Intensiteitsgemoduleerde Radiotherapie (IMRT)

KCE reports vol. 62A

Federaal Kenniscentrum voor de Gezondheidszorg
Centre fédéral d'expertise des soins de santé
2007

Het Federaal Kenniscentrum voor de Gezondheidszorg

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KCE reports vol. 62A

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Belangenconflictt:	Sommige experten verklaren een onderzoeksbeurs te hebben ontvangen van Elekta (De Neve Wilfried), van TomoTherapy (Scalliet Pierre, Storme Guy en Verellen Dirk) of van BrainLAB (Storme Guy en Verellen Dirk) voor het uitvoeren van onderzoek en produktontwikkeling.
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Layout:	Ine Verhulst

Brussel, 25 juli 2007

Studie nr 2006-23
Domein : Health Technology Assessment (HTA)

MeSH : Radiotherapy, Intensity-Modulated ; Radiotherapy, Conformal

NLM classification : WN250

Taal : Nederlands, Engels
Formaat : Adobe® PDF™ (A4)

Wettelijk depot : D2007/10.273/32

Dit document is beschikbaar van op de website van het Federaal Kenniscentrum voor de gezondheidszorg.

Hoe refereren naar dit document?
Van den Steen D, Hulstaert F, Camberlin C. Intensiteitsgemoduleerde Radiotherapie (IMRT). Health Technology Assessment (HTA). Brussel: Federaal Kenniscentrum voor de Gezondheidszorg (KCE); 2007. KCE reports 62A (D2007/10.273/32)

Voorwoord

Vandaag zijn bepaalde vormen van kanker niet langer fataal dankzij het therapeutisch arsenaal waarover het medisch korps beschikt, onder andere de externe radiotherapie. Eventueel gecombineerd met chirurgie en/of chemotherapie, beoogt deze therapie de kankercellen te vernietigen via ioniserende stralen die in het lichaam door dringen. Deze behandeling heeft ook nevenwerkingen of kan zelfs secundaire kankers induceren bij bestraling van gezond weefsel. Daarom is het belangrijk de tumor nauwkeurig te af te lijnen en de bestralingsdosis zo accuraat mogelijk toe te dienen.

De vooruitgang op gebied van beeldvorming en informatica hebben de conformele radiotherapie mogelijk gemaakt waarbij het te bestralen gebied in drie dimensies gevisualiseerd wordt (3DCRT). De intensiteitsgemoduleerde radiotherapie (IMRT) gaat nog verder via het veranderen of moduleren van de intensiteit van de stralingsbundels. Zo laat IMRT toe om tumoren met een concave vorm nauwkeurig te bestralen, om een hogere stralingsdosis te richten op de tumor en/of de toxiciteit te beperken voor de omringende gezonde weefsels.

IMRT wordt in België gebruikt in een stijgend aantal centra en is terugbetaald sinds 2001. Binnen de twee jaar zal ongeveer elk Belgische radiotherapie centrum beschikken over IMRT. Deze installatie vereist een niet onbelangrijke investering van de betrokken ziekenhuizen maar heeft ook gevolgen voor de uitgaven van de ziekteverzekering. Bovendien vereist de complexiteit van Deze behandeling een doorgedreven expertise en kwaliteitsgarantie.

IMRT is een « emerging technology ». Zulke nieuwe technologieën worden in een steeds toenemend ritme geintroduceerd in de gezondheidszorg. Een evaluatie van de klinische werkzaamheid en veiligheid, alsook een gezondheidseconomische, organisatorische en budgettaire studie in de Belgische context drongen zich op.

Het KCE dankt de experten in radiotherapie en stralingsfysica voor hun waardevolle wetenschappelijke inbreng, alsook de vertegenwoordiging vanuit de industrie voor hun medewerking.

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Samenvatting

INTRODUCTIE

Intensiteitsgemoduleerde radiotherapie (IMRT) onderscheidt zich van standaard externe radiotherapie technieken door een meer accurate bestraling van de tumor. De techniek laat toe gevoelige organen te sparen die omgeven zijn door tumoren met een concaaf oppervlak. Dit gebeurt bij IMRT via het controleren – of moduleren – van de intensiteit van de componenten van de stralingsbundel. Dit kan bereikt worden op een aantal manieren: via een multileaf collimator (MLC) met bladen die al of niet bewegen tijdens de bestraling, of met een bestralingskoepel die beweegt tijdens de bestraling zoals bij tomotherapie.

Alvorens de radiotherapie behandeling te starten, zal de arts aan de hand van beelden verkregen via computed tomography (CT) en andere technieken zorgvuldig het te bestralen gebied afbakenen ten opzichte van de stralingsgevoelige gezonde organen. Via software voor het plannen van de behandeling worden dosis-volume histogrammen berekend. Een accurate bestraling met IMRT vereist een correcte positionering van de patiënt, met de hulp van (soms dagelijkse) beeldvorming.

Gezien de complexiteit van IMRT is het noodzakelijk te beschikken over deskundigen in stralingsfysica en dosimetrie. Een doorgedreven kwaliteitsbewaking voor de verschillende stappen is essentieel.

DOELSTELLINGEN

In deze "rapid health technology assessment" onderzoeken we via literatuurstudie de klinische werkzaamheid en de kosten-effectiviteit van IMRT (intensity-modulated radiation therapy) in vergelijking met de standaard conformele 3D radiotherapie (3DCRT) technologie. We belichten de kost van IMRT en ramen de impact van IMRT op het budget van de Belgische ziekteverzekering met een economisch model.

De antwoorden op deze onderzoeksvragen kunnen vervolgens omgezet worden in aanbevelingen over het gebruik, de financiering, de organisatie en kwaliteitsopvolging van IMRT.

KLINISCHE GEGEVENS

We hebben in de literatuur gezocht naar patiëntstudies waarbij IMRT wordt vergeleken met een standaard uitwendige radiotherapeutische techniek. Gezien slechts weinig en eerder kleine gerandomiseerde studies (RCT) werden gevonden, hebben we ook niet-gerandomiseerde vergelijkende patiëntstudies weerhouden. Deze rapporten vergelijken vooral de nevenwerkingen van IMRT behandelde patiënten met controlepatiënten die voorheen in hetzelfde centrum werden behandeld met externe radiotherapie. Het moge duidelijk zijn dat de bewijskracht van zulke historische vergelijkingen zwak is vergeleken met een RCT.

We identificeerden in totaal 19 rapporten van vergelijkende studies. De publicaties betreffen kanker van hoofd en hals (9 rapporten, inclusief 1 RCT), prostaatkanker (6 rapporten, geen RCT), borstkanker (3 rapporten, inclusief 2 RCT's), en medulloblastoom (1 rapport, geen RCT).

Gezien de beperkte mogelijkheid van orgaanbeweging, vormt kanker van hoofd en hals een gepaste kandidaat indicatie voor hoog accurate bestraling, zoals mogelijk is met IMRT. Het voordeel van IMRT tov 3DCRT is vooral gerapporteerd voor het ontzien van stralingsgevoelige gezonde organen zoals de speekselklieren, en in een enkele studie ook de oogzenuw. Gebaseerd op de gepubliceerde studies kan besloten worden dat een goed uitgevoerde IMRT de levenskwaliteit van de patiënt met kanker van hoofd en hals kan verbeteren (bvb minder xerostomie). Er zijn geen afdoende gegevens die een vergelijking toelaten tussen IMRT en 3DCRT op het vlak van tumor herval of overleving.

Gezien volgens bepaalde auteurs de radiotherapie van kanker van hoofd en hals niet overal optimaal gebeurt en IMRT moeilijk blijft in planning en uitvoering, wordt gesuggereerd IMRT behandelingen te beperken tot centra die beschikken over de nodige expertise (zoals aangetoond door onderzoeksactiviteiten rond IMRT, de opvolging van patiënten, enz.).

De standaard curatieve behandelingen voor prostaatkanker zijn radicale prostatectomie en radiotherapie (externe bestraling of brachytherapie). Er zijn voldoende gegevens die aantonen dat patiënten met een gelokaliseerde prostaatkanker met een intermediair of hoog risico, met andere woorden patiënten die normaal gezien niet in aanmerking komen voor chirurgie, voordeel halen uit een hogere dan conventionele stralingsdosis dosis zoals die kan worden toegediend met 3DCRT of IMRT. Er is evenwel vooralsnog geen bijkomend voordeel in overleving aangetoond. IMRT laat een steile dosisgradiënt toe tussen het doelvolume en de omliggende gevoelige normale structuren zoals rectum, darm en blaas. Om deze reden werd in vele centra IMRT eerst gebruikt bij prostaatkanker. De meeste vergelijkende studies (hierbij was geen enkele RCT) rapporteren minder rectale toxiciteit na IMRT dan na 3DCRT, ook bij hoge dosis. De uitdaging blijft om tijdens elke sessie de prostaat (en soms de lymfeklieren) zo accuraat mogelijk te bestralen. Frequente correcties van de bestraling gebaseerd op beeldvorming kunnen hierbij helpen.

Bij standaard radiotherapie voor borstkanker met gebruik van tangentiële velden bij vrouwen met grote borsten kan de dosisverdeling inhomogeen zijn, wat aanleiding kan geven tot een verhoogde laattijdige huidtoxiciteit (cosmetisch effect, fibrosevorming en pijn). Twee RCT's (waarvan één rapport enkel in abstract formaat) en een retrospectieve vergelijking van IMRT met conventionele radiotherapie bevestigen dat er na IMRT minder huidcomplicaties optreden. Algemene levenskwaliteit kon niet aangetoond worden met behulp van standaardtechniek. Langetermijnstudies zijn noodzakelijk om het risico na IMRT te kennen op het ontstaan van een tumor in de contralaterale borst.

Een kleinere retrospectieve vergelijking bij kinderen behandeld met cisplatin voor medulloblastoma suggereert dat IMRT de ototoxiciteit kan doen dalen in vergelijking met 3DCRT.

Het optreden van fatale secundaire kankers wordt beschouwd als het belangrijkste risico van radiotherapie. De totale stralingsdosis voor het lichaam is hoger bij IMRT en dit zou theoretisch de incidentie van fatale secundaire kankers kunnen doen verdubbelen in vergelijking met de standaard radiotherapeutische technieken. Vooral jongere patiënten lopen een verhoogd risico.

Er bestaan grote variaties in totale lichaamsbelasting tussen de verschillende IMRT technieken. Ook het dagelijks positioneren van de patiënt met beeldvorming gebaseerd op straling verhoogt de algemene stralingsbelasting. Producenten en gebruikers van IMRT hardware en software dienen hiervan op de hoogte te zijn. Verdere productverbetering dient te worden gestimuleerd om zo het risico op secundaire tumoren te verminderen.

LOKALE SITUATIE

De 25 Belgische centra voor radiotherapie namen deel aan een enquête voor deze studie. Twaalf centra gebruiken momenteel IMRT en, op één enkel centrum na, hebben alle centra de intentie deze techniek in de twee volgende jaren te gebruiken. De centra rapporteerden 2150 behandelingen in 2006 vergeleken met 1400 in 2005, wat neerkomt op respectievelijk 20% vergeleken met 15% van alle behandelingen met uitwendige bestraling in de centra die over IMRT beschikken. De verstrekkingcode voor de planning van een IMRT behandeling werd voor ongeveer 700 patiënten in 2005 aangerekend. Het verschil met het opgegeven aantal in de enquête is wellicht te wijten aan klinische indicaties waarvoor IMRT niet terugbetaald wordt en de wijze van facturering.

ECONOMISCHE LITERATUUR

We doorzochten de economische literatuur over IMRT aan de hand van een zo ruim mogelijke scope. De bedoeling hiervan was, naast gezondheidseconomische evaluaties waarbij het klinische effect van IMRT vergeleken wordt met dat van een alternatieve therapie, ook zuiver beschrijvende studies evenals boekhoudkundige costing analyses van IMRT te vinden.

Vijf publicaties werden uiteindelijk geselecteerd voor verdere analyse. Drie publicaties betreffen gezondheidseconomische evaluaties, waaronder een kosten-minimalisatie-analyse en twee kosten-utiliteitsanalyses. De kwaliteit van deze drie studies werd als laag beoordeeld. Een vierde studie betreft een beschrijvende kostenvergelijking van diverse radiotherapeutische technieken. De vijfde geselecteerd publicatie is een costing studie van IMRT.

De drie beschouwde gezondheidseconomische evaluaties en de beschrijvende kostenvergelijking hebben betrekking op de klinische context in de Verenigde Staten van Amerika en verwijzen naar behandelprotocols die weinig relevant blijken vanuit een Belgische invalshoek. Daarenboven werd de kost van IMRT geraamd aan de hand van Medicare honoraria.

Beide kosten-utiliteitsanalyses besluiten dat IMRT kosten-effectief is in vergelijking met 3DCRT voor patiënten met prostaatkanker bij een drempelwaarde van 50 000$ per QALY. Deze resultaten werden echter afgeleid van klinische gegevens voor patiëntcasussen en afzonderlijke enquêtes over levenskwaliteit in beperkte en heterogene populaties.

De beschouwde costing studie benadert de kost van IMRT empirisch voor patiënten in Frankrijk met hoofd- en halskanker tussen 2003 en 2005. Een gemiddelde kost van 10 916€ werd berekend en vergeleken met de publieke terugbetaling van 6 987€. Twee belangrijke beperkingen doen afbreuk aan de relevantie van deze bevindingen. In de eerste plaats werden indirecte kosten, die goed zijn voor 45% van de geraamde totaalkost, afgeleid aan de hand van referentiewaarden die voor Franse ziekenhuizen in het algemeen van toepassing zijn. Ten tweede is de bestudeerde populatie beperkt tot patiënten met hoofd- en halskanker.

Geen duidelijk besluit kan gemaakt worden omtrent de kosten-effectiviteit van IMRT in vergelijking met alternatieve interventies, in het bijzonder met 3DCRT. Idealiter dienen kosten- en utiliteitswaarden verzameld te worden binnen het ruimere kader van een RCT. Een noodzakelijke beginvoorwaarde hierbij is dat verdere costing studies in ziekenhuizen, bij voorkeur activity based costing studies, voorafgaandelijk plaatsvinden.

ORGANISATORISCHE AANDACHTSPUNTEN

Onze analyse van de economische literatuur leverde achtentwintig publicaties op die betrekking hebben op de organisatorische aspecten van IMRT. Dit resultaat werd verder aangevuld met grijze literatuur. De doelstelling van deze zoektocht bestond erin aandachtspunten op te lijsten in verband met de introductie en toepassing van IMRT door Belgische radiotherapiediensten.

Allereerst werd vastgesteld dat de opstartkost voor specifieke uitrusting bij IMRT aanzienlijk is. Als men akte neemt van aanduidingen dat geschikte werkprocedures het gebruik van minstens twee operationele en gelijkaardige deeltjesversnellers vergen per behandelcentrum, vertaalt dat zich in een minimale opstartkost voor een behandelcentrum dat IMRT kan verstrekken, van 7 100 000€. De uitbouw van een enkele operationele 3DCRT eenheid naar een IMRT eenheid kan dan weer een bijkomende investering voor hard- en software vragen tot 750 000€, een toename van de oorspronkelijke kost voor hardware en software met 40%-50%. In het algemeen dient evenwel aangestipt te worden dat de gevonden kostenramingen sterk variëren.

Verder kan besloten worden dat de werktijd voor stralingsfysici zal toenemen met een factor van ongeveer 3 bij toepassing van IMRT. Het moet eveneens benadrukt worden dat de eigenlijke behandeltijd met IMRT sterk schommelt naargelang de IMRT techniek

en de behandelde tumor. Dit kan een invloed hebben op de algemene capaciteit van een radiotherapiedienst.

Tot slot bemerken we dat geen sluitende conclusie geldt wat betreft de dekking van reële kosten door de bijhorende publieke terugbetaling. Geen enkele activity based costing studie werd vooralsnog uitgevoerd voor IMRT. Daarenboven dienen leereffecten in detail geëvalueerd te worden om een gedegen lange termijn kostenbepaling te kunnen maken. Hoewel er aanwijzingen zijn dat de terugbetaling voor uitwendige bestralingstherapie danig varieert binnen Europa, dienen gedetailleerde analyses die alle mogelijke aspecten rond terugbetaling omvatten, hierrond uitsluitsel te bieden. Een laatste vaststelling is, dat Amerikaanse gegevens lijken te suggereren dat de vergoeding voor IMRT in het Amerikaanse Medicare programma gunstig uitvalt in vergelijking met de schaarse en onvolledige cijfers voor Europa.

BUDGET IMPACT SCENARIO'S

Aan de hand van epidemiologische gegevens voor Vlaanderen in 2001, internationale gegevens over het percentage externe bestralingstherapieën en de geldende regelgeving rond de publieke terugbetaling van radiotherapie in België, hebben we mogelijke impact van IMRT op het publieke budget voor gezondheidszorg geraamd. Hiervoor werden budgetsimulaties voor de periode tussen 2002 en 2006 uitgevoerd. De fundamentele hypothese die hierbij gehanteerd werd, is dat een met IMRT behandelde patiënt in afwezigheid van IMRT als therapeutische optie met 3DCRT (prostaatkanker, hoofd- en halskanker) of conventionele radiotherapie (borstkanker) behandeld zou zijn.

De budget impact voor 2003 werd geraamd op ongeveer 5 000 000€ indien dat jaar alle extern bestraalde patiënten met prostaat-, hoofd- of halskanker met IMRT behandeld werden (van dit bedrag ging 73,3% naar extra honoraria, 7,4% naar investeringskosten en 20,4% naar werkingskosten). Dit zou betekenen dat het totale budget voor externe bestralingstherapie toegenomen zou zijn met 5,4%. Daarenboven zou de uitbreiding van de huidige terugbetaling voor IMRT naar patiënten met borstkanker bijzonder kostenverhogend kunnen uitvallen met een toename van het totale budget in 2003 van ongeveer 17 000 000€. Dit komt neer op een geschatte stijging van het gehele budget voor uitwendige bestraling met 18,7%. Dit resultaat is gemodelleerd aan de hand van de aanname dat alle bestraalde patiënten met borstkanker klinisch in aanmerking zouden komen voor IMRT, wat zou betekenen dat 50% van alle uitwendig bestraalde patiënten met IMRT behandeld zouden worden. Experts schuiven echter eerder 40% als realistisch percentage naar voren. Bijgevolg dient de budget impact in het tweede scenario als maximaal ingeschat te worden.

Met opzet worden de budgettaire bevindingen voorgesteld als de uitkomst van een wijzigbaar model. Toekomstige aanvullingen van het model dienen allereerst een gedetailleerde analyse in te houden van de verdeling van bestraalde patiënten over de diverse radiotherapiediensten. Daarnaast is het aangewezen specifiek Belgische percentages voor het aantal stralingstherapieën te hanteren en kunnen netto budgettaire effecten geraamd worden als gevolg van therapeutische substitutie met alternatieve behandelwijzen die geen uitwendige uitstraling omvatten (chemotherapie, brachietherapie, etc.) .

Aanbevelingen

- **In het algemeen zijn meer lange termijn gegevens nodig van met IMRT behandelde patiënten, om een mogelijk overlevingsvoordeel te documenteren en het verhoogde risico op secundaire kankers in te schatten in vergelijking met standaard uitwendige radiotherapie. Zowel de gebruikers als de producenten van IMRT hardware en software dienen meer bewust gemaakt te worden van het risico op het ontstaan van secundaire kankers. Productverbeteringen in die zin dienen te worden gestimuleerd.**
- **Gezien de complexiteit van planning en gebruik van IMRT voor kanker van hoofd en hals, en gezien het domein nog volop in onderzoek is, wordt aanbevolen de uitvoering van deze behandeling te beperken tot centra die beschikken over de nodige expertise, bij voorkeur in centra waar onderzoek naar IMRT plaatsvindt. De IMRT expertise van een centrum kan geëvalueerd worden aan de hand van de procedures voor kwaliteitsborging, de opvolging van de outcome van de patiënten en de deelname aan clinical trials. Een aangepaste financiering van de complexe planning van IMRT voor kanker van hoofd en hals dient overwogen te worden.**
- **IMRT of (3D) conformele radiotherapie (3DCRT) is aanbevolen wil men in hoge dosis externe radiotherapie toepassen bij prostaatkanker.**
- **Het gebruik van IMRT kan leiden tot minder huidcomplicaties na radiotherapie voor borstkanker bij vrouwen met grote borsten. Lange termijn studies zijn noodzakelijk om het risico te kennen op het ontstaan van een tumor in de contralaterale borst na IMRT alvorens het routinematig gebruik ingevoerd kan worden. Specifieke onderzoeksfinanciering van IMRT in borstkanker kan aangewezen zijn.**
- **Door een meer frequent gebruik van beeldvorming voor IMRT verwacht men de werkzaamheid en veiligheid van IMRT te verhogen, vooral voor doelorganen die een zekere beweging vertonen in het lichaam, zoals het geval is bij prostaatkanker. De financiering van beeldvorming voor IMRT dient opnieuw te worden geëvalueerd in de toekomst.**

Scientific Summary

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ABBREVIATIONS

2DRT	Two-dimensional (conventional) radiotherapy / radiation therapy
3DCRT	Three-dimensional conformal radiotherapy / radiation therapy
ABC	Activity based costing
CPI	Consumer price Index
CRT	Conventional radiotherapy
CT	Computed tomography
FDA	Food and drug administration
IGRT	Image-guided radiotherapy
IMRT	Intensity-modulated radiotherapy
Gy	Gray
kv	kilovoltage
MLC	Multileaf collimator
MRI	Magnetic resonance imaging
MV	Megavoltage
NCCN	National comprehensive cancer network
NCRP	National council of radiation protection and measurements
NICE	National institute of clinical excellence
Sv	Sievert
OAR	Organ at risk
PET	Positron emission tomography
PSA	Prostate specific antigen
QOL	Quality of life
RCT	Randomized controlled trial
RT	Radiotherapy / Radiation therapy
RTOG	Radiation therapy oncology group
SEER	Surveillance epidemiology and end results
SPS	Stimulated parotid salivary
SWS	Stimulated whole salivary
TNM	Tumour node metastasis

1 AIMS OF THE STUDY

The present report will address the following research questions:

- 1. to review the literature in order to assess the clinical effectiveness of IMRT, including the safety and the quality of life of the treated patients,
- 2. to review the literature in order to evaluate the cost-effectiveness of the therapy, compared with the 3DCRT technology without modulated intensity,
- 3. to analyze the costs of IMRT in Belgium and to estimate the budget impact for the Belgian Health insurance with model-based simulations.

Based on the results obtained to these research questions recommendations on IMRT use, financing, organisation and quality assurance may be formulated.

2 INTRODUCTION TO IMRT

2.1 THE TECHNOLOGY

Radiation therapy (RT) is the specific use of high-energy radiation from X-rays, gamma rays, neutrons and other sources to treat cancer. Radiation may be delivered from an external source or from a source that is placed close to the tumour inside the body. Three-dimensional conformal radiation therapy (3DCRT) is an advanced form of external beam radiation therapy that uses computers to create a three-dimensional (3D) picture of the tumour so that multiple radiation beams can be shaped exactly (i.e. conform) to the contour of the treatment area.

Intensity-modulated radiation therapy (IMRT) evolved out of the inability of 3DCRT to irradiate tumours that are concave, surrounded by normal tissue, or in very close proximity to sensitive normal tissue, without causing excessive radiation exposure of adjacent normal tissue. IMRT utilizes computer-controlled X-ray accelerators to deliver precise radiation doses to a malignant tumour. The radiation dose is designed to conform to the three-dimensional (3D) shape of the tumour by modulating-or controlling-the intensity of the sub-components of each radiation beam.[1] Treatment planning is achieved in most systems using inverse planning software algorithms. Sometimes subtly modified forward-planning methods can be used.[1] Using IMRT a higher radiation dose can be focused to the tumour while minimizing radiation exposure to surrounding normal tissues. IMRT also has the potential to reduce treatment toxicity, even when doses are not increased. In particular, IMRT provides the ability to spare organs at risk that are surrounded by targets with concave surfaces. Traditional external radiation therapy techniques, including 3DCRT with uniform radiation intensity and/or with simple beam fluency modifying devices like wedges, do not provide a method for sparing critical structures that push into and are partially or fully surrounded by a target or combination of targets.

The first clinical IMRT with modern technology for delivery was in March 1994, or nearly 100 years after the discovery of the X-ray in November 1895.[1] Typically, patients are scheduled for IMRT sessions five days during a number of weeks. Treatment sessions usually take between 15 and 30 minutes. The IMRT process requires a coordinated team effort between the radiation oncologist, the medical physicist, the treatment planner, and the radiation therapist.

2.2 IMPLEMENTING IMRT

Implementing IMRT in clinical practice requires several steps, both for treatment planning and for treatment delivery.[2, 3]

1. First, careful delineation using computed tomography (CT) and other images by the clinician of both target tissues and tissues at risk is required to lower doses to volumes of nontarget tissue while achieving prescription doses to the target. Delineation for IMRT inverse planning is less forgiving for the clinician compared with conventional external radiotherapy.
2. Second, a customized (optimized) treatment plan is developed that respects the target dose requirements, as well as the dose constraints of the surrounding dose-limiting structures. 3D computed tomography images of the patient in conjunction with computerized dose calculations are used for this purpose.
3. Third, treatment delivery involves the field-by-field, day-by-day reproduction of the treatment plan within the patient. Patient positioning and localisation of the target organ become more important than before.

Throughout the process, careful quality assurance is necessary to achieve the preferred dose distribution, accuracy, and reproducibility that distinguish such precision treatment. For verification purposes the patient's plan can be applied to a CT study of a

phantom, in which dose measurements can be made using ion chambers and/or film. Compared with conventional radiotherapy in vivo dosimetry for IMRT is more complex and still a challenge to perform.

The dose distribution within the target can be made more homogeneous using IMRT, but inhomogeneity will often be observed due to the overriding need to protect organs-at-risk and limitations of the planning systems. On the other hand inhomogeneity can be the aim as in ongoing IMRT research targeting an increased dose to specific tumour area's. In theory, IMRT also allows for a reduction in the margin for dose fall-off at the beam edges ("penumbra") by the use of compensating rinds of increased beam intensity.

2.3 DELIVERY TECHNIQUES

IMRT can be produced through numerous delivery methods.

1. Fixed gantry during irradiation, adding different sub-multileaf collimator (MLC) fields to each field (multiple static field or step-and-shoot MLC technique)
2. Fixed gantry, changing the dwell time for each MLC leaf during a treated field by moving the MLC leaves with the radiation on (dynamic MLC technique)
3. Moving gantry with the treatment beam on, using an arcing or tomotherapy (serial or spiral delivery) method with dynamic collimation.

In MLC-based IMRT the orientations of the multiple beams still have to be manually pre-selected, while in fully rotational approaches such as tomotherapy, individual beams do not exist, nor the possibility to select beam angles. In the future it is expected all radiation treatment delivery machines will be optimized to also deliver IMRT. Ongoing product enhancements by accelerator vendors (Varian, Elekta, TomoTherapy, Siemens) and treatment planning companies should lead to improvements in efficiency in planning and delivery, safety (less radiation leakage) and quality assurance.

The U.S. Food and Drug Administration (FDA) has approved a number of medical charged-particle radiation therapy system devices and radiation therapy treatment planning system devices. A few examples include: the TomoTherapy Hi•Art System® (TomoTherapy Inc., Madison, WI); the Peacock™ System (NOMOS Corp., Sewickley, PA); and SmartBeam™ IMRT (Varian Medical Systems, Inc. Palo Alto, CA).

An instrument which cannot be classified under IMRT but shows some similarities is the Cyberknife (Accuray, Sunnyvale, CA). This system is used for stereotactic radiosurgery of intracranial and extracranial tumours.

2.4 PRECAUTIONS

The process of IMRT implementation and delivery remains complex. It requires a much expanded emphasis on quality assurance procedures to guarantee its proper implementation. In the US and Europe, the evolution is towards more and more radiotherapy departments with limited physics and dosimetry support starting IMRT. The possibility that patient safety will be compromised is of great concern.[3] Training of physicists and dosimetrists is essential in this regard. Using inverse planning for IMRT will not guarantee an optimum treatment plan. It has been recommended to assess the difference between dose-volume histograms obtained after planning optimisation and the final calculation used for dose delivery which take into account the optimization of the apertures.[3] The issue is compounded by the multitude of combinations possible of inverse planning approaches and dose delivery methods, each requiring their own quality assurance procedures. Also error free data communication between systems requires attention, since information transfer is a common source of treatment error. It has been advised to start with a single technique in routine practice.[3]

2.5 IMAGING AND IMAGE-GUIDED RADIOTHERAPY

The high degree of dose conformality achievable with IMRT creates some challenges. It creates a challenge for the radiotherapist to accurately delineate the target and the organs at risk. It is also a challenge to reduce the variation between clinicians. Another challenge is the accuracy and precision with which the target volume and critical structures can be localized day to day, especially in indications other than head and neck. Image guided corrections for day to day set up errors or for internal organ motion have become important issues. Intrafraction organ motion has become the limiting factor for margin reduction around the clinical target volume. Image-guided radiotherapy (IGRT) is therefore a growth area. Recent reviews on the subject have been published.[4, 5]

In some cases, a treatment preparation session may be necessary to mold a special device that will help the patient maintain an exact treatment position. Prior to treatment, the patient's skin may be marked or tattooed with colored ink to help align and target the equipment. Radio-opaque markers may also be use, e.g. gold marker seeds in case of prostate treatment.

In IMRT images are acquired for three reasons.

