HTA Positronen Emissie Tomografie in België

KCE reports vol.22 A

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
2005

Het Federaal Kenniscentrum voor de Gezondheidszorg

Voorstelling :	Het Federaal Kenniscentrum voor de Gezondheidszorg is een parastatale, opgericht door de programma-wet van 24 december 2002 (artikelen 262 tot 266) die onder de bevoegdheid valt van de Minister van Volksgezondheid en Sociale Zaken. Het centrum is belast met het realiseren van beleidsondersteunende studies binnen de sector van de gezondheidszorg en de ziekteverzekering.

Raad van Bestuur

Effectieve leden :	Gillet Pierre (Président), Cuypers Dirk (Vice-Président), Avontroodt Yolande, Beeckmans Jan, Bovy Laurence, De Cock Jo (Vice-Président), Demaeseneer Jan, Dercq Jean-Paul, Goyens Floris, Keirse Manu, Kesteloot Katrien, Maes Jef, Mariage Olivier, Mertens Pascal, Mertens Raf, Moens Marc, Ponce Annick, Smiets Pierre, Van Ermen Lieve, Van Massenhove Frank, Vandermeeren Philippe, Verertbruggen Patrick, Vranckx Charles
Plaatsvervangers :	Boonen Carine, Cuypers Rita, De Ridder Henri, Decoster Christiaan, Deman Esther, Désir Daniel, Heyerick Paul, Kips Johan, Legrand Jean, Lemye Roland, Lombaerts Rita, Maes André, Palsterman Paul, Pirlot Viviane, Praet François, Praet Jean-Claude, Remacle Anne, Schoonjans Chris, Servotte Joseph, Vanderstappen Anne
Regeringscommissaris :	Roger Yves

Directie

Algemeen Directeur :	Dirk Ramaekers
Algemeen Directeur adjunct :	Jean-Pierre Closon

HTA Positronen Emissie Tomografie in België

KCE reports vol. 22A

CLEEMPUT I, DARGENT G, POELMANS J, CAMBERLIN C, VAN DEN BRUEL A, RAMAEKERS D

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
2005

KCE reports vol.22A

Titel :	HTA Positronen Emissie Tomografie in België
Auteurs :	Cleemput I, Dargent G, Poelmans J, Camberlin C, Van den Bruel A, Ramaekers D
Externe experten:	De Neve W, Flamen P, Goldman S, Hustinx R, Jerusalem G, Lonneux M, Maes A, Moons K, Mortelmans L, Salmon E, Uyl-de Groot C
Externe validatoren :	Buntinx F, Facey K, Winnen B
Conflicts of interest :	De meerderheid van de experts werkt in een ziekenhuis met PETscanner. Eén van de onafhankelijke reviewers die het rapport goedkeurden, K Facey, werkt momenteel aan een systematisch overzicht over het gebruik van PET scans in kanker voor het DoH van Groot Brittanië. De experts en validatoren werkten mee aan het wetenschappelijke rapport. Experts en validatoren stonden niet in voor de aanbevelingen voor het beleid. Deze aanbevelingen vallen onder de volledige verantwoordelijkheid van het KCE .
Dankwoord:	Federaal Agentschap voor Nucleaire Controle (FANC), Federale Overheidsdienst Volksgezondheid, Veiligheid van de Voedselketen en Leefmilieu (DG3), producenten van FDG and PET scanners, Belgisch Genootschap voor Nucleaire Geneeskunde- Werkgroep PET, Nationaal Kankerregister, RIZIV, de leden van INAHTA die deelgenomen hebben aan de enquête
Layout:	Bogaerts Dimitri, Chalon Patrice
Brussel:	Juni 2006 (2nd edition), Oktober 2005 (1st edition)
MeSH :	Tomography, Emission-Computed; Fluorodeoxyglucose F18/*diagnostic use; Technology Assessment, Biomedical; Sensitivity and specificity
NLM classificatie :	W74

Taal : Nederlands
Format : Adobe® PDF™ (A4)

Wettelijk depot : D2005/10.273/29

Dit document is beschikbaar vanop de website van het Fedeaal Kenniscentrum voor de Gezondheidszorg.

Hoe refereren naar dit document?
Cleemput I, Dargent G, Poelmans J, Camberlin C, Van den Bruel A, Ramaekers D. HTA Positronen Emissie Tomografie in België. Bruxelles : Federaal Kenniscentrum voor de Gezondheidszorg (KCE); Oktober 2005. KCE Reports vol. 22A. Ref. D2005/10.273/29.

Federaal Kenniscentrum voor de Gezondheidszorg - Centre Fédéral d'Expertise des Soins de Santé.

Résidence Palace (10de verdieping-10ème étage)
Wetstraat 155
B-1040 Brussel
België

Tel: +32 [0]2 287 33 88
Fax: +32 [0]2 287 33 85

Email : info@kenniscentrum.fgov.be , info@centredexpertise.fgov.be
Web : http://www.kenniscentrum.fgov.be , http://www.centredexpertise.fgov.be

Voorwoord

In de gezondheidszorg is men voortdurend op zoek naar goede alternatieven voor ingrijpende interventies. Positron Emission Tomography (PET) scanners zijn hiervan een mooi voorbeeld. PET is een niet-invasieve techniek met weinig risico's die o.a. toelaat om metastasen op te sporen bij sommige patiënten met sommige kankers en waardoor mogelijks invasieve ingrepen vermeden kunnen worden. Voor de patiënt en de arts klinkt dit uiteraard zeer aantrekkelijk.

PET is echter ook een zware medische technologie. Tegenover de potentiële voordelen van PET staan de hoge kosten. Naast de evaluatie van de diagnostische doeltreffendheid moeten ook de kosten bekeken worden en moet afgewogen worden of de baten opwegen tegen de bijkomende kosten van PET. Nog voor er duidelijke bewijzen waren van die klinisch diagnostische meerwaarde van PET nam de vraag van diverse belangengroepen naar (de financiering van) PET scanners toe en ontstond er een niet aflatende druk om de technologie ruim beschikbaar te maken in meer ziekenhuizen.

De hamvraag blijft hoeveel PET-scanners België nu nodig heeft? Internationaal is België, met momenteel 13 erkende en een handvol niet-erkende PET scanners, duidelijk koploper. Uit onze enquête blijkt dat de planning in een aantal landen in de richting gaat van de Belgische (officiële) situatie. Het is onduidelijk of klinisch-wetenschappelijke argumenten, dan wel juist het opbod door de vergelijking met landen met hoge aantallen scanners zoals België daar als leidraad dienen.

Het KCE toont zich met dit onderzoek ook voor het eerst op internationaal vlak. De internationale enquête wordt geïntegreerd in het werk van INAHTA over PET[1] en andere landen kijken uit naar dit rapport om het te kunnen gebruiken in hun eigen assessments. Omdat zowat alle Europese landen in het algemeen met een toenemende technology push worden geconfronteerd, is het in de steigers staande Europese HTA netwerk[2], EUNetHTA, vanuit beleidsmatig standpunt een belangrijk Europees initiatief dat hopelijk de efficiëntie en impact van HTA op het gezondheidsbeleid nog zal verhogen.

Dit HTA is het resultaat van een vruchtbare samenwerking tussen het KCE en externe instanties. Hierbij wensen wij hen van harte te bedanken voor de nuttige input: de Belgische en buitenlandse experten, het Belgish Genootschap voor Nucleaire Geneeskunde-Werkgroep PET, het Federaal Agentschap voor Nucleaire Controle, het Directoraat Generaal Geneesmiddelen van de FOD Volksgezondheid, Veiligheid van de Voedselketen en Leefmilieu, en het Nationaal Kankerregister. Verder willen wij ook de leden van INAHTA danken die hebben deelgenomen aan de enquête over PET in de verschillende landen. Tot slot wensen wij onze waardering uit te spreken voor de input van de producenten van PET scanners en van FDG.

Jean-Pierre CLOSON
Adjunct Algemeen Directeur

Dirk RAMAEKERS
Algemeen Directeur

[1] http://www.inahta.org and visit section on PET
[2] http://www.eunethta.net

Samenvatting

Inleiding

"Positron Emission Tomography" (PET) is een niet-invasieve diagnostische technologie die in welbepaalde aandoeningen een afwijkend metabolisme in aangetaste organen of weefsels kan aantonen. PET maakt gebruik van een radioactieve merkstof gekoppeld aan een biochemische stof zoals bv. 18 Fluoro-deoxy-glucose (FDG). FDG wordt in grote hoeveelheden opgenomen door bepaalde types van kankercellen en ontstekingscellen.

PET lijkt een aantrekkelijke optie te zijn voor een aantal indicaties maar het is wel een zeer dure technologie. De investeringskosten en de werkingskosten zijn hoog. Bijgevolg heeft PET een grote impact op het gebruik van middelen binnen de gezondheidszorg. Een aantal vragen dient dan ook gesteld bij beslissingen over de implementatie en planning van PET. Ten eerste, is deze technologie klinisch nuttig, meer bepaald wat is de waarde van PET voor het verbeteren van de diagnose en de uitkomst voor de patiënt (verminderde morbiditeit of mortaliteit)? Ten tweede, rechtvaardigt de toegevoegde waarde de extra kosten? En ten derde, wat is de te verwachten impact van PET op de organisatie van de gezondheidszorg in België?

Doelstellingen

De doelstellingen van dit Health Technology Assessment (HTA) zijn drieledig:

- De klinische doeltreffendheid en de doelmatigheid (kosten-effectiviteit) van PET voor verschillende indicaties evalueren op basis van de literatuur;
- De huidige situatie van PET in België beschrijven, met inbegrip van de regulering, frequentie van gebruik en kosten voor het gezondheidszorgbudget, en de Belgische situatie vergelijken met andere Westerse landen;
- Aanbevelingen formuleren voor de organisatie en financiering van PET diensten in België.

Methodologie

Dit HTA volgt de standaard methodologie voor HTA van het KCE. Een multidisciplinair team van externe experten las voorlopige versies van het rapport regelmatig kritisch na en gaf de nodige feedback en input. Producenten en verdelers van PET scanners en FDG werden gecontacteerd en verstrekten informatie over hun producten. Het Belgische Genootschap voor Nucleaire Geneeskunde - Workgroup PET stelde gegevens ter beschikking over het gebruik van PET in België. Het finale rapport werd gevalideerd door drie externe validatoren.

Recente HTA rapporten en systematische literatuuroverzichten vormden de basis voor de beoordeling van de klinische doeltreffendheid van PET. Bij gebrek aan éénduidigheid van besluiten over de klinische doeltreffendheid of bij het ontbreken van een HTA rapport of systematisch literatuuroverzicht (na 2002) werden voor welbepaalde indicaties bijkomende primaire studies gezocht.

De doeltreffendheid van PET werd geëvalueerd in oncologie, cardiologie, neurologie en andere potentiële indicaties. De keuze van de studies werd beperkt tot deze waarbij een 'dedicated PET' scanner werd gebruikt met FDG als merkstof. Twee onderzoekers van het KCE selecteerden de studies op een systematische wijze en onafhankelijk van elkaar. Hierbij werd gebruik gemaakt van standaard lijsten voor de beoordeling van de kwaliteit van de studies. Uit de weerhouden studies werd de belangrijkste informatie geselecteerd en ondergebracht in een hiërarchische classificatie van diagnostische doeltreffendheid bij technologieën voor medische beeldvorming. Het laagste niveau in deze classificatie bevat informatie die beperkt is tot evidence op het louter technische niveau (het technisch functioneren van de technologie). Het hoogste niveau bevat

evidence van klinische doeltreffendheid (effecten van de diagnostische technologie op de uitkomst voor de patiënt) en van kosten-effectiviteit (niveau 1: technische doeltreffendheid; 2: diagnostische accuraatheid; 3: invloed op diagnostisch denken; 4: invloed op therapeutisch beleid; 5: invloed op de uitkomst voor de patiënt; 6: kosten-effectiviteit).

Bij gebrek aan systematische literatuuroverzichten werd voor de evaluatie van de kosten-effectiviteit van PET gezocht naar primaire studies bij elke indicatie. De kwaliteitscontrole van deze studies gebeurde met behulp van een standaard instrument.

In 12 landen werd een enquête uitgevoerd om de ervaringen met PET in het buitenland te schetsen en te vergelijken met de Belgische situatie. Op basis van de gevonden evidence voor klinische doeltreffendheid en doelmatigheid van PET bij verschillende indicaties schatten wij vervolgens het aantal PET scanners nodig in België. Hierbij werden verschillende hypotheses gehanteerd met betrekking tot het minimale vereiste niveau van evidence en met betrekking tot de gebruiksintensiteit van een PET scanner.

Klinische doeltreffendheid en kosten-effectiviteit

PET wordt het meest frequent gebruikt in de oncologie. Alle HTA rapporten en systematische literatuuroverzichten geven aan dat de methodologische kwaliteit van studies over PET in oncologie doorgaans zwak tot matig is. Verschillende bronnen van vertekening werden geïdentificeerd. Meestal leidt deze vertekening tot een overschatting van de diagnostische doeltreffendheid van PET. Dit is minder het geval bij studies over het gebruik van PET bij longkanker: meerdere studies werden uitgevoerd bij een voldoende aantal patiënten en deze studies waren vaker van een betere kwaliteit dan de meeste studies bij andere oncologische indicaties. In weerwil van de bedenkelijke methodologische kwaliteit van de meeste studies, hebben meerdere auteurs toch pragmatische aanbevelingen geformuleerd voor het gebruik van PET. Zo werden in Australië bijvoorbeeld tijdelijke fondsen vrijgemaakt voor beloftevolle indicaties om aanvullende gegevens te verzamelen en bewijskracht van een hogere kwaliteit te leveren. Deze informatie kan dan verder gebruikt worden om toekomstige beleidsbeslissingen over het routinematige gebruik van PET te ondersteunen.

De evidence voor de klinische doeltreffendheid van PET is het meest overtuigend bij het initiële stadiëringsonderzoek van niet-kleincellig longcarcinoom en voor de opsporing en de plaatsbepaling van recidieven van colorectaal carcinoom (lokaal recidief, intra- of extrahepatisch recidief). Bij deze indicaties biedt PET de mogelijkheid om veralgemeende uitzaaiingen uit te sluiten vooraleer men overgaat tot een mogelijk curatieve heelkundige ingreep.

Hoewel men, bij een aantal indicaties, de evidence over de diagnostische waarde van PET als voldoende kan beschouwen blijft er toch voor een aantal van hen een grote mate van onzekerheid bestaan over de klinische doeltreffendheid meer bepaald over de rol van PET voor de uiteindelijke uitkomst voor de patiënt op het vlak van mortaliteit en morbiditeit. De indicaties waar minstens een invloed op diagnostisch denken werd bewezen, zijn de volgende:

- diagnose van een solitaire nodule in de long >1cm (op basis van een negatief PET scan resultaat kan een invasieve biopsieprocedure worden vermeden),
- evaluatie van een residuele lymfoommassa na therapie (hiervoor is ook een PET scan noodzakelijk bij de initiële stadiëring): de behandeling kan vervolgens aangepast worden op basis van het resultaat van deze PET scan,
- stadiëring (detectie van regionale lymfekliermetastasen) en restadiëring (detectie van resterende of recidiverende tumor na behandeling) van hoofd- en halscarcinoom,
- bepaling van het behandelingseffect van neoadjuvante therapie en van de prognose bij patiënten met slokdarmcarcinoom waarbij curatieve heelkunde gepland wordt,

- bepaling van het behandelingseffect bij gastrointestinale stromale tumoren (GIST) (dit is evenwel een zeer zeldzame aandoening),
- en bepaling van de myocardiale viabiliteit bij patiënten die in aanmerking komen voor een revacularisatie.

Bij een aantal andere indicaties is er slechts evidence tot het niveau van diagnostische accuraatheid. Aanvullende studies zijn nodig om de diagnostische waarde van PET in deze indicaties te bewijzen. Deze indicaties zijn de volgende:

- diagnose van residueel of recidiverend niet-kleincellig longcarcinoom en pleuracarcinoom;
- stadiëring en restadiëring van kleincellig longcarcinoom;
- initiële stadiëring en diagnose van recidiverend lymfoom (er zijn enkele studies over veranderingen in therapeutisch beleid, doch met belangrijke heterogeniteit); prognose en evaluatie van het behandelingseffect bij lymfoom,
- diagnose van een occulte primaire tumor waarvan de aanwezigheid vermoed wordt op basis van een positieve halsklier of solitaire metastase en waarbij de klassiek uitgevoerde onderzoeken negatief zijn;
- initiële diagnose en stadiëring van colorectaal carcinoom;
- stadiëring van maligne melanoom (voor uitzaaiingen op afstand bij patiënten met een primair of recidiverend maligne melanoom);
- stadiëring en restadiëring van borstcarcinoom;
- stadiëring van slokdarmcarcinoom, meer bepaald voor uitzaaiingen op afstand;
- detectie van recidief van een epitheliaal thyroid carcinoom bij gestegen biomarkers maar niet bevestigd door ^{131}I scintigrafie;
- stadiëring, evaluatie van een residuele massa en detectie van recidief van cervixcarcinoom;
- initiële diagnose en detectie van recidief van ovariumcarcinoom;
- stadiëring van niercarcinoom;
- stadiëring en evaluatie van een residuele massa van testiscarcinoom;
- diagnose van de ziekte van Alzheimer (de therapeutische consequenties zijn onduidelijk; de doeltreffendheid van cholinesterase inhibitoren wordt momenteel in vraag gesteld).

Er werd slechts beperkte evidence gevonden over de diagnostische accuraatheid in ondermeer de volgende indicaties: diagnose van primair hoofd- en halscarcinoom wanneer de resultaten van CT/MRI onduidelijk zijn; diagnose en detectie van uitzaaiingen van pancreascarcinoom; diagnose van hersentumor, meer bepaald het onderscheiden van een hoog-gradig en laag-gradig glioma; diagnose van hersentumor, meer bepaald het meebepalen van het biopsie-traject en afgrenzing van de zone voor therapie; restadiëring van hersentumor meer bepaald het onderscheiden van een recidief van maligniteit en bestralingsnecrose; pre-chirurgische evaluatie van refractaire epilepsie.

Een belangrijke opmerking hierbij is dat dit meestal zeldzame indicaties zijn en dat voldoende grote en conclusieve klinische studies over de diagnostische waarde geen sinecure zijn.

Voor andere indicaties zoals koorts van onbekende oorsprong is de huidige evidence nog te summier om besluiten te kunnen trekken over de diagnostische doeltreffendheid van PET. Ook dit is een weinig voorkomende indicatie.

Voor een aantal indicaties werd evidence gevonden tegen het gebruik van PET: diagnose bij patiënten verwezen met een afwijkende mammografie of een palpabele massa in de borst, stadiëring van oksel-lymfeklieren bij patiënten met borstcarcinoom maar zonder palpabele oksel-lymfeklieren en zonder evidentie voor uitzaaiingen op afstand, diagnose van een primitive maligne levertumor. Bij deze indicaties is het risico op vals negatieve PET resultaten te hoog. Indien het medische beleid gebaseerd wordt op een dergelijk misleidend PET scan resultaat (vermijden van een biopsie bij de eerste en derde indicatie, vermijden van een sentinel lymfeklier biopsie en/of uitruiming van de okselklieren bij de derde indicatie) kan dit bij een te grote groep patiënten aanleiding geven tot onderbehandeling en een verhoogde mortaliteit.

Organisatie en patiëntenperspectief

Van alle landen die geantwoord hebben op onze enquête heeft België het grootste aantal PET scanners en het grootste aantal PET scans per jaar. Er zijn 13 erkende PET scanners in België (dit zijn er 1,26 per miljoen inwoners), maar er zijn sterke aanwijzingen (uit gegevens van het Federaal Agentschap voor Nucleaire Controle (FANC) over het transport van FDG) dat er ook een aantal niet-erkende PET scanners werkzaam zijn in België. Per jaar worden ongeveer 12.000 PET scans uitgevoerd voor terugbetaalde indicaties. Het totale aantal scans, inclusief PET voor niet-terugbetaalde indicaties en voor wetenschappelijke onderzoeksdoeleinden, is bijna 20.000 per jaar. De meest frequente indicaties voor PET zijn longcarcinoom, colorectaal carcinoom, non-Hodgkin lymfoom, hoofd- en halscarcinoom, en Hodgkin lymfoom. Buiten Hodgkin lymfoom zijn dit de meest frequente kankers in België.

De geografische spreiding van PET centra reflecteert in eerste instantie de lokalisatie van academische ziekenhuizen, in tweede instantie de lokalisatie van een ziekenhuis gespecialiseerd in oncologie en tenslotte de bevolkingsdichtheid. Er is een hoge concentratie van PET scanners in Brussel, dat de dichtstbevolkte regio is van België. Zes PET centra hebben een eigen cyclotron voor de productie van FDG. De 7 andere PET centra moeten beroep doen op één van de twee commerciële producenten die een toelating hebben voor de productie en verdeling van FDG in België. Gegevens over transport van FDG tonen echter aan dat PET centra frequent beroep doen op niet-commerciële academische centra die een eigen cyclotron hebben voor de toelevering van FDG.

Financiering van PET gebeurt via drie kanalen: (1) een jaarlijks vast bedrag voor apparatuur, uitrusting, onderhoud en werking, (2) een honorarium per scan en (3) een bedrag per eenheid FDG.

Vanuit het standpunt van de patiënt is het voornaamste potentiële voordeel van PET dat het, bij bepaalde indicaties, medische beslissingen kan beïnvloeden en daardoor mogelijks bepaalde invasieve (diagnostische) procedures kan vermijden. Daarnaast kan het voor een patiënt ook waardevol zijn om met PET een bevestiging van een eerder gestelde diagnose te krijgen.

Voor de grote meerderheid van patiënten kan PET als een uiterst veilige techniek beschouwd worden. Nochtans kan een patiënt ook schade ondervinden die te maken heeft met de onduidelijkheid die heerst over de klinische doeltreffendheid van PET. Schade kan ontstaan indien beslissingen voor patiëntenbeleid genomen worden op basis van een vals positief of vals negatief PET resultaat. Het gevolg van verkeerde testresultaten kan dus leiden tot onjuiste of suboptimale behandeling.

Conclusies en aanbevelingen

In een gezondheidszorgsysteem dat geconfronteerd wordt met beperkte middelen en steeds toenemende behoeften moeten keuzen gemaakt worden. Keuzen in de gezondheidszorg kunnen geïnspireerd worden door een combinatie van factoren: wetenschappelijke bewijsvoering, financiële overwegingen, druk van belangengroepen, maatschappelijke waarden… Efficiënt gebruik van middelen vereist een benadering die

gebaseerd is op evidence van klinische doeltreffendheid en doelmatigheid. In het geval van PET is de evidence van impact op behandelingsstrategieën en/of uitkomst voor de patiënt beperkt tot slechts enkele indicaties. Meer frequent is er evidence van diagnostische accuraatheid, wat erop wijst dat PET mogelijks van enig bijkomend diagnostisch nut kan zijn ten opzichte van andere diagnostische technieken.

Voor een mogelijke verbetering van het therapeutische beleid en de mortaliteit en morbiditeit van de patiënt zijn 3 PET scanners in België voldoende. Een meer toegeeflijke benadering, die alle indicaties meeneemt waarvoor PET nuttig kan zijn in termen van het veranderen/verbeteren van een diagnose, leidt tot een schatting van maximum 10 PET scanners, afhankelijk van het jaarlijkse volume PET onderzoeken per scanner (zie tabel). Daarbuiten kan PET beschouwd worden als een technologie bestemd voor klinisch wetenschappelijk onderzoek. Zelfs indien het aantal PET scans voor terugbetaalde indicaties gedurende het voorbije jaar licht zou zijn toegenomen (in 2004 werden de RIZIV nomenclatuurcodes van PET aangerekend voor 13.500 scans), dan nog zullen er zeker niet meer dan 26.000 scans zijn uitgevoerd. Dit is de theoretische capaciteit van de 13 "erkende" PET scanners. Bovendien blijkt uit onze gegevens en onze contacten met experten dat een aantal PET scanners momenteel nog steeds niet hun volle capaciteit benutten. Meer PET scanners zullen de behandeling en/of de mortaliteit/morbiditeit van patiënten niet verbeteren en zullen bijgevolg leiden tot een inefficiënt gebruik van middelen.

Tabel: Schatting van de behoefte aan PET scanners in België gebaseerd op de gebruiksintensiteit van 11 van de 13 "erkende".

	Aantal scans in 2003, voor terugbetaalde en niet-terugbetaalde indicaties en voor onderzoeksdoeleinden	Behoefte aan PET scanners in België in functie van de gebruiksintensiteit van PET	
		1500 scans per PET scanner per jaar	2000 scans per PET scanner per jaar
Niveau van evidence ≥ 4	5 078	3	3
Niveau van evidence ≥ 3	7 379	5	4
Niveau van evidence ≥ 2	14 408	10	7
Alle indicaties, los van het niveau van evidence	19 727	13	10

Momenteel is er een overcapaciteit aan PET in België. Het hoge aantal (erkende en niet-erkende) PET scanners kan niet gerechtvaardigd worden op basis van wetenschappelijke bewijsvoering en demografische gegevens alleen. Meer dan 10 PET scanners houden in België leidt tot inefficiënties in het gebruik van middelen: de bijkomende kosten gaan niet gepaard met een betere klinische uitkomst. Maar efficiënt gebruik van middelen is niet de enige drijfveer van het gezondheidsbeleid. Andere doelstellingen kunnen eveneens een belangrijke rol spelen in het beslissingsproces over PET.

Een eerste argument om overcapaciteit in PET te behouden zijn eventuele nieuwe indicaties voor PET waarvoor onderzoek nu nog loopt, de veroudering van de bevolking en de toenemende incidentie van de huidige indicaties voor PET. Het behouden of creëren van overcapaciteit omwille van onzekere toekomstige baten is duur, zeker in een domein dat gekenmerkt wordt door voortdurende technologische ontwikkelingen en een relatief snelle veroudering van bestaande uitrusting.

Een tweede argument voor het instandhouden van een beperkte overcapaciteit is gelijke toegang tot zware medische technologie. Een groter aantal PET scanners zou een meer gelijke toegang tot PET kunnen realiseren, maar dit rechtvaardigt niet de hoge concentratie van PET scanners in het centrum van het land.

Een derde argument om de 13 erkende PET scanners te behouden is wetenschappelijk onderzoek. Er gebeurt heel wat klinisch onderzoek in België, zij het op een eerder beperkt deel van de (erkende) PET scanners. Slechts enkele onderzoeksgroepen publiceren regelmatig in belangrijke internationale tijdschriften. Met de overcapaciteit aan PET scanners kan en zou België verder een leidende rol moeten spelen in klinisch PET onderzoek, meer bepaald naar de impact van PET op het therapeutisch beleid, de uiteindelijke uitkomst voor de patiënt en de kosten-effectiviteit. Deze elementen zijn cruciaal voor zowel de patiënten als de ziekteverzekering. Indien financiële middelen voor onderzoek uit het gezondheidszorgbudget komen, moet dit transparant zijn en mag dit niet overlappen met andere financiële stromen voor onderzoeksdoeleinden, bijvoorbeeld vanwege de industrie.

PET scanners worden soms onderbenut om financiële redenen. PET centra die geen cyclotron hebben, moeten FDG aankopen bij commerciële ondernemingen. De prijs van een dosis FDG is hoger dan de terugbetaling. Onderaanneming van FDG productie naar academische centra met een eigen cyclotron is wettelijk niet toegelaten, maar gegevens van het FANC tonen aan dat onderaanneming frequent gebeurt in België. Volgens de Federale Overheidsdienst van Volksgezondheid, Veiligheid van de Voedselketen en Leefmilieu leidt deze situatie tot onduidelijkheden over verantwoordelijkheid, veiligheid en kwaliteit van de producten. Er wordt momenteel een wettelijke regeling uitgewerkt voor de onderaanneming van magistrale bereidingen, inclusief radiofarmaceutica. Daarnaast worden er praktijkrichtlijnen ontwikkeld voor ziekenhuisapotheken.

De nieuwe regulering zal de productiekost van FDG in niet-commerciële cyclotrons beïnvloeden. Bijkomende investeringen zullen nodig zijn voor onder meer kwaliteitscontrole, opleiding van personeel en werkingsprocedures. Momenteel rekenen de niet-commerciële centra met een cyclotron lagere prijzen aan voor FDG dan de commerciële firma's. Dit zal wellicht niet zo blijven onder de nieuwe reglementering. De terugbetaling van FDG moet in verhouding zijn met de eisen die gesteld worden aan de productie en verdeling van FDG door de overheid.

Een klein deel van de overcapaciteit aan PET zal misschien nodig zijn om de toegenomen vraag aan PET scans op te vangen ten gevolge van de mogelijke sluiting van illegale PET scanners. Het financieringssysteem moet efficiënt gebruik van zware medische technologie zoals PET scanners stimuleren. Een semi-vast budget voor kosten van uitrusting, onderhoud en werkingkosten, gecombineerd met een adequate terugbetaling van FDG zou een meer efficiënt gebruik van erkende PET scanners aanmoedigen. De indicaties waarvoor PET beeldvorming is terugbetaald in de huidige Belgische terugbetalingsregeling stemmen min of meer overeen met de indicaties in dit rapport, tenminste indien het criterium van diagnostische accuraatheid (niveau 2) voldoende wordt geacht voor het veralgemeende gebruik van PET voor bepaalde indicaties. Een eventuele verdere uitbreiding van terugbetaalde indicaties moet rekening houden met de mogelijke impact van PET op het therapeutische beleid en de uitkomst voor de patiënt. Ten slotte is het niet onbelangrijk te weten dat voor niet-terugbetaalde indicaties andere facturatiecodes voor nucleaire geneeskunde worden gebruikt. Deze codes kunnen eveneens gebruikt worden door specialisten nucleaire geneeskunde in centra met een niet-erkende PET scanner.

Beleidsmakers in de gezondheidszorg moeten kiezen tussen efficiënt gebruik van schaarse middelen en andere beleidsdoelstellingen voor PET. De doelstelling van doelmatigheid kan in conflict komen met andere doelstellingen zoals het garanderen van gelijke toegang tot dure medische technologie. Meer efficiëntie vraagt om het verdwijnen van PET scanners in België. Andere doelstellingen zoals toegankelijkheid kunnen pleiten voor het behoud van het huidige aantal PET scanners, op voorwaade dat de nodige aandacht wordt gegeven aan een gelijkmatige geografische spreiding.

Als het beleid ervoor kiest om de overcapaciteit te behouden, opent dit perspectieven voor meer wetenschappelijk onderzoek. België kan op die manier een leidende rol spelen in het wetenschappelijk onderzoek met PET. Een duidelijk onderzoeksplan moet gecreëerd worden, met speciale aandacht voor onderzoek dat kan leiden naar mogelijke verbeteringen in het therapeutisch beleid en de uitkomst voor de patiënt door PET. Financiering van PET onderzoek moet transparant zijn en gebaseerd op criteria zoals publicaties en impact factor.

Het KCE bevelt aan om een udpdating van deze studie in enkele jaren uit te voeren.

Kernboodschappen

- In vergelijking met vele andere Westerse landen heeft België momenteel het grootste aantal PET scanners en het grootste aantal scans per jaar. Dit kan niet gerechtvaardigd of verklaard worden op basis van alleen maar klinisch-wetenschappelijke evidence of demografische kenmerken.
- Het aantal erkende PET scanners in België overtreft het aantal PET scanners dat België nodig heeft op basis van behoefteschattingen. Er is bijgevolg een overcapaciteit aan PET scanners. Er zijn bovendien aanwijzingen dat er in België nog steeds een aantal niet-erkende PET scanners werkzaam zijn.
- Hoewel er voor een aantal indicaties evidence bestaat dat PET in vergelijking met andere technieken een diagnostisch voordeel kan hebben is er slechts voor zeer weinig indicaties evidence voor een betere klinische uitkomst voor de patiënt. Voor de meeste indicaties is er geen evidence dat PET bijdraagt tot een betere uitkomst.
- Er is nood aan een wettelijk kader voor de uitbesteding van FDG productie aan niet-commerciële PET centra met een eigen cyclotron. Hoewel dit wettelijk niet is toegelaten gebeurt uitbesteding frequent in België.
- De prijs die de PET centra betalen voor extern toegeleverde FDG is hoger dan de terugbetaling per dosis vanwege het RIZIV. De terugbetaling voor FDG moet aangepast zijn aan de eisen die door de overheid gesteld worden voor de productie en levering van FDG.
- Voor de diagnose/behandeling van patiënten met indicaties waarvoor er evidence is dat PET kan bijdragen tot een lagere mortaliteit en morbiditeit volstaan 3 PET scanners in België. Rekening houdend met de huidige prevalentie van indicaties waar PET slechts nut op het vlak van diagnostische accuraatheid heeft, zijn 10 PET scanners voldoende in België.
- Omdat ontwikkelingen in diagnostische technologiën kunnen vooruitlopen op ontwikkelingen in behandeling, is het mogelijk dat de klinische doeltreffendheid en kosten-effectiviteit van PET slechts duidelijk worden op langere termijn. Het in stand houden of creëren van overcapaciteit ten behoeve van een potentieel voordeel in de toekomst is niet alleen erg kostelijk maar ook niet echt nuttig gegeven de voortdurende technologische vernieuwingen op dit terrrein.

- Maximaal gebruik van de huidige (over)capaciteit en doelmatig gebruik van middelen in de gezondheidszorg zijn twee niet verenigbare doelstellingen in de context van PET. Gebruik van de volledige capaciteit van alle goedgekeurde PET scanners impliceert hogere kosten die niet in verhouding staan tot verbeteringen in termen van uitkomsten die voor patiënten belangrijk zijn, zoals therapeutische planning en mortaliteit en morbiditeit.
- Beleidsverantwoordelijken in de gezondheidszorg moeten een keuze maken tussen doelmatigheid (met name het gebruik van PET beperken tot indicaties waarbij het klinisch nut van PET al duidelijk is aangetoond), hetgeen de sluiting impliceert van een aantal PET scanners, en andere politieke doelstellingen, zoals het verzekeren van de toegankelijkheid van PET.
- Indien de optie wordt genomen om een overcapaciteit aan PET scanners te behouden, is er een belangrijke opportuniteit voor wetenschappelijk onderzoek met PET in België. Aangezien er publieke middelen zullen gebruikt worden voor dit wetenschappelijk onderzoek, moet dit onderzoek duidelijke doelstellingen hebben die relevant zijn voor de samenleving. Als er middelen uit het gezondheidszorgbudget worden geïnvesteerd in dergelijk onderzoek, moet dit transparant zijn voor de bevolking en mag dit niet overlappen met andere geldstromen naar de ziekenhuizen voor wetenschappelijk onderzoek (bv. afkomstig van de industrie).

Table of contents

LIST OF ABBREVIATIONS

Organizations

AETMIS Agence d'Évaluation des Technologies et des Modes Intervention en Santé (Québec)
AETS Agencia de Evaluación de Tecnologias Sanitarias (Spain)
AETSA Agencia de Evaluación de Tecnologias Sanitarias de Andalucia (Spain)
AHCPR Agency for Health Care Policy and Research, Center for Practice and Technology Assessment (USA)
AHFMR Alberta Heritage Foundation for Medical Research (Canada)
AHRQ Agency for Health Research and Quality (USA)
BCBSA-TEC Blue Cross-Blue Shield Association -Technology Evaluation Center (USA)
BCBS Blue Cross-Blue Shield (see BCBSA-TEC)
CAHTA - AATRM Catalan Agency for Health Technology Assessment, Barcelona (Spain)
CCOHTA Canadian Coordinating Office for Health Technology Assessment (Canada)
CEDIT Comité d'Evaluation et de Diffusion des Innovations Technologiques (France)
CIHR Canadian Institute of Health Research
CMS Centers for Medicare and Medicaid Services (USA - ex-HCFA)
DACEHTA Danish Centre for Evaluation and Health Technology Assessment (Danemark)
DARE Database of Abstracts of Reviews of Effects
ECRI Emergency Care Research Institute (Pennsylvania, USA)
FNCLCC Fédération Nationale des Centres de Lutte Contre le Cancer (France)
HCFA Health Care Financing Administration (USA – see now CMS)
HTAi Health Technology Assessment international
HTBS Health Technology Board of Scotland (Scotland)
HSTAT NLM Health Services/technology Assessment Text – National Library of Medicine
ICES Institute for Clinical Evaluative Sciences (Canada)
ICP Institute for Clinical PET (USA)
ICSI Institute for Clinical Systems Improvment
INAHTA International Network of Agencies for Health Technology
MINNESOTA DoH Minnesota Department of Health
MIHSR Monash Institute of Health Services Research
MSAC Medical Services Advisory Committee (Australia)
NCCHTA National Coordinating Centre for Health Technology Assessment (UK)
NHS National Health Services (UK)
NHSEED NHS Economic Evaluation Database
NHSCRD NHS Centre for Reviews and Dissemination University of York (UK)
NHS R&D Programme National Health Service Research and Development Programme
NICE National Institute for Health and Clinical Excellence (UK)
NZHTA New Zealand Health Technology Assessment
OHPPR Office of Oregon Health policy and Research
RAND Rand Corporation
RIZIV/INAMI Rijksinstituut voor Ziekte- en Invaliditeitsverzekering/Institut National d'Insurance Maladie et Invalidité
SNHTA Swiss network for HTA
VATAP Veterans Affairs, Technology Assessment Program (USA)
WHO World Health Organisation

Terms

AC Adenocarcinoma
AJCC American Joint Committee on cancer
ALN Axillary lymph nodes
ALND Axillary lymph node dissection
APR-DRG All Patients Revised - Diagnostic Related Groups

BAC Bronchio alveolar carcinoma
Bq Becquerel
c clinically
C Carbon
^{11}C Radioactive carbon
CA 125 Cancer Antigen 125
CABG Coronary artery bypass graft
CEA Carcino embryonic antigen
CI Confidence Interval
Cont Contralateral
CRT Chemoradiotherapy
CT Computed Tomography
CWU Conventional work up
Cyto Cytology
DEALE Declining exponential approximation of life expectancy
DOR Diagnostic odds ratio
EEG Electroencephalography
e.g. exempli gratia
ERCP Endoscopic retrograde cholangiopancreaticography
EUS Esophageal (endoscopic) ultrasound
FDG Fluoro-deoxy-glucose
FN False negatives
FNAB Fine needle aspiration biopsy
FP False positives
FU Follow up
FUO Fever of Unknown Origin
g gram
Ga Scinti Gallium scintigraphy
GIST Gastrointestinal Stromal Tumour
GMP Good manufacturing practices
HD Hodgkin's disease
HNSCC Head and Neck squamous cell carcinoma
HTA Health Technology Assessment
HVMR Hippocampal formation volumetric assessment
I Iodium
ICER Incremental cost-effectiveness ratio
i.e. id est
IMT Iodo-Methyl-Tyrosine
LE Life expectancy
LR Likelihood ratio
LR+ Positive likelihood ratio
LR- Negative likelihood ratio
LYS Life year saved
Mets Metastases
mos months
MRI Magnetic resonance imaging
MRM Magnetic resonance mammography
n number
N Node
^{13}N Radioactive nitrogen
NHL Non Hodgkin's lymphoma
N0 Node negative
NPV Negative predictive value
NSCLC Non-small cell lung cancer
^{15}O Radioactive oxygen
OPT Occult primary tumour

PET Positron emission tomography
PET/CT Positron emission tomography combined with computed tomography
PPV Positive predictive value
PTCA Percutaneous transluminal coronary angioplasty
Pts Patients
QALY Quality-adjusted life year
^{83}Rb Radioactive rubidium
ROC Receiver operating characteristics
ROI Region of interest
RX Radiography
SCC Squamous cell carcinoma
SCLC Small cell lung cancer
SD Standard deviation
Se Sensitivity
SLN Sentinel lymph node
SLNB Sentinel lymph node biopsy
SNB Sentinel node biopsy
Sp Specificity
SPECT Single photon emission computed tomography
SPET Single Photon Emission Tomography
SPN Solitary pulmonary nodule
SR Systematic Review
sROC summary receiver operating characteristics
surv survival
SUV Standardized uptake value
T Tumour
TBC Tuberculosis
^{99}Tc Radioactive technetium
TN True negatives
TP True positives
US Ultrasonography
Vs versus
Yr Year

1. INTRODUCTION

Positron Emission Tomography (PET) scanning is a non-invasive imaging procedure used for measuring the concentration of positron-emitting radio-isotopes within tissue in malignant and benign disease.

Expectations about the utility of PET are high within the medical community, because this technique combining metabolic and localisation approaches could, in theory, detect pathologic processes still invisible for classical imaging techniques.

On the other hand PET is a very expensive technology: investment costs are between 1.5 and 3 millions euros, depending on whether a cyclotron is installed on-site, and operating costs are high. Therefore, public authorities in charge of health care financing are concerned about the diffusion and application of this technology and try to carefully assess not only the clinical indications of PET but also its cost–effectiveness relative to other diagnostic tools.

There is often debate about the place of PET in the diagnostic work up and whether it should be additional to or in replacement of other diagnostic procedures. In terms of costs, using PET as an additional diagnostic tool has clear implications. If PET can replace other diagnostic tests, the costs of PET need to be balanced with the savings from avoided tests. Finally, the main question is whether the benefits of PET are worth the extra costs.

Various countries have already evaluated PET in the past few years in order to plan the supply of PET services. In Belgium, the diffusion of the technology took place before a careful health technology assessment was done. As a consequence, Belgium is one of the countries with the highest number of PET per million people in the world. There are currently 1.3 officially registered PET scanners per million inhabitants in Belgium. Concerns about the appropriateness of this number and its economic implications are now being raised, which has led to this HTA report.

The assessment of PET scanners in Belgium raises several questions: What are the clinical evidence-based indications? What is the cost effectiveness for these indications? How many PET scans are needed to meet the indications? How to finance this technology and what are the perspectives for the future? This HTA report looks at these questions and formulates recommendations for health care policy.

2. OBJECTIVES

The aims of this study are:

- to review the existing evidence on the diagnostic accuracy, clinical effectiveness and cost-effectiveness of PET;

Based on HTA reports, systematic reviews and some primary studies, the objective of this work is to give a good and clear synthesis of the existing evidence on PET, including for clinical indications and cost-effectiveness. To fulfil this goal, it is important to rest upon a good methodology in the process of selecting studies and evidence. Therefore, we used several well validated quality appraisal tools.

- to describe the current situation of PET in Belgium, including regulation, frequency of use and costs for the national health insurance RIZIV/INAMI;

The objective is to describe the situation of PET in Belgium on the basis of existing databases or surveys. Belgium is not starting from scratch because PET has already several years of history in our country and, fortunately, that activity has been registered. Therefore it is important to confront the evidence from the literature with the existing situation.

- to formulate recommendations for the organisation of PET services in Belgium based on the existing evidence and data.

Finally, the main objective of this HTA report is to formulate practical recommendations to the health authorities about planning, organisation, financing, research and development of PET in Belgium. In this context, it is important to consider the ethical aspects, such as accessibility and patient preferences.

3. TECHNOLOGY DESCRIPTION

3.1. PET

PET imaging is a non invasive nuclear medicine examination based on the detection of metabolic abnormalities of disease processes through the use of short-lived radiopharmaceuticals. Where classical imaging techniques give information on the structure and localisation of lesions, PET imaging is used, as a complementary tool, to characterise the function, the metabolism, the biochemical processes and the blood flow of organs and when possible, to detect a greater or lesser radiopharmaceuticals uptake. To reach this goal, a radiopharmaceutical is combined with a biochemical substance, active in the tissues. This is the case of glucose becoming 18 Fluoro-deoxy-glucose when combined with a radiopharmaceutical. Glucose is an interesting tracer because it is absorbed in great amount by cancerous or inflammatory cells. Moreover, the development of vascularisation in the cancerous process reinforces this glucose uptake. Once in the organism, 18FDG-glucose emits positrons detected by gamma cameras and then, an image is produced, to be read by the nuclear medicine specialist.

The determination of a positive result depends on the comparison between a specific region and the adjacent "normal" regions. But certain regions of the body are known to be physiologically glucose-avid. Therefore, the categorization of a region with augmented uptake is a very difficult process, based on a careful inspection of the region of interest, contrasting the supposed lesion with the adjacent tissue.

With such a process, the experience of the reader, specialist in nuclear medicine, is the most important issue. For that reason, there have been various attempts to make the reading objective, at least in a semi-quantitative way. So far, two techniques are used in that goal: the Lesion to Back Ratio and the Standardized Uptake Value (SUV). The last one is certainly the most common. It is based on the normalisation of attenuation-corrected images for injected dose and body mass. The SUV is the ratio between the tissue concentration of the radiopharmaceutical (in Bq/g) and the injected dose (in Bq) divided by the body mass (in g). The tissue concentration is evaluated on the scanner with a linear grey scale. The difficulty to standardize the reading of PET images explains why sensitivity and specificity may show such variations for the same indication.[1-7]

PET and conventional nuclear imaging both are diagnostic radionuclide imaging techniques and involve the use of radiopharmaceuticals (pharmaceuticals labelled with a radioactive isotope). These radionuclides can be localized in a variety of physiological or pathological processes using sophisticated imaging systems. Unlike conventional imaging techniques (RX, CT, MRI and ultrasound) which provide predominantly anatomical information, radionuclide imaging provides functional information on metabolic activity in physiological or pathological processes and only limited anatomical information. The detection of an abnormal lesion with these modalities is based on the differential radionuclide uptake within the lesion and the surrounding tissues. Whether or not a lesion can be detected is related to the degree of radionuclide avidity, size of the lesion and background activity.

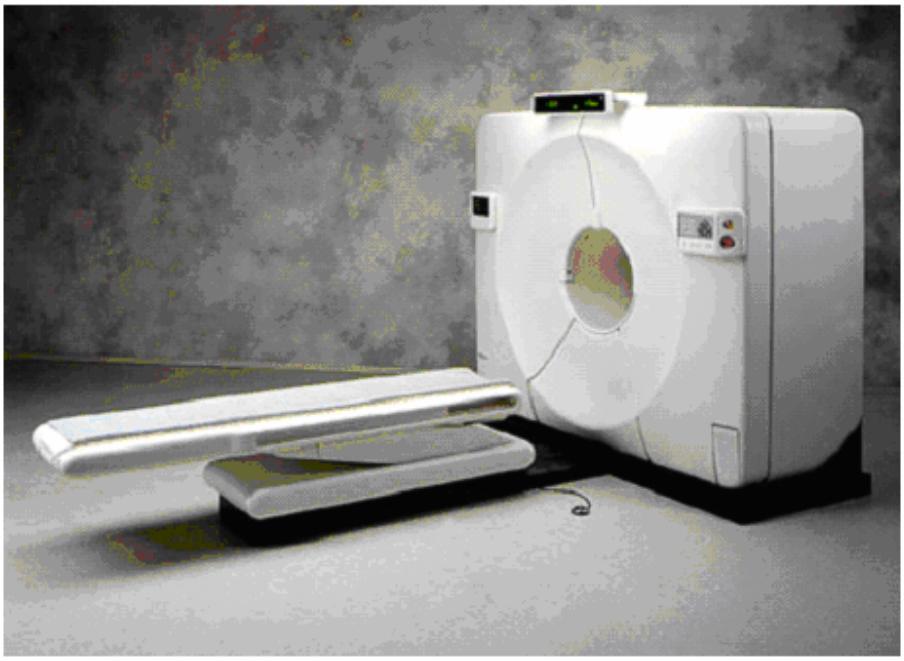
Most radioisotopes used in PET are produced in a cyclotron and once incorporated in biological molecules become positron-emission radionuclides allowing imaging of a variety of physiological or pathological process within the human body. Positrons are positively charged electrons emitted from instable nuclei with an excess of protons. These positrons combine with electrons resulting in pairs of positive and negative electrons which rapidly annihilate converting their mass into energy in the form of two gamma rays travelling at 180 from each other. Modern PET imaging systems are designed for the detection of the simultaneous arrival of each pair of gamma rays and hence, collimators are not required. The location of the emission can be computed as lying on the line connecting the 2 rays and combining results from multiple emissions, an image is constituted with localisation of the sources of emissions. A dedicated PET system consists of a ring detector surrounding the patient and collects the pairs of gamma rays emitted.

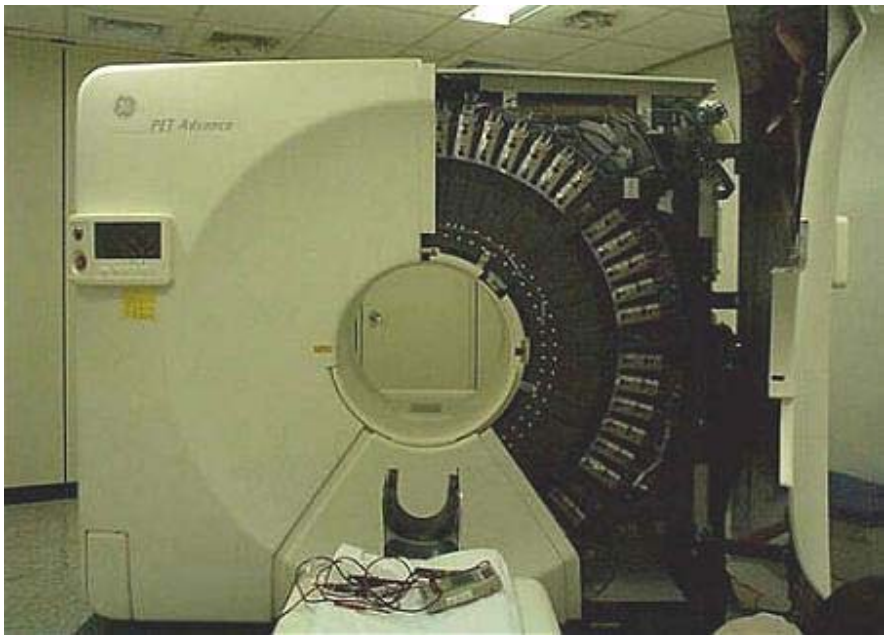
The coincident arrival of pairs of gamma rays is subsequently recorded and transformed into images. Compared to gamma cameras, PET has a better spatial resolution and is able to identify lesions typically down to the 7- to 8-mm range [8]. An external positron-emission source mounted on the PET imaging system allows for attenuation measurement and correction (attenuation refers to the loss of photons through scatter or absorption). This transmission scan is done while the patient remains in position and takes 20 minutes in addition to the time needed for the emission scan. A major limitation of PET is the lack of anatomical details. Therefore, interpretation of PET images requires anatomical information from CT or MRI.

The most commonly used radionuclide in PET is an analogue of glucose labelled with ^{18}Fluorine (FDG or 2-deoxy-2-{Fluorine-18}fluoro-D-glucose) with a half-life of 110 minutes allowing commercial distribution of synthesised FDG within 2 hours. For other isotopes with much shorter half-lives (ranging from 2 minutes for ^{15}Oxygen to 20 minutes for ^{11}Carbon), on-site production is required. In this report, we focus on FDG-PET. For convenience, the term PET is used for FDG-PET unless otherwise specified (e.g. for cardiology and neurology).

FDG-PET imaging in cancer is based on the property of increased glucose uptake into and glycolysis within several malignant cell types. FDG undergoes glycolysis within tumour cells. However, in all tissues except the liver, FDG-6-phosphate is only slowly metabolized and is "trapped" within the cell allowing its detection by PET. Intracellular concentrations of FDG reach a plateau when rates of cellular uptake and dephosporylation have become equal. As this occurs at 50-60 minutes following intravenous administration of FDG, clinical PET imaging is performed after this time interval. In a standard dedicated PET scanner, about 1 hour is required to complete the emission and transmission acquisitions from skull base to thigh. The recent development of faster scintillating crystals and PET/CT systems has reduced total scanning time to less than 30 minutes.

Most frequently clinical PET is used for the detection of lesions and images are qualitatively assessed. It has been suggested that both attenuation corrected and uncorrected images should be used for lesion detection. While the need for attenuation correction for lesion detection remains debatable, it is certainly required in quantitative measurements of lesion uptake [9].




PET Advance

3.2. ALTERNATIVES TO PET

3.2.1. Gamma Cameras

Gamma cameras are used in conventional diagnostic nuclear imaging procedures in which radionuclides emitting single gamma ray photons are used. Technetium-99m (Tc-99m) is the most commonly used radioisotope that can be added to a variety of pharmaceuticals. These gamma rays are emitted during decay of the radiopharmaceutical and are detected externally by a gamma camera used in a planar or tomographic mode, the latter known as SPECT. The diagnostic information obtained depends on the type and properties of the radiopharmaceutical used. Gamma rays cannot be focused by an optical lens and instead a collimator, a lead plate with an array of small holes, is used to only detect those photons that travel almost perpendicular to the surface of the detector and excluding all other radiation. Therefore, images of the distribution of the radiopharmaceutical obtained with parallel collimators have a low spatial resolution (above 1.5 cm) [10].

Theoretically, dual- or multi-headed planar gamma cameras could be used for PET as an alternative to dedicated PET imaging. However, only few comparative studies with small sample sizes have been performed. Initial studies reported a similar performance of gamma cameras and dedicated PET in the detection of lesions >2 cm but dedicated PET is more accurate in the detection of small lesions [9].

3.2.2. PET/CT

PET/CT is an emerging technology, where a CT scanner (emitting x-rays) is combined with a PET imager in the same gantry. Typically, the CT acquisition is performed first followed by PET acquisition. This set-up allows co-registration of PET data and CT data producing fusion images with combined functional and anatomical details. In addition, attenuation correction is based on CT data thereby reducing the total scanning time to less than 30 minutes. It has been proposed that PET/CT could be used to improve the PET image through fast and accurate attenuation correction, improve localisation of abnormalities detected on PET, radiotherapy and surgery planning, evaluation of therapy outcome by localising regions of oedema and scarring and produce the highest quality PET and CT information with the least inconvenience [9]. The costs related to the acquisition and the maintenance of a PET/CT scanner may be higher than that of a PET scanner only but may be outweighed by the potential of producing diagnostically superior images and reducing scan time, thus allowing higher patient throughput.

The authors of the HTA-HTBS 2002 report summarize some of the questions that would need to be answered before deciding whether PET/CT will be effective in practice:

- What percentage of PET scans requires quantitation? In some cases the aim is to detect the spread of a cancer. While correcting for attenuation may improve the accuracy of the image, it is uncertain whether it improves the ability to detect metastatic spread. If quantitation is not required, then a PET/CT scanner does not offer any improvement in throughput, thus negating one of its advantages.
- What percentage of PET scans requires anatomical registration? In some cases the fact that a tumour has spread is enough to change the management of the patient (i.e. make them unsuitable for surgery). In these cases there is no need for any anatomical registration.
- Is the registration that can be obtained by the combined scanner significantly better than that using two separate scans? Clearly, it is easier to co-register a PET and a CT image if they are taken with the patient in the same position. However, even in this phase, co-registration may not be perfect. For example, in order to get good diagnostic CT images patients are frequently asked to hold their breath during the CT scan. This is not possible for the PET scan since it takes too long. Therefore breathing motion will introduce some error. Also, in some cases the CT scan may be taken with the arms above the head (to improve quality) and this position may be too uncomfortable for the longer PET scan so

the arms may be placed by the patients side, thereby changing the position of internal organs.

A recent Spanish HTA report highlighted the poor methodological quality of the studies comparing PET or CT and PET/CT. Moreover, the clinical impact on patients has still to be evaluated and this new technology has to be compared to the results given by images fusion through software. More studies are needed. [11].

4. LITERATURE REVIEW

4.1. METHODS

4.1.1. Diagnostic efficacy

In order to assess the evidence on diagnostic accuracy and clinical effectiveness of PET, HTA reports and systematic reviews were first searched. The search terms were: PET/Title & Abstract OR Positron emission tomography/Title & Abstract. The following databases were searched up till April 2005:

Health Technology Assessment Database (HTA), NHS Economic Evaluation Database (NHS EED), Database of Abstracts of Reviews of Effects (DARE) and PubMed Clinical Queries – Systematic Reviews.

- The websites of the following HTA agencies were visited between January and March 2005 and the HTA reports on PET downloaded: AETMIS, AETS, AETSA, AHRQ, AHFMR, CIHR, CAHTA - AATRM, CEDIT, Sundhedsstyrelsen, DACEHTA, NHS, NICE, FNCLCC, HAYES, HSTAT-NLM, Minnesota DoH, NCCHTA, CRD, HTAi, ICES, ICSI, INAHTA, MSAC, NZHTA, OHPPR, RAND, SNHTA, Blue Cross Blue Shield, MIHSR, CCOHTA. The complete search strategy and history are presented with all details in appendix.

- Systematic reviews published between December 2001 and April 2005 were searched in Medline (Clinical Queries: Systematic reviews) and Embase using an update of the strategy used by Mijnhout et al for FDG-PET (see appendix) [12].

HTA reports and systematic reviews were independently critically appraised by two experts of the KCE, using the INAHTA checklist for the HTA reports and the Dutch Cochrane checklist for the systematic reviews (see appendix). Several HTA reports integrate findings and conclusions from previous reports. In that case, only the most recent report was retained. The selected HTA reports were: HTBS, FNCLCC, MSAC, DACEHTA, BCBS, AHRQ and ICES and for specific indications, AETMIS, ICSI and AETS.

The evidence for each clinical indication was synthesized and, according to the level of evidence, indications with no clear conclusion and/or without search update since 2002 were selected for a primary studies search. These indications are: melanoma, lymphoma, colorectal cancer and breast cancer. The search was performed in Ovid-Medline and Embase, using the updated version of Mijnhout et al. strategy with general terms for cancer (cancer, oncology, neoplasm, malignancy, tumour) and specific terms by indications (colon, rectum, lymphoma,…) on 1/3/2005 for colorectal cancer, 2/3/2005 for lymphoma, 10/3/2005 for breast cancer and 14/4/2005 for melanoma (see appendix). The selection criteria were: published after 1/1/2002, diagnostic studies, with abstract, with at least 10 patients, in English, Dutch, French, German or Spanish. After reviewing the available evidence from HTA reports, we decided to search additional primary studies for SPN as well, up till April 2005, because there was a large variation in the reported sensitivity and specificity of PET for this indication.

For some indications (in non-small cell lung cancer, gastro-intestinal stromal tumour, oesophageal cancer and brain tumour), the external expert group provided additional literature that was either not covered by our search strategy or too recent to show up in databases (e.g. articles in press). For these indications a systematic search was not performed. Therefore, some conclusions based on these studies might be more favourable for PET. However, when studies provided by external experts are used in our review, this is explicitely mentioned in the text.

The methodological quality (patient spectrum, verification, blinding and replication) of the studies was assessed with the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) checklist [13]. Studies were selected according to evaluation criteria of the American College of Physicians, already used in evaluating literature on MRI. These criteria formerly have been used by several HTA agencies in their evaluation of literature on PET [14 15]. Grade A and B studies were selected. The assessments

were performed independently by two experts of the KCE. Disagreements between experts were discussed and, when no consensus was reached, a third expert was asked to arbitrate.

4.1.2. Cost-effectiveness

Economic evaluations were searched in Medline, Embase, Econlit, HTA database, DARE and NHSEED. The full search strategy is presented in appendix. Studies on the cost-effectiveness of PET, compared to appropriate alternatives, were searched for all indications for which at least evidence of level 3 is available. Publication year was limited to 2000 or later. Quality of the studies was assessed with the "Drummond" checklist for economic evaluations.[16] Studies were selected and their quality was assessed independently by two experts of the KCE. Initially, 44 articles were retained on the basis of title and/or abstract. Of these, 12 were found relevant for this HTA. A flow chart with exclusion criteria and tables with extracted data are presented in appendix. Two additional reference works[17, 18], published before 2000, were added because many subsequent models use the same model construct, and models published as part of HTA reports [9].

All the studies are summarized in tabulated form in appendix. The tables outline all the characteristics and relevant assumptions used in the cost-effectiveness models as well as any remarks that led to the quality tag. Only the results of studies of fair to good quality are presented in this HTA. The major weaknesses of the studies are presented under 'remarks' in the summary tables. All results are presented with confidence intervals and or P value whenever available in the HTA report, systematic review or original study. For indications not mentioned in the table (e.g. breast cancer, renal cancer) no economic evidence was found.

Economic studies are of variable methodological quality, as was already pointed out in a methodological review of economic evaluation studies in nuclear medicine in 2000.[19] In addition, the economic studies are hardly comparable, as they often use very different diagnostic pathways and models, different perspectives, different cost-effectiveness thresholds and different time windows (e.g. diagnostic process, lifetime). The results of the models are often very country-specific, especially when the perspective of the reimbursement agencies is used.

Therefore, the conclusions from literature generally have weak relevance for Belgium: the Belgian diagnostic pathways may not resemble those used in the cost-effectiveness analyses and reimbursement conditions are different.

It has been pointed out in the economic literature on PET that besides large practice variations between countries there are also large practice variations within countries: different hospitals and different physicians use different diagnostic pathways. The results of the economic evaluations are hence only relevant in as far as they resemble the current practice of the hospital or physician.

4.2. EVIDENCE LEVELS

The studies retrieved from the literature were critically appraised using quality assessment tools. On the basis of available studies for an indication and their quality, a level of evidence was attributed for the diagnostic efficacy of PET in each indication. For some indications, evidence was limited or absent. This could be related to the low quality of published studies, to the mere absence of clinical diagnostic studies or to the fact that the sample size of the study was too low. For very rare indications however, it is often quite difficult to obtain a sufficient number of patients to perform a well powered diagnostic study and hence the evidence base for certain of these indications will remain weak. On the other hand, the mere existence of publications is not sufficient to conclude that there is evidence for the clinical diagnostic efficacy of PET for a certain indication. Diagnostic studies can be of low quality, the research questions might be irrelevant and several sources of bias can be present.

Fryback and Thornbury described a hierarchy of diagnostic efficacy, which is used as the basis of this report [20] Efficacy is defined as the probability of benefit from a medical technology to individuals in a defined population under ideal conditions of use [21]. In other words: can the diagnostic test work?

This is not the same as effectiveness, which assesses the test's ability to work in the real world: does it work in clinical practice? Finally, in efficiency the test's financial implications are considered: is it worth it? [22]

The model is characterized by a change in perceived goals. It is hierarchical: on one extreme are endpoints describing only the technical performance of the test, on the other extreme are endpoints pertaining to the value of the diagnostic technology to society. If a test performs poorly at one level, it is unlikely to perform well at a higher level. The reverse, however, is not true: increases in the technical performance of a test will not necessarily guarantee improvement at a higher level, for example effect on patient outcome.

A diagnostic test does not necessarily have to demonstrate effectiveness at each level before it can be used in clinical practice [23], but the possible gain and remaining uncertainty on the test's efficacy is clearly presented by this approach.

Level 1: technical efficacy

The technical efficacy of a test refers to the ability to produce usable information.

The *test's feasibility* and *operator dependence* refer to in what circumstances and by whom the test can be performed.

The *analytical sensitivity* is the ability to detect small quantities of the measured component. This should be distinguished from the diagnostic sensitivity, the ability of a test to detect disease.

The precision or *reproducibility* of results is the ability to obtain the same test results on repeated testing or observations. It is influenced by analytical variability and observer interpretation. Analytical variability consists of inaccuracy and imprecision. Inaccuracy implies systematic error, such as calibration error. Imprecision implies random error. Agreement between two continuous test methods can be expressed in a regression analysis or Bland & Altman plots [24]. A correlation coefficient does not provide information on agreement. The agreement between two observers (interobserver) or the same observer on different occasions (intraobserver) can be expressed with a kappa statistic.

It is often assumed that the technical efficacy does no longer need to be evaluated once a test is being used in clinical practice.

Level 2: diagnostic accuracy

This level refers to the test's ability to detect or exclude disease in patients compared with a criterion standard or reference test. Test characteristics are sensitivity, specificity, predictive values, likelihood ratios and ROC curves. Definitions of these and other terms are provided in appendix.

Sensitivity and specificity are the most widely used outcome measures, but are sensitive to spectrum bias. Spectrum bias may occur when the study population has a different clinical spectrum (more advanced cases, for instance) than the population in whom the test is to be applied [25, 26]. If sensitivity is determined in seriously diseased subjects and specificity in clearly healthy subjects, both will be grossly overestimated relative to practical situations where diseased and healthy subjects cannot be clinically distinguished in advance[27, 28]. This design has been called 'inappropriate case-control design' in the pilot assessments.

Predictive values, with the positive predictive value being the proportion of patients with a positive test result that actually has the disease and the negative predictive value the proportion of patients with a negative test result that does not have the disease, are dependent on disease prevalence in the study sample. For example, in a situation where disease prevalence is very low, say 1%, the negative predictive value of the test will be easily over 95% as already 99% of the population do not have the

disease. Prevalence and the setting in which patients were recruited should be noted to reflect on this.

The *likelihood ratios* show how a test result alters the pre-test probability into a post-test probability, using Bayesian reasoning. The pre-test probability depends on the prevalence of the target condition and the results of previous tests, for example history, clinical examination, imaging or laboratory tests.

Another outcome measure which is sometimes used, is the *number needed to diagnose*, analogous to the number needed to treat in intervention studies. However, using this measure it is assumed that diagnostic testing is always done to rule in a target condition, to diagnose the target condition, while in clinical practice tests are also used to rule out a target condition.

Finally, test accuracy can be illustrated using an *ROC curve*. The ROC curve graphs test sensitivity versus 1-specificity for various cut-off points. The area under the curve provides a summary measure of the test performance. It also allows comparison of two different tests by testing the two areas under the curve or by testing partial areas under the curve in which the test is most useful.

Clearly, the first level of diagnostic efficacy, technical efficacy, contributes to the diagnostic accuracy. But it also becomes apparent that there may be a point beyond which improvement in technical performance no longer improves diagnostic accuracy. Assuming therefore that diagnostic accuracy can be estimated on the basis of technical accuracy studies is not correct.

Level 3: diagnostic thinking

This level of diagnostic efficacy is concerned with assessment of the effect of test information on diagnostic reasoning and disease categorization. Studies on diagnostic thinking serve as a proxy for estimating the effect of a test on patient care. Patients' outcome can not be influenced by the diagnostic technology unless the physician is led to do something different than would have been done without the test information.

Using the *likelihood ratio* and calculating the post-test probability, this change in diagnostic thinking can be computed. However, the pre-test probability of a disease is not always available in clinical practice and depends not only on setting, but also on patient characteristics and other selection processes, such as referral and the results or previous tests. Clinicians who wish to apply the Bayesian properties of diagnostic tests require accurate estimates of the pre-test probability of target disorders in their area and setting. These estimates can come from five sources personal experience, population prevalence figures, practice databases, the publication that described the test or one of a growing number of primary studies of pre-test probability in different settings[29].

An alternative are studies that empirically test the *change in the physician's subjective assessment* on the probability of disease. In these studies, physicians are asked to estimate the probability of disease before knowing the test result, and estimating it again after the test result has been disclosed. Efficacious tests are those that significantly increase or lower pre-test probabilities assumed by the physician or computed by likelihood ratios using Bayesian reasoning.

One major difficulty with this level of diagnostic efficacy is that it is not always known what post-test probability of disease should be used as a threshold. Which probability of disease is low enough to exclude disease, which is high enough to treat the patient? These thresholds will differ according to the target condition and the treatments that are available [30].

Level 4: therapeutic impact

The most efficacious tests at this level are those that lead to the institution of a new management strategy. Studies can assess this empirically by comparing the intended management before the test result is known with that after the test result has been disclosed. In what *proportion of patients did the information change the intended management*? In some cases, management changes are considered not only in the patient himself, but also in other persons, for example prophylactic

measures in case of an infectious outbreak. These prospective case-series, however, can be subject to bias such as selection bias. The lack of a concurrent control group may lead to confounding, as there is no information on those patients not enrolled in the study and therefore not receiving the new technology. These considerations underscore the need for randomized controlled trials. But, in the absence of RCT's they do play an important role as an intermediate.

Level 5: patient outcome

The ultimate goal of health care is to improve patient outcome. For diagnostic tests that are expensive, dangerous or widely used, knowledge about patient outcome efficacy seems particularly important. It is at this level that expected harm, such as burden, pain, risk, can be weighed directly against its expected benefit, such as improving life expectancy, quality of life, disease related morbidity, etcetera.

The *randomized controlled trial* is the study design the least prone to bias to estimate these risks and benefit. However, it is not always feasible to perform an RCT for ethical, financial or other reasons. In those cases, case-series collected before and after the introduction of a new test technology or case-control studies may provide some of the answers.

A methodological difficulty with this level is that the independent contribution of test technology to patient outcomes may be small in the context of all the other influences and therefore very large sample sizes may be required. But, in spite of these difficulties, RCT's on diagnostic tests are feasible. Various designs are possible, according to the specific research question [31].

Some tests, however, will never be able to prove a change in 'objective' patient outcomes such as mortality or morbidity, simply because there is no treatment available at this moment that has an impact on these outcomes. This is the case in for example dementia or Amyotrophic Lateral Sclerosis (ALS). A diagnostic test will therefore never produce a difference in mortality, but may improve *quality of life measures* by giving the patient (and the carer) an affirmative diagnosis and providing an explanation for the signs and symptoms the patient experiences.

Level 6: cost-effectiveness analysis

This level goes beyond the individual risks and benefits, but assesses whether the cost for use of a given test is acceptable for society. Is the price for the positive effect on patient outcome worthwhile? Resources can not be allocated twice; money spent on one technology can not be spent on another.

Cost-effectiveness studies compute a cost per unit of output. Any of the measures of the previous levels can be used as input, for example cost per surgery avoided, cost per appropriately treated patient, cost per life year gained or cost per quality adjusted life year gained. Final outcomes, such as life years gained or QALYs gained, are preferred over intermediate outcomes in economic evaluations, as they allow comparisons across a broader range of health interventions, e.g. diagnostic and therapeutic interventions. Because data on these outcomes and costs of the diagnostic and subsequent therapeutic paths are not routinely available from observations, modelling becomes inevitable to examine the cost-effectiveness of diagnostic tests. The validity of the model input parameters is crucial for the credibility of the model. The values of all input variables must be based on solid evidence obtained from literature or observations. Sensitivity analyses can illustrate the robustness of the conclusions, by demonstrating the sensitivity of the results to changes in the values of remaining uncertain input parameters.

Cost-effectiveness models can only upgrade the level of evidence if level 5 evidence was available on the outcomes used in the model (be it life years gained or procedures avoided) and if this evidence was actually used in the model. More specifically, models that base their outcome estimation on non-PET related evidence (e.g. on the survival after surgery, regardless of the diagnostic work up prior to the treatment decision) can not upgrade the level of evidence from, for instance, 4 to 6. There must be at least level of evidence 5 for PET to reach level 6 with cost-effectiveness models.

For rare diseases, it is again more difficult to reach higher levels of evidence, as the patient numbers that can be included in a clinical trial are small. As a consequence, it is more difficult to reach statistical significance.

Key Messages

- **The literature review of the diagnostic efficacy and economic value of PET was based on existing HTA reports and systematic reviews. For emerging indications a review of primary studies was performed.**
- **Quality of the studies was assessed using standard quality assessment tools.**
- **The levels of evidence attributed to each indication depend on the level reached on the hierarchic scale for diagnostic procedures and on the quality of the existing studies. Mere existence of studies does not imply that there is clinical evidence. Lack of evidence does not imply that a diagnostic test is not useful in experienced settings.**

5. PET FOR CANCER MANAGEMENT

At present, the evidence on the use of PET in oncology is considered sufficient in some selected indications. While PET is not useful at all in some indications, the utility of PET in several other potential indications remains uncertain and additional well-designed studies are needed. However, when an indication may be regarded as doubtful today this may be related to a lack of methodologically sound studies performed on that issue.

This report summarizes the available evidence on PET in lung cancer, lymphoma, head and neck cancer, colorectal cancer, malignant melanoma, breast cancer, oesophageal cancer, thyroid cancer, pancreatic cancer, liver cancer, cervical cancer, ovarian cancer, renal cancer, testicular cancer, gastrointestinal stromal tumours and other tumours.

5.1. LUNG CANCER

Material reviewed: HTA reports, Systematic Reviews and primary studies whithout time limit (SPN)

Lung cancer includes non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Pleural and mediastinal cancer will also be reviewed in this section. The use of PET has been evaluated in diagnosis, initial staging, monitoring of treatment response, and evaluation of recurrence or residual disease. Some studies also addressed prediction of survival and optimization of irradiated volume.

5.1.1. Diagnosis of malignancy of a solitary pulmonary nodule (SPN)

Diagnostic efficacy

PET may be useful in the diagnosis of malignancy of a Solitary Pulmonary Nodule (SPN). We present hereafter the principal results found in the selected HTA reports.

PET may be indicated in the initial diagnosis of a SPN > 1cm when no clear signs of a benign tumour are found on classical imaging procedures (sensitivity varies from 50% to100% for malignancy of nodule < 3 cm and from 93% to 100% for a mass > 3 cm) [32 8 9 33, 15]. The most important cause of false negative results is related to the size of the lesion. A frequently used reference diameter is 1 cm because PET results are related to tumour size and also to an absolute FDG uptake value within the tumour. [32] PET may be used in SPN < 1 cm but with less evidence [8, 32]. The specificity of PET in SPN varies from 40% to 100% (due to increased FDG uptake in inflammatory or granulomatous lesions such as TBC or histoplasmosis)) [32 8 9 15 } [33] In case of a negative biopsy result or contra-indication of biopsy, the sensitivity of PET in the diagnosis of malignancy of a SPN varies between 86% and 100%. The specificity varies between 40% and 90%, the positive predictive value between 88% and 95%, and the negative predictive value between 55% and 100% [15]. Further studies are needed to assess this indication [34].

Due to the variation of sensitivity and specificity among the HTA reports and systematic reviews, and the mix between dedicated PET and gamma camera, FDG and other tracers in the existing reviews, we tried to pool the studies in order to draw a Summary ROC curve. The SPN is indeed a good example of indication where it is possible to study the medical decision process on the basis of a pooled value of sensitivity and specificity.

Therefore, after a search in Medline and Embase and on the basis of the references of existing systematic reviews and HTA reports (see appendix), we selected 32 studies fulfilling our criteria (stated in the methods section) with a total of 1897 patients (Table 1).

Table 1: SPN – Primary studies

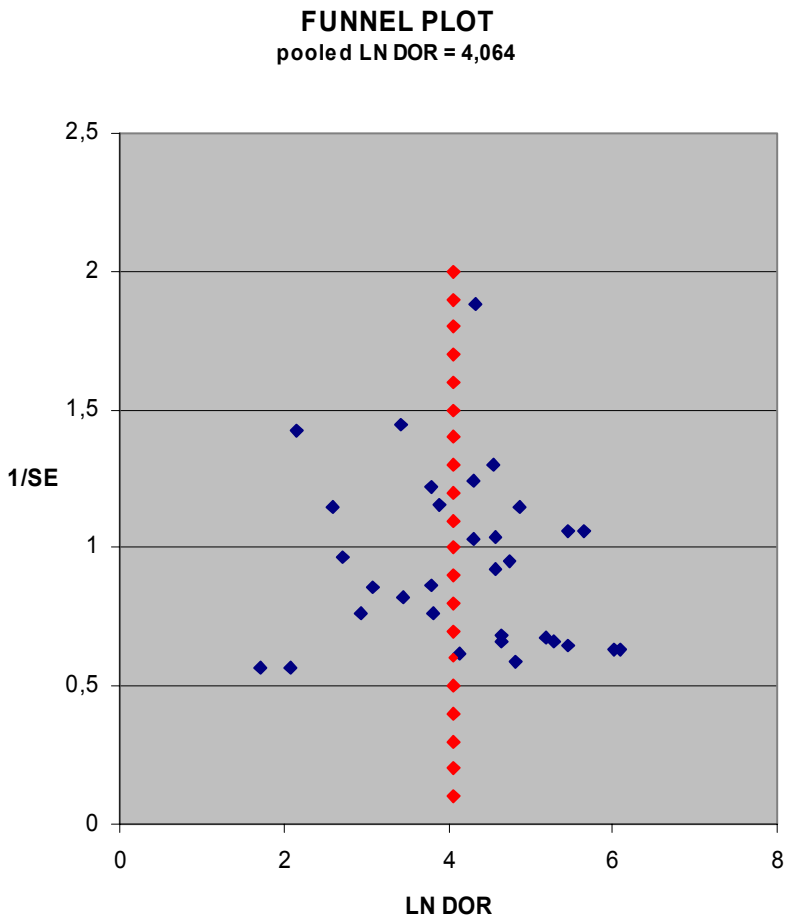
Setting	Grade	Study design	Author	Yr	Pts	Compare	Blinded

Diagnosis	B	Prospective	Kubota[35]	1990	22	Histology (21) cyto(1)	Y
Diagnosis	B	Prospective	Gupta [36]	1992	20	Histology(19)FU(1)	Y
Diagnosis	B	Prospective	Slosman[37]	1993	36	Histology(33)FU(3)	Y(?)
Diagnosis	B	Prospective	Patz[38]	1993	51	Histology(49)cyto(1)FU(1)	Y
Diagnosis	B	Prospective	Lowe[39]	1994	88	Histology(87) FU(1)	Y
Diagnosis	B	Prospective	Duhaylongsod[40]	1995	87	Histology(84)FU(3) ?(13)	Y
Diagnosis	B	Prospective	Bury[41]	1996	50	Histology	Y
Diagnosis	B	Prospective	Sazon[42]	1996	127	Histology or cyto	Y
Diagnosis	B	Prospective	Gupta[43]	1996	61	Histology(60)FU(1)	Y
Diagnosis	B	Prospective	Knight[44]	1996	48	Histology(36)FU(12)	Y
Diagnosis	B	Retrospective	Dewan[45]	1997	52	Histology	Y
Diagnosis	B	Retrospective	Lowe[46]	1997	197	Histology(173)FU(24)	Y
Diagnosis	B	Prospective	Prauer[47]	1998	54	Histology	Y
Diagnosis	A	Prospective	Lowe[48]	1998	89	Histology	Y
Diagnosis	B	Prospective	Gupta[49]	1998	19	Histology	Y
Diagnosis	B	Prospective	Vaylet[50]	1998	11	Histology	Y
Diagnosis	B	Retrospective	Graeber[51]	1999	96	Histology	Y
Diagnosis	B	Prospective	Richter[52]	1999	55	Histology(48)FU(7)	Y
Diagnosis	B	Prospective	Halter[53]	2000	35	Histology(30)	Y
Diagnosis	B	Prospective	Indahl[54]	2001	87	Histology	Y
Diagnosis	B	Retrospective	Lee[55]	2001	58	Histology(36) FU(22)	Y
Diagnosis	B	Prospective	Hain[56]	2001	63	Histology(44)FU(19)	Y
Diagnosis	B	Prospective	Hung[57]	2001	26	Histology	Y
Diagnosis	B	Prospective	Croft[58]	2002	85	Histology	Y
Diagnosis	B	Prospective	Wilkomm[59]	2002	10	Histology(9) FU(3)	Y
Diagnosis	B	Retrospective	Hickeson[60]	2002	47	Histology(37) FU(10)	Y
Diagnosis	B	Prospective	Pitman[61]	2002	50	Histology(27)cyto(5)FU(3) CWU(15)	Y
Diagnosis	B	Prospective	Buck[62]	2003	26	Histology	Y
Diagnosis	B	Prospective	Demura[63]	2003	80	Histology	Y
Diagnosis	B	Retrospective	Ruiz-hernandez[64]	2004	67	Histology(49) cyto(3) FU(15)	Y
Diagnosis	B	Prospective	Oturai[65]	2004	84	Histology(81)FU(3)	Y
Diagnosis	B	Retrospective	Herder[66]	2004	36	Histology(15) FU(21)	Y

Cyto = cytology, FU = follow up, CWU = Clinical work up, Pts = number of patients

Then, we drew a Funnel Plot in order to detect publication bias, plotting the log of Diagnostic Odds Ratio (DOR = Rate of sensitivity/(1 - sensitivity) over (1 – specificity)/specificity) against 1/Standard Error of DOR[67]. The results are presented in Figure 1.

Figure 1: Funnel Plot



Although the plot gives a relative symmetrical view, we executed a Trim and Fill procedure to identify the eventual lack of small negative studies, but got a kappa equal to 0 at the first iteration, which indicates the absence of publication bias[68].

We computed the Confidence Interval (CI) for each sensitivity and specificity and put the results in graphs (see Figure 2 and Figure 3) with Metadisc software [69]. These graphs show the relative homogeneity of sensitivities, but also the greater variability of specificities.

Figure 2: Sensitivity of the selected studies with 95% CI

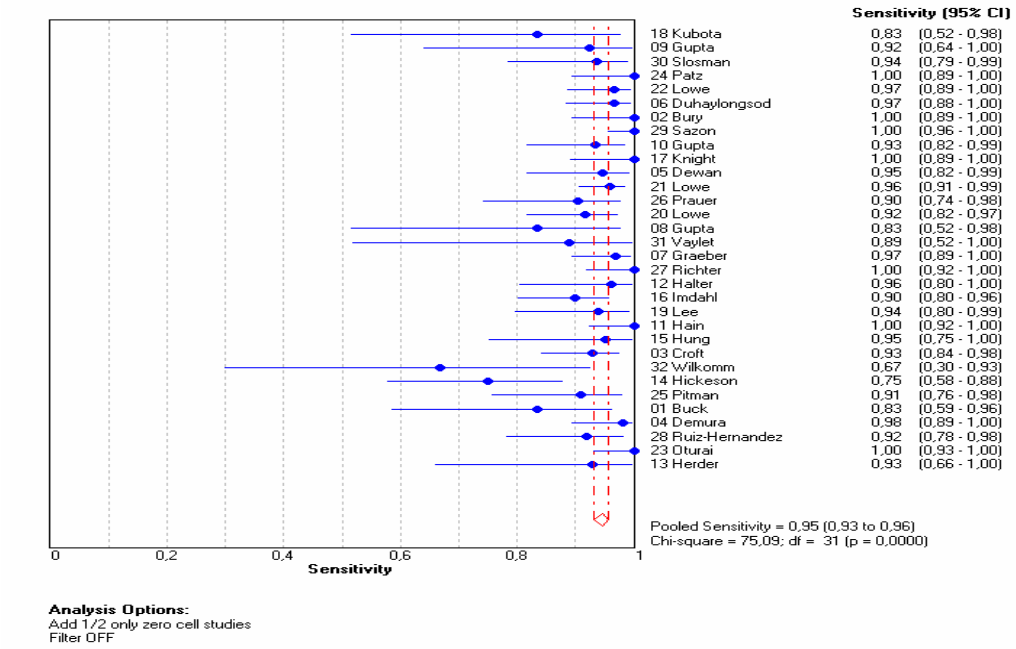
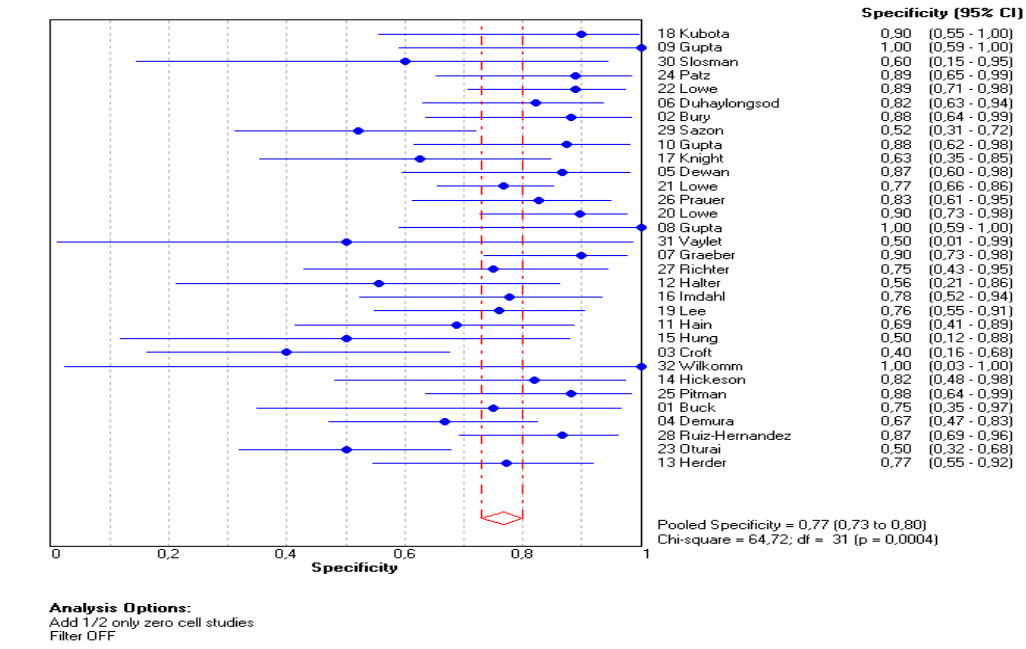
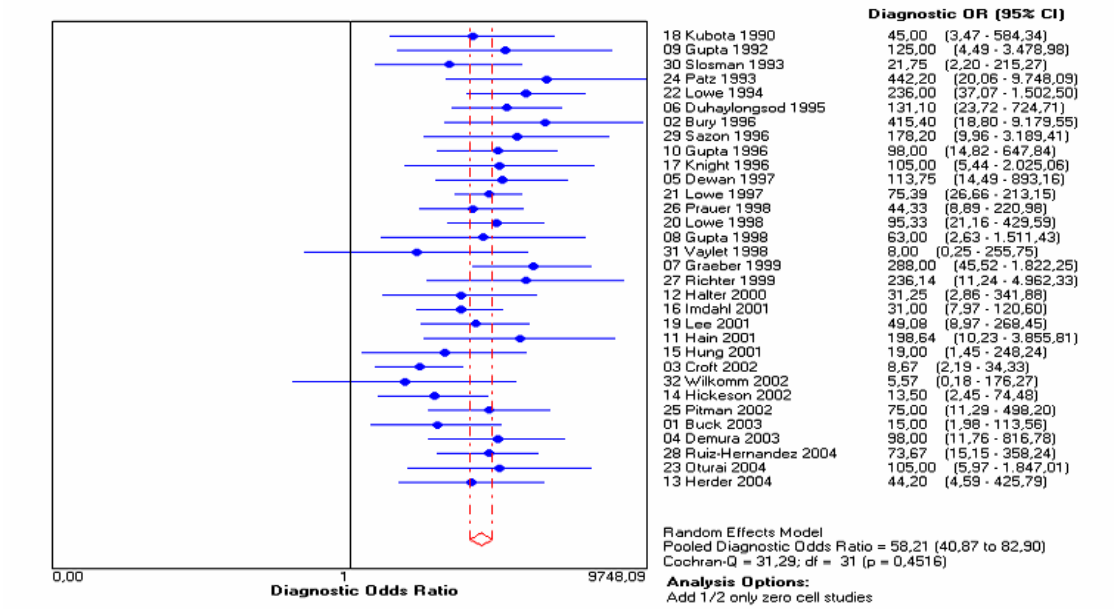


Figure 3: Specificity of the selected studies with 95% CI



We tested the homogeneity of the studies, computing the weighted summary Odds Ratio under the random effects model [70] assuming inter-studies variability of the pooled Diagnostic Odds Ratio (DOR) as shown in Figure 4.

Figure 4: Diagnostic Odds Ratio with 95% CI



The pooled DOR is 58.21 (95% CI 40.87 – 82.9), the test of heterogeneity (Q or Chi^2 = 31.29) is not statistically significant (p = 0.45), and the I^2 = 0.9 % which indicates homogeneity [71]. We also computed the DOR using the fixed effect model (Mantel Haenszel) and found a result of 59.47 for the pooled DOR (65% CI 42.59 – 83.03) with Q = 35.82 (p = 0.25) not statistically significant. The difference between the 2 models is small and therefore, we decided to keep the random effect model in our analysis.

Then, we built the Summary ROC curve, computing D, the diagnostic log-Odds Ratio (ln OR) which conveys the test's accuracy in discriminating cases from non-cases, and S which is a measure of the diagnostic threshold [72] .To handle the problem of zero values, we used a correction factor of 0.5 in the 2 X 2 tables, when needed. We applied the Moses regression model (D=a+ bS) on these data to achieve a smoothed fitting of the ROC curve, weighing the regression with the inverse of study variance.[72]

The results, computed with Metadisc software, are presented in Table 2 and Figure 5.

Table 2: Analysis of Diagnostic threshold

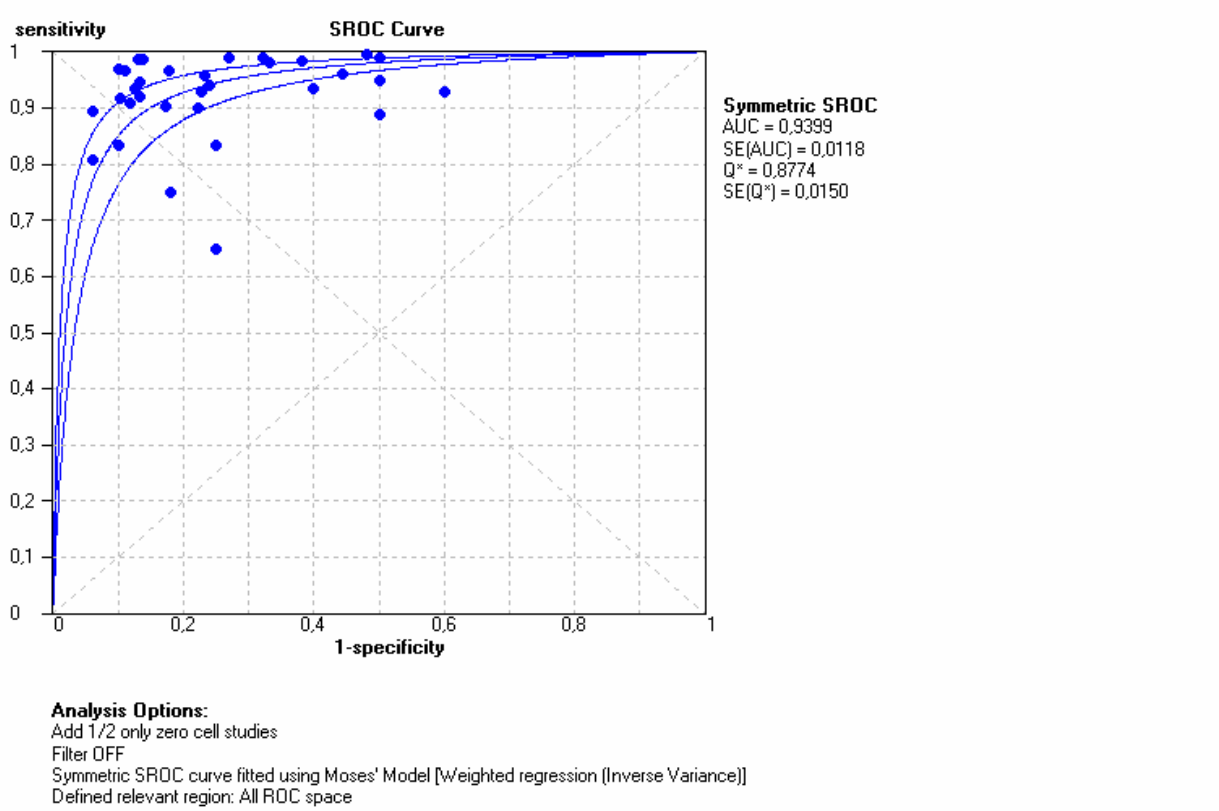
Spearman correlation coefficient : 0.314 p-value= 0.080 (Logit(True Positive Rate) vs Logit(False Positive Rate)

Moses' model (D = a + bS) Weighted regression (Inverse Variance)

Var	Coeff.	Std. Error	T	p-value
a	3.936	0.279	14.122	< 0.0001
b(1)	0.086	0.143	0.603	0.5510

Nber. studies = 32 Filter OFF Add ½ only zero cell studies

Figure 5: sROC curve



If b = 0, the studies are homogeneous and the sROC curve is a good reflection of the sensitivity and specificity. The value of b in our curve is not significantly different from 0 as attested by a Student T test with p = 0.551.

The Q* point represents the diagnostic threshold at which the probability of a correct diagnosis is constant for all subjects. On the sROC curve, this is the point where TPR = 1 – FPR (sensitivity = specificity). In our case, Q* = 0,887 (0.912 for Gould, the only systematic review on SPN with a sROC curve) [8]. This value has no clinical impact, but is used to compare the sROC curve of different tests. That is the reason why we took the median specificity among our selected studies and the corresponding sensitivity to draw the graph of post-test probability as function of test result and pre-test probability: At median specificity of 77 %, sensitivity is 94.6 %. The results of other meta-analyses on the subject : median specificity: 77.8% and sensitivity at that point: 96.8% [73] pooled sensitivity of

96±1% and a pooled specificity of 80±2% [74] . Generally SPN has a malignancy pre-test probability between 15 and 75% before PET [47 58 60 73 75 48]. If we choose a median pre-test probability of 40%, the post-test probability in case of a positive result is a little less than 75% in both graphs and, in case of a negative PET result, the post-test probability is 2.7% for Gould and 4.5% in our study: Figure 6 and **Figure** 7. [76]

In case of a SPN > 1cm, a malignancy may be excluded based on a negative PET and the need for an additional biopsy (FNAB or thoracotomy) may become obsolete. To improve the reproducibility of PET results, a threshold value based on a SUV semiquantitative analysis should be established. For nodule <1cm, the evidence of PET diagnostic efficacy is still lacking.

Figure 6: SPN: Gould study

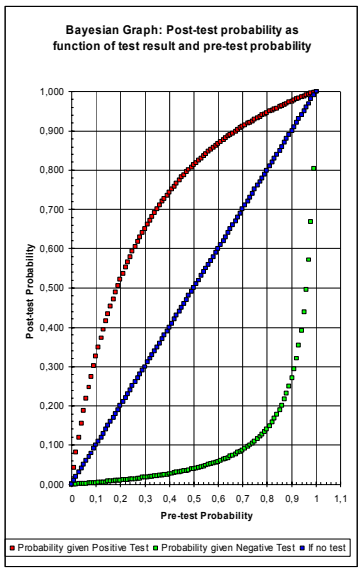


Figure 7: SPN: KCE Study

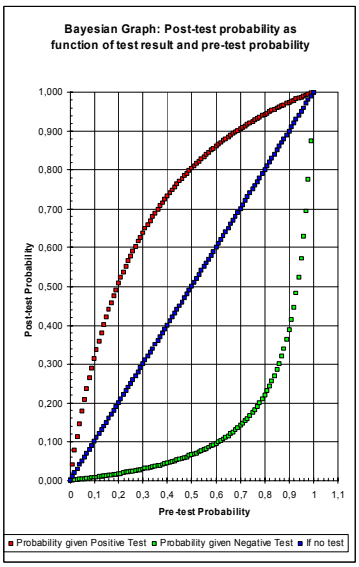


Table 3: Table of evidence for SPN

Type of cancer	Cancer management decision	Source and search period	Evidence	Diagnostic efficacy
Lung cancer SPN	Malignancy diagnosis I	HTA-FNCLCC 1991-10/2002	30 articles (10 retrospective and 20 prospective) n = 1550 patients + n = 518 lesions Se = 50% to 100% and Sp = 50% to 100% for nodule < 3cms, results per patient Se = 81% to 86% and Sp = 40% to 100% results per lesion, for nodule < 3cms Se = 93% to 100% and Sp = 52% to 90% per patient, for mass > 3 cms Se = 94% to 100% and Sp 67% to 83% per lesion for mass > 3 cms LHR + = 7.11 to 9 and LHR - = 0.06 to 0.09 (on 202 patients) Reference standard used in the studies not stated in the report	Level 3
Lung cancer SPN	Malignancy diagnosis II	HTA-DACEHTA from 1999 to 6/2001	Update of VHA (1996 – 1999) and NHS – HTA (1999) reports 12 publications included among which 9 give Se, Sp and LHR values. All 9 are included in the FNCLCC review Reference standard: pathology and follow up in 1 study	Level 3
Lung cancer SPN	Malignancy diagnosis III	HTA-ICES - up to 1 April 2004	1 prospective observational studies with histology as gold standard and only in case of contraindicated or failed FNAB), all included in the FNCLCC review, in Gould and in DACEHTA report. Se = 86% to 100% and Sp 40% to 90% PPV = 88% to 95% and NPV 55% to 100% Reference standard: pathology	Level 3
Lung cancer SPN	Malignancy diagnosis IV	SR-Gould meta analysis 1/1996 – 9/2000	40 articles (Retrospective ? Prospective ?) n = 1474 focal lesions. Study included in the FNCLCC review and DACEHTA report, 6 studies on patients with known lung cancer, 3 studies on gamma camera sROC analysis Maximum joint Se and Sp = 91.2% (95%CI 96.8% - 77.8%), In current practice: Se 96.8% and Sp 77.8% No difference between nodule or mass, between dedicated Pet and gamma camera, nor between SUV method or qualitative method. Reference standard: pathology and/or 2 year follow up	Level 3

Cost-effectiveness of PET in diagnosis of SPN

The cost-effectiveness of PET in the diagnosis of malignant solitary pulmonary nodules was examined in five studies of good quality and two of fair quality. The most comprehensive model with the clearest exposition of all assumptions imputed in the model was developed by Gould and colleagues. [77] The Markov model considered 40 clinically plausible sequences of CT, FDG-PET, transthoracic needle biopsy, surgery and watchful waiting. All sequences started with CT or FDG-PET. A hypothetical cohort of 62-year old men and women with new, non-calcified solitary pulmonary nodules ran through the model. Three levels of pre-test probability of malignancy were considered: low (26%), intermediate (55%) and high (79%). A strategy was cost-effective if its cost-effectiveness ratio (cost per QALY gained compared to the next most effective, non-dominated[iii], alternative) fell below US$100,000/QALY. A societal perspective was taken.

