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

Hadrontherapie

KCE reports vol. 67A

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Contact

Federaal Kenniscentrum voor de Gezondheidszorg (KCE)
Wetstraat 62
B-1040 Brussel
Belgium

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

Email : info@kce.fgov.be
Web : http://www.kce.fgov.be

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MICHEL HUYBRECHTS, CAROLINE OBYN, JEANNINE GAILLY,
FRANÇOISE MAMBOURG, IMGARD VINCK, DIRK RAMAEKERS

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Titel : Hadrontherapie

Auteurs : Michel Huybrechts, Caroline Obyn, Jeannine Gailly, Françoise Mambourg, Imgard Vinck, Dirk Ramaekers

Externe experten: Yves Benoît (Pediatrische oncologie, UZ Gent, RUGent), Wilfried De Neve (Radiotherapie, UZ Gent, RUGent), Steven De Vleeschouwer (Neurochirurgie, St Raphaël Kliniek, KULeuven), Katrien Kesteloot (Faculteit Economische Wetenschappen, KULeuven; Financieel Directeur, Universiteitsziekenhuizen, Leuven), Philippe Lambin (Radiotherapie, Maastro Clinic, Maastricht, Netherland), Françoise Renard (Kankerregister, Brussels), Laurette Renard (Ophtalmologie, St Luc Universitair Ziekenhuis, UCL, Brussel)

Externe validatoren: Madelon Pijls-Johannesma (Maastro Clinic, Maastricht, Nederland), Philippe Stevens (Relatiemanager zieken- en rusthuizen, Dexia Social Profit Vlaanderen, Dexia Bank, Antwerpen), Walter Van den Bogaert (Oncologie-Radiotherapie, UZ Gasthuisberg, KULeuven)

Conflict of interest : Michel Huybrechts is eigenaar van 75 gewone aandelen van Siemens AG en heeft een familielid (de zoon van zijn tweelingbroer) die tewerkgesteld is bij IBA NV, beide ondernemingen met activiteiten in de ontwikkeling van medische synchrotrons/cyclotrons. Wilfried De Neve en Walter Van den Bogaert zijn leden van het Belgische Consortium voor onderzoek, ontwikkeling en validatie van hadrontherapie. Madelon Pijls-Johannesma heeft onderzoeksfondsen ontvangen.

Disclaimer: De experts en validatoren werkten mee aan het wetenschappelijke rapport maar werden niet betrokken in de aanbevelingen voor het beleid. Deze aanbevelingen vallen onder de volledige verantwoordelijkheid van het KCE.

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Voorwoord

Kanker is en blijft één van de belangrijkste uitdagingen in onze moderne geneeskunde. Elke innovatie hoe klein ook die mogelijks in staat is de behandeling van deze ziekte te verbeteren brengt telkens grote verwachtingen met zich mee. Enthousiasme en gedrevenheid zijn noodzakelijke voorwaarden voor verdere vooruitgang in de kankerzorg. Jammer genoeg weten we dat de oorspronkelijke geestdrift voor een nieuwe interventie niet steeds in verhouding staat tot de uiteindelijk objectief geconstateerde resultaten voor de patiënt, vaak jaren later.

Voor een aantal ontluikende zware medische technologieën dienen beleidsmakers regelmatig voordat er voldoende bewijzen van de klinische en maatschappelijke meerwaarde beschikbaar zijn al investerings- of terugbetalingsbeslissingen te nemen. Het vormt voor het KCE dan ook een bijzondere uitdaging om dergelijk nog onontgonnen terrein te onderzoeken, zodat goed geïnformeerde beslissingen kunnen worden genomen zonder te grote overhaasting maar ook zonder nodeloos uitstel.

Hadrontherapie of radiotherapie met ionenstralen is zo een nieuwe aanpak van kankerbehandeling. De fysische eigenschappen van ionen die versneld worden tot bijna 80% van de lichtsnelheid zijn al enige tijd gekend, maar de toepassingen in de geneeskunde zijn van recentere datum. De techniek vereist een aanzienlijke financiële investering en een multidisciplinaire hooggeschoold team met fysici, ingenieurs, informatici, en - uiteraard - artsen en verpleegkundigen. De behandelingscentra zijn momenteel nog maar beperkt verspreid in de wereld.

Dient deze behandeling ontwikkeld te worden in België, op welke schaal, met welke middelen, voor welke patiënten? Dit rapport tracht deze vragen te verhelderen en een overzicht te geven van de beschikbare resultaten uit klinisch onderzoek en maakt een financiële simulatie.

Het KCE dankt van harte de meerdere experts in radiotherapie voor hun waardevolle wetenschappelijke inbreng, alsook de buitenlandse hadron centra, de financiële experts en de industrie voor hun bereidwillige medewerking.

Jean-Pierre Closon
Adjunct Algemeen Directeur

Dirk Ramaekers
Algemeen Directeur

Samenvatting

PRINCIPES VAN HADRONTHERAPIE

Radiotherapie is een lokale kankerbehandeling, die frequent wordt toegepast in combinatie met chirurgie. Aan deze lokale behandeling wordt soms chemotherapie toegevoegd als systemische behandeling.

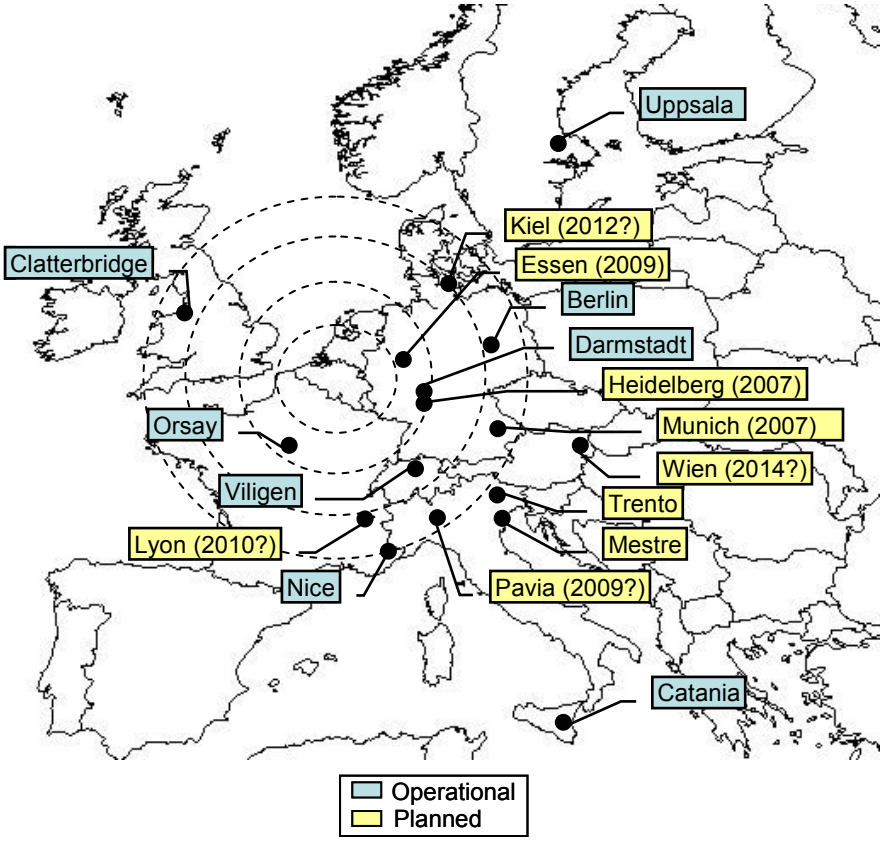
Klassieke radiotherapie of fotontherapie gebruikt externe radioactiviteit om patiënten te bestralen met fotonstralen (X- of ^{57}kobalt-stralen), op conventionele, 3D-conforme of intensiteitsgemoduleerde wijze. Aangezien bij intensiteitsgemoduleerde radiotherapie (IMRT) hoge bestralingsdosissen op precieze manier kunnen worden toegediend, vertegenwoordigt deze therapie een vooruitgang in de behandeling van een aantal dieper gelegen tumoren (zie KCE rapport 62A). Met deze therapie wordt evenwel nog steeds een groot volume normaal weefsel bestraald. Dit stelt het probleem dat, na verloop van tijd, deze extra blootstelling van normale cellen, ondanks de eerder geringe hoeveelheid bestraling, kan leiden tot secundaire kwaadaardige tumoren.

Hadrontherapie, bestraling met geladen deeltjes, is relatief nieuw. Strikt genomen wordt de patiënt niet blootgesteld aan rechtstreekse radioactieve stralen, aangezien de aangewende projectielen geen radioactieve maar "gewone" waterstof- of koolstof-ionen zijn (protontherapie en koolstof-ion therapie). Deze therapie is gebaseerd op de observatie dat geladen atomen (ionen) hun energie op een specifieke wijze verliezen, namelijk op het einde van hun traject, daar waar hun snelheid sterk afneemt. Op deze locatie wordt een erg geconcentreerde energie-piek bereikt: de Bragg-piek, genaamd naar de fysicus die in 1905 de verhoging in ionisatie-dichtheid op het einde van de baan van alfa-deeltjes beschreef.

Een andere ontwikkeling bij hadrontherapie bestaat erin de behandeling op te volgen met een PET-scan. Radioactieve ^{15}O en ^{11}C die ontstaan zijn uit de botsing tussen afgevuurde protonen en gewone ^{16}O en ^{12}C uit de celkernen, kunnen gebruikt worden om de diepte van ionenstralen in de tumor op te volgen. Meer bepaald zijn ^{15}O en ^{11}C radioactieve nevenproducten die desintegreren door een β^+ afgifte, gepaard gaande met de productie van 2 lichtfotonen. Deze fotonen (flitsen) kunnen worden geregistreerd met een gevoelige PET-scan. Het tumorvolume wordt opgedeeld in een groot aantal cilindervormige staafjes. Dankzij de precieze visualisatie van de impact van elk ion, kan in ieder tumorstaafje de behandeling gecontroleerd worden.

Momenteel zijn er wereldwijd 28 protontherapie-centra, waarvan 8 in Europa. (Fig. I). Voor Koolstof-ion therapie daarentegen, zijn er momenteel 3 centra (2 in Japan en 1 part-time in Darmstadt, Duitsland). Negen nieuwe hadrontherapiecentra zijn momenteel goedgekeurd of in constructie.

Figure I : Operationele en niewe hadron centra in Europa



KLINISCHE EVIDENCE VOOR HADRONTHERAPIE

OOGMELANOMA'S

Verschillende behandelingen zijn momenteel beschikbaar voor oogmelanoma's. Protontherapie is een mogelijk alternatief voor fotontherapie wanneer brachytherapie ongeschikt is, namelijk wanneer de rand van de achterkant van het melanoom zich uitstrekt tot dicht bij de optische schijf of de fovea, of wanneer de dikte 5.5 mm overschrijdt.

Overtuigende bewijzen ontbreken momenteel om een gefundeerde keuze tussen proton- en fotontherapie te maken, aangezien lokale controle, oogretentie na bestraling en overleving equivalent waren in niet-vergelijkende gevallenreeksen. Er was geen verschil in verlies van visuele scherpte en gezichtsveld. Het voorkomen van neovasculaire glaucoma was in geringe mate minder frequent bij protontherapie. Koolstofiontherapie blijkt een minder interessante therapie dan proton- of fotontherapie voor oogmelanoma's. Er is geen evidence om het gebruik van protontherapie te verdedigen voor andere oogziektes zoals neovasculaire leeftijdgerelateerde maculaire degeneratie.

SCHEDELBASISTUMOREN

Chordomas

Chordomas van de schedelbasis zijn zeldzame tumoren met een slechte prognose. Chirurgie blijft de best beschikbare optie. Radiotherapie wordt gebruikt om lokale controle te verbeteren in geval van een residuele of niet-operabele tumor.

Gevallenseries met protontherapie tonen een verbeterde lokale progressievrije overlevingsgraad en algemene overlevingsgraad t.o.v. de historische respons. Series van patiënten met moderne chirurgie en stereotactische fotontherapie geven ook goede resultaten.

Er is echter geen duidelijke klinische evidence van vergelijkende studies die het verschil in doeltreffendheid nagaat tussen proton- en klassieke fotontherapieën (of hun combinatie, of hoge precisie fotontherapie) of tussen radiotherapie en moderne chirurgische ingrepen (slechts 20% met radiotherapie). Resultaten zijn gebaseerd op heterogene gevallenreeksen zonder vergelijkende controlegroep

De veiligheid lijkt acceptabel (weinig gevallen met graad 3 en 4 toxiciteit). Hersenstamschade kan ook optreden met protontherapie. Het risico is gerelateerd aan het volume van de hersenstam dat meer dan 60 GyE ontving. Er zijn onvoldoende data beschikbaar om de toxiciteit geïnduceerd door foton- of protontherapie te vergelijken.

Gevallenreeksen met koolstof-ion bestraling toonden ook goede resultaten in chordomas van de schedelbasis zonder ernstige toxische reacties. Er zijn echter geen vergelijkende studies tussen koolstof-ion therapie en de huidige behandeling.

Chondrosarcomas

Chondrosarcomas van de schedelbasis zijn zeldzame tumoren met een goede prognose. Chirurgie blijft de hoofdbehandeling. Radiotherapie wordt gebruik om lokale controle te verbeteren in geval van een overblijvende tumor.

In gevallenreeksen van chondrosarcomas van de schedelbasis, werden geen verschillen geconstateerd tussen foton- en protontherapie op vlak van lokale controlegraad en algemene overleving. Koolstof-iontherapie lijkt momenteel minder doeltreffend dan de huidige behandeling. De inbegrepen studies zijn kleine heterogene niet-vergelijkende gevallenreeksen. Een selectie-bias kan niet uitgesloten worden.

Er is geen evidence voor het gebruik van proton- of koolstof-iontherapie voor de behandeling van andere kwaadaardige of goedaardige intracraniële tumoren.

TUMOREN VAN DE RUGGEGRAAT EN HET SACRUM

Voor andere niet-schedelbasis chordomas en chondrosarcomas is er geen evidence ter verdediging van proton- of koolstof-iontherapie. Er zijn geen vergelijkende studies en de gevallenreeksen zijn heterogeen wat betreft de studiepopulatie en de geselecteerde behandeling.

PEDIATRISCHE TUMOREN VAN HET CENTRAAL ZENUWSTELSEL

Protontherapie lijkt veilig en goed getolereerd door kinderen in geval van tumoren van het centraal zenuwstelsel (doch geen gerandomiseerde gecontroleerde studies zijn beschikbaar, en slechts geringe retrospectieve evidence). Er is momenteel geen evidence om het gebruik van protontherapie als eerstelijnsbehandeling toe te passen bij pediatrische tumoren van het centraal zenuwstelsel.

KWAADAARDIGE SPEEKSELKLIERTUMOREN

Eén gerandomiseerde gecontroleerde studie toont een significant betere locale controlegraad met neutronen (versus conventionele fotontherapie) bij niet-opereerbare of terugkerende kwaadaardige tumoren van de speekselklieren, maar geen verschil in overleving. Neutrontherapie is stopgezet en is niet meer beschikbaar.

Een vergelijkende gevallenreeks toonde ook een betere lokale controle bij een combinatie van koolstof-ion en fotontherapie versus fotontherapie alleen bij patiënten met cystische adenoïde carcinoma zonder significant verschil in overleving tot nog toe.

GASTROINTESTINALE TUMOREN

Het klinische nut van protontherapie in slokdarmkanker blijft onduidelijk. De gerapporteerde resultaten met proton- of koolstofionentherapie voor levercarcinoma zijn gelijkaardig aan deze met conventionele radiotherapie. Ook voor gastro-intestinale tumoren blijft de rol van protonen of koolstofionen onduidelijk.

LONGTUMOREN

Het nut van proton- en koolstofiontherapie bij longkankers in een vroeg stadium is onduidelijk. De resultaten gerapporteerd voor proton- en koolstofiontherapie voor longkanker zijn vergelijkbaar met deze voor conventionele radiotherapie.

PROSTAATKANKERS

Het nut van proton- en koolstofiontherapie voor prostaatkankers is nog onduidelijk. Ten opzichte van conventionele dosis toonde hoge dosis radiotherapie, waarbij fotontherapie in beide armen gecombineerd werd met protontherapie, geen significant verschil in algemene overlevingsgraad maar wel een reductie in het risico van biochemische mislukking (PSA niveau) maar. Hoge dosis radiotherapie met combinatie van foton- en protontherapie dient vergeleken met conventionele en nieuwe behandelingen.

UROGENITALE KANKERS

Het nut van proton- en koolstofiontherapie in baarmoederhalskanker is ongekend. Het nut van protontherapie in blaaskanker is ongekend.

SAMENVATTEND: WELKE TUMOREN VOOR HADRONTHERAPIE ?

Voor geen enkele indicatie is er reeds overtuigende evidence dat proton- of koolstofiontherapie resulteert in verbeterde locale controle, ziektevrije overlevingsgraad of algemene overlevingsgraad. Hadrontherapie blijft een experimentele behandeling. Wereldwijd werden er ondertussen naar schatting reeds meer dan 50 000 patiënten behandeld. We vinden voorlopig maar een beperkt aantal studies, die een potentiële verbetering van de locale controle ten opzichte van de conventionele behandeling, aanduiden (tabel A.1 en A.2). Op basis van data van het Kankerregister is een schatting gemaakt van het aantal in aanmerking komende patiënten. In totaal gaat het over maximum 51 patiënten vandaag tot maximum 100 patiënten op middellange termijn.

Tabel A.1: Mogelijke actuele indicaties met een laag niveau van evidence

Indicatie	Proton of koolstofion	Aantal patiënten in België per jaar
Oogmelanoma wanneer dicht bij de optische schijf of fovea, of wanneer de dikte > 5 mm	*Proton*	2 kinderen* 11 volwassenen
Niet-opereerbare schedelbasis chordomas	*Proton*	Een deel van de 7 niet-opereerbare chordomas (van de schedelbasis, ruggengraat en staartbeen)
Schedelbasis chondrosarcomas	*Proton*	3 kinderen 22 volwassenen

* Retinoblastomas worden niet in rekening gebracht aangezien chemotherapie hiervoor de algemene behandeling is

Tabel A.2: Mogelijke toekomstige indicaties, maar onvoldoende data om tot een conclusie te komen

Indicatie	Proton of koolstofion	Aantal patiënten in België per jaar
Cystische adenoïde carcinomas, lokaal vergevorderd (≥T3) bij volwassenen maar… evidence enkel voor neutronen	*Koolstofion*	6 volwassenen
Chordomas van de ruggengraat, staart- en heiligbeen	*Proton*	Het complementaire deel van de 7 niet-opereerbare chordomas (van de schedelbasis, ruggengraat en staartbeen)
Zeldzame en specifieke tumoren in selectieve patiëntengroepen waar conventionele therapie een significant risico meebrengt voor gevoelige weefsels in de buurt	*Proton*	*< 50 (kinderen of volwassenen)*

Kernboodschappen

- **Hadrontherapie is een behandeling van kanker met niet radioactieve ionen. Vandaag wordt vooral gebruik gemaakt van protonen.**
- **Protontherapie kan een indicatie vormen voor zeldzame en specifieke tumoren in selectieve patiëntengroepen waar conventionele therapie een significant risico met zich meebrengt voor gevoelige weefsels in de buurt. Momenteel zijn er slechts weinig betrouwbare wetenschappelijke bewijzen uit klinisch onderzoek.**
- **Koolstofiontherapie is een veelbelovende maar nog steeds experimentele behandeling. Verder klinisch onderzoek is dus noodzakelijk.**
- **Een totaal van maximaal 51 patiënten zou vandaag baat hebben bij hadrontherapie (proton- en koolstofion therapie).**

KOST VAN EEN HADRON CENTRUM IN BELGIË

Op basis van prijsinformatie van meerdere constructeurs, kan voor een koolstof-ion en protontherapie-centrum met 3 behandelruimtes een totaal investeringsbedrag verwacht worden van naar schatting 159 miljoen € (inclusief kosten van het gebouw en architect, alle materiaal en installatie, project management, BTW, financieringskost en uitgaven om het centrum op te starten). Indien het centrum 12,5 uur per werkdag actief is, dan kunnen jaarlijks een 900-tal patiënten behandeld worden. Op voorwaarde dat het centrum goedgekeurd is in het zorgstrategisch plan van de bevoegde minister, zou het centrum in aanmerking kunnen komen voor de klassieke ziekenhuissubsidies ter hoogte van 60%. Dit zou zich vertalen in een totaal subsidiebedrag van 95.4 miljoen € (de betalingsmodaliteiten kunnen verschillen van regio tot regio, zo zou in Vlaanderen het subsidiebedrag gespreid kunnen worden in 20 jaarlijkse betalingen van 6,2 m€). Het jaarlijkse budget voor terugbetaling van deze therapie door het RIZIV zou dan 22.2 miljoen € bedragen, of 24 700 € gemiddelde terugbetaling per patiënt. Gezien de hoge overhead kosten (van het gebouw en de versneller) is een kleiner centrum geen aanbevolen optie. Op langere termijn is het mogelijk dat ontwikkelingen op vlak van technologie tot kleinere en goedkopere hadron centra leidt.

BEHANDELINGSMOGELIJKHEDEN IN HET BUITENLAND

Aangezien momenteel slechts een beperkt aantal patiënten een indicatie vormt voor hadrontherapie, werd onderzocht of de centra in het buitenland over voldoende capaciteit beschikken om Belgische patiënten te behandelen. De nodige informatie werd verkregen via een vragenlijst die verstuurd werd naar zowel de bestaande als de nieuwe centra in Europa en daarbuiten.

Voor oogmelanoma blijkt er meer dan voldoende capaciteit beschikbaar om alle betreffende Belgische oogpatiënten te behandelen. In Europa wordt momenteel in 5 centra oogbehandelingen aangeboden: Berlijn, Catania, Clatterbridge, Nice en Villigen. Vanaf 2010 kunnen oogpatiënten ook in Essen terecht. Alle vermelde centra (behalve Catania) beschikken over vrije capaciteit om Belgische patiënten op te nemen.

Voor behandeling van andere tumoren (met proton- of koolstof-ion therapie), is er momenteel weinig beschikbare capaciteit in Europa. Afspraken voor Belgische patiënten kunnen dan ook niet gemakkelijk worden bekomen. Dankzij de constructie van nieuwe grote behandelcentra en de uitbreiding van de bestaande centra, kan verwacht worden dat op korte termijn alle momenteel in aanmerking komende patiënten kunnen worden behandeld in het buitenland. In 2008 gaat het nieuwe Heidelbergse koolstof-ion en proton-centrum van start. Dit centrum met 3 behandelkamers verwacht een 1500-tal patiënten jaarlijks te behandelen, waaronder een relatief groot aantal Belgische patiënten. In 2010 wordt het nieuwe protoncentrum in Essen operationeel. Ook dit centrum verwacht een groot aantal Belgische patiënten te kunnen behandelen. In hetzelfde jaar gaat ook het nieuwe koolstof-ion en proton-centrum van start in Lyon. In dit centrum zullen Belgische patiënten geselecteerd worden op basis van de toekomstige bewezen klinische indicaties.

De prijs voor oogbehandeling kan varieert van 3 400€ tot 20 000€. De prijs van proton en koolstofionbehandeling fluctueert van 15 000€ tot 40 000€. Het benodigd budget voor behandeling van 51 patiënten (inclusief reis- en verblijfskosten) wordt geschat op maximum 1,7 miljoen €, in de veronderstelling dat de oogpatiënten worden behandeld in Nice, de paediatrische patiënten in Villigen en de overige in Heidelberg.

Momenteel is er geen omkaderde terugbetaling voorzien voor hadrontherapie (maar terugbetaling van behandelingskost kan eventueel wel bekomen worden via een E 112 formulier). Daarnaast kan een tussenkomst bekomen worden via het Solidariteitsfonds (voor de behandelings- en/of reiskosten) of de Stichting tegen Kanker (voor de reiskosten). We raden aan dat het RIZIV op basis van de huidige klinische bewijzen een beslissing neemt over de terugbetaling van deze therapie. Indien beslist wordt voor de 50-tal patiënten terugbetaling te voorzien, dan is het aangewezen een standaardprocedure binnen een wettelijk kader te voorzien dat vlotte toegang tot de

buitenlandse centra verzekert. Vermits het hier handelt over een experimentele behandeling, is de inclusie van de patiënten in klinische studies binnen een strikt reglementair kader sterk aan te bevelen. De contracten met die centra dienen "all-in" prijzen te voorzien, met zowel de kost van behandeling als accommodatie en transport.

CONCLUSIES EN AANBEVELINGEN

Sedert 1961 zijn wereldwijd meer dan 50 000 patiënten behandeld met protontherapie. Ondanks dit hoge aantal leverden slechts 2 bescheiden studies zwakke klinische evidence voor protontherapie. Voor de meer recent gestarte koolstof-ion therapie, waarmee ondertussen 3 500 patiënten werden behandeld, zijn zelfs nog geen gerandomiseerde gecontroleerde klinische studies gestart. We kunnen enkel veronderstellen" dat de goede resultaten die behaald werden met neutronen voor speekselkliertumoren kunnen worden gereproduceerd met koolstof-ion therapie.

Het totale aantal in aanmerking komende patiënten ligt momenteel ver beneden het minimum aantal benodigde patiënten om de investeringskost van een Belgisch hadroncentrum (van 159 miljoen €) te verantwoorden en het centrum op efficiënte manier te runnen (zonder dat een overgrote meerderheid van patiënten in het buitenland zou moeten worden gerekruteerd).

Overeenkomsten met buitenlandse centra zijn daarom, alvast op korte termijn, een te overwegen optie. Hiervoor is er nood aan een standaardprocedure die voorafgaande betaling kan voorzien en vlotte toegang tot behandeling garandeert. Een centraal comité dient te worden opgericht dat de aanvragen van Belgische radiotherapeuten centraliseert, de patiënten selecteert, de effectieve deelname van iedere patiënt aan een gecontroleerde klinische studie verzekert en eventuele secundaire kankers bij die patiënten levenslang registreert.

Gegeven de huidige afwezigheid van voldoende betrouwbare wetenschappelijke bewijzen voor de klinische doeltreffendheid, is het moeilijk te verantwoorden om de investering in een Belgisch centrum ten laste te brengen van de ziekteverzekering. Desalniettemin kan omwille van redenen van stimuleren van biomedisch onderzoek, innovatie en ondersteuning van lokale industriële partners een investering in de ontwikkeling van een veelbelovende technologie overwogen worden. Hiervoor dienen dan aangepaste financiële bronnen te worden aangesproken.

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Glossary

Carbon-ion	Positively charged carbon atom that has lost 6 electrons
CPT:	Charged particle therapy
CTC:	Common Toxicity Criteria, NCI, Bethesda
GSI:	Gesellschaft für Schwerionenforschung, Darmstadt
Hadron	From the Greak "heavy", strongly interacting particles as protons, ions, neutrons
HICAT:	Heavy-Ion Cancer Therapy, Heidelberg, Germany
HIMAC:	Heavy-Ion Medical Accelerator Complex, Chiba, Japan
IMPT:	Intensity Modulated Proton Therapy
IMRT:	Intensity Modulated Radiotherapy
Ions	Positively charged particle
LET:	Linear Energy Transfer (in keV/µm)
MeV:	Mega electron volt
Proton	Positively charged hydrogen atom that has lost his only electron
RBE	Relative Biologic Effectiveness
SOBP	Spread-out Bragg peak

1 INTRODUCTION

Radiotherapy with photon beams (X-rays), either conventional, 3D-conformal or intensity modulated radiation therapy, is frequently used in the local treatment of cancer. Radiations damage the DNA and in turn block the cell division what leads to the death of cancer cells and the destruction of the tumour. Experimentally, theses approaches can eliminate even the most radio-resistant cancers. In real life however, high doses cause a significant morbidity to the healthy adjacent tissues. Intensity-modulated radiation therapy (IMRT), which can deliver higher doses of radiotherapy to tumoural targets while reducing the dose delivered to selected normal tissues a represents a major advance in the treatment of deeply located tumours. But this still leads to the irradiation of a larger volume of normal tissue what raises the concern that, over time, this extra-exposure of normal cells although at a low-level of radiation will cause secondary malignancies. This adverse effect is a serious threat for paediatric patients, who after initial treatment success would have an almost normal life expectancy. While this risk is also present after treatment in adult cancer patients, the median age at diagnosis is in the seventh decade, and therefore, secondary malignancies after radiotherapy are uncommon.

Charged particle therapy (CPT) in cancer treatment offers theoretical advantages to photon beam radiation. Proton therapy represents a highly conformal technique that combines the advantages of a unique dose distribution in tissues through a sharply localised peak-dose, described as the 'Bragg Peak, of a stereotactic alignment and of a fractionation of the dose. Schematically, the indications for proton therapy are twofold: (a) pushing the dose to aggressive tumours above the conventional limits by 20 to 30% in exploiting the balistic advantages of accelerated protons over photons while decreasing the integral dose to large anatomical structures surrounding the target such as the cerebral hemispheres: typical types of tumours are chordomas and chondrosarcomas of the skull base and cerebellar primitive neuroectodermal tumours (PNET), (b) sparing as much as possible critical normal structures whose proximity to the target could compromise an appropriate delivery of a uniform dose using photons alone: typical situations are tumours close to the optic nerve.

Heavy protons (hadrontherapy), in contrast to photon and lighter particles, can penetrate very deeply losing only a small fraction of their initial energy before reaching the tumour to then transfer almost all their energy at the very end of their track. The depth where the Bragg peak takes place is directly related to the mass and the square of the speed of the charged particle. Therefore, the desired dose can be precisely targeted anywhere in the patient, and by varying the beam energy and intensity the desired dose can be spread out over the whole tumour volume (using the 'Spread-out Bragg peak', SOBP), achieving a plateau of irradiation within a slice of the tumour. In that process, during each session, a few hundred millions heavy protons are accelerated with the aim to reach as many nuclei of cancer cells.

Intensity-modulated proton therapy is, at this moment, mainly experimental although the results of a limited number of case studies are promising. Initially, patients were treated at facilities designed for basic research in high-energy physics and not for the patient care, what obviously often made individual treatments cumbersome. Individual dosage control and precise patient positioning are essential ingredients for the success of this treatment. Moreover, the energy of the beam (that determines the depth of the Bragg peak) in many of the early proton beam machines was only sufficient to treat superficial lesions (such as eye tumours) or intermediate lesions (such as the spinal lesions). Therefore, initial attention was mostly paid to uveal melanomas in the eyes and base of skull sarcomas, and the major emphasis for proton therapy was dose escalation for tumours adjacent to critical normal structures that constrained the doses that could be given with photons and where the success rate of conventional radiotherapy was low. More potent cyclotrons can now deliver hadrons to a depth of up to 27 cm and can thus hit deeply-rooted tumours.

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[a] Levin, WP,Kooy, H,Loeffler, JS,DeLaney, TF. Proton Beam Therapy, Minireview. British Journal of Cancer 2005; 93, 849-54.

Particle beam therapy is therefore an experimental but emerging and promising technology, requiring however, large budgets, both for the building and maintenance of the needed facilities as for the running of the centre with highly skilled physicists and radiotherapists. It was estimated that by the end of 2006 about 49.000 patients had received radiation therapy by proton beams in the 25 active centres worldwide of which 9 in Europe (none in Belgium).[b] The building of a single Belgian centre, capable of treating approximately 1000 patients yearly would be a heavy investment. In countries where proton therapy is available, cost per patient treated are around 20.000 €, excluding the cost for building the infrastructure, or approximately 2.5 times the cost for comparable photon beam radiotherapy.

It is, at this moment, difficult to predict the possible and probably extension of indications that could be the consequence of the local availability of such a centre. A further extension of indications could indeed lead to an important increased cost for the community.

In this report we will present the rationale behind the use of ions in the treatment of cancer, review the medical evidence with regard to the efficacy and safety of hadrontherapy, calculate the number of patients who could reasonably beneficiate for the relevant indications considered. The last part is devoted to the costs of building and running a hadrontherapy centre in Belgium.

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[b] Sisteron, J. World wide charged particle patients Totals. Particles (2004); 30:20

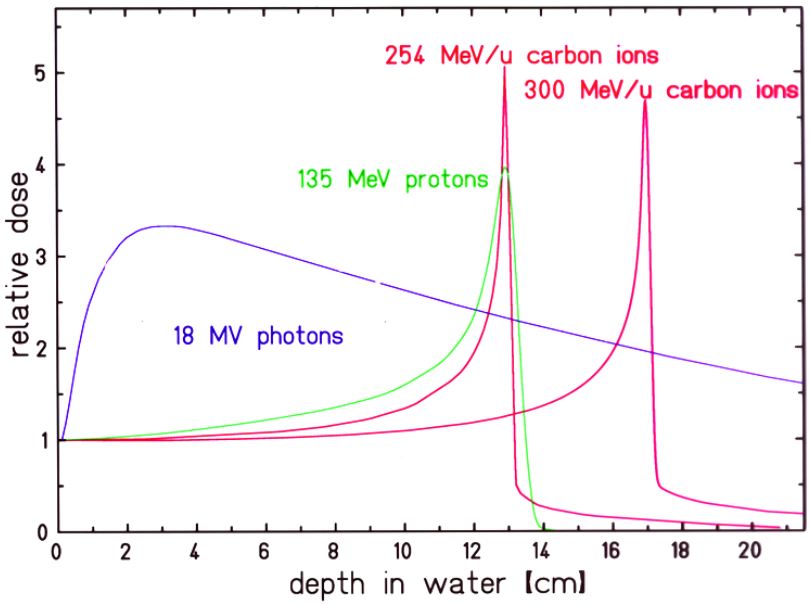
2 BACKGROUND

2.1 PHYSICAL PROPERTIES OF IONS BEAMS

Robert Wilson was the first to investigate the depth dose profile of protons, positively charged hydrogen ions, produced at the Berkeley cyclotron in 1946 and to see the medical potential of this form of radioactivity.