1. Treatment planning i.e. delineation of target and normal structures, typically created once prior to treatment. IMRT planning may include positron emission tomography (PET)[6] and magnetic resonance imaging (MRI). Typically, IMRT sessions begin about a week after simulation. It is expected this model will become outdated and be replaced by image guided IMRT.

2. Image guidance and/or treatment verification, for setup verification and correction. Some treatment machines already have a scanner integrated. The frequency of imaging (CT or other) will vary based on characteristics of the tumour dose gradient and the patient, e.g. daily (often on-line) imaging can be required for a pelvic irradiation of an obese patient.

3. Follow-up of treatment response, CT, MRI and PET scans are often used for this purpose.

Exchange of image data is important. Electronic standards exist and are used, e.g. DICOM and DICOM-RT.

Key points

- **Intensity-modulated radiation therapy (IMRT) involves the delivery of optimized, non-uniform irradiation beam intensities, thereby improving the accuracy of tumour targeting.**
- **Expertise in physics and dosimetry as well as complex quality assurance measures are needed when IMRT is started.**

3 CLINICAL DATA

3.1 CLINICAL EFFECTIVENESS

3.1.1 Literature search

3.1.1.1 Methods

A literature search was conducted in January and February 2007 using the following databases: Medline (Pubmed), Embase, Cochrane. In addition, manufacturers and distributors of IMRT systems were requested to provide any clinical evaluations of their equipment.

Inclusion criteria

Type of publication: systematic review, meta-analysis, controlled clinical trial. Only patient efficacy or safety studies comparing IMRT with another type of external radiotherapy for the same target were included. Comparative studies without use of randomisation, e.g. comparisons with a historical control group, are included with the limitation that the resulting evidence can be considered supportive at most. Clinical reports without control group, dosimetric studies, planning studies, animal studies or studies concerning only technical aspects or phantoms were excluded. The type of pathology studied did not constitute an exclusion criterion.

Language: reports in English.

Method: full articles were searched only if the title or abstract suggested the report could be included.

Medline/Pubmed search

"Radiotherapy, Intensity-Modulated"[MeSH] has been included as MESH term only recently (2006), so the term "Radiotherapy, Conformal", introduced in 1999, was used.

This MESH term was used in Pubmed Clinical Queries. "Therapy" was used as Clinical Study Category and the scope was set to broad and sensitive. Only reports published in 2004 and later were considered, as a systematic search had been conducted up to March 2004 and reported in a HTA report by the Gallician Agency for Health Technology Assessment.[7] The 4 study reports retained in this HTA report have been added to our search results.

Pubmed search: (Radiotherapy, Conformal[MeSH]) AND ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading])

Limits: added to PubMed in the last 3 years. The PubMed search was done on January 4, 2007 and repeated February 8, 2007 for the 2006 period.

Titles and abstracts were scanned and full articles retrieved where clinical outcome measures were used, at least one treatment arm used IMRT and was compared with a control group.

Embase search (13 februari 2007): ('intensity modulated radiation therapy'/exp OR 'intensity modulated radiation therapy' OR 'intensity modulated radiotherapy' OR 'imrt') AND (('clinical trial'/exp OR 'clinical trial') OR (random*) OR ('clinical trial':it)) AND [2004-2007]/py

3.1.1.2 Results of search

218 hits were found for articles added to Pubmed during 2004.

267 hits were found for articles added to Pubmed during 2005.

214 hits were found for articles added to Pubmed starting January 1, 2006 or later.

Embase search generated 300 hits.

Two study reports [8, 9] were identified using this Embase search, which had been missed using the PubMed search criteria.

Using hand searching an abstract of a randomized controlled trial in breast cancer [10] was included for which no full paper was available at the time of writing of this report. Also a report from 2002 on the use of IMRT versus 3DCRT in medulloblastoma in children was identified and included.

Overall, we identified 19 comparative trial reports. The reports concerned head and neck cancer (n=9, including 1 RCT), prostate cancer (n=6, no RCT), breast cancer (n=3, including 2 RCT's) and medulloblastoma (n=1, no RCT).

3.1.2 IMRT Indications and Impact on Clinical Outcomes

IMRT is being rapidly adopted despite an incomplete understanding of its strengths and weaknesses. Reasons for the early adoption in the US are the culture of implementation of new technology "because it is there" and the early reimbursement of IMRT.[1] In Germany, uptake has been slower and the total number of IMRT treatments has been estimated at 5 000 in 2006.[11] The strongest evidence for clinical utility should come from randomized controlled trials, but such trials are hard to set up.[1] This may be the case for skull base tumours where conventional radiotherapy results are unsatisfactory.[11] In centres where many patients were referred for treatment long term patient follow-up may be a challenge in clinical routine, as patients may not always return for long term follow-up visits.

IMRT can be used to escalate the tumour volume to a higher dose while maintaining normal tissue toxicity at the same level. Alternatively, IMRT can be used to deliver conventional doses to the tumour bed, resulting in lower dose to normal tissues, with hopes of reducing toxicity. IMRT is currently used mainly for prostate cancer and head and neck cancer. Breast cancer, non small cell lung cancer, intracranial tumours, mesothelioma, pancreatic cancer, and gynaecologic cancers are other possible indications. IMRT may also be beneficial for treating specific paediatric malignancies, but specific safety concerns exist. [12]

In a two-part review article, Guerrero Urbano et al.[13, 14] noted that the majority of reports concern patients treated in the context of clinical trials, and for most tumour types longer term follow up of treated patients will be required to confirm the clinical benefits of IMRT. Most studies have been small Phase I or II trials where there has been no true comparison of IMRT with the conventional radiotherapy technique. The authors concluded that further data from randomized trials are required to confirm the anticipated benefits of IMRT in patients. To this point, only a limited number of trials comparing IMRT with conventional techniques have been reported, including a few reports of prospective randomized clinical studies (tables IA, IB, IC). Many clinical studies have verified the superior dose distributions, however, and have reported on small numbers of patients. Many authors have completed treatment planning comparisons between IMRT plans and conventional treatment plans. Dosimetric studies in radiotherapy can predict efficacy and toxicity. The dosimetric advantages of IMRT are considered by some as a clinical advantage. In the present assessment however, we have restricted the search to studies with clinical endpoints.

Table IA. Head and Neck Cancer

Study and Institution	Period and Design	Patients and Primary Tumour	Results	Comment
Chao et al, 2001.[15] Mallinckrodt Institute, Washington University, St. Louis, US.	1970 to 1999. Single centre retrospective comparison of conventional RT (CRT) and IMRT.	430 (preop CRT 109, postop CRT 142, definitive CRT 153, postop IMRT 14, definitive IMRT 12) patients with oropharyngeal carcinoma	Less xerostomia at 6 months or later after IMRT. Tendency for better loco-regional control and disease-free survival at 2 years after IMRT.	
Duthoy et al, 2005.[16] Ghent University Hospital, Belgium	Single centre retrospective comparison of IMRT 1998 to 2003 (mainly 70 Gy) vs conventional RT 1985 to 1998 (median 65 Gy) in adenocarcinoma of ethmoid sinuses.	58 (IMRT 28, conventional RT 30) patients with adenocarcinoma of ethmoid sinus.	Survival rates similar at 2 years. Low rates of acute and chronic ocular toxicity, and no IMRT induced blindness.	Patients treated with palliative intention in pre-IMRT period, would receive high dose IMRT.
Jabbari et al, 2005.[17] University of Michigan, Ann Arbor, US	1997 to 2002. Prospective study. Patients treated at affiliated clinics using standard CRT were matched with multiple IMRT patients treated locally and compared using xerostomia and head and neck HNQOL questionnaires.	112 (IMRT 96, CRT 16) patients with head and neck cancer	66 patients with results at 12 months were analysed (IMRT 56, CRT 10). Trend for improvement in HNQOL and xerostomia in IMRT starting at 6 months (not in CRT).	Cases and controls may differ in other variables (comorbidity and cotreatment).
Braam et al, 2006.[18] University Medical Center, Utrecht, The Netherlands.	1996 to 2005. Single centre prospective non randomized comparison (IMRT alone vs CRT alone) of SPS flow rate.	56 (IMRT 30, CRT 26) patients with oropharyngeal cancer.	SPS flow rate of at least 25% (all parotid glands) At 6 weeks: IMRT 21/47 vs CRT 5/37 At 6 months: IMRT 17/39 vs CRT 6/32.	More postoperative radiotherapy in CRT Group.
Lee et al, 2006.[19] Memorial Sloan-Kettering, New York, US	September 1998 to June 2004, IMRT mainly since 2003. Single centre retrospective comparison IMRT vs delayed accelerated boost radiotherapy (CBRT) (both median 70 Gy)	112 (IMRT 41, CBRT 71) patients with stage III/IV oropharyngeal carcinoma treated with chemotherapy	At median 46 months CBRT and 31 months IMRT: similar survival outcome, but at 2 years less grade 2+ xerostomia and less dependency on percutaneous endoscopic	34/41 IMRT since 2003, vs 10/71 CBRT.

Study and Institution	Period and Design	Patients and Primary Tumour	Results	Comment
			gastrostomy after IMRT.	
Pow et al, 2006.[20] Queen Mary Hospital, Hong Kong.	June 2000 to July 2004. Single centre randomized controlled trial (IMRT alone vs CRT alone) to compare change in stimulated whole salivary (SWS) flow rate.	51 (IMRT 25, CRT 26) patients with stage 2 nasopharyngeal carcinoma (T2, N0/N1, M0)	For 45 patients at 12 months in remission, recovery of flow rate of at least 25%. SWS: IMRT 12/24 versus CRT 1/21. SPS: IMRT 20/24 versus CRT 2/21	At baseline less dry mouth as symptom in IMRT Group. Change in this symptom after treatment did not differ between groups (trend only). Dry mouth and SPS (SWS?) significantly correlated.
Fang et al, 2006.[21] Chang Gung University College of Medicine, Taiwan	January 1998 to December 2003; IMRT and 3DCRT started March 2002; other techniques before. Retrospective comparison, mainly conformal versus not conformal.	Data were analysed for 237 patients with nasopharyngeal carcinoma with cancer free survival of at least 2-3 years and completed questionnaire, for 85 out of 129 patients (IMRT 52, 3DCRT 33) versus 152 out of 261 patients (2DCRT + 3DCRT boost 91, 2DCRT 61)	Radiation technique (conformal vs not) was associated with a good global QOL and less high level xerostomia.	Prospective QOL collection started July 2000, retrospective for others. No difference IMRT vs 3DCRT reported.
Münter et al, 2007.[22] University of Heidelberg, Germany	Single centre retrospective comparison of IMRT with CRT and CRT plus i.v. Amifostine for relative excretion rate based on scintigraphy (parotid gland only and combined with submandibular gland).	75 (IMRT 19, CRT 33, CRT+amifostine 23) patients with head and neck cancer.	Reduction in parotid salivary rate was higher 3 months after CRT than IMRT. Amifostine protected only if dose < 40,6 Gy.	Only parotid gland was spared using IMRT.
Graff et al, 2007.[23] Six centres in France.	Januari 2001 to Januari 2005, Cross-sectional QOL (EORTC QLQ-C30 and QLQ-H&N35) comparison in matched patients treated at 6 centres with bilateral (>=45Gy) IMRT vs CRT.	67 IMRT and 67 matched CRT patients (questionnaires had been mailed to 235 patients) with head and neck cancer, minimum one year of follow-up	IMRT scored better for dry mouth and sticky saliva.	Study not corrected for a possible treatment centre effect.

CRT= conventional radiotherapy; SWS= stimulated whole salivary; SPS=stimulated parotid salivary; QOL=Quality of Life

Table IB. Prostate Cancer

Study and Institution	Period and Design	Patients and Primary Tumour	Results	Comment
Zelefsky et al, 2000.[24] Memorial Sloan Kettering, New York, US.	September 1992 to February 1998; IMRT started April 1997? Single centre retrospective comparison of 81 Gy treatment using IMRT with 3DCRT	232 (IMRT 171, 3DCRT 61) clinical stage T1c-T3 prostate cancer patients.	Less acute grade 1 and 2 rectal toxicity after IMRT. Also less late grade 2 (and 3) rectal bleeding: at 2 years 2% IMRT vs 10% 3DCRT; at 3 years: 17% 3DCRT	T1c + T2a patients: 141/171 IMRT vs 9/61 3DCRT. Planned target volume was similar between groups.
Zelefsky et al, 2001.[25] Memorial Sloan Kettering, New York, US.	October 1988 to December 1998. Single centre retrospective comparison of 81 Gy treatment using IMRT with 3DCRT (also lower doses studied with 3DCRT)	250 (IMRT 189, 3DCRT 61) clinical stage T1c-T3 prostate cancer patients	3y actuarial rate of grade 2 rectal toxicity: 14% after 3DCRT vs 2% after IMRT (similar rate as 3DRCT at 64.6-70.2Gy); no change in urinary toxicity.	PSA relapse was lower after 3DCRT dose escalation. No IMRT vs 3DRCT comparison for PSA relapse. Patients overlap with Zelefsky et al. [24]. Author reported 4.5% grade 2 rectal toxicity in 772 IMRT patients.[26]
Shu et al, 2001.[27] UCSF San Francisco, US	June 1992 to August 1998. Single centre retrospective comparison of at least Dmax of 82 Gy treatment using IMRT with 3DCRT.	44 (IMRT 18, 3DCRT 26) patients with prostate cancer.	More acute grade 2+ gastrointestinal toxicity after IMRT (21% vs 3%) mainly because of more whole pelvis radiation in IMRT group. No differences in late morbidity after median 18.7 months for IMRT and 30.1 months for 3DCRT.	Gleason score < 7: 4/18 IMRT vs 17/26 3DCRT. Whole pelvis radiation: 13/18 IMRT vs 1/26 3DCRT.
Kupellian et al, 2002.[28] Cleveland Clinic, Cleveland, US	January 1998 to December 1999; IMRT started October 1998. Single centre retrospective comparison of short course IMRT 70 Gy in 28 fractions and 3DCRT 78 Gy in 39 fractions	282 (IMRT 166, 3DCRT 116) patients with localized prostate cancer	Follow-up median IMRT 21 months, 3DCRT 32 months. PSA relapse free survival rates similar (trend towards better outcome for IMRT in multivariate analysis). Less acute rectal toxicity after IMRT. Late rectal toxicity similar.	3DCRT patients had more advanced T stages and Gleason score. Second report on (IMRT only) outcome after median 66 months.[29]
Ashman et al, 2005.[30] Memorial Sloan Kettering, New York, US.	December 1996 to January 2004. Single centre retrospective comparison of rectal toxicity after whole pelvis radiation, IMRT vs 3DCRT	27 (13 IMRT, 14 3DCRT) patients with prostate cancer	Acute (< 3 months) RTOG grade 2 gastrointestinal toxicity: IMRT 1/13, 3DCRT: 8/14.	Confounding: GI toxicity mainly in patients who also received chemotherapy.
Sanguineti et al, 2006.[9] Galveston, US and Genoa, Italy.	Retrospective comparison of late (>90 days) grade 2+ rectal toxicity after whole pelvis IMRT (April 2002 to August 2004 in Galveston) vs prostate only 3DCRT (1995 to 1999 in Genoa) (prostate dose 76 Gy for both regimens).	133 (45 IMRT, 68 CRT) patients with prostate cancer.	Estimated cumulative incidence late rectal toxicity grade 2+: 6% for IMRT whole pelvis and 21% for 3DCRT prostate only, confirmed in multivariate analysis.	IMRT site (Galveston, US) was different from CRT site (Genoa, Italy).

Table IC. Breast Cancer

Study and Institution	Period and Design	Patients and Primary Tumour	Results	Comment
Pignol et al, 2006.[10] Sunnybrook, Toronto, Canada	RCT in 2 centres, comparing acute skin toxicity after IMRT vs standard irradiation using wedge compensation (up to 50 Gy).	358 (331 analysed) patients undergoing adjuvant radiotherapy of breast cancer.	Less severe moist desquamation after IMRT.	Abstract only.
Freedman et al, 2006.[8] Fox Chase Cancer Center, Philadelphia, US	Single centre retrospective comparison of IMRT (January 2003 to January 2004) with conventional RT (November 1985 to August 2000). Patients were matched and compared for acute (<6 weeks) skin toxicity.	151 (IMRT 73, CRT 58) patients undergoing adjuvant radiotherapy of breast cancer.	Less acute desquamation after IMRT (21%) compared with matched controls (38%). Use of IMRT and breast size were predictors for moist desquamation.	Chemotherapy before IMRT, but during or after CRT.
Donovan et al, 2007.[31] Royal Marsden, Sutton and Chelsea, UK	1997 to 2000. RCT in 2 centres, comparing breast appearance (photographs) and QOL after IMRT vs standard 2D radiotherapy.	306 (IMRT 150, 2D-RT 156) patients randomized with early breast cancer (T1-3a N0-1 M0). 240 analysed.	Change in breast appearance up to 5 y in 47/118 (40%) IMRT vs 71/122 (58%) after 2D-RT. Less palpable indurations after IMRT. No differences in QOL.	IMRT was delivered using physical compensators or step-and-shoot MLC.

3.1.2.1 Head and Neck cancer and skull base tumours

Most head and neck cancers occur after age 50 and begin in the squamous cells that line the mucosal surfaces in the head and neck (squamous cell cancer of the head and neck). This category includes tumours of the paranasal sinuses, the oral cavity, the nasopharynx, the oropharynx, hypopharynx and larynx. Some head and neck cancers begin in cells of the salivary glands or the thyroid.

The three main types of treatment for managing head and neck cancer are radiation therapy, surgery and chemotherapy. About one third of the patients have localized disease without lymph node involvement or distant metastases. For those patients the primary treatments with curative intent are radiation therapy or surgery. The choice will depend on the tumour location but also on the institutional expertise. Radiotherapy is often preferred for laryngeal cancer to preserve voice function. Patients who have more extensive cancers are often treated with a combination of surgery and radiation therapy or with radiation therapy combined with chemotherapy.

Head and neck cancer radiation treatment is reportedly not being performed optimally by many radiation oncologists.[32] As IMRT is more difficult to plan and deliver, it has been suggested to restrict such IMRT treatments to large volume centres with the necessary expertise.[32] Also the NCCN (National comprehensive cancer network) for radiation treatment of head and neck cancer state consider IMRT still an area of active investigation. Standards for target definition, dose specification, fractionation (with and without concurrent chemotherapy) and normal tissue constraints are expected to be developed further within the next few years. Initial experience of FDG-PET/CT guided IMRT of head and neck cancer has also been published.[6]

Long term complications of radiotherapy of head and neck cancers include xerostomia, loss of taste, decreased tongue mobility, second malignancies, dysphagia, dental decay, and neck fibrosis. Radiation-induced xerostomia is a frequent and usually permanent side effect.[33] Parotid salivary flow rates return to normal when the mean dose is below 25 Gy, but not at higher dose levels.[34] Head-and-neck cancer represents an attractive site for IMRT. Organ motion is practically absent, and only the setup uncertainties need to be addressed. Tight dose gradients around the targets, limiting the doses to the noninvolved tissue, offer the potential for a therapeutic gain. Among the organs at risk the benefit of IMRT has focussed mainly on the sparing of the salivary glands, and the optic nerves.

Our literature search identified 9 publications where IMRT treated patients are studied with a control group (table IA). One publication did not report on the comparison between IMRT and 3DCRT treated patients in the study.[21] Four of the studies published on IMRT and 3DCRT in head and neck tumours are single institution comparisons with a historical control group.[15, 16, 19, 22] Such comparisons try to isolate the absolute benefit from IMRT. Care must be taken when interpreting such reports as IMRT may not emerge as an independent prognostic factor and e.g. the impact of IMRT in oropharynx cancer may get overstated in non-randomized single institution series.[35] Also three non-randomized studies only provide weak quality evidence.[17, 18, 23] A single centre randomized trial was conducted in Hong-Kong demonstrating in 48 patients a more rapid recovery of salivary flow rate after IMRT compared with 3DCRT.[20] In conclusion, there is moderate quality evidence for a more rapid recovery of xerostomia after IMRT and one report showing less ocular toxicity after IMRT. There are no robust data comparing IMRT with 3DCRT with regard to relapse or survival. A phase III trial comparing IMRT plus cisplatin versus conventional radiotherapy plus cisplatin is ongoing in France (study NCT00158678 at www.clinicaltrials.gov).

Tumours of the skull base can often be treated only with IMRT and require referral to a reference centre.[11]

In conclusion, the planning of IMRT for head and neck cancer is very complex and is best conducted in centres which have the necessary expertise. Well-performed IMRT can improve quality of life (e.g. less xerostomy complications) in head and neck cancer patients.

3.1.2.2 Prostate cancer

According to autopsy studies, about half of the men aged 60 have localised prostate cancer irrespective of the cause of death. Most of these localised prostate cancers are slowly progressive and will not lead to clinically significant disease or potential years of life lost.

Most prostate tumours are adenocarcinoma's. The Gleason score, based on low-power architectural findings, provides some prognostic information. Staging is performed using the TNM (tumour, node, metastasis) classification. PSA (prostate specific antigen) is a prognostic marker as well as a marker for treatment outcome. It is however not a perfect surrogate for clinical outcome.[36, 37]

Treatment for prostate cancer may involve watchful waiting, surgery, radiation therapy, or hormonal therapy. Some men receive a combination of therapies. The choice for a curative treatment will depend on the patient life expectancy.[37] The standard curative treatments for cancer are radical prostatectomy and radiotherapy (external beam or internal brachytherapy). No option has proven its superiority over the other. However, compared with I-125 seed brachytherapy IMRT has been suggested to provide at least as good PSA outcomes in low risk prostate cancer, while being associated with less long term genito-urinary grade 2+ RTOG toxicity.[38]

There is fairly strong evidence that patients with localised, intermediate risk, and high risk (pre-treatment PSA >= 10 and/or Gleason score >= 7 and/or T2) disease, i.e. patients normally not suited for surgery, benefit from higher than conventional total radiation dose. No overall survival benefit has been shown.[39, 40]. High risk patients may benefit from additional therapy, such as androgen deprivation.[40]

Treatment-related mortality is very low (0.1 to 0.2% for surgery, <1% for radiotherapy). Erectile dysfunction, urinary incontinence and bowel dysfunction are well-known and relatively common negative effects of surgery or radiotherapy. It is difficult to obtain an exact estimation of these effects, because they are surgeon-dependent and the definition of negative effects varies between the studies.[37]

The National Institute of Clinical Excellence (NICE) has recommended in 2002 conformal radiotherapy as the new technique standard for prostate external-beam irradiation.[41] According to recent practice guidelines for prostate cancer radiation therapy by the National Comprehensive Cancer Network (NCCN) [42] 3DCRT or IMRT techniques should be employed over conventional techniques.

IMRT can produce better sculpturing of the high-dose region to concave-shaped target volumes, such as the coverage of the seminal vesicles. IMRT plans can provide a steep high to low-dose gradient at the edge of the target volume for improved avoidance of adjacent normal structures, such as the rectum, bowel and bladder. For this reason IMRT was used first for prostate cancer treatment in many centres.[11] Six reports of comparative studies[24, 27, 25, 28, 30, 9] were identified, but no randomized study (table IB). One centre published two reports with overlapping patient populations.[24, 25] Rectal toxicity was reportedly lower after IMRT, also at high doses. Higher-dose escalation may be achieved more safely using IMRT. De Meerleer et al[43] compared retrospectively IMRT 76 Gy (n=82) with 74 Gy (n=51) (maximum rectum dose 74 Gy and 72 Gy, respectively). PSA relapse at 3 years was higher in 74 Gy patients but this group contained more high risk patients and received less androgen deprivation. The lower GI toxicity seen after 76 Gy was attributed to an improved treatment planning. In Germany IMRT is the recommended technique if the planned dose is more than 70 Gy.[11]

Also irradiation of pelvic nodes (U-shaped pelvic nodal target volume) while reducing the dose given to the bowel can now be studied using IMRT in intermediate- to high-risk prostate cancer patients. In the report by Shu et al[27] whole pelvic 3DCRT or IMRT was associated with a higher incidence of GI toxicity compared with prostate only 3DCRT or IMRT. Ashman et al[30] reported whole pelvic radiation was associated with less rectal toxicity after IMRT compared with 3DCRT. Sanguineti et al[9] compared results at two institutions and showed more rectal sparing using IMRT, even covering also the pelvic nodes and seminal vesicles, compared with 3DCRT to the prostate only (prostate treated at 76 Gy in both regimens).

Hypofractionation (a larger dose per fraction, e.g. 3 Gy instead of 1.8 or 2 Gy, and less number of fractions) is also being investigated using IMRT in good prognosis prostate cancer patients.[40]

The mean interfraction displacement of the prostate gland has been reported to range between 3 and 7 mm.[40] Treatment margins are used to compensate for this uncertainty but excessive margins need to be avoided. Image guidance can reduce set-up variability and can be obtained using ultrasound, electronic portal imaging devices (e.g. using three gold marker seeds, as technique does not provide internal soft-tissue verification), a kv-cone-beam CT, or a MV-CT scanner as part of the tomotherapy machine (also allowing for transit dosimetry). In patients with hip replacement MV-CT produces less 'scatter' artefact compared with kv-cone beam.

In conclusion, IMRT or 3DCRT are recommended if high doses of external radiotherapy are delivered for prostate cancer. The challenge is to precisely target the prostate with or without the pelvic lymph nodes each session. The use of specific localisation techniques such as imaging are expected to improve the efficacy and safety of high dose external radiotherapy of the prostate.

3.1.2.3 Breast cancer

Post-operative radiotherapy in patients with breast cancer has been shown to improve locoregional disease-free survival and overall survival. Treatment to the whole breast with standard tangential fields produces rather inhomogeneous dose distributions due to the variations in thickness across the target volume, in particular in large breasted women. Based on the opinion of the external expert group such patients constitute about a quarter of all patients undergoing radiotherapy for breast cancer. Such dose inhomogeneities, may lead to increased late skin toxicity (poor cosmesis, fibrosis, pain) and increased cardiac and lung morbidity.[14]

A 2006 technology assessment report from Blue Cross Blue Shield concluded available data were insufficient to determine whether IMRT is superior to 3DCRT for improving health outcomes of patients with breast cancer.[44]

Two randomized trials (one abstract[10], one full paper[31]) and one retrospective comparison[8] of IMRT with conventional radiotherapy confirm that IMRT reduces the frequency of skin complications (table IC), which are more frequently seen in large breasted patients. However no improvement in overall quality of life could be demonstrated using standard techniques.[31]

The risk of tumour induction in the contralateral breast has often led to a restriction of the IMRT fields to two tangents.[45] Conventional radiotherapy plus physical wedges as a compensation technique resulted in 2.4 to 3.3 times more total body exposure compared with IMRT, because the physical wedges scattered a lot of the radiation.[46]

IMRT is also being developed to treat the whole breast and thoracic wall with or without irradiation of surrounding lymph node areas, including the internal mammary nodes. When multiple field IMRT is used to also treat the chest wall and the nodal areas, a higher mean dose to the contralateral lung (12 Gy) and breast (6 Gy) are delivered compared with the standard technique. This limits the use of IMRT in this indication.[45]

In conclusion, use of IMRT may reduce skin complications in breast cancer external radiotherapy. Long term studies are required to assess the risk of induction of a secondary tumour in the contralateral breast after IMRT.

3.1.2.4 Other indications

Ototoxicity is common after cisplatin chemotherapy and radiation therapy for medulloblastoma. In a retrospective study of 26 children treated for medulloblastoma at the Baylor College of Medecine, Houston, the mean dose delivered to the auditory apparatus was 36.7 Gy for 15 patients treated using IMRT and 54.2 Gy for 11 children treated using 3DCRT. 64% (7 out of 11) of the 3DCRT treated patients developed grade 3 to 4 hearing loss, compared to only 13% (2 out of 15) in the IMRT group.[47] This retrospective study published in 2002 is limited by its small sample size and requires confirmation.

3.2 PATIENT AND SAFETY ISSUES

3.2.1 Vigilance

As mentioned above the administration of radiotherapy, and even more IMRT, requires of a number of quality assurance steps in order to avoid errors, which may sometimes be fatal. Doses delivered may not be targeted correctly or may be too high or too low. Because immediate side effects are missing, doses which are too low may remain unnoticed for longer period and affect more patients. The International Atomic Energy Agency has produced a number of accident reports covering also adverse events associated with radiotherapy (http://www.iaea.org). A number of serious adverse events associated with radiotherapy in France were recently reviewed.[48] Most of the events were the result of the administration by error of a dose which was too high and showed either as acute or chronic (mostly irreversible) complications. The error often occurred because of miscommunication between operators, e.g. in one case in Lyon in 2004, a too large cerebral field was irradiated with fatal outcome. Another type of error, as occurred in Épinal in May 2004 to May 2005, was linked to the dosimetric instrument and software. A major issue with such more systematic errors is that they may get repeated patient after patient. Radiotherapy centres in France have to report immediately any events to the authorities. Patients and caregivers have however been informed late when such adverse events occurred. The article calls for more transparency from the side of the authorities in the communication of such radiotherapy errors. More recently, in 2006, a 16 year old girl died after having received a number of overdoses during treatment for a brain tumour in Glasgow. According to the investigation the error had occurred because one of the treatment planners was not aware of all features of the new version of the treatment planning software which had been installed. (http://rpop.iaea.org/RPoP/RPoP/Content/Documents/Whitepapers/27_10_06_lisa.pdf)

3.2.2 Secondary Malignancies

The induction of fatal secondary malignancies is considered the greatest risk associated with treatment radiation and justifies efforts of long term patient follow up. Secondary malignancies are expected mainly in patients surviving at least 5 years, because of the latency period of tumours. The theoretical risk of secondary cancer after radiotherapy is based on measured X-ray dose and published risk data. Risk coefficients have been compiled by the National Council of Radiation Protection and Measurements (NCRP report 116, 1993), based primarily on data from Japanese atomic bomb survivors. In addition, tumours which can be treated either using surgery or radiotherapy allow for a comparison of this risk. By 10 years after prostate cancer treatment with conventional radiotherapy or surgery (Surveillance epidemiology and end results, SEER program), 1973-1993, the incidence of a radiotherapy-induced malignancy is about 1.5% based on epidemiological data. The principal sites are rectum, bladder, colon and lung.[49] Results are to be interpreted with caution as e.g. heavy smokers with prostate cancer may get referred preferably to radiotherapy instead of surgery. A report by Dorr[50] describes 85 patients re-admitted with secondary cancers among 31 000 patients treated using conventional external radiotherapy between 1969 and 1989. The majority of second cancers were within 5 cm from the radiation portal edge, corresponding to regions which received less than 6 Gy.