Pre-test probability of malignancy is a critical factor for the effectiveness and cost-effectiveness of a strategy. Pre-test probability depends on age, smoking status, history of cancer, nodule diameter, spiculation and upper lobe location.

Table 4 presents the strategies for which the incremental cost-effectiveness ratio satisfies the acceptability criterion of < 100,000 US$/QALY. All other strategies were dominated by another strategy. For an intermediate pre-test probability of malignancy all PET strategies were dominated by one of the other strategies considered in the model.

Table 4: Incremental cost-effectiveness ratios of non-dominated strategies according to the pre-test probability of malignancy [77]

Pre-test probability malignancy	Strategy	ICER[a] (US$/QALY)
Low (26%)	CT, followed by biopsy if CT indeterminate or followed by watchful waiting if CT benign	10 935
	CT, followed by PET if CT indeterminate, followed by surgery if PET positive or by biopsy if PET negative; if CT benign, watch and wait.	20 445
	CT, followed by PET if CT indeterminate, followed by surgery if PET positive or by biopsy if PET negative; if CT benign, biopsy	45 838
Intermediate (55%)	CT, followed by biopsy if CT indeterminate or followed by watchful waiting if CT benign	7 625
	CT-guided biopsy	14 981
	CT, followed by surgery if CT indeterminate, if CT benign, biopsy	17 649
High (79%)	CT, followed by surgery if CT indeterminate, if CT benign, watch and wait	6 515
	CT, followed by surgery if CT indeterminate or followed by PET if CT benign; if PET positive, biopsy; if PET negative, wait and see.	16 261
	CT, followed by surgery if CT indeterminate or followed by PET if CT benign; if PET positive, surgery; if PET negative, wait and see.	50 839
	CT, followed by surgery if CT indeterminate or followed by PET if CT benign; if PET positive, surgery; if PET negative, biopsy.	67 568

[a] ICER: Incremental cost-effectiveness ratio, expressed as cost (US$) per QALY gained of the strategy compared to the next most effective strategy that was not dominated.

[iii] An intervention is dominated if it is more costly and less effective than the alternative. In this case the alternative is clearly preferred.

PET strategies are most cost-effective in patients with a high or low pre-test probability of malignancy, especially when used selectively, i.e. when CT results and pre-test probability are discordant. In patients with intermediate pre-test probability of malignancy, PET is only marginally more effective and much more costly than CT followed by biopsy and/or surgery. The surgical risk also plays a role, albeit a more modest one than pre-test probability. PET strategies are more cost-effective if the surgical risk is high and pre-test probability of malignancy low to intermediate. The sensitivity analysis revealed that it is cost-effective to do a PET after CT if the CT results suggest malignancy and if pre-test probability of malignancy is between 10% and 55%. If the CT results are benign, PET is cost-effective if the pre-test probability of malignancy is between 77% and 89%. For patients with very high pre-test probability of malignancy (>90%), immediate surgery is more cost-effective than CT and/or PET strategies. [77]

A much cited study by Gambhir concludes that a CT+PET strategy is especially cost-effective (compared to watchful waiting) for a pre-test probability of malignancy between 12% and 69%.[18] Above this range, CT alone becomes the most cost-effective strategy. This is from the perspective of the Medicare reimbursement system. The key variables that influenced the cost-effectiveness of the strategies in this model were pre-test probability of malignancy, specificity of CT, percentage of biopsy procedures used and the cost of surgery. At extremely low pre-test probabilities of malignancy, watchful waiting is the most cost-effective strategy. At extremely high pre-test probabilities, immediate surgery is most efficient. High CT specificity (e.g. 0.91) improves the cost-effectiveness of CT alone compared to CT+PET, assuming that improvements in specificity do not compromise CT sensitivity. Unfortunately, the authors did not look at the impact of CT sensitivity on the results of the cost-effectiveness analysis.[18]

In a German cost-effectiveness analysis by Dietlein et al, four strategies were compared: watchful waiting (with CT every 3 months), explorative surgery, transthoracic needle biopsy (TNB), and PET [78]. Strategies were compared with either watchful waiting or exploratory surgery. The hypothetial cohort for this decision analytic model consists of 62-year old men with SPN of up to 3 cm diagnosed by CT, without calcification, without spicula and without enlargement of mediastinal lymph nodes (on a CT scan). Compared to watchful waiting, the ICER of the FDG-PET branch was €3,218 /LYS against €4,210 /LYS for the exploratory surgery and €/6,120LYS for the transthoracic needle biopsy. Compared to exploratory surgery the FDG-PET strategy was dominant (higher life expectancy and cost savings). Watchful waiting and TNB generated cost savings relative to exploratory surgery but these savings did not justify the loss of life expectancy. FDG-PET remains the most cost-effective strategy for risk and non-risk patients when SPN malignancy is between 10%-80%, specificity/sensitivity PET for SPN≤3cm above 88%/73% and for nodal involvement 67%/89% (=penalization -7% on each baseline parameter). Compared to other models, the advantage of this model is that involvement of mediastinal lymph nodes and efficacy of PET for detecting nodal metastases are taken into account. Hence the additional effects of PET in nodal staging explain the fact that life expectancy is more influenced by PET than in the previous one [18].

A replication of two existing models (the ICP model [79] and the Gambhir model[18]) for Australia, found that both PET alone and CT+PET dominated CT alone, i.e. both PET-strategies were more accurate and less costly than the CT only strategy.[80] This result was maintained with and without modelling the follow up. Follow up consisted of 4 chest X-rays over 2 years. The results of the models were robust. The one-way sensitivity analysis[iv] showed that the PET strategies have a lower cost per accurately treated patient than the CT alone strategy up to a prior probability of malignancy level of 0.8 (Gambhir model) or 0,9 (ICP model). The perspective of the analysis was not specified.

Finally, an Italian model analyzed the cost-benefit of diagnosis of SPN with CT+PET as compared to CT alone from the perspective of the Italian National Reimbursement System.[81] In Italy, patients with positive CT are referred to oncological assessment. In case of uncertain results or negative clinical examination, a biopsy is performed (about 20% in the base case scenario). Other patients undergo a thoracoscopy (80%). The model revealed a cost saving of € 48 per patient with CT+PET. The results were sensitive for the value of sensitivity of CT (baseline 0.53) and the percentage of surgical

[iv] A one-way sensitivity analysis tests the sensitivity of the results of the model to one of the uncertain parameters used in the model. The value of one parameter is changed and all others are kept constant at their baseline value.

interventions (baseline 80%) and biopsy (baseline 20%). At a sensitivity level of 70% or higher for CT, CT+PET becomes more costly than CT alone. For a percentage of immediate surgery after positive CT of less than 69% -and thus a percentage of biopsy of more than 31%- CT+PET is more costly than CT alone. As in most models, the prevalence of malignancy determines the results of the model. A prevalence level of less than 31% renders the CT+PET strategy less costly as compared to CT alone.[81]

In general, we can conclude from the economic models on PET for the diagnosis of malignant SPNs that the determinant factors for the cost-effectiveness of PET-strategies are the pre-test probability of malignancy and the sensitivity of CT. First, PET is economically justified for patients with a pre-test probability between 10% and 55% if CT results are positive, and for patients with a pre-test probability of malignancy between 77% and 89% if CT results are negative. For very high pre-test probabilities of malignancy (>90%), immediate surgery is the most cost-effective strategy. Second, the higher the sensitivity of CT, the lower the cost-effectiveness of PET-strategies compared to CT-only strategies.

Conclusion

Based on the diagnostic efficacy and cost effectiveness studies, the use of PET in SPN diagnosis can be rated at level 3. The economic models indeed, estimated the post-test probabilities threshold for which PET is economically justified. This threshold can hence be used for medical decision making: beyond the threshold value, the invasive procedures (FNAB or thoracotomy) can be avoided.

5.1.2. Initial staging and prognosis of NSCLC

Diagnostic efficacy

For initial staging of NSCLC, the reported sensitivity of PET for local disease assessment varies between 61 and 100%, the specificity between 64 and 100%, compared with CT sensitivity of 20% – 83% and specificity of 25% – 100% [32 33 15]. The point on the ROC curve with equal sensitivity and specificity (Q*) was 0.9 for PET and 0.7 for CT (p<0.0001) in detecting mediastinal lymph nodes metastases. This point located in the most left upper zone of the graph has no clinical impact per se but is useful to compare the sROC curve of 2 tests. The clinical impact of a sROC curve depends indeed on the chosen threshold between positive and negative result of the test. Overall estimate of the DOR was 5.4 for CT and 76.4 for PET [82] .

Several HTA reports made a distinction between the different stages of disease. In case of disease N2, the performance values for PET and CT are respectively 67%-100% and 20%-79% for sensitivity, and 76%-100% and 63%-98% for specificity in detecting mediastinal involved lymph nodes, even with size <1cm [32 73]. Compared to CT, PET better detects N1 disease (42% vs 13%) and N2/N3 disease (58% vs 32%) [15].

Based on three meta-analyses on CT Nodes Negative patients, PET has a sensitivity of 86% (CI: 79%-86%) at the specificity of 90% (CI: 87%-93%). In CT Nodes Positive patients, PET sensitivity is 92% (CI: 87%-95%) at the specificity of 76% (CI: 69%-82%) [9] and Figure 9 present the graph of post-test probability as function of test result and pre-test probability in these cases [76]:

Figure 8: PET after CT Nodes negative

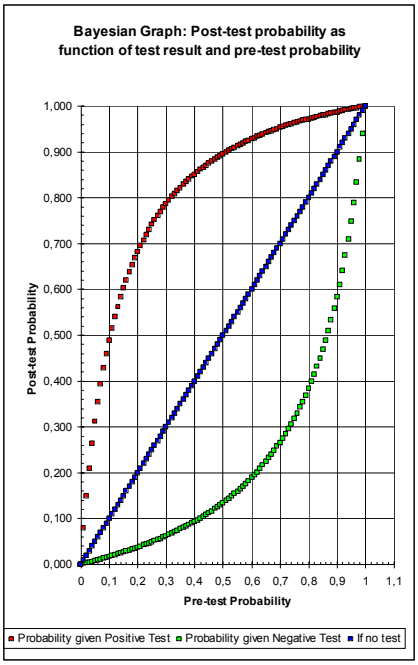
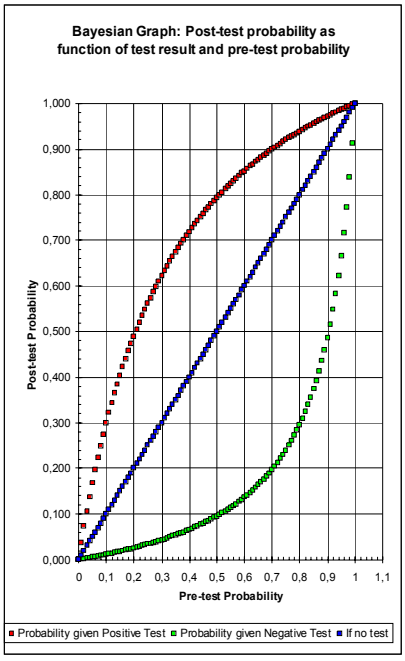


Figure 9: PET after CT Nodes positive



Nevertheless, the utilisation of PET is not expected to reduce the number of CT because the anatomical information provided by CT is still needed for the T classification ([15], External Experts group). PET has a limited ability in detecting micro-metastases in lymph nodes and false positive results may occur in granulomatous lesions such as sarcoidosis and anthracosis [32 83] . This is the reason why PET is considered most useful for its negative predictive value (87 to 97%), potentially allowing surgery without preoperative mediastinoscopy and cytological/histological confirmation in stage I and II patients (N0 or N1 and M0), candidates for surgery on basis of CT and PET negative results, and in N2/N3 patients in case of a negative PET.[9, 32].

Evaluation of PET in the detection of distant metastases in case of NSCLC is difficult because there is no reference technique allowing an objective detection of the lesions. It is clear that, for ethical reasons, it is not possible to biopsy any positive site to make sure it is a metastasis (External Experts group). However, RCTs on patient outcomes may be an alternative to the absence of a reference standard. Nevertheless, of NSCLC patients surgically treated with a curative intent, 5% to 7% had a non-resectable tumour and 14% died during the first year following surgery [84]. For that reason, the role of PET in preoperative staging has been studied. PET should identify those patients who are not candidate for resection because of metastases in 8% to 15% of the cases [85] but, anyway, the localisation of metastases depends on the stage of the disease (7.7% for stage I, 18% for stage II and 24% for stage III [86]). PET apparently allows a change in staging for 13% to 47% of cases (N disease), and for 11% to 30% of cases (M disease) [32], and, finally, reduces the number of not indicated thoracotomies according to several studies including 1 RCT (41% of "futile" thoracotomies for classical imagery, 21% for PET) [32 15]. Other studies show a change in the management of patient treatment in 29% to 65% of the cases [32 9]. There are 2 RCTs on PET in NSCLC patient management, one undertaken in Europe and the other in Australia, with discordant results. The European study shows a change in patient management (reduction of futile thoracotomies) but not the Australian one [34]. The difference may be due to the way in which the surgeons use the additional information that PET provided: with the procedures used in Europe, would the Australian study have lead to the same conclusions [34]. Current management protocol should be outlined before studying the way PET changes patient management. This is not just the technology that is changing but also cancer management decisions: the emerging dilemma in NSCLC is to identify the patients who should be selected for combination treatment [34]. The conclusion of most HTA reports and Systematic Reviews is that PET plays a role in initial staging of NSCLC [9, 32 84 15 83 34]. In a recent study (198 patients), it has been reported that systematically applied PET scanning has a significant impact on patient management, altering diagnosis or therapeutic intervention in 72.2% of patients with potentially life-saving consequences in 2% [87]. However, direct evidence of PET ability to improve patient outcome is lacking.[83]

Remarks:

- The advantage of PET in the assessment of prognosis of NSCLC is not well established except for pT1 patients with a lower FDG uptake who have a better prognosis, [32 85 83].
- There is no difference between NSCLC and most bronchiolo-alveolar carcinoma (BAC) for PET indications (FNCLCC), although PET may be false negative or give only a low FDG uptake in this subtype (External Experts Group).
- Most carcinoid (neuroendocrine) tumours are considered not FDG-avid [32].

Table 5: Table of evidence for NSCLC staging

Type of cancer	Cancer mangmnt decision	Source & search period	Evidence	Diagnostic efficacy
Lung cancer NSCLC	Initial staging I	HTA-FNCLCC 1991-10/2002	27 articles (17 prospective and 10 retrospective) 1,030 patients Local extension: Results per patient in 17 studies, per lesion (node, nodes group or mediastin) in 9 studies and both in 1 study; All studies with dedicated PET except 1, Comparison with CT in 22 studies Se = 67 – 100%, Sp =76% – 100% PPV = 43% – 93%, NPV = 87% – 99% for PET ; Se= 20% – 79%, Sp = 63% – 100%, PPV = 23% – 76%, NPV = 64% – 96% for CT Distant metastases 6 articles, no precision about typology Sites investigated: every sites in 3 studies, bone in 2 and the pleura in 1 Se= 81% – 100% and Sp = 67%– 99% Change in patient management 18 articles (9 prospective, 3 retrospective and 6 not mentioned); Change of N stage: 13 – 47% Change of M stage: 11% – 30%; Change, no other mention: 18%– 62% Reference standard: pathology and follow up	Level 4
Lung cancer NSCLC	Initial staging II	HTA-HTBS July 2001 update of DACEHTA	3 SR, 33 papers on mediastinal staging, 19 papers on distant metastases, 2 RCT , a meta-analysis has been done with 16 selected studies (9 papers not found in the FNCLCC report and 9 papers found in the FNCLCC report but not found here) There is overlap between these studies. if CT negative: PET Sp = 0,9 and Se at this specificity = 0.86; if CT positive: PET Sp = 0.76 and Se at this specificity is 0.92 2 RCT with contradictory results about reduction of futile thoracotomies (1 = 51% reduction in thoracotomies rate, no reduction for the other, but variation among surgical procedures in use) Published studies suffer from deficiencies, further studies are needed Reference standard: pathology and follow up	Level 4
Lung cancer NSCLC	Initial staging III	HTA-DACEHTA up to 1/5/2001	31 papers, 30 in HTBSreport and 28 in FNCLCC (there is overlap between these studies), For mediastinal staging: Se= 63% – 100% and Sp = 67% – 100% for PET, Se = 20% – 83% and Sp = 25% – 100% for CT For distant metastases: Se = 90% – 100% and Sp = 80% – 100% for PET, Se = 80% – 100% and Sp = 0% – 89% for CT Reference standard: pathology and follow up	Level 2
Lung cancer NSCLC	Initial staging IV	HTA-ICES up to 1 April 2004	15 studies, all in the precedent reports, except 1 (Vesselle 2002) but with results similar to other studies. Se = 61% – 98% and Sp = 64% – 97% for PET; Se = 20% – 72% and Sp = 30% – 64% for CT Reference standard: surgery, pathology or follow up	Level 2
Lung cancer NSCLC	Initial staging V	HTA-MSAC 1996 – 1/2000	14 studies selected, all in other reports, conclusion similar to others Reference standard: pathology and follow up	Level 2
Lung cancer NSCLC	Initial staging VI	SR -Gould, M.K., et al., 2003	39 studies (n=18-237) 28 studies by patient analysis, 6 studies by lymph nodes analysis Median Se = 61% (95%CI 50% - 71%) and Sp = 79% (95%CI 66% - 89%) for CT; 85% (95%CI 67% - 91%) and 90% (95%CI 82%-96%)for PET. If CT+, PET Se = 91% (95%CI 79%-96%) for Sp = 78%; If CT -, PET Se = 75% (95%CI 59% -87%) for SP = 93% Q* = 70% (95%CI 67%-73%) for CT; Q* = 86% (95%CI 84%-88%) for PET Reference standard used in the primary studies: not stated	Level 2
Lung cancer NSCLC	Initial staging VII	SR -Birim, O., et al 2005	17 studies (n=833, 18-102/study) Median Se = 59% (95%CI 50%-67%) and Sp = 78% (95%CI 70%-84%) for CT; 83% (95%CI 77%-87%) and 92% (95%CI 89%-95%)for PET. Q* = 70% (95%CI 65%-71%) for CT; Q* = 90% (95%CI 86%-95%) for PET Overall estimate of the DOR was 5.4 for CT and 76.4 for FDG PET. Reference standard: pathology	Level 2

Cost-effectiveness of PET in staging of NSCLC

Six studies of good quality and one of fair quality were found on the cost-effectiveness of PET for pre-operative staging of NSCLC [17, 9, 88]

A Canadian cost-effectiveness analysis, based on a decision analytic model, concludes that FDG-PET is cost-effective in pre-operative staging of NSCLC. [88] A strategy that includes PET in addition to CT is cost saving and offers a better life expectancy than CT alone (3.1 days of life gained). About 9% of unnecessary surgery can be avoided through a diagnostic path with PET. This leads to a net cost saving of CA$1,455 per patient (price year 2000). The conclusion that CT+PET is cost saving relative to CT alone holds, ceteris paribus, for a prevalence of unresectable disease > 12.9%, a PET cost <CA$2,484, a surgical cost > CA$1,729, CT sensitivity <86.3% or PET sensitivity >37.8% (one-way sensitivity analyses). PET+CT offers better life expectancy than CT alone as long as the prevalence of unresectable disease is > 2,8%, CT sensitivity <97.9% or PET specificity >35.4% (one-way sensitivity analysis). [88]

Gambhir and colleagues reach similar conclusions from their model: under base-case assumptions CT+PET dominates CT alone, in that it offers a slightly better life expectancy (3 days) for a lower cost (savings US$1,154). In a conservative model, where every patient gets an anatomical CT prior to surgery and/or biopsy and every patient who is PET positive gets a biopsy to confirm unresectability, CT+PET remains cost saving as long as, ceteris paribus, the prevalence of unresectable disease >16.9%, CT sensitivity <82.3%, PET sensitivity >48.2%, PET specificity >12.3%, PET cost <US$2,354, biopsy cost <US$ 11,398 or surgical cost >US$17,485 (one-way sensitivity analysis). PET+CT offers better life expectancy than CT alone as long as the prevalence of unresectable disease is > 5.6%, CT sensitivity <95.7%, PET sensitivity >11.9%, PET specificity >31.7%, mortality associated with PET <0.16% and with biopsy <2.3% (one-way sensitivity analysis). The results are roughly the same as those found by Sloka in 2004, with small differences in threshold values for cost-benefit and effectiveness.

The German cost-effectiveness analysis by Dietlein et al. concluded to a clear cost-effectiveness of use of whole-body full ring PET in the preoperative staging of patients with NSCLC and normal-sized lymph nodes. The decision analytic model compared five strategies on a hypothetical cohort of 62-year old men with NSCLC histologically established and assessed as locally resectable [78]. The analysis was performed from the perspective of the reimbursement system. The conventional strategy was CT alone, with surgery or confirmation by mediastinoscopy if CT is negative (normal-sized mediastinal lymph nodes) and mediastinoscopy if CT is positive (enlarged mediastinal lymph nodes). The four other strategies included PET after CT; for patient with normal-sized mediastinal lymph nodes, for all patients, for all patients but without surgical procedures when both CT and PET were nodal-positive and finally for all patients but without surgical procedures when PET alone was nodal-positive. The use of whole-body PET in patients with normal-sized nodes leads to a better patient selection for surgery and is the most cost-effective strategy. In this case, the ICER is €143 per Life Year Saved (LYS) (against €36,667 /LYS if PET is used for all patients). Patients with a positive PET result should not be excluded from mediastinoscopy confirmation, as the cost savings did not justify the expected life years lost. The model was robust to one-way sensitivity analysis of prevalence and lowered specificity or sensitivity of PET. If the reimbursement decreases to €1,225, the ICER became negative due to cost savings. On the contrary, the use of a thoracic PET raised the ICER to €28,000 /LYS.

The Health Technology Board for Scotland modelled the cost-utility of PET for staging of NSCLC in Scotland.[9] Seven strategies with PET were considered and compared to the least costly alternative. The model assumed that every patient gets a CT scan before further testing. The calculation of costs and outcomes is hence performed for CT positive and CT negative patients respectively. The results of the model show that one specific strategy is more cost-effective than the current practice in CT-negative patients, but not equally cost-effective in CT-positive patients. This strategy involves sending all patients to PET, if PET is negative: send to surgery, if PET is positive and there are distant metastases: send to non-surgical treatment, otherwise: send to mediastinoscopy (if this is positive: non-surgical treatment, if this is negative: surgery). The incremental cost-effectiveness of this strategy

is £ 58,951/QALY compared to the current practice in CT-positive patients and £ 7,909/QALY compared to sending all patients to surgery without further testing in CT-negative patients.

The Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé for Québec built a decision analysis model with two competing strategies: CT alone versus CT followed by PET [84]. The population is a hypothetical cohort of 100 65-years old male patients with a metastatic conventional diagnosis negative and costs are tariffs and reimbursements from the Healthcare system perspective except for PET that are real costs transmitted by the Association of Nuclear Medicine Physicians. CT scan is used on every patient to detect mediastinal metastases. In the branch with PET, PET is used for mediastinal metastases if CT negative and is afterwards always used to detect distant metastases. Biopsy and mediastinoscopy are used to confirm the diagnosis, respectively of distant metastases or mediastinal metastases. The ICER for CT+PET is CA$ 4,689 per life year gained, the incremental effectiveness being 0.27 life year. One-way sensitivity-analysis and Monte-Carlo dynamic simulations did not affect the results. For the Monte-Carlo simulations, 95% of simulated ICER stay below the threshold of CA$ 50,000.

In a cost-outcome description by Verboom et al.[89] the difference in costs and number of futile operations between 188 patients randomly assigned to Conventional work up (CWU) or CWU + PET were computed. The study was based on the PLUS Randomized Controlled trial. All the patients had suspected NSCLC and were clinically estimated potentially resectable. The number of futile surgeries was higher in the CWU alone group, the absolute difference being 41% (39/96) - 21% (19/92) =20% (95% CI: 9% - 28%). This is equivalent to 5 patients needing PET to avoid 1 futile thoracotomy (95% CI: 3-14). The average cost per patient in the CWU alone group was € 9,573 (+/- SD 12072), compared to € 8,284 (+/- SD € 7,462) in the PET+CWU group. The median, however, was higher in the PET+CWU group than in the CWU alone group (€ 7,592 versus € 7,480). The presence of an outlier in the CWU group (61 ICU days) might explain the difference in results when looking at means versus medians. The one-way sensitivity analysis on efficacy or setting of PET showed the results were robust, although a PET scan price of € 1,588 and worst efficacy (>=36 futile operations after PET) would make the CWU arm more favorable (€ 542). The authors conclude that use of PET in staging of patients with NSCLC is feasible, safe and cost saving from a clinical and an economic perspective. This conclusion was, however, not entirely supported by the results. While the strengths of the study are that the costs and outcomes are observed instead of modelled, two main weaknesses remain. First, the outcome measure used in this study is an intermediary outcome (number of futile operations avoided), due to the short time window of the RCT. Final outcomes (life years gained and QALYs) are not considered, although they may be more important than the intermediary outcome, especially in view of the ongoing discussion about the effectiveness of surgery in specific NSCLC patients [9]. Second, the computation of futile surgery on the total number of patients of a group implies certainty that the higher number of non-operated patients in the CWU+PET group effectively should not have been operated or that PET cannot lead to false-positive results. If we only consider the avoided futile operations in those who are operated upon, the absolute difference would be less: 50% (39/78) – 31.7% (19/60) = 18.3%.

In conclusion, the economic models conclude that the addition of PET to CT is cost-effective in staging NSCLC. Although the incremental benefits in terms of life expectancy gained are small, considerable costs can be saved from avoiding unnecessary surgery as well as quality of life impairments.

5.1.3. Small cell lung cancer (SCLC)

For SCLC diagnosis, based on 2 studies (71 patients), the sensitivity and specificity of PET were both100%, compared with CT which has 90 to 93% sensitivity (25 patients) [90]. On the basis of 3 retrospective [91] [92] [93] and 1 prospective [94] studies, added by the External Experts Group and not yet reviewed by any HTA reports, PET was able to change the staging or management for 8% to 40% of patients. Anyway, the sample size of these studies is too small and the only prospective study shows a positive effect for only 13 patients on 120 (~12%) which is not enough to change the level of evidence [94]. Further studies are needed. However, SCLC typically disseminates before diagnosis and is treated with chemotherapy rather than surgery [34] [85] [32].

A single study with multiple methodological flaws addressed the use of FDG-PET in the diagnosis of SCLC patients with paraneoplastic syndrome [90].

A single high quality study found a 96% sensitivity and 69% specificity for PET in the detection of residual or recurrent disease with survival as outcome [90].

Table 6: Table of evidence for SCLC Staging

Type of cancer	Cancer Management decision	Source & search period	Evidence	Diagnostic efficacy
Lung cancer SCLC	Staging I	AHRQ 2004 Until 18 April 2003	2 studies (n=71) Se = 100% for PET, Se = 90% – 93% for CT Reference standard: pathology and follow up	Level 2

Table 7: SCLC – Primary studies

Setting	Grade	Study design	Author	Yr	Pts	Compare	Outcome	Blinded
Staging	C	Retrospective	Blum	2004	40	Histology and follow up	5/15 patients : upstaging (33%) 10/25 patients: change in therapy management, after restaging (40%)	N
Staging	B	Retrospect.	Bradley	2004	48	Histology	2/24 patients: upstaging (8%) 6/24 patients: change in radiation therapy plan (25%)	Y
Staging	B	Retrospect.	Kamel	2003	42	Histology and clinical workup	8/42 patients: change in radiation therapy (19%) 1/42 patients: downstaging (2.4%) 2/42 patients : chemotherapy stopped (4.8%) 1/42 patients: chemotherapy restarted (2.4%)	Y
Staging	B	Prospective	Brink	2004	120	Histology and clinical workup	10/120 patients: upstaging (8%) 3/120 patients: downstaging (2.5%) 1/120 patients: incorrect downstaging (0.8%) For lymph nodes detection: Se= 100% Sp= 98% for PET, Se= 70% Sp = 94% for CT For distant metastases (except brain): Se = 98% Sp = 92% for PET, Se = 83% Sp = 79% for CT	Y

Legend: Yr=year published; Pts=number of patients.

5.1.4. Irridiated volumes optimisation and therapy monitoring

On average, the information added by PET has reduced bone marrow irradiation but not the total dose of lung or mediastinal irradiation. There is still a great inter-observer variability and the number of patients concerned by the studies on that subject is small [32]. The combination of PET with CT might improve these results: compared with CT only, Planning Target Volume has been reduced in 24 to 70% of cases and increased in 30 to 76% of cases in a study on 30 patients [32 83].

Therapy monitoring with PET is based on the idea that therapy not only reduces tumour metabolism but also FDG uptake [32] . The Standardized Uptake Value of FDG is often used to assess the impact of therapy on the tumour. It is recommended to wait until 3 weeks after chemotherapy and until 4 months after radiotherapy before performing a PET, in order to reduce the interference risk between PET and therapy [32]. PET has been shown more accurate than CT to evaluate the response of stage IIIa-N2 disease after neoadjuvant chemotherapy [95] In this patient population, a decision has to be made as to whether the N stage has been reduced to N1 or N0 before operating the patient although a recent EORTC study reports an equal result for surgery and radiotherapy in that case [96].

Response to treatment remains an important prognosis factor (External Experts Group). Anyway, more studies are needed [32 84 97].

5.1.5. Residual and recurrent disease

Due to the difficulty in assessing residual or recurrent disease, which is only possible on long term follow up, evidence is actually lacking on a potential role for PET in the diagnosis of residual or recurrent lung cancer (sensitivity between 70% and 100%, specificity between 61% and 100%) [32 84 15]. Anyway, the potential of improved detection of bone metastases, frequently present in residual or recurrent disease, may argue in favour of PET in this indication [15].

Table 8: Evidence for NSCLC irradiation, therapy monitoring, residual/recurrent disease

Type of cancer	Cancer management decision	Source and search period	Evidence	Diagnostic efficacy
Lung cancer NSCLC	Irradiated volumes optimization I	HTA-FNCLCC 1991-10/2002	11 studies, including the 2 of MASC report between 13% and 70% of change in radiotherapy field, but small series of patients, great variability inter-observers and no outcomes assessment Reference standard: pathology in 1 study, not stated for the others	Level <2
Lung cancer NSCLC	Irradiated volumes optimization II	HTA-MSAC 1996 – 1/2000	2 studies (1 prospective, 1 retrospective) change of radiotherapy field in one quarter to one third of patients no change in outcomes reported Reference standard: not sated	Level <2
Lung cancer NSCLC	Therapy monitoring I	HTA-FNCLCC 1991-10/2002	7 studies (Needs better standardisation, and large scale experience in that indication) PET results show better correlation with survival than CT Great variability between patients and design among the studies Reference standard: surgery and follow up	Level <2
Lung cancer NSCLC	Therapy monitoring II	SR-Vansteenkiste, J., et al., 2004 1993 – 2003	4 studies on therapy monitoring (189 patients) 7 studies on prognostic value after treatment (397 patients) Overlapping between studies PET is a sensitive method of measuring biological effect of anticancer therapy but needs better standardisation and large-scale experience. Reference standard: follow up	Level <2
Lung cancer NSCLC	Residual and recurrent disease I	HTA-FNCLCC 1991-10/2002	8 studies: 2 prospective, results per patient, 4 retrospective, results per patient, 2 retrospective, results per lesion Se = 70% – 98%, Sp = 63% – 100% Reference standard: lack of histological controls (histology and follow up in 1 study, partial histology in 1 study)	Level 2
Lung cancer NSCLC	Residual and recurrent disease II	HTA-ICES Up to April 2004	1 study (58 patients) Reference standard: pathology and clinical Work Up	Level <2 Lack of studies

Remark: On a number of indications in this Table a level <2 was attributed based on the presence of relevant information beyond technical efficacy, but insufficient to reach a level 2.

5.1.6. Pleural and mediastinal disease

On the basis of the three studies on the role of PET in diagnosing pleural malignancy, a sensitivity ranging between 89% and 100%, and a specificity between 78% and 100% was reported [32, 15].The External Experts Group added 8 more primary studies with a total of 336 patients giving similar results of sensitivity and specificity [98 99 100 101 102 103 104 105].

There is only one study (n = 22) for mediastinal disease reporting a sensitivity of 90% and a specificity of 92%, compared with CT values: 70% and 83% [32].

Lung Cancer - Key Messages

- **For malignancy diagnosis of a SPN > 1cm, there is evidence of diagnostic efficacy up to diagnostic thinking based on the existence of a pre-test probability and a likelihood ratio, allowing the computation of a post-test probability. In addition, a post-test probability threshold for cost-effectiveness is provided by economic models: evidence is supportive for the use of PET (level 3).**
- **For the initial staging of a Non Small Cell lung Cancer, there is evidence of diagnostic accuracy. In addition, there is evidence that adding PET to CT is cost-effective, although the incremental benefit in terms of life years gained is small (level 6).**
- **For residual and recurrent disease, there is evidence of diagnostic accuracy including the determination of sensitivity and specificity (level 2).**
- **For therapy monitoring, there is a lack of evidence for diagnostic efficacy.**
- **For irradiated volume optimization, there is a lack of evidence for diagnostic efficacy.**
- **For staging/restaging SCLC, there is evidence of diagnostic accuracy including the determination of sensitivity and specificity (level 2).**
- **For pleural disease, there is evidence of diagnostic accuracy including the determination of sensitivity and specificity (level 2). For mediastinal disease, there is no evidence.**

5.2. LYMPHOMA

Material reviewed: HTA reports, Systematic Reviews and primary studies edited from 2002/1/1 for treatment response evaluation.

Following the WHO classification, Lymphoma may be divided into various groups, i.e. Hodgkin's lymphoma, Large B Cell Non Hodgkin's lymphoma, Follicular NHL…. The conclusions, presented in the following section, apply to all types, except if mentioned. The potential indications for the use of PET use are initial diagnosis, staging (lymph nodes and extra adenomatous) and recurrence diagnosis, residual mass evaluation (at the end of treatment), prognosis and treatment response (after initial therapy).

5.2.1. Initial diagnosis

Due to the necessity of a histological diagnosis, the role of PET in the initial diagnosis of lymphoma is very limited [32 34].

5.2.2. Staging and recurrence diagnosis

FDG uptake seems related to the histological grade of lymphoma with higher uptake in the more aggressive forms (high grade lymphoma according to the European American Lymphoma classification from the International Lymphoma Study Group) [106]. However, PET could give very good results in low grade Follicular NHL[32].

The role of PET in the initial staging of the disease implies a non-invasive evaluation of lymph node involvement and locating the preferred biopsy sites with more accuracy than CT [32]. In that indication, the sensitivity of PET is 99.2% and the specificity is 100%, compared with CT sensitivity of 83.2% and specificity of 99.8% [84]. PET done in the staging process could represent a good reference investigation allowing comparison with a PET done in the follow up process [32 107].

For other localisations of the disease, PET has a global sensitivity of 77% to 100%, specificity of 72% to 100% and an accuracy of 83% to 100%, compared with 50% to 95%, 51% to 95% and 63% respectively for gallium scintigraphy and 20% to 100%, 33% to 100 % and 73% for CT [32 84 108]. The positive predictive value of PET varies between 62% to 100%, and the negative predictive value from 50% to 100% [108].

For bone marrow involvement, PET showed a sensitivity of 79%, a specificity of 76%, a positive predictive value of 62% and a negative predictive value of 90% and bone marrow biopsy showed a sensitivity of 58% and specificity of 100% [108 107] . The role of PET for detection of lesions in bones or bone marrow is controversial [32].

For evaluation of spleen involvement, PET has a sensitivity of 92%, specificity of 100% and an accuracy of 97%, compared with 50%, 95% and 78% respectively for gallium scintigraphy [32]. The overall sensitivity of gallium is high but its usefulness in abdominal regions is limited as a result of bowel excretion of gallium [32].

For the evaluation of extra lymphatic localisations, several studies have shown that PET is responsible for a change in patient management in 14% to 23% of cases (change in staging or change in treatment) [32 107]. Therefore, PET could be indicated in addition to classical imaging techniques in the initial staging of Hodgkin's disease, aggressive NHL and low grade Follicular NHL if a staging change could affect the therapy [32 84 108]. The recurrence diagnosis is not different from initial staging ([32]. There are no studies reporting the impact of PET on patient outcomes [108].

Table 9: Evidence for Lymphoma staging and recurrence

Type of cancer	Cancer management decision	Source and search period	Evidence	Diagnostic efficacy
Lymphoma	Staging I	HTA-FNCLCC 1991-10/2002	17 studies: 466 Hodgkin patients and 357 NHL patients comparison with CT in 10 studies, with Ga scintigraphy in 5 studies, with clinical work up in 1 study Overall Se = 86% – 100% (8 studies) and Sp = 72% – 100% (8 studies) for PET For CT, Se = 81% – 91% (2 studies) Sp = 41% – 100 %(2 studies) For Ga scinti, Se = 50% – 95% (5 studies) Sp = 51% – 95% (4 studies) For spleen involvement: Se = 92%, Sp = 100% and accuracy = 97% for PET; Se = 50%, Sp =95% and accuracy = 78% for Ga scinti Change in staging due to PET (7 studies) Change in therapeutic management: 23% of patients (1 study) Reference standard: for lymph nodes, histology; for extra lymphatic localisations: histology of positive cases in 1 study, conventional imaging in the others	Level 3 Insufficient evidence to include results about change in patient management
Lymphoma	Staging II	HTA-HTBS July 2001 update of DACEHTA	7 studies: Studies mainly retrospective and with small number of patients Unclear if change in staging due to PET leads to a change in patient management Reference standard: follow up	Level 2 Insufficient evidence to include results about change in patient management
Lymphoma	Staging III	HTA-MSAC 1996 - 3/2001	7 studies: 369 patients (4 already in the FNCLCC report) For PET, Se = 79% – 100%, Sp = 78% – 100%, PPV = 67% – 100%, NPV = 50% – 100% For CT, Se = 20% – 100%, Sp = 33% – 100% For Bone marrow biopsy, Se = 58%, Sp = 100% For Bone scinti, Se = 80%, Sp = 92% For Ga Scinti, Se = 89% Clinical management presented in 12 studies, with great variability No studies about patients outcomes Reference standard: conventional imaging or follow up and CT or follow up and pathology	Level 2 Insufficient evidence to include results about change in patient management
Lymphoma	Staging IV	HTA-ICES - up to 1 April 2004	2 studies: 133 patients (already in the FNCLCC report) PET Se = 96%, Sp = 94% Change in patient therapeutic management due to PET : 14% Comparisons with Bone Marrow Biopsy: Se = 79%, Sp = 76%, PPV = 58% and NPV = 90% for PET Reference standard: pathology for 1 study, not stated in the other	Level 2 Insufficient evidence to include results about change in patient management
Lymphoma	Staging V	HTA-AETMIS up	3 Studies (2 prospective, 1 retrospective) : 107 patients (2 already in the	Level 2

		to February 2001	FNCLCC report) Se = 77% - 100% and Sp = 89% - 100% for PET ; Se = 80% - 95% and Sp = 39% for CT; Se = 80% for Ga scinti PET for nodes: Se = 99.2%, Sp = 100%; extra-lymphatic: Se = 100% and Sp = 99.4%; under-diaphragmatic: Se = 99% and Sp = 99.8% (1 study). Reference standard: biopsy or conventional imaging or follow up if discordance between PET and CT in 1 study, not stated for the others	

5.2.3. Residual mass evaluation, prognosis and treatment response

For the evaluation of a residual mass the sensitivity and specificity of PET spans from 43% to 100% and from 69% to 100%, compared with CT sensitivity of 71% to 100% and specificity of 17% to 65% [108]. The positive predictive value of PET spans from 44% to100% and the negative predictive value from 67% to 100%, compared with CT PPV and NPV of 19% to 60% and 50% to 100%, respectively [108 32]. In case of a positive PET the global survival of patients is 20%± 18% after 1 year and 0% to 4% after 2 years with 100% recurrence, but in case of a negative PET, the survival is 87%± 7% to 100% after 1 year and 68% ± 11% to 85% after 2 years with 17% recurrence [32]. Therefore, PET should be indicated for the diagnosis of residual disease (Hodgkin's disease and aggressive or follicular Non Hodgkin's lymphoma) in case of intense FDG uptake during initial staging [32 84] and for early evaluation of therapeutic response [32 107]. Clearly in that case, it is assumed that a PET examination would have to be done during the initial staging work up to all patients with Hodgkin's disease and aggressive or follicular non Hodgkin's lymphoma. Furthermore, the NHS Scotish Executive Health Department recommends on the basis of the HTBS HTA report, the use of PET in case of Diffuse Large B Cell Non Hodgkin's lymphoma, after 6 weeks treatment for patients with extensive disease to assess response to treatment and at the completion of chemotherapy to assess the need for consolidation radiotherapy [109]. However, the external Experts Group found that PET is not indicated to decide whether to irradiate or not because it is unable to detect a small amount of residual disease (External Experts Group). Mostly, PET is indicated for Hodgkin's disease patients after initial therapy in order to select those for whom no further treatment is needed or additional consolidation is needed [34]. For that indication, Facey report stated that there is consistent evidence of clinical effectiveness and that PET is suitable for routine use in stated pathway with audit [34]. A pathway is a tool used to plan healthcare for a specific patient [110]. The DACEHTA report did not provide any information on that setting.

The intensity of FDG uptake before treatment could serve as a prognosis indicator. The standardised uptake value (SUV) or other semi-quantitative methods like the distribution absorption ratio may be used to estimate the ratio between lesions and healthy tissue with a worse prognosis in case of high value of the ratio. The interest of disposing a good prediction technique rests on the possibility for the clinician to intensify the treatment and to plan a bone marrow transplant [32 108]. Several studies have shown the good prognosis value of PET for recurrence before and after bone marrow transplant [32]. Other studies have shown that the FDG uptake estimated with SUV has dropped down after chemotherapy. The best results to estimate the prognosis seem to be obtained after one course of chemotherapy (sensitivity of 82%, positive predictive value of 90%), or at mid term of the treatment and not after completion of treatment (sensitivity of 45%, positive predictive value of 83%) [32 107, 108]. However, the best moment is unknown (External Experts Group). In 2 prospective studies on 23 + 70 patients, it has been shown that, after one course of chemotherapy, 90% to 100% of PET positive patients have relapsed and ~85% of PET negative patients are still alive after 18 months in one study and after 36 months in the second one [32].

The role of PET in the evaluation of lymphoma treatment response has been evaluated through a search for primary studies from 2002 to 2005 (see selection methodology in the appendix). From our search, we selected 5 primary studies. For Hodgkin's disease, a study on 36 patients showed that midway through therapy, 4 of the 5 positive PET patients relapsed as well as 1 of the 3 Gallium scintigraphy positive patients. At conclusion of chemotherapy, 4 of the 8 PET positive patients relapsed as well as 2 of the 3 Gallium scintigraphy positive patients. PET had significance in predicting subsequent relapse (P=0.04) with a positive predictive value of 0.49 vs 0.65 for Gallium scintigraphy. The negative predictive value of PET is 0.96 vs 0.90 for Gallium. The sensitivity of PET at the end of therapy is 0.8 vs 0.4 for gallium [111]. A second study on 36 patients showed that PET could be positive up to 9 months before histological confirmation of an asymptomatic relapse, with 5 relapses among the 11 PET positive patients and no relapse among the PET negative patients [112]. PET could not replace bone marrow biopsy but provides the appropriate localisation [113].

From a first study on 50 patients with aggressive NHL, it appeared that survival could be predicted from the PET result following 2 chemotherapy courses (P<0.001 – Kaplan-Meier) (**Table 11**). The importance of histopathologic sub-types differentiation is underlined in that study [114].

A second study on 59 patients with Hodgkin's disease (16) and aggressive NHL (53), was a comparative study on the diagnostic accuracy of PET versus CT in the detection of recurrent disease following chemotherapy. PET has a sensitivity and specificity of 82% and 92% respectively, while CT had a sensitivity and specificity of 73% and 15% respectively. Local recurrence or disease progression was detected in 70% of patients with a positive PET result and in only 2 patients with a negative PET result ($P<0.001$) [115]. Due to the small sample size of these studies, it is impossible to draw conclusions on the role of PET in the follow up of lymphoma.

Table 10: Lymphoma Residual mass evaluation, prognosis and treatment response

Type of cancer	Cancer management decision	Source and search period	Evidence	Diagnostic efficacy
Lymphoma	Residual mass evaluation I	HTA-FNCLCC 1991-10/2002	11 studies: 204 Hodgkin patients, 158 NHL patients and 56 patients with no precision For PET, Se = 42% – 100% (6 studies), Sp = 69% – 100% (6 studies) For CT, Se = 25% – 100% (6 studies), Sp = 17% – 74% (6 studies) PET+: 1year survival = 20%+/-18%, 2 years = 0% - 4%, with 100% recurrence; PET -: 1year survival= 87% +/-7%, 2 years 68% +/-11%, allowing the identification of patients where therapy intensification is needed Reference standard: follow up in 1 study, not stated for the others	Level 3
Lymphoma	Residual mass evaluation II	HTA-HTBS July 2001 update of DACEHTA	- 7 studies: 194 Hodgkin patients and 71 NHL patients, 4 retrospective and 3 prospective studies In case of positive CT, PET Se = 80% (95%CI 59%-94%), Sp = 89% (95%CI 74% -97%) (metanalysis) - 7 retrospective studies: 193HD, 222 NHL patients For PET alone, Se = 81% (95%CI 63% -92%), Sp = 95% (95%CI 90% -99%); (meta analysis) - 5 retrospective, 1 prospective studies 223 HD and 82 NHL patients For CT alone, Se = 75 (95% CI 58%-88%), Sp = 45% (95%CI 27%-64%) (meta analysis) Reference standard: follow up	Level 2
Lymphoma	Residual mass evaluation III	HTA-MSAC 1996 - 3/2001	6 studies (5 already in the FNCLCC report): 241 patients For PET: Se = 43% – 100%, Sp = 69% – 100% For CT (3 studies), Se = 71% – 100% Sp = 4% – 65% For MRI (1 study), Se = 45%, Sp = 74% No impact on clinical management reported Reference standard: pathology and follow up in 2 studies, follow up in 1 study, not stated for others	Level 2
Lymphoma	Residual mass evaluation IV	HTA-ICES - up to 1 April 2004	1 retrospective study, already cited by other reports Reference standard: follow up	Level 2
Lymphoma	Prognosis I	HTA-FNCLCC 1991-10/2002	8 studies: 326 patients - After chemotherapy, positive PET patients have a lower progression free survival and overall survival at one year - Decrease in SUV is associate with low risk of recurrence Reference standard: follow up in 2 studies, not stated for the others	Level 2
Lymphoma	Prognosis II	HTA-MSAC 1996 - 3/2001	4 studies: (2 already in the FNCLCC report) - After chemotherapy, positive PET patients have a lower progression free survival and overall survival at one year - After 1 cure chemotherapy: Se = 82% and PPV = 90% for PET; after completion of treatment, Se = 45% and PPV = 83% for PET (1 study) - Decrease in SUV is associate with low risk of recurrence - For PET, Se = 70%, Sp = 100% in prognosis Reference standard: follow up	Level 2
Lymphoma	Treatment response I	HTA-FNCLCC 1991-10/2002	4 studies: 16 Hodgkin patients, 115 NHL patients At mid treatment, 87% – 100% of patients relapse if PET is positive and 84% – 87% of patients without recurrence if PET negative, at least after 1 year Reference standard: follow up	Level 2
Lymphoma	Treatment response II	HTA-MSAC 1996 - 3/2001	4 studies: (already in the FNCLCC report) For PET, Se = 93 %, Sp = 100%, PPV = 100%, NPV = 97% in diagnosing response to treatment. For CT, Se = 100%, Sp = 23%, PPV = 38%, NPV = 100% Reference standard: follow up	Level 2

Table 11: Lymphoma Treatment response - Primary studies

Setting	Grade	Study design	Author	Yr	Pts	Compare	Outcome	Blinded
Treatment response	B	Prospect.	Friedberg	2004	36 HD	Follow up (median = 24 months, range 10-32) Ga scinti	Mid therapy: Ga sci - PET - relapse: 1/16pts Ga sci - PET + relapse: 2/3pts Ga sci + PET + relapse: 2/2 pts Ga Sci + PET- relapse: 1/1 pts Post chemotherapy: Ga sci - PET - relapse: 1/24pts Ga sci - PET + relapse: 2/5pts Ga sci + PET + relapse: 2/3 pts Ga sci + PET- relapse: 0 pts	Y
Treatment response HD	B	Prospect.	Jerusalem	2003	36 HD	Follow up 3 years	CT- PET - relapse: 0/11 pts CT- PET + relapse: 3/36pts CT+ PET + relapse: 2/5 pts CT+ PET - relapse: 0/14 pts	Y
Treatment response HD	B	Prospect.	Döbert	2003	28 HD	Follow up at least 3 months CT Bone marrow biopsy	PET Se for residual mass = 30% PET Sp for residual mass = 100% With SUV cutoff of 2.5, PET provides appropriate localisation for bone marrow infiltration	unclear
Treatment response	B	Prospect.	Zinzani	2002	59 16HD 43 NHL	Follow up 60 months CT	Survival after radiochemotherapy CT- PET - relapse: 0/7 pts CT- PET + relapse: 3/3 pts CT+ PET + relapse: 6/10 pts CT+ PET - relapse: 2/39 pts	unclear
Treatment response	B	Prospect.	Itti	2004	50 NHL	Follow up (median = 28 months)	Survival correlated with PET result after 2 chemotherapy courses (Kaplan Meier $p<0.001$)	unclear

Legend: Yr=year published; Pts=number of patients.

5.2.4. Cost-effectiveness of PET in re-staging Hodgkin's disease

The evidence on cost-effectiveness of PET in lymphoma is limited to one model that examines the cost-effectiveness of PET in re-staging Hodgkin's disease.[9] The potential advantage of PET in addition to CT in this patient population is that it may avoid unnecessary radiotherapy and the associated morbidity and mortality.

The economic model showed that all strategies involving PET are more cost-effective to allocate patients to consolidation radiotherapy or surveillance than strategies that do not involve PET. It is more cost-effective to use PET in all patients (and not preceded by CT) than to use PET only in CT-positive patients. Nevertheless, *both* strategies are cost-effective for a wide range of assumptions

about the uncertain modelling variables, if the willingness to pay for a life year gained is equal to £ 5,000 (price year 2002).

With a strategy of CT alone, 36% of the patients will receive unnecessary consolidation radiotherapy. With the PET alone strategy, this percentage decreases to 4% and with PET after positive CT, the percentage of unnecessary radiotherapy is 6%.[9]

The model reflects the current clinical practice in Scotland. It is unclear whether the same effects will be reached in a Belgian context. It would be useful to apply the model to the Belgian diagnostic and treatment pathways for patients with Hodgkin's disease to see whether the conclusions hold. This was beyond the scope of this review.

Lymphoma - Key Messages

- **PET is not an indicated in the initial diagnosis.**
- **For initial staging and recurrence diagnosis (lymph nodes involvement and extra lymphatic localisation), there is evidence for diagnostic accuracy including the determination of sensitivity and specificity but without mentioning a post-test probability or diagnostic threshold. There are some studies treating changes in patient management but with high heterogeneity (level 2).**
- **For residual mass evaluation, there is clinical evidence up to the diagnostic thinking level because PET allows directing the medical decision on the follow up strategy (level 3). There is evidence from one modelling study for cost-effectiveness of PET for re-staging Hodgkin's disease.**
- **For prognosis, there is evidence of diagnostic accuracy including the determination of sensitivity and specificity (level 2).**
- **For evaluation of treatment response, there is evidence of diagnostic accuracy including the determination of sensitivity and specificity (level 2).**

5.3. HEAD AND NECK CANCER

5.3.1. Diagnosis of an occult primary tumour (suspected from a metastatic cervical lymph node)

The HTA-BCBS 2000 (OPT) report (Table 12-Diagnosis I) assessed the diagnostic accuracy of PET in the diagnosis of an occult primary tumour (OPT) following detection of metastases to cervical lymph nodes [116]. A first indication addressed in this report was related to the diagnostic accuracy of PET in the detection of an OPT not identified on clinical examination and imaging. A second indication addressed in this report was related to the diagnostic accuracy of PET in the detection of an OPT when results of other imaging modalities were not necessarily negative. Eight studies reporting on sensitivity and specificity and meeting the BCBS inclusion criteria were retrieved from January 1966 up to May 2000. Five studies from this report were also included in the HTA-DACEHTA 2001 report [117]. Another study in the HTA-DACEHTA 2001 report [117] is included in the HTA-MSAC 2001(ii) report [108]. One study from this report is not included in the HTA-MSAC 2001(ii) report and another study is updated in the HTA-MSAC 2001(ii) report [108]. The diagnostic reference standard in these studies was histopathology. All 8 studies reported hierarchy of diagnostic efficacy level 2 evidence. Studies had small sample sizes (n=10 to 29 patients/study; total n=138 patients) and a variety of comparators was used. Overall, the frequency of true positive PET results was 32% (range: 13% to 56%). The frequency of false positive PET results ranged from 0% to 40%. The reported PET sensitivity was 69% (range: 44% to 100%); PET specificity was 69% (range: 20% to 100%). No pooled analysis of sensitivity was performed. In the first indication (4 studies), the pooled estimate of true positive PET-results was 28%. A primary tumour was identified in 1 of 4 patients with a prior negative diagnostic work up. In the second indication (4 studies), the pooled estimate of true positive PET-results was 36%. True positive results of PET versus other comparators are summarized in Table 12. The benefit of PET over MRI remains unclear and also noted that the HTA-DACEHTA 2001 report [117] recognises a potential benefit of PET in both indications (based on the true positive rates). However, rates of false positives may weaken this benefit [34].

The HTA-MSAC 2001(ii) report (Table 13- Diagnosis II) [108] addresses the diagnosis of an occult primary tumour (OPT) following detection of metastases to cervical lymph nodes. A first indication addressed in this report was related to the diagnostic accuracy of PET in the detection of an occult primary squamous cell carcinoma (SCC). A second indication addressed in this report was related to the diagnostic accuracy of PET in the detection of an occult primary tumour (SCC or different histopathology: mixed study populations). Overall, 8 studies reporting on sensitivity and specificity and meeting the MSAC inclusion criteria, were retrieved up to March 2001. Five studies were also included in the HTA-DACEHTA 2001 report [117]. One study from this report was not included in the HTA-BCBS 2000 (OPT) report [116]. In this report, 1 study from the HTA-BCBS 2000 (OPT) report [116] is updated. The diagnostic reference standards in these studies were PET directed biopsies and clinical follow up. All 8 studies reported hierarchy of diagnostic efficacy level 2 evidence. In the first indication (5 studies), the pooled estimate of true positive PET results was 27%. In the second indication (mixed study population; 4 studies), the pooled estimate of true positive PET results was 30%. About two thirds of occult SCC primary tumours were detected in the head and neck region, another third was found in the lung. Two occult primary tumours in the mixed study population appeared to be primary breast tumours. The detection rate of true positives was similar for SCC metastases and metastases with mixed histopathology. Vermeersch et al. noted that some small head and neck tumours detected on clinical examination and pan-endoscopy may not be detected by PET [118]. Four studies reported level 4 evidence. PET assisted in the detection of primary tumours in 26/90 patients which in 19 cases led to a change in planned patient management. Three studies included some level 5 evidence information on survival. Only small numbers of patients have been analysed in each of the 3 studies that included some information about survival (with a maximum number of 29 patients evaluated for survival in 1 study). This information did not always include patients with primary tumours detected by PET. Therefore, these data on survival are considered insufficient and should be viewed with caution [34]. Patients in whom the primary tumour is large enough to be detected by PET or conventional examinations may also have more advanced disease and consequently poorer outcomes than those where no primary lesion can be found.

Occult Primary Tumour (suspected from a metastatic cervical lymph node) - Key Message

- **For diagnosis of an Occult Primary Tumour suspected from a cervical lymph node metastasis when clinical examination, panendoscopy with biopsy and/or conventional imaging modalities (CT/MRI) have failed to identify a primary tumour, there is evidence of diagnostic accuracy including the determination of sensitivity and specificity (level 2).**

5.3.2. Diagnosis of an occult primary tumour (suspected from a metastatic carcinoma outside the cervical lymph nodes)

The HTA-BCBS 2002 report studied the use of PET in patients with a metastatic carcinoma outside the cervical lymph nodes and an occult primary tumour (OPT) (4 studies; total of 47 patients) [119]. Evidence was considered sufficient to permit conclusions on the outcome of PET only after an initially unsuccessful diagnostic work up in patients with an OPT and with a single metastatic site outside the cervical lymph nodes. PET shows adequate diagnostic performance in the detection of additional metastatic sites in patients eligible for local or regional therapy of a single metastatic site from an OPT. Information from PET resulted in changes in patient management in 15 of 42 patients (36%; pooled results from 3 reports). PET has the ability to confirm a suspected malignancy and may contribute to an appropriate treatment i.e. when breast or colon cancer is found in patients with isolated metastasis in the axilla or liver. The use of PET after a negative initial work up for an OPT to rule out or detect additional metastasis meets the BCBS criteria for patients in whom local or regional therapy is considered as part of a treatment plan for a single site of metastatic carcinoma outside the cervical lymph nodes. BCBS criteria are not met for the use of PET instead of or as part of the initial work up for OPT. Moreover, BCBS criteria are neither met for patients with an OPT with multiple metastatic sites [119].

In a systematic review and meta-analysis by Delgado-Bolton et al. 2003, the diagnostic performance of PET was assessed in OPT in the detection of the primary tumour [120]. A literature search was performed from January 1994 up to May 2001. A meta-analysis was performed on patient-data from 15 eligible studies (298 patients). Reference standards in the studies were histopathology and imaging procedures or clinical follow up if no histopathological proof could be obtained. Study design was prospective (8 studies), retrospective (4 studies) or was not stated (3 studies). Assessments of the validity and quality of the research methods classified all studies in grade of evidence C. Grade C is considered weak evidence and includes studies with several flaws in research methods, small sample sizes, or incomplete reporting; these studies represent a narrow spectrum of generalizability. All studies included fewer than 35 patients, except for 1 study. The combined study populations consisted of 199 patients with metastatic cervical and supraclavicular lymph nodes 99 patients with a metastasis outside these regions. In addition, different histopathological cancer types were also mixed (SCC, ACC, undifferentiated or other). Studies had no control groups. Six studies were comparative with CT or MRI (4 studies), CT or MRI or direct pan-endoscopy with biopsy (1 study) and MRI (1 study). Pooled estimates of PET-sensitivity and specificity were 0.87 (95% CI: 0.81-0.92) and 0.71 (95% CI: 0.64-0.78) respectively. A sROC curve was provided. A funnel plot of specificity, not of sensitivity, suggests the presence of publication bias. The authors conclude that PET has intermediate specificity and high sensitivity for the detection of an OPT and suggest that PET could be useful in this indication. However, more data are needed to determine the clinical utility of PET in the assessment of patients with an OPT. Evaluation of the role of PET in OPT patients' management has yet to be assessed with properly designed studies [120].

Occult Primary Tumour (suspected from a metastatic carcinoma outside the cervical lymph nodes) - Key Messages

For diagnosis of an Occult Primary Tumour (suspected from a metastatic carcinoma outside the cervical lymph nodes)

- suspected from a single metastatic site outside the cervical lymph nodes following an unsuccessful initial diagnostic work up,
- as well as for the detection or exclusion of additional metastases following an unsuccessful initial diagnostic work up for an Occult Primary Tumour when local or regional therapy is considered as part of a treatment plan for a single metastatic carcinoma outside the cervical lymph nodes,

there is evidence of diagnostic accuracy (level 2).

Table 12: Head and Neck cancer (suspected from Occult Primary Tumour)

Type of cancer	Cancer management decision	Source and Search period	Evidence	Diagnostic efficacy
Head and neck cancer (suspected from occult primary tumour - OPT)	Diagnosis I	HTA-BCBS 2000 (OPT) - up to May 2000	8 studies (10 to 29 patients/study, total n=138 patients) PET Se = 69% (range 44% to100%) and PET Spec = 69% (range 20% to100%) PET-TP=32% (range 13%-56%) and PET-FP (range = 0-40%) 4 studies on detection of an OPT not identified on clinical examination and imaging: Pooled PET-TP=28% 4 studies on detection of a primary tumour with results, not necessarily negative on other imaging modalities Pooled PET-TP = 36% TP's from comparative studies: PET-TP=47% vs CT/MRI-TP=33% (n=15) ; PET-TP=31% vs Endoscopy-TP=8% (n=13) ; PET-TP=50% vs CT-TP=0% (n=10) ; PET-TP=35% vs MRI-TP=36% vs CT-TP=22% (n=20)	Level 2 Small studies with a variety of comparators
Head and neck cancer (suspected from occult primary tumour - OPT)	Diagnosis II	HTA-MSAC 2001 (ii) - up to March 2001	8 studies (total n=166 patients) 5 studies on detection of an occult SCC primary tumour: PET-TP=27% 3 studies on detection of an OPT (SCC or other histopathology; mixed study populations): PET-TP=33% Hierarchy 4 evidence is reported in 4 studies: PET assisted in the detection of primary tumours in 26 out of 90 patients leading to changes management decisions in 19 patients Some hierarchy 5 evidence (on survival) is reported in 3 studies	Level 2

Table adapted from: K Facey, I Bradbury, G Laking and E Payne. Positron Emission Tomography (PET) Imaging in Cancer Management. Ultra Rapid Review. July 2004. Health Technology Assessment NHS R&D HTA Programme.

5.3.3. Diagnosis of head and neck cancer

In a systematic review by Vermeersch et al 2003 (Table 13-Diagnosis), the diagnostic accuracy of PET in the diagnosis of primary head and neck cancer was assessed [118]. Head and neck cancer was defined as squamous cell carcinoma of the upper aerodigestive tract including the pharynx, larynx, oral cavity and lips. Studies were retrieved from 1989 up to February 2003. Four comparative studies (comparative with CT/MRI), reporting on sensitivity and specificity were selected. Study sizes were not reported. The reference standards were not stated. All 4 studies reported hierarchy of diagnostic efficacy level 2 evidence. In these 4 studies, the diagnostic accuracy of PET versus CT/MRI was assessed. The sensitivity of PET varied from 85% to 95% while its specificity varied from 80% to 100%. The sensitivity of the CT/MRI comparator test varied from 67% to 88% and its specificity varied from 44% to 75%. PET specificity was not statistically different from the specificity of CT/MRI. In most cases, the diagnosis of primary head and neck cancer is made on clinical examination, endoscopy with biopsies and imaging with CT/MRI and/or US. Morphological imaging such as CT/MRI is irreplaceable to determine the extension of the tumour in adjacent structures but may lack specificity. "Where doubt exists" PET may be used to improve the specificity of CT/MRI [34].

5.3.4. Staging of head and neck cancer

The HTA-BCBS 2000 report (Table 13-Staging I) addresses the cancer management decision on initial staging of head and neck cancer. Head and neck cancer in this report included a variety of malignancies but predominantly SCC of the pharynx, larynx, oral cavity, lip and salivary glands. The diagnostic accuracy of PET was assessed in the staging of regional lymph node metastases in established primary head and neck cancer, in order to determine whether to perform neck dissection or irradiation. Studies were retrieved up to May 2000. Eight of 11 studies in HTA-DACEHTA 2001 [117] are included in this report. Seventeen studies reporting on patients, lesions or affected neck sides were selected. The reference standard was not stated. All 17 studies reported hierarchy of diagnostic efficacy level 2 evidence. In 8 studies on a total of 239 patients the unit of analysis was the patient and not the lesion. Results from 4 studies, comparing PET with CT, were pooled by patient results. The estimated sensitivity and specificity of PET was 81% and 97% respectively. The estimated sensitivity and specificity of CT was 72% and 89% respectively. Results from 3 studies, comparing PET with MRI were also pooled by patient results. The estimated sensitivity and specificity of PET was 91% and 82% respectively. The estimated sensitivity and specificity of MRI was 82% and 83% respectively. A single study with small sample size evaluated the diagnostic accuracy of PET in addition to morphological imaging. Correct stage classifications were reported with CT in 9 of 13 patients and with CT+PET in 12 of 13 patients. Correct stage classifications were reported with MRI in 2 of 5 patients and with MRI+PET in all 5 patients. A sROC analysis was not performed.

The HTA-MSAC 2001(ii) report (Table 13-Staging II) [108]addresses the cancer management decision on initial staging of head and neck cancer. Head and neck cancer consisted predominantly of SCC of the upper aerodigestive tract. The diagnostic accuracy of PET was assessed in the staging of regional lymph node involvement in patients with newly diagnosed head and neck cancer. Studies were retrieved up to March 2001. Fourteen comparative studies (comparative with CT/MRI), reporting on sensitivity and specificity were selected.The reference standard was histopathology. All 14 studies reported hierarchy of diagnostic efficacy level 2 evidence. Six studies used the patient as the unit of analysis. The specificity of PET was similar or higher than comparators' specificity and only below 90% in 1 study. The sensitivity of PET is similar to the comparators' sensitivity in 3 studies (83%, 100%, 75%). In the other 3 studies, the sensitivities of PET are 100%, 57% and 50% and the sensitivities of the comparator are 78%, 80% and 40%.Correct lymph node staging was assessed in 3 studies: 65%, 75% and 88% of the patients were correctly staged. Two studies reported hierarchy 4 evidence. One study reported that 8 of 32 patients had management changed or were intended to have management changed. In another study on 12 patients, PET correctly indicated all cases of metastatic involvement (number of patients not stated) but incorrectly indicated the need for surgery in 5 of 12 patients. It was noted that some papers combined SCC and non-SCC but also that pooling of all comparators (selected patients had MRI instead of CT) is not ideal [34].

In a systematic review by Goerres et al 2003 (Table 13-Staging III), the diagnostic accuracy of PET was assessed in the staging of regional lymph node involvement in patients with cytology or histology proven primary head and neck cancer [121]. Head and neck cancer in this review included SCC and adenocarcinoma (AC) but without specifications of tumour sites. Studies were retrieved up to October 2001. Eleven studies, reporting on sensitivity, specificity and likelihood ratios were selected. The reference standard was histopathology. All 11 studies reported hierarchy of diagnostic efficacy level 3 evidence. The sensitivity and specificity of PET were 81% and the 79% respectively. Positive and negative log-likelihoods were calculated as weighted means and reported by patient and by lymph node. Analysis by lymph node (n=3294) revealed a positive likelihood ratio of 17.3 (95% CI 10.9 - 17.3) and a negative likelihood ratio 0.19 (95% CI 0.13 - 0.27). Analysis by patient (n=369) revealed a positive likelihood ratio of 3.9 (95% CI 2.6 - 5.9) and a negative likelihood ratio 0.24 (95% CI 0.14 - 0.41). Few details were provided on the include studies. No comparative data were presented and some small studies were reported with a large number of lymph nodes per patient. In methodological terms, an analysis with the patient as unit of analysis is more reliable. Pre-test probabilities from a register of 98 Swiss patients were combined with likelihood ratios to calculate post-test probabilities.

In a systematic review by Vermeersch et al 2003 (Table 13-Staging IV), the diagnostic accuracy of PET in the staging of regional lymph node involvement in primary head and neck SCC was assessed. Head and neck cancer was defined as SCC of the upper aerodigestive tract including the oral cavity, pharynx and larynx. Studies were retrieved from 1989 up to February 2003 [118]. Seventeen comparative studies (comparative with CT/MRI), reporting on sensitivity and specificity were selected. Study sizes were not reported. The reference standard was not stated. All 17 studies reported hierarchy of diagnostic efficacy level 2 evidence. A sROC curve was provided, but no estimates were reported. Sensitivity was 80% or more and specificity was 90% or more for PET in 6 studies. A similar sensitivity and specificity for CT/MRI was found in only 1 study. PET sensitivity (p=0.01) and specificity (p=0.01) were significantly higher than CT/MRI sensitivity and specificity. Poor standardisation across studies was noted of patient population, reference standard or CT/MRI positive definition. Results by lesion and patient were not differentiated. As the studies used disparate proportions, the authors restricted their analysis to a paired comparison of PET with CT/MRI. An analysis by each comparator would have been preferable [34].

In the same systematic review by Vermeersch et al 2003 (Table 13-Staging V), the diagnostic accuracy of PET in the detection of distant metastases and synchronous primaries in patients diagnosed with primary squamous cell head and neck cancer was assessed [118]. Head and neck cancer was defined as SCC of the upper aerodigestive tract including the oral cavity, pharynx and larynx. Studies were retrieved from 1989 up to February 2003. Four studies were selected (reported in narrative).The reference standard was histopathology, clinical or radiographic follow up. All 4 studies reported hierarchy of diagnostic efficacy level 2 evidence. In a first study on 59 patients, a superior "accuracy" was reported for PET compared to bronchoscopy in the detection of synchronous lung lesions (80% versus 50%). A second study on 45 patients found 2 true positive and 4 false positive lesions in the chest. A third study on 28 patients found true positives in 9 out of 10 patients and true negatives in 17 out of 18 patients. In a fourth study on 12 patients, PET found mediastinal disease undetected by prior investigation in 2 patients. Results by lesion and patient were mixed. From the first study it was unclear whether "accuracy" referred to diagnostic accuracy or sensitivity. No pathological data were given in the second study [34].

In the "ICES 2004 Quarterly update" of the original ICES 2001 HTA-report, a literature review and critical appraisal of articles on the use of PET scan in head & neck cancer has been performed until April 2004 [15]. The authors noted that PET may potentially influence some processes of care in selected patients with head & neck squamous cell carcinoma (HNSCC). Four prospective studies on the detection of metastases from newly diagnosed HNSCC (n=48-78 patients per study; total n= 244) were discussed. Three studies were comparative (3 studies comparative with CT and 1 study with CT and MRI). The reference standard was histopathology. All studies reported hierarchy of diagnostic efficacy level 2 evidence. PET-sensitivity was similar to CT-sensitivity in 2 studies (81% and 72% versus 81% and 67%) and superior to CT-sensitivity in 1 study (87% versus 65%). PET-specificity was superior to CT-specificity in 2 studies (100% and 94% versus 81% and 47%) and similar to CT-specificity in 1 study (99% versus 97%). In 1 study with MRI as a comparator PET-sensitivity was similar (87% versus 88%) but PET-specificity was higher (94% versus 41%). It was noted that PET may

be superior to CT in the pre-treatment evaluation of clinically uninvolved lymph nodes in the neck. No study has examined the likelihood that doctors would use this information to alter therapy or to improve outcomes. In a study on 56 HNSCC patients, PET of the thorax produced additional information in only 1 patient compared to conventional imaging (evidence of otherwise undetected metastases). More accurate assessment of cervical lymph node metastasis has the potential to reduce the frequency of unnecessary lymph node dissections in patients with HNSCC. It appears that PET may be equivalent or superior to classical morphological imaging methods in the evaluation of cervical lymph node metastases. Superior specificity and sensitivity of PET compared to CT scan has been reported. However, it remains unclear whether the use of PET would reduce the utilization of CT or MRI. In addition, it is also unclear which changes in treatment and outcome would be observed if PET is implemented. Furthermore, HNSCC at various locations have varying probabilities of lymph node metastases and presently, studies are lacking on which different anatomic cancer sites within the head and neck region would or would not be most appropriate for PET [15].

5.3.5. Restaging of head and neck cancer

The HTA-BCBS 2000 report (Table 14-Restaging I) addresses the cancer management decision on restaging in follow up after primary treatment for head and neck cancer with surgery or radiotherapy. Head and neck cancer in this report included diverse malignancies but predominantly SCC including pharynx, larynx, oral cavity, lip and salivary glands. Studies were retrieved up to May 2000. Twenty-four studies were selected. Eighteen studies evaluated patients as the unit of analysis. The reference standard was not stated. All 24 studies reported hierarchy of diagnostic efficacy level 2 evidence. Eighteen studies evaluated patients as the unit of analysis. The sensitivity of PET was 80% or more in 16 out of 18 studies (range=33% to 100%). The specificity of PET was 80% or more in 11 out of 18 studies (range=33% to 100%). Results from 18 studies were pooled by patient results. Pooled sensitivity and specificity of PET was 90% and 76% respectively. PET performed better than comparators in 6 studies (n=140 patients). PET results were mixed or neutral in 4 studies (n=152 patients). PET performed worse than CT in 1 study (n=13 patients). A single study with small sample size evaluated the diagnostic accuracy of PET in addition to morphological imaging. Correct restaging was reported with CT in 7 out of 8 patients and with CT+PET also in 7 out of 13 patients. Correct restaging was reported with MRI in 1 out of 2 patients and with MRI+PET in 2 out of 2 patients. In 1 study (n=29 patients), PET results led to recommendations for palliative treatment instead of surgery in 9 patients. Not all studies were comparative and results were not pooled in a formal model due to different comparators, sites of residual/recurrent disease. The lower specificity in restaging may be related to a higher FDG uptake in regions with treatment-induced inflammation. The timing of PET imaging may be important, but this has not been clearly reported. A small study shows no added benefit of PET. In another study reporting recommendation of palliative treatment instead of surgery in 9 patients based on PET results, no information was provided that PET results were eventually used to alter patient management [34].

The HTA-MSAC 2001(ii) report (Table 14-Restaging II) assessed the diagnostic accuracy of PET in the detection of residual or recurrent head and neck cancer. Head and neck cancer mainly consisted of SCC of the upper aerodigestive tract. Studies were retrieved up to March 2001[108]. Fifteen comparative studies (comparative with CT/MRI and analysed with the patient as a unit of analysis) were selected. The reference standards were clinical follow up, sometimes with histopathology of lesions obtained by biopsy or surgery. All 15 studies reported hierarchy of diagnostic efficacy level 2 evidence. PET sensitivity was 85% or more in 14/15 studies; CT/MRI sensitivity was 85% or more in 4/15 studies. PET specificity was 80% or more in 10/15 studies; CT/MRI specificity was 80% or more in 6/15 studies. In 1 study, PET correctly predicted the need for pan-endoscopy in 30/38 patients versus 19/38 patients for CT+MRI. Eight studies reported hierarchy 4 evidence. Three of these studies are notable. In a first study, PET results correctly indicated the need for biopsy in 16 out of 17 patients compared to 11 out of 17 patients for CT/MRI results. Biopsy was correctly avoided in 14 of 21 cases. In a second study, PET detected distant metastases in 7 out of 22 patients and treatment changed from surgery to palliation in these 7 patients. In a third study PET results led to management change in 26 out of 66 patients. It was found that this change was correct in 23 patients. It was noted

that most studies assessed detection of residual or recurrent disease in patients who had undergone radiation. PET sensitivity was higher than comparators' sensitivity and PET specificity was similar or higher than the comparators' specificity. In some cases PET accuracy was slightly better for local disease than for nodal disease. Several studies reporting hierarchy 4 evidence had small sample sizes and provided incomplete information on how management was changed [34].

In the systematic review by Goerres et al. 2003 (Table 14-Restaging III), head and neck cancer included SCC and adenocarcinoma (AC) but without specifications of tumour sites [121]. The diagnostic accuracy of PET was assessed in the restaging of regional lymph node involvement in patients with recurrent head and neck cancer. PET was performed on follow up but only after a time-interval of at least 1 month following the end of treatment. Studies were retrieved up to October 2001. Ten studies, reporting on sensitivity, specificity and likelihood ratios were selected. The reference standard was histopathology. These 10 studies reported hierarchy of diagnostic efficacy level 3. Positive and negative log-likelihoods were calculated as weighted means and were reported with the patient as a unit of analysis. Analysis by patient revealed a positive likelihood ratio of 4.0 (95% CI 2.8 - 5.6) and a negative likelihood ratio 0.16 (95% CI 0.10 - 0.25).The sensitivity and specificity of PET were 88% and 78% respectively. It was noted that only few details were provided on the included studies, no comparative data were presented and generally only small studies were reported [34].

In a systematic review by Vermeersch et al 2003 (Table 14-Restaging IV), the diagnostic accuracy of PET in the staging of regional lymph node involvement in residual or recurrent squamous cell head and neck cancer was assessed. Head and neck cancer was defined as SCC of the upper aerodigestive tract including the oral cavity, pharynx and larynx [118]. Studies were retrieved from 1989 up to February 2003. Fifteen comparative studies (comparative with CT/MRI) reporting on sensitivity and specificity were selected. The reference standard was not stated. All 15 studies reported hierarchy of diagnostic efficacy level 2 evidence. A sROC curve was provided, but no estimates were reported. PET sensitivity was 80% or more and PET specificity was 90% or more in 6 studies. A similar sensitivity and specificity for CT/MRI was found in 1 study. PET sensitivity (p=0.01) and specificity (p=0.02) were significantly higher than CT/MRI sensitivity and specificity. Poor standardisation across studies was noted of patient population, reference standard or CT/MRI positive definition. Results by lesion and patient were mixed. Separate analyses of CT and MRI comparators would have been preferable, but the combined sensitivity of comparators appears lower than PET [34].

In the "ICES 2004 Quarterly update", 2 prospective studies on the detection of recurrent HNSCC were selected. Both studies reported hierarchy of diagnostic efficacy level 2 evidence [15]. In one study 30 patients with initially stage III or Stage IV disease had a complete response to treatment and were followed for signs of recurrence. The reference standard was clinical follow up. For the detection of recurrence within 1 year of treatment, PET had a sensitivity of 100% compared to 38% for CT and 44% for clinical examination. All 3 methods had good to excellent specificity: PET 93%, CT 85% and clinical examination 100%. Another prospective study of 44 patients with suspected HNSCC recurrence found that PET had sensitivity of 96% and specificity of 61%, which was superior to the combination of CT plus MRI (sensitivity 73%, specificity 50%). The reference standard was unclear. The authors note that early detection of tumour recurrence in HNSCC is considered important for prompt institution of salvage therapy. Distortion of tissue structures following surgery and radiation therapy may limit the diagnostic abilities of anatomic imaging techniques. The diagnostic accuracy of PET in the detection of early tumour recurrence seems superior to CT or MRI. Therefore, the use of PET in identifying recurrent HNSCC may be appropriate in the following conditions: if conventional methods of diagnosing recurrence are inconclusive and if a recurrence could be cured by subsequent definitive therapy [15].

Table 13: Head and Neck cancer – Diagnosis and Staging

Type of cancer	Cancer management decision	Source and Search period	Evidence	Diagnostic efficacy
Head and neck cancer	Diagnosis	SR-Vermeersch 2003 1989 to February 2003	4 comparative studies with CT/MRI PET Se range = 85% to 95% and PET Sp range = 67% to 100% CT/MRI Se range = 67% to 88% and CT/MRI Sp range = 44% to 75% PET Sp > CT/MRI Sp (p=0.06)	Level 2
Head and neck cancer	Staging I	HTA-BCBS 2000 - up to May 2000	17 studies based on neck sides, lesions, or patients (8 studies, n=239 patients) 4 comparative studies with CT (n=123 patients) Pooled results (by patient): PET Se = 81% and PET Sp 97% vs CT Se = 72% and CT Sp=89% 3 comparative studies with MRI (n=106 patients) Pooled results (by patient): PET Se = 91% and PET Sp 88% vs MRI Se = 82% and CT Sp=83% 1 small study on the value of PET in addition to other imaging Correct staging with CT in 9 and with CT+PET in 12 out of 13 patients. Correct staging with MRI in 2 and with MRI+PET in 5 out of 5 patients	Level 2
Head and neck cancer	Staging II	HTA-MSAC 2001 (ii) - up to March 2001	14 comparative studies with CT/MRI 6 studies with the patient as the unit of analysis (n=12 to 41 patients/study) PET Sp > comparators Sp and < 90% in a single study PET Se similar to comparators Se in 3 studies (83%, 100%, 75%). In the other 3 studies: PET Se =100%, 57%, 50% and comparator Se=78%, 80%, 40%. In 3 studies correct lymph node staging was evaluated: 65%, 75%, 88% of the patients were staged correctly 2 studies reported hierarchy 4 evidence In1 study, 8 out of 32 patients had management or "intent of management changed" In 1 study (12 patients) PET correctly indicated all cases of metastatic involvement (number of patients not stated) but incorrectly indicated need for surgery in 5 out of 12 patients	Level 2
Head and neck cancer	Staging III	SR-Goerres 2003 - up to October 2001	11 studies (n=8 to 106 patients per study) Positive and negative log-likelihoods calculated as weighted means and reported by patient and by lymph node By patient (n=369): LR+=3.9 (95% CI 2.5-5.9) and LR-=0.24 (95%CI 0.14-0.41) By lymph node (n=3294): LR+=17.3 (95% CI 10.9-27.3) and LR-= 0.19 (95% CI 0.13-0.27) PET Se=81%, PET Sp=79%	Level 3
Head and neck cancer	Staging IV	SR-Vermeersch 2003 1989 to	17 comparative studies using CT or MRI (study sizes not reported) sROC curve, but no estimates reported PET Se > 80% and PET Sp > 90% in 6 studies vs similar CT/MRI Se/ Sp in 1 study PET significantly higher Se (p=0.01) and higher Sp (p=0.01) than	Level 2

		February 2003	CT/MRI	
Head and neck cancer	Staging V	SR-Vermeersch 2003 1989 to February 2003	4 studies reported in narrative study1 (n=59): PET superior "accuracy" to bronchoscopy in detection of synchronous lung lesions (80% vs 50%) study2 (n=45): 2 TP, 4 FP in chest study3 (n=28): TP=9/10, TN=17/18 study4 (n=12): PET detected mediastinal disease in 2 patients, not otherwise detected	Level 2

Table adapted from: K Facey, I Bradbury, G Laking and E Payne. Positron Emission Tomography (PET)) Imaging in Cancer Management. Ultra Rapid Review. July 2004. Health Technology Assessment NHS R&D HTA Programme.

Table 14: Head and Neck cancer – Restaging

Type of cancer	Cancer management decision	Source and Search period	Evidence	Diagnostic efficacy
Head and neck cancer	Restaging I	HTA-BCBS 2000 up to May 2000	24 studies 18 studies evaluated patients as the unit of analysis (n=10 to 48 patients per study) PET Se>80% in 16/18 studies and PET Sp>80% in 11/18 studies (range=33% to 100%) Pooled PET Se=90%, pooled PET Sp=76% PET better than comparators in 6 studies (n=140 patients); PET results mixed or neutral in 4 studies (n=152 patients); PET worse than CT in 1 study (n=13 patients) 1 small study evaluated the value of PET in addition to other imaging Correct restaging with CT in 7 and CT+PET in 7 out of 8 patients. Correct restaging with MRI in 1 and MRI+PET in 2 out of 2 patients. In 1 study (n=29), PET results led to recommendations for palliative treatment instead of surgery in 9 patients	Level 2
Head and neck cancer	Restaging II	HTA-MSAC 2001(ii) up to March 2001	15 comparative studies with CT/MRI and the patient as the unit of analysis (n=10 to 66 patients per study) PET Se >85% in 14/15 studies, CT/MRI Se >85% in 4/15 studies PET Sp >80% in 10/15 studies, CT/MRI Se >80% in 6/15 studies In 1 study the need for panendoscopy was correctly predicted in 30/38 patients by PET results and in 19/38 patients by CT+MRI results	Level 2
Head and neck cancer	Restaging III	SR-Goerres 2003 up to Oct 2001	10 studies (n=13 to 50 patients/study, total n=350 patients) Positive and negative log-likelihoods calculated as weighted means and reported by patient By patient: LR+=4.0 (95% CI: 2.8-5.6) and LR-=0.16 (95% CI: 0.10-0.25) PET Se =88%, PET Sp =78%	Level 3
Head and neck cancer	Restaging IV	SR-Vermeersch 2003 1989 to February 2003	15 comparative studies with CT/MRI (study sizes not reported) sROC curve, but no estimates reported PET Se >80% and PET Sp >90% in 6 studies vs similar CT/MRI Se/ Sp in 1 study PET significantly higher Se (p=0.01) and higher Sp (p=0.02) than CT/MRI	Level 2

Table adapted from: K Facey, I Bradbury, G Laking and E Payne. Positron Emission Tomography (PET) Imaging in Cancer Management. Ultra Rapid Review. July 2004. Health Technology Assessment NHS R&D HTA Programme.

5.3.6. Cost-effectiveness of PET in head and neck cancer

The evidence on cost-effectiveness of PET for diagnosis and staging or for restaging and monitoring of response is limited. One study modelled the cost-effectiveness (cost per life year gained) and cost-utility (cost per QALY) of CT+FDG-PET as compared to CT alone for classification N0 HNSCC patients. The perspective was that of a large university hospital. No cost savings were associated with the use of PET, but the cost-effectiveness as well as the cost-utility ratio was lower than US$10,000 perlife year or QALY gained. [122] According to this model, the PET strategy remained cost-effective as long as the prevalence of disease was between 16% and 32%. The model had a number of weaknesses, in particular with respect to the input variables used for the model. The values for the sensitivity and specificity of PET were determined from publications of PET in all types of HNSCC patients and not from publications about PET in classification of N0 HNSCC. The sensitivity of the modelling results to this assumption was not tested.

Head and Neck Cancer - Key Messages

- **For diagnosis of primary head and neck cancer, limited evidence seems supportive for the use of PET in the diagnosis of primary head and neck cancer when CT/MRI results are indeterminate (level 2).**
- **For staging in head and neck cancer, i.e. assessment of regional lymph node involvement, there is evidence of diagnostic efficacy up to diagnostic thinking based on calculated positive and negative likelihood ratios (level 3).**
- **For staging in head and neck cancer, i.e. detection of distant metastases and synchronous primary tumours, there is some evidence of diagnostic accuracy (level 2).**
- **For restaging in head and neck cancer, i.e. assessment of residual or recurrent disease during follow up after treatment, there is evidence of diagnostic efficacy up to diagnostic thinking based on calculated positive and negative likelihood ratios (level 3).**

5.4. COLORECTAL CANCER

Material reviewed: HTA reports, Systematic Reviews and primary studies edited from 2002/1/1

The use of PET has been studied in various indications in colorectal cancer including initial diagnosis, initial staging, restaging after chemo or/and radiotherapy, detection and localization of recurrences or metastasis, and treatment monitoring. We found 26 primary studies on colorectal cancer and PET from 2002 to 2005. Among these, we selected 3 relevant studies (see appendix).

5.4.1. Initial diagnosis and initial staging

One HTA report (February 2001) has not found any evidence or even studies on the utility of PET in the initial diagnosis of colorectal cancer [84].

In another HTA report [32], including a literature search performed until October 2002, the few existing studies on the role of PET in initial diagnosis and staging show better sensitivity and specificity for PET than for CT, except for the detection of lymph node metastasis. However, more studies are needed, particularly prospective studies, to assess the role of PET in case of discordant results between classical imaging and a rising level of carcinoembryonic antigen (CEA) [32].

We found 2 recent primary studies on this indication, one of which was selected on the basis of our criteria as presented in the appendix.The results of that prospective study in 38 patients with confirmed colorectal cancer show that PET detected 95% of primary tumours (49% for CT and 14% for Sonography). Sensitivity, specificity and accuracy of PET in detecting lymph node involvement was 29%, 88% and 75% respectively (CT and US did not detect any lymph node). In detecting liver metastases, PET had a sensitivity of 78%, specificity of 96% and accuracy of 91% (CT sensitivity: 67%, specificity: 100%, accuracy: 91%; Sonography sensitivity: 25%, specificity: 100%, accuracy: 81%). Levels of CEA and Carbohydrate Antigen were elevated in only 33% and 8% of patients with established colorectal cancer. Finally, PET results led to changes in treatment modality in 8% and the range of surgery in 13% of the patients (16% of patients had a treatment management change in total). [123].

5.4.2. Restaging after chemo- and/or radiotherapy

This indication is not covered by any HTA report or systematic review, but we found 5 primary studies between January 2002 and February 2005 on that topic (restaging after chemo-radiotherapy or assessment of prognosis after chemo-radiotherapy in rectal cancer). The quality of these studies has been assessed and none met our selection criteria.

5.4.3. Detection and localisation of recurrences or metastasis

Diagnostic efficacy

This is a widely covered topic in colorectal cancer. For this indication, the reported sensitivity of PET varies between 87% and 100%, and the specificity between 79% and 100%, always superior to CT sensitivity (61% to 100%) and specificity (50% to 96%) [32 84 83 33, 15 124].

This indication includes the following categories:

Detection and localisation of recurrence

An isolated elevation of CEA could be the first sign of a recurrence. The sensitivity of CEA varies between 76% and 89% and the specificity between 90% and 100%. In case of CEA increase with a normal CT, the sensitivity of PET varies between 77% and 94% and specificity between 80% and 100%.

In case of hepatic metastases and elevated CEA, PET sensitivity varies between 93% and 100% , a specificity between 57% and 98%, a positive predictive value between 89% and 96% and a negative predictive value between 67% and 100%, compared with CT sensitivity of 83%, specificity of 91%, positive predictive value of 83% and negative predictive value of 93% [32] [15] [84]. Moreover, an isolated CEA elevation is unable to give a localisation of the recurrence [85] . In case of increased CEA level in a patient who underwent surgery for colorectal cancer, PET is indicated [32]. For the MSAC, after a first report where PET was evaluated as not indicated for colorectal cancer, an update, based on 2 new high quality papers concluded that in detecting local recurrence, the concordance between PET and CT is high but that PET allows the detection of smaller lesions than CT [83]. For AETMIS, the localisation of a recurrent disease when classical investigations or CEA level are not normal, or the distinction between recurrent disease and scar tissue are selected indications [84]. We found one primary study on diagnosis of recurrences in rectal cancer by patients with elevated CEA, positive morphological imaging or inconclusive clinical investigation: this prospective study on 36 patients gives for PET a sensitivity of 100%, a specificity of 85%, a positive predictive value of 92% and a negative predictive value of 100% [125].

Detection of local recurrences

On the basis of 2 studies, the sensitivity of PET varies from 92% to 96% and the specificity is 87%, compared to CT sensitivity of 88% and specificity of 89%, and to MRI sensitivity of 83% and specificity of 100% [84] [83].

Detection of hepatic metastasis

PET is better in this indication than other techniques, including CT [32] [83]. PET allows the detection of smaller lesions [83]. One HTA report concluded, on the basis of 3 studies, that it is not clear if PET would replace any currently applied investigation but it is possible that PET will reduce the number of laparotomies (patient management changes in 29% of the cases) [15].

For that indication, PET sensitivity varies from 90% to 100% and specificity from 81% to 100%. For the same indication, the values of CT vary from 69% to 100% for sensitivity and from 58% to 95% for specificity. Some studies also report values for MRI investigation: sensitivity 100% and specificity 100% and for Sonography: sensitivity 87% and specificity 93% [32] [83] [84]. A systematic review also recommends PET for the diagnosis of hepatic metastasis, in case of CEA elevation or abnormal imaging findings when hepatic resection is planned. In that case and for a specificity greater than 85%, the values of sensitivity are 90% for PET, 70% for MRI, 72% for CT and 55% for Ultrasound [124]. We also found 1 primary studies which met our selection criteria. This prospective study in 58 patients reported a sensitivity of 100% and specificity of 98% for PET in detecting liver metastases prior to resection and a sensitivity of 14%, andspecificity of 98% for CT. In more than 1 patient on five, PET avoided unnecessary surgery [126].

Detection of extrahepatic metastasis

For that indication, sensitivity of PET varies from 10% to 100% and specificity from 92% to 100%, compared with sensitivity between 33% and 94% and specificity between 71% and 100% for CT, depending of the localisation (pelvic, abdominal, retroperitoneal, pulmonary, other) [84] [32] [83]. The MSAC concluded that PET is better than CT for that indication [83]. The conclusion of AETMIS agency is that the most important added value of PET in colorectal cancer is related to the identification of extrahepatic metastasis in order to avoid surgery [84].

Localisation of metastasis

PET is indicated for localization of metastasis in case of increasing CEA level following surgery in a patient with colorectal cancer, as showed in table 13 [32].

Assessment before resection of recurrences or metastasis

PET is better than CT in the assessment of surgical possibilities for resection of recurrence or metastasis, as showed in table 13 [127, 32].

Globally, for detection of metastases in patients with recurrent colorectal cancer, the Facey et al report stated that there is consistent evidence of clinical effectiveness and that PET is suitable for routine use in stated pathway with audit [127, 34]. A pathway is a tool used to plan healthcare for a specific patient [110].

Table 15: Table of evidence for Colorectal cancer: diagnosis and staging

Type of cancer	Cancer management decision	Source and search period	Evidence	Diagnostic efficacy
Colorectal	Diagnosis & Staging I	HTA - FNCLCC 1991-10/2002	5 studies: 97 patients for 2 studies, other unknown Diagnosis (3 studies): Se = 24% – 100%, Sp = 43% – 96% Nodes (2 studies): Se = 22% - 29%, for PET & CT Hepatic metastasis (1 study): Se = 88%, Sp = 100% for PET; Se = 38%, Sp = 97% for CT PET leads to a change in staging in 42% of patients and influences the therapeutic management for 62% of patients, but no evaluation of impact on outcomes (1 study) Reference standard used in the studies not stated in the report	Level 2
Colorectal	Diagnosis & Staging II	HTA - DACEHTA up to 1/5/2001	7 studies: 16 – 115 patients per study Diagnosis (2 studies): PET Se > 85%, Sp = 67% (1 study) Staging: Se >90%, Sp > 95%(6 studies) = 57%(1 study) Reference standard: pathology (+ follow up for 1 study)	Level 2

Table 16: Table of evidence for Colorectal cancer: recurrence

Type of cancer	Cancer management decision	Source and search period	Evidence	Diagnostic efficacy
Colorectal	Recurrence I	HTA - FNCLCC 1991-10/2002	12 studies (3 prospective, 9 retrospective): 683 patients All recurrences, for PET Se = 87% – 100%, Sp = 79% – 100% (9 studies), for CT Se = 61% – 100%, Sp = 50 %– 91% (9 studies) Hepatic recurrence: PET Se = 90% – 100% (6 studies), Sp = 81% – 100% (3 studies), CT Se = 69% – 86% (6 studies), Sp = 58% – 85%(3 studies) Other localization: PET Se = 10% – 100% (5 studies), Sp = 92% – 100% (3 studies), CT Se = 33% – 84% (4 studies), Sp = 71% – 80% (2 studies) In case of CEA increase and CT normal (5 studies, 2 prospective, 3 retrospective, 231 patients) PET Se = 77% – 94%, Sp = 80% – 100% In 6 studies, therapeutic decision is modified in 23% -84% of patients by PET results Reference standard: pathology in case of CEA increase, not stated for the other studies	Level 4
Colorectal	Recurrence II	HTA - DACEHTA up to 1/5/2001	13 studies (n=15-105 per study) PET Se 85% in12 studies, 79% in other, Sp =90% in 7 studies, 43% - 83% in other Se and Sp higher than CT in 4 studies, than MRI in 4 studies	Level 2
Colorectal	Recurrence III	HTA - MSAC 2000 1996 - 1/2000	5 studies (already in the FNCLCC report) : 384 patients Local recurrence : PET has higher Se than CT (3 studies) Hepatic metastasis :PET Se > 90%, CT Se = 74% – 100% Extrahepatic metastasis: PET Se = 90% – 100%, CT Se = 57% – 74% PET result leads to changes in patient management Reference standard used in the studies not stated in the report	Level 4
Colorectal	Recurrence IV	HTA - ICES - up to 1 April 2004	3 prospective studies: (2 in the FNCLCC report) patients with rising CEA Hepatic metastasis: PET Se = 93% – 100%, Sp = 57% – 98%, PPV = 89% - 96%, NPV = 67% - 100%; CT Se = 83%, Sp = 91%, PPV = 83% and NPV = 93% Change in patient care in 29% of patients (1 study) Reference standard: surgery or clinical work up	Level 4
Colorectal	Recurrence V	HTA - AETMIS – up to February 2001	5 studies (4 already in the FNCLCC report and among these 4, 1 in the MSAC report)): 394 patients Globally: Se = 93% - 100% and Sp = 90% - 99% for PET (5 studies); Se = 69% - 91% and Sp = 72% - 96% for CT (5 studies); Se = 76% - 89% and Sp = 90% - 100% for CEA (2 studies) For local recurrence (2 studies): Se = 92% to 96% and Sp = 87% for PET; Se = 88% and Sp = 89% for CT; Se = 83% and Sp = 100% for MRI For other recurrence (1 study): Se = 79% - 100% and Sp = 95% - 100% for PET; Se = 33% - 94% and Sp = 90% - 100% for CT, depending on the localisation of recurrence Reference standard: surgery and follow up in 1 study, conventional imaging in 4 studies	Level 2
Colorectal	Recurrence VI (and staging)	SR – Kinkel et al 2002 (Dec 1985 – Dec 2000)	9 PET studies (n = 423), 11 MRI studies (n=401), 25 CT studies (n = 1371), 9 US studies (n = 509) PET Sp = 85% in all studies, Se = 90% (95%CI 80% -97%) CT Se = 72% (95%CI 63% -80%) MRI Se = 76% (95%CI 57% -91%) US Se = 55% (95%CI 41% -68%) Change in patient management after PET in 61% – 94% of patients (2 studies) Reference standard: histology, cytology and follow up	Level 4
Colorectal	Recurrence VII	SR – Dietlein et al. 2003 (1997 – 2002)	15 studies (n = 40-120) Se = 94% (95% CI 91% - 96%), Sp = 78% (95%CI 69% - 86%) for PET Se = 73% (95%CI 68% - 78%), Sp = 62% (95%CI 52% - 72%)for CT Staging correctly changed: 27% of patients, incorrectly changed : 4% of patients, change in patient management : 34% (95% CI 31% -38%) Reference standard: histology or follow up minimum 6 months	Level 4

Table 17: Colorectal cancer - Primary studies

Setting	Grade	Study design	Author	Yr	Pts	Compare	Outcome	Blinded	Se (%)	Sp (%)	PPV (%)	NPV (%)
Staging	B	Prospect	Kantorova	2003	38	Histology or follow up	PET Se = 78%, Sp = 96% CT Se = 67%, Sp = 100% US Se = 25%, Sp = 100% Change in treatment modality for 8% of patients and range of surgery in 13% of patients	unclear	78	96	-	-
Recurrence	B	Prospect	Timm	2002	36	Histology and/or CWU (n=23) FU 12 months(n=13)	Se, Sp, PPV and NPV	unclear	100	85	92	100
Recurrence (extrahepatic metastases before resection of hepatic metastases)	B	Prospect	Rosa	2004	58	Histology and/or FU (6-24 months)	Change in patient management: correctly upstaged: 12 pts/58, no change for the others	Y	100	97.7	-	-

Legend: Yr=year published; Pts=number of patients; Se=sensitivity; Sp=specificity; PPV=Positive Predictive Value; NPV=Negative PredictiveValue; Prospect.= Prospective; - data unavailable.