Protons, like all charged particles, slow down as they travel through a material as a result of electromagnetic interactions. But unlike the X-rays or photons that start loosing their energy as soon as they hit the surface of the body, ions loose their energy only in the end of their track- the so-called Bragg peak, named after the physicist who as early as 1905 described the increase in ionization density at the end of the alpha particles range - while the dose elsewhere is low. The slower the ions move, the more efficient they are at ionizing atoms in their path and the more likely they are to interact with atomic nuclei. The increase in ionization density towards the end of the particle track allows to let a higher energy in a deep-seated tumour than would be possible using conventional photon beams (Fig. A) while sparing the healthy tissues in front of the tumour and the surrounding organs.

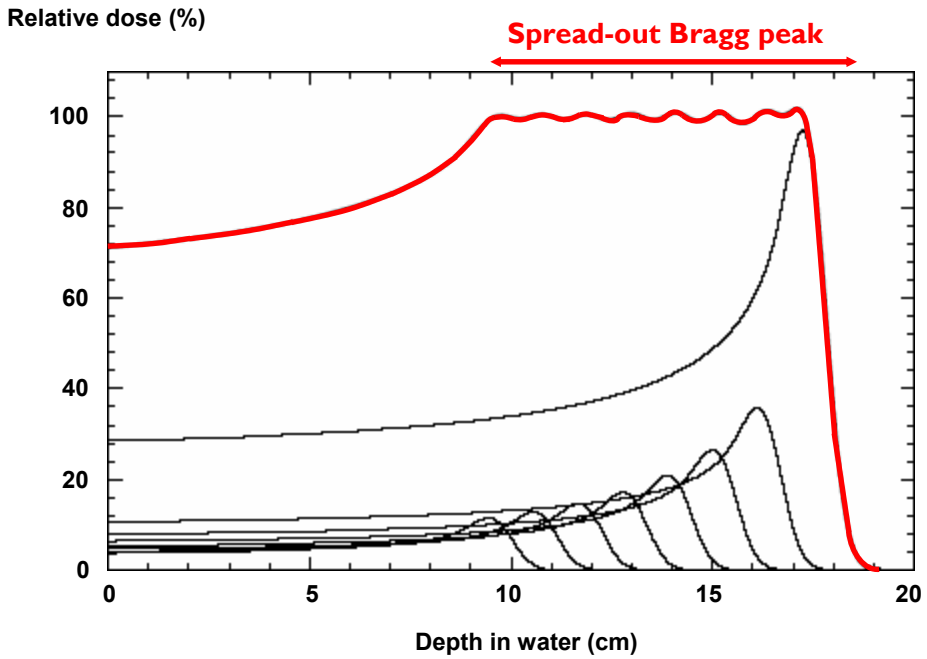
Fig. A: Depth dose profiles of photons, protons and carbon ions of 250 MeV/n and 300 MeV/n [Kraft from Weber]**.**



2.2 SPREAD-OUT BRAGG PEAKS IONS BEAMS

One single Bragg peak alone is not suitable for tumour treatments, simply because the spatial dimensions of the peak region are too small. To irradiate a cylindrical slice in the tumour, one has to sum up several single peaks of decreasing energy from the same incident beam to create a spread-out Bragg peak (SOBP). By using appropriate weights for every peak, a homogeneous high dose region can be achieved (Fig. B). This process will be repeated for each successive rod.

Fig. B: Dose distribution in a spread-out Bragg peak (thick redline) with a modulation width of 9 cm. In this example, the SOBP is the sum of eight single peaks with different positions and intensities (thin lines) of the protons beam *[from Wilkens, PhD thesis, Heidelberg, 2004]*.



2.3 RADIOBIOLOGICAL PROPERTIES OF IONS BEAMS

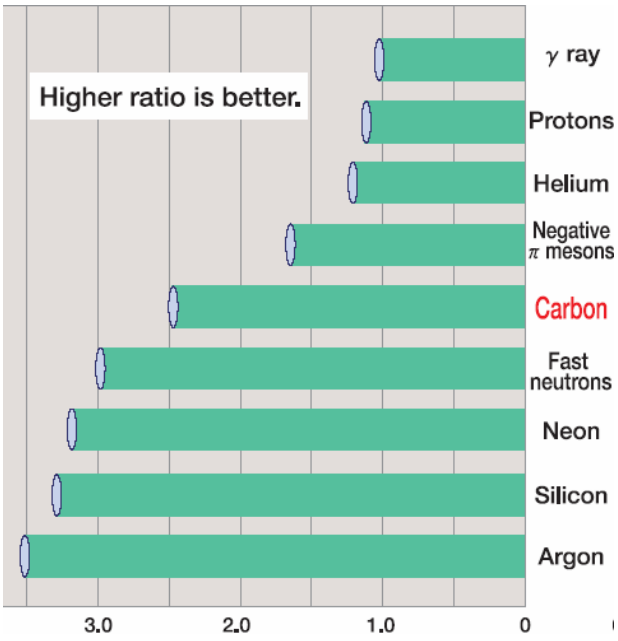
Radiation quality is defined by the nature, charge and energy spectrum of the particles and can be characterized by their Linear Energy Transfer (LET in keV/µm). LET depends on the energy and particle species: Photons, including X rays and gamma rays, possess LET values of 0.1-10 keV/µm. The largest biological effectiveness is achieved by charged particles possessing an intermediate LET value of 150 keV/µm. High-LET radiotherapy results in better tumour control.

The Relative Biologic Effectiveness (RBE) depends of the energy loss per unit length of particle track travelling in water but also of her radial distribution according to the projectile energy. At high energies the track is wide and LET is low, therefore, the ionization events are well separated and light particles of high energy mostly act as sparsely ionizing radiation. Consequently, the combination of the two parameters, LET and energy, determine the RBE and its position in the LET spectrum. With decreasing energy the track narrows and the energy loss or LET becomes larger. Consequently, the produced damage has a higher local density resulting in a diminished reparability of the lesion and a greater RBE [Heilmann 1996]. Finally, at the very end of the track the diameter shrinks and LET increases further, yielding an overproduction of local damage where the major dose is wasted as an overkill of the system [Butts 1967]. Therefore, RBE decreases rapidly behind the Bragg maximum towards the end of the track.

For protons, the RBE is increased only for the last fraction of a centimetre of the range. For clinical use, RBE has been determined for extended volumes and an increase of 10 to 20 % was found. Therefore, in treatment planning for proton irradiations, the

absorbed physical dose is currently multiplied with the global factor RBE = 1.1 to RBE = 1.2. This dose is then called the biological effective dose and is given in GyE (Gray equivalent). The mean RBE calculated at the centre of the Bragg peak is more than 2 times higher than with protons (Fig. C).

Fig C: RBE for different particles



2.4 PROTONS AND HEAVY IONS RADIOTHERAPY

The energy of the proton beam is adjusted to match the tumour depth. Moreover, by combining protons with different energies in a single beam, the Bragg peak can be modulated into a plateau that dumps a high dose of radiation throughout the depth of the tumour.

Newer than protons on the particle-therapy scene is carbon therapy. Heavy ions, such as carbon, have a higher RBE than protons and are thought to provide more effective treatment for certain, deep-seated tumours that are often "radioresistant".

This is because the rate at which a charged particle loses energy in a material - which is quantified by its linear energy transfer (LET) - increases with the mass of the particle. Helium ions were first used at Berkeley in 1957, while neon ions have been used to treat only a few hundreds patients. As the mass of the particle increases there is a higher relative biological effectiveness. But the ratio of RBE between the peak at the end of the track and the initial plateau gets worse when using a particle with a higher mass. The optimal RBE using ions has since been found to lie in the range between lithium and carbon. Fast neutrons have a higher RBE than carbon ions but there is actually no more facility in activity.

For an extended tumour volume, the RBE increases to the distal part, i.e., to the maximal range because there Bragg peak ions contribute mostly to the dose. In the region closes to the surface, the RBE is small. In order to achieve a homogeneous biological effect across the complete tumour, the physical dose has to be decreased to the distal end. This has to be taken into account in the entire planning procedure. There are currently just three heavy-ion treatment facilities in the world - two in Japan and one in Germany - all of which use carbon ions.

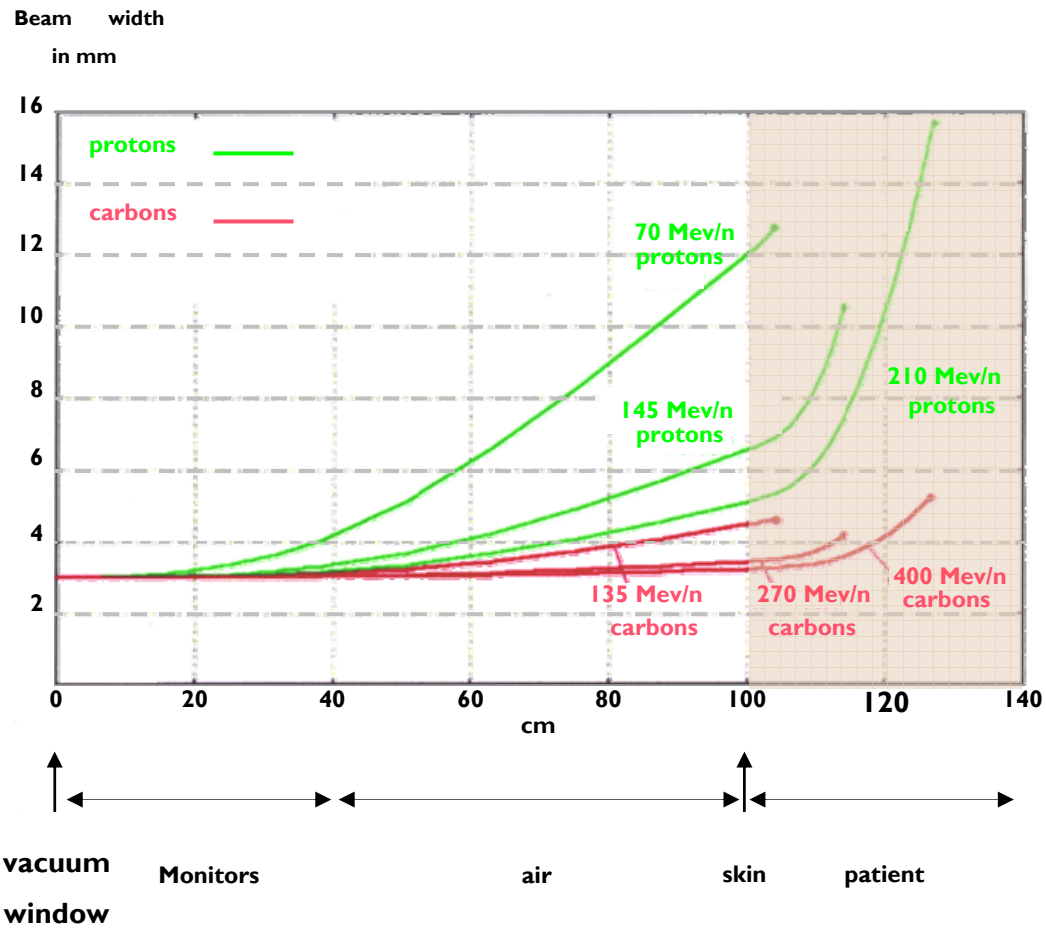
2.5 LATERAL SCATTERING

For the clinical application, the lateral scattering of the beam is more important than the longitudinal. Because of possible range uncertainties the treatment planning will avoid a beam directly stopping in front of a critical structure. Therefore, tumour volumes close to critical structures can only be irradiated with the beam passing by. How close the beam can get is consequently determined by the lateral scattering.

Lateral scattering results from weak magnetic interactions of the projectiles with the target nuclei but depends also of the kinematic of nuclear reactions, especially at the distal side of the Bragg peak where the primary projectiles are stopped [Weber 1999].

In figure D, the lateral scattering of a therapy beam in a real setup is compared for protons and carbon ions from the vacuum window to the position of the patient and then up to 27 cm in water (corresponding to the distal edge of the Bragg peak for carbon ion with an energy of 400 MeV/n). The lateral deflection of 400 MeV/n carbon beam is approximately 1 mm up to a penetration depth of 20 cm in contrast to 3 and 5 mm at a depth of 10 cm for proton beams of 210 and 145 MeV respectively. The lateral deflection of carbon beams is thus far less than with any proton beam.

Fig. D: Comparison of the lateral scattering of proton and carbon beams as function of the penetration depth from exit window to the patient [Weber 1996].



3 THE PRODUCTION OF IONS

3.1 THE INJECTOR SYSTEM

At present all carbon ion facilities use an electron cyclotron resonance (ECR) ion-source for injection. Very different ions can be produced: from H_2^+, H_3^+, Ne^+ to C^{4+} or O^{5+}.

The ions are usually accelerated by a linear accelerator (linac) to an output energy of around 6 to 7 MeV/n. The linac consists of a Radio Frequency Quadrupole (RFQ) accelerator followed by a Drift Tube Linac (DTL). The 'drift-tube' is made of a series of co-linear tubes connected alternately to opposite ends of a high-frequency HT generator. The particles experience an energy gain each time they cross a gap. The entire accelerating structure is held under high vacuum. It suits only to the acceleration of heavier particles where the increase in velocity is relatively modest. The C^{4+} ions are fully stripped to C^{6+} before being injected and accumulated into a synchrotron or a cyclotron.

3.2 THE ACCELERATOR

The ion beam is accelerated from 6-7 Mev/n at the entry to several hundreds of MeV/n.

For proton therapy, there seems to be no preference for cyclotrons or synchrotrons. Both types of accelerators have their benefits and shortcomings. Cyclotrons produce a very stable beam intensity that is suitable for beam scanning but the energy variation has to be performed with absorber systems and this is at the expense of a higher radioactive background for the patient. Cyclotrons are smaller but heavier than synchrotrons. At present, both, cyclotrons and synchrotrons are used for proton therapy with good results.

For heavier ions like carbon, a synchrotron appears to be preferable since a cyclotron would become very heavy and probably more expensive than a synchrotron. In addition, synchrotrons can accelerate ion beams up to energies of around 400 MeV/n and offers the unique possibility to change the extracted beam energy from pulse to pulse within about 1 second, the typical time in between 2 spills, and the next scan can be performed with a different radiological depth. More than 250 different accelerator energies can be produced.

Residual range and beam energy

The depth required for irradiating the tumour till the distal edge, or residual range, depends on the beam energy. The deeper the tumour is located, the higher the energy needed to accelerate the particle, the more powerful the accelerator required. The energy required for carbon ions to reach the depths of 18, 22, or 30 cm in water is respectively 310, 350 or 430 MeV/n. Obviously the kind of indications and organs will influence the power needed. A 17 cm range is sufficient to treat 70% of the head and neck tumours, 65% of the brain, oesophagus and lung tumours, 55% of the liver tumours but only a very small fraction of bone and soft tissue sarcomas, prostate and rectum tumours. A 310 MeV/n represents probably a good compromise. If needed, a linear accelerator could be added to boost the carbon ions up to 435 MeV/n.

The second important parameter is the spread-out Bragg peak (SOBP), to say the thickness of the slice that can be treated at once. A 12 cm range for the SOBP is already sufficient to treat more than 90% of tumours. The last parameter, the field diameter, is no more relevant in case of an active scanning system.

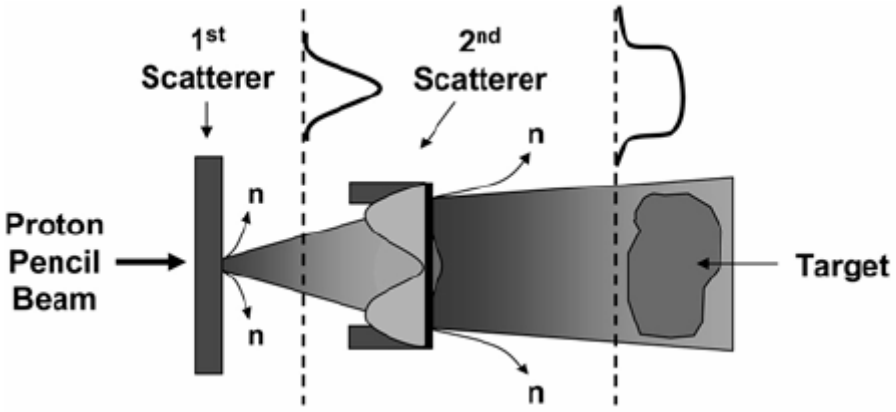
3.3 THE ION DELIVERY SYSTEMS

The ions emerging from a cyclotron or synchrotron form a narrow pencil beam (4-10 mm in diameter). To cover a treatment field of practical size, the pencil beam must be spread laterally. Several techniques exist for this:

Passive scattering

Passive scattering is by far the simplest technique: A scattering metal foil is used to scatter sideways the beam of protons and thus to cover a larger area, large enough for therapy. (Fig. E: 1st & 2d scatterers). In a radiation field produced by a passive absorber, the RBE depends only on the depth and there is no lateral RBE variation.

Fig E: Passive scattering



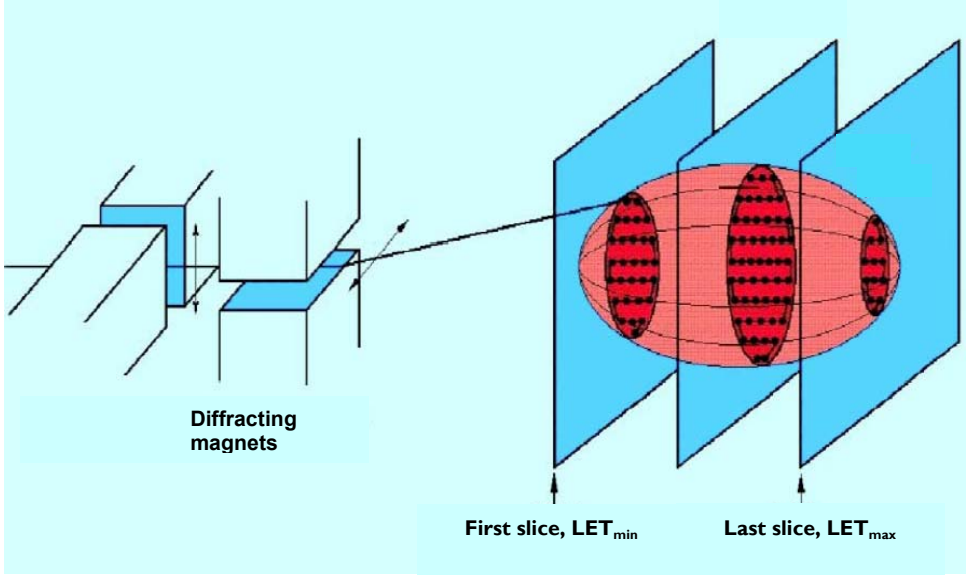
From Hall et all IMRT, Protons & the risk of second cancer 2006

Active scanning

This technique uses magnetic fields to steer the beam in the desired direction (Fig. F). The small circular beam is deflected (bended) in vertical and horizontal directions by using 2 pairs of fast scanner (weighty) magnets and scanned many times across the defined treatment field, with the energy and intensity varying so that the dose in each micro volume of the tumour can be optimized.

The beam intensity is controlled accurately at every instant in such a way that the delivered dose is adapted to the depth of the slice. The whole tumour volume is not irradiated at the same time but spot after spot and slice after slice. This technique, called "intensity modulated proton therapy" is able to contour the proximal edge of the spread out Bragg peak (SOBP) as well as the distal edge. This method has the advantage of not degrading the beam and of not producing unwanted secondary neutron radiation. Scanning beams are available only in European facilities.

Fig. F: The ions emerge from a cyclotron or synchrotron as a narrow pencil beam. To cover a treatment field of practical size, the beam is scanned.



Passive scattering or active scanning

Passive scattering is by far the simplest technique but suffers the disadvantage of increased total-body effective dose to the patient. The scattering foil hit by protons inevitably produces neutrons that deliver a total-body equivalent dose that is even larger than the leakage radiation from conventional linear accelerators.

Doses outside the edge of the treatment field

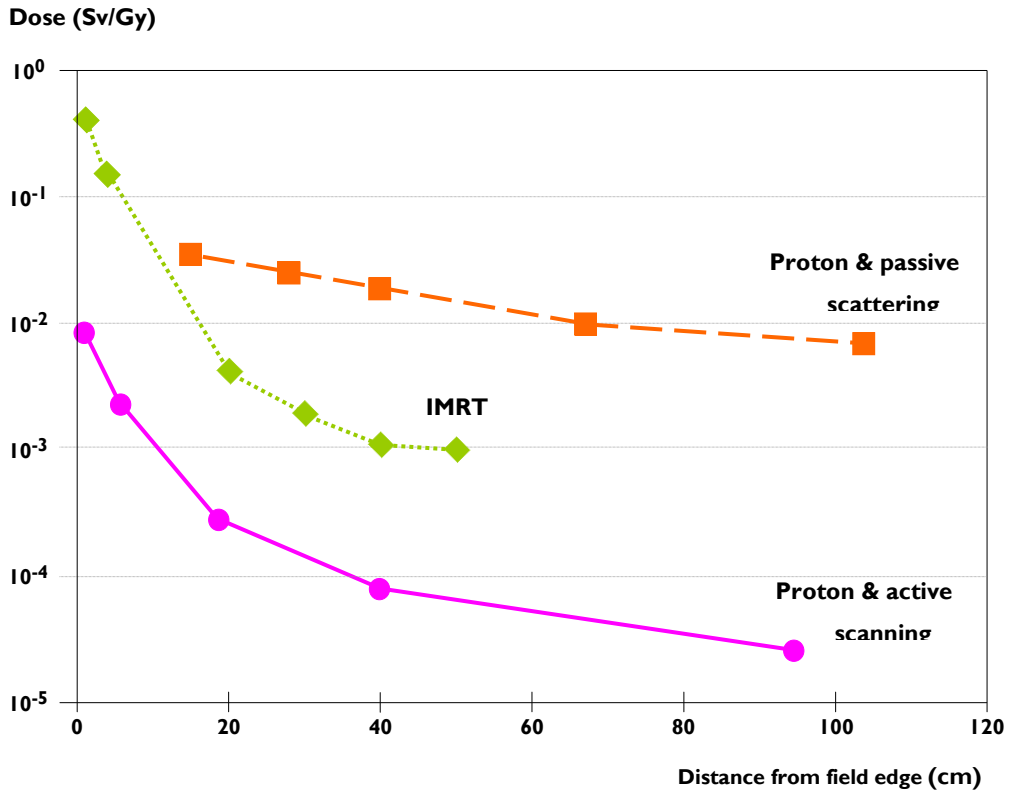
Intensity-modulated radiation therapy allows dose to be concentrated in the tumour volume while sparing normal tissues. This property is a major step forward, especially for children, in whom sparing normal tissues to avoid a subsequent growth detriment is critically important. However, the downside to IMRT is the increase in total-body dose.

Delivery of a specified dose to the isocenter from a modulated field delivered by IMRT requires the accelerator to be energized for a longer time. The total-body dose will be increased because of leakage radiation.

In the case of X-rays, secondary photon radiation consists of scatter, which predominates near the treatment field, and leakage, which predominates away from the treatment field. At this point, we might be tempted to suggest that X-rays should be replaced by protons, because this type of particle irradiation results in a reduced volume of normal-tissue exposure, with a consequent reduction in the incidence of second cancers.

Many proton facilities use passive modulation to produce a field of sufficient size; that is, the pencil beam of protons that emerges from the cyclotron or synchrotron is made simply to impinge on a scattering foil to produce a field of useful size. The scattering foil becomes a source of neutrons, which results in a total body dose to the patient. The consequences of this exposure are shown dramatically in Fig G. Passive modulation results in doses distance from the field edge that are 10 times higher than those characteristic of IMRT with X-rays. The full benefit of protons is achieved only if a scanning beam is used in which doses are 10 times lower than the doses from X-rays. However, this risk reduction should the pencil scanning beam system be used is not yet supported by evidence.

Fig. G: The equivalent dose outside the edge of the treatment field as a fraction of the dose at the isocenter for protons with passive modulation, with active scanning and for IMRT.



The doses are rough estimates and are facility dependent.IMRT was administered with a 6-MV X-rays 4-field The passive modulation data are from Yan et al., renormalized to a 10-cm X 10-cm field and to a neutron RBE of 10. The pencil-beam scanning data are from Schneider et al., renormalized to a 10-cm X 10-cm field and an RBE of 10. Both proton curves were produced by Dr. Harald Paganetti, Massachusetts General Hospital and Harvard Medical School. X-ray data are 4-field IMRT. Unpublished data for a 6-MV linear accelerator were provided by Dr. C. W. Wuu, Columbia University Medical Center, New York.

3.4 THE GANTRY

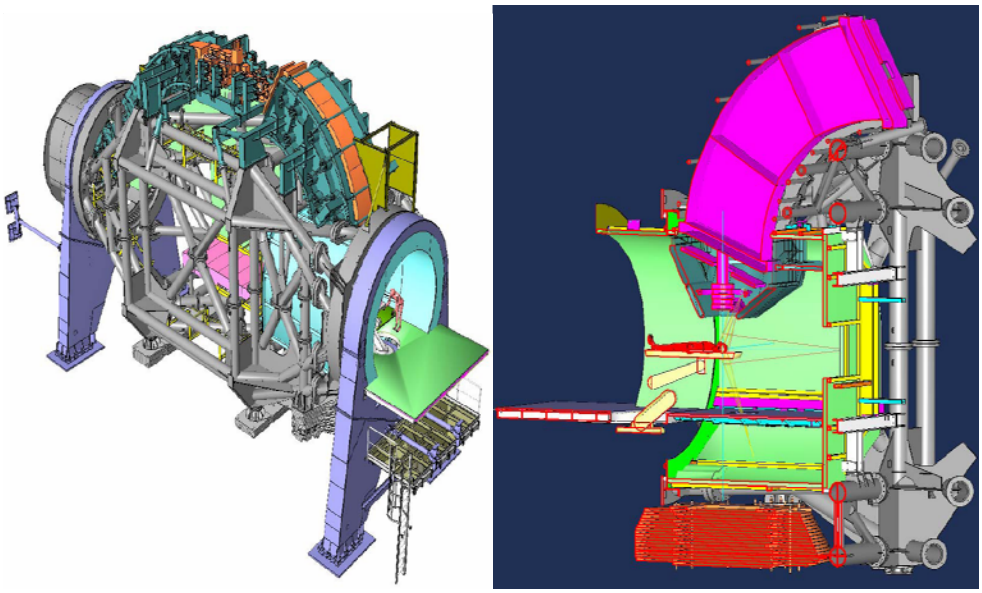
The term "gantry" stands for a rotating system of beam delivery (a kind of spotlight) that allows flexible irradiation from any desired angle one to administer the beam in any direction to a lying patient.

In photon therapy, the radiation source is moved around the patient.

In particle therapy, it is impossible to move the accelerator around the patient. Instead, deflection magnets are mounted on a turnable system. But at present the systems are not equipped with scanning. An excentric gantry has been built at PSI, Villigen, and three gantry systems are installed at the NPTC, Boston.

For carbon ions, the first gantry system will soon be realized at Heidelberg (Fig. H). Because of the greater ion energies necessary to obtain the same penetration depth and because of the higher magnetic rigidity of the beam, the design of a rotating carbon gantry cannot be a straightforward blow-up of a proton design. Upstream scanning can reduce the gantry radius. The maximum displacement of the iso-center is in the range of 1 mm under any rotation angle. As a result of the mechanical design, the weight of a carbon gantry is between 300 and 600 tons i.e. six times larger than that of a proton gantry.

Fig H: Layout of the HICAT Carbon Gantry



Goal for beam reproducibility in the iso-center: ± 0.5 mm
Total rotating weight: 570 tons of which 145 tons of beam transport components
Weight of room fixed components: 130 tons

3.5 TREATMENT PLANNING

Before the actual dose calculation starts, the target volume is divided into slices of equal radiological depth (Fig. I). Each slice then corresponds to the range of ions at a defined energy of the accelerator. The scan positions of the raster scanner are then defined as a quadratic grid for every energy. In the last step, the particle number at each scan point is optimized iteratively until a predefined dose at each point is reached.

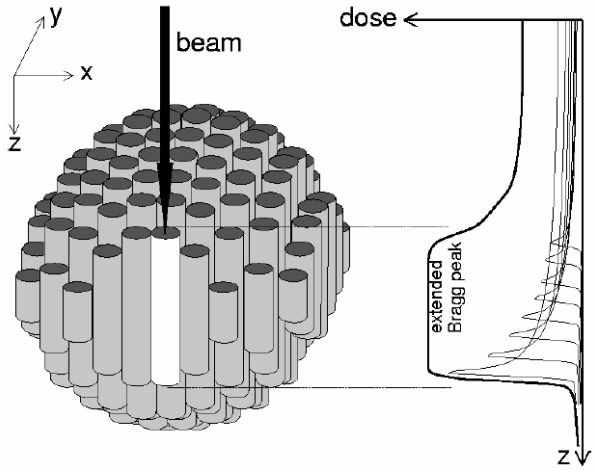


Fig. I Principle of depth scanning: the tumour volume is dissected in rods that are filled with a non-linear superposition of Bragg peaks by changing the particle energy From Weber, 2000

3.5.1 Clinical dosimetry of ion beams

Measurement of Absorbed Dose

The determination of absorbed dose to water in all operating ion facilities is currently based on ionization chamber dosimetry. For this purpose, commercial ionization chambers (mainly thimble type chambers) are used which are calibrated by the manufacturer in a field of Co-60 in terms of absorbed dose to water. Initially at HIMAC chambers calibrated in terms of air kerma were used, but the transition to water absorbed dose was performed recently.

This procedure is recommended also in the latest Code of Practice of the International Atomic Energy Agency, the technical report series TRS-398, which is currently the only international guideline for clinical dosimetry of ion beams.

Dose Verification

The verification of the dose delivered to a patient by a certain treatment plan is one of the crucial points of any quality assurance system in radiotherapy. In conventional therapy with photons it is common to measure the dose delivered by a treatment plan at a single point in a phantom in order to check the calculation of monitor units as well as the monitor calibration.

This procedure is used also for the passive field shaping systems, like HIMAC, where every treatment field is checked every day before delivery. This procedure is sufficient for a static treatment field.

For a dynamic dose delivery, like the 3D raster scanning system, this procedure is not sufficient, since the dose delivery may be correct at one point in the treatment field, but deviations may appear at another point. Therefore, the dose has to be verified simultaneously at many points in the field. Such a method was introduced at the GSI, using a set of 24 small volume ionization chambers connected to a motor-driven phantom. It allows an efficient check of the absorbed dose in the treatment field at many points and furthermore the direct comparison with the treatment planning dose at these points.

3.5.2 Imaging for in vivo verification of treatment delivery

Production of positron-emitting nuclei by protons and carbon ions

With the irradiation concentrated on the tumour it is very important to evaluate accurately the irradiated volume. A very clean method to visualize the target is to register the photons emitted by the target through a PET scanner.

In the case of a protons beam (Fig. J), ^{11}C, ^{10}C and ^{15}O are created mostly via (p,n) or (p,2n) reactions on ^{12}C and ^{16}O nuclei. In this case all the positron-emitting nuclei are fragments of target carbon and oxygen nuclei at rest.

In contrast, carbon beams (Fig. K), produce ^{11}C and ^{10}C nuclei mostly via fragmentation of the ^{12}C projectile while ^{15}O nuclei are produced from the target ^{16}O nuclei. The stripping of one or two neutrons converts the stable ^{12}C isotope into the positron-emitting isotopes ^{11}C or ^{10}C respectively.

Fig. J: Production of β+ emitters with protons beam

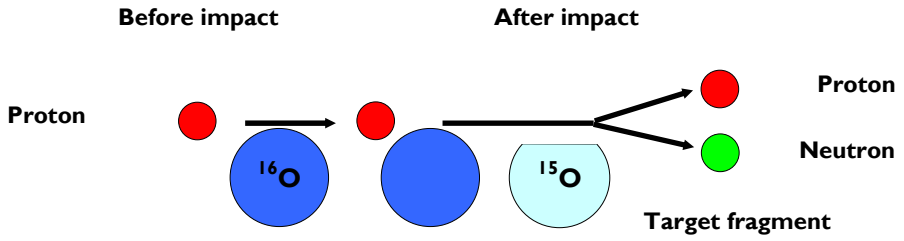
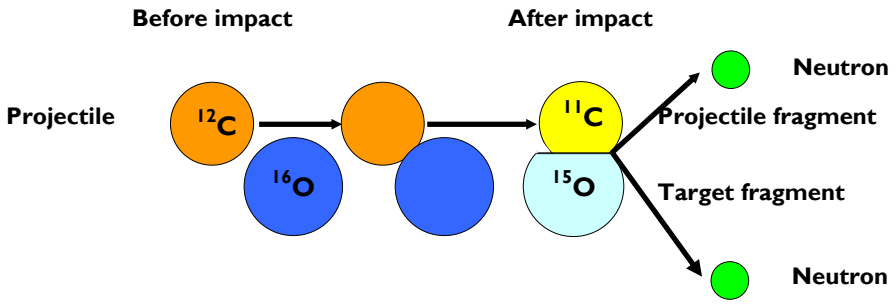


Fig. K: Production of β+ emitters with carbon-ions beam



The most abundant products suitable for PET detection after proton and carbon ion irradiations are ^{11}C (T1/2 = 20.334 min), ^{15}O (T1/2 = 2.037 min.) and ^{10}C (T1/2 = 19.3 s)(Table 1). These radioactive isotopes decay by β^+-particle emission. As soon as the β^+-particles combine with electrons, they annihilated. Each event gives rise to two photons that are emitted in opposite directions and simultaneously registered by the gamma camera.