Three different components of peripheral dose of radiation treatment have been described.[51]

1. linear accelerator head leakage (limited to 0.1% of the dose at the isocentre) and a greater leakage from the multileaf collimator (MLC) (about 1 to 3%) which affects the entire body equally and is proportional to monitor units (beam-on time). For the Hi-Art II TomoTherapy machine patient leakage was estimated at 1% of the prescription dose.[52] Leakage radiation in the patient area was almost entirely due to leakage through closed MLC leaves. Leakage dose was higher in case of a shorter duration treatment with a wider field width.
2. internal scatter, which primarily affects tissues several centimetres from the beam edge and is directly proportional to field size, and
3. entrance and exit extra-target dose wherein more beams will expose more tissues to lower doses in the plane of the beams (IMRT is often obtained with 5 to 7 beams).

A report comparing a slice-by-slice arc rotation technique for IMRT with a conventional technique (both 70 Gy with a 6-MV photon beam) estimated an increase in the whole-body equivalent dose from 242 mSv to 1969 mSv. This was estimated to correspond to an eightfold increased risk of secondary malignancy.[53] The amount of secondary radiation is a linear function of the amount of beam-on time. Depending on the treatment energy, the step-and-shoot IMRT treatments require 3.5 to 4.9 times as many monitor units as the conventional radiotherapy.[54] Three dimensional conformal radiation therapy (3DCRT) for prostate cancer is most commonly delivered with high-energy photons, typically in the range of 10-21 MV. With the advent of IMRT, an increase in the number of monitor units relative to 3DCRT has lead to a concern about secondary malignancies. This risk becomes more relevant at higher photon energies where there is a greater neutron contribution. Subsequently, the majority of IMRT prostate treatments are being delivered with 6-10 MV photons where neutron production is negligible. In a population of all ages, the maximum risk of fatal secondary malignancy after conventional radiation therapy varied from 1.7% for conventional radiation, 2.1% for IMRT using 10-MV X-rays, to 5.1% for IMRT using 18-MV X-rays.[54] When used for a population of prostate patients these estimates constitute a conservative maximal risk, when used in a paediatric population the estimates will be higher.

Hall[49] concluded that IMRT may double the incidence of solid cancers in long-term survivors because of a combination of the increase in monitor units and the changed dose distribution. In addition, some machines leak a little more than others. In prostate cancer patients an increase of the 10 year secondary cancer incidence from 1.5% to 3% may be acceptable if it is balanced by a substantial improvement in local tumour control and reduction in acute toxicity. The problem can further be mitigated by the manufacturers. They can reduce both leakage from the treatment head as well as leakage through the MLC by implementing some steps as suggested by Hall.[49] Also manufacturers of inverse planning software should be stimulated to improve their products in an effort to further reduce the risk for secondary malignancies.[11] Schneider et al[55] have argued that the relative risk increase is not so high when also secondary tumours induced by the primary dose field are accounted for. For prostate radiotherapy using a 6-MV IMRT plan the risk was estimated to be 15% higher than after a conventional 15-MV four-field plan. In case of tomotherapy the user has three options if leakage radiation is higher than the desired value: limit the number of sweeps of the gantry, using a larger tomotherapy aperture, or using an IMRT dose delivery technique that is more monitor unit efficient.[3] Similar arguments can be made for the number of segments used for step-and-shoot dose delivery.[3]

In addition, introducing IMRT may require an upgrade of the room shielding, because of the higher number of monitoring units.

3.2.3 IMRT in Children

Radiotherapy in children represents a special case for three reasons.[49]

1. Children are more sensitive to radiation-induced cancer than adults by a factor of at least 10.[56]
2. Compared with adults radiation scattered from the treatment volume is more important in the small body of the child.
3. The question of genetic susceptibility arises because many childhood cancers involve a germline mutation.

In a study reported by Koshy[57] the dose was measured at extra-target organs (thyroid, breast, testis) in 23 MLC-based IMRT treated children and in 7 controls treated using conventional radiotherapy or 3DCRT. No significant difference was seen in the thyroid and breast doses (too few cases to compare testis dose). Most of the extra-target dose in IMRT was attributed to internal scatter and not to leakage radiation (increase fourfold, despite a 23.5 times increase in monitor units). Long term follow-up of IMRT treated children will allow a more accurate benefit-risk evaluation. When IMRT (DMLC "sliding window") was compared with 3DCRT in 5 cases using a paediatric-sized anthropomorphic phantom it was observed that the smaller effective field size resulted in less internal scatter to points at small distance.[51] With regard to more distant points IMRT was associated with an increased dose, resulting from an increased number of monitor units. Whereas the overall peripheral dose was reportedly similar, it was concluded that the tumour distance to critical structures might help in the selection of the most optimal technique (3DCRT or IMRT).

3.2.4 Imaging

In adults and children, concomitant CT scanning gives a small but significant contribution to the total dose to most organs and tissues outside the target volume, as indicated in the report of the Hoge Gezondheidsraad/Conseil supérieur de la Santé in December 2006 (www.healh.fgov.be/HGR_CSS ref.8080). Generally this has been reported to be in the range 5-10% of the total organ dose, but it can be as high as 20% for bone surfaces.[58] These numbers are relevant as new imaging techniques are used more often, e.g. in the (sometimes daily) on-line verification of the treatment field positions (megavoltage portal imaging devices, image guided radiotherapy techniques, cone beam CT, and tomotherapy).

Key points

- **Weak to moderate quality of evidence exists demonstrating a reduction in toxicity after IMRT compared with 2D radiotherapy or 3DCRT for head and neck cancer, prostate cancer and breast cancer. Current reports do no allow for a good comparison of relapse or survival data between IMRT and conventional techniques.**
- **As IMRT for head and neck cancer is more difficult to plan and deliver, and still an area of investigation, it has been suggested restrict to this treatment to centres with the necessary expertise.**
- **IMRT or (3D) conformal radiation therapy (3DCRT) can be used to deliver high doses for prostate cancer. The challenge is to precisely target the prostate with or without the pelvic nodes each session. Frequent image-based adjustments help to achieve this.**
- **Use of IMRT may reduce skin complications in breast cancer radiotherapy, primarily in heavy breasted women. Long term studies are required to assess the risk of induction of a secondary tumour in the contralateral breast after IMRT before introduction into common practice.**
- **The induction of fatal secondary malignancies is considered the greatest risk associated with treatment radiation. Total body irradiation is higher using IMRT and, in theory, may overall double the incidence of fatal secondary malignancies compared with standard external radiotherapy techniques. Especially younger patients are at risk.**
- **Large variations exist in total body irradiation between various IMRT techniques. Also use of daily radiation-based imaging for treatment set-up verification adds to the overall exposure. Manufacturers and users of IMRT hardware and software should be aware of this. Further product improvement should be stimulated in an effort to reduce the risk for secondary malignancies.**

4 LOCAL SITUATION

4.1 INCIDENCE OF SPECIFIC MALIGNANCIES IN BELGIUM

Cancers are the second cause of mortality in Europe and in Belgium, after the cardiovascular diseases.

In the Belgian Cancer Register, Walloon and Brussels figures are underestimated. The cancer incidence rates in Belgium were extrapolated from the Flemish figures, standardized by age and gender.

About 56 000 new cases of malignant cancer were diagnosed in Belgium in 2001, which represents 547 cases per 100 000 inhabitants. The five most common localisations accounting for those cases were: breast (C50), prostate (C61), bronchus and lung (C34), colon (C18) and malignant neoplasms of skin (C44).

Head and neck cancer

Based on the Flanders Cancer Registry, 1973 cases of head and neck cancer were estimated in Belgium for 2001. This is similar to other European countries or regions. In women, the incidence was almost five times lower than in men. Tobacco and alcohol use are the most important risk factors. In Flanders, as for chronic liver disease, the incidence of head and neck cancer is somewhat lower in the eastern parts of Flanders.

Prostate cancer

Based on the Flemish Cancer Registry, prostate cancer was the most frequently diagnosed tumour in males and accounted for 8884 new diagnoses (29.1% of the male tumours) for 2001. In Belgium, the cumulative incidence of prostate cancer up to the age of 75 increased from 2% to 6% between 1990 and 1998.[37] This trend was also seen in other regions where PSA tests are frequently used for screening of prostate cancer. The cumulative mortality of prostate cancer to the age of 75 has remained stable at approximately 1.1% in Belgium.

Breast cancer

Over 9500 patients in Belgium are diagnosed with breast cancer each year. In 80% of these patients the treatment regimen will include radiotherapy.[59]

4.2 EXTERNAL RADIOTHERAPY AND IMRT IN BELGIUM

4.2.1 Local Regulations

Radiotherapy facility approvals are determined by the Royal Decree of 5 April 1991 that imposes minimal requirements to general hospitals in terms of infrastructure, equipment and staff in function of the activity. The Royal Decree of 9 July 2000 restricted the number of radiotherapy centres to existing facilities at that time; except in provinces that had no facility. New facilities could open if located at more than 50 km of existing centres. There are now 25 radiotherapy facilities in Belgium, listed in appendix 1.

The installation of IMRT equipment in itself is not legally limited in Belgium. Nevertheless, the devices used for IMRT fall under the Royal Decree of 18 March 1999, that translate the European directive 93/42 concerning medical devices. According to this decree, the producer, the authorized representative, the distributors, the notified bodies, the physicians and the persons responsible for the reception and the distribution of devices have to report any incident to the Ministry of Health (federal public service of health, food chain safety and environment). In the case of radiotherapy devices, each reported incident transmitted to the federal public service is automatically transferred also to the federal Agency for Nuclear Control. Information on incidents and failures of devices is currently not publicly accessible. For more information on the

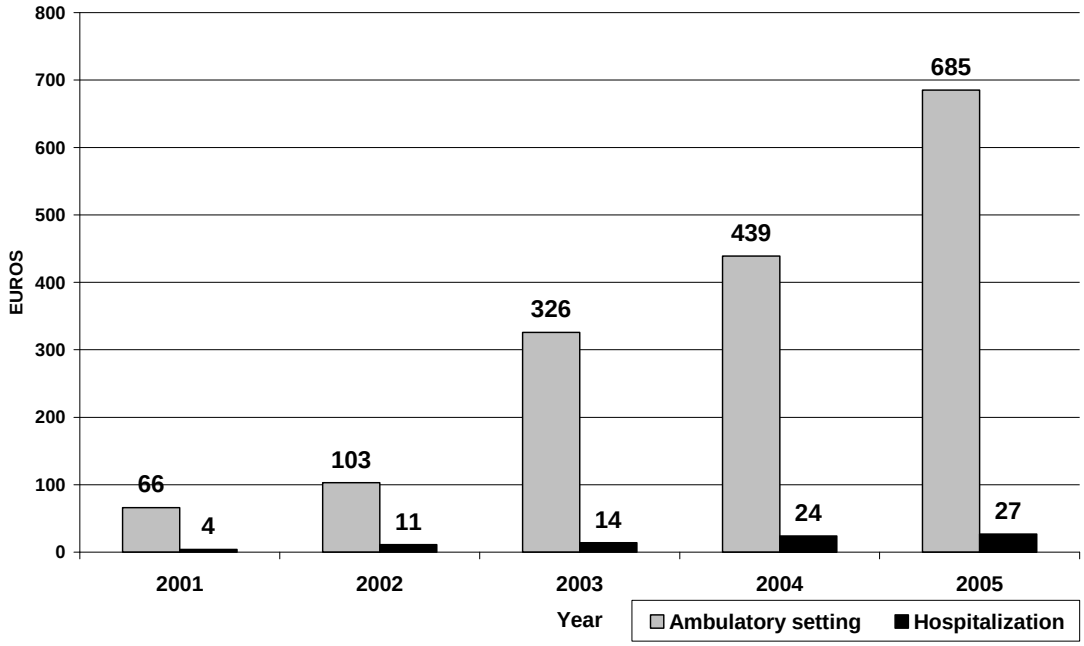
Vigilance reports process and on the European Commission position, please consult the KCE report 44 An evaluation procedure for the emerging medical technologies. [60]

4.2.2 Centres and Activity

Amongst the 25 registered radiotherapy centres in Belgium (see appendix 1), 12 centres currently use the IMRT technology.

Several reimbursement codes are used to cover the different steps of a radiotherapy treatment (planning, dosimetry, etc). Since June 2001, an additional code is charged in case of intensity modulation amounting to € 115 per treatment (444452 in ambulatory setting or 444463 for hospitalized patient). In 2005, the reimbursement based on this code amounted to €74 500, for almost 700 patients treated. Figure 1 shows that the number of patients treated with IMRT increased more than tenfold in four years.

Figure 1 : NUMBER of IMRT-plannings reimbursed (2001-2005)



Source: INAMI-RIZIV

These figures must be taken cautiously. There is probably an underestimation of the numbers of IMRT. First, IMRT breast treatments cannot be billed under the same reimbursement category as other indications treated with IMRT such as prostate or head and neck cancers, so that the billed number of codes 444452 – 444463 may not take IMRT treated breast cancers into account. Second, there are probably flaws in the available 2005 data. Indeed, the numbers of cancer treatments are expected to grow from one year to another, yet the number of started treatment courses (RIZIV/INAMI billing data) decreases from 2004 to 2005 in each reimbursement categories, as seen in appendix 6. Third, recording of billed treatments is delayed in comparison with the moment the treatment is started, which can affect the number of treatments reported, especially for establishing technologies such as IMRT.

4.2.3 Belgian Centres Survey

Based on the French practice survey developed in the 2003 HTA report of the French National Authority for Health [61], a questionnaire was sent in February 2007 to each radiotherapy centre in order to obtain a snapshot of the Belgian IMRT situation (see appendix 2).

All twenty-five centres responded (two centres work in collaboration) from which 12 centres already use IMRT, 11 other centres plan to develop this activity soon (9 in 2007 and 2 in 2008) and one does not plan to install IMRT in the coming years.

The number of patients treated with IMRT was respectively (at least) 760, 1411 and 2154 patients in 2004, 2005 and 2006 (figures from one major centre are missing in 2004 and 2006). In 2007, 2795 patients are expected to start IMRT. As noted in the previous section (in Figure 1), the number of billed IMRT plannings in 2005 is inferior to the effective number of treatments begun in 2005.

The increase in IMRT use as presented in Table 1 will probably level-off in the coming years as not every indication will benefit from IMRT. The percentage is the number of patients treated with IMRT divided by the number of patients treated with external radiotherapy (IMRT included) in the centres that offer IMRT.

Table 1 : Percentages of IMRT patients of all patients treated with radiotherapy

2001	2002	2003	2004	2005	2006	2007 (exp)
2.1%	2.6%	2.7%	5.6%	9.3%	15.0%	20.8%

The average number of sessions per indications is presented in Table 2 and is based on the 11 centres that provided the number of patients and the number of sessions. Thirty-nine patients treated by stereotactic way were not included in the calculation of the number of sessions. As some centres grouped some indications, the same grouping was kept.

Table 2 : Average number of sessions per patient per indication (2006)

Localisation	N patients	Average N of sessions
Prostate	697	35.4
Head and Neck (+skull base and paraspinal)	400	28.2
Breast (incl. forward technique)	469	25.8
Lung	159	13.5
Central Nervous System	282	13.2
Gynaecologic	19	24.5
Liver metastasis	1	25
Rectum	16	24.1
Others	178	
Total	2221	

The category others includes amongst others gastrointestinal cancers, sarcoma, lymphoma, skin cancers, bone cancers, etc.

Equipment manufacturers VARIAN, Elekta, TomoTherapy, BrainLAB, Siemens and Philips were cited in the survey as suppliers of IMRT equipment.

Among the reasons to adopt IMRT in the near future, the reduction of adverse events and the higher dose offered by IMRT were the most cited; other reasons were concave organs treatment possibility, regional accessibility (for patients), better dose repartition, radiotherapy visibility and possibility to do cerebral stereotaxy. Head and neck cancer was the first indications declared to require future IMRT use (8 out of 10 centres), followed by prostate cancer (7), lung cancer (3), breast cancer, central nervous system cancer, lever/abdominal mestatases, gynaecologic cancer (2) and finally paraspinal cancer and rectum cancer (1).

In order to compare Belgium with the international situation, a written survey questionnaire was distributed in February 2007 by e-mail to the HTA agencies from the different countries belonging to the INAHTA network. Intensity-Modulated Radiotherapy is not included within the service portfolio of the public health system in Andalucia, due to the lack of evidence to support its use; but the Agencia de Evaluación de Tecnologías Sanitarias de Andalucía is going to conduct a report on the subject. In Switzerland, IMRT is reimbursed without any limitations by the mandatory health insurance package for all Swiss inhabitants. Israël reported to have 3 major hospitals performing IMRT. A more complete response was sent by Denmark. Last year, between 150 and 200 Danish patients were treated. Denmark has 80 radiation oncologists and 80 radiophysicists operating six IMRT centres, which is qualified as an insufficient number of radiophysicists by the Danish survey respondents. Beside a possibility of state guarantee loans for IMRT acquisition, there is neither a particular financing of the equipment nor a specific radiotherapist fee-for-service. Finally, the number of 160 Brazilian radiophysicists was also considered as insufficient by the Brazilian respondents. Fifteen hospitals are IMRT-equipped in Brazil and approximatively 450 patients have been treated in 2006, mostly for prostate cancer, head and neck cancer, breast cancer, lung cancer and central nervous system cancer. Maintenance of public devices are financed by the government in Brazil but no quality assurance process nor guidelines officially exist. Other countries did not answer or were still waiting for information to be transmitted when the present report was finalized.

Key points

- **Twelve of the 25 Belgian radiotherapy centres currently use IMRT and all but one remaining centres are planning to use this technology in the forthcoming two years.**
- **Centres reported 2150 IMRT treatments in 2006 which represents 20% of all external radiotherapy treatments in our survey.**

5 ECONOMIC LITERATURE

5.1 METHODS

A comprehensive literature search for economic studies on IMRT was performed in November and December 2006 covering the following databases: Medline, CINAHL (Cumulative Index to Nursing & Allied Health Literature), Econlit, BNI (British Nursing Index), CRD (Centre for Reviews and Dissemination) dababases, Embase (Evidence-based Medicine). In addition, Belgian representatives of manufacturers were addressed with the request to provide relevant documents with regard to economic aspects of the IMRT technology.

Searches in the Medline, CINAHL, CRD and Embase databases were limited to publications from 2000 onward. Publication languages were restricted (when limits apply in the various filters) to English, Dutch/Flemish, French, German, Italian, Spanish or "multilingual". Detailed search filters featuring precise entry terms, boolean operators and query limitations can be found in appendix 4.

Next, abstracts of the selected publication were screened and ordered by relevance of content. Full text versions of relevant publications were requested for further scrutiny. Publications focusing mainly on technology, medical outcomes and organisational issues were distinguished from publications relating to cost analyses on the topic of IMRT. By intent a broad scope was set to capture publications of which the study design encompasses full health economic evaluations as well as descriptive cost analyses and accounting (costing) analyses.

5.2 RESULTS

5.2.1 Global overview

Table 3 summarizes overall numbers of publications yielded by the various search filters we applied. Next, the found publications were centralized in a consolidated database, counting 1 118 entries after removal of double entries.

Table 3 Global Overview of Economic Literature Search

Searched Database	Number of Hits
Medline (R), accessed through OVID platform	580
Medline ® In-Process & Other Non-Indexed Citations (OVID)	56
CINAHL (OVID)	38
Econlit (OVID)	4
BNI (OVID)	6
CRD (DARE, NHS EED, HTA, Ongoing Reviews)	279
Embase	365

Based on title and abstract 97 publications were selected for further scrutiny: full text versions were explored and publications were classified by main theme. In all, five cost analyses were found. Twenty-eight publications were found to relate to the organisational aspects of IMRT and/or mention price/cost data in respect to IMRT. These publications are of relevance to the chapter on organisational issues in our report (cf. infra). The remainder of the full-text studies dealt more specifically with medical outcomes, technological aspects or other topics of lower relevance to the economic and organisational assessment of IMRT.

5.2.2 Selected publications

As stated in the above paragraph, five cost analyses relating specifically to IMRT were found.

Three publications [62] [63] [64] were identified as full health economic evaluations, respectively a cost minimization analysis and two cost-utility analyses, all three found to be of poor quality. A fourth paper [65] offers a descriptive cost comparison of various radiation therapy techniques including IMRT. Finally, the fifth publication [66] is a costing analysis of IMRT. Evidence tables for these studies are included in appendix 4.

Bonastre 2006 [66] estimates the average cost of a full IMRT treatment plan for head and neck cancer patients applying to France based on patients treated between July 1st 2003 and April 30th 2005. Separate cost estimates are made for each of the 9 participating hospitals. These calculations result from a full costing (absorption costing) approach based both on empirical observations (chronometric measuring, etc.) and financial (accounting) data for each hospital. This way, aggregate overall costs for each of the 99 patients in the analyzed case series are derived and compared with the applying public reimbursement. An average cost of 10 916€ (breaking down to 2 773€ for the planning stage and 8 143€ for the actual irradiation) is calculated and compared to the corresponding public reimbursement of 6 987€. The authors consequently conclude that current public payments do not cover the actual cost. In an assessment of cost variability among patient cases, the authors indicate learning effects are at work. This would imply more "experienced" hospitals incur lower overall cost, probably lowering the long term difference between actual cost and public reimbursement. A recent publication[67] exploring the impact of learning effects through a multi-level analysis for the same data set found that 42% of variation in costs between centres could be attributed to centre-specific experience in IMRT delivery. The authors, however, concede that given the particularly complex planning for head and neck cancers, it is likely similar analyses for other cancer types would be less striking.

As overheads and logistics costs (which were attributed to the IMRT protocol by means of a general distribution factor) on average account for about 45% of the estimated overall IMRT cost it may be argued that more detailed activity based costing analyses in the participating hospitals would be better suited to attribute indirect costs with greater accuracy. Nevertheless, this would have implied a substantial increase in required research means, in particular given the multi-centric outline of the study. The Bonastre analysis has the unique advantage among the four selected cost analyses that it assesses costs for the IMRT protocol in an empiric framework (although limited to head and neck cancers) and does not exclusively resort to theoretic modelling of cost aggregates.

Suh 2005 [65] develops a descriptive cost comparison of eight distinct radiotherapy regimens including IMRT in treating early-breast cancer patients who underwent breast-conserving surgery. Costs are estimated from a societal perspective, i.e. the United States, and limited to direct costs: patient costs and health care payer costs. Patient costs apply to time and transportation costs associated with an outpatient radiotherapy treatment plan and payer costs are derived from (theoretical) sets of cost item combinations based on prevailing Medicare reimbursement fees. The authors argue that the least costly technique would be the accelerated conventional whole breast radiotherapy protocol as opposed to the most costly whole breast IMRT protocol. Estimates per treated patient range respectively from 6 100$ to 19 300$. It should be noted, however, that deriving cost input variables from reimbursement schemes may skew ensuing conclusions. As established by various authors [68-71] IMRT reimbursement fees in the United States are perceived as generous compared to reimbursement fees for alternative radiotherapy interventions. The cost estimates made for partial breast irradiation treatments seem to lack in relevance in light of the standard clinical practices (i.e. whole breast irradiation), at least in the way they apply to Belgium today. A further criticism concerns the assumption put forth by the authors that patients will remain in full time employment throughout the course of the radiotherapy treatment. When comparing cost outcomes of alternative interventions from a societal perspective this assumption tends to bias the cost comparison against interventions lasting over a shorter term (as IMRT compared to conventional radiotherapy for instance).

Konski 2004 [62] presents a cost-minimization analysis comparing conventional whole breast irradiation with partial breast irradiation (including IMRT) in early-stage breast cancer patients. The cost assessment is limited to Medicare reimbursed items, based on theoretical item combinations, and consequently takes on a health care payer perspective. Authors conclude that IMRT accelerated partial breast irradiation ranks third at 10 872$ among the four considered interventions (with 3-D conformal accelerated partial breast irradiation ranking first at 4 533$). It should duly be noted that this analysis may be distorted due to the applying reimbursement scheme. Again, given the clinical standard of whole breast irradiation the chosen design seems to bear little relevance (at least to the Belgian context). Moreover, the author concedes that "the best way to evaluate the cost-effectiveness of different accelerated partial breast irradiation treatment techniques would be for an economic analysis to be incorporated into clinical trials." Further, in contradiction of the developed cost-minimization analysis he observes that "a prospective randomized trial evaluating efficacy, QALY or utilities, and cost […] is needed" to address cost-effectiveness for the selected interventions.

Konski 2005 [63] performs a cost-utility analysis comparing IMRT to 3DCRT therapy in a hypothetical cohort of 70-year old males suffering from good-risk or intermediate-risk prostate cancer. As such, the study design encompasses two subgroup analyses. At an estimated 16 182$ and 17 448$ per added QALY respectively for good-risk and intermediate-risk patients and assumed willingness-to-pay of 50 000$ per added QALY the authors state IMRT is cost-effective compared to 3DCRT. Cost outcomes were obtained from actual Medicare reimbursements at the Fox Chase Center (Pennsylvania, USA). A main shortcoming of the analysis is that modelled probabilities and clinical effects are derived from separate patient case series for compared groups. Furthermore, the applied patient utilities, were estimated from two distinct primary data sources, obtained through two different methods[a] relating to particularly small

[a] EQ-5D survey (IMRT group) and TimeTradeOff (3DCRT group)

patient samples (of 17 and 34 patients for the IMRT and 3DCRT group respectively). Moreover, it would appear the utilities for the IMRT group were obtained from a group of intermediate-risk patients and related conclusions were extended to good-risk patients. The make-up of the 3DCRT group for which utilities were determined was not detailed.

Konski 2006 [64] analyzes the cost-utility of IMRT compared with three-dimensional conformal radiation therapy (3DCRT) in a hypothetical cohort of 70-year old males, limited to patients suffering from intermediate-risk prostate cancer. At an estimated 40 101$ per added QALY and assumed willingness-to-pay of 50 000$ per added QALY the authors state IMRT is cost-effective compared to 3DCRT with a 55.1% probability. As cost data were based on theoretically modelled sets of Medicare reimbursement fees overall cost outcomes were found to be substantially higher, in turn feeding into a less favourable cost-effectiveness ratio for IMRT compared to 3DCRT[b]. Further outcome data in Konski 2006 correspond to data already applied in Konski 2005 (cf. supra) with the noteworthy observation that the former publication only develops an economic evaluation for intermediate-risk patients, which seems more fitting given the applied utility outcomes. Other points of criticism raised for the 2005 analysis remain valid, including the restricted samples derived utility data stem from. Not surprisingly, the authors' main conclusion proved sensitive to changes in applied utility values.

5.2.3 Conclusion

At present, no conclusive economic evaluation of the IMRT technique has been made. As a result, no firm conclusion can be drawn on the cost-effectiveness of IMRT in comparison to alternative health care interventions, in particular 3DCRT. Ideally, (direct medical) cost and utility data would be collected within the wider framework of a randomized controlled trial. In this respect, further full costing analyses, preferably activity based, at hospital-level are a prerequisite necessity to establish the relative financial impact with respect to the indirect costs of alternative radiotherapy techniques in routine practice. It should, however, be stressed that prevailing reimbursement schemes may prohibit the set-up of such a comparative design as IMRT may evolve into a universally promoted standard before its incremental cost-effectiveness has been established.

Key points

- **No firm conclusion can be drawn on the cost-effectiveness of IMRT in comparison to alternative interventions, in particular 3DCRT.**
- **IMRT may evolve into a universally promoted standard before its incremental cost-effectiveness has been established.**

[b] Authors commented that lower actual reimbursement "can be a result of negotiated discounts with managed Medicare insurance products or inefficient charge capture."

6 ORGANISATIONAL ISSUES

This chapter offers a succinct description of the principal organisational issues at stake in the adoption and implementation of IMRT. We will discuss equipment and staffing needed to implement an IMRT program and the possible tensions at play between ruling levels of reimbursement and actual costs. The main perspective chosen for our discussion is that of a provider (radiotherapy department) already equipped with 3DCRT technology as this reference case was considered most in keeping with the Belgian context.

6.1 METHODS

As stated in the preceding chapter (cf. supra), our general economic search filter yielded twenty-eight publications with regard to the organisational aspects of IMRT. These results were further complemented through a google-based grey search and contacts with the group of external experts linked to our research project. Furthermore, Belgian industry representatives were contacted with the request to transmit relevant information.

6.2 RESULTS

6.2.1 Equipment needs

Five separate sources [72], [73], [74], [75],[76] offer a full overview of minimal equipment needs for the implementation of IMRT for (country, year of reference): the USA 2002, the USA 2003, France 2003, Spain 2005, Belgium 2006. A detailed overview of these cost estimates can be found in appendix 5.