Cost-effectiveness of PET in staging recurrent colorectal cancer

Two decision models of fair quality were published that examined the cost-effectiveness of CT+PET as compared to CT alone for the pre-operative staging of recurrent colorectal cancer.[128, 129] One study concluded that, under baseline assumptions, CT+PET dominates CT alone in that it offers a better outcome, both in terms of life expectancy (3.8 days) and in terms of avoided surgery (125 on 1,000 patients), at a lower cost (saving CA $1,758).[129]

One-way sensitivity analyses revealed that CT+PET remained cost saving as long as the disease prevalence was >22.4%, PET cost <CA $2,787, surgery cost >CA $2,922, chemotherapy cost <CA $ 100,000, CT sensitivity <87.3%, PET sensitivity >73.8%, PET specificity >65.3%, avoidance of surgery >3.2% and non-resectable disease <95%. Life expectancy is better for CT+PET if disease prevalence >17.5%, CT sensitivity <91.8%, PET sensitivity >44.3%, PET specificity >51.2%, avoidance of surgery >11.3% and non-resectable disease is <71.6% (one-way sensitivity analyses).[129]

The second study concluded that CT+PET offers a slightly better life expectancy (9.5 days) at a higher cost (US $429). [128] Although CT+PET did not dominate CT alone in this latter model, the incremental cost-effectiveness ratio was favourable at US $16,437 per life year gained, compared to the incremental cost-effectiveness ratio of other interventions (a threshold value of US $50,000 per life year gained was used).

The incremental cost-effectiveness ratio of CT+PET exceeds US $50,000 per life year gained if the prevalence of disease is <49%, sensitivity of CT > 87.9%, specificity of biopsy < 80.3%, life expectancy of untreated patient with recurrence >2.57 years and life expectancy of patients with recurrence undergoing chemotherapy <1.75 year.[128]

5.4.4. Treatment monitoring

In February 2001, there was no study evaluating PET in the assessment of treatment response, although some HTA agencies had mentioned this indication. The conclusion of AETMIS, at that time was that PET has a potential in treatment response monitoring [84]. For the FNCLCC, on the basis of 2 studies (n = 18 and n =15), PET seems to have a place in monitoring the treatment (chemo and radiotherapy), which could be an important element in the decision of a sphincter preservation for rectal cancer. Anyway, further studies are needed [32].

Colorectal cancer - Key Messages

- **For initial diagnosis and staging of colorectal cancer, there is evidence of diagnostic accuracy inlcuding the determination of sensitivity and specificity (level 2).**
- **For restaging after chemo/radiotherapy, there is no evidence.**
- **For detection and localization of local, hepatic and extrahepatic recurrence, the diagnostic efficacy includes changes in patient management and therapeutic decision (level 4). In addidition, there is limited evidence for cost-effectiveness.**
- **For treatment monitoring, there is no evidence.**

5.5. MALIGNANT MELANOMA

5.5.1. Diagnosis

PET has no role in the initial diagnosis of malignant melanoma. Diagnosis is made by inspection, biopsy or surgical excision and histopathology.

5.5.2. Staging

In a systematic review and meta-analysis Mijnhout et al. 2001 (Table 18- Staging I) assessed the diagnostic accuracy of PET in cutaneous melanoma patients [130]. Studies were identified by a comprehensive search without any language restrictions in the databases Medline, Embase, and Current Contents databases up to July 1999. Potential indications for PET in patients with histologically proven cutaneous melanoma include the detection of occult regional lymph node involvement or distant metastatic disease in patients with primary or suspected recurrent melanoma. Eleven studies meeting the authors' inclusion criteria were selected. All the studies included in the earlier HTA-MSAC 2000 report [83] were also included in this review. Reference standards included histopathology, follow up, imaging in 2 studies with primary cases, sentinel lymph node biopsy (SLNB) in 1 study. All 11 studies reported hierarchy of diagnostic efficacy level 2 evidence. Seven studies provided enough data for the evaluation of index test characteristics and were available for a quantitative analysis and statistical pooling; after exclusion of 1 low outlier study with stage I/II patients (the study with SLNB as a reference standard), 6 studies were pooled in a summary receiver operating characteristic (sROC) analysis using a random effects model of meta-analysis. Both distant and regional metastatic spread was included in the pooled analysis (n=360). The pooled sensitivity of the 6 studies was 78% (95% CI, 70%-84%) and the pooled specificity was 88% (95% CI, 82%-92%). The pooled Diagnostic Odds Ratio (DOR) of the six studies was 33.1 (95% CI 21.8 - 54.0). Subgroup analysis (based on subgroup classification by AJCC Stage prior to PET) revealed that PET is more accurate for regional staging in patients with AJCC Stage III disease (DOR=18.3; 95% CI 0.4-127.5) than in patients with Stage II disease (DOR=5.5; 95% CI 1.0-31.5) and Stage I disease (DOR=7.4; 95% CI 0.1-462.5). The HTA-MSAC 2000 report [83] noted that 1 study reported that 22/100 pats had change in management as a result of PET. Patients with recurrent melanoma were evaluated in 5 studies, patients with primary melanoma in 1 study and a mixed group of primary and recurrent melanoma in another 5 studies. Distant metastases were evaluated in 6 studies, regional lymph node metastases in 4 studies; both, distant metastases together with regional lymph node metastases were evaluated in 1 study. The methodological quality of the studies was poor with major problems of verification, review and selection bias. Methodologically flawed studies are likely to provide biased results. Therefore the favourable findings of the studies included in this review and meta-analysis may represent an overestimation of diagnostic accuracy. Reporting of index test comparators was poor. Major problems of the included studies were the lack of a valid reference test, the absence of an independent, blind comparison of PET and the reference test in all subjects. Also considered major problems in the studies were high test probabilities and repetitive PET scans. The study (74 patients), using SLNB as the reference standard, showed a poor sensitivity (17%) in Stage I/II patients and was excluded from the meta-analysis. Therefore, heterogeneity of sensitivity is greater than the model shows. Except from the excluded study, there was only one study with one Stage I patient. The diagnostic accuracy of PET in staging regional lymph nodes seems better in Stage III patients. It was noted that in the introduction to the review, the author states that PET has been promoted for the evaluation of patients with recurrent melanoma but also that reports concerning the use of PET in primary melanoma are controversial. Currently, there are no analyses by primary versus recurrent disease. The HTA-MSAC 2000 report [83] addressed recurrent melanoma but found only 1 study.

The HTA-DACEHTA 2001 report (Table 18- Staging II) assessed the diagnostic accuracy of PET in the staging of patients with primary or suspected recurrent melanoma [117]. Studies were retrieved from 1990 up to May 2001. Nine of these studies are included in Mijnhout 2001 [130], 5 later ones from 1999/2000 are included in this report as well as 1 study from 1995. Fifteen studies meeting the HTA-DACEHTA 2001 report's inclusion criteria, were selected. All 15 studies reported hierarchy of

diagnostic efficacy level 2 evidence. The reference standard was histopathology (12 studies) or unclear (3 studies). Four out of 5 studies published after Mijnhout 2001 [130] show a PET sensitivity >85%. One study in stage II patients shows a PET sensitivity of 78%. PET specificities were: 95%, 84%, 44%, 56% and 87%. In three studies, the diagnostic accuracy of PET and CT scan were compared. In these studies the sensitivity of PET varied from 94% to 100% while its specificity varied from 56% to 95%. The sensitivity of the CT comparator test varied from 55% to 92% and its specificity varied from 22% to 84%. However, the study populations were not clearly delineated and the analysis of the results was probably mixed by patient and lesion. One study was reported in Mijnhout but the CT results were not reported there. The author of the report notes that many studies found that PET had the highest precision for visceral and lymphatic metastases, while CT was more accurate for diagnosing smaller pulmonary metastases. No analyses were presented separately for patients with primary or recurrent disease [34].

In the "ICES 2004 Quarterly updates", 3 prospective studies on the staging of newly diagnosed malignant melanoma were selected. All studies reported hierarchy of diagnostic efficacy level 2 evidence [15]. The reference standard was conventional imaging in the first study and histopathology in the other 2 studies. In a first study on 52 patients with newly diagnosed high-risk malignant melanoma (i.e. thickness >1.5 mm or suspected recurrence) PET was compared to "conventional imaging" (radiography, ultrasonography, CT and MRI). PET sensitivity versus "conventional imaging" sensitivity was 100% versus 85% and PET specificity versus "conventional imaging" specificity was 96% versus 58%. In a second study on 38 newly diagnosed melanoma patients, staging PET results were compared with histopathology results following dissection of 56 lymph node basins. PET sensitivity was 95% and PET specificity was 84%. PET detected 83% of metastases 6-10 mm in size, but only 23% of those <6 mm. In a third study on 67 patients, PET sensitivity for lymph node metastases was 91.7% and PET specificity was 97.7%. The authors commented that PET is not indicated in the initial T- and N-staging of primary melanoma. T-staging of primary melanoma (ulceration and vertical height) is assessed by inspection and biopsy or surgical excision. PET has a limited ability to detect small (< 5 mm) nodal metastases and, because of their safety and better accuracy, lymphatic mapping and sentinel lymph node biopsy (SLNB) procedures remain the procedures of choice in N-staging. In another study on 38 patients PET was compared to "routine methods" (including clinical examination, radiography, CT, ultrasound and serum profiles of liver enzymes) in the follow up detection of silent metastases. PET sensitivity versus "routine methods"-sensitivity was 97% versus 62% and PET-specificity versus "routine methods" specificity was 56% versus 22%. PET may be superior to conventional imaging in the detection of metastatic disease. While test characteristics of PET seem favourable in various scenarios of malignant melanoma, evidence about the nature and benefit in these patients is lacking [15].

Table 18: Malignant melanoma – Staging

Type of cancer	Cancer management decision	Source and Search period	Evidence	Diagnostic efficacy
Malignant melanoma	Staging I	SR-Mijnhout 2001 up to July 1999	11 studies (n=12 to 100 patients/study) 7 studies provided enough data to calculate index test characteristics, 6 in sROC analysis Both distant and regional spread included in the pooled analysis (n=360) sROC, random effects model: PET Se 78% (95%CI 70%-84%) and PET Sp 88% (95%CI 82%-92%) Overall DOR=33.1 DOR by AJCC classification (stage prior to PET): PET-DOR stage III =18.3 (95%CI: 0.4 - 127.5), PET-DOR stage II =5.5 (95%CI:1.0 - 31.5), PET-DOR stage I =7.4 (95%CI: 0.1 – 462.5) (excluding low outlier with stage I/II patients) HTA-MSAC 2000 notes that 1 study reported that PET results led to management change in 22/100 patients	Level 2
Malignant melanoma	Staging II	HTA-DACEHTA 2001 1990-May2001	15 studies (n=12 to100 patients/study) 4 out of 5 studies published after Mijnhout show PET Se >85%, 1 study in stage II patents shows PET Se=78%. PET Sp = 95%, 84%, 44%, 56%, 87% 3 studies showed CT comparators: study 1 (n=76): PET Se =94%, PET Sp =83% vs CT Se =55%, CT Sp = 84% study 2 (n=50): PET Se =100%, PET Sp =95% vs CT Se =92% , CT Sp =82% study 3 (n=38): PET Se =97%, PET Sp =56% vs CT Se =62%, CT Sp =22%	Level 2

Table adapted from: K Facey, I Bradbury, G Laking and E Payne. Positron Emission Tomography (PET)) Imaging in Cancer Management. Ultra Rapid Review. July 2004. Health Technology Assessment NHS R&D HTA Programme.

Table 19: Malignant melanoma - Primary studies

Setting	Grade	Study design	Author	Yr	Pts	Compare	Outcome	Blinded	Se (%)	Sp (%)	PPV (%)	NPV (%)
Staging	B	Prospect.	Havenga	2003	53	Sentinel Lymph Node Biopsy (SLNB)/ Histology	Lymph Node Mets	-	15	87	40	78
Staging	B	Prospect.	Fink	2004	48	Sentinel Lymph Node Biopsy (SLNB)/ Histology	Lymph Node Mets	Yes	13	100	100	85
Staging	B	Prospect.	Vereecken	2005	39	Sentinel Lymph Node Biopsy (SLNB)/ Histology	Lymph Node Mets	-	40	-	-	-

Legend: Yr=year published; Pts=number of patients; Se=sensitivity; Sp=specificity; PPV=Positive Predictive Value; NPV=Negative PredictiveValue; Prospect.= Prospective; - data unavailable; SLNB=sentinel lymph node biopsy; Mets=Metastases(For Se/Se, Sp/Sp, PPV/PPV and NPV/NPV= single value refers to PET)

Primary studies

All primary studies on PET in malignant melanoma were about staging. Havenga et al. reported the value of sentinel lymph node biopsy (SLNB) and PET in relation to SLNB in staging primary cutaneous melanoma. The reference standard was histopathology. Fifty-five patients with primary cutaneous melanoma > 1 mm Breslow thickness and no palpable regional lymph nodes, scheduled to undergo SLNB, underwent a FDG-PET scan prior to SLNB. SLN were retrieved from 53 patients. Melanoma metastases were found in the SLN of 13 patients. PET detected the lymph node metastases in 2 of the 13 patients with SLN metastases. In 5 patients FDG accumulation was recorded in a regional basin, while no tumour positive SLN was found. In 8 patients PET showed increased activity at a site of possible distant metastasis. Metastatic disease was confirmed in 1 patient. No explanation for the positive PET result could be found in 5 cases. The authors concluded that PET should not be considered in this group. SLNB reveals regional metastases that are too small to be detected by PET. The prevalence of distant metastases is too small to justify routine use of PET (Table 19) [131].

Fink et al. reported the value of SLNB and PET in relation to SLNB in staging primary malignant melanoma (AJCC stages I and II). The reference standard was histopathology. Forty-eight consecutive patients with primary cutaneous melanoma stage I (Breslow thickness > 1mm) and II and with no clinical or sonographically suspicious regional lymph nodes underwent a PET scan prior to SLNB. PET and SLNB results were interpreted independently. Eight patients (16.7%) had a positive SLNB. PET was positive in only 1 patient with a positive SLNB, yielding a sensitivity of 13%. All other positive sentinel lymph nodes remained undetected on PET. PET is obviously not an adequate screening test for subclinical and sonographically inconspicuous lymph node metastases in patients with melanoma stage I and II. The low sensitivity is probably due to the small size of metastatic deposits in sentinel nodes (Table 19) [132].

Vereecken et al. reported the value of SLNB and PET in relation to SLNB in staging intermediate/poor prognosis primary melanoma patients and no palpable regional lymph nodes.

Patients were classified as intermediate or at high risk (≥ 50%) for recurrence according to the depth of their melanoma, measured by the Breslow index (≥ 1 mm, but ≤ 4 mm), and/or to the presence of histological criteria indicating a poor prognosis. The reference standard was histopathology. Forty-three patients with intermediate/ poor prognosis primary melanoma, scheduled to undergo SLNB, underwent a complete staging procedure including PET prior to SLNB. They also underwent additional imaging procedures as a routine screening procedure for distant metastases (CT scan of the chest, CT of the abdomen, CT or NMR of the brain). SLN were retrieved from 39 patients. Melanoma metastases were found in the SLN of 10 patients. PET detected the lymph node metastases in 4 of the 10 patients with SLN metastases. Although 13 unexplained hypermetabolic spots were reported in 9 patients (false positives), no distant metastatic disease was found. Twenty-six hypermetabolic spots in 19 patients could be explained by inflammation, contusion, prostatitis, hiatus hernia, tuberculosis, intramuscular injection, thyroiditis; one hypermetabolic spot on PET in a single patient represented an incidental finding of a second primary cancer (pulmonary adenocarcinoma). An incidental finding on CT in another patient represented a hypernephroma. The authors concluded that PET is not useful to detect micro-metastases and cannot replace SLNB in initial regional staging (Table 19) [133].

Malignant Melanoma - Key Message

- **For staging in malignant melanoma, i.e. assessment of regional lymph node involvement or distant metastatic disease in patients with primary or suspected recurrent melanoma, there is evidence of diagnostic accuracy including the determination of sensitivity and specificity (level 2). Evidence on the use of PET in initial staging is conflicting.**

5.6. BREAST CANCER

5.6.1. Diagnosis

The HTA-DACEHTA 2001 report (Table 20- Diagnosis I) assessed the diagnostic accuracy of PET in the diagnosis of breast cancer and more specifically in the differentiation of malignant and benign breast mass [117]. Six studies meeting the authors' inclusion criteria were retrieved from 1990 up to May 2001. None of these studies are included in the HTA-BCBS 2003 report [134]. The diagnostic reference standard in these studies was histopathology. All 6 studies reported hierarchy of diagnostic efficacy level 2. Reported PET sensitivities and specificities were >80% in 5 studies and 80% and 76% respectively in the 6th study. PET sensitivity was comparable to scintimammography in 2 studies. It was noted that some studies not only evaluated diagnosis (differentiation of malignant and benign breast mass) but also lymph node metastases. Analysis of the results was probably mixed by patient and lesion [34].

The first indication addressed in the HTA-BCBS 2001 report (Table 20- Diagnosis II) was related to the diagnostic accuracy of PET in patients who have an abnormal mammogram or palpable breast mass and are recommended to undergo biopsy diagnosis in order to avoid breast biopsy in case of a negative PET result [135]. Thirteen studies meeting the BCBS inclusion criteria were retrieved from January 1966 up to March 2001. None of these studies are included in the HTA-DACEHTA 2001 report [117]. The diagnostic reference standards in these studies were cytological aspiration and histopathology. All 13 studies were reported hierarchy of diagnostic efficacy level 2 evidence. A sROC analysis of all 13 studies predicts a sensitivity of 89% and a specificity of 80%. From the perspective of an individual with a negative PET scan, the patient has already made the choice to undergo PET scanning and is considering using its results to guide whether to undergo biopsy. From this patient's perspective, the crucial measure is PET negative predictive value (NPV). The NPV is the probability that a negative PET result has correctly assessed that the patient has no disease. At a prior prevalence (probability) of malignancy of 50%, the NPV is 88%, thus the false-negative risk is

12%. At a prior prevalence (probability) of malignancy of 75%, the risk of false-negative is 29%.Three studies that used the lesion as the unit of analysis were excluded. Ten studies used the patient as unit of analysis (n=415 patients). A random effects model of meta-analysis, applied in these 10 studies, produced a pooled sensitivity estimate of 88% (95% CI 83% - 92%) and a pooled specificity estimate of 79% (95%CI 71% - 85%). It was noted that although a separate sROC analysis of patient-based studies was not performed, results of the sROC analysis of all 13 studies were almost identical to the results of the patient-based meta-analysis. For an individual with a negative PET scan, the risk of a false-negative result is considered too high when the only benefit consists of avoiding a biopsy. A false-negative result in this case may lead too often to a missed or delayed diagnosis. The studies in this report only include patients with suspicious mammograms or palpable masses. Therefore, compared to the prior prevalence of malignancy of 20% -30% in the general population, the prior prevalence of malignancy on biopsy (50% -95%) is high and the mean tumour size was large, ranging from 2 cm to 4 cm. Evidence on the diagnostic performance of PET for differential diagnosis of breast lesions among patients with abnormal mammograms or palpable masses is lacking for patients with indeterminate mammograms and small, non-palpable lesions [34]. The second indication addressed in this report was related to the diagnostic accuracy of PET in patients with small non-palpable lesions and low suspicion findings on mammography and other routine imaging, and have been referred for a 3 to 6 months imaging follow up, in order to elect early biopsy or avoid short-interval imaging follow up. These patients have a prior malignancy between 20% and 50%. No studies were found in these patients and therefore evidence is lacking on this subject [135].

In the "ICES 2004 Quarterly updates", 1 prospective study on 42 patients compared PET with MR mammography (MRM) in the diagnosis of suspected breast cancer (primary tumour), confirmed by histology [15]. This study reported hierarchy of diagnostic efficacy level 2 evidence. The reference standard was histopathology. In the diagnosis of the primary tumour PET sensitivity versus MRM sensitivity was 93% versus 100%. For diagnosis of contralateral tumours, both PET and MRM were 100% sensitive and the specificity of MRM versus PET was 100% versus 97.5% [15].

5.6.2. Staging

The HTA-DACEHTA 2001 report (Table 21- Staging I) assessed the diagnostic accuracy of PET in the detection of breast cancer lymph node metastases [117]. Ten studies meeting the authors' inclusion criteria were retrieved from 1990 up to May 2001. None of these studies are included in the HTA-BCBS 2001 report. Nine studies reported on sensitivity and specificity. The diagnostic reference standard in these studies was histopathology. All 10 studies reported hierarchy of diagnostic efficacy level 2 evidence. Reported PET sensitivities and specificities were $\geq$ 85% in 7 studies and 50% and 79% in the other 2 studies. PET specificities were $\geq$ 90% in 6 studies and 66%, 75% and 86% in the other 3 studies. It was noted that the analysis of the results was probably mixed by patient and lesion [34].

The HTA-BCBS 2003 report (Table 21- Staging II) assessed the diagnostic accuracy of PET in the initial staging evaluation of the axillary lymph nodes in breast cancer [134]. Eight studies on the assessment of tumour extent in axillary lymph nodes (ALN) in patients with confirmed primary breast cancer, no palpable ALN metastases (clinically node negative = cN0) and no evidence of distant metastases were retrieved from January 1966 up to October 2003. In clinical practice, patients with palpable lymph nodes are likely to undergo ALN dissection (ALND) even when metastases remain undetected by imaging. Therefore, PET results are unlikely to have impact on management in patients with palpable nodes and the diagnostic accuracy of PET has not been assessed in this indication. All studies from the HTA-BCBS 2001 report [135] are also included in this report. The diagnostic reference standards in the selected studies were ALND alone (ALND: 4 studies) or the combination of ALND with sentinel node biopsy (SNB) (ALND plus SNB: 4 studies). ALND plus SNB is a more sensitive reference standard than ALND alone. In addition to providing information on nodal status, ALND may be therapeutic, if removing tumour-involved nodes improves local control. SNB is a more recent, less invasive, technique and ALND is performed only when the sentinel node is positive. All 8 studies reported hierarchy of diagnostic efficacy level 2 evidence. Six studies included only patients with non-palpable nodes (cN0), while in two other studies 71% and 94% of the patients were cN0.

When the reference standard is ALND only, estimates of sensitivity range from 40% to 93% and estimates of specificity range from 87% to 100%. When SNB is added to the reference standard, PET sensitivity ranges from 20% to 50% and specificity ranges from 82% to 100%. Negative predictive values from studies with ALND only as a reference standard ranged from 68% to 96%. NPV from studies that included SNB in the reference standard ranged from 57% to 80%. If one considers the prevalence of node positive disease in studies with ALND plus SNB (which ranges from 33% to 64%) as a reference standard, then a patient with a negative PET would face a 36% to 67% chance of having her axillary metastases undetected when PET was used to avoid ALND plus SNB. Most studies had a prospective design with more than 30 patients in 5 studies. The studies with a mixed population of cN0 patients and cN+ (clinically node positive) patients did not analyse cN0 patients separately. This is acceptable because the percentage of cN0 patients was high. Evaluation of PET against the more sensitive reference standard of ALND plus SNB results in a lower diagnostic accuracy for PET. If PET were used to decide whether to perform axillary lymph node dissection, then all patients with negative PET results would avoid further axillary evaluation with either SNB or ALND. If the sensitivity of PET is estimated to be between 20% and 50%, then approximately 50% to 80% of patients with axillary metastases would be undetected (false negative PET results). Under-treatment in this case would be associated with an absolute difference in 10-year survival of 8.2%. The report concludes that, given the high individual risk of false negatives, PET cannot be reliably used to avoid ALND [34].

In the "ICES 2004 Quarterly updates", 6 prospective studies were selected (n= 42-167/study) with PET results of axillary lymph nodes prior to axillary dissection compared with histopathology (reference standard) [15]. All studies reported hierarchy of diagnostic efficacy level 2 evidence. Sensitivity ranged from 50% to 94%, specificity from 86% to 100%.

Primary studies

All additional primary studies on PET in breast cancer retrieved were on staging. Two recent studies, both published in 2004, were commented on in the "ICES 2004 Quarterly updates" of the original ICES 2001 HTA-report [15]. These studies suggested that PET should not be routinely recommended in the detection of axillary lymph node metastases [136 137]. In a multicenter prospective study by Wahl et al., PET was reported to have moderate accuracy, compared to axillary lymph node pathology, for detecting axillary metastases in 360 women with newly diagnosed invasive breast cancer (308 patients with accessible axillae). The reference standard was histopathology. The mean sensitivity and specificity of PET (with at least one abnormal axillary focus considered to be positive) was 61% and 80%, respectively. Under these same conditions, the positive and negative predictive value for PET was 62% and 79%, respectively. The authors concluded that PET should not be "routinely recommended" for axillary staging in newly diagnosed breast cancer (

Table 22) [136]. In a paper by Zornoza et al., a series of 200 patients with breast cancer were studied with PET. The reference standard was histopathology. One hundred patients had axillary dissection (regardless of PET results). The sensitivity, specificity, positive predictive value and negative predictive value of PET in this group were 90.9%, 100%, 100% and 90% respectively. The other 100 patients had a subsequent sentinel node biopsy (in the absence of suspicious axilla on the PET scan). The sensitivity, specificity, positive predictive value and negative predictive value of PET in this group were 76.9, 95.8, 95.2 and 79.3 % respectively. The authors concluded that PET can avoid routine sentinel node study in breast cancer cases where there is axillary uptake, but should be complemented by sentinel node biopsy where there is no pathological uptake on PET (

Table 22) [137]. The authors noted that the practice regarding axillary assessment varies widely at present. Some practitioners perform axillary dissection routinely for most patients with newly diagnosed carcinoma of the breast while others perform it only if a SLNB is positive. A SLNB consists

of injecting the patient's breast cancer with a blue dye and nuclear medicine marker 24 hours before surgery. By the time of surgery the injected material has been taken up by the lymph nodes in the axilla, which is examined histologically during the operation. Proponents of this technique maintain that if this node does not contain metastases, then the axilla need not to be dissected [15].

5.6.3. Restaging

The HTA-DACEHTA 2001 report (Table 21- Restaging I) assessed the diagnostic accuracy of PET in the evaluation of breast cancer recurrence [117].Three studies meeting the authors' inclusion criteria were retrieved from 1990 up to May 2001. One of these studies is included in the HTA-BCBS 2003 report [134]. One study is non comparative. Three studies reported on sensitivity and specificity. The diagnostic reference standard in these studies was histopathology. All 3 studies reported hierarchy of diagnostic efficacy level 2 evidence. Reported PET sensitivities were 73%, 93% and 91%. PET specifities were 96%, 79% and 96%. It was noted that only 23-60 patients per study were noted to have "recurrence". It is unclear whether these patients had true recurrent disease while the others had primary disease. It is likely that the studies combined loco-regional and distant metastases. The analysis of the results was probably mixed by patient and lesion [34].

The HTA-BCBS 2003 report (Table 21- Restaging II) assessed the diagnostic accuracy of PET in the detection of loco-regional recurrence in patients with breast cancer [134]. Studies may include those who present with pain in the arm or other symptoms referable to the brachial plexus. Three comparative studies on the detection of loco-regional recurrence were retrieved from January 1966 to October 2001. This report includes the studies from the HTA-BCBS 2001 report [135]. The diagnostic reference standards in these studies were histopathology and follow up. All 3 studies reported hierarchy of diagnostic efficacy level 2 evidence. In a retrospective study with a mixed patient population, only 25 of 57 patients had suspected recurrent or metastatic disease. A second study included information on 10 patients. In a third prospective study on 75 patients, PET had a lower sensitivity for local recurrence than CT/MRI (80% versus 93%) and similar specificity (96% versus 98%). It was not only noted that 7 non-comparative studies were excluded but also that it appears from the report's tables and text that 142 patients are implied instead of a total number of 152 patients mentioned in the report. The report states that there were data inconsistencies and confused reporting, combining patients with loco-regional recurrence and patients with distant metastases. Other patients (disease-free patients and patients with elevated tumour markers) were also included in the total group. In the third study, PET specificity was comparable to CT/MRI specificity, but PET sensitivity was lower than CT/MRI sensitivity. The authors of the report express their concerns about insufficient details on the reference standard and therefore also on the validity of accuracy calculations.

5.6.4. Staging/restaging

The HTA-BCBS 2003 report (Table 21- Staging and Restaging) also assessed the diagnostic accuracy of PET in the detection of distant metastases/recurrence in patients with breast cancer who are undergoing a staging evaluation [134]. A complete staging evaluation is recommended if clinical suspicion for metastatic disease is high at initial diagnosis or when recurrent breast cancer (following treatment) is suspected. There is considerable variation in the patterns of metastasis and the aggressiveness of metastatic progression of disease. Ten comparative studies were retrieved from January 1966 up to October 2003. This report includes the studies from the HTA-BCBS 2001 report [135]. The diagnostic reference standards in this study were histopathology and follow up. All 10 studies reported hierarchy of diagnostic efficacy level 2 evidence. Four comparative studies used the patient as the unit of analysis. In a first retrospective study on 50 patients, PET had a higher sensitivity and specificity than conventional work up (CWU) (sensitivity 86% versus 57%; specificity 90% versus 81%). In a second retrospective study with a mixed population (group A consisted of 40 patients with suspected distant metastases and group B consisted of 33 patients with suspected loco-regional recurrence), PET had a higher sensitivity and specificity versus CT (PET sensitivity 85% in both patient groups

versus CT sensitivity 40% in group A and 54% in group B; PET specificity 90% in both groups and CT specificity 85% in both groups). In a third study on 54 patients, PET had a higher sensitivity and specificity versus CT (PET sensitivity 86% and specificity 73% versus CT sensitivity 73% and CT specificity 54%). In a fourth study on 39 patients, PET sensitivity (94%) was higher than CWU (18%) while PET specificity was 50% and CWU specificity not stated. Three non-comparative studies were excluded. PET appears to be more accurate than CT or CWU (stated in the fourth study as chest Xray, radionuclide bone scan, liver ultrasound/CT, oriented CT/MRI). However, PET specificity was <80% in 2 out of the 4 studies [34]. The report concluded that studies comparing PET and alternative imaging modalities suggest better diagnostic performance for PET, however the quality of study methods was generally poor. It is unclear whether studies of better methodological quality would obtain similar results. Overall, evidence on the use of PET in detecting distant recurrence or metastasis is insufficient to permit conclusions about diagnostic performance.

In the "ICES 2004 Quarterly updates" of the original ICES 2001 HTA-report, the authors commented on 1 study from which PET appears to be more effective than radionuclide bone scanning in the detection of bone metastases due to breast cancer [15]. The reference standard was unclear. The area under the ROC-curve was 1.00 for PET and 0.82 for bone scanning ($p<0.05$). However, it is difficult to draw definitive conclusions due to small sample size (34 patients).

In a recent systematic review by Isasi et al. 2005 the diagnostic performance of PET was assessed in the evaluation of breast cancer recurrence and metastases [138]. A literature search was performed from Januari 1995 up to June 2004. Eighteen studies reporting hierarchy of diagnostic accuracy level 2 evidence and meeting inclusion criteria were retrieved. Reference standards in the studies were histopathology (n=3), clinical follow up (n=5) or a combination of histopathology and clinical follow up (n=10). Study design was prospective (n=6), retrospective (n=7) or was not stated (n=5). The study was funded by a grant of Philips Medical Systems and Integral PET associates. Sixteen studies included patient-based data on a total of 808 patients. Six from these studies are also included in the HTA-BCBS 2003 report [134]. Two studies here were excluded from the HTA-BCBS 2003 report [134] because PET was not compared with diagnostic alternatives. Eight studies here, including 1 study after October 2003, were not included in the HTA-BCBS 2003 report [134]. The HTA-BCBS 2003 report included 6 studies not presented in this systematic review [134]. From the studies with patient-based data, pooled estimates of PET sensitivity and PET specificity were calculated. Pooled PET sensitivity and specificity were 90.3% and 87.3% respectively. Tests for homogeneity indicated the presence of statistical heterogeneity ($p< 0.05$) which affects the generalizability of the results. After exclusion of 3 outlier studies (2 studies with low specificity and 1 with low sensitivity), the pooled sensitivity and specificity were 90% (95% CI 86.8%-93.2%) and 88% (95% CI 85.4%-92.2%). A sROC curve was provided. The authors conclude that their results indicate that PET is a valuable tool for detecting breast cancer recurrence and metastases. As is noted by the authors, loco-regional recurrence is a clearly different situation from distant recurrence and/or distant metastases from which the prognosis of 5-year survival is much worse. However, the authors did not analyse both groups separately and only estimates were provided on the mixed group of patients with loco-regional recurrence and those with distant recurrence and/or distant metastases. Neither did the authors attempt to provide a separate analysis of comparative studies [138].

Table 20: Breast cancer - Diagnosis

Type of cancer	Cancer management decision	Source and Search period	Evidence	Diagnostic efficacy
Breast cancer	Diagnosis I	HTA - DACEHTA 2001 1990-May2001	6 studies (n=14 to144 patients/study) PET Se and PET Sp >80% in 5 studies; PET Se=80% and PET Sp= 76% in 6th study PET Se comparable to scintimammography in 2 studies	Level 2

Breast cancer	Diagnosis II	HTA - BCBS 2001 Jan 1966-March 2001	13 studies (n=16 to144 patients/study; total n=606 patients) sROC analysis of all 13 studies predicts: PET Se=89%, PET Sp =80% and NPV=88% For an individual patient with a negative PET and prior prevalence (probability) of malignancy of 50%, risk of false negative = 12%; for prior prevalence of 75%, risk of false negative = 29% 10 studies with patient data (n=415 patients) (exclusion of 3 studies with lesion-based analysis) Random effects meta-analysis of 10 studies gives pooled estimate: PET Se =88% (95%CI 83%-92%), PET Sp = 79% (95%CI 71%- 85%)	Level 2

Table adapted from: K Facey, I Bradbury, G Laking and E Payne. Positron Emission Tomography (PET) Imaging in Cancer Management. Ultra Rapid Review. July 2004. Health Technology Assessment NHS R&D HTA Programme.

Table 21: Breast cancer – Staging and Restaging

Type of cancer	Cancer management decision	Source and Search period	Evidence	Diagnostic efficacy
Breast cancer	Staging I	HTA – DACEHTA 2001 1990-May 2001	10 studies (n=18-167 per study) 9 studies with Se/Sp: PET Se > 85% in 7 studies; 50%, 79% in others. PET Sp > 90% in 6 studies; 66%, 75%, 86% in others.	Level 2
Breast cancer	Staging II	HTA- BCBS 2003 Jan 1966-October 2003	8 studies (n=15-129 per study; total n=337) 6 studies with cNO (non-palpable lymph nodes) patients only, 2 with 71% and 94% cNO patients: with ALND (axillary lymph node dissection) as reference standard: PET Se =40% -93% and PET Sp =87% -100%; NPV for PET=68% -96% with ALND+SLNB as reference standard: PETSe =20% -50% and PET Sp =82% -100%; NPV for PET=57% -80% As the prevalence of node positive disease in studies with ALND+SLNB as reference standard = 33% -64%, axillary metastase would remain undetected in 36% to 67% of patients with a negative PET when PET was used to avoid ALNB+SLNB	Level 2
Breast cancer	Restaging I	HTA - DACEHTA 2001 1990-May 2001	3 studies (n=30-75 per study): PET Se =73%,93%,91% and PET Sp = 96%, 79%, 96%	Level 2
Breast cancer	Restaging II	HTA- BCBS 2003 Jan 1966-October 2003	3 comparative studies (n=10-75 per study; total n=142) study1 (retrospective study, in mixed population, only 25/57 with suspected recurrent/metastatic disease) study2 (n=10) study3 (Prospective study, n=75): PET Se =80% and PET Sp =96% vs CT/MRI Se =93% and CT/MRI Sp =98%	Level 2
Breast cancer	Staging/ Restaging	HTA- BCBS 2003 Jan 1966-October 2003	10 comparative studies (n=484) 4 comparative studies with patient data (n=217) Study 1 (n=50): PET Se = 86% and PET Sp = 90% vs (conventional work up) CWU Se = 57% and CWU Sp =81% Study 2 (n=40 distant, 33 recurrent): PET Se =85%, 85% and PET Sp =90%, 90% vs CT Se =40%, 54% and CT Sp =85%, 85% Study3 (n=54): PET Se=86% and PET Sp=73% vs CT Se=73% and CT Sp=54% Study4 (n=39): PET Se=94% and PET Sp=50% vs CWU Se=18% and CWU Sp=not stated	Level 2

Table adapted from: K Facey, I Bradbury, G Laking and E Payne. Positron Emission Tomography (PET)) Imaging in Cancer Management. Ultra Rapid Review. July 2004. Health Technology Assessment NHS R&D HTA Programme.

Table 22: Breast cancer - Primary studies

Setting	Grade	Study design	Author	Yr	Pts	Compare	Blinded	Se (%)	Sp (%)	PPV (%)	NPV (%)
Axillary lymph node staging	A	Prospect. multicenter	Wahl	2004	305	ALND Histology	Yes	61	80	62	79
Axillary lymph node staging	B	Prospect.	Zornoza	2004	200	ALND & SLNB Histology	Yes	90.9 ALND 76.9 SNB	100 ALND 95.8 SNB	100 ALND 95.2 SNB	90 ALND 79.3 SNB

Legend: Yr=year published; Pts=number of patients; Se=sensitivity; Sp=specificity; PPV=Positive Predictive Value; NPV=Negative PredictiveValue; MRM=MR mammography; PT=primary tumour; Cont=contralateral; - = data unavailable; SLNB=sentinel lymph node biopsy; ALND=axillary lymph node dissection (For Se/Se, Sp/Sp, PPV/PPV and NPV/NPV: single value refers to PET, subsequent values, if any, refer to comparator)

5.6.5. Assessment of treatment response

It was noted that assessing tumour response to treatment has become an area of enthusiasm for the potential value of PET. A few meta-analyses did mention the use of PET for evaluation of response to treatment. The largest body of evidence was presented in breast cancer in the HTA-BCBS 2003 report. This report found 7 studies on a total of 211 patients undergoing multi-course treatment for breast cancer. However, this evidence could not be summarised due to the major differences in study designs. PET was used to assess response before, during, immediately after or several months after a variety of forms of treatment (neoadjuvant chemotherapy, chemohormonotherapy, hormone therapy, or surgery with or without chemotherapy and radiation), in different patient populations and with different reference standards. Furthermore, individual studies were generally too small to lead to clear recommendations. So the overall conclusion related to treatment response is that further diagnostic studies are required. The design of such studies would be helped if the timing and rationale for PET response assessments could be organised within some explicit, systematic framework of theory [134 34].

A study of 30 patients receiving neoadjuvant or primary chemotherapy for carcinoma of the breast underwent PET before the first course and after the second and fifth courses of chemotherapy. Regression of PET uptake in the primary tumour or lymph nodes was related to histological evidence of therapy response. Neoadjuvant or primary chemotherapy prior to surgery and/or radiation therapy at present is applied chiefly in the setting of locally advanced breast cancer. It is unclear whether information from PET about a poor prognosis or response to chemotherapy would prompt a change in therapy that would improve clinical outcomes (because of the likelihood in this clinical setting that other therapies would also fail) [15].

Breast Cancer - Key Messages

- **For diagnosis in patients referred for breast biopsy with abnormal mammogram or palpable breast mass, there is evidence of diagnostic inaccuracy. Benefits do not appear to outweigh risks (level 2 against the use of PET).**
- **For staging/restaging in breast cancer, i.e. detection of distant metastatic disease if clinical suspicion for metastatic disease is high at initial diagnosis or when recurrent breast cancer is suspected, there is evidence of diagnostic accuracy including the determination of sensitivity and specificity (level 2). Evidence seems supportive for the use of PET.**
- **For staging in breast cancer, i.e. staging of axillary lymph nodes in patients with no palpable axillary lymph nodes metastases and no evidence of distant metastases, there is evidence of diagnostic inaccuracy. Benefits do not appear to outweigh risks (level 2 against the use of PET).**
- **For restaging in breast cancer, i.e. detection of loco-regional recurrence, there is evidence of diagnostic accuracy including the determination of sensitivity and specificity (level 2). There is inconclusive evidence that PET is superior to CT/MRI.**
- **For assessment of treatment response, further diagnostic studies are needed**

5.7. OESOPHAGEAL CANCER

5.7.1. Diagnosis

The HTA-BCBS 2002 report (Table 23- Diagnosis I) intended to assess the diagnostic accuracy of PET in the initial detection of primary oesophageal tumours [139]. Oesophageal cancer includes squamous cell carcinoma (SCC) and adenocarcinoma (AC). The diagnostic reference standard was histopathology. A literature search was performed up to March 2002. No evidence was found on this subject. It was noted that evidence on the differentiation of oesophageal cancer and benign conditions is lacking. Because studies only include patients with the disease, the specificity cannot be determined [34].

The HTA-MSAC 2001(i) report (Table 23- Diagnosis II) adressed the diagnostic accuracy of PET in the assessment of the primary tumour in patients with established oesophageal cancer (SCC and AC) [140]. A literature search was performed up to March 2001. Eight studies were selected. Although this report is superseded by the HTA-BCBS 2002 report [139], this report provides more details on this subject. The diagnostic reference standard was histopathology. In 4 studies, PET identified all primary tumours. In another 4 studies, the sensitivity of PET in the visualisation of primary tumour was 95% to 99%. However, PET has a low sensitivity (38%) for patients with T1 (early stage) disease compared to 100% sensitivity for patients with T2-T4 disease. It was noted that some authors suggest that PET may not be useful for the staging of the primary tumour given its limited ability to define tissues planes in relation to other structures [34].

5.7.2. Staging

The HTA-MSAC 2001(i) report (Table 24- Staging I) assessed the diagnostic accuracy of PET in the staging of regional lymph node metastases in patients with oesophageal cancer (SCC and AC), in order to assist in the selection of treatment modalities for these patients (surgery, radiotherapy or chemo-radiotherapy) [140]. A literature search was performed up to March 2001. Although this report is superseded by the HTA-BCBS 2002 report [139], some earlier studies were reported here with a different analysis of lymph nodes and comparison with esophageal ultrasound (EUS). Eight studies were selected. The diagnostic reference standards consisted of laparoscopy, a variety of surgical resection procedures and histopathology in some patients. All 8 studies reported hierarchy of diagnostic efficacy level 2 evidence. The sensitivity of PET varied from 10% to 100% and the specificity varied from 71% to 100%. The sensitivity of CT ranged from 0% to 68% and its specificity ranged from 73% to 100%. The study (on 45 patients) with CT and EUS as comparators for nodal staging showed a sensitivity and specificity for PET of 81% and 88% respectively versus a sensitivity and specificity for CT of 41% and 100% respectively versus a sensitivity and specificity for EUS of 50% and 73% respectively. It was noted that some papers included patients with gastric or gastro-oesophageal cancer. Several summaries were based on nodes and/or sites and not on patients; patient numbers were not stated. Study results were heterogeneous, but the specificity was fairly high and similar for PET and CT. PET sensitivity was slightly higher than CT sensitivity in these studies. In the study with CT and EUS as comparators, PET sensitivity is significantly higher than combined CT or EUS sensitivity [34].

The HTA-BCBS 2002 report (Table 24- Staging II) assessed the diagnostic accuracy of PET in the staging of loco-regional lymph nodes in patients with biopsy proven oesophageal cancer (SCC and AC) [139]. Nine studies were retrieved from a literature search performed up to March 2002. The diagnostic reference standard was histopathology. All 9 studies reported hierarchy of diagnostic efficacy level 2 evidence. Seven studies with a total of 302 patients were comparative. A random effects meta-analysis by patient revealed a sensitivity for PET of 51% (95% CI 31% - 70%) versus a sensitivity for CT of 42% (95% CI 25% - 61%). PET specificity was 89% (95% CI 81% - 94%) versus specificity for CT of 87% (95% CI 67% - 96%). In a single study on 39 patients, CT and EUS were used as comparators. In this study, the sensitivity of PET was 33% while the sensitivity of CT, EUS and "CT+EUS" were 0%, 81% and 62% respectively. The specificity of PET was 89% while the specificity of CT, EUS and "CT+EUS" were 100%, 67% and 67% respectively. It was noted that on all

oesophageal indications in this HTA, several instances or centres produced multiple publications. Each analysis used just one paper from each centre. PET specificity and CT specifity were similar. PET sensitivity is low but slightly higher than CT sensitivity. In the study with CT and EUS comparators, EUS sensitivity was much higher than PET sensitivity. Findings from this study are the opposite of those from another study with EUS as a comparator (study included in the MSAC 2001(i) report) [140] [34].

The HTA-BCBS 2002 report (Table 24- Staging III) evaluated the diagnostic accuracy of PET in the staging of distant lymph nodes in patients with biopsy proven oesophageal cancer (SCC and AC) [139]. Four studies were retrieved from a literature search performed up to March 2002. The diagnostic reference standards were histopathology and clinical follow up. All 4 studies reported hierarchy of diagnostic efficacy level 2 evidence. Two studies with a total of 77 patients were comparative. In one study on 42 patients (SCC/AC), PET sensitivity and CT sensitivity were 77% and 46% respectively while PET specificity and CT specificity were 90% and 69% respectively. In another study on 35 patients (SCC/AC), PET sensitivity and CT sensitivity were 25% and 0% respectively and PET specificity and CT specificity were 96% and 100% respectively. PET sensitivity is low in 1 study but higher than CT sensitivity. PET specificity is high in both studies and CT specificity is high in 1 study.

The HTA- MSAC 2001 (i) report (Table 24- Staging IV) assessed the diagnostic accuracy of PET in the staging of all lymph nodes (no specific region) in patients with biopsy proven oesophageal cancer (SCC and AC) [140]. The diagnostic reference standards were histopathology and histopathology combined with clinical follow up and clinical follow up in 10 patients in a single study. Three studies were retrieved from a literature search performed up to March 2001. All 3 studies reported hierarchy of diagnostic efficacy level 2 evidence. Three studies on 201 patients were comparative. In one study on 53 patients (436 metastases, SCC), PET sensitivity and CT sensitivity were 52% and 15% respectively while PET specificity and CT specificity were 94% and 97% respectively. In a second study on 39 patients (221 metastases, SCC/AC), PET sensitivity and CT sensitivity were 39% and 22% respectively. EUS sensitivity and "CT+EUS" sensitivity were 63% and 54% respectively. PET specificity compared to specificities of CT, EUS and "CT+EUS" was 97% versus 96%, 88% and 90% respectively. In a third study on 109 patients (276 metastases), PET sensitivity and CT sensitivity were 80% and 68% respectively and PET specificity and CT specificity were 95% and 81% respectively. It was noted that results had probably been analysed by lymph nodes or nodal regions. When compared to CT, PET has a higher sensitivity and a similar or higher specificity. In 1 study however, PET sensitivity is lower than EUS sensitivity [34].

The HTA-BCBS 2002 report (Table 24- Staging V) assessed the diagnostic accuracy of PET in the staging of distant sites, other than lymph nodes, in patients with biopsy proven oesophageal cancer (SCC and AC) [139]. Three studies were retrieved from a literature search performed up to March 2002. This report supersedes the HTA-MSAC 2001(i) report (metastases were not analysed separately from lymph nodes in the HTA-MSAC 2001(i) report) [140]. The diagnostic reference standards were histopathology and follow up. All 3 studies reported hierarchy of diagnostic efficacy level 2 evidence. Three studies with a total of 196 patients were comparative. In one study on 79 patients (SCC/AC), PET sensitivity compared to sensitivities of CT, EUS and "CT+EUS" was 74% versus 41%, 42% and 47% respectively. PET specificity compared to specificities of CT, EUS and "CT+EUS" was 90% versus 83%, 94% and 78% respectively. In a second study on 91 patients (100 metastases, SCC/AC), PET sensitivity compared to CT sensitivity was 69% and 46% respectively while PET specificity compared to CT specificity was 93% and 74% respectively. In a third study on 26 patients (SCC/AC), PET sensitivity compared to CT sensitivity was 100% and 50% respectively and PET specificity compared to CT specificity was 90% and 95% respectively. It was noted that the author of the report had stated that only one study avoided verification bias, PET was interpreted blinded to the results of the reference standard in only one study and that there was no study with the reference standard interpreted blind to PET results. Therefore, evidence is considered insufficient to draw conclusions on PET diagnostic performance in this indication. It was noted that PET sensitivity was higher than CT sensitivity in the 3 studies (and higher than EUS sensitivity in 1 study). PET specificity was similar or higher than CT specificity in the 3 studies and similar to EUS specificity in 1 study.

In order to achieve a higher evidence level, the HTA-BCBS 2002 report (Table 24- Staging VI overview) provided an overview of all diagnostic studies on staging of oesophageal cancer [119]. The HTA-MSAC 2001(i) report included 5 studies with some hierarchy 4 evidence mainly predicting surgery that would be avoided [140]. K. Facey et al. commented that the evidence provided was insufficient to quantify the actual changes in patient management. The HTA-BCBS 2002 report included 2 survival analyses determining the predictive value of PET [119]. One study on 91 patients assessed the 30-month survival comparing PET predicted disease state with CT predicted disease state. With PET predicted local disease, survival was 60%; with PET predicted distant disease, survival was only 20% (p=0.01). With CT predicted local disease, survival was 52%; with CT predicted distant disease, survival was 38% (p>0.05). Another study on 48 patients assessed the Standard Uptake Value (SUV) as a predictor of median survival. A SUV>7 indicated survival of 10 months; a SUV<7 indicated survival of 35 months. It was noted that evidence on survival is not robust category 5 evidence. It was stated that 30 month survival is significantly better when PET predicted local disease but the analysis is unclear and probably not robust. The authors state that robust multivariate analyses including other potential prognostic factors are needed.

A recent systematic review assessed the staging performance of PET in oesophageal cancer [141]. Twelve studies (n=18-81patients per study) meeting inclusion criteria were analysed. The reference standard was histopathology. Eight studies were prospective. In most studies, all stages of disease were included. The studies had limited methodological quality with several deficiencies in their design i.e. diagnostic bias, verification bias and spectrum bias. The results of this systematic review should therefore be interpreted with caution. PET showed moderate sensitivity and specificity for the detection of loco-regional metastases: pooled sensitivity and specificity of 51% (95% CI 34% - 69%) and 84% (95% CI 76% - 91%), respectively. PET showed reasonable sensitivity and specificity in detection of distant lymphatic and hematogenous metastases: pooled sensitivity and specificity of 67% (95% CI 58% - 76%) and 97% (95% CI 90% - 100%), respectively. Different studies have shown a high accuracy of PET. However, the hallmark for implementation in diagnostic work up is the ability to change patient management due to more accurate staging. Of the included studies, the change in patient management ranged from 3% to 20% due to addition of PET to preoperative work up. However, these studies involved only a limited number of patients. Larger prospective studies should quantify to what extent the routine use of PET leads to changes in management and better health care for these patients [141].

5.7.3. Assessment of treatment response

The HTA- MSAC 2001(i) report [140] with a literature search performed up to March 2001, found no evidence on restaging oesophageal cancer following neoadjuvant therapy.

A most recent systematic review was provided by the external experts' group (electronic publication ahead of print). This review assessed the diagnostic performance of PET in restaging oesophageal cancer following neoadjuvant therapy [142]. Response to therapy is currently evaluated by morphological imaging such as CT and EUS. General restrictions of these methods are the difficulty in distinguishing viable tumour from necrotic or fibrotic tissue and the delay between cell kill and tumour shrinkage. PET has the ability to reflect alterations in tissue metabolism that generally precede anatomic changes. Therefore, the diagnostic accuracy of CT, EUS and PET were compared in the assessment of the response of oesophageal cancer to neoadjuvant therapy in patients eligible for curative surgery. A literature search was performed up to January 2004. Four studies with CT (n =13-50 patients per study), 13 studies with EUS (n =11-87 patients per study) and 7 studies with PET (n =10-40 patients per study) met inclusion criteria. The reference standard was histopathology. Six studies with PET, 3 studies with CT and 7 studies with EUS had a prospective study design. The included papers were of variable methodological quality with percentages of the maximum score for methodological quality varying between 15% and 100%. A summary ROC analysis could be performed for 3 studies with CT, 4 studies with EUS and 4 studies with PET. The maximum joint values for sensitivity and specificity were 54% for CT, 86% for EUS and 85% for PET. The overall accuracy of CT was reported to be significantly lower than that of PET (p< 0.006) and of EUS (p<0.003). The overall accuracy of PET and EUS were similar (p<0.893). In all patients, CT was always feasible

whereas EUS and PET were not feasible in 6% and 1% of the patients respectively. In addition, in all four studies with PET, a significantly longer survival in metabolically responding patients was found. Only if evaluation is performed early in the course of neoadjuvant therapy and the test accurately discriminates responders from nonresponders can the test results be used to aid in the decision about whether this toxic therapy should be continued, as in responders or stopped, as in nonresponders. General limitations to this review were the limited number of studies and patients, the poor to moderate methodological quality of the four studies with CT and the fact that in none of the studies a head to head comparison was used to test directly for a difference in accuracy between the three imaging modalities. Some potential sources of heterogeneity included important differences in neoadjuvant therapeutic schemes among the studies and the possibility of spectrum bias. It was concluded that CT has poor accuracy for assessment of response to neoadjuvant therapy in patients with oesophageal cancer. EUS and PET have a similar good accuracy but EUS is not always feasible following chemotherapy and radiation therapy. The authors consider PET to be a promising non-invasive tool for assessment of neoadjuvant therapy in patients with oesophageal cancer [142].

Findings from this systematic review are in line with results from studies published after January 2004 and provided by the external expert's group. In a study by Wieder et al. 38 consecutive patients with histologically proven intrathoracic oesophageal squamous cell carcinoma (cT3, cN0/+, cMO) and eligible for curative surgery were recruited from a phase II trial of neoadjuvant chemoradiotherapy (CRT). It appeared that changes in tumour metabolic activity after 14 days of preoperative chemoradiotherapy were significantly correlated with tumour response and patient survival. In histopathologic responders (<10% viable cells in the resected specimen), the decrease in standardized uptake value (SUV) from baseline to day 14 was 44% $\pm$ 15%, whereas it was only 21% $\pm$ 14% in nonresponders (p=0.005). Metabolic changes at this time point were also correlated with patient survival (p=0.011) [143]. From a retrospective evaluation of 83 consecutive patients with resectable oesophageal carcinoma who underwent preoperative chemoradiotherapy (CRT) and PET and tumour resection, it appeared that post-CRT PET was predictive of pathologic response and survival. Most patients (89%) were men. Most tumours were adenocarcinomas (88%) and clinical EUS T3/4 (83%) or N1 (55%) tumours. PET after preoperative CRT identified pathologic responders but failed to rule out microscopic residual tumour in 11% of the patients. Pathologic response was found to correlate with the post-CRT PET standardized uptake value (SUV) (P=0.03) and a post-CRT PET SUV of $\geq$ 4 was found to be the only preoperative factor to correlate with decreased survival (2-year survival rate of 33% versus 60%; p=0.01). On univariate Cox regression analysis, only post-CRT PET was found to be correlated with post-CRT survival (p=0.04). As microscopic residual disease cannot be ruled out, oesophagectomy should still be considered even if the post-CRT PET scan is normal [144] (based on references provided by the external experts group).

Table 23: Oesophageal cancer – Diagnosis

Type of cancer	Cancer management decision	Source and Search period	Evidence	Diagnostic efficacy
Oesophageal cancer	Diagnosis I	HTA-BCBS 2002 up to March 2002	None	
Oesophageal cancer	Diagnosis II	HTA-MSAC 2001(i) up to March 2001	8 studies In 4 studies PET was able to identify all primary tumours In another 4 studies, high PET Se =95%-99% for primary tumour visualisation but low PET Se of 38% for patients with early stage disease (T1) vs 100% for patients with T2-T4 lesions	

Table adapted from: K Facey, I Bradbury, G Laking and E Payne. Positron Emission Tomography (PET) Imaging in Cancer Management. Ultra Rapid Review. July 2004. Health Technology Assessment NHS R&D HTA Programme.

Table 24: Oesophageal cancer – Staging

Type of cancer	Cancer management decision	Source and Search period	Evidence	Diagnostic efficacy
Oesophageal cancer	Staging I	HTA-MSAC 2001(i) up to March 2001	8 studies: PET Se =10-100% and PET Sp =71-100% vs CT Se =0-68% and CT Sp =73-100% Report involving esophageal ultrasound (EUS) for nodal staging (n=45): PET Se =81% and PET Sp = 88% vs CT Se =41% and CT Sp =100% vs EUS Se =50% and EUS Sp =73%	Level 2
Oesophageal cancer	Staging II	HTA-BCBS 2002 up to March 2002	9 studies 7 comparative studies (n=302), random effects meta-analysis by patient: PET Se =51% (95%CI 31% -70%) and PET Sp =89% (95%CI 81%-94%) vs CT Se =42% (95%CI 25% - 61%) and CT Sp =87% (95%CI 67% - 96%) 1 study with EUS comparator (n=39, SCC/AC): PET Se =33% and PET Sp =89% vs CT Se =0% and CT Sp =100% vs EUS Se =81% and EUS Sp =67% vs CT+EUS Se =62% and CT+EUS Sp=67%	Level 2
Oesophageal cancer	Staging III	HTA-BCBS 2002 up to March 2002	4 studies 2 comparative studies (n=77) Study1 (n=42, SCC/AC): PET Se =77% and PET Sp =90% vs CT Se =46% and CT Sp =69% Study2 (n=35, SCC/AC): PET Se =25% and PET Sp =96% vs CT Se =0% and CT Sp=100%	Level 2
Oesophageal cancer	Staging IV	HTA-MSAC 2001(i) up to March 2001	3 comparative studies (n=201) Study1 (n=53, m =436, SCC): PET Se =52% and PET Sp =94% vs CT Se =15% and CT Sp =97% Study2 (n=39,m =221, SCC/AC): PET Se =39% and PET Sp =97% vs CT Se =22% and CT Sp =96% vs EUS Se =63% and EUS Sp =88% vs CT+EUS Se =54% and CT+EUS Sp =90% Study3 (n=109, m=276): PET Se =80% and PET Sp =95% vs CT Se =68% and CT Sp =97%	Level 2
Oesophageal cancer	Staging V	HTA-BCBS 2002 up to March 2002	3 comparative studies (n=196) Study1 (n=79, SCC/AC): PET Se =74% and PET Sp =90% vs CT Se =41% and CT Sp =83% vs EUS Se =42% and EUS Sp =94% vs CT+EUS Se =47% and CT+EUS Sp =78% Study2 (n=91, m=100, SCC/AC): PET Se =69% and PET Sp =93% vs CT Se =46% and CT Sp =74% Study3 (n=26, SCC/AC): PET Se =100% and PET Sp =90% vs CT Se =50% and CT Sp =95%	Level 2
Oesophageal cancer	Staging VI Overview		HTA-MSAC 2001(i) reports 5 studies with some hierarchy 2 evidence mainly predicting surgery that would be avoided HTA-BCBS 2002 reports 2 survival analyses determining predictive value of PET Study 1 (n=91, 30-month survival): PET predicted disease state (Local, surv =60%; Distant, surv =20%, p =0.01)	

			CT predicted disease state (Local, surv=52%; Distant, surv=38%, p>0.05) Study 2 (n=48): SUV predictive of median survival (SUV>7, survival=10 mos; SUV<7, survival=35 mos)	

Table adapted from: K Facey, I Bradbury, G Laking and E Payne. Positron Emission Tomography (PET) Imaging in Cancer Management. Ultra Rapid Review. July 2004. Health Technology Assessment NHS R&D HTA Programme

Oesophageal Cancer - Key Messages

- **For diagnosis, i.e. the initial detection of a primary tumour, there is lack of evidence.**
- **For staging in oesophageal cancer, i.e. staging of lymph nodes (loco-regional, distal or all lymph nodes) and distant sites other than lymph nodes, there is evidence of diagnostic accuracy including the determination of sensitivity and specificity. Evidence, although limited, seems supportive for the use of PET (level 2)**
- **For staging in oesophageal cancer, i.e. staging of distant sites, there is evidence of diagnostic accuracy including the determination of sensitivity and specificity (level 2).**
- **For assessment of treatment response after patients, eligible for curative surgery, have received neoadjuvant therapy (comparative with initial staging PET result), there is evidence up to diagnostic thinking based on diagnostic accuracy and prognosis (level 3).**

5.8. THYROID CANCER

5.8.1. Diagnosis and staging

No HTA-reports or systematic reviews were found on these indications.

5.8.2. Restaging (recurrence)

In a systematic review, Hooft et al. 2001 (Table 25- Restaging I) intended to assess the diagnostic accuracy of PET in the detection of recurrent disease in previously treated thyroid cancer patients with elevated biomarkers but not confirmed by ^{131}I scintigraphy [145]. Medullary or Huertle thyroid were excluded where possible. Eleven studies were retrieved from a literature search performed up to October 2000. In this review are included 6 studies of epithelial thyroid cancer and 2 studies of medullary thyroid cancer already included in the HTA-AHRQ 2002 report. The diagnostic reference standards were histopathology, imaging and follow up. All 11 studies reported hierarchy of diagnostic efficacy level 2 evidence. PET detected "possible disease" in 115 out of 140 patients. However, these results were adequately validated only in 68 patients, 90% of which had recurrent disease. Recurrent thyroid cancer was not detected by PET in 6 patients (false negatives). False positive results were reported in 6 out of 156 patients. Inadequate reference standards were used in some studies. The authors were unable to extract adequate data to undertake their planned meta-analyses. Therefore, only narrative reports were presented without calculations of sensitivity or specificity.

The HTA-AHRQ 2002 report (Table 25- Restaging II) assessed the diagnostic accuracy of PET in the detection of recurrent disease in previously treated thyroid cancer patients with metastatic disease suspected from elevated biomarkers but not confirmed by ^{131}I scintigraphy [146]. Thyroid cancer included epithelial cancer i.e. differentiated and well-differentiated follicular, papillary, mixed follicular-papillary and Huertle thyroid cancer. Eleven studies were retrieved from a literature search performed from 1980 up to September 2001. Six studies already included in Hooft SR 2001 [145] are also included in this report. The diagnostic reference standards were histopathology, imaging and follow up. All 11 studies reported hierarchy of diagnostic efficacy level 2 evidence. Eleven studies with at least 10 patients in each study were retrieved with a total number of 244 patients. Approximately 65% of the patients had papillary cancer and approximately 35% had follicular cancer. A random effects meta-analysis yielded a PET sensitivity of 84% (95% CI 73% - 91%) and a PET specificity of 56% (95% CI 27% - 82%). Seven studies included some hierarchy 4 evidence on patient management and outcomes following a positive PET result. In 5 studies, 71% of the patients were treated for recurrent disease. In 4 studies, successful treatment or cure was reported in 0% to 48% of the patients. In 3 studies, 34% of the patients treated after a positive PET result developed recurrent disease. In 4 studies, a positive PET scan did not result in a change in patient management. It was noted that sub-group analyses were reported for Huertle thyroid cancer and poorly differentiated tumours but only on a small number of patients. Heterogeneity is noted by the authors and therefore estimates of sensitivity and specificity are preliminary and should be "interpreted with caution". However, heterogeneity is predominantly related to PET specificity. PET sensitivity is rather high given the negative results of other imaging modalities. Cure and recurrence were not defined consistently and reported with insufficient details.

The HTA-AHRQ 2002 report (Table 25- Restaging III) intended to assess the diagnostic accuracy of PET in the detection of recurrent disease in previously treated medullary thyroid cancer patients with metastatic disease suspected from elevated biomarkers but not confirmed by other imaging modalities [146]. Six studies were retrieved from a literature search performed from 1980 up to September 2001. The diagnostic reference standards were histopathology, imaging and follow up. All 6 studies with a total of 17 patients reported hierarchy of diagnostic efficacy level 2 evidence. Actual documentation on the diagnostic accuracy of PET in the evaluation of disease recurrence or metastatic spread following thyroid cancer treatment is considered too weak to draw any conclusions. Only two studies had sufficient power to estimate diagnostic accuracy in these indications: sensitivity 88% and 96%; specificity 100% and 76% [146].

In a systematic review, Hooft et al. 2001 (Table 25- Restaging IV) assessed the diagnostic accuracy of PET in the detection of recurrent disease in patients without elevated biomarkers and no evidence of disease by ^{131}I scintigraphy, but with clinical suspicion of recurrence (e.g. equivocal imaging results) [145]. Medullary and Huertle thyroid cancer were excluded where possible. Five studies were retrieved from a literature search performed from 1980 up to October 2000. The diagnostic reference standards were histopathology, imaging and follow up. All 5 studies reported hierarchy of diagnostic efficacy level 2 evidence. The number of patients in each study varied from 2 to 21 patients with a total number of 50 patients. Thirty-five out of 50 PET scans were negative. After 1 year clinical follow up, only one of these 35 negative scans appeared a false negative result. Six out of 50 PET scans were false positive results. The authors were unable to extract adequate data to undertake their planned meta-analyses. Therefore, only narrative reports were presented without calculations of sensitivity or specificity. Verification was inadequate in some studies (neither histopathology nor follow up). It was noted that the rate of false positives was higher than in the group with elevated biomarkers [34].

In a systematic review, Hooft et al. 2001 attempted to evaluate the diagnostic accuracy of PET in detecting recurrent disease in thyroid cancer patients with otherwise established neoplastic foci [145]. A literature search was performed from 1980 up to October 2000. Eligible patients were included in 6 papers but only 1 paper was specifically designed to include these patients. The authors did not review these data and stated that it was unclear for which clinical problem PET had been performed.

Table 25: Restaging (recurrence) – Thyroid cancer

Type of cancer	Cancer management decision	Source and Search period	Evidence	Diagnostic efficacy
Thyroid cancer	Restaging I	SR-Hooft 2001- up to Oct 2000	11 studies (total n=156) PET found "possible disease" in 115/140 patients, but adequate valdation only done on 68 of them, 90% of which were recurrent disease PET missed recurrence in 6 cases (FN); FP=6/156	Level 2
Thyroid cancer	Restaging II	HTA-AHRQ 2002 1980-Sept 2001	11 studies on >10 pats (total n=244); 65% papillary cancers, 35% follicular cancers Random effects meta-analysis: PET Se = 84% (95%CI 73% - 91%) and PET Sp = 56% (95%CI 27% - 82%) 7 studies included some hierarchy 2 evidence on patient management and outcome following positive PET In 5 studies, 71% of patients had treatment for recurrence In 4 studies, 0%-48% of patients had successful treatment or cure In 3 studies, 34% of patients treated after a positive PET had recurrence In 4 studies, 21% patients had no change in management despite a positive PET	Level 2
Thyroid cancer	Restaging III	HTA-AHRQ 2002 1980-Sept 2001	6 studies (total n=17): medullary cancer	Level 2
Thyroid cancer	Restaging IV	SR-Hooft 2001 1980-Oct 2000	5 studies (n=2-21 per study, total n=50) 34/50 scans were negative. After 1 year of clinical follow up only 1 of these scans appeared false negative (FN) false positives (FP)=6/50	Level 2

Table adapted from: K Facey, I Bradbury, G Laking and E Payne. Positron Emission Tomography (PET)) Imaging in Cancer Management. Ultra Rapid Review. July 2004. Health Technology Assessment NHS R&D HTA Programme.

Thyroid Cancer - Key Messages

- For restaging, i.e. detection of recurrence of epithelial thyroid cancer in previously treated patients with elevated biomarkers not confirmed by ^{131}I scintigraphy, there is evidence of diagnostic accuracy including the determination of sensitivity and specificity (level 2).
- For restaging, i.e. detection of recurrence of medullary thyroid cancer in previously treated patients with elevated biomarkers not confirmed by other imaging, there is some evidence of diagnostic accuracy (level2).
- For restaging, i.e. detection of recurrence of thyroid cancer (no differentiation between epithelial and medullary) in previously treated patients without elevated biomarkers and no evidence of disease by ^{131}I scintigraphy but with clinical suspicion of recurrence, there is some evidence of diagnostic accuracy (level2).
- For restaging, i.e. detection of recurrence of thyroid cancer (no differentiation between epithelial and medullary) in patients with otherwise established neoplastic foci, there is some evidence of diagnostic accuracy (level2).

5.9. PANCREATIC CANCER

5.9.1. Diagnosis

A recent meta-analysis assessed the diagnostic accuracy of PET in the detection of pancreatic cancer [147]. Seventeen studies were included in the analysis. None of the studies described the patient population or recruitment procedures in detail. All studies used histopathology or long-term follow up of the patients as the reference standard for detection of pancreatic malignancy. In 9 studies, it was possible to extract information about the results of PET, CT and the reference standard.The summary estimate and 95% confidence interval for sensitivity and specificity were: for CT 81% (95%CI 72%-88%) and 66% (95%CI 53%-77%), for PET after a positive CT 92% (95%CI 87%-95%) and 68% (95%CI 51%-81%), for PET after a negative CT 73% (95%CI 50%-88%) and 86% (95%CI 75%-93%) and for PET after an indeterminate CT 100% and 68% (results based on a single study). The area under the sROC was 0.82 for CT and 0.94 for PET. There was no heterogeneity or publication bias. These results suggest that although adding PET to the diagnostic work up may enhance the diagnosis of pancreatic malignancy, its usefulness will vary depending upon the pre-test probability of the patient, the CT-results and the provider's testing thresholds. The studies included in this meta-analysis had limited methodological quality with several deficiencies in their design i.e. a lack of clear recruitment procedures and limited descriptions of the study populations. Many were unable to account for possible bias in referral for PET. In the diagnosis of pancreatic cancer, a significant number of CT results may be indeterminate. Only one study specifically assessed the impact of an indeterminate CT on the usefulness of PET. The others did not describe whether indeterminate CT results were treated as positive or negative. Therefore, the estimates for PET sensitivity and specificity in these subpopulations are imprecise. Finally, sensitivity and specificity of PET in those with a positive or negative CT were not statistically different as the CI overlapped, although the trend was suggestive. A definitive assessment of the role for PET as an adjunct test for the detection of pancreatic cancer awaits a large prospective study designed to detect the differences in sensitivity and specificity for all three populations: positive CT, negative CT and indeterminate CT along with a prospectively designed cost-effectiveness analysis and the need to determine change in patient management as a result of PET. In the current studies, the benefit derived from the addition of PET to CT for the detection of pancreatic carcinoma depends upon the results of the CT. At present, published studies do not adequately answer the question of who will benefit the most from PET. [147].

In the HTA-AHRQ 2004 report [90], the diagnostic accuracy of PET as an adjunct to conventional imaging in differentiating benign from malignant pancreatic lesions (18 studies) was comparable or slightly better than the comparator alone (CT: 14 studies and ERCP: 6 studies). PET sensitivity ranges from 71% to 100% and CT ranges from 51.6% to 100%; PET specificity ranges from 50% to 100% and CT specificity ranges from 0% to 87.2%. Data from 6 studies: ERCP sensitivity ranges from 60% to 100% and ERCP specificity ranges from 37.5% to 92.3%.

5.9.2. Staging

In the HTA-AHRQ 2004 report [90], the diagnostic accuracy of PET as an adjunct to conventional imaging in detecting metastatic pancreatic cancer was assessed(9 studies). A trend towards greater sensitivity but lower specificity than comparators for the detection of metastases was found. The reference standard was histopathology or clinical follow up. Future studies need to be larger in order to provide a more definitive assessment of relative test performance. The authors of the report were unable to identify a subpopulation of patients with metastatic pancreatic cancer that might achieve a substantial greater benefit because details regarding the patient populations and tumour characteristics were incompletely reported.

5.9.3. Restaging

The HTA-AHRQ 2004 report [90] found only one study in 32 patients on the diagnostic accuracy of PET in the detection of residual or recurrent disease after primary treatment for pancreatic carcinoma. This study indicated greater discrimination between patients using PET compared to CT [90]. The reference standard in these studies was histopathology or clinical follow up.

Pancreatic Cancer - Key Messages

- **For diagnosis, i.e. the detection of pancreatic cancer, there is limited evidence of diagnostic accuracy including the determination of sensitivity and specificity (level 2). The clinical utility and advantage over other imaging techniques remain to be established.**
- **For staging, i.e. detection of metastatic disease, there is limited evidence of diagnostic accuracy including determination of sensitivity and specificity (level 2). The clinical utility and advantage over other imaging techniques remain to be established.**
- **For restaging, i.e. detection of residual or recurrent disease, there is lack of evidence.**

5.10. LIVER CANCER

Material reviewed: HTA reports and Systematic Reviews

The diagnosis of a liver tumour is complicated, especially in case of associated cirrhosis where the classical imaging techniques show limitations. Therefore, the role of PET has been studied, principally to differentiate benign from malignant tumours, but until now with no conclusive results. The FNCLCC is the only agency that included liver tumours in its report, on the basis of 11 primary studies with histology as reference standard. Indeed, due to a low sensitivity in case of hepatocellular carcinoma, PET is not indicated to diagnose the malignancy of a liver tumour [32]. PET has low sensitivity to detect lymph node involvement, metastasis and hepatocellular carcinoma. In that case, sensitivity of PET varies between 50% and 55%, sensitivity is 100% for sonography and varies between 78% and 90% for CT [32].

PET could play a role to differentiate between focal nodular hyperplasia and metastasis if the positive PET investigation is completed with a CT, MRI and biopsy, or surgery but there is still no evidence (1 study with 16 patients) [32]. The role of PET in detecting liver metastases has been reviewed together with colorectal cancer (staging: level 2, recurrence detection: level 4).

In one study, PET investigation has shown a good sensitivity (24/26 patients) for early detection in case of primary sclerosing cholangitis by patients with a high risk of cholangiocarcinoma (7% to 10% of patients - [148]) [32].

Liver tumour - Key Message

For diagnosing malignancy of a liver tumour, clinical evidence does not support the use of PET (level 2 against the use of PET).

5.11. CERVICAL CANCER

Material reviewed: HTA reports and Systematic Reviews

5.11.1. Staging

The spread of cervical cancer is an important factor to decide which treatment is the most appropriate and to assess the prognosis of the patient. The conventional imaging techniques give bad results for the initial staging of the tumour [32].

PET seems to give better results than CT allowing a reduction of the radiotherapy fields [32 140 90]. Indeed, extended field radiotherapy leading to increased morbidity is necessary in patients treated with curative intent. If PET were able to detect para-aortic nodes involvement, it could appropriately define which patients will benefit from radiotherapy and which ones will have no need of such a therapy. Also, by defining the spread of disease, PET will be able to orientate patients to curative or palliative treatment [140 90].

For staging, PET has a sensitivity of 57% to 100% and a specificity of 83% to100%. In comparison, classical imaging techniques exhibit the following values: 0% to 73% for sensitivity, 0% to 100% for specificity [32 140 90]. In assessment of nodal involvement, PET has a lower sensitivity for the detection of para-aortic nodes when compared with its ability to detect pelvic nodes [140].

However, there is no evidence of any advantage using PET in the detection of microscopic metastases [140 32]. The progression-free survival has been studied: 18% of patients with a negative CT but a positive PET for aortic lymph nodes have a 2-year progression-free survival, compared with 64% of patients in case of PET negative and CT negative, and 14% in case of PET and CT positive [90]. However, in one study patients with PET positive lymph nodes have better overall and progression-free survival at 2.5 years, indicating a potential treatment bias. Para-aortic radiation therapy indeed was given to 7 of 7 patients with positive nodes by CT, to only 4 of 14 of those with positive nodes only on PET [90].

5.11.2. Residual mass evaluation and recurrence

PET has been evaluated for residual mass evaluation after treatment although it is difficult to compare with a good standard because surgery is generally preceded by radio-chemotherapy and there is a non specific FDG uptake by the urinary tract[32, 90]. For that indication, PET has a sensitivity of 100%, a specificity of 60% [90 32]. The 2 year progression-free survival was 40% among patients with positive PET following treatment compared to 86% for patients with negative PET [90].

Early detection of a recurrence has the potential to improve survival (AHRQ 2004). In the diagnosis of recurrence, PET has sensitivity between 90% and 100%, and specificity between 0% to 77%, compared with 48% to 77% and 83% to 85% for CT [32, 90]. All HTA agencies which have evaluated this indications conclude that there is not enough evidence so far to propose cervical cancer as a indication for PET[32, 90 140].

Table 26: Table for evidence for cervical cancer

Type of cancer	Cancer management decision	Source and search period	Evidence	Diagnostic efficacy
Cervical cancer	Staging I	HTA-FNCLCC 1991-10/2002	8 studies (4 retrospective and 4 prospective with N = 112 patients) Se = 57% - 100% and Sp = 83% - 100% for PET Se = 57% and Sp = 100% for CT (1study) Se = 50% - 73% and Sp = 83% for IRM (2 studies) Reference standard: pathology and follow up	Level 2
Cervical cancer	Staging II	HTA-MSAC 03/2001	4 studies N = 115 patients (already in the FNCLCC report) Para-aortic nodes: 59 patients in average, Averaged Se = 67%; Sp = 95%; PPV = 83%; NPV = 80% Pelvic nodes: 41 patients in average Averaged Se = 91%; Sp = 94%; PPV = 95%; NPV = 89% Reference standard: pathology	Level 2
Cervical cancer	Staging III	HTA-AHRQ 2004 Up to April 03	8 studies N = 342 patients For lymph nodes : Se = 70% - 100% and Sp = 92% - 100% for PET Se = 0% – 73% and Sp = 0% – 100% for classical imagery 2 years progression free survival in case of PET + and CT +: 14% , in case of PET – and CT +: 18%, in case of PET– AND CT- : 64% Reference standard: pathology in 4 studies, follow up in 2 studies, both in 2 studies	Level 2
Cervical cancer	Residual mass after treatment	HTA-FNCLCC 1991-10/2002 AND HTA-AHRQ 2004 Up to April 03	2 studies N = 96 patients Se = 100% and Sp = 60% PET result is the most significant survival factor: 40% if PET +, 86% if PET – Reference standard: not stated	Level 2 but lack of studies
Cervical cancer	Recurrence diagnosis	HTA - AHRQ 2004 Up to April 063 AND HTA-FNCLCC 1991-10/2002	4 studies N = 353 patients Se = 90% - 100% and Sp = 0% – 77% for PET If local recurrence: Se = 86% Sp = 83%, if pelvic recurrence: Se = 100%, Sp = 75% and, if distant metastasis: Se = 100% and Sp = 100% for Pet (1 study) Se = 48% - 77% and Sp = 83% - 85% for CT (2 studies) Reference standard: pathology and follow up	Level 2

Cervical cancer - Key Message

- **For staging, residual mass evaluation and recurrence diagnosis of cervical cancer, there is evidence of diagnostic accuracy including the determination of sensitivity and specificity (level 2).**
- **For recurrence diagnosis, there is inconclusive evidence that PET is superior to CT, because the specificity of PET is low compared with CT.**

5.12. OVARIAN CANCER

Material reviewed: HTA reports and Systematic Reviews

5.12.1. Primitive tumour diagnosis and staging

The role of PET in diagnosis ovarian primitive tumour remains uncertain because the few studies treating that subject are inconclusive or exhibit great variability of results. The sensitivity of PET varies from 58% to 100% and the specificity from 67% to 80% [140, 32].

The initial staging of an ovarian cancer is frequently determined during surgery because classical imaging techniques are not useful. The diagnosis of recurrence, suspected in case of serum tumour marker elevation (CA 125), needs a second look laparotomy to get confirmation. However, 10% of women with advanced cancer have no CA 125 elevation [140 32 90]. Therefore, it is theoretically sound to test PET investigation in order to get a good staging without surgical intervention[140 32 90]. For staging, the sensitivity of PET is 72% and the specificity is 92% for lymph nodes detection and respectively 71% and 100% for peritoneal carcinomatosis detection. Anyway, these results are presented on the basis of only one study [140]. The literature search done by the AHRQ in 2004 did not show any new study for that indication [90].

5.12.2. Diagnosis of recurrence

For diagnosis of recurrence, the sensitivity of PET varies between 18% and 100% with a specificity of 45% to 100%, compared to classical imaging (CT or MRI) with a sensitivity of 55% to 91% and a specificity of 46% to 100%, or to CA 125 serum tumour marker with a sensitivity of 75% to 91% and specificity of 77% to 100% [140 32 90]. Among patients who are clinically free of disease, the sensitivity and specificity of PET are 67% and 89%, compared with 67% to 94% and 89% when there is clinical suspicion of recurrence [90]. If PET investigation is made after classical imaging, the global sensitivity and specificity are 92% and 100% respectively [32, 90]. Anyway, microscopic lesions often escape PET detection: for peritoneal carcinomatosis, the sensitivity of PET is 44% [32, 90].

The use of PET has been proposed in the assessment of treatment response, as measured by CA 125 in 2 studies but there is no evidence to support this point[140, 90].

The MSAC HTA report concluded that there were neither studies of the impact of PET on clinical management nor on patient outcomes. The apparent improved diagnostic accuracy of PET over conventional imaging in detecting recurrent cancer was based on small numbers of patients with differences in test performance and may not be statistically significant [140]. The conclusion of FNCLCC and AHRQ HTA reports is that evidence is insufficient to recommend the use of PET in ovarian cancer. However, the AHRQ stated that there is fair evidence to support the use of PET for the detection of recurrent ovarian cancer when the CA 125 is elevated and classical imaging is negative or equivocal [32, 90]. In any case, further studies are needed [140 32 90].

Table 27: Table of evidence for ovarian cancer

Type of cancer	Cancer management decision	Source and search period	Evidence	Diagnostic efficacy
Ovarian cancer	Diagnosis of primitive tumour	FNCLCC 1991-10/2002	3 prospective studies N = 49 patients Se = 58 % – 100%, Sp = 67% - 80%, PVV = 28% - 82%, NPV = 92% - 100% Reference standard: pathology and follow up	Level 2 Few studies great variability
Ovarian cancer	Diagnosis of primitive tumour	MSAC 03/2001	2 studies N = 109 patients Se = 58% - 100%; Sp = 67% - 80% for PET Se = 100%, Sp = 67%, PPV = 80%, NPV = 100% for CT (1 study) Se = 92%, Sp = 60%, PPV = 23%, NPV = 98% for US (1 study) Se = 83% - 100%; Sp = 84% - 100%; PPV = 42% - 100%; NPV = 97% - 100% for MRI (2 studies) Reference standard: pathology and follow up	Level 2 Few studies
Ovarian cancer	Staging	MSAC 03/2001	1 prospective study N= 14 patients For lymph nodes: Se = 72%, Sp = 92%, PPV = 80%, NPV = 89% For peritoneal carcinomatosis: Se = 71%, Sp = 100%, PPV = 100%, NPV = 76% Reference standard: pathology and follow up	Level <2 Only 1 study with few patients
Ovarian cancer	Recurrence diagnosis	FNCLCC 1991-10/2002	13 prospective studies, 2 retrospective N = 362 patients Se = 55% - 100% ; Sp = 50% - 100% ; PPV = 89% - 100% ; NPV = 17% - 100% for PET Se = 55% - 100%; Sp = 46% - 100%; PPV = 90% - 92%; NPV = 92% for classical imagery Se = 95% and Sp = 77% for CA 125 (1 study) Reference standard: pathology and follow up	Level 2
Ovarian cancer	Recurrence diagnosis	MSAC 03/2001	6 studies (1 retro and 5 prospective) N = 132 Se = 55% - 100%; Sp = 50% – 100%; PPV = 17% - 100%; NPV = 54% - 90% for PET Se = 40% - 82%; Sp = 50% - 53%; PPV = 67% - 77%; NPV = 25% - 62% for CT (2 studies) Se = 86%, Sp = 100%, PPV = 100%, NPV = 67% for MRI (1study) Reference standard: pathology and follow up.	Level 2
Ovarian cancer	Recurrence diagnosis	AHRQ 2004 Up to April 03	8 studies (3 prospective, 2 retrospective) N = 221 patients Se = 18% - 95%; Sp = 45% - 100% for PET Se = 65% - 67%; Sp = 71% - 89% if diagnosis not suspected before PET (2 studies) Se = 55% - 100%; Sp = 46% - 90% for Classical imagery (4 studies) Se = 92% - 100%; Sp = 90% - 100% for PET+CT (2 studies) Se = 75% - 91%; Sp = 77% - 100% for CA 125 (2 studies) Reference standard: pathology and/or follow up	Level 2

Ovarian cancer - Key Messages

- **For diagnosis, there is evidence of diagnostic accuracy including the determination of sensitivity and specificity (level 2).**
- **For initial staging, there is no evidence.**
- **For diagnosis of recurrence, there is evidence of diagnostic accuracy including the determination of sensitivity and specificity (level 2).**
- **For evaluation of treatment response, there is no evidence.**

5.13. RENAL CANCER

Material reviewed: HTA reports and Systematic Reviews

There are few studies on PET and renal tumour. PET investigation could be useful to detect recurrences and metastases in case of symptoms like pain or if standard imaging techniques are unclear[32]. Until now, PET utility in the initial diagnosis of renal cancers has not been shown, but a recent study has concluded that images taken 3 hours after injection could help in diagnosing primary renal cancer in case of inconclusive CT or in inoperable patients [32]. Also, following surgery, PET could be useful in the detection of metastases in patients at risk of dissemination (tumour aggressiveness assessed by histology or loco-regional extension). The reference standard used in the studies is not stated in the HTA report. [32].

Table 28: Table of evidence for renal cancer

Type of cancer	Cancer management decision	Source and search period	Evidence	Diagnostic efficacy
Renal	Diagnosis of primitive tumour	HTA-FNCLCC 1991-10/2002	6 studies n = 110 tumours Se = 47% - 100% and Sp = 0% – 100% Great variability among studies	Level 2
Renal	Staging	HTA-FNCLCC 1991-10/2002	4 studies Se = 89% and Sp =100%	Level 2
Renal	Recurrence	HTA-FNCLCC 1991-10/2002	2 studies for locoregional recurrences : inconclusive 4 studies for metastatic recurrences : inconclusive	Level <2

Remark: Some evidence presented in this table is insufficient to reach a level 2. However, there is more than technical efficacy in these studies. That is the reason why we decided to give a <2 level.

Renal cancer- Key Messages

- **For initial diagnosis and detection of recurrence, there is a lack of evidence for diagnostic accuracy.**
- **For staging, there is evidence of diagnostic accuracy including the determination of sensitivity and specificity (level 2).**

5.14. TESTICULAR CANCER

Material reviewed: HTA reports and Systematic Reviews

Testicular cancer occurs in young people and has a good prognosis if correctly treated. Therefore it is important to get a good initial staging of the tumour in order to provide the right treatment without excessive aggressiveness because the treatment side effects could dramatically affect these young men [32]. Also, the residual mass detection after therapy is important because in case of active residual mass, it would be possible to surgically resect the tumour with complete remission. In both cases often classical imaging does not offer conclusive indications and this is the reason why PET has been studied [32 90].

Finally, in case of elevated serum tumour markers, PET could play a role as CT is not able to detect tumour smaller than 1 cm [90]. However, it is quite clear that there is no utility of PET in the initial diagnosis of testicular tumour, because physiologic uptake of FDG in testicular tissue is high [32].

5.14.1. Initial staging

Due to the difficulties for classical imaging techniques to evaluate small volume metastasis, every patient receives chemotherapy or radiotherapy (or retroperitoneal lymph nodes resection) but this is not needed in 70% of patients with non germ cell tumour and in 80% of patients with germ cell tumour. Nevertheless, the sensitivity of PET between 70% and 90% with specificity between 94% and 100% is not high enough to diminish the value of adjuvant therapies in case of negative results. Indeed the risk of a false negative result for nodes smaller than 1 cm is too high [32 90].

5.14.2. Residual mass evaluation after chemotherapy

There are few studies on the role of PET in residual mass evaluation. These studies show that PET is better than CT for that indication, with sensitivity 59% to 89%, specificity 92% to 100% for PET, 26% to 55% and 86% to 100% for CT, 42% and 100% for serum tumour markers [32, 90]. PET distinguishes between an active tumour (15% – 20% of cases) and a mature or immature teratoma (30% – 40%) or necrosis and/or fibrosis lesion (40% – 50%), but not between mature teratoma and necrosis and/or fibrosis lesion [32, 90]. For non-seminomatous germ cell, PET is useful to identify a residual mass too big to be resected. In the other cases, PET will probably not change patient management. For seminoma > 3 cms, all patients with a positive PET need a surgical exploration and if < 3cms, CT is enough because the prognosis of patients is good (External Experts Group).

5.14.3. Occult recurrence diagnosis

In case of elevation of serum tumour markers, PET can be used to diagnose a recurrence; the classical imaging techniques are not helpful. The sensitivity and specificity were 82% and 88% for PET, 55% and 0% for CT, 100% and 0% for serum tumour markers. In case of normal CT, the sensitivity and specificity of PET are 73% and 88% [90].

5.14.4. Prediction of therapeutic response

On the basis of a single study, sensitivity, specificity, positive predictive value and negative predictive value of PET, compared with CT and/or MRI, with serum tumour markers and the two last combined together are as presented in Table 29.

Table 29: Sensitivity and specificity of PET, classical imagery and markers

	Sensitivity	Specificity	PPV	NPV
PET	100%	78%	88%	100%
CT/MRI	43%	88%	86%	47%
Markers	15%	100%	100%	47%
CT/MRI + Markers	38%	100%	100%	47%

These findings need to be confirmed by more studies [32]. Another study finds that, based on PET findings, 57% of patients had a change in management [90].

Table 30: Table of evidence for testicular cancer

Type of cancer	Cancer management decision	Source and search period	Evidence	Diagnostic efficacy
Testicular	Staging	HTA - FNCLCC 1991-10/2002 and AHRQ 2004 Up to April 03	3 studies N = 118 patients + 1 study 23 patients (AHRQ) Se = 70% - 90% and Sp = 94% - 100% for PET Se = 40% - 60% and Sp = 78% -100% for CT (2studies) Reference standard: pathology and follow up	Level 2
Testicular	Residual mass detection	HTA - FNCLCC 1991-10/2002 and HTA - AHRQ 2004 Up to April 03	6 studies N = 177 patients + 1 study 29 patients (AHRQ) Se = 59% - 89% and Sp = 92% - 100% for PET (3studies, 107 patients) Se = 26% - 55% and Sp = 86% for CT (2 study, 75patients) Se = 42% and Sp = 100% for tumour markers (1 study, 45 patients) If teratoma considered as false negative: Se = 16% - 67% and Sp = 90% - 100% (3 studies, 84 patients) If teratoma considered as true negative: Se = 75% - 100% and Sp = 77% - 100% (3 studies, 66 patients) After salvage chemotherapy: Se = 0% and Sp = 80% for PET, Se = 50% and Sp = 100% for CT (1 study 29 patients) Reference standard: pathology and follow up	Level 2
Testicular	Occult recurrence diagnosis	HTA - AHRQ 2004 Up to April 2003	1 study N = 55 patients Se = 89%, Sp = 95% for PET; Se = 100%, Sp = 0% for CT; Se = 62%, Sp = 95% for tumour markers in case of residual mass (47 patients) If elevated tumour markers, Se = 82% and Sp = 88% for PET, Se = 55% and Sp = 0% for CT, Se = 100% and Sp = 0% for tumour markers (41 patients) If elevated markers but normal CT, Se = 73% and Sp = 88% for PET Reference standard: pathology and follow up	Level 2 But lack of studies
Testicular	Prediction of therapeutic response	HTA- FNCLCC 1991-10/2002	1 study N = 23 patients Se = 100%, Sp = 78%, PPV = 88%, NPV = 100% for PET Se = 43%, Sp = 88%, PPV = 86%, NPV= 47% for CT Se = 15%, Sp = 100%, PPV = 100%, NPV = 42% for tumour markers Se = 38%, Sp = 100%, PPV = 100%, NPV = 47% for markers and classical imagery	Level 2 But lack of studies

			Reference standard: pathology and follow up	

Testicular cancer - Key Messages

- **For staging and residual mass detection, there is evidence of diagnostic accuracy including the determination of sensitivity and specificity (level 2).**
- **For therapeutic response and detection of occult recurrence, there is a lack of evidence for the use of PET.**

5.15. GASTROINTESTINAL STROMAL TUMOURS

Material reviewed: HTA reports and primary studies.

The sensitivity of PET for detecting gastrointestinal stromal tumours depends on the growth of the tumour: FDG uptake is better than scintigraphy for aggressive tumours. However, these results are based on 4 studies only with few patients [32]. More studies are needed to confirm these results. For that reason, we rated the diagnostic efficacy at level 1.

On basis of five primary studies, added by the External Experts Group, PET could have a role to play in the evaluation of the response of gastrointestinal stromal tumours after treatment with Imatinib Mesylate [149] [150] [151] [152] [153].

Table 31 : Table of evidence for Gastrointestinal Stromal Tumour

Type of cancer	Cancer management decision	Source and search period	Evidence	Diagnostic efficacy
Gastro intestinal Stromal Tumour	Diagnosis	HTA - FNCLCC 1991-10/2002	4 studies (n=16 patients for 1 study, n =7 tumours for a second one and n=19 tumours for a third one) Se = 14% – 100%	Level 2

Table 32: Gastrointestinal Stromal Tumour – Primary studies

Type of cancer	Cancer management decision	Source and search period	Evidence	Diagnostic efficacy
Gastro intestinal Stromal Tumour	Therapy monitoring I (Imatinib Mesylate)	Gayed et al J Nucl Med 2004; 45: 17-21	N=54 patients Se = 86% and PPV=98% for PET, Se = 93% and PPV = 100% for CT but difference not stat. significant PET predicts response to therapy earlier than CT in 22.5% of patients	Level 3
Gastro intestinal Stromal Tumour	Therapy monitoring II (Imatinib Mesylate)	Jager et al Nuclear Med Comm 2004; 25:433-438	N = 16 consecutive patients with irresectable or metastasized GIST Separation between PET responders and non responders after 1 week treatment matched almost perfectly with overall treatment response (prediction sensitivity 93%) and progression free survival (median 8 months) was better in patients with PET response	Level 3
Gastro intestinal Stromal Tumour	Therapy monitoring III (Imatinib Mesylate)	Antoch et al J Nucl med 2004; 45:357-365	N = 20 patients with proven GIST Detection of lesions: 135 with PET, 249 with CT, 279 side by side and 282 on fused PET/CT Accuracy of tumour response diagnosis at 1, 3 and 6 months: 85% of patients for PET at 1 month, 100% at 3 and 6 months 44% for CT at 1 month, 60% at 3months and 57% at 6 months	Level 2
Gastro intestinal Stromal Tumour	Therapy monitoring IV (Imatinib Mesylate)	Choi et al AJR 2004; 183:1619-1628	N = 36 patients, retrospective 70% of patients showing response on PET exhibited at least a partial response but PET cannot be used in patients with baseline negative PET.	Level 2
Gastro intestinal Stromal Tumour	Therapy monitoring V (Imatinib Mesylate)	Goerres et al Eur J Nucl Med Mol Imaging 2005; 32:153-162	N = 28 patients, prospective CT detect more lesions than PET (66 lesions with PET, 96 lesions with CT). A post treatment PET without FDG uptake was predictive of better overall survival and longer time to progression. In contrast, CT was not suitable for prognosis after treatment.	Level 3

Gastrointestinal stromal tumour - Key Messages

- **For diagnosis, there is no evidence for the use of PET.**
- **For therapy monitoring, there is evidence of diagnostic efficacy up to the level of diagnostic thinking based on the distinction between treatment responders and non responders (level 3) and a potential impact of PET on therapy planning but more studies are needed. However, it must be kept in mind that this is a rare disease.**

5.16. OTHER TUMOURS

Material reviewed: HTA reports and Systematic Reviews

The following tumours have a low evidence level on basis of HTA reports and Systematic Reviews: salivary glands cancer, non melanoma skin cancer, gastric cancer, endometrial and vaginal cancer, prostate cancer, bladder cancer, myeloma and sarcoma. These cancers will not be presented in further detail.

6. PET IN CARDIOLOGY

Material reviewed: HTA reports and primary studies.

The use of radiopharmaceuticals in cardiology is not new. Technetium or Thallium scintigraphy is a classical diagnosis too I[107, 33, 84].

PET has also been used with other radiopharmaceuticals in cardiology and various studies have demonstrated its efficacy [107]. In this section, the statement that 'PET' implies 'FDG-PET' holds true. When other tracers are used, they will be mentioned.

6.1. PERFUSION OF MYOCARDIUM

For myocardium perfusion evaluation, products with short half life time are used (^{83}Rb: T1/2 = 76 sec, ^{15}O: T1/2 = 2 min, ^{13}N: T1/2 = 10 min, ^{11}C: T1/2 = 20 min) and therefore a cyclotron must be just beside the examination location [84]. An HTA report comparing PET and SPECT in ischemic disease diagnosis has found sensitivity between 53% and 76% for SPECT and between 85% and 93% for PET (ECRI in Agencia de Evaluacion de Tecnologias, 1995 [154]). Another one comparing angiography and either ^{83}Rb PET (sensitivity between 76% and 95% and specificity between 86% and 100%) or ^{13}N (sensitivity between 94% and 98%, specificity between 93% and 100%) insisted on the selection bias of the primary studies (AHCPR in Agencia de Evaluacion de Tecnologias, 1995 [154]). The added value of PET compared to classical techniques (coronary angiography, scintigraphy) is still not clear [107 84].