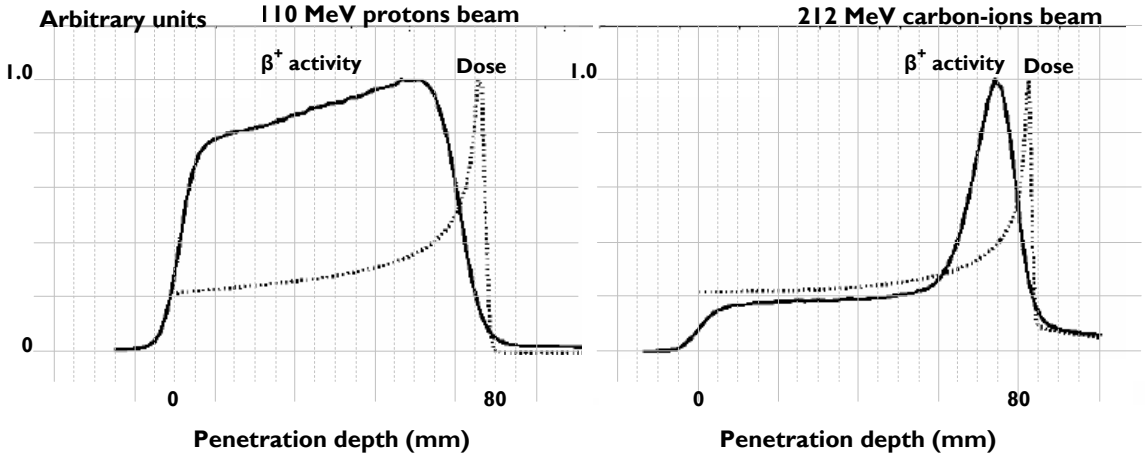
Table 1: Measured yields of positron-emitting nuclei (per beam particle, in %)

	Proton	Proton	Proton	^{12}C	^{12}C	^{12}C
	110 MeV	140 MeV	175 MeV	212 MeV	260 MeV	343 MeV
^{11}C	2.2%	3.4%	4.7%	10.5%	14.7%	19.9%
^{10}C	0.1%	0.2%	0.2%	0.8%	1.2%	1.5%
^{15}O	0.8%	1.2%	1.6%	2.1%	3.1%	5.0%

Parodi K 2004 On the feasibility of dose quantification with in-beam PET data in radiotherapy with 12C and proton beams PhD Dissertation Technische University of Dresden

Because the loss of one or two neutrons causes only small perturbations, these isotopes continue to travel with almost the same velocity to almost the same range. Therefore, the measurement of the coincident emission of the two annihilation gamma quanta can be used to trace back the stopping points of the carbon ions. In contrast to the proton irradiation, the maximum of β^+-activity produced by carbon ions is located very close to the Bragg peak and thus clearly marks its position (Fig. L).

Fig. L: Pattern of β+ emission by protons and carbon-ions beams with identical penetration depths



3.5.3 Beam on-line PET

PET images are constructed by using only the detection events after the beam irradiation stop. The measured activity distribution corresponded to the irradiated dose distribution. The distinctness of the PET image increased as the time of the measurement since more events are detected. However, the number of positrons/cm³ measured in the target is 200 times lower than during an ordinary PET scan. Since the spatial relationship between delivered dose and induced β^+ activity is complex, a sophisticated software has to be included to take into account the mean distance covered by the positron and then by the 2 annihilation photons until they hit the detectors.

For useful clinical interpretation, measured PET images have to be compared with corresponding PET expectations calculated on the basis of the planned treatment. The quantities of main interest are the distal dose fall-off and the lateral field dimension which influence the accuracy of range and field position verification respectively.

In situ PET represents thus a powerful tool for the visualization of the particle distribution inside the patient's body in the course of the treatment.

It allows a comparison between the planned treatment and the one actually performed. Furthermore is capable of detecting unpredictable deviations between planned and delivered treatment due to minor positioning errors.

3.5.4 Quality control

3.5.4.1 PET images for quality control

A PET image is taken every day and compared to the PET image of the first day of treatment with each PET image during the comparatively long period of treatment. Wherewith, if the difference between both images is confirmed by reducing the tumour size and changing the body shape, then the first proton treatment plan is immediately corrected to a new plan. As a result, proton or carbon treatments of high accuracy can be offered to the patient. In practice, the daily precision of the patient positioning and the irradiated beam condition is evaluated with the change of the measured activity distribution. The change is then used for the setup of the margin in the proton treatment planning system.

3.5.4.2 Machine control data

Position, energy, particle numbers used for each beam spot in a treatment field, all are registered. With this information, it is possible to calculate the absorbed dose and the biological effective dose.

In case of an interruption of the electric supply, as the last treated spot has been registered with the applied dose, the treatment can resume exactly at the next beam spot in accordance with the planning.

3.5.4.3 Reporting

The electronic record includes for each patient all the data used or generated during the treatment planning like CT- and MR-images, PET images gained during the irradiations for each fraction. The record also contains the measured actual position of the beam at every beam spot, as well as the measured intensity at each spot, as well as the deviation from the planned values.

4 CLINICAL EFFECTIVENESS

4.1 CLINICAL RESEARCH QUESTIONS

The clinical research questions we will try to answer are:

1. For which cancers has hadrontherapy (proton beam therapy, carbon ion therapy) a superior efficacy with regard to the current treatment by improving local control tumour, disease free survival and/or overall survival?
2. In which treatments has hadrontherapy less side effects than the actual one?
3. What is the place of hadrontherapy in actual clinical pathways?
4. Is there room for hadrontherapy in the treatment of other diseases than cancer?

4.2 LITERATURE REVIEW

The literature review complies with the search procedure in use at the Belgian Health Care Knowledge Centre (KCE).

4.2.1 Systematic search

HTA reports were searched in the CRD database (http://www.crd.york.ac.uk/crdweb/) with the terms "hadrontherapy" and "proton beam therapy". We found 8 HTA reports.

Studies were also searched in Medline (126 references) and Embase (41 references) from 2000 to 2007 according to the following strings. The term "charged particles" is binded to the Meshterm "heavy ions".

Search string for Medline (19/03/2007):

1 Database: Ovid MEDLINE(R) 1950 to Present with Daily Update

Search Strategy:

---

1 *Elementary Particles/ae, tu [Adverse Effects, Therapeutic Use] (11)

2 *Heavy Ions/ae, tu [Adverse Effects, Therapeutic Use] (116)

3 *Protons/ae, tu [Adverse Effects, Therapeutic Use] (358)

4 *Radiotherapy, High-Energy/ae, ec [Adverse Effects, Economics] (484)

5 *Alpha Particles/ae, tu [Adverse Effects, Therapeutic Use] (105)

6 Hadron therapy.mp. (29)

7 Proton therapy.mp. (318)

8 Carbon-ion therapy.mp. (27)

9 Heavy-ion radiotherapy.mp. (33)

10 Carbon beam.mp. (40)

11 Heavy ion.mp. (634)

12 Ion gantry.mp. (3)

13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (1873)

14 limit 13 to yr="2000 - 2007" (814)

15 limit 14 to humans (582)

16 limit 15 to (clinical trial or consensus development conference or consensus development conference, nih or controlled clinical trial or government publications or guideline or meta analysis or practice guideline or randomized controlled trial or "review") (126)

17 from 16 keep 1-126 (126)

Search string for Embase (11 apr 2007):

#1. elementary AND particles AND [2003-2007]/py	97
#2. ('elementary particles'/exp OR 'elementary particles') AND [2003-2007]/py6	196 43
#3. 'heavy ion'/exp/dd_dt AND [2000-2007]/py	382
#4. 'heavy ion'/exp AND [2000-2007]/py	6
#5. 'proton'/exp/dd_dt/mj AND [english]/lim AND [huma s]/lim AND [2000-2007]/py	1,357 23
#6. 'proton'/exp AND [english]/lim AND [humans]/lim AN D [2000-2007]/py	332 39
#7. 'ion therapy'/exp AND [humans]/lim AND [2000-2007] /py	48
#8. 'alpha radiation'/exp AND [english]/lim AND [human s]/lim AND [2000-2007]/py	4 2,342
#9. 'hadron therapy' AND [2000-2007]/py	
#10. 'carbon-ion therapy'/exp AND [2000-2007]/py	1,844
#11. 'ion gantry' AND [2000-2007]/py	1,534
#12. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	
#13. # AND 12 AND #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR # 7 OR #8 OR #9 OR #10 OR #11 AND [humans]/lim AND [2000-2007]/py	65
#14. # AND 13 AND # AND 12 AND #1 OR #2 OR #3 OR #4 OR #5 OR #6	
OR #7 OR #8 OR #9 OR #10 OR #11 AND [humans]/lim AND [2000-2007]/py AND ([article]/lim OR [review]/lim OR [short survey]/lim) AND [humans]/lim AND [2000-2007]/py	**41**
#15. # AND 14 AND # AND 13 AND # AND 12 AND #1 OR #2 OR #3 OR #4 OR #5 OR	
#6 OR #7 OR #8 OR #9 OR #10 OR #11 AND [humans]/lim AND [2000-2007]/py AND ([article]/lim OR [review]/lim OR [short survey]/lim) AND [humans]/lim AND [2000-2007]/py AND ([cochrane review]/lim OR [controlled clinical trial]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim AND [2000-2007]/py	
#16. # AND # 15 AND 14 AND # AND 13 AND # AND 12 AND #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 AND [humans]/lim AND [2000-2007]/py AND ([article]/lim OR [review]/lim OR [short survey]/lim) AN D [humans]/lim AND [2000-2007]/py AND ([cochrane r eview]/lim OR [controlled clinical trial]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim) AND [2000-2007]/ py AND [embase]/lim	
Emtree terms : 'elementary particle', 'heavy ion radiation' (1978),'ion therapy' (2006), 'fast proton radiation', 'drug therapy', 'adverse drug reaction'	

4.2.2 INAHTA agencies and research

We sent mails to the INAHTA agencies for unpublished and/or HTA reports in progress. For new references, we contacted several hadron therapy centres in Europe (Austria, MedAustron; Berlin, Charité University Hospital; Catttania, INFN; Clatterbridge, Centre for Oncology; Darmstadt, GSI; Essen, WPE; Heidelberg, HIT; Lyon, Etoile ; Munchen, RPTC1 ; Nice, Centre Antoine-Lacassagne ; Orsay, CPO; Pavia, CNAO; Uppsala, The Svedberg Laboratory; Villigen, PSI) in Asia (Chiba HIMAC; Hyogo HIBMC; Kashiwa NCC; Tsukuba) in North-America (Bloomington, MPRI; Boston, Harvard; Boston, MGH Cancer center; Houston, MDAnderson; Illinois, Northern Illinois University; Jacksonville, Florida Proton Center; California, Loma Linda; Vancouver, BC Cancer Agency) and in Russia (St Petersburg, CRIRR; Moscow).

4.2.3 Hand searching

In addition, the reference lists of the selected articles and HTA reports were searched for any missing relevant publications.

4.2.4 Studies in progress

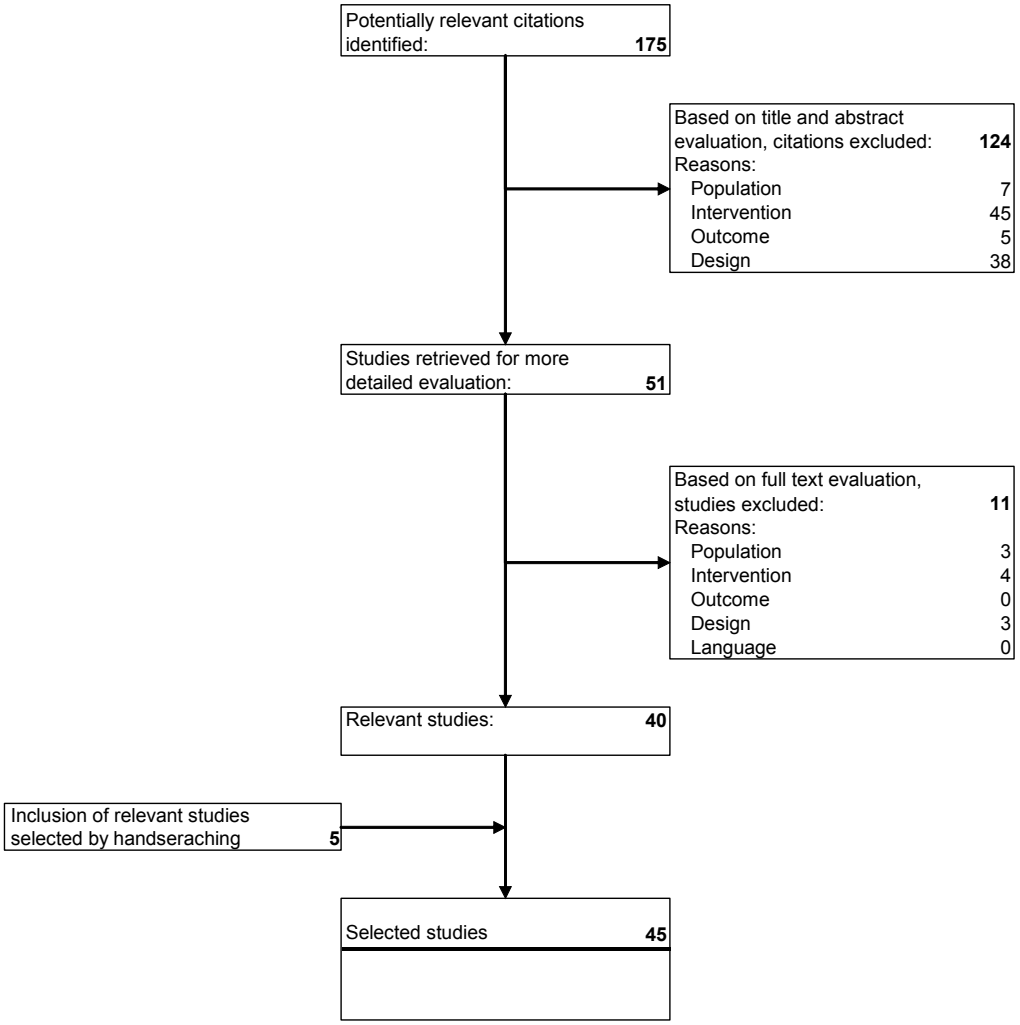
An additional search has been done for studies in progress on the site http://www.controlled-trials.com/mrct/search.html which include a metaregister of controlled trials (including 13 databanks of trials in progress). The terms "carbon ion", "hadron", "proton beam" and "proton radiation" have successively been used. Our search does not found controlled trials in progress with carbon ion. Three protocols have been found about proton therapy: one for patients with resectable pancreatic cancer (proton beam and capecitabine) in Massachusetts General Hospital, one for patients with stage I and II prostate cancer (comparison of two doses proton beam) in Loma Linda and Massachusetts and finally one in patients with chordomas (comparison between two doses) in Houston Texas.

The database ClinicalTrials available on the site http://clinicaltrials.gov/ interrogated with the terms "proton beam" reported non controlled trials in progress in patients with "retinoblastoma" (phase II trial, children), "medulloblastoma or pineoblastomas" (phase II trial), "chondrosarcomas" (phase II trial) or "unresectable hepatocellular cancer or hepatic metastasis" (phase I trial). The search with the terms "carbon ions" or with "carbon ion" or with "carbon" did not find relevant studies in progress.

4.2.5 Studies selection

We used the following criteria

- Selection criteria based on title and abstract:
    - Inclusion: HTA reports, systematic reviews and clinical studies, patients with cancer (and ocular diseases), intervention (hadrontherapy, proton beam therapy, carbon ion therapy)
    - Exclusion: Duplicates, physiological studies, not human population, other intervention, design (letter, comment, narrative review), and language (other than English, Dutch or French); systematic reviews and HTA reports older than 5 yearsThe studies on what doubt existed were included to the selection on base of the full text.
- Selection criteria based on full text:
    - Inclusion: (HTA reports, systematic reviews and clinical trials), studies with at least 10 patients; patients with cancer (or ocular diseases), intervention (hadrontherapy, proton beam therapy, several ion therapy), outcome (local control rate, overall survival, disease free survival and safety parameters)
    - Exclusion: Other design (letter, comment, narrative review, case reports), patients with others conditions, other intervention or non clinical outcome



4.2.6 Critical appraisal

The critical appraisal was done for HTAs, SRs and additional studies.

4.2.6.1 Critical appraisal of HTA reports

For the critical appraisal of the HTA reports the INAHTA HTA checklist was used (see results in Appendix from Chapter 4 in table AA)

The following HTA reports were considered for critical appraisal: the AETMIS (Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé) report 2003 [1], the ANZHSN (Australia and New Zealand Horizon Scanning network) report 2006 [2], the CEDIT (Comité d'Evaluation et de Diffusion des innovations Technologiques) report 2002[3], the NHSC (National Horizon Scanning Centre) report 2006 [4].

Two reports [1, 2] get a high score and two others a poor score [3, 4].

4.2.6.2 Critical appraisal of systematic reviews

The following reviews have been considered for critical appraisal: Hug [5], Noël [6], Jereczek-Fossa[7], Pijls-Johannesma [8], Greco [9], Brada[10],Lodge [11], Olsen[12]. More details on the critical appraisal of the systematic reviews are given in table AB.

The review from Hug, Noël and Greco doesn't contain a description of the literature search and of the selection criteria. Therefore, it's impossible to consider them as a systematic review. Using the Cochrane checklist , the clinical review from B. Jereczek-Fossa [7] about head and neck tumours was evaluated to be of lesser quality. The search was performed in Medline only and a description on the selection criteria used is lacking ("studies were selected on relevance"). Furthermore, this review was older than three systematic reviews [10-12] of better quality considered in this report.

The articles from Brada and Lodge are based on the same systematic review of the literature performed by Madelon Pijls-Johannesma [8]. That review is a particularly exhaustive literature review carried out in 12 databases according to the Cochrane Collaboration systematic review methodology. Manual searches of bibliographies and journals were also performed notably on SIGLE (System for Information on Grey Literature in Europe).

For the original studies, the inclusion criteria were: at least 20 patients and a follow-up of at least 2 years. Quality appraisals from selected studies were performed according to the Cochrane Collaboration guidelines. Relevance studies were entered onto a study register in order to facilitate updates of the review.

A review article published by Brada in March 2007 contains the results from the studies selected by Madelon Pijls-Johannesma about the most frequent tumours treated by protons. This publication is however less complete than that of Lodge.

The literature review published in may 2007 by M. Lodge and M Pijls-Johannesma may be considered the most accurate review published to date for four reasons: The methodology used (see critical appraisal), the high number of tumours studied, the description of results obtained with protons and with ions and the comparison performed between proton/ion therapy and historical series with photon therapy.

Another publication [12] also published in May 2007, is included but the inclusions criteria for original studies varied in comparison to the publication by Lodge et al. The review by Olsen included papers involving at least 50 patients (except studies in children) and describing a "reasonable" follow-up. All studies were scored with the SIGN system and sixty publications were finally included in the review.

The results extracted from those "good quality" reviews are described here (with agreements and differences) for each tumour site.

4.2.6.3 Critical appraisal for additional studies

Most additional studies are observational studies or case series of patients treated in several centres or proton or carbon ion therapy without group control. The description of the studies is included in the evidence tables.

4.3 RESULTS

4.3.1 Introduction

In this chapter, the clinical evidence is discussed in detail for each indication found in the literature. The HTA reports and the systematic reviews lead to global conclusions about the use of proton or carbon ion therapy.

4.3.2 Proton therapy

Globally, the HTA reports favour a limited use of hadrontherapy for selected groups of patients. Their conclusions are based on evidence of low quality.

The ANZHSN HTA report [2] concludes that *"there is a large body of poor quality evidence indicating the successful use of proton beam therapy in a diverse patient base. Proton therapy may be of great benefit to a group of vulnerable patients who either have untreatable cancers with conventional therapies, or conventional therapies would put them at high risk of future, secondary disease".*

The National Horizon Scanning Technology briefing [4] reports that *"charged particle therapy is indicated for rare and specific tumours in both adult and paediatric patients, particularly tumours which have been identified due their proximity to critical structures such as spinal cord, brainstem and heart."*

The very recent systematic reviews (SR) of Brada and Lodge [10-12] agree on that the quality of the evidence is poor and that further research is needed. The SR of Lodge [11] concludes that "*existing data do not suggest that the rapid expansion of hadrontherapy as a major treatment modality would be appropriate.*" The SR of Olsen[12] states that *"proton therapy offers the option to deliver higher radiation doses and/or better confinement of the treatment of intracranial tumours in children and adults, but reported studies are heterogeneous in design and do not allow for strict conclusions".* The SR of Brada [10] does not

give a global conclusion but merely conclusions according to specific localizations of tumours. The detailed discussion about selected groups of patients in the 3 SR is considered by tumour site.

4.3.3 Carbon ion therapy

Carbon ions are described as "particles of experimental interest" in the Horizon Scanning Technology briefing [4] but there is not specific discussion about carbon ion therapy. The systematic review of Lodge [11] is the only that treated heavy ion therapy (carbon beam ion but also others ions such helium ion are included in this term). It concludes that *"heavy ion therapy is still in experimental phase"*. The detailed discussion about results with carbon ion is included in the results by tumour site.

Key points

- **Proton beam therapy can represent an indication for rare and specific tumours in selected groups of patients where conventional therapy presents a significant risk for fragile structures in the vicinity. The quality of actual evidence is nevertheless poor and further research is thus needed.**
- **Carbon ion therapy is an appealing but still experimental approach.**

4.3.4 Results by tumour site

The disappointing results observed with conventional radiotherapy for ocular, skull base and paediatric tumours have stimulated the use of hadron therapy in these indications. For several kinds of tumours experiments have been performed with proton or carbon ion therapy. The precise targeting achievable with hadrontherapy and its sparing potential towards fragile structures explain why ocular tumours and skull base tumours such as chordomas or chondrosarcomas were first studied. For the same reason, paediatric tumours and other site adult tumours have been studied such as other intracranial tumours, face and neck tumours (especially salivary gland tumours) but also prostate (or other pelvic tumours such cervix or bladder), lung, gastrointestinal or breast cancer. In many situations, the aim was to limit the damage to the surrounding tissues but also to improve the prognosis with regard to the current treatment.

In addition, some studies investigate hadron therapy in non-cancerous diseases near or within fragile tissues like neovascular age-related macular degeneration and non cancerous intracranial tumours or malformations. These indications are also discussed.

If available, the adverse events are also discussed for each tumour site. A grading severity scale is used according to the US National Cancer Institute common terminology criteria for adverse events http://ctep.cancer.gov/forms/CTCAEv3.pdf)

Grade 1 is used for mild adverse events; grade 2 for moderate adverse events; grade 3 for severe adverse events; grade 4 for life-threatening complication or disabling adverse effects and grade 5 for death related to adverse event

4.3.4.1 Ocular tumours

Different treatments' options are used in uveal melanoma such as local resection, enucleation, transpupillary thermotherapy, photodynamic therapy, episcleral brachytherapy with ^{106}ruthenium or ^{125}iodine, and photon or proton therapy. The proton has been considered an appropriate option for tumours where the posterior margin extends close to the optic disc or close to the fovea, or where the thickness exceeds 5.5 mm [10]: In these patients, brachytherapy may cause optic neuropathy and the only alternative is fractioned stereotactic radiotherapy. The rate of complications during the treatment of ocular tumours is related to the therapy used for the treatment but also to several initial factors such as the localization and the volume of the tumour as well as the characteristics of the treated eye. The large differences in volume of the tumours or in their localisation within the different groups are important confounding factors that preclude a firm conclusion. Moreover the choice of the treatment is often bound to the localization and the grade of tumours. Indirect comparison between results in different groups of patients with different treatments is hazardous according to numerous biases.

RESULTS WITH CURRENT TREATMENT

In the selected studies using stereotactic photon therapy (n = 350 patients), the 5-year weighted mean for local tumour control was 97%, the weighted mean for eye retention was 90%. Neovascular glaucoma occurred in 16% of patients[11]. A 5-year overall survival is not yet available.

RESULTS WITH PROTON THERAPY

This topic is considered in one HTA report [2] and in 3 systematic reviews [10-12]. The studies included were 1 RCT that compared doses of proton therapy[13], 2 cohort studies comparing groups with proton therapy and groups with enucleation as treatment[14, 15] and one comparative study between proton beam radiation versus 125I and 106Ru episcleral radiation therapy (brachytherapy)[16]. All the other included studies are prospective or retrospective case series. The HTA report [2] includes only a case series [17] and gives no conclusion. Our systematic search found 3 studies not included in the SR [18-20]. More details are given in table AC, AD.

In most selected studies, the proton beam radiation total dose for ocular melanomas is between 50 to 60 CGE (Cobalt Gray Equivalent) fractioned on 4 consecutive days. Few studies related to a total dose of 70 CGE, in 5 or 6 fractions.

COMPARATIVE STUDIES

The cohort studies [14, 15] followed patients (440 eyes) with uveal melanomas treated with enucleation or with proton beam irradiation. Cox regression analysis adjusted for prognostic variables found no difference in disease free survival (RR 1.0 [95% CI 0.7-1.4]) or overall survival (RR 1.2 [95% CI 0.9-1.2])[12].

A retrospective comparative case series [16] studied 597 patients with choroidal melanomas treated either with proton beam irradiation either with episcleral (^{106}Ru and ^{125}I) brachytherapy. Local recurrence was better with proton therapy but with a higher mortality rate. The model was not appropriately adjusted for possible confounders [12].

The RCT of Gragoudas [13] assessed the clinical effects of two doses of either 50 or 70 CGE (Cobalt Gray Equivalent) in 188 patients with small or medium size melanomas (< 15 mm in diameter and < 5 mm in height) near the optic disc or macula. Local tumour recurrence and metastatic death rates were similar. Visual acuity loss was similar. The lower-dose group did experience significantly less visual field loss. The trial was underpowered to conclude for difference in cancer control rates [12].

Our systematic search found an additional study not included in the systematic reviews: Char 2002 [18] compared late recurrence between 3 different treatments (retrospective cases series) for uveal melanomas (^{125}I brachytherapy; proton therapy; helium therapy) after long term follow-up and concluded that more late recurrences (5 to 15 years) occur with extended follow-up after brachytherapy but not after proton or helium therapy. Many potential biases are possible in such a retrospective design study.

NON COMPARATIVE STUDIES

There are conflicting conclusions between the systematic reviews.

The SR of Olsen [12] reported 5-year survival rates of 70 to 95%, reflecting the diversity in population, indications and patient risk, and disease free survival varying of 85 to 96% for 5 years follow-up, of 76 to 95% for 10 years follow-up and of 73% for 15 years follow-up in the cases series with proton therapy. The systematic review concluded that no proper comparison with other alternative has been undertaken, that reported studies are heterogeneous and do not allow strict conclusions.

In the SR of Lodge, the weighted mean for local tumour control in case series (n = 4972 patients) was 97%, overall survival was 85%, and the cause specific survival was 85%. The weighted mean for eye retention was 90%, whereas neovascular glaucoma occurred in 12% of patients [11]. The SR of Lodge came to the conclusion that proton is superior to photons therapy (based upon a lower incidence of neovascular glaucomas with protons and on the fact that photons studies have a shorter follow-up).

The SR of Brada [10] however with the same results (but they did not account for neovascular glaucomas) concluded that there is currently no clear evidence that proton therapy is superior to photon therapy in patients with ocular melanomas. Only 40% of

patients had preservation of vision of 20/40 or better with protons. Ten percent died from metastatic tumours with protons and less than 10% with photons [10].

Our search found 2 additional studies. The study of Spatola 2003 [19] is a preliminary search with a short follow-up and few patients, and the study of Höcht 2005[20] was not a clinical study but treated about deposition dose.

RESULTS WITH CARBON ION THERAPY

This topic is considered in one systematic review[11]. Our search did not find additional clinical studies not included in the SRs or HTA reports: More details are given in table AE and AF.

In the systematic review of Lodge [11], two studies dealt with Helium ion therapy [21, 22]. The two other studies of Tsuji and Hirasawa [23, 24] are prospective phase I/II clinical trials in which eye retention rates and severe side effects such as neovascular glaucoma were analyzed. The rates with carbon ion (84% eye retention and neovascular glaucoma > 40%) seems less interesting than proton or photon therapy rates [11].

Key points

- **Several treatments are possible for eye's melanomas. Proton therapy is a possible alternative to photon therapy when brachytherapy is inappropriate, to say when the posterior margin extends close to the optic disc or to the fovea, or when the thickness exceeds 5.5mm.**
- **Convincing arguments are currently lacking to allow a choice between proton and photon therapy since local control, eye retention after radiation and survival were equivalent in the non comparative cases series. There were no differences in visual acuity loss and visual field loss. Occurrence of neo vascular glaucoma was slightly less frequent with proton therapy.**
- **Carbon ion therapy seems less interesting than proton or photon therapy for ocular melanomas.**

4.3.4.2 Proton therapy for neovascular age-related macular degeneration

Macular degeneration is the leading cause of blindness in the elderly. It can be associated with subfoveal choroidal neovascularisation. Radiotherapy has been proposed to prevent new vessel growth. A Cochrane systematic review about radiotherapy for neovascular age-related macular degeneration concluded however that there was no evidence that external beam (photon) radiotherapy is an effective treatment for neovascular age-related degeneration [25].

Proton beam treatment has also been experimented used for neovascular age-related macular degeneration. Our systematic search found 3 clinical trials? on this topic [26-28] The 3 studies are of poor quality. Biases are not excluded. The validity of the results is uncertain. More details are given in table AG.

The study of Ciulla [27] compared proton beam therapy with sham therapy in neovascular age-related macular degeneration. There is no statistical difference between the 2 groups. The two other studies [26, 28] that compared the effect of 2 different doses of proton therapy it was concluded that there is no significant differences in rates of visual loss between the 2 doses. There is thus currently no evidence for the use of proton therapy in neovascular age-related macular degeneration.

Key points

- **There is no evidence to support the use of proton beam therapy for other ocular diseases such as neovascular age-related macular degeneration.**

4.3.4.3 Skull base chordomas

Chordomas are tumours (<1% CNS tumours) that arise from embryonic notochordal remnants along the length of the neuraxis (sacrum, intracranial or along the spinal axis). Most studies with proton beam radiation concerned? skull base chordomas, according to the proximity of delicate organs.

The role of surgery remains paramount in the treatment but surgical complete removing of skull base chordomas is difficult, caused by the proximity of the brainstem and cranial nerves. The residual/ unresectable chordoma after surgery is of progressive nature and conventional radiotherapy is used to improve the local control. Radiotherapy is introduced to treat the remaining tumour or in case of an unresectable tumour.

The evidence for a benefit of conventional photons radiotherapy over surgery alone in tumour control and survival is not clear. It is discussed in several systematic reviews, from a benefit based on little prospective data but not sufficient documentation on dose relationship [10] to not sufficient cancer control with doses 50-60 Gy and toxic effects with higher doses [12].

The choice of a treatment with proton beam irradiation (in place of photon beam irradiation) is linked to the fact that proton beam therapy can be focused on the target with the hope of reducing the side effects to the brainstem. Proton therapy is used after surgery (except in the case of inoperable tumours), alone or combined with photon therapy. Carbon ion therapy is also used in several studies on chondromas.

Surgical techniques are not always comparable in several studies and thus better global results in case series can be linked either to surgery or to radiotherapy.

RESULTS WITH CURRENT TREATMENT

In base skull chordomas, the reported local progression free survival rate after conventional photons therapy ranges from 17% to 65% after 5 years [10] (17 to 33% in the studies cited in the systematic review of Lodge [11]). The wide range in the results provided probably results from biases in patient selection and changing surgical techniques [10]. The most recent surgical series (with only 20% conventional radiotherapy) reports a 5 years local progression free survival rate of 65% [10, 11]. Surgery followed by fractioned stereotactic radiotherapy resulted in a 5 years progression free survival of 50% [10, 11].

The mean 5-year overall survival with photons has a rate of 44% in the series (n=100) cited by the systematic review of Lodge [11]. This rate is of 82% in surgery followed by fractioned stereotactic radiotherapy [11].

All these results are based on retrospective or prospective non-comparative case series.

RESULTS WITH PROTON THERAPY

This topic is considered in one HTA report [2] and in the 3 recent systematic reviews [10-12]. The systematic reviews of Lodge and Brada considered two retrospective non-comparative case series [29, 30] about proton therapy. The third study included is a more recent prospective non-comparative case serie [31-33] of combined proton and photons beams treatment. The HTA report [2] included only one case series study [30] and concluded that comparative studies are missing. The systematic review of Olsen[12] included one poor quality RCT [34] and 9 case series [35-38, 29-32]. Our systematic search found one more study [39]. More details are given in table AH and AJ .

In most selected studies, the proton beam fractioned radiation total dose for chordomas is between 64.8 to 79.2 CGE (Cobalt Gray Equivalent). Several studies used a combination of photons and protons fractioned irradiation.

For patients treated with proton, there are conflicting results between the systematic reviews.

According to Brada, median 5-year local progression free survival rate is the most appropriate measure to assess the efficacy of surgery and radiotherapy in chordomas. The rate is of 60% by summary statistics of existing studies (n = 302 patients). There is no clear superiority of proton therapy in terms of local control of the tumour [10].