As can be concluded from these sources capital start-up costs both for 3DCRT and IMRT therapy are considerable, especially when taking into account that there are indications that proper working conditions require at least two functioning and similar linear accelerators at each treatment site [73]. Martin 2003 [73] offers the most complete cost estimate, reaching the conclusion that the minimal set-up cost for a new IMRT-capable radiotherapy unit will be around 7 100 000€. This amount covers bunker facilities for a cost ranged between 380 000€ and 600 000€.

A further point of interest is the substantial cost added by upgrading an already operational 3DCRT treatment unit to an IMRT unit (up to 50% of the initial capital cost of the 3DCRT unit).

Through our grey search we identified various independent sources quoting cost estimates for IMRT-capable linear accelerators (see Table 4). Cost estimates range between 1 200 000$ (around 900 000€) and 1 300 000£ (around 1 900 000€), illustrating the fact that a large part of overall start-up equipment costs can be accounted for by the purchasing cost of a linear accelerator. As the (often concise) cost item description indicates, however, differences in (optional) functionalities may go some way in accounting for the price variation.

Table 4 Various cost estimates reported for IMRT-capable linear accelerators ("linacs")

Description	Indicated Cost	Country	Year	Reference
"Linac IMRT"	1 600 000€	Germany	2006	77
"IMRT, portal imaging, multi leaf collimation and respiratory gating"	3 500 000$ (NZD)	New-Zealand	2004	78
"High Energy Linac with MLC and portal vision facilities"	1 300 000£	United Kingdom	2004	79
"MV Cone Beam with a Linac" (Siemens)	1 200 000$	United States of America	2004	80
"Average Sales Price IMRT" (Varian)	1 900 000$		2005	81

A similar assessment can be made with regard to prices quoted for quality assurance software, for which we found a (single source) table of comparison (Table 5): wide variation in price in connection with a marked diversity in options bundled in various software packages.

Table 5 Cost estimates reported for IMRT Quality Assurance software (USA, 2003) [82]

Company	Software	Description	Licensing Fee
Elekta	PrecisePLAN	"Aperture-based inverse planning for IMRT, patient plan calculation on (selectable) phantoms, export plan and dose to linac and dose QA-system"	"100 000$"
LifeLine Software	radCalc	"FDA 510(k)-approved for independent MU or point-dose verification for conventional and IMRT treatment planning systems"	"7000$ - 17 500$ / site"
NMPE (MEDTEC)	pReference Qatool	"Fluence and film data importing; image registration; spatial and density calibration; histograms; registered line profiles; 2-D/3-D prescribed and delivered substraction analysis; composite isolines and continuously variable isoline pairs"	"9 500$ delivered on laptop computer"
	ProCheckTM	"Fluence and film data importing; image registration; spatial and density calibration; histograms; registered line profiles; 2-D/3-D prescribed and delivered substraction analysis; composite isolines and continuously variable isoline pairs; gamma analysis; flatness and symmetry"	"15 500$ ProCheck QA software delivered on a Dell workstation or laptop computer, includes a flatbed scanner and color printer"
RIT	RIT113 Film Dosimetry Software	"Film dosimetry by scanning films at 12- or 16-bit depth and performing software analysis. Offers a host of QA options including plan/film analysis, profiles and isodose curves. Also provides MLC routines like transmission analysis, 50 percent fluence analysis, interrupted treatment and more."	"12 500$, additional site licenses are available for 2 500$ each."
Sun Nuclear	MapCHECK	"IMRT plan verification is electronic, using 445 detectors: uses percent difference and distance-to-agreement (user adjustable) to quickly perform plans in absolute dose; film analysis software is also included; available gantry attachment allows measurement at any gantry angle"	"1st year free, 2 500$/year for software thereafter"
Varian	Argus QA Products	"machine QA"	"12 600$"
	Portal Dosimetry	"Pretreatment QA for IMRT plans; constancy checks for machine QA tests"	"Individual floating license modules 5 000$ - 25 000$, full capability starting under 55 000$ including training"

We conclude that the initial start-up cost for IMRT specific equipment is considerable, amounting up to several million euro for a newly operational unit. Nevertheless, published cost estimates vary widely, which could be explained by pointing to the distinct and often supplier-specific options bundled in hardware and software packages.

6.2.2 Staffing needs

As pointed out in the introductory chapter of our report, the implementation of IMRT implies a higher workload with regard to treatment planning and quality assurance procedures. As a consequence, it should be expected that physics time, i.e. working

time spent by medical physicists, will increase drastically. Two surveys [83] [84] carried out in the USA for the years 2001 and 2003 confirm this. Both surveys were conducted by the American Association of Physicists in Medicine (AAPM) Professional Council and the American College of Medical Physics (ACMP). The survey carried out by Herman in 2003 was based on the output of thirty completed surveys sent out to medical physics departments and groups in 2001. The survey carried out by Mills in 2005 (the "Abt survey") was based on surveys sent to 100 qualified medical physicists (QMP) in 2005, chosen to reflect overall practice type and geographic location for the QMP profession. Consequently, the design of the Abt survey is superior to that of the Herman survey. Both surveys drew on procedure descriptions applying to Medicare billing codes.

As illustrated by Table 6 physics time for IMRT compared to 3DCRT increases by a factor of around 3. This increase in time spent by a physicist will only in part be offset by a decrease in support staff time[c] (see Table 7).

Table 6 Physics Time for 3DCRT and IMRT

Procedure Description	Herman Survey	Abt Survey
	Physicist Hours per Patient	
IMRT Treatment Planning	12,03	10
Therapeutic radiology simulation-aided field setting, 3-dimensional	3,51	3,75
Relative Impact IMRT versus 3DCRT	3,4	2,7

Table 7 Physics Support Staff Time for 3DCRT and IMRT

Procedure Description	2003 Abt Survey Support Staff Estimates (Hours)
IMRT Treatment Planning	3
Therapeutic radiology simulation-aided field setting, 3-dimensional	3,75
Relative Impact IMRT versus 3DCRT	0,8

Since the main and methodologically most compelling source comparing treatment preparation times between 3DCRT and IMRT applies to time spent by American physicists and "physics support staff", we have no reliable means at present to assess to which extent these findings apply to physics time spent by Belgian professionals, nor to time spent by related categories of (para)medical health professionals involved in the preparation, delivery and follow-up of IMRT in a specifically Belgian context.

Through our grey search we found a single-centre comparison made between planning times for 3DCRT and IMRT treatment of respectively prostate and Head and Neck cancer[85]. These figures (Table 8) indicate that the average planning times vary more by radiated tumour site (irrespective of the chosen technique) than they do between techniques (irrespective of tumour site).

[c] Mills 2005 defines physics support staff as "medical dosimetrists, physics assistants, equipment engineers, physics technologists, physics residents and so on"

Table 8 Physics planning times at Mc Anderson Cancer Centre (Gillin 2003)

Technique	Prostate	Head and Neck
3DCRT	6 hours	Intital effort: 2 days
		Rework effort: 1.5 days
IMRT	8 hours	Initial effort: 3 days
		Rework Effort: 2 days

Miles 2005 [86] corroborates the strong impact the tumour location has on overall planning time (Table 9). Furthermore, the effect the specific subtype of IMRT-technique has on treatment times is also demonstrated here.

Table 9 IMRT overview of planning times and treatment times

Source	Planning Time (hours)	Treatment Time (minutes)	Technique	Treatment Site
Boehmer 2004 [87]	4.25	No data	Dynamic	Prostate only
Adams 2004 [88]	3-5	28 (mean)	Dynamic 5-field	Prostate plus pelvic nodes
		24 (mean)	Step and shoot 5-field	
Munter 2003 [89]	No data	12.6 (mean, beam-on time only)	Step and shoot 5-9 field	Head and Neck
Clark 2002 [90]	10	15-20	Dynamic 5-field	Prostate plus pelvic nodes
Ozyigit 2002 [91]	4	35	MLMiC (NOMOS)	Head and Neck
Hunt 2001 [92]	8	20-25	Dynamic 7-field	Nasopharynx
Xia 2000 [93]	4-8 (no QA)	25-30	MLMiC 5-field	Nasopharynx
Butler 1999 [94]	Two days (with QA)	20 (mean)	MLMiC 3-5 field	Head and Neck
Grant 1999 [95]	No data	15-20	MLMiC 3-field	Head and Neck
Miles 2005 [86]	11 (median, with QA)	20 (standard time slot, with median beam-on time: 12)	Dynamic 5-field	Prostate plus pelvic nodes
	14 (median, with QA)			Head and Neck

We conclude that physics time can be expected to increase drastically with IMRT implementation. Currently[d], 87 qualified medical physicists are registered (as actively in service) with the Belgian public authorities [96]. In pursuance of a royal decree specifying legally binding criteria for radiotherapy departments [97] for every additional 750 patients a given department treats an extra physicist (full-time equivalent) has to be recruited. This would imply that, abiding by present rules, the total number of physicists is scheduled to treat a maximum of 65 250 patients (750 multiplied by 87). Going by estimates based on RIZIV/INAMI billing code data for 2004, it would appear the number of physicists leaves sufficient a margin: 30 666 treatments were started for treatment through external radiotherapy or (exclusive) treatment by brachytherapy. Details on the derived number of treatments and treatment categories can be found in appendix 6. Assuming that every treatment corresponds to one patient we can estimate a (theoretical) minimum number of 41 qualified medical physicists needed by current regulations.

[d] Reference date: 23rd April 2007

When measured by comparable guidelines applying to neighbouring countries the Belgian standard pales: 300-400, 600 and 650 patients per physicist respectively for France, Luxembourg and the Netherlands ([98]). Admittedly, a large part of this variation may perhaps be absorbed by (correcting for) the assignment of various tasks between physicists and allied health professionals [98].

Finally, it should duly be stressed that actual IMRT treatment time can vary strongly by type of IMRT technique and (case-mix of) treated tumour site(s), which in turn may influence a radiotherapy department's patients capacity and hence the overall number of linear accelerators required.

6.2.3 IMRT Cost versus reimbursement

6.2.3.1 IMRT Cost

We found five separate sources quoting cost estimates for an IMRT treatment course. These publications include: an empiric full costing analysis [66], 2 theoretically modelled costing analyses [99], [100]. The cost estimate, covering both direct and indirect costs, in the Projet Etoile publication[100] was derived from direct costs in a separate study, Marchal 2004[101]. Finally, we found one site-specific cost quote without further methodological development [74]. Table 10 summarizes the main findings.

We dealt extensively with Bonastre 2006, the most detailed of the above analyses in our review of the economic literature. Once more, it should be emphasized that no activity based full costing analysis on the specific topic of IMRT was found, implying that the precise cost impact of IMRT is still to a large extent a pending question. Given the expected differences in planning times (cf. infra), it may be anticipated, however, that tumour type will wield a considerable impact on the actual cost of IMRT.

Table 10 Cost estimates for an IMRT treatment course

Country	Tumour Site	Year(s) data apply to	Cost Estimate
France[66]	Head and Neck	2003-2005	10 916€
France[100]	Head and Neck	2003	6 432€
	Prostate	2003	6 416€
Switzerland[99]	NA	2003	10 600€
Argentine[74]	Head and Neck	2004	10 000€ - 12 000€

6.2.3.2 IMRT Reimbursement

International data

In our review of the economic literature we already indicated that various authors describe the ruling reimbursement under Medicare provisions in the USA as favourable compared to alternative forms of radiotherapy. In spite of the fact that IMRT reimbursement compared to conventional treatment was revised downward in 2004 (decreasing the relative reimbursement from a factor 4 to 2.8) [102] IMRT still attracts a comparatively advantageous reimbursement.

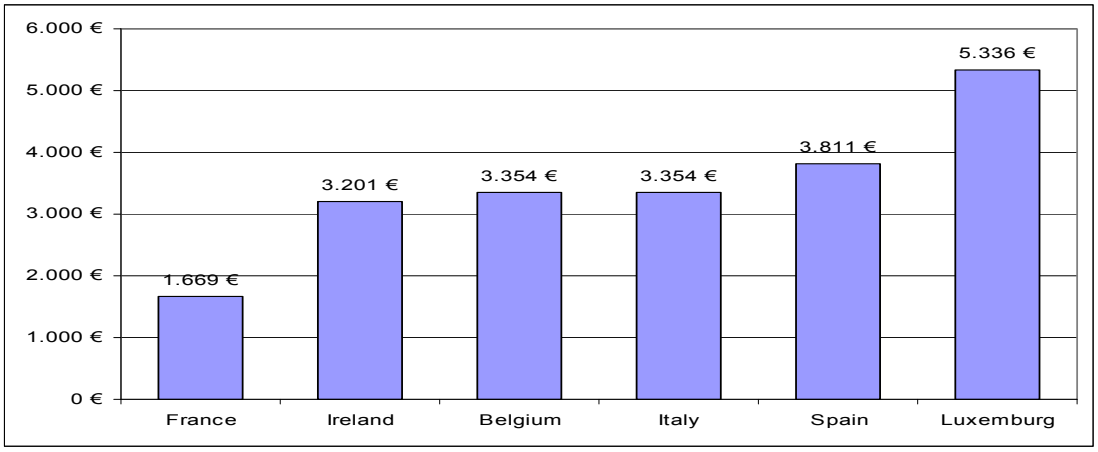
Based on a recent publication outlining Medicare reimbursement practices for various radiotherapy techniques [103] we derived aggregate fee-for-service reimbursements applying to respectively hospital and free-standing facilities (Table 11). These figures apply to reimbursement levels posterior to the aforementioned downward revision.

Table 11 Medicare reimbursement for course of IMRT (2005$)

IMRT SERVICES		Medicare Unit Reimbursement		Quantity (25 fractions/5 weeks schedule)	Medicare Overall Reimbursement	
		Hospital	Free-Standing Facility		Hospital	Free-Standing Facility
9924X	Initial Consult	$264.11	$0.00	1	$264.11	$0.00
77263	Physician Plan	$167.13	$0.00	1	$167.13	$0.00
77290	Pretreatment Simulation	$305.17	$259.98	1	$305.17	$259.98
76370	CT Guidance	$142.04	$117.86	1	$142.04	$117.86
77301	IMRT Plan (after CT imaging)	$1 228.55	$1 114.57	1	$1 228.55	$1 114.57
77334	Treatment Devices (after planning)	$228.10	$129.61	1	$228.10	$129.61
77418	Daily Treatment Delivery	$309.20	$687.84	25	$7 730.00	$17 196.00
76950	Daily Ultrasound set Up OR	$97.76	$52.30	25	$2 444.00	$1 307.50
77417	Port films if no other guidance	$43.87	$23.88	0	$0.00	$0.00
77336	Weekly QA (after planning)	$97.48	$119.00	4	$389.92	$476.00
77427	Weekly Physician Management	$172.05	$0.00	5	$860.25	$0.00
77470-59	Special Treatment Procedure	$441.37	$444.92	1	$441.37	$444.92
TOTAL					**$14 200.64**	**$21 046.44**

In comparison to the reimbursement levels Martin 2003 [73] quotes for radiotherapy in various European fee-for-service schemes (see Figure 2), it appears evident that the Medicare reimbursement levels stand out as exceptionally high. It should, however, be stressed that the figures in table 13 refer to average reimbursements for treatment course of all types of external radiation therapy. Moreover, these figures only cover the fee-for-service part of overall reimbursements, without taking into account possible costs financed by health care payers for IMRT equipment, inpatient facilities, etc. The variation in reimbursement levels among European countries appears to be wide. To which extent this may reflect alternative sources of financing for radiotherapy services at work, is not clear.

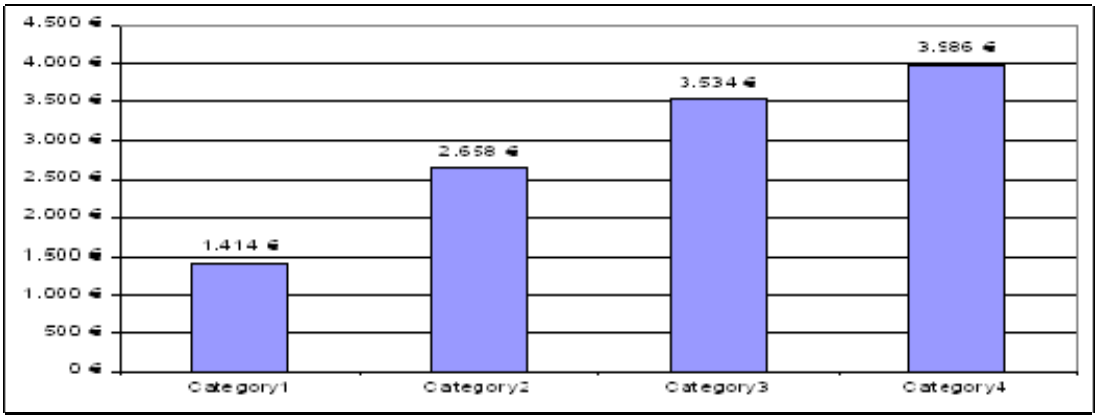
Figure 2 Average reimbursement of external radiotherapy in fee-for-service schemes



Belgian data

Based on the Belgian "nomenclature" billing code scheme we derived maximum reimbursements for external beam radiotherapy treatment courses according to the four related reimbursement categories (see Figure 3). IMRT treatments would typically be covered under category 4 following current reimbursement regulations. For the precise development of the maximum reimbursements and billing code descriptions we refer readers to appendix 7. These amounts apply to the fee-for-service reimbursement (article 18) in 2003 as to allow for a comparison with the figures from Figure 2.

Figure 3 Maximum fee-for-service reimbursement of external radiation therapy courses applying to Belgium (2003€)



When we multiply the numbers of started treatments by category (see appendix 6) with the maximum reimbursements per category, we can derive a maximum overall budget for external radiotherapy for Belgium in 2003 of 68 058 433€, which would imply at most an average amount of 2 562€ was reimbursed per started treatment course. In applying the actually reimbursed amount (see appendix 6) of 62 588 987 we find an

average reimbursement of 2 318€ per started course of external radiotherapy, a result that would invalidate the quoted amount in Figure 2.

6.2.3.3 Cost coverage by reimbursement

Based on the above analyses we conclude that no firm assessment can be made at present with regard to the coverage of actual costs for IMRT by current provisions in reimbursement.

No ABC analysis has been performed for IMRT up to date. Furthermore, so-called "learning effects" as reported in publications discussed in our economic literature review would have to be analyzed in detail to make a valid long term cost analysis.

Although reimbursement levels across European countries for external radiotherapy appear to vary widely, more detailed analyses incorporating a wider range of public reimbursements such as in appendix 8 would be required to validate this. No specific reimbursement analysis applying to IMRT was found for European countries. American Medicare billing data suggest that the prevailing Medicare reimbursement is favourable when compared to the (few and incomplete) figures for Europe.

6.2.4 Conclusion and discussion

There are clear indications that the introduction and implementation of IMRT wields a formidable cost impact for radiotherapy departments, both with regard to equipment and staffing needs. Comparability of data in this respect, however, is hampered by the fact that published equipment costs often apply to very heterogeneous products bundling an array of diverging functionalities. In addition, publications probing the effect of IMRT implementation on staffing needs should be read with an understanding of the possible wide-ranging differences in treatment protocols and task descriptions applying to health professionals in varying countries.

This lack of comparability is coupled with a dearth of studies addressing the cost analysis of IMRT treatment courses (which should ideally correct to great detail for "tumour case-mix" and applied IMRT technique at departmental level). Finally, findings on current reimbursement levels of IMRT are scarce and often only partially take all aspects of public reimbursement into account.

We conclude that in all of the above fields there is an apparent need for further research before reimbursement levels could be fine-tuned to induce optimal IMRT service levels.

Key points

- **The initial start-up cost for IMRT specific equipment is considerable, especially when taking into account indications that proper working conditions require at least two functioning and similar linear accelerators at each treatment site, leading to a minimal set-up cost for a new IMRT-capable radiotherapy unit of up to 7100 000€.**
- **Upgrading an already operational 3DCRT treatment unit to an IMRT unit can incur an extra investment of up to 50%.**
- **Published cost estimates vary widely, which could be explained by pointing to often specific options bundled in hardware and software packages.**
- **There are indications that time spent by medical physicists on treatment planning and quality assurance can be expected to increase drastically -by a factor of around 3- with IMRT compared to 3DCRT.**
- **Actual IMRT planning and treatment times vary strongly by type of IMRT technique and treated tumour site.**
- **No firm assessment can be made at present with respect to the coverage of actual costs for IMRT by current reimbursement.**
- **More detailed analyses such as ABC studies and comprehensive reimbursement estimates on the topic of IMRT are required.**
- **There are indications reimbursement levels vary strongly across Europe and that Medicare reimbursement levels (USA) stand out as particularly high.**

7 BUDGET IMPACT SCENARIOS

7.1 RATIONALE

The purpose of the present analysis is to offer Belgian policy makers an insight into the possible impact the further diffusion of IMRT may hold on the overall size of public funding, in particular annual budgets running within the current regulatory framework. As such, the results of the analysis will apply from a Belgian public payer's perspective at short term. The analysis of clinical data will be rooted in available scientific findings. Inevitably, institutional factors such as reimbursement tariffs will refer exclusively to the Belgian context. Expected, but as yet unquantifiable budget impact drivers will be identified. The main outcome of this analysis will be the design of an updatable reference frame laying bare the principal operational elements and relationships influencing the budgetary endpoint.

7.2 KEY ASSUMPTIONS

7.2.1 Baseline Scenario

Our base case scenario will start from the assumption no IMRT treatments are performed within reimbursed health care. IMRT, however, cannot be considered a newly introduced technology from the Belgian public payer's perspective as IMRT treatments have been reported from 2001 on (see Figure 1). Consequently, we will have to correct for distortions in our baseline stemming from this observation (cf. infra).

Furthermore, a new legal framework for public financing of radiotherapy departments was introduced as of April 25th 2005 [104] basing departmental funding for investment and operational costs on the annual number of treatment courses weighted by category types that apply to external radiotherapy (categories 1-4, see appendix 6). This implies the departmental funding is directly impacted by the IMRT delivery, which is reimbursed under category 4. More details can be found in appendix 8. Prior to this regulation, RT investment and operational costs were reimbursed dependent on the annual number of treated patients without further distinction.

The current billing code scheme distinguishing between various categories of RT (Article 18) came into effect from June 1st 2001. As we dispose of observations on the number of delivered billing code items on an annual base, we shall take 2002 (first full year after the introduction of the new billing code scheme) as the first year of our simulation and will include the following years up to 2006, the most recent year for which we extrapolated cancer incidences (cf. infra).

Our intent is to apply the current regulatory framework (including the new financing scheme for investment and operational costs at RT department level) to the period 2002-2006 and to assess which would be the feasible budget impact of IMRT implementation going by various scenarios (differences of comparator scenarios and baseline scenario). Our budgetary endpoint will be measured in euro (nominal values). As we dispose of the complete number of annually delivered RT courses by category, including the indication of the number of IMRT courses (subgroup of category 4 courses) from 2002 on, we are able to simulate the category-weighted RT departmental financing as if the current regulation would have applied to the period between 2002 and 2006. Moreover, we will correct for historically reported IMRT courses to simulate the absence of IMRT courses in our baseline scenario.

Key points

- **We will apply the current regulatory framework to the period between 2002 and 2006 to assess the possible budget impact of IMRT.**
- **Our baseline scenario assumes no IMRT has been delivered and will be compared with various scenarios of IMRT delivery.**
- **The budgetary endpoints of our model will concern the monetary differences between various IMRT delivery scenarios and our baseline scenario.**

7.2.2 Epidemiologic Assumptions

Based on published cancer incidence data applying to Flanders 2001 and official demographic data on all residents of Belgium we extrapolated incidence figures, correcting[e] for age and sex, for the years 2002-2006. The results, ordered following the same lay-out presented in Table 1 in the first chapter of this report, can be found below (see Table 12). These data will help to set the number of patients involved in our analysis.

Table 12 Cancer Incidence in Belgium (2002-2006) extrapolated according to the international morphology classification ICD-10

	Year				
Localisation	2002	2003	2004	2005	2006
Breast (C50)	9 364	9 462	9 560	9 667	9 771
Prostate (C61)	9 025	9 165	9 314	9 478	9 626
Bronchus and lung (C34)	6 250	6 338	6 431	6 527	6 611
Rectum (C20)	2 100	2 132	2 164	2 199	2 231
Cervix uteri & corpus uteri (C53 & C54)	2 008	2 042	2 074	2 106	2 135
Head & Neck (C00-14, C30-32)	2 055	2 072	2 090	2 110	2 129
Central Nervous System (C70-72)	734	740	746	752	758
Liver and intrahepatic bile ducts (C22)	369	375	380	386	391
Mesothelium (C45)	243	247	250	254	258
Other	24 777	25 113	25 444	25 834	26 214
Total	56 926	57 686	58 453	59 313	60 124

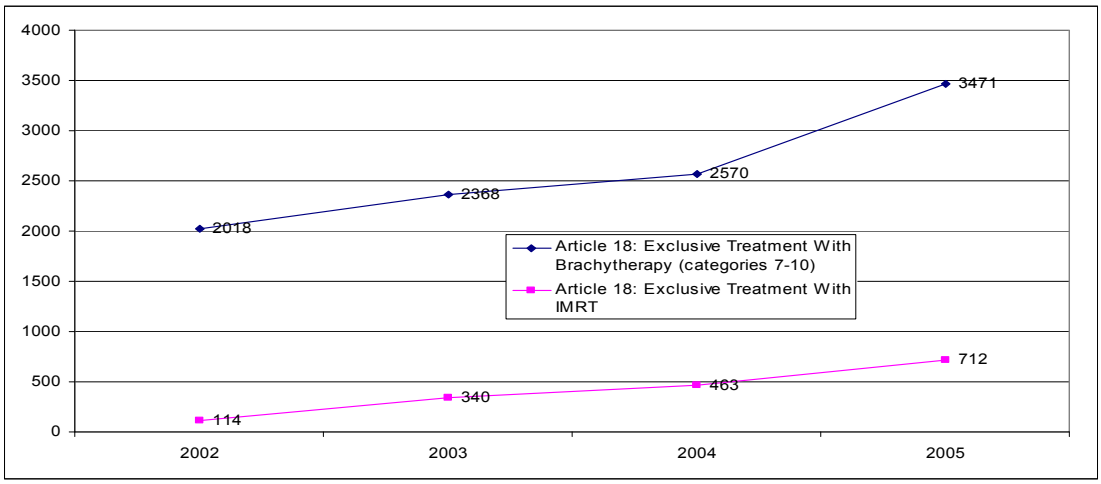
Based on Flemish Cancer Register : www.kankerregister.be and population data from ECODATA, FOD Economie, KMO, Middenstand & Energie

[e] incidence rates per sex-age (5-year groups) profile applying to Flanders 2005 were multiplied by demographic frequencies for Belgium 2002-2006.

7.2.3 Assumptions for IMRT delivery

The principal therapeutic assumption we made is that patients being treated with IMRT would otherwise, i.e. in absence of IMRT as a therapeutic choice, have been treated with 3DCRT (prostate cancer, head and neck cancer) or 2DRT (breast cancer)[f]. The main implication of this assumption is that alternative treatment shifts, e.g. from patients who would have been treated (exclusively) with brachytherapy for prostate cancer, are excluded from our analysis. Given the absence of data on the clinical outcome of therapeutic substitution between IMRT and brachytherapy in prostate cancer patients, it was deemed judicious to approach the introduction of IMRT as a "ceteris paribus" transition from patients treated with 3DCRT to patients treated with IMRT. This assumption is corroborated by Figure 4, indicating no apparent substitution effects have been playing that would divert patient treatment preferentially to IMRT. It would also seem that the newly introduced regulation on the reimbursement of investment and operational costs from April 2005 on has not considerably influenced the delivery of brachytherapy. As the new regulation is solely based on the number of deliveries through categories 1-4 it tends to favour the implementation of brachytherapy (categories 6-10) less than the former regulation did.

Figure 4 Brachytherapy versus IMRT under article 18: number of treatment courses



External beam radiotherapy uptake as a percentage of newly diagnosed patients by tumour type was derived from CCORE 2003[105]. This publication sets "optimal", i.e. evidence-based, radiotherapy uptake rates through a systematic review for a comprehensive range of cancers with a view to facilitating further planning efforts for external radiotherapy infrastructure needs. These data have already been applied internationally in estimating external radiotherapy investment costs [106] [107] [98]. Table 13 summarizes the uptake rates that are most pertinent to our analysis.

Table 13 Uptake rate for external beam radiotherapy by type of cancer

Tumour type	Proportion of all cancers	Patients receiving RT (%)
Breast	13%	83%
Prostate	12%	60%
Head and Neck	4%	78%

[f] At present, breast cancer patients are excluded from reimbursement for 3DCRT (see appendix 6).

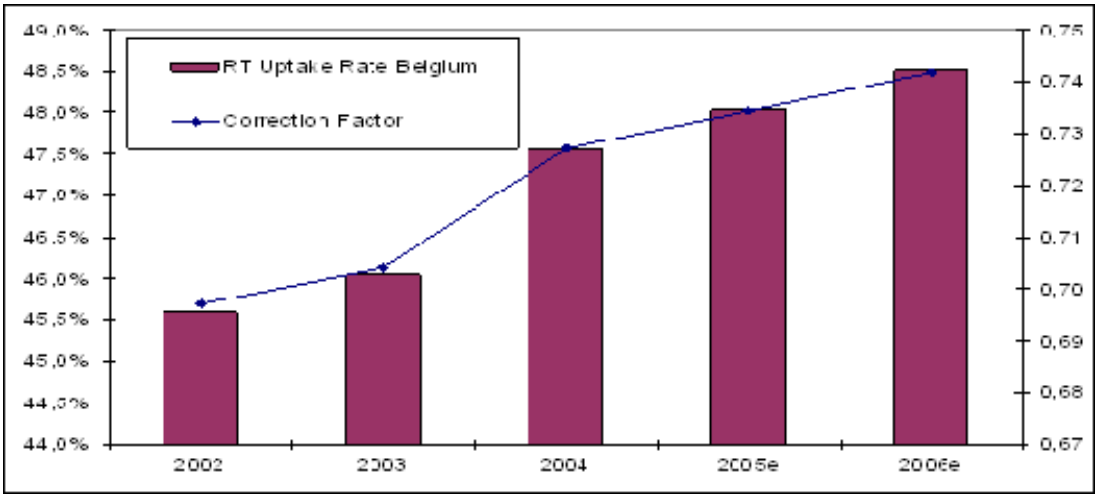
Overall, an optimal external radiotherapy rate of 52.3% is put forth for newly diagnosed cancer patients. Adding 25% of cancer patients requiring re-treatment through external radiation (regardless of tumour type), an optimal level of 65.4 treatment courses per one hundred cancers is assumed [105].