6.2. MYOCARDIAL VIABILITY

6.2.1. Diagnostic effectiveness

The study of myocardial viability for patients with ischemic disease is important. Indeed, the success of a revascularization will depend on the myocardial viability [84]. In that goal, the use of PET with FDG could be interesting because a maintained or increased uptake in an area with reduced perfusion could indicate reversible ischemia, and conversely, reduced FDG uptake in an area with reduced perfusion could indicate irreversible ischemia [33].

Among the studies on PET and myocardial viability, the sensitivity of PET varies between 71% and 100%, the specificity between 33% and 91%, the positive predictive value from 46% to 88% and the negative predictive value from 66% to 96% [84 107, 33]. An important issue is the added value of PET to what would be known from previous investigation. The Australians have compared PET with SPECT for that indication in their HTA report, with the following results:

	SPECT	PET
Sensitivity	86%	90%
Specificity	47%	74%
Positive predictive value	72%	83%
Negative predictive value	70%	84%

After searching for head to head comparisons between both techniques, 2 studies demonstrated a change in patient management after PET in 50% of patients (from transplant workup to revascularisation in 7/11 patients, from medical therapy to revascularisation in 8/18 patients and from revascularisation to medical therapy in16/38 patients). However, these 2 studies had unclear selection processes. This report concluded that the concordance between SPECT and PET for myocardial viability is good and that the outcome of revascularisation after positive PET but negative SPECT is not clear [83]. The performance of FDG PET compared to other imaging techniques is presented in Table 33.

Table 33: Performance of FDG PET and other techniques

	N	Se	(95 %CI)	Sp	(95%CI)
^{99}Tc SPECT	207	83%	(77-89)	69%	(63-74)
Dobutamine Echo	448	84%	(82-86)	81%	(79-84)
Thallium reinjection	209	86%	(83-89)	47%	(43-51)
FDG PET	332	88%	(84-91)	73%	(69-77)
Thallium rest redistribution	145	90%	(87-93)	54%	(49-60)

The impact of these differences on the clinical management of the patient is, however, not known [107]. A "class A" quality, randomized controlled, double blinded clinical trial of 103 patients with left ventricular dysfunction, considered for revascularization, compared ^{13}N PET, FDG-PET and ^{99}Tc-SPECT in order to determine the best management strategy (PTCA, CABG, medical therapy). There were no differences between PET and SPECT in assessing the viability of myocardium, in the therapeutic decision choice and in cardiac event-free survival. Unfortunately, the generalisation of this study to the spectrum of patients of most interest is hampered because the patients of this study had a relatively high functional status. However, the good qualities of this study raise doubt about the utility of PET compared to other techniques [107].

Further large scale, multi-centre investigations studying a higher evidence level are necessary to assess the role of PET for ischemic heart disease[83, 107 33].

Table 34: Table of evidence for myocardial viability

Management decision	Source and search period	Evidence	Diagnostic efficacy
Myocardial viability diagnosis I	HTA- DACEHTA 2001 From 1999 to 6/2001	14 articles (13 with selection bias, 13 without control group, 6 without blinding) n = 415 patients (from 14 to 48) Se = 71% to 90% and Sp = 64% to 84% PPV = 46% to 85% and NPV = 66% to 96%	Level 2
Myocardial viability diagnosis II	HTA- ICES 2001 Until December 2000	17 articles (7 already in DACEHTA report, patients with generally mild to moderate left ventricular dysfunction) n = 661 (from 11 to 193) Se = 71% to 100%, Sp = 33% to 91% 1 RCT on patients best management strategy	Level 3
Myocardial viability diagnosis II	HTA- MSAC 2000 1996 – 1/2000	133 studies In 2 studies, change in patient management reported for 50% of patients	Level 3

6.2.2. Cost-effectiveness of PET in the assessment of myocardial viability

The evidence on cost-effectiveness of PET for this indication is limited. The AETMIS in Québec built a decision analysis model with two competing strategies: Thallium test alone versus Thallium test + PET [84]. The population is a hypothetical cohort of patients with 30% left ventricular ejection fraction. The costs are tariffs and reimbursements from the Healthcare system perspective except for PET for which they are real costs transmitted by the Association of Nuclear Medicine Physicians. Costs of medical treatment and transplantation, as well as some input probabilities in the model were derived from expert opinions. If the first step is positive (Thallium test in both strategies) the patient is revascularized. If the result is equivocal, the clinical work up determines the myocardial viability (which allows revascularization) in the first strategy, while a PET determines the viability in the second one. If the myocardium is judged non viable, between 60% and 95% of the patients will receive a medical treatment, while the remaining others will be transplanted. The main probabilistic difference between both strategies lies in the myocardial viability probability after equivocal test: between 15% and 50% (from expert opinions) in the first strategy and 50% in the Thallium test + PET one (from literature). The Monte Carlo simulation resulted in a Thallium test + PET incremental costs comprised between CA$ -7,182 (thus cost saving) and CA$ + 687, while the incremental effectiveness was comprised between 2% and 7% (5-year survival probability). Hence, the conclusion is that the strategy Thallium test + PET may be cost-effective to assess myocardial viability, given the hypothetical population. The main weakness of the model is that it does not take into account the rate of false positives from clinical work up (leading to revascularization) and from PET. Similarly, the mortality probability after a revascularization in case of positive clinical decision should not be equal to the mortality probability after a positive PET. False positive patients with a failed revascularization (since their myocardium is not viable) should be able to receive a medical treatment or a transplant afterwards in the model. In this case, the complete costs of transplantation should be computed (ignoring organ acquisition and organizational costs in the transplantation process costs would only improve further the ICER of the strategy with PET in the present model).

Cardiology - Key Messages

- For myocardial perfusion evaluation, there is no evidence.
- For myocardial viability, there is evidence of diagnostic efficacy up to diagnostic thinking to select the patients eligible for revascularisation (level 3). The total number of patients for this indication is limited.

7. PET IN NEUROLOGY

7.1. ALZHEIMER DISEASE AND OTHER DEMENTIA

Material reviewed: HTA reports and primary studies.

Alzheimer Disease (AD) is an age-related degenerative disease of the brain, primarily occurring after age 60 and is characterized by the insidious onset of dementia. Impairment of memory, judgment, attention span, and problem solving skills are followed by severe apraxias and a global loss of cognitive abilities. AD is pathologically marked by severe cortical atrophy and the triad of senile plaques, neurofibrillary tangles and neutrophil threads [155]. Causes and pathophysiology of AD remain incompletely understood.

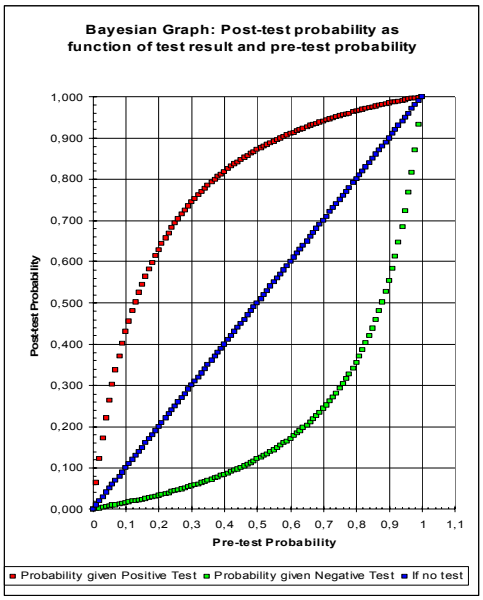
As more people are getting older, AD is also expected to become more prevalent. Diagnosing a condition like AD early in the disease process is critical only when treatments are available with a proven effectiveness on outcomes that truly matter. Recently, the true effectiveness of commonly used pharmacological treatments (i.e. cholinesterase inhibitors) has been questioned. With these agents, some short-term effects on intermediate endpoints may be observed [156] [157] [158] but there are no established effects on more essential endpoints such as delayed institutionalisation, disease progression and mortality [159] [160, 161]. Based on the lack of effectiveness of these drugs, NICE has recently recommended their withdrawal from the UK market [162].

A potential usefulness of PET in the early diagnosis of AD may be related to its ability to demonstrate a reduced glucose metabolism in certain areas of the brain i.e. the medial temporal cortex, posterior cingulated and temporo-parietal cortices (the basal nuclei of Meynert are more difficult to visualize) [33].

Several HTA reports and systematic reviews assessed the role of PET in the diagnosis of AD and in the differentiation of AD from other forms of dementia. Among these evaluations, the AHRQ report is not only the most recent but also the most complete one on this issue [163].

In this report, for mild to moderate dementia, 15 case-control studies have been selected to evaluate the role of PET in the diagnosis of AD compared to normal subjects [164]. The sensitivity of PET varies from 75% to 100% and the specificity varies from 17% to 100% (the number of subjects per study varies from 21 to 91) [164]. Globally, on the basis of a sROC curve, a pooled sensitivity was estimated for PET at 88% (95%CI: 79% to 94%) and a pooled specificity at 87% (95% CI: 77% - 93%)[164]. The graph of pre-test/post test probability is presented in Figure 10 [76].

Figure 10: Pretest/Post test probabilities of AD



In diagnosing AD among other forms of dementia, the sensitivity of PET varies from 86% to 95% and its specificity from 61% to 73%, on the basis of 3 studies [164].

For mild cognitive impairment, 2 studies only evaluate the role of PET. The sensitivity varies from 79% to 100% [164]. The conclusion of the AHRQ is that for patients with dementia, treatment without further testing is superior to treating based on additional test using PET, since treatment is viewed, at best, as moderately effective and relatively benign. In case of possible extrapolation of the effect of treatment, if any, for mild cognitive impairment patients, then the same conclusion is true[164]. The update of 2004 added 1 study on diagnosis of AD from Parkinson dementia and 2 studies on progression of disease, but with small sample (n = 38, n = 20) and 1 retrospective study on progression of disease but showing no statistically difference compared with clinical work up [163].

The HTA report of the DACEHTA selected 7 studies and the Veteran Administration HTA report (USA 1996) selected 7 studies too on the role of PET in AD diagnosis. All are already included in the AHRQ report [33 165]. The AETS report (Spain 1999) selected 8 studies, among which 2 are included in the AHRQ report, 3 are technical reports (evidence level 1) and 3 are different from AHRQ report with sensitivity from 71% to 100%, and specificity only given by one study of 83% [166]. The conclusions of these 3 agencies are that the use of PET in AD should await the results of further multicenter studies with histopathology as diagnosis standard and the development of more effective treatments [165]. PET cannot be considered as a much more useful tool than the clinical tools available at the present time [166] and, due to selection bias in the primary studies, there is no evidence that PET increases diagnostic accuracy compared with SPECT [33].

Two recent systematic reviews on that subject were selected too. The first one after reviewing HTA reports, guidelines, systematic reviews and primary studies, does not give any new evidence compared with the AHRQ report and concluded that the routine use of PET cannot be recommended in the diagnosis of AD. The existing original literature offers important methodological limitations [159]. The second one, after an extensive systematic review of the literature has not selected new papers compared with the AHRQ report and concluded that specificity and sensitivity are limited by study design and patient characteristics. Therefore, the clinical value of these parameters is uncertain [167].

Table 35: Table of evidence for Alzheimer disease

Type of disease	Management decision	Source and search period	Evidence	Diagnostic efficacy
Alzheimer disease (AD)	Diagnosis I	HTA - AHRQ 2001	Diagnosis AD from normal patients: 15 studies, N = 21 to 91/study Se = 75% - 100% and Sp = 17% - 100% Diagnosis AD from other dementia: 3 studies Se = 86% - 95% and Sp = 61% - 73% Diagnosis of mild cognitive impairment: 2 studies Se = 79% - 100%	Level 2
Alzheimer disease (AD)	Diagnosis II	HTA - DACEHTA (and VHA 1996)	7 studies, all already included in the AHRQ report	Level 2
Alzheimer disease (AD)	Diagnosis III	HTA - AETS 1999	8 studies, 2 already in the AHRQ report, 5 = Technical reports Se = 71% - 100% and Sp = 83% (1 study)	Level 2
Alzheimer disease (AD)	Diagnosis IV	SR - Patwardhan, M.B., et al., 2004	15 studies (n=494, 11 – 97/study) pooled Se = 86% (95%CI 76% -93%) pooled Sp = 86% (95%CI 72% -93%)	Level 2
Alzheimer disease (AD)	Diagnosis V	SR - Carnero-Pardo, C 2003	8 HTA reports, 5 SR, 3 studies for AD prediction (n=306), 2 studies on diferantial diagnosis (n=160). A pooled Se or Sp are not presented. The number of original works available is low and, they offer important methodological limitations	Level 2
Alzheimer disease (AD)	Progression of disease prediction	HTA - AHRQ 2004 (30/04/2004)	3 studies (n = 32, n = 20, n = 167) For PET : Se = 95% (CI 95% 90% -100%), Sp = 79% (CI 95% 66% -92%) For CWU : Se = 77% (CI 95% 66% -87%), Sp = 76% (CI 95% 63% -90%), Difference not statistically significant	Level 2

Alzheimer disease - Key Messages

- **For Alzheimer disease, there is evidence of diagnostic accuracy including the determination of sensitivity and specificity (level 2).**
- **Possible therapeutic consequences are uncertain. The effectiveness of pharmacological treatment of Alzheimer disease, e.g. by cholinesterase inhibitors, is being questioned.**

7.2. BRAIN TUMOUR

7.2.1. Diagnosis

The HTA-AHRQ 2004 report [90], the most recent one on this issue, assessed the diagnostic accuracy of PET in the management of brain tumours. A first question assessed the diagnostic accuracy of PET in the diagnosis of brain cancer more specifically in distinguishing high-grade from low-grade glioma when a tumour is deemed indeterminate by biopsy. On occasion, a biopsy specimen may not provide sufficient tissue to distinguish low-grade tumour (WHO class I or II). This is most likely when the actual tumour class is either II or III. Patients with high-grade tumours are generally treated more aggressively than patients with low-grade tumours. No studies were found on PET performance in clarifying the grade of tumour in patients with indeterminate biopsy. However, 4 studies provided data on patients with definite biopsy grade (Table 36-Diagnosis). These studies evaluated the role of PET in newly identified primary brain tumours in differentiating between grade II and III tumours. Studies were retrieved from January 1966 up to April 2003. The diagnostic reference standards varied across studies and were: histology (2 studies), histology or clinical follow up (1 study), histology or clinical follow up or radiology (1 study). All 4 studies reported hierarchy of diagnostic accuracy level 2 evidence. Estimates of PET sensitivity for high-grade tumour ranged from 69% to 100% and specificity from 57% to 100%. In 1 study on 23 patients, the diagnostic accuracy of PET and MRI were compared. PET sensitivity was equal to MRI sensitivity (69%) but PET specificity was lower than MRI specificity (57% versus 100%).There were important limitations common to all studies. First, none of them specifically evaluated those grade II/III tumours where biopsy histology was indeterminate. Second, none of the studies were blinded to the reader of the gold standard. In addition, cut-points related to interpretation of PET results were not provided in 2 studies but were assumed from the data by the authors of the report. Study design was retrospective in 2 studies and not stated in 2 other studies. The authors conclude that it remains unclear from these results to which degree PET performance for patients with truly indeterminate biopsy results will resemble the reviewed studies [90].

A member of the external experts group noted that the lack of data on the pre-surgical diagnostic accuracy of PET does not mean that biopsy analysis has become obsolete. In case of an indetermined biopsy result, additional efforts to establish a diagnosis should be considered. At the pre-surgical stage of brain tumour evaluation, PET has been applied for other purposes than the distinction between low-grade and high-grade tumour. In particular, PET has been added to MRI for the targeting of brain biopsy [168 169]. PET may improve the diagnostic yield of this procedure but PET/MRI-targeted procedures have not been directly compared to MRI-targeted procedures. At the pre-surgical stage, PET has also been added to MRI in order to better delineate brain tumour area. Delineation is an essential step for the resection of these tumours under imaging-guided neurosurgery (neuronavigation). A study reported on the use of PET in 91 patients (103 consecutive resections) with an infiltrating brain mass lesion with unclear boundaries on MRI imaging. PET images were combined with MRI images in navigation planning for image-guided tumour resection. Study design was not stated. PET was reported to improve tumour delineation and to define a final target contour different from that with MRI alone in 83/103 (80%) procedures. Total resection of the increased PET tracer uptake was achieved in 54/103 (52%) procedures (Pirotte B; article in press). Radiosurgery is an alternative treatment for gliomas and other brain tumours. PET may also modify the planning of

this treatment [170] [171](based on comments, references and studies provided by a member of the external experts group). Currently, in this indication, the use of PET in a multimodality integrated approach is limited to a number of highly specialised neurosurgical centres around the world and as technological developments are continuously evolving, results presented by these centres are likely to be highly dependent on the operator (an experienced team with particular skills in brain imaging and neurosurgery). Therefore, these results may not be generalisable to other settings.

7.2.2. Staging

No HTA-reports or systematic reviews were found on this indication.

7.2.3. Restaging

A second question in the HTA-AHRQ 2004 report [90] adressed the diagnostic accuracy of PET in the restaging of brain cancer i.e. in performing guided lesion biopsy for patients with a recurrent brain tumour and indeterminate MRI, compared with biopsy performed with conventional imaging (Table 36- Restaging II). Glial tumours are frequently heterogeneous. For recurrent tumour, abnormalities may be particularly unevenly distributed since high grade tumours often originate from malignant degeneration of lower grade tumours. By identifying the tissue with the highest metabolic activity, it may be possible to improve the yield of biopsy, decrease the number of biopsies required, and increase the likelihood that the specimen will correctly represent the worst histology. This could improve the appropriateness of therapy. A literature search was performed from January 1966 up to April 2003 but no studies were found on this subject [90].

A member of the external experts group provided comments on the potential use of tracers different from FDG. Amino-acid tracers such as ^{11}C-labeled methionine may be a valuable tool in the detection of recurrence of low grade and high grade gliomas and in revealing evolution from low to high grade. Currently, in this indication, the use of PET in a multimodality integrated approach is limited to a number of highly specialised neurosurgical centres throughout the world and as technological developments are continuously evolving, results presented by these centres are likely to be highly operator dependent (an experienced team with particular skills in brain imaging and neurosurgery). Therefore, these results may not be generalisable to other settings.

A final question in the HTA-AHRQ 2004 report [90] addressed the diagnostic accuracy of PET in the restaging of brain cancer i.e. in distinguishing tumour from radiation necrosis in recurrent brain lesions, compared with conventional imaging (Table 36- Restaging II). Radiation treatment may lead to necrosis. Tissue necrosis can be difficult to distinguish from recurrent malignancy using conventional imaging. The distinction between recurrent malignancy and necrosis can be of clinical importance since uncertainty may lead to biopsy, and because therapy and prognosis are different. Seven studies were retrieved from January 1966 up to April 2003. Five studies reported hierarchy of diagnostic accuracy level 2 evidence. The diagnostic reference standards were histology or clinical follow up. Study design was not stated. With the exception of 1 study with only 1 patient without recurrence and another study performed on a dual (IMT) SPET/PET scanner model, the sensitivity of PET in the context of distinguishing tumour from radiation necrosis appears to be in the range of 76% to 83% with specificity from 50% to 62%. The conclusion that PET may be a valuable modality is tempered by the results of 3 studies in which PET had more comparable characteristics to the more accessible radionuclide studies (SPET/SPECT). Two retrospective chart reviews of poor methodological quality reported some hierarchy 4 evidence. In 1 study, PET did not appear to have an evident advantage over MRI. In a study on 55 patients using a Cox regression model, median survival was associated with age, recurrence number and qualitative assessment of PET. No coefficient estimates were provided, so the extra contribution of PET in predicting survival beyond conventional imaging and clinical information cannot be assessed [90].

The HTA-MSAC 2000 report [83] assessed the value of PET in distinguishing tumour from radiation necrosis in patients with residual or recurrent mass after treatment for malignant glioma. Studies

were searched up to January 2000. The reference standard was histopathology or clinical follow up. A first group of 11 studies examined PET use related to the clinical question. Five studies are included in the HTA-AHRQ 2004 report [90]. The remaining 6 studies all reported hierarchy of diagnostic accuracy level 2 evidence. While 5 studies were represented only in the evidence tables, 1 study has been discussed in detail. In this study, PET was compared to iodomethyltyrosine IMT-SPECT. PET correctly diagnosed 12/19 patients (with concordant results between observers) compared to 18/19 for IMT-SPECT. It was concluded that IMT SPECT was superior to PET in the detection and delineation of tumour. The authors of the report concluded that there is insufficient information to conclude that PET is superior to SPET/SPECT in differentiating radionecrosis from tumour recurrence. A second group of 5 studies examined PET use in grading gliomas. All studies reported hierarchy of diagnostic accuracy level 2 evidence. One study is included in the HTA-AHRQ 2004 report [90]. The studies were of varying methodological quality. Most patients included in the studies were not the patient group of interest; instead of having suspected recurrence, they were often patients at the stage of primary diagnosis with no prior treatment and therefore no radiation necrosis. Therefore the results of these studies are not generalisable to the patient population of interest. The authors of the report suggested that a comprehensive and systematic review on this indication should be conducted [90].

In the HTA-ICES 2001 report [107], with a literature search until December 2001, no studies of sufficient quality were found neither on the subject of distinguishing recurrent glioma from radiation necrosis nor on the subject of the efficacy of PET in radiation treatment planning. The authors concluded that the use of PET in the processes of care for glioma is not established by the literature and remains an experimental question [107].

Table 36: Brain tumour – Diagnosis and Restaging

Type of cancer	Cancer management decision	Source and Search period	Evidence	Diagnostic efficacy
Primary brain cancer	Diagnosis	HTA-AHRQ 2004 up to April 2003	No studies were found on PET in clarifying the grade of tumor for patients with indeterminate biopsy 4 studies with data on patients with definite biopsy grade (n=23-45 per study, total n=136): PET Se =69% - 100% and PET Sp =57% - 100% 1 comparative study with MRI (n=23): PET Se =69% and PET Sp=100% vs MRI Se =69% and MRI Sp=100%	Level 2
Primary brain cancer	Restaging I	HTA-AHRQ 2004 up to April 2003	No evidence	
Primary brain cancer	Restaging II	HTA-AHRQ 2004 up to April 2003	7 studies (n=16-55 patients per study, total n=170) 3 comparative studies on recurrence diagnosis Study1 (n=19): PET Se=80% and PET Sp =50% vs SPECT Se=75% and SPECT Sp=50% Study2 (n=16): PET Se=67% and PET Sp=100% vs TI-SPET Se=100% and TI-SPET Sp=100% Study3 (n=30): PET Se=76% and PETSp=100% vs IMT-SPET Se =70% and IMT-SPET Sp=100% 1 study (n=50), patients with abnormal MRI suggesting recurrence: PET Se=83%, PET Sp=62% In another study (n=55) using a Cox regression model, median survival was associated with age, recurrence number and qualitative assessment of FDG-PET 2 studies reported hierarchy 4 evidence. In 1 study, PET did not appear to have an evident advantage over MRI	Level 2

Brain Tumour - Key Messages

- **For diagnosis, i.e. distinguishing high-grade from low-grade glioma, there is evidence of diagnostic accuracy including the determination of sensitivity and specificity (level 2)**
- **For diagnosis, i.e. biopsy targeting and delineation of lesion for therapy planning, there is some evidence of diagnostic accuracy (level 2)**
- **For restaging, i.e. distinguishing recurrent malignancy from radiation necrosis, there is some evidence of diagnostic accuracy (level 2)**

7.3. EPILEPSY

The HTA-MSAC 2004 report [172] assessed the value of PET in the pre-surgical evaluation of patients with refractory epilepsy where there is no focus with concordant results on usual structural imaging and EEG. The medical literature was searched to identify relevant studies and reviews for the period between 1999 and June 2004, in order to update the previous HTA-MSAC 2000 report [83]. Twelve studies (n=12 to 118 patients; total n=635) were selected for inclusion in the review. All studies were case series (retrospective: 6 studies; unclear design or design not stated: 5 studies).The reference standard was surgical outcome. Due to fundamental limitations in the reference standard (partial verification bias) not all patients with an informative PET may have proceeded to surgery; in studies without additional testing for PET negative patients, an estimation of "true" and "false" negatives is not possible and the results are limited to an estimation of the proportion of patients with a PET-defined seizure focus who have a positive surgical outcome (positive predictive value). Due to these fundamental limitations of the reference standard, this review reports on evidence about the proportion of patients with a lesion localised by PET (diagnostic yield) as well as estimates of the rate of correct localisation achieved by PET. Another possible source of bias, limiting the generalisability of the rates of localisation to the patient group of interest, lies in a possible inappropriate selection of eligible patients (spectrum bias; it was sometimes unclear to what extent prior testing was unhelpful in the patients enrolled and patients may have been included regardless of the PET result). There is no evidence from controlled trials on the effectiveness of PET to proceed to surgery in patients with insufficient results from EEG and MRI. Evidence from case series suggests that PET provides localisation information in some patients (median 70%, range 39-100%), and that some patients (median 67%, range 29-100%) have good post-surgical outcomes after having a PET scan in their pre-surgical work up. The accuracy in this group cannot be estimated due to problems in defining a reference standard. A single study investigating the impact of PET on clinical management suggests that PET is promising in this regard. Any conclusions made by linking the evidence of extra localisation data provided by PET to improved surgical outcomes assume firstly that the efficacy of surgery is equivalent in patients with structural and functional foci, and secondly that PET results in altered management. If, based on current clinical expertise, these assumptions are judged to be reasonable, then it may be concluded that PET provides extra localisation information in some patients with medically refractory epilepsy, in whom MRI and EEG had not been able to localise a seizure focus, and that some of these patients will have good post-surgical seizure control outcomes. There is insufficient evidence to determine the size of this effect.

The HTA-MSAC 2000 report [83] assessed the value of PET in the pre-surgical evaluation of patients with refractory epilepsy, more specifically in patients where no focus was identified on the basis of concordant results on usual structural imaging and EEG. Five studies were retrieved from January 1966 up to January 2000. The number of patients included in these studies ranged from 32 to 67 patients. Usual imaging varied across studies. Study design was retrospective (n=3), prospective (n=1) or unclear (n=1). All studies reported hierarchy of diagnostic accuracy level 2 evidence. The reported sensitivity of PET in these studies is relatively high (76% to 90%). However, a number of problems

arise in the interpretation of these results. The reference standard was based on a combination of tests (including PET) which leads to overestimation of test accuracy. When using the outcome of surgery to estimate test accuracy, only patients with positive PET result are having surgery, resulting in test sensitivity close to 100%. Most studies selected patients who already had undergone surgery and did not report information on patients who underwent pre-surgical work up but were not operated on and who may have had a negative result if they had had a PET scan. The result of this omission is that the true negatives are missing from the diagnostic accuracy equation. Nevertheless, the authors of the report stated that it was reasonable to conclude that a subset of patients who would be helped by surgery will benefit as a result of a positive PET scan. It is unclear how much PET would be helpful in all patients with refractory epilepsy [83].

The HTA-DACEHTA 2001 report [117] also assessed the value of PET in the pre-surgical evaluation of patients with refractory epilepsy. Eight studies were retrieved from January 1966 up to May 2001. Study sizes were not reported. All studies reported hierarchy of diagnostic accuracy level 2 evidence. The reference standard was not stated. None of the studies were included in the HTA-MSAC 2000 report [83]. Most studies were performed on children and had no control groups. The diagnostic accuracy of PET ranged from 15% to 95% with a concordance between PET, SPECT and MRI of approximately 65%. Results of a comparative retrospective study in children were discussed. Fifty-six children on whom inter-ictal PET was performed were compared with a control group of 44 children without inter-ictal PET. There were no differences between both groups in age distribution, therapy and outcome of therapy. The hypo-metabolic area demonstrated on PET was consistent only with ictal recordings in 2/13 children and there was general poor correlation between PET and ictal EEG. The authors of the report concluded that results are still too preliminary and too few to give an overall picture of the diagnostic value of PET for epilepsy. There appears to be no evidence that PET can replace perfusion investigations with SPECT, which is much more easily accessible. As the affected patient group in Denmark is relatively small, there appears to be no need for clinical use of PET in assessing the operation indication with uncontrolled complex, partial epilepsy. PET may possibly be a supplement to SPECT after MR scanning and EEG, if the location of the trigger zone is still unresolved.

In the HTA-ICES 2001 report [107], with a literature search until December 2001, 6 "quality grade B" studies were retrieved assessing the use of PET in localizing epileptic foci in the pre-surgical evaluation of intractable epilepsy. In general, these studies had small sample sizes possibly reflecting the small number of patients with intractable epilepsy who undergo pre-surgical evaluation. The reference standard was not stated. The authors stated that PET may have a limited role in the evaluation of patients with intractable epilepsy being considered for neurosurgery. Although PET may have a potential to decrease the need for invasive diagnostic procedures and to facilitate localization of seizure focus, there is a need to compare PET to other non-invasive diagnostic procedures such as EEG, MRI, SPECT and hippocampal formation volumetric assessment (HVMR) in high quality clinical trials. Overall quality of the research evidence is relatively poor and more definite studies are needed.

Epilepsy - Key Message

- **For pre-surgical evaluation of refractory epilepsy, there is some evidence of diagnostic accuracy but the added clinical value of PET is unclear (level 2). However, this is a rare indication.**

7.4. OTHER POTENTIAL INDICATIONS

Other potential indications for the use of PET may include an assessment of fever of unknown origin (FUO), and inflammatory disorders such as chronic osteomyelitis and inflammatory or infectious sequelae following implant-surgery (i.e. hip or knee arthroplasty and spine surgery). On the subjects of the role of PET in FUO, infection or inflammation, neither a HTA report nor a systematic review was found.

In a search for primary studies a search in MEDLINE was performed on 11 July 2005 using the updated version of the Mijnhout strategy for PET (see appendix) combined with the MeSH terms (Fever of Unknown Origin OR Inflammation OR Infection). Two grade B studies were retained.

In the first study the diagnostic accuracy of PET was prospectively assessed for the differentiation between infection and aseptic loosening in total hip replacements in 35 patients suspected of having infected total hip replacements. PET results were compared with three-phase bone scintigraphy and serial conventional radiographs (available in 32 patients). The reference standard consisted of microbiologic examinations of surgical specimens in 26 patients and results of joint aspiration plus clinical follow up of at least 6 months in the remaining 9 patients. Results of PET, conventional radiography and three-phase bone scintigraphy each were interpreted by two independent observers blinded to the results of other imaging studies. It was not stated whether the reference standard was interpreted blinded to imaging results or clinical findings. Nine patients had septic and 21 patients had aseptic loosening. In 5 patients, neither loosening nor infection was confirmed. Sensitivity values for diagnosing infection with PET, conventional radiography and three-phase bone scintigraphy for readers 1 and 2 were respectively 33% and 22%, 89% and 78%, and 56% and 44%, while specificity values were 81% and 85%, 50% and 65%, and 88% and 92% and accuracy values were 69% for both readers, 60% and 69%, and 80% for both readers. PET was more specific (p=0.035) but less sensitive (p=0.016) than conventional radiography for the diagnosis of infection. In this study population, PET performed similarly to three-phase bone scintigraphy. PET was more specific but less sensitive than conventional radiography for the detection of infection. The authors concluded from their results that PET as an imaging modality offers no benefit in addition to three-phase bone scintigraphy in patients with prosthetic joint replacement [173].

In the second study the clinical value of PET was prospectively assessed in 58 consecutive patients with FUO. PET results were compared with results from Ga scintigraphy (available in 40 patients). PET and Ga scintigraphy were used as a second step examination in a three step approach. The reference standard consisted of the final diagnosis. In light of these outcomes, PET and Ga scintigraphy results were retrospectively evaluated for their diagnostic contribution. Twenty-four PET scans (41% of the total number of scans) were considered helpful in the diagnosis in 41% of the patients (a final diagnosis was established in 64% of the patients) and 22 PET scans (38% of the total number) were considered noncontributory. PET scan and Ga scintigraphy were considered helpful in the diagnosis in 35% and 25% of the patients respectively (not statistically significant). The authors conclude that PET compares favourably with Ga scintigraphy for the evaluation of patients with FUO [174].

Other Potential Indications - Key Messages

- A primary study of moderate methodological quality concluded that PET as an imaging modality offers no benefit in addition to three-phase bone scintigraphy in patients with prosthetic hip joint replacement
- From another primary study of moderate methodological quality, it appeared that PET may be useful in the diagnostic work up of patients with fever of unknown origin
- Currently, the evidence is limited and considered too preliminary to support the widespread use of PET in these indications.

8. ORGANISATION AND PLANNING OF PET SERVICES

The development and operation of a PET facility is expensive. The cost of a cyclotron and a PET scanner was £1,469,700 (€ 2,179,423) and £1,285,050 (€ 1,905,605) respectively in the UK in 2003 [175]. The French estimation was €2.3 million for the installation of a single PET scanner in 2001. Operational costs (1800 screenings, excluding transportation of FDG) were estimated at €2 million per year [176]. The prices are dropping. A PET scanner currently costs around € 1 million (personal communication PET industry). This excludes the capital investments, such as buildings and radioprotection, needed to install a PET scanner and/or a cyclotron. The total capital investment is more likely to be around £2 million (€3 million) for one PET scanner.

In the German HTA report of DIMDI, the average costs per FDG dose produced in-house was estimated at € 254 and the average costs of one scan amounted to € 382 (price year 1997 – on average 27.5 patients a week) [177].

The start-up costs of a PET centre include the initial capital outlay for the PET scanner, the cyclotron (if applicable, including a radiochemistry lab), minor equipment, facility construction, regulatory compliance, legal fees and salaries of initial personnel. Several business models are possible for PET facilities: the PET centre can have a full-service in-house cyclotron operation, or it can develop a cyclotron distribution service for other PET centres in case of excess capacity of production of radiopharmaceuticals, or it can purchase its radiopharmaceuticals from a distribution centre [178].

The capacity of a cyclotron exceeds the demand of a single PET centre. Therefore, one cyclotron can in principle furnish multiple PET centres. Transportation to a PET centre implies that an extra amount of FDG production is needed to meet the radioactive decomposition across the distance. Also the possibility to use other radioisotopes such as ^{11}C, ^{13}N or ^{15}O that have a shorter half-lifetime can also have some influence in the decision process of building an in-house cyclotron.

A survey in 10 PET facilities in the US found no cost advantage for facilities that purchase FDG over facilities that manufacture FDG on site [179]. The average cost per PET scan was only slightly lower for the centres that manufacture FDG themselves compared to centres that purchase FDG ($1,885 versus $1,898). The discrepancy in results between this survey and previous analyses may be explained by insufficiently detailed responses to the survey by some centres, which led to an underestimation of the costs of FDG production.

The HTBS modelling demonstrated that the in-house FDG production facility in combination of the sharing of a cancer centre staff was the cheapest option [9]. The estimated cost per scan would then be £677 (€ 1,005), assuming 1500 patients a year. The annual operating costs would be 1 million £ (€1.5 million) and the capital costs £ 4.25 million (€6.3 million). In a German context, collaboration between hospitals with a PET-scanner and satellite suppliers of FDG has proven to be the least costly business model [177].

Likewise, the provision of the radiopharmaceuticals by centralized cyclotrons and purchase by remote PET facilities proved to be the least costly business model in a US environment in 2001. [178]. Under the assumption that a PET scanner would be used for 7 years, about 7 patients can be scanned per day and a dose of radiopharmaceuticals costs $700 (€564), the average total cost of one PET scan was estimated to be $1,602 (€ 1,292). Under the existing reimbursement scheme for PET scans in the US at that time ($2,185-2,301 per scan, depending on the indication), the business model of a dedicated PET with radiopharmaceuticals purchased from a distributing cyclotron centre showed a positive net present value (i.e. the revenues are higher than the costs) over a 7-year period of operation. However, if on average there would be less than 3.45 patients receiving a PET scan per day, the model is no longer profitable [178].

Throughput is a critical factor for the costs of a PET scan. Centres with a larger number of scans per year had lower average unit costs per scan, due to the high fixed costs of the PET equipment and the staff. [179]. For a whole-body scan, 61% of the (in-house) production costs of FDG and 85% of the costs of the scanner itself were considered to be fixed costs in 1999 in a German study [177]. Note that staff is a semi-fixed costs, which means that the economies of scale can only be exploited up to a certain level of volume, after which new staff must be hired to cope with the volume increase.

Potential throughput depends on the frequency of production or delivery of radiopharmaceuticals. A twice daily delivery (or in-house production) of FDG allows a throughput of 1500 to 2000 PET scans a year. Less frequent delivery of FDG leads to PET scanners remaining idle, which induces inefficiency in the use of this equipment.

In this chapter we first briefly discuss the experiences of other countries with the introduction and planning of PET services. The discussion is based on the results of a survey we performed in different countries. Next, the current Belgian situation is described in more detail.

Key messages:

- **PET is an expensive diagnostic technique. The average cost of a PET scan was estimated to be around $ 1,600 (€ 1,300) in the US and around € 1000 in Europe in 2001.**
- **FDG can be manufactured on-site if PET centres have their own cyclotron or purchased from a commercially exploited cyclotron. The supply of radiopharmaceuticals (FDG) needs to be efficient and timely for the efficient use of a PET scanner.**
- **Patient throughput is a critical factor for the cost of a PET-facility.**

8.1. EXPERIENCE IN OTHER COUNTRIES

In June 2005, INAHTA published a draft report on the experiences with PET in member countries. The report was based on the responses of 16 countries on a written survey, first performed in 1999 and updated in 2003/2004. We updated the survey once again in February/March 2005.

The questionnaire was distributed by e-mail to the HTA agencies in the different countries. A reminder was sent to non-responders three weeks after the first mailing. Eleven countries responded, with the UK providing separate answers for Scotland and for England and Wales. The results of the survey are presented in Table 37.

United States (Veterans Affairs)

Until last year, Veterans Affairs (VA) had a moratorium on purchasing additional scanners. Now, VA allows each of the 22 regional Veteran Integrated Service Networks (VISN) to plan and purchase their own scanners without approval from the headquarters.

The initial purchasing decision will be based on current workload projections, inter-facility referral patterns, distance patients must travel, and presence of knowledgeable and willing nuclear medicine staff. Each VISN can add more scanners in the future as workload warrants but they must produce at least 714 studies per year to justify additional purchases. Indications for PET scans are limited to conditions covered by Medicare or approved research.

VISNs can provide PET services either in-house or with mobile, fee, contract or sharing arrangements. Each VISN will make this as a business decision in an effort to maximize access and minimize cost. In-house PET scanners will be placed at medical centres that already serve as tertiary referral centres, as evidenced by, for example, the presence of a Nuclear Medicine Service, Cardiac Catheterization Laboratory and accredited cancer programs.

There are 5 cyclotrons that serve multiple PET centres and all are located very close to VA PET facilities. In the US there is an extensive commercial network of FDG suppliers, so there are no plans to purchase more cyclotrons in the near future.

Canada

In Canada, decisions on public PET scanners are made at the provincial level. There is little information on how the decisions are made but one deciding factor is probably the location of cyclotron facilities (maximum distance of 2 hours from the PET centre). PET radiopharmaceuticals are presently regulated as experimental drugs by the federal goverment (Health Canada) and can only be used in clinical trials sanctioned by Health Canada or under its Special Access Program.

The province of Ontario is currently evaluating PET in 5 clinical trials. The trials are funded by the Ontario government and relate to the use of PET in the staging of resectable and advanced non small cell lung cancer, head and neck cancer, breast cancer and colorectal cancer with liver metatstasis. In addition, a registry is being established to track the use of PET in people with a solitary pulmonary nodule or with suspected recurrent thyroid cancer, germ cell cancer and colorectal cancer characterized by elevated biomarker and negative imaging findings. Finally, PET is also used in other research in the province including cardiac studies at the University of Ottawa Heart Institute. Capital costs relating to PET scanning are paid by hospitals from donated funds.

An Ontario PET Steering Committee is monitoring results of the Ontario trials and research in other jurisdictions, and will provide evidence-based advice to the Ministry of Health and Long-Term Care regarding the introduction of PET as an insured health service.

Spain

The Spanish Public Health System has a limited number of indications for PET approved based on scientific evidence. This can influence the number of scanners in the public (not the private) system. There are 2 companies that deliver FDG. Eight cyclotrons supply multiple PET centres and all are located near the PET centre.

The Netherlands

Until 2000, there was a governmental planning system for PET. This was abandoned in 2002. Now, every institution can buy a PET scanner. Since Dutch hospitals are private institutions, they can decide themselves whether or not they install a PET scanner. Once a reimbursement tariff for a PET scan is fixed by the government, the door is open for additional PET scanners. On July 1, 2004, a tariff was fixed for PET scan in the Netherlands.

Israel

Decisions on the number of PET scanners to be installed in Israel were based on a process involving needs assessment using the registry of cancer incidence rates and expert consultation. It is the Parliament who decides on additional PET s.canners It is planned to review the situation of PET in a few years following experience gained in the field and data collection which is compulsory.

Each centre independently organizes the provision of PET-tracers. There are two cyclotrons in Israel. One cyclotron is located in Jerusalem, in the same hospital as the PET device and the other is located in the Tel Aviv region serving other areas.

France

In 2001, the number of authorisations was 1 PET scanner per million inhabitants. In 2004 this number was updated to 1/800, 000 inhabitants.

Decisions on PET are taken by the French Minister of Health. Several criteria are taken into account:

(1) centres (public or private) must have a nuclear medicine ward;

(2) oncological activity must be important (no precise data on the number of patient per year or number of beds in the ward);

(3) centres must be included in a medical care multidisciplinary network for cancer disease;

(4) registered indications of FDG will probably be extended to other cancer and non oncologic disease (neurology, cardiology) (so medical need will increase).

PET-tracers with a marketing authorisation (only FDG today) have to be provided by industrials who received this authorisation. Other tracers can be produced for research. Twelve cyclotrons supply multiple PET scanners. Most often the cyclotrons are implanted in hospital.

Denmark

The decision on the number of PET/CT scanners is de-centralised in Denmark. Central health authorities have no direct influence on the number of PET/CT scanners taken into use.

The debate in Denmark revolves around the use of better PET/CT scanners instead of gammaPET-scanners, which are then used as 'ordinary' gamma-cameras instead of being closed down. This causes some problems with hospitals that do not have PET/CT scanners but still insist on running their own limited amount of tests.

There are two cyclotrons in Denmark. Both cyclotrons are located at hospitals with scanners. One supplies most of the existing scanners and therefore also sets the price of FDG. The other cyclotron supplies mostly just its own hospital's scanner. Other hospitals are also working to get their own cyclotron. At the moment there is one cyclotron on the way for research purposes only.

Finland

Finland has 4 fixed PET scanners located in on PET centre in Turku and one mobile PET that visits Finland for a few weeks every second week of the month. The need for clinical PET in oncology was based on literature reviews and expert opinion on clinical indications and patient populations. Finland is planning to install new PET scanners in Helsinki (May 2005) and in Tampere (2007).

There are four cyclotrons that supply multiple PET scanners. Three of them are located at Turku and supply the three PETs in the Turku PET centre. There is one commercial cyclotron located in Helsinki that supplies the mobile PET service in Helsinki and Tampere.

UK

As of April 2005 there were about 21 PET scanners in the entire UK, of which 4 were for research purposes only (www-pet.umds.ac.uk/UKPET/)

In Scotland, the HTA report from the Health Technology Assessment Board for Scotland drove the decision on the provision of PET services [9]. The report stipulated that, based on detailed cost-effectiveness calculations and a throughput scenario of 1,500 patient images per machine per year, at least 1 PET scanner was needed in Scotland. The scanner should be linked to a cancer centre. In March 2004 the financial resources were freed for the installation of 3 PET scanners (1 for each of the 3 cancer centres).

There is currently one cyclotron in Scotland, attached to a university PET unit.

In England and Wales there are about 16 PET scanners for 50 million people. The government is heading towards a rate of 1 per million people, following the projected rate in other European countries. The provision of PET-tracers is mixed public/private. There is one authorised manufacturer for FDG who may also set up in Scotland.

Australia

Australia currently has 13 PET scanners, 9 publicly funded and 4 privately funded. Eight cyclotrons serve the 13 PET scanners. Five cyclotrons are located at the PET centres.

In 1999, in response to the increasing interest in PET from physicians and nuclearists and the uncertainty about its clinical and cost effectiveness, the Australian Government conducted a national PET review. The Medical Services Advisory Committee (MSAC) evaluated the scientific evidence base of PET. The review found insufficient evidence to draw definitive conclusions about PET's clinical and

cost-effectiveness, but envisaged that PET is potentially clinically effective and potentially cost-effective and that further evaluation was warranted.

The reviewers recommended an expansion of PET funding to enable further evaluation of the technology. This would require public funding for a total of seven facilities nationally. The funding for these facilities should be dependent upon the facilities' participation in a national PET data collection. The data collection program is intended to provide sufficient evidence to enable the Government to make more long-term decisions regarding the role of PET in Australian clinical practice.

The PET review determined that seven PET facilities was a reasonable number given Australia's population, and the need to balance PET's unproven status with the need to establish a data collection infrastructure of sufficient scope to provide the data for further evaluation of PET. Ultimately, eight facilities were granted public funding to participate in the evaluation. The eight facilities are distributed roughly with Australia's population density.

Sweden

Sweden currently has 7 PET scanners, to be augmented to 10 within 3 years. There are 3 cyclotrons, all located at the PET centres.

Decisions about the planning of PET scanners are made on a regional level, e.g. the Uppsala University Hospital decided they needed an additional PET scanner for research purposes. In Gothenburg a separate needs analysis has been made on the basis of regional conditions.

General findings

Most of the PET scanners in responding countries are in the public sector. A few countries also use mobile PET scanners, but the majority relies on dedicated PET scanners in PET centres. The interest in PET/CT hybrid scanners is growing.

Almost all countries adopt a system of registration or participation in a clinical trial to further assess the clinical utility of PET scan in different indications. These assessments will guide future decisions on PET.

There are on average 0.72 PET scanners per million people available in the surveyed countries. Belgium currently has 1.26 approved PET scanners per million people. Most countries are heading towards a rate of 1 PET scanner per 800,000 people (1.25 scanners per million people).

In terms of the total number of PET scans, Belgium leads with more than 12,000 scans in 2003 (for approved indications only). Australia had the second highest annual throughput, with 8,146 scans in 2003, followed by Canada with 4,700 scans in 2002. It should be noted that both Australia and Canada have a population size of at least twice that of Belgium (Australia has 20 million inhabitants, Canada almost 26 million).[180]

The number of PET scanners per million people is only a rough indicator of the need for PET scanners. The actual need in a country should be estimated on the basis of incidence figures of the different indications for which PET is deemed useful. This will be discussed in the next chapter.

Key Messages

- Belgium still has the highest number of PET scanners per million people and the highest annual number of scans amongst 12 European and non-European countries.
- Most countries are planning additional PET scanners, up till a rate of 0.5 to 1.3 PET scanners per million people in the forthcoming years.

Table 37: Results of the survey on PET in a number of countries

Country	Number of PETs	Number planned or expected (*)	Time frame planned PETs	Stakeholders demand for PETs	Closing PETs	Number of Cyclotrons
Belgium	13 PETs (**1.26 pmp**)					
France	9 PETs, 23 PET-CTs, 23 PET-CT scanners in process of installation for 60 million people (**0.96 pmp**)	1 per 800 000 inhabitants (75 PET or PET-CT scanners authorised in total; 45 operational) (**1.25 pmp**)	2006	nuclear physicians, oncologists	No	12
Finland	5 PET scanners+5 gamma cameras for 5.2 million people (**0.96 pmp**)	1 replacement, 2 new (**1.34 pmp**)	2005 and 2007	oncologists	No	4
Denmark	4 PET-CT, 2 PET (of which one only used for brain research), 4 gamma PET scanners in use (6 available) but <100 gamma PET examinations performed a year; for 5.4 million people (**0.92 pmp**).	3 PET-CT scanners granted for 2 hospitals that do not already have PET/CT scanners. Plans for scanners at 5 additional hospitals. (**1.29 pmp**)		Nuclear medicine physicians/physiologist, oncologists. Patients are frustrated with the waiting period, which puts pressure on all parties involved.		2
Netherlands	12 – 15 for 16 million people (**0.75-0.93 pmp**)	20 to 25, one in every region (**1.25-1.56 pmp**)		nuclearists working in hospitals		
USA (VHA)	6 for 7 million people (**0.83 pmp**) + academic affiliates in the private sector to provide PET	Each of the 22 Veteran Integrated Service Networks (VISN) can plan and purchase their own scanner without approval from the headquarters.		imaging departments and oncologists	VA has closed down 5 PET facilities over the years, mainly because of aging equipment.	5
Canada	22 for 32 million people (**0.69 pmp**)	5 approved or in progress (**0.84 pmp**)			No – only for issues of private vs public scanners and attrition through the normal lifespan of the technology (use as backup when the newer	7

					units are not available).	
Spain	28 (19 full ring PET scanners, 6 PET-CT and 3 coincidence cameras), both private and public, for 43 million people (**0.65 pmp**)	10 PET-CTs and 2 PET cameras (**0.93 pmp**)	2005	oncologists	No	8
Israel	3 for 6 million people (**0.5 pmp**)	3 (**1 pmp**)	2005	1) Ministry of Health (MOH) and the Certificate of Need (CON); 2) The Health Funds and the hospitals	No	2
Scotland	1 per 5 million people (**0.2 pmp**)	2-3 (**0.4-0.6 pmp**)	2006-2007	Patients, oncologists, hospitals	No	1
England and Wales	16 for 50 million people, of which at least 5 purely for research (**0.22 pmp**)	Not yet decided		Medics, politicians, National Institute for Clinical Excellence	No	8
Australia	13 for 20,3 million people (**0,66 pmp**)	3 (**0,8 pmp**)	Early 2006	nuclear physicians, oncologists	No	8
Sweden	7 for 8,9 million people (**0,78 pmp**)	3 (**1,12 pmp**)	2007	University hospitals and physicians	No	3

(*) Given that the Netherlands has abandoned a governmental planning system, the number presented is the expected number of PET scanners.

8.2. PET IN BELGIUM

8.2.1. Population impact

The estimation of the population impact of PET in Belgium requires an overview of the incidence of the different indications for which PET may produce a benefit. We focus on the indications for which diagnostic evidence was reviewed in the previous chapters.

Cancer

The most recent data on cancer incidence in Belgium date from 1998 (www.kankerregister.be). The figures underestimate the real incidence of cancer in Belgium, as compliance with the registration is poor in some regions (personal communication, Dr. L. Van Eycken). More recent data exist for Flanders (www.tegenkanker.be - 2000). In addition, the International Agency for Research on Cancer (www.iacr.com.fr) estimated cancer incidences for 2002. Table 38 presents the incidences of the cancer types discussed in the previous chapter.

Table 38: Incidence of most frequent cancers

Cancer site	Incidence 1998*	Incidence in Flanders 2000**	Estimated incidence 2002***
Breast	6697	4934	7429
Lung	5185	3598	7707
Colon+rectum	4724	3943	6434
Oesophagus+stomach	1647	1266	2126
Non-Hodgkin's lymphoma	1307	927	1606
Pancreas+liver	1171	770	1558
Head & Neck	1127	1069	1483
Kidney	931	773	1330
Ovary	813	627	1073
Melanoma	690	722	756
Brain	643	471	981
Cervix	531	411	667
Thyroid and other endocrine glands	397	194	254
Hodgkin's Lymphoma	212	133	250

* Source: Kankerregister
** Source: Vlaamse Liga tegen Kanker.
*** Source: International Agency for Research on Cancer, Globocan (www-dep.iarc.fr)

Other indications

The number of patients with cardiologic or neurologic indications for PET scan is difficult to estimate, given the paucity of data on these specific indications. The number is presumably relatively small.

8.2.2. PET scanners in Belgium: number, dispersion and activity

Number and dispersion

In comparison with other countries, Belgium is in a particular situation in terms of PET services. Whereas other countries mainly struggle with the question of how many new PET scanners should be introduced in their health care system, Belgium has to evaluate whether the number of already installed PET scanners is appropriate for the expected need. Belgium currently has the highest number of PET scanners per million inhabitants among the 11 countries surveyed by INAHTA. In other countries, centres are often reluctant to install a PET, given the high financial risk involved with its installation (high up-front costs, high operating expenses and possibly inappropriate reimbursement).

The Belgian PET market is divided between three companies: Siemens, Philips and General Electric.

There are currently 13 approved PET scanners in Belgium. Several Royal Decrees organized the planning of approved PET scanners in 2000 (Table 39; situation on August 12, 2000)[5]. The seven academic hospitals all received an approval as well as the Institute Jules Bordet in Brussels, specialized in oncology. The remaining approvals were granted on basis of population density (one per complete bracket of 1,600,000 inhabitants: 3 in Flanders, 2 in Wallonia). The legislation imposes minimal requirements in terms of equipment, staff, number of admissions and activity (especially in lung oncology). Before the limitation of the number of PET scanners in 2000, Belgium had 18 dedicated PET scanners. There are strong indications that Belgium still has more operational PET scanners than the 13 officially approved shown in Table 39.

Table 39: Hospitals with an approved PET scanner and the number of scans reimbursed per centre (based on billing codes INAMI/RIZIV for the year 2003).

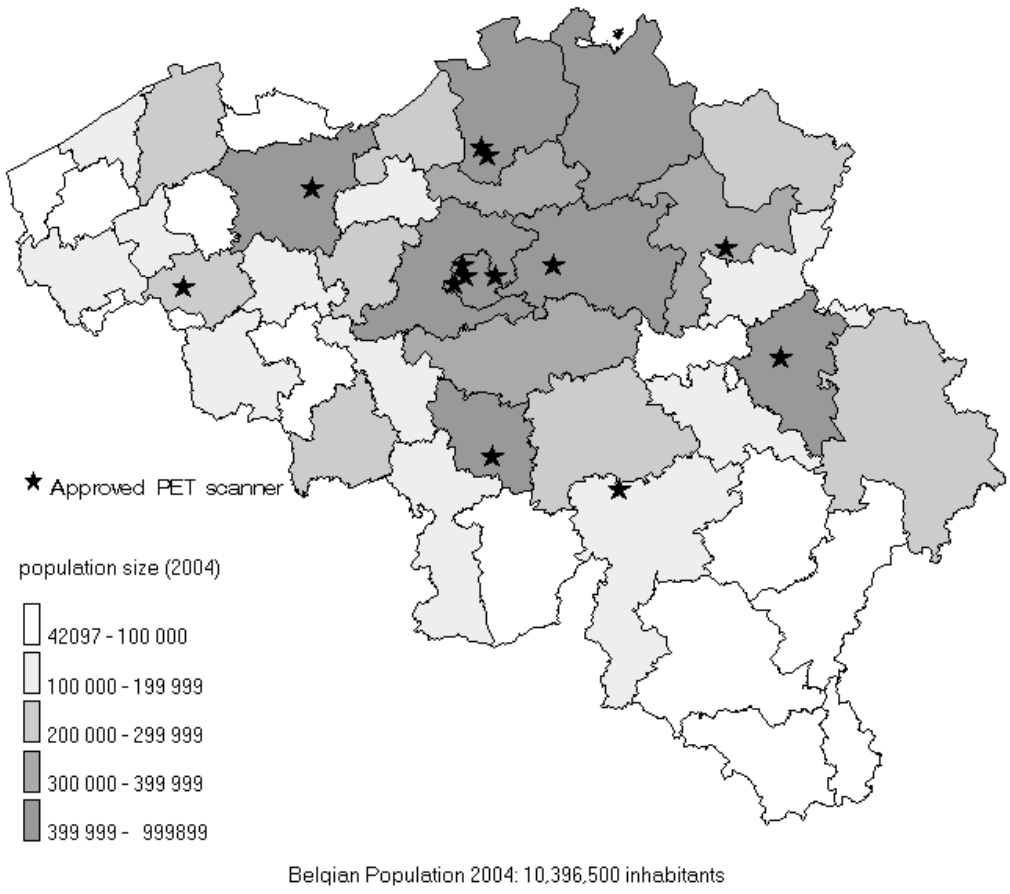
HOSPITAL	LOCATION	NUMBER OF REIMBURSED SCANS
UNIVERSITAIRE ZIEKENHUIZEN K.U.L.	LEUVEN	2 460
ALGEMEEN ZIEKENHUIS ST. AUGUSTINUS (*)	WILRIJK (ANTWERP)	1185
CENTRE HOSPITALIER UNIV. DE LIEGE	LIEGE	1 156
CLINIQUES UNIVERSITAIRES ST. LUC	BRUXELLES	1 080
CLINIQUES UNIVERSITAIRES (U.C.L.)	MONT-GODINNE	920
CLIN. UNIV. DE BRUXELLES - HOPITAL ERASME	BRUXELLES	898
ALGEMEEN ZIEKENHUIS SALVATOR-St.URSULA(**)	HASSELT	771
INSTITUT J. BORDET	BRUXELLES	724
AKADEMISCH ZIEKENHUIS (V.U.B.)	BRUSSEL	717
UNIVERSITAIR ZIEKENHUIS ANTWERPEN	EDEGEM (ANTWERP)	578
UNIVERSITAIR ZIEKENHUIS	GENT	417
ALGEMEEN ZIEKENHUIS GROENINGE (***)	KORTRIJK	-
CENTRE HOSPITALIER UNIV. DE CHARLEROI (***)	CHARLEROI	-
TOTAL OF REIMBURSED PET-SCANS		**10906**

(*) PET-scan shared with AZ Middelheim in Antwerp.
(**)The PET-scanner located in Hasselt is shared by several hospitals from the same province.
(***) Recent approbation, no data 2003.

[5] The Royal Decrees have recently been given force of law and inserted in different healthcare laws by the law of 27 April 2005 ("Law concerning the control of the health care budget and containing miscellaneous regulations on health").

The numbers in the table refer to the number of reimbursed scans, excluding PET scans performed for research or other non-reimbursed clinical purposes. In total, the INAMI/RIZIV reimbursed 11,618 scans in 2003. Of these 10906 were reimbursed to approved PET-scanners.
Figure 11shows the geographical repartition of the approved scanners.

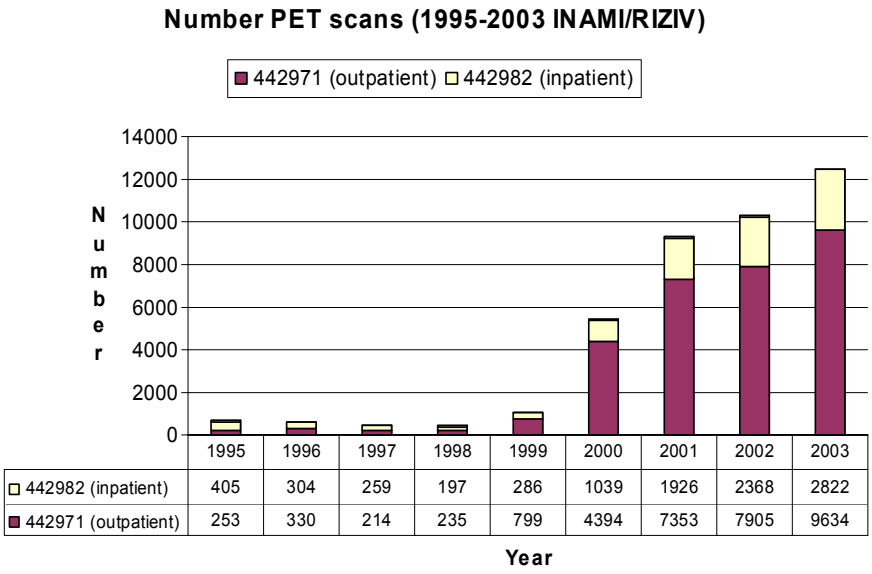
Figure 11: Geographic localisation of approved PET centres in Belgium.



Activity

The number of PET scans reimbursed during a year is drawn from the invoiced billing codes for the medical act of scanning transmitted by hospitals to health insurers who send the information to the INAMI-RIZIV (National Insurance Institute for Illness and Disability). A PET scan can be invoiced under two different codes, according to the inpatient or outpatient status of the patient. Medical fee for service paid per code will be discussed in section 5.2.3.

Figure 12: Number of PET scans reimbursed (1995-2003).



There can be some delay between the moment of the diagnostic act of scanning, the transmission of billing codes and the reimbursement itself. The year unit presented in Figure 12 is the accounting year (reimbursement year), that can be superior or equal to the year during which the procedure was done (examination year). Some acts executed in 2003 may not be processed into the data yet, causing a slight underestimation of the number of reimbursed procedures in 2003.

The regulation and approbation of the 13 PET centres by Royal Decree was accompanied by the creation of a compulsory internal registry of PET activities for each PET centre. The (unchanged) specifications of the register are now inserted in the Law on Hospitals coordinated on 7 August 1987, modified by the law of 30 December 1988 and more recently by the law of 27 April 2005. The register must contain information on the type of tumour, the initial staging pre-PET, the proposed therapy, the clinical reason for the request of a PET scan, indication (staging, therapeutic response, re-staging), information on other imaging modalities, result and influence on diagnosis, staging and therapy.

According to the national registry for PET scans, 19,727 scans have been performed between September 2003 and September 2004 in 11 of the 13 Belgian PET centres (one centre did not participate and one did not provide their data yet). One centre started its activities halfway the registration period. Of these, 17,645 were for oncological indications, 1,224 for neurological indications, 120 for cardiological indications and 138 for infections.

The number of PET scans per type of tumour and indication is presented in Table 40. The levels of evidence for PET scan in these indications are presented in parentheses.

Table 40: Number of PET images per type of tumour and indication (level of evidence)

Cancer site	Total number of PETs performed#	Diagnosis	Recurrence	Treatment
Breast	927	233 (2 against)	550 (2)	131
Lung	5335	3834 (3; 6-staging)	928 (2)	523 (<2)
Colon+rectum	1871	294 (2)	1244 (4)	324 (<2)
Oesophagus+stomach	892	430 (<2; 2-staging)	267	189 (3)
Non-Hodgkin's lymphoma	1307	531 (<2; 2-staging)	613 (2)	775 (3)
Pancreas+liver	556	(pancr: 2; liver: 2 against)		
Head & Neck	1127	388 (2; 3-staging)	501 (3)	154
Kidney	160	(<2; 2-staging)	(<2)	
Ovary	267	(2; <2-staging)	(2)	(<2)
Melanoma	690	278 (2-staging)	399 (2-staging)	65
Brain	586	(2)	(2)	
Cervix	211	(2)	(2)	
Thyroid and other endocrine glands	149		(2)	
Hodgkin's Lymphoma	1077	315 (<2; 2-staging)	374 (2)	376 (3)
Testicular	126	(2)	(2)	(<2)

Source: Belgian Society of Nuclear Medicine - Workgroup PET

The data on changes in diagnosis, staging and therapy compared to the diagnosis, staging and therapy suggested by conventional imaging techniques have not been analysed yet.

8.2.3. Supply of radiopharmaceuticals

The radiopharmaceutical FDG is produced in a cyclotron. The cyclotron renders a non-radioactive target material radioactive by bombarding it with high-energy charged particles. Once the radioactive fluorine-18 is synthesized, it is incorporated into a glucose molecule.

FDG has a half-life of about 2 hours (109 minutes). Therefore, it is important that the cyclotrons are located in the vicinity (100-200 km depending on traffic) of the PET centres or that timely supply is possible. The production of FDG is limited to two cycles a day, and can serve up to 50 patients (doses) a day. More production cycles would expose the personnel working at the cyclotron to higher levels of radioactivity.

The production and distribution of FDG, the radiopharmaceutical used for PET scanning, is regulated in Belgium. Only registered manufacturers of FDG are allowed to sell FDG to PET centres that have no cyclotron on-site. There are two private manufacturers of FDG in Belgium that have a marketing authorisation: MDS Nordion, located in Fleurus, and IBA, located in Brussels and Ghent. IBA starts its activities in Belgium in September.

The two cyclotrons will be used as each other's back-up in case of a defect of one of the two cyclotrons.

MDS Nordion, located in Fleurus, and the University of Liège (ULg) that has its own cyclotron have signed an agreement for the production and marketing of FDG. MDS Nordion is a part of MDS Inc, an originally Canadian international company.

A third private company, Tyco Healthcare/Mallinckrodt, supplies Belgian PET centres from abroad (the Netherlands). According to our information, this company does not have a marketing authorisation for FDG in Belgium.

Data of the Federal Agency for Nuclear Control (FANC/AFCN) show that FDG is not only supplied to the approved PET centres, but also to several other hospitals where legally no PET scanningss are expected to be performed.

In addition to the commercial producers of FDG, a number of academic hospitals produce FDG in-house. Besides ULg, there are five academic centres with a cyclotron in-house: Erasmus (Brussels), KULeuven, UCL (Brussels), UZ Gent and AZ-VUB (Brussels).These centres are only allowed to produce FDG for personal use. When not involved in commercial production, they do not have to comply with GMP-guidelines. Manufacturing criteria are hence less strict for academic centres with a non-commercially exploited cyclotron than for the companies that commercialize FDG.

Inspection of FDG produced in-house at academic centres is organised by the Belgian Ministry of Public Health (FOD Volksgezondheid/SPF Santé Publique) and the Federal Agency for Nuclear Control (FANC/AFCN). FDG produced in-house is considered as a magistral formula[6] and as such subject to the regulations for such substances.

Outsourcing of FDG production between a PET centre without a cyclotron and a PET-centre with a cyclotron on-site is not allowed for two reasons. First, from the perspective of the sub-contractor, sale of FDG is not allowed. Selling FDG is a commercial activity which is only allowed for holders of a marketing authorisation. Second, there is an issue of split of responsibilities. A hospital pharmacist carries the final responsibility for all products delivered by the hospital pharmacy and produced between the walls of this pharmacy. Whenever the FDG is not produced in-house but by a colleague at an academic centre that has no license to sell FDG, there is a conflict of responsibilities: the pharmacist of the non-registered centre is responsible for the product produced in his centre and the pharmacist of the outsourcing centre is responsible for the FDG delivered by his pharmacy. It is hence unclear who carries final responsibility.

Nevertheless, data of the Federal Agency of Nuclear Control (FANC/AFCN) show that outsourcing of FDG supply to centres with an in-house cyclotron occurs frequently in Belgium.

The base price of FDG fixed by the Ministry of Economical Affairs is € 375, but FDG is sold to the PET centres at € 300 to € 370 per dose by the private companies, including transport. Academic cyclotrons that supply other PET centres adopt a lower price per dose, but charge transport separately. In France, the price was € 416 in 2001, including transport [176]. In Scotland the same year, the price was between £353 and £376 (€ 524 and -€ 558), excluding transport, depending on whether the supplier was a NHS facility or a commercial entity [9]. These foreign prices may have changed since 2001.

[6] A magistral formula is a pharmaceutical preparation, made by a pharmacist following the procedures stipulated in the farmacopea or following a specific prescription of a physician for a particular patient.

8.2.4. Financing of PET in Belgium

Since 2002, reimbursement has three components: the annual flat-rate amount paid per approved PET scanner as indicated in the planning Royal Decree (hospital fee), the medical act of scanning (medical fee for service) and finally the FDG reimbursement.

Annual flat-rate amount

The hospital fee is currently fixed at € 282,599 to cover the PET infrastructure plus a basis of € 198,315 to cover the personnel and organisational costs. This latter amount follows indexation and amounts now to € 215,633 (July 2005).

Medical fee for service

The fee for service amounts to € 159.99 per imaging procedure (same rate for outpatient as inpatient examination). This fee is only applicable for the indications presented in Table 41.

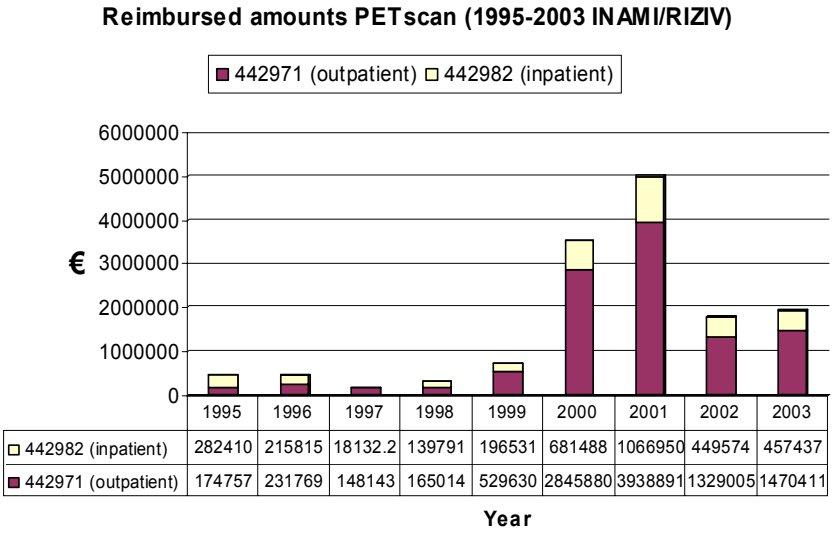
Table 41: Reimbursed indications for PET with their levels of evidence

Reimbursed indication	Level of evidence
Oncology:	
Evaluation of solitary pulmonary nodule (SPN) before surgery	level 3
Evaluation of residual mass or in case of objective suspicion of recurrent	
cerebral,	level 2
oral or pharyngeal malignancy	level 3
Whole-body examination for initial staging of	
malignant non-small cell lung cancer (NSCLC),	level 6
oesophageal or	level 2
pancreatic malignancy,	level 2
malignant melanoma (IIc or more),	level 2
malignant lymphoma (HL and NHL),	level 2
if the therapy, particularly curative surgery, is decisively influenced by the examination.	
Whole-body examination for evaluation of residual mass or in case of confirmed suspicion of recurrent	
malignant melanoma,	level 2
malignant NSCLC,	level 2
colorectal,	level 4
lymphomatous,	level 3
pancreatic or	level 2
ovarian malignancy	level 2
Cardiology: Myocardial viability if surgery is planned for a recent well-documented coronary failure.	level 3
Neurology: Epilepsy that does not respond to medication if the scan can decisively influence the therapeutic management towards curative surgery	level 2

There is no fee for service for other indications.

The following Figure 13 presents the reimbursed amount for PET-scan, broken down between the billing code for outpatient examination and inpatient examination.

Figure 13: Reimbursement PET 1995-2003.



	1995	1996	1997	1998	1999	2000	2001	2002	2003
442982 (inpatient)	282410	215815	18132.2	139791	196531	681488	1066950	449574	457437
442971 (outpatient)	174757	231769	148143	165014	529630	2845880	3938891	1329005	1470411

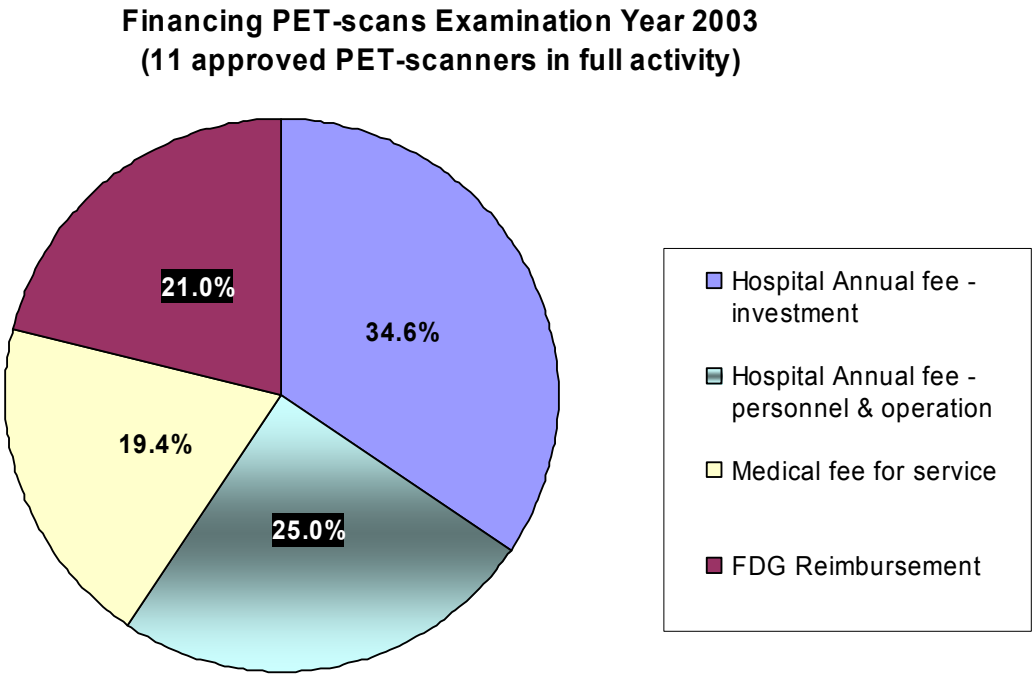
The trend modification between 2001 and 2002 is due to the new system of financing introducing a flat-rate hospital fee; before this date, there was no annual flat-rate fee but on the other hand the medical fee for service was € 733.57 high. The equivalent expenditure (FDG excluded) in 2002 would be: € 1,778,580 + 13 x (€ 282,599 + € 198,315) = € 8.03 million in comparison with € 5.01 in 2001.

FDG reimbursement

Finally, the FDG reimbursement fee is fixed at € 173.53 per dose. The reimbursement is hence lower than the prices charged for a dose of FDG (€ 300 - € 370). The real cost of the production of FDG is unknown. It is beyond the scope of this HTA to calculate this cost, but a Belgian research group is currently planning a study on the real cost of FDG production (B. Krug, personal communication).

The repartition of the financing of PET scanners is shown on Figure 14.

Figure 14: Repartition of different financing flows for PET scan (for PET scans reimbursed in 2002)



The repartition was computed on data from 2003 (that may still lack a few examinations due to billing delays). In 2003 11 PET scanners out of 13 were already in full activity (some approbations were granted more recently). They were reimbursed for 10,906 PET scans out of 11,618 for the whole country, the rest (712) was done by non-approved PET-centres that do not receive any hospital annual fee.

Key Messages

- **With 13 approved PET scanners performing around 20,000 PET scans a year, Belgium has a high number of PET scanners per million inhabitants.**
- **Six academic centres have their own FDG producing cyclotron. There are two other commercial cyclotrons located in Belgium delivering FDG to other centres.**
- **PET is currently most frequently used for lung cancer, followed by colorectal cancer, non-Hodgkin's lymphoma, head and neck cancer and Hodgkin's lymphoma.**
- **PET scanning has a triple funding source: annual flat-rate amount per centre, medical fee for service per scan and FDG reimbursement per dose.**

9. PATIENT ISSUES

A number of patient issues are associated with diagnostic techniques in general and PET imaging in particular. These issues relate to access to PET services, benefits of PET scanning and information on risks of PET scanning. As policy decisions are not only based on objective elements of evidence, the patient perspective needs to be highlighted.

9.1. ACCESS TO PET SERVICES

Geographical dispersion of PET scanners is an important determinant for accessibility. Despite the fact that Belgium is relatively small, dispersion of PET services should take the population density of a region into account or even better the prevalence of the most important indications for PET. There is a high concentration of PET facilities in the centre of the country, related to the granting in the legislation of a PET scanner to every university and the Bordet institute. There is a good distribution of PET scanners in the rest of the country, guaranteeing good accessibility otoPET services.

9.2. BENEFITS OF PET FROM THE PATIENT'S PERSPECTIVE

A major advantage of PET is its minimally invasive nature. Especially compared to invasive diagnostic strategies, such as biopsy, mediastinoscopy, this is an important asset from the perspective of the patient. Obviously, the diagnostic efficacy remains crucial: without a clear positive added value of PET in terms of changes in further diagnostic follow up or treatment, the benefit is small (apart from the value of additional information, cfr. below). In case of large benefits, e.g. in terms of avoided surgery, PET clearly has an added value to patients.

In case of a very small benefit of PET or a potential benefit for a small number of patients, other issues arise. The trade-off between the benefit of a minimal invasive procedure and the cost-effectiveness of this procedure then becomes much more pertinent. If a strategy with PET avoids an invasive procedure in a very small percentage of patients compared to a strategy without PET, the question arises whether this small percentage is worth the extra costs of PET imaging. From the patients' perspective, a small chance of avoiding an invasive procedure (with its associated risks) may be very important. From the societal perspective, we are also faced with the need to spend resources efficiently. Economic evaluations that incorporate quality of life (e.g. cost-per-QALY analyses) may help to make this trade-off.

A Scottish survey in patient representatives and voluntary organisations revealed that PET may also be valuable for the confirmation of an earlier made diagnosis based on, for instance, CT.[9] It improves the certainty about a previous diagnosis. This highlights the importance of accurate patient information. On the one hand, the reliability of PET imaging and the extent to which PET imaging can actually confirm the results of previous diagnostic procedures should be clearly explained in order to avoid unrealistic patient expectations. On the other hand, the value of information is often neglected in assessments of diagnostic technologies, while it may often provide reassurance to patients.

9.3. INFORMATION ON RISKS OF PET SCANNING

Patients may be concerned about the risks of injection of the radiopharmaceutical, both for themselves and their family. Clear information, in simple language, should be provided to the patient. The innocuous nature of FDG, except for specific patients such as pregnant women, is largely recognized. A large scale American retrospective study in 22 PET centres found no reaction following the 80 000 doses of radiopharmaceuticals (mainly but not only FDG) recorded between 1994 and 1997 (95% CI 0-3.7/100,000

doses) [181]. The other potential complications due to injection and placement of the patient in a bed in a semi-close environment are not exclusive to PET scanning [182].

The very rare contra-indications for PET scanning are claustrophobia (<0.5%) especially for the longer tunnel of PET combined with CT and obesity (patients weighting more than 158,5 kg who cannot enter the tunnel) [84].

Patients should be well-informed about the scanning process in order to avoid anxiety and to guarantee that the patient does not eat for at least 4 hours before the scan [9]. This is particularly important for the technical success of PET imaging. Anxiety may increase muscle tension, which increases glucose uptake and may hence distort the PET image. For similar reasons of technical success the patient needs to be sober. Additional requirements to increase the chances of success need to be set out clearly in advance to the patients.

Key Messages

- **Accessibility of PET services is good in Belgium. There is a relatively equal geographical distribution of PET facilities according to population density, with a high concentration of PET centres in Brussels.**
- **PET is a non-invasive diagnostic technique; a feature that may be valued highly by patients compared to other invasive diagnostic techniques.**
- **The value of additional information or confirmation of an earlier diagnosis is often neglected in the assessment of PET, although it may be an important asset of PET from the patients' point of view.**
- **The risks associated with PET scanning are limited.**

10. GENERAL CONCLUSIONS AND RECOMMENDATIONS

10.1. EXISTING CLINICAL EVIDENCE

The existing evidence for clinical indications for PET is often still limited to level 2 or 3, according to the grading system we adopted. Very often, there is only evidence for diagnostic accuracy of PET (level 2 - sensitivity and specificity) and only for some indications there is also evidence for an effect of PET on diagnostic thinking (level 3). For some rare indications, it is obviously difficult to obtain a solid evidence base, as it takes long to gather the data.

The reading of PET is mostly qualitative. Semi-quantitative measures, like Standardized Uptake Value, are not yet used uniformly and there are only few studies about inter- and intra-observer reliability [183 3].

Evidence of PET cost-effectiveness in different indications is limited. There is evidence that PET is cost-effective for the diagnosis of a solitary pulmonary nodule and for the staging of non-small cell lung cancer. Furthermore, there is some evidence that PET is cost-effective in the re-staging of Hodgkin's disease and the staging of recurrent colorectal cancer. More information is needed about the cost-effectiveness of PET in other indications before routine use in these indications can be economically justified.

From the perspective of the patient, there are three major issues related to PET: accessibility, benefits and risks. Accessibility is determined by the dispersion of PET centres across the country. The benefits of PET are its minimal invasive nature compared to some other diagnostic procedures and its value of additional information or confirmation of an earlier diagnosis. Risks of PET imaging are limited.

10.2. BELGIAN SITUATION

Belgium is among the countries with the highest number of PET scanners per million people but other countries are planning a higher number of PET scanners, possibly approaching the rate of Belgium (1.26 PET scanners per million people) in the future. Belgium currently has 13 approved PET scanners. There is a relatively high concentration of PET scanners in Brussels (4), due to the allocation criteria used at the time of approval of PET scanners. The first criterion was the academic nature of a hospital, second, one centre specialised in oncology got an approval and finally, population density was looked at to determine the need for PET imaging. Next to the approved PET scanners, a number of non-approved scanners are operational in Belgium.

The indications for which PET imaging is reimbursed under the current reimbursement scheme of Belgium are more or less concordant with the indications found in our review, at least if diagnostic accuracy (level 2) is regarded as sufficient for widespread use of PET in an indication. Only a few of the reimbursed indications (SPN, NSCLC, head and neck cancer, colorectal cancer and myocardial viability) currently reach a higher level of evidence. For future possible expansion of reimbursed indications impact on patient management and therapeutic consequences should be considered as well.

For the supply of the most commonly used radiopharmaceutical FDG, PET centres have to rely on the production of one of the two private companies that are licensed to produce and distribute FDG in Belgium or to their own production in-house, in their own cyclotron. Outsourcing of FDG production by a PET centre without a cyclotron to a PET centre with a cyclotron on-site is not allowed for legal reasons.

10.3. NUMBER OF PET SCANNERS NEEDED IN BELGIUM

Based on the literature review of possible indications for PET imaging, the levels of evidence and the number of PETs performed between September 2003 and September 2004 by 11 of the 13 approved PET scanners[7], we can make a rough estimation of the number of PET scanners needed in Belgium. The table on which the calculations are based are presented in appendix. We estimated the number of PET scanners needed in function of the level of evidence for diagnostic efficacy for all indications, and under two different assumptions about case load per PET scanner per year: 1,500 or 2,000.

The data from the Belgian Society of Nuclear Medicine - Workgroup PET were presented per disease and for most cancer types per indication (diagnosis, recurrence and treatment). For diagnosis, there was a different level of evidence for initial diagnosis and staging in head and neck cancer and in lung cancer. In both cases, we retained the highest level and we assumed that all the patients who received a PET scan in 2003-2004 for diagnosis of head and neck cancer or lung cancer received this scan for the purpose with the highest level of evidence. For cervical cancer, ovarian cancer and testicular cancer, we did not receive different numbers of scans for diagnosis, recurrence or treatment. The levels of evidence differ, however, for the three indications. We conservatively assumed that all scans for these cancers were performed for the indication with the highest level of evidence. Likewise, the number of scans for pancreas cancer was merged with the number of scans for liver cancer in the database of the Belgian Society of Nuclear Medicine - Workgroup PET, although there are different levels of evidence for both types of cancer. Again, we conservatively assumed that all patients who received a PET were pancreas cancer patients, for which the level of evidence is highest.

The data from the Belgian Society of Nuclear Medicine - Workgroup PET include both scans performed for routine diagnostic work up, for which reimbursement is foreseen in the Belgian reimbursement scheme, and PET imaging performed for research purposes or non-reimbursed indications where the utility is unclear. A comparison between the numbers presented by the Belgian Society of Nuclear Medicine - Workgroup PET and the numbers of PET scans reimbursed shows that between 30% and 40% of the PET scans performed in Belgium in 2003 were for research or other purposes. In a 1,500 annual case load scenario, this would mean that only about 1000 scans per year would be for reimbursed indications and 500 for research purposes or non-reimbursed indications.

On the one hand, this conservative approach leads to an overestimation of the number of PET scanners needed in Belgium. On the other hand, there are also elements that may lead to an underestimation. First, the calculations are based on the number of scans performed in 11 PET centres, while there are currently 13 approved PET scanners in Belgium. Second, we could not take PET imaging performed on illegal scanners into account, although some of these scans may also be justified based on the existing evidence. However, based on recent data of FANC/AFNC on FDG transport towards individual hospitals, it can be deducted that the case load on these non-approved PET scanners only amounts to a few percentages of the total number of PET scans performed in Belgium.

The existing data did not allow a more refined analysis, but we can expect that the estimate will not deviate too much from the one presented below, given that the justification for one additional PET scanner would need an additional 1,500 to 2,000 patients eligible for PET imaging according to the state-of-the art evidence.

The results of our calculations are presented in Table 42. The results show that Belgium currently needs at least 3 and at most 10 PET scanners, depending on the level of evidence considered acceptable for routine use of PET imaging in different indications. The absolute minimal requirement is that PET imaging has proven diagnostic accuracy, i.e. PET imaging is more or equally able to detect or exclude disease in patients than a reference test. Technical efficiency (level of evidence 1) is clearly not enough to justify

[7] Data provided by the Belgian Society of Nuclear Medicine Workgroup PET. Data were available for 11 of the 13 approved PET scanners.

routine use of PET in clinical practice. On the one hand, this a a very expensive technique where most of the countries have had a much more prudent health care policy and where from a health insurers point of view clinical evidence of a higher level than just the determination of sensitivity and specificity (i.e. level 2) can be demanded. On the other hand this is still an emerging technology where the evidence base is still building up for several indications. Lack of evidence in itself does not mean that PET is not useful for an individual patient under specific conditions (expertise, multidisciplinary team, etc). So again, we used a quite conservative approach, that surely would be challenged in a context that strives towards the most efficient and equitable use of health care resources from the perspective of society and health insurance.

The calculations presented in Table 42 take both reimbursed and non-reimbursed PET scans into account, for all cut-off values for level of evidence. Without consideration of the level of evidence in different indications, and thus assuming that all PET scans performed in 2003 were either for appropriate indications or for research purposes, between 10 and 13 PET scanners were needed in Belgium. The actual number of PET scanners that performed that number of scans at that time was 11.

With the current evidence, there is no medical or scientific justification for more PET scanners in Belgium. For the reimbursed indications, a number between 7 and 9 PET scanners should be sufficient (in 2003, almost 12,000 PET scans were reimbursed). However, PET centres, many of which are academic, also do research, which can be used as an argument to increase the number of PET scanners. According to our calculations, 10 PET scanners would be highly sufficient for both routine clinical care and research purposes.

There is currently still a potential for growth in PET scanning: first, there are emerging indications (e.g. treatment follow up for Non-Hodgkin's Lymphoma) and it is probable that other indications for PET imaging will emerge in the future, increasing the need for PET scanners. Indications for which there is only evidence of level 2 now can have a higher level of evidence in four years. Second, PET imaging is currently mostly used for elderly patients. In an ageing population, it is likely that the need for PET scanners will also increase. Third, the incidence of indications for PET may increase, which may be used as an argument to maintain excess capacity. These should not, however, be used as arguments in favour of the installation of more PET scanners in Belgium at this moment. Firstly, it is important that PET proves its diagnostic efficacy in these new indications or even cost-effectiveness before it becomes routine practice. Secondly, the technology, both hard- and software is in constant evolution, which means that a current state-of-the-art scanner probably will be outdated in a few years without additional investments. Thirdly, the incidence of diseases potentially eligible for PET scanning may also decrease in the future. Prognostic incidence models may be useful for the planning of PET services.

The National Health and Disability Insurance (RIZIV/INAMI) risks to be confronted with an uncontrolled increase in budgetary outlays for PET scanning if it leaves the door open for additional PET scanners for the sake of 'emerging indications'. This is not desirable, given the scarcity of resources and especially the urge to use the existing resources and capacity more efficiently. Before a new PET scanner is installed, a critical mass eligible for PET imaging must be present that cannot be captured by the existing capacity.

The 13 existing PET scanners in Belgium are highly sufficient for PET imaging needed in routine clinical practice and for research purposes. Belgium is still amongst the countries with the highest number of PET scanners per million people. With this number of PET scanners, there is actually excess capacity. This excess capacity could be used to catch up with the demand of illegal PET scanners, if these would close down.

PET/CT scanners are an emerging technology. Although this analysis did not specifically look at PET/CT, there are no indications that the number of PET/CT scanners needed in Belgium would be higher than the number of PET scanners. As we did not assess the diagnostic efficacy and cost-effectiveness of PET/CT, we cannot state on the basis of this HTA whether PET/CT is to replace PET. PET/CT needs further assessment and

research before firm conclusions about appropriateness of implementation and diffusion in Belgium can be drawn.

Table 42: Estimated number of PET scanners needed in Belgium, based on the throughput of 11 out of 13 approved PET scanners that were already operational in 2004

	Number of scans done Sept 2003 – Sept 2004 *for reimbursed indications, non-reimbursed indications and research*	Number of PET scanners needed in function of annual throughput	
		1500 imaging procedures per PET scanner per year	2000 imaging procedures per PET scanner per year
Level of evidence ≥ 4	5,078	3	3
Level of evidence ≥ 3	7,379	5	4
Level of evidence ≥ 2	14,408	10	7
All indications, irrespective of level of evidence	19,727	13	10

10.4. USE OF AVAILABLE CAPACITY ON APPROVED PET SCANNERS

In principle it is possible to perform up to 2,000 scans annually per PET scanner. In 2003, eleven centres did less than 20000 scans, representing an average case load of about 1,800 examinations per year, including both scans done for reimbursed indications and research. This shows that there is room for more efficient use of the available official PET capacity. Increasing the number of scans performed on the existing approved PET scanners would allow meeting the additional demand in case of closure of the illegal PET scanners.

However, from the organizational point of view, a number of conditions have to be met to increase efficiency of capacity usage:

- Firstly, in order to guarantee equitable access to this technique, a PET centre needs to collaborate with other hospitals that do not have a PET scanner on their own premises, e.g. through a service level agreement. Only about 1 out of 10 Belgian hospitals have a PET scanner. Sufficient slots should hence be allocated for external referrals. There are already examples of existing networks around several of the approved PET scanners. However, so far networking is not compulsory.
- Secondly, for an optimal use of a PET scanner, the FDG radio-isotope needs to be delivered in a timely fashion to the PET centres, possibly twice a day. FDG is commercialized by two companies in Belgium. In addition, some academic hospitals have their own cyclotron and produce FDG in-house. The two private companies sell FDG to PET centres at a price between € 300 -€ 370. Twice daily delivery to PET centres is without doubt feasible for the companies. The PET centres, however, are apparently not always ordering a twice daily delivery of FDG, because the price they pay for FDG is higher than the reimbursement for this product. Reimbursement of FDG should be framed in the broader context of financing PET centres, which is discussed in paragraph 10.6.

Thirty to 40% of the capacity is currently used for research purposes. If we suppose that this percentage of PET imaging devoted to research remains the same and that the 13 PET scanners are used at full capacity (this presumes that the number of patients falling within the reimbursed indications increases, e.g. because of population aging), the number of PET scannings available for research purposes can be calculated. We do this for the two case load scenarios. With an assumed annual case load of 2,000 scans, the maximum number of scans is 26,000 per year, for 13 PET scanners. Likewise, the maximum number of scans with an annual case load of 1,500 is 19,500.

The results are presented in Table 43. The figures show that there is room for at least 5,850 PET images for research purposes each year if the conditions for optimal use of capacity are met. If we assume that the number of PET images needed for reimbursed indications does not increase but remains at a level of 12,000 to 12,500 per year, there is room for 13,500 to 14,000 PET images for research purposes.

Table 43: Number of PET scans available for research purposes in case of full capacity use of the 13 approved PET scanners

	Case load	
% of scans devoted to research	1500 scans/year	2000 scans/year
30%	5 850	7 800
40%	7 800	10 400

The current number of PET scans for research purposes or non-reimbursed indications is about 7500, which suggests that a lot of PET research is going on in Belgium. However, this is not confirmed by publications in high impact peer-reviewed journals for all approved PET-centres. There is a lot of ongoing research in Belgian centres that is concentrated in only part of the PET centres. Research on patient outcomes is rare in Belgium, while this is the major gap in current PET literature. More research should be devoted to this aspect.

10.5. CURRENT FINANCING MECHANISMS AND POSSIBLE AMELIORATIONS

There are currently three flows of funding for PET centres: an annual flat-rate for fixed costs (depreciation and personnel), a fee per medical service and a fee per unit of FDG delivered. Expenses for the fixed and operating costs of PET are more than 60% of the total outlay for PET by the health care system.

There are several indications that in addition to the 13 approved PET scanners other, illegal, PET scanners are still operational in Belgium. Although these hospitals do not receive the flat-rate amount for fixed costs, they can use alternative codes of nuclear medicine for their fees for service (i.e. "assimilation") and possibly charge part or the entire amount to the patient. On the first of July 2005, a legal framework was created by the Law of 27 April 2005 that gives the inspectors from the National Insurance Institute for Illness and Disability (INAMI/RIZIV) the authority to record the use of illegal medical equipment. The incurred fine is a percentage up to 10% of medical fees reimbursed during the semester of the infraction of the law; this fine cannot be charged to the patient. A Royal Decree is to be taken to determine the percentage and to list the medical fees for service used for the calculation of the fine.

Revision of the financial arrangements for PET imaging is desirable for a more efficient use of available resources. More efficiency would mean that PET is used for indications where there is evidence of clinical usefulness and that this is done at a minimal cost. Over-use as well as under-use of PET should be avoided. There are currently no indications that PET is being under-used in Belgium. The high volume of PET scans performed in Belgium in comparison with other countries cannot be explained by demographical variables. However, with the current information, it is neither possible to conclude that there is over-use of PET. The data on cancer incidence alone do not allow an estimation of the number of PET scans required for each indication. For such estimate more information is needed about the numbers of patients eligible for PET for initial diagnosis, staging, recurrence assessment or treatment evaluation.

A financing system that wants to ensure efficiency, should be developed in a way that it stimulates an appropriate use of PET at minimal costs. Financing of health care services

can range from completely fixed budget systems to completely variable funding systems. All kinds of hybrid models, combining fixed with variable funding are possible.

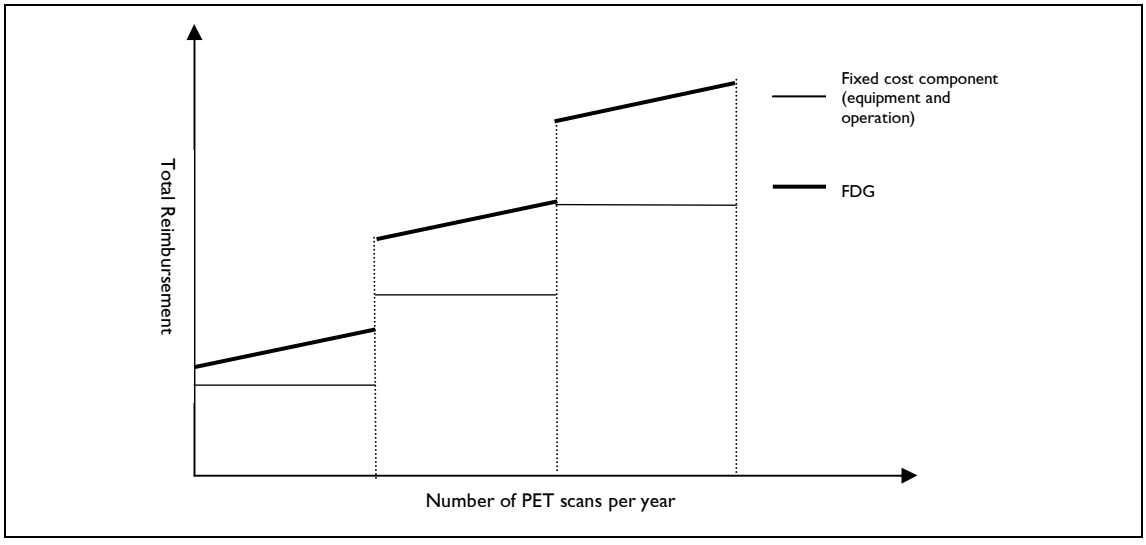
An optimal financing system for PET takes the cost structure of a PET service into account, without giving incentives for inappropriate use of PET. The cost structure of a PET centre consists of a fixed cost component (related to the PET scanner and its maintenance), a semi-fixed cost component (related to para-medical and non-medical personnel and general operating costs) and a variable cost component (FDG, medical personnel). It is clear that some financing systems are more or less indicated for each of these components. For instance, a fixed budget for a completely variable component such as FDG would give an incentive for under-use of PET. Similarly, financing of PET equipment in function of actual number of scans performed would give an incentive for over-use.

The current reimbursement system consists of a fixed budget for equipment, maintenance and operation, combined with a variable reimbursement per service provided (fee for service) and per unit of FDG delivered. This system does not reflect the semi-fixed nature of the operational costs.

A semi-fixed reimbursement for semi-fixed costs, in function of the pre-defined volume ranges, grants high volume centres a higher budget for equipment, maintenance and operating costs than low volume centres. It is a stepwise reimbursement system, intended to stimulate efficient use of available capacity and takes into account the semi-fixed nature of costs with increasing volumes. For example, if a PET scanner is used for 3 patients per day, fewer personnel (e.g. nurses, administrative staff) will be needed than if it is used for 10 patients per day. The additional personnel drive the fixed costs upward where it remains fixed up to a certain volume of scans. The volume of PET images taken into account for this semi-fixed reimbursement system should be based on the incidence figures of cancer for the area in which the PET network operates.

If the system of fee for service and fee per dose of FDG delivered remains as it is now, the funding system can be graphically presented as in Figure 15.

Figure 15: Budgetary system with semi-fixed reimbursement for fixed costs and variable reimbursement for FDG



The definition of volume is crucial in this financing system. If it only includes PET for reimbursed indications and the number of PET images for research purposes is not taken into account, research on PET will be slowed down. As research was one of the arguments to approve PET scanners in academic centres, such perverse effects of the financing system should be avoided. On the other hand, if PET imaging performed for research or non-reimbursed purposes is included in the calculation of annual volume to

define the amount of fixed reimbursement, research will (partly) be financed out of the health care budget. But research is not routine clinical practice. It can be seriously questioned whether it is desirable that research would be financed out of the health care budget. With a separate budget for research, a regularisation of the allocated budget could be pursued, but only under specific conditions. These conditions could relate to the obligation to prove research activities (e.g. by means of research protocols and publications in peer reviewed journals), registration of PETs performed for research purposes. Centres that can prove active research with PET can obtain additional semi-fixed reimbursement out of the budget for scientific research, if the volume performed for research purposes brings them to a volume range that corresponds with higher reimbursement for equipment and personnel.