Based on 2 studies [29, 30] (n= 202), the systematic review of Lodge [11] reported a 5-year local progression free survival rate of 65%. It reported also a mean 5-year overall survival of 81% with protons [29, 33] (n= 133). The systematic review concluded that patients with base of the skull chordomas seem to have a better outcome when treated with protons.

Based on a wider selection of cases series (n = 500), the systematic review of Olsen [12] concluded that 5 and 10 years survival was high in these studies and that grade 3 and 4 toxicity was limited. The reported studies are heterogeneous in design (proton therapy alone or as supplement to conventional radiotherapy, either for primary tumours or for recurrences) and do not allow for strict conclusions [12].

The additional study founded by our systematic search [39] is a retrospective case series with only 13 patients (overall survival at 5 years of 66% and 5 years disease free survival of 42.2%).

There are not comparative studies between the different treatment options. Differences may be due to several biases, surgical treatment change or patients' selection.

There are insufficient data available to compare toxicity induced by photon or proton beam therapies. Grade 3 and 4 toxicity was limited in the case series reports [12] The use of proton therapy can result in brainstem damage, and the risk is related to the volume of the brainstem irradiated with doses more than 60 GyE [10].

RESULTS WITH CARBON ION THERAPY

This topic is considered in the systematic review of Lodge [11] which reported 2 retrospectives case series on carbon ion therapy [40, 41]. Our systematic search found 6 non-comparative case series [42-44, 41, 45, 24]. More details are given in table AK and AL.

The total mean dose used in the studies was between 57 to 65 Gy delivered in 16 to 20 fractions.

Based on 2 retrospectives cases series (n= 107), the systematic review of Lodge [11] reported a mean 2-year local progression free survival rate of 72% with carbon ion and a mean 5-year overall survival of 81%. Grade 4 and 5 toxicity has not been observed.

One additional study related only a 1-year local control rate (94%) and showed no severe toxicity[42]. Three studies were preliminary results of studies all included in the systematic review of Lodge [43, 44, 41]. Two phase I/II studies [45, 24] showed a 3-year local control of 93% and a 5-year overall survival of 87% in patients with skull base chordomas treated by carbon ion irradiation.

Key points

- **Chordoma of the skull base is a rare tumour with a poor prognosis. Surgery remains the best available option. Radiotherapy is used to improve the local control in case of residual tumour or in case of an inoperable tumour.**
- **Case series with proton beam therapy show high results of local progression free survival rate and overall survival rates. Modern surgical series and stereotactic photon irradiation also have good results.**
- **There is however currently no clear clinical evidence from comparative studies to assess the clinical superiority in efficacy between proton and classical photon therapies (or their combination, or high precision photons therapy) or between radiotherapy and the modern surgical series (with only 20% of radiotherapy). Results are based on heterogeneous non-comparative case series.**
- **The safety seems acceptable (little grade 3 and 4 toxicity). Proton therapy may lead to brainstem damage. The risk is related to the volume of the brainstem irradiated with a dose higher than 60 GyE. There are insufficient data available to compare toxicity induced by photon or proton beam therapy.**
- **Case series with carbon ion irradiation also showed good results in chordomas of the skull base without serious toxic reactions. There are however no comparative studies between carbon ion therapy and current treatment.**

4.3.4.4 Skull base chondrosarcomas

Chondrosarcomas are rare cancerous bone tumours developing from cartilage. They can be localized in the skull base, but also somewhere else in the skeleton. Such as for chordomas, complete surgical resection is difficult due to the proximity of brainstem and nerves.

RESULTS WITH CURRENT TREATMENTS

In chondrosarcomas, the prognosis is often good. The outcome after surgery (usually followed by photon therapy) is reported as 90% to 100% actuarial local control at 5 years [10]. The 5-Year overall survival [11] is 100% (n=8) with stereotactic photon irradiation post surgery. These results are based on non-comparative case series.

RESULTS WITH PROTONS

This topic is considered in the same studies as chordomas of the skull base.

In published studies about proton therapy, the 5 year local tumour control is of 95%, which is not different from the results of conventional photon therapy [10, 11]. The 5-year overall survival is 100% (n = 25). The systematic review of Olsen [12] doesn't give a specific conclusion for skull base chondrosarcomas. The discussion is the same as for chordomas.

RESULTS WITH CARBON ION THERAPY

This topic is considered in the same studies as chordomas of the skull base.

The systematic review of Lodge [11] reported a 5-year local control rate of 86% with carbon ion and a mean 5-year overall survival of 93% (n=81) in retrospective cases series. This result seems low. There are no comparative studies.

Key points

- **Chondrosarcomas of the skull base are rare tumours with a good prognosis. Surgery remains the main treatment. Radiotherapy is used to improve the local control in case of a remaining tumour.**
- **In chondrosarcomas of the skull base, there are no differences between photon and proton irradiation in the results of case series for both local control rate and for overall survival. Carbon ion therapy seems currently less effective than existing treatment. The included studies are small heterogeneous non-comparative case series. Biases are not excluded.**

4.3.4.5 Other non skull base chordomas and chondrosarcomas

There are few publications about other localizations of chordomas and chondrosarcomas. Only the systematic review of Olsen [12] (based on the study of Munzenrider 1999 [30]) gives results on this topic. Our systematic search found 2 additional studies with carbon ion [46, 41].More details are given in table AM and AN.

The case series of Munzenrider 1999 [30] described a 10-year disease free survival for cervical spine chordomas of 54% and of 48% for non-skull chondrosarcomas with proton beam irradiation.

The retrospective case series of Imai 2004 [46] studied 30 patients (41-85 years) with unresectable sacral chordomas treated with carbon ion radiotherapy. The overall and cause-specific survivals at 5 year were 52 and 94% respectively and the overall local control rate at 5 years was 96%. Two patients had severe skin/soft tissue complications requiring skin grafts.

A non comparative case series [41] included 9 spinal and 8 sacrococcygeal chordomas and chondrosarcomas treated with combined photon RT and carbon ion boost. A 3-year local control persist in 8/9 spinal and 7/8 sacral tumours. Grade 4 and 5 toxicity was not observed.

Key point

- **For other non-skull base chordomas and chondrosarcomas, there is no evidence in favour of proton or carbon ion therapy. There are no comparative studies and the case series are heterogeneous with regard to the included population and the selected treatment.**

4.3.4.6 Other intracranial tumours

Proton therapy has also been used in several other (malignant or not) tumours such as low grade glioma, glioblastoma multiforme, acoustic neuroma, low grade astrocytomas, cavernous malformation or benign meningioma.

This topic is considered in the systematic review of Lodge and of Brada [10, 11]. Two prospective cases series [47, 48] about gliomas and glioblastomas and several retrospective case series [49-52]are included. More details are given in table AO and AP and AQ And AR.

Glioma is currently not an indication for proton therapy. The 2 systematic reviews [10, 11] came to the same conclusion for gliomas: "*Dose escalation with protons has not demonstrated convincing survival benefit in malignant glioma other than would be expected due to patient selection*". A phase I/II clinical trial (Mizoe 2007) described a potential efficacy in patients with malignant gliomas who receive higher doses of carbon ion therapy combined with X-ray radiotherapy and chemotherapy. For the other kinds of intracranial tumours, there is not evidence in favour of proton or carbon ion therapy.

Key point

- **There is no evidence for the use of proton or carbon ion therapy in the other malignant or not malignant intracranial tumours.**

4.3.4.7 Paediatric cranial tumours

Olsen referred to six cases series reporting the experience form three well-known centres: Loma Linda University, Massachusetts General Hospital and "le Centre de Protonthérapie d'Orsay".

The first study was performed at the Massachusetts General Hospital: 18 children with base of skull or cervical spine chordomas were treated by high dose irradiation, with a 5-year actuarial survival rate of 68% and a 5-year disease-free survival rate (DFS) of 63%. The authors concluded that "chordomas in children behave similarly to those in adults; the only significant prognostic factor was the location". [53] At Orsay, 17 children with selected central nervous system (CNS) tumours were treated with a combination of proton and photon irradiation (photons 24-54 Gy and protons 9-31 CGE) between 1994 and 2000. At 36 months, the local control rate was 92% and overall survival rate was 83 %. The authors concluded that "with a mean 27 months follow-up, protontherapy was well tolerated for doses up to 69 CGE and with an excellent local control rate". [54]

Twenty-eight children with CNS tumours and 27 with astrocytomas were treated at Loma Linda in the United States. For these 28 children treated between 1991 and 1994, 16 suffered from a benign tumour of the brain and twelve from a malignant one. With a follow-up of 7 to 49 months, three patients died (grade 2 to 4 gliomas), one is living with a persistent disease and four had treatment-related toxicity. [55] Twenty-seven patients (44% for unresectable primary disease and 56% for residual or recurrent disease) were also treated by proton therapy for low-grade astrocytoma. At 3.3 years, local control rate was 78% and overall survival rate was 86%. The authors concluded that "*proton radiation therapy is a safe and efficacious 3-D conformal treatment modality. Longer follow-up time is needed to fully evaluate the benefits of normal tissue sparing*". [56]

At Loma Linda and Massachusetts General Hospital, 29 children that suffered from skull base tumours were treated and follow-up between 1992 and 1999, 13 patients underwent fractioned protons and 16 combined proton and photon irradiation because despite maximal surgical resection, 97% of patients had gross disease. Target doses ranged between 50.4 and 78.6 CGE. With a follow-up of 13 to 92 months (mean 40) after proton RT, the actuarial 5-year local control and overall survival rate was 72% and 56%. The authors concluded that : "Proton RT for children with aggressively recurring tumours after major skull base surgery can offer a considerable prospect of tumour control and survival, but longer follow-up is necessary. [57]. Mac Allister analyzed the morbidity of 28 children identified as at risk for brain injury from treatment by proton therapy [58]. With a follow-up of 7 to 49 months (median 25), he noted in 4 out of 28 cases of early morbidity, in 26 cases disease related morbidity, 4 local failures and 3 deaths. The authors concluded that early treatment-related morbidity associated with therapy is low, but that it is nonetheless necessary to assess long-term follow-up.

Since treatments for childhood cancer are often more effective, authors pay particular attention to adverse outcomes in long term survivors of childhood cancer. The major risk for children treated by radiotherapy is a secondary tumour. For children having radiotherapy centred on head and neck, late neuropsychologic morbidity (effects on neurocognitive, developmental and behavioural development) represents another major risk. Oeffinger and Geenen followed up children survivors from a cancer in order to assess theirs chronic health conditions. Oeffinger performed a retrospective cohort study (Chilhood Cancer Survivor Study) of 10,397 at least five-year survivors of childhood cancer treated in United States between 1970 and 1986. Thirty years after the cancer diagnosis, the cumulative incidence of a chronic health condition reached 42.4% (95% CI, 33.7 to 51.2) for severe, disabling, or life-threatening conditions or death due to a chronic condition. CNS tumour was present in groups having the highest risk for severe or life-threatening condition (RR 12.6; 95% CI, 10.3 to 15.5).[59] Geenen performed a retrospective cohort study of 1362 five-year survivors of childhood cancer treated in Amsterdam between 1966 and 1996. With a median follow-up from 17.0 years a high or severe burden of adverse events was observed in 55% of survivors who received radiotherapy. Conventional radiotherapy on head and neck was the most important risk factor for obesity (RRs from 1.63 to 1.97). The risks for endocrine (RRs from 4.25 to 8.83) and neurologics events (RRs from 3.06 to 3.20) were also

significantly increased compared with the general population. .[60] . Both authors concluded that adult survivors of childhood cancer must benefit from adequate monitoring and that the risks associated with treatments should be minimized. Proton therapy could be a promising way to reduce the risks of radiation by better focusing radiation beams.

In this way, Miralbell *et al*. performed 2 preclinical studies with the aim to quantify the dose reduction delivered to the surrounding (normal) tissues with regard to classical radiotherapy. The first study was a comparative dosimetric study in a virtual 3-year old child in which the effect of a three field (two laterals and one posterior) proton plan is compared with a two-field conventional x-ray plan, a 6-field hand made plan and a computer-optimized 9-field "inverse" plan. A 3D treatment-planning, based on CT-scan measures in a 3-year old child, was used to generate each of these treatment plans. Proton beams succeeded better in reducing the irradiation of the nontarget brain volume and eye globes than any of the photon plans. Therefore, a lower intelligence quotient deficit, could theoretically be expected after treatment with proton beams especially in 4-year old children with an unfavourable localisation.[61] The second paper applied several treatment plans to 2 patients, the one suffering of a parameningeal rhabdomyosarcoma, the other of a medulloblastoma, in order to estimate the incidence of secondary cancers. Their model used figures from Publication N°. 60 of the International Commission on Radiologic Protection.

Proton beams may reduce the expected incidence of radiation-induced secondary cancers by a factor of ≥2 in rhabdomyosarcoma and by a factor of 8 to 15 for the medulloblastoma with regard to conventional X-ray plans or IMRT.

On the other hand, the treatment is complex : positioning and fixation of the patient require insertion of radio-opaque bony landmarks, cast systems to fix the bony structure, head mask to limit movements to 1-2 mm of the skull in the cranio-caudal direction, all elements required as part of the planning in order to achieve correct guidance of the radiation beam; On top very young children must be anesthetized to keep them immobile . [6] Today the theoretical gain of proton therapy for the treatment of brain tumours in children has not been demonstrated by rigorous follow-up studies.

More information about the studies is available in tables AS and AT.

Key points

- **Proton radiation therapy seems to be safe and well tolerated by children suffering from CNS tumours (no RCTs available, sparse retrospective evidence)**
- **There is currently no evidence to support the use of proton therapy as first line treatment in CNS tumours by children.**

4.3.4.8 Salivary gland tumours

Salivary gland tumours are a heterogeneous group of tumours. Cystic adenoid carcinoma accounts for 5 to 10% of salivary gland tumours [1]). The most studied tumour with neutron or carbon ion therapy is the cystic adenoid carcinoma of the parotid glands, which is a rare cancer. Cystic adenoid carcinoma grows slowly but is an infiltrating tumour with a strong recurrence potential. Neutron therapy is intended for inoperable and unresectable salivary gland tumours.

RESULTS WITH CONVENTIONAL THERAPY

After surgical resection, the standard treatment, the recurrence rate is 50%. For operable cases with adjuvant radiation photon therapy, the 5-year survival rate can be 60 to 75% (AETMIS HTA report Québec 2003 [1].

The 5-year local control with photons related in the systematic review of Lodge[11] gets from 50 to 70% for salivary gland tumours and 24.6% at 4 year for locally advanced adenoid cystic carcinoma.

RESULTS WITH PROTON THERAPY

Our search does not find studies using proton therapy in salivary gland tumours.

RESULTS WITH NEUTRON THERAPY

This topic is considered in one HTA report [1] and one systematic review [11]. In the included studies, there is a randomized control trial (in 2 publications [62, 63]) and comparative or non-comparative cases series[64-69]. Our systematic review found an additional study about carbon ion [24]. More details are given in table AU and AV.

In salivary glands tumours, the studied treatment is neutron therapy (slow or fast neutrons produced by cyclotrons). The total mean dose used in the studies was between 16 to 20 GyE in 12 to 17 fractions.

The AETMIS HTA report Québec 2003 [1] concluded, based on scientific data up to march 2003 that *"the efficacy of neutron therapy is well established only for the treatment of inoperable or unresectable salivary gland tumours, regardless of their degree of malignancy or stage of progression, and for the treatment of large residual tumours after surgical resection"*. There is a significant difference in local tumour control but there is however no difference in survival between the group treated with photons and the group treated with protons in the RCTs and in the comparative studies. The 10-year local control rate 56% for neutrons and 17% for photons ($p<0.009$) and the 10-year survival rates 15% for neutrons and 25% for photons ($p=0.5$) [63]. The first RCT of Griffin has been published in 1988 followed by a final report (with ten years results of the same RCT) published by Laramore in 1993. Treatment with fast neutron radiotherapy has however been discontinued and is not yet available.

RESULTS WITH CARBON ION THERAPY

The systematic review of Lodge concludes that local control rate is higher with carbon ions [11]. A comparative case series [67] found a 4-year local control rate of 77.5% (photons and carbon ions) and of 24.6% (photons alone) ($p= 0.08$) in patients with cystic adenoid carcinoma. The 4 year overall survival rates were 75.8% (photons and carbon ions) and 77.9% (photons alone). There was thus also a significant difference for local control but no difference for survival. Rates for severe late toxicity were < 5% in both groups. The additional study with carbon ion therapy [24] is a non-comparative case series. }. More details on the studies are given in table AU, AV and AW.

Key points

- **One randomized controlled trial showed a significantly better local control rate with neutrons (*vs* conventional photons therapy) in inoperable, unresectable or recurrent malignant salivary gland tumours but no difference in survival. Neutrons therapy has been discontinued and is no more available.**
- **A comparative case series found also a better local control with carbon ion and photons than with photons alone in patients with cystic adenoid carcinoma without any significant difference in survival so far.**

4.3.4.9 Other head and neck tumours

This group of indications is heterogeneous and included patients with several locally advanced or recurrent cancers of the head and neck. The topic is considered for proton in two systematic reviews [10, 11]. The included studies are prospective or retrospective non-comparative case series [70, 71]. For carbon ion, the systematic review of Lodge [11] considered a prospective comparative case serie [72] comparing two different fractions of the same total dose and the study of Schulz-Ertner [67] included in the salivary gland tumour topic. One additional study was found by our systematic search [24]. More details are given in table AX and AY and AZ.

According to the systematic reviews, the results for protons were similar to those achieved with photons RT. Severe late complication rates were 10 to 18% [10, 11]. The study of Tsuji 2007 [24] related a 5-year overall survival of 37%in locally advanced or recurrent head and neck tumours.

4.3.4.10 Gastrointestinal tumours

RESULTS WITH PROTONS OR CARBON ION THERAPY

The two studies cited by the systematic reviews from Olsen [12], Brada [10] and Lodge [11]for oesophageal tumours were performed in Japan. Kyoma[73] included 30 patients in one prospective study and Sugahara [74] included 46 patients in one retrospective study. Tumour control rates after proton seem superior to historical controls treated with radiotherapy (RT) alone, but they are similar to modern therapy. Those apparently more favourable results may be accounted for by patient selection, and long term survival rates are low (10 to 15%) in line with conventional RT.

For liver carcinoma also, most studies were performed in Japan. Olsen referred to one case serie of 162 patients [75](mainly stage I and II) that received proton irradiation to 50-88 CGE. But, it was impossible to conclude about overall survival or local control because a quality problems with the study (variation in dose and heterogeneity in patient population). Brada cited one retrospective study [76] and two prospective studies [77, 78] where +/- 300 patients were treated by protons but report results are similar than those achieved by conventional RT. Besides Kawashima and Bush, Lodge referred to other studies performed by Hata [79] for protons and Kato[80] for carbon ions. Their conclusions were also that results report with protons or carbon ions are similar than those achieved by RT.

For unresectable adenocarcinoma of the pancreas, one phase III trial [81] using carbon ion therapy was identified by M. Lodge. In this old study, local control rates were slightly higher (10% vs 5%) with carbon ion than with photons, but the small numbers of patients preclude firm conclusions. Results on those studies are depicted in table A1.

Key points

- **The clinical value of proton therapy in oesophageal cancer remains unclear**
- **The results reported with proton or C-ions therapy for liver carcinoma are similar to those achieved by conventional RT.**
- **For gastrointestinal tumours, the role of protons or C-ions remains unclear.**

4.3.4.11 Lung cancer

RESULTS WITH PROTONS OR CARBON ION THERAPY

Most studies are observational studies (prospective or retrospective) performed in patients suffering from early-stage, medically inoperable non-small cell lung cancer. Two prospective studies (Bush)[82] and two retrospective studies (Nihei) [83] (Shioyama)[84] using proton therapy were included in the systematic review of Lodge. Those studies were also included by Brada. Olsen included the same studies and in addition the study from Nihei focussing on safety issues. Lodge also included three studies performed with C-ions therapy. Results of those studies are depicted on table A2

Olsen concluded that analysis of outcomes was difficult because of heterogeneity of the patient population and treatment given. Lodge performed a comparison with conventional radiotherapy and concluded that proton and C-ions achieved equivalent outcomes than those achieved with photon therapy.

Key points

- **The value of proton and C-ions therapy in early-stage lung cancer remains unclear.**
- **The results reported with protons or C- ions therapy for lung cancer are similar to those achieved by conventional radiotherapy.**

4.3.4.12 Prostate cancer

RESULTS WITH PROTONS

Lodge and Olsen included two RCT's performed in the Massachusetts General Hospital (Boston) and at Loma Linda University. Shipley [85]described treatments for patients suffering from advanced stages (T3-T4) of adenocarcinoma of the prostate comparing high dose irradiation boosting of conformal protons with conventional dose irradiation using photons alone. High dose irradiation with protons improved local control only in patients with poorly differentiated tumours, but also increased late radiation sequelae and has not increased overall survival at 5 year. Zietman[86]performed a comparison of conventional-dose versus high-dose conformal radiation therapy using photons and protons combined in clinically localized prostate cancer. High dose demonstrated a significant (P<0.001) reduction in the risk of biochemical failure (PSA level) by low-risk subgroup (stage T1b through T2b prostate cancer and PSA levels less than 15 ng/mL), but this reduction is not significantly different for higher-risk subgroups. There has been no significant difference in overall survival rates. Furthermore, the optimum treatment for localized stages prostate cancer with an intermediate or good prognosis remains unknown. [87] Slater[88]performed a retrospective study including 1255 patients treated by protons and photons combined or proton alone for patients at lower risk (< 15% risk for micrometastases in pelvic lymph nodes). Results were similar than those found in RCT's published by Shipley and Zietman.

RESULTS WITH CARBON ION THERAPY

Lodge included three prospective studies performed by Akakura [89], Ishikawa [90] and Tsuji performed in Chiba (Japan) using carbon ions beams for prostate cancer. The article from Tsuji summarized those three studies emphasizing tissue morbidity and biochemical relapse-free rate. Only low risk patients (T1-T2a, Gleason score <7 and PSA<20ng/ml) were treated by C-ion RT alone, high risk patients received hormonal therapy in combination with the C-ion RT. The overall 5-year biochemical relapse-free survival was 83.2% without any local recurrence. Results were impaired due to the high number of patients lost to follow up (235 treated and 201 followed up at least 6 months). [91]Results on those studies are depicted on table A3.

High dose radiation given in combination of protons and photons seems to provide better intermediate outcomes ((biochemical disease- free survival) for clinically localised prostate (T1b-T2b) cancer than photon alone (level of evidence 1). Survival rate at 5-year are comparable with those reported for other modalities intended for cure but, as yet, long-term survival outcomes were lacking. Because several old studies were accompanied by a little increase in gastrointestinal (grade III) morbidity further studies are necessary [92]. It's not possible to conclude about efficacy of protons due to the absence of comparative study between proton therapy and conventional therapy [93].

Key points

- **The value of proton and C-ions therapy in prostate cancer remains unclear.**
- **High dose RT combining photons and protons has shown a significant (P<0.001) reduction in the risk of biochemical failure (PSA level) but no significant difference in overall survival rates.**
- **It's necessary to compare high dose RT combining photons and protons with conventional and emerging treatments**

4.3.4.13 Cervical cancer

Lodge included one study performed with proton at Tsukuba (Japan) and two others performed with C-Ions at Tsukuba and Chiba. Twenty five patients were treated at Tsukuba by external photon irradiation to the pelvis, followed by proton irradiation [94]. The results showed that tumour control, survival, and morbidity are similar to those achieved with conventional radiotherapy. Kato and Nakano reported a prospective study involving 49 patients at stage IIIB and IVA cervical cancer disease. Kato performed a dose escalation study of carbon ion radiotherapy for locally advanced carcinoma of the uterine cervix and concluded that the dose to the intestines should be limited to <60 GyE to avoid major complications.[95] Nakano focused on potential difference between hypoxic and oxygenated tumours, but concluded that the role of the tumour oxygenation status was not so important in local control. [96]

RESULTS WITH CARBON ION THERAPY

For cervical cancer, no firm conclusion about the clinical efficacy of carbon ion therapy can be drawn in view of the small number of patients. Furthermore, more studies are needed on treatment-related morbidity.

4.3.4.14 Bladder cancer

Lodge included two retrospective studies on proton therapy for bladder cancer performed by Hata and Tsuji. Hata included 25 patients receiving transurethral resection of bladder tumour(s), followed by pelvic X-ray irradiation combined with intra-arterial chemotherapy with methotrexate and cisplatin. Patients (92%) who were free of residual tumour at the time of re-evaluation received also proton beam. Proton beam therapy might improve local control and facilitate bladder preservation. [97] Tsuj had obtained the same results in the past and considered treatment combining definitive RT and intra-arterial administration of chemotherapy as an effective bladder-preserving strategy. [98] Lodge concluded that outcomes reported after combined treatment with proton therapy and were similar than those achieved with conventional therapy.

For bladder cancer, two small retrospective studies showed better results, in fact a higher bladder preservation rate. Results of those studies are depicted on table A4.. Further comparative studies concerning more patients are necessary to firm those results.

Key points

- **The value of proton and C-ions therapy in cervix cancer remains unclear.**
- **The value of proton therapy in bladder cancer remains unclear.**

4.4 ANSWERS TO THE CLINICAL QUESTIONS

The answer to the clinical research questions are:

1. For which cancers has hadrontherapy (proton beam therapy, carbon ion therapy) a superior efficacy with regard to the current treatment by improving local control tumour, disease free survival and/or overall survival? Our research was not able to show any evidence in favour of hadrontherapy. The only RCT with neutrontherapy (vs photons) was in the treatment of salivary glands tumours. It showed a better local control without improvement of survival.
2. In which treatments has hadrontherapy less side effects than the actual one? There were no comparative studies with regard to the toxicity of hadrontherapy. There were no reports of patients with toxicity Grade $\geq$ 4 severity.
3. What is the place of hadrontherapy in actual clinical pathways? Proton beam therapy can represent an indication for rare and specific tumours in selected groups of patients where conventional therapy presents a significant risk for fragile structures in the vicinity. The quality of actual evidence is nevertheless poor. Carbon ion therapy is an appealing but still experimental approach.
4. Is there room for hadrontherapy in the treatment of other diseases than cancer? There is currently no evidence for the use of hadrontherapy in the treatment of non-malignant diseases.

5 EPIDEMIOLOGY

5.1 EPIDEMIOLOGIC RESEARCH QUESTIONS

In this part, we envisage to give an estimate of the potential number of Belgian patients that are eligible for proton and carbon-ion beam therapy.

5.2 METHODOLOGY

First of all, based on the results from chapter 4 and on cancer incidence data from the Belgian Cancer Registry, the number of possible Belgian patients has been estimated. In Belgium, central data collection on cancer incidence has started only relatively recently, in 1993. Due to methodological reasons, the data have been systematically underestimated at the beginning of the data collection. Since 1997, the quality of data in Flanders has considerably improved. In Walloon and Brussels however, they are still unreliable. Therefore, we have based our study on data of Flanders and extrapolated this to the other regions. In Flanders 1/1/2003 there are 5, 996 million inhabitants of the Flemish region, on a total population of 10,356 million in Belgium. The latest data available are from 2003. The yearly incidence of concerned cancers in Belgium is therefore derived from the age related incidence observed in Flanders in the period 2000-2003. We assumed that the distribution of tumours by stage of Flanders was representative for the Belgian situation. This distribution was applied to the Belgian age related incidence to give the estimated number of concerned cancer types.

Secondly, an overview is given of other international epidemiologic studies on hadrontherapy, followed by a projection of their results to the Belgian situation. However, the indications taken into account in these studies are far larger than discussed in the clinical chapter.

5.3 CANCERS ELIGIBLE FOR HADRON THERAPY

For none of the indications there is evidence yet from randomized controlled trials that hadron therapy results in improved local control, disease free survival or overall survival. Until evidence becomes available, hadron therapy remains an experimental treatment. Still, we find that the limited studies done indicate a potential improvement in local control for the following tumours:

Table 5.1: Defendable indications with a poor level of evidence

	Protons radiotherapy	Carbon-ion radiotherapy
Children & Adults	Uveal melanoma if close to optic disk or fovea or thickness >5 mm	
	Unresectable skull base chordomas	None
	Skull base chondrosarcomas	None

Table 5.2: Potential indications

	Protons radiotherapy	Carbon-ion radiotherapy
Children & Adults	*Spinal & sacrococcygeal chordomas*	
	Rare and specific tumours in selected groups of patients where conventional therapy presents a significant risk for fragile structures in the vicinity	
Adults		*Cystic adenoid carcinomas locally advanced ≥T3 but evidence only for neutrons*

5.4 NUMBER OF PATIENTS ELIGIBLE FOR HADRON THERAPY

Extrapolated from average 2000-2003 cancer data (according to the methodology mentioned above), the number of patients in 2006 is estimated as follows:

Table 5.3 :Number of paediatric and adult patients currently eligible for Hadrontherapy in Belgium

	# patients
Paediatric	5: – 3 low-grade skull base chondrosarcomas (chondrosarcomas: ~40% of C 41) – 2 uveal melanoma (malign melanomas of the eye, retinoblastomas not taken into account, since these are generally treated with chemotherapy)
Adult	46: – 22 low-grade skull base chondrosarcomas (~40% C41); chondrosarcomas are usually low-grade tumours (Brada 2007) – 7 unresectable chordomas (skull base, spinal and sacral) and/or residual tumours after surgery. The tumour is usually unresectable because its location makes it surgically unreachable. – 11 uveal melanoma (~1/6th of malign melanoma of the eye) – 6 cystic adenoid carcinoma of the parotid and salivary glands (cystic adenoid carcinoma: ~12% of C07-08; stage ≥3: ~50% of cystic adenoid carcinoma
Total	51

Taking into account the evolution of the Belgian population (derived from data of the National Institute for Statistics [99]) and a constant incidence rate[c], the number of new cases currently in scope for hadron therapy is expected to increase from 51 in 2006 to 63 in 2040 – an average increase of 0.6% per year.

In the hypothesis where rare and specific tumours in selected groups of patients for whom conventional therapy presents a significant risk for fragile structures in the vicinity would be added, we do not expect to find more than 100 patients a year.

Key points

- **Taking into account the indications with little, though poor, evidence and potential other indications, the total Belgian patient base is estimated at 51 (maximum 100) patients**

5.5 COMPARISON WITH INTERNATIONAL EPIDEMIOLOGICAL STUDIES FOR PROTON/CARBON-ION THERAPY

In this part we calculate the number of patients eligible for proton/carbon-ion therapy based on international epidemiological studies. The following studies are taken into account:

1. In Sweden [101] a group of radiation oncologists and hospital physicists have estimated the number of patients suitable for proton beam therapy. The potential proportion of patients for *proton therapy* constitutes 14-15% of all irradiated cancer patients.
2. In France [102] a survey amongst 5 radiation therapy departments was performed (as part of the Etoile project, integrated into the European Enlight network). Results indicated that 14.5% of all irradiated cancer patients are eligible for proton- and carbon-ion therapy.

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[c] Moller (2005) [100] recommends for cancer predictions to assume a constant incidence rate by age group for less common types of cancer. For more common types of cancer, however, a projection based on trends in the last one or two decennials is the preferred method.

3. In Italy the numbers of patients suitable for the TERA project were estimated by using Category A and Category B indications. In Category A, hadron therapy can be regarded as the treatment of choice, including tumours like uveal melanoma, chondrosarcoma, chordoma, meningioma of the skull base, paraspinal tumours and retinoblastoma. Category B includes tumours in which local control will be affected favourably in obtaining higher percentages of cure like brain, lung, rectal, prostate and gynaecological tumours. Results show a proportion of 10-15% of all irradiated patients in Italy (according to [103]).
4. At five European University hospitals (Heidelberg, Milano, Lyon, Vienna and Innsbruck), a calculation of the proportion suitable for hadron therapy by tumour subgroup was performed. Based on the mean values of these estimates, Mayer (2004) [104] estimated the proportion of eligible patients in Austria at 13.5% of all irradiated cancer patients and at 5.6% of all newly diagnosed cancer patients (Fig. H.)

Tabel 5.4 Projection of eligible patients for P or C ions in several countries

	Patients eligible for P or C ion therapy as a proportion of all irradiated patients
Sweden (Glimelius, 2005)	14-15% (P)
Austria (Mayer, 2004)	13.5% (P + C ion)
France (Baron, 2004),	14.5% (P + C ion)
Italy (Orrechia, 1998?) (see Mayer, 2004)	16% (P + C ion)

With nearly 30 000 irradiated cancer patients in Belgium in 2003, and a range of 15% eligible for proton/carbon ion therapy, some experts predict that figure could grow till up 3 945 patients . However, as discussed in the clinical chapter, we were not able to find evidence that this new therapy has better results than conventional therapy.

6 REIMBURSEMENT POLICIES WORLDWIDE

6.1 RESEARCH QUESTION

In this part, we aim to give an overview of the current reimbursement policies in other countries.

6.2 METHODOLOGY

The following information on reimbursement policies was obtained through contacts with hadron centres, healthcare policy institutions and grey literature on the internet.

6.3 OVERVIEW

6.3.1 Overview of proton therapy reimbursement

Table 6.1: Current reimbursement policies in other countries for <u>proton</u> therapy

	Uveal melanomas	Meningiomas	Low grade gliomas	Skull-base tumours	ORL tumours	Bone and soft tissue sarcomas	Paediatric	Prostate	Other
Switzerland		■	■	■	■	■	■		
Italy	■								
UK	■								
Sweden	■	■	■	■	■	■	■	■	■
USA	■	■	■	■	■	■	■	■	■
Netherlands*	■			■					

■ Reimbursed □ Not reimbursed

*Evidence based reimbursement: no general reimbursement, but case by case reimbursement for uveal melanoma and skull base tumours.