Comparing the number of external RT treatment courses for 2002-2003-2004 (see appendix 6) to the extrapolated cancer incidence for the same year, we obtain percentages of respectively 45.6%, 46.1% and 47.5% for Belgium. Although the uptake rates are persistently below the rate put forth by CCORE 2003, a trend towards a higher uptake rate is observed (geometric average for year-to-year growth rates of 1,02%). In applying the average geometric growth rate for 2002-2004 we can extrapolate uptake rates for 2005 and 2006 of respectively 48.03% and 48.52% (see Figure 5).

The lower uptake rates for Belgium may imply alternative therapeutic interventions are preferred over external radiotherapy or indicate differences in average numbers of fractions per course, etc. Furthermore, current treatment practice in Europe has been reported to be "about 45-55%" of new cancer patients receiving external radiation [108], putting the CCORE optimal uptake rate at the upper end of estimated current treatment practices.

In order to assess the short-term budget impact of IMRT we will correct RT uptake rates in our model with year-to-year downward correction factors ranging from of 0.7 (2002) to 0.74 (2006) as this would be more in line with the actual Belgian situation (see Figure 5). These correction factors were obtained by dividing the actual RT uptake rates for Belgium by the optimal uptake rate of 65.4% estimated by CCORE 2003.

Figure 5 Overall RT uptake rates for Belgium



Extrapolated rates ("e") for 2005 and 2006

The eventually applied RT uptake rates and resulting patient numbers can be found in Table 14 and Table 15 (see also appendix 10). In our model we will additionally explore the impact the higher CCORE uptake rates have on our endpoint as well as the higher uptake rate of 80% reported for breast cancer patients in Belgium [59].

Table 14 (IM)RT uptake rates in model

Localisation	2002	2003	2004	2005	2006
Breast (C50)	73%	74%	76%	77%	77%
Prostate (C61)	53%	53%	55%	55%	56%
Head & Neck (C00-14, C30-32)	68%	69%	71%	72%	73%

Table 15 (IM)RT patients in model

Localisation	2002	2003	2004	2005	2006
Breast (C50)	6 813	6 955	7 255	7 411	7 567
Prostate (C61)	4 747	4 870	5 110	5 253	5 389
Head & Neck (C00-14, C30-32)	1 405	1 431	1 491	1 520	1 550

Furthermore, we will hypothesize that the number of RT fractions under IMRT is equal for the number of RT fractions under 3DCRT/2DRT for a similar patient case. Expert opinion has suggested [109] the number of fractions may be expected to drop under IMRT compared to 3DCRT/2DRT, in particular for head and neck cancers, but this has not yet been clinically established and thus is not in agreement with current clinical practices for IMRT delivery. If the average number of fractions would differ between IMRT and 3DCRT/2DRT for a given patient case, additional cost items such as number of days spent in hospital, reimbursed taxi fares to and from the RT department, etc. would have to be accounted for in our model as it addresses the incremental cost between 3DCRT/2DRT and IMRT.

A final assumption with respect to therapeutic aspects is that, were a 3DCRT/2DRT patient in our base case scenario treated as an inpatient/outpatient (s)he will be treated accordingly as an IMRT patient. This assumption is equivalent to stating there is no reason to assume that patients undergoing IMRT or 3DCRT/2DRT treatment would tend to be more or respectively less hospitalized.

7.2.4 Cost Assumptions

Given the applied assumptions the only cost items varying in our incremental analysis will be those taking into account the reimbursement category of external radiotherapy, i.e. the cost for treating a patient in a higher reimbursement category (category 4) than (s)he would otherwise, in the absence of IMRT as a therapeutic choice, have been (category 3 for prostate, head and neck cancer patients, category 2 for breast cancer patients). As reimbursements for category 2 compared to category 3 patients are markedly lower, the incremental cost for breast cancer IMRT in our model will be consistently higher. A detailed overview of relevant budgetary regulations applying to Belgian radiotherapy departments will be found in appendix 8. Consequently, the cost differences in these two variables can be assessed as follows:

- Fee-for-service: ranging (between 2002 and 2006) from 549€ to 573€ or 1 291€ to 1 347€ added per IMRT treatment course for prostate / head and neck cancer patients or breast cancer patients respectively. These differences in reimbursement have been derived in appendix 7 by means of example for 2003 and apply to historically reported RIZIV/INAMI reimbursement tariffs for 2002-2006. It is assumed the extra reimbursement for head and neck / prostate cancer patients is equal to the difference between maximum reimbursements for category 4 and for category 3 patients (see last table of appendix). The additional reimbursement for breast cancer patients is hypothesized to concur with the difference between maximum reimbursements for respectively category 4 and category 2 patients (ibidem) as found to be in line with current regulations (see appendix 6).
- Annual increase in reimbursed investments costs for the radiotherapy department (chapter A3 of the financial regulation): about 60€ or 120€ for every IMRT treated prostate/head and neck cancer patient or respectively breast cancer patient (see appendix 8). In agreement with present regulations we assumed an annual lump sum of 90 000€ was reimbursed for every additional "750 points" with category 1, 2, 3, 4 treatment courses accounting for 1, 2, 2.5 and 3 points respectively. We attributed an average marginal value of (around) 120€ for every additional point.
- Annual increase in reimbursed operational costs for medical-technical departments (chapter B3 of the financial regulation): about 170€ or 340€ in 2006 for every IMRT treated prostate/head and neck cancer patient or breast cancer patient respectively will be hypothesized (see appendix 8). These amounts were corrected for inflation[g] on a yearly basis and are made up of two components: a lump sum of around 180€ per additional point and varying lump sums depending on the size of the related radiotherapy department (as measured by its points total). For the latter component we calculated average marginal values per additional point for the various size categories (corresponding to specific lump sum reimbursements) and included the average marginal value in our model. A detailed analysis can be found in appendix 8.

g general cost of living as measured by the Belgian CPI[110]

Key points

- **Epidemiologic input data for Belgium were obtained through linear extrapolations of Flemish data, corrected by age and sex, over the years 2002-2006.**
- **The principal therapeutic assumption is that patients being treated with IMRT would otherwise, i.e. in absence of IMRT as a therapeutic choice, have been treated with 3DCRT (prostate, head and neck cancers) or 2DRT (breast cancers).**
- **External beam radiotherapy uptake as a percentage of newly diagnosed patients by tumour type was derived from an international review (CCORE 2003) and adapted to be more in line with the Belgian situation.**
- **Fee-for service costs were derived from the prevailing RIZIV/INAMI tariff regulations (article 18).**
- **The annual increase in reimbursed investment and operational costs for the radiotherapy department were based on the current regulatory framework.**

7.2.5 Simulations

The budget impact simulations will follow the main outline of our clinical discussion, which dealt primarily with IMRT in prostate cancer, head and neck cancer and breast cancer in agreement with the bulk of published research on IMRT.

Simulation outcomes are reported as differences between comparator scenario costs and baseline scenario costs. Outcomes are reported in going values (euro, nominal values over the period 2002-2006).

7.2.6 Comparator Scenarios

A first scenario will take the treatment of all projected prostate and head and neck cancers expected to undergo external radiation by IMRT into consideration: "P-H-N" scenario. This scenario would cover more than 23% of all patients treated with external radiotherapy.

A second scenario will simulate the budgetary outcome when, in addition to the patient populations in scenario 1, all breast cancer patients qualifying for external radiation therapy are treated with IMRT= "P-H-N-B" scenario. This scenario would include almost 50% of all patients treated with external radiotherapy, more than the 40% mentioned by some experts. [109]

7.2.7 Results

Detailed developments and aggregates for our model outcomes are shown in appendix 10. Table 17 is derived from those figures and gives an overview of the differences in overall budgets between comparator scenarios and the baseline scenario. For 2003, the total budget impact for the P-H-N scenario is estimated at around 5 000 000€ (breaking down into 72.2% of added fee-for-service expenses, 7.4% of investment costs and 20.4% of operational costs). We estimated the overall public payer cost in 2003 for external radiotherapy at about 91 000 000€ (see appendix 9). As a consequence, we conclude there would be a budgetary impact of about 5.4% added to the running budget for external radiotherapy resulting from the delivery of IMRT to patients suffering from prostate and head and neck cancers.

From the below table it also becomes apparent that the extension of current category 4 reimbursement for IMRT to breast cancer patients (currently reimbursed under category 2) may prove to be a sizeable cost inducing measure. Setting the IMRT reimbursement for breast cancer patients at the same level as the ruling level for prostate, head and neck cancer would imply a (maximum) further raise of the 2003 budget for external radiotherapy with approximately 12 000 000€. This means a total increase with 18.7% of the overall budget for external RT. Of course, this figure is estimated starting from the assumption all externally radiated breast cancer patients would clinically qualify for an IMRT treatment, which seems unlikely. Setting the IMRT uptake variable at 25% (flat rate for 2002-2006) of all breast cancer patients (as suggested by some of the external experts related to this report) brings the overall budget impact for the P-H-N-B scenario down to around 9 000 000€ (a decrease of our initial outcome with over 47%). However, we are foremost concerned with the maximum budget impact that would apply if the current regulation on IMRT would be extended to breast cancer patients. As this regulation is mostly based on the anatomic localisation of tumours, our model estimates hold true as estimations of maximal budget impacts. A further exploration of breast cancer IMRT uptake is made by setting the uptake rate at 80% for 2002-2006, a percentage found in a recent Belgian publication[59]). The result for this simulation is a total budget impact of about 18 200 000€ for 2003, an increase of our initial estimate by 6,3%.

Finally, we can derive (through appendices 7, 8 and 10) the overall reimbursement per treatment course for category 4 patients as shown in Table 16 (see also Table 18). Adding a further 7.4% for inpatient daily bed costs and outpatient transportation cost (in keeping with our overall budget analysis in appendix 8) this leads to a comprehensive estimate of 5 682€ (2003 € value).

Table 16 Overall Reimbursement (Category 4, € in 2003 value)

ITEM	REIMBURSEMENT 2003 €	
Fee -for Service (Article 18)	3 986 €	75%
Investment Costs (A3)	352 €	7%
Operational Costs: Departmental Lump Sums (B3)	439€	8%
Operational Costs: Point Lump Sums (B3)	511 €	10%
Total	5 288 €	100%

Key points

- **For 2003 the total budget impact for the P-H-N scenario is estimated at around 5 000 000 € (breaking down into 72.2% of added fee-for-service expenses, 7.4% of investment costs and 20.4% of operational costs). There would be an estimated maximum budgetary impact of about 5.4% added to the running budget for external radiotherapy resulting from the delivery of IMRT to patients suffering from prostate and head and neck cancers.**
- **The extension of current category 4 reimbursement for IMRT to breast cancer patients may prove to be a sizeable cost inducing measure, setting the overall increase at a maximum of around 17 000 000€ for 2003. This would add 18.7% to the running budget for external radiotherapy, assuming all externally radiated patients suffering from prostate, head and neck or breast cancer receive IMRT.**

Table 17 Model Scenarios Overview

PATIENT GROUP	2002		2003		2004		2005		2006	
	#Pat	BUDGET IMPACT	#Pat	BUDGET IMPACT	#Pat	BUDGET IMPACT	#Pat	BUDGET IMPACT	#Pat	BUDGET IMPACT
Prostate	4 747	3 626 877 €	4 870	3 808 710 €	5 110	4 056 581 €	5 253	4 194 615 €	5389	4.313.074 €
Head & Neck	1 405	1 073 596 €	1 431	1 119 383 €	1 491	1 183 351 €	1 520	1 213 951 €	1550	1.240.110 €
Breast	6 813	11 721 521 €	6 955	12 262 951 €	7 255	12 975 251 €	7 411	13 323 467 €	7567	13.630.892 €
BUDGET IMPACT										
P-H-N	4 700 472 €		4 928 093 €		5 239 932 €		5 408 566 €		5 553 184 €	
P-H-N-B	16 421 993 €		17 191 043 €		18 215 182 €		18 732 033 €		19 184 076 €	
BUDGET IMPACT (% OF OVERALL PUBLIC BUDGET)										
P-H-N	0.03%		0.03%		0.03%		0.03%		No Data	
P-H-N-B	0.12%		0.11%		0.11%		0.11%			

Table 18 Total Reimbursement per Category (2003€)

	Category1	Category2	Category3	Category4
Fee–for-service (Article 18)	1 414 €	2 658 €	3 534 €	3 986 €
Investment Costs (A3)	117 €	235 €	293 €	352 €
Operational Costs: Departmental Lump Sums (B3)	146 €	293 €	366 €	439 €
Operational Costs: Point Lump Sums (B3)	170 €	341 €	426 €	511 €
TOTAL	1 848 €	3 526 €	4 619 €	5 289 €

7.3 VALIDATION

7.3.1 Main Limitations

As external radiotherapy uptake percentages have been shown to vary widely across countries/regions, it would have been preferable to dispose of uptake rates specified by tumour type applying to Belgium. Therefore we will explore the possible uncertainty of applied uptake rates in our sensitivity analysis.

A further limitation in our model is related to the assumption that all patients qualifying for external radiation will undergo IMRT. It is clear that certain indications, e.g. calling for palliative radiation, are unlikely to receive IMRT treatment. Nevertheless, as current regulations do not restrict radiotherapy reimbursements in this regard (see appendix 6) our estimates correctly allow in this case for maximum budget impacts given current regulations.

In setting the public payer reimbursement of operational costs we assumed external radiotherapy courses (as measured by departmental point scores, corrected for historically reported IMRT courses) are distributed uniformly over existing RT departments, which we concretized in our model by calculating an average marginal reimbursement per added point to the departmental points score. Our analysis did indicate a wide difference between possible marginal reimbursements depending on the historic RT department size. We will assess the possible impact of this variable by running the model for respectively minimum and maximum values of this variable.

Given the fact that our model is foremost concerned with making a short-term assessment of potential budget impact going by current reimbursement practices, additional analyses are required in order to successfully assess potential long term evolutions:

- ABC analyses needed to establish long term equilibrium reimbursement levels,
- Assessments of potential treatment shifts toward IMRT deriving from alternative therapeutic interventions (brachytherapy, chemotherapy, etc.). Future updates of the model in this direction may result into overall savings for health care budgets as radiotherapy is reportedly a relatively inexpensive component of cancer care. [98]

7.3.2 Sensitivity Analysis

Based on percentages CCORE 2003 quotes as outer values for uptake rates in breast, prostate, head and neck cancer patients[105] and outer values we derived for the marginal operational cost per added score point contributing to departmental lump sum reimbursements (see appendix 8) univariate alterations were made to the initial simulation.

As limited data on the distribution of the above variables were available we did not undertake a probabilistic sensitivity analysis. Other input parameters concern arbitrarily fixed values that are at the discretion of policy makers (billing code fees, etc.). Therefore we did not alter these parameters in various accessory simulations.

The values applied in our sensitivity analysis are summarized in Table 19.

Table 19 Parameter values altered in sensitivity analysis

Variabele	Minimum	Maximum
Breast Cancer IMRT Uptake (CCORE 2003)	82.95%	85.25%
Prostate Cancer IMRT Uptake (CCORE 2003)	55.00%	67.00%
Head & Neck Cancer IMRT Uptake (CCORE 2003)	74.00%	84.00%
(Reimbursement of) Operational Costs	0 €	339 €

The results of these simulations (see Table 20) indicate that the highest impact on the modelled budget impact from feasible variations in input parameters can be traced to changes in the marginal operational costs. In order to amend for this uncertainty detailed information on the exact size (number of treatments by patient category on an annual basis) of various radiotherapy departments in Belgium would be required.

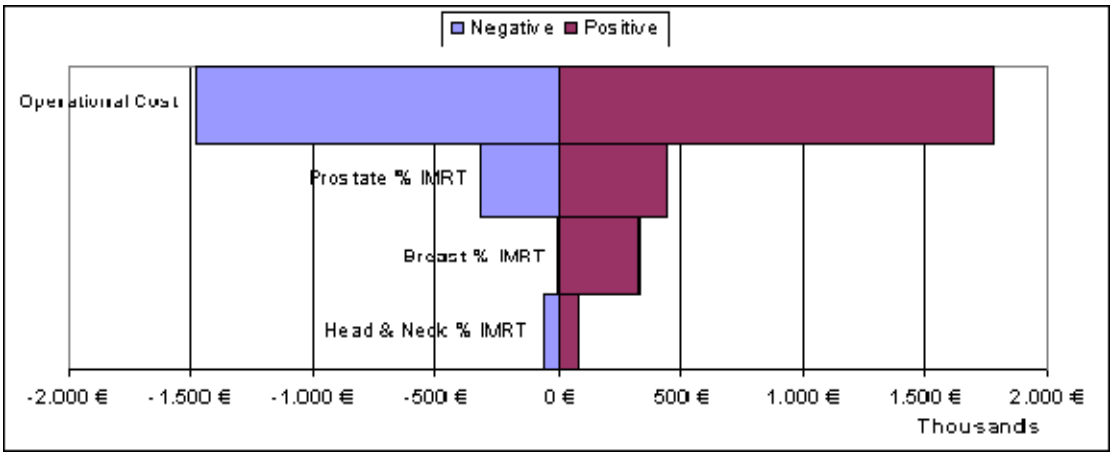
The possible variation in the model outcome associated to variations in Operational Costs is up to five times higher than the possible outcome variation related to uncertainty in the uptake rate for prostate cancer patients. Further, given the smaller margin of uncertainty with breast cancer IMRT uptake and the low incidence of head and neck cancer patients, model uncertainty dependent on these latter parameters is less marked. Uncertainty in uptake rates can be mitigated through the use of rates specifically applying to a Belgian population.

Figure 6 plots the data from Table 20 as deviations (in thousands of euros) from the initial model outcome for P-H-N-B 2003, allowing for a more graphical understanding of parameter influence in model uncertainty.

Table 20 Simulation outcomes for the sensitivity analysis

Simulation (P-H-N-B 2003)	Min	Max
Initial Simulation	17 200 000 €	
(Reimbursement of) Operational Cost	15 700 000 €	19 000 000 €
Prostate Cancer IMRT Uptake (CCORE 2003)	16 900 000 €	17 600 000 €
Head & Neck Cancer IMRT Uptake (CCORE 2003)	17 200 000 €	17 500 000 €
Head & Neck (C00-14, C30-32) Uptake	17 100 000 €	17 300 000 €

Figure 6 Tornado diagram (one-way sensitivity simulations)



7.3.3 Conclusion and discussion

Given the adopted assumptions in our model the budget impact of IMRT delivery to head and neck / prostate cancer patients would amount to about 5 000 000€ (2003 €) or an estimated 5.4% added to the running budget for external radiotherapy (0.03% of the overall reimbursements budget that year).

Our simulations also indicate that by reimbursing IMRT for breast cancer patients under category 4 regulations alongside prostate / head & neck cancer patients, the current standard for IMRT reimbursement, could potentially lead to total increase of the budget for external radiotherapy with approximately 17 000 000€ (2003 €) or an additional 18.7% (0.11% of the overall reimbursements budget that year) following the P-H-N-B implementation scenario.

Future improvements/extensions of the model would principally concern:

- An empirical assessment of the actual point allocation across all Belgian RT departments to allow for a more precise estimate for the applied marginal operational cost reimbursements, which proved a salient point of interest in our sensitivity analysis.
- The importance of setting correct uptake rates, as illustrated through our sensitivity analysis.
- The net budgetary effect generated by therapeutic shifts from cancer care interventions other than external radiotherapy, which may incur overall budget savings.

As updatability is an important requirement for any budget impact analysis, the authors actively encourage further research input.

8 GENERAL CONCLUSIONS

Our general discussion will be structured following the answers our report prompted in response to the main research questions invoked in our opening chapter.

Clinical effectiveness

We conclude that weak to moderate quality evidence is available demonstrating a reduction in toxicity after IMRT compared with 2DRT or 3DCRT for head and neck cancer, prostate cancer and breast cancer. Current reports do no allow for a good comparison of relapse or survival data between IMRT and conventional techniques.

Patient safety

On the topic of patient safety we observe that total body irradiation is higher using IMRT and, in theory, may overall double the incidence of fatal secondary malignancies compared with standard external radiotherapy techniques. Especially younger patients are at risk. Large variations exist in total body irradiation between various IMRT techniques. Also use of daily radiation-based imaging for treatment set-up verification adds to the overall exposure.

Cost-effectiveness

In respect of the cost-effectiveness of the IMRT compared with 3DCRT our report indicates that no firm conclusion can be drawn on the cost-effectiveness of IMRT in comparison to alternative interventions, in particular 3DCRT. Furthermore, IMRT may evolve into a universally promoted standard before its incremental cost-effectiveness has been established, especially as regards the clinical context in the USA given prevailing (Medicare) reimbursement levels.

Cost of IMRT

We showed that the start-up cost for IMRT specific equipment is considerable, amounting up to 7 million euro for a newly operational unit. Upgrading an already operational 3DCRT treatment unit to an IMRT unit can incur an extra investment of up to 50%. Cost estimates vary widely as often specific options are bundled in hardware and software packages. With regard to staffing costs, these can be expected to increase drastically (by a factor of around 3) for physicists with IMRT implementation. The workload of related health professionals (physicians, etc.) may be expected to increase for IMRT as well. However, no publications specifically addressing the comparison between IMRT and 3DCRT for this aspect were found. If the optimality of current reimbursement levels is to be assessed detailed analyses such as ABC studies and comprehensive reimbursement estimates on the topic of IMRT would be required.

Budget impact

We estimated the budget impact of treating all prostate and head and neck cancer patients, given current (2007) regulations would apply, with IMRT at around 5 000 000 € in 2003 (breaking down into 72.2% of added fee-for-service expenses, 7.4% of investment costs and 20.4% of operational costs). This would imply that about 5.4% would be added to the running budget for external radiotherapy. The extension of current category 4 reimbursement for IMRT to breast cancer patients may prove to be a sizeable cost inducing measure, more than tripling the modelled impact for prostate and head and neck cancers. By intent we publish our estimates as the results of an updatable model. Future innovations should foremost concern an analysis of patient distribution across RT departments, the inclusion of IMRT uptake rates per tumour site applying specifically to Belgium and the extension to the net budgetary effect generated by therapeutic shifts from cancer care interventions other than external radiotherapy (chemotherapy, etc.).

9 RECOMMENDATIONS

- **In general, more long term data are needed for IMRT treated patients, to confirm any survival advantage and to assess the increased risk of secondary malignancies in comparison with standard external radiotherapy techniques. Manufacturers and users of IMRT hardware and software should be made more aware of this risk of induction of secondary malignancies, and product improvement is to be stimulated.**
- **As IMRT for head and neck cancer is more difficult to plan and deliver, and still an area of investigation, for the time being its use in these patients should be restricted to centres with the necessary expertise and preferentially those that are performing research in this area. The IMRT expertise at a centre could be assessed based on quality assurance measures in place, monitoring of patient outcomes and participation in clinical trials. A more appropriate financing of complex IMRT planning in head and neck cancer is to be considered.**
- **IMRT or (3D) conformal radiation therapy (3DCRT) is recommended for high dose external radiotherapy in prostate cancer.**
- **Use of IMRT may reduce skin complications in breast cancer radiotherapy, primarily in heavy breasted women. Long term studies are required to assess the risk of induction of a secondary tumour in the contralateral breast after IMRT before introduction into common practice. Specific research financing of IMRT in breast cancer should be considered.**
- **More frequent imaging for guidance of IMRT is expected to further improve the efficacy and safety of IMRT, particularly in targets showing internal movement, e.g. in case of prostate cancer. Financing of imaging for IMRT should be re-assessed in the future.**

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11 APPENDICES

APPENDIX 1: RADIOTHERAPY CENTRES

Registration	Institution	Localisation
008	RESEAU HOSPITALIER DE MEDECINE SOCIALE	BAUDOUR
009	ALGEMEEN ZIEKENHUIS MIDDELHEIM	ANTWERPEN-2
010	HOPITAL ST.-JOSEPH, STE.-THERESE ET IMTR.	GILLY
020	C.H. PELTZER - LA TOURELLE	VERVIERS
026	ALGEMEEN ZIEKENHUIS ST. MAARTEN	DUFFEL
049	ALGEMEEN ZIEKENHUIS ST.-JAN (A.V.)	BRUGGE
063	ST.-ELISABETHZIEKENHUIS	TURNHOUT
079	INSTITUT JULES BORDET	BRUXELLES--1
099	ALGEMEEN ZIEKENHUIS ST. AUGUSTINUS	WILRIJK
110	ALGEMENE KLINIEK ST.-JAN	BRUSSEL--1
111	V.Z.W. EUROPAZIEKENHUIZEN	BRUSSEL-18
117	HEILIG HART ZIEKENHUIS V.Z.W.	ROESELARE
126	ONZE LIEVE VROUW ZIEKENHUIS	AALST
143	AKADEMISCH ZIEKENHUIS (V.U.B.)	BRUSSEL--9
146	CENTRE HOSPITALIER DE JOLIMONT - LOBBES	HAINE-SAINT-PAUL
166	CLINIQUE STE.-ELISABETH	NAMUR
243	VIRGA JESSE ZIEKENHUIS (A.V.) Limburgs Oncologisch Centrum	HASSELT
290	ALGEMEEN ZIEKENHUIS SINT - LUCAS	GENT
322	UNIVERSITAIRE ZIEKENHUIZEN K.U.L.	LEUVEN
332	C.H. INTERREGIONAL EDITH CAVELL (CHIREC)	BRUXELLES-18
396	ALGEMEEN ZIEKENHUIS GROENINGE	KORTRIJK
403	CLINIQUES UNIVERSITAIRES ST.LUC	BRUXELLES-20
670	UNIVERSITAIR ZIEKENHUIS	GENT
707	CENTRE HOSPITALIER UNIV. SART-TILMAN	LIEGE-1 (SART-TILMAN)
718	C.H.U. A. VESALE	MONTIGNY-LE-TILLEUL
718	CENTRE HOSPITALIER DE CHARLEROI	CHARLEROI

C.H.U. VESALE and CENTRE HOSPITALIER DE CHARLEROI share the same registered radiotherapy facility.

APPENDIX 2: BELGIAN RADIOTHERAPY CENTRES SURVEY (FRENCH AND DUTCH)

1. Votre centre a-t-il traité des patients par IMRT en 2006?
   - Oui/Non: ……
   - Si oui, passez au point suivant, sinon passez à la dernière question (point 8).
2. Depuis quand votre centre a-t-il recours à l'IMRT? Année+mois: ……..
3. Radiothérapie externe : IMRT versus autres : patients ayant débuté leur traitement dans l'année.

	2001	2002	2003	2004	2005	2006	2007 (attendu)
IMRT							
Non-IMRT							

4. Matériel IMRT installé dans votre centre:

Equipement/logiciel	Spécifiez (indiquez le nombre entre parenthèses)
Type d'accélérateur	
Verification system	
Planning station and software	
Système d'imagerie dédiée	
Système de dosimétrie	

5. Quelles procédures d'assurance qualité spéficiques à l'IMRT suivez-vous dans votre centre ?……
6. Combien d'équivalents temps plein (ETP) ont travaillés spécifiquement à l'IMRT dans votre centre en 2006? (correspondant au volume traité au Point 7):.... ETPs radiothérapeutes, …. ETPs radiophysicien/ingénieur, ... ETPs infirmiers
7. Volume traité par IMRT en 2006 par indication, exprimé en nombre de patients ayant débuté leur traitement dans l'année et en nombre de séances de radiothérapie:

Indication	Nombre de patients ayant débuté un traitement IMRT par indication en 2006	Nombre total de séances effectuées par indication en 2006
Prostate		
Tête et cou		
Sein		
Poumon		
Système Nerveux Central		
Col de l'utérus et endomètre		
Métastases hépatiques		
Rectum		
Base du crâne et paraspinal		
Mésothélium		
Pédiatrie		

Autres (à spécifier):
…
…
…

8. Si vous avez répondu non à la première question, envisagez-vous l'acquisition de matériel IMRT?
   - Oui/Non: ……
   - Pour quelles raisons ?

   ……

   - Si oui, dans quel délai cette acquisition est-elle envisagée ? ……..
   - Dans quelles indications :

   ……

   ……

   ……

SURVEY (DUTCH)

1. Heeft uw centrum IMRT behandelingen uitgevoerd in 2006?

   Ja/nee: ……

   Indien ja ga naar punt 2. Indien nee ga naar laatste vraag (punt 8).

2. Sinds wanneer voert uw centrum IMRT behandelingen uit? Jaar+maand: …….

3. Externe radiotherapie: IMRT versus niet IMRT, patiënten gestart per jaar:

	2001	2002	2003	2004	2005	2006	2007 (expect)
IMRT							
Niet-IMRT							

Nota : gelieve alleen de behandelingen met intensiteitsgemoduleerde bundels te registreren als IMRT (en niet alle categorie 4 behandelingen)

4. IMRT materiaal in uw centrum

Toestellen/software	Specifieer (plus aantal)
Accelerator hardware	
Verification system	
Planning station and software	
Dedicated imaging system	
Dosimetry system	

5. 5. Welke specifieke QA/kwaliteitscontroles voert uw centrum uit voor IMRT?