The variable financing of FDG should be in line with the specific requirements imposed by the government on the production and distribution of FDG. If specific conditions are set for the production and distribution of FDG that drive the costs upwards, this must reasonably be reflected in the reimbursement system. The current fee per unit of FDG delivered is lower than the price charged by the companies that sell FDG in Belgium.

A public outsourcing mechanism can in principle push the price of FDG downwards. However, it is uncertain whether this will actually happen, given the small number of FDG producers currently active in the Belgian market and the legal constraints still present to enlarge the number of producers.

A final possibility is to reimburse all costs, both fixed and variable, with one lump sum or with a semi-fixed budget including all costs. A lump sum has the major disadvantage that it gives no incentive whatsoever for efficient use of the PET scanner. A semi-fixed budget is, from the perspective of the health insurance not very different from the earlier described option of semi-fixed budget for fixed costs combined with a variable reimbursement for FDG. The major difference is that the honorarium fee is included, which may actually be an important difference from the hospital point of view.

From an aggregate health care sector perspective, efficiency would be improved by limiting the number of PET scanners in Belgium to maximum 10. With 10 PET scanners, all the patients with indications for which the clinical value of PET has been proven, could be served. More PETs implies additional costs without additional benefits and thus inefficient use of scarce health care resources. However, other elements may plea for more PET scanners than the suggested 10. Examples are accessibility to PET services, development of research with PET, aging population… This cannot, however, justify the high concentration of PET scanners in the centre of the country.

If these arguments outweigh the efficiency argument, there is, from the health care sector's point of view, no problem with under-use of PET capacity. On the contrary, under-use of capacity would in this case be better than inappropriate use of PET, as this would only be more costly and would add nothing to patients' management or outcomes. The semi-fixed reimbursement system allows a better fit with the actual cost structure of a PET centre and hence ensures that the volume performed on the PET scanners is performed at minimal costs for the health care payer.

From the societal point of view, however, important opportunities are lost if part of the PET capacity remains idle. The spare capacity could be used for research. With the current PET capacity in Belgium, there is so much room for research that Belgium could and perhaps should play a leading role in PET research. The societal resources consumed to keep the overcapacity of PET for the sake of research should be justified by research with societal relevance, i.e. the results of this research should allow improvements in patient management and outcomes or health care policy.

In conclusion, health care policy is not inspired by efficiency considerations alone. Other elements may inform policy makers' decision, such as accessibility to care. It is important, however, to be conscious of the opportunities this creates in the case of PET. With the excess capacity of PET in case of 13 PET scanners, Belgium should be a pioneer in PET research.

10.6. ORGANISATION OF FDG SUPPLY AND DISTRIBUTION

The Ministry of Public Health is now working on a regulatory framework to organize the outsourcing of pharmaceutical preparations. The framework includes radiopharmaceuticals but is actually larger and encompasses a number of pharmaceutical preparations that will be specified by Royal Decree. In addition, GMP-like guidelines are being developed for hospital pharmacies, i.e. Good Officinal Practices (GOP). Both initiatives will improve safety, efficacy and quality of the officinal products and the regulatory framework will moreover solve the responsibility issue.

The new regulation will impact upon the production cost of FDG at non-commercial cyclotrons of academic centres. It will require investments in increased quality control mechanisms, education of personnel and stricter operating procedures. Currently, the prices charged for FDG by non-commercial cyclotrons are lower than the prices charged by the commercial suppliers. There are different reasons for this, but one is probably the cost of production and control. Compliance with GMP-guidelines requires large investments in infrastructure, standard operating procedures, education, etcetera. On the other hand, the private companies have the comparative advantage of larger production volumes, which allows them to benefit from economies of scale. Another reason for the higher prices charged by commercial suppliers is obviously profit margins. Because of the increased measures for quality control that will have to be imposed to non-commercial cyclotrons and their associated costs, it is uncertain whether the pressure on the prices due to increased competition will compensate the upward pressure on prices due to increased production costs. This has to be investigated further.

10.7. GEOGRAPHICAL DISPERSION OF PET CENTRES

PET centres are dispersed over the entire Belgian territory. There is a high concentration of PET centres in Brussels and there are two PET scanners in the city of Antwerp.

Part of the problem is the criteria for the initial approval of PET centres. The academic nature of a hospital should in fact not be a decisive criterion. If the argument for allocating PET scanners primordially to academic centres is scientific research, prove of such research with PET, including a research framework with clear objectives and publications in high impact peer-reviewed journals, should be provided to obtain approval for a PET scanner. Not all academic centres may wish to do research on PET and not all are publishing results of PET research in high impact journals.

In addition, there is a problem of lack of networking between Belgian hospitals. Hospitals without a PET scanner should be encouraged to set up a network with hospitals with a PET scanner. This guarantees equal access to PET services for all patients.

10.8. INFORMATION TO PRESCRIBERS

Prescribers of PET should be better informed about the usefulness of PET imaging in different indications. The law defines a number of indications for PET imaging, but not all are evidence based (cfr. pancreatic cancer). Prescribers, i.e. oncologists, hematologists and related specialists, should be informed about the clinical utility of PET scanning in different indications and settings. This can be done through the circuit of continuing medical education. This report can serve as guidance. In addition, specialists in nuclear medicine of the 13 approved PET centres have an important role to play in the transformation of information to other professions.

10.9. CONCLUSION

The existence of 13 approved PET scanners in Belgium cannot be justified on the basis of objective scientific evidence. Even with a very conservative approach, keeping all indications for which there is only evidence for diagnostic accuracy and assuming an annual throughput of 1,500 scans, there is only evidence for a maximum of 10 PET scanners in Belgium. The approach we used for the estimation of the number of PET scanners needed in Belgium is extremely lenient. For diagnostic procedures, it may at least be expected that they have reached the level of diagnostic thinking (level 3) before they are used routinely. This means that the test results should at least have the potential to change the categorisation of patients. Only then the test may lead to a change in treatment decisions (level 4). Under this more restrictive condition, requiring evidence of level 3 or higher, there is only room for 5 PET scanners in Belgium.

The calculations are based on figures reflecting the actually performed number of scans in 2003-2004. They included the scans performed for research purposes or for other, non-reimbursed indications. With 13 approved PET scanners, there is much room for research in Belgium. Unfortunately, little research focuses on impact on patient outcomes, which is actually the most important gap in the evidence on PET. Research efforts from Belgian centres are not always well reflected in publications in high impact internationally peer-reviewed journals.

PET capacity is currently under-used in Belgium. Some PET scanners are kept idle for financial reasons. Part of this excess capacity could be used to catch up with the increased demand related to the closing of illegal PET scanners. Another part could be used for research purposes. However, this would require a financing system that stimulates instead of frustrates the efficient use of PET scanners.

A semi-fixed budget for costs of equipment and maintenance and operating costs, combined with an adequate reimbursement of FDG would stimulate more efficient use of existing PET scanners. Because there are not enough patients with reimbursed indications to occupy the 13 PET scanners full time, additional imaging will be done for research or other purposes. However, it is questionable whether this should be financed from the health care budget. Health care should be financed by the health care budget, but research should be financed by research budgets and financial resources from the industry that has an interest in the distribution of this technology. If research with PET increases, and if society has to pay for this research, prove of this research should be provided. Granting budgets to PET centres for research purposes should be subject to clear conditions.

Keeping the 13 approved PET scanners in Belgium will lead to societal costs that are, certainly in the short term, not reflected in better clinical outcomes, as only very limited evidence was found for the clinical utility of PET imaging in terms of impact on patient outcomes. In the longer run, with emerging indications, changing incidences of diseases where PET can be useful, ageing population, evolving technological possibilities and more research, it may become useful to have more PET. However, this is all very speculative and may even work in the opposite direction, i.e. that less PET scanners are needed. In the meantime, the additional costs are not justified by the better outcomes.

However, policy is not only inspired by objective scientific evidence or efficiency considerations. Other (societal or political) elements may play a role in the decision process. If such elements are used to justify the existence of 13 PET scanners in Belgium, this should at least be transparent, as it has consequences for societal resource use.

Key Messages

- **Belgium has the highest number of PET and the highest annual throughput amongst many Western countries. To date, this cannot be justified nor explained on the basis of only scientific evidence or demographic data.**

- The number of approved PET is higher than the need for PET services in Belgium. As a consequence, there is an overcapacity in PET. In addition, there are indications that some non-approved PET scanners are still operational in Belgium.
- Although there is evidence that PET may offer some diagnostic advantages compared with other techniques, the evidence of improved clinical outcomes is limited to a limited number of indications. For most indications, there is no evidence that PET improves patient outcomes.
- A legal framework is needed for the outsourcing of FDG production to non-commercial academic PET centres with a cyclotron on-site. Although legally not allowed, outsourcing occurs frequently in Belgium, creating potential problems of responsibility, safety and quality.
- The fee per dose of FDG delivered is lower than the price charged for FDG by the companies with a marketing authorisation for FDG in Belgium. Reimbursement of FDG should be in line with requirements imposed for production and delivery of FDG.
- In terms of clinical use to improve patient outcomes, 3 PET scanners would be sufficient. Given the current prevalence of indications, for which PET imaging may be useful in terms of merely diagnosis, about 10 PET scanners would suffice for Belgium.
- Because developments in diagnostic techniques may precede developments in treatment, the clinical effectiveness and cost-effectiveness of PET may only become clear in the longer term. Maintaining or creating an overcapacity for the sake of a potential future benefit is, however, very costly and not very useful given the continuing technological developments in this field.
- Full use of existing (over)capacity and efficient use of health care resources are not compatible in the context of PET. Full capacity use of all approved PET scanners implies higher costs that are not proportional to improvements in patient management or patient outcomes.
- Health care policy makers have to make a trade-off between efficiency (i.e. using PET for indications where the clinical usefulness of PET is firmly established), implying the closure of some PET scanners, and other policy objectives, such as ensuring accessibility to PET services.
- If overcapacity of PET is to be maintained, there is a huge opportunity for research with PET in Belgium. As societal resources will be used for such research, proof of such research and its societal relevance should be provided. If financial resources for research came from the health care budget this should be publicly transparent and should not overlap with other financial streams for research purposes towards the hospitals.

11. REFERENCES

1. Calvo R, Marti-Climent JM, Richter JA, Penuelas I, Crespo-Jara A, Villar LM, et al. Three-dimensional clinical PET in lung cancer: validation and practical strategies. J Nucl Med. 2000;41(3):439-48.
2. Chin BB, Patel PV, Nakamoto Y, Cohade C, Osman M, Marshall LT, et al. Quantitative evaluation of 2-deoxy-2-[18F] fluoro-D-glucose uptake in hepatic metastases with combined PET-CT: iterative reconstruction with CT attenuation correction versus filtered back projection with 68Germanium attenuation correction. Mol Imaging Biol. 2002;4(6):399-409.
3. Paquet N, Albert A, Foidart J, Hustinx R. Within-patient variability of (18)F-FDG: standardized uptake values in normal tissues. J Nucl Med. 2004;45(5):784-8.
4. Bergmann H, Dobrozemsky G, Minear G, Nicoletti R, Samal M. An inter-laboratory comparison study of image quality of PET scanners using the NEMA NU 2-2001 procedure for assessment of image quality. Phys Med Biol. 2005;50(10):2193-207.
5. Coles JP, Fryer TD, Bradley PG, Nortje J, Smielewski P, Rice K, et al. Intersubject variability and reproducibility of (15)O PET studies. J Cereb Blood Flow Metab. 2005.
6. Van Laere K, Ceyssens S, Van Calenbergh F, de Groot T, Menten J, Flamen P, et al. Direct comparison of 18F-FDG and 11C-methionine PET in suspected recurrence of glioma: sensitivity, inter-observer variability and prognostic value. Eur J Nucl Med Mol Imaging. 2005;32(1):39-51.
7. Wells P, Gunn RN, Steel C, Ranicar AS, Brady F, Osman S, et al. 2-[11C]thymidine positron emission tomography reproducibility in humans. Clin Cancer Res. 2005;11(12):4341-7.
8. Gould MK, Maclean CC, Kuschner WG, Rydzak CE, Owens DK. Accuracy of positron emission tomography for diagnosis of pulmonary nodules and mass lesions: a meta-analysis. Jama. 2001;285(7):914-24.
9. Health Technology Board for S. Positron emission tomography (PET) imaging in cancer management. Glasgow: Health Technology Board for Scotland (HTBS) (merged into NHS Quality Improvement Scotland (NHS QIS)); 2002.
10. Wanet PM, Sand A, Abramovici J. Physical and clinical evaluation of high-resolution thyroid pinhole tomography. J Nucl Med. 1996;37(12):2017-20.
11. Reza M. Efectividad, seguridad, e indicaciones del sistema hibrido PET/TAC. madrid: Agencia Lain Entralgo; 2004 octubre 2004.
12. Mijnhout GS, Riphagen, II, Hoekstra OS. Update of the FDG PET search strategy. Nucl Med Commun. 2004;25(12):1187-9.
13. Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol. 2003;3:25.
14. Adams E FK. Positron emission tomography: descriptive analysis of experience with PET in VA. A systematic review update of FDG-PET as a diagnostic test in cancer and Alzheimer's disease. Boston: U. S. Department of Veterans Affairs. 1998:55 (+ appendices).
15. ICES, Laupacis A, Paszat L, Hodgson D, Institute for Clinical Evaluative S. Health technology assessment of positron emission tomography in oncology - a systematic review. Toronto: Institute for Clinical Evaluative Sciences (ICES); 2004.
16. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. Bmj. 1996;313(7052):275-83.

17. Gambhir SS, Hoh CK, Phelps ME, Madar I, Maddahi J. Decision tree sensitivity analysis for cost-effectiveness of FDG-PET in the staging and management of non-small-cell lung carcinoma. J Nucl Med. 1996;37(9):1428-36.

18. Gambhir SS, Shepherd JE, Shah BD, Hart E, Hoh CK, Valk PE, et al. Analytical decision model for the cost-effective management of solitary pulmonary nodules. J Clin Oncol. 1998;16(6):2113-25.

19. Gambhir SS, Schwimmer J. Economic evaluation studies in nuclear medicine: a methodological review of the literature. Q J Nucl Med. 2000;44(2):121-37.

20. Fryback DG, Thornbury JR. The efficacy of diagnostic imaging. Med Decis Making. 1991;11(2):88-94.

21. Brook RH, Lohr KN. Efficacy, effectiveness, variations, and quality. Boundary-crossing research. Med Care. 1985;23(5):710-22.

22. Haynes B. Can it work? Does it work? Is it worth it? The testing of healthcareinterventions is evolving. Bmj. 1999;319(7211):652-3.

23. Pearl WS. A hierarchical outcomes approach to test assessment. Ann Emerg Med. 1999;33(1):77-84.

24. Bland JM, Altman DG. Measuring agreement in method comparison studies. Stat Methods Med Res. 1999;8(2):135-60.

25. Feinstein A. Clinical Epidemiology. The architecture of clinical research. Philadelphia: WB Saunders; 1985.

26. Begg CB. Biases in the assessment of diagnostic tests. Stat Med. 1987;6(4):411-23.

27. Lijmer JG, Mol BW, Heisterkamp S, Bonsel GJ, Prins MH, van der Meulen JH, et al. Empirical evidence of design-related bias in studies of diagnostic tests. Jama. 1999;282(11):1061-6.

28. Knottnerus JA, van Weel C, Muris JW. Evaluation of diagnostic procedures. Bmj. 2002;324(7335):477-80.

29. Sackett DL, Haynes RB. The architecture of diagnostic research. Bmj. 2002;324(7336):539-41.

30. Pauker SG, Kassirer JP. The threshold approach to clinical decision making. N Engl J Med. 1980;302(20):1109-17.

31. Bossuyt PM, Lijmer JG, Mol BW. Randomised comparisons of medical tests: sometimes invalid, not always efficient. Lancet. 2000;356(9244):1844-7.

32. FNCLCC, Bourguet P, Bosquet L, Corone C, Devillers A, Foehrenbach H, et al. Recommandations pour la pratique clinique :Standards, Options et Recommandations 2003 pour l'utilisation de la tomographie par émission de positons au [18F]-FDG (TEP-FDG) en cancérologie (rapport intégral). Paris: FNCLCC; 2003 novembre 2003. Recommandations pour la pratique clinique Available from: http://www.fnclcc.fr/

33. Lassen U. Positron emissions tomography (PET) with 18-F-fluorodeoxyglucose (FDG). A survey of the literature with regard to evidence for clinical use in oncology, cardiology and neurology (english translation). Copenhagen: Danish Centre for Evaluation and Health Technology Assessment (DACEHTA) (formerly DIHTA); 2001 june 2001. Available from: http://www.sst.dk/

34. Facey K, Bradbury I, Laking G, Payne E. Ultra Rapid review

Positron Emission Tomography (PET) Imaging in Cancer management. NHS; 2004 july 2004.

35. Kubota K, Matsuzawa T, Fujiwara T, Ito M, Hatazawa J, Ishiwata K, et al. Differential diagnosis of lung tumor with positron emission tomography: a prospective study. J Nucl Med. 1990;31(12):1927-32.

36. Gupta NC, Frank AR, Dewan NA, Redepenning LS, Rothberg ML, Mailliard JA, et al. Solitary pulmonary nodules: detection of malignancy with PET with 2- F-18 -fluoro-2-deoxy-D-glucose. Radiology. 1992;184(2):441-4.

37. Slosman DO, Spiliopoulos A, Couson F, Nicod L, Louis O, Lemoine R, et al. Satellite PET and lung cancer: a prospective study in surgical patients. Nucl Med Commun. 1993;14(11):955-61.

38. Patz EF, Jr., Lowe VJ, Hoffman JM, Paine SS, Burrowes P, Coleman RE, et al. Focal pulmonary abnormalities: evaluation with F-18 fluorodeoxyglucose PET scanning. Radiology. 1993;188(2):487-90.

39. Lowe VJ, Hoffman JM, DeLong DM, Patz EF, Coleman RE. Semiquantitative and visual analysis of FDG-PET images in pulmonary abnormalities. J Nucl Med. 1994;35(11):1771-6.

40. Duhaylongsod FG, Lowe VJ, Patz EF, Jr., Vaughn AL, Coleman RE, Wolfe WG. Detection of primary and recurrent lung cancer by means of F-18 fluorodeoxyglucose positron emission tomography (FDG PET). J Thorac Cardiovasc Surg. 1995;110(1):130-9; discussion 9-40.

41. Bury T, Dowlati A, Paulus P, Corhay JL, Benoit T, Kayembe JM, et al. Evaluation of the solitary pulmonary nodule by positron emission tomography imaging. European Respiratory Journal. 1996;9(3):410-4.

42. Sazon DA, Santiago SM, Soo Hoo GW, Khonsary A, Brown C, Mandelkern M, et al. Fluorodeoxyglucose-positron emission tomography in the detection and staging of lung cancer. Am J Respir Crit Care Med. 1996;153(1):417-21.

43. Gupta NC, Maloof J, Gunel E. Probability of malignancy in solitary pulmonary nodules using fluorine-18-FDG and PET. J Nucl Med. 1996;37(6):943-8.

44. Knight SB, Delbeke D, Stewart JR, Sandler MP. Evaluation of pulmonary lesions with FDG-PET. Comparison of findings in patients with and without a history of prior malignancy. Chest. 1996;109(4):982-8.

45. Dewan NA, Shehah CJ, Reeb SD, Gobar LS, Scott WJ, Ryschon K. Likelihood of malignancy in a solitary pulmonary nodule: Comparison of Bayesian analysis and results of FDG-PET scan. Chest. 1997;112(2):416-22.

46. Lowe VJ, Duhaylongsod FG, Patz EF, Delong DM, Hoffman JM, Wolfe WG, et al. Pulmonary abnormalities and PET data analysis: a retrospective study. Radiology. 1997;202(2):435-9.

47. Prauer HW, Weber WA, Romer W, Treumann T, Ziegler SI, Schwaiger M. Controlled prospective study of positron emission tomography using the glucose analogue 18f fluorodeoxyglucose in the evaluation of pulmonary nodules. Br J Surg. 1998;85(11):1506-11.

48. Lowe VJ, Fletcher JW, Gobar L, Lawson M, Kirchner P, Valk P, et al. Prospective investigation of positron emission tomography in lung nodules. J Clin Oncol. 1998;16(3):1075-84.

49. Gupta N, Gill H, Graeber G, Bishop H, Hurst J, Stephens T. Dynamic positron emission tomography with F-18 fluorodeoxyglucose imaging in differentiation of benign from malignant lung/mediastinal lesions. Chest. 1998;114(4):1105-11.

50. Vaylet F, Foehrenbach H, De Dreuille O, Maszelin P, Merlet P, Bendriem B, et al. Fluorodeoxyglucose and bronchopulmonary cancer. Initial French results with positron emission tomography. Rev Pneumol Clin. 1998;54(4):187-95.

51. Graeber GM, Gupta NC, Murray GF. Positron emission tomographic imaging with fluorodeoxyglucose isefficacious in evaluating malignant pulmonary disease. J Thorac Cardiovasc Surg. 1999;117(4):719-27.

52. Richter JA, Torre W, Gamez C, Aramendia JM, Crespo A, Nicolas A, et al. Value of PET-18FDG in lung cancer. Medicina Clinica. 1999;113(15):567-71.

53. Halter G, Storck M, Guhlmann A, Frank J, Grosse S, Liewald F. FDG positron emission tomography in the diagnosis of peripheral pulmonary focal lesions. Thorac Cardiovasc Surg. 2000;48(2):97-101.

54. Imdahl A, Jenkner S, Brink I, Nitzsche E, Stoelben E, Moser E, et al. Validation of FDG positron emission tomography for differentiation of unknown pulmonary lesions. Eur J Cardiothorac Surg. 2001;20(2):324-9.

55. Lee J, Aronchick JM, Alavi A. Accuracy of F-18 fluorodeoxyglucose positron emission tomography for the evaluation of malignancy in patients presenting with new lung abnormalities: a retrospective review. Chest. 2001;120(6):1791-7.

56. Hain SF, Curran KM, Beggs AD, Fogelman I, O'Doherty MJ, Maisey MN. FDG-PET as a "metabolic biopsy" tool in thoracic lesions with indeterminate biopsy. Eur J Nucl Med. 2001;28(9):1336-40.

57. Hung GU, Shiau YC, Tsai SC, Ho YJ, Kao CH, Yen RF. Differentiation of radiographically indeterminate solitary pulmonary nodules with. Jpn J Clin Oncol. 2001;31(2):51-4.

58. Croft DR, Trapp J, Kernstine K, Kirchner P, Mullan B, Galvin J, et al. FDG-PET imaging and the diagnosis of non-small cell lung cancer in a region of high histoplasmosis prevalence. Lung Cancer. 2002;36(3):297-301.

59. Willkomm P, Bangard M, Guhlke S, Sartor J, Bender H, Gallkowski U, et al. Comparison of [18F]FDG-PET and L-3[123I]-iodo-alpha-methyl tyrosine (I-123 IMT)-SPECT in primary lung cancer. Ann Nucl Med. 2002;16(7):503-6.

60. Hickeson M, Yun M, Matthies A, Zhuang H, Adam L-E, Lacorte L, et al. Use of a corrected standardized uptake value based on the lesion size on CT permits accurate characterization of lung nodules on FDG-PET. European Journal of Nuclear Medicine. 2002;29(12):1639-47.

61. Pitman AG, Hicks RJ, Binns DS, Ware RE, Kalff V, McKenzie AF, et al. Performance of sodium iodide based (18)F-fluorodeoxyglucose positron emission tomography in the characterization of indeterminate pulmonary nodules or masses. Br J Radiol. 2002;75(890):114-21.

62. Buck AK, Halter G, Schirrmeister H, Kotzerke J, Wurziger I, Glatting G, et al. Imaging proliferation in lung tumors with PET: 18F-FLT versus 18F-FDG. J Nucl Med. 2003;44(9):1426-31.

63. Demura Y, Tsuchida T, Ishizaki T, Mizuno S, Totani Y, Ameshima S, et al. 18F-FDG accumulation with PET for differentiation between benign and malignant lesions in the thorax. J Nucl Med. 2003;44(4):540-8.

64. Ruiz-Hernandez G, de Juan R, Samanes A, Verea H, Penas JM, Veres A, et al. Positron emission tomography using 18-FDG-PET in radiologically indeterminate pulmonary lesions. An Med Interna. 2004;21(1):12-6.

65. Oturai PS, Mortensen J, Enevoldsen H, Eigtved A, Backer V, Olesen KP, et al. Gamma-camera 18F-FDG PET in diagnosis and staging of patients presenting with suspected lung cancer and comparison with dedicated PET. J Nucl Med. 2004;45(8):1351-7.

66. Herder GJ, Golding RP, Hoekstra OS, Comans EF, Teule GJ, Postmus PE, et al. The performance of 18F-fluorodeoxyglucose positron emission tomography in small solitary pulmonary nodules. European Journal of Nuclear Medicine and Molecular Imaging. 2004;31(9):1231-6.

67. Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. J Clin Epidemiol. 2001;54(10):1046-55.

68. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics. 2000;56(2):455-63.

69. Zamora J, Muriel A, Abraira V. Meta-Disc for Windows: a software package for the metaanalysis of Diagnostic Tests. In: Colloquium XC, editor. Barcelona; 2003.

70. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177-88.

71. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Bmj. 2003;327(7414):557-60.

72. Walter SD. Properties of the summary receiver operating characteristic (SROC) curve for diagnostic test data. Stat Med. 2002;21(9):1237-56.

73. Gould MK, Kuschner WG, Rydzak CE, Maclean CC, Demas AN, Shigemitsu H, et al. Test performance of positron emission tomography and computed tomography for mediastinal staging in patients with non-small-cell lung cancer: a meta-analysis. Ann Intern Med. 2003;139(11):879-92.

74. Hellwig D, Ukena D, Paulsen F, Bamberg M, Kirsch CM. [Meta-analysis of the efficacy of positron emission tomography with F-18-fluorodeoxyglucose in lung tumors. Basis for

discussion of the German Consensus Conference on PET in Oncology 2000]. Pneumologie. 2001;55(8):367-77.

75. Blum J, Handmaker H, Lister-James J, Rinne N. A multicenter trial with a somatostatin analog (99m)Tc depreotide in the evaluation of solitary pulmonary nodules. Chest. 2000;117(5):1232-8.

76. Hamm R. Clinical decision making spreadsheet calculator. In: Oklahoma DofmUo, editor.

77. Gould MK, Sanders GD, Barnett PG, Rydzak CE, Maclean CC, McClellan MB, et al. Cost-effectiveness of alternative management strategies for patients with solitary pulmonary nodules. Annals of Internal Medicine. 2003;138(9):724-35.

78. Dietlein M, Weber K, Gandjour A, Moka D, Theissen P, Lauterbach KW, et al. Cost-effectiveness of FDG-PET for the management of solitary pulmonary nodules: a decision analysis based on cost reimbursement in Germany. European Journal of Nuclear Medicine. 2000;27(10):1441-56.

79. Force. IoCPSNT. Clinical application and economic implications of PET in the assessment of solitary pulmonary nodules: a retrospective study. Foothill Ranch, California: ICP; 1994.

80. Keith CJ, Miles KA, Griffiths MR, Wong D, Pitman AG, Hicks RJ. Solitary pulmonary nodules: accuracy and cost-effectiveness of sodium iodide FDG-PET using Australian data. European Journal of Nuclear Medicine & Molecular Imaging. 2002;29(8):1016-23.

81. Gugiatti A, Grimaldi A, Rossetti C, Lucignani G, De Marchis D, Borgonovi E, et al. Economic analyses on the use of positron emission tomography for the work-up of solitary pulmonary nodules and for staging patients with non-small-cell-lung-cancer in Italy. The Quarterly Journal of Nuclear Medicine. 2004;48(1):49-61.

82. Birim O, Kappetein AP, Stijnen T, Bogers AJ. Meta-analysis of positron emission tomographic and computed tomographic imaging in detecting mediastinal lymph node metastases in nonsmall cell lung cancer. Ann Thorac Surg. 2005;79(1):375-82.

83. Medical Services Advisory C. Positron emission tomography. Canberra: Medical Services Advisory Committee; 2000.

84. Agence d'Evaluation des Technologies et des Modes d'Intervention en S. La tomographie par émission de positrons au Québec. Montréal: 2003. (AETMIS 01-3 RF) Available from: http://www.aetmis.gouv.qc.ca

85. Institute for Clinical Systems I. PET scans for solitary pulmonary nodules, non-small cell lung cancer, recurrent colorectal cancer, lymphoma, and recurrent melanoma. Bloomington, MN: Institute for Clinical Systems Improvement (ICSI); 2001.

86. MacManus MP, Hicks RJ, Ball DL, Ciavarella F, Binns D, Hogg A, et al. Imaging with F-18 FDG PET is superior to Tl-201 SPECT in the staging of non-small cell lung cancer for radical radiation therapy. Australasian Radiology. 2001;45(4):483-90.

87. Sachs S, Bilfinger TV. The impact of positron emission tomography on clinical decision making in a university-based multidisciplinary lung cancer practice. Chest. 2005;128(2):698-703.

88. Sloka JS, Hollett PD, Mathews M. Cost-effectiveness of positron emission tomography for non-small cell lung carcinoma in Canada. Medical Science Monitor. 2004;10(5):MT73-80.

89. Verboom P, van Tinteren H, Hoekstra OS, Smit EF, van den Bergh JH, Schreurs AJ, et al. Cost-effectiveness of FDG-PET in staging non-small cell lung cancer: the PLUS study. European Journal of Nuclear Medicine & Molecular Imaging. 2003;30(11):1444-9.

90. Matchar DB, Kulasingam SL, Havrilesky L, Mann LO, Myers ER, McCrory DC, et al. Positron emission testing for six cancers (brain, cervical, small cell lung, ovarian, pancreatic and testicular). Rockville: Agency for Healthcare Research and Quality (AHRQ); 2004.

91. Kamel EM, Zwahlen D, Wyss MT, Stumpe KD, von Schulthess GK, Steinert HC. Whole-body (18)F-FDG PET improves the management of patients with small cell lung cancer. J Nucl Med. 2003;44(12):1911-7.

92. Bradley JD, Dehdashti F, Mintun MA, Govindan R, Trinkaus K, Siegel BA. Positron emission tomography in limited-stage small-cell lung cancer: a prospective study. J Clin Oncol. 2004;22(16):3248-54.

93. Blum R, MacManus MP, Rischin D, Michael M, Ball D, Hicks RJ. Impact of positron emission tomography on the management of patients with small-cell lung cancer: preliminary experience. Am J Clin Oncol. 2004;27(2):164-71.

94. Brink I, Schumacher T, Mix M, Ruhland S, Stoelben E, Digel W, et al. Impact of [18F]FDG-PET on the primary staging of small-cell lung cancer. Eur J Nucl Med Mol Imaging. 2004;31(12):1614-20.

95. Mikhaeel NG, Hutchings M, Fields PA, O'Doherty M J, Timothy AR. FDG-PET after two to three cycles of chemotherapy predicts progression-free and overall survival in high-grade non-Hodgkin lymphoma. Ann Oncol. 2005;16(9):1514-23.

96. van Tinteren H, Hoekstra OS, Smit EF, van den Bergh JH, Schreurs AJ, Stallaert RA, et al. Effectiveness of positron emission tomography in the preoperative assessment of patients with suspected non-small-cell lung cancer: the PLUS multicentre randomised trial. Lancet. 2002;359(9315):1388-93.

97. Vansteenkiste J, Fischer BM, Dooms C, Mortensen J. Positron-emission tomography in prognostic and therapeutic assessment of lung cancer: systematic review. Lancet Oncol. 2004;5(9):531-40.

98. Benard F, Sterman D, Smith RJ, Kaiser LR, Albelda SM, Alavi A. Prognostic value of FDG PET imaging in malignant pleural mesothelioma. J Nucl Med. 1999;40(8):1241-5.

99. Duysinx B, Nguyen D, Louis R, Cataldo D, Belhocine T, Bartsch P, et al. Evaluation of pleural disease with 18-fluorodeoxyglucose positron emission tomography imaging. Chest. 2004;125(2):489-93.

100. Kramer H, Pieterman RM, Slebos DJ, Timens W, Vaalburg W, Koeter GH, et al. PET for the evaluation of pleural thickening observed on CT. J Nucl Med. 2004;45(6):995-8.

101. Schaffler GJ, Wolf G, Schoellnast H, Groell R, Maier A, Smolle-Juttner FM, et al. Non-small cell lung cancer: evaluation of pleural abnormalities on CT scans with 18F FDG PET. Radiology. 2004;231(3):858-65.

102. Carretta A, Landoni C, Melloni G, Ceresoli GL, Compierchio A, Fazio F, et al. 18-FDG positron emission tomography in the evaluation of malignant pleural diseases - a pilot study. Eur J Cardiothorac Surg. 2000;17(4):377-83.

103. Bury T, Paulus P, Dowlati A, Corhay JL, Rigo P, Radermecker MF. Evaluation of pleural diseases with FDG-PET imaging: preliminary report. Thorax. 1997;52(2):187-9.

104. Toaff JS, Metser U, Gottfried M, Gur O, Deeb ME, Lievshitz G, et al. Differentiation between malignant and benign pleural effusion in patients with extra-pleural primary malignancies: assessment with positron emission tomography-computed tomography. Invest Radiol. 2005;40(4):204-9.

105. Balogova S, Grahek D, Kerrou K, Montravers F, Younsi N, Aide N, et al. [[18F]-FDG imaging in apparently isolated pleural lesions]. Rev Pneumol Clin. 2003;59(5 Pt 1):275-88.

106. Harris NL. Principles of the revised European-American Lymphoma Classification (from the International Lymphoma Study Group). Ann Oncol. 1997;8 Suppl 2:11-6.

107. ICES, Laupacis A, Institute for Clinical Evaluative S. Health technology assessment of PET (positron emission tomography). Toronto: Institute for Clinical Evaluative Sciences (ICES); 2001.

108. Medical Services Advisory C. Positron emission tomography [Part 2(ii)]. Canberra: Medical Services Advisory Committee (MSAC); 2001.

109. Scottish-Executive. Implementation of HTBS' Health Technology Assessment of Positron-Emission Tomography in Scotland

Report and Recommendations. Scottish Executive Health Departmrnt, NHS Scotland; 2003 October 2003. (HHS HDL (2003)63) Available from:

http://web.archive.org/web/20041128042520/www.show.scot.nhs.uk/sehd/cancerinscotland/Documents/PETFinalreport.pdf

110. Middleton J, Reeves D. What is an integrated care pathway? 2003. What is....?

111. Friedberg JW, Fischman A, Neuberg D, Kim H, Takvorian T, Ng AK, et al. FDG-PET is superior to gallium scintigraphy in staging and more sensitive in the follow-up of patients with de novo Hodgkin lymphoma: a blinded comparison. Leukemia & Lymphoma. 2004;45(1):85-92.

112. Jerusalem G, Beguin Y, Fassotte MF, Belhocine T, Hustinx R, Rigo P, et al. Early detection of relapse by whole-body positron emission tomography in the follow-up of patients with Hodgkin's disease. Annals of Oncology. 2003;14(1):123-30.

113. Dobert N, Menzel C, Berner U, Hamscho N, Wordehoff N, Mitrou P, et al. Positron emission tomography in patients with Hodgkin's disease: correlation to histopathologic subtypes. Cancer Biotherapy & Radiopharmaceuticals. 2003;18(4):565-71.

114. Itti E, Haioun C, Rahmouni A, Reyes F, Meignan M. Agressive large cell lymphoma: Early assessment of therapeutic efficacy by positron emission tomography. Medecine Nucleaire. 2004;28(7):327-32.

115. Zinzani PL, Chierichetti F, Zompatori M, Tani M, Stefoni V, Garraffa G, et al. Advantages of positron emission tomography (PET) with respect to computed tomography in the follow-up of lymphoma patients with abdominal presentation. Leukemia and Lymphoma. 2002;43(6):1239-43.

116. BCBS. FDG Positron Emission Tomography in Head and Neck Cancer. Chicago IL: Blue Cross Blue Shield Association (BCBS); 2000.

117. Danish Centre for E, Health Technology A. Positron emissions tomography (PET) with 18-F-fluorodeoxyglucose (FDG). A literature review of evidence for clinical use in the fields of oncology, cardiology and neurology. Copenhagen: Danish Centre for Evaluation and Health Technology Assessment (DACEHTA) (formerly DIHTA); 2001.

118. Vermeersch H, Loose D, Ham H, Otte A, Van de Wiele C. Nuclear medicine imaging for the assessment of primary and recurrent head and neck carcinoma using routinely available tracers. Eur J Nucl Med Mol Imaging. 2003;30(12):1689-700.

119. Blue Cross Blue Shield A. FDG PET to manage patients with an occult primary carcinoma and metastasis outside the cervical lymph nodes. Chicago IL: Blue Cross Blue Shield Association; 2002.

120. Delgado-Bolton RC, Fernandez-Perez C, Gonzalez-Mate A, Carreras JL. Meta-analysis of the performance of 18F-FDG PET in primary tumor detection in unknown primary tumors. J Nucl Med. 2003;44(8):1301-14.

121. Goerres GW, Mosna-Firlejczyk K, Steurer J, von Schulthess GK, Bachmann LM. Assessment of clinical utility of 18F-FDG PET in patients with head and neck cancer: a probability analysis. Eur J Nucl Med Mol Imaging. 2003;30(4):562-71.

122. Hollenbeak CS, Lowe VJ, Stack BC, Jr. The cost-effectiveness of fluorodeoxyglucose 18-F positron emission tomography in the N0 neck. Cancer. 2001;92(9):2341-8.

123. Kantorova I, Lipska L, Belohlavek O, Visokai V, Trubac M, Schneiderova M. Routine 18F-FDG PET preoperative staging of colorectal cancer: Comparison with conventional staging and its impact on treatment decision making. Journal of Nuclear Medicine. 2003;44(11):1784-8.

124. Kinkel K, Lu Y, Both M, Warren RS, Thoeni RF. Detection of hepatic metastases from cancers of the gastrointestinal tract by using noninvasive imaging methods (US, CT, MR imaging, PET): a meta-analysis. Radiology. 2002;224(3):748-56.

125. Timm S, Sailer MA, Baum RP, Debus ES, Thiede A. The value of positron-emission tomography (PET) in the follow-up of patients with rectal carcinoma. Coloproctology. 2002;24(4):197-202.

126. Rosa F, Meimarakis G, Stahl A, Bumm R, Hahn K, Tatsch K, et al. Colorectal cancer patients before resection of hepatic metastases. Impact of (18)F-FDG PET on detecting extrahepatic disease. Nuclear Medizin. 2004;43(4):135-40.

127. Dietlein M, Weber W, Schwaiger M, Schicha H. [18F-Fluorodeoxyglucose positron emission tomography in restaging of colorectal cancer]. [German]. Nuclear-Medizin. 2003;42(4):145-56.

128. Park KC, Schwimmer J, Shepherd JE, Phelps ME, Czernin JR, Schiepers C, et al. Decision analysis for the cost-effective management of recurrent colorectal cancer. Annals of Surgery. 2001;233(3):310-9.

129. Sloka JS, Hollett PD, Mathews M. Cost-effectiveness of positron emission tomography in recurrent colorectal cancer in Canada. McGill Journal of Medicine. 2004;7(2):165-74.

130. Mijnhout GS, Hoekstra OS, van Tulder MW, Teule GJ, Deville WL. Systematic review of the diagnostic accuracy of (18)F-fluorodeoxyglucose positron emission tomography in melanoma patients. Cancer. 2001;91(8):1530-42.

131. Havenga K, Cobben DCP, Oyen WJG, Nienhuijs S, Hoekstra HJ, Ruers TJM, et al. Fluorodeoxyglycose-positron emission tomography and sentinel lymph node biopsy in staging primary cutaneous melanoma. European Journal of Surgical Oncology. 2003;29(8):662-4.

132. Fink AM, Holle-Robatsch S, Herzog N, Mirzaei S, Rappersberger K, Lilgenau N, et al. Positron emission tomography is not useful in detecting metastasis in the sentinel lymph node in patients with primary malignant melanoma stage I and II. Melanoma Research. 2004;14(2):141-5.

133. Vereecken P, Laporte M, Petein M, Steels E, Heenen M. Evaluation of extensive initial staging procedure in intermediate/high-risk melanoma patients. Journal of the European Academy of Dermatology & Venereology. 2005;19(1):66-73.

134. Blue Cross Blue Shield A. FDG positron emission tomography for evaluating breast cancer. Chicago IL: Blue Cross Blue Shield Association; 2003.

135. BCBS. FDG positron emission tomography for evaluating breast cancer. Chicago IL: Blue Cross Blue Shield Association; 2001.

136. Wahl RL, Siegel BA, Coleman RE, Gatsonis CG, Group PETS. Prospective multicenter study of axillary nodal staging by positron emission tomography in breast cancer: a report of the staging breast cancer with PET Study Group. Journal of Clinical Oncology. 2004;22(2):277-85.

137. Zornoza G, Garcia-Velloso MJ, Sola J, Regueira FM, Pina L, Beorlegui C. 18F-FDG PET complemented with sentinel lymph node biopsy in the detection of axillary involvement in breast cancer. European Journal of Surgical Oncology. 2004;30(1):15-9.

138. Isasi CR, Moadel RM, Blaufox MD. A meta-analysis of FDG-PET for the evaluation of breast cancer recurrence and metastases. Breast Cancer Res Treat. 2005;90(2):105-12.

139. Blue Cross Blue Shield A. FDG positron emission tomography for evaluating esophageal cancer. Chicago IL: Blue Cross Blue Shield Association; 2002.

140. Medical Services Advisory C. Positron emission tomography [Part 2(i)]. Canberra: Medical Services Advisory Committee (MSAC); 2001. Available from: http://www.msac.gov.au/reports.htm

141. van Westreenen HL, Westerterp M, Bossuyt PM, Pruim J, Sloof GW, van Lanschot JJ, et al. Systematic review of the staging performance of 18F-fluorodeoxyglucose positron emission tomography in esophageal cancer. J Clin Oncol. 2004;22(18):3805-12.

142. Westerterp M, van Westreenen HL, Reitsma JB, Hoekstra OS, Stoker J, Fockens P, et al. Esophageal Cancer: CT, Endoscopic US, and FDG PET for Assessment of Response to Neoadjuvant Therapy--Systematic Review. Radiology. 2005;236(3):841-51.

143. Wieder HA, Brucher BL, Zimmermann F, Becker K, Lordick F, Beer A, et al. Time course of tumor metabolic activity during chemoradiotherapy of esophageal squamous cell carcinoma and response to treatment. J Clin Oncol. 2004;22(5):900-8.

144. Swisher SG, Erasmus J, Maish M, Correa AM, Macapinlac H, Ajani JA, et al. 2-Fluoro-2-deoxy-D-glucose positron emission tomography imaging is predictive of pathologic response and survival after preoperative chemoradiation in patients with esophageal carcinoma. Cancer. 2004;101(8):1776-85.

145. Hooft L, Hoekstra OS, Deville W, Lips P, Teule GJ, Boers M, et al. Diagnostic accuracy of 18F-fluorodeoxyglucose positron emission tomography in the follow-up of papillary or follicular thyroid cancer. J Clin Endocrinol Metab. 2001;86(8):3779-86.

146. AHRQ. Systematic review of positron emission tomography for follow-up of treated thyroid cancer. Rockville: Agency for Health Care Research and Quality (AHRQ); 2002.

147. Orlando LA, Kulasingam SL, Matchar DB. Meta-analysis: the detection of pancreatic malignancy with positron emission tomography. Aliment Pharmacol Ther. 2004;20(10):1063-70.

148. Merck & Co., Merck Sharp & Dohme., Merck Research Laboratories. The Merck manual of diagnosis and therapy. In. Rahway, N.J.: Merck; 1950. p. v.

149. Goerres GW, Stupp R, Barghouth G, Hany TF, Pestalozzi B, Dizendorf E, et al. The value of PET, CT and in-line PET/CT in patients with gastrointestinal stromal tumours: long-term outcome of treatment with imatinib mesylate. Eur J Nucl Med Mol Imaging. 2005;32(2):153-62.

150. Choi H, Charnsangavej C, de Castro Faria S, Tamm EP, Benjamin RS, Johnson MM, et al. CT evaluation of the response of gastrointestinal stromal tumors after imatinib mesylate treatment: a quantitative analysis correlated with FDG PET findings. AJR Am J Roentgenol. 2004;183(6):1619-28.

151. Antoch G, Kanja J, Bauer S, Kuehl H, Renzing-Koehler K, Schuette J, et al. Comparison of PET, CT, and dual-modality PET/CT imaging for monitoring of imatinib (STI571) therapy in patients with gastrointestinal stromal tumors. J Nucl Med. 2004;45(3):357-65.

152. Jager PL, Gietema JA, van der Graaf WT. Imatinib mesylate for the treatment of gastrointestinal stromal tumours: best monitored with FDG PET. Nucl Med Commun. 2004;25(5):433-8.

153. Gayed I, Vu T, Iyer R, Johnson M, Macapinlac H, Swanston N, et al. The role of 18F-FDG PET in staging and early prediction of response to therapy of recurrent gastrointestinal stromal tumors. J Nucl Med. 2004;45(1):17-21.

154. Agencia de Evaluacion de Tecnologias S. Positron emission tomography (PET) in cardiology. IPE-95/e (Public report). Madrid: Agencia de Evaluacion de Tecnologias Sanitarias (AETS); 1995.

155. Adams RD, Victor M. Principles of neurology, fifth edition. Companion handbook. New York: McGraw-Hill, Health Professions Division; 1994.

156. Areosa SA, Sherriff F, McShane R. Memantine for dementia. Cochrane Database Syst Rev. 2005(3):CD003154.

157. Seltzer B, Zolnouni P, Nunez M, Goldman R, Kumar D, Ieni J, et al. Efficacy of donepezil in early-stage Alzheimer disease: a randomized placebo-controlled trial. Arch Neurol. 2004;61(12):1852-6.

158. Petersen RC, Thomas RG, Grundman M, Bennett D, Doody R, Ferris S, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med. 2005;352(23):2379-88.

159. Carnero-Pardo C. [Systematic review of the value of positron emission tomography in the diagnosis of Alzheimer's disease]. Rev Neurol. 2003;37(9):860-70.

160. Courtney C, Farrell D, Gray R, Hills R, Lynch L, Sellwood E, et al. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. Lancet. 2004;363(9427):2105-15.

161. Kaduszkiewicz H, Zimmermann T, Beck-Bornholdt HP, van den Bussche H. Cholinesterase inhibitors for patients with Alzheimer's disease: systematic review of randomised clinical trials. Bmj. 2005;331(7512):321-7.

162. Kmietowicz Z. NICE proposes to withdraw Alzheimer's drugs from NHS. Bmj. 2005;330(7490):495.

163. Matchar DB, Kulasingam SL, Huntington A, Patwardhan M, Mann LO, Agency for Healthcare R, et al. Positron emission tomography, single photon emission computed tomography, computed tomography, functional magnetic resonance imaging, and magnetic resonance spectroscopy and for the diagnosis and management of Alzheimer's dementia. Rockville: Agency for Healthcare Research and Quality (AHRQ); 2004.

164. Matchar DB, Kulasingam SL, McCrory DC, Patwardhan MB, Rutschmann OT, Samsa GP, et al. Use of positron emission tomography and other neuroimaging techniques in the diagnosis and management of Alzheimer's disease and dementia. Rockville: Agency for Healthcare Research and Quality (AHRQ); 2001.

165. Adams E, Technology Assessment U, Management D, Research C, Affairs USDoV. Evaluating diagnostic tests: a guide to the literature. Boston: U. S. Department of Veterans Affairs; 1997.

166. Agencia de Evaluacion de Tecnologias S. Positron emission tomography with fluordeoxyglucose (FDG-PET) in neurology. IPE-99/18. Madrid: Agencia de Evaluacion de Tecnologias Sanitarias (AETS); 1999.

167. Patwardhan MB, McCrory DC, Matchar DB, Samsa GP, Rutschmann OT. Alzheimer disease: operating characteristics of PET--a meta-analysis. Radiology. 2004;231(1):73-80.

168. Pirotte B, Goldman S, Massager N, David P, Wikler D, Vandesteene A, et al. Comparison of 18F-FDG and 11C-methionine for PET-guided stereotactic brain biopsy of gliomas. J Nucl Med. 2004;45(8):1293-8.

169. Levivier M, Goldman S, Pirotte B, Brotchi J. First year experience using the Fischer ZD-Neurosurgical Localizing Unit with particular reference to the development of PET-guided stereotactic biopsy. Acta Neurol Belg. 1993;93(1):5-22.

170. Levivier M, Massager N, Wikler D, Lorenzoni J, Ruiz S, Devriendt D, et al. Use of stereotactic PET images in dosimetry planning of radiosurgery for brain tumors: clinical experience and proposed classification. J Nucl Med. 2004;45(7):1146-54.

171. Levivier M, Wikler D, Jr., Massager N, David P, Devriendt D, Lorenzoni J, et al. The integration of metabolic imaging in stereotactic procedures including radiosurgery: a review. J Neurosurg. 2002;97(5 Suppl):542-50.

172. MSAC. Positron emission tomography (PET) for epilepsy. Canberra: Medical Services Advisory Committee (MSAC); 2004. (26)

173. Stumpe KD, Notzli HP, Zanetti M, Kamel EM, Hany TF, Gorres GW, et al. FDG PET for differentiation of infection and aseptic loosening in total hip replacements: comparison with conventional radiography and three-phase bone scintigraphy. Radiology. 2004;231(2):333-41.

174. Blockmans D, Knockaert D, Maes A, De Caestecker J, Stroobants S, Bobbaers H, et al. Clinical value of [(18)F]fluoro-deoxyglucose positron emission tomography for patients with fever of unknown origin. Clin Infect Dis. 2001;32(2):191-6.

175. Bedford M, Maisey MN. Requirements for clinical PET: comparisons within Europe. Eur J Nucl Med Mol Imaging. 2004;31(2):208-21.

176. Comite d'Evaluation et de Diffusion des Innovations T. Positron emission tomography. Paris: Comite d'Evaluation et de Diffusion des Innovations Technologiques (CEDIT); 2001.

177. Muller A, Stratmann-Schone D, Klose T, Leidl R, German Agency for Health Technology Assessment at the German Institute for Medical D, Information. Positron emission tomography - the economic efficacy. Koln: German Agency for Health Technology Assessment at the German Institute for Medical Documentation and Information; 2000.

178. Keppler JS, Conti PS. A cost analysis of positron emission tomography. Ajr. 2001;American Journal of Roentgenology. 177(1):31-40.

179. Berger M, Gould MK, Barnett PG. The cost of positron emission tomography in six United States Veterans Affairs hospitals and two academic medical centers. Ajr. 2003;American Journal of Roentgenology. 181(2):359-65.

180. Hastings J, Adams E, Almazàn C, Morland B, Bradbury I, King R, et al. Positron Emission Tomography: update of members' experiences with PET. Stockholm: International Network of Agencies for Health Technology Assessment; 2005 June 2005.

181. Silberstein EB. Prevalence of adverse reactions to positron emitting radiopharmaceuticals in nuclear medicine. Pharmacopeia Committee of the Society of Nuclear Medicine. J Nucl Med. 1998;39(12):2190-2.

182. Sciences IfCE. Health technology assessment of positron emission tomography in oncology - a systematic review. Toronto: Institute for Clinical Evaluative Sciences (ICES); 2003.

183. Weber WA, Ziegler SI, Thodtmann R, Hanauske AR, Schwaiger M. Reproducibility of metabolic measurements in malignant tumors using FDG PET. J Nucl Med. 1999;40(11):1771-7.

12. APPENDIX

DEFINITIONS

METHODOLOGIES USED FOR SUMMARISING DIAGNOSTIC STUDIES

TP, FP, TN, FN

In diagnostic studies, the most common method of evaluating diagnostic accuracy is by the calculation of sensitivity and specificity.

True positives (TP) are the subjects with the condition of interest (e.g. disease, tumour,....) and a positive test result. False positives (FP) are the subjects without the condition of interest but with a positive test result.

True negatives (TN) are the subjects without the condition of interest and a negative test result. False negatives (FN) are the subjects with the condition of interest but with a negative test result.

Sensitivity is the probability of a positive test result in a subject with the condition of interest.

Specificity is the probability of a negative test result in a subject without the condition of interest.

These can be calculated as follows:

Sensitivity (sens) = TP/(TP+FN)

Specificity (spec) = TN/(TN+FP)

Accuracy is calculated as (TP+TN)/(TP+FN+TN+FP)

When the prevalence of a condition is known, the negative predictive value (NPV) can be calculated:

NPV = (prevalence of condition absent) (spec)

((prev. of condition absent) (spec) + (prev. of condition present)(1-sens))

To summarise the discriminative value of a test, the diagnostic odds ratio (DOR) is often used. This is the ratio of the odds of a positive test result in patients with the condition of interest over the odds of a positive test result in patients without the condition.

DOR = sensitivity/(1-sensitivity)

(1-specificity)/specificity

DOR=1 implies that the odds of a positive result in those with and without the condition of interest is equal, so the test has no discriminative power. Values >1 imply better discrimination of those with the condition of interest, with higher levels implying better discrimination.

One method of summarising diagnostic study results is to pool the estimates of sensitivity and to separately pool the estimates of specificity, using two separate analyses. For this, two forms of meta-analysis models can be used. A fixed effects model, which only includes within study variation or a random effects model, which includes within study and between study variation. The latter gives wider confidence intervals and is probably more appropriate given the obvious heterogeneity in the studies. However, in some cases a random-effects model may give a negative variance estimate, indicating that the true between study variance is small. In this situation, a fixed effect model should be used.

Sensitivity and specificity are inter-related and depend on the characteristics of the condition of interest in the study. Separate analyses of sensitivity and specificity ignore this and tend to underestimate the true parameters. Alternative methods of summarising the sensitivity and specificity across studies are the summary receiver operating characteristic, or the likelihood ratio. (adapted from K Facey).

LITERATURE REVIEW

Introduction:

In order to assess the evidence on diagnostic accuracy and clinical effectiveness of PET, HTA reports, and systematic reviews were first searched. The evidence for each clinical indication was synthesized and, according to the level of evidence, indications without clear conclusion and/or with no search update after the year 2002 were selected for a primary studies search. For specific reasons explained in the report, a search of literature for SPN was also performed.

The assessments were performed independently by two experts of the KCE. Disagreements between experts were discussed and, when no consensus was reached, a third expert was asked to arbitrate.

HTA REPORTS:

How?

The search terms were: PET/Title & Abstract OR Positron emission tomography/Title & Abstract first and then PET/All fields.

When?

The search was performed on 19/1/2005, and then updated up to April 2005

Where?

The following databases were searched:

Health Technology Assessment Database (HTA), NHS Economic Evaluation Database (NHS EED), Database of Abstracts of Reviews of Effects (DARE).

The websites of the following HTA agencies were searched and when available, a report on PET downloaded:

1. Aetmis http://www.aetmis.gouv.qc.ca/
2. INAHTA http://www.inahta.org/
3. AHRQ http://www.ahrq.gov/
4. AHFMR http://www.ahfmr.ab.ca/
5. Blue Cross Blue Shield http://www.bcbs.com/
6. DACEHTA – Sundhedsstyrelsen http://www.sst.dk/Planlaegning_og_behandling/Medicinsk_teknologivurdering.aspx?lang=en or http://www.cemtv.dk
7. Centers for Medicare and Medicaid Services http://www.cms.hhs.gov
8. Intercollegiate Standing Committee on Nuclear Medicine UK http://www.rcplondon.ac.uk/pubs/wp_pet.pdf
9. NHS Scotland http://www.show.scot.nhs.uk/ and HTBS http://www.htbs.org.uk/board.htm
10. FNCLCC http://www.fnclcc.com/
11. ICES http://www.ices.on.ca/
12. ICSI http://www.icsi.org/
13. MSAC http://www.msac.gov.au/
14. CEDIT http://cedit.aphp.fr/
15. AETS http://sid.usal.es/
16. AETSA http://www.juntadeandalucia.es/

17. Veterans Health Administration http://www.va.gov/

18. HSTAT NLM http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat

19. NCCHTA http://www.ncchta.org/

20 Norway http://www.kunnskapssenteret.no/index.php?back=2&artikkelid=73

21 Catalan agency for HTA http://www.aatrm.net/html/en/dir407/

22 SNHTA http://www.snhta.ch/home/portal.php

23 Hayes http://www.hayesinc.com/

24 Rand corporation http://www.rand.org/

25. HTAi http://www.htai.org/

26. NZHTA http://nzhta.chmeds.ac.nz/

27. ECRI http://www.ecri.org/

28. University of Birmingham http://www.pcpoh.bham.ac.uk/publichealth/wmhtac/

29. CIHR http://www.cihr-irsc.gc.ca/

30. CCOHTA http://www.ccohta.ca/entry_e.html

31.MIHSR http://www.med.monash.edu.au/healthservices/cce/

32. Royal Australian College of Surgeons
http://www.surgeons.org/Content/NavigationMenu/ResearchandExternalAffairs/Research/ASERNIPS/default.htm

33. OHPPR http://www.ohppr.state.or.us/hrc/welcome_hrcreport.htm

34. Instituto de Salud Carlos III http://www.isciii.es/publico/

35. German Institute of Medical Documentation and Information DIMDI
http://www.dimdi.de/static/en/hta/

36. NHS DoH http://www.dh.gov.uk/Home/fs/en

37. Nasjonalt kunnskapssenteret for helsetjenesten http://www.kunnskapssenteret.no/

The following reports were downloaded:

1. La tomographie par émission de positrons au Québec (PDF 2 282 K)
Montréal: AETMIS, 2001, xvi-270 p. (ISBN2-550-37972-1).

http://www.aetmis.gouv.qc.ca/fr/publications/scientifiques/imagerie_medicale/2001_03_fr.pdf

2. INAHTA Positron Emission Tomography Experience with PET and Synthesis of the Evidence.
Stockholm: International Network of Agencies for Technology Assessment, 1999

http://www.inahta.org/Reports.asp?name=Content11%2Fpublikationer%2F9%2Fpet%2Epdf

3. AHRQ

Positron Emission Tomography (FDG) for Brain, Cervical, Ovarian, Pancreatic, Small Cell Lung, and Testicular Cancers (2003) (Zipped File, 400 KB)
Positron Emission Tomography (FDG) for Breast Cancer (2001) (PDF File, 890 KB)
Positron Emission Tomography (FDG) for Myocardial Viability (2001) (PDF File, 200 KB)
Positron Emission Tomography (FDG) for Soft Tissue Sarcoma (2002) (Zipped File, 18 KB)
Positron Emission Tomography (FDG) for Thyroid Cancer (2002) (Zipped File, 83 KB)
Use of Positron Emission Tomography and Other Neuroimaging Techniques in the Diagnosis and Management of Alzheimer's

Disease and Dementia (2001) (PDF File, 800 KB)
Use of Positron Emission Tomography (FDG) for Alzheimer's
Disease and Dementia Update (2004) In work

http://www.ahrq.gov/clinic/techix.htm

http://www.bcbs.com/sitesearch/search.asp?QueryText=DiagnosticImaging%20(category)

4. AHFMR Functional diagnostic imaging in epilepsy – Technology Assessment Report

Paula Corabian, David Hailey August 1998, HTA10

http://www.ahfmr.ab.ca/publications.html

5. Blue Cross Blue Shield

FDG PET to Manage patients with an Occult primary Carcinoma and Metastasis Outside the Cervical Lymph Nodes

FDG Positron Emission Tomography for Evaluating Breast cancer

6. Denmark

http://www.cemtv.dk/publikationer/docs/PET/Redegoerelse.pdf

http://www.cemtv.dk/publikationer/docs/PET/katalog.pdf

7. DoH NHS

http://www.cms.hhs.gov/manuals/pm_trans/R171CIM.pdf

8. Intercollegiate Standing Committee on Nuclear Medicine UK

http://www.rcplondon.ac.uk/pubs/wp_pet.pdf

9. NHS Scotland

http://www.show.scot.nhs.uk/sehd/cancerinscotland/Documents/PETFinalreport.pdf

10. FNCLCC

http://www.fnclcc.com/fr/sor/pdf/rapport_integral/BP_EVA_Util-TEP-FDG_int.pdf

11. ICES

http://www.ices.on.ca/webpage.cfm?site_id=1&org_id=68&morg_id=0&gsec_id=0&item_id=1536&type=report

12. ICSI

http://www.icsi.org/knowledge/browse_bydate.asp?catID=107&page=7

13. MSAC

http://www.msac.gov.au/reports.htm

14. CEDIT 1997 et 2001

http://cedit.aphp.fr/index_pub.html

http://cedit.aphp.fr/index_nouv.html

15. AETS

http://sid.usal.es//webexterna.asp?url=http%3A%2F%2Fwww%2Eisciii%2Ees%2Faets%2F&origen=http%3A%2F%2Fsid%2Eusal%2Ees%2Fmostrarficha%2Easp%3FID%3D9803%26fichero%3D2%2E1%2E3

http://sid.usal.es//webexterna.asp?url=http%3A%2F%2Fwww%2Eisciii%2Ees%2Faets%2F&origen=http%3A%2F%2Fsid%2Eusal%2Ees%2Fmostrarficha%2Easp%3FID%3D9803%26fichero%3D2%2E1%2E3

16. AETSA

http://www.juntadeandalucia.es/salud/orgdep/AETSA/pdf/pet_pub.pdf

17. Veterans Health Administration

http://www.va.gov/vatap/pubs/petupdate_list.htm

18. Surgeon General of Minnesota

http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat6.chapter.2219

19. NCCHTA

http://www.ncchta.org/fullmono/mon316.pdf or via
http://www.ncchta.org/execsumm/SUMM316.HTM

20. HTBS http://www.nhshealthquality.org/nhsqis/files/as%20one.doc#_Toc37828407

21. Norway http://www.kunnskapssenteret.no/filer/Rapport6-03.pdf

Selection process:

The reports were critically appraised with the help of the INAHTA checklist:

Checklist for HTA - INAHTA			
	Yes	Partly	No
Preliminary			
Are contact details available for further information?			
Authors identified?			
Statement regarding conflict of interest?			
Statement on whether report externally reviewed?			
Short summary in non-technical language?			
Why?			
Reference to the question that is addressed and context of assessment?			
Scope of the assessment specified?			
Description of the health technology?			
How?			
Details on sources of information?			
Information on selection of material for assessment?			
Information on basis for interpretation of selected data?			
What?			
Results of assessment clearly presented?			
Interpretation of assessment results included?			
What then?			
Findings of the assessment discussed?			
Medico-legal implications considered?			
Conclusions from assessment clearly stated?			
Suggestions for further action?			

Results: Several HTA reports integrate findings and conclusions from previous reports. In that case, only the most recent report was retained. The selected HTA reports were:

1) HTBS,

2) FNCLCC,

3) MSAC 200 and 2001

4) DACEHTA,

5)BCBS,

6) AHRQ 2001 and 2004

7) ICES

and for specific indications, AETMIS, ICSI and AETS.

We received also the Ultra Rapid Review of K.Facey et al, and after critical appraisal, decided to include it in our selection.

The evidence tables for HTA reports are presented hereunder:

HTA REPORTS

HTA-reports were identified and selected following a search on 19/01/2005 in the CRD database using the following search string: "PET/All fields".

The Norwegian HTA-update Report on PET (NHSRC 2003; SMM-report 6/2003) summarizes conclusions and recommendations of relevant HTA reports (n=14) and Systematic Reviews (n=3) published after the INATHA joint project on PET (1999) and a first SMM report (2000).

The following databases were searched: HTA databases, DARE, NHSEED, TRIP database. Search terms: "positron AND emission OR PET AND HTA reports". Time limits: 2001-2003. Language: Norwegian (Scientific Summary in English on p.31; Summary also in INATHA Briefs Issue 2004/80).General conclusions and results: "PET is more accurate than other diagnostic procedures for several indications in oncology and should therefore be used. This applies mainly in diagnosing non-small cell lung cancer (NSCLC), identifying metastasis from malignant melanoma and colorectal cancer and in finding tumors in the head/neck. It is important to note that PET is still in the development phase. Hence, examinations should be performed within the framework of clinical trials since there is a need for knowledge collected systematically". HTA-reports summarized in the SMM-report 6/2003 are the following: ICES 2003; AETMIS 2002; HTBS 2002; AHRQ 2002 (SR); AHRQ 2002 (TA); AHRQ 2001(TA); AHRQ 2001(SR); DACEHTA 2001a; DACEHTA 2001b; ICES 2001; CEDIT 2001; MSAC 2001 [part 2(i)]; MSAC 2001 [part 2(ii)]; MSAC 2000.

http://www.kunnskapssenteret.no/smm/Publications/Engsmdrag/FramesetPublications.htm

ONCOLOGY

BRONCHOPULMONARY AND PLEURAL CANCERS

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
ICES *Canada* April 2004 (Quarterly updates i.e. Jan 2004, Sept 2003, May 2003)	Health technology assessment of PET (positron emission tomography): a systematic review. Lauparis A, Paszat L, Hodgson D, Benk V. (ICES) 2004. (health technology assessment of positron emission tomography (PET) in oncology-a systematic review-ICES investigative report)	PET	Fair	PET literature review and assessment of articles Update from Nov 1,2002 up to and including Apr 1, 2004. (updates on ICES 2001 original report)	*-Populations studied (2 "A" Grade, 21 "B" Grade studies)*: *Studies on diagnosis of the solitary pulmonary nodule; staging of primary carcinoma of the lung/evaluation of mediastinal lymph nodes; detection of residual or recurrent carcinoma of the lung; detection of bone metastases from primary carcinoma of the lung; detection of malignant pleural effusion; prediction of survival.* *-Potential impact of PET on processes of care for carcinoma of the lung* There is evidence for the efficacy of PET in distinguishing benign from malignant solitary pulmonary nodules (SPN). The use of PET in this context would reduce patient morbidity by reducing the number of unnecessary thoracotomies performed for SPN. There is conflicting evidence about whether or not preoperative PET among patients with a diagnosis of lung cancer would reduce the number of unnecessary thoracotomies in this setting. Possibly, PET may achieve reductions in the rate of unnecessary thoracotomies only if there is strict to guidelines about processes of care for various results of preoperative PET among patients with a diagnosis of lung cancer. There is evidence for the efficacy of PET in predicting the histological status of mediastinal lymph nodes and in detecting malignant pleural effusion in patients with carcinoma of the lung, and that PET is more efficacious than CT. However, staging and preoperative procedures prior to attempted resection of carcinoma of the lung vary among practitioners. Among those who use *mediastinoscopy* as a staging procedure would be avoidable if PET were available. Among those who do not use mediastinoscopy and take patients with CT negative mediastinal nodes to resection directly, some thoracotomies might be avoided. It is unclear if the utilization of CT would decrease at all if PET were available, because the anatomical information provided by CT (which is better than that provided by PET) might still be needed. No study has been published evaluating the effect of PET upon the frequency of thoracotomy in this setting. Although recurrent carcinoma of the lung is usually incurable, residual or recurrent

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
					carcinoma may be detected most accurately by PET, and would coincidentally provide better assessment of the possibility of bone metastases which frequently accompany residual or recurrent carcinoma. The number of bone scans would likely decrease. In addition, PET appears to provide important prognostic information about patients with carcinoma of the lung, and might allow radiation therapy for carcinoma of the lung to be designed in a manner which would reduce the amount of normal lung tissue exposed to radiation. The role of PET as a predictor of survival in patients with NSCLC has recently been demonstrated.
AHRQ *USA* 2004	Positron emission testing for six cancers (brain, cervical, small cell lung, ovarian, pancreatic and testicular). Matchar D B, Kulasingam S L, Havrilesky L, Mann L O, Myers E R, McCrory D C, Patwardhan M, Prosnitz R. Agency for Healthcare Research and Quality (AHRQ) 2004 (Technology Assessment): 221.	Performance of FDG-PET compared to conventional imaging (CT/MRI) in Small Cell Lung Cancer (SCLC)	Good (but without clear recom-menda-tions)	Search: MEDLINE <1966 to April Week 1 2003>	-Staging: inconclusive evidence due to limited ability to comment on the comparative test accuracy performance of PET in 3 studies and small sample sizes in 2 studies. -Restaging post treatment (detect residual or new disease sites): suggestive of a role of PET but not definitive due to a lack of comparative data on CT/MRI performance. -Diagnosis of occult SCLC in patients with paraneoplastic syndrome(s): role of PET suggested but only a single study with too small sample size and no comparator test.

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
FNCLCC *France* 2003	Recommandations pour la pratique clinique : standards, options et recommandations 2003 pour l'utilisation de la tomographie par émission de positrons au [18-F]-FDG (TEP-FDG) en cancérologie (rapport intégral) (FNCLCC) 2003 :290.	FDG-PET in pulmonary nodules and masses. In particular: also assessment of PET in small cell lung cancer, bronchiolo-alveolar carcinoma, carcinoid tumors	Fair	*Translation of French* Search from January 1966 until October 2002 *The difference between nodules and masses is related to tumor size (usually 3 cm)*	-Place of PET in the diagnosis of malignity in bronchopulmonary lesions. *Standards*: PET is indicated in the diagnosis of a solitary pulmonary nodule >1cm, without definite signs of benignity on imaging (calcifications) (evidence level A). However, certain inflammatory lesions (tuberculosis and histoplasmosis in particular) may cause false positive results while bronchiolo-alveolar cancers and malignant carcinoid tumors may cause false negative results. *Option:* PET may be utilized in the diagnosis of a pulmonary lesion <1cm (evidence level B2) but underestimation of fixation may occur depending on the resolution characteristics of the PET infrastructure. *Recommendations:* PET may be utilized in the diagnosis of cystic or necrotic lesions. However, underestimation of fixation may occur due to an effect of partial volume (experts' agreement). In light of the established limitations of FDG, protocols for PET using other metabolic tracers should be developed to improve the differential diagnosis between malignant lesions (malignant carcinoid tumors and bronchiolo-alveolar carcinomas in particular) and inflammatory granulomatous lesion (experts' agreement). -Place of PET in the staging of bronchopulmonary cancers. *Standards*: PET is indicated in the staging of broncho-pulmonary cancers (i.e. documentation of locoregional extension and distant metastatic spread, more specifically in the adrenal glands) (evidence level A). However, certain inflammatory adenopathies (sarcoidose and anthracose in particular) may cause false positive results. PET is not indicated in the detection of intracranial metastasis of bronchopulmonary cancers (experts' agreement). *Recommendations*: additional studies are needed to document the different performances of PET and bone scintigraphy with diphosphanates in detecting bone metastasis of bronchopulmonary cancers (experts' agreement). Future studies are also needed to confirm the prognostic value of the initial pre-therapeutic fixation-intensity of FDG and its correlation with patient survival (experts' agreement). -Place of PET in the optimization of irradiated volumes. *Standards*: no standard applicable. *Option*: PET may be utilized in addition to tomodensitometry to better define the irradiated volumes in bronchopulmonary oncology (evidence level B2). *Recommendation*: technical developments are needed to further improve correlations between PET-imaging and tomodensitometric findings in bronchopulmonary cancers (experts' agreement). -Place of PET in the assessment of therapy response in bronchopulmonary cancers. *Standard*: no standard applicable. *Indication requiring confirmation within the*

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
					framework of evaluated protocols: PET may be utilized in the early evaluation of tumor response to anti-tumoral therapy in bronchpulmonary cancer (evidence level B2). *Recommendations*: to avoid interferences related to the effects of treatments, evaluation by PET of therapy response in bronchopulmonary oncology should be planned only after a delay of at least 3 weeks following completion of a chemotherapy-cure and only after a delay of at least 4 months following completion of irradiation (evidence level D). Additional studies are required to document the predictive value of PET in terms of survival of these patients (experts' agreement). -Place of PET in the evaluation of recurrences and residual disease in bronchopulmonary cancer. *Standard*: no standard applicable. *Option*: PET may be utilized in bronchopulmonary oncology in the differential diagnosis of recurrence or residual disease and post-therapy fibrosis. However, a delay of at least 4 months following completion of radiotherapy should be respected (experts' agreement). -Place of PET in the diagnosis of malignity of pleural lesions. *Standard*: no standard applicable. *Option*: PET may be utilized in the diagnosis of malignity of pleural lesions (evidence level B2). However, false positive results may arise from pleural granulomas while false negative findings may result from small malignant pleural lesions (partial volume effect). *Indications requiring confirmation within the framework of evaluated protocols*: PET may contribute in guiding a diagnostic biopsy of the pleura (evidence level D). PET may be utilized in the staging of regional and distant extension of malignant pleural lesions (evidence level D). -Place of PET in the diagnosis of malignity of mediastinal lesions. *Standard*: insufficient evidence for defining standards and options. *Recommendation*: additional studies are needed to define the role of PET in the diagnosis of primary malignant mediastinal lesions.

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
NHSRC *Norway* 2003	Positron emission tomography (PET) - diagnostic and clinical use. Morland B. Norwegian Health Services Research Centre (NHSRC) 2003 (SMM-Report 6/2003).	PET		*Short review* Update based on 14 HTA reports and 3 SR's (2001-2003). Update of reports of INATHA 1999 and SMM 2000 Survey and synthesis of the evidence	-There are many overlapping references in the reports and they generally conclude in agreement. -The clinical use of PET as a diagnostic tool has increased in the period, despite the lack of Fair documentation regarding clinical effectiveness. -The main areas of use are still within oncology, neurology and cardiology. -HTA-reports published after the INATHA-report of 1999 and the SMM-report in 2000, concludes that PET is more accurate than other diagnostic procedures for several indications within oncology and should therefore be used. -This applies mainly in diagnosing of non-small cell lung cancer (NSCLC) and solitary pulmonary nodules, in staging of Hodgkin's lymphoma, in identifying metastasis from malignant melanoma and colorectal cancer and, in the diagnosis of head and neck tumors. -It is important to notice that PET is still in the developing phase. Examinations should therefore be performed within the framework of clinical trials, since there is still a great need for knowledge collected systematically. -It is also important to notice that "PET scanning should only be used if the results of the test will affect patient management".
HTBS *Scotland* 2002	HTA Report 2: Positron emission tomography (PET) imaging in cancer management; HTA Advice 2: Positron emission tomography (PET) imaging in cancer management; Understanding HTBS Advice: Positron emission tomography (PET) imaging in cancer management. Health Technology Board for Scotland (HTBS) (merged into NHS	FDG-PET	Excellent	Basis for evaluation: Existing HTA-reports by DACEHTA and MSAC. Updated search in Medline, Embase, Cochrane. Models for cost-effectiveness. Populations studied:	*Translation (norwegian into english) of the Evidence table in NHSRC 2003* Indications studied: Staging of NSCLC (52)* (*number of studies); treated Hodgkin's lymphoma. Some other cancers were also evaluated (clinical data and economic analyses): other lymphomas; head/neck cancer; colorectal cancer; malignant melanoma; breast cancer. Outcomes studied: Histopathology; choice of therapy; clinical outcomes; cost-effectiveness (cost per quality adjusted life years compared to alternative treatment strategies). Results/Comments: -NSLCC: Almost all studies show an increased diagnostic accuracy of PET compared to CT in mediastinal staging of NSCLC and a somewhat improved detection of distant metastases.

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
	Quality Improvement Scotland (NHS QIS)) 2002.			Patient series with and without positive CT (mediastinal staging) in NSCLCC and Hodgkin's disease	There are contradictory results (from two RCT's) on the choice of therapy. There is no documentation on the quality of life or clinical outcome. The economic model does not show with enough certainty which treatment strategy will be the most cost-effective. -Hodgkin's disease: Most studies show PET to be more specific and somewhat more sensitive than CT in the detection of recurrence of Hodgkin's disease. PET: sensitivity 0.81 (95% CI. 0.63-0.92); specificity 0.95 (95% CI. 0.90-0.99). The economic model (Markov) indicates that the use of PET is cost-effective in helping avoiding unnecessary toxic treatment.
AETMIS *Canada* 2002	Positron emission tomography in Quebec. Dussault F P, Nguyen V H, Rachet F. Agence d'Evaluation des Technologies et des Modes d'Intervention en Sante (AETMIS) 2002 (AETMIS 01-3 RE): 260.	FDG-PET	Fair	Basis for evaluation: Existing technology assessments with updated search in Medline, Cochrane, Embase, Cancerlit, HTA-economic databases Purpose of the evaluation: -collect and evaluate documentation on the clinical use of PET. -formulate	*Translation (norwegian into english) of the Evidence table in NHSRC 2003* Indications studied: NSCLC and solitary lung infiltrates; colorectal cancer; malignant melanoma; head & neck cancer; lymphoma; breast cancer; prostate cancer. Dementia and Alzheimer's disease; refractory epilepsy; brain tumor (glioma). Myocardial viability; coronary perfusion. Outcomes studied: Results/Comments: - PET has a demonstrated diagnostic benefit in certain indications in lung cancers, colorectal cancers, malignant melanomas, head& neck cancers, lymphoma (i.e. in the initial staging, detection of metastases and/or monitoring of therapy response: indication dependent on the type of cancer). - PET is effective in the diagnosis of epileptic foci and may differentiate between tumor tissue and radiation necrosis in brain tumors. - PET is effective in the evaluation of myocardial viability and myocardial perfusion. - Models for the assessment of the cost-effectiveness of PET in NSCLC and myocardial viability have been developed.

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
				recommendations on the clinical use of PET in Quebec	
HAYES 2002	Positron emission tomography (PET) for lung cancer. HAYES, Inc. 2002: 95.	N.A. (Not Available)	N.A	N.A.	N.A
DACEHTA *Danmark* 2001b	Positron emissions tomography (PET) with 18-F-fluorodeoxyglucose (FDG). A literature review of evidence for clinical use in the fields of oncology, cardiology and neurology. Danish Centre for Evaluation and Health Technology Assessment (DACEHTA) (formerly DIHTA) 2001.	FDG-PET. Standard PET versus "hybrid-PET" With and without blinded evaluation of test results. With and without comparison with alternative methods.	Fair	*Report in Danish* Basis for evaluation: Systematic literature review. Search in Medline, Embase, Cochrane. Inclusion criteria: English language. RCT/Case-control/Cohort studies. 363 articles included. Patient series >12 patients with clear inclusion criteria for disease.	*Translation (norwegian into english) of the Evidence table in NHSRC 2003* *Systematic review of literature* Indications studied: NSCLC (53); Solitary Pulmonary Infiltrates >4cm (12); ; Colorectal cancer (32); Malignant Melanoma (20); Head & Neck cancer (42); Breast cancer (37). Alzheimer's disease (41); Epilepsy foci (23). Ischemic Heart Disease (52). Outcomes studied: Histopathology; choice of therapy; clinical outcome. Results/Comments: -PET has a higher sensitivity, specificity, positive and negative predictive value compared to CT in the initial staging and detection of metastases (however: low evidence degree). -Most studies find a high sensitivity and specificity of PET in patient with malignant lung infiltrates (however: selected patients with high degree malignancy grades). -PET is presumed to be better than CT/MRI in the detection of head & neck cancer recurrence. -PET is better than CT for initial staging and detection of liver metastases in colorectal cancer (however: low evidence degree). -PET has a higher diagnostic precision compared to CT in the detection of metastases (other than in the lungs) from malignant melanoma. -PET may become a tool for dealing with lymph node metastases from breast cancer (however; too few and bad studies).

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
					-PET is not better than SPECT in the detection of Alzheimer's disease or epileptic foci. -Variable results for the use of PET in ischemic heart disease. -No documentation on clinical outcome.
DACEHTA *Danmark* 2001a	Paper concerning clinical PET-scanning using FDG - with focus on diagnosis of cancer. Danish Centre for Evaluation and Health Technology Assessment (DACEHTA) (formerly DIHTA) 2001.	FDG-PET		*Danish* Recommendations based on SR's as described in DACEHTA, *Denmark*, 2001b and critically reviewed by oncologists.	*Translation (norwegian into english) of the Evidence table in NHSRC 2003* *Recommendations:* The documented benefit of PET in diagnosis: Lung cancer : good Solitary lung mass : good Colorectal cancer : good Head & Neck cancer : good Malignant melanoma: good Breast cancer : scant Other cancers : scant Alzheimer : lacking Epilepsy : unclear Ischemic heart disease: lacking The documented benefit of PET in therapy: Lung cancer : scant Other : lacking
ICES *Canada* 2001	Health technology assessment of PET (positron emission tomography). Laupacis A. Institute for Clinical Evaluative Sciences (ICES) 2001: 116.	FDG-PET	Fair	Systematic review of the English peer-reviewed, grey and web-based PET scanning literature up to December 2000 Inclusion criteria: Case-series of	*Translation (norwegian into english) of the Evidence table in NHSRC 2003)* Indications studied: Lung cancer(12);Solitary pulmonary nodule (12);Head & Neck cancer(15);Breast cancer(5);Hodgkin lymphoma (5); malignant melanoma (3); colorectal cancer (2); brain tumor: recurrence or irradiation necrosis(0); myocardial viability (?);epilepsy (?); dementia(?) Outcomes studied: Histopathology; choice of therapy; clinical outcome. Results/Comments:

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
				>12 patients Economic evaluations	PET is considered useful in the diagnosis of all studied indications in oncology. PET may affect patient management i.e. avoidance of unnecessary aggressive (surgery) treatment. PET has no shown benefit over existing alternatives in the evaluation of myocardial viability. PET may have a role in the diagnosis of epileptic foci but most likely not in the diagnosis of dementia. PET may be cost-effective in the evaluation of lung-cancer, in cases of solitary pulmonary infiltrates and in patients treated for Hodgkin's lymphoma.
ICSI *USA* 2001	PET scans for solitary pulmonary nodules, non-small cell lung cancer, recurrent colorectal cancer, lymphoma, and recurrent melanoma. Institute for Clinical Systems Improvement (ICSI) 2001 (Technology Assessment Report).	FDG-PET	Poor	No details on Search strategy	-PET scans are safe – there are no reports of morbidity or mortality as a result of a PET scan. -The potential for misuse of PET exists; PET scans are inappropriate if used a) as a screening tool in the general population, b) when the results would not alter the treatment approach, c) to evaluate neoplasms that are not glucose avid with FDG PET, d) within 2 months of an operative procedure or within 3-4 months after the completion of treatment, or e) for patients with uncontrolled diabetes or glucose levels above 200 mg/dL. -SPN's: PET scans can correctly distinguish benign from malignant indeterminate SPN's in 87% to 94% of the cases. However, PET scan results do not provide a definitive diagnosis that is possible only with biopsy and tissue diagnosis. (Conclusion Grade I based on Class C evidence). -NSCLC: PET is more sensitive, specific, and accurate than VT in evaluating thoracic nodes and extra-thoracic abnormalities for the purpose of staging NSCLC. Based on th positive and negative predictive values of PET scans for mediastinal lymph node metastases, a negative PET scan may not require invasive follow-up but a positive PET scan should be followed by mediastinoscopy. PET scans have also been found to identify patients not suitable for resection because of distant metastases in 8% to 15% of the cases or N3 disease in 6% of the cases. (Conclusion Grade I based on Class C evidence). -Recurrent Colorectal Cancer: PET scans may be used to evaluate patients with elevated levels of CEA but negative CT scans. For detection of local recurrence of colorectal cancer, PET scans have been found to be more sensitive, specific, and accurate than CT scans. For detection of hepatic metastases, PET and CT are at

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
					least comparable, but PET provides more information about the extent of disease. Total body PET is superior to CT in identifying extrahepatic disease. Unnecessary operative procedures may be avoided in up to 20% of patients studied. (Conclusion Grade II based on Class C evidence). -Lymphoma: PET has been found to identify more nodal and more extranodal disease in lymphoma patients. In patients whose disease status has been verified by biopsy, PET scans were more accurate than CT scans for staging. PET scans have a high sensitivity and specificity for staging disease prior to treatment. For the evaluation of residual masses, Pet scans have been found to be at least as sensitive and more specific than CT. (Conclusion Grade II based on Class C evidence). -Recurrent Melanoma: PET scans are superior to conventional imaging methods in identifying systemic melanoma metastases with the exception of lung metastases where the various approaches are comparable. Unnecessary operative procedures may be avoided in up to 17% of patients with clinical suspicion of progressive disease. Pet scans do not appear to have a primary role in staging regional lymph nodes in patients with localized cutaneous melanoma. (Conclusion Grade II based on Class C evidence). -To date, there are limited survival data. RCT's to determine a survival benefit are not likely. The major benefit of PET scans is in identifying patients who will not benefit from operative resection thereby sparing them from the morbidity and the costs of the procedure. PET is not designed as a tool that will ultimately impact survival but rather as a tool to assist in selection of optimum treatment.
MSAC *Australia* 2000	Positron emission tomography. Medical Services Advisory Committee (MSAC) 2000 (MSAC Application 1025): 124.	FDG-PET compared to conventional techniques: CT/MRI/*Rtg. /Ultralyd*	Excellent	Basis for evaluation: Systematic reviews (3) and primary studies (54) Search in Medline, Cochrane, HTA database, DARE, NHS EED, Healthstar,	*Translation (norwegian into english) of the Evidence table in NHSRC 2003* Indications studied: Pre-operative staging and detection of metastases from NSCLC (17). Metastases from malignant melanoma (11). Recurrence following treatment of malignant glioma (11). Metastases from colorectal cancer (2). Epileptic foci in the brain (5). Myocard viability (?) Outcomes studied: Histopathology (confirmed); choice of therapy; clinical outcome, cost-effectiveness..

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
				Cinahl, Embase Inclusion criteria: Only english language Prospective patient series >10 patients with clear inclusion criteria for disease. Casuistic studies excluded.	Results/Comments: Higher diagnostic accuracy, i.e. higher sensitivity for staging of NSCLC and detection of metastases from malignant melanomas and colorectal cancer. Improved differentiation between tumor tissue and radiation necrosis following treatment of glioma. Change in choice of therapy for NSCLC and potential for change in case of metastases from colorectal cancer. No documented effect on clinical outcome. No adequate knowledge of cost-effectiveness. In some patients, PET may be helpful in improving diagnosis for epilepsy surgery, but uncertainty persists related to the real amount of false negatives/positives. No conclusion on the use of PET in coronary heart disease.
INATHA *Joint Project* 1999	Positron emission tomography: experience with PET and synthesis of the evidence (INAHTA Joint Project). Adams E, Asua J, Conde Olasagasti J, Erlichman M, Flynn K, Hurtado-Saracho I. Technology Assessment Unit, Management Decision & Research Center, US Department of Veterans Affairs (VATAP) MDRC, OSTEBA, AETS, AHRQ, INAHTA 1999: 41.	FDG-PET		Survey and synthesis of the evidence	Potential clinical PET indications identified by INATHA PET Collaboration participants: -Diagnosing and staging of NSCLC. Evidence suggests PET may be cost-effective for staging lung cancer to confirm respectability in patients with a negative mediastinum on CT. -Characterizing solitary pulmonary nodule. Evidence suggests PET may have utility when other tests are inconclusive.

GYNAECOLOGICAL CANCER

Breast cancer

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
ICES *Canada* April 2004 (Quarterly updates i.e. Jan 2004, Sept 2003, May 2003)	Health technology assessment of PET (positron emission tomography): a systematic review. Lauparis A, Paszat L, Hodgson D, Benk V. (ICES) 2004. (health technology assessment of positron emission tomography (PET) in oncology-a systematic review-ICES investigative report)	PET	Fair	PET literature review and assessment of articles Update from Nov 1,2002 up to and including Apr 1, 2004. (updates on ICES 2001 original report)	*-Populations studied (2 "A" Grade, 9 "B" Grade studies)*: *Studies on pre-operative staging, detection of axillary lymph node metastasis, detection of bone metastasis, early assessment of response to chemotherapy.* *-Potential impact of PET on processes of care for breast cancer* These studies appear to provide additional information on the selection of therapy for carcinoma of the breast. However, it is unclear if PET would replace the utilization of any currently used assessment procedures. The practice regarding axillary assessment varies widely at present. Some practitioners perform axillary dissection routinely for most patients with newly diagnosed carcinoma of the breast while others perform it only if a sentinel lymph node biopsy is positive. At present, there is no evidence to support the routine use of sentinel lymph node biopsy. For surgeons routinely performing axillary dissection, PET might reduce the rate of axillary dissection in patients with PET-negative axillary imaging. There has been no comparison of PET imaging of the axilla to sentinel lymph node biopsy. In one study, PET appears to be more effective than radionuclide bone scanning in the detection of bone metastasis due to carcinoma of the breast. However, it is difficult to draw definitive conclusions from these study results due to the relatively small number of patients included (34 patients). Neoadjuvant, or primary chemotherapy prior to surgery and/or radiation therapy, at present is applied chiefly in the setting of locally advanced breast cancer. It is unclear if information from PET about a poor prognosis or response to chemotherapy would prompt a change in therapy that would improve clinical outcomes (because of the likelihood in this clinical setting that other therapies would also fail).
FNCLCC *France* 2003	Recommandations pour la pratique clinique : standards, options et recommandations 2003 pour l'utilisation de la tomographie par	FDG-PET	Fair	*Translation of French* Search from January 1966	-Place of PET in the initial diagnosis of breast cancer. *Standard*: PET is not indicated in the diagnosis of breast cancer (evidence level A). *Recommendations*: comparing the diagnostic performance of PET and MRI in the surveillance of women with a genetically predisposition for breast cancer within the framework of a prospective study. -Place of PET in the initial staging of breast cancer. *Standard*: PET is unable to detect

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
	émission de positrons au [18-F]-FDG (TEP-FDG) en cancérologie (rapport intégral) (FNCLCC) 2003 :290.			until October 2002	microscopic lymph node metastasis (evidence level B2). *Option*: PET enables documentation of loco-regional invasion and metastatic spread in the initial staging of invasive breast cancer (evidence level B2). *Recommendation*: the place of PET in the initial staging of invasive breast cancer remains to be established. Therefore, a comparison of the performance of PET relative to other diagnostic techniques should be made within the framework of properly designed prospective, multicenter and comparative studies (experts'agreement). -Place of PET in the restaging of recurrent and metastatic breast cancer. *Standard*: no standard applicable. *Option*: PET may be proposed in case of suspected local recurrence or metastatic spread (evidence level B2). *Recommendations*: the role of PET in the early diagnosis of recurrence (compared with MRI) and metastatic spread of breast cancer should be determined more precisely within the framework of prospective, multicenter and comparative studies (experts'agreement). -Place of PET in the evaluation of therapy response following neo-adjuvant chemotherapy in breast cancer. *Standard*: no standard applicable. *Indications requiring confirmation within the framework of evaluated protocols*: indications for PET remain to be determined more precisely in prospective, multicenter and comparative studies (evidence level D). -Place of PET in the evaluation of residual disease in breast cancer. *Standard, Option*: neither standard nor option applicable. *Indications requiring confirmation within the framework of evaluated protocols*: PET may be proposed in the evaluation of residual disease within the framework of evaluated protocols (evidence level C).
NHSRC *Norway* 2003	Positron emission tomography (PET) - diagnostic and clinical use. Morland B. Norwegian Health Services Research Centre (NHSRC) 2003 (SMM-Report 6/2003).	PET		*Short review* Update based on 14 HTA reports and 3 SR's (2001-2003). Update of reports of INATHA 1999 and SMM 2000 Survey and synthesis of the	-There are many overlapping references in the reports and they generally conclude in agreement. -The clinical use of PET as a diagnostic tool has increased in the period, despite the lack of good documentation regarding clinical effectiveness. -The main areas of use are still within oncology, neurology and cardiology. -HTA-reports published after the INATHA-report of 1999 and the SMM-report in 2000, concludes that PET is more accurate than other diagnostic procedures for several indications within oncology and should therefore be used. -This applies mainly in diagnosing of non-small cell lung cancer (NSCLC) and solitary pulmonary nodules, in staging of Hodgkin's lymphoma, in identifying metastasis from malignant melanoma and colorectal cancer and, in the diagnosis of head and neck

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
				evidence	tumors. -It is important to notice that PET is still in the developing phase. Examinations should therefore be performed within the framework of clinical trials, since there is still a great need for knowledge collected systematically. -It is also important to notice that "PET scanning should only be used if the results of the test will affect patient management".
BCBS (TEC) *USA* 2003	FDG positron emission tomography for evaluating breast cancer. Blue Cross Blue Shield Association (BCBS) 2003 (TEC Assessment 18(14)): 45.	FDG-PET compared to an appropriate reference standard Technology assessment by AHRQ for Blue Cross Blue Shield Association	Fair	Basis for evaluation: Review of articles in peer-reviewed journals in MEDLINE, between January 1966 and October 2003. 6 studies (range: 10 to 61 patients) included	Indication and outcome studied: FDG-PET performance for evaluation of treatment response in breast cancer patients (6). Comparison of FDG-PET findings with an appropriate reference standard, for both patients with disease and without (permitting calculation of both sensitivity and specificity) Results/Comments: -In the absence of adequate evidence to estimate diagnostic performance, the outcomes of using PET to evaluate response to treatment cannot be determined. -A comparison of net health outcome for use of PET in management versus alternative management cannot be conducted for any of these indications: staging axillary lymph nodes; detecting loco-regional recurrence or distant recurrence/metastasis; and evaluating response to treatment. Thus, whether net health outcome is improved with the use of PET, compared to alternative management strategies, cannot be determined for these uses of PET. -Whether FDG PET imaging for evaluating breast cancer improves health outcomes has not been established in investigational settings. For the above reasons, FDG-PET imaging for evaluating response to treatment for breast cancer does not meet the TEC criteria.
HAYES 2003	Positron emission tomography (PET) for breast cancer. HAYES, Inc. 2003: 88.	N.A.	N.A.	N.A.	N.A.
AETMIS *Canada* 2002	Positron emission tomography in Quebec. Dussault F P, Nguyen V H, Rachet F. Agence	FDG-PET	Fair	Basis for evaluation: Existing technology	*Translation (norwegian into english) of the Evidence table in NHSRC 2003* Indications studied: NSCLC and solitary lung infiltrates; colorectal cancer; malignant melanoma; head &

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
	d'Evaluation des Technologies et des Modes d'Intervention en Sante (AETMIS) 2002 (AETMIS 01-3 RE): 260.			assessments with updated search in Medline, Cochrane, Embase, Cancerlit, HTA-economic databases. Purpose of the evaluation: -collect and evaluate documentation on the clinical use of PET. -formulate recommendations on the clinical use of PET in Quebec	neck cancer; lymphoma; breast cancer; prostate cancer. Dementia and Alzheimer's disease; refractory epilepsy; brain tumor (glioma). Myocardial viability; coronary perfusion. Outcomes studied: Results/Comments: - PET has a demonstrated diagnostic benefit in certain indications in lung cancers, colorectal cancers, malignant melanomas, head& neck cancers, lymphoma (i.e. in the initial staging, detection of metastases and/or monitoring of therapy response: indication dependent on the type of cancer). - PET is effective in the diagnosis of epileptic foci and may differentiate between tumor tissue and radiation necrosis in brain tumors. - PET is effective in the evaluation of myocardial viability and myocardial perfusion. - Models for the assessment of the cost-effectiveness of PET in NSCLC and myocardial viability have been developed.
DACEHTA *Danmark* 2001b	Positron emissions tomography (PET) with 18-F-fluorodeoxyglucose (FDG). A literature review of evidence for clinical use in the fields of oncology, cardiology and neurology. Danish Centre for Evaluation and Health Technology Assessment (DACEHTA) (formerly	FDG-PET. Standard PET versus "hybrid-PET" With and without blinded evaluation of test results. With and without comparison	Fair	*Report in Danish* Basis for evaluation: Systematic literature review. Search in Medline, Embase, Cochrane. Inclusion criteria: English language. RCT/Case-control/Cohort	*Translation (norwegian into english) of the Evidence table in NHSRC 2003* *Systematic review of literature* Indications studied: NSCLC (53); Solitary Pulmonary Infiltrates >4cm (12); ; Colorectal cancer (32); Malignant Melanoma (20); Head & Neck cancer (42); Breast cancer (37). Alzheimer's disease (41); Epilepsy foci (23). Ischemic Heart Disease (52). Outcomes studied: Histopathology; choice of therapy; clinical outcome. Results/Comments: -PET has a higher sensitivity, specificity, positive and negative predictive value

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
	DIHTA) 2001.	with alternative methods.		studies. 363 articles included. Patient series >12 patients with clear inclusion criteria for disease.	compared to CT in the initial staging and detection of metastases (however: low evidence degree). -Most studies find a high sensitivity and specificity of PET in patient with malignant lung infiltrates (however: selected patients with high degree malignancy grades). -PET is presumed to be better than CT/MRI in the detection of head & neck cancer recurrence. -PET is better than CT for initial staging and detection of liver metastases in colorectal cancer (however: low evidence degree). -PET has a higher diagnostic precision compared to CT in the detection of metastases (other than in the lungs) from malignant melanoma. -PET may become a tool for dealing with lymph node metastases from breast cancer (however; too few and bad studies). -PET is not better than SPECT in the detection of Alzheimer's disease or epileptic foci. -Variable results for the use of PET in ischemic heart disease. -No documentation on clinical outcome.
DACEHTA *Danmark* 2001a	Paper concerning clinical PET-scanning using FDG - with focus on diagnosis of cancer. Danish Centre for Evaluation and Health Technology Assessment (DACEHTA) (formerly DIHTA) 2001.	FDG-PET		*Danish* Recommendations based on SR's as described in DACEHTA, *Denmark*, 2001b and critically reviewed by oncologists.	*Translation (norwegian into english) of the Evidence table in NHSRC 2003* *Recommendations:* The documented benefit of PET in diagnosis: Lung cancer : good Solitary lung mass : good Colorectal cancer : good Head & Neck cancer : good Malignant melanoma: good Breast cancer : scant Other cancers : scant Alzheimer : lacking Epilepsy : unclear Ischemic heart disease: lacking The documented benefit of PET in therapy:

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
					Lung cancer : scant Other : lacking
BCBS (TEC) *USA* 2001	FDG positron emission tomography for evaluating breast cancer. Blue Cross Blue Shield Association (BCBS) 2001 (TEC Assessment 16(05)): 73.	FDG-PET compared to CT/MRI/ Scintigraphy Technology assessment by AHRQ for Blue Cross Blue Shield Association	Fair	Basis for evaluation: search in Medline, Cancerlit 25 studies included Population studied: Prospective studies on >10 patients with breast cancer	*Translation (norwegian into english) of the Evidence table in NHSRC 2003* Indications studied: Breast cancer: primary diagnosis (13); lymph node spread (4); recurrence (2); distant metastases; therapy monitoring (4). Outcomes studied: Histopathology. Results/Comments: -PET in the primary diagnosis. Sensitivity: 88% (95% CI 83-92%). Specificity: 80% (95% CI 71-85%) -Spread to lymph nodes. PET sensitivity 80% (46-95%). PET specificity 89% (83-94%). -Too few studies to conclude on disease recurrence, distant metastases and therapy monitoring. -Assessment of diagnostic accuracy yields a too high risk for false negative results. -In general: the quality of the studies is too low (among other problems: a too high degree of malignancy of the included patients) to recommend the use of PET in breast cancer.
ICES *Canada* 2001	Health technology assessment of PET (positron emission tomography). Laupacis A. Institute for Clinical Evaluative Sciences (ICES) 2001: 116.	FDG-PET	Fair	Systematic review of the English peer-reviewed, grey and web-based PET scanning literature up to December 2000 Inclusion criteria: Case-series of >12 patients Economic evaluations	*Translation (norwegian into english) of the Evidence table in NHSRC 2003* Indications studied: Lung cancer(12);Solitary pulmonary nodule (12);Head & Neck cancer(15);Breast cancer(5);Hodgkin lymphoma (5); malignant melanoma (3); colorectal cancer (2);brain tumor: recurrence or irradiation necrosis(0); myocardial viability (?);epilepsy (?); dementia(?) Outcomes studied: Histopathology; choice of therapy; clinical outcome. Results/Comments: PET is considered useful in the diagnosis of all studied indications in oncology. PET may affect patient management i.e. avoidance of unnecessary aggressive (surgery) treatment.