6.3.2 Overview of carbon-ion therapy reimbursement

Carbon-ion therapy is currently only reimbursed in Germany and in Japan. In the US, this therapy is not (yet) covered by Medicare.

6.4 THE NETHERLANDS

Proton- and carbon-ion therapy in general is not part of the basis Insurance package. In the past, a limited number of cases have been reimbursed, only in case of rare tumours as uveal melanome, skull base tumours as chordoma and chondrosarcoma.[d]

[d] Source : contact with CVZ

6.5 SWITZERLAND

Since January 1, 2002, reimbursement of proton therapy costs for the following tumour types has been mandatory for Swiss health insurance providers:

- meningiomas
- low-grade gliomas (grade 1 and 2)
- skull base tumours and ORL tumours impacting clinical structures
- bone and soft tissue sarcomas
- for children – tumours needing treatment that spares the growing organism.

6.6 UK

In the UK treatment of all eye tumours with proton therapy is reimbursed.

6.7 SWEDEN

All cases currently treated with proton therapy are reimbursed by the national insurance: prostate cancer, intracranial and skull base tumours, miscellaneous tumours.

6.8 ITALY

All cases currently treated in the centre in Catania are reimbursed: uveal melanoma and a number of other e.g. conjuctival and iris melanoma.

6.9 USA

More than 150 insurance carriers, including Medicare, cover proton therapy for a range of tumours, also including prostate cancer.[e]

6.10 GERMANY

Different policies applied by the numerous health insurers (~250). The hadron centres are discussing reimbursement with each health insurer individually. The general reimbursement rate for proton and carbon-ion therapy is 19 500€ per patient.

[e] Source: www.mdanderson.org/care_centers/radiationonco/ptc/ July 2007

7 ORGANISATIONAL ASPECTS

7.1 ORGANISATIONAL ASPECTS: RESEARCH QUESTION

In the following part, some organisational/legal aspects attached to the options of the construction of a local centre and the referrals of Belgian patient to centres abroad are highlighted.

7.2 SENDING PATIENTS ABROAD: POSSIBILITIES OF REIMBURSEMENT FOR HADRON THERAPY PROVIDED IN CENTRES ABROAD

7.2.1 The E 112 form

Patients can go abroad for treatment on their *own initiative*. Care will then be paid for through out – of pocket payments by the patient with possible reimbursement by private insurance or by the procedure provided in the Council regulation 1408/71 for sickness fund patients, the so called E 112 form. The E 112 procedure includes that for any planned hospital care to which the patient is entitled in his own Member State he may also seek in any other Member State provided he first has the authorisation of his own system. This authorisation must be given if the system cannot provide care within a medically acceptable time limit, considering the patient's condition. The patient will be reimbursed up to at least the level of reimbursement provided by his own system. These rules are only applicable for treatment in countries of the European Economic Area or Switzerland.

Up to now a few cases have been reimbursed under the E 112 procedure. There's no regular reimbursement by national social security (hadron therapy is not included as such in nomenclature of RIZIV/INAMI) for patients treated with hadron therapy since the therapy doesn't exist in Belgium. This implies that the concept of care to which the patient is "entitled" in his own member state was interpreted very largely (probably as cancer therapy in general).

7.2.2 Reimbursement by the National Solidarity Fund

Patients can obtain reimbursement for medical treatment abroad, travelling costs and costs of his/her stay and the accompanying person from a Special Solidarity Fund (Bijzonder Solidariteitsfonds - Fonds Spécial de Solidarité) of the RIZIV/INAMI if the following general conditions have been met:

1. The case is worthy of consideration
2. The treatment abroad and the date of it have been approved by the advisory physician of the patients' insurance prior his/her departure
3. The care provided abroad has been prescribed beforehand by a specialist registered as medical practitioner in Belgium.

Up to now only 3 patients obtained reimbursement for medical costs via the Special Solidarity Fund. Since the electronic processing of files by the Special Solidarity Fund has started (1/7/2002), solely data starting from this date can be provided. The age of the patients at the moment of treatment was 13 years (2001), 41 years (treatment has not started yet – agreement is given) and 14 years (2000). The centres where patients were treated are:

- Paul Scherrer Institute – Villigen-Zwitserland
- Massachusetts General Hospital - Boston-USA
- Institut Curie – Orsay-France

It was however impossible to determine the amount of reimbursement for medical costs of protontherapy since other costs were taken into account. Travel costs were reimbursed by the "Stichting tegen kanker". This charity foundation agreed to contribute in the financing of travel costs to Villigen (Switzerland) for the child, one family's member and the accompanying Belgian radiotherapist.

It is obvious however that the current situation is not satisfying. The procedure of reimbursement through the special solidarity fund is tricky and patients will often have to prepay the full cost in order to be treated in time. Moreover the best centres select patients who fit in the inclusion rules of their ongoing clinical trials.

As more patients will be eligible for carbon therapy, there is need for systematic procedure embedded in a legal framework affording a guaranteed access of patients to hadron therapy.

7.2.3 Cross border contracting

Planned care can also be provided and paid for through *direct contracts* between health care providers and purchasers[f]. In that case hospitals are directly reimbursed by either the health care purchaser (for instance the National Health insurance System) without intervention of the patient. This care can be funded at the national rate[g] or at higher prices, depending on what has been stipulated in the cross border contract.

In order to control patient flows, guarantee continuity, access and quality of care and manage patient mobility in a more systematic way, contracting long term agreements with foreign hadron therapy centres is the best option in expectation of the construction of a Belgian center. The purchasing party can be national health insurance RIZIV/INAMI setting up a national program for patients to go abroad for hadron therapy[h]. The other side of the agreement is the provider of care, in case the hadron therapy centre. The formal contractual arrangements can be embedded in a bilateral framework agreement between Member States[i].

Today there is no such thing as an EU level legal framework for cross border contracts. Recently there have been some initiatives of a European Commission working group, the High Level Group on health services and medical care[j]. The working group set out some key issues that should be taken into account when drawing up agreements or contracts related to purchase of health care abroad. The main aim was to provide an EU level framework for cross border contracts between providers and purchasers, guaranteeing the involvement of the public authority of the home country and the country where the intervention is performed. With regard to the general content of the contract, regulations setting the applicable law, medical malpractice and liability regulation, sharing of information, price and administrative procedures are essential issues.

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f For an overview of cross border contracted care in Belgium http://www.iese.edu/en/files/6_22160.pdf

g Through council regulation nr. 1408/71

h The purpose of the agreements is not necessarily to purchase health care, but parties can also agree on co-financing medical equipment and sharing of facilities for hadron therapy so that patients from both sides of the border can access the facilities in question. For instance there's an agreement between Aachen and Maastricht to co-invest in centre for protontherapy.

i http://www.espaces-transfrontaliers.org/document/Practical_guide_COE_MOT_EN.pdf

j http://ec.europa.eu/health/ph_overview/co_operation/mobility/docs/highlevel_2005_013_en.pdf

THE SPECIFIC CONTENT OF CROSS BORDER CONTRACTS FOR HADRON THERAPY SHOULD INCLUDE

- The type of therapy covered by the contract
- The number of sessions
- The patient pathway and referral system
- The collaboration modalities between the referring physicians and the receiving physicians
- The indicative number of patients covered by the contract.
- The duration of the contract and mechanisms for renewal and termination of the contract.
- The use of personal and clinical data (for instance for medical research)
- Special requirements, journey, frequency of controls, medication, time limits for exchange of medical records
- A provision on the responsibility for provision of clear and understandable information and communication to patients (service level agreement) in the following phases:
    - admission: e.g. what to bring, diagnostic results
    - treatment e.g. how to prepare, what will be undertaken
    - travel e.g. how to get to the provider in another Member State
    - financing e.g. what the patient and purchaser are expected to pay
    - follow-up and exchange of information with the patient's doctor in their Member State;
- The financial arrangements
    - when the payment will take place e.g. after the treatment takes place, when the patient returns, regularly
    - what is included and how the payment is calculated e.g. length of stay, procedure, cost of capital, medication, overhead costs
    - what the patient is charged e.g. medication, medical devices, meals, telephone, travel expenses, changes to planned treatment
    - arrangements for accompanying persons
- the administrative arrangements

Recently new Belgian legislation regarding patient mobility has been ratified[k]. In that scope an Observatory for patient mobility is created by national health insurance (RIZIV/INAMI). Today patient mobility is mainly a matter of one way traffic from patients abroad to Belgium. In that scope the new law mainly focuses on mobility from patients abroad towards Belgium.

In order to guarantee continuity, access, quality of care and manage patient mobility contracting long term agreements with foreign hadron therapy centres is the best option as long as there is no Belgian centre.

k Wet van 4 juni 2007 tot wijziging van de wetgeving met het oog op de bevordering van de patiëntenmobiliteit, *B.S.* 25 juli 2007, not entered into force yet

Key points

- **The contracts should include "package prices" which covers all cost components of the treatment based on official national tariffs (of the providing country) and secondary costs such as accommodation and travel cost.**
- **A central committee which centralizes the requests from Belgian radiotherapists, prioritizes the patients and manages the necessary agreements with the centres abroad should be established**

7.3 CONSTRUCTION OF A BELGIAN CENTRE

In the start up phase of a hadron therapy centre, capacity will increase gradually. Probably full capacity will be reached after 3 or 4 years. One possibility to optimize activity is to restrict indications for which treatment will be provided. Eventually spare capacity can be filled up by actively recruiting foreign patients. As Belgian doctors (including hospital doctors) are paid on a fee-for-service basis, they have a direct financial incentive to treat more patients as it increases their income. Additional patients also implies increased experience, competence and prospects for career development.

The following criteria should be taken into account when considering a local construction[l]:

- Proximity of several reknown academic hospital providing appropriate secondary services such as anaesthesia, imaging, etc.
- Proximity of accommodation for treated patients and accompanying persons to stay overnight
- Easy accessible location from patients all over Belgium; Optimum location with regard to the catchment area (South of England, North West of France, South of The Netherlands);
- Multilingual (English, Dutch, French, German…);
- Outstanding and scientifically proven knowledge and expertise in radiotherapy invasive treatment, patient positioning and immobilization, radiation therapy planning, IMRT, IGRT, stereotactic techniques
- Capacity to produce and adhere to good practice guidelines and to implement outcome measures and quality control;
- Demonstration of a multi-disciplinary approach;
- Expertise in radiotherapy related research; clinical study design, data management, endpoint analysis and reporting
- Strong commitment to collaborative research programs in radiobiology, clinical research, basic physics research such as microdosimetry, materials sciences etc.
- Administrative life-long follow-up of cases treated and epidemiological surveillance of secondary cancers.
- Other aspects such as financial participation and logistic support, both at institution's level as at regional level.

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l The criteria are partly based on the criteria formulated by the private foundation "Belgian Hadron Therapy Centre" and partly on the criteria for European networks of reference for rare diseases formulated by the rare diseases task force working group of the European Commission (DG Sanco) http://ec.europa.eu/health/ph_threats/non_com/rare_8_en.htm

8 COST ANALYSIS INTRODUCTION

8.1 RESEARCH QUESTIONS

In this chapter, a brief introduction is given on the cost analysis (viewpoint of the analysis, what costs are covered and how non-market costs are treated). Consequently, in chapters 9 and 10 a cost calculation will be given of treating patients abroad and starting a Belgian centre respectively.

8.2 SOCIETAL POINT OF VIEW

In this study we are looking from the societal point of view, which is the broadest point of view for cost analysis. In case of treatment abroad, we include the full costs for the patients (including traveling and lodging costs for the patient and accompanying person). In case of treatment in a new Belgian centre, we include all costs to start up and run the centre and treating the patient. This cost evaluation is independent from the type and size of reimbursement, since the reimbursement flows are considered as transfer payments (from government to patient), and mean no extra cost to society (they are a gain for the patient and a loss for the government). Note that our societal point of view equals the governmental point of view, on the condition that the government reimburses exactly all of the costs occurred to the patients and the proton therapy centre.

8.3 COSTS COMMON TO BOTH OPTIONS

In this study we compare the costs of two options: 1) sending patients for treatment abroad; 2) treating patients in a new centre in Belgium. Costs that are common to both options will not affect the choice between the two options. Therefore they need not be considered.

The following costs are considered to be equal in both options:

- Cost of selection and referral

After the diagnostic phase, a local radiation oncologist will decide on the treatment of the patient, based on approved treatment protocols. In case of treatment with protons/ions, the oncologist will contact the proton centre, be it in Belgium or abroad, for scheduling the treatment. In case of treatment abroad, the diagnosis will not be repeated abroad.

- Cost of meals for patient:

As a patient is forced to take meals at a restaurant in the option of treatment abroad, one could argue that this is more expensive than taking a meal in the option of treatment in Belgium (as one may take the meal at home). Nevertheless, we assume that the costs of meals are equal in both options for two reasons. First of all, the cost of meals is, compared to the other costs, of relatively small order, and will unlikely make any difference to the study result. Secondly, the meals can most likely be taken at the hospital restaurant, where in most cases relatively cheap meals are offered.

8.4 NON-MARKET COSTS

For most cost items, cost calculation is relatively unambiguous since market price estimates are available. However, there are a number of costs incurring to patients that are more difficult to value. This issue arises with the valuation of the time lost by patients and relatives, both work and leisure time. In both treatment options, we can assume that the patient stops working during the treatment period. But clearly there is a different quality of "leisure" time. In the case of treatment abroad, the patient stays abroad for the full period of treatment, whereas in the case of local treatment, the patient can stay at home. Also, in the case of treatment abroad, there is the time loss for the accompanying person, either work loss or leisure loss, depending on the situation of this person.

As the market value of this work and leisure time is not straightforward to assess, we do not take these costs into account.

Key points

- **In this study we are looking from a societal point of view**
- **Costs that are common to both options (option 1: treatment abroad and option 2: treatment at a local centre) are not considered**
- **Non-market costs (such as time loss for patients) are not considered**

9 POSSIBILITY AND COST FOR TREATING BELGIAN PATIENTS ABROAD

9.1 RESEARCH QUESTIONS

In this chapter the research questions covered are as follows:

1. Do centres abroad have capacity available to treat Belgian patients? If yes, how much?
2. At what cost could Belgian patients be treated abroad?

First of all, an overview is given of the existing and planned centres abroad. Consequently, the possibility and cost of treatment abroad is analysed. The methodology applied can be found under 9.2.1

9.2 EXISTING AND PLANNED CENTRES ABROAD

9.2.1 European centres

9.2.1.1 Operational centres in Europe

In Europe there are currently eight operational particle therapy centres. (see table 9.1) These centres have treated more than 15 000 patients in total in the past.

Four of the centres (Berlin, Catania, Clatterbridge and Nice) are suitable for eye-treatments only, since they have an accelerator of low clinical energy (60-72 MeV). Amongst these four, only Nice is fully dedicated to treatments. The other low-energy centres also devote considerable time to research activities.

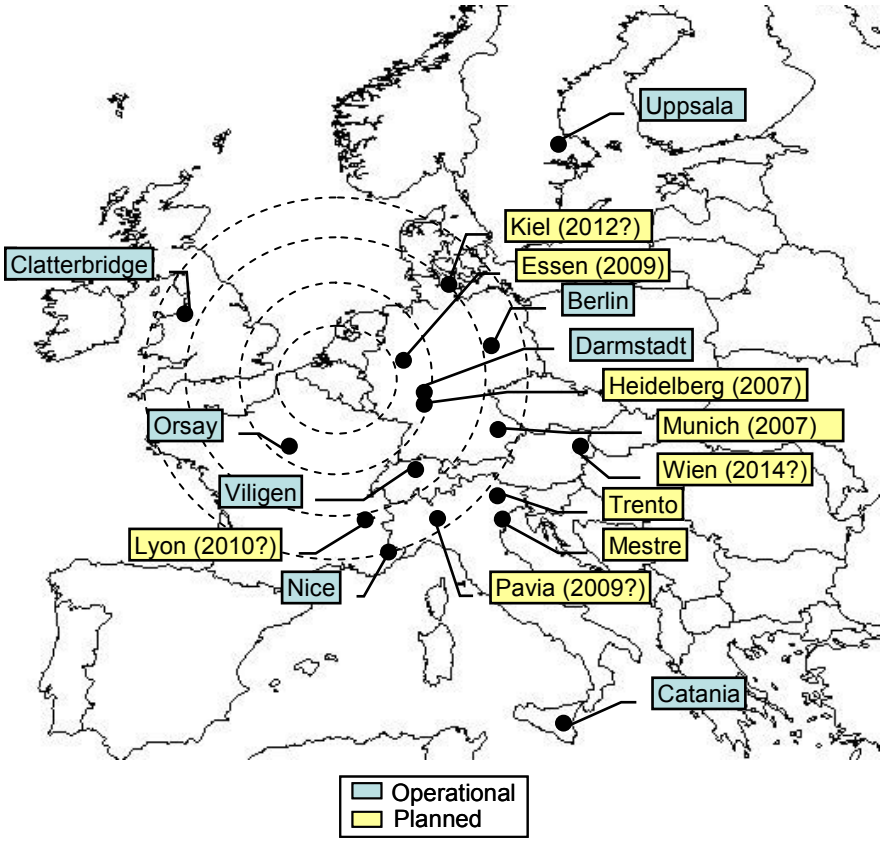
Orsay, Uppsala and Villigen are the proton centres with higher energy accelerators. Darmstadt is the only currently operational European carbon-ion centre. Orsay, Uppsala and Villigen are significantly expanding their activities. The medical activities in Darmstadt will be stopped and patients will be referred to the new centre in Heidelberg.

9.2.1.2 Planned centres in Europe

Nine new European centres are currently under construction or approved. Four of the centres are for proton treatment: in Essen (Nov 2009), Munich (2007), Trento and Mestre. Five of them are also for carbon-ion treatment: Heidelberg (end 2007) (in collaboration with Darmstadt), Pavia (2009), Lyon (end 2010?), Vienna (2014?), Kiel (2012?). With these new centres and the expansion of the existing centres, the capacity for treating patients with hadron therapy will be more than eight-folded in the coming six years.

Numerous other centres all over Europe are proposed and in preparation, but as no tender for construction has started yet, their construction is still uncertain. Most of the proposed centres are in Germany (amongst other in Marburg, Köln, Aachen, Dresden, Erlangen ...). Also in the Netherlands there are a number of initiatives: Maastricht, Groningen, Utrecht and Rotterdam.

Figure A : Operational and new hadron centres in Europe



9.2.2 Centres outside Europe

Outside Europe, there are currently 20 particle therapy facilities in operation, amongst which 8 in the USA and Canada, 7 in Japan, 3 in Russia, 1 in South-Africa and 1 in China. 1 centre in Seoul is under construction.

Figure B : Existing hadron centres outside Europe

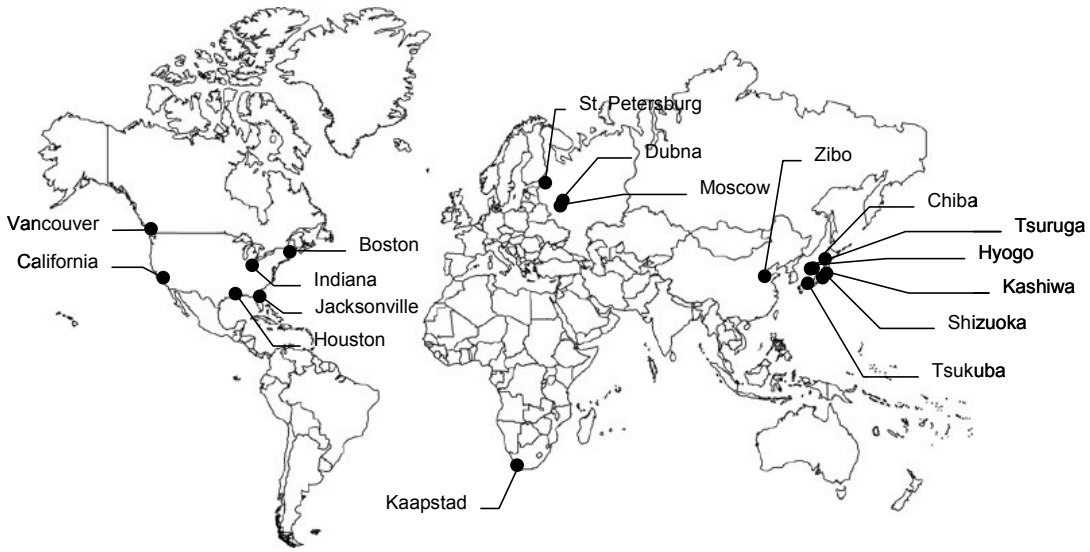
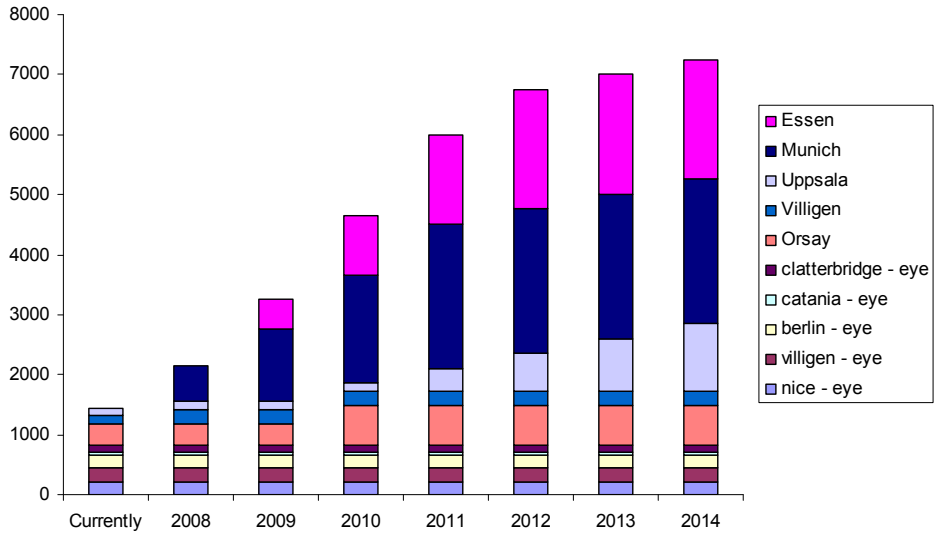


Table 9.1 : European centres (partly based on source: PTCOG)

Location and name of centre	P and/or C ion	Max. clinical energy (MeV)	Date of First patient	Total patients treated (Jul 06-Dec 06)
Centres in operation				
Villigen, PSI (2 accelerators)	P	72	1984	4646 (eyes only)
	P	230	1996	262
Clatterbridge, Centre of Oncology	P	62	1989	1584 (eyes only)
Uppsala, The Svedberg Laboratory	P	200	1989	738
Nice, Centre Antoine Lacassagne	P	65	1991	3129 (eyes mostly)
Orsay, Centre de Protonthérapie	P	200	1991	3766
Darmstadt, Biophysics and therapy Centre GSI	C ion	430	1997	316
Berlin, Proton Therapy, ISL/HMI	P	72	1998	829 (eyes mostly)
Catania, INFN	P	60	2002	114 (eyes only)
Approved projects in expansion/under construction				
Villigen, PSI	P	250	2007/2008	
Uppsala, University Hospital	P		2011	
Orsay, Centre de Protonthérapie	P	230	2010	
Essen, WPE	P	230	Nov 2009	
Munich, RPTC	P	250	2007	
Trento	P		?	
Mestro	P		?	
Pavia	P+C ion	430	2009?	
Heidelberg	P+C ion	430	Winter 2007/2008	
Lyon, Etoile	P+C ion		End 2010	
Vienna, Med Austron	P+C ion		2014	
Kiel	P+C ion		2012?	
Initiatives for centres (still in planning stage)				
Marburg			2010?	
Köln			2009?	
Berlin				
Dresden				
...				

Figure C: Proton therapy capacity in Europe (number of patients yearly) (Source: estimates provided by the centres, ramp-up period of 4 years assumed)



*Munich project currently endangered by delays in VARIAN / ACCEL´s product development

Figure D : Carbon-ion therapy capacity in Europe (number of patients yearly) (Source: estimates provided by the centres, ramp-up period of 4 years assumed)

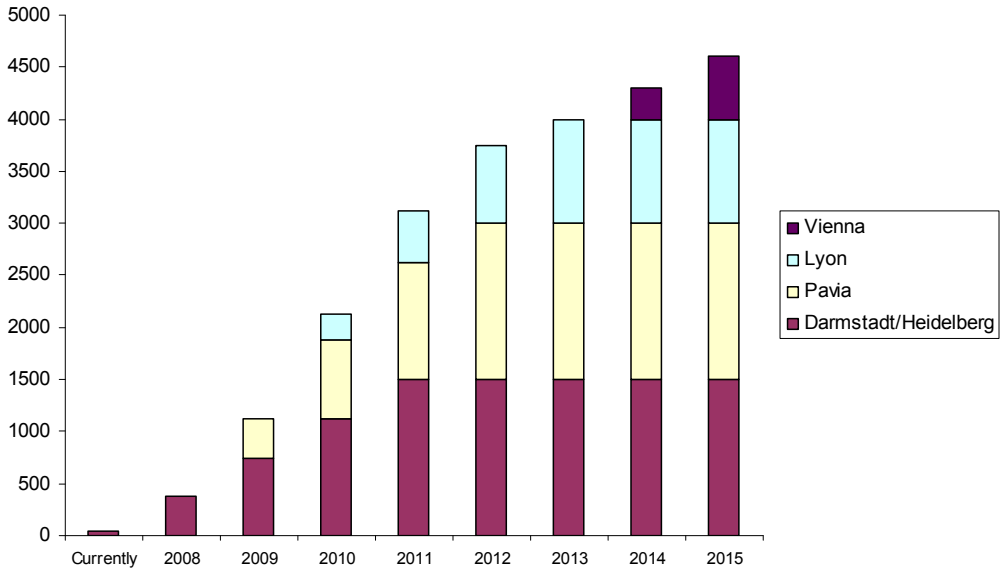


Table 9.2 : Centres outside Europe (source: PTCOG)

Location	P and/or C ion	Max. clinical energy (MeV)	Date of First patient	Total patients treated (Jul 06-Dec 06)
Centres in operation				
Boston, Harvard	P	160	1961	9116
Moscow, ITEP	P	200	1969	3927
St. Petersburg	P	1000	1975	1320
Chiba, Japan	C ion	800/u	1994	2867
Tsukuba, Japan, PMRC	P	250	2001	930
Dubna, Russia	P	200	1999	318
California, Loma Linda	P	250	1990	11414
South Africa	P	200	1993	486
Indiana, MPRI	P	200	1993	220
California, UCSF	P	60	1994	920
Vancouver, TRIUMF	P	72	1995	111
Kashiwa, Japan, NCC	P	235	1998	462
Hyogo, Japan, HIBMC	P	230	2001	1099
Hyogo, Japan, HIBMC	C ion	320	2002	131
Boston, NPTC, MGH	P	235	2001	2080
Shizuoka, Japan	P	235	2003	410
Tsuruga, Japan	P	200	2002	33
Zibo, China	P	230	2004	270
Houston, MD Anderson Cancer Center	P	250	2006	114
Jacksonville, FPTI	P	230	2006	15
Centres in construction				
Seoul	P	230	2007	
Centres in planning stage				
iThemba Labs, South Africa	P	230	~2009	
Chicago	P	250	2011	
UPenn, US	P	230	2009	

9.3 AVAILABLE CAPACITY IN CENTRES AND TREATMENT PRICE

9.3.1 Methodology

In order to investigate whether the centers abroad foresee to have free capacity in the future and whether they are interested to accept Belgian patients, a questionnaire was sent to the existing centers worldwide, including those that are currently under construction. We requested an estimate of the number of Belgian patients that could be treated at their centre in the future, as well as the treatment price. The planned centers that have not started a tender procedure yet, have not been taken into account, given the large uncertainty of their future. We received answers from 15 European centers and 4 centers outside Europe.

9.3.2 Results

Following the expansion of the current centers and the construction of new large centers outside research facilities, the centers foresee to have considerably large

capacity for treating Belgian patients in the near future. Two new large German centers, Heidelberg (start of operation foreseen end 2007) and Essen (start 2010) expect both to be able to treat up to 500 Belgian patients per year. For this, Heidelberg would be interested to construct a treatment room exclusively for Belgian patients. Also Lyon (start in 2010) foresees to be able to treat a number of Belgian patients, according to their priority criteria. The centre Etoile in Lyon has a strong European vocation and therefore prefers to select patients based on clinical priorities, rather than on nationality. Villigen, Orsay and Uppsala currently have limited capacity and therefore treatment of Belgian patients is restricted to strict priority cases. After expansion of these centers (foreseen in respectively 2009, 2010 and 2011), a larger number of Belgian patients could be treated.

In the uveal centers Nice, Berlin, Clatterbridge and Villigen, in total 75-100 Belgian eye patients could be treated (which is more than the actual number of Belgian eye patients).

In Table 9.3 the estimates for available capacity and price at the centers abroad are summarized.

Table 9.3 : Estimates for available capacity and price for Belgian patients

Centre	P/C ion	Estimated capacity for treating Belgian patients	Average price indication all-inclusive*
High MeV centres			
Villigen	P	Currently: limited availability From 2009: more capacity but still limited to priority patient cases only	15-18 k€
Orsay	P	Currently: a small number of Belgian patients can be treated. Priority is given to intracranial tumours and other priority tumours jointly agreed From 2010: more capacity available	1 544 € by fraction
Uppsala	P	Currently: ~20 From 2011: ~110	
Heidelberg	P+C ion	From 2008: up to 400-500 Belgian patients (in case of construction of room exclusively for Belgian patients)	40 k€
Essen	P	From 2010: up to 500 Belgian patients	25 k€
Lyon	P+C ion	From 2010/2011: 100 Belgian patients	20 k€
Vienna	P+C ion	From 2014: about 300 patients from abroad could be treated	~20 k€
Munchen	P	Unclear, but large amount of patients expected from abroad. Patients selected on first come first serve basis	
Houston	P	Currently: 100	83-98 kUSD
Hyogo	P+C ion	Currently: "A small number"	20-25 k€
Darmstadt	C ion	None (medical activities will be transferred to Heidelberg)	
Cattania	P	None	
Pavia	P + C ion	None	
Vancouver, Canada	P	None	
Chiba	C ion	None	
Low MeV centres (for eye treatments)			
Nice	P	30-40	10 k€
Berlin	P	25 or more	15.2-16.9 k€
Essen	P	40-50	20 k€
Clatterbridge	P	10-15	14.6 k€
Villigen	P	10-15	3.4 k€

K€ : thousand EURO

* Including 1st examination, treatment planning, treatment and 1st after treatment control. Both technical and professional fees are included.

**High-priority criteria still to be defined by Lyon

9.4 COST OF TREATMENT ABROAD

9.4.1 Considered costs

The costs considered for treatment abroad include:

- Cost of full treatment in the centre: including cost of tumour localization, immobilization devices, irradiation, doctor's fees
- Cost of transport to the centre (flight or train and taxi), for both the patient and an accompanying person (in case of a paediatric patient) (see Appendix)
- Lodging in a furnished rental apartment near the centre for the full length of treatment, for two persons (see Appendix)

9.4.2 Patient allocation

For the budget calculation, the following patient allocation is taken. Note that contracts can be agreed with other centers as well:

Table 9.4 Patient allocation assumed for the budget calculation

Patient type	N° of patients	Centre
Eye patients	~13	Nice (from today onwards)
Paediatric patients (no eye tumour)	~3	Villigen
Adult patients (no eye tumour)	~35	Heidelberg (from 2008) or Essen (from 2009/10)

9.4.3 Resulting yearly reimbursement budget requirement

Given the assumed above mentioned patient allocation, the cost of treatment of about 51 patients abroad, including cost of transport and lodging is estimated at 1,7 m€ or on average of 11,4 k€ for eye patients, 21,8k€ for paediatric patients treated in Villigen and 43,4 k€ for patients treated in Heidelberg (P or C ion). From 2009/10 patients could also be treated in Essen which would likely lead to a price reduction compared to Heidelberg.

Table 9.5 Total budget requirement

	Cost / Budget required
Approximation of total budget required	1 732 k€
Average total cost per eye patient	11,4 k€
Average total cost for paediatric patient treated in Villigen	21,8k€
Average total cost for patients treated in Heidelberg (P or C ion)	43,4 k€
Included Average Travel cost	0,4 k€
Included Average Lodging cost	2, 5 k€

Key points

- **Currently 8 hadron centers are operational in Europe, all of which originated from physics research activities. 4 of the centres are suitable for eye treatments only (Nice, Clatterbridge, Berlin and Catania). 3 of the centres are proton centers (Villigen, Orsay and Uppsala). Only 1 of the centers is a carbon-ion centre (Darmstadt). A new large center in Heidelberg (for carbon-ion and proton therapy) will be operational in 2007-2008.**
- **Following the expansion of the existing centers and the construction of new centers, the capacity for both Proton and Carbon ion therapy will be significantly increased in the short-term future**
- **It is expected that all of the currently eligible Belgian patients can be treated abroad in the short term future.**
- **The total budget required for treatment of 51 patients abroad is estimated at 1,7 million € (including traveling and accommodation costs)**

10 INVESTMENT ANALYSIS BELGIAN HADRONTHERAPY CENTRE

10.1 RESEARCH QUESTION AND METHODOLOGY

The aim of this chapter is to study the costs of a hadron therapy centre in Belgium. All costs are considered, including construction, finance and operational costs over an expected lifetime of 30 years. Current subsidy possibilities for hospitals are taken into account (for both the Flemish and Walloon region). Based on a cash flow model, the minimum required reimbursement from RIZIV/INAMI is calculated. We received cost data from IBA, Siemens, Hitachi and Accel.