   ……
   ……..…..

   ……
   ……..…..

6. Hoeveel FTEs werkten in 2006 op uw dienst radiotherapie specifiek op IMRT (corresponderend met de werkbelasting gedetailleeerd hieronder): ....

FTEs radiotherapeuten, …. FTEs radiotherapie ingenieur/physici, ... FTEs verpleging

7. Werkbelasting IMRT per indicatie, in aantal gestarte patiënten in 2006 en totaal aantal radiotherapie sessies in 2006:

Indicatie	Patiënten in 2006 gestart met IMRT	Totaal aantal IMRT sessies in 2006 per indicatie
Prostaat		
Hoofd-hals		
Borst		
Long		
Centraal Zenuwstelsel		
Cervix & endometrium		
Lever/abdominale metastasen		
Rectum		
Schedelbasis en paraspinale		
Mesothelioom		
Pediatrie		
Andere (specifieer): … … …		

8. Indien nee op eerste punt: overweegt u aankoop IMRT? Wanneer? Waarom wel/niet? Indicaties?

   - Ja/nee: ……
   - Waarom wel/niet?

   ……

   ……

   ……

   - Indicaties?

   ……

   ……

   ……

APPENDIX 3 : INAHTA SURVEY

ORGANISATION AND FINANCING OF INTENSITY-MODULATED RADIOTHERAPY

International Comparison: Questionnaire

Introduction

The Belgian Health Care Knowledge Centre is currently conducting a rapid HTA of Intensity-Modulated Radiotherapy.

We would like to compare the Belgian situation with other countries. Such a comparative analysis might also be of interest to other members of INAHTA. We would therefore very much appreciate if you could take some time of the answer the following questions. May we ask to send the completed questionnaire to Cecile.camberlin@kce.fgov.be before March the 1st.

9. The questions in **black and bold** are the **most important** for us. If it is difficult for you to answer one of these questions (e.g. because the data are not available in your country), just skip the question. To allow for a more in depth comparison between countries, we have also added some questions in blue colour. It may take more time for answering these questions (or for finding the source of information). They should be considered as OPTIONAL and should not discourage you from answering the rest of the questionnaire. But, of course, it would be great if some of you are able to answer these questions too.

1. Which country or region are you representing?
2. National population size of your country (2006)

Supply – Statistics

3. How many IMRT-installation are in operation in your country?
4. How many radiation oncologists are operating in your country?
5. How many radiophysicists are operating in your country?
6. Is there any shortage of radiophysicists in your country? ☐ YES ☐ NO
7. How many of IMRT-installations are located in a hospital?
8. How many are located in an ambulatory setting?

Activity – Statistics

Please provide ACTIVITY data for 2006 Which country or region are you representing?

National population size of your country (2006)

or (if not available for 2006) most recent year, namely:

Total number of IMRT-treated patients in your country?

If further breakdowns are available, how many per type of indication (number of patients and number of sessions overall)?

- Prostate cancer: patients sessions
- Head and neck cancer: patients sessions
- Breast : patients sessions
- Lung: patients sessions

- Central nervous system patients sessions
- Gynaecological : patients sessions
- Liver: patients sessions
- Rectum: patients sessions
- Skull base and paranasal: patients sessions
- Mesothelium : patients sessions
- Paediatrics: patients sessions
- Other: patients sessions

Financing

How are the IMRT-treatments reimbursed in your country?

1. No separate reimbursement (within the hospital budget) ☐ YES ☐ NO
2. Separate financing of the equipment ☐ YES ☐ NO
   a. How, subsidized by the govt? ☐ YES ☐ NO
   b. Size of this financing (currency and/or %):
   c. Other, please specify:
3. Separate financing of the equipment – operating costs? ☐ YES ☐ NO
   d. How, subsidized by the govt? ☐ YES ☐ NO
   e. Size of this financing (currency and/or %):
   f. Other, please specify:
4. Separate remuneration of the radiotherapist ☐ YES ☐ NO
   g. How, fee for service? ☐ YES ☐ NO
   h. Size of this financing (currency and/or %):
   i. Other, please specify:

Quality Assurance :

How is the internal and external Quality Assurance of IMRT-treatments organized in your country?

Are there any official treatment guidelines? ☐ YES ☐ NO

Are there any official radiotherapy equipment guidelines? ☐ YES ☐ NO

Are there any official IMRT specific equipment guidelines? ☐ YES ☐ NO

THANK YOU VERY MUCH FOR YOUR COOPERATION!!!

Your e-mail address: *Your tel. number:*

APPENDIX 4: HEALTH ECONOMIC ANALYSIS

LITERATURE REVIEW: SEARCH FILTERS

Date	29 11 2006
Database	Database: CINAHL - Cumulative Index to Nursing & Allied Health Literature
Date covered	<1982 to November Week 3 2006>
Search Strategy	1 (radiotherap$ and computer$).tw. (23) 2 (intensi$ adj2 modul$ adj2 radioth$).tw. (12) 3 (arc and $therap$).tw. (46) 4 IMRT.tw. (32) 5 RCMI.tw. (1) 6 exp Radiotherapy, computer-assisted/ (19) 7 or/1-6 (122) 8 cost$.tw. (29168) 9 quality.tw. (48878) 10 survival.tw. (9880) 11 econom$.tw. (10941) 12 exp RADIOTHERAPY, COMPUTER-ASSISTED/ (19) 13 exp "COSTS AND COST ANALYSIS"/ (21034) 14 exp "Quality of Life"/ (16200) 15 Life Table Method/ (220) 16 exp SURVIVAL ANALYSIS/ (9653) 17 or/8-16 (112178) 18 7 and 17 (45) 19 limit 18 to yr="2000-2007" (38)

Date	29 11 2006
Database	Database: **Econlit**
Date covered	1969 to November 2006 (OVID)
Search Strategy	1 IMRT.tw. (0) 2 RCMI.tw. (0) 3 (((intensi$ and modul$) or arc$) and $therap$).tw. (4) 4 (conform$ and $therap$).tw. (0) 5 or/1-4 (4)

Date	12 12 2006
Database	Database: **BNI**
Date covered	1985 to November 2006 (OVID)
Search Strategy	1 IMRT.tw. (0) 2 RCMI.tw. (0) 3 (((intensi$ and modul$) or arc$) and $therap$).tw. (5) 4 (conform$ and $therap$).tw. (1) 5 or/1-4 (6)

Date	01 12 2006
Database	**CRD: HTA, NHS EED, DARE**
Search Strategy	IMRT OR RCMI OR (((intensit* AND modul*) OR arc*) AND *therap*) OR (conform* AND *therap*) restrict yr 2000 2007: 279 documents found

Date	13 12 2006
Database	EMbase
Search Strategy	#1. 'computer assisted radiotherapy'/exp 2 946 #2. 'imrt'/exp OR 'imrt' 2 107 #3. intensit* AND modul* AND radioth* 2 347 #6. arc AND (therap* OR radioth*) 2 481 #7. conforma* AND radioth* 3 328 #8. rcmi 29 #9. #1 OR #2 OR #3 OR #6 OR #7 OR #8 9 082 #10. 'quality of life'/ 114 247 #11. (((fiscal:ab,ti,de OR financial:ab,ti,de OR finance:ab,ti,de OR funding:ab,ti,de) OR ((variable*:ab, ti,de OR unit*:ab,ti,de OR estimate*:ab,ti,de) AND cost*:ab,ti,de) OR ('socioeconomics'/ OR 'cost benefit analysis'/ OR 'cost effectiveness analysis'/OR 'cost of illness'/ OR 'cost control'/ OR 'economic aspect'/ OR 'financial management'/ OR 'health care cost'/ OR 'health care financing'/ OR 'health economics'/ OR 'hospital cost'/ OR 'cost minimization analysis'/)) OR ('economic evaluation'/ OR 'cost'/ OR 'reimbursement'/ OR 'cost utility analysis'/ OR 'drug cost'/ OR 'energy cost'/ OR 'hospital cost'/ OR 'hospital running cost'/ OR 'biomedical technology assessment'/)) 569 350 #12. #10 OR #11 664 096 #13. #9 AND #12 598 #14. #13 AND [embase]/lim 477 #15. #14 AND ([dutch]/lim OR [english]/lim OR [french]/lim OR [german]/lim OR [italian]/lim OR [spanish]/lim) 462 #16. #15 AND [2000-2007]/py 364

Date	12 12 2006
Database	**Database: Ovid MEDLINE(R)**
Date covered	<1966 to November Week 3 2006>
Search Strategy	1 exp Radiotherapy, Computer-Assisted/ (8724) 2 (intensi$ adj2 modul$ adj2 radioth$).mp. (900) 3 (arc and $therap$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (793) 4 IMRT.mp. (1392) 5 RCMI.mp. (18) 6 or/1-5 (9669) 7 ec.fs. (227199) 8 cost$.tw. (192360) 9 exp "Quality of Life"/ (59942) 10 exp "Costs and Cost Analysis"/ (131639) 11 exp life tables/ (9050) 12 exp Survival Analysis/ (85765) 13 (or/7-12) and 6 (782) 14 limit 13 to yr="2000-2007" (594) 15 limit 14 to (dutch or english or flemish or french or german or italian or multilingual or spanish) (580)

Date	12 12 2006
Database	**Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations**
Date covered	<December 07, 2006>
Search Strategy	1 (radiotherap$ and computer$).tw. (22) 2 (intensi$ adj2 modul$ adj2 radioth$).tw. (79) 3 (arc and $therap$).tw. (33) 4 IMRT.tw. (151) 5 RCMI.tw. (0) 6 or/1-5 (225) 7 cost$.tw. (7809) 8 quality.tw. (13547) 9 survival.tw. (10865) 10 econom$.tw. (3682) 11 or/7-10 (32719) 12 6 and 11 (61) 13 limit 12 to yr="2000-2007" (59) 14 limit 13 to (dutch or english or flemish or german or italian or spanish or multilingual) (56)

ECONOMIC LITERATURE REVIEW: EVIDENCE TABLES

Economic evaluations summary sheet: Bonastre 2006

Author	Bonastre e.a. [66]
Country	France
Design	Costing analysis (full costing: absorption costing)
Perspective	Direct medical costs from hospital's perspective
Time window	Average overall treatment time for IMRT patient
Interventions	IMRT treatment protocol: irradiation preparation + actual irradiation
Population	Multi-centric patient case series: 99 patients diagnosed with either Oropharynx (55) or Nasopharnyx (44) cancer, recruited from 9 hospitals between July 1st 2003 and April 31st 2005.
Assumptions	Most cost components were estimated empirically. Financial data for each hospitals regarding direct costs were applied: directly involved staff, equipment, consumables and software. Applying overhead costs for each hospital were attributed to the IMRT protocol by means of a national (French) general distribution key.
Data source for costs	Data were collected from 9 participating hospitals. A general distribution key was used for overheads.
Cost items included	Main cost components: personnel, equipment, software, consumables and overheads.
Data source for outcomes	Does not apply
Discounting	Does not apply
Costs	Average overall IMRT treatment cost: 10 916€: 2 773€ for the planning stage and 8 143€ for the irradiation stage. Overhead costs amount to 4.955€ (or 45% of overall cost).
Outcomes	Does not apply
Cost-effectiveness	Does not apply
Sensitivity analysis	Does not apply as an empirical cost description was made. However, cost variability was assessed through a multilevel analysis. Authors found learning effects (experience of treating hospitals with the IMRT technique) to be the main cost driver.
Conclusions	High costs related to the introduction of the IMRT technique and the observed difference between actual cost and public reimbursement for the IMRT preparation phase warrant higher state subsidies for hospitals acquiring the IMRT technique.
Remarks	In all, patient numbers given the number of hospitals are limited: 99 patients / 9 hospitals. Important differences in treatment protocols between hospitals apply with regard to quality assurance (control of dosimetry and positioning). As overhead costs (which are attributed by means of a general factor) account for 45% of overall estimated costs one might argue that activity based (ABC) analyses in the 9 participating hospitals would allow for a higher degree of accuracy. It should be noted, however, that ABC analyses require a substantial added investment of means.

Economic evaluations summary sheet: Suh 2005

Author	Suh e.a. [65]
Country	United States
Design	Cost Comparison Analysis
Perspective	Societal cost perspective
Time window	Ranging from 5 to 30 treatment days depending on the intervention type
Interventions	Whole-breast Radiation Therapy (WBRT) Whole-breast Radiation Therapy with a Boost (WBRT-B) Whole-breast Accelerated Radiation Therapy (WBRT-AC) Whole-breast Intensity Modulated Radiation Therapy (WBRT-IMRT) Accelerated Partial Breast Irradiation (APBI-IC) Accelerated Partial Breast Irradiation – Interstitial (APBI-IT) Accelerated Partial Breast Irradiation – 3D Conformal RT (APBI-3DCRT) Accelerated Partial Breast Irradiation – Intensity Modulated RT (APBI-IMRT)
Population	60-year-old woman with stage I breast cancer in hospital-based outpatient setting
Assumptions	Patient lives approximately 20 miles from the facility Patient can maintain work full-time throughout treatment 0.5 hours spent at facility per treatment fraction
Data source for costs	Direct non-medical costs: theoretical estimates Direct medical costs: based on Medicare reimbursement scheme (CPT codes)
Cost items included	Direct medical costs: Medicare fee items Direct non-medical costs: time and transportation costs
Data source for outcomes	Does not apply given the study design
Discounting	Does not apply given the limited time frame assumed in the analysis.
Costs	WBRT: 8 500$ WBRT-B: 10 900$ WBRT-AC: 6 100$ WBRT-IMRT: 19 300$ APBI-IC: 18 300$ APBI-IT: 17 300$ APBI-3DCRT: 7 700$ APBI-IMRT: 9 700$
Outcomes	Does not apply given the study design
Cost-effectiveness	Does not apply given the study design
Sensitivity analysis	Patient Distance from Facility
Conclusions	Based on societal cost considerations, WBRT-AC appears to be the preferred approach. In case of a partial-breast RT regimen, external beam-based approaches would be more advantageous from a societal perspective than a brachytherapy approach.
Remarks	Applying Medicare reimbursement fees as (relative) costs may skew the resulting conclusion. The standard treatment involves whole breast radiation as opposed to partial breast radiation. As a consequence, the relevance of this study design for Belgium is questionable. The assumption that patients will remain in full time employment throughout the course of the radiotherapy treatment is not self-evident. When comparing cost outcomes of alternative interventions from a societal perspective this assumption tends to bias cost comparison against interventions lasting over a shorter terms (as IMRT compared to conventional radiotherapy for instance).

Economic evaluations summary sheet: Konski 2004

Author	Konski [62]
Country	United States
Design	Cost Minimization Analysis
Perspective	Payer's perspective (i.e. Medicare perspective)
Time window	Ranging from 2 weeks to 6/7 weeks depending on type of intervention
Interventions	Whole Breast Irradiation, conventional radiation (WBI) Accelerated Partial Breast Irradiation, 3D conformal radiation (APBI-3DC) Accelerated Partial Breast Irradiation, IMRT (APBI-IMRT)
	Accelerated Partial Breast Irradiation, interstitial brachytherapy (APBI-IBT)
Population	Patients with early stage breast cancer
Assumptions	WBI: 30-35 treatments over 6-7 weeks APBI: 10 treatments over 2 weeks Brachytherapy (MammoSite®): 10 treatments over 1 week
Data source for costs	Expected Medicare reimbursement (derived from Current Procedural Terminology (CPT) codes and Health care common procedure coding system (HCPCS) codes)
Cost items included	Limited to costs for radiation therapy as set out by Medicare codes
Data source for outcomes	Comparability of outcomes between WBI and various forms of PBI is put forth based on two research articles referring to primary clinical findings (Koo 2003, Vicini 2003)
Discounting	Does not apply given short time frame
Costs	WBI: $6 542, APBI-3DC: $4 553, APBI-IMRT: $10 872, APBI-IBT: $14 505
Outcomes	Assumed to be equal
Cost-effectiveness	Does not apply given study design
Sensitivity analysis	Applying lower reimbursement rates for technical interventions (of which APBI-3D has less) does not alter the conclusion
Conclusions	APBI-3DC is cost-minimizing compared to WBI "A prospective randomized trial evaluating efficacy, QALY or utilities and costs between WBI and APBI is needed to fully answer the question of whether APBI is a cost-effective alternative to WBI in selected patients with breast cancer"
Remarks	The standard treatment involves whole breast radiation as opposed to partial breast radiation. As a consequence, the relevance of this study design for Belgium is questionable. In light of expected difference in patient outcomes (avoided mastectomy, shorter treatment time, etc.) a cost-minimisation assessment is unsatisfactory. Applying theoretic cost estimates based on the Medicare reimbursement scheme does not allow for a realistic approximation of actual costs.

Economic evaluations summary sheet: Konski 2005

Author	Konski [63]
Country	United States
Design	Cost-Utility-Analysis (probabilistic model)
Perspective	Payer's perspective (i.e. Medicare perspective)
Time window	Time horizon of 10 years
Interventions	Intensity-modulated radiation therapy (IMRT) compared to three-dimensional conformal radiation therapy (3DCRT)
Population	70-year old with prostate cancer: a) subpopulation of patients with good-risk b) subpopulation of patients with intermediate-risk
Assumptions	Markov-model covering various states: post-treatment, hormone therapy, chemotherapy and death Transition probabilities were derived from various clinical publications.
Data source for costs	Radiation Therapy: Actual Medicare Reimbursement at Fox Chase Center (PA, USA) Hormone Therapy: Wholesale price from Drug Red Book + assumed fee for administration Chemotherapy: based on publication by Piper (Cost description 2002)
Cost items included	Radiation Therapy: Medicare CPT Code items Hormone Therapy Chemotherapy
Data source for outcomes	IMRT-group: utilities derived from in-house clinical trial based on administering EQ-5D questionnaire to 17 patients with intermediate-risk prostate cancer 3DCRT-group: utilities derived from separate in-house study using time-trade off interviews for 34 men
Discounting	3% discounting of costs and benefits
Costs	Mean cost for patients with good-risk prostate cancer in IMRT protocol: $31 950
	Mean cost for patients with good-risk prostate cancer in 3DCRT protocol: $19 213 Mean cost for patients with intermediate-risk prostate cancer in IMRT protocol: $33 837 Mean cost for patients with intermediate-risk prostate cancer in 3DCRT protocol: $21 377
Outcomes	Mean survival for patients with good-risk prostate cancer in IMRT protocol: 6.44 QALYs Mean survival for patients with good-risk prostate cancer in 3DCRT protocol: 5.71 QALYs Mean survival for patients with intermediate-risk prostate cancer in IMRT protocol: 6.29 QALYs Mean survival for patients with intermediate-risk prostate cancer in 3DCRT protocol: 5.52 QALYs
Cost-effectiveness	Patients with good-risk prostate cancer: $17 448/added QALY
	Patients with intermediate-risk prostate cancer: $16 182/added QALY
Sensitivity analysis	One-way analyses on cost, utility values and time window. Conclusions were robust for changes in cost inputs. Conclusions were not robust for changes in utility outcomes. Authors suggest IMRT would be more cost effective in longer time window.
Conclusions	Given a willingness-to-pay of 50.000 per extra QALY, IMRT is cost-effective compared to 3DCRT
Remarks	Clinical data were not collected from 1 single RCT. Cost data were based on (actual) Medicare reimbursements for case series'. Utilities for compared intervention groups were taken from two distinct in-house studies (without further formal reference): utility estimation methodology differed for both groups and sample sizes are particularly low, which is reflected in the ranges that were used in various sensitivity analyses, invalidating robustness of the general conclusion. Moreover, the utilities for the IMRT group were derived exclusively from intermediate-risk cancer patients whereas the patient group for which 3DCRT utilities were derived remains unspecified. Suggestions that cost-effectiveness of IMRT is an increasing function of time should be counterbalanced by the likelihood that the incidence of secondary malignancies after radiation therapy will increase over time.

Economic evaluations summary sheet: Konski 2006

Author	Konski e.a. [64]
Country	United States
Design	Cost-Utility-Analysis (probabilistic model)
Perspective	Payer's perspective (i.e. Medicare perspective)
Time window	Projected (markov-modelled) further life expectancy (average of 7 years for IMRT-patients)
Interventions	Intensity-modulated radiation therapy (IMRT) compared to three-dimensional conformal radiation therapy (3DCRT)
Population	70-year old with intermediate-risk prostate cancer
Assumptions	Markov-model covering various states: post-treatment, hormone therapy, chemotherapy and death Transition probabilities were derived from various clinical publications.
Data source for costs	Radiation Therapy: Medicare Reimbursement Fees (2004 conversion factors) Hormone Therapy: Wholesale price from Drug Red Book + assumed fee for administration Chemotherapy: based on publication by Piper (Cost description 2002)
Cost items included	Radiation Therapy: Medicare CPT Code items Hormone Therapy Chemotherapy
Data source for outcomes	IMRT-group: utilities derived from in-house clinical trial based on administering EQ-5D questionnaire to 17 patients with intermediate-risk prostate cancer. 3DCRT-group: utilities derived from separate in-house study using time-trade off interviews for 34 men
Discounting	3% discounting of costs and benefits
Costs	Mean cost for patients in IMRT protocol: $47 931 Mean cost for patients in 3DCRT protocol: $21 865
Outcomes	Mean survival for patients in IMRT protocol: 6,27 QALYs Mean survival for patients in 3DCRT protocol: 5,62 QALYs
Cost-effectiveness	$40 101/added QALY
Sensitivity analysis	One-way and two-way analyses on cost, utility values and time window. Conclusions were robust for changes in cost inputs. Conclusions were not robust for changes in utility outcomes. Authors suggest IMRT would be more cost effective in longer time window.
Conclusions	Given a willingness-to-pay of $50 000 per extra QALY, IMRT is cost-effective compared to 3DCRT with a 55.1% probability.
Remarks	Clinical data ("transitional probabilities") were not collected from 1 single RCT, but based on two separate patient case series (both collected at the Fox Chase Center). Cost data were estimated under a "theoretical" scheme and not derived from real-life trials. For instance, the modelled cost for medical imagery is assumed to be equal for both interventions: 1 CT scan for each protocol, which seems unlikely given the particular demands of IMRT in this field. Utilities for compared intervention groups were taken from two distinct (and unspecified) in-house studies: utility estimation methodology differed for both groups and sample sizes are particularly low, which is reflected in the ranges that were used in various sensitivity analyses, invalidating the robustness of the general conclusion. Suggestions that cost-effectiveness of IMRT is an increasing function of time should be counterbalanced by the likelihood that the incidence of secondary malignancies after radiation therapy will increase over time.

APPENDIX 5: IMRT EQUIPMENT COSTS

Capital start-up and upgrade costs for IMRT: USA 2003 [72]

Equipment	Description	Indicated Cost
Linear Accelerator (LINAC)	Full System (including MLC)	1 500 000$ - 2 000 000$
Multi-leaf Collimator (MLC)	Retrofit MLC	425 000$
Treatment Planning System (TPS)	Inverse Treatment Planning System	75 000$ - 125 000$
Auto Field Sequencing	Exchanges data between IMRT components	40 000$
IMRT Quality Assurance Software	NA	25 000$
Derived total for retrofitting existing system (3DCRT)		565 000$ - 615 000$
Derived total for new System		1 640 000$ - 2 190 000$

Capital start-up and upgrade costs for IMRT: France 2003 [73]

Equipment		Description	Indicated Cost
3DCRT Equipment	Linear Accelerator (LINAC)	Bi-energy Linac (basic version)	1 150 000€ - 1 250 000€
	Multi-leaf Collimator (MLC)	80 leaf - 120 leaf MLC	335 000€ - 490 000€
	Portal Vision	Real-Time medical imaging	290 000€
	Dosimetry Workstation	NA	183 000€
	Contouring Workstation	NA	66 000€
	Simulator	With-Without "option scanner"	472 000€ - 640 000€
	Other	Not specified, amount derived from overall amount mentioned for "preparation equipment 3DCRT""	751 000€
IMRT Specific Equipment	Inverse Treatment Planning System	NA	200 000€
Derived total for retrofitting existing system (3DCRT)			200 000€
Derived total for new System			3 447 000€ - 3 870 000€

Capital start-up and upgrade costs for IMRT: Spain 2005 [7]

Equipment		Description	Indicated Cost
3DCRT Equipment	Linear Accelerator (LINAC)	LINAC with 2 photon beams and 5 electron beams	1 235 000€
	Multi-leaf Collimator (MLC)	Full segment MLC	429 000€
	Portal Vision	Real-Time medical imaging	276 000€
	Integrated IT Network	Integration of LINAC, planification, imaging, verification, various workstations, etc.	297 000€
	Dosimetry Workstation	NA	145 000€
	Contouring Workstation	NA	65 000€
IMRT Specific Equipment	Dynamic Multi-leaf Upgrade	Sliding windows + control software	44 000€
	Inverse Treatment Planning System	NA	174 000€
Derived total for retrofitting existing system (3DCRT)			218 000€
Derived total for new System			2 665 000€

Capital start-up and upgrade costs for IMRT: Belgium 2006 [76]

Equipment		Description	Indicated Cost
3DCRT Equipment	Linear Accelerator (LINAC)	Standard LINAC	1 000 000€ - 1 250 000€
	Treatment Planning System (TPS)	Standard TPS	250 000€ - 400 000€
IMRT Specific Equipment	Linear Accelerator IMRT upgrade	NA	50 000€ - 150 000€
	Treatment Planning System IMRT upgrade	NA	250 000€ - 400 000€
	IMRT specific software	NA	150 000€ -200 000€
Derived total for retrofitting existing system (3DCRT)			450 000€ - 750 000€
Derived total for new System			1 700 000€ - 2 400 000€

Capital start-up costs for IMRT: USA 2002 [75]

Table B – Equipment needed for full implementation of above five-year upgrade plan

Potential Equipment	Quantity	Estimated Cost	Total Costs	Description
120 MLC Upgrade	2	$400,000	$800,000	Enhances ability to deliver conformal and IMRT treatments
Dynamic MLC (dMLC)	2	$80,000	$160,000	Enables the linear accelerator to deliver higher resolution dynamic treatments, which are also more efficient
Exact Couch Top	2	$30,000	$60,000	Facilitates consistent positioning
Auto Field Sequencing	2	$40,000	$80,000	Improves productivity by eliminating multiple trips into the treatment room by technologists
PortalVision	2	$250,000	$500,000	Provides for electronic imaging for positioning, improving productivity and effectiveness of care and eliminating film
Portal Dosimetry	2	$100,000	$200,000	Allows for comparison of actual delivered dose with prescribed dose
Upgrades – Console Replacement	2	$5,000	$10,000	Allows linear accelerator to accept new technologies like MLC, and PV
Upgrades – 6.0 Software	2	$10,000	$20,000	Allows linear accelerator to accept new technologies like MLC, and PV
Add CMS Inverse planning capability	1	$100,000	$100,000	Allows for the development of inverse treatment plans for delivering IMRT
Vision System	1	$100,000	$100,000	Provides for a filmless imaging network so images can be reviewed anywhere in the system. Eliminates film, improves productivity.
VARiS 6.0 Upgrade	1	Included w/ Service Contract	$100,000	Improves network
Upgrades to VARiS	1	$200,000	$200,000	Allocation for new hardware and upgrades to software
HL7 PA	1	$25,000	$25,000	For communication between hospital information system and VARiS to avoid redundant data entry and allow direct transfer of charge information
HL7 ADT	1	$25,000	$25,000	Provides communication between hospital information system and VARiS to allow direct transfer of ADT information
CT Simulator	1	$850,000	$850,000	Provides CT Simulation in the department increasing efficiency for Radiology and Radiation Therapy and possibly increasing revenue
Respiratory Gating	3	$100,000	$300,000	Allows for gating of beam to better target tumors affected by respiratory motion
Replace Treatment Planning	1	$300,000	$300,000	Upgrade or replace treatment planning system - forecasting improvements in technology (e.g., fusion, new algorithms, etc)
TOTAL			**$3,830,000**	

Source: Reproduced from Berkowitz 2002 [75]

APPENDIX 6: RADIATION THERAPY CATEGORIES

Various radiation treatment course categories (RIZIV/INAMI article 18) and indicated relevance to this report