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
					PET has no shown benefit over existing alternatives in the evaluation of myocardial viability. PET may have a role in the diagnosis of epileptic foci but most likely not in the diagnosis of dementia. PET may be cost-effective in the evaluation of lung-cancer, in cases of solitary pulmonary infiltrates and in patients treated for Hodgkin's lymphoma.

Cervical cancer

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
AHRQ *USA* 2004	Positron emission testing for six cancers (brain, cervical, small cell lung, ovarian, pancreatic and testicular). Matchar D B, Kulasingam S L, Havrilesky L, Mann L O, Myers E R, McCrory D C, Patwardhan M, Prosnitz R. Agency for Healthcare Research and Quality (AHRQ) 2004 (Technology Assessment): 221.	Performance of FDG-PET compared to conventional imaging	Fair (but without clear recom-menda-tions)	Search: MEDLINE <1966 to April Week 1 2003>	-Fair to good evidence that PET is more sensitive than CT or MRI for detection of pre-treatment retroperitoneal nodal metastastes in patients with newly diagnosed cervical cancer. Given the potential for PET to have a substantial impact on patient outcomes and costs by altering management strategies, a well-designed study addressing issues of sample size and bias should be a high priority. -Detection of residual and recurrent cervical cancer following treatment. Data from three retrospective studies suggest that PET is more sensitive than conventional imaging for detection of recurrent cervical cancer. However, these data are limited by small sample size. In addition, it is unclear whether improved whether improved early diagnosis of extra-pelvic recurrent cervical cancer leads to improved patient outcomes except in the setting of patients who have not previously received radiation.
FNCLCC *France* 2003	Recommandations pour la pratique clinique : standards, options et recommandations 2003 pour l'utilisation de la tomographie par émission de positrons au [18-F]-FDG (TEP-FDG) en cancérologie (rapport intégral) (FNCLCC) 2003 :290.	FDG-PET in cancer of the uterus, including cervical cancer, and vagina	Fair	*Translation of French* Search from January 1966 until October 2002	-Place of PET in the management of patients with cancer of the uterus or vagina. *Standard*: PET is, other than in evaluated protocols, actually not indicated in patients with endometrial cancer. *Option*: PET may be proposed in cervical cancer to improve documentation of lymph node involvement (evidence level B2). *Indications requiring confirmation within the framework of evaluated protocols*: utilization of PET in cervical cancer may include evaluation of residual disease following treatment (evidence level C) and detection of recurrence (evidence level C) within the framework of evaluated protocols. *Recommendation*: the performance of PET in endometrial and vaginal cancers remains to be determined more precisely in prospective, multicenter and comparative studies (experts' agreement).
NHSRC *Norway* 2003	Positron emission tomography (PET) - diagnostic and clinical use. Morland B. Norwegian Health Services Research Centre (NHSRC) 2003	PET		*Short review* Update based on 14 HTA reports and 3 SR's (2001-2003). Update of reports of	-There are many overlapping references in the reports and they generally conclude in agreement. -The clinical use of PET as a diagnostic tool has increased in the period, despite the lack of good documentation regarding clinical effectiveness. -The main areas of use are still within oncology, neurology and cardiology. -HTA-reports published after the INATHA-report of 1999 and the SMM-report in

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
	(SMM-Report 6/2003).			INATHA 1999 and SMM 2000 Survey and synthesis of the evidence	2000, concludes that PET is more accurate than other diagnostic procedures for several indications within oncology and should therefore be used. -This applies mainly in diagnosing of non-small cell lung cancer (NSCLC) and solitary pulmonary nodules, in staging of Hodgkin's lymphoma, in identifying metastasis from malignant melanoma and colorectal cancer and, in the diagnosis of head and neck tumors. -It is important to notice that PET is still in the developing phase. Examinations should therefore be performed within the framework of clinical trials, since there is still a great need for knowledge collected systematically. -It is also important to notice that "PET scanning should only be used if the results of the test will affect patient management".
MSAC (i) *Australia* 2001	Positron emission tomography [Part 2(i)]. Medical Services Advisory Committee. Medical Services Advisory Committee (MSAC) 2001 (MSAC reference 10): 126.	FDG-PET compared to conventional techniques: CT/MRI/*Rtg. /Ultralyd*	Excellent	Basis for evaluation: Systematic reviews and primary studies Search in Medline, Cochrane, HTA database, DARE, NHS EED, Healthstar, Cinahl, Embase Inclusion criteria: Only english language Prospective patient series >10 patients with clear inclusion criteria for disease. Casuistic studies	*Translation (norwegian into english) of the Evidence table in NHSRC 2003* Indications studied: Recurrence of ovarian cancer (7). Staging of cervical cancer (5) or endometrial cancer (0). Staging of esophageal (12) or gastric cancer (4). Outcomes studied: Histopathology (confirmed); choice of therapy; clinical outcome, cost-effectiveness.. Results/Comments: PET shows, compared to CT, a higher specificity and positive predictive value for recurrence of ovarian cancer. Higher sensitivity for the diagnosis of metastatic lymph nodes and staging of cervix cancer No documentation on therapy choice, but assumed potential to change from curative to palliative surgery. No documented effects on clinical outcome. No adequate knowledge of cost-effectiveness

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
				excluded.	

Ovarian cancer

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
AHRQ *USA* 2004	Positron emission testing for six cancers (brain, cervical, small cell lung, ovarian, pancreatic and testicular). Matchar D B, Kulasingam S L, Havrilesky L, Mann L O, Myers E R, McCrory D C, Patwardhan M, Prosnitz R. Agency for Healthcare Research and Quality (AHRQ) 2004 (Technology Assessment): 221.	Utility of FDG-PET compared to conventional imaging.	Fair (but without clear recom-menda-tions)	Search: MEDLINE <1966 to April Week 1 2003>	-PET for staging at initial diagnosis: no studies. -PET for detecting recurrence following treatment: PET is not suspected to be useful in the routine surveillance of patients with a history of ovarian cancer. However, there is fair evidence to support the use of PET for the detection of recurrent ovarian cancer when the CA 125 is elevated and conventional imaging is negative or equivocal. An adequate powered prospective study to confirm this, ideally with survival as one of the primary outcomes, would be very helpful. -PET for monitoring effect of chemotherapy: no studies.
FNCLCC *France* 2003	Recommandations pour la pratique clinique : standards, options et recommandations 2003 pour l'utilisation de la tomographie par émission de positrons au [18-F]-FDG (TEP-FDG) en cancérologie (rapport intégral) (FNCLCC) 2003 :290.	FDG-PET	Fair	*Translation of French* Search from January 1966 until October 2002	-Place of PET in the management of patients with ovarian cancer. *Standard*: no standard applicable. *Option*: PET may be proposed in case of suspected local recurrence or metastatic spread taken into consent the knowledge that microscopic peritoneal disease may cause false negative results (evidence level B2). *Recommendation*: the indications for PET remain to be determined more precisely in prospective, multicenter and comparative studies (experts' agreement).
NHSRC *Norway* 2003	Positron emission tomography (PET) - diagnostic and clinical use. Morland B. Norwegian Health	PET		*Short review* Update based on 14 HTA reports and 3 SR's (2001-2003).	-There are many overlapping references in the reports and they generally conclude in agreement. -The clinical use of PET as a diagnostic tool has increased in the period, despite the lack of good documentation regarding clinical effectiveness.

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
	Services Research Centre (NHSRC) 2003 (SMM-Report 6/2003).			Update of reports of INATHA 1999 and SMM 2000 Survey and synthesis of the evidence	-The main areas of use are still within oncology, neurology and cardiology. -HTA-reports published after the INATHA-report of 1999 and the SMM-report in 2000, concludes that PET is more accurate than other diagnostic procedures for several indications within oncology and should therefore be used. -This applies mainly in diagnosing of non-small cell lung cancer (NSCLC) and solitary pulmonary nodules, in staging of Hodgkin's lymphoma, in identifying metastasis from malignant melanoma and colorectal cancer and, in the diagnosis of head and neck tumors. -It is important to notice that PET is still in the developing phase. Examinations should therefore be performed within the framework of clinical trials, since there is still a great need for knowledge collected systematically. -It is also important to notice that "PET scanning should only be used if the results of the test will affect patient management".
MSAC (i) *Australia* 2001	Positron emission tomography [Part 2(i)]. Medical Services Advisory Committee. Medical Services Advisory Committee (MSAC) 2001 (MSAC reference 10): 126.	FDG-PET compared to conventional techniques: CT/MRI/*Rtg. /Ultralyd*	Excellent	Basis for evaluation: Systematic reviews and primary studies Search in Medline, Cochrane, HTA database, DARE, NHS EED, Healthstar, Cinahl, Embase Inclusion criteria: Only english language Prospective patient series >10 patients with clear inclusion criteria	*Translation (norwegian into english) of the Evidence table in NHSRC 2003)* Indications studied: Recurrence of ovarian cancer (7). Staging of cervical cancer (5) or endometrial cancer (0). Staging of esophageal (12) or gastric cancer (4). Outcomes studied: Histopathology (confirmed); choice of therapy; clinical outcome, cost-effectiveness.. Results/Comments: PET shows, compared to CT, a higher specificity and positive predictive value for recurrence of ovarian cancer. Higher sensitivity for the diagnosis of metastatic lymph nodes and staging of cervix cancer No documentation on therapy choice, but assumed potential to change from curative to palliative surgery. No documented effects on clinical outcome. No adequate knowledge of cost-effectiveness

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
				for disease. Casuistic studies excluded.	
HAYES 2001	Positron emission tomography (PET) for ovarian cancer. HAYES, Inc. 2001: 32.	N.A.	N.A.	N.A.	N.A.

HEAD AND NECK CANCER

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
ICES *Canada* April 2004 (Quarterly updates i.e. Jan 2004, Sept 2003, May 2003)	Health technology assessment of PET (positron emission tomography): a systematic review. Lauparis A, Paszat L, Hodgson D, Benk V. (ICES) 2004. (health technology assessment of positron emission tomography (PET) in oncology-a systematic review-ICES investigative report)	PET	Fair	PET literature review and assessment of articles Update from Nov 1,2002 up to and including Apr 1, 2004. (updates on ICES 2001 original report)	*-Populations studied (7 "B" Grade studies)*: *Studies on detection of metastases from newly diagnosed squamous carcinoma of the head and neck; detection of recurrent squamous carcinoma of the head and neck.* *-Potential impact of PET on processes of care for squamous carcinoma of the head and neck.* More accurate assessment of cervical lymph node metastasis has the potential to reduce the frequency of unnecessary lymph node dissections for patients with cancer of the head and neck. For the evaluation of lymph node metastases , PET appears to have superior specificity and may have superior sensitivity compared to CT scanning. It is unclear if adoption of PET would reduce the utilization of CT or MRI. It is also unclear what changes in treatment and outcomes would be observed if implemented. While there are studies of adequate quality of PET test characteristics compared to CT, squamous carcinomas at various anatomic locations of the head and neck have varying probabilities of lymph node metastases, and there has not been sufficient examination of which anatomic cancer sites in the head and neck would or would not be most appropriate for PET. The ability of PET to identify recurrent disease seems strong. The routine use of PET to identify recurrent cancer of the head and neck may be appropriate in the following conditions: if conventional methods of diagnosing recurrence are inconclusive and if a recurrence could be cured by subsequent definitive therapy.
FNCLCC *France* 2003	Recommandations pour la pratique clinique : standards, options et recommandations 2003 pour l'utilisation de la tomographie par émission de positrons au [18-F]-FDG (TEP-FDG) en cancérologie (rapport intégral) (FNCLCC) 2003: 290.	FDG-PET	Fair	*Translation of French* Search from January 1966 until October 2002	-Place of PET in the characterization of tumors of the UAS and of a second cancer, whenever applicable. *Standard*: no standard applicable. *Options*: PET may be indicated in the differential diagnosis of benign and malign tumors of the UAS when biopsy results are inconclusive (evidence level B2). PET, when used in the staging of an already known primary malignant tumor of the UAS, is also useful as an add-on examination in the search for a second cancer (evidence level B2). *Recommendation*: FDG-fixation within a tumor of the UAS, with an already established diagnosis of malignancy, may be quantified in the initial staging in order to provide information on the prognosis of survival or on the probability of recurrent disease following treatment. -Place of PET in the search of a primary tumor in case of cervical metastatic nodal

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
					involvement with an unknown primary tumor. *Standard*: literature findings are heterogeneous and don't allow for definition of a standard. *Option*: PET may be indicated in the search of a primary tumor in case of cervical metastatic nodal involvement with an unknown primary tumor (evidence level C). -Place of PET in the staging of an untreated cancer of the UAS. *Standard*: PET is indicated in the staging of untreated cancers of the UAS (evidence level B2). *Recommendations*: In this situation, a single whole body PET-scan allows for a precise evaluation of loco-regional extension and metastatic spread (experts' agreement). FDG-fixation within a tumor of the UAS, with an already established diagnosis of malignancy, may be quantified in the initial staging in order to provide information on the prognosis of survival or on the probability of recurrent disease following treatment. -Place of PET in the evaluation of therapy response of cancers of the UAS. *Standard*: no standard applicable. *Option*: PET may be used in the evaluation of therapy response (evidence level B2) as well as in the characterization of residual masses. -Place of PET in the detection recurrent cancer of the UAS. *Standard*: PET is indicated in the diagnosis of recurrent cancer of the UAS (evidence level B2). *Recommendation*: prospective studies are needed to determine the frequency of PET required in the follow up of these patients. - Place of PET in the management of patients with cancer of the salivary glands. *Standard*: no indication for PET in the management of patients with cancer of the salivary glands other than in the context of clinical trials.
NHSRC *Norway* 2003	Positron emission tomography (PET) - diagnostic and clinical use. Morland B. Norwegian Health Services Research Centre (NHSRC) 2003 (SMM-Report 6/2003).	PET		*Short review* Update based on 14 HTA reports and 3 SR's (2001-2003). Update of reports of INATHA 1999 and SMM 2000 Survey and synthesis of	-There are many overlapping references in the reports and they generally conclude in agreement. -The clinical use of PET as a diagnostic tool has increased in the period, despite the lack of good documentation regarding clinical effectiveness. -The main areas of use are still within oncology, neurology and cardiology. -HTA-reports published after the INATHA-report of 1999 and the SMM-report in 2000, concludes that PET is more accurate than other diagnostic procedures for several indications within oncology and should therefore be used. -This applies mainly in diagnosing of non-small cell lung cancer (NSCLC) and solitary pulmonary nodules, in staging of Hodgkin's lymphoma, in identifying metastasis from

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
				the evidence	malignant melanoma and colorectal cancer and, in the diagnosis of head and neck tumors. -It is important to notice that PET is still in the developing phase. Examinations should therefore be performed within the framework of clinical trials, since there is still a great need for knowledge collected systematically. -It is also important to notice that "PET scanning should only be used if the results of the test will affect patient management".
AETMIS *Canada* 2002	Positron emission tomography in Quebec. Dussault F P, Nguyen V H, Rachet F. Agence d'Evaluation des Technologies et des Modes d'Intervention en Sante (AETMIS) 2002 (AETMIS 01-3 RE): 260.	FDG-PET	Fair	Basis for evaluation: Existing technology assessments with updated search in Medline, Cochrane, Embase, Cancerlit, HTA-economic databases. Purpose of the evaluation: -collect and evaluate documentation on the clinical use of PET. -formulate recommendations on the clinical use of PET in Quebec	*Translation (norwegian into english) of the Evidence table in NHSRC 2003* Indications studied: NSCLC and solitary lung infiltrates; colorectal cancer; malignant melanoma; head & neck cancer; lymphoma; breast cancer; prostate cancer. Dementia and Alzheimer's disease; refractory epilepsy; brain tumor (glioma). Myocardial viability; coronary perfusion. Outcomes studied: Results/Comments: - PET has a demonstrated diagnostic benefit in certain indications in lung cancers, colorectal cancers, malignant melanomas, head& neck cancers, lymphoma (i.e. in the initial staging, detection of metastases and/or monitoring of therapy response: indication dependent on the type of cancer). - PET is effective in the diagnosis of epileptic foci and may differentiate between tumor tissue and radiation necrosis in brain tumors. - PET is effective in the evaluation of myocardial viability and myocardial perfusion. - Models for the assessment of the cost-effectiveness of PET in NSCLC and myocardial viability have been developed.

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
DACEHTA *Danmark* 2001b	Positron emissions tomography (PET) with 18-F-fluorodeoxyglucose (FDG). A literature review of evidence for clinical use in the fields of oncology, cardiology and neurology. Danish Centre for Evaluation and Health Technology Assessment (DACEHTA) (formerly DIHTA) 2001.	FDG-PET. Standard PET versus "hybrid-PET" With and without blinded evaluation of test results. With and without comparison with alternative methods.	Fair	*Report in Danish* Basis for evaluation: Systematic literature review. Search in Medline, Embase, Cochrane. Inclusion criteria: English language. RCT/Case-control/Cohort studies. 363 articles included. Patient series >12 patients with clear inclusion criteria for disease.	*Translation (norwegian into english) of the Evidence table in NHSRC 2003* *Systematic review of literature* Indications studied: NSCLC (53); Solitary Pulmonary Infiltrates >4cm (12); ; Colorectal cancer (32); Malignant Melanoma (20); Head & Neck cancer (42); Breast cancer (37). Alzheimer's disease (41); Epilepsy foci (23). Ischemic Heart Disease (52). Outcomes studied: Histopathology; choice of therapy; clinical outcome. Results/Comments: -PET has a higher sensitivity, specificity, positive and negative predictive value compared to CT in the initial staging and detection of metastases (however: low evidence degree). -Most studies find a high sensitivity and specificity of PET in patient with malignant lung infiltrates (however: selected patients with high degree malignancy grades). -PET is presumed to be better than CT/MRI in the detection of head & neck cancer recurrence. -PET is better than CT for initial staging and detection of liver metastases in colorectal cancer (however: low evidence degree). -PET has a higher diagnostic precision compared to CT in the detection of metastases (other than in the lungs) from malignant melanoma. -PET may become a tool for dealing with lymph node metastases from breast cancer (however; too few and bad studies). -PET is not better than SPECT in the detection of Alzheimer's disease or epileptic foci. -Variable results for the use of PET in ischemic heart disease. -No documentation on clinical outcome.
DACEHTA *Danmark*	Paper concerning clinical PET-scanning using FDG - with focus on diagnosis of cancer. Danish Centre for	FDG-PET		*Danish* Recommendations based on SR's as	*Translation (norwegian into english) of the Evidence table in NHSRC 2003)* *Recommendations:* The documented benefit of PET in diagnosis:

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
2001a	Evaluation and Health Technology Assessment (DACEHTA) (formerly DIHTA) 2001.			described in DACEHTA, *Denmark*, 2001b[32] and critically reviewed by oncologists.	Lung cancer : good Solitary lung mass : good Colorectal cancer : good Head & Neck cancer : good Malignant melanoma: good Breast cancer : scant Other cancers : scant Alzheimer : lacking Epilepsy : unclear Ischemic heart disease: lacking <u>The documented benefit of PET in therapy:</u> Lung cancer : scant Other : lacking
MSAC (ii) *Australia* 2001	Positron emission tomography [Part 2(ii)]. Medical Services Advisory Committee. Medical Services Advisory Committee (MSAC) 2001 (MSAC reference 10): 169.	FDG-PET compared to conventional techniques: CT/MRI/*Rtg./Ultralyd* Bone marrow biopsy Bone marrow scintigraphy	Excellent	<u>Basis for evaluation:</u> Systematic reviews and primary studies Search in Medline, Cochrane, HTA database, DARE, NHS EED, Healthstar, Cinahl, Embase <u>Inclusion criteria:</u> Only english	*Translation (norwegian into english) of the Evidence table in NHSRC 2003* <u>Indications studied</u>: Recurrence of lymphoma before treatment (38). Staging of head & neck cancer (spinocellular carcinoma) before treatment (48). Sarcoma: staging, biopsy, recurrence, distant metastases, monitoring of therapy (24). <u>Outcomes studied:</u> Histopathology (confirmed); choice of therapy; clinical outcome, cost-effectiveness.. <u>Results/Comments:</u> -Increased utility of PET for staging of lymphoma and evidence for effect on choice of therapy. -PET has a similar or even better diagnostic accuracy compared to CT/MRI for head & neck cancer and PET is better in the detection of recurrence or residual tumor. No evidence for an effect on the choice of therapy. -Unclear evidence for a significance of PET compared to CT for sarcoma in staging or detection of recurrence; improvement in "guided biopsy". No effect on the choice of therapy.

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
				language Prospective patient series >10 patients with clear inclusion criteria for disease. Casuistic studies excluded.	-PET has no documented effect on clinical outcome in some indications. -No adequate knowledge of cost-effectiveness.
ICES *Canada* 2001	Health technology assessment of PET (positron emission tomography). Laupacis A. Institute for Clinical Evaluative Sciences (ICES) 2001: 116.	FDG-PET	Fair	Systematic review of the English peer-reviewed, grey and web-based PET scanning literature up to December 2000 Inclusion criteria: Case-series of >12 patients Economic evaluations	*Translation (norwegian into english) of the Evidence table in NHSRC 2003* Indications studied: Lung cancer(12);Solitary pulmonary nodule (12);Head & Neck cancer(15);Breast cancer(5);Hodgkin lymphoma (5); malignant melanoma (3); colorectal cancer (2);brain tumor: recurrence or irradiation necrosis(0); myocardial viability (?);epilepsy (?); dementia(?) Outcomes studied: Histopathology; choice of therapy; clinical outcome. Results/Comments: PET is considered useful in the diagnosis of all studied indications in oncology. PET may affect patient management i.e. avoidance of unnecessary aggressive (surgery) treatment. PET has no shown benefit over existing alternatives in the evaluation of myocardial viability. PET may have a role in the diagnosis of epileptic foci but most likely not in the diagnosis of dementia. PET may be cost-effective in the evaluation of lung-cancer, in cases of solitary pulmonary infiltrates and in patients treated for Hodgkin's lymphoma.
HAYES 2001	Positron emission tomography (PET) for non-central nervous system	N.A.	N.A.	N.A.	N.A.

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
	head and neck tumors. HAYES, Inc. 2001: 45.				
BCBS USA 2000	FDG positron emission tomography in head and neck cancer. BCBS 2000, Vol 15 No 4	FDG-PET	Fair	Search up to May 2000	

HODGKIN'S AND NON-HODGKIN'S LYMPHOMA (HL AND NHL)

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
ICES *Canada* April 2004 (Quarterly updates i.e. Jan 2004, Sept 2003, May 2003)	Health technology assessment of PET (positron emission tomography): a systematic review. Lauparis A, Paszat L, Hodgson D, Benk V. (ICES) 2004. (health technology assessment of positron emission tomography (PET) in oncology-a systematic review-ICES investigative report)	PET	Fair	PET literature review and assessment of articles Update from Nov 1,2002 up to and including Apr 1, 2004. (updates on ICES 2001 original report)	*-Populations studied (1"A" Grade, 4"B" Grade studies)*: *Studies on staging of newly diagnosed malignant lymphoma and Hodgkin's disease; evaluation of response to treatment.* *-Potential impact of PET on processes of care for malignant lymphoma and Hodgkin's disease* We lack evidence about whether the addition of PET to conventional staging investigations would lead to appropriate modifications in treatment for HD or NHL. Most of the retrospective evidence indicates that an abnormal PET scan following initial therapy is associated with a poor outcome. This conclusion is supported by a recent prospective study indicating that PET midway through anthracycline-based chemotherapy for aggressive NHL clearly distinguishes patients with favourable and unfavourable prognosis. However, it is currently known that gallium scintigraphy with PET scanning would provide marginally better prognostic information. Also, there are limited data to indicate whether using PET scan results to intensify treatment for poor responders will produce a clinically significant improvement in outcome.
FNCLCC *France* 2003	Recommandations pour la pratique clinique : standards, options et recommandations 2003 pour l'utilisation de la tomographie par émission de positrons au [18-F]-FDG (TEP-FDG) en cancérologie (rapport intégral) (FNCLCC) 2003 :290.	FDG-PET	Fair	*Translation of French* Search from January 1966 until October 2002	Place of PET in the management of patients with lymphoma. *Standards*: PET is indicated, complementary to conventional imaging, in the initial staging of disease extent in Hodgkin's lymphoma (HL), in non-Hodgkin's malignant lymphoma (NHML) and in follicular lymphoma (evidence level B2). PET is also indicated in the diagnosis of residual disease in aggressive HL and NHML in case of demonstrated localisations of intensive FDG-fixation in the initial staging bilan (evidence level B2). Finally, PET is indicated in the early evaluation of therapy response (evidence level B2). *Recommendation*: the place of PET should be evaluated in the different histological subgroups according to the recent classification.
NHSRC *Norway* 2003	Positron emission tomography (PET) - diagnostic and clinical use. Morland B. Norwegian Health Services Research	PET	Fair	Update based on 14 HTA reports and 3 SR's (2001-2003). Update	-There are many overlapping references in the reports and they generally conclude in agreement. -The clinical use of PET as a diagnostic tool has increased in the period, despite the lack of good documentation regarding clinical effectiveness.

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
	Centre (NHSRC) 2003 (SMM-Report 6/2003).			of reports of INATHA 1999 and SMM 2000	-The main areas of use are still within oncology, neurology and cardiology. -HTA-reports published after the INATHA-report of 1999 and the SMM-report in 2000, concludes that PET is more accurate than other diagnostic procedures for several indications within oncology and should therefore be used. -This applies mainly in diagnosing of non-small cell lung cancer (NSCLC) and solitary pulmonary nodules, in staging of Hodgkin's lymphoma, in identifying metastasis from malignant melanoma and colorectal cancer and, in the diagnosis of head and neck tumors. -It is important to notice that PET is still in the developing phase. Examinations should therefore be performed within the framework of clinical trials, since there is still a great need for knowledge collected systematically. -It is also important to notice that "PET scanning should only be used if the results of the test will affect patient management".
HTBS*Scotland* 2002	HTA Report 2: Positron emission tomography (PET) imaging in cancer management; HTA Advice 2: Positron emission tomography (PET) imaging in cancer management; Understanding HTBS Advice: Positron emission tomography (PET) imaging in cancer management. Health Technology Board for Scotland (HTBS) (merged into NHS Quality Improvement Scotland (NHS QIS)) 2002.	FDG-PET	Excellent	Existing HTA-reports by DACEHTA and MSAC. Updated search in Medline, Embase, Cochrane. Models for cost-effectiveness. Population studied: Patient series with and without positive CT (mediastinal staging) in	*Translation (norwegian into english) of the Evidence table in NHSRC 2003* Indications studied: Staging of NSCLC (52); treated Hodgkin's lymphoma. Some other cancers were also evaluated (clinical data and economic analyses): other lymphomas; head/neck cancer; colorectal cancer; malignant melanoma; breast cancer. Outcomes studied: Histopathology; choice of therapy; clinical outcomes; cost-effectiveness (cost per quality adjusted life years compared to alternative treatment strategies). Results/Comments: -NSLCC: Almost all studies show an increased diagnostic accuracy of PET compared to CT in mediastinal staging of NSCLC and a somewhat improved detection of distant metastases. There are contradictory results (from two RCT's) on the choice of therapy. There is no documentation on the quality of life or clinical outcome. The economic model does not show with enough certainty which treatment strategy will be the most cost-effective. -Hodgkin's disease:

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
				NSCLCC and Hodgkin's disease	Most studies show PET to be more specific and somewhat more sensitive than CT in the detection of recurrence of Hodgkin's disease. PET: sensitivity 0.81 (95% CI. 0.63-0.92); specificity 0.95 (95% CI. 0.90-0.99). The economic model (Markov) indicates that the use of PET is cost-effective in helping avoiding unnecessary toxic treatment.
AETMIS *Canada* 2002	Positron emission tomography in Quebec. Dussault F P, Nguyen V H, Rachet F. Agence d'Evaluation des Technologies et des Modes d'Intervention en Sante (AETMIS) 2002 (AETMIS 01-3 RE): 260.	FDG-PET	Fair	Basis for evaluation: Existing technology assessments with updated search in Medline, Cochrane, Embase, Cancerlit, HTA-economic databases. Purpose of the evaluation: -collect and evaluate documentation on the clinical use of PET. -formulate recommendations on the clinical use of PET in Quebec	*Translation (norwegian into english) of the Evidence table in NHSRC 2003* Indications studied: NSCLC and solitary lung infiltrates; colorectal cancer; malignant melanoma; head & neck cancer; lymphoma; breast cancer; prostate cancer. Dementia and Alzheimer's disease; refractory epilepsy; brain tumor (glioma). Myocardial viability; coronary perfusion. Outcomes studied: Results/Comments: - PET has a demonstrated diagnostic benefit in certain indications in lung cancers, colorectal cancers, malignant melanomas, head& neck cancers, lymphoma (i.e. in the initial staging, detection of metastases and/or monitoring of therapy response: indication dependent on the type of cancer). - PET is effective in the diagnosis of epileptic foci and may differentiate between tumor tissue and radiation necrosis in brain tumors. - PET is effective in the evaluation of myocardial viability and myocardial perfusion. - Models for the assessment of the cost-effectiveness of PET in NSCLC and myocardial viability have been developed.
MSAC (ii)	Positron emission tomography [Part 2(ii)].	FDG-PET compared	Excellent	Basis for evaluation:	*Translation (norwegian into english) of the Evidence table in NHSRC 2003*

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
Australia 2001	Medical Services Advisory Committee. Medical Services Advisory Committee (MSAC) 2001 (MSAC reference 10): 169.	to conventional techniques: CT/MRI/*Rtg. /Ultralyd* Bone marrow biopsy Bone marrow scintigraphy		Systematic reviews and primary studies Search in Medline, Cochrane, HTA database, DARE, NHS EED, Healthstar, Cinahl, Embase Inclusion criteria: Only english language Prospective patient series >10 patients with clear inclusion criteria for disease. Casuistic studies excluded.	Indications studied: Recurrence of lymphoma before treatment (38). Staging of head & neck cancer (spinocellular carcinoma) before treatment (48). Sarcoma: staging, biopsy, recurrence, distant metastases, monitoring of therapy (24). Outcomes studied: Histopathology (confirmed); choice of therapy; clinical outcome, cost-effectiveness.. Results/Comments: -Increased utility of PET for staging of lymphoma and evidence for effect on choice of therapy. -PET has a similar or even better diagnostic accuracy compared to CT/MRI for head & neck cancer and PET is better in the detection of recurrence or residual tumor. No evidence for an effect on the choice of therapy. -Unclear evidence for a significance of PET compared to CT for sarcoma in staging or detection of recurrence; improvement in "guided biopsy". No effect on the choice of therapy. -PET has no documented effect on clinical outcome in some indications. -No adequate knowledge of cost-effectiveness.
ICES *Canada* 2001	Health technology assessment of PET (positron emission tomography). Laupacis A. Institute for Clinical Evaluative Sciences (ICES) 2001: 116.	FDG-PET	Fair	Systematic review of the English peer-reviewed, grey and web-based PET scanning literature up	*Translation (norwegian into english) of the Evidence table in NHSRC 2003* Indications studied: Lung cancer(12);Solitary pulmonary nodule (12);Head & Neck cancer(15);Breast cancer(5);Hodgkin lymphoma (5); malignant melanoma (3); colorectal cancer (2);brain tumor: recurrence or irradiation necrosis(0); myocardial viability (?);epilepsy (?); dementia(?)

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
				to December 2000 Inclusion criteria: Case-series of >12 patients Economic evaluations	Outcomes studied: Histopathology; choice of therapy; clinical outcome. Results/Comments: PET is considered useful in the diagnosis of all studied indications in oncology. PET may affect patient management i.e. avoidance of unnecessary aggressive (surgery) treatment. PET has no shown benefit over existing alternatives in the evaluation of myocardial viability. PET may have a role in the diagnosis of epileptic foci but most likely not in the diagnosis of dementia. PET may be cost-effective in the evaluation of lung-cancer, in cases of solitary pulmonary infiltrates and in patients treated for Hodgkin's lymphoma.
ICSI 2001	PET scans for solitary pulmonary nodules, non-small cell lung cancer, recurrent colorectal cancer, lymphoma, and recurrent melanoma. Institute for Clinical Systems Improvement (ICSI) 2001 (Technology Assessment Report).	FDG-PET	Poor	No details on Search strategy	-PET scans are safe – there are no reports of morbidity or mortality as a result of a PET scan. -The potential for misuse of PET exists; PET scans are inappropriate if used a) as a screening tool in the general population, b) when the results would not alter the treatment approach, c) to evaluate neoplasms that are not glucose avid with FDG PET, d) within 2 months of an operative procedure or within 3-4 months after the completion of treatment, or e) for patients with uncontrolled diabetes or glucose levels above 200 mg/dL. -SPN's: PET scans can correctly distinguish benign from malignant indeterminate SPN's in 87% to 94% of the cases. However, PET scan results do not provide a definitive diagnosis that is possible only with biopsy and tissue diagnosis. (Conclusion Grade I based on Class C evidence). -NSCLC: PET is more sensitive, specific, and accurate than VT in evaluating thoracic nodes and extra-thoracic abnormalities for the purpose of staging NSCLC. Based on th positive and negative predictive values of PET scans for mediastinal lymph node metastases, a negative PET scan may not require invasive follow-up but a positive PET scan should be followed by mediastinoscopy. PET scans have also been found to identify patients not suitable for resection because of distant metastases in 8% to 15% of the cases or N3 disease in 6% of the cases. (Conclusion Grade I based on Class C evidence). -Recurrent Colorectal Cancer: PET scans may be used to evaluate patients with

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
					elevated levels of CEA but negative CT scans. For detection of local recurrence of colorectal cancer, PET scans have been found to be more sensitive, specific, and accurate than CT scans. For detection of hepatic metastases, PET and CT are at least comparable, but PET provides more information about the extent of disease. Total body PET is superior to CT in identifying extrahepatic disease. Unnecessary operative procedures may be avoided in up to 20% of patients studied. (Conclusion Grade II based on Class C evidence). -Lymphoma: PET has been found to identify more nodal and more extranodal disease in lymphoma patients. In patients whose disease status has been verified by biopsy, PET scans were more accurate than CT scans for staging. PET scans have a high sensitivity and specificity for staging disease prior to treatment. For the evaluation of residual masses, Pet scans have been found to be at least as sensitive and more specific than CT. (Conclusion Grade II based on Class C evidence). -Recurrent Melanoma: PET scans are superior to conventional imaging methods in identifying systemic melanoma metastases with the exception of lung metastases where the various approaches are comparable. Unnecessary operative procedures may be avoided in up to 17% of patients with clinical suspicion of progressive disease. Pet scans do not appear to have a primary role in staging regional lymph nodes in patients with localized cutaneous melanoma. (Conclusion Grade II based on Class C evidence). -To date, there are limited survival data. RCT's to determine a survival benefit are not likely. The major benefit of PET scans is in identifying patients who will not benefit from operative resection thereby sparing them from the morbidity and the costs of the procedure. PET is not designed as a tool that will ultimately impact survival but rather as a tool to assist in selection of optimum treatment.
HAYES 2000	Positron emission tomography (PET) for malignant lymphoma. HAYES, Inc. 2000: 37.	N.A.	N.A.	N.A.	N.A.

MALIGNANT MELANOMA

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
ICES *Canada* April 2004 (Quarterly updates i.e. Jan 2004, Sept 2003, May 2003)	Health technology assessment of PET (positron emission tomography): a systematic review. Lauparis A, Paszat L, Hodgson D, Benk V. (ICES) 2004. (health technology assessment of positron emission tomography (PET) in oncology-a systematic review-ICES investigative report)	PET	Fair	PET literature review and assessment of articles Update from Nov 1,2002 up to and including Apr 1, 2004. (updates on ICES 2001 original report)	*-Populations studied (4"B" Grade studies)*: *Studies on staging of newly diagnosed malignant melanoma and follow-up of malignant melanoma* *-Potential impact of PET on processes of care for malignant melanoma* It appears that PET may be superior to conventional imaging in the detection of metastatic disease. However, PET is limited in its ability to detect small (≤ 5mm) nodal metastases. While the test characteristics of PET in various scenarios of malignant melanoma are favourable, we lack evidence about the nature and magnitude of benefit among these patients.
FNCLCC *France* 2003	Recommendations pour la pratique clinique : standards, options et recommandations 2003 pour l'utilisation de la tomographie par emision de positrons au [18-F]-FDG (TEP-FDG) en cancerologie (rapport integral) (FNCLCC) 2003 :290.	FDG-PET	Fair	*Translation of French* Search from January 1966 until October 2002	-Place of PET in the management of patients with cutaneous malignant melanoma. *Standard*: PET is not indicated in the detection of nodal micrometastasis (evidence level B2). *Options*: PET is no alternative to sentinel ganglion biopsy (evidence level B2) but may be utilized as a non invasive technique in the detection of nodal metastasis (evidence level B2). PET may be utilized in the initial staging of melanoma patients at high risk for metastasis (stage III AJCC) in a perspective of a possible curative treatment (evidence level B2) and in the assessment of the operability of a presumed unique metastasis (evidence level B2). *Indication requiring confirmation within the framework of evaluated protocols*: PET may be indicated in the detection of recurrent disease in the follow up within the framework of evaluated protocols (evidence level B2). *Recommendation*: additional studies are needed to more precisely determine the place of PET in the decision tree and its association with other imaging techniques in the follow up of patients and in the evaluation of therapy response (experts' agreement), thereby also considering therapeutic evolutions. -Place of PET in the management of patients with other than cutaneous melanoma. *Standard,Option*: no indication for PET in these patients. *Recommendations*: additional studies are needed to confirm the potential of PET in the detection of metastasis (experts'agreement), in the detection of primary mucosal tumors (experts'agreement) and in the follow up of patients (experts'agreement)

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
NHSRC *Norway* 2003	Positron emission tomography (PET) - diagnostic and clinical use. Morland B. Norwegian Health Services Research Centre (NHSRC) 2003 (SMM-Report 6/2003).	PET		*Short review* Update based on 14 HTA reports and 3 SR's (2001-2003). Update of reports of INATHA 1999 and SMM 2000 Survey and synthesis of the evidence	-There are many overlapping references in the reports and they generally conclude in agreement. -The clinical use of PET as a diagnostic tool has increased in the period, despite the lack of good documentation regarding clinical effectiveness. -The main areas of use are still within oncology, neurology and cardiology. -HTA-reports published after the INATHA-report of 1999 and the SMM-report in 2000, concludes that PET is more accurate than other diagnostic procedures for several indications within oncology and should therefore be used. -This applies mainly in diagnosing of non-small cell lung cancer (NSCLC) and solitary pulmonary nodules, in staging of Hodgkin's lymphoma, in identifying metastasis from malignant melanoma and colorectal cancer and, in the diagnosis of head and neck tumors. -It is important to notice that PET is still in the developing phase. Examinations should therefore be performed within the framework of clinical trials, since there is still a great need for knowledge collected systematically. -It is also important to notice that "PET scanning should only be used if the results of the test will affect patient management".
AETMIS *Canada* 2002	Positron emission tomography in Quebec. Dussault F P, Nguyen V H, Rachet F. Agence d'Evaluation des Technologies et des Modes d'Intervention en Sante (AETMIS) 2002 (AETMIS 01-3 RE): 260.	FDG-PET	Fair	Basis for evaluation: Existing technology assessments with updated search in Medline, Cochrane, Embase, Cancerlit, HTA-economic databases. Purpose of the evaluation:	*Translation (norwegian into english) of the Evidence table in NHSRC 2003)* Indications studied: NSCLC and solitary lung infiltrates; colorectal cancer; malignant melanoma; head & neck cancer; lymphoma; breast cancer; prostate cancer. Dementia and Alzheimer's disease; refractory epilepsy; brain tumor (glioma). Myocardial viability; coronary perfusion. Outcomes studied: Results/Comments: - PET has a demonstrated diagnostic benefit in certain indications in lung cancers, colorectal cancers, malignant melanomas, head& neck cancers, lymphoma (i.e. in the initial staging, detection of metastases and/or monitoring of therapy response: indication dependent on the type of cancer). - PET is effective in the diagnosis of epileptic foci and may differentiate between

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
				-collect and evaluate documentation on the clinical use of PET. -formulate recommendations on the clinical use of PET in Quebec	tumor tissue and radiation necrosis in brain tumors. - PET is effective in the evaluation of myocardial viability and myocardial perfusion. - Models for the assessment of the cost-effectiveness of PET in NSCLC and myocardial viability have been developed.
DACEHTA *Danmark* 2001b	Positron emissions tomography (PET) with 18-F-fluorodeoxyglucose (FDG). A literature review of evidence for clinical use in the fields of oncology, cardiology and neurology. Danish Centre for Evaluation and Health Technology Assessment (DACEHTA) (formerly DIHTA) 2001.	FDG-PET. Standard PET versus "hybrid-PET" With and without blinded evaluation of test results. With and without comparison with alternative methods.	Fair	*Report in Danish* <u>Basis for evaluation:</u> Systematic literature review. Search in Medline, Embase, Cochrane. <u>Inclusion criteria:</u> English language. RCT/Case-control/Cohort studies. 363 articles included. Patient series >12 patients with clear	*Translation (norwegian into english) of the Evidence table in NHSRC 2003* *Systematic review of literature* <u>Indications studied</u>: NSCLC (53); Solitary Pulmonary Infiltrates >4cm (12); ; Colorectal cancer (32); Malignant Melanoma (20); Head & Neck cancer (42); Breast cancer (37). Alzheimer's disease (41); Epilepsy foci (23). Ischemic Heart Disease (52). <u>Outcomes studied:</u> Histopathology; choice of therapy; clinical outcome. <u>Results/Comments:</u> -PET has a higher sensitivity, specificity, positive and negative predictive value compared to CT in the initial staging and detection of metastases (however: low evidence degree). -Most studies find a high sensitivity and specificity of PET in patient with malignant lung infiltrates (however: selected patients with high degree malignancy grades). -PET is presumed to be better than CT/MRI in the detection of head & neck cancer recurrence. -PET is better than CT for initial staging and detection of liver metastases in colorectal cancer (however: low evidence degree). -PET has a higher diagnostic precision compared to CT in the detection of

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
				inclusion criteria for disease.	metastases (other than in the lungs) from malignant melanoma. -PET may become a tool for dealing with lymph node metastases from breast cancer (however; too few and bad studies). -PET is not better than SPECT in the detection of Alzheimer's disease or epileptic foci. -Variable results for the use of PET in ischemic heart disease. -No documentation on clinical outcome.
DACEHTA *Danmark* 2001a	Paper concerning clinical PET-scanning using FDG - with focus on diagnosis of cancer. Danish Centre for Evaluation and Health Technology Assessment (DACEHTA) (formerly DIHTA) 2001.	FDG-PET		*Danish* Recommendations based on SR's as described in DACEHTA, *Denmark*, 2001b[32] and critically reviewed by oncologists.	*Translation (norwegian into english) of the Evidence table in NHSRC 2003* *Recommendations:* The documented benefit of PET in diagnosis: Lung cancer : good Solitary lung mass : good Colorectal cancer : good Head & Neck cancer : good Malignant melanoma: good Breast cancer : scant Other cancers : scant Alzheimer : lacking Epilepsy : unclear Ischemic heart disease: lacking The documented benefit of PET in therapy: Lung cancer : scant Other : lacking
ICES *Canada* 2001	Health technology assessment of PET (positron emission tomography). Laupacis A. Institute for Clinical Evaluative Sciences (ICES) 2001: 116.	FDG-PET	Fair	Systematic review of the English peer-reviewed, grey and web-based PET scanning literature up	*Translation (norwegian into english) of the Evidence table in NHSRC 2003* Indications studied: Lung cancer(12);Solitary pulmonary nodule (12);Head & Neck cancer(15);Breast cancer(5);Hodgkin lymphoma (5); malignant melanoma (3); colorectal cancer (2);brain tumor: recurrence or irradiation necrosis(0); myocardial viability (?);epilepsy (?); dementia(?)

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
				to December 2000 Inclusion criteria: Case-series of >12 patients Economic evaluations	Outcomes studied: Histopathology; choice of therapy; clinical outcome. Results/Comments: PET is considered useful in the diagnosis of all studied indications in oncology. PET may affect patient management i.e. avoidance of unnecessary aggressive (surgery) treatment. PET has no shown benefit over existing alternatives in the evaluation of myocardial viability. PET may have a role in the diagnosis of epileptic foci but most likely not in the diagnosis of dementia. PET may be cost-effective in the evaluation of lung-cancer, in cases of solitary pulmonary infiltrates and in patients treated for Hodgkin's lymphoma.
ICSI 2001	PET scans for solitary pulmonary nodules, non-small cell lung cancer, recurrent colorectal cancer, lymphoma, and recurrent melanoma. Institute for Clinical Systems Improvement (ICSI) 2001 (Technology Assessment Report).	FDG-PET	Poor	No details on Search strategy	-PET scans are safe – there are no reports of morbidity or mortality as a result of a PET scan. -The potential for misuse of PET exists; PET scans are inappropriate if used a) as a screening tool in the general population, b) when the results would not alter the treatment approach, c) to evaluate neoplasms that are not glucose avid with FDG PET, d) within 2 months of an operative procedure or within 3-4 months after the completion of treatment, or e) for patients with uncontrolled diabetes or glucose levels above 200 mg/dL. -SPN's: PET scans can correctly distinguish benign from malignant indeterminate SPN's in 87% to 94% of the cases. However, PET scan results do not provide a definitive diagnosis that is possible only with biopsy and tissue diagnosis. (Conclusion Grade I based on Class C evidence). -NSCLC: PET is more sensitive, specific, and accurate than VT in evaluating thoracic nodes and extra-thoracic abnormalities for the purpose of staging NSCLC. Based on th positive and negative predictive values of PET scans for mediastinal lymph node metastases, a negative PET scan may not require invasive follow-up but a positive PET scan should be followed by mediastinoscopy. PET scans have also been found to identify patients not suitable for resection because of distant metastases in 8% to 15% of the cases or N3 disease in 6% of the cases. (Conclusion Grade I based on Class C evidence). -Recurrent Colorectal Cancer: PET scans may be used to evaluate patients with

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
					elevated levels of CEA but negative CT scans. For detection of local recurrence of colorectal cancer, PET scans have been found to be more sensitive, specific, and accurate than CT scans. For detection of hepatic metastases, PET and CT are at least comparable, but PET provides more information about the extent of disease. Total body PET is superior to CT in identifying extrahepatic disease. Unnecessary operative procedures may be avoided in up to 20% of patients studied. (Conclusion Grade II based on Class C evidence). -Lymphoma: PET has been found to identify more nodal and more extranodal disease in lymphoma patients. In patients whose disease status has been verified by biopsy, PET scans were more accurate than CT scans for staging. PET scans have a high sensitivity and specificity for staging disease prior to treatment. For the evaluation of residual masses, Pet scans have been found to be at least as sensitive and more specific than CT. (Conclusion Grade II based on Class C evidence). -Recurrent Melanoma: PET scans are superior to conventional imaging methods in identifying systemic melanoma metastases with the exception of lung metastases where the various approaches are comparable. Unnecessary operative procedures may be avoided in up to 17% of patients with clinical suspicion of progressive disease. Pet scans do not appear to have a primary role in staging regional lymph nodes in patients with localized cutaneous melanoma. (Conclusion Grade II based on Class C evidence). -To date, there are limited survival data. RCT's to determine a survival benefit are not likely. The major benefit of PET scans is in identifying patients who will not benefit from operative resection thereby sparing them from the morbidity and the costs of the procedure. PET is not designed as a tool that will ultimately impact survival but rather as a tool to assist in selection of optimum treatment.
MSAC *Australia* 2000	Positron emission tomography. Medical Services Advisory Committee (MSAC) 2000 (MSAC Application 1025): 124.	FDG-PET compared to conventional techniques: CT/MRI/*Rtg./Ultralyd*	Excellent	Basis for evaluation: Systematic reviews (3) and primary studies (54) Search in Medline, Cochrane,	*Translation (norwegian into english) of the Evidence table in NHSRC 2003* Indications studied: Pre-operative staging and detection of metastases from NSCLC (17). Metastases from malignant melanoma (11). Recurrence following treatment of malignant glioma (11). Metastases from colorectal cancer (2). Epileptic foci in the brain (5). Myocard viability (?)

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
				HTA database, DARE, NHS EED, Healthstar, Cinahl, Embase Inclusion criteria: Only english language Prospective patient series >10 patients with clear inclusion criteria for disease. Casuistic studies excluded.	Outcomes studied: Histopathology (confirmed); choice of therapy; clinical outcome, cost-effectiveness.. Results/Comments: Higher diagnostic accuracy, i.e. higher sensitivity for staging of NSCLC and detection of metastases from malignant melanomas and colorectal cancer. Improved differentiation between tumor tissue and radiation necrosis following treatment of glioma. Change in choice of therapy for NSCLC and potential for change in case of metastases from colorectal cancer. No documented effect on clinical outcome. No adequate knowledge of cost-effectiveness. In some patients, PET may be helpful in improving diagnosis for epilepsy surgery, but uncertainty persists related to the real amount of false negatives/positives. No conclusion on the use of PET in coronary heart disease.
HAYES 2000	Positron emission tomography (PET) for malignant melanoma. HAYES, Inc. 2000: 33.	N.A.	N.A.	N.A.	N.A.

CANCERS OF THE DIGESTIVE SYSTEM

Esophageal cancer

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
FNCLCC *France* 2003	Recommendations pour la pratique clinique : standards, options et recommandations 2003 pour l'utilisation de la tomographie par emision de positrons au [18-F]-FDG (TEP-FDG) en cancerologie (rapport integral) (FNCLCC) 2003 :290.	FDG-PET	Fair	*Translation of French* Search from January 1966 until October 2002	-Place of PET in the management of patients with esophageal cancer. *Standard*: PET is indicated, in addition to scanner and echo-endoscopy, in the pre-therapeutic evaluation of nodal involvement and metastatic spread of esophageal cancers (evidence level B2). *Recommendation*: the place of PET in the evaluation of therapeutic response and the diagnosis of recurrent disease remains to be established in prospective studies (experts' agreement).
NHSRC *Norway* 2003	Positron emission tomography (PET) - diagnostic and clinical use. Morland B. Norwegian Health Services Research Centre (NHSRC) 2003 (SMM-Report 6/2003).	PET		*Short review* Update based on 14 HTA reports and 3 SR's (2001-2003). Update of reports of INATHA 1999 and SMM 2000 Survey and synthesis of the evidence	-There are many overlapping references in the reports and they generally conclude in agreement. -The clinical use of PET as a diagnostic tool has increased in the period, despite the lack of good documentation regarding clinical effectiveness. -The main areas of use are still within oncology, neurology and cardiology. -HTA-reports published after the INATHA-report of 1999 and the SMM-report in 2000, concludes that PET is more accurate than other diagnostic procedures for several indications within oncology and should therefore be used. -This applies mainly in diagnosing of non-small cell lung cancer (NSCLC) and solitary pulmonary nodules, in staging of Hodgkin's lymphoma, in identifying metastasis from malignant melanoma and colorectal cancer and, in the diagnosis of head and neck tumors. -It is important to notice that PET is still in the developing phase. Examinations should therefore be performed within the framework of clinical trials, since there is still a great need for knowledge collected systematically. -It is also important to notice that "PET scanning should only be used if the results of the test will affect patient management".

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
BCBS *USA* 2002	FDG positron emission tomography for evaluating esophageal cancer. Blue Cross Blue Shield Association (BCBS) 2002 (TEC Assessment 16(21)): 31.	PET	Fair	Search up to March 2002	Evidence is insufficient to permit conclusions about diagnostic performance and health outcomes for use of PET in detecting primary esophageal tumours, staging, or evaluation of treatment response. While the greatest amount of evidence is available on staging, concerns about questionable study quality and inconsistent results preclude conclusions about the relative diagnostic performance of PET and CT. The random effects model (REM) estimates of sensitivity for PET and CT for detecting locoregional lymph node involvement have very wide confidence intervals with a high dgree of overlap. Without a clear indication of relative diagnostic performance, it cannot be concluded how management and outcomes would be affected by use of PET in evaluating esophageal cancer.
MSAC (i) *Australia* 2001	Positron emission tomography [Part 2(i)]. Medical Services Advisory Committee. Medical Services Advisory Committee (MSAC) 2001 (MSAC reference 10): 126.	FDG-PET compared to conventional techniques: CT/MRI/*Rtg./Ultralyd*	Excellent	Basis for evaluation: Systematic reviews and primary studies Search in Medline, Cochrane, HTA database, DARE, NHS EED, Healthstar, Cinahl, Embase Inclusion criteria: Only english language Prospective patient series >10 patients with clear inclusion	*Translation (norwegian into english) of the Evidence table in NHSRC 2003* Indications studied: Recurrence of ovarian cancer (7). Staging of cervical cancer (5) or endometrial cancer (0). Staging of esophageal (12) or gastric cancer (4). Outcomes studied: Histopathology (confirmed); choice of therapy; clinical outcome, cost-effectiveness.. Results/Comments: PET shows, compared to CT, a higher specificity and positive predictive value for recurrence of ovarian cancer. Higher sensitivity for the diagnosis of metastatic lymph nodes and staging of cervix cancer No documentation on therapy choice, but assumed potential to change from curative to palliative surgery. No documented effects on clinical outcome. No adequate knowledge of cost-effectiveness

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
				criteria for disease. Casuistic studies excluded.	
HAYES 2001	Positron emission tomography (PET) for oesophageal cancer. HAYES, Inc. 2001: 35.	N.A.	N.A.	N.A.	N.A.

Gastric cancer

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
FNCLCC *France* 2003	Recommendations pour la pratique clinique : standards, options et recommandations 2003 pour l'utilisation de la tomographie par emision de positrons au [18-F]-FDG (TEP-FDG) en cancerologie (rapport integral) (FNCLCC) 2003 :290.	FDG-PET	Fair	*Translation of French* Search from January 1966 until October 2002	-Place of PET in the management of patients with gastric cancer. *Standard*: insufficient evidence in literature to define standards or options. *Recommendation*: the impact of PET in the therapeutic management remains to be established in prospective studies (experts' agreement).
NHSRC *Norway* 2003	Positron emission tomography (PET) - diagnostic and clinical use. Morland B. Norwegian Health Services Research Centre (NHSRC) 2003 (SMM-Report 6/2003).	PET		*Short review* Update based on 14 HTA reports and 3 SR's (2001-2003). Update of reports of INATHA 1999 and SMM 2000 Survey and synthesis of the evidence	-There are many overlapping references in the reports and they generally conclude in agreement. -The clinical use of PET as a diagnostic tool has increased in the period, despite the lack of good documentation regarding clinical effectiveness. -The main areas of use are still within oncology, neurology and cardiology. -HTA-reports published after the INATHA-report of 1999 and the SMM-report in 2000, concludes that PET is more accurate than other diagnostic procedures for several indications within oncology and should therefore be used. -This applies mainly in diagnosing of non-small cell lung cancer (NSCLC) and solitary pulmonary nodules, in staging of Hodgkin's lymphoma, in identifying metastasis from malignant melanoma and colorectal cancer and, in the diagnosis of head and neck tumors. -It is important to notice that PET is still in the developing phase. Examinations should therefore be performed within the framework of clinical trials, since there is still a great need for knowledge collected systematically. -It is also important to notice that "PET scanning should only be used if the results of the test will affect patient management".
MSAC (i) *Australia*	Positron emission tomography [Part 2(i)]. Medical Services	FDG-PET compared to	Excellent	Basis for evaluation:	*Translation (norwegian into english) of the Evidence table in NHSRC 2003*

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
2001	Advisory Committee. Medical Services Advisory Committee (MSAC) 2001 (MSAC reference 10): 126.	conventional techniques: CT/MRI/*Rtg. /Ultralyd*		Systematic reviews and primary studies Search in Medline, Cochrane, HTA database, DARE, NHS EED, Healthstar, Cinahl, Embase Inclusion criteria: Only english language Prospective patient series >10 patients with clear inclusion criteria for disease. Casuistic studies excluded.	Indications studied: Recurrence of ovarian cancer (7). Staging of cervical cancer (5) or endometrial cancer (0). Staging of esophageal (12) or gastric cancer (4). Outcomes studied: Histopathology (confirmed); choice of therapy; clinical outcome, cost-effectiveness.. Results/Comments: PET shows, compared to CT, a higher specificity and positive predictive value for recurrence of ovarian cancer. Higher sensitivity for the diagnosis of metastatic lymph nodes and staging of cervix cancer No documentation on therapy choice, but assumed potential to change from curative to palliative surgery. No documented effects on clinical outcome. No adequate knowledge of cost-effectiveness

Colorectal cancer

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
ICES *Canada* April 2004 (Quarterly updates i.e. Jan 2004, Sept 2003, May 2003)	Health technology assessment of PET (positron emission tomography): a systematic review. Lauparis A, Paszat L, Hodgson D, Benk V. (ICES) 2004. (health technology assessment of positron emission tomography (PET) in oncology-a systematic review-ICES investigative report)	PET	Fair	PET literature review and assessment of articles Update from Nov 1,2002 up to and including Apr 1, 2004. (updates on ICES 2001 original report)	*-Populations studied (3"B" Grade studies)*: *Studies on detection of recurrent/metastatic colorectal carcinoma* *-Potential impact of PET on processes of care for colorectal carcinoma* It is not clear that PET in this context would replace any currently applied investigations; the slightly higher values for PET might slightly reduce the number of laparotomies performed in this clinical setting. Ruers et al. 2002 compared PET to conventional imaging and reported that patient cre was chaged by PET results for 29% of patients.
FNCLCC *France* 2003	Recommandations pour la pratique clinique : standards, options et recommandations 2003 pour l'utilisation de la tomographie par émission de positrons au [18-F]-FDG (TEP-FDG) en cancérologie (rapport intégral) (FNCLCC) 2003 :290.	FDG-PET	Fair	*Translation of French* Search from January 1966 until October 2002	-Place of PET in the initial staging of colorectal cancers. *Standard*: no standard applicable. *Indication requiring confirmation within the framework of evaluated protocols*: place of PET in the initial preoperative staging of colorectal cancers (evidence level C). *Recommendation*: the indication of PET in the initial staging of colorectal cancers needs to be evaluated within the framework of prospective studies, more specifically in case of discordance between conventional imaging judged "normal" and a preoperative elevated concentration of ACE (experts' agreement). -Place of PET in the detection of recurrent disease and metastasis in colorectal cancers. *Standards*: PET is indicated in the pre-operative staging of local recurrence and metastasis of colorectal cancers (evidence level B2). PET is indicated to localize recurrence in case of confirmed elevated ACE in patients who have already had surgical resection for colorectal cancer (evidence level B2). *Recommendations*: the impact of PET on patients' survival should to be evaluated within the framework of prospective studies addressing the follow up of colorectal cancers stages II and III (experts' agreement).
NHSRC *Norway* 2003	Positron emission tomography (PET) - diagnostic and clinical use. Morland B.	PET	Fair	*Short review* Update based on 14 HTA	-There are many overlapping references in the reports and they generally conclude in agreement. -The clinical use of PET as a diagnostic tool has increased in the period, despite the lack

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
	Norwegian Health Services Research Centre (NHSRC) 2003 (SMM-Report 6/2003).			reports and 3 SR's (2001-2003). Update of reports of INATHA 1999 and SMM 2000 Survey and synthesis of the evidence	of good documentation regarding clinical effectiveness. -The main areas of use are still within oncology, neurology and cardiology. -HTA-reports published after the INATHA-report of 1999 and the SMM-report in 2000, concludes that PET is more accurate than other diagnostic procedures for several indications within oncology and should therefore be used. -This applies mainly in diagnosing of non-small cell lung cancer (NSCLC) and solitary pulmonary nodules, in staging of Hodgkin's lymphoma, in identifying metastasis from malignant melanoma and colorectal cancer and, in the diagnosis of head and neck tumors. -It is important to notice that PET is still in the developing phase. Examinations should therefore be performed within the framework of clinical trials, since there is still a great need for knowledge collected systematically. -It is also important to notice that "PET scanning should only be used if the results of the test will affect patient management".
AETMIS *Canada* 2002	Positron emission tomography in Quebec. Dussault F P, Nguyen V H, Rachet F. Agence d'Evaluation des Technologies et des Modes d'Intervention en Sante (AETMIS) 2002 (AETMIS 01-3 RE): 260.	FDG-PET	Fair	Basis for evaluation: Existing technology assessments with updated search in Medline, Cochrane, Embase, Cancerlit, HTA-economic databases. Purpose of the evaluation: -collect and evaluate documentation	*Translation (norwegian into english) of the Evidence table in NHSRC 2003* Indications studied: NSCLC and solitary lung infiltrates; colorectal cancer; malignant melanoma; head & neck cancer; lymphoma; breast cancer; prostate cancer. Dementia and Alzheimer's disease; refractory epilepsy; brain tumor (glioma). Myocardial viability; coronary perfusion. Outcomes studied: Results/Comments: - PET has a demonstrated diagnostic benefit in certain indications in lung cancers, colorectal cancers, malignant melanomas, head& neck cancers, lymphoma (i.e. in the initial staging, detection of metastases and/or monitoring of therapy response: indication dependent on the type of cancer). - PET is effective in the diagnosis of epileptic foci and may differentiate between tumor tissue and radiation necrosis in brain tumors. - PET is effective in the evaluation of myocardial viability and myocardial perfusion. - Models for the assessment of the cost-effectiveness of PET in NSCLC and myocardial

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
				on the clinical use of PET. -formulate recommendations on the clinical use of PET in Quebec	viability have been developed.
DACEHTA *Danmark* 2001b	Positron emissions tomography (PET) with 18-F-fluorodeoxyglucose (FDG). A literature review of evidence for clinical use in the fields of oncology, cardiology and neurology. Danish Centre for Evaluation and Health Technology Assessment (DACEHTA) (formerly DIHTA) 2001.	FDG-PET. Standard PET versus "hybrid-PET" With and without blinded evaluation of test results. With and without comparison with alternative methods.	Fair	*Report in Danish* Basis for evaluation: Systematic literature review. Search in Medline, Embase, Cochrane. Inclusion criteria: English language. RCT/Case-control/Cohort studies. 363 articles included. Patient series >12 patients with clear inclusion criteria for disease.	*Translation (norwegian into english) of the Evidence table in NHSRC 2003* *Systematic review of literature* Indications studied: NSCLC (53); Solitary Pulmonary Infiltrates >4cm (12); ; Colorectal cancer (32); Malignant Melanoma (20); Head & Neck cancer (42); Breast cancer (37). Alzheimer's disease (41); Epilepsy foci (23). Ischemic Heart Disease (52). Outcomes studied: Histopathology; choice of therapy; clinical outcome. Results/Comments: -PET has a higher sensitivity, specificity, positive and negative predictive value compared to CT in the initial staging and detection of metastases (however: low evidence degree). -Most studies find a high sensitivity and specificity of PET in patient with malignant lung infiltrates (however: selected patients with high degree malignancy grades). -PET is presumed to be better than CT/MRI in the detection of head & neck cancer recurrence. -PET is better than CT for initial staging and detection of liver metastases in colorectal cancer (however: low evidence degree). -PET has a higher diagnostic precision compared to CT in the detection of metastases (other than in the lungs) from malignant melanoma. -PET may become a tool for dealing with lymph node metastases from breast cancer (however; too few and bad studies). -PET is not better than SPECT in the detection of Alzheimer's disease or epileptic foci. -Variable results for the use of PET in ischemic heart disease.

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
					-No documentation on clinical outcome.
DACEHTA *Danmark* 2001a	Paper concerning clinical PET-scanning using FDG - with focus on diagnosis of cancer. Danish Centre for Evaluation and Health Technology Assessment (DACEHTA) (formerly DIHTA) 2001.	FDG-PET		*Danish* Recommendations based on SR's as described in DACEHTA, *Denmark*, 2001b and critically reviewed by oncologists.	*Translation (norwegian into english) of the Evidence table in NHSRC 2003*[7] *Recommendations:* The documented benefit of PET in diagnosis: Lung cancer : good Solitary lung mass : good Colorectal cancer : good Head & Neck cancer : good Malignant melanoma: good Breast cancer : scant Other cancers : scant Alzheimer : lacking Epilepsy : unclear Ischemic heart disease: lacking The documented benefit of PET in therapy: Lung cancer : scant Other : lacking
ICES *Canada* 2001	Health technology assessment of PET (positron emission tomography). Laupacis A. Institute for Clinical Evaluative Sciences (ICES) 2001: 116.	FDG-PET	Fair	Systematic review of the English peer-reviewed, grey and web-based PET scanning literature up to December 2000 Inclusion criteria: Case-series of >12 patients	*Translation (norwegian into english) of the Evidence table in NHSRC 2003* Indications studied: Lung cancer(12);Solitary pulmonary nodule (12);Head & Neck cancer(15);Breast cancer(5);Hodgkin lymphoma (5); malignant melanoma (3); colorectal cancer (2);brain tumor: recurrence or irradiation necrosis(0); myocardial viability (?);epilepsy (?); dementia(?) Outcomes studied: Histopathology; choice of therapy; clinical outcome. Results/Comments: PET is considered useful in the diagnosis of all studied indications in oncology. PET may affect patient management i.e. avoidance of unnecessary aggressive (surgery) treatment.

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
				Economic evaluations	PET has no shown benefit over existing alternatives in the evaluation of myocardial viability. PET may have a role in the diagnosis of epileptic foci but most likely not in the diagnosis of dementia. PET may be cost-effective in the evaluation of lung-cancer, in cases of solitary pulmonary infiltrates and in patients treated for Hodgkin's lymphoma.
ICSI 2001	PET scans for solitary pulmonary nodules, non-small cell lung cancer, recurrent colorectal cancer, lymphoma, and recurrent melanoma. Institute for Clinical Systems Improvement (ICSI) 2001 (Technology Assessment Report).	FDG-PET	Poor	No details on Search strategy	-PET scans are safe – there are no reports of morbidity or mortality as a result of a PET scan. -The potential for misuse of PET exists; PET scans are inappropriate if used a) as a screening tool in the general population, b) when the results would not alter the treatment approach, c) to evaluate neoplasms that are not glucose avid with FDG PET, d) within 2 months of an operative procedure or within 3-4 months after the completion of treatment, or e) for patients with uncontrolled diabetes or glucose levels above 200 mg/dL. -SPN's: PET scans can correctly distinguish benign from malignant indeterminate SPN's in 87% to 94% of the cases. However, PET scan results do not provide a definitive diagnosis that is possible only with biopsy and tissue diagnosis. (Conclusion Grade I based on Class C evidence). -NSCLC: PET is more sensitive, specific, and accurate than VT in evaluating thoracic nodes and extra-thoracic abnormalities for the purpose of staging NSCLC. Based on th positive and negative predictive values of PET scans for mediastinal lymph node metastases, a negative PET scan may not require invasive follow-up but a positive PET scan should be followed by mediastinoscopy. PET scans have also been found to identify patients not suitable for resection because of distant metastases in 8% to 15% of the cases or N3 disease in 6% of the cases. (Conclusion Grade I based on Class C evidence). -Recurrent Colorectal Cancer: PET scans may be used to evaluate patients with elevated levels of CEA but negative CT scans. For detection of local recurrence of colorectal cancer, PET scans have been found to be more sensitive, specific, and accurate than CT scans. For detection of hepatic metastases, PET and CT are at least comparable, but PET provides more information about the extent of disease. Total body PET is superior to CT in identifying extrahepatic disease. Unnecessary operative procedures may be avoided in up to 20% of patients studied. (Conclusion Grade II based on Class C evidence). -Lymphoma: PET has been found to identify more nodal and more extranodal disease in

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
					lymphoma patients. In patients whose disease status has been verified by biopsy, PET scans were more accurate than CT scans for staging. PET scans have a high sensitivity and specificity for staging disease prior to treatment. For the evaluation of residual masses, Pet scans have been found to be at least as sensitive and more specific than CT. (Conclusion Grade II based on Class C evidence). -Recurrent Melanoma: PET scans are superior to conventional imaging methods in identifying systemic melanoma metastases with the exception of lung metastases where the various approaches are comparable. Unnecessary operative procedures may be avoided in up to 17% of patients with clinical suspicion of progressive disease. Pet scans do not appear to have a primary role in staging regional lymph nodes in patients with localized cutaneous melanoma. (Conclusion Grade II based on Class C evidence). -To date, there are limited survival data. RCT's to determine a survival benefit are not likely. The major benefit of PET scans is in identifying patients who will not benefit from operative resection thereby sparing them from the morbidity and the costs of the procedure. PET is not designed as a tool that will ultimately impact survival but rather as a tool to assist in selection of optimum treatment.
MSAC *Australia* 2000	Positron emission tomography. Medical Services Advisory Committee (MSAC) 2000 (MSAC Application 1025): 124.	FDG-PET compared to conventional techniques: CT/MRI/*Rtg. /Ultralyd*	Excellent	Basis for evaluation: Systematic reviews (3) and primary studies (54) Search in Medline, Cochrane, HTA database, DARE, NHS EED, Healthstar, Cinahl, Embase Inclusion criteria: Only english	*Translation (norwegian into english) of the Evidence table in NHSRC 2003)* Indications studied: Pre-operative staging and detection of metastases from NSCLC (17). Metastases from malignant melanoma (11). Recurrence following treatment of malignant glioma (11). Metastases from colorectal cancer (2). Epileptic foci in the brain (5). Myocard viability (?) Outcomes studied: Histopathology (confirmed); choice of therapy; clinical outcome, cost-effectiveness.. Results/Comments: Higher diagnostic accuracy, i.e. higher sensitivity for staging of NSCLC and detection of metastases from malignant melanomas and colorectal cancer. Improved differentiation between tumor tissue and radiation necrosis following treatment of glioma. Change in choice of therapy for NSCLC and potential for change in case of metastases

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
				language Prospective patient series >10 patients with clear inclusion criteria for disease. Casuistic studies excluded.	from colorectal cancer. No documented effect on clinical outcome. No adequate knowledge of cost-effectiveness. In some patients, PET may be helpful in improving diagnosis for epilepsy surgery, but uncertainty persists related to the real amount of false negatives/positives. No conclusion on the use of PET in coronary heart disease.
HAYES 2000	Positron emission tomography (PET) for colorectal cancer. HAYES, Inc. 2000: 36.	N.A.	N.A.	N.A.	N.A.

Pancreatic cancer

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
AHRQ *USA* 2004	Positron emission testing for six cancers (brain, cervical, small cell lung, ovarian, pancreatic and testicular). Matchar D B, Kulasingam S L, Havrilesky L, Mann L O, Myers E R, McCrory D C, Patwardhan M, Prosnitz R. Agency for Healthcare Research and Quality (AHRQ) 2004 (Technology Assessment): 221.	Performance of FDG-PET	Fair (but without clear recom-menda-tions)	Search: MEDLINE <1966 to April Week 1 2003>	-Diagnostic test performance of PET as an adjunct to conventional imaging in differentiating benign from malignant pancreatic lesions. PET sensitivity and specificity were generally slightly better than the comparator alone. One study suggests that the additional clinical impact of PET compared to CT is mixed. Using SUV to define PET positively shows little additional benefit over visual assessment. PET performed reasonably well when compared to state of the art imaging techniques such as MRI and EUS. No sub-populations with more or less benefit from PET than the general study population were identified; however insufficient information and the generally homogeneous populations limited assessment. -Diagnostic test performance of PET as an adjunct to conventional imaging in detecting metastatic pancreatic cancer. PET shows a trend towards greater sensitivity but somewhat lower specificity for the detection of metastasis than the comparators. Future studies need to be larger in order to provide a more definitive assessment of relative test performance. -Identifying a sub-population of patients with metastatic pancreatic carcinoma in which PET might achieve a substantially greater benefit is difficult due to incomplete reporting of details regarding the patient populations and tumor characteristics. -Diagnostic test performance for detection of residual or recurrent disease after primary treatment for pancreatic carcinoma. A single study was identified related to this question and indicated greater discrimination between patients using PET compared to CT and the distinctions were clinically useful.
FNCLCC *France* 2003	Recommandations pour la pratique clinique: standards, options et recommandations 2003 pour l'utilisation de la tomographie par émission de positrons au [18-F]-FDG (TEP-FDG) en cancérologie (rapport intégral) (FNCLCC) 2003 :290.	FDG-PET	Fair	*Translation of French* Search from January 1966 until October 2002	-Place of PET in the management of patients with pancreatic cancer. *Standards*: only in case of a glycemia < 7.2 mmol.L-1, PET is indicated in the differential diagnosis of pancreatic cancer and chronic pancreatitis (evidence level B2). PET is a useful additional examination in the assessment of the extension of pancreatic cancers (evidence level B2) and allows for not proposing radical surgery in patients who already have metastatic disease (experts' agreement). *Indication requiring confirmation within the framework of evaluated protocols*: utility of PET in addition to scanner in the diagnosis of malignancy of cystic pancreatic tumors (evidence level C).

HAYES 2001	Positron emission tomography (PET) for pancreatic cancer. HAYES, Inc. 2001: 40.	N.A.	N.A.	N.A.	N.A.

Liver cancer

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
FNCLCC *France* 2003	Recommandations pour la pratique clinique : standards, options et recommandations 2003 pour l'utilisation de la tomographie par émission de positrons au [18-F]-FDG (TEP-FDG) en cancérologie (rapport intégral) (FNCLCC) 2003: 290.	FDG-PET	Fair	*Translation of French* Search from January 1966 until October 2002	- Place of PET in the management of patients with liver cancer. *Standard*: PET is indicated in the differential diagnosis of liver metastasis, cholangiosarcomas and benign tumors in case of an isolated liver localisation (evidence level B2). *Option*: indication for PET in the staging of extension of hepatocellular carcinomas (evidence level B2). *Indication requiring confirmation within the framework of evaluated protocols*: PET may be useful in the early diagnosis of cholangiosarcomas in patients with sclerosing cholangitis (evidence level B2).
HAYES 2002	Positron emission tomography (PET) for liver cancer. HAYES, Inc. 2002: 60.	N.A.	N.A.	N.A.	N.A.

Digestive neuro-endocrine tumors

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
FNCLCC *France* 2003	Recommandations pour la pratique clinique : standards, options et recommandations 2003 pour l'utilisation de la tomographie par émission de positrons au [18-F]-FDG (TEP-FDG) en cancérologie (rapport intégral) (FNCLCC) 2003: 290.	FDG-PET	Fair	*Translation of French* Search from January 1966 until October 2002	- Place of PET in the management of patients with a neuro-endocrine tumor. *Standards*: PET is not indicated in the initial diagnosis and staging of digestive neuro-endocrine tumors (evidence level B2). PET may only be considered in case of a normal scintigraphy with pentétréotide, which is the initial standard examination (experts' agreement). *Recommendation*: the combination of PET and scintigraphy with pentétréotide may serve as a basis for an isotopic classification of neuro-endocrine tumors within the framework of prospective studies (experts' agreement).

UROGENITAL CANCER

Prostate cancer

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
FNCLCC *France* 2003	Recommandations pour la pratique clinique : standards, options et recommandations 2003 pour l'utilisation de la tomographie par émission de positrons au [18-F]-FDG (TEP-FDG) en cancérologie (rapport intégral) (FNCLCC) 2003 :290.	FDG-PET	Fair	*Translation of French* Search from January 1966 until October 2002	-Place of PET in the management of patients with prostate cancer. *Standard*: no indication for PET in the diagnosis of a primary cancer of the prostate (evidence level B2
NHSRC *Norway* 2003	Positron emission tomography (PET) - diagnostic and clinical use. Morland B. Norwegian Health Services Research Centre (NHSRC) 2003 (SMM-Report 6/2003).	PET		*Short review* Update based on 14 HTA reports and 3 SR's (2001-2003). Update of reports of INATHA 1999 and SMM 2000 Survey and synthesis of the evidence	-There are many overlapping references in the reports and they generally conclude in agreement. -The clinical use of PET as a diagnostic tool has increased in the period, despite the lack of good documentation regarding clinical effectiveness. -The main areas of use are still within oncology, neurology and cardiology. -HTA-reports published after the INATHA-report of 1999 and the SMM-report in 2000, concludes that PET is more accurate than other diagnostic procedures for several indications within oncology and should therefore be used. -This applies mainly in diagnosing of non-small cell lung cancer (NSCLC) and solitary pulmonary nodules, in staging of Hodgkin's lymphoma, in identifying metastasis from malignant melanoma and colorectal cancer and, in the diagnosis of head and neck tumors. -It is important to notice that PET is still in the developing phase. Examinations should therefore be performed within the framework of clinical trials, since there is still a great need for knowledge collected systematically.

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
					-It is also important to notice that "PET scanning should only be used if the results of the test will affect patient management".
AETMIS *Canada* 2002	Positron emission tomography in Quebec. Dussault F P, Nguyen V H, Rachet F. Agence d'Evaluation des Technologies et des Modes d'Intervention en Sante (AETMIS) 2002 (AETMIS 01-3 RE): 260.	FDG-PET	Fair	Basis for evaluation: Existing technology assessments with updated search in Medline, Cochrane, Embase, Cancerlit, HTA-economic databases. Purpose of the evaluation: -collect and evaluate documentation on the clinical use of PET. -formulate recommendations on the clinical use of PET in Quebec	*Translation (norwegian into english) of the Evidence table in NHSRC 2003*[7] Indications studied: NSCLC and solitary lung infiltrates; colorectal cancer; malignant melanoma; head & neck cancer; lymphoma; breast cancer; prostate cancer. Dementia and Alzheimer's disease; refractory epilepsy; brain tumor (glioma). Myocardial viability; coronary perfusion. Outcomes studied: Results/Comments: - PET has a demonstrated diagnostic benefit in certain indications in lung cancers, colorectal cancers, malignant melanomas, head& neck cancers, lymphoma (i.e. in the initial staging, detection of metastases and/or monitoring of therapy response: indication dependent on the type of cancer). - PET is effective in the diagnosis of epileptic foci and may differentiate between tumor tissue and radiation necrosis in brain tumors. - PET is effective in the evaluation of myocardial viability and myocardial perfusion. - Models for the assessment of the cost-effectiveness of PET in NSCLC and myocardial viability have been developed.
HAYES 2001	Positron emission tomography (PET) for prostate cancer. HAYES, Inc. 2001:	N.A.	N.A.	N.A.	N.A.

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
	36.				

Testicular cancer

Study ID	Source/reference	Technology considered	Quality	Remarks	Conclusions/Recommendations "Role of PET"
AHRQ *USA* 2004	Positron emission testing for six cancers (brain, cervical, small cell lung, ovarian, pancreatic and testicular). Matchar D B, Kulasingam S L, Havrilesky L, Mann L O, Myers E R, McCrory D C, Patwardhan M, Prosnitz R. Agency for Healthcare Research and Quality (AHRQ) 2004 (Technology Assessment): 221.	Performance of FDG-PET	Fair (but without clear recom-menda-tions)	Search: MEDLINE <1966 to April Week 1 2003>	-Performance of PET compared to conventional imaging modalities or histology with respect to initial staging in patients with germ cell tumors. Five studies, all limited by small sample size, provide fairly consistent evidence of PET being more sensitive and specific than CT in this indication. However, the clinical relevance of most of these studies is hampered by failure to report results for seminoma and non-seminoma patients separately and failure to report results separately by clinical stage. (Upstaging or downstaging by an improved imaging test would have implications for therapy, which would differ by stage). -Diagnostic performance of PET compared to conventional imaging in the evaluation of residual masses or suspected recurrent disease to reliably distinguish between viable tumor and necrosis/fibrosis. No studies found which evaluated the role of PET in detecting recurrent disease following initial treatment for germ cell tumors. Eight studies, meeting inclusion criteria within this review, assessed the ability of PET to characterize residual post chemotherapy masses as viable tumor or necrosis/fibrosis. For various reasons, estimates of the sensitivity of PET to detect viable tumor, varied widely (four studies showed relatively low sensitivity in the range of 16-67% and four other studies showed relatively high sensitivity in the range of 75-100%). On the other hand, the specificity of PET was consistently higher than that of CT. From a clinical point of view, a high specificity means that a positive PET scan indicates a high probability of residual viable tumor while a low specificity means that a negative PET scan does not provide complete assurance that a patient does not have a mass, which requires surgical resection, esp. in patients with non-seminomatous germ cell tumors. -Diagnostic performance of PET compared to conventional imaging in determining if there has been a recurrence of tumor in patients with rising serum tumor markers and a normal CT. A single study found PET having a sensitivity of 73% and a specificity of 88% for the diagnosis of recurrent germ cell tumor in patients with rising tumor markers but

Study ID	Source/reference	Technology considered	Quality	Remarks	Conclusions/Recommendations "Role of PET"
					a normal CT.
FNCLCC *France* 2003	Recommandations pour la pratique clinique : standards, options et recommandations 2003 pour l'utilisation de la tomographie par émission de positrons au [18-F]-FDG (TEP-FDG) en cancérologie (rapport intégral) (FNCLCC) 2003 :290.	FDG-PET	Fair	*Translation of French* Search from January 1966 until October 2002	-Place of PET in the management of patients with prostate cancer. *Standard*: PET is not indicated in the diagnosis of a primary testicular tumor. PET can not differentiate between a residual fibrous mass and a mature teratoma.
HAYES 2001	Positron emission tomography (PET) for testicular cancer. HAYES, Inc. 2001: 37.	N.A.	N.A.	N.A.	N.A.

Renal cancer

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
FNCLCC *France* 2003	Recommandations pour la pratique clinique : standards, options et recommandations 2003 pour l'utilisation de la tomographie par émission de positrons au [18-F]-FDG (TEP-FDG) en cancérologie (rapport intégral) (FNCLCC) 2003 :290.	FDG-PET	Fair	*Translation of French* Search from January 1966 until October 2002	- Place of PET in the management of patients with renal cancer. *Standard*: no standard applicable. *Option*: PET may be indicated in the search of local recurrences or distant metastasis in case of suspected signs (pain, equivocal results of morphological imaging) (evidence level C). *Indications requiring confirmation within the framework of evaluated protocols*: the place of PET in the diagnosis of a primary tumor (evidence level C) and the initial staging of disease extension (evidence level C) remains to be determined in prospective studies. *Recommendation*: the utility of PET in the evaluation of therapy response requires assessment in prospective studies (experts' agreement).

Bladder cancer

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
FNCLCC *France* 2003	Recommandations pour la pratique clinique : standards, options et recommandations 2003 pour l'utilisation de la tomographie par émission de positrons au [18-F]-FDG (TEP-FDG) en cancérologie (rapport intégral) (FNCLCC) 2003 :290.	FDG-PET	Fair	*Translation of French* Search from January 1966 until October 2002	-Place of PET in the management of patients with bladder cancer. *Standard, Option*: insufficient evidence in literature to define standards or options.

OTHER CANCERS

Thyroid cancer

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
FNCLCC *France* 2003	Recommandations pour la pratique clinique : standards, options et recommandations 2003 pour l'utilisation de la tomographie par émission de positrons au [18-F]-FDG (TEP-FDG) en cancérologie (rapport intégral) (FNCLCC) 2003 :290.	FDG-PET	Fair	*Translation of French* Search from January 1966 until October 2002	-Place of PET in the diagnosis of malignity of thyroid nodules. *Standard*: no indication in the diagnosis of malignity of thyroid nodules. -Place of PET in the detection of nodal metastasis in recurrent disease and distant metastasis of differentiated thyroid cancers. *Standard*: PET is indicated in case of suspected residual disease or recurrence of differentiated thyroid cancers when results of conventional imaging (including radioactive iodium) are equivocal and useful indications for a complementary therapy (in general: surgery) can be expected from PET (evidence level B2). *Recommendations*: clinical studies should continue to more precisely document the diagnostic value of PET compared to dosage of thyroglobuline (experts' agreement) and the influence of endogeneous TSH-levels or the administration of rh TSH on the detection of tumoral sites (experts' agreement). -Place of PET in the management of patients with medullary thyroid cancer (MTC). *Standard*: no standard. *Option*: in case of a new surgical intervention for persistent or recurrent MTC, PET may be included in the preoperative bilan (evidence level B2). *Recommendation*: ongoing research on the role of PET in the management of CMT in addition to the other diagnostic approaches is recommended (experts' agreement).
NHSRC *Norway* 2003	Positron emission tomography (PET) - diagnostic and clinical use. Morland B. Norwegian Health Services Research Centre (NHSRC) 2003 (SMM-Report 6/2003).	PET		*Short review* Update based on 14 HTA reports and 3 SR's (2001-2003). Update of reports of INATHA 1999 and SMM 2000 Survey and synthesis of the evidence	-There are many overlapping references in the reports and they generally conclude in agreement. -The clinical use of PET as a diagnostic tool has increased in the period, despite the lack of good documentation regarding clinical effectiveness. -The main areas of use are still within oncology, neurology and cardiology. -HTA-reports published after the INATHA-report of 1999 and the SMM-report in 2000, concludes that PET is more accurate than other diagnostic procedures for several indications within oncology and should therefore be used. -This applies mainly in diagnosing of non-small cell lung cancer (NSCLC) and solitary pulmonary nodules, in staging of Hodgkin's lymphoma, in identifying metastasis from malignant melanoma and colorectal cancer and, in the diagnosis of head and neck tumors. -It is important to notice that PET is still in the developing phase. Examinations should therefore be performed within the framework of clinical trials, since there is still a great

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
					need for knowledge collected systematically. -It is also important to notice that "PET scanning should only be used if the results of the test will affect patient management".
HAYES 2003	Positron emission tomography (PET) for thyroid cancer. HAYES, Inc. 2003: 68.	N.A.	N.A.	N.A.	N.A.
AHRQ (SR) *USA* 2002	Systematic review of positron emission tomography for follow-up of treated thyroid cancer. Balk E, Lau J. Agency for Healthcare Research and Quality (AHRQ) 2002: 34.	FDG-PET Technology assessment conducted by the New England Medical Center EPC, Boston for AHRQ	Fair	Basis for evaluation: search in Medline, Cancerlit 11 studies included Population studied: patient series >10 patients with or without control groups	*Translation (norwegian into english) of the Evidence table in NHSRC 2003*[7] Indications studied: Treated thyroid cancer; therapy monitoring. Outcomes studied: Histopathology; choice of therapy; clinical outcome. Results/Comments: Only two studies had sufficient power to assess the diagnostic accuracy for disease recurrence or metastases. Sensitivity: 88% and 96%. Specificity: 100% and 76%. In general, the documentation is too weak to draw any conclusions.

Myeloma

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
FNCLCC *France* 2003	Recommandations pour la pratique clinique : standards, options et recommandations 2003 pour l'utilisation de la tomographie par émission de positrons au [18-F]-FDG (TEP-FDG) en cancérologie (rapport intégral) (FNCLCC) 2003 :290.	FDG-PET	Fair	*Translation of French* Search from January 1966 until October 2002	-Place of PET in the management of patients with myeloma. *Standard, Option*: insufficient evidence in literature to define standards or options.

Soft-tissue sarcoma; osseous sarcoma

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
FNCLCC *France* 2003	Recommandations pour la pratique clinique : standards, options et recommandations 2003 pour l'utilisation de la tomographie par émission de positrons au [18-F]-FDG (TEP-FDG) en cancérologie (rapport intégral) (FNCLCC) 2003 :290.	FDG-PET	Fair	*Translation of French* Search from January 1966 until October 2002	-Place of PET in the management of patients with soft-tissue sarcoma. *Standard*: no standard. - Place of PET in the management of patients with soft-tissue sarcoma. *Standard*: insufficient evidence in literature to define standards.
NHSRC *Norway* 2003	Positron emission tomography (PET) - diagnostic and clinical use. Morland B. Norwegian Health Services Research Centre (NHSRC) 2003 (SMM-Report 6/2003).	PET		*Short review* Update based on 14 HTA reports and 3 SR's (2001-2003). Update of reports of INATHA 1999 and SMM 2000 Survey and synthesis of the evidence	-There are many overlapping references in the reports and they generally conclude in agreement. -The clinical use of PET as a diagnostic tool has increased in the period, despite the lack of good documentation regarding clinical effectiveness. -The main areas of use are still within oncology, neurology and cardiology. -HTA-reports published after the INATHA-report of 1999 and the SMM-report in 2000, concludes that PET is more accurate than other diagnostic procedures for several indications within oncology and should therefore be used. -This applies mainly in diagnosing of non-small cell lung cancer (NSCLC) and solitary pulmonary nodules, in staging of Hodgkin's lymphoma, in identifying metastasis from malignant melanoma and colorectal cancer and, in the diagnosis of head and neck tumors. -It is important to notice that PET is still in the developing phase. Examinations should therefore be performed within the framework of clinical trials, since there is still a great need for knowledge collected systematically. -It is also important to notice that "PET scanning should only be used if the results of the test will affect patient management".

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
AHRQ (TA) *USA* 2002	FDG-PET for the diagnosis and management of soft tissue sarcoma. Ioannidis J P A, Lau J. Agency for Healthcare Research and Quality (AHRQ) 2002 (Technology Assessment).	FDG-PET compared to MRI/CT Technology assessment conducted by the New England Medical Center EPC, Boston for AHRQ	Fair	Basis for evaluation: search in Medline, Embase 20 studies included Population studied: patient series >5 patients	*Translation (norwegian into english) of the Evidence table in NHSRC 2003* Indications studied: Soft tissue sarcoma (diagnosis, recurrence; distant metastases). Outcomes studied: Histopathology; therapy monitoring; clinical outcome. Results/Comments: -PET in the primary diagnosis. Sensitivity: 64%-100%. Specificity: 71%-100%. The available studies don't allow a comparison of PET with CT/MRI. -Pet is comparable to CT/MRI in the diagnosis of recurrence or distant metastases -No documentation on therapy monitoring or on clinical outcome.
HAYES 2002	Positron emission tomography (PET) for soft-tissue sarcoma. HAYES, Inc. 2002: 57.	N.A.	N.A.	N.A.	N.A.
MSAC (ii) *Australia* 2001	Positron emission tomography [Part 2(ii)]. Medical Services Advisory Committee. Medical Services Advisory Committee (MSAC) 2001 (MSAC reference 10): 169.	FDG-PET compared to conventional techniques: CT/MRI/*Rtg. /Ultralyd* Bone marrow biopsy Bone marrow scintigraphy	Excellent	Basis for evaluation: Systematic reviews and primary studies Search in Medline, Cochrane, HTA database, DARE, NHS EED, Healthstar, Cinahl, Embase	*Translation (norwegian into english) of the Evidence table in NHSRC 2003* Indications studied: Recurrence of lymphoma before treatment (38). Staging of head & neck cancer (spinocellular carcinoma) before treatment (48). Sarcoma: staging, biopsy, recurrence, distant metastases, monitoring of therapy (24). Outcomes studied: Histopathology (confirmed); choice of therapy; clinical outcome, cost-effectiveness.. Results/Comments: -Increased utility of PET for staging of lymphoma and evidence for effect on choice of therapy. -PET has a similar or even better diagnostic accuracy compared to CT/MRI for head & neck cancer and PET is better in the detection of recurrence or residual tumor. No evidence for an effect on the choice of therapy.

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
				Inclusion criteria: Only english language Prospective patient series >10 patients with clear inclusion criteria for disease. Casuistic studies excluded.	-Unclear evidence for a significance of PET compared to CT for sarcoma in staging or detection of recurrence; improvement in "guided biopsy". No effect on the choice of therapy. -PET has no documented effect on clinical outcome in some indications. -No adequate knowledge of cost-effectiveness.

Metastasis and occult primary carcinoma

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
FNCLCC *France* 2003	Recommandations pour la pratique clinique : standards, options et recommandations 2003 pour l'utilisation de la tomographie par émission de positrons au [18-F]-FDG (TEP-FDG) en cancérologie (rapport intégral) (FNCLCC) 2003 :290.	FDG-PET	Fair	*Translation of French* Search from January 1966 until October 2002	-Place of PET in the management of patients with an unknown primary tumor. *Standard*: no standard. *Option:* PET may be indicated in the search for a primary tumor in case of a cervical metastatic adenopathy with an unknown primary tumor (evidence level C). *Indication requiring confirmation within the framework of evaluated protocols*: PET may be utilized in the identification of a primary site in patients with an unknown primary tumor but without a cervical adenopathy within the framework of evaluated protocols (evidence level C). *Recommendation*: complementary and methodologically appropriate studies are recommended to more precisely determine the place of PET in this indication (experts' agreement).
BCBS *USA* 2002	FDG PET to manage patients with an occult primary carcinoma and metastasis outside the cervical lymph nodes. Blue Cross Blue Shield Association (BCBS) 2002 (TEC Assessment 17(14)): 23.	FDG-PET	Fair	Basis for evaluation Search in MEDLINE from January 1990 through September 2002. 4 studies (total of 47 patients)	Indication studied: The use of FDG PET for patients with a metastatic carcinoma outside the cervical lymph nodes from an occult primary tumor (OPT)(4). Results/Comments: -Evidence was sufficient to permit conclusions on the outcomes of FDG-PET only after an unsuccessful initial diagnostic work-up for patients with one metastatic site from an OPT (indication 1c). Evidence was insufficient to permit conclusions on outcomes of FDG-PET instead of (indication 1a) or as part of (indication 1b) a conventional work-up. -Results demonstrate adequate diagnostic performance for use of PET to detect metastatic sites in patients eligible for local or regional therapy of a single metastatic site from an occult carcinoma. -Three studies reported that information from FDG-PET altered management for 25-41% of patients with metastatic carcinoma outside the cervical nodes from an OPT. Pooled analysis yielded an overall rate of 36% (15 of 42 patients in the 3 reports); -PET can confirm a suspected malignancy and the appropriateness of the planned treatment (e.g., in cases of breast or colon cancer found in patients with isolated metastasis in the axilla or liver).

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
					-The available evidence is insufficient to determine whether FDG-PET improved health outcomes, and whether it was as beneficial as alternatives, for patients with metastatic carcinoma from an OPT who are not candidates for local or regional therapy. -Evidence was also insufficient to permit conclusions on effects of FDG PET imaging on outcomes when used instead or as part of the initial work-up for OPT (indications 1a and 1b), or for patients with multiple sites of metastasis from an OPT (indications 2a, 2b, and 2c). Thus, whether FDG PET imaging improves net health outcome of these patients and whether it is as beneficial as alternatives cannot be determined. Based on the above, the use of FDG PET after a negative initial diagnostic work-up for an OPT to rule out or detect additional metastatic sites meets the TEC criteria for patients considering local or regional therapy as part of the treatment plan for a single site of metastatic carcinoma outside the cervical lymph nodes; The use of FDG-PET instead of or as part of the initial work-up for OPT, or for patients with multiple sites of metastasis from an OPT, does not meet the TEC criteria.

Bone cancer

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
HAYES 2002	Positron emission tomography (PET) for bone cancer. HAYES, Inc. 2002: 57.	N.A.	N.A.	N.A.	N.A.

Oncology

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
CEDIT *France* 2001	Positron emission tomography. Comite d'Evaluation et de Diffusion des Innovations Technologiques (CEDIT) 2001 (01.01).	FDG-PET		Basis for evaluation: Recommendations based on previous technology evaluations (french language).	*Translation (norwegian into english) of the Evidence table in NHSRC 2003* Indications studied: Various oncological indications; neurology; myocardial viability. Outcomes studied: Diagnostic benefit; choice of therapy; clinical outcome; Results/Comments: -In oncology, PET shows an improved sensitivity and specificity in several indications. There is also some shown effect on choice of therapy. No documented effect on clinical outcome. -In neurology, PET is used in research but has no established clinical value. -PET is described as useful in the analysis of myocardial viability, but has no documented benefit compared to the alternative Thallium SPECT (single-photon emission-computed tomography).