As starting point, the cost is calculated for a base case scenario, which consists of a carbon-ion and proton therapy facility, with 3 treatment rooms, operated in 2 shifts for 12,5 hrs treatment per day and 5 days per week. In the sensitivity analysis, multiple other scenarios are assessed, amongst which also a scenario for a proton-only therapy facility and a carbon-ion centre with 2 or 4 treatment rooms. Different operational scenarios and their impact on the potential number of patients treated are also examined.

10.2 GENERALCONSIDERATIONS ON INFRASTRUCTURE AND EQUIPMENT

10.2.1 Carbon-ion and proton facility as base case scenario

Two main options are investigated:

1. A carbon-ion and proton therapy facility (used for the base case analysis)
2. A proton-only therapy facility (this scenario will be examined in the sensitivity analysis)

Both for proton and for heavy-ion therapy there is currently little clinical evidence. As, however, carbon-ion therapy combines the advantages of dose delivery with the biological advantage, a carbon-ion and proton facility is considered as the base case investment for our study. Proton therapy is expected to result in marginal improvements compared with photon therapy (which is already very advanced in Belgium), whereas carbon-ion therapy is expected to result in significant improvements, at only a relatively higher price than proton therapy. As however, for paediatric patients, proton therapy would still be preferred above carbon-ion therapy, we will consider an investment in a combined carbon-ion and proton therapy facility.

10.2.2 Number of treatment rooms

Three treatment rooms are taken as base case scenario. This is considered as a minimum to cover the large investment in the building. A scenario with 2 and 4 treatment rooms will be treated in sensitivity analysis as well.

10.2.3 Type of accelerator and treatment rooms

There are two main options for an accelerator that can accelerate both carbon-ions and protons (a superconducting cyclotron and a synchrotron). Both can reach an energy level of ~400 MeV/u for carbon-ions and ~230 MeV for protons. For the type of treatment rooms there are two options:

1. Fixed beam room

A fixed beam room requires rotating the patient to aim ions to various anatomical regions. The fixed beam rooms can be equipped with a horizontal beam and/or a 45° or vertical beam in order to be able to reach all tumours.

2. Gantry

A gantry is used to rotate the radiation delivery apparatus around the patient so that he can be treated from different angles. The position of the patient remains unchanged. This type of rooms is typically installed in combination with a fixed horizontal beam room, so that all tumours can be treated at a minimum investment cost.

For our study, we have asked the constructors a price for a fully equipped centre that can treat all relevant indications, independently of the type of accelerator or treatment room configuration, according to their best solution.

10.2.4 Eye apparatus

For the treatment of eye tumours, a separate apparatus and line would need to be installed. As however, for eye treatment, only a low level of energy is required (60 MeV), the considered accelerator types (of ~400 MeV/u for carbon-ions and ~230 MeV for protons) that are much more expensive, can more efficiently be used for treating other tumours. Taking also into account the required ophthalmologic competencies, the limited number of eligible eye patients in Belgium and the relatively short treatment (of 4 to 5 fractions), we consider for our analysis that no eye treatment line is installed and that the eye patients will be sent to dedicated eye-treatment centres abroad, which are specialized in this particular type of radiation. As mentioned in the chapter on treatment abroad, the centres in Nice, Berlin and Clatterbridge are interested in receiving Belgian patients.

10.2.5 Treatment planning equipment

Standard treatment planning software and computers are foreseen. On top of this, a centre typically needs 1 PET CT, MRI CT or MR-PET scan. For our study 1 PET CT is assumed.

10.3 TREATMENT PROCESS AND WORKFLOW

Based on information from other centres[m] the treatment process for a Belgian hadron centre is assumed to be as follows.

10.3.1 Referrals and selection: at local radiotherapy centre

Based on approved treatment protocols or clinical trial protocols, the radiation oncologists team at the local radiotherapy department decides on what therapy is needed for the patient. In case hadron therapy is needed, after discussion of the proposed treatment with the patient, the team will refer its patient to the hadron centre.

10.3.2 Treatment planning: at national hadron centre

10.3.2.1 Examination

Upon referral to the centre, a surgeon and radiation oncologist review the patient case, assessing his medical and treatment history, medications and prior imaging studies to determine the best hadron treatment for the patient.

10.3.2.2 Production of immobilisation devices and fiducials

For a CT scan and the actual treatment, it is crucial that the patient remains still. Therefore, the patient is fit with an immobilization device, which will minimize patient motion and a light sedative is administered.

For patients with tumours within the head, the treatment requires fiducials to be implanted in the surface of the skull. The fiducials help to insure that the proton beam is precisely aimed at the target. The fiducials are put in place by a neurosurgeon using a small needle, with a local anaesthetic.)

10.3.2.3 CT scan

Once the immobilization frame is in place, an IV contrast is injected in preparation for a CT scan. The CT scan will create a precise three-dimensional picture of the area to be treated. This delivers the framework for calculating the radiation dose and designing the treatment.

Once the CT scan is completed, the physicians use the scan, in addition to other studies the patient has had, to outline the treatment plan. Once the treatment plan is finalized,

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m Massachusetts General Hospital Cancer Center [105]

customized equipment is fabricated to shape the proton beam. This equipment is designed for each direction from which the beam will be aimed. This treatment planning takes a couple of hours.

10.3.3 Irradiation

Once the treatment plan is finalized, actual treatment can start.

10.3.3.1 Patient preparation and immobilisation

The gantry utilization is clearly the bottleneck of the facility. Therefore it is important to minimize the time spent in the gantries and to prepare the next patient during the treatment of the previous patient, by helping him into his specific mold or cast (for body treatments) so that he is ready for treatment, on a transporting cart, when the previous patient comes out.

10.3.3.2 Position verification and correction

The patient needs to lie on a treatment bed with the immobilization device secured. Position verification and correction can be done by X-rays directly in the treatment room, or with a CT in a separate CT room (for efficiency reasons).

10.3.3.3 Irradiation

The beam is then turned on to deliver the precise radiation dose. One field takes about 5 minutes on average (including switching time of the accelerator). On average, a patient will receive about 2 fields per fraction.

10.3.3.4 Verification

After the irradiation, the precision of the irradiation can be verified with a PET-CT. The positrons emitted by the irradiated cells will enable an in situ check of the dose deposition within the target. It is assumed for our study that the majority of patients will undergo this PET verification.

10.4 RESEARCH

In this field of radiation oncology, important research is still needed relating to clinical care, physics and biology. As there is limited clinical evidence, one would suppose that all patients would be entered into a clinical protocol. In the physics area, research can be done for designing and implementing new technology for beam delivery, treatment planning and verification of treatment delivery. In the biological field, research is needed, amongst other, on the precise estimation of the relative biological effectiveness of particles relative to standard radiotherapy.

For our analysis a number of personnel is foreseen for the clinical research.

10.5 OPERATIONAL MODEL

As base case analysis, a treatment schedule is foreseen from 07:30 to 20:00, from Monday to Friday. In the sensitivity analysis, the impact of shorter treatment hours (from 09:00 to 17:00 from Monday to Saturday) and longer hours (from 07:00 to 22:00, from Monday to Saturday) is assessed.

10.5.1 Work schedules

Table 10.1: Daily work schedule

	Base case scenario: 12,5 operating hrs / day 2 shifts
Quality assurance and calibration	05:30-07:30
Patient treatment	07:30-20:00
Quality assurance and calibration	20:00-21:00

Table 10.2: Weekly/Yearly work schedule:

Treatment days/week	5 days/week (Monday to Friday)
Treatment weeks/year	48 weeks/year
Time for (un)scheduled closures	Calculated in weekends and week 49, 50 and 51
Number of hours for operation per year (per room)	3000

10.5.2 Patient flow

Table 10.3.A: Patient flow

	Carbon-ion and proton therapy
Average number of fractions per patient	18
Average time per fraction (min)	30
Maximum capacity patients per year	900
Patients treated	25% of max. capacity in year 1 50% in year 2 75% in year 3 100% from year 4. Yearly increase of 1% after year 4*
Percentage usage of treatment rooms	90%
Number of treatment rooms	3

* Shorter time per fraction or smaller number of fractions per patient should be feasible in the future

Table 10.3.B Calculation of number of patients

Calculation of available operation time		
Number of hours operation per day	12,5	hrs
Number of weeks operation per year	48	weeks
Number of days operation per week	5	days
➔ Number of hrs available for operation per year	3000	hrs

Calculation of total number of fractions per year		
Number of rooms	3	rooms
Total # working min / year for all rooms	540.000	min
% utilization of rooms	90%	
Available minutes for all gantries	86.000	min
Time per fraction (minutes)	30	min
➔ Number of fractions available per year	16.200	fractions

Average number of fractions / patient	18	fractions
⇓		
Number of patients	900	patients

According to Tsujii [106] the following dose-fractionations for carbon-ion therapy are currently employed at the National Institute of Radiological Sciences (NIRS) in Chiba.

The average number of fractions per patient at the NIRS was 12 in 2006. For our analysis, and based on benchmarking with business plans from other centres (amongst which Heidelberg), we assume conservatively 18 fractions per patient. The more precise the beam delivery, the lesser fractions are needed.

Table 10.4: Dose-fractionations for carbon-ion therapy at the National Institute of Radiological Sciences (NIRS) in Chiba [106]

Site	Number of fractions
Head & Neck (ACC, MM etc + Sarcoma)	16
CNS	20
Skull Base	16
NSCLC (Non-Small Cell Lung Cancer) Peripheral type	Clinical study not concluded yet: 18/9/4/1/9
NSCLC - Hilar type	9
Liver HCC	Clinical study not concluded yet: 15/12/8/4/2
Bone/Soft tissue	16
Prostate	20
Pancreas Pre-operative	8
Pancreas Radical	12
Rectum	16

30 minutes for treatment per patient is also a conservative option. Business plans of other carbon-ion and proton centres calculate down to 20 minutes.

10.5.3 Personnel parameters

Table 10.5: Personnel parameters

Working hours / week per FTE	38	
Working weeks / year per FTE	45	Taking into account vacation and bank holidays
Percentage productive hrs / total working hrs / FTE	88%	Taking into account sick time and other service-related duties
Total productive hrs / year per FTE	1500	
Number of shifts required	2	

See Appendix for benchmark data on operational models of hadron therapy centres or studies

10.6 STAFFING

10.6.1 Employment status of physicians

The employment status of physicians in Belgium is depending from the type of hospital. At university hospitals, physicians have an employment contract. At general hospitals, physicians are self-employed. Given that very likely the hadron therapy centre will be affiliated with a university hospital, most likely the physicians will have an employment contract.

10.6.2 Staffing in phase of routine

The necessary staffing for the facility is based on staffing of existing centres in Europe and the US (data provided by IBA), in function of the number of shifts and treatment rooms and diagnosis equipment (PET-CT). The cost per FTE is based on wage scales and personnel costs at Belgian (university) hospitals.

Table 10.6: staffing plan for a centre with 3 rooms, operated in 2 shifts, in phase of routine

	# FTE's	Cost per FTE p.a. (k€)*	Rationale for staffing	Cost per FTE based on
Management & Administration & Research fellows				
Facility General Manager	1	180		Average cost at Belgian university hospitals
Chief Physicist	1	140		
Chief Medical Doctor	1	180		
Administration senior (management)	3	55	1 per treatment room	Barema 305.01 B 163 "Administratie – bestuurschef" 15 ys seniority
Administration junior (secretary)	3	46	1 per treatment room	Barema 305.01 B139 Administratie – Directiesecretaris 15 ys seniority
Research fellows	3	46	1 per treatment room	
Medical doctors				
Radiation oncologist	7	180	1 per shift per treatment room for follow-up of patients + 1 for research and training	Average cost at Belgian university hospitals
Nurses				
Senior Radiographer	1	56	1 in charge of supervision of diagnosis operations	Barema 305.01 Q143 Gebrevetteerde verpleger 20 ys seniority
Radiographers	2	50	2 radiographers for PET CT scanner	Barema 305.01 Q143 Gebrevetteerde verpleger 10 ys seniority
Therapist senior	14	56	2 per shift per treatment room for patient treatment + 2 for research and training	Barema 305.01 Q143 Gebrevetteerde verpleger 20 ys seniority
Therapist junior	9	50	1,5 per shift per treatment room for patient treatment	Barema 305.01 Q143 Gebrevetteerde verpleger 10 ys seniority
Physicists				
Dosimetrist (with degree in Physics)	6	93	1 per shift per treatment room for treatment plans preparation.	Based on higher salary range for hospital physicists in Belgium (survey BVZF-SBPH)
Physicist (therapy)	7		1 per shift per treatment for morning quality assurance, fields calibration + 1 for research and training	
Total staff employed by centre	58			
Staff provided by constructor for maintenance	13			
Total staff	71			

*Total cost for centre (including gross wage, RSZ, holiday pay,…)

10.6.3 Staffing during ramp-up phase

Table 10.8: Staffing during start up phase

	Commissioning year	1 st year of operations	2nd year	3rd year	4th year
Staffing assumptions (% of full staffing)	15%	40%	65%	90%	100%
% of patients treated	0%	25%	50%	75%	100%

10.7 VAT

It is assumed that the centre does not pay taxes on its profits, as the centre is not expected to be profit-making. The centre does however pay VAT on all of its purchases, according to the following general tariffs:

Table 10.9: General VAT rate

	VAT rate
Building costs	21%
Cost of accelerator and medical equipment and IT	21%
Maintenance of building and medical equipment	21%
Other operational costs (medical supplies, utility costs, security, courier, …)	21%

10.8 INFLATION OF COSTS AND REVENUES

10.8.1 Inflation of operational costs other than maintenance, energy and personnel

'Het Federaal Planbureau' forecasts an average inflation rate of 1,9% for the period 2007-2012 [107]. The average inflation rate of the period 2001-2006 was 2.1%. Based on these figures a general inflation rate of 2.0% is assumed for the full lifetime of the facility.

10.8.2 Inflation of maintenance costs

The inflation of the maintenance costs (of building, equipment and medical IT) needs to take into account labour and material cost increase on one hand and efficiency gains on the other hand.

The Agoria data from June 1994 to June 2007 shows a labour cost increase of 2.485% yearly (source: Agoria, Federation for the Technology Industry). Taking into account the efficiency gains, also a 2% inflation is assumed for all maintenance costs.

10.8.3 Inflation of personnel costs

Also all personnel costs are assumed to rise by 2.0% per year. As relatively high seniority of personnel is foreseen for the initial personnel cost, this yearly increase should be sufficient. Likely lower start salaries will balance out larger wage increases.

10.8.4 Inflation of energy costs

Energy costs are assumed to rise by 2.5% per year.

10.8.5 Indexation of reimbursement revenues

The revenues for the centre (the reimbursement from RIZIV/INAMI) are considered partly fixed (the investment fee), and partly variable (the operational fee, depending on the number of treatment sessions). In line with the reimbursement of actual radiotherapy services (according to the Royal Decree of 11 July 2005 [108], an indexation is foreseen for the operational reimbursement part, in line with the health index, but no

indexation is foreseen for the investment reimbursement part. The health index is assumed to be at 2.0% for the full lifetime of the facility.

10.9 TIMELINE

Design, construction, installation and commissioning of a hadron centre are assumed to take 4 years. This timing takes into account sufficient margin for testing and training.

The minimum expected lifetime of the cyclotron/synchrotron is 30 years. This is in line with literature on hadron therapy (amongst other Cohilis (1999) [109] and Goitein (2003) [110] and business plans of other centres (amongst other the Etoile centre at Lyon).

10.10 INVESTMENT COSTS

10.10.1 Building, accelerator, beam lines and equipment

For the price of a fully equipped turn-key hadron centre, we obtained price data from different constructors, notably IBA, Siemens, Hitachi and Accel. The following price information was obtained from the constructors (excl. VAT):

Table 10.10: Price data for a fully equipped hadron centre obtained from the constructors excl. VAT

	Average of base prices* (m€)	Range** (m€)	Average of base prices – 15% (m€)
Building for a centre with 3 treatment rooms. Including – architect costs – project management – provision of utilities – furnishings and office supplies Assuming that the centre is located next to a hospital. Cost of ground not included.	39	35 – 60	33
Price per m^2 (for a centre of 9 000 to 11 000m^2)			⇓ 3000–3667€/m^2
Accelerator, beam lines and 3 treatment rooms – either 2 gantries and 1 fixed beam room or 3 fixed beam rooms – according to the recommended set-up by the constructor to treat all patients fully equipped with scanning and patient couches etc.	93	83 - 107	79
Treatment planning soft- and hardware (m€)	2.3	1.2 – 3.5	2.0
Total (m€)	135	120-158	114

* Some constructors provided a base and a maximum price (E.g. for the building price the maximum price takes into account extra costs for difficult subsoil and extra costs due to stringent regulations in terms of radiation protection). For our analysis, base price was used to calculate the average.

** Showing variation from the lowest base price to the highest maximum price

As we may expect from the constructors to give considerably higher prices than the actual price, we have applied a discount on their offer. Based on comparison with cost information from existing centres, we have applied a realistic discount of 15%.

The cost of a built-in PET scan is estimated at 2.3 m€. That brings the total investment cost to116.3 m€.

10.10.2 Intermediate finance cost

As construction costs are paid stepwise during the construction period, an intermediate finance cost is foreseen covering the full construction and installation process. The following timing is foreseen for finance:

- Building funds from start year 1
- Accelerator and treatment room funds from start year 2 (1/3) and start year 3 (2/3)
- Diagnosis and Treatment planning equipment from start year 4

10.10.3 Operational expenditures to commission the centre

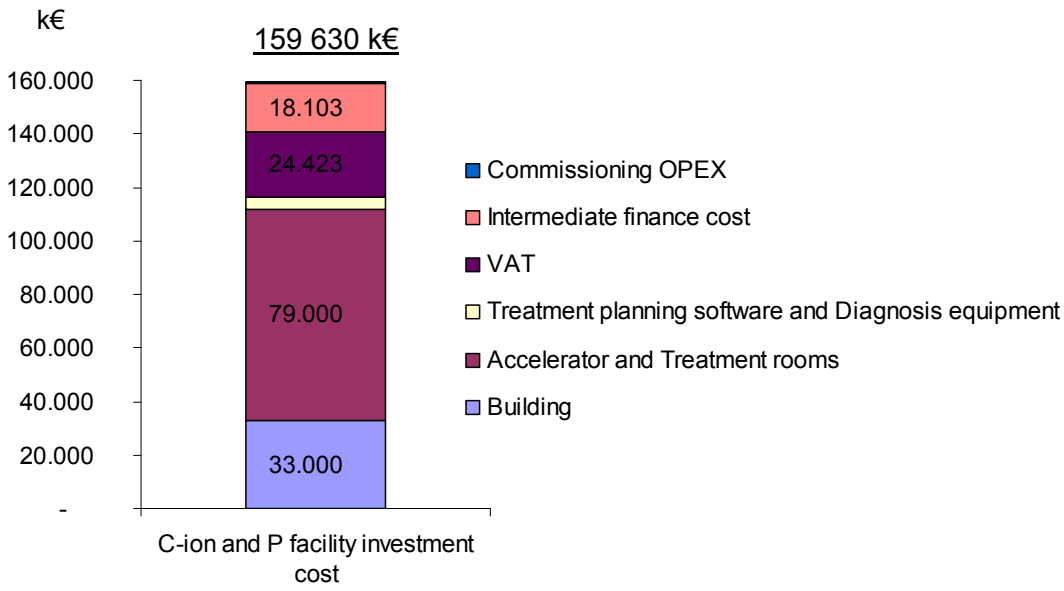
In the 4th year, the year before the start of operations, 15% of personnel is foreseen (8.7 FTEs) for clinical testing and training. These costs are considered as part of the initial investment.

10.10.4 Contingency margin for unforeseen expenditures

For this type of projects, usually a contingency fund is foreseen of minimum 15% of the construction costs (Goitein & Jermann, 2003). As we assume however that the investment costs are prudently estimated, no contingency is included in this study.

10.10.5 Capital cost overview

Figure A Capital cost distribution



10.10.6 Depreciation

The depreciation rates for the asset base are as follows:

	Depreciation period (n° of years)
Building and infrastructure	30
Accelerator and treatment rooms	30
Diagnosis equipment	10
Treatment planning equipment	5

A proton/carbon-ion accelerator has a considerable longer expected lifetime than electron linacs. According to Cohilis (1999) [109], experience has shown that cyclotrons exhibit very long lifetimes, typically up to 30 years, if the main decommissioning criterion is the loss of reliability. Exclusive reliance on solid state technology for power supplies and controls is likely to make the new generation of cyclotrons even more rugged than the earlier units. Therefore the authors are confident that a 30-year lifetime can be expected for a hadron therapy facility. Also according to Gotein and Jermann (2003) [110], a lifetime of 30 years is a conservative assumption, given the experience at existing proton facilities.

As in Belgium, electron linacs are depreciated in 10 years, and A3 financing of hospitals for these linacs is limited to 10 years, adjusted regulation would be required for depreciation and financing of a hadron cyclotron.

10.11 OPERATING COSTS

10.11.1 Ground rent

The land required for a hadron facility varies largely from project to project. Goitein & Jermann (2003) measure the land needed for a proton facility at 6 000m^2. The land budgeted for the Etoile project in Lyon however is 30 000 m^2 which is considered "large enough to be able to accommodate additional buildings for new technical facilities and to house patients or research staff on a temporary basis". Based on information from constructors, the footprint of a centre varies around 4000-6000 m^2, the total gross space around 9 000-11 000 m^2 and based on this, a ground size of 10 000 m^2 should be a reasonable size for the Belgian centre.

Although land is non-depreciable and will return (more than) its original value at the end of the project, there is still a cost for using the land. This cost is the lost opportunity to use or rent the land for another venture. The opportunity costs can never be known with certainty, neither can the future resale value. In the economic literature, the cost is usually valued by applying an interest rate (equal to the discount rate used in the study) to the amount of capital invested. [111].

In order to include this opportunity cost in the total costs of the centre, it is assumed that the ground will be borrowed from government at 3% of the value of the ground.

As a price indicator we apply the average price for industrial grounds sold in 2006 in Belgium (source: NIS), which is 34.6€/m^2. Depending on the type of ground, the price may be considerably higher (in the case of grounds currently owned by an existing hospital), or may be lower (in the case that the ground is sold as pasture land).

Table 10.11: Ground assumptions

Size of land	10 000 m^2
Cost per m^2	34.6 €/m^2
Value land	346 000 €
Assumed Yearly rent (opportunity cost)	10 380 €

10.11.2 Hard facility operating costs: Building and equipment maintenance

Maintenance includes both preventive and corrective maintenance and covers both cost of labour and all parts.

10.11.2.1 Building and equipment maintenance

Building maintenance - including estate and property management, energy and utilities management, fire safety maintenance, statutory inspections etcetera - is estimated at 3% of the building price, the average of the prices provided by the constructors, from year 1 of operations.

Equipment maintenance/updates – including accelerator and beamline maintenance, treatment rooms and medical equipment – is at 7.27% of the purchase price according to the average price of the constructors, from year 1 of operations.

Table 10.12: Price of building and equipment maintenance data obtained from constructors

Cost as % of purchase price	Average of base price* (%)	Range
Building maintenance	3.0	-
Equipment*	7.27	5.0 – 9.0

* In case a range was given by the constructors, the lower range was applied for the average

The impact of lower and higher maintenance price is measured in the sensitivity analysis.

10.11.2.2 Medical IT and software maintenance and updates

Maintenance of medical IT and software – including treatment planning software and computer updates – is estimated at 20% of the purchase price, from year 1 of operations.

10.11.2.3 Furniture, office IT and standard equipment renewal cost

For renewal of furniture, Office IT and standard equipment, a renewal cost is foreseen at 90 k€ per year from year 3 of operations.

10.11.2.4 Cost for disposal and decommissioning

A cost is foreseen of 1 000 k€ (inflated for 30 years) after 30 years operation for closing down the facility.

10.11.3 Soft facility operating costs

Soft facilities management costs include telecommunications, waste disposal, linen service, domestic services (cleaning and housekeeping), sterile services, courier/postal/printing services, security, medical supplies (in particular the patient immobilisation devices) and insurance costs for patients in trials.

All soft facilities management costs are assumed to rise by 2.0% per year.

Table 10.13: Soft facility operating costs assumptions

	Total yearly cost (k€) VAT excluded	Rate (assuming gross floor space of 10 000m²)
Telecommunications	100	0.010 k€/m2 gross floor space
Waste disposal	40	0.004 k€/m2 gross floor space
☐Linen services	4	
Domestic services	350	0.035 k€/m2 gross floor space
☐Sterile services	20	0.002 k€/m2 gross floor space
☐Courier, postal & printing services	40	0.004 k€/m2 gross floor space
Security	20	0.002 k€/m2 gross floor space
Medical supplies (including patient enclosures and immobilisation devices)	0.75 k€/patient	
Insurance for patient trials	30	

10.11.4 Energy and utilities

Energy and utilities include costs for gas, electricity, water and sewerage. The electricity consumption of the hadron equipment is an estimate provided by one of the constructors.

Table 10.14: Energy and utilities costs

	Total yearly cost (k€) (VAT excl.)	Rate (VAT excl.)
Electricity	1003	0.098 k€/MWh* 8 450 MWh
Gas	60	0.006 k€ /m2 gross floor space**
Water	40	0.004 k€ /m2 gross floor space
Sewerage	30	0.003 k€ /m2 gross floor space

* 70€/MWh for electricity (estimate provided by Electrabel) + 40% mark-up estimate for transport (transmission and distribution) and taxes

** Consumption of 122 kWh / m² at a price of 35 €/MWh for gas (estimate provided by Electrabel) + 40% for transport and taxes

Table 10.15: Electricity consumption parameter:

Hadron equipment consumption	C ion + P
Consumption during treatment, validation and testing	900 kW/h
N° hours/day	15.5
N° days/year	240
Consumption during maintenance and time without treatment or test: all other time	375 kW/h
N° hours/year	5040

Other consumption	C ion + P
	5000 MWh/year

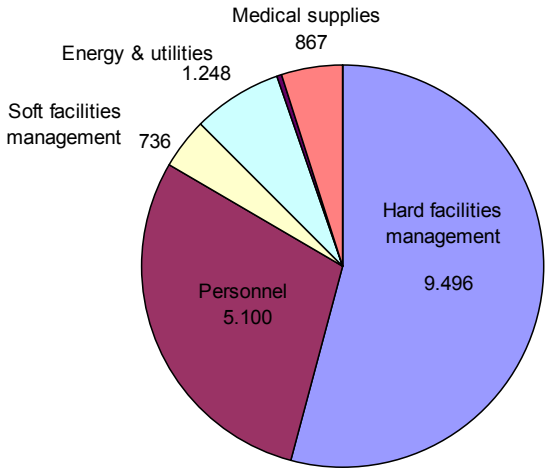
10.11.5 Personnel

See 1.5 Staffing.

10.11.6 Operating cost overview

Figure B : Operational cost distribution (first year running at full capacity) (k€)

17 496 k€



10.12 LEGAL AND FINANCING STRUCTURE

10.12.1 Legal structure

Given the uniqueness of the project (a single hadron therapy centre in Belgium) and the large investment, a specific statute for this centre is recommended. Similarly to the Military hospital, the centre could fall under authority of the RIZIV/INAMI and be directly financed by it, instead of through the Federal Public Service of Social Security.

10.12.2 Subsidies

The hadron therapy centre could be subsidized either by means of hospital subsidies and/or by means of R&D or European subsidies. The first option is examined more closely hereafter. The second option will be briefly discussed after.

10.12.2.1 Hospital subsidies

The subsidies of hospital infrastructure are regulated in the national law of 23 December 1963 on hospitals, article 46. This article stipulates that the regions can subsidize the costs for the building or reconditioning of a hospital or a service, as well as the costs of the first equipment and the first purchase of apparatus and heavy medical equipment. The subsidy percentage is determined at 60% by the royal decree of 13 December 1968.

Depending on the region, there is a different subsidizing body for the health care sector. For Flanders and the Flemish (monolingual) institutes in the Brussels region, there is the Flemish Infrastructure Fund VIPA ("Vlaams Infrastructuurfonds voor Persoonsgebonden Aangelegenheden"). For Walloon, the division of Health and Infrastructures at the Ministry of the Walloon region, is responsible. For the bilingual institutes in the Brussels region, the COCOM ("Commission communautaire commune"/"Gemeenschappelijke Gemeenschapscomissie") is in charge. For the monolingual French institutes in the Brussels region, there is the COCOF ("Commission communautaire française"). For the university hospitals in the French

community, the French community intervenes. Each of these subsidizing bodies follows the 60% rule of the royal decree of 1968.

In order to make the full investment, including the heavy equipment, eligible for subsidies, a number of steps would need to be taken. First of all, the Minister would need to approve the project (from healthcare strategic point of view). Secondly, the Federal resolution of 11 May 2007 (regarding maximum cost for subsidies for hospitals) would need to be complemented with a clause regarding subsidies for heavy medical equipment outside the maximum cost prices. Thirdly, specific maximum prices for the building of this new radiation therapy would need to be approved (currently the maximum size per bunker is 500m2 which is not sufficient for this new radiation therapy). Once these conditions are fulfilled, then the centre could apply for a subsidy of 60% of the accepted construction cost, including the heavy medical equipment.

The VIPA has introduced recently the 'alternative' finance system, which implies the possibility to spread the subsidies over 20 years. The settlement of the future subsidy payments is then linked to the fulfilment of certain utilization standards. This 'alternative' finance system is considered for the investment under analysis.

As construction cost, the costs for the building, the accelerator, the treatment rooms, the treatment planning software and other treatment material are included. The first subsidy payment is settled at earliest 1 year after the date the order is given to start the works. The following 19 payments are settled each one year later.

The fixed nominal annual amount paid is calculated as follows (formula of VIPA):

$$60\% * \text{Accepted investment cost} * \frac{R}{1-(\frac{1}{1+R})^{20}}$$

With R being the average 10 year OLO rate from 1 September to 30 November of the preceding year, increased by 15 basis points.

For projects approved by VIPA in year 2007, the coefficient is 7,3222.

As the depreciation of the accelerator is at 30 years, possibilities should be examined to have the subsidies (and loan guarantees) over 30 years instead of 20. In this case the cash flow position of the centre would be less subject to large fluctuations. (see under 1.13)

10.12.2.2 Other subsidies

As long as the project is not approved in the healthcare strategic plan, the project would need to call upon other subsidy possibilities, or a public-private-partnership (see under 10.11.4). Other possible subsidy channels are the Flemish IWT ("Instituut voor de aanmoediging van innovatie door Wetenschap & Technologie in Vlaanderen") and the FRIA in Walloon ("Fonds pour la formation à la recherche dans l'industrie et dans l'Agriculture") for R&D subsidies. On European level, the EU programme for Large Research Infrastructures, the European fund for Regional Development or the European Social Fund (for the training of the international workforce) could be considered. However, the competition with other centres for EU funds is high.

10.12.3 Loans

In order to cover the remainder of the investment; the centre would need to take on loans. This loan financing can be provided by either private or public financing institutions (as the European Investment Bank). On the condition that the project is eligible for hospital subsidies, the subsidizing institutions are offering guarantees for these loans. By VIPA 90% of the loan is guaranteed.

A Belgian bank (Dexia) gave us an indicative interest rate of 4.887% (June 2007) for a loan which is guaranteed by the subsidizing institution, on 20 years with half-yearly progressive repayments.

Table 10.16: Loan terms

Loan pay-back period	Construction period + 20 years
Repayment in construction years	Subsidies received are used for repayment (yearly payment)
Repayment after construction years	Fixed semestrial payments
Interest rate (fixed)	4.887%

(OLO $_{20\ years}$ (June 2007): 4.61%)

10.12.4 Alternative financing option: Public-Private Partnership

An alternative option for financing the centre is through a Public-Private Partnership (PPP). In this case the government gives a concession to a private vendor in order to construct, commission and operate the centre for a certain period (a BOT-operation: Build-Operate-Transfer). The private partner funds the equity part (10% or more) of the investment, and subsidies can be minimized. The remainder of the investment is funded by bank loans. Loans for the investment will only be provided for a period between 10 and 15 years. In exchange for the work carried out and the operations, the private beneficiary of the concession receives payment, including a return on the equity provided. At the end of the concession agreement, the centre is transferred to the local authority. The three main risks are spread amongst the public and private partners. The three big risks are the construction risk, the availability risk (linked with maintenance risk) and the demand risk ("market" risk or technology risk: will there be sufficient patients and will there not be competition of a better treatment technology). If at least two[n] out of these three risks are transferred to the private partner, then the investment is not calculated as public debt, according to the ESR 95 norms (of EUROSTAT).

There are pros and contras to a PPP. On one hand, a PPP ensures that no (large) public budget needs to be spent, and therefore, a PPP would be the required method in case that no subsidies can be obtained. Involving an industrial partner can also ensure the commercial drive to make the project a (financial) success. On the other hand, however, one can also be concerned about the commercialization of the project. How can be ensured that quality of health care and research do not become subordinate to the financials of the project? Also, from financing point of view, a PPP is more expensive than the classical financing option. First of all, the loans provided by the banks will be at higher interest rate in the case of a PPP. According to the Basel II norms, loans at public hospitals are considered equivalent to loans to government institutions and therefore the risk premium is minimal. However, if a commercial organization is an important partner in the project, the risk premium will be assessed considerably higher. Secondly, the vendor also asks a return on equity which is significantly higher than the loan interest rate, since equity funds bear more risk.

10.13 REIMBURSEMENT BY RIZIV/INAMI

There are multiple options for the reimbursement of hadron therapy. The reimbursement can be per patient or per session or per "protocol", or specific for preparation and irradiation phases.