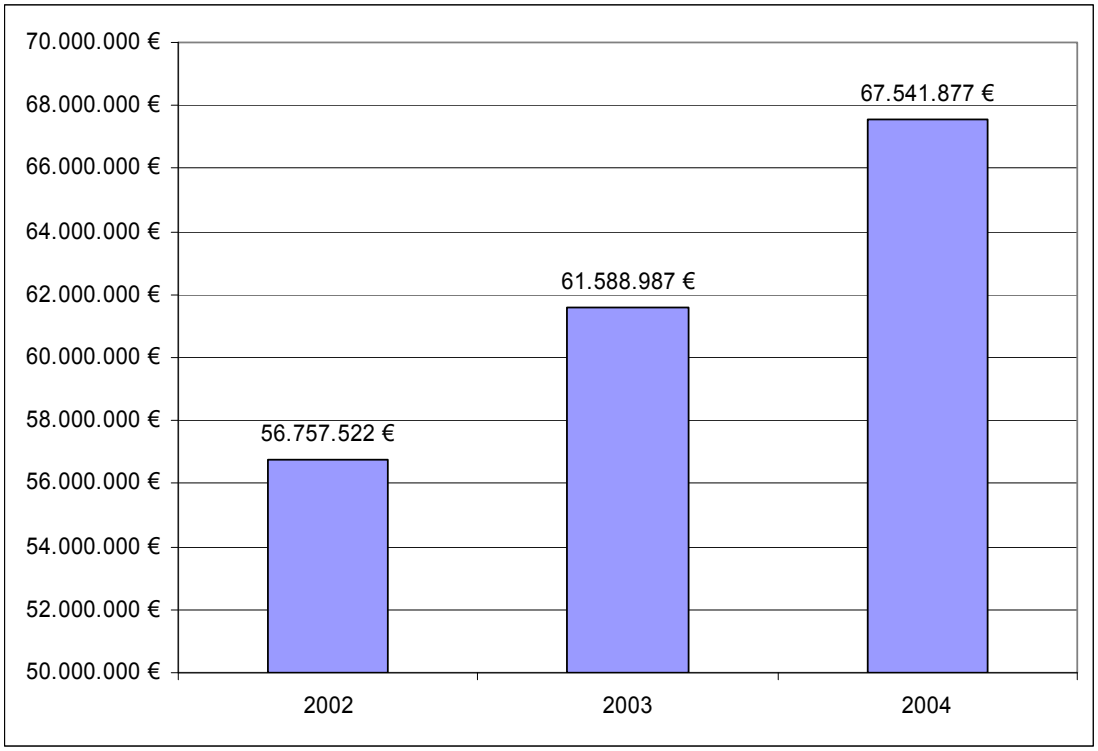
Category of Treatment Course	Label (Dutch)	Main Indication
1	Patiënten behandeld met uitwendige bestraling wegens volgende maligne en niet-maligne aandoeningen :Maligne tumoren :- metastasen (bot, hersenen, huid, lever, weke delen)- bestralingen met curatief oogmerk waarbij minder dan 11 fracties worden toegediend. Niet-maligne aandoeningen- heterotope botaanmaak- hypersplenisme (miltbestraling)- radiocastratie (ovarieel)- preventie gynecomastie (bestraling borst bij prostaatcarcinoma)- Graves' exophtalmie	Conventional external beam radiotherapy, maximum of 10 fractions per course **Up to three per year per patient for varying RT target areas.**
2	Patiënten behandeld met uitwendige bestraling met curatief oogmerk of met oog op definitieve tumorcontrole binnen een bestraald gebied wegens maligne of één van de volgende niet-maligne aandoeningen :Niet-maligne aandoeningen :- vertebrale hemangiomen- hypophysetumoren- goedaardige hersentumoren, ook meningeomen en craniopharyngeomen- cerebrale arterioveneuze malformaties of hemangiomen- chordoma- midline granuloma- agressieve fibromatose	Conventional external beam radiotherapy, between 11 and 35 fractions per course **Up to three per year per patient for varying RT target areas.**
3	Driedimensionele behandelingen bij patiënten van categorie 2 wegens hersentumoren, hoofd-hals tumoren (behalve larynx T1N0 en T2N0),longtumoren, pancreastumoren, pelvische tumoren, slokdarmtumoren, maagtumoren, weke delen tumoren.- Mantelvelden (ziekte van Hodgkin) of infradiafragmatische complexegrote velden (ziekte van Hodgkin, testis of ovarium-carcinomen oflymfomen).- Complexe velden voor medulloblastomen of ependymomen en anderekindertumoren.- Hyperfractionering bij patiënten van categorie 2."	3D radiotherapy (**does not apply to breast cancer patients**)
4	Totale lichaamsbestraling in het kader van een beenmergtransplantatie.- Peroperatieve elektronenbestraling of fotonenbestraling via lineaire versneller uitgerust met specifieke applicatoren.De dosimetrische karakteristieken van de applicatoren moeten individueel voor elke beschikbare elektronenergie in 3 dimensies zijn opgemeten.- Totale huid elektronentherapie (minimaal 15 fracties).De dosimetrische karakteristieken van de gebruikte velden en hunaansluitingen moeten opgemeten zijn.- Stereotactische radiotherapie voor AVM behandeling, meningiomen, hypofysetumoren en acusticus neurinomen, of bij maligne hersentumorenkleiner dan 3 cm. Hersenmetastasen worden als maligne hersentumoren beschouwd. - Radiotherapie met gemoduleerde intensiteit (IMRT) bij patiënten van categorie 3 volgens eén der volgende technieken :tomotherapie, statische gesegmenteerde bundels (min 15 segmenten),dynamische multileafcollimatie (sliding window, close-in, dynamische wig is geen IMRT), patiënt individueel vervaardigde compensatoren of IMAT.Minstens 15 fracties dienen volgens IMRT toegediend te worden.Voor de technieken met statische bundelincidenties, dienen de berekende fluentieprofielen van elke bundel bij het patiëntdossier te worden gevoegd.	Several indications, including IMRT (at least 15 fractions), **only applies to patients meeting criteria for category 3**
5	Patiënten behandeld met curietherapie, waarbij voorafgaandelijke en/of aansluitende externe bestraling wordt toegepast voor localisaties in neus-keel- en orengebied, oog, huidepitheliomen van meer dan 3 cm, sarcomen,pelvische, retroperitoneale en cerebrale lokalisaties. Beide behandelingstypes zijn cumuleerbaar tijdens éénzelfde behandelingsperiode.	Brachytherapy in combination with external radiation
6	Patiënten behandeld met curietherapie, waarbij voorafgaandelijke en/ofaansluitende externe bestraling wordt toegepast voor borsttumoren enintraluminele toepassingen op slokdarm, bronchus of galwegen.Beide behandelingstypes zijn cumuleerbaar tijdens éénzelfdebehandelingsperiode.	
7	Patiënten die beantwoorden aan de criteria of lijden aan een aandoeningopgenomen in categorie 1, exclusief behandeld met curietherapie.	(Mainly) applying to exclusive brachytherapy treatments
8	Patiënten die beantwoorden aan de criteria of lijden aan een aandoeningopgenomen in categorie 2, exclusief behandeld met curietherapie.	

Category of Treatment Course	Label (Dutch)	Main Indication
9	Patiënten exclusief behandeld met curietherapie of electronen wegensvolgende maligne of niet-maligne aandoeningen :Maligne tumoren :- huidepitheliomen van minder dan 3 cm zonder metastasen.Bij ontstentenis van fotografisch bewijs wordt elk huidepithelioom zondermetastase geacht de 3 cm niet te overschrijden.Niet-maligne aandoeningen- keloiden, keratoacanthoma- pterygium	
10	Patiënten behandeld met intraluminele curietherapie voor coronaire ofvasculaire restenosepreventie na angioplastie.	
11	Patiënten behandeld met conventionele bestraling of contacttherapie vooreen van volgende maligne of niet-maligne aandoeningen.Maligne tumoren :- huidepitheliomen van minder dan 3 cm zonder metastasen Bij ontstentenis van fotografisch bewijs wordt elk huidepithelioom zondermetastase geacht de 3 cm niet te overschrijden.Niet-maligne aandoeningen :- keloiden, keratoacanthoma- pterygium	Other

Number of started treatment courses per year of delivery per treatment course category (RIZIV/INAMI billing data)

Treatment Course Category	Year of Delivery	Number of Courses
C1	2003	7 335
C2	2003	11 250
C3	2003	7 108
C4	2003	872
C5	2003	304
C6	2003	33
C7	2003	83
C8	2003	741
C9a	2003	207
C9b	2003	675
C10	2003	662
C11	2003	410
C1	2004	7 425
C2	2004	10 159
C3	2004	8 937
C4	2004	1 270
C5	2004	290
C6	2004	30
C7	2004	99
C8	2004	1 133
C9a	2004	111
C9b	2004	566
C10	2004	661
C11	2004	305
C1	2005	5 579
C2	2005	7 807
C3	2005	7 279
C4	2005	1 228
C5	2005	226
C6	2005	12
C7	2005	82
C8	2005	1 035
C9b	2005	528
C10	2005	453
C11	2005	221

Fee-for-Service (article 18) budget for categories 1-4 (external radiotherapy) by year of delivery



APPENDIX 7 RIZIV/INAMI ARTICLE 18: MAXIMUM REIMBURSEMENTS BY TREATMENT CATEGORY

Description of billing codes pertaining to Article 18 (RIZIV/INAMI)

RIZIV Billing Code	Label_NL	Label_FR
444113	Forfaitair honorarium voor een eenvoudige uitwendige bestralingsreeks van 1 tot 10 fracties voor een patiënt die beantwoordt aan de criteria of lijdt aan een aandoening opgenomen in categorie 1	Honoraires forfaitaires pour une série d'irradiations externes simples de 1 à 10 fractions chez un patient qui répond aux critères ou pathologie repris en catégorie 1
444135	Forfaitair honorarium voor een eenvoudige uitwendige bestralingsreeks van minstens 11 tot 35 fracties voor een patiënt die beantwoordt aan de criteria of lijdt aan een aandoening opgenomen in categorie 2	Honoraires forfaitaires pour une série d'irradiations externes simples de 11 à 35 fractions chez un patient qui répond aux critères ou pathologie repris en catégorie 2
444150	Forfaitair honorarium voor een complexe uitwendige bestralingsreeks voor een patiënt die beantwoordt aan de criteria of lijdt aan een aandoening opgenomen in categorie 3	Honoraires forfaitaires pour une série d'irradiations externes complexes chez un patient qui répond aux critères ou pathologie repris en catégorie 3
444172	Forfaitair honorarium voor een complexe uitwendige bestralingsreeks voor een patiënt die beantwoordt aan de criteria of lijdt aan een aandoening opgenomen in categorie 4	Honoraires forfaitaires pour une série d'irradiations externes complexes chez un patient qui répond aux critères ou pathologie repris en catégorie 4
444194	Forfaitair honorarium voor een uitwendige bestralingsreeks met uitsluitend elektronen voor een patiënt die beantwoordt aan de criteria of lijdt aan een aandoening opgenomen in categorie 9	Honoraires forfaitaires pour une série d'irradiations externes exclusives par électrons chez un patient qui répond aux critères ou pathologie repris en catégorie 9
444216	Forfaitair honorarium voor exclusieve curietherapie voor een patiënt die beantwoordt aan de criteria of lijdt aan een aandoening opgenomen in categorie 7	Honoraires forfaitaires pour curiethérapie exclusive chez un patient qui répond aux critères ou pathologie repris en catégorie 7
444231	Forfaitair honorarium voor exclusieve curietherapie voor een patiënt die beantwoordt aan de criteria of lijdt aan een aandoening opgenomen in categorie 9	Honoraires forfaitaires pour curiethérapie exclusive chez un patient qui répond aux critères ou pathologie repris en catégorie 9
444253	Forfaitair honorarium voor exclusieve curietherapie voor een patiënt die beantwoordt aan de criteria of lijdt aan een aandoening opgenomen in categorie 8	Honoraires forfaitaires pour curiethérapie exclusive chez un patient qui répond aux critères ou pathologie repris en catégorie 8
444275	Forfaitair honorarium voor exclusieve curietherapie voor een patiënt die beantwoordt aan de criteria of lijdt aan een aandoening opgenomen in categorie 10 (restenosepreventie)	Honoraires forfaitaires pour curiethérapie exclusive chez un patient qui répond aux critères ou pathologie repris en catégorie 10 (prévention de resténose)
444290	Forfaitair honorarium voor curietherapie gecombineerd met uitwendige bestralingsreeks voor een patiënt die beantwoordt aan de criteria of lijdt aan een aandoening opgenomen in categorie 5	Honoraires forfaitaires pour curiethérapie combinée à une série d'irradiations externes chez un patient qui répond aux critères ou pathologie repris en catégorie 5
444312	Forfaitair honorarium voor curietherapie gecombineerd met uitwendige bestralingsreeks voor een patiënt die beantwoordt aan de criteria of lijdt aan een aandoening opgenomen in categorie 6	Honoraires forfaitaires pour curiethérapie combinée à une série d'irradiations externes chez un patient qui répond aux critères ou pathologie repris en catégorie 6

RIZIV Billing Code	Label_NL	Label_FR
444334	Forfaitair honorarium voor een conventionele behandeling (röntgentherapie 200 tot 300 KV, contacttherapie 50 KV) van 1 tot 15 fracties voor een patiënt die beantwoordt aan de criteria of lijdt aan een aandoening opgenomen in categorie 11	Honoraires forfaitaires pour un traitement conventionnel (röntgenthérapie de 200 à 300 KV, thérapie de contact de 50 KV) de 1 à 15 fractions chez un patient qui répond aux critères ou pathologie repris en catégorie 11
444356	Forfaitair honorarium voor de voorbereidingen met simulator van een behandeling met uitwendige bestraling of curietherapie, per bestralingsreeks voor een patiënt van categorie 1, 2, 3, 4, 5, 6, 7 of 8, eerste simulatie	Honoraires forfaitaires pour les préparations avec simulation d'un traitement par irradiation externe ou de curiethérapie, par série d'irradiation pour un patient de catégorie 1, 2, 3, 4, 5, 6, 7 ou 8, la première simulation
444371	Forfaitair honorarium voor de voorbereidingen met simulator van een behandeling met uitwendige bestraling of curietherapie, per bestralingsreeks voor een patiënt van categorie 2, 3,4, 5, 6 of 8, tweede simulatie	Honoraires forfaitaires pour les préparations avec simulation d'un traitement par irradiation externe ou de curiethérapie, par série d'irradiation pour un patient de catégorie 2, 3, 4, 5, 6 ou 8, deuxième simulation
444393	Forfaitair honorarium voor de berekening van de individuele dosisverdeling van een behandeling met uitwendige bestraling of curietherapie voor patiënten van categorie 1, 2, 3, 4, 5, 6, 7 of 8, eerste planning	Honoraires forfaitaires pour le calcul de la distribution de la dose individuelle d'un traitement par irradiation externe ou de curiethérapie chez des patients de catégorie 1, 2, 3, 4, 5, 6, 7 ou 8, premier planning
444415	Forfaitair honorarium voor de berekening van de individuele dosisverdeling van een behandeling met uitwendige bestraling of curietherapie voor patiënten van categorie 2, 3, 4, 5, 6 of 8 , tweede planning	Honoraires forfaitaires pour le calcul de la distribution de la dose individuelle d'un traitement par irradiation externe ou de curiethérapie chez des patients de catégorie 2, 3, 4, 5, 6 ou 8 , deuxième planning
444430	Bijkomend honorarium bij de verstrekking 444393 - 444404 (eerste planning) voor de berekening van de individuele driedimensionele dosisverdeling voor uitwendige bestraling voor patiënten van categorie 3 of 4	Honoraires supplémentaires lors de la prestation 444393 - 444404 (premier planning) pour le calcul de la distribution tridimensionnelle de la dose individuelle pour irradiation externe chez des patients de catégorie 3 ou 4
444452	Bijkomend honorarium bij de verstrekking 444393 - 444404 (eerste planning) voor de individuele dosisberekening met gebruik van een intensiteitsmodulatieprogramma voor bestraling met multileafcollimator voor patiënten van categorie 3 of 4	Honoraires supplémentaires lors de la prestation 444393 - 444404 (premier planning) pour le calcul de la dose individuelle avec utilisation d'un programme de modulation d' intensité pour irradiation avec un collimateur multi-lames chez des patients de catégorie 3 ou 4
444474	Honorarium voor gammagrafie bij een patiënt behandeld met uitwendige bestraling van categorie 1, 2, 3 of 4, maximum 4 per bestralingsreeks	Honoraires pour gammagraphie chez un patient de catégorie 1, 2, 3 ou 4 traité par irradiation externe,maximum 4 par série d'irradiation
444496	Honorarium voor on-line imaging bij een patiënt behandeld met uitwendige bestraling categorie 1, 2, 3 of 4, maximum 4 per bestralingsreeks	Honoraires pour imagerie portale en ligne chez un patient de catégorie 1, 2, 3 ou 4 traité par irradiation externe, maximum 4 par série d'irradiation
444511	Honorarium voor in-vivo dosimetrie bij patiënten behandeld met uitwendige bestraling van categorie 1, 2, 3 of 4, maximum 4 per bestralingsreeks	Honoraires pour dosimétrie in vivo chez des patients de catégorie 1, 2, 3 ou 4 traités par irradiation externe, maximum 4 par série d'irradiation
444533	Bijkomend honorarium voor bestraling met een multileafcollimator voor de patiënten van categorie 3 of 4 per bestralingsreeks	Honoraires supplémentaires pour irradiation avec un collimateur multi-lames chez des patients de catégorie 3 ou 4, par série

RIZIV Billing Code	Label_NL	Label_FR
		d'irradiation
444555	Bijkomend honorarium bij curietherapie voor gebruik van een automatische afterloading apparaat op afstand voor de patiënten van categorie 5, 6, 7 of 8, per bestralingsreeks	Honoraires supplémentaires pour curiethérapie avec utilisation d'un système de chargement différé avec projecteur automatique de sources chez des patients de catégorie 5, 6, 7 ou 8, par série d'irradiation
444570	Maskers of individuele fixatiesystemen bij uitwendige bestraling voor de patiënten van categorie 1 voor de regio hoofd en hals en voor de patiënten van categorie 2, 3 of 4, per bestralingsreeks	Masques ou systèmes de fixation individuelle lors d'irradiation externe chez des patients de catégorie 1 pour localisations tête et cou et chez des patients de catégorie 2, 3 ou 4, par série d'irradiation
444592	Individuele blokken bij een behandeling met uitwendige bestraling en/of curietherapie van patiënten van categorie 1, 2, 3, 4, 5, 6, 7 of 8, per bestralingsreeks	Blocs individualisés pour traitement par irradiation externe et/ou par curiethérapie des patients de catégorie 1, 2, 3, 4, 5, 6, 7 ou 8, par série d'irradiation
444124	Forfaitair honorarium voor een eenvoudige uitwendige bestralingsreeks van 1 tot 10 fracties voor een patiënt die beantwoordt aan de criteria of lijdt aan een aandoening opgenomen in categorie 1	Honoraires forfaitaires pour une série d'irradiations externes simples de 1 à 10 fractions chez un patient qui répond aux critères ou pathologie repris en catégorie 1
444146	Forfaitair honorarium voor een eenvoudige uitwendige bestralingsreeks van minstens 11 tot 35 fracties voor een patiënt die beantwoordt aan de criteria of lijdt aan een aandoening opgenomen in categorie 2	Honoraires forfaitaires pour une série d'irradiations externes simples de 11 à 35 fractions chez un patient qui répond aux critères ou pathologie repris en catégorie 2
444161	Forfaitair honorarium voor een complexe uitwendige bestralingsreeks voor een patiënt die beantwoordt aan de criteria of lijdt aan een aandoening opgenomen in categorie 3	Honoraires forfaitaires pour une série d'irradiations externes complexes chez un patient qui répond aux critères ou pathologie repris en catégorie 3
444183	Forfaitair honorarium voor een complexe uitwendige bestralingsreeks voor een patiënt die beantwoordt aan de criteria of lijdt aan een aandoening opgenomen in categorie 4	Honoraires forfaitaires pour une série d'irradiations externes complexes chez un patient qui répond aux critères ou pathologie repris en catégorie 4
444205	Forfaitair honorarium voor een uitwendige bestralingsreeks met uitsluitend elektronen voor een patiënt die beantwoordt aan de criteria of lijdt aan een aandoening opgenomen in categorie 9	Honoraires forfaitaires pour une série d'irradiations externes exclusives par électrons chez un patient qui répond aux critères ou pathologie repris en catégorie 9
444220	Forfaitair honorarium voor exclusieve curietherapie voor een patiënt die beantwoordt aan de criteria of lijdt aan een aandoening opgenomen in categorie 7	Honoraires forfaitaires pour curiethérapie exclusive chez un patient qui répond aux critères ou pathologie repris en catégorie 7
444242	Forfaitair honorarium voor exclusieve curietherapie voor een patiënt die beantwoordt aan de criteria of lijdt aan een aandoening opgenomen in categorie 9	Honoraires forfaitaires pour curiethérapie exclusive chez un patient qui répond aux critères ou pathologie repris en catégorie 9
444264	Forfaitair honorarium voor exclusieve curietherapie voor een patiënt die beantwoordt aan de criteria of lijdt aan een aandoening opgenomen in categorie 8	Honoraires forfaitaires pour curiethérapie exclusive chez un patient qui répond aux critères ou pathologie repris en catégorie 8
444286	Forfaitair honorarium voor exclusieve curietherapie voor een patiënt die beantwoordt aan de criteria of lijdt aan een aandoening opgenomen in categorie 10 (restenosepreventie)	Honoraires forfaitaires pour curiethérapie exclusive chez un patient qui répond aux critères ou pathologie repris en catégorie 10 (prévention de resténose)

RIZIV Billing Code	Label_NL	Label_FR
444301	Forfaitair honorarium voor curietherapie gecombineerd met uitwendige bestralingsreeks voor een patiënt die beantwoordt aan de criteria of lijdt aan een aandoening opgenomen in categorie 5	Honoraires forfaitaires pour curiethérapie combinée à une série d'irradiations externes chez un patient qui répond aux critères ou pathologie repris en catégorie 5
444323	Forfaitair honorarium voor curietherapie gecombineerd met uitwendige bestralingsreeks voor een patiënt die beantwoordt aan de criteria of lijdt aan een aandoening opgenomen in categorie 6	Honoraires forfaitaires pour curiethérapie combinée à une série d'irradiations externes chez un patient qui répond aux critères ou pathologie repris en catégorie 6
444345	Forfaitair honorarium voor een conventionele behandeling (röntgentherapie 200 tot 300 KV, contacttherapie 50 KV) van 1 tot 15 fracties voor een patiënt die beantwoordt aan de criteria of lijdt aan een aandoening opgenomen in categorie 11	Honoraires forfaitaires pour un traitement conventionnel (röntgenthérapie de 200 à 300 KV, thérapie de contact de 50 KV) de 1 à 15 fractions chez un patient qui répond aux critères ou pathologie repris en catégorie 11
444360	Forfaitair honorarium voor de voorbereidingen met simulator van een behandeling met uitwendige bestraling of curietherapie, per bestralingsreeks voor een patiënt van categorie 1, 2, 3, 4, 5, 6, 7 of 8, eerste simulatie	Honoraires forfaitaires pour les préparations avec simulation d'un traitement par irradiation externe ou de curiethérapie, par série d'irradiation pour un patient de catégorie 1, 2, 3, 4, 5, 6, 7 ou 8, la première simulation
444382	Forfaitair honorarium voor de voorbereidingen met simulator van een behandeling met uitwendige bestraling of curietherapie, per bestralingsreeks voor een patiënt van categorie 2, 3,4, 5, 6 of 8, tweede simulatie	Honoraires forfaitaires pour les préparations avec simulation d'un traitement par irradiation externe ou de curiethérapie, par série d'irradiation pour un patient de catégorie 2, 3, 4, 5, 6 ou 8, deuxième simulation
444404	Forfaitair honorarium voor de berekening van de individuele dosisverdeling van een behandeling met uitwendige bestraling of curietherapie voor patiënten van categorie 1, 2, 3, 4, 5, 6, 7 of 8, eerste planning	Honoraires forfaitaires pour le calcul de la distribution de la dose individuelle d'un traitement par irradiation externe ou de curiethérapie chez des patients de catégorie 1, 2, 3, 4, 5, 6, 7 ou 8, premier planning
444426	Forfaitair honorarium voor de berekening van de individuele dosisverdeling van een behandeling met uitwendige bestraling of curietherapie voor patiënten van categorie 2, 3, 4, 5, 6 of 8 , tweede planning	Honoraires forfaitaires pour le calcul de la distribution de la dose individuelle d'un traitement par irradiation externe ou de curiethérapie chez des patients de catégorie 2, 3, 4, 5, 6 ou 8 , deuxième planning
444441	Bijkomend honorarium bij de verstrekking 444393 - 444404 (eerste planning) voor de berekening van de individuele driedimensionele dosisverdeling voor uitwendige bestraling voor patiënten van categorie 3 of 4	Honoraires supplémentaires lors de la prestation 444393 - 444404 (premier planning) pour le calcul de la distribution tridimensionnelle de la dose individuelle pour irradiation externe chez des patients de catégorie 3 ou 4
444463	Bijkomend honorarium bij de verstrekking 444393 - 444404 (eerste planning) voor de individuele dosisberekening met gebruik van een intensiteitsmodulatieprogramma voor bestraling met multileafcollimator voor patiënten van categorie 3 of 4	Honoraires supplémentaires lors de la prestation 444393 - 444404 (premier planning) pour le calcul de la dose individuelle avec utilisation d'un programme de modulation d' intensité pour irradiation avec un collimateur multi-lames chez des patients de catégorie 3 ou 4
444485	Honorarium voor gammagrafie bij een patiënt behandeld met uitwendige bestraling van categorie 1, 2, 3 of 4, maximum 4 per bestralingsreeks	Honoraires pour gammagraphie chez un patient de catégorie 1, 2, 3 ou 4 traité par irradiation externe, maximum 4 par série d'irradiation

RIZIV Billing Code	Label_NL	Label_FR
444500	Honorarium voor on-line imaging bij een patiënt behandeld met uitwendige bestraling categorie 1, 2, 3 of 4, maximum 4 per bestralingsreeks	Honoraires pour imagerie portale en ligne chez un patient de catégorie 1, 2, 3 ou 4 traité par irradiation externe, maximum 4 par série d'irradiation
444522	Honorarium voor in-vivo dosimetrie bij patiënten behandeld met uitwendige bestraling van categorie 1, 2, 3 of 4, maximum 4 per bestralingsreeks	Honoraires pour dosimétrie in vivo chez des patients de catégorie 1, 2, 3 ou 4 traités par irradiation externe, maximum 4 par série d'irradiation
444544	Bijkomend honorarium voor bestraling met een multileafcollimator voor de patiënten van categorie 3 of 4 per bestralingsreeks	Honoraires supplémentaires pour irradiation avec un collimateur multi-lames chez des patients de catégorie 3 ou 4, par série d'irradiation
444566	Bijkomend honorarium bij curietherapie voor gebruik van een automatische afterloading apparaat op afstand voor de patiënten van categorie 5, 6, 7 of 8, per bestralingsreeks	Honoraires supplémentaires pour curiethérapie avec utilisation d'un système de chargement différé avec projecteur automatique de sources chez des patients de catégorie 5, 6, 7 ou 8, par série d'irradiation
444581	Maskers of individuele fixatiesystemen bij uitwendige bestraling voor de patiënten van categorie 1 voor de regio hoofd en hals en voor de patiënten van categorie 2, 3 of 4, per bestralingsreeks	Masques ou systèmes de fixation individuelle lors d'irradiation externe chez des patients de catégorie 1 pour localisations tête et cou et chez des patients de catégorie 2, 3 ou 4, par série d'irradiation
444603	Individuele blokken bij een behandeling met uitwendige bestraling en/of curietherapie van patiënten van categorie 1, 2, 3, 4, 5, 6, 7 of 8, per bestralingsreeks	Blocs individualisés pour traitement par irradiation externe et/ou par curiethérapie des patients de catégorie 1, 2, 3, 4, 5, 6, 7 ou 8, par série d'irradiation

Billing codes for which the penultimate number is even/uneven apply respectively to inpatient/outpatient settings.