NEUROLOGY

BRAIN TUMOUR

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
AHRQ *USA* 2004	Positron emission testing for six cancers (brain, cervical, small cell lung, ovarian, pancreatic and testicular). Matchar D B, Kulasingam S L, Havrilesky L, Mann L O, Myers E R, McCrory D C, Patwardhan M, Prosnitz R. Agency for Healthcare Research and Quality (AHRQ) 2004 (Technology Assessment): 221.	Performance of FDG-PET in selected clinical situations in primary brain tumors	Fair	Search: MEDLINE <1966 to April Week 1 2003>	-Performance of PET in guided lesion biopsy for recurrent brain tumors associated with an indeterminate MRI, compared with biopsy performed with conventional imaging: no studies identified. -Performance of PET in distinguishing tumor from radiation necrosis in recurrent brain lesions, compared with conventional imaging: the conclusion that PET may be valuable is tempered by the results of three studies in which PET had comparable operating characteristics to the more accessible studies (SPET/SPECT). -Performance of PET in distinguishing high-grade from low-grade gliomas in newly diagnosed patients with brain tumor and indeterminate (grade II/III) biopsy: no studies. It is unclear whether estimates of sensitivity (range: 69% to 100%) and specificity (range: 57% to 100%) for high-grade tumor, based on data provided in four studies, will resemble PET performance for patients with truly indeterminate biopsy results.
NHSRC *Norway* 2003	Positron emission tomography (PET) - diagnostic and clinical use. Morland B. Norwegian Health Services Research Centre (NHSRC) 2003 (SMM-Report 6/2003).	PET		*Short review* Update based on 14 HTA reports and 3 SR's (2001-2003). Update of reports of INATHA 1999 and SMM 2000	-There are many overlapping references in the reports and they generally conclude in agreement. -The clinical use of PET as a diagnostic tool has increased in the period, despite the lack of good documentation regarding clinical effectiveness. -The main areas of use are still within oncology, neurology and cardiology. -HTA-reports published after the INATHA-report of 1999 and the SMM-report in 2000, concludes that PET is more accurate than other diagnostic procedures for several indications within oncology and should therefore be used.

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
				Survey and synthesis of the evidence	-This applies mainly in diagnosing of non-small cell lung cancer (NSCLC) and solitary pulmonary nodules, in staging of Hodgkin's lymphoma, in identifying metastasis from malignant melanoma and colorectal cancer and, in the diagnosis of head and neck tumors. -It is important to notice that PET is still in the developing phase. Examinations should therefore be performed within the framework of clinical trials, since there is still a great need for knowledge collected systematically. -It is also important to notice that "PET scanning should only be used if the results of the test will affect patient management".
AETMIS *Canada* 2002	Positron emission tomography in Quebec. Dussault F P, Nguyen V H, Rachet F. Agence d'Evaluation des Technologies et des Modes d'Intervention en Sante (AETMIS) 2002 (AETMIS 01-3 RE): 260.	FDG-PET	Fair	Basis for evaluation: Existing technology assessments with updated search in Medline, Cochrane, Embase, Cancerlit, HTA-economic databases. Purpose of the evaluation: -collect and evaluate documentation on the clinical use of PET. -formulate recommendations on the clinical use of	*Translation (norwegian into english) of the Evidence table in NHSRC 2003*[7] Indications studied: NSCLC and solitary lung infiltrates; colorectal cancer; malignant melanoma; head & neck cancer; lymphoma; breast cancer; prostate cancer. Dementia and Alzheimer's disease; refractory epilepsy; brain tumor (glioma). Myocardial viability; coronary perfusion. Outcomes studied: Results/Comments: - PET has a demonstrated diagnostic benefit in certain indications in lung cancers, colorectal cancers, malignant melanomas, head& neck cancers, lymphoma (i.e. in the initial staging, detection of metastases and/or monitoring of therapy response: indication dependent on the type of cancer). - PET is effective in the diagnosis of epileptic foci and may differentiate between tumor tissue and radiation necrosis in brain tumors. - PET is effective in the evaluation of myocardial viability and myocardial perfusion. - Models for the assessment of the cost-effectiveness of PET in NSCLC and myocardial viability have been developed.

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
				PET in Quebec	
ICES *Canada* 2001	Health technology assessment of PET (positron emission tomography). Laupacis A. Institute for Clinical Evaluative Sciences (ICES) 2001: 116.	FDG-PET	Fair	Systematic review of the English peer-reviewed, grey and web-based PET scanning literature up to December 2000 Inclusion criteria: Case-series of >12 patients Economic evaluations	*Translation (norwegian into english) of the Evidence table in NHSRC 2003* Indications studied: Lung cancer(12);Solitary pulmonary nodule (12);Head & Neck cancer(15);Breast cancer(5);Hodgkin lymphoma (5); malignant melanoma (3); colorectal cancer (2);brain tumor: recurrence or irradiation necrosis(0); myocardial viability (?);epilepsy (?); dementia(?) Outcomes studied: Histopathology; choice of therapy; clinical outcome. Results/Comments: PET is considered useful in the diagnosis of all studied indications in oncology. PET may affect patient management i.e. avoidance of unnecessary aggressive (surgery) treatment. PET has no shown benefit over existing alternatives in the evaluation of myocardial viability. PET may have a role in the diagnosis of epileptic foci but most likely not in the diagnosis of dementia. PET may be cost-effective in the evaluation of lung-cancer, in cases of solitary pulmonary infiltrates and in patients treated for Hodgkin's lymphoma.
HAYES 2001	Positron emission tomography (PET) for central nervous system (CNS) tumors. HAYES, Inc. 2001: 57.	N.A.	N.A.	N.A.	N.A.
MSAC *Australia* 2000	Positron emission tomography. Medical Services Advisory Committee (MSAC) 2000 (MSAC	FDG-PET compared to conventional techniques:	Excellent	Basis for evaluation: Systematic reviews (3) and primary	*Translation (norwegian into english) of the Evidence table in NHSRC 2003*[7] Indications studied: Pre-operative staging and detection of metastases from NSCLC (17). Metastases from malignant melanoma (11).

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
	Application 1025): 124.	CT/MRI/*Rtg. /Ultralyd*		studies (54) Search in Medline, Cochrane, HTA database, DARE, NHS EED, Healthstar, Cinahl, Embase <u>Inclusion criteria:</u> Only english language Prospective patient series >10 patients with clear inclusion criteria for disease. Casuistic studies excluded.	Recurrence following treatment of malignant glioma (11). Metastases from colorectal cancer (2). Epileptic foci in the brain (5). Myocard viability (?) <u>Outcomes studied:</u> Histopathology (confirmed); choice of therapy; clinical outcome, cost-effectiveness.. <u>Results/Comments:</u> Higher diagnostic accuracy, i.e. higher sensitivity for staging of NSCLC and detection of metastases from malignant melanomas and colorectal cancer. Improved differentiation between tumor tissue and radiation necrosis following treatment of glioma. Change in choice of therapy for NSCLC and potential for change in case of metastases from colorectal cancer. No documented effect on clinical outcome. No adequate knowledge of cost-effectiveness. In some patients, PET may be helpful in improving diagnosis for epilepsy surgery, but uncertainty persists related to the real amount of false negatives/positives. No conclusion on the use of PET in coronary heart disease.
INATHA *Joint Project* 1999	Positron emission tomography: experience with PET and synthesis of the evidence (INAHTA Joint Project). Adams E, Asua J, Conde Olasagasti J, Erlichman M, Flynn K, Hurtado-Saracho I.	PET		Survey and synthesis of the evidence	<u>Potential clinical PET indications identified by INATHA PET Collaboration participants:</u> -Diagnosing brain tumor recurrence vs. radiation necrosis. Evidence suggests PET's diagnostic accuracy was superior to conventional diagnostic techniques (CT, MRI) but not to SPECT.

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
	Technology Assessment Unit, Management Decision & Research Center, US Department of Veterans Affairs (VATAP) MDRC, OSTEBA, AETS, AHRQ, INAHTA 1999: 41.				

EPILEPSY

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
MSAC *Australia* 2004	Positron emission tomography (PET) for epilepsy. Medical Services Advisory Committee (MSAC) 2004 (MSAC Reference 26): 124.	FDG-PET	Fair	Search up to June 2004	In the pre-surgical evaluation of patients with refractory epilepsy where there is no focus with concordant results on usual structural imaging and electroencephalogram, PET provides additional localising information in some patients and a proportion of them will have good post-surgical outcomes as a consequence. MSAC recommends that public funding should be reported.
NHSRC *Norway* 2003	Positron emission tomography (PET) - diagnostic and clinical use. Morland B. Norwegian Health Services Research Centre (NHSRC) 2003 (SMM-Report 6/2003).	PET		*Short review* Update based on 14 HTA reports and 3 SR's (2001-2003). Update of reports of INATHA 1999 and SMM 2000 Survey and synthesis of the evidence	-There are many overlapping references in the reports and they generally conclude in agreement. -The clinical use of PET as a diagnostic tool has increased in the period, despite the lack of good documentation regarding clinical effectiveness. -The main areas of use are still within oncology, neurology and cardiology. -HTA-reports published after the INATHA-report of 1999 and the SMM-report in 2000, concludes that PET is more accurate than other diagnostic procedures for several indications within oncology and should therefore be used. -This applies mainly in diagnosing of non-small cell lung cancer (NSCLC) and solitary pulmonary nodules, in staging of Hodgkin's lymphoma, in identifying metastasis from malignant melanoma and colorectal cancer and, in the diagnosis of head and neck tumors. -It is important to notice that PET is still in the developing phase. Examinations should therefore be performed within the framework of clinical trials, since there is still a great need for knowledge collected systematically. -It is also important to notice that "PET scanning should only be used if the results of the test will affect patient management".
HAYES 2003	Positron emission tomography (PET) for epilepsy. HAYES, Inc. 2003: 87.	N.A.	N.A.	N.A.	N.A.
AETMIS *Canada*	Positron emission tomography in Quebec. Dussault F	FDG-PET	Fair	Basis for evaluation: Existing	*Translation (norwegian into english) of the Evidence table in NHSRC 2003* Indications studied:

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
2002	P, Nguyen V H, Rachet F. Agence d'Evaluation des Technologies et des Modes d'Intervention en Sante (AETMIS) 2002 (AETMIS 01-3 RE): 260.			technology assessments with updated search in Medline, Cochrane, Embase, Cancerlit, HTA-economic databases. Purpose of the evaluation: -collect and evaluate documentation on the clinical use of PET. -formulate recommendations on the clinical use of PET in Quebec	NSCLC and solitary lung infiltrates; colorectal cancer; malignant melanoma; head & neck cancer; lymphoma; breast cancer; prostate cancer. Dementia and Alzheimer's disease; refractory epilepsy; brain tumor (glioma). Myocardial viability; coronary perfusion. Outcomes studied: Results/Comments: - PET has a demonstrated diagnostic benefit in certain indications in lung cancers, colorectal cancers, malignant melanomas, head& neck cancers, lymphoma (i.e. in the initial staging, detection of metastases and/or monitoring of therapy response: indication dependent on the type of cancer). - PET is effective in the diagnosis of epileptic foci and may differentiate between tumor tissue and radiation necrosis in brain tumors. - PET is effective in the evaluation of myocardial viability and myocardial perfusion. - Models for the assessment of the cost-effectiveness of PET in NSCLC and myocardial viability have been developed.
DACEHTA *Danmark* 2001b	Positron emissions tomography (PET) with 18-F-fluorodeoxyglucose (FDG). A literature review of evidence for clinical use in the fields of oncology, cardiology and neurology. Danish	FDG-PET. Standard PET versus "hybrid-PET" With and without blinded evaluation of test results. With and	Fair	*Report in Danish* Basis for evaluation: Systematic literature review. Search in Medline, Embase,	Translated version, edited in HTBS*Scotland* 2002 The results are too preliminary and too few to give an overall picture of the diagnostic value of PET for epilepsy. There appears to be no evidence that PET can replace perfusion investigations with SPECT, which is much more easily accessible. As the affected patient group in Denmark is relatively small, there appears to be no need for clinical use of PET in assessing the operation indication with uncontrolled complex, partial epilepsy. PET may possibly be a supplement to SPECT after MR scanning and electroencephalogram, if the location of the trigger zone is still unresolved. *Translation (norwegian into english) of the Evidence table in NHSRC 2003*[7]

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
	Centre for Evaluation and Health Technology Assessment (DACEHTA) (formerly DIHTA) 2001.	without comparison with alternative methods.		Cochrane. Inclusion criteria: English language. RCT/Case-control/Cohort studies. 363 articles included. Patient series >12 patients with clear inclusion criteria for disease.	*Systematic review of literature* Indications studied: NSCLC (53); Solitary Pulmonary Infiltrates >4cm (12); ; Colorectal cancer (32); Malignant Melanoma (20); Head & Neck cancer (42); Breast cancer (37). Alzheimer's disease (41); Epilepsy foci (23). Ischemic Heart Disease (52). Outcomes studied: Histopathology; choice of therapy; clinical outcome. Results/Comments: -PET has a higher sensitivity, specificity, positive and negative predictive value compared to CT in the initial staging and detection of metastases (however: low evidence degree). -Most studies find a high sensitivity and specificity of PET in patient with malignant lung infiltrates (however: selected patients with high degree malignancy grades). -PET is presumed to be better than CT/MRI in the detection of head & neck cancer recurrence. -PET is better than CT for initial staging and detection of liver metastases in colorectal cancer (however: low evidence degree). -PET has a higher diagnostic precision compared to CT in the detection of metastases (other than in the lungs) from malignant melanoma. -PET may become a tool for dealing with lymph node metastases from breast cancer (however; too few and bad studies). -PET is not better than SPECT in the detection of Alzheimer's disease or epileptic foci. -Variable results for the use of PET in ischemic heart disease. -No documentation on clinical outcome.
DACEHTA *Danmark* 2001a	Paper concerning clinical PET-scanning using FDG - with focus on diagnosis of cancer. Danish Centre for Evaluation and	FDG-PET		*Danish* Recommendations based on SR's as described in DACEHTA, *Denmark*,	*Translation (norwegian into english) of the Evidence table in NHSRC 2003* *Recommendations:* The documented benefit of PET in diagnosis: Lung cancer : good Solitary lung mass : good Colorectal cancer : good

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
	Health Technology Assessment (DACEHTA) (formerly DIHTA) 2001.			2001b[32] and critically reviewed by oncologists.	Head & Neck cancer : good Malignant melanoma: good Breast cancer : scant Other cancers : scant Alzheimer : lacking Epilepsy : unclear Ischemic heart disease: lacking The documented benefit of PET in therapy: Lung cancer : scant Other : lacking
ICES *Canada* 2001	Health technology assessment of PET (positron emission tomography). Laupacis A. Institute for Clinical Evaluative Sciences (ICES) 2001: 116.	FDG-PET	Fair	Systematic review of the English peer-reviewed, grey and web-based PET scanning literature up to December 2000 Inclusion criteria: Case-series of >12 patients Economic evaluations	*Translation (norwegian into english) of the Evidence table in NHSRC 2003*[7] Indications studied: Lung cancer(12);Solitary pulmonary nodule (12);Head & Neck cancer(15);Breast cancer(5);Hodgkin lymphoma (5); malignant melanoma (3); colorectal cancer (2);brain tumor: recurrence or irradiation necrosis(0); myocardial viability (?);epilepsy (?); dementia(?) Outcomes studied: Histopathology; choice of therapy; clinical outcome. Results/Comments: PET is considered useful in the diagnosis of all studied indications in oncology. PET may affect patient management i.e. avoidance of unnecessary aggressive (surgery) treatment. PET has no shown benefit over existing alternatives in the evaluation of myocardial viability. PET may have a role in the diagnosis of epileptic foci but most likely not in the diagnosis of dementia. PET may be cost-effective in the evaluation of lung-cancer, in cases of solitary pulmonary infiltrates and in patients treated for Hodgkin's lymphoma.
MSAC	Positron emission tomography. Medical	FDG-PET compared to	Excellen t	Basis for evaluation:	*Translation (norwegian into english) of the Evidence table in NHSRC 2003*

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
Australia 2000	Services Advisory Committee (MSAC) 2000 (MSAC Application 1025): 124.	conventional techniques: CT/MRI/*Rtg./ Ultralyd*		Systematic reviews (3) and primary studies (54) Search in Medline, Cochrane, HTA database, DARE, NHS EED, Healthstar, Cinahl, Embase Inclusion criteria: Only english language Prospective patient series >10 patients with clear inclusion criteria for disease. Casuistic studies excluded.	Indications studied: Pre-operative staging and detection of metastases from NSCLC (17). Metastases from malignant melanoma (11). Recurrence following treatment of malignant glioma (11). Metastases from colorectal cancer (2). Epileptic foci in the brain (5). Myocard viability (?) Outcomes studied: Histopathology (confirmed); choice of therapy; clinical outcome, cost-effectiveness.. Results/Comments: Higher diagnostic accuracy, i.e. higher sensitivity for staging of NSCLC and detection of metastases from malignant melanomas and colorectal cancer. Improved differentiation between tumor tissue and radiation necrosis following treatment of glioma. Change in choice of therapy for NSCLC and potential for change in case of metastases from colorectal cancer. No documented effect on clinical outcome. No adequate knowledge of cost-effectiveness. In some patients, PET may be helpful in improving diagnosis for epilepsy surgery, but uncertainty persists related to the real amount of false negatives/positives. No conclusion on the use of PET in coronary heart disease.
INATHA *Joint Project* 1999	Positron emission tomography: experience with PET and synthesis of the evidence (INAHTA Joint Project). Adams E, Asua J,	PET		Survey and synthesis of the evidence	Potential clinical PET indications identified by INATHA PET Collaboration participants: Diagnosing seizure foci in intractable epilepsy. Evidence suggests PET's diagnostic accuracy was comparable or superior to other functional imaging modalities used to confirm foci identified by EEG or MRI, but PET is not yet able to replace invasive EEG or structural imaging. The diagnostic contribution of all functional imaging for this indication is still questioned.

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
	Conde Olasagasti J, Erlichman M, Flynn K, Hurtado-Saracho I. Technology Assessment Unit, Management Decision & Research Center, US Department of Veterans Affairs (VATAP) MDRC, OSTEBA, AETS, AHRQ, INAHTA 1999: 41.				

ALZHEIMER'S DISEASE (AD)

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
NHSRC *Norway* 2003	Positron emission tomography (PET) - diagnostic and clinical use. Morland B. Norwegian Health Services Research Centre (NHSRC) 2003 (SMM-Report 6/2003).	PET		*Short review* Update based on 14 HTA reports and 3 SR's (2001-2003). Update of reports of INATHA 1999 and SMM 2000 Survey and synthesis of the evidence	-There are many overlapping references in the reports and they generally conclude in agreement. -The clinical use of PET as a diagnostic tool has increased in the period, despite the lack of good documentation regarding clinical effectiveness. -The main areas of use are still within oncology, neurology and cardiology. -HTA-reports published after the INATHA-report of 1999 and the SMM-report in 2000, concludes that PET is more accurate than other diagnostic procedures for several indications within oncology and should therefore be used. -This applies mainly in diagnosing of non-small cell lung cancer (NSCLC) and solitary pulmonary nodules, in staging of Hodgkin's lymphoma, in identifying metastasis from malignant melanoma and colorectal cancer and, in the diagnosis of head and neck tumors. -It is important to notice that PET is still in the developing phase. Examinations should therefore be performed within the framework of clinical trials, since there is still a great need for knowledge collected systematically. -It is also important to notice that "PET scanning should only be used if the results of the test will affect patient management".
AETMIS *Canada* 2002	Positron emission tomography in Quebec. Dussault F P, Nguyen V H, Rachet F. Agence d'Evaluation des Technologies et des Modes d'Intervention en Sante (AETMIS) 2002 (AETMIS 01-3 RE): 260.	FDG-PET	Fair	Basis for evaluation: Existing technology assessments with updated search in Medline, Cochrane, Embase, Cancerlit, HTA-economic databases.	*Translation (norwegian into english) of the Evidence table in NHSRC 2003* Indications studied: NSCLC and solitary lung infiltrates; colorectal cancer; malignant melanoma; head & neck cancer; lymphoma; breast cancer; prostate cancer. Dementia and Alzheimer's disease; refractory epilepsy; brain tumor (glioma). Myocardial viability; coronary perfusion. Outcomes studied: Results/Comments: - PET has a demonstrated diagnostic benefit in certain indications in lung cancers, colorectal cancers, malignant melanomas, head& neck cancers, lymphoma (i.e. in the initial staging, detection of metastases and/or monitoring of therapy response: indication dependent on the type of cancer).

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
				Purpose of the evaluation: -collect and evaluate documentation on the clinical use of PET. -formulate recommendations on the clinical use of PET in Quebec	- PET is effective in the diagnosis of epileptic foci and may differentiate between tumor tissue and radiation necrosis in brain tumors. - PET is effective in the evaluation of myocardial viability and myocardial perfusion. - Models for the assessment of the cost-effectiveness of PET in NSCLC and myocardial viability have been developed.
HAYES 2002	Positron emission tomography (PET) for Alzheimer's disease (AD). HAYES, Inc. 2002: 76.	N.A.	N.A.	N.A.	N.A.
DACEHTA *Danmark* 2001b	Positron emissions tomography (PET) with 18-F-fluorodeoxyglucose (FDG). A literature review of evidence for clinical use in the fields of oncology, cardiology and neurology. Danish Centre for Evaluation and Health Technology Assessment (DACEHTA) (formerly DIHTA)	FDG-PET. Standard PET versus "hybrid-PET" With and without blinded evaluation of test results. With and without comparison with alternative	Fair	*Report in Danish* Basis for evaluation: Systematic literature review. Search in Medline, Embase, Cochrane. Inclusion criteria: English language.	Translated version, edited in HTBS*Scotland* 2002 There is selection bias with the investigations of PET in Alzheimer's disease (AD). There is little evidence from prospective investigations in patients with possible AD, but some evidence in probable AD. However, there is no evidence that PET increases diagnostic certainty compared with perfusion investigations using single photon emission computed tomography (SPECT), which is a more readily available imaging technique. Perfusion investigations with dedicated PET and for example, O^{15}-H_2O may possibly be a supplement, but this tracer is very short) lived and therefore cannot be distributed outside departments with their own cyclotron. *Translation (norwegian into english) of the Evidence table in NHSRC 2003* *Systematic review of literature*

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
	2001.	methods.		RCT/Case-control/Cohort studies. 363 articles included. Patient series >12 patients with clear inclusion criteria for disease.	Indications studied: NSCLC (53); Solitary Pulmonary Infiltrates >4cm (12); ; Colorectal cancer (32); Malignant Melanoma (20); Head & Neck cancer (42); Breast cancer (37). Alzheimer's disease (41); Epilepsy foci (23). Ischemic Heart Disease (52). Outcomes studied: Histopathology; choice of therapy; clinical outcome. Results/Comments: -PET has a higher sensitivity, specificity, positive and negative predictive value compared to CT in the initial staging and detection of metastases (however: low evidence degree). -Most studies find a high sensitivity and specificity of PET in patient with malignant lung infiltrates (however: selected patients with high degree malignancy grades). -PET is presumed to be better than CT/MRI in the detection of head & neck cancer recurrence. -PET is better than CT for initial staging and detection of liver metastases in colorectal cancer (however: low evidence degree). -PET has a higher diagnostic precision compared to CT in the detection of metastases (other than in the lungs) from malignant melanoma. -PET may become a tool for dealing with lymph node metastases from breast cancer (however; too few and bad studies). -PET is not better than SPECT in the detection of Alzheimer's disease or epileptic foci. -Variable results for the use of PET in ischemic heart disease. -No documentation on clinical outcome.
DACEHTA *Danmark* 2001a	Paper concerning clinical PET-scanning using FDG - with focus on diagnosis of cancer. Danish Centre for Evaluation and Health Technology Assessment	FDG-PET		*Danish* Recommendations based on SR's as described in DACEHTA, *Denmark*, 2001b[32] and	*Translation (norwegian into english) of the Evidence table in NHSRC 2003* *Recommendations:* The documented benefit of PET in diagnosis: Lung cancer : good Solitary lung mass : good Colorectal cancer : good Head & Neck cancer : good

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
	(DACEHTA) (formerly DIHTA) 2001.			critically reviewed by oncologists.	Malignant melanoma: good Breast cancer : scant Other cancers : scant Alzheimer : lacking Epilepsy : unclear Ischemic heart disease: lacking The documented benefit of PET in therapy: Lung cancer : scant Other : lacking
ICES *Canada* 2001	Health technology assessment of PET (positron emission tomography). Laupacis A. Institute for Clinical Evaluative Sciences (ICES) 2001: 116.	FDG-PET	Fair	Systematic review of the English peer-reviewed, grey and web-based PET scanning literature up to December 2000 Inclusion criteria: Case-series of >12 patients Economic evaluations	*Translation (norwegian into english) of the Evidence table in NHSRC 2003* Indications studied: Lung cancer(12);Solitary pulmonary nodule (12);Head & Neck cancer(15);Breast cancer(5);Hodgkin lymphoma (5); malignant melanoma (3); colorectal cancer (2);brain tumor: recurrence or irradiation necrosis(0); myocardial viability (?);epilepsy (?); dementia(?) Outcomes studied: Histopathology; choice of therapy; clinical outcome. Results/Comments: PET is considered useful in the diagnosis of all studied indications in oncology. PET may affect patient management i.e. avoidance of unnecessary aggressive (surgery) treatment. PET has no shown benefit over existing alternatives in the evaluation of myocardial viability. PET may have a role in the diagnosis of epileptic foci but most likely not in the diagnosis of dementia. PET may be cost-effective in the evaluation of lung-cancer, in cases of solitary pulmonary infiltrates and in patients treated for Hodgkin's lymphoma.
AHRQ *USA*	Use of positron emission tomography and other	FDG-PET (test results compared	Fair	Basis for evaluation: Comprehensiv	*Translation (norwegian into english) of the Evidence table in NHSRC 2003*

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
2001	neuroimaging techniques in the diagnosis and management of Alzheimer's disease and dementia. Matchar D B, Kulasingam S L, McCrory D C, Patwardhan M B, Rutschmann O T, Samsa G P, Schmechel D E. Agency for Healthcare Research and Quality (AHRQ) 2001 (Technology Assessment): 152.	with the decision on medically treatment of dementia- or Alzheimer patients) Technology assessment by the Duke Evidence-based Practice Center for AHRQ		e literature review, meta-analysis and decision analysis. Search in Medline, Cinahl, Healthstar. 15 studies included. Inclusion citeria: Dementia patients; persons with a nearby family member with Alzheimer; persons with mild cognitive impairment.	Indication studied: Can the decision on medical treatment in dementia or Alzheimer patients be based on the results of PET? Outcomes studied: Clinical diagnosis; quality of life; length of life (survival). Results/Comments: PET sensitivity 88% (95% CI 79-94%) and specificity 87% (95% CI 77-93%) in differentiating Alzheimer patients from healthy persons. Conclusion: too many false negative findings to use PET findings as a basis for decision of medical treatment (when therapy is judged safe enough).
INATHA *Joint Project* 1999	Positron emission tomography: experience with PET and synthesis of the evidence (INAHTA Joint Project). Adams E, Asua J, Conde Olasagasti J, Erlichman M, Flynn K, Hurtado-Saracho I. Technology	PET		*Short review* Update based on 14 HTA reports and 3 SR's (2001-2003). Update of reports of INATHA 1999 and SMM 2000 Survey and synthesis of	Potential clinical PET indications identified by INATHA PET Collaboration participants: Diagnosing Alzheimer's dementia. Evidence suggests PET's diagnostic accuracy was comparable or superior to competing technologies (CT, MRI, SPECT, EEG), but the value of improved diagnostic information to management of AD patients or to improved clinical results was unknown.

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
	Assessment Unit, Management Decision & Research Center, US Department of Veterans Affairs (VATAP) MDRC, OSTEBA, AETS, AHRQ, INAHTA 1999: 41.			the evidence	

Huntington's disease

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
HAYES 2004	Positron emission tomography (PET) for Huntington's disease (HD). HAYES, Inc. 2004: 53.	N.A.	N.A.	N.A.	N.A.

Parkinson's disease

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
HAYES 2004	Positron emission tomography (PET) for Parkinson's disease. HAYES, Inc. 2004: 84.	N.A.	N.A.	N.A.	N.A.

Neurology

Study ID	Source/reference	Technology considered	Quality	Remarks	Conclusions/Recommendations "Role of PET"
CEDIT *France* 2001	Positron emission tomography. Comite d'Evaluation et de Diffusion des Innovations Technologiques (CEDIT) 2001 (01.01).	FDG-PET		Basis for evaluation: Recommendations based on previous technology evaluations (french language).	*Translation (norwegian into english) of the Evidence table in NHSRC 2003* Indications studied: Various oncological indications; neurology; myocardial viability. Outcomes studied: Diagnostic benefit; choice of therapy; clinical outcome; Results/Comments: -In oncology, PET shows an improved sensitivity and specificity in several indications. There is also some shown effect on choice of therapy. No documented effect on clinical outcome. -In neurology, PET is used in research but has no established clinical value. -PET is described as useful in the analysis of myocardial viability, but has no documented benefit compared to the alternative Thallium SPECT (single-photon emission-computed tomography).
AETS *Andalucia* 1999	Positron emission tomography with fluordeoxyglucose (FDG-PET) in neurology. IPE-99/18. Agencia de Evaluacion de Tecnologias Sanitarias (AETS) 1999.			In Spanish	

CARDIOLOGY

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
NHSRC *Norway* 2003	Positron emission tomography (PET) - diagnostic and clinical use. Morland B. Norwegian Health Services Research Centre (NHSRC) 2003 (SMM-Report 6/2003).	PET		*Short review* Update based on 14 HTA reports and 3 SR's (2001-2003). Update of reports of INATHA 1999 and SMM 2000 Survey and synthesis of the evidence	-There are many overlapping references in the reports and they generally conclude in agreement. -The clinical use of PET as a diagnostic tool has increased in the period, despite the lack of good documentation regarding clinical effectiveness. -The main areas of use are still within oncology, neurology and cardiology. -HTA-reports published after the INATHA-report of 1999 and the SMM-report in 2000, concludes that PET is more accurate than other diagnostic procedures for several indications within oncology and should therefore be used. -This applies mainly in diagnosing of non-small cell lung cancer (NSCLC) and solitary pulmonary nodules, in staging of Hodgkin's lymphoma, in identifying metastasis from malignant melanoma and colorectal cancer and, in the diagnosis of head and neck tumors. -It is important to notice that PET is still in the developing phase. Examinations should therefore be performed within the framework of clinical trials, since there is still a great need for knowledge collected systematically. -It is also important to notice that "PET scanning should only be used if the results of the test will affect patient management".
HAYES 2003	Positron emission tomography (PET) for cardiac applications. HAYES, Inc. 2003: 97.	N.A.	N.A.	N.A.	N.A.
AETMIS *Canada* 2002	Positron emission tomography in Quebec. Dussault F P, Nguyen V H, Rachet F. Agence d'Evaluation des Technologies et des Modes d'Intervention en Sante (AETMIS) 2002 (AETMIS 01-3	FDG-PET	Fair	Basis for evaluation: Existing technology assessments with updated search in Medline, Cochrane, Embase,	*Translation (norwegian into english) of the Evidence table in NHSRC 2003* Indications studied: NSCLC and solitary lung infiltrates; colorectal cancer; malignant melanoma; head & neck cancer; lymphoma; breast cancer; prostate cancer. Dementia and Alzheimer's disease; refractory epilepsy; brain tumor (glioma). Myocardial viability; coronary perfusion. Outcomes studied: Results/Comments:

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
	RE): 260.			Cancerlit, HTA-economic databases. <u>Purpose of the evaluation:</u> -collect and evaluate documentation on the clinical use of PET. -formulate recommendations on the clinical use of PET in Quebec	- PET has a demonstrated diagnostic benefit in certain indications in lung cancers, colorectal cancers, malignant melanomas, head& neck cancers, lymphoma (i.e. in the initial staging, detection of metastases and/or monitoring of therapy response: indication dependent on the type of cancer). - PET is effective in the diagnosis of epileptic foci and may differentiate between tumor tissue and radiation necrosis in brain tumors. - PET is effective in the evaluation of myocardial viability and myocardial perfusion. - Models for the assessment of the cost-effectiveness of PET in NSCLC and myocardial viability have been developed.
DACEHTA *Danmark* 2001b	Positron emissions tomography (PET) with 18-F-fluorodeoxyglucose (FDG). A literature review of evidence for clinical use in the fields of oncology, cardiology and neurology. Danish Centre for Evaluation and Health Technology Assessment (DACEHTA) (formerly DIHTA) 2001.	FDG-PET. Standard PET versus "hybrid-PET" With and without blinded evaluation of test results. With and without comparison with alternative methods.	Fair	*Report in Danish* <u>Basis for evaluation:</u> Systematic literature review. Search in Medline, Embase, Cochrane. <u>Inclusion criteria:</u> English language. RCT/Case-	Translated version, edited in HTBS*Scotland* 2002 Many of the included studies were not blinded and without control groups. All of the studies were case series with indirect diagnostic tests and a low evidence level, corresponding to category III for clinical evidence. The larger scale investigations were unable to retrieve the high sensitivity and specificity of studies published earlier. On the basis of the smaller investigations with 20-40 patients, concordance appears to exist between PET and other studies such as SPECT and low-dose dobutamine echocardiography regarding sensitivity. The positive predictive values of 66-96% are very unreliable, since KAG control is lacking. The fluctuating results with FDG uptake can be due to fluctuating inclusion criteria and varying evaluation methods. It is possible that the contractile reserve cannot be described on the basis of single metabolic investigations. Intensive research is being conducted within this area, and increased knowledge of pathophysiological mechanisms may possibly lead to the development of new, better diagnostic methods; Large scale, multi centre investigations with a higher evidence level are necessary before the ultimate role of PET for ischaemic heart disease can be determined. However, it is doubtful whether these studies will be carried out since very ill patients are involved,

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
				control/Cohort studies. 363 articles included. Patient series >12 patients with clear inclusion criteria for disease.	who in many instances are in urgent need of revascularization. *Translation (norwegian into english) of the Evidence table in NHSRC 2003* *Systematic review of literature* Indications studied: NSCLC (53); Solitary Pulmonary Infiltrates >4cm (12); ; Colorectal cancer (32); Malignant Melanoma (20); Head & Neck cancer (42); Breast cancer (37). Alzheimer's disease (41); Epilepsy foci (23). Ischemic Heart Disease (52). Outcomes studied: Histopathology; choice of therapy; clinical outcome. Results/Comments: -PET has a higher sensitivity, specificity, positive and negative predictive value compared to CT in the initial staging and detection of metastases (however: low evidence degree). -Most studies find a high sensitivity and specificity of PET in patient with malignant lung infiltrates (however: selected patients with high degree malignancy grades). -PET is presumed to be better than CT/MRI in the detection of head & neck cancer recurrence. -PET is better than CT for initial staging and detection of liver metastases in colorectal cancer (however: low evidence degree). -PET has a higher diagnostic precision compared to CT in the detection of metastases (other than in the lungs) from malignant melanoma. -PET may become a tool for dealing with lymph node metastases from breast cancer (however; too few and bad studies). -PET is not better than SPECT in the detection of Alzheimer's disease or epileptic foci. -Variable results for the use of PET in ischemic heart disease. -No documentation on clinical outcome.
DACEHTA *Danmark* 2001a	Paper concerning clinical PET-scanning using FDG - with focus on diagnosis of cancer. Danish	FDG-PET		*Danish* Recommendations based on SR's as described in	*Translation (norwegian into english) of the Evidence table in NHSRC 2003* *Recommendations:* The documented benefit of PET in diagnosis: Lung cancer : good

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
	Centre for Evaluation and Health Technology Assessment (DACEHTA) (formerly DIHTA) 2001.			DACEHTA, *Denmark*, 2001b and critically reviewed by oncologists.	Solitary lung mass : good Colorectal cancer : good Head & Neck cancer : good Malignant melanoma: good Breast cancer : scant Other cancers : scant Alzheimer : lacking Epilepsy : unclear Ischemic heart disease: lacking The documented benefit of PET in therapy: Lung cancer : scant Other : lacking
ICES *Canada* 2001	Health technology assessment of PET (positron emission tomography). Laupacis A. Institute for Clinical Evaluative Sciences (ICES) 2001: 116.	FDG-PET	Fair	Systematic review of the English peer-reviewed, grey and web-based PET scanning literature up to December 2000 Inclusion criteria: Case-series of >12 patients Economic evaluations	*Translation (norwegian into english) of the Evidence table in NHSRC 2003* Indications studied: Lung cancer(12);Solitary pulmonary nodule (12);Head & Neck cancer(15);Breast cancer(5);Hodgkin lymphoma (5); malignant melanoma (3); colorectal cancer (2);brain tumor: recurrence or irradiation necrosis(0); myocardial viability (?);epilepsy (?); dementia(?) Outcomes studied: Histopathology; choice of therapy; clinical outcome. Results/Comments: PET is considered useful in the diagnosis of all studied indications in oncology. PET may affect patient management i.e. avoidance of unnecessary aggressive (surgery) treatment. PET has no shown benefit over existing alternatives in the evaluation of myocardial viability. PET may have a role in the diagnosis of epileptic foci but most likely not in the diagnosis of dementia. PET may be cost-effective in the evaluation of lung-cancer, in cases of solitary pulmonary infiltrates and in patients treated for Hodgkin's lymphoma.

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
CEDIT *France* 2001	Positron emission tomography. Comite d'Evaluation et de Diffusion des Innovations Technologiques (CEDIT) 2001 (01.01).	FDG-PET		Basis for evaluation: Recommendations based on previous technology evaluations (french language).	*Translation (norwegian into english) of the Evidence table in NHSRC 2003* Indications studied: Various oncological indications; neurology; myocardial viability. Outcomes studied: Diagnostic benefit; choice of therapy; clinical outcome; Results/Comments: -In oncology, PET shows an improved sensitivity and specificity in several indications. There is also some shown effect on choice of therapy. No documented effect on clinical outcome. -In neurology, PET is used in research but has no established clinical value. -PET is described as useful in the analysis of myocardial viability, but has no documented benefit compared to the alternative Thallium SPECT (single-photon emission-computed tomography).
MSAC *Australia* 2000	Positron emission tomography. Medical Services Advisory Committee (MSAC) 2000 (MSAC Application 1025): 124.	FDG-PET compared to conventional techniques: CT/MRI/*Rtg. /Ultralyd*	Excellent	Basis for evaluation: Systematic reviews (3) and primary studies (54) Search in Medline, Cochrane, HTA database, DARE, NHS EED, Healthstar, Cinahl, Embase Inclusion criteria: Only english	*Translation (norwegian into english) of the Evidence table in NHSRC 2003* Indications studied: Pre-operative staging and detection of metastases from NSCLC (17). Metastases from malignant melanoma (11). Recurrence following treatment of malignant glioma (11). Metastases from colorectal cancer (2). Epileptic foci in the brain (5). Myocard viability (?) Outcomes studied: Histopathology (confirmed); choice of therapy; clinical outcome, cost-effectiveness.. Results/Comments: Higher diagnostic accuracy, i.e. higher sensitivity for staging of NSCLC and detection of metastases from malignant melanomas and colorectal cancer. Improved differentiation between tumor tissue and radiation necrosis following treatment of glioma.

Study ID	Source/reference	Technology	Quality	Remarks	Conclusions/Recommendations "Role of PET"
				language Prospective patient series >10 patients with clear inclusion criteria for disease. Casuistic studies excluded.	Change in choice of therapy for NSCLC and potential for change in case of metastases from colorectal cancer. No documented effect on clinical outcome. No adequate knowledge of cost-effectiveness. In some patients, PET may be helpful in improving diagnosis for epilepsy surgery, but uncertainty persists related to the real amount of false negatives/positives. No conclusion on the use of PET in coronary heart disease.
INATHA *Joint Project* 1999	Positron emission tomography: experience with PET and synthesis of the evidence (INAHTA Joint Project). Adams E, Asua J, Conde Olasagasti J, Erlichman M, Flynn K, Hurtado-Saracho I. Technology Assessment Unit, Management Decision & Research Center, US Department of Veterans Affairs (VATAP) MDRC, OSTEBA, AETS, AHRQ, INAHTA 1999: 41.	PET		Survey and synthesis of the evidence	<u>Potential clinical PET indications identified by INATHA PET Collaboration participants:</u> -Assessing myocardial perfusion in patients with coronary artery disease (CAD). Evidence suggests PET's diagnostic accuracy is improved over other imaging alternatives, particularly thallium-201 SPECT, but the extent of improvement is unclear. PET is more costly than all other individual non-invasive strategies. PET is unable to replace coronary angiography as the definitive standard for CAD assessment in most patients. -Assessing myocardial viability. Evidence suggests PET has comparable sensitivity and superior specificity to other modalities. Quality of data for evaluating the performance of SPECT, dobutamine ECHO and MRI are similarly limited.

SYSTEMATIC REVIEWS

How? Updated Minhout strategy with cancer terms

((deoxyglucose[mh] OR deoxyglucose[tw] OR desoxyglucose[tw] OR deoxy-glucose[tw] OR desoxy-glucose[tw] OR deoxy-d-glucose[tw] OR desoxy-d-glucose[tw] OR 2deoxyglucose[tw] OR 2deoxy-d-glucose[tw] OR fluorodeoxyglucose[tw] OR fluorodesoxyglucose[tw] OR fludeoxyglucose[tw] OR fluordeoxyglucose[tw] OR fluordesoxyglucose[tw] OR 18fluorodeoxyglucose[tw] OR 18fluorodesoxyglucose[tw] OR 18fluordeoxyglucose[tw] OR fdg*[tw] OR 18fdg*[tw] OR 18f-dg*[tw] OR ((fluor[tw] OR 2fluor*[tw] OR fluoro[tw] OR fluorodeoxy[tw] OR fludeoxy[tw] OR fluorine[tw] OR 18f[tw] OR 18flu*[tw]) AND glucose[tw])) AND (pet[tw] OR pet/*[tw] OR petscan*[tw] OR tomography, emission-computed[mh] OR (emission[tw] AND (tomograph [tw] OR tomographs [tw] OR tomographic*[tw] OR tomography[tw] OR tomographies[tw]))))) AND (oncolog* OR cancer* OR neoplas* OR neoplasms[mesh] OR tumour* OR tumor* OR carcinom* OR melanom* OR lymphoma* OR leukemi* OR malignan* OR cancer[sb])

When? After 1/1/2001

Where? Pubmed clinical queries systematic reviews

Selection process:

The quality of SR was appraised through the Dutch Cochrane checklist for the systematic reviews

Checklist for diagnostic systematic reviews (Dutch Cochrane Centre)	Yes/No/not enough information
Are the research questions adequately described?	
Has the literature seach been adequately performed?	
Has the selection of articles been adequately performed?	
Has the quality appraisal been adequately performed?	
Has the procedure for data-extraction been adequately described?	
Are the characteristics of the included studies adequately described?	
Has the meta-analysis been performed adequately?	
overall quality assessment	

Results: see evidence table hereunder

Systematic reviews evidence table (> 2001):

N	STUDY	Conclusions/Recommendations	Quality assessment
1	Kinkel, K., et al., Detection of hepatic metastases from cancers of the gastrointestinal tract by using noninvasive imaging methods (US, CT, MR imaging, PET): a meta-analysis. Radiology, 2002. 224(3): p. 748-56.	At equivalent specificity, FDG PET is the most sensitive imaging modality for the diagnosis of hepatic metastases from colorectal, esophagal and gastric cancers. PET might be particularly helpful in patients with increasing CEA levels and normal imaging findings when hepatic resection is planned. Mean weight sensitivity for studies with specificity>85%: 55% for US, 72% for CT, 76% for MR and 90% for FDG PET	Good
2	Gould, M.K., et al., Test performance of positron emission tomography and computed tomography for mediastinal staging in patients with non-small-cell lung cancer: a meta-analysis. Ann Intern Med, 2003. 139(11): p. 879-92	FDG PET is more accurate than CT for mediastinal staging, is more sensitive but less specific when CT shows enlarged mediastinal lymph nodes. Median sensitivity and specificity were 61% and 79% for CT; 85% and 90% for FDG Pet.	Good
3	Mijnhout, G.S., et al., Systematic review of the diagnostic accuracy of (18)F-fluorodeoxyglucose positron emission tomography in melanoma patients. Cancer, 2001. 91(8): p. 1530-42.	Detection of melanoma metastases: pooled Se 0.79, Sp 0.86. Pooled diagnostic odds ratio: 36.4, BUT, due to the poor methodologic quality of the available studies, it is yet not possible to develop guidelines for the effective use of PET in patients with melanoma. Future accuracy studies are needed.	Good
4	Birim, O., et al., Meta-analysis of positron emission tomographic and computed tomographic imaging in detecting mediastinal lymph node metastases in nonsmall cell lung cancer. Ann Thorac Surg, 2005. 79(1): p. 375-82.	FDG PET is more accurate than CT in detecting mediastinal lymph node metastases. The point on the ROC curve with equal Se and Sp was 0.9 for FDG PET and 0.7 for CT (difference significant with $p < 0.0001$). Overall estimate of the DOR was 5.4 for CT and 76.4 for FDG PET.	Good
5	Orlando, L.A., S.L. Kulasingam, and D.B. Matchar, Meta-analysis: the detection of pancreatic malignancy with positron emission tomography. Aliment Pharmacol Ther, 2004. 20(10): p. 1063-70.	Detection of pancreatic cancer: CT: Se 81% Sp 66% PET after a +CT: Se 92% Sp 68% PET after a –CT: Se 73% Sp 86% PET after indeterminate CT: Se 100% Sp 68% AUC of ROC: 0.82 for CT and 0.94 for PET	Good

N	STUDY	Conclusions/Recommendations	Quality assessment
		Conclusion: further studies are needed.	
6	Patwardhan, M.B., et al., Alzheimer disease: operating characteristics of PET--a meta-analysis. Radiology, 2004. 231(1): p. 73-80.	The Sp and Se of FDG PET are limited by both study design and patient characteristics. Therefore, the clinical value of these parameters is uncertain. Future research needs to focus on current limitations.	Good
7	van Westreenen, H.L., et al., Systematic review of the staging performance of 18F-fluorodeoxyglucose positron emission tomography in esophageal cancer. J Clin Oncol, 2004. 22(18): p. 3805-12.	Preoperative staging performance of FDG PET in esophageal cancer: locoregional metastases: Se 0.51 Sp 0.84 distant metastases: Se 0.67 Sp 0.97 FDG PET should carry more weight than its role in N staging as M stage determines patient management. Further larger and prospective studies are needed.	Good
8	Westerterp M Esophageal cancer: CT, endoscopic US, and FDG PET for assessment of response to neoadjuvant therapy – systematic review Radiology 2005; 236(3): 841-51.	Comparative assessment of PET versus CT and EUS performance in the assessment of response to neoadjuvant therapy in patients with esophageal cancer: maximum joint values for sensitivity and specificity were 54% for CT, 86% for EUS and 85% for PET. FDG PET seems to be a promising tool for assessment of response to neoadjuvant therapy in patients with esophageal cancer.	Good
9	Vermeersch H et al. Nuclear medicine imaging for the assessment of primary and recurrent head and neck carcinoma using routinely available tracers. Eur J Nucl Med Mol Imaging 2003; 30 (12): 1698-700.	Comparative assessment of PET versus conventional morphological imaging in the diagnosis and staging of primary and recurrent HNSCC. Compared with conventional imaging PET proves as sensitive and specific for the detection of primary HNSCC but more sensitive and specific for the detection of regional lymph node involvement and recurrence of HNSCC.	Good
10	Goerres GW et al. Assessment of clinical utility of 18F-FDG PET in patients with head and neck cancer: a probability analysis. Eur J Nucl Med Mol Imaging 2003; 30 (4): 562-71.	Assessment of the diagnostic accuracy of PET in the primary assessment and follow-up of patients with HNSCC. The main ability of PET in this setting lies in ruling out the presence of of disease in both staging and restaging. Further studies are needed to derive probabilities for individual patients from sequential testing as applied in the diagnostic work-up of HNSCC patients.	Good
11	Isasi SR et al. A meta-analysis of FDG-PET for the evaluation of breast	Evaluation of FDG PET performance in the evaluation of breast cancer recurrence and metastases. Statistical heterogeneity affects the	Good

N	STUDY	Conclusions/Recommendations	Quality assessment
	cancer recurrence and metastases. Breast Cancer Res Treat 2005; 90(2); 105-12.	generalizibility of the results: pooled sensitivity: 90% (95%CI: 86.8-93.2) pooled false positive rate: 11% (95%CI: 7.8-14.6) PET may be a valuable tool for detecting breast cancer recurrence and metastases.	
12	Hooft L et al. Diagnostic accuracy of 18F-fluorodeoxyglucose positron emission tomography in the follow-up of papillary or follicular thyroid cancer. J Clin Endocrin and Metab 2001; 86(8): 3779-86.	Determination of the diagnostic accuracy of FDG PET in patients with suspected recurrent papillary or follicular thyroid carcinoma. Heterogeneous reviewed material. Results seem supportive for the use of PET in identifying and localizing foci of recurrent cancer. However, implementation of PET in a routine diagnostic algorithm requires additional avidence.	Good
13	Carnero-Pardo, C Systematic Review of the value of positron emission tomography in the diagnosis of Alzheimer disease (Spanish) Revista de Neurologia 2003 37:9 (860-870)	At present, and according to available evidence, the routine use of PET cannot be recommended in the diagnostic assessment of AD. The number of original works available is very low and, generally speaking, they offer important methodological limitations	Good, but no meta-analysis
14	Vansteenkiste, J., et al., Positron-emission tomography in prognostic and therapeutic assessment of lung cancer: systematic review. Lancet Oncol, 2004. 5(9): p. 531-40.	FDG uptake on PET has independent prognostic value in newly diagnosed NSCL cancer but is less substantiated in treated lung cancer. PET is a sensitive method of measuring biological effect of anticancer therapy but needs better standardisation and large-scale experience. Further studies are needed to define the role of FDG PET in restaging after induction therapy. There is good prospective evidence of effectiveness of PET over CT for correct identification of recurrent lung cancer.	Fair, but poor information about selection of articles, quality appraisal, data extraction and no meta-analysis performed
15	Silverman, D.H., et al., Added clinical benefit of incorporating 2-deoxy-2-[18F]fluoro-D-glucose with positron emission tomography into the clinical evaluation of patients with cognitive impairment. Mol Imaging Biol, 2002. 4(4): p. 283-93.	Comparison of 2 strategies for diagnostic of Alzheimer disease: standards of American Academy of Neurology (AAN) and AAN + Petscan. PET decreased false negative (from 8.3% to 3.1%) and false positive (from 23% to 11.9%). When coupled with AAN treatment recommendations, it corresponds to a ~62% decrease in avoidable months of nursing home care and a ~48% decrease of unnecessary drug therapy resulting from inaccurate diagnoses.	Fair, but the assumptions over avoidable nursing home care are contestable and over unnecessary drug therapy

N	STUDY	Conclusions/Recommendations	Quality assessment
			depends on the therapeutic strategy in use in the country
16	Bastiaannet, E. et al The value of FDG-PET in the detection, grading and response to therapy of soft tissue and bone sarcomas; a systematic review and meta-analysis Cancer Treat Rev, 2004. 30(1) : p 83-101	There were few studies with comparable outcome parameters and moreover, the quality of these studies was poor. Nevertheless, in general, PET has the potential to discriminate between sarcomas and benign tumours, as well as between low and high grade sarcomas. The major drawback in the diagnostic phase is the lack of studies that look at the clinical relevant issues such as differentiation between benign tumour and low grade sarcomas, and detection of recurrences, and sarcomas difficult to approach by surgery. In the therapeutic phase, PET has not yet proven its place.	Good
17	Delgado-Bolton, R. C.et al. Meta-analysis of the performance of 18F-FDG PET in primary tumor detection in unknown primary tumors J Nucl Med, 2002, 44(8) :1301-14	The contribution of an imaging procedure to the management of a patient is difficult to measure because many variables and effects must be considered. The Fryback & Thornbury model assigns each of these variables an efficacy level that would indicate the contributions of the study. The patient outcome efficacy is reached by only 1 study on 15. Six studies on 15 reach the level of therapeutic efficacy. Results indicate that PET could be useful in patients with UPT for the detection of the primary tumour. PET has intermediate specificity and high sensitivity. However, more data are needed to determine the clinical uttlity of PET in assessing patients with UPT	Good
18	Ioannidis, J. P., Lau, J. 18F-FDG PET for the diagnosis and grading of soft-tissue sarcoma: a meta-analysis J Nucl Med, 2003.44(5) :717-24	FDG PET has good discriminating ability in the evaluation of both primary and recurrent soft tissue lesions but offers inadequate discrimination between low grade and benign lesions (PET was positive in all intermediate/high grade tumours, 74.4% of low grade tumour and 39.3% of benign lesions). Limiting data on comparisons with MRI and CT showed no differences against PET in diagnosing recurrent and metastatic disease.	Good
19	Bourguet, P., et al., Summary of the Standards, Options and Recommendations for the use of positron emission tomography with 2-	See FNCLCC HTA report	See HTA report

N	STUDY	Conclusions/Recommendations	Quality assessment
	[18F]fluoro-2-deoxy-D-glucose (FDP-PET scanning) in oncology (2002). Br J Cancer, 2003. 89 Suppl 1: p. S84-91.		
20	Jereczek-Fossa, B.A., J. Jassem, and R. Orecchia, Cervical lymph node metastases of squamous cell carcinoma from an unknown primary. Cancer Treat Rev, 2004. 30(2): p. 153-64.	FDG PET allows detection of primary tumour in about 25% of cases of cervical lymph node metastase of squamous cell carcinoma from an unknown primary. This procedure is still considered investigational.	Poor: no information about search, data extraction, inclusion/exclusion criteria…
21	Schrevens, L., et al., The role of PET scan in diagnosis, staging, and management of non-small cell lung cancer. Oncologist, 2004. 9(6): p. 633-43.	PET is useful in the assessment of SPN and in the staging of NSCLC patients, considered to be candidates for radical treatment. The main additional interest of PET is to assess locoregional lymph node spread more precisely than CT, to detect metastatic lesions and to help in the differentiation of lesions equivocal after conventional imaging.	Poor: no information about search, data extraction, inclusion/exclusion criteria…
22	Knuuti, J., H.R. Schelbert, and J.J. Bax, The need for standardisation of cardiac FDG PET imaging in the evaluation of myocardial viability in patients with chronic ischaemic left ventricular dysfunction. Eur J Nucl Med Mol Imaging, 2002. 29(9): p. 1257-66.	FDG PET used to predict improvement in left ventricular function after revascularisation have reported wide ranges for Se 71 to 100% and for Sp: 33 to 91%. In addition, evaluation of patients with insulin resistance appears to represent a specific challenge. It appears that the optimisation and standardisation of study protocols and analysis of FDG images for the assessment of myocardial viability are critical.	Poor: no information about search, data extraction, inclusion/exclusion criteria…
23	Simon, G.R. and H. Wagner, Small cell lung cancer. Chest, 2003. 123(1 Suppl): p. 259S-271S.	For the routine staging of patients with SCLC, Pet scanning is not recommended outside of a clinical trial.	Poor: no information about search, data extraction, inclusion/exclusion criteria…

N	STUDY	Conclusions/Recommendations	Quality assessment
24	Pastor-Gomez, J., P. Pulido-Rivas, and R.G. Sola, [Review of the literature on the value of magnetoencephalography in epilepsy]. Rev Neurol, 2003. 37(10): p. 951-61.	No clear results for PET	Gives a list of papers for Pet and epilepsy with critical appraisal
25	Shvarts, O., et al., Positron emission tomography in urologic oncology. Cancer Control, 2002. 9(4): p. 335-42.	Testicular cancer: PET has a higher diagnostic accuracy than CT for staging and restaging, and should be test of choice for assessment of CT visualized residual mass following chemotherapy. Prostate, Renal and Bladder: the current role of PET is still being defined, but can be used for problem solving in patients with indeterminate findings on conventional imaging.	Poor, not a systematic review
26	Hersh, M.R., E.L. Knapp, and J. Choi, Newer imaging modalities to assess tumor in the prostate. Cancer Control, 2004. 11(6): p. 353-7.	PET has proven less successful than MRI, US and lymphotropic contrast agents at staging prostate cancer. Other radiopharmaceuticals than FDG, as C-choline have been used successfully in identifying both local and metastatic disease.	Poor, not a systematic review
27	Schlumberger, M., et al., Follow-up of low-risk patients with differentiated thyroid carcinoma: a European perspective. Eur J Endocrinol, 2004. 150(2): p. 105-12.	Differentiated thyroid carcinoma: if the post therapy Whole Body Scan does not show any uptake, other imaging modalities may be employed: spiral CT of neck and chest, bone scintigraphy and FDG PET. FDG PET may be more sensitive when performed following rhTSH stimulation.	Poor, not a systematic review
28	De Santis, M. and J. Pont, The role of positron emission tomography in germ cell cancer. World J Urol, 2004. 22(1): p. 41-6.	FDG PET predicts the persistence of viable tumour in post chemotherapy residual lesions with a high diagnostic accuracy. It should therefore be used as a standard tool in patients with residual seminomatous lesions. NSGCT patients with residual masses do not derive any therapeutic benefits from PET. Preliminary data suggesting that PET is an early predictor of response in GCT patients carrying a poor prognosis need to be confirmed. In relapses with a mismatch between tumour marker levels and imaging data, PET may have a place in selected cases.	Poor, not a systematic review
29	Segall, G., Assessment of myocardial viability by positron emission tomography. Nucl Med Commun, 2002. 23(4): p. 323-30.	FDG PET is the most accurate test to evaluate myocardial viability preoperatively. FDG is superior to PET Rb, PET N-amonia, and to SPECT agent like Thallium & TC. It is expected that the test will become	Poor., not a systematic review

N	STUDY	Conclusions/Recommendations	Quality assessment
		the standard of care when the availability is universal.	
30	Curran, W.J., Jr., Evolving chemoradiation treatment strategies for locally advanced non-small-cell lung cancer. Oncology (Huntingt), 2003. 17(12 Suppl 13): p. 7-14.	Technological advances such as FDG-PET staging can be used to improve patient selection and predict survival in NSCL stage III cancer.	Poor, not a systematic reviewIt's an evaluation of treatment strategies

PRIMARY STUDIES

The indications for primary search are: melanoma, lymphoma, colorectal cancer and breast cancer

How?

using the updated version of Mijnhout et al. strategy with general terms for cancer (cancer, oncology, neoplasm, malignancy, tumour) and specific terms by indications (colon, rectum, lymphoma,…)

Where?

The search was performed in Ovid-Medline and Embase

Ovid-Medline:

#	Search History
1	exp Deoxyglucose/
2	deoxyglucose.mp.
3	desoxyglucose.mp.
4	deoxy-glucose.mp.
5	desoxy-glucose.mp.
6	deoxy-d-glucose.mp.
7	desoxy-d-glucose.mp.
8	2deoxyglucose.mp.
9	2deoxy-d-glucose.mp.
10	fluorodeoxyglucose.mp.
11	fluorodesoxyglucose.mp.
12	fludeoxyglucose.mp.
13	fluordeoxyglucose.mp.
14	fluordesoxyglucose.mp.
15	18fluorodeoxyglucose.mp.
16	18fluorodesoxyglucose.mp.
17	18fluordeoxyglucose.mp.
18	fdg$.mp.
19	18fdg$.mp.
20	18f-dg$.mp.
21	((fluor or 2fluor$ or fluoro or fluorodeoxy or fludeoxy or fluorine or 18f or 18flu$) and glucose).mp.
22	(pet or pet$).mp.
23	petscan$.mp.
24	exp Tomography, Emission-Computed/
25	(emission and (tomograph or tomographs or tomographic$ or tomography or tomographies)).mp.

26	exp animals/ not exp humans/
27	or/1-21
28	((22 not 26) or 23 or 24 or 25) and 27

AND for colon carcinoma: exp colon/ OR exp rectum/

for lymphoma: exp lymphoma/

for melanoma: exp melanoma/

for breast cancer: exp breast/

with limits: after 1/1/2002,

Embase

((((('computer assisted emission tomography'/exp OR 'positron emission tomography'/exp OR 'whole body tomography'/exp) OR 'positron emission tomography':ti,ab,tn,mn,de OR pet*:ti,ab,de,tn,mn OR petscan*:ti,ab,de,tn,mn OR (pet*:ti,ab,tn,mn,de NOT (animal:ti,ab,tn,mn,de NOT human:ti,ab,tn,mn,de AND animal:ti,ab,tn,mn,de))) AND (('deoxyglucose':ti,ab,de,mn,tn OR 'desoxyglucose':ti,ab,de,mn,tn OR 'deoxy-glucose':ti,ab,de,mn,tn OR 'desoxy-glucose':ti,ab,de,mn,tn OR 'deoxy-d-glucose':ti,ab,de,mn,tn OR 'desoxy-d-glucose':ti,ab,de,mn,tn OR '2deoxyglucose':ti,ab,de,mn,tn OR '2deoxy-d-glucose':ti,ab,de,mn,tn OR 'fluorodeoxyglucose':ti,ab,de,mn,tn OR 'fluorodesoxyglucose':ti,ab,de,mn,tn OR 'fludeoxyglucose':ti,ab,de,mn,tn OR 'fluordeoxyglucose':ti,ab,de,mn,tn OR 'fluordesoxyglucose':ti,ab,de,mn,tn OR '18fluorodeoxyglucose':ti,ab,de,mn,tn OR '18fluorodesoxyglucose':ti,ab,de,mn,tn OR '18fluordeoxyglucose':ti,ab,de,mn,tn OR fdg*:ti,ab,de,mn,tn OR 18fdg*:ti,ab,de,mn,tn OR '18f-dg':ti,ab,de,mn,tn OR ((fluor:ti,ab,de,mn,tn OR 2fluor*:ti,ab,de,mn,tn OR fluoro:ti,ab,de,mn,tn OR fluorodeoxy:ti,ab,de,mn,tn OR fludeoxy:ti,ab,de,mn,tn OR fluorine:ti,ab,de,mn,tn OR 18f:ti,ab,de,mn,tn OR 18flu*:ti,ab,de,mn,tn) AND glucose:ti,ab,de,mn,tn)) OR ('deoxyglucose'/exp OR 'deoxyglucose')) AND [2002-2005]/py) AND (oncolog* OR cancer* OR neoplas* OR 'neoplasms'/exp OR tumour* OR tumor* OR carcinom* OR 'cancer'/exp))

AND for colon carcinoma: (colon* OR rect*)

for lymphoma: (lymphom* OR leukemi*)

for melanoma: melanom*

for breast cancer: breast

AND [embase]/lim

When?

on 1/3/2005 for colorectal cancer, 2/3/2005 for lymphoma, 10/3/2005 for breast cancer and 14/4/2005 for melanoma.

Selection process:

The selection criteria were: published after 1/1/2002, diagnostic studies, with abstract, with at least 10 patients, in English, Dutch, French, German or Spanish.

The methodological quality (patient spectrum, verification, blinding and replication) of the studies was assessed with the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) checklist [13].

The QUADAS tool

Item		Yes	No	Unclear
1.	Was the spectrum of patients representative of the patients who will receive the test in practice?	( )	( )	( )
2.	Were selection criteria clearly described?	( )	( )	( )
3.	Is the reference standard likely to correctly classify the target condition?	( )	( )	( )
4.	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	( )	( )	( )
5.	Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?	( )	( )	( )
6.	Did patients receive the same reference standard regardless of the index test result?	( )	( )	( )
7.	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	( )	( )	( )
8.	Was the execution of the index test described in sufficient detail to permit replication of the test?	( )	( )	( )
9.	Was the execution of the reference standard described in sufficient detail to permit its replication?	( )	( )	( )
10.	Were the index test results interpreted without knowledge of the results of the reference standard?	( )	( )	( )
11.	Were the reference standard results interpreted without knowledge of the results of the index test?	( )	( )	( )
12.	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	( )	( )	( )
13.	Were uninterpretable/ intermediate test results reported?	( )	( )	( )
14.	Were withdrawals from the study explained?	( )	( )	( )

Studies were selected according to evaluation criteria of the American College of Physicians, already used in evaluating literature on MRI. These criteria formerly have been used by several HTA agencies in their evaluation of literature on PET [14 15]. Grade A and B studies were selected:

To further refine judgment of methodological quality, grade **diagnostic accuracy or thinking efficacy** studies:

Grade A- Studies with broad generalizability to a variety of patients and no significant flaws in research methods

Grade B- Studies with a narrower spectrum of generalizability, and with only a few flaws that are well described (and impact on conclusions can be

assessed)

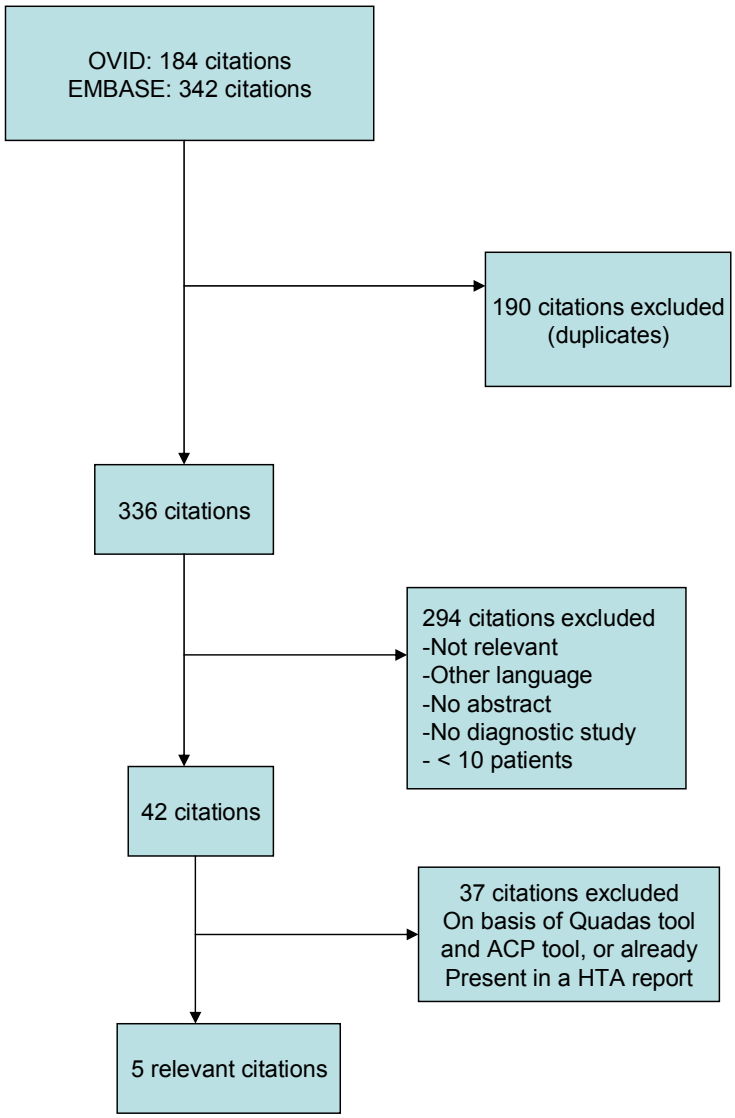
Grade C- Studies with several methods flaws, small sample sizes, incomplete reporting or retrospective studies of diagnostic accuracy

Grade D- Studies with multiple flaws in methods, no credible reference standard for diagnosis, evidence of work up, test review, or diagnostic review

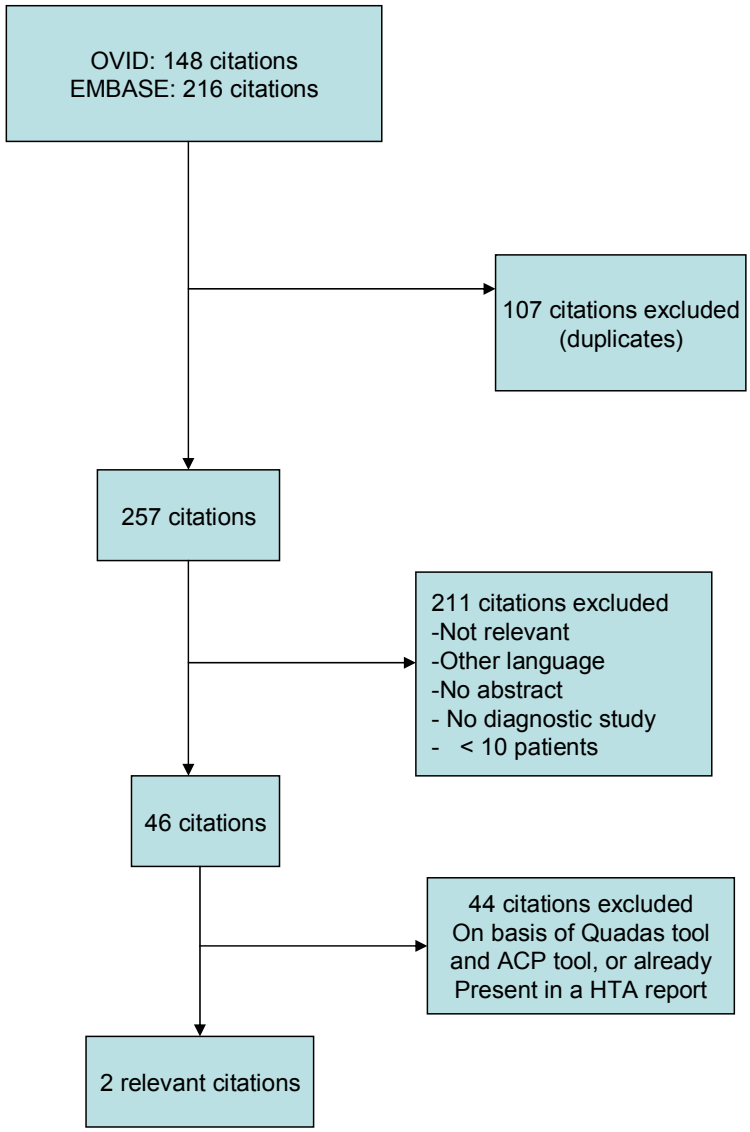
bias, or opinions without substantiating data

Results: see flowcharts hereunder and evidence tables in the report

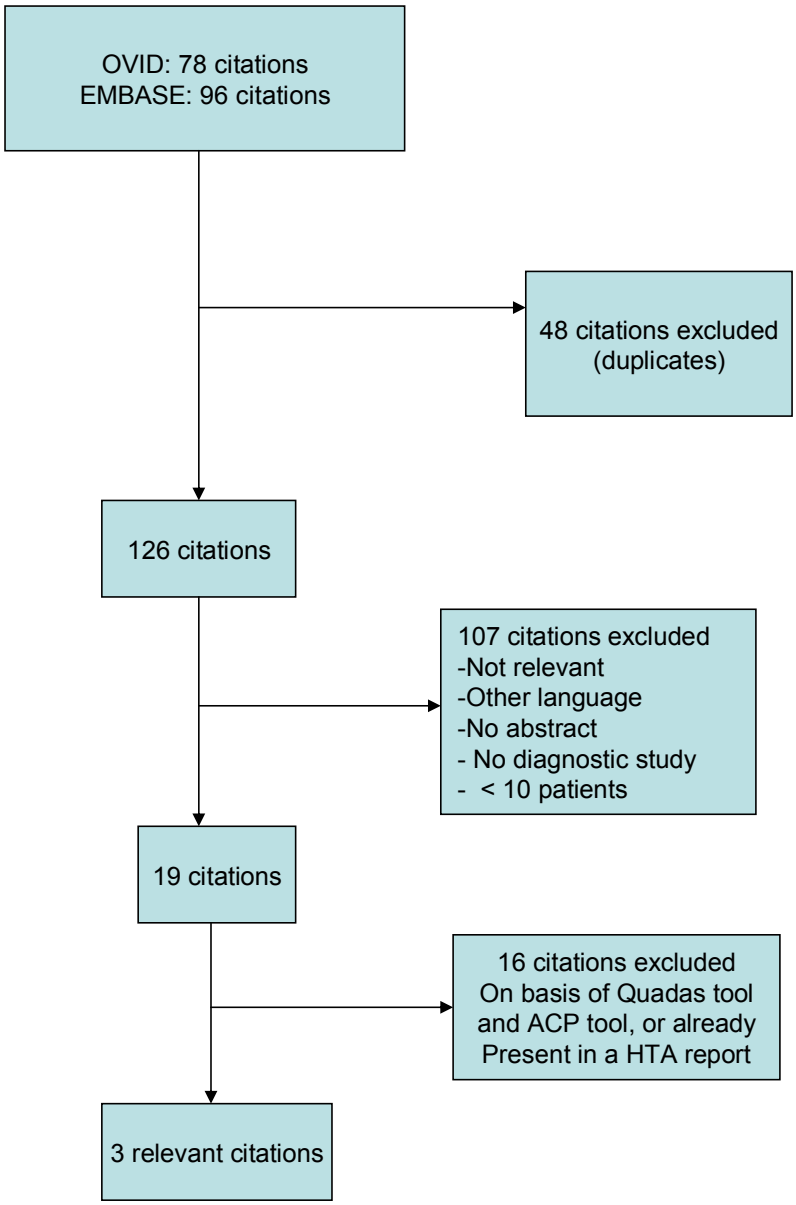
LYMPHOMA Primary studies search : 2 march 2005



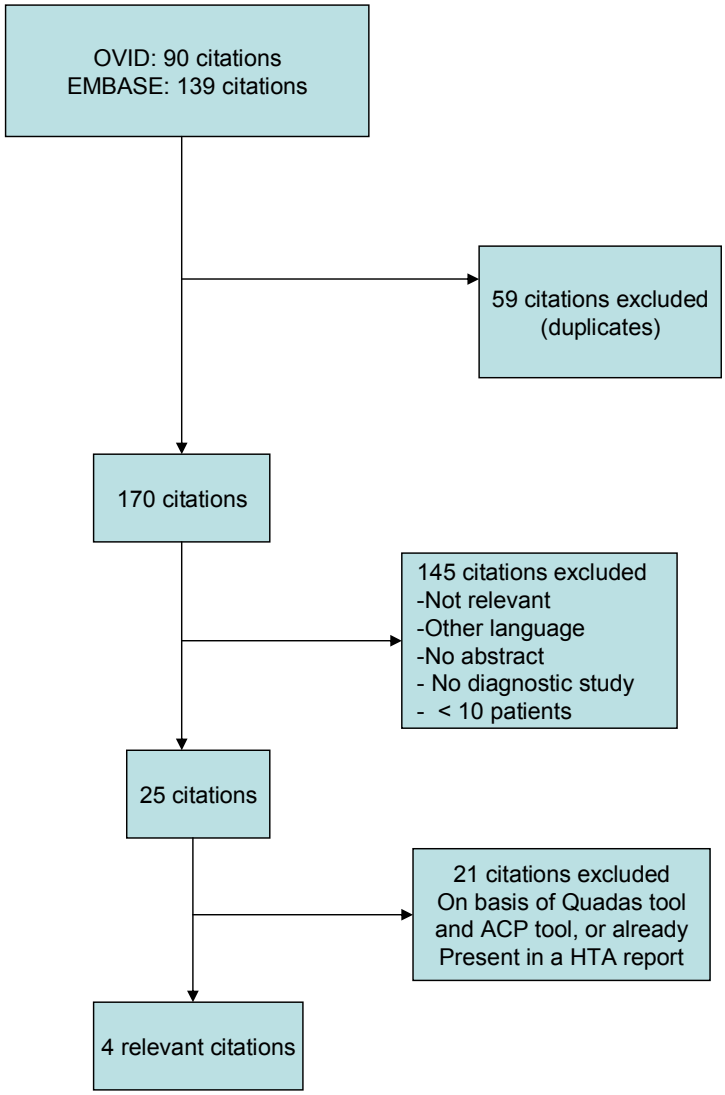
BREAST Primary studies search : 10 march 2005



MELANOMA Primary studies search : 14 april 2005



COLORECTAL Primary studies search : 1 march 2005



SPN

After reviewing the available evidence from HTA reports, we decided to search additional primary studies for SPN as well, up till April 2005, because there was a large variation in the reported sensitivity and specificity of PET for this indication.

How? using the updated version of Mijnhout et al. strategy with general terms for cancer (cancer, oncology, neoplasm, malignancy, tumour) and specific terms for SPN

Where?

Pubmed

((deoxyglucose[mh] OR deoxyglucose[tw] OR desoxyglucose[tw] OR deoxy-glucose[tw] OR desoxy-glucose[tw] OR deoxy-d-glucose[tw] OR desoxy-d-glucose[tw] OR 2deoxyglucose[tw] OR 2deoxy-d-glucose[tw] OR fluorodeoxyglucose[tw] OR fluorodesoxyglucose[tw] OR fludeoxyglucose[tw] OR fluordeoxyglucose[tw] OR fluordesoxyglucose[tw] OR 18fluorodeoxyglucose[tw] OR 18fluorodesoxyglucose[tw] OR 18fluordeoxyglucose[tw] OR fdg*[tw] OR 18fdg*[tw] OR 18f-dg*[tw] OR ((fluor[tw] OR 2fluor*[tw] OR fluoro[tw] OR fluorodeoxy[tw] OR fludeoxy[tw] OR fluorine[tw] OR 18f[tw] OR 18flu*[tw]) AND glucose[tw])) AND (pet[tw] OR pet/*[tw] OR petscan*[tw] OR tomography, emission-computed[mh] OR (emission[tw] AND (tomograph [tw] OR tomographs [tw] OR tomographic*[tw] OR tomography[tw] OR tomographies[tw]))) AND (oncolog* OR cancer* OR neoplas* OR neoplasms[mesh] OR tumour* OR tumor* OR carcinom* OR malignan* OR cancer[sb]) AND (solitary pulmonary nodule[tw] OR lung[tw])

Embase

((((('computer assisted emission tomography'/exp OR 'positron emission tomography'/exp OR 'whole body tomography'/exp) OR 'positron emission tomography':ti,ab,tn,mn,de OR pet*:ti,ab,de,tn,mn OR petscan*:ti,ab,de,tn,mn OR (pet*:ti,ab,tn,mn,de NOT (animal:ti,ab,tn,mn,de NOT human:ti,ab,tn,mn,de AND animal:ti,ab,tn,mn,de))) AND (('deoxyglucose':ti,ab,de,mn,tn OR 'desoxyglucose':ti,ab,de,mn,tn OR 'deoxy-glucose':ti,ab,de,mn,tn OR 'desoxy-glucose':ti,ab,de,mn,tn OR 'deoxy-d-glucose':ti,ab,de,mn,tn OR 'desoxy-d-glucose':ti,ab,de,mn,tn OR '2deoxyglucose':ti,ab,de,mn,tn OR '2deoxy-d-glucose':ti,ab,de,mn,tn OR 'fluorodeoxyglucose':ti,ab,de,mn,tn OR 'fluorodesoxyglucose':ti,ab,de,mn,tn OR 'fludeoxyglucose':ti,ab,de,mn,tn OR 'fluordeoxyglucose':ti,ab,de,mn,tn OR 'fluordesoxyglucose':ti,ab,de,mn,tn OR '18fluorodeoxyglucose':ti,ab,de,mn,tn OR '18fluorodesoxyglucose':ti,ab,de,mn,tn OR '18fluordeoxyglucose':ti,ab,de,mn,tn OR fdg*:ti,ab,de,mn,tn OR 18fdg*:ti,ab,de,mn,tn OR '18f-dg':ti,ab,de,mn,tn OR ((fluor:ti,ab,de,mn,tn OR 2fluor*:ti,ab,de,mn,tn OR fluoro:ti,ab,de,mn,tn OR fluorodeoxy:ti,ab,de,mn,tn OR fludeoxy:ti,ab,de,mn,tn OR fluorine:ti,ab,de,mn,tn OR 18f:ti,ab,de,mn,tn OR 18flu*:ti,ab,de,mn,tn) AND glucose:ti,ab,de,mn,tn)) OR ('deoxyglucose'/exp OR 'deoxyglucose')) AND [2002-2005]/py) AND (oncolog* OR cancer* OR neoplas* OR 'neoplasms'/exp OR tumour* OR tumor* OR carcinom* OR malignan* OR 'cancer'/exp)) AND (lung AND nodule) AND [embase]/lim

When? In May 2005, up till April 2005

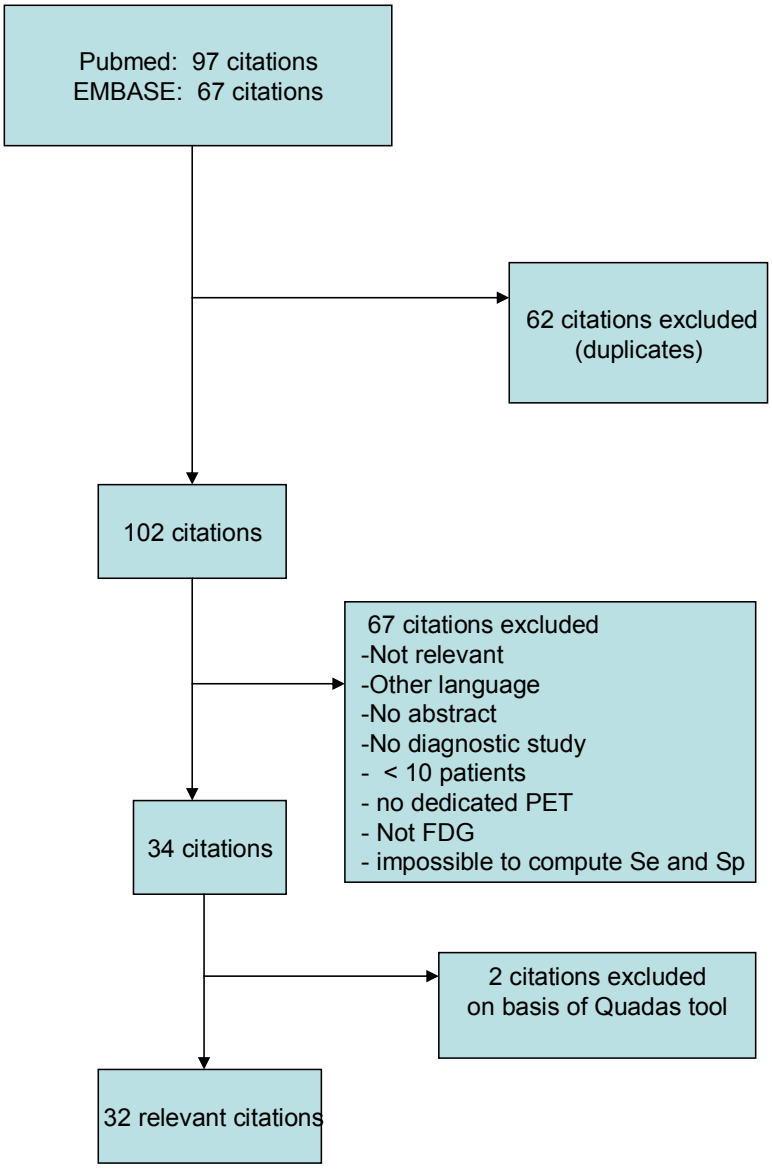
Selection process:

The selection criteria were: diagnostic studies, with abstract, with at least 10 patients, in English, Dutch, French, German or Spanish, over dedicated PET using FDG as tracer, giving all necessary information to compute Se and Sp .

The methodological quality (patient spectrum, verification, blinding and replication) of the studies was assessed with the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) checklist [13].

Results: the results are presented in the flowchart hereunder and in the report.

SPN Primary studies search : 1 march 2005



STUDYING THE ECONOMIC ASPECTS OF PET-SCAN

The assessment of the economic value of diagnostic tests is fraught with difficulties. The aim of economic evaluations is to assess whether the additional benefits of an intervention are worth the extra costs. Although this can eventually be considered a moral discussion, economic evaluation can provide support to the decision making process, by making explicit what can be made explicit: the costs associated with the technology/intervention and the outcomes that can be obtained with it. If this information is available for a large number of interventions, policy makers can start to discuss the relative importance, e.g. from the societal point of view, of the outcomes.

The problem that arises with diagnostic technology is that the outcome is rarely expressed in generic terms. While you can easily express the outcome of, for example, a surgical intervention in terms of life years gained, this is rarely done in diagnostic research. The final outcomes are much less clear and highly depend on the treatment path the patient follows once the diagnosis is made. Much of the clinical literature in diagnostic research focuses on intermediary endpoints, such as sensitivity and specificity of the test.

Because for economic evaluation we need information on how the diagnostic technology influences the final treatment outcome, modelling becomes inevitable. A useful approach to compare the economic value of different diagnostic interventions (without having comparability with other, non-diagnostic interventions) is to express the outcome of the intervention in terms of "patients appropriately treated". For example, if the diagnostic intervention avoids surgery in patients without a tumour, it increases the proportion of patients appropriately treated.

SEARCH STRATEGY

Medline (Ovid) (including Medline in process)

#	Search History
1	exp Deoxyglucose/
2	deoxyglucose.mp.
3	desoxyglucose.mp.
4	deoxy-glucose.mp.
5	desoxy-glucose.mp.
6	deoxy-d-glucose.mp.
7	desoxy-d-glucose.mp.
8	2deoxyglucose.mp.
9	2deoxy-d-glucose.mp.
10	fluorodeoxyglucose.mp.
11	fluorodesoxyglucose.mp.
12	fludeoxyglucose.mp.
13	fluordeoxyglucose.mp.
14	fluordesoxyglucose.mp.
15	18fluorodeoxyglucose.mp.
16	18fluorodesoxyglucose.mp.
17	18fluordeoxyglucose.mp.
18	fdg$.mp.
19	18fdg$.mp.
20	18f-dg$.mp.
21	((fluor or 2fluor$ or fluoro or fluorodeoxy or fludeoxy or fluorine or 18f or 18flu$) and glucose).mp.
22	(pet or pet$).mp.
23	petscan$.mp.

24	exp Tomography, Emission-Computed/
25	(emission and (tomograph or tomographs or tomographic$ or tomography or tomographies)).mp.
26	exp animals/ not exp humans/
27	or/1-21
28	((22 not 26) or 23 or 24 or 25) and 27
29	Positron-Emission Tomography/ec [Economics]
30	randomized controlled trial.pt. or cost effectiveness.tw. or cost effective.tw. or ec.fs. or cost.tw. or health care costs.sh.
31	limit 28 to ("costs (sensitivity)" or "costs (specificity)" or "costs (optimized)" or "economics (sensitivity)" or "economics (specificity)" or "economics (optimized)")
32	(28 and 30) or 29 or 31
33	exp economics/
34	exp "quality of life"/
35	(economic$ or cost$).tw.
36	"quality of life".tw.
37	qol$.tw.
38	quality adjusted life year$.tw.
39	qaly$.tw.
40	or/33-39
41	28 and 40
42	41 OR 32

DARE

Same strategy

EMBASE

(((((('computer assisted emission tomography'/exp OR 'computer assisted emission tomography') OR ('positron emission tomography'/exp OR 'positron emission tomography') OR ('whole body tomography'/exp OR 'whole body tomography') AND [2001-2005]/py AND [2001-2005]/py) OR (emission:ab,ti,de,mn,tn AND (tomograph:ab,ti,de,mn,tn OR tomographs:ab,ti,de,mn,tn OR tomographic*:ab,ti,de,mn,tn OR tomography:ab,ti,de,mn,tn OR tomographies:ab,ti,de,mn,tn) AND [2001-2005]/py AND [2001-2005]/py) OR ((pet:ab,ti,de,mn,tn OR pet*:ab,ti,de,mn,tn OR petscan*:ab,ti,de,mn,tn AND [2001-2005]/py) NOT ('non human' NOT 'human'/exp AND [2001-2005]/py))) AND (((fluor:mn,de,tn,ab,ti OR 2fluor:mn,de,tn,ab,ti OR fluoro:mn,de,tn,ab,ti OR fluorodeoxy:mn,de,tn,ab,ti OR fludeoxy:mn,de,tn,ab,ti OR fluorine:mn,de,tn,ab,ti OR 18f:mn,de,tn,ab,ti OR 18flu:mn,de,tn,ab,ti) AND glucose:mn,de,tn,ab,ti AND [2001-2005]/py AND [2001-2005]/py) OR (((deoxyglucose:ab,ti,mn,tn,de OR 'deoxy glucose':ab,ti,mn,tn,de OR desoxyglucose:ab,ti,mn,tn,de OR 'desoxy glucose':ab,ti,mn,tn,de OR deoxy-d-glucose:ab,ti,mn,tn,de OR desoxy-d-glucose:ab,ti,mn,tn,de OR 2deoxyglucose:ab,ti,mn,tn,de OR 2deoxy-d-glucose:ab,ti,mn,tn,de OR fluorodeoxyglucose:ab,ti,mn,tn,de OR fluorodesoxyglucose:ab,ti,mn,tn,de OR fludeoxyglucose:ab,ti,mn,tn,de OR fluordeoxyglucose:ab,ti,mn,tn,de OR fluordesoxyglucose:ab,ti,mn,tn,de OR 18fluorodeoxyglucose:ab,ti,mn,tn,de OR 18fluorodesoxyglucose:ab,ti,mn,tn,de OR 18fluordeoxyglucose:ab,ti,mn,tn,de OR fdg:ab,ti,mn,tn,de OR 18fdg:ab,ti,mn,tn,de OR 18-fdg:ab,ti,mn,tn,de AND [2001-2005]/py) AND [2001-2005]/py) OR ((fluor:mn,de,tn,ab,ti OR 2fluor:mn,de,tn,ab,ti OR fluoro:mn,de,tn,ab,ti OR fluorodeoxy:mn,de,tn,ab,ti OR fludeoxy:mn,de,tn,ab,ti OR fluorine:mn,de,tn,ab,ti OR 18f:mn,de,tn,ab,ti OR 18flu:mn,de,tn,ab,ti) AND glucose:mn,de,tn,ab,ti AND [2001-2005]/py AND [2001-2005]/py)))) AND (('economic evaluation'/ OR 'cost'/ OR 'reimbursement'/ OR 'cost utility analysis'/ OR 'drug cost'/ OR 'energy cost'/ OR 'hospital cost'/ OR 'hospital running cost'/ OR 'biomedical technology assessment'/ AND [2001-2005]/py AND [2001-2005]/py) OR ((fiscal:ab,ti,de OR financial:ab,ti,de OR finance:ab,ti,de OR funding:ab,ti,de AND [2001-2005]/py AND [2001-2005]/py) OR ((variable*:ab,ti,de,mn,tn OR unit*:ab,ti,de,mn,tn OR estimate*:ab,ti,de,mn,tn AND [2001-2005]/py) AND (cost*:ab,ti,de,mn,tn AND [2001-2005]/py)) OR ('socioeconomics'/ OR 'cost benefit analysis'/ OR 'cost effectiveness analysis'/ OR 'cost of illness'/ OR 'cost control'/ OR 'economic aspect'/ OR 'financial management'/ OR 'health care cost'/ OR 'health care financing'/ OR 'health economics'/ OR 'hospital cost'/ OR 'cost minimization analysis'/ AND [2001-2005]/py AND [2001-2005]/py)))) AND [embase]/lim AND [2001-2005]/py

NHS EED (CRD)

de?oxy?glucose OR flu?de?oxyglucose OR fdg OR 18f?fg/All fields AND

pet OR tomography computer assisted OR (emission and tomograph)/All Fields

EconLit (Ovid)

(pet or positron emission tomography or computer assisted tomography).mp. [mp=heading words, abstract, title, country as subject]

Quality checklist for economic evaluations[16]

Study design

The research question is stated

The economic importance of the research question is stated

The viewpoints of the analysis are clearly stated and justified

The rationale for choosing the alternative programmes or interventions compared is stated

The alternatives being compared are clearly described

The form of economic evaluation used is stated

The choice of form of economic evaluation is justified in relation to the questions addressed

Data collection

The sources of effectiveness estimates used are stated

Details of the design and results of effectiveness study are given (if based on a single study)

Details of the method of synthesis or meta-analysis of estimated are given (if based on an overview of a number of effectiveness studies)

The primary outcome measure(s) for the economic evaluation are clearly stated

Methods to value health states and other benefits are stated

Details of the subjects from whom valuations were obtained are given

Productivity changes (if included) are reported separately

The relevance of productivity changes to the study question is discussed

Quantities of resources are reported separately from their unit costs

Methods for the estimation of quantities and unit costs are described

Currency and price data are recorded

Details of currency of price adjustments for inflation or currency conversion are given

Details of any model used are given

The choice of model used and the key parameters on which it is based are justified

Analysis and interpretation of results

Time horizon of costs and benefits is stated

The discount rate(s) is stated

The choice of rate(s) is justified

An explanation is given if costs or benefits are not discounted

Details of statistical tests and confidence intervals are given for stochastic data

The approach to sensitivity analysis is given

The choice of variables for sensitivity analysis is justified

The ranges over which the variables are varied are stated

Relevant alternatives are compared

Incremental analysis is reported

Major outcomes are presented in a disaggregated as well as aggregated form

The answer to the study question is given

Conclusions follow from the data reported

Conclusions are accompanied by the appropriate caveats

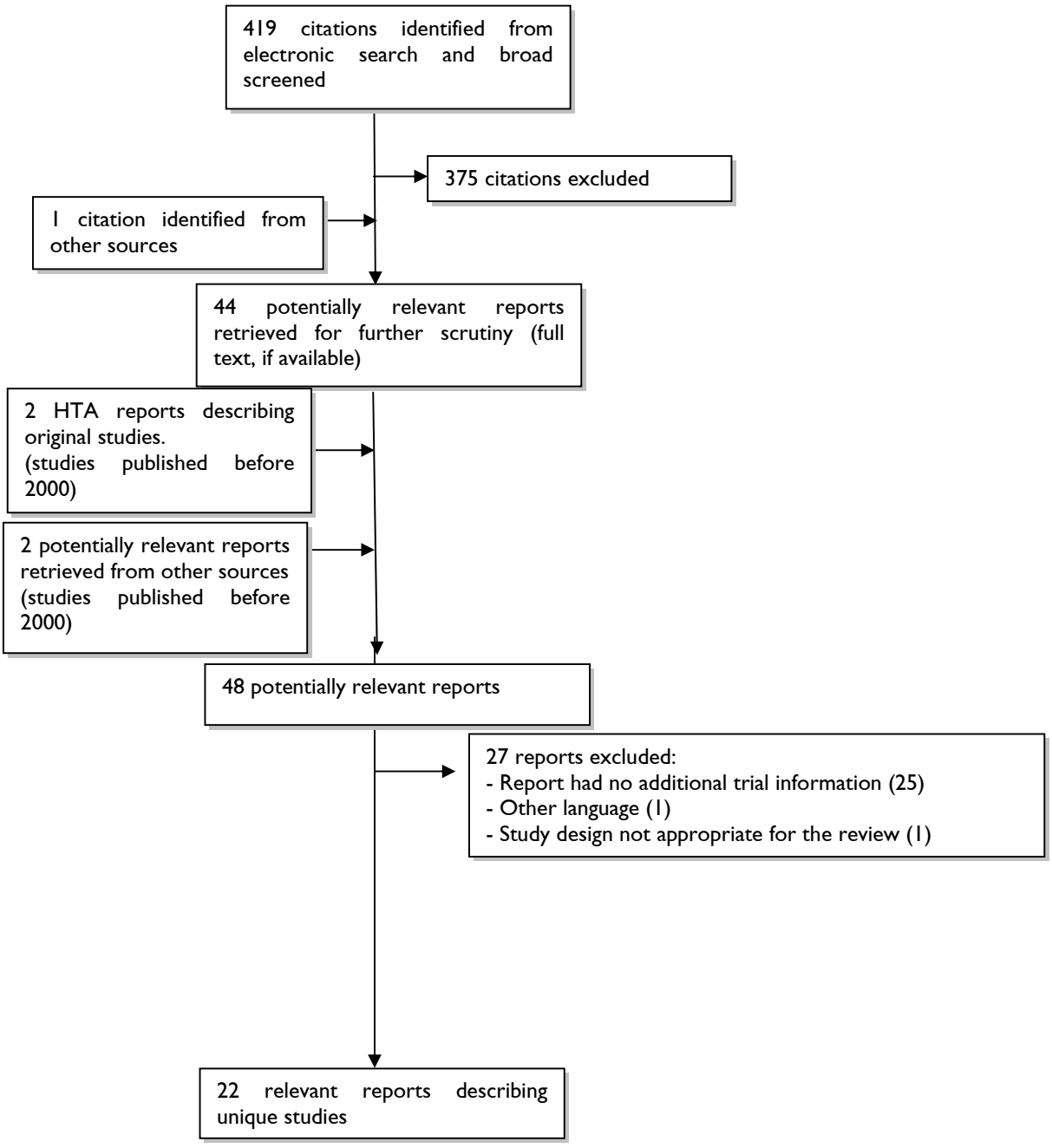
RESULTS ECONOMIC LITERATURE SEARCH

The search for economic literature revealed 22 relevant articles. The results of the quality assessment per indication are presented in the table. Some studies examined different indications and are therefore mentioned more than once in the table. For indications not mentioned in the table (e.g. breast cancer, renal cancer) no economic evidence was found.