As the centre is facing large loan repayment costs in the first 20 years, and as in the ramp-up years only a limited number of patients are treated, we recommend to have a combination of a fixed yearly reimbursement for the investment plus a variable reimbursement (per treatment session) for the operational costs, in line with actual radiotherapy reimbursement. It is assumed that both the operational fee and investment fee are indexed with the health index. We assume a 50-50 split between investment (fixed) and operational (variable) reimbursement for a centre in full operation, reflecting the large proportion of investment costs in overall costs.

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[n] Note that in most cases the private partner takes the construction and availability risk and leaves the market risk to the public partner.

10.14 BASE CASE RESULTS

Base case results

- **Number of patients[a] (after ramp-up period): 900**
- **Average reimbursement price per patient (after ramp-up period)[b]: 24.7 k€**
- **Yearly budget for RIZIV/INAMI[c]: 22.2 m€**
- **Subsidies: 20 yearly payments of 6.2 m€**

a) Increase of 1%/year
b) Price including both fixed investment reimbursement and variable operational reimbursement. Increase of about 1.5%/year due to indexation of reimbursement, slightly counterbalanced by an increasing number of patients.
c) Increase of roughly 2.5% per year given indexation of the price per patient combined with a slightly increasing amount of patients

Break-even point	After 20 years of operation
Operational credit line	At 5%, guaranteed by government or hospitals

The minimum reimbursement fee is calculated so that the centre is break-even after 20 years of operation in the base case. At that point in time all loans (investment and operational loan) are paid back, and the centre starts making profits.

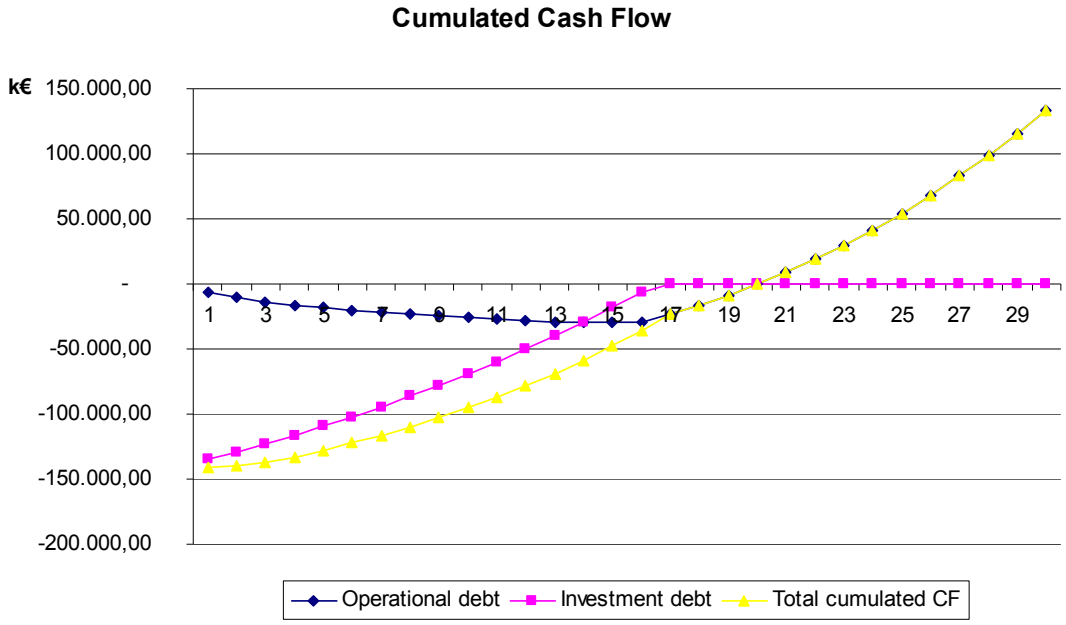
As a constant evolution of the reimbursement rates is assumed, and as the investment is paid back in 20 years whilst the centre has a lifetime of 30 years, in the first years the centre will deal with a negative cash flow and the centre will therefore need to take on extra "operational" debt. On the condition that this extra "operational" loan would be guaranteed° (by either the regional subsidizing instance, the federal government or a conglomerate of hospitals), the banks would be willing to provide this debt. For our base case analysis it is assumed that this guarantee would be available. Should however, there would be no possibility for such a guarantee, then a higher reimbursement would be required in order to have a positive cash flow earlier on. In the latter case the centre would already be break-even at the end of operational year 16 (see sensitivity scenario) and reimbursement price could be reviewed downwards after this period.

An operational credit line is assumed to be provided by a private bank, at an interest rate of 5%.

Based on the estimated costs and the estimated number of patients that will be treated, the average cost of treatment per patient results in the following prices and budget for reimbursement:

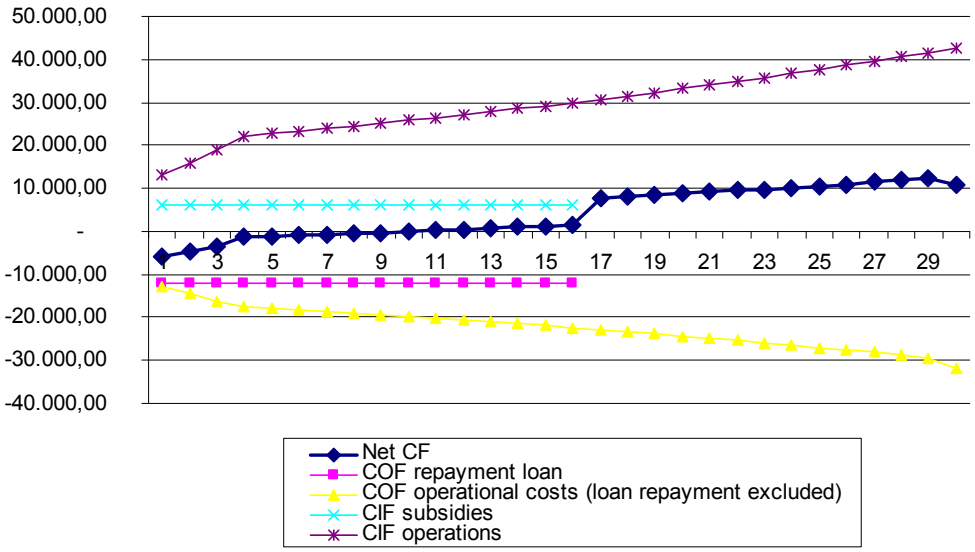
° Note that the guarantee of debt does not appear as debt in the accounts of government, unless the guarantee is called upon.

Figure C : Cumulated CF / Debt evolution of the hadron facility



Note: year 1 on this graph is the first operational year

Figure D : Cash flow evolution per year



Note: year 1 is first operational year (with treatment of 25% patients). 100% capacity is reached in the 4th operational year. Until year 16 the investment loan needs to be paid back (in the 4 preceding construction years the subsidies are used to settle the first 4 repayments). In the last year, a cost is foreseen for disposal and decommissioning of the centre.

10.15 SENSITIVITY ANALYSIS

10.15.1 Scenario summary

Scenario	N° of patients		Yearly subsidies (for 20 years)		Total yearly cost for RIZIV/INAMI		Average cost per patient for RIZIV/INAMI		CF: maximum operational debt		Cumulative CF after 30 years operation	
m€	n°	Δ with base case	m€	Δ with base case	m€	Δ with base case	k€	Δ with base case	m€	Δ with base case	m€	Δ with base case
Base Case	900	-	6.2	-	22.2	-	24.7	-	-29.5	-	132.7	-
1) Carbon ion + Proton versus Proton-only therapy												
Base case: Carbon-ion + proton												
Scenario: Proton-only	884	-2%	4.2	-33%	16.9	-24%	19.1	-23%	-20.3	-31%		-31%
2) Number of treatment rooms (Carbon-ion therapy												
Base case: 3 rooms												
Scenario: 2 rooms	600	-33%	5.5	-11%	19	-14%	31.7	28%	-26.6	-10%		-11%
Scenario: 4 rooms	1200	33%	6.8	10%	25.4	14%	21.2	-14%	-32.5	+10%		+11%
3) Working hours												
Base case: 12,5 hrs/day; 5 days/week												
15 hrs/day; 6 days/week	1296	44%	b.c.	-	24.4	10%	18.8	-24%	-29.6	<1%		1%
8 hrs/day, 6 days/week	691	-23%	b.c.	-	21.4	-4%	31	26%	-29.5	<1%		<1%
4) % utilization of rooms												
Base case: 90%												
Optimistic scenario: 95%	950	6%	b.c.	-	22.3	<1%	23,5	-5%	-29,5	<1%		<1%
Pessimistic scenario: 75%	850	-6%	b.c.	-	22.2	<1%	26,1	6%	-29,6	<1%		<1%
5) Number of fractions per patient												
Base case: 18 fractions												
16 fractions	1013	13%	b.c.	-	22.3	<1%	22,1	-11%	-29,5	<1%		<1%
20 fractions	810	-10%	b.c.	-	22.1	<1%	27.3	11%	-29.6	<1%		<1%
6) Financing: break-even point												

Base case: Break-even after 20 years operation											
after 25 yrs	b.c.	-	b.c.	-	21.2	-5%	23.6	-4%	- 53.8	+82%	-60%
after 15 years	b.c.	-	b.c.	-	23.6	6%	26.2	6%	-2.5	-58%	+81%
7) Financing: subsidy percentage											
Base case: 60% subsidies											
50% subsidies	b.c.	-	5.2	-16%	23.4	5%	26	5%	-35.3	+20%	+18%
10% subsidies	b.c.	-	1	-84%	27.9	26%	31	26%	- 58.5	+98%	+92%
8) Change in investment price											
Base case: 116,3 m€											
Optimistic scenario: -10%	b.c.	-	5,6	-10%	20.8	-6%	23.1	-6%	-26.7	-9%	-9%
Pessimistic scenario: +10%	b.c.	-	6.8	+10%	23.6	+6%	26.3	+6%	-32.3	9%	+9%
9) Change in maintenance price of building and equipment											
Base case: 7,27% for equipment, 3% for building											
-20% on maintenance costs	b.c.	-	b.c.	-	20.3	-9%	22.6	-9%	-28.6	-3%	-4%
+10% on maintenance costs	b.c.	-	b.c.	-	23.2	+5%	25.8	+4%	-30.0	+2%	+9%

Note: b.c.: Base case results

10.15.2 Explanation of scenarios

10.15.2.1 Proton-only therapy instead of Carbon-ion and proton therapy

Table 10.17: Price data obtained from constructors for a fully equipped proton therapy centre

	Average of base prices* (m€)	Range** (m€)	Average of base prices – 15% (m€)
Building for a centre with 3 treatment rooms. Including – architect costs – project management – provision of utilities – furnishings and office supplies Assuming that the centre is located next to a hospital. Cost of ground not included.	36	30-42	31
Accelerator, beam lines and 3 treatment rooms fully equipped with scanning and patient couches etc.	50	45-67	43
Treatment planning soft- and hardware (m€)	2.5	1.2–7.0	2.1
Total (m€)	88.5	76.2-116	75.2

* Some constructors provided us with a base and a maximum price. For our analysis, base price was used to calculate the average.
** Showing variation from the lowest base price to the highest maximum price

Table 10.18: Price of building and equipment maintenance obtained from constructors for a proton therapy centre

Cost as % of purchase price	Average of base price* (%)	Range
Building maintenance	3.0	-
Equipment*	6.7	5.0 % – 10.0 %

* In case a range was given by the constructors, the lower range was applied for the average

Table 10.19: Adjusted operational parameters for a proton-only centre

	Proton-only centre
Average time per fraction (min)	22
Average number of fractions per patient	25
Maximum capacity patients per year	884
Patients treated	25% of max. capacity in year 1 50% in year 2 75% in year 3 100% from year 4. Yearly increase of 0.5% after year 4 (Efficiency gains (shorter time per fraction) should be feasible in the future).
Percentage usage of treatment rooms	90%
Number of treatment rooms	3

According to Goitein [110], an average of 25 fractions per patient is a reasonable estimate for proton therapy. The number of fractions varies highly from treatment to treatment.

Also the energy consumption is adapted accordingly:

Table 10.20: Energy parameters for a proton therapy centre

	Proton only centre
Consumption during treatment, validation and testing	600 kW/h
N° hours/day	15.5
N° days/year	240
Consumption during maintenance and time without treatment or test: all other time	250 kW/h
N° hours/year	5040

Other consumption	Proton only
	5000 MWh/year

10.15.2.2 Number of treatment rooms

- Two treatment rooms

As a number of overhead costs are to be spread over a smaller number of treatment rooms, the price for the accelerator + treatment rooms is decreased by 11.5 m€ (from 79 to 67.5m€), assuming that the cheapest room is taken out (and potential extra costs need to be done to ensure that the remaining 2 rooms can treat all indications). The staffing plan is adapted downwards accordingly (only 43 FTE's employed by the centre). Ceteris paribus, only 600 patients can be treated.

- Four treatment rooms

The investment price raises by 11.5 m€, expected to cover both the extra cost for the building and the treatment room. Another 0.67 m€ is foreseen for extra treatment planning soft- and hardware. As many overhead costs can be spread over the 4 rooms, the price increase is estimated significantly lower than proportional. The staffing number is reviewed upwardly to 73 FTEs. Keeping the base case working hours, 1200 patients can be treated.

10.15.2.3 Working hours

Operating hours from 8:00 to 22:00, instead of 12.5 hours in the base case scenario. This operational model needs 2.3 shifts instead of 2. Bonuses for evening and weekend work are applied accordingly.

Table 10.7 : Bonuses for P.C. nr. 305.01.00-00.00

Bonuses		
Saturday	26%	
Sunday	56%	
Official holiday	56%	
Night	35%	On work day or Saturday
	50%	On Sunday or official holiday

Key points

- **Based on price information obtained from four constructors (Accel, IBA, Hitachi and Siemens), the investment cost of a centre for Proton and Carbon-ion therapy centre with 3 treatment rooms is estimated at 159,6 m€**
- **Yearly operational costs are estimated at 17,5 m€**
- **Operated 12,5 hrs per workday, the centre is estimated to treat about 900 patients yearly**
- **On the condition that the centre would be eligible for hospital subsidies of 60%, RIZIV annual reimbursement for patient treatment would be 22,2 m€ per year, or an average reimbursement of 24 700€ per patient**

11 APPENDICES

APPENDIX FROM CHAPTER 4

Table AA Critical appraisal of the HTA reports with the INAHTA HTA Checklist

Item	Adelaïde ANZHSN 2006 [2]	AETMIS 2003[1]	CEDIT 2002[3]	NHSC 2006[4]
Preliminary				
1. Appropriate contact details for further information?	Yes	Yes	Yes	Yes
2. Authors identified?	Yes	Yes	No	No
3. Statement regarding conflict of interest?	Unclear	No	No	No
4. Statement on whether report externally reviewed?	No	Yes	No	No
5. Short summary in non-technical language?	Yes	Yes	Yes	Yes
Why?				
6. Reference to the question that is addressed and context of the assessment?	No	Yes	Yes	No
7. Scope of the assessment specified?	Yes	Yes	Yes	Yes
8. Description of the health technology?	Yes	Yes	Yes	Yes
How?				
9. Details on sources of information?	Unclear	Yes	Unclear	Unclear
10. Information on selection of material for assessment ?	Unclear	Yes	No	No
11. Information on basis for interpretation of selected data?	Yes	Unclear	Unclear	Unclear
What?				
12. Results of assessment clearly presented?	Yes	Yes	No	Yes
13. Interpretation of the assessment results included?	Yes	Yes	No	Unclear
What then?				
14. Findings of the assessment discussed?	Yes	Yes	No	No
15. Medico-legal implications considered?	No	No	No	No
16. Conclusions from assessment clearly stated?	Yes	Yes	Yes	Yes
17. Suggestions for further action?	Yes	Unclear	Unclear	No
	11Y, 3U, 3N	13Y, 2U, 2N	6Y, 3U, 8N	6Y, 3U, 8N

Table AB Critical appraisal of the systematic reviews

Dutch Cochrane collaboration Formulier Vc	Olsen 2007[12]	Lodge 2007[11]	Brada 2007[10]	Greco 2007[9]	Pijls – Johannesma 2006[8]	Jereczek-Fossa 2006[7]	Noel 2003[6]	Hug 2000[5]
Vraagstelling adequaat geformuleerd	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Zoek actie adequaat uitgevoerd	Yes	Yes	Yes	No	Yes	Unclear	No	No
Adequate selectie van artikels	Yes	Yes	Yes	No	Yes	Yes	No	No
Adequate kwaliteitsbeoordeling van artikels	Yes	Yes	Unclear	No	Unclear	Unclear	No	No
Adequate beschrijving data extractie	Unclear	Unclear	Unclear		Unclear	Unclear		
Belankrijste kenmerken oorspronkelijk onderzoeken beschreven	Yes	Yes	Yes		Unclear	No		
Adequaat omgegaan met klinische en statistische heterogeneiteit	Unclear	Unclear	Unclear		Unclear	Unclear		
Statistiche pooling correct uitgevoer	Not applicable	Not applicable	Not applicable		Not applicable	Not applicable		

Table AC: HTA and SR description for ocular tumours for proton beam therapy

Reference	Included studies	Conclusion
ANZHSN AHTA 2006[2]	Egger 2003 [17]	Optimisation of the treatment technique improves the 5-year eye retention from 97 to 100% for small, from 86 to 99% for medium and from 71 to 89 % for large tumours. There are no data for eye retention with other therapies. Comparative studies of the gold standard radiotherapy and proton beam therapy will be conducted
Brada 2007[10]	Courdi 1999[112] Damato 2005a[113] Dendale 2006[114] Egger 2003[17] Fuss 2001[115] Gragoudas 2002[116] Wilson 1999 [16]	Local tumour control and complications rate similar for protons and photons. No clear evidence that protons should be superior to photons for ocular melanoma. Only studies with 5-year results are shown in the table.
Lodge 2007[11]	Courdi 1999[112] Damato 2005a[113] Damato 2005b[117] Dendale 2006[114] Egger 2003[17] Fuss 2001[115] Gragoudas 2002[116] Höcht 2004[118] Naeser 1998[119] Wilson 1999[16]	Based on prospective and retrospective studies proton irradiation emerges as the treatment of choice for some ocular tumours. Arguments: Stereotactic radiotherapy (SRT) with photons gives similar results to protons. But, 5-year results for protons studies with regard to 2 to 3-year results with photons series. Incidence of neovascular glaucoma seems to be lower with proton therapy than with SRT photons (12% versus 16%) based on non comparative cases series.
Olsen 2007[12]	RCT: Gragoudas 2000[13] Cohort studies: Seddon 1985[14] and Seddon 1990[15] Foss 1997[120] and Wilson 1999[16] Cases series: Massachusetts general hospital (Egan 1998[121], 1989[122]; Glynn 1989[123]; Gragoudas 1985[124], 1986[125], 1987[126], 1988[127], 1992[128], 1999[129], 2002[116]; Guyer 1992[130], Li 2000[131], 2003[132]; Seddon 1986[133]) Loma Linda (Fuss 2001[115]) Lausanne (Bercher 1992[134]; Egger 2001[135], Zografos 1988[136], 2003[137]) and Orsay (Courdi 1999[112]; Desjardins 1997[138], 2003[139]; Lumbroso 2002[140] and Schlienger 1996[141])	Large number of patients treated with proton therapy with ocular tumour, but no proper comparison with other treatment alternatives; One low quality RCT (dose study of Gragoudas 2000).

Table AD: Description of studies in for ocular tumours and proton beam therapy

Reference	Location	Population	Intervention	Design	Results
Bercher 1992[134]	Lausanne, Switzerland	934 patients with choroidal melanoma	Proton beam radiation	Retrospective non comparative cases series study	4 years survival 60% in patients with extrascleral extension and 85% in patients without
Char 2002 [18]	California, USA	996 patients with uveal melanoma	^{125}I brachytherapy (n = 449) *vs* proton therapy (n= 199) *vs* helium therapy (n= 348)	Comparison of 3 retrospective partially randomized cases series Possible bias Valid and applicable results unclear	Late recurrence (5 to 15 years) continued with increased follow-up after brachytherapy and not after radiation
Courdi 1999[112]	Nice, France	538 patients with uveal melanoma	Proton beam radiation with 52 Gy/4 consecutive days	Retrospective non comparative cases series study	Cause specific survival 77.4% at 78 months, overall survival 73.8 and local control 89.0.
Damato 2005a[113]	Clatterbridge, UK	349 patients with choroidal melanoma	Proton beam radiation with 53.1 Gy/4 consecutive days	Prospective non comparative cases series study Phase I/II study	5 year actuarial rate for local recurrenc: 3.5%, 9.4% for enucleation
Damato 2005b[117]	Clatterbridge UK	88 patients with iris melanoma	Proton beam radiation total dose 53.1 Gy on 4 consecutive days	Retrospective non comparative cases series study	Cataract rate of 63% at 4 years
Dendale 2006[114]	Orsay France	1406 patients with uveal melanomas	Proton beam radiation total dose 60 CGE on 4 consecutive days	Retrospective non comparative case series	5 year overall survival: 79% and metastases free survival: 80.6% Prognosis factors for complications
Desjardins 1997[138]	Orsay France	612 choroidal melanomas	Proton beam radiation	Prospective non comparative cases series study	Follow up between 1 and 3 years
Desjardins 2003[139]	Orsay France	1272 uveal melanomas	Iodine 125 plaques (n= 346) or proton beam therapy (n=926)	Retrospective comparative cases series study	Similar recurrence if iodine 125 for anterior tumours
Egan 1989[122]	Massachusetts general hospital Boston USA	994 eyes with uveal melanoma	Proton beam radiation	Retrospective non comparative case series	Probability of eye retention 95 and 90% 2 and 5 years post irradiation
Egan 1998[121]	Massachusetts general hospital Boston USA	1541 consecutive patients with choroidal melanomas	Proton beam radiation total dose 70 CGE on 5 to 7 fractions	Prospective case series	In the absence of tumour viability enucleation has no deleterious effect on patient's survival
Egger 2001[135]	Lausanne Suisse	2435 uveal melanomas	Proton beam radiation	Retrospective non comparative case series	5 year local control: 90.6 ± 1.7% if treated before 1988 to 98.9 ± 0.6% after 1993
Egger 2003 [17]	PSI Villingen Switzerland	2648 eyes with uveal melanoma	Proton beam radiation	Prospective non comparative cases series	Overall eye retention rate at 5, 10 and 15 years were 88.9%, 86.2%

Reference	Location	Population	Intervention	Design	Results
				study	and 83.7%.
Foss 1997 [120]	London England (links with Wilson)	127 patients with uveal melanoma	Proton beam radiation	Cohort with retrospective data	Predictive factors for rubeosis
Fuss 2001[115]	Loma Linda California USA	78 patients with medium and large melanoma	Proton beam radiation	Retrospective non comparative case series	5 year local control: 90.5 ± 3.7%; 5 year metastases free survival: 76.2 ± 6.7% 5 year disease specific survival: 75.6 ± 7.6%
Glynn 1989[123]	Massachusetts general hospital Boston USA	700 patients with uveal melanomas	Proton beam radiation	Retrospective non comparative case series	Predictors of metastasis
Gragoudas 1985[124]	Massachusetts general hospital Boston USA	241 patients with uveal melanomas	Proton beam radiation	Retrospective non comparative case series	Visual acuity: 20/40 or better in 47% and 20/100 or better in 66% 13 patients with metastasis
Gragoudas 1986[125]	Massachusetts general hospital Boston USA	510 patients with uveal melanomas	Proton beam radiation	Retrospective non comparative case series	Predictors of metastasis
Gragoudas 1987[126]	Massachusetts general hospital Boston USA	128 consecutive patients with uveal melanoma	Proton beam radiation	Prospective non comparative cases series study	Visual acuity: 20/40 or better in 35% and 20/100 or better in 58% 26 patients with metastases
Gragoudas 1988[127]	Massachusetts general hospital Boston USA	780 consecutive patients with uveal melanoma	Proton beam radiation	Retrospective non comparative case series	5 years cumulative probability of metastasis: 20%
Gragoudas 1992[128]	Massachusetts general hospital Boston USA	1077 patients with uveal melanomas	Proton beam radiation	Retrospective non comparative case series	5 year probability of local tumour control: 97 ± 1%
Gragoudas 1999[129]	Massachusetts general hospital Boston USA	558 patients with choroidal melanoma	Proton beam radiation	Retrospective non comparative case series	Cumulative 5 Year rates for vision loss were 68%
Gragoudas 2000[13]	Massachusetts general hospital Boston USA	188 patients with choroidal melanoma	Proton beam radiation Comparison between 2 doses 70 CGE versus 50 CGE	RCT	Dose reduction did not result in a lesser degree of visual acuity loss but significant less visual field loss
Gragoudas 2002[116]	Massachusetts general hospital Boston USA	1922 patients with choroidal/ciliary melanoma	Proton beam radiation	Retrospective non comparative cases series study	5 year and 10 years recurrence: 3.2% (95%CI 2.5-4.2) and 4.3% (95%CI 3.3-5.6)
Guyer 1992[130]	Massachusetts general hospital Boston USA	218 patients with paramacular choroidal melanomas	Proton beam radiation	Retrospective non comparative cases series study	Radiation maculopathy is common 1 year visual acuity at 20/200 or better in 90% of eyes and at 3 year: 67%
Höcht 2004[118]	Hahn-Meitner Institute of Berlin	245 patients with uveal melanomas	Proton beam radiation total dose 60 CGE on 4 consecutive days	Prospective non comparative cases series	At 3 years, local control of 95.5% and eyes retention of 87.5%

Reference	Location	Population	Intervention	Design	Results
	Germany			study Phase I/II study	
Höcht 2005[20]	Berlin Germany	10 patients posterior uveal melanoma in proximity to optic disk and fovea centralis	first treated by 68-MeV protons Stereotactic radiotherapy with 6-MV photons consecutively planned	Comparative planning study	Not selected: Not clinical: dose deposition study
Li 2000[131]	Massachusetts general hospital Boston USA	1848 patients with primary choroidal melanoma or ciliary body melanoma	Proton beam radiation total dose 70 CGE on 5 fractions	Retrospective non comparative cases series study	Covariate adjusted 5 year death rates for ciliary body origin and choroidal origin were 15.9% (95%CI 11.3-21.2) and 9.8% (95%CI 8.3-11.7)
Li 2003[132]	Massachusetts general hospital Boston USA	1204 consecutive patients with primary choroidal melanoma	Proton beam radiation total dose 70 CGE on 5 fractions	Retrospective non comparative cases series study	5 and 10 years metastatic deaths rates were 12.8% and 20.7%
Lumbroso 2002[140]	Orsay France	1062 patients with choroidal melanomas	Proton beam radiation	Retrospective non comparative cases series study	Survival rate: 92% at 2 years and 78% at 5 years
Naeser 1998[119]	Uppsala Sweden	20 patients with uveal melanoma	Proton beam radiation total dose 54.6 Gy on 4 consecutive days	Prospective non comparative cases series study	At 5 years, successful treatment in 8 patients
Schlienger 1996[141]	Orsay France	The first 146 patients with uveal melanomas	Proton beam radiation	Retrospective non comparative cases series study	One year follow up See Dendale and Desjardin
Seddon 1985[14]	Massachusetts general hospital Boston USA	516 patients with uveal melanoma	120 treated by proton beam radiation from 1975 to 1981 235 treated by enucleation from 1953 to 1973 161 treated by enucleation from 1975 to 1981	Cohort studies (comparative groups)	Estimated rate ratio death from all causes: similar
Seddon 1986[133]	Massachusetts general hospital Boston USA	440 eyes with uveal melanoma	Proton beam radiation	Retrospective non comparative cases series study	Prognostic factors for visual outcomes
Seddon 1990[15]	Massachusetts general hospital Boston USA	1051 patients with uveal melanoma	556 treated by proton beam radiation from 1975 to 1984 238 treated by enucleation from 1975 to 1984 257 treated by enucleation from 1965 to 1975	Cohort studies (comparative groups)	Survival of patients similar Overall rate ratio for all cause mortality 1.2 (95%CI 0.9-1.6) for concurrent enucleation series versus proton beam
Spatola 2003[19]	Catania Italy	30 patients with uveal melanoma	Proton beam radiation 4 fractions to a total dose of 54.5 Gy (= 60 CGE)	Non comparative cases series study	Not selected: Only preliminary results at 6-8 months for 13 patients

Reference	Location	Population	Intervention	Design	Results
Wilson 1999[16]	St Bartholomeus hospital London UK	597 patients with choroidal melanoma	Proton beam radiation versus Iodine-125 and Ruthenium-106 episcleral plaque radiation therapy	Retrospective comparative case series study	Local recurrence 106 RU > 1125 : P= 0.0133; RR 2.97; CI 1.26-7.02 Local recurrence 106 RU > proton : P= 0.0097; RR 2.94; CI 1.30-6.66
Zografos 1988[136]	Lausanne Suisse	310 uveal melanomas	Proton beam radiation	Prospective non comparative cases series study	Follow up only one year
Zografos 2003[137]	Lausanne Suisse	Metastatic melanoma in the eye and orbit	Various protocol	Retrospective non comparative cases series study	Palliative treatment

Table AE HTA and SR description for ocular tumours and carbon ion therapy

Reference	Included studies	Conclusion
Lodge 2007[11]	Castro 1997[22] Char 1993[21] Tsuji 2006 (published in 2007)[24] Hirasawa 2006 (published in 2007)[23]	The studies of Castro and Char are about Helium ion radiotherapy. The studies of Tsuji and Hirasawa are prospective phase I/II clinical trials in which eye retention rates and severe side effects such as neovascular glaucoma were analyzed. The rates with carbon ion (84% eye retention and neovascular glaucoma > 40%) seems less interesting than proton or photon therapy rates

Table AF Description of studies for ocular tumours and carbon ion therapy

Reference	Location or institution	Population	intervention	Design	Results
Castro 1997[22]	California San Fransisco USA	347 patients with uveal melanoma	Helium ion radiotherapy from 1978 to 1992	Retrospective non comparative cases series study	Not about carbon ion therapy
Char 1993[21]	California San Francisco USA	86 patients with helium and 98 with brachytherapy	Helium ions versus iodine 125 brachytherapy	Prospective randomized trial	Not about carbon ion therapy
Hirasawa 2007[23]	Chiba Japan	55 patients with choroidal melanoma	Carbon ion beam based on computer tomography treatment	Prospective non comparative cases series Phase I/II clinical trial	3 year cumulative neovascular glaucoma = 42.6 ± 6.8% (the enucleation rate was small: 3/55)
Tsuji H 2007[24]	Chiba Japan	59 patients with locally advanced or unfavorably located choroidal melanoma	Carbon ion beam Dose escalation study with an initial dose of 70 GyE in 5 fractions	Prospective non comparative cases series Phase I/II clinical trial	23 (40%) neovascular glaucoma 3 enucleations for intraocular pressure 3 year overall survival: 88.2% 3 year disease free survival: 84.8% Local control rates: 97.4%

Table AG Description of studies for neovascular age related macular degeneration and proton beam therapy

Reference	Location or institution	Population	intervention	Design	Results
Ciulla T 2002[27]	Indianapolis USA	37 Exudative age related macular degeneration (AMD)with subfoveal choroidal neovascular membranes (CNVM)	16 GyE Proton beam irradiation delivered in 2 fractions 24 hours apart versus sham control treatment	Randomized sham-controlled clinical trial Brief report only (description of the study)	Proton irradiation was associated with a trend toward stabilization of visual acuity, but this association did not reach statistical significance
Flaxel C 2000[26]	Loma Linda California USA	46 consecutive patients with Subfoveal choroidal neo-vascularisation in age-related macular degeneration CNVM	Proton beam irradiation 2 dose regimens: 8 CGE and 14 CGE 12 months follow up	Prospective clinical case series study No randomization No criteria for the group allocation	At 1 year follow-up, 44% (8CGE) and 75% (14 CGE) had stabilized or improved visual acutiy
Zambarakji 2006[28]	Massachusetts general hospital Boston USA	166 patients Subfoveal neovascular age related macular degeneration	Proton beam irradiation Comparison between 2 doses: 16-cobalt gray equivalent (CGE) or 24-CGE proton radiation in 2 equal fractions	Randomized dose ranging clinical trial Validation Cochrane RCT Randomisation Yes Blind randomisation No Patient blind : unclear Operator blind: No Examiner blind: yes Equivalent groups: Yes Loss to follow-up: 16 Intention to treat analyse No Similar care except intervention unclear Valid and applicable results unclear	No significant differences in rates of visual loss between the 2 groups doses

Table AH HTA and SR description for skull base chordomas and chondrosarcomas and proton therapy

Reference	Included studies	Conclusion
ANZHSN AHTA 2006[2]	Munzenrider 1999[30]	Case series results; No data were provided for other therapy modalities used to treat these conditions. Comparative studies of the gold standard radiotherapy and proton beam therapy will be conducted
Brada 2007 [10]	Skull based chordomas Noel 2005[33] Hug 1999[29] Munzenrider 1999[30] Skull based chondrosarcomas Hug 1999[29] Munzenrider 1999[30]	Chordomas: No superiority on efficacy with classical treatment (surgery + photons) for 5 year local control No comparison studies available for safety For chondrosarcomas, no difference with classical radiotherapy for 5 year progression free survival
Lodge 2007 [11]	Skull based chordomas Noel 2005[33] Hug 1999[29] Munzenrider 1999[30] Skull base chondrosarcomas Hug 1999[29] Munzenrider 1999[30]	Conflicting conclusions with Brada 2007 for chordomas (seem better for 5 year overall survival) Based on only 2 studies (Noel non included n= 202), 5-years local progression free survival rate of 65% and compared it with a rate of 25% with photons. 5 year overall survival of 81% with protons (only 2 studies, Munzenrider non included n= 133) and a rate of 44% with photons Same conclusion with Brada for chondrosarcomas
Olsen 2007[12]	Santoni 1998[34] Austin-Seymour 1999/2000[35] Debus 1997/2000[38, 142] Fagundes 1995[37] Munzenrider 1999[30] Hug 1999[29] Noel 2002/2003[31, 32]	One RCT (Santoni 1998 : High dose proton and photon irradiation in combination Comparison between two doses: 66.6 or 72 CGE no difference but publication “without analysing by initial allocation group”) overall temporal lobe damage was 7.6% at 2 years and 13.2% after 5 years. 9 cases series No conclusion possible, too heterogeneous studies No specific discussion about chondrosarcoma or about chordomas

Table AJ Description of studies for skull base chordomas and chondrosarcomas and proton beam therapy

Reference	Location or institution	Population	Intervention	Design	Results
Austin-Seymour 1989[35]	Massachusetts general hospital Boston USA	68 patients with chordomas or chondrosarcomas of the skull base	Fractioned proton radiation therapy 69 CGE	Prospective non comparative case series	Same study: patients also included in 1990
Austin-Seymour 1990[36]	Massachusetts general hospital Boston USA	110 patients with chordomas or chondrosarcomas of the skull base	Fractioned proton radiation therapy 69 CGE	Prospective non comparative case series	actuarial 5 year local control rate = 82% disease free survival rate is 76%
Debus 1997[38]	Massachusetts general hospital Boston USA	367 patients with chordomas or chondrosarcomas of the skull base	combination proton and photons	Retrospective non comparative case series	Brainsterm toxicity in 17/367 patients with 3 deaths Increased toxicity associated with maximum dose to brainstem and volume of brainstem receiving a dose > 50, 55 or 60 CGE.
Debus 2000a[142]	Heidelberg Germany	45 patients with chordomas or chondrosarcomas of the skull base	postoperative fractioned photons stereotactic radiotherapy 66.6 Gy for chordomas 64.9 for chondrosarcomas	Retrospective non comparative case series	Chondrosarcomas: local control rate at 5 years: 100% Chordomas: local control rate at 5 years: 50%% (82% at 2 years) survival at 5 years: 82% (97% at 2 years)
Fagundes 1995[37]	Massachusetts general hospital Boston USA	63 patients with relapse between 204 patients with chordomas of the skull base or cervical spine	combination proton and photons	Retrospective non comparative case series	patterns of failure and outcomes after relapses
Hug 1999 [29]	Loma Linda California USA	33 patients with chordomas and 25 patients with chondrosarcomas	Proton beam radiation: 64.8 to 79.2 Co Gy equivalent	Retrospective non comparative case series	actuarial 5 year survival rate = 100 % for chondrosarcomas and 79% for chordomas grade 3 and 4 toxicity in 7% of patients
Igaki H 2004 [39]	Tsukuba Japan	13 patients with skull base chordoma	Proton beam therapy Median total tumour dose 72 Gy	Retrospective non comparative case series	5 year local control rate : 46% Overall survival at 5 years: 66% and 5 years disease free survival: 42.2%
Munzenrider 1999[30]	Massachusetts general hospital Boston USA	Tumours of the skull base: chordomas (169) and chondrosarcomas (165)	Proton beam radiation	Retrospective non comparative case series	10 years local control rates 94% in chondrosarcomas, 65% in male chordomas and 42 in female chordomas
Noel 2002[31]	Orsay France	67 consecutive patients with chordoma or	Fractionated irradiation combining proton	Prospective non comparative	Same population than 2005

Reference	Location or institution	Population	Intervention	Design	Results
		chondrosarcoma of the base of the skull or cervical spine	and photons beams	case series	
Noel 2003[32]	Orsay France	67 consecutive patients with chordoma or chondrosarcoma of the base of the skull or cervical spine	Fractionated irradiation combining proton and photons beams	Prospective non comparative case series	Same publication than 2002
Noel 2005[33]	Orsay France	100 consecutive patients with chordoma of the base skull or upper cervical spine	Fractionated irradiation combining proton and photons beams	Prospective non comparative case series	2 year local control: 86.3% ± 3.9%, 4 year: 53.8% ± 7.5% 2 year overall survival: 94.3% ± 2.5%, 5 year: 80.5% ± 7.2%
Santoni 1998[34]	Massachussets general hospital Boston USA	96 patients with chordomas or chodrosarcomas of the skull base	High dose proton and photon irradiation in combination Comparison between 2 doses: 66.6 or 72 CGE	RCT poor quality (see discussion)	temporal lobe damage at 2 years: 7.6% and at 5 years: 13.2%

Table AK HTA and SR description for skull base chordomas and chondrosarcomas and carbon ion therapy

Reference	Included studies	Conclusion
Lodge 2007[11]	Castro 1994[40] Schultz-Ertner 2004 [143]	Outcomes seem better with carbon ion than with photons therapy.