Suggested translations for most relevant article 18 billing codes

RIZIV/INAMI billing code	Label_ENG (translation suggested by KCE)
444555	Additional fee per treatment cycle for brachytherapy by used of an automatic afterloading apparatus for a patient in categories 6,5,7 or 8
444566	Additional fee per treatment cycle for brachytherapy by used of an automatic afterloading apparatus for a patient in categories 6,5,7 or 8
444430	Additional fee for billing code 444393 - 444404 (first planning) for an individual threedimensional dosimetry for an external radiation treatment for a patient in categories 3 or 4
444441	Additional fee for billing code 444393 - 444404 (first planning) for an individual threedimensional dosimetry for an external radiation treatment for a patient in categories 3 or 4
444452	Additional fee for billing code 444393 - 444404 (first planning) for an individual dosimetry by use of an intensity modulated program for radiation with a multi leaf collimator of a patient in categories 3 or 4
444463	Additional fee for billing code 444393 - 444404 (first planning) for an individual dosimetry by use of an intensity modulated program for radiation with a multi leaf collimator of a patient in categories 3 or 4
444533	Additional fee per treatment cycle for radiation with a multi leaf collimator for a patient in categories 3 or 4
444544	Additional fee per treatment cycle for radiation with a multi leaf collimator for a patient in categories 3 or 4
444290	Lump sum fee for a brachytherapy combined with an external radiation treatment cycle for a patient complying with the criteria/affections applying to category 5
444301	Lump sum fee for a brachytherapy combined with an external radiation treatment cycle for a patient complying with the criteria/affections applying to category 5
444312	Lump sum fee for a brachytherapy combined with an external radiation treatment cycle for a patient complying with the criteria/affections applying to category 6
444323	Lump sum fee for a brachytherapy combined with an external radiation treatment cycle for a patient complying with the criteria/affections applying to category 6
444393	Lump sum fee for individual dosimetry for an external radiation or brachytherapy treatment for a patient in categories 1, 2, 3, 4, 5, 6, 7 or 8, first planning
444404	Lump sum fee for individual dosimetry for an external radiation or brachytherapy treatment for a patient in categories 1, 2, 3, 4, 5, 6, 7 or 8, first planning
444415	Lump sum fee for individual dosimetry for an external radiation or brachytherapy treatment for a patient in categories 2, 3, 4, 5, 6 or 8, second planning
444426	Lump sum fee for individual dosimetry for an external radiation or brachytherapy treatment for a patient in categories 2, 3, 4, 5, 6 or 8, second planning
444356	Lump sum fee for preparation by use of a simulator of an external radiation or brachytherapy per treatment cycle for a patient in categories 1,2,3,4,5,6,7 or 8, first simulation
444360	Lump sum fee for preparation by use of a simulator of an external radiation or brachytherapy per treatment cycle for a patient in categories 1,2,3,4,5,6,7 or 8, first simulation

RIZIV/INAMI billing code	Label_ENG (translation suggested by KCE)
444371	Lump sum fee for preparation by use of a simulator of an external radiation or brachytherapy per treatment cycle for a patient in categories 1,2,3,4,5,6,7 or 8, second simulation
444382	Lump sum fee for preparation by use of a simulator of an external radiation or brachytherapy per treatment cycle for a patient in categories 1,2,3,4,5,6,7 or 8, second simulation
444150	Lump sum fee for a complicated external radiation treatment cycle for a patient complying with the criteria/affections applying to category 3
444161	Lump sum fee for a complicated external radiation treatment cycle for a patient complying with the criteria/affections applying to category 3
444172	Lump sum fee for a complicated external radiation treatment cycle for a patient complying with the criteria/affections applying to category 4

Derived maximum fee-for-service reimbursements per treatment course by patient category (C1-C4, 2003): outpatient billing codes (same tariffs for inpatients)

RIZIVcode	Tariff 2003	MAX # / COURSE	C1	C2	C3	C4	C1	C2	C3	C4
444113	565 €	1	X				565 €	0 €	0 €	0 €
444135	1.357 €	1		X			0 €	1 357 €	0 €	0 €
444150	1.809 €	1			X		0 €	0 €	1 809 €	0 €
444172	2.262 €	1				X	0 €	0 €	0 €	2 262 €
444356	339 €	1	X	X	X	X	339 €	339 €	339 €	339 €
444371	170 €	1		X	X	X	0 €	170 €	170 €	170 €
444393	283 €	1	X	X	X	X	283 €	283 €	283 €	283 €
444415	141 €	1		X	X	X	0 €	141 €	141 €	141 €
444430	141 €	1			X	X	0 €	0 €	141 €	141 €
444452	113 €	1				X	0 €	0 €	0 €	113 €
444474	28 €	4	X	X	X	X	113 €	113 €	113 €	113 €
444496	28 €	0*	X	X	X	X	0 €	0 €	0 €	0 €
444511	28 €	4	X	X	X	X	113 €	113 €	113 €	113 €
444533	170 €	1			X	X	0 €	0 €	170 €	170 €
444570	141 €	1		X	X	X	0 €	141 €	141 €	141 €
444592	85 €	0*	X	X	X	X	0 €	0 €	0 €	0 €
Maximum Reimbursement per Course (as derived from billing code labels and article 18 provisions)							1 414 €	2 658 €	3 421 €	3 986 €
Derived Difference between maximum reimbursements for category 4 and 2								1 328 €		
Derived Difference between maximum reimbursements for category 4 and 3									565 €	

* billing items cannot be combined with other items already in list

APPENDIX 8: IMRT BUDGET ESTIMATIONS

The main legal source for deriving the impact of IMRT on operational and investment costs at departmental level is a royal decree dated July 11th 2005[104]. Financing of radiotherapy departments is defined by the number of delivered treatment courses, weighted by category type through a point-based system (see table below).

Point-based weighting of radiotherapy department activity: 2003 example

CATEGORIES	POINTS	# COURSES 2003	# POINTS 2003 (OVERALL)
1	1	7 335	7 335
2	2	11 250	22 500
3	2.5	7 108	17 770
4	3	872	2 616
		TOTAL 2003	50 221

Investment Costs

With regard to investment costs (chapter A3 of the hospitals budget) the public payer reimburses 90 000€ per operational linac annually (for a period of ten years following the year the investment is made). The below table gives an overview of the maximum number of reimbursed linacs at recognized radiotherapy departments. Per 750 additional points beyond the shown point ranges an extra linac will be reimbursed (or 120€ per point). Given the fact that an average points total of 2 009 applied to the 25 Belgian radiotherapy centres in 2003, we will hypothesize that per extra point 120€ will be reimbursed to the department.

Points-based allocation of linacs per department

Point Range		Range	#Reimbursed Linacs	Reimbursement	Marginal Reimbursement (by endpoints of range per extra linac)
1	1 124	1124	1	90 000 €	80 €
1 225	1 874	650	2	180 000 €	138 €
1 875	2 624	750	3	270 000 €	120 €
2 625	3 374	750	4	360 000 €	120 €
3 375	4 124	750	5	450 000 €	120 €
4 125	4 874	750	6	540 000 €	120 €

As the point difference between respectively a category 3 and category 4 patients is equal to 0.5 points, 1 500 patients switching from 3DCRT (category 3) to IMRT (category 4) will make up the equivalent of an additional linac, reimbursed at 90 000€ annually or an estimated incremental effect of 60€ per IMRT patient. Implicitly we assume the number of patients/treatment courses/points scores to be distributed uniformly across the various RT departments, meaning that on average (across all RT departments) the above assumption is correct.

No date of reference (allowing to correct for inflation) is indicated for this amount. In our calculations we will deflate this amount by one year (based on the inflation rate of the following year) as the first reimbursement is made one year after the purchasing date. This implies we estimate this cost item at 88 110€ or around (slightly less than) 60€ per IMRT patient suffering from prostate or head and neck cancer. For patients

suffering from breast cancer around (slightly less than) 120€ will be estimated as these patients would switch from category 2 to category 4, implying a one-point difference.

Operational Costs

With regard to the reimbursement of operational costs (chapter B3 of the hospitals budget) the public payer reimburses 179.3€ per point plus a departmental lump sum depending on the (points-measured) size of the department (see table and figure below). The specified amounts bear July 1st 2005 as a date of reference and will be deflated/inflated accordingly in our model.

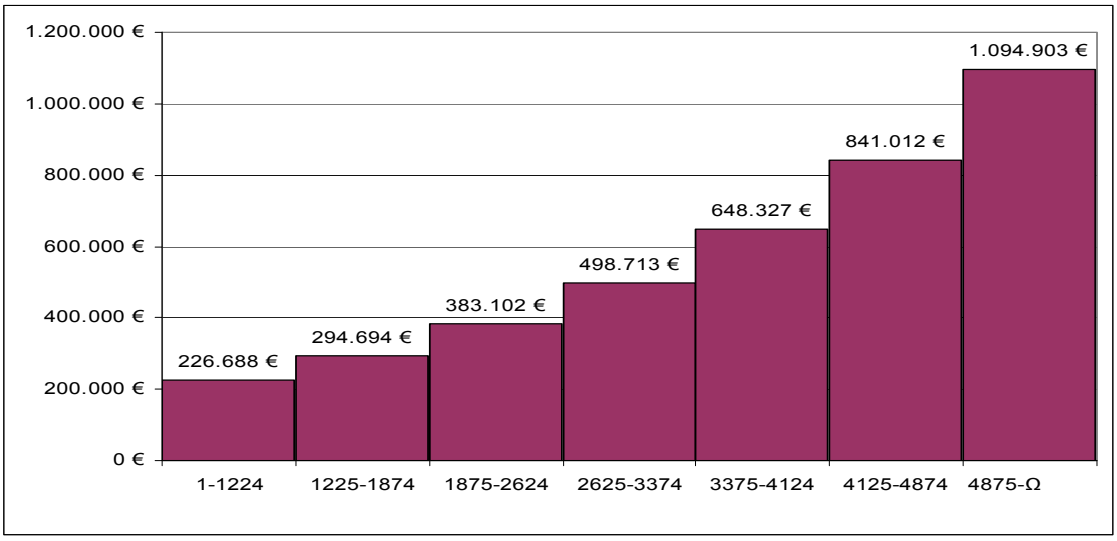
The table and figure give below an indication of the size-dependent reimbursed cost categories. Reimbursement can be considered a discrete function of departmental size (measured by points score).

Points-based allocation of operational costs per department

Point Range		Range Size	Reimbursement
1	1 124	1 124	226 688 €
1 225	1 874	650	294 694 €
1 875	2 624	750	383 102 €
2 625	3 374	750	498 713 €
3 375	4 124	750	648 327 €
4 125	4 874	750	841 012 €
4 875	Ω*	NA	1 094 903 €

*"Ω" stands for (positive) infinity

Points-based allocation of operational costs per department: reimbursement per points range.



In the table below we re-arranged the data from the previous table and figure as to derive average marginal values for every point in a given point range. We limit our range of interest to 2-5625 because:

- We assume no new RT departments will gain governmental funding, meaning the marginal value of point 1, i.e. 226 688€, will not be included in our derived average marginal value. This assumption is tantamount to stating new IMRT treatments will only be performed at already existing RT departments.
- Based on our survey results (see appendix 2) we put the highest maximum points score for a given department at around 5 000 in Belgium (2006 data). Leaving some leeway for a further increase of the points score due to the switch from 3DCRT to IMRT (0.5 point increase per IMRT course), we set the upper limit at 5 625 points.

Marginal Value of Points

Points Set		Reimbursement	# Points in Set	Marginal Value of Points Set	Average Marginal Values of Points by Set
	1	226 688 €	1	226 688 €	226 688 €
2	1225	294 694 €	1224	68 006 €	56 €
1226	1875	383 102 €	650	88 408 €	136 €
1876	2625	498 713 €	750	115 611 €	154 €
2626	3375	648 327 €	750	149 614 €	199 €
3376	4125	841 012 €	750	192 685 €	257 €
4126	4875	1 094 903 €	750	253 891 €	339 €
4876	5625	1 094 903 €	750	0 €	0 €

The last column contains the average marginal value for a point in a given points set. Let us assume an RT department sees its score rise from 2 to 1 225, leading to a budgetary increase of 68 006€. The average marginal contribution of each point in the point set/range 2-1225 would then be 56€ (68 006€ divided by 1224 points). If we assume point scores are distributed in a uniform way across all RT departments, we can apply the average marginal values across point sets to estimate the impact of IMRT on the average operational costs across departments.

We estimate the average marginal value per point at 154€, using the set size (column 4) as weights: this is the average monetary contribution by a(n additional) point to an overall rise in the budget for operation costs given the aforementioned hypotheses hold. Applied to our case we will assume a marginal contribution of 154€ per IMRT treated breast cancer patient (one-point difference between category 2 and 4) and 77€ per IMRT treated prostate or head and neck patient (half a point of difference between category 3 and 4).

APPENDIX 9: EXTERNAL RADIOTHERAPY BUDGET ESTIMATIONS

We estimate the overall budget for external radiotherapy in 2003 by separate cost items (governmental perspective):

- Fee-for-service (article 18)
- Investment Costs (A3)
- Operational Costs (B3)
- Inpatient Overhead Costs

Fee-for-service Cost

In appendix 6 we calculated the actual fee-for-service budget for external radiotherapy in 2003: 61 588 987€. By correcting for the 340 IMRT treatments in 2003 (by subtracting 565€ per IMRT, "equalizing" the IMRT reimbursement to a 3DCRT reimbursement) we obtain a "net" fee-for-service budget of 61 396 887€.

Investment Costs

We first subtract 170 points from the 50 221 (point-weighted) started courses for external radiotherapy in 2003 as to correct for IMRT courses delivered in 2003. Then, we divide this number by 750, obtaining a minimum of 67 linacs for Belgium that year. Estro 2005 puts the number of linacs for Belgium at 70[98]. By multiplying this latter figure by 90 000€, we obtain an estimate of 6 300 000€, which we deflate by one year to obtain an estimate of 6 160 743€ for reimbursed "net" investments costs in 2003.

Operational Costs: departmental lump sums

By taking the point-weighted total of treatments in categories 1-4 for 2003 we can derive an aggregated total score for all RT departments. After subtracting this total by (340*0.5) we obtain 50 051 as a "net" overall points aggregate. Divided by 25 we have an average "net" score of 2002 per centre. Consequently, on average centres are entitled to a departmental lump sum of 383 102€ (deflated to 2003), leading to a "net" overall reimbursement for departmental lumps sums of 9 104 384€.

Operational Costs: point lump sums

By taking the 50 051 "net" aggregate point score for 2003 and multiplying it by (the deflated value of) 179.3€ we obtain an overall "net" reimbursement of 8 374 923€.

Inpatient Overhead Costs

We apply an estimated maximum number of fractions per external radiation treatment category type based on present reimbursement regulations: 10 fractions for category 1 and 35 fractions for categories 2-4. The following table gives an overview of this calculation leading to a maximum number of 746 400 fractions in 2003, or 10 663 fractions per linear accelerator. It should be noted that this derived average "linac throughput capacity" is on the high side given the maximizing hypotheses applied with regard to the number of fractions per course.

Overall maximum fractions for external radiation therapy (2003)

Category (external radiation)	Maximum # Fractions	Treatment courses started		Derived Overall # Fractions	
		Outpatient Setting	Inpatient Setting	Outpatient Setting	Inpatient Setting
Category 1	10	4 820	2 515	48 200	25.150
Category 2	35	10 691	559	374 185	19 565
Category 3	35	6 494	614	227 290	21 490
Category 4	35	513	359	17 955	12 565
Total		22 518	4 047	667 630	78 770

Finally, we estimate an additional daily bed cost, covering the additional hospital overhead costs for inpatient treatment delivery. In assuming that all fractions for treatment courses started in hospital settings are delivered to inpatients (again a cost maximizing assumption) and that fractions are delivered according to a 5 fractions per 7 days scheme we are able to derive estimates for public payer reimbursement of daily bed costs. Based on publicly available daily bed costs for Belgium applying to 2003 [111] and data on cancer incidence by tumour location (see data for 2001 in Table 1 of our report) we derived APR-DRG weighted daily bed cost averages per treatment category. The observed difference between the daily bed costs for categories 1 and 2 versus categories 3 and 4 can be explained by the fact that breast cancer patients are exempt from treatment as category 3 or 4 patients. Hence daily bed costs for APR-DRG 382 "MALIGNANT BREAST DISORDERS" taken into account for categories 3-4. Further details for these calculations can be found the next table.

Base values for estimating daily bed costs

Localisation	2001 Incidence	2001% Incidence	APrDRG (version 15)	Daily Bed Cost	% Art 18 billing codes in total of professional fees
Breast (C50)	9 265	16.5%	382	277 €	5.66%
Prostate (C61)	8 884	15.8%	500	265 €	4.54%
Bronchus and lung (C34)	6 163	11.0%	144	269 €	0.40%
Rectum (C20)	2 067	3.7%	240	272 €	2.08%
Cervix uteri & corpus uteri (C53 & C54)	2 037	3.6%	511 - 530	274€ -291€	0.01% - 6.83%
Head & Neck (C00-14, C30-32)	1 973	3.5%	110	290 €	8.26%
Central Nervous System (C70-72)	729	1.3%	41	292 €	12.90%
Liver and intrahepatic bile ducts (C22)	364	0.6%	281	331 €	0.91%
Mesothelium (C45)	240	0.4%	NA	No data	No data
Other	24 413	43.5%	NA	No data	No data
Total	56 136	100.0%			

The table below depicts two overall cost estimates: the full cost estimate attributes all overhead costs to the external radiation course whereas the proportional estimate attributes overheads proportional to the stake average radiotherapy fees (article 18 billing code items) hold in the overall expenses for specialist fees.

Table Overall maximum daily bed costs for external radiotherapy (2003)

Category (external radiation)	Derived Overall # Fractions Inpatient Setting	Average Daily Bed Cost: Full Cost	Average Daily Bed Cost: Proportional Cost
Category 1	25 150		
Category 2	19 565	278.6 €	12.5 €
Category 3	21 490		
Category 4	12 565	279.6 €	11.7 €
Total	78 770	30 772 461€	1 338 345€

Outpatient Transportation costs

As an exception to the general rule, outpatient transportation costs are reimbursed under public regulations for patients undergoing RT following a ministerial decree dated July 6th 1989[112], which specifies cost will be reimbursed in correspondence to public transports travel expenses. We did not manage to obtain detailed data on the precise amounts that are reimbursed by the health insurers ("mutualities"). In keeping with a forthcoming decree (coming into effect 1st July 2007 REF) we put the maximum reimbursed amount at a reimbursement of 0.25€ per kilometre for a (two-way) travelling distance between the patient's home and RT department of 60 kilometres Taking the total number of estimated fractions for outpatients in 2003 we obtain a figure of 667 630 fractions. If we assume per day one fraction is performed in patients, we obtain an overall cost of 5 007 225€. It should nevertheless be observed that the reimbursement of transportation costs is potentially a sizeable cost factor for which little information is at hand.

Overall budget estimate

Below we derive an overall budget estimate for external radiotherapy applying to Belgium in 2003 assuming the present. The amounts have been corrected for possible costs related to the delivery of IMRT. As such, this can be regarded a "net" estimate.

Overall Reimbursements for External Radiotherapy (estimate in 2003€)

ITEM	**REIMBURSEMENT 2003**	
Fee for Service (Article 18)	61 588 987 €	67%
Investment Costs (A3)	6 160 743 €	7%
Operational Costs: Departmental Lump Sums (B3)	9 104 385 €	10%
Operational Costs: Point Lump Sums (B3)	8 374 924 €	9%
Inpatient Daily Bed Costs	1 338 345 €	1%
Oupatient Transporation Costs	5 007 225 €	5%
Total	**91 574 609 €**	**100%**

APPENDIX 10: OUTPUT DETERMINISTIC MODEL

Modelled IMRT patient numbers

EXTRAPOLATED INCIDENCES					
Localisation	2002	2003	2004	2005	2006
Breast (C50)	9364	9462	9560	9667	9771
Prostate (C61)	9025	9165	9314	9478	9626
Head & Neck (C00-14, C30-32)	2055	2072	2090	2110	2129

CCORE 2003 EXTERNAL RT UPTAKE RATE (FIRST-TIME PATIENTS)					
Localisation	2002	2003	2004	2005	2006
Breast (C50)	83%	83%	83%	83%	83%
Prostate (C61)	60%	60%	60%	60%	60%
Head & Neck (C00-14, C30-32)	78%	78%	78%	78%	78%

CCORE 2003 INCLUSION FACTOR FO SECONDARY CANCER TREATMENT BY EXTERNAL RT
1.25

CCORE 2003 EXTERNAL RT UPTAKE RATE (25% OF SECOND TREATMENT RT INCLUDED)					
Localisation	2002	2003	2004	2005	2006
Breast (C50)*	104%	104%	104%	104%	104%
Prostate (C61)	75%	75%	75%	75%	75%
Head & Neck (C00-14, C30-32)	98%	98%	98%	98%	98%

* Flat mark-up of 25% applied as CCORE did not specify per tumour type

GENERAL EXTERNAL RT UPTAKE RATE BELGIUM					
	2002	2003	2004	2005	2006
General RT Uptake Rate Belgium	45.6%	46.1%	47.5%	48.03%	48.52%
Correction Factor	0.70	0.71	0.73	0.74	0.75

EXTERNAL RT UPTAKE RATES BELGIUM					
Localisation	2002	2003	2004	2005	2006
Breast (C50)	73%	74%	76%	77%	77%
Prostate (C61)	53%	53%	55%	55%	56%
Head & Neck (C00-14, C30-32)	68%	69%	71%	72%	73%

DERIVED NUMBERS OF RT PATIENTS					
Localisation	2002	2003	2004	2005	2006
Breast (C50)	6813	6955	7255	7411	7567
Prostate (C61)	4747	4870	5110	5253	5389
Head & Neck (C00-14, C30-32)	1405	1431	1491	1520	1550

Cost items

FEE FOR SERVICE ARTICLE 18 (BASED ON RIZIV/INAMI TARIFFS)					
Localisation	2002	2003	2004	2005	2006
Breast (C50)	1 291 €	1 329 €	1 347 €	1 347 €	1 347 €
Prostate (C61)	549 €	565 €	573 €	573 €	573 €
Head & Neck (C00-14. C30-32)	549 €	565 €	573 €	573 €	573 €

INVESTMENT COSTS (A3)					
Localisation	2002	2003	2004	2005	2006
Breast (C50)	117.3 €	117.3 €	117.3 €	117.3 €	117.3 €
Prostate (C61)	58.7 €	58.7 €	58.7 €	58.7 €	58.7 €
Head & Neck (C00-14. C30-32)	58.7 €	58.7 €	58.7 €	58.7 €	58.7 €

OPERATIONAL COSTS (B3_a): LUMP SUM PER POINT					
Localisation	2002	2003	2004	2005	2006
Breast (C50)	167.7 €	170.4 €	174.3 €	179.3 €	181.2 €
Prostate (C61)	83.9 €	85.2 €	87.1 €	89.7 €	90.6 €
Head & Neck (C00-14. C30-32)	83.9 €	85.2 €	87.1 €	89.7 €	90.6 €

OPERATIONAL COSTS (B3_b): LUMP SUM PER DEPART (PER EXTRA POINT) (2005/06)					
Localisation	2002	2003	2004	2005	2006
Breast (C50)	144.1 €	146.4 €	149.7 €	154.0 €	155.6 €
Prostate (C61)	72.0 €	73.2 €	74.9 €	77.0 €	77.8 €
Head & Neck (C00-14. C30-32)	72.0 €	73.2 €	74.9 €	77.0 €	77.8 €

OPERATIONAL COSTS (B3)					
Localisation	2002	2003	2004	2005	2006
Breast (C50)	311.8 €	316.8 €	324.0 €	333.3 €	336.8 €
Prostate (C61)	155.9 €	158.4 €	162.0 €	166.7 €	168.4 €
Head & Neck (C00-14. C30-32)	155.9 €	158.4 €	162.0 €	166.7 €	168.4 €

BELGIAN CPI (BELGIAN NATIONAL BANK[110])		
REFERENCE DATE	BASE 2002	BASE 2005
2002/06	100.00	93.55
2003/06	101.61	95.06
2004/06	103.91	97.21
2005/06	106.89	100.00
2006/06	108.01	101.05

INVESTMENT COSTS (A3) PER POINT
120 €
OPERATIONAL COSTS (B3_a): LUMP SUM PER POINT (2005/06)
179.30 €
OPERATIONAL COSTS (B3_b): MARGINAL SUM PER POINT
154 €

Detailed model results (€)

	Year														
	2002			2003			2004			2005			2006		
Scenario	ART 18	A3 (INV)	B3 (OP)	ART 18	A3 (INV)	B3 (OP)	ART 18	A3 (INV)	B3 (OP)	ART 18	A3 (INV)	B3 (OP)	ART 18	A3 (INV)	B3 (OP)
PROST	2 608 255	278 526	740 096	2 751 492	285 735	771 483	2 929 042	299 796	827 743	3 011 072	308 192	875 351	3 089 337	316 202	907 535
H-N	772 072	82 447	219 077	808 665	83 978	226 739	854 435	87 454	241 462	871 425	89 193	253 333	888 257	90 916	260 937
BREAST	8 797 475	799 533	2 124 512	9 243 194	816 152	2 203 605	9 773 334	851 342	2 350 575	9 983 703	869 666	2 470 098	10 194 220	888 004	2 548 668
P-H-N	4 700 472 €			4 928 093 €			5 239 932 €			5 408 566 €			5 553 184 €		
P-H-N-B	16 421 993 €			17 191 043 €			18 215 182 €			18 732 033 €			19 184 076 €		

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Wettelijk depot : D/2007/10.273/32

KCE reports

1. Effectiviteit en kosten-effectiviteit van behandelingen voor rookstop. D/2004/10.273/1.
2. Studie naar de mogelijke kosten van een eventuele wijziging van de rechtsregels inzake medische aansprakelijkheid (fase 1). D/2004/10.273/2.
3. Antibioticagebruik in ziekenhuizen bij acute pyelonefritis. D/2004/10.273/5.
4. Leukoreductie. Een mogelijke maatregel in het kader van een nationaal beleid voor bloedtransfusieveiligheid. D/2004/10.273/7.
5. Het preoperatief onderzoek. D/2004/10.273/9.
6. Validatie van het rapport van de Onderzoekscommissie over de onderfinanciering van de ziekenhuizen. D/2004/10.273/11.
7. Nationale richtlijn prenatale zorg. Een basis voor een klinisch pad voor de opvolging van zwangerschappen. D/2004/10.273/13.
8. Financieringssystemen van ziekenhuisgeneesmiddelen: een beschrijvende studie van een aantal Europese landen en Canada. D/2004/10.273/15.
9. Feedback: onderzoek naar de impact en barrières bij implementatie – Onderzoeksrapport: deel 1. D/2005/10.273/01.
10. De kost van tandprothesen. D/2005/10.273/03.
11. Borstkankerscreening. D/2005/10.273/05.
12. Studie naar een alternatieve financiering van bloed en labiele bloedderivaten in de ziekenhuizen. D/2005/10.273/07.
13. Endovasculaire behandeling van Carotisstenose. D/2005/10.273/09.
14. Variaties in de ziekenhuispraktijk bij acuut myocardinfarct in België. D/2005/10.273/11.
15. Evolutie van de uitgaven voor gezondheidszorg. D/2005/10.273/13.
16. Studie naar de mogelijke kosten van een eventuele wijziging van de rechtsregels inzake medische aansprakelijkheid. Fase II : ontwikkeling van een actuarieel model en eerste schattingen. D/2005/10.273/15.
17. Evaluatie van de referentiebedragen. D/2005/10.273/17.
18. Prospectief bepalen van de honoraria van ziekenhuisartsen op basis van klinische paden en guidelines: makkelijker gezegd dan gedaan.. D/2005/10.273/19.
19. Evaluatie van forfaitaire persoonlijk bijdrage op het gebruik van spoedgevallendienst. D/2005/10.273/21.
20. HTA Moleculaire Diagnostiek in België. D/2005/10.273/23, D/2005/10.273/25.
21. HTA Stomamateriaal in België. D/2005/10.273/27.
22. HTA Positronen Emissie Tomografie in België. D/2005/10.273/29.
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.
30. Inventaris van databanken gezondheidszorg. D2006/10.273/14.
31. Health Technology Assessment prostate-specific-antigen (PSA) voor prostaatkankerscreening. D2006/10.273/17.
32. Feedback : onderzoek naar de impact en barrières bij implementatie – Onderzoeksrapport : deel II. D/2006/10.273/19.
33. Effecten en kosten van de vaccinatie van Belgische kinderen met geconjugeerd pneumokokkenvaccin. D/2006/10.273/21.
34. Trastuzumab bij vroegtijdige stadia van borstkanker. D/2006/10.273/23.
35. Studie naar de mogelijke kosten van een eventuele wijziging van de rechtsregels inzake medische aansprakelijkheid (fase III)- precisering van de kostenraming. D/2006/10.273/26.
36. Farmacologische en chirurgische behandeling van obesitas. Residentiële zorg voor ernstig obese kinderen in België. D/2006/10.273/28.
37. HTA Magnetische Resonantie Beeldvorming. D/2006/10.273/32.

38. Baarmoederhalskankerscreening en testen op Human Papillomavirus (HPV). D/2006/10.273/35
39. Rapid assessment van nieuwe wervelzuil technologieën : totale discusprothese en vertebro/ballon kyfoplastie. D/2006/10.273/38.
40. Functioneel bilan van de patiënt als mogelijke basis voor nomenclatuur van kinesitherapie in België? D/2006/10.273/40.
41. Klinische kwaliteitsindicatoren. D/2006/10.273/43.
42. Studie naar praktijkverschillen bij electieve chirurgische ingrepen in België. D/2006/10.273/45.
43. Herziening bestaande praktijkrichtlijnen. D/2006/10.273/48.
44. Een procedure voor de beoordeling van nieuwe medische hulpmiddelen. D/2006/10.273/50.
45. HTA Colorectale Kankerscreening: wetenschappelijke stand van zaken en budgetimpact voor België. D/2006/10.273/53.
46. Health Technology Assessment. Polysomnografie en thuismonitoring van zuigelingen voor de preventie van wiegendood. D/2006/10.273/59.
47. Geneesmiddelengebruik in de belgische rusthuizen en rust- en verzorgingstehuizen. D/2006/10.273/61
48. Chronische lage rugpijn. D/2006/10.273/63.
49. Antivirale middelen bij seizoensgriep en grieppandemie. Literatuurstudie en ontwikkeling van praktijkrichtlijnen. D/2006/10.273/65.
50. Eigen betalingen in de Belgische gezondheidszorg. De impact van supplementen. D/2006/10.273/68.
51. Chronische zorgbehoeften bij personen met een niet- aangeboren hersenletsel (NAH) tussen 18 en 65 jaar. D/2007/10.273/01.
52. Rapid Assessment: Cardiovasculaire Primaire Preventie in de Belgische Huisartspraktijk. D/2007/10.273/03.
53. Financiering van verpleegkundige zorg in ziekenhuizen. D/2007/10 273/06
54. Kosten-effectiviteitsanalyse van rotavirus vaccinatie van zuigelingen in België
55. Evidence-based inhoud van geschreven informatie vanuit de farmaceutische industrie aan huisartsen. D2007/10.273/12.
56. Orthopedisch Materiaal in België: Health Technology Assessment. D2007/10.273/14.
57. Organisatie en Financiering van Musculoskeletale en Neurologische Revalidatie in België. D2007/10.273/18.
58. De Implanteerbare Defibrillator: een Health Technology Assessment. D2007/10.273/21.
59. Laboratoriumtesten in de huisartsgeneeskunde. D2007/10.273/24.
60. Longfunctie testen bij volwassenen. D2007/10.273/27.
61. Vacuümgeassisteerde Wondbehandeling: een Rapid Assessment. D2007/10.273/30
62. Intensiteitsgemoduleerde Radiotherapie (IMRT). D2007/10.273/32.
63. Wetenschappelijke ondersteuning van het College voor Oncologie: een nationale praktijkrichtlijn voor de aanpak van borstkanker. D2007/10.273/35.