Table: Yield of the literature search for economic evaluations

Indication	Quality		
	Good	Fair	Poor
Diagnosis SPN	3 [18, 78, 77]	2 [80, 81]	2 [184, 185]
Staging NSCLC	4 [78, 9, 84, 88]	1 [17 89]	5 [186, 187, 81, 188 189]
Head and Neck cancer	0	1 [122]	0
Colorectal cancer	0	2 [128, 129]	0
Miscellaneous (different indications in one article)	0	0	1 [190]
Lymphoma	1 [9]	0	1 [191]
Assessment Myocardial viability	0	1 [84]	0

FLOW CHART ECONOMIC LITERATURE SEARCH



ECONOMIC EVALUATIONS OF PET

Diagnosis of Solitary Pulmonary Nodules

<table>
<tr><td>Author</td><td colspan="4">Gould et al. 2003</td></tr>
<tr><td>Country</td><td colspan="4">US</td></tr>
<tr><td>Design</td><td colspan="4">Cost-effectiveness analysis
Markov model</td></tr>
<tr><td>Perspective</td><td colspan="4">Societal</td></tr>
<tr><td>Time window</td><td colspan="4">Lifetime</td></tr>
<tr><td>Interventions</td><td colspan="4">40 clinically plausible sequences of CT, FDG-PET, transthoracic needle biopsy, surgery and watchful waiting were considered.
All sequences start with either CT, FDG-PET. If the biopsy revealed malignancy, surgery would be performed.</td></tr>
<tr><td>Population</td><td colspan="4">Adult patients with new, noncalcified solitary pulmonary nodule.
Base case: hypothetical cohort of 62-year old men and women.</td></tr>
<tr><td rowspan="5">Assumptions</td><td colspan="4">Pre-test probability of malignancy: low (26%), intermediate (55%), high (79%)
(Pre-test probability of malignancy depends on age, smoking status, history of cancer, nodule diameter, spiculation and upper lobe location - to be determined on individual basis)
Watchful waiting consists of chest radiographs at 1, 2, 4 and 6 months and every 3 months thereafter.
Monthly probability of cancer recurrence after surgery derived from survival data from the Surveillance, Epidemiology and End Results (SEER) tumor registry.
Diagnostic accuracy derived from literature (meta-analysis performed):</td></tr>
<tr><td></td><td>Sensitivity</td><td>Specificity</td><td>Cost</td></tr>
<tr><td>CT</td><td>0,965</td><td>0,558</td><td>US$ 285</td></tr>
<tr><td>FDG-PET</td><td>0,942</td><td>0,833</td><td>US$ 1980</td></tr>
<tr><td>CT-guided needle biopsy</td><td>0,963</td><td>0,98</td><td>US$ 583</td></tr>
<tr><td colspan="4">Probability of minor pneumothorax: 24%
Probability of major pneumothorax, requiring chest tube drainage: 5%
Probabilities of fatal and non-fatal surgical complications derived from literature.</td></tr>
<tr><td>Data source for costs</td><td colspan="4">Imaging tests and needle biopsy: Medicare reimbursement rates
Surgical procedures and complications: professional fees+median cost-adjusted charges
Long term costs: Medicare claims linked with data from SEER tumor registry.
Health care costs for patients with benign nodules or survival >5 years, age-specific annual health care expenditures derived from Consumer Expenditures Study.
Price year: 2001
Currency: US$</td></tr>
<tr><td>Cost items included</td><td colspan="4">CT scan: US$ 285
PET scan: US$1980
CT guided needle biopsy: US$583</td></tr>
</table>

	Fluoroscope-guided needle biopsy: US$283 Minor pneumothorax: US$72 Major pneumothorax: US$2566 Surgery for malignant nodule (lobectomy): US$14875 Surgery for benign nodule: US$11625 Fatal or nonfatal surgical complications: US$8624 Chest radiograph and physician office visit during wait-and-watch period: US$ 72 Monthly cost of living with lung cancer for patients with local stage disease, regional stage disease, distant stage disease: different cost figure for 1-12 months (monthly variable, based on average Medicare expenditures) and for 13-60 months (fixed cost per month) Monthly health care cost of living with benign disease or being disease-free: variable cost based on average monthly age-specific health care expenditures for US citizens.
Data source for outcomes	Utilities: Beaver Dam Health Outcomes study and literature Mortality from recurrent cancer: SEER tumor registry Mortality from other causes: 1996 US life tables
Discounting	3%
Costs	(Selected examples of non-dominated strategies) Low pre-test probability of malignancy (26%): watchful waiting: $ 51 419 CT, if indeterminate: biopsy, if benign: watch and wait: $55 217 CT, if indeterminate: PET, if PET positive: surgery, if PET negative: biopsy, if CT benign: watch and wait: $55 552 Intermediate probability of malignancy (55%) watchful waiting: $ 58 511 CT, if indeterminate: biopsy, if benign: watch and wait: $64 234 CT, if indeterminate: PET, if PET positive: surgery, if PET negative: biopsy, if CT benign: biopsy: $65 387 High probability of malignancy (79%) watchful waiting: $ 64 381 CT, if indeterminate: surgery, if benign: watch and wait: $71 713 CT, if indeterminate: surgery, if CT benign: PET, if PET positive: biopsy, if PET negative: watch and wait: $72 306
Outcomes	Low pre-test probability of malignancy (26%): watchful waiting: 10,089 QALYs CT, if indeterminate: biopsy, if benign: watch and wait: 10,437 QALYs CT, if indeterminate: PET, if PET positive: surgery, if PET negative: biopsy, if CT benign: watch and wait: 10,453 QALYs Intermediate probability of malignancy (55%) watchful waiting: 8,130 QALYs CT, if indeterminate: biopsy, if benign: watch and wait: 8,881 QALYs CT, if indeterminate: PET, if PET positive: surgery, if PET negative: biopsy, if CT benign: biopsy: 8,932 QALYs

	High probability of malignancy (79%) watchful waiting: 6,509 QALYs CT, if indeterminate: surgery, if benign: watch and wait: 7,634 QALYs CT, if indeterminate: surgery, if CT benign: PET, if PET positive: biopsy, if PET negative: watch and wait: 7,671 QALYs
Cost-effectiveness	cost per QALY gained; Comparator: watchful waiting Cost-utility threshold: $100 000/QALY Low pre-test probability of malignancy (26%): CT, if indeterminate: biopsy, if benign: watch and wait: ICER: 10935 $/QALY CT, if indeterminate: PET, if PET positive: surgery, if PET negative: biopsy, if CT benign: watch and wait: 20445 $/QALY Intermediate probability of malignancy (55%) CT, if indeterminate: biopsy, if benign: watch and wait:7625 $/QALY CT, if indeterminate: PET, if PET positive: surgery, if PET negative: biopsy, if CT benign: biopsy: 229260 $/QALY High probability of malignancy (79%) CT, if indeterminate: surgery, if benign: watch and wait: 1125 $/QALY CT, if indeterminate: surgery, if CT benign: PET, if PET positive: biopsy, if PET negative: watch and wait: 16261 $/QALY
Sensitivity analysis	Variables considered in sensitivity analyses: diagnostic accuracy, utilities, costs, transition probabilities One-way sensitivity analysis: pre-test probability impacts upon results; sensitivity of CT (not specificity), probability of non-diagnositic needle biopsy in patients with malignant nodules and patient preferences for time spent under observation impact upon choice of strategy for patients with intermediate pretest probability, Probabilistic sensitivity analysis: In patients with low and high pretest probability, PET strategies were cost-saving or cost less than $100 000 per QALY gained in 76,7% and 99,9% of all simulations, respectively. For patients with intermediate pretest probability, PET strategies were cost saving or economically attractive in fewer than 25% if all simulations.
Conclusions	Effectiveness and cost-effectiveness of management strategies depend critically on the pretest probability of malignancy and, to a lesser extent, the risk of surgical complications CT was recommended as the initial test in nearly all circumstances, except when pretest probability was extremely high, in which case immediate surgery is recommended. Selective use of PET is more cost-effective than non-selective use, especially when pretest probability and CT results are discordant It is both effective and cost-effective to use surgery and needle biopsy aggressively once the results of imaging tests are known. Recommendations for the use of PET: 1. when pre-test probability is low (10%-50%) and CT results are possibly malignant 2. when pre-test probability is high (77%-89%) and CT results are benign 3. when surgical risk is high, pretest probability is low to intermediate (<65%) and CT results are possibly malignant 4. when CT results suggest a benign cause and the probability of nondiagnostic biopsy is high, or the patient in uncomfortable with a strategy of watchful waiting.

Remarks	
Author	Gambhir et al.1998
Country	US
Design	Cost-effectiveness analysis Decision analytic model
Perspective	Medicare
Time window	Lifetime
Interventions	CT CT+PET
Population	Baseline: - 64-year old white man, 1.5 pack/day smoker, with a 2.5 cm nodule and a 14.8 year life expectancy (pre-test likelihood 0.83) Other: - 35-year old, non-smoker, 1.0 cm nodule (pre-test likelihood 0.001) - 50-year old, 1 pack/day smoker, 2.0-cm nodule (pre-test likelihood 0.34) - 75-year old, non-smoker, 2.0-cm nodule (pre-test likelihood 0.23) - 75-year old, 1.5 pack/day smoker, 2.0-cm nodule (pre-test likelihood 0.80)

Assumptions

	sensitivity	specificity	costs
CT	0.999	0.610	US$ 378
PET	0.925	0.830	US$ 1000
Needle Biopsy	0.895	0.959	US$ 692
Video-assisted thoracoscopy	1	1	US$ 5132

Morbidity:

Biopsy 0.0008 years

Surgery: 0.08 years

Thoracoscopy: 0.0126 years

Mortality:

Biopsy: 0.2%

Thoracoscopy: 2.5%

Surgery (curative): 4%

Surgery (exploratory): 0.5%

Life expectancy:

Normal: 14.8 years

Unresectable disease: 1.24 years

Surgical cure: 6.62 years

Surgical cure postobservation: 5.67 years

Probability

Resectable SPN: 0.8

Resectable SPN postobservation: 0.78

Mixed strategy to surgery: 0.80 (80% goes directly to surgery, 20% to biopsy)

	Biopsy (transthoracic needle aspiration biopsy): 0.85 Pneumothorax from biopsy: 0.24 Pneumothorax from thoracoscopy: 1.00 Indeterminate biopsy: 0.06 Indeterminate thoracoscopy: 0.02 Benign observation period: 2 years Malignant observation period: 0.25 years
Data source for costs	Medicare reimbursement
Cost items included	Chest radiograph: US$ 44 CT: US$ 378 PET: US$ 1000 Needle biopsy: US$ 692 Chest tube: US$ 2497 Video-assisted thoracoscopy: US$ 5132 Surgery: US$ 14121
Data source for outcomes	Probabilities: Literature Life expectancy: calculated using the Declining Exponential Approximation of Life Expectancy (DEALE)
Discounting	Unclear
Costs	Baseline: Watch and wait: US$ 11886 CT: US$ 13541 CT+PET: US$ 13928 Effect of pre-test likelihood The CT+PET strategy is the least costly alternative to wait and watch at low pretest likelihood, but beyond a pre-test likelihood of 0.72, the CT strategy becomes the least expensive alternate strategy.
Outcomes	Life expectancy (baseline): Watch and wait: 6.35 years CT: 6.86 years CT+PET: 6.83 years Effect of pre-test likelihood: The CT+PET strategy has the greatest incremental life expectancy gain for pretest likelihood between 0.02 and 0.44.
Cost-effectiveness	Incremental cost-effectiveness ratio: cost per life year gained comparator=watch and wait (~observation with serial chest x-rays or alternately serial CT scans) Baseline: CT: 3266 US$/life year gained CT+PET: 4273 US$/life year gained

	Effect of pre-test likelihood: At low pre-test likelihood, up to 0.12, wait and watch is the most cost-effective strategy. From 0.12 to 0.69, the CT+PET strategy is the most cost-effective. Between 0.69 and 0.90, the CT strategy is the most cost-effective and above 0.90, the most cost-effective strategy is immediate surgery.
Sensitivity analysis	Determination of the break-even point of each uncertain variable where the cost, life expectancy or ICER of competing strategies equal each other. Threshold value for ICER: US$ 50 000/life year saved One-way sensitivity analysis: altering a single parameter in the model, does not alter the conclusion that CT+PET is more cost-effective when pre-test likelihood is low, and CT alone is more cost-effective if pre-test likelihood is high.
Conclusions	PET is potentially cost-effective in the management of SPN. The use of PET in addition to CT can provide an advantage in terms of incremental cost-effectiveness (compared to watch and wait or to CT alone) as well as in terms of cost savings (as compared to the CT alone strategy). At a pretest likelihood between 0.69 and 0.90, CT alone is the preferred strategy. In this range, the low specificity of CT affects few patients; more than 70% are malignant, so the additional cost of PET is not balanced by avoiding unnecessary surgeries or biopsies.
Remarks	

Author	Dietlein et al, 2000
Country	Germany
Design	Cost-effectiveness analysis Decision analytic model
Perspective	Healthcare system
Time window	Lifetime
Interventions	A. 2 years Watchful waiting (first baseline strategy) (CT every 3 months) B. Transthoracic needle biopsy (TNB) C. Exploratory surgery (second baseline strategy) D. FDG-PET
Population	Hypothetical cohort of 62-year old men with SPN of up to 3 cm diagnosed by CT, without calcification, without spicula and without enlargement of mediastinal lymph nodes
Assumptions	<u>Probability:</u> Malignancy of SPN: 65% (5% - 95%) N2/3 when normal-sized lymph nodes on CT (thus undetected): 7% Distant metastasis: 0% (as not described in any study about PET in SPN). Growth of benign SPN to malignant SPN: 10% Drop-out during observation period: 5% Malignant SPN: CT after 3 months if 50% of patients, 6 months for the remaining 50%. Locally respectable SPN: 94% Pneumothorax requiring intubation due to TNB: 24% Indeterminate TNB results: 10% <u>Mortality</u> TNB: 0.2% Mediastinoscopy: 0.2% Exploratory surgery: 0.5% surgery , resection: 2.9% <u>Morbidity</u> TNB: 0.02 year Mediastinoscopy: 0.02 year Exploratory surgery: 0.1 year Surgery, resection: 0.2 year

((*) pooled from literature)	Sensitivity	Specificity
PET SPN<=3cm	95% (80% - 100%) (*)	80% (65% - 85%) (*)
PET mediastinal lymph nodes	73.9% (59% - 74%) (*)	96.5% (81% - 100%) (*)
TNB SPN<=3cm	90% (90% - 100%)	100%
Mediastinoscopy	72% (62% - 87%)	100%

<table>
<tr><td></td><td>Life expectancy:
Benign SPN: 16 years
Watchful waiting: 6.5 years (reduced because resection performed after doubling of tumour volume).
Resected NSCLC pT1 without mediastinal involvement: 7 years.
Non curative therapy NSCLC: 1.5 years</td></tr>
<tr><td>Data source for costs</td><td>Costs reimbursed by german public health provider in 1999.</td></tr>
<tr><td>Cost items included</td><td>Reimbursement:
CT: € 117.8
Whole-body FDG PET: €1227.1 (627 – 1827)
TNB (hospitalization): € 1035.74 (5 days + 1 ICU day)
Mediastinoscopy (hospitalization): € 1137.78 (4 days + 1 ICU day)
Surgery, exploratory: € 5232.37 (6 days + 1 ICU day)
Surgery, resection: € 4467.63 (+ 5 days + 2 ICU days)
Palliative: € 11378 (5689 – 22756) (30 days)</td></tr>
<tr><td>Data source for outcomes</td><td>Life expectancy and survival rates calculated from data taken from literature (Gambhir and Cummings method: life expectancy = 1 / (annual mortality rate general population + annual mortality rate of disease)).</td></tr>
<tr><td>Discounting</td><td>5%</td></tr>
<tr><td>Costs</td><td>cf. costs-effectiveness analysis</td></tr>
<tr><td>Outcomes</td><td>cf. costs-effectiveness analysis</td></tr>
<tr><td>Cost-effectiveness</td><td>
<table>
<tr><td>Strategy</td><td>Life Expenctancy</td><td>Costs</td><td colspan="2">ICER (in €/LYS)</td></tr>
<tr><td></td><td></td><td></td><td>vs A</td><td>vs C</td></tr>
<tr><td>A</td><td>9031 LYS</td><td>€ 9405</td><td></td><td>4210 (- / -)</td></tr>
<tr><td>B TNB</td><td>9139 LYS</td><td>€ 10066</td><td>6120</td><td>3343 (- / -)</td></tr>
<tr><td>C Surgery</td><td>9378 LYS</td><td>€ 10866</td><td>4210</td><td></td></tr>
<tr><td>D PET</td><td>9412 LYS</td><td>€ 10631</td><td>3218</td><td>-6912</td></tr>
</table>
</td></tr>
<tr><td>Sensitivity analysis</td><td>One-way sensitivity analyses of the following variables:</td></tr>
<tr><td></td><td>Pretest Probability of SPN malignancy: 5%, 50%, 35%, 50%, 80%, 95%.
=> If watchful waiting is the comparator: PET algorithm showed best ICER for probability from 10 to 70%. <10%: ICER PET > 50000 €/LYS, watchful waiting is preferred. >70% : exploratory surgery is preferred.
=> If explorative surgery is comparator: PET algorithm showed best ICER (reducing costs and life saving) for probability up to 70%. Between 75% and 80%, the higher costs were justified by increased life expectancy. But from 85%, the explorative surgery became the best strategy.
Sensitivity and Specificity of FDG-PET for detecting metastases in normal-sized and mediastinal lymph nodes: -15%, -10%, -5%, +5%
=> If watchful waiting is the comparator: PET algorithm showed best ICER when test</td></tr>
</table>

	parameters are penalized to 7%, beyond this point, explorative surgery has a better ICER. . => If explorative surgery is comparator: idem beyond 6%. TNB sensitivity => If watchful waiting is the comparator: TNB showed best ICER when its sensitivity reached 95%. => If explorative surgery is comparator: TNB was preferred to PET only if its sensitivity was100%. Mortality rate of surgery: x0.85, x0.9, x0.95, x1.05 => No change of ICER ranges. Risk Patients (x2, x3) => No change of ICER ranges. Reimbursement of FDG-PET (-600, -400, -200, +200, +400, +600) => If watchful waiting is the comparator: PET showed best ICER up to € 1605. => If explorative surgery is comparator: PET showed best ICER up to € 1605.. Reimbursement of palliative therapy (x2, x0.5) => No change of ICER ranges.
Conclusions	FDG-PET is potentially cost-effective for evaluating SPN.
	FDG-PET remains the most cost-effective strategy for a SPN malignancy between 10%-80%, and penalization of PET parameters up to -7%.
Remarks	PET Advantage in life expectancy in comparison with Gambhir model: additional effects of nodal staging in FDG-PET taken into account. Implemenation of PET would lead to an estimated increased cost of less than € 1per patient for the public health provider. Transferring the diagnostic efficacy from controlled studies to routine user, keeping it cost-effective, would need obligatory protocol for data acquisitions Further clinical trials should help to validate results.

Author	Keith et al. 2002			
Country	Australia			
Design	Cost-effectiveness analysis Published decision models (ICP and Gambhir) adjusted for Australian data			
Perspective	Not specified			
Time window	Diagnostic process until 2-years follow up			
Interventions	2 models replicated from literature: 1. ICP: PET alone versus CT alone 2. Gambhir: CT alone versus CT+FDG-PET 2 approaches for follow-up of nodules considered benign on CT or PET: (1) no follow-up; (2) four chest X-rays over 2 years			
Population	Observational retrospective cohort of 92 patients, mean age 66,7 years (range 48-84), with no history of malignancy for the previous 5 years			
Assumptions		Sensitivity	Specificity	Costs
	CT	0,97-0,99	0,53-0,61	€ 235
	FDG-PET	0.92	0.95	€ 706
	Biopsy	0,90-0,95	0,88-0,96	€ 707
	Baseline prior probability of malignancy: 0,54			
Data source for costs	Surgery and other hospital-based procedures: published hospital cost-weights			
Cost items included	CT: € 235 (A$400) serial X-rays (4): € 105 (A$178) biopsy: € 707 (A$1202) thoracotomy: € 4 460 (A$7 585) PET scan: € 706 (A$1 200), calculated based on assumption of 1 000 scans per year, 8 years operational (€ 147), and operational costs (€ 559)			
Data source for outcomes	Observational data from 2 hospitals			
Discounting	Unclear			
Costs	ICP, no follow-up: CT: € 3 479 PET: € 3 024 Incremental savings: € 455 ICP, with follow-up CT: € 3 712 PET: € 3 462 Incremental savings: € 250 Gambhir, no follow-up			

	CT: € 3 339 CT+PET: € 3 014 Incremental savings: € 325 Gambhir, with follow-up CT: € 3 567 CT+PET: € 3 544 Incremental savings: € 23
Outcomes	Proportion of appropriately managed patients: ICP, no follow-up: CT: 80% PET: 93% ICP, with follow-up CT: 79% PET: 93% Gambhir, no follow-up CT: 84% CT+PET: 94% Gambhir, with follow-up CT: 82% CT+PET: 95%
Cost-effectiveness	Incremental cost-accuracy ratio (incremental cost per appropriately treated patient): ICP, no follow-up: PET dominates CT ICP, with follow-up: PET dominates CT Gambhir, no follow-up: CT+PET dominates CT Gambhir, with follow-up: CT+PET dominates CT
Sensitivity analysis	One-way sensitivity analysis on prior probability of malignancy: PET strategy remains more cost-effective than the CT strategy until the prior probability of disease reaches 0,8 (Gambhir model) or 0,9 (ICP model) Two-way sensitivity analysis: cost FDG-PET and prior probability of malignancy A prior probability of malignancy of 0,54 would result in cost savings with PET costs as high as € 736 for the Gambhir model with follow up and € 1161 for the ICP model without follow-up. Alternatively, with a PET cost of € 706, the use of PET would remain cost saving with values for prior probability of malignancy up to 56% (Gambhir with follow-up) and 90% (ICP without follow-up).
Conclusions	PET, either in addition or in place of CT, is advantageous in terms of both absolute cost savings and cost-effectiveness. The CT strategy only becomes more cost-effective if the proportion of patients with

	malignancies exceeds 80%, as the low specificity of CT then affects fewer patients and the additional costs of PET scanning is not offset by avoiding unnecessary biopsy and/or surgery.
Remarks	The usefulness of PET for staging is not considered but should be included in cost-effectiveness analyses of PET scan. The ratio of surgical costs to PET costs (6,3/1 in this study) is the major determinant of the extent of cost savings produced. The perspective of the analysis is unclear, which makes it unclear to who the savings will accrue.

Author	Comber et al. 2003			
Country	Australia			
Design	Cost-effectiveness analysis Decision model			
Perspective	Not specified			
Time window	Diagnostic process			
Interventions	1. CT alone 2. CT + Quantitative contrast enhanced CT (QECT) when SPN not benign according to CT 3. CT + FDG-PET when SPN not benign according to CT 4. CT + QECT when SPN not benign + FDG-PET when QECT positive			
Population	Not specified			
Assumptions	Follow-up strategy: 4 chest radiographs over 2 years Prevalence of malignancy: 54%			
		Sensitivity	Specificity	Cost
	CT	0.99	0.61	A$ 400
	QECT	0.98	0.58	A$ 110
	FDG-PET	0.92	0.95	A$ 1200
	Biopsy	0.9	0.96	A$ 1204
	Serial chest x-ray	1	0.9	A$ 178
	surgery	1	1	A$ 7585
Data source for costs	Diagnostic procedures: Australian Medicare Benefits Schedule Surgical and other hospital-based procedures: DRG Cost Weights for Australian public hospitals			
Cost items included	FDG-PET=A$1200 Chest radiographs= A$178			
Data source for outcomes	Literature			
Discounting	No			
Costs	CT alone: A$6065/patient CT+QECT: A$5560/patient CT+FDG-PET: A$6027/patient CT+QECT+FDG-PET: A$5910/patient			
Outcomes	CT alone: 0.82 CT+QECT: 0.90 CT+FDG-PET: 0.95 CT+QECT+FDG-PET: 0.95			
Cost-effectiveness	Cost per appropriately treated patient (incremental cost-accuracy ratio, diagnostic strategy compared to "no investigation or treatment" option): QECT+FDG-PET: A$12059/patient			

	FDG-PET: $12300/patient QECT: $12636/patient CT: $16847/patient
Sensitivity analysis	One-way sensitivity analysis: prevalence of disease At prevalence levels <54% same relative cost-effectiveness relationships At prevalence levels >60%, QECT more cost-effective than QECT+FDG-PET At prevalence levels at 90%, ICER of CT approaches ICER QECT Two-way sensitivity analysis: cost FDG-PET/surgery ratio and prevalence QECT more likely to be cost-effective as the FDG-PET/surgery cost ratio increases and with higher probability of malignancy.
Conclusions	QECT is always preferred to CT alone in the investigation of SPNs CT+FDG-PET is more cost-effective than CT alone, except at high levels of disease prevalence CT+QECT+FDG-PET is more cost-effective than CT+FDG-PET, except at high levels of disease prevalence where their cost-effectiveness is approximately equal. As CT+QECT does not provide superior staging information as compared to CT+FDG-PET in patients with malignant nodules, patients with malignant nodules may require CT+QECT+FDG-PET in any case, thereby reducing the cost-savings associated with the CT+QECT strategy.
Remarks	The comparator for the incremental cost-effectiveness ratio is probably not realistic. The "no diagnostic intervention or treatment" will not be used in practical situations. Costs and outcomes of the comparator are not reported.

<table>
<tr><td>Author</td><td>Tsushima et al. 2004</td></tr>
<tr><td>Country</td><td>Japan</td></tr>
<tr><td>Design</td><td>Cost-effectiveness analysis
Decision model</td></tr>
<tr><td>Perspective</td><td>Not specified</td></tr>
<tr><td>Time window</td><td>Diagnostic process</td></tr>
<tr><td>Interventions</td><td>1. CT alone (comparator)
2. CT + FDG-PET
3. CT + FDG-PET + CT-guided needle biopsy in 80% and direct surgery in 20%
4. CT + CT-guided needle biopsy</td></tr>
<tr><td>Population</td><td>1000 individuals with SPNs</td></tr>
<tr><td>Assumptions</td><td>Prevalence of malignancy: 10%
Strategy 3: in case of positive CT and subsequent negative PET, 20% of the patients will undergo CT-guided needle biopsy and 80% will be followed up by unenhanced chest CT.
sensitivity and specificity derived from literature:
<table>
<tr><td></td><td>Sensitivity</td><td>Specificity</td><td>Cost</td></tr>
<tr><td>CT</td><td>0.99</td><td>0.63</td><td>US$ 129</td></tr>
<tr><td>FDG-PET</td><td>0.968</td><td>0.778</td><td>US$ 669</td></tr>
<tr><td>CT-guided needle biopsy</td><td>0.769</td><td>0.936</td><td>US$ 590</td></tr>
</table>
Follow-up strategy: unhenanced chest CT (frequency unclear)
Cost thoracotomy: 13398 US$
Complication rate CT-guided needle biopsy: 2,9% pneumothorax in which chest tube placement was necessary (literature - Japan)
Length of stay for treatment of pneumothorax: 6,3 days (literature)</td></tr>
<tr><td>Data source for costs</td><td>Thoracotomy: hospital bills of 10 procedures in one hospital (2002)
Diagnostic procedures: Ministry of Health (Nat. Health Insurance)</td></tr>
<tr><td>Cost items included</td><td>Chest CT without contrast enhancement: ¥15420 (US$ 129)
Surgical resection of SPN: ¥1607 (US$13398)</td></tr>
<tr><td>Data source for outcomes</td><td>Literature</td></tr>
<tr><td>Discounting</td><td>No</td></tr>
<tr><td>Costs</td><td>CT alone: US$6337/patient
CT+PET: US$3383/patient
CT+PET+Biopsy: US$2739/patient
CT+Biopsy: US$2573/patient</td></tr>
<tr><td>Outcomes</td><td>accuracy CT: 0,67
accuracy CT+PET:0,92
accuracy CT+PET+biopsy: 0,96</td></tr>
</table>

	accuracy CT+biopsy:0,95
Cost-effectiveness	incremental cost-accuracy ratio all strategies are dominant compared to CT alone at a prevalence level of 10%: lower costs and higher accuracy. CT+CT-guided needle biopsy was the most cost-effective approach (highest cost savings per unit of increase in accuracy)
Sensitivity analysis	Prevalence of malignancy: The higher the disease prevalence, the smaller the difference in costs between the different strategies Costs increase with higher prevalence of malignancy. At prevalence rates up to 55%, all strategies were dominant relative to CT alone Only at a prevalence of more than 80%, CT alone becomes cost-effective (higher accuracy for equal costs)
Conclusions	CT-guided needle biopsy and FDG-PET in addition to CT is potentially cost-effective in Japan. The advantage of CT+PET is that it is noninvasive, easy to perform, has few contra-indications, can be done in outpatient setting and has little co-morbidity. CT-guided biopsy is slightly more invasive, has some contraindications and some complications (e.g. pneumothorax, hemoptysis)
Remarks	The model assumes that all SPNs which are diagnosed as lung cancer are operated upon, regardless of cancer staging.

Diagnosis of Solitary Pulmonary Nodules + Staging of NSCLC

Author	Gugiatti et al. 2004		
Country	Italy		
Design	Cost-benefit analysis for SPN assessment Cost-effectiveness for staging of NSCLC Decision model		
Perspective	Servizio Sanitario Nazionale: Italian National Reimbursement System		
Time window	SPN: diagnostic process staging NSCLC: lifetime		
Interventions	SPN: X-ray CT versus CT+PET NSCLC: X-ray CT+PET if negative or indefinite diagnosis versus X-ray CT+diagnostic thoracotomy (mediastinoscopy) in all patients		
Population	Not specified		
Assumptions	1. Cost analysis SPN assessment Prevalence SPN: 25%		
		Sensitivity	Specificity
	CT	0,53	0,75
	PET	0,92	0,95
	Probability of CT-guided needle biopsy: 20% Probability of thoracotomy: 80% Probability pneumothorax without cardiac csqs during CT guided fine needle biopsy: 28% Probability pneumothorax with cardiac csqs during biopsy: 2% Probability pneumothorax and complications during thoracotomy: 0% 2. Cost-effectiveness analysis NSCLC staging Prevalence NSCLC: 30% (pre-test % of expected positive patient)		
		Sensitivity	Specificity
	CT	0,67	0,73
	PET	0,90	0,91
	Mortality PET 0% Mortality CT: 0.0025% Mortality thoracotomy: 3.0% Mortality Mediastinoscopic biopsy: 0.3 % Life expectancy NSCLC resectable: 7 years Life expectancy NSCLC unresectable: 0.5 year (Life expectancies from Gambhir et al. 2000 (valuable for a 64-year old white male))		
Data source for costs	Costs parameters from national tariffs (2nd analysis with tariffs from Lombardy; not presented in this table)		
Cost items included	National tariffs (ROD-DRGs): Pneumothorax without cardiac consequences: € 2255.37		

	Pneumothorax with cardiac consequences: € 4289.69 Thoracotomy: € 2680.93 Resectional surgery: € 7333.7 Mediastinoscopy pre-thoracotomy: € 2680.93 WB-PET: € 1071.65 CT (2 exams): € 275.8 Agobiopsy with CT: € 165,25
Data source for outcomes	Literature
Discounting	No
Costs	Cost analysis SPN assessment Expected reimbursement cost X-ray CT only: € 1598 Expected reimbursement cost SPN PET+CT: € 1550 -> Incremental savings: € 48
Outcomes	Cost-effectiveness of NSCLC staging Additional years of life calculated following Declining Exponential Approximation of Life expectancy (DEALE)
Cost-effectiveness	Cost-effectiveness of NSCLC staging Expected average cost per year of life X-ray CT+mediastinoscopy: € 1607 per year added Expected average cost per year of life CT + PET: € 1499 per year added -> difference: € 108 per year saved
Sensitivity analysis	Cost analysis of SPN assessment CT+PET only becomes more costly than CT for high values of CT sensitivity (above 70%) or for low percentages of surgical interventions (less than 69%) or for higher percentages of agobiopsy (>31%). One-way sensitivity analysis on prevalence, %biopsy, sensitivity, specificity PET & CT, %pneumothorax (w/ and w/o cardiac csqs): CT+PET is cost saving if: prevalence<31%, %biopsy<32%, sensit.PET>36%, spec.PET>85%, sens.CT<70%, spec.CT<77%, %pneumothorax between 20-50%, %pneumothorax+cc between 2-10% Cost-effectiveness of NSCLC staging One-way sensitivity analysis on prevalence, likelihood death in mediatinsocopy, sensitivity, specificity PET & CT CT+PET has a lower average cost-effectiveness ratio than CT+mediastinoscopy (< €1844/year of life gained) if **% malignancy<66%**, likelihood of death in mediatinoscopy in 0.1-0.5%, sensitivity of PET 60-90%, specificity of PET>51.4%, sensitivity CT 40-90%, specificity CT 50-90%, % pneumothorax between 20-50%, % pneumothorax+complications between 2-10% **(model only sensitive for parameter in bold)**
Conclusions	PET for SPN assessment Due to the high sensitivity and specificity of PET, a reduction of biopsies and thoracotomies for diagnostic purposes can be obtained. This reduction in turn has the indirect effect of reducing the number of complications arising from these invasive methodologies. Adding PET brings about a low but significant cost reduction for the Italian National Health Service. The costs of CT+PET compared to CT alone depend crucially on the prevalence of patients

	actually affected by pulmonary carcinoma and the distribution of patients between the 2 types of invasive investigation techniques (fine needle-biopsy and thoracotomy). PET for staging of NSCLC Due to the higher accuracy of the CT+PET strategy, there is a fall in mortality in relation to mediastinoscopy and surgical resection in unresectable patients. This makes the strategy cost-effective as compared to CT+mediastinoscopy. The model results are sensitive to variations in the percentage of positive (i.e. unresectable) patients.
Remarks	No incremental cost-effectiveness ratios were calculated. Cost-effectiveness was concluded based on average cost-effectiveness ratios. As outcomes in terms of life expectancy for each strategy were not reported, it is not possible to calculate the incremental cost-effectiveness ratio. Savings less evident compared with USA and Germany because of low values of surgical DRG's. Substitution of CT by PET is possible but unlikely as Italian surgeons always attend to have CT scan. CT prior to PET minimizes the number of patients with potential curative surgical resection excluded from this opportunity =>"conservative" model with higher costs

Staging of Non-Small Cell Lung Cancer

Author	Sloka et al. 2004				
Country	Canada				
Design	Cost-effectiveness analysis Decision model				
Perspective	Health care system				
Time window	From the initial diagnostic studies to the end of initial treatment				
Interventions	CT alone				
	CT + FDG-PET				
Population	Hypothetical cohort of 1000 65-year old patients with suspected NSCLC				
Assumptions	5-year survival rate: 44% (literature) 33,5% surgically unresectable (literature) sensitivity and specificity derived from literature (meta-analyses):				
		Sensitivity	Specificity	Cost	Mortality
	CT	0,67	0,73	290 CA$	0.0025%
	FDG-PET	0,91	0,96	1029 CA$	0%
	Biopsy	1	1	588 CA$	0.3%
	Mortality radiation therapy: 0% Mortality CT contrast material: 0,0025% Risk mortality surgical resection lung cancer: 3% Life expectancy of a 65 year old with resectable NSCLC is 4,6 years (calculated) Life expectancy of a 65 year old with unresectable NSCLC is 9-10 months (literature) Life expectancy of a 65 year old local population: 18.3 years				
Data source for costs	Literature (Canadian)				
Cost items included	PET: CA$1029 mediastinoscopy & biopsy: CA$588 lung resection surgery: CA$17521 treatment non-resectable NSCLC: CA$10474,98 Radiation therapy: CA$ 10475 price year 2000				
Data source for outcomes	Life expectancy: literature Unnecessary surgery avoided: results from the model				
Discounting	No				
Costs	CT alone: CA$17595/patient PET+CT: CA$16140/patient Cost saving PET+CT: CA$1455				
Outcomes	avoided unnecessary surgery: 9% life years gained: 3,1 days				

Cost-effectiveness	ICER not calculated due to clinical insignificance of the outcome difference in terms of life years gained Cost-benefit: $1455 per patient
Sensitivity analysis	outcomes in terms of avoided surgery highly depend on accuracy of biopsy, assumed to be 100% PET+CT less costly than CT alone as long as disease prevalence >12,9%, PET cost <$2484, surgery cost >$1729, CT sensitivity <86,3%, PET sensitivity >37,8% PET+CT offers better life expectancy than CT alone as long as disease prevalence >2,8%, CT sensitivity <97,9%, PET specificity >35,4% All the described scenarios are met in reality.
Conclusions	CT+PET is a cost-effective approach to determining the management of NSCLC.
Remarks	Cost items not included: cost of palliative care, chemotherapy, cost of emotional support

Author	Gambhir et al.1996		
Country	US		
Design	Cost outcome description/cost-benefit analysis Decision analytic model		
Perspective	Institutional		
Time window	Lifetime		
Interventions	2 models are considered: Conservative model: CT alone versus CT+PET: all patients have anatomical CT prior to surgery and/or biopsy and every patient who is PET positive (regardless of CT results) gets a biopsy to confirm unresectability Less conservative model: CT alone versus CT+PET: if CT and PET positive: inoperable; CT and PET negative: surgery; discordant results: biopsy.		
Population	64-year old man with 2.3-cm lung cancer		
Assumptions		Sensitivity	Specificity
	CT	0.67	0.73
	PET	0.90	0.91
	Prevalence: 31% Mortality PET: 0% CT: 0.0025% Surgery: 3.0% Biopsy: 0.3% Morbidity Surgery: 0.083 years Biopsy: 0.007 years Life expectancy Surgical cure: 7.0 years Unresectable disease: 1.0 year		
Data source for costs	Billed costs in one institution		
Cost items included	Thoracic CT: US$ 700 Thoracic PET: US$ 1200 Biopsy: US$ 3000 Surgery: US$ 30000		
Data source for outcomes	Literature Life expectancy: calculated using the Declining Exponential Approximation of Life Expectancy (DEALE)		
Discounting	Unclear		
Costs	CT alone: US$ 25 634 CT+PET: US$ 24 480		

<table>
<tr><td></td><td colspan="3">-> savings: US$ 1 154 per patient
2. CT alone: US$25 634
CT+PET: US$ 23 367
->savings of CT+PET relative to CT alone: US$ 2 267 per patient</td></tr>
<tr><td>Outcomes</td><td colspan="3">Incremental life expectancy of CT+PET relative to CT alone: 2.96 days</td></tr>
<tr><td>Cost-effectiveness</td><td colspan="3">Not assessed</td></tr>
<tr><td>Sensitivity analysis</td><td colspan="3">One-way sensitivity analysis – threshold sensitivity analysis: search for cut-off values beyond which CT+PET is the strategy of choice when trying to minimize costs (generate savings) or maximize life expectancy.

Model 1 (conservative):
PET+CT better life expectancy, resp. cost saving if</td></tr>
<tr><td></td><td>Better life expectancy</td><td>Cost saving</td></tr>
<tr><td>Prevalence</td><td>>5.6%</td><td>>16.9%</td></tr>
<tr><td>CT sensitivity</td><td><95.7%</td><td><82.3%</td></tr>
<tr><td>PET sensitivity</td><td>>11.9%</td><td>>48.2%</td></tr>
<tr><td>PET specificity</td><td>>31.7%</td><td>>12.3%</td></tr>
<tr><td>Mortality PET</td><td><0.16</td><td></td></tr>
<tr><td>Mortality biopsy</td><td><2.3%</td><td></td></tr>
<tr><td>Morbidity biopsy</td><td><0.066</td><td></td></tr>
<tr><td>Cost PET</td><td></td><td><US$ 2 354</td></tr>
<tr><td>Cost biopsy</td><td></td><td><US$ 11 398</td></tr>
<tr><td>Cost surgery</td><td></td><td>>US$ 17 485</td></tr>
<tr><td colspan="3">Model 2 (less conservative):
PET+CT better life expectancy, resp. cost saving if</td></tr>
<tr><td></td><td>Better life expectancy</td><td>Cost saving</td></tr>
<tr><td>Prevalence</td><td>>76.3%</td><td>>6.4%</td></tr>
<tr><td>CT specificity</td><td>>96.7%</td><td></td></tr>
<tr><td>PET sensitivity</td><td></td><td>>23.0%</td></tr>
<tr><td>PET specificity</td><td>>98.7%</td><td></td></tr>
<tr><td>Cost PET</td><td></td><td><US$ 3 466</td></tr>
<tr><td>Cost surgery</td><td></td><td>>US$ 9 191</td></tr>
<tr><td>Conclusions</td><td colspan="3">The model shows that CT+PET is cost saving and has a marginal increase in life expectancy as compared to CT alone over a wide range of values for the uncertain model input variables.</td></tr>
<tr><td>Remarks</td><td colspan="3">The model actually does not examine the cost-effectiveness of CT+PET. Instead, it models the costs of CT+PET and the effects, without bringing the two outcomes together.
Costs and outcomes of the two models are not fully presented. The sensitivity analyses look at the threshold values of uncertain parameters for one outcome: either costs or life years gained.
The study, which is published early 1995, still has many methodological weaknesses as far as</td></tr>
</table>

	the economic analysis is concerned. The model, though, may be a useful basis for studies that wish to examine the cost-effectiveness of PET-strategies for staging of NSCLC and has therefore been replicated by other authors.

Author	Dietlein et al, 2000		
Country	Germany		
Design	Cost-effectiveness analysis Decision analytic model		
Perspective	Healthcare system		
Time window	Lifetime		
Interventions	A. CT (conventional strategy=comparator) B. PET when normal size mediastinal lymph nodes C. PET D. PET without supplementary mediastinoscopy when both CT and PET positive for mediastinal lymph nodes E. PET without supplementary mediastinoscopy when PET alone positive for mediastinal lymph nodes		
Population	Hypothetical cohort of 62-year old men with NSCLC histologically established and assessed as locally respectable by thoracic CT and bronchoscopy		
Assumptions	Prevalence N2/N3 in locally respectable NSCLC: 30% (10% - 60%) Probability of upstaging to M1 by using PET after CT: 5% (0% - 5%) (Se: 93% - Sp: 98%) downstaging:11%. Use of Mediastinoscopy in patients with normal-sized mediastinal lymph nodes: 42% (0% - 100%) Mortality surgery: 3.7% Mortality mediastinoscopy: 0.5% Recurrence after curative resection: 38% (after 4 years) Morbidity surgery: 0.1 year Morbidity mediastinoscopy: 0.02 year		
	((*) pooled from literature)	Sensitivity	Specificity
	PET normal-sized mediastinal lymph nodes	73.9% (59% - 79%) (*)	96.5% (80% - 100%) (*)
	PET enlarged mediastinal lymph nodes	95.4% (81% - 100%) (*)	75.7% (61% - 81%) (*)
	CT	60%	77%
	Mediastinoscopy	72% (62% - 87%)	100%
	Life Expectancy	M0	M1
		N0/N1	N2/3
	Surgery	4.5 years	1.8 years	0.5 years
	Palliative	2.6 years	1.8 years	0.5 years
Data source for costs	Costs reimbursed by german public health provider in 1999.		

<table>
<tr><td>Cost items included</td><td colspan="7">Reimbursement:

CT: € 585
Whole-body FDG PET: €1227 (627 – 1827)
Mediastinoscopy (hospitalization): € 1138 (3 days)
Surgery: € 11656 (11 days + 3 ICU days)
Palliative: € 11378 (5689 – 22756) (30 days)</td></tr>
<tr><td>Data source for outcomes</td><td colspan="7">Life expectancy and survival rates calculated from data taken from literature (Gambhir and Cummings method: life expectancy = 1 / (annual mortality rate general population + annual mortality rate of disease)).</td></tr>
<tr><td>Discounting</td><td colspan="7">5%</td></tr>
<tr><td>Costs</td><td colspan="7">cf. costs-effectiveness analysis</td></tr>
<tr><td>Outcomes</td><td colspan="7">cf. costs-effectiveness analysis</td></tr>
<tr><td rowspan="7">Cost-effectiveness</td><td>Strategy</td><td>Life Expencta ncy</td><td>Costs</td><td colspan="3">ICER (in €/LYS)</td><td></td></tr>
<tr><td></td><td></td><td></td><td>vs A</td><td>vs B</td><td>vs C</td><td></td></tr>
<tr><td>A</td><td>3308 LYS</td><td>€ 16890</td><td></td><td></td><td></td><td></td></tr>
<tr><td>B</td><td>3322 LYS</td><td>€ 16892</td><td>143</td><td></td><td></td><td></td></tr>
<tr><td>C</td><td>3328 LYS</td><td>€ 17112</td><td>11100</td><td>36667</td><td></td><td></td></tr>
<tr><td>D</td><td>3282 LYS</td><td>€ 16279</td><td></td><td>15325</td><td>18109</td><td>saving / lowering LE</td></tr>
<tr><td>E</td><td>3255 LYS</td><td>€ 15839</td><td></td><td>15716</td><td>17438</td><td>saving / lowering LE</td></tr>
<tr><td rowspan="2">Sensitivity analysis</td><td colspan="7">One-way sensitivity analyses of the following variables:</td></tr>
<tr><td colspan="7">Pretest Probability of N2/N3: 10%, 20%, 40%, 50%, 60%.

=> B remains dominant (ICER B-A <0) when Prob>=30%, ICER C-B > €/LYS 50000, D & E should only be considered if Prob > 50% (ICER> 50000 saved per Life year lost).

Sensitivity and Specificity of FDG-PET for detecting metastases in normal-sized and mediastinal lymph nodes: -15%, -10%, -5%, +5%

=> B remains dominant when Sp and Se lowered.

Thoracic PET in place of whole-body scan

=> Acceptable only in strategy B (ICER Whole-body PET much better than thoracic PET): 143 €/LYS versus 28000).

Use of mediastinoscopy (0% or 100%) in conventional strategy A (patients with normal-sized lymph nodes) or sensitivity modification: -10%, -5%, +5%, +10%, 15%.

=> B remains the most cost-effective strategy.

Reimbursement of FDG-PET (-600, -400, -200, +200, +400, +600)

=> ICER B-A <0 when reimbursement below € 1225. If reimbursement above € 1460, ICER C-B > € 50000.

Reimbursement of palliative therapy (x2, x0.5)

=> No change of ICER ranges.</td></tr>
<tr><td>Conclusions</td><td colspan="7">Costs of selective use of PET in patients with normal-sized mediastinal lymph nodes being</td></tr>
</table>

	nearly compensated by the appropriate selection for beneficial surgery makes it clearly cost-effective.(strategy B) Cost-effectiveness analysis appears robust for a wide range of assumptions. In patients with enlarged mediastinal lymph nodes PET would be cost-effective if the test parameters from literature could be transferred directly to daily routine practice (strategy C). From a point of view of cost-effectiveness, a positive PET for N2/N3 staging cannot replace mediastinoscopy or histological verification (strategies D & E).
Remarks	Direct costs only Productivity gains excluded. The analysis was applied to full ring PET. Implemenation of PET would lead to an estimated increased cost of less than € 1per patient for the public health provider. Transferring the diagnostic efficacy from controlled studies to routine user, keeping it cost-effective, would need obligatory protocol for data acquisitions Further clinical trials should help to validate results.

Author	HTA report HTBS, 2002		
Country	Scotland		
Design	Cost-utility analysis Decision analytic model (based on Dietlein et al. 2000)		
Perspective	NHS Scotland		
Time window	Lifetime		
Interventions	send all patients to surgery without further testing (hypothetical intervention to show limits of model, not in clinical practice) send all patients to non-surgical treatment without further testing (hypothetical) all patients to mediastinoscopy, if negative: surgery, if positive: non-surgical treatment (current practice) all patients to mediastinoscopy, if negative: PET (if neg: surgery; if pos: non-surgical treatment), if positive: non-surgical treatment all patients to PET, if negative: surgery, if positive: non-surgerical treatment all patients to PET, if negative: mediastinoscopy (if neg: surgery; if pos: non-surgical treatment), if positive: non-surgical treatment all patients to PET, if negative: surgery, if positive and distant metastasis: non-surgical treatment, otherwise: mediastinoscopy (if neg: surgery, if pos: non-surgical treatment)		
Population	Hypothetical cohort of 100 62-year olds fit for either surgery or non-surgical treatment		
Assumptions	**Prevalence** of N2/N3: 30% Mortality: CT and PET: 0% Mediastinoscopy: 0.5% Surgery: 3.7% Life expectancy after surgery: N0/1, M0: 4.5 years N2/3, M0: 1.8 years M1: 0.5 years Life expectancy after palliation: N0/1, M 0: 2.6 years N2/3, M0: 1.8 years M1: 0.5 years Utility: N0/N1, M0, surgical treatment: 0.88 N0/N1, M0 non-surgical treatment; N0-3, M0-1 non-surgical treatment and N2-3, M0-1 surgical treatment: 0.65		
		Sensitivity	Specificity
	PET	86% if CT negative 92% if CT positive	90% if CT negative 76% if CT positive
	Mediastinoscopy	72%	100%
Data source for costs	HTBS calculations		

<table>
<tr><td>Cost items included</td><td colspan="4">FDG-PET: £ 677
Mediastinoscopy: £ 375
Surgery: £ 3 419
Radical radiotherapy: £ 2 120
Chemotherapy: £ 4 003
Best supportive care: £ 3 371
Price year: 2002-2003</td></tr>
<tr><td>Data source for outcomes</td><td colspan="4">Literature</td></tr>
<tr><td>Discounting</td><td colspan="4">Costs: 0%
Outcomes: 1.5%</td></tr>
<tr><td>Costs</td><td colspan="4">Cfr. Cost-effectiveness results</td></tr>
<tr><td>Outcomes</td><td colspan="4">Cfr. Cost-effectiveness results</td></tr>
<tr><td rowspan="15">Cost-effectiveness</td><td colspan="4">For CT-positive patients:
Comparator: strategy 3 (least costly strategy: cost = £191 295; Outcomes: 71.86 QALYs)</td></tr>
<tr><td></td><td>Incremental cost</td><td>Incremental QALYs</td><td>ICER</td></tr>
<tr><td>Strategy 1</td><td>£ 5 952</td><td>-2.05</td><td>Dominated by 3</td></tr>
<tr><td>Strategy 4</td><td>£ 12 425</td><td>-5.83</td><td>Dominated by 3</td></tr>
<tr><td>Strategy 6</td><td>£ 13 862</td><td>-5.71</td><td>Dominated by 3</td></tr>
<tr><td>Strategy 7</td><td>£ 14 803</td><td>0.25</td><td>£ 58 951/QALY</td></tr>
<tr><td>Strategy 5</td><td>£ 1 592</td><td>-5.94</td><td>Dominated by 7</td></tr>
<tr><td>Strategy 2</td><td>£ 3 440</td><td>-27.66</td><td>Dominated by 7</td></tr>
<tr><td colspan="4">For CT-negative patients:</td></tr>
<tr><td colspan="4">Comparator: strategy 1 (least costly strategy: cost = £293 127; Outcomes: 189.01 QALYs)</td></tr>
<tr><td></td><td>Incremental cost</td><td>Incremental QALYs</td><td>ICER</td></tr>
<tr><td>Strategy 3</td><td>£11,501</td><td>0.62</td><td>£18,589</td></tr>
<tr><td>Strategy 7</td><td>£11,490</td><td>1.45</td><td>£7,909</td></tr>
<tr><td>Strategy 5</td><td>£2,949</td><td>-8.98</td><td>Dominated by 7</td></tr>
<tr><td>Strategy 6</td><td>£17,727</td><td>-9.57</td><td>Dominated by 7</td></tr>
<tr><td>Strategy 4</td><td>£18,573</td><td>-9.67</td><td>Dominated by 7</td></tr>
<tr><td>Strategy 2</td><td>£82,071</td><td>-95.26</td><td>Dominated by 7</td></tr>
<tr><td>Sensitivity analysis</td><td colspan="4">For CT-positive patients: Assuming improved accuracy of PET in detecting M1 disease has the greatest effect upon the ICER. If PET is as accurate at detecting M1 disease as it is at detecting N2/3 disease, the ICER of moving from strategy 3 to strategy 7 in CT-positive patients is £30 881 per QALY.
For CT-negative patients: within all sensitivity analyses, strategy 7 is cost-effective compared with strategy 3.</td></tr>
<tr><td>Conclusions</td><td colspan="4">Three treatment strategies stand out in terms of either better outcomes, lower costs or both: strategy 1 (hypothetical), strategy 3 (no PET, current practice) and strategy 7 (with PET).
The principle potential benefit of PET scanning is to limit the number of futile operations carried out. Strategy 7 is cost-effective in CT-negative patients: strategy 3 produces roughly</td></tr>
</table>

	double the number of futile operations and slightly fewer correct operations than strategy 7. PET is not equally cost-effective in CT-positive patients: only around 1% of the patients would avoid futile operations when strategy 7 would be employed as compared to strategy 3.
Remarks	

Author	Verboom et al 2003
Country	Netherlands
Design	RCT
Perspective	Hospital
Time window	1 year
Interventions	1. Conventional Work-up (CWU) alone 2. PET + CWU
Population	188 patients with suspected or proven NSCLC, potentially resectable on basis of clinical staging (randomly assigned).
Assumptions	
Data source for costs	Method bottom-up applied on real costs in one centre of the RCT (incl. expensive-university PET variant). In between & cheap PET variants based on expert opinions.
Cost items included	X-ray € 35 (33-35) Abdominal ultrasound € 57 (24-74) Bone scan € 199 (170-260) CT € 123 (92 – 175) MRI € 229 (169 – 290) Bronchoscopy € 394 (349 – 440) Video Assisted Thoracic Surgery € 244 (202-333) Mediastinoscopy € 400 (383 – 433) Surgery € 1408 (1275 – 1797) Hospital day € 220 (187 – 216) ICU day € 1080 (898 – 1238) PET 3 variants: cheap (12 scans a day – NM department community hospital) € 736 In between (8 sc. A day – community hospital with on-site cyclotron) € 1020 Expensive (8 sc. A day – university with on-site cyclotron and function research) € 1588
Data source for outcomes	
Discounting	No
Costs	Operated patients € 11486 +/- 12628 SD p. patient CWU (Avg futile € 12473, non futile € 10489) € 10709 +/- 7727 SD p. patient CWU+PET (futile € 13689, non futile € 9487) Non-oper. patients € 1287 +/- 1609 SD per patient CWU € 3736 +/- 4137 SD per patient CWU + PET All patients € 9573 +/- 12072 SD per patient CWU € 8284 +/- 7462 SD per patient CWU + PET
Outcomes	Futile surgery CWU + PET: 21% (39/96) versus 41%(19/92) for CWU alone group. =20% absolute difference (95% CI:9% - 28%) or 5 patients undergoing PET to avoid 1 futile

	thoracotomy (95%CI : 3-14)
Cost-effectiveness	
Sensitivity analysis	PET outcome efficacy: between 3 PET to avoid 1 and 14 PET to avoid 1, the cost difference ranges from €759 to €2123 in favor of PET+CWU; even at 1 surgery prevented for 3 PET (9%), cost of the group CWU alone is still higher. Variants on PET scan per patient cost: PET-CWU remains favourable up to the break-even point of € 2350 per PET. When highest PET scan price (€ 1588) and worst efficacy (36 futile operations remaining after PET) were taken into account, CWU arm was more favourable (€ 542).
Conclusions	The additional use of PET in staging of patients with NSCLC is feasible, safe and cost-saving from a clinical and an economic perspective Major costs drivers were hospital days, post-operative ICU care and operation itself. The one-way sensitivity analysis on efficacy or setting of PET showed the results were robust. But highest PET scan price and worst efficacy make CWU arm was more favourable (€ 542).
Remarks	Therapeutic interventions as chemotherapy and radiotherapy were not taken into account in the costs. Some operations were refused by the patient. Among this population of potentially respectable, some had severe co-morbidity or tumour type for which surgery was not optimal (these belonged thus to the non-operated group) One outlier operated patient in the CWU group stayed 61 days in the ICU.

Author	HTA report AETMIS, 2003		
Country	CANADA (Québec)		
Design	Cost-effectiveness analysis Decision analytic model		
Perspective	Healthcare system		
Time window	1 year		
Interventions	CT alone for mediastinal metastases (mediastinoscopy If positive, surgery if negative) CT for mediastinal metastases first + PET (for distant metastases if CT positive, for mediastinal metastases if CT negative). PET results confirmed by biopsy (distant metastases) and mediastinoscopy (mediastinal metastases).		
Population	Hypothetical cohort of 100 65-year olds with NSCLC confirmed and negative metastatic diagnosis		
Assumptions	Prevalence of N2/N3: 31% (28% - 38%) Mortality: CT: 0.0025 % (0% – 1%) Surgery: 3% (0% - 20%) Life expectancy after surgery: 7 years (1 - 15) Life expectancy after palliation: 1 year (0.1 - 2)		
		Sensitivity	Specificity
	CT PET	75% (60% - 90%) mediastinal:91% (81% - 100%) distant: 82% (64% - 100%)	66% (55% - 77%) mediastinal:86%(78% - 94%) distant: 93% (88% - 98%)
	Biopsy	100%	100%
Data source for costs	Honorarium (tariffs) and costing from Manuel des Médecins spécialistes du Québec and APR-DRG 1998-1999 reimbursement databank		
Cost items included		Tariffs	Hospital stay (APR-DRG)
	Biopsy CT Mediastinoscopy PET Surgery Biopsy+mediastinoscopy+surgery	CA$ 75 CA$60 CA$280 CA$250 CA$672	CA$ 6130 (5517 – 6743) CA$ 5054 (4977 – 7932) CA$ 8424 (7544 – 11781) CA$ 9163 (7609 – 12147)
	FDG-PET: CA$ 1313		
Data source for outcomes	Life-expentancy following Declining Exponential Approximation of Life Expentacy		
Discounting	No		

Costs	CT CA$ 8455 CT + PET CA$9723
Outcomes	CT 4551 life years CT + PET 4823 life years 12% surgery avoided
Cost-effectiveness	Incremental Cost CT + PET: CA$ 1268 Incremental Effectiveness CT + PET: 0.27 year Incremental Cost-effectiveness Ratio CT + PET: CA$ 4689 per life year gained (CA$ 1983 without PET capital investment)
Sensitivity analysis	- One-way analysis : ICER stays superior in case of CT + PET (ICER between CA$ 3000 – CA$ 7000) - Monte-Carlo 1000 simulation: 95% simulated ICER < CA$ 50000 (50% < CA$ 5000).
Conclusions	PET is a cost-effective technique in Québec for this indication requiring an acceptable investment per life year gained. The intermediary measure is the mortality reduction by surgery. On short term, PET is not likely to increase survival of lung cancer patients, but may improve quality of life, avoiding impairing useless surgery, reducing waiting lists and allow more participation from patient in management. Studies about quality of life and patients preferences should be developed. ICER may be lower as PET capital expenditure should also be incremented on other indications
Remarks	Costs of radiotherapy and chemotherapy not included

Author	Kosuda et al. 2000		
Country	Japan		
Design	Cost-effectiveness analysis – decision analytic model		
Perspective	Not specified (National reimbursement system? Hospital?)		
Time window			
Interventions	1. Chest CT alone 2. Chest CT+PET		
Population	1000-patients simulation with suspected NSCLC, stage IIIB or less		
Assumptions	Lung cancer Prevalence:71.4% (in hospital, based on 56 pts with PN in 1 year) Lymph node (N3) Prevalence: 31% *Mortality PET 0% *Mortality CT: 0.0025% *Mortality thoracotomy: 3.0% *Mortality Mediastinoscopic biopsy: 0.3 % *Life expectancy surgical cure: 7 years *Life expectancy radiotherapy in patients with N3: 1 year *Life expectancy no therapy in patients with curable cancer: 1 year *Life expectancy radiotherapy in patients with curable cancer: 2 years *Life expectancy surgical cure: 7 years		
		PET	CT
	Sensitivity detection lung cancer	96.3%	Not incorporated*
	Specificity detection lung cancer	78.6%	Not incorporated
	Sensitivity lymph nodes	90%	67%
	Specificity lymph nodes	91%	73%
	Accuracy mediastinoscopy: 100% * chest CT findings have hardly any influence on the diagnosis of lung cancer in the hospital and therefore this is not incorporated in the model.		
Data source for costs	Outpatient & inpatient bills in hospital (April 1996-March 1997)		
Cost items included	Bronchofibroscopy ¥74,150 $ 530 Mediastinoscopy ¥120,450 $ 860 Outpatient examinations (malignant) ¥79,682 $ 569 Outpatient examinations (benign) ¥53,003 $ 379 Thoracotomy (malignant) ¥2,292,768 $16,377 Thoracotomy (benign) ¥1,165,284 $ 8,323 ¥140=$ 1		
Data source for outcomes	Observational data from one hospital Literature		
Discounting	No		
Costs	Expected incremental cost: ¥ 132000 (US$943)		

Outcomes	Expected life expectancy gain: 0.607 year/patient for CT+PET
Cost-effectiveness	Expected-cost per life year gained (*if cost of 1 PET = ¥ 100000*): ¥218000 (US$1557)
Sensitivity analysis	Sensitivity analysis on cost of FDG-PET (NB: before introduction of approbation by the Ministry) Sensitivity Analysis on FDG-PET specificity diagnosis of lung cancer & Sensitivity FDG-PET diagnosis of N3 (because variation from hospital to hospital): marginal costs decreases with both BUT life expectancy gain stable Two-way sensitivity analysis Prevalence of malignant disease from 10% to 90%: large variation of marginal cost and life expectancy gain. If prevalence is 40%, costs are equal; at a prevalence of 50%, life expectancy gain of CT+PET is 0.
Conclusions	CT+FDG-PET is unlikely to be cost-saving in Japan. NSCLC patients would gain 7.3 months of life for an outlay of US$943.
Remarks	Chest CT sensitivity (100%) was not included because of low level of specificity (57.9%) - Chest CT findings have hardly any influence on the diagnosis of lung cancer in the hospital Depreciation of PET, personnel expenses and overhead costs were not taken into account, the first two are estimated to total approximately ¥ 20000 per examination. In the discussion it is stated that depreciation and personnel expenses should be counterbalanced by the avoided mediastinoscopic costs Lung cancer prevalence data and success rate of transbronchial lung biopsy were obtained from observational data of 56 patients with pulmonary nodules. Question is how representative this is for the actual prevalence of lung cancer. Impact of this assumption tested in sensitivity analyses.

Author	Verboom et al. 2002
Country	Netherlands
Design	Decision model
Perspective	Direct costs made within the healthcare sector, real resource use
Time window	Diagnosis until surgery or follow-up
Interventions	Current: current diagnosis strategy PET1: Current + PET in initial diagnosis phase PET2: Current + PET after imaging but prior to invasive staging (mediastinoscopy) PET3: Current + PET after imaging & mediatinoscopy (only patients eligible for surgery are diagnosed by PET)
Population	Observational data: 117 patients with suspicion of NSCLC of which 10 patients were excluded because they were eligible for surgery but not operated on because of other medical reasons.
Assumptions	Accuracy PET1 and PET2 = 80% Accuracy PET3 = 75%
Data source for costs	Diagnostic tests (CT, Bone scan, MRI, Bronchoscopy, Mediastinoscopy) and operation: observational data from all consecutive patients with NSCLC diagnosed in 1993-1994 in two hospitals PET-scan: calculations based on data from one PET centre (6 PET/day; 1500 PET/year, cyclotron on site)
Cost items included	Manpower, materials, equipment, overhead Hospital day: € 216 (€1=2.2037 GLD) IC day: € 1163 Ultrasound of abdomen: € 68 CT scan: € 123 Bone scan: € 243 MRI: € 185 Bronchoscopy (flexible): € 62 Bronchoscopy (rigid): € 167 Mediatin oscopy: € 361 PET: € 1588
Data source for outcomes	Outcome measure: accuracy of diagnostic strategy (avoided futile surgical interventions); source: literature
Discounting	No
Costs	Without substitution of other diagnostic procedures by PET: PET1: incremental cost of initial staging € 1588/patient (incremental total costs not presented) PET2: incremental total cost of € 221/patient PET3: incremental total savings of € 146/patient
Outcomes	PET1 decreases the number of futile operations from 38 to 17 PET2 decreases the number of futile operations from 13 to 8 in patients who have had mediatinoscopy

	PET3 decreases the number of futile operations from 38 to 17
Cost-effectiveness	Not presented
Sensitivity analysis	
Conclusions	Introduction of PET will inevitably lead to an increase in staging costs, irrespective of the strategy. By declining the number of futile operations, the total costs can be contained. PET1 significantly increases the costs of initial staging but avoids many futile operations. PET2 costs less but avoids less futile operations. From a cost point of view, the evaluation of PET in a strategy after diagnosis imaging but prior to invasive staging seems most optimal.
Remarks	Costs of subsequent therapeutic interventions were excluded (chemotherapy, radiotherapy). The relevance of some of the analyses is doubtful. The explanation does not allow a clear understanding of the goal and relevance of the analyses. E.g. what does it mean that PET substitutes 50% of the diagnostic procedures and how realistic is it to assume that this will not impact upon the accuracy of the diagnostic process?

Author	Abe et al. 2003		
Country	Japan		
Design	Cost-benefit analysis – Decision analytic model		
Perspective	National reimbursement system		
Time window	Lifetime		
Interventions	Conventional Imaging (CT, MRI, Bone scintigraphy) Chest FDG-PET, followed by Whole-body FDG-PET + Brain MRI if positive		
Population	Hypothetical cohort of 1000 patients suspected of having NSCLC in each branch		
Assumptions	Prevalence of cancer: 75% Prevalence of metastasis: 2 hypothesis: 20% or 40% Life expectancy benign disease: 28.2 years Life expectancy NSCLC surgical cure: 7 years Life expectancy NSCLC Follow-up in pts with surgically curable disease: 1 year Life expectancy NSCLC Follow-up/chemo/thoraco pts with metastasis: 0.5 year Mortality PET: 0% Mortality CT: 0.0025% Mortality thoracotomy: 3%		
		Sensitivity	Specificity
	Conventional imaging	90%	90%
	Chest PET	96.3%	78.6%
	WB PET and brain MRI	90%	90%
	Accuracy biopsy: 100%		
Data source for costs	Insurance reimbursement system bills		
Cost items included	Bone scan: ¥ 41490 Brain MRI with contrast: ¥ 30670 Abdominal CT with contrast: ¥ 33540 FDG-PET: ¥ 75000 (=$ 625) Thoracotomy: ¥ 331450 Excisional biopsy: ¥ 32450 ¥120=$ 1		
Data source for outcomes	Literature		
Discounting	No		
Costs	Cost-savings: Net costs minus costs of hospitalization, radiotherapy and chemotherapy Cost savings: $ 697.69 (preval.metas.20%) - $ 683.52 (preval.metas.40%)		
Outcomes	Gain in life expectancy/patient: 0.04 years (11.06-11.02) (prev.metas. 20%) - 0.10 years (10.13 -10.03) (prev.metas 40%)		
Cost-	Cost of PET per patient in case of prevalence of NSCLC <80%: $ 1322.68/patient		

effectiveness	
Sensitivity analysis	Uncertain parameters: prevalence of NSCLC Prevalence of distant metastasis 20% Prevalence of distant metastasis 40% Expected cost savings and expected life expectancy decrease as NSCLC increases Break-even point at 80%: prevalence of NSCLC must be <80%in order for the WB-FDG-PET to gain Life expectancy Cost (reimbursement) of FDG-PET examination per patient is $ 1322.68 (with prevalence NSCLC 75% - prevalence distant metas 20%)
Conclusions	Conventional imaging: low NSCLC prevalences result in high costs because all patients with benign disease will end up undergoing unnecessary thoracotomies. The WB-PET strategy reduced the number of benign disease thoracotomies to approximately 20% (==> cost savings). Whole-Body FDG-PET is cost-effective in the Japanese insurance reimbursement system (present cost very low from the industrial point of view).
Remarks	The decision-tree does not include Chest CT scan, transbronchial lung biopsy & transcutaneous needle biopsy (reim.PET limited to patients suspected of lung cancer who Mediastinoscopy was not included as japanese practioners do not perform it or less often Hospital charge and costs related to examinations and surgical procedures were not included.

Assessment myocardial viability

Author	HTA report AETMIS, 2003		
Country	CANADA (Québec)		
Design	Cost-effectiveness analysis Decision analytic model		
Perspective	Healthcare system		
Time window	5 years		
Interventions	Thallium test: if positive => revascularization, if equivoqual=> clinical decision (medical treatment or transplantation). Thallium test + PET =>idem.		
Population	Hypothetical cohort of patients with less than 30% left ventricular ejection fraction		
Assumptions	5 years Survival Probability : Revascularization: 80% Medical treatment: 50% Transplantation: 75% Medical treatment probability: 60% - 95%. Non equivoqual Thallium test probability: 30% - 40% Myocardial viability probability after equivoqual Thallium test (first strategy): 15% - 30% Myocardial viability probability after equivoqual Thallium test (Thallium + PET): 50%		
Data source for costs	Honorarium (tariffs) and costing from Manuel des Médecins spécialistes du Québec, APR-DRG 1998-1999 reimbursement databank and expert opinions		
Cost items included		Tariffs	Hospital stay (APR-DRG)
	Thallium test PET Revascularization	CA$94.4 CA$225 - 275	 CA$ 8262 -10099
	FDG-PET: CA$ 1050 – 1575 Thallium test: CA$ 315 -385 Medical treatment: $CA 16000 - 24000 Transplantation: $CA 48000 - 72000		
Data source for outcomes	Average 5 years Survival Probability after medical treatment, revascularization or transplantation		
Discounting	No		
Costs	Thallium test: CA$ 10547 - 29993 Thallium test + PET: CA$ 10119 - 24753		
Outcomes	Thallium test: 63% - 71% 5 years survival probability Thallium test+ PET: 69% - 73% 5 years survival probability		
Cost-effectiveness	Incremental Cost Thallium test + PET: CA$ -7182 – (+)687		

	Incremental Effectiveness Thallium test + PET: 2% - 7%.
Sensitivity analysis	- Monte Carlo 1000 simulation: 95% simulated ICER < 0 (costs saving with higher effectiveness). - Sensitivity analysis of constant (uniformly distributed) variables shows no effect on results
Conclusions	Thallium test + PET may be very cost-effective. [This strategy may avoid coronarographies in case of perfusion examination]
Remarks	Direct costs only Transplantation costs do not include organ acquisition and coordination costs. Limited population and limited hypotheses

Miscellaneous: Diagnosis SPN, staging NSCLC, axillary staging breast cancer, recurrency colorectal cancer, assessment myocardial viability

Author	Miles et al. 2001
Country	Australia
Design	Cost-benefit analysis and cost-effectiveness analysis Based on published decision models (e.g. ICP and Gambhir for SPN) and adjusted for Australian data on costs and specificity of PET Based on published cost-effectiveness analyses based on actual experience
Perspective	Not specified
Time window	Following the published model
Interventions	Solitary Pulmonary Nodes: Model ICP (1994): PET alone versus CT alone Model Gambhir (1998) and observations Valk et al. (1996): CT alone versus CT+FDG-PET Preoperative staging of lung cancer Model Gambhir (1998) and observations Valk et al. (1996): CT alone versus CT+FDG-PET Axillary staging of breast cancer (ICP model and observational analysis of Adler et al. 1997): Comparator for PET unclear Preoperative evaluation of recurrent colorectal cancer (ICP model and observational analysis of Valk et al. 1996, Lai et al. 1996 and Debelke et al. 1997) CT+PET versus CT alone Assessment of myocardial viability (ICP model and observational analysis of Beanlands et al. 1997) Coronary angiography alone versus PET+coronary angiography (??)
Population	As in the published models or analyses
Assumptions	pneumothorax rate: 5%
Data source for costs	Diagnostic procedures: Medicare Benefits Schedule In-patient care: National Hospital Cost Data Collection AN-DRG PET scan: operational cost of one PET centre
Cost items included	PET scan: A$ 950 CT scan: A$ 412.70 Chest/abdomen needle biopsy: A$1107.08-1109.60 Thoracotomy: A$ 7462.59 Mediastinoscopy A$2466 Lung resection: A$ 7539.25 (weighted sum of uncomplicated, minor cc and major cc DRG) Mastectomy&axillary node dissection: A$ 4399 Partial mastectomy: A$ 2365 Laparotomy w/o resection: A$ 2636

	Laparotomy w/ resection: A$ 8262.60
Data source for outcomes	As in the published models or analyses
Discounting	Unclear
Costs	Solitary Pulmonary Nodules Decision analyses CT: A$ 5813.54 /patient (Gambhir) - 6169.26 A$/patient (ICP) PET: A$ 5663.76 /patient (ICP) CT+PET: A$ 4878.77 /patient (Gambhir) -> Incremental saving of PET relative to CT (ICP): A$ 505.50 -> Incremental saving of CT+PET relative to CT (Gambhir): A$934.78 Observational study (Valk et al.) CT+PET: A$ 36100 for 38 scans -> Incremental savings PET relative to CT: A$1325/patient -> Incremental savings CT+PET relative to CT: A$ 912.41/patient Pre-operative staging of lung cancer Decision analysis (Gambhir) no PET: A$ 7353.26 /patient CT+PET: A$ 7318.61 /patient -> Incremental saving of CT+PET relative to CT: A$ 34.65/patient Observational study CT+PET: A$ 51300 for 54 scans -> Incremental savings CT+PET relative to CT: A$ 390.03/patient Axillary staging of breast cancer Decision analysis (ICP) No PET: A$ 4399 /patient PET: A$ 3849 /patient -> Incremental savings PET relative to no PET: A$550.08/patient Observational study (Adler) PET: A$ 47500 for 50 scans -> Incremental cost PET relative to no PET: A$55.04/patient Preoperative evaluation of recurrent colorectal cancer Decision analysis (ICP) CT: A$ 5045 /patient PET: A$ 2744 /patient -> Incremental cost saving of A$2301.27/patient Observational studies Valk, Delbeke, Lai: PET: A$ 154850 for 163 scans -> Incremental savings: A$249.06/patient

	Lai: PET: A$ 32300 for 34 scans -> Incremental savings: A$1723.19/patient Assessment of myocardial viability Decision analysis (ICP) No PET: A$ 8129 /patient PET: A$ 7828 /patient -> incremental savings PET relative to no PET: A$300.24/patient Observational study (Beanlands) PET: A$ 275258 for 87 scans + A$ 193608 for additional procedures (15 CABGs) -> Incremental saving PET relative to no PET: A$2069.65/patient
Outcomes	Solitary Pulmonary Nodules Observational study (Valk et al.) Procedures saved with PET versus CT alone : 8 thoracotomies, 10 needle biopsies -> savings from avoided procedures: A$ 70772 for 38 PET scans Pre-operative staging of lung cancer Decision analysis (Gambhir) Life expectancy PET = life expectancy CT+PET: 4.9 years Observational study (Valk et al.) Procedures saved with PET versus CT alone : 6 thoracotomies, 11 mediastinoscopies -> Savings from avoided procedures: A$ 72361 Axillary staging of breast cancer Observational study (Adler) Savings from avoided procedures: A$ 44748 for 50 scans Preoperative evaluation of recurrent colorectal cancer Observational studies Valk, Delbeke, Lai: Savings from avoided procedures: A$ 245022 for 163 scans Lai: Savings from avoided procedures: A$ 58589 for 34 scans Assessment of myocardial viability Observational study (Baenlands) Savings from avoided procedures: A$ 456317 for 87 scans
Cost-effectiveness	Cost-benefit measure: Savings per patient Solitary Pulmonary Nodules Decision models PET relative to CT: A$ 505.5 CT+PET relative to CT: A$ 934.78 Observational study PET relative to CT: A$ 1325.11 CT+PET relative to CT: A$912.41 Pre-operative staging of lung cancer

	Decision analysis CT+PET relative to CT: A$ 34.65 Observational study CT+PET relative to CT : A$ 390.03 Axillary staging of breast cancer Decision analysis PET relative to no PET: A$ 550.08 Observational study (Adler) PET relative to no PET: A$ -55.04 (incremental cost) Preoperative evaluation of recurrent colorectal cancer Decision analysis PET relative to CT: A$ 2301.27 Observational studies CT+PET relative to no PET: A$ 249.06 CT+PET relative to no PET: A$ 1723.19 Assessment of myocardial viability Decision analysis PET relative to no PET: A$ 300.24 Observational study PET relative to no PET: A$ 2069.65
Sensitivity analysis	Sensitivity analysis for decision tree analyses on (1) disease prevalence and (2) specificity of FDG-PET Solitary Pulmonary Nodules PET remains cost-effective for all values of prevalence up to 0.8 (0.9 in model 2) and for all specificity of PET as low as 0.72 (0.3 in model 2). Pre-operative staging of lung cancer CT+PET remains cost-saving for disease prevalence above 0.3. Reducing specificity of PET does not remove cost-effectiveness but decreases life expectancy. Axillary staging of breast cancer FDG-PET remains cost-effective for values of prevalence up to 0.57 and for PET specificity as low as 0.59. Preoperative evaluation of recurrent colorectal cancer PET remains cost-effective for all values of prevalence and specificity. Assessment of myocardial viability PET remains cost-effective for values of prevalence up to 0.76 and values of speficity of PET as low as 0.63.
Conclusions	FDG-PET is cost-effective in Australia for all described indications *if* PET costs $950. If costs were higher, PET may not be cost-effective for some indications, particularly the pre-operative staging of lung cancer. A fee for PET of $1500 would be in danger of removing the cost-effectiveness of PET in all of the clinical situations described.

Remarks	In contrast to what the authors describe, these are not a cost-effectiveness analyses but cost-benefit analyses. The cost-benefit measure is "savings per patient." The paper contains many inconsistencies between the numbers in the text and the numbers in the tables. Few details on the models are given, which precludes proper quality assessment.

Head and Neck cancer

Author	Hollenbeak et al. 2001
Country	US
Design	Cost-effectiveness analysis + cost-utility analysis Decision model
Perspective	large university medical centre
Time window	Lifetime
Interventions	CT alone versus CT+FDG-PET
Population	Patients with N0 Neck squamous cell carcinoma with no evidence of lymph node involvement
Assumptions	Prevalence of disease given a negative CT scan: 28,6% (literature) PET sensitivity: 86,9% (literature) PET specificity: 94,8% (literature) Probability of a positive PET scan: 26.6% Probability of a negative PET result: 71.50% Probability of lymph node involvement, given positive PET: 87.00% Probability of lymph node involvement, given negative PET: 2.10% Utility(modified neck dissection): 0,925 U(Radiation+modified neck dissection): 0,913 U(Radiation): 0,875 U(radical neck dissection): 0,763 U(radiation+radical neck dissection): 0,675
Data source for costs	accounting database of a large Midwestern university hospital Estimates by a variant of cost-to-charges methodology
Cost items included	PET scan: 1075$ Modified neck dissection: 6791,73$ Radical neck dissection: 8083,73$ Radiation: 4399,51$
Data source for outcomes	Survival estimated using data from the Surveillance, Epidemiology and End Results (SEER) Database Utilities derived from Time Trade-off survey in 8 patients
Discounting	Not specified
Costs	CT alone: 3571,5$ CT+PET: 4678,7$
Outcomes	CT alone: 9,93 life years; 9,38 QALYs CT+PET: 10,06 life years; 9,82 QALYs
Cost-effectiveness	Cost per QALY: 2505 $/QALY Cost per life year saved: 8718 $/LYS
Sensitivity	One-way sensitivity analysis on cost of PET and prevalence of occult disease:

analysis	PET strategy remains cost-effective (cost per QALY<$50 000) as long as the cost of the scan was less than $50 052
Conclusions	PET is cost-effective as part of a strategy for treating N0 neck in head and neck squamous cell carcinoma (HNSCC) patients No cost savings are associated with the use of PET, but the value gained may be considered worthwhile.
Remarks	Sensitivity and specificity of PET were determined from recent publications of PET scans of cervical lymphatics. They were not specific for N0 Neck squamous cell carcinoma.

Pre-operative staging of recurrent colorectal cancer

Author	Sloka et al. 2004			
Country	Canada			
Design	Cost-effectiveness analysis Decision model			
Perspective	Unclear			
Time window	from initial diagnosis to final treatment modalities of the first disease recurrence			
Interventions	CT alone versus CT+PET			
Population	Hypothetical sample of 1000 65-year old person with suspected recurrent colorectal cancer			
Assumptions	Prevalence of recurrent disease: 85% All patients have colonoscopy after CT or CT+PET with subsequent biopsy if positive; if negative diagnosis confirmed with biopsy (with CT) or diagnostic surgery Sensitivity and specificity of PET and CT derived from literature (meta-analysis):			
		Sensitivity	Specificity	Mortality
	CT	0,762	0,694	0,0025%
	FDG-PET	0,933	0,927	0%
	Colonoscopy	0,93	0,85	6,5%
	Biopsy	1	1	0,0054%
	Life expectancy for all patients with unstaged recurrent colorectal cancer is 2,6 years Mean survival of patient with untreated extensive colorectal metastasis is 13,1 months (literature) Mean survival of patient with extensive colorectal metastasis treated with chemotherapy is 16 months (literature) Full utilisation of PET and cyclotron			
Data source for costs	Canadian fee schedules and cost accounting systems Literature Price year: 2000 Currency: CA$			
Cost items included	PET scan: CA$1029 surgery: CA$16479,34 thorax, abdomen and pelvic CT: CA$462 CT-guided biopsy: CA$118 colonoscopy: CA$168 chemotherapy: CA$10000			
Data source for outcomes	Literature			
Discounting	Not specified			
Costs	CT strategy: CA$9523 per person PET strategy: CA$7765 per person			

	Expected savings: CA$1758 per person		
Outcomes	Life expectancy: increase of 3,8 days		
	Number of surgeries: 125 avoided surgical procedures (CT: 580; PET: 455)		
Cost-effectiveness	PET dominates CT strategy		
Sensitivity analysis	One-way sensitivity analysis on disease prevalence, CT cost, PET cost, Surgery cost, Biopsy cost, Chemotherapy cost, CT sensitivity, CT specificity, PET sensitivity, PET specificity, avoidance of surgery, percentage non-resectable. CT+PET better life expectancy, resp. cost saving if		
		Better life expectancy	Cost saving
	Disease prevalence	>17.5%	>22.4%
	CT cost		Any
	PET cost		< CA$2787
	Surgery cost		> CA$2922
	Biopsy cost		Any
	Chemotherapy cost		< CA$100 000
	CT sensitivity	<91.8%	<87.3%
	CT specificity	Any	Any
	PET sensitivity	>44.3%	>73.8%
	PET specificity	>51.2%	>65.3%
	Avoidance of surgery	>11.3%	>3.2%
	Non-resectable	<71.6%	<95.0%
Conclusions	CT+PET is a cost-effective approach to determining the management of recurrent colorectal cancer. The additional PET cost is compensated for by the savings realised from avoided surgeries.		
Remarks	There are some inconsistencies between the numbers mentioned in the text and the numbers mentioned in the tables.		

Author	Park et al. 2001			
Country	US			
Design	Cost-effectiveness analysis Decision model based on Gambhir et al. (1998)			
Perspective	Not specified (probably Medicare)			
Time window	Lifetime			
Interventions	CT alone versus CT+PET			
Population	Patients with recurrence of colorectal cancer who had undergone surgical resection of their primary colorectal cancer and who were suspected of having recurrence based on elevated levels of carcinoembryonic antigen.			
Assumptions	70% of the patients with primary colorectal cancer are eligible for curative resection. 40% of the patients who have undergone curative resection for their primary colorectal cancer will experience recurrence within 2 years. according to conventional imaging techniques, 30% of the postsurgical patients with recurrence are potential candidates for surgery, but only 25% can truly benefit from surgery Morbidity biopsy: 0,001 years Morbidity surgery: 0,024 years % death biopsy: 0,2 % death surgery: 3,4 Life expectancy normal post-surgical patient (60 years of age): 5.681 years Life expectancy recurrent patient (no treatment): 2 years Life expectancy recurrent patient (surgical cure): 3.804 years Life expectancy recurrent patient (chemotherapy): 2.663 years Life expectancy normal post-surgical patient with chemotherapy: 4.545 years			
		Sensitivity	Specificity	Cost
	CT	0,757	0,557	US$ 789
	FDG-PET	0,97	0,756	US$ 2000
	Biopsy	1	1	US$ 692
	Probability hepatic involvement: 0.285 Probability hepatic + extrahepatic involvement: 0.81 Prevalence of recurrence in follow-up: 0.702 Probability liver-only recurrence (resectable): 1 (??)			
Data source for costs	Medicare reimbursement fees			
Cost items included	CT: US$ 789 PET: US$ 2000 Biopsy: US$ 692 Surgery: US$ 22039 Chemotherapy: US$ 7927			
Data source	Literature			

for outcomes	
Discounting	Yes, percentage unclear
Costs	CT: US$ 8354 CT+PET: US$ 8783 -> Incremental cost CT+PET relative to CT alone: US$ 429
Outcomes	Life expectancy CT: 3.563 years Life expectancy CT+PET: 3.589 years -> incremental life expectancy CT+PET relative to CT alone: 0.0261 years (9,527 days) 2.77% of the patients entering the decision tree would be correctly directed away from surgery by the additional PET scan.
Cost-effectiveness	Cost-effectiveness ratio threshold: US$ 50000 Cost per life year gained CT+PET relative to CT alone: 16437 US$/year
Sensitivity analysis	Most influential variables for the results of the decision analysis: Prevalence of disease (baseline prevalence 70.2%): At a prevalence of 91% or higher, CT+PET becomes dominant (cost saving and better life expectancy) At a prevalence of 49% or lower, the ICER exceeds 50000 US$/life year gained. At a prevalence of 8% or less, CT becomes dominant. Sensitivity of CT (baseline value 75.7%) At a sensitivity of CT of 0.879 or higher, the ICER exceeds 50000 US$/life year gained. Specificity of biopsy (baseline 1) At a specificity of biopsy of 0.803 or lower, the ICER exceeds 50000 US$/life year gained. Cost of PET (baseline US$ 2000) At a cost of US$ 1171, CT+PET becomes dominant Frequency of hepatic involvement (baseline 28.5%) When the frequency of hepatic recurrence exceeds 46%, CT+PET becomes dominant. Life expectancy of untreated patient with recurrence (baseline 2 years) At a life expectancy of 2.569 years or more, the ICER exceeds 50000 US$/life year gained. Life expectancy of a patient with recurrence undergoing chemotherapy (baseline 2.663 years) At a life expectancy of 1.75 years or less, the ICER exceeds 50000 US$/life year gained.
Conclusions	Higher accessibility of PET would be a potential for significant life expectancy gains and if costs of PET were lowered, cost savings may also accrue by avoiding unnecessary surgeries. Despite the high cost of FDG-PET relative to other imaging modalities, it can be more cost-effective because of the increased performance of detecting and evaluating tumours throughout the body at minimal risk to the patient.
Remarks	Performing a biopsy based on FDG-PET information alone was assumed to be possible. In the clinical setting, it is difficult and often impossible to perform biopsy based only on a positive PET finding. The study focussed on hepatic recurrences and respectability. It is unclear why the probability of liver-only recurrence is 1.

Re-staging Hodgkin's disease

Author	HTA report HTBS, 2002		
Country	Scotland		
Design	Cost-effectiveness analysis Markov model		
Perspective	NHS Scotland + patient travel costs		
Time window	30 year (proxy for lifetime)		
Interventions	all for surveillance (hypothetical intervention to show limits of model, not in clinical practice) all for consolidation (hypothetical) CT alone, if positive: consolidation, if negative: surveillance (current practice) CT+PET: first CT, if positive: PET (if positive: consolidation, if negative: surveillance), if negative: surveillance PET, if positive: consolidation, if negative: surveillance (CT also performed but results not used to allocate patients to surveillance or consolidation)		
Population	Patients who have achieved a partial or complete response to induction therapy for Hodgkin's disease		
Assumptions	Relapse: Years 1-2 post ABVD: 26.5% Years 3-5 post ABVD: 6% Years 1-5 post RT: 11.5% In-field relapse from RT (assumed to occur in years 1-2): 37% After surveillance suitable for salvage (years 1-2): 25% After surveillance suitable for salvage (years 3-5): 85% 5-year survival: relapse free after salvage: 52% Post High-Dose Chemotherapy (HDCT): 60% Percentage of patients moving from IVE re-induction to HDCT: 52% Percentage toxic deaths under IVE: 1% Percentage toxic deaths under HDCT: 7% RR of breast cancer post RT: 12.7 RR of leukaemia post RT: 24.3-34.7 RR of lung cancer post RT: 3.7 – 10.3 Relative risk of death from heart disease post RT: 3.1		
		Sensitivity	Specificity
	CT alone	0.75	0.45
	CT+PET	0.80	0.89
	PET alone	0.81	0.95
Data source	HTBS calculations		

<table>
<tr><td>for costs</td><td colspan="4"></td></tr>
<tr><td>Cost items included</td><td colspan="4">FDG-PET: £ 678
CT: £ 146
RT: £ 2 494</td></tr>
<tr><td></td><td>Surveillance</td><td>post ABVD</td><td>Post conservative/salvage</td><td>Post autologous PBSCT</td></tr>
<tr><td></td><td>Year 1
Year 2
Year 3
Year 4
Year 5+</td><td>£ 265
£ 89
£ 89
£ 59
£ 30</td><td>£ 411
£ 235
£ 89
£ 59
£ 30</td><td>£ 649
£ 59
£ 59
£ 59
£ 30</td></tr>
<tr><td></td><td colspan="4">IVE re-induction: £ 6 832
HDCT therapy and autologous peripheral blood stem cell support: £ 19 172
Non-curative therapy for IVE failures: £ 524 per year
Long term toxicities – lung cancer: £ 500 per year
Long term toxicities – breast cancer: £ 200 per year
Long term toxicities – leukaemia: £ 1 500 per year
Price year: 2002-2003</td></tr>
<tr><td>Data source for outcomes</td><td colspan="4">Literature</td></tr>
<tr><td>Discounting</td><td colspan="4">Costs: 0%
Outcomes: 1.5%</td></tr>
<tr><td>Costs</td><td colspan="4">Costs calculated for different patient types: male/female, 20/40/60 years old at end of induction therapy.</td></tr>
<tr><td>Outcomes</td><td colspan="4">Outcomes calculated for different patient types: male/female, 20/40/60 years old at end of induction therapy.</td></tr>
<tr><td>Cost-effectiveness</td><td colspan="4">Costs and life years saved calculated for the different patient types: male/female, 20/40/60 years old at end of induction therapy.</td></tr>
<tr><td>Sensitivity analysis</td><td colspan="4">Extensive probabilistic sensitivity analysis performed.
Cost-effectiveness conclusions are maintained if quality adjusted life year gains are calculated based on the available quality weights (high uncertainty), if very unfavourable assumptions are made about the actual false-positive rates associated with FDG-PET or if the discount rate on benefits is increased to 6%.</td></tr>
<tr><td>Conclusions</td><td colspan="4">The PET alone strategy (strategy 5) to assign patients to consolidation or surveillance, gives the largest expected value of life years and the lowest expected cost and is cost-effective for essentially all plausible input values, for any value of willingness to pay greater than £ 5 000. Strategy 4 is a poorer strategy than strategy 5 but still cost-effective relative to interventions that do not contain PET.
The use of the PET alone strategy appears to be cost saving compared with current practice.

The use of PET scanning in this indication is cost-effective.</td></tr>
<tr><td>Remarks</td><td colspan="4"></td></tr>
</table>

Primary staging malignant lymphoma

Author	Klose et al 2000
Country	Germany
Design	Cost-effectiveness analysis Observational design
Perspective	Hospital
Time window	Diagnostic process
Interventions	1. No diagnosis (comparator) 2. CT 3. FDG-PET
Population	22 patients of a clinical trial April 1997-May 1998
Assumptions	No diagnosis: cost and effects = 0 7.4 scans a day can be done on one PET scanner
Data source for costs	Micro-costing in Ulm Univ. Hospital for directs costs of FDG-PET and CT (staff, materials, investment, maintenance & overheads)
Cost items included	Investment cyclotron: € 1.66 mio (=€2673/week +maintenance.1286/week) Investment CT: € 670 900 (€1613/week (loan) +maint.1947/week) Investment PET: € 394 036 + workstation € 13 273 Cost/min. €0.73 physisican, chem, eng. €0.36/ technician
Data source for outcomes	Surrogate endpoint: correct staging Outcomes based on results of trial
Discounting	No
Costs	CT: € 391 FDG-PET: € 961
Outcomes	Upstaging in 4 patients
Cost-effectiveness	Incremental cost per correctly staged patient: CT: € 478/patient compared to no diagnosis PET: € 3 133/patient compared to CT
Sensitivity analysis	6 scenarios on costs: lower/upper limits on PET utilisation time, working time, number of films + CT use of materials, staff 3: % FDG in cyclotron radiation time (achieved and potential devel.) 4: optimized full util.PET and CT (daily staff and material assumed to increase by 40%) /5: cyclotron serves 4 instead of 2 PETS (staff and material raised by 75%) /6:5+4
Conclusions	FDG-PET is more accurate than CT. PET might result in cost savings because of better planning of further diagnostic procedures and treatment. Sensitivity analysis with full utilisation reduces costs for PET (and with cyclotrons serving more scanners). Cost-effectiveness of PET could be improved (in procedure itself or regional planning of PET facilities). More research is needed to assess long term treatment and cost effects of more accurate staging.

Remarks	The study has many weaknesses. 1. The gold standard used for this analysis is not really a gold standard. Used as a gold standard are "concordant and clarified discrepant findings", which means that if PET and CT give the same result, this result is assumed to be 100% correct. If results of PET and CT are discordant, a biopsy is done to obtain a final result. 2. while it is stated that a societal viewpoint is taken, the viewpoint is actually more limited. 3. long term consequences of changes in staging were not assessed. 4. Costing CT versus PET but findings come from confrontation of discrepancies.

BASELINE DATA FOR THE CALCULATION OF THE NUMBER OF PET SCANNERS NEEDED IN BELGIUM

	Levels of evidence			Number of PET scans			
	Diagnosis	Recurrence	Treatment	Diagnosis	Recurrence	Treatment	Total n scans
Lung	3 (6-staging)	2	1	3834	928	523	5335
Colorectal	2	4	1	294	1244	324	1871
Non-Hodgkin lymphoma	1 (2-staging)	2	2	531	613	775	1936
Hodgkin Lymphoma	1 (2-staging)	2	2	315	374	376	1077
Head & Neck	2 (3-staging)	3		388	501	154	1060
Breast	2 (against)	2		233	550	131	927
Oesophagus & Stomach	2 (staging)		3	430	267	189	892
Melanoma	2 (staging)	2 (staging)		278	399	65	746
Thyroid		2					149
Pancreatic+Liver	Pancreas: 2 Liver: 2 (against)						556
Cervical	2	2					211
Ovarian	2	2	1				267
Renal	1	1					160
Testicular	2	2	1				126
Occult Primary Tumour	2						
Other							2332
Brain tumour	2		3				586
Epilepsy			2				277
Dementia	2						145
Movement disorders							40
General neuro							158
Psychiatry							18
Cardiac viability	3						72
Cardiac flow reserve	1						48
FUO							328
Systemic							258
Other inflam							152
ALL INDICATIONS							19727

This page is left intentionaly blank.

Wettelijk depot : D/2005/10.273/29

KCE reports

1. Effectiviteit en kosten-effectiviteit van behandelingen voor rookstop. D/2004/10.273/1.
2. Studie naar de mogelijke kosten van een eventuele wijziging van de rechtsregels inzake medische aansprakelijkheid (fase 1). D/2004/10.273/2.
3. Antibioticagebruik in ziekenhuizen bij acute pyelonefritis. D/2004/10.273/5.
4. Leukoreductie. Een mogelijke maatregel in het kader van een nationaal beleid voor bloedtransfusieveiligheid. D/2004/10.273/7.
5. Het preoperatief onderzoek. D/2004/10.273/9.
6. Validatie van het rapport van de Onderzoekscommissie over de onderfinanciering van de ziekenhuizen. D/2004/10.273/11.
7. Nationale richtlijn prenatale zorg. Een basis voor een klinisch pad voor de opvolging van zwangerschappen. D/2004/10.273/13.
8. Financieringssystemen van ziekenhuisgeneesmiddelen: een beschrijvende studie van een aantal Europese landen en Canada. D/2004/10.273/15.
9. Feedback: onderzoek naar de impact en barrières bij implementatie – Onderzoeksrapport: deel 1. D/2005/10.273/01.
10. De kost van tandprothesen. D/2005/10.273/03.
11. Borstkankerscreening. D/2005/10.273/05.
12. Studie naar een alternatieve financiering van bloed en labiele bloedderivaten in de ziekenhuizen. D/2005/10.273/07.
13. Endovasculaire behandeling van Carotisstenose. D/2005/10.273/09.
14. Variaties in de ziekenhuispraktijk bij acuut myocardinfarct in België. D/2005/10.273/11.
15. Evolutie van de uitgaven voor gezondheidszorg. D/2005/10.273/13.
16. Studie naar de mogelijke kosten van een eventuele wijziging van de rechtsregels inzake medische aansprakelijkheid. Fase II: ontwikkeling van een actuarieel model en eerste schattingen. D/2005/10.273/15.
17. Evaluatie van de referentiebedragen. D/2005/10.273/17.
18. Prospectief bepalen van de honoraria van ziekenhuisartsen op basis van klinische paden en guidelines: makkelijker gezegd dan gedaan.. D/2005/10.273/19.
19. Evaluatie van forfaitaire persoonlijk bijdrage op het gebruik van spoedgevallendienst. D/2005/10.273/21.
20. HTA Moleculaire Diagnostiek in België. D/2005/10.273/23, D/2005/10.273/25.
21. HTA Stomamateriaal in België. D/2005/10.273/27.
22. HTA Positronen Emissie Tomografie in België. D/2005/10.273/28.

Inlichtingen

Federaal Kenniscentrum voor de Gezondheidszorg - Centre Fédéral d'Expertise des Soins de Santé.
Résidence Palace (10de verdieping-10ème étage)
Wetstraat 155 Rue de la Loi
B-1040 Brussel-Bruxelles
Belgium
Tel: +32 [0]2 287 33 88
Fax: +32 [0]2 287 33 85
Email : info@kenniscentrum.fgov.be , info@centredexpertise.fgov.be
Web : http://www.kenniscentrum.fgov.be , http://www.centredexpertise.fgov.be