Table AL Description of studies for skull base chordomas and chondrosarcomas with carbon ion therapy

Reference	Location or institution	Population	intervention	Design	Results
Castro 1994[40]	Berkeley California US	223 patients with skull base tumours: chordomas (53), chondrosarcomas (27), meningioma (27) nasopharynx (31) salivary gland (44) paranasal sinuses (22) (primary or recurrent lesions)	Charged particle Mean of 65 Gy equivalent	Retrospective non comparative case series	5 year local control 78% for chondrosarcomas and 63% for chordomas
Debus 2000b[42]	Heidelberg Germany	group 1 17 chordomas 10 chondrosarcomas Group 2 Other skull base tumours (18)	group 1 Carbon ion irradiation Median total dose 60 Gye in 20 consecutive days Group 2: stereotactic radiotherapy conbined with carbon ion	Non comparative case series	One year local control rate 94% No severe toxicity
Schultz-Ertner 2003a [43] Schultz-Ertner 2003b[44] Schultz-Ertner 2004b[143]	Heidelberg Germany				same participants as Schultz-Ertner 2004 all included in the systematic review of Lodge 2007
Schultz-Ertner 2004[143]	Heidelberg Germany	87 skull base chordomas and chondrosarcomas	carbon Ion RT (60 Gye)	Retrospective non comparative case series	3-year local control 81% for chordomas and 100% for chondrosarcomas, grade 4 and 5 toxicity non observed
Tsujii 2004[45] Tsujii 2007[24]	Chiba Japan	(2867 patients in total) 40 skull base chordomas	carbon ion irradiation median 57.6 Gy in 16 fractions	Phase I/II non comparative case series study	3-year local control: 93% 5-year overall survival: 87%

Table AM HTA and SR description for other localization's chordomas and chondrosarcomas and proton therapy

Reference	Included studies	Conclusion
Brada 2007 [10]	None	No discussion about others localizations
Lodge 2007[11]	None	No discussion about others localizations
Olsen 2007[12]	Austin-Seymour 1999/2000[35, 36, 12] Debus 1997[38] Fagundes 1995[37] Munzenrider 1999[30]	Five studies of the Massachusetts General Hospital (USA) 5-year overall survival for cervical spine chondrosarcomas: 48% 5-year disease free survival for cervical spine chondrosarcomas: 54% NB. Only the study of Munzenrider 1999 related results on cervical tumours and the results are: 10-year disease free survival for cervical spine chordomas: 54% and chondrosarcomas: 48%

Table AN Description of studies for other localization's chordomas and chondrosarcomas and proton beam therapy

Reference	Location or institution	Population	Intervention	Design	Results
Imai R 2004[46]	Chiba Japan	30 patients (41-85 years) with unresectable sacral chordomas (23 prior treatment and 7 local recurrence) Follow up 30 months (median)	Carbon ion radiotherapy Median clinical target volume = 546 cm3. Applied dose from 52.8 to 73.6 GyE in 16 fixed fractions over 4 weeks	Retrospective non comparative case series	Overall and cause specific survival at 5 years: 52 and 94% respectively Overall local control rate at 5 years: 96% 2 patients with severe skin/soft tissue complication requiring skin grafts.
Munzenrider 1999[30]	Massachusetts general hospital Boston USA	Tumours of cervical spine: chordomas and chondrosarcomas	Proton beam radiation	Retrospective non comparative case series	10-year disease free survival for cervical spine chordomas: 54% and chondrosarcomas: 48%
Schulz-Ertner 2004[41]	Heidelberg Germany	9 spinal and 8 sacrococcygeal chordomas and chondrosarcomas	combined photon RT with a carbon ion boost	non comparative case series	3-year local control in 8/9 spinal and 7/8 sacral grade 4 and 5 toxicity non observed

Table AO HTA and SR description for other intracranial tumours and proton therapy

Reference	Included studies	Conclusion
Lodge 2007[11]	Fitzek 2001[48] Fitzek 1999[47] Bush 2002[52] Amin-Hanjani 1998[49] Wenkel 2000[50] Vernimmen 2001[51]	Dose escalation with protons has not demonstrated convincing survival benefit in malignant glioma other than would be expected due to patient selection
Brada 2007[10]	Fitzek 2001[48] Fitzek 1999[47] Bush 2002[52] Vernimmen 2001[51] Wenkel 2000[50]	studies do not allow for conclusion about superiority of protons

Table AP Description of studies for other intracranial tumours and proton therapy

Reference	Location or institution	Population	intervention	Design	Results
Amin-Hanjani 1998[49]	Massachusetts Boston USA	98 patients with cavernous malformations	stereotactic radio surgery with proton beam therapy	retrospective non comparative case series	radio surgery reduce hemorrhage but there is a potential for complications and continued lesion progression
Bush 2002[52]	Loma Linda California USA	31 acoustic neuromas	proton therapy 54.0 CGE in grade 1 and 60.0 CGE in grade 2	retrospective non comparative case series	11/31 local regression 31% maintained useful hearing
Fitzek 1999[47]	Massachusetts Boston USA	23 patients with glioblastoma multiforme	proton/photons radiotherapy to 90 CGE	phase II trial prospective non comparative case series	Actuarial rates survival at 2 and 3 years : 34 and 18%
Fitzek 2001[48]	Massachusetts Boston USA	20 patients with grade 2/4 (n=7) and grade ¾ (n= 13) gliomas	Dose escalation with proton/photons radiotherapy 68.2 CGE in grade 2 and 79.2 CGE in grade 3	phase I/II trial prospective non comparative case series	Actuarial 5-year survival rate for grade 2 of 71% and for grade 3 of 23% 2 patients with radiation necrosis (one death of radiation necrosis)
Vernimmen 2001[51]	Tygeberg South Africa	46 patients with large and complex meningioma of the skull base	Stereotactic radiotherapy (SRT, 54. to 61.6 in 16 or more fractions) versus hypofractionated stereotactic radiotherapy (HSRT, 20.3 CGE in 3 fractions)	retrospective comparative case series	HSRT: 16/18 (89%) clinically stable or improved and 11% deteriorated SRT: 2/5 clinically better and 3/5 stables
Wenkel 2000[50]	Massachusetts Boston USA	46 patients with benign meningioma partially resected or recurrent	combined proton and photons therapy 59.0 CGE	retrospective non comparative case series	Overall survival at 5 and 10 years was 93 and 88%. Recurrence free rate at 5 and 10 years was 100% and 88%. 8/46 severe long term toxicity

Table AQ HTA and SR description for other intracranial tumours and carbon ion therapy

Reference	Included studies	Conclusion
Lodge 2007[11]	Fabrikant 1992 [144]	Not specific conclusion

Table AR Description of studies for other intracranial tumours and carbon ion therapy

Reference	Location or institution	Population	intervention	Design	Results
Fabrikant 1992[144]	Berkeley California USA	patients with intracranial vascular malformations	charged particle radiosurgery	retrospective non comparative case series	Rate of complete angiographic obliteration 3 years after treatment 90 to 95% for volumes < 4 cm3 or 4-14 cm3 and 60 to 70% for volumes < 14 cm3.
Mizoe 2007-08-[145]	Chiba japan	48 patients with malignant glioma (16 anplastic astrocytomas and 32 glioblastoma)	carbon ion radiotherapy combined with x-ray radiotherapy and chemotherapy	phase I/II clinical trial non comparative case series	Potential efficacy in patients who receive higher carbon doses. No grade 3 or acute reaction in the brain 4 cases of grade 2 brain morbidity and 4 cases of grade 2 brain reaction

Table AS Description of included studies in HTA and SR for paediatric cranial tumours

Reference	Location or institution	Population	Intervention	Design	Results
Benk 1995 [53]	MGH	18 children (4-18 year old) with skull chordomas	Postoperative radiation, photons and protons mixed (69 CGE)	Retrospective study	5-Y SR : 68% 5-Y DFS : 63%
Habrand 1999 [55]	Orsay, Fr (1994-1998)	9 children, intra-cranial malignancies		Retrospective study	Follow-up : 2 to 5 months : 7 alive, 2 local recurrences
Habrand 1999 [55]	Loma Linda, US (1991-1994)	28 children: 16 benign tumour, 12 malignant one		Retrospective study	Follow-up : 7 to 49 months : 24 alive, 3 died, 1 local recurrences 4 treatment related toxicity
Noel 2003 [54]	Orsay, Fr (1994-2000)	27 children (5 to 17 years)with CNS tumour	Photons 24-54 (Gy) and protons 9-31 (CGE)	Retrospective study	3-Y SR : 83% Local control at 3 y : 92%
Hug 2002 [56] [56]	Loma Linda, US (1991-1997)	27 children (2 to 18 years) with astrocytoma	50.4 to 63 CGE	Retrospective study	3-Y SR : 86% Local control : 88%
Hug 2002 [57] [56]	Boston & Loma Linda, US (1992-1999)	Skull base tumours 17 in Boston, 12 in Loma Linda	Proton or proton (40-72 CGE) + RT (12.6-31.6 CGE)	Retrospective study	5-Y SR : 56% 5-Y L.C : 63%
McAllister 1997 [58]	Loma Linda, US (1991-1994)	28 children with skull base tumours	See above	Morbidity from children treated by proton (see above)	Follow-up : 7 to 49 months : 4 cases of early morbidity, 26 cases of disease related morbidity, 4 local failure, 3 deaths

Table AT Secondary cancers after radiotherapy

Reference	Location or institution	Population	Intervention	Design	Results
Geenen 2007 [60]	Amsterdam, NI (1966 - 1996)	1 362 children with childhood cancer & at least 5-year survival	Comparative study : Children treated for cancer versus general population	Retrospective cohort: Treatment-specific prevalence of AE at end of follow-up	median follow-up, 17.0 years 75%: 1 or more adverse events, 24.6% 5 or more 40% : 1 severe or life-threatening 55% with radiotherapy : high or severe burden of adverse events
Oeffinger 2006 [59]	United States (1970 -1986)	10 397 survivors of childhood cancer	Comparative study : Children treated for cancer versus siblings		30 y after the diagnostic 73%: 1 chronic health condition 42% : 1 severe or life-threatening ?% with radiotherapy : high or severe burden of adverse events
Miralbell 1997[61] [61]	Geneva, CH	Virtual theoretic study	Brain sparing effect from dosimetric study in a 3-year old child	Modelling late neuropsychologic deficit after x-rays *vs* protons	Absolute risk reduction of 3.6% in 4-year old children with protons *vs* photon optimized plan
Miralbell 2002 [146]	Geneva, CH	1 parameningeal rhabdomyosarcoma; 1 medulloblastoma	4 treatment plans; 3 treatment plans	Modelling risk of 2^{ry} cancer	Protons reduce risk by ≥ 2; protons reduce risk by 8 to15

Table AU HTA and SR description for salivary glands tumours and neutron therapy

Reference	Included studies	Conclusion
AETMIS 2003[1]	Griffin 1988[62] Laramore 1993[63] Breteau 2000[64] Huber 2001[66] Douglas 2000[65]	The efficacy of neutron therapy is well established only for the treatment of inoperable or unresectable salivary gland tumours, regardless of their degree of malignancy or stage of progression, and for the treatment of large residual tumours after surgical resection NB No difference in survival
Lodge 2007[11]	Chen 2006[69] Schulz- Ertner 2005[67] Terhaardt 2005[68]	Local control rate higher with carbon ion (> 75%) than with photons (< 50%)

Table AV Description of studies for salivary gland tumours with neutron therapy

Reference	Location or institution	Population	intervention	Design	Results
Griffin 1988[62]	Washington center USA	32 patients with inoperable, recurrent or unresectable malignant salivary gland tumours (mix of tumours histology)	Fast neutron radiotherapy (n=17) 16,5 to 22,0 Gy in 12 fractions comparing with conventional photon radiotherapy (n=15) 55 to 70 Gy	RCT	complete tumour clearance rates 85% with neutrons and 33% with photons (p= 0.01) 2-year local control rate 67% for neutrons and 17% for photons (p<0.005) 2-year survival rates 62% for neutrons and 25% for photons (p=0.10)
Laramore 1993[63]	Washington center USA	follow up of the study of Griffin 1986 in 1993: 25 admissible patients	13 neutrons 12 photons	RCT	10-year local control rate 56% for neutrons and 17% for photons (p<0.009) 10-year survival rates 15% for neutrons and 25% for photons (p=0.5)
Breteau 2000[64]	France (Italy)	75 patients with cystic adenoid carcinoma (following radical microscopically and complete surgery)	LET radiation therapy (photons, electrons) Neutrons 17 Gy (1 Gy 3 X /week) photons 60 to 70 Gy	retrospective comparative case series	3-year local control rate 74% for neutrons and 34% for photons
Chen 2006[69]	San Fransisco USA	45 patients with newly diagnosed salivary gland carcinomas (mix of tumours histology and stages)	radiation alone Photons 66 Gy	retrospective non comparative case series	5 and 10-year local control rate 70% and 57% respectively 10-year overall survival rates 46% 10-year metastases free survival rates 67%
Douglas 2000[65]	Washington center USA	159 patients with cystic adenoid carcinoma locally advanced or recurrent	Neutrons median total dose 19.2 Gy (1.05 4x / week to 1.7 Gy 3x /week)	retrospective non comparative case series	5-year local control rate 57 5-year overall survival rates 72% 5-year cause specific survival rates 77% No difference in outcomes between gland sites
Huber 2001[66]	Heidelberg Germany	75 patients with inoperable, recurrent or incompletely resected cystic adenoid carcinoma	Neutrons 16 Gy (1 Gy 3 X /week) photons 64 Gy or both	retrospective comparative case series	Actuarial 5-year local control rate 75% for neutrons and 32% for photons Not difference in survival (p>0.1) Severe late grade 3 and 4 toxicity: 19% with neutrons, 10% with mix beam and 4% with photons (p>0.1)
Terhaardt 2005[68]	Utrecht Nederlands	538 patients with malignant salivary gland tumours	surgery + photon radiotherapy (62 Gy) n= 386 primary radiotherapy	retrospective comparative case series	Indications of radiotherapy in malignant salivary tumours

Table AW Description of studies for salivary gland tumours with carbon ion therapy

Reference	Location or institution	Population	intervention	Design	Results
Schulz-Ertner 2005[67]	Heidelberg Germany	63 patients with cystic adenoid carcinoma	group A: Photons and carbon (n= 29) group B: photons alone (n= 34)	Retrospective comparative case series	2-year local control rate 77.5% (photons and carbon ion) and 72.6% (photons alone) 4-year local control rate 77.5% (photons and carbon ion) and 24.6 (photons alone) (p= 0.08) 4 year overall survival rate 75.8% (photons and carbon ion) and 77.9% (photons alone) Rates for severe late toxicity < 5% in both groups
Tsujii 2007[24]	Chiba Japan	(2867 patients in total) 64 locally advanced cystic adenoid carcinoma	carbon ion irradiation median 57.6 Gy in 16 fractions	non comparative case series	3-year local control: 82% 5-year overall survival: 68%

HTA and SR description for other head and neck tumours and proton therapy

Reference	Included studies	Conclusion
Brada 2007[10]	Tokuuye 2004 [70] Slater 2005[71]	the results are similar to those achieved with photons RT
Lodge 2007[11]	Tokuuye 2004 [70] Slater 2005[71]	Severe late complication rate was 10 to 18%.

Table AX Description of studies for other head and neck tumours and proton therapy

Reference	Location or institution	Population	intervention	Design	Results
Slater 2005[71]	Loma Linda USA	29 patients with localized stage II-IV oropharyngeal cancer	photon and proton radiation 75.9 GyE in 45 fractions	retrospective non comparative case series	Actuarial 5-year control for local disease was 88% Actuarial 5 year survival was 65%
Tokuuye 2004 [70]	Tsukuba Japan	33 patients with head and neck malignancies but no history of surgical resection	protons with or without X-rays irradiation	retrospective non comparative case series	overall 5-year survival and local control were 44 and 74% 6/33 > grade 3 toxicity (acute or late toxicity)

Table AY HTA and SR description for other head and neck tumours and carbon ion therapy

Reference	Included studies	Conclusion
Lodge 2007[11]	Mizoe 2004[72] Schulz-Ertner 2005 [67]	.

Table AZ Description of studies for other head and neck tumours and carbon ion therapy

Reference	Location or institution	Population	intervention	Design	Results
Mizoe 2004[72]	Chiba Japan	36 patients with locally advanced or recurrent cancer of the head and neck	Carbon ion group A: 17 patients, 70.2 GyE in 18 fractions in 6 weeks Group B: 19 patients 70.2 GyE in 16 fractions in 4 weeks	prospective comparative case series	equal clinical outcomes in terms of morbidity and local control
Schulz-Ertner 2005 [67]	Heidelberg Germany	63 patients with cystic adenoid carcinoma			about salivary gland all included in this topic
Tsujii 2007[24]	Chiba Japan	(2867 patients in total) locally advanced or recurrent head and neck tumours heterogeneous group	carbon ion irradiation median 49 to 70 Gy in 16 to 18 fractions	non comparative case series	3-year local control: 81% 5-year overall survival: 37%

Table A1 : Description of studies included in HTA and SR for gastrointestinal tumours

Reference	Location or institution	Population	intervention	Design	Results
Koyama 2003 [73]	Japan	30 patients with oesophagus tumour	photon therapy followed by proton, doses of 77 to 80 CyE	Prospective study	LC : 56.6 and 49.0% (advanced or not) 5y SR : 78.3 and 38.1%
Sugahara, 2005 [74]	Japan	46 patients with oesophagus tumour	40 received combinations of X-rays (median, 48 Gy) and protons (median, 31.7 Gy) as a boost, median total : 76.0 Gy	Retrospective Studies	LC for T1 : 83% , T2-T4 : 29%. 5-Y SR : T1 : 34 %, T2-T4 : 55%, and 13%
Chiba, [75] 2005		162 patients with liver carcinoma unsuitable for surgery	72 Gy in 16 fractions over 29 days	Retrospective Studies	LC rate at 5 years was 86.9% among the 162 patients. 5-Y SR : 23.5% 5 For 50 patients having a solitary tumour, 5-Y SR : 53.5%.
Nemoto,[76] 2004	No abstract				
Kawashima2005 [78]	Chiba, Japan.	30 patients with solitary hepatocellular carcinoma (HCC); no indication for surgery	76 cobalt gray equivalent in 20 fractions for 5 weeks without other treatment	Retrospective Studies	Recurrence : 1/30 median follow-up period of 31 months 2-Y SR : 66% (48% to 84%)
Bush [77] 2004	Loma Linda, California	34 patients with locally unresectable hepatocellular carcinoma	63 cobalt Gray equivalents, in 15 fractions for 3 weeks	phase II trial	LC rate at 2 years : 75% 2-Y SR : 55%
Hata[79] 2006	Possible interference with studies from Sugahara, Takayuki,		63 grays (Gy) to 84 Gy (median, 73 Gy) in 13 to 27 fractions	Retrospective Studies	overall and cause-2-Y SR 62% and 82% 5-Y SR : 33% and 67%

Reference	Location or institution	Population	intervention	Design	Results
	Nemoto				
Kato[80] 2004	Japan (ions)		step-wise dose-escalation study.	toxicity study (Phase I-II trial)	no severe adverse effects and no treatment-related deaths occurred, LC rate at 5 years : 81% 5-Y SR : 25%
Linstadt [81] 1998	Berkeley US (ions)	49 patients with locally advanced carcinoma of the pancreas	6,000 cGy over a period of 10 weeks	randomized, prospective study comparing helium ion radiation therapy proton	LC rate slightly higher in the helium-treated patients no significant difference in survival

Table A2: Description of studies included in HTA and SR for lung tumours

Reference	Location or institution	Population	Total dose	Design	Results
Bush 1999 [82]	Loma Linda, US	37 patients with early-stage, medically inoperable non-small cell lung cancer	73.8 CGE given over 5 weeks (if poor CV function 51 CGE to the tumour only)	prospective study	LC rate at 2 years : 87% 5-Y SR : for the entire group was 63%; for stage I patients: 86%.
Bush 2004 [147]	Loma Linda, US	68 patients with inoperable stage I non-small cell lung cancer	From 51 (CGE) to 60 CGE in 10 fractions over 2 weeks	prospective phase 2 clinical trial.	LC rate at 3 years : 74%, 3-Y SR : 72%,
Nihei 2006 [83]	Chiba Japan	37 patients with Stage I, tumour size < or =5 cm, medically inoperable	70-94 Gy(E) was delivered in 20 fractions (3.5-4.9 Gy(E) per fraction)	Retrospective study (safety and efficacy)	LC at 2-year : 80% 3-Y SR : 84%
Shioyama 2003 [84]	Tsukuba, Japan	37 patients	76.0 Gy (range 49.0-93.0 Gy)	Retrospective study	LC rate at 5-year for patients with Stage IA (89%), with Stage IB (39%) 5-Y SR : 29% for all patients, (70% for Stage IA patients, and 16% Stage IB)
Koto 2003 [148]	Chiba (ions) Japan	82 patients stage I non-small cell lung cancer	59.4 to 95.4 gray equivalents (GyE)	prospective study	LC rate at 3.5-year: 77%
Miyamoto [149]	Similar with study from Koto	82 patients	59.4 to 95.4 (GyE) in incremental steps	prospective study (phase I/II trial)	LC rate at 3.5-year: 77%
Nishimura 2003 [150]	Chiba (ions) Japan	Post treatment radiographic lung damage by 43 patients	59.4 to 95.4 (GyE) in incremental steps	prospective study (phase I/II trial)	Severity of pulmonary reactions was correlated with dose-volume factors.

Table A3 : Description of included studies in HTA and SR for prostate tumours

Reference	Location or institution	Population	Total dose	Design	Results
Shipley 1995 [85]	Massachusetts General Hospital	202 patients with advanced T3-T4 prostate cancer	Start common dose : 50.4 Gy by four-field photons plus	RCT Arm 1 : additional 25.2 CGE by conformal protons (total dose 75.6 CGE) or arm 2 : additional 16.8 Gy by photons	local control improved only in patients with poorly differentiated tumours, but, late radiation sequelae also increased,.No change on overall survival
Zietman 2005 (also Rossi) [86]	Massachusetts General Hospital and Loma Linda University	393 patients, stages T1b through T2b and PSA< 15 ng/ml	Protons and photons combined in the two arms	RCT :conventional dose of 70.2Gy, versus high dose of 79.2Gy	No significant difference in survival rate, but in biochemical failure 1% -2% acute or late GI-GU morbidity
Slater, 2004 [88]	Loma Linda University	1255 patients, stages Ia-III	30CGE plus 45 Gy or 75 Gy alone	Retrospective study First group : proton and photons combined Second group : protons alone for patients at less risks	biochemical disease-free survival rate at 5 year : 73% no difference in toxcity
Tsuji (Akukara, Ishikawa) [91]	Chiba, Japan	201 patients, stages T1-T3	54-72 GyE with hormonotherapy for high risk, without for low risk (T1-T2a , Gleason score <7 and PSA<20ng/ml)	Prospective study	LC rate at 5 year : 95-100% 5-6% acute or late GI-GU morbidity

Table A4 : Description of studies included in HTA and SR for pelvis tumour

Reference	Location or institution	Population	Total dose	Design	Results
Kagei K 2003 [94]	Tsukuba (Japan)	25 patients with squamous cell carcinoma of the uterine cervix (stage IIB-IVA)	Curative intent by external photon irradiation to the pelvis, followed by proton irradiation to the primary tumour (86 Gy median dose)	Retrospective case study	10Y OS: 89% for stage IIB and 40% for stage IIIB-IVA 5Y LC: 100% and 61% respectively 4% severe (grade 4 or more) late complications (at 5 years)
Kato [95]	Chiba (Japan)	49 patients, stage IIIB and IVA disease	First study :total dose 52.8 to 72.0 , second study : 68.8 to 72.8 Gy	Prospective study	8 patients major late GI complications LC at 5-year in the first and second studies was 45%and 79%, respectively.
Nakano 2006 [96]	Chiba (Japan)	49 patients with stage IIIb bulky and IVa uterine cervical cancer	NR	Prospective study	no significant prognostic difference between hypoxic and oxygenated tumours
Hata 2006 [97]	Tsukuba (Japan)	25 patients, stage cT2-3N0M0	transurethral resection + RT+ chemotherapy + proton irradiation boost	Retrospective study	26 %major late complications survival at 5-year : 60% bladder preservation : 96%
Tsuji [98]	Chiba (Japan)	35 patients , clinical stages T2 to T4	transurethral resection + RT+ chemotherapy with or without proton irradiation boost (60-80 Gy)	Retrospective study	9 %major late complications survival(time unclear) : 59 % bladder preservation: 68%

APPENDIX FROM CHAPTER 9: COST OF TRANSPORT TO THE CENTRE AND LODGING

The transport mean and cost is assumed as follows:

- The train is the transport mean for the following centres: Orsay (Paris), Lyon, Nice, Essen, Darmstadt and Heidelberg. Prices are requested at the NMBS for 2nd class tickets, without any promotion, June 2007.
- The plane is the transport mean for all other centres. Air fares are taken from the Brussels Airlines website, June 2007, for economy class with departure foreseen in one and a half month time, and return after approximately 8 weeks, including luggage insurance and annulation fee.
- Taxi transport foreseen from railway station/airport to the centre for a cost of 75€.

Table: Train fares

Centre	Railway station	Price of return ticket per person
Heidelberg	Heidelberg	216€
Essen	Essen	106€
Orsay	Paris	156€
Lyon	Lyon	201€
Nice	Nice	287€

Table: Flight fares

Centre	Airport	Price of return ticket per person
Berlin	Berlin	342€
Munich	Munich	243€
Villigen	Zurich	508€
Clatterbridge	Manchester	276€
Uppsala	Stockholm	321€

The cost of lodging is assumed as follows:

Cost per night:

Prices vary considerably depending from the location of the centre and the type of lodging.

As approximation, for all centres we take a lodging price of 75€ per night, which should come close to the actual rental for a furnished apartment for up to 2 persons, with bedroom, kitchenette, bathroom, washer/dryer and internet connection.

Length of stay:

The patient first needs to do a pre-examination and then it takes about a week for the treatment planning, before the actual irradiation treatment starts. Usually one fraction per day is delivered, so for proton treatment, on average 25 fractions are needed and therefore 5 weeks + 1 week for the pre-treatment. (In reality the patient has the choice either to come back home in the pre-treatment week, either to stay nearby the centre). For carbon-ion, an average of 18 fractions can be assumed.

APPENDIX FROM CHAPTER 10: BENCHMARK DATA ON OPERATIONAL MODELS

	Goitein 2003 **P**	Cohilis, Jongen, Strahlentherapie und Onkologie **P**	Lyon **P+C ion**	Heidelberg **P+C ion**
Average time per fraction	22 min. (in 5-10 years : 11 min.)	13 min for gantry treatment 11 min for fixed beam treatment 15 min for eye treatment + 50% inefficiency factor (50% increase of treatment times)	25 min.*: « hypothèse très prudente »	20-30 min.
Patient treatm. hrs. /day	13	12	13,2	12
# Operational days /week		6	5	6
# Weeks /year		50	45	
% usage of treatm. hours	90%			
# patients yearly			"Minimum 1000"	
# patients in ramp-up period			20% (200) in year 1 50% (500) in year 2 75% (750) in year 3 100% (1000) from year 4	

*http://etoile.in2p3.fr/texte%20par%203%20base/09.pdf

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Wettelijk depot : D/2007/10.273/50

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.
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21. HTA Stomamateriaal in België. D/2005/10.273/27.
22. HTA Positronen Emissie Tomografie in België. D/2005/10.273/29.
23. HTA De electieve endovasculaire behandeling van het abdominale aorta aneurysma (AAA). D/2005/10.273/32.
24. Het gebruik van natriuretische peptides in de diagnostische aanpak van patiënten met vermoeden van hartfalen. D/2005/10.273/34.
25. Capsule endoscopie. D/2006/10.273/01.
26. Medico–legale aspecten van klinische praktijkrichtlijnen. D2006/10.273/05.
27. De kwaliteit en de organisatie van type 2 diabeteszorg. D2006/10.273/07.
28. Voorlopige richtlijnen voor farmaco-economisch onderzoek in België. D2006/10.273/10.
29. Nationale Richtlijnen College voor Oncologie: A. algemeen kader oncologisch kwaliteitshandboek B. wetenschappelijke basis voor klinische paden voor diagnose en behandeling colorectale kanker en testiskanker. D2006/10.273/12.
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31. Health Technology Assessment prostate-specific-antigen (PSA) voor prostaatkankerscreening. D2006/10.273/17.
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63. Wetenschappelijke ondersteuning van het College voor Oncologie: een nationale praktijkrichtlijn voor de aanpak van borstkanker. D/2007/10.273/35.
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65. Organisatie en financiering van genetische diagnostiek in België. D/2007/10.273/44.
66. Health Technology Assessment: Drug-Eluting Stents in België. D/2007/10.273/47.
67. Hadrontherapie. D/2007/10.273/50.