CANCER PLAN

ACTION 30

(Financed by the Federal Public Service of Health, Food Chain Safety and Environment)

Feasibility study of a Hadron Therapy Centre in Belgium

EXECUTED BY

THE BELGIAN HADRON THERAPY CENTRE (BHTC) FOUNDATION

IN COLLABORATION WITH

BELGIAN UNIVERSITIES, UNIVERSITY HOSPITALS, BELGIAN CANCER REGISTRY, RESEARCH INSTITUTES, EXPERTS FROM THE BELGIAN SOCIETY OF PAEDIATRIC HEMATOLOGY AND ONCOLOGY

AND

INTERNATIONAL EXPERTS IN HADRON THERAPY

GUIDED BY THE CANCER PLAN UNIT

REVIEWED BY THE STEERING COMMITTEE OF ACTION 30

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(Financed by the Federal Public Service of Health, Food Chain Safety and Environment)

Guided by the **Unit Cancer Plan**

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RÉSUMÉ

Contexte général

1. L'hadronthérapie est un nom générique qui englobe les traitements par faisceaux de hadrons. Les hadrons sont des particules susceptibles d'interaction forte (άδρός = fort), à savoir, en pratique, protons, neutrons ou noyaux atomiques. À l'heure actuelle, les protons et les ions carbone sont les plus investigués.
2. En 2012, la Belgique comptait 25 centres de radiothérapie externe et 11 satellites traitant environ 30,000 patients/an par photons ou électrons. L'hadronthérapie n'est pas disponible en Belgique.
3. L'Europe comptait 14 centres d'hadronthérapie opérationnels (protons: 12, ions carbone et protons: 2). Le coût est de 18,000-40,000 €/patient. Les USA sont le leader mondial en protonthérapie; les coûts/patient y dépassent souvent les 100,000 $. Le Japon est le leader mondial en thérapie par ions carbone. Les coûts/patient y sont d'environ 40,000 €, soutien logistique inclus.
4. Très peu de patients belges sont adressés à des centres d'hadronthérapie en raison de difficultés multiples : listes d'attente, barrières linguistiques, déplacements longs, hébergement coûteux, raisons sociales, problèmes logistiques et financiers.

Justification physique : Peu devant, presque rien derrière.

1. Les faisceaux d'électrons ne sont pas bien délimités et ne conviennent donc pas pour un traitement de haute précision. Les faisceaux de photons sont bien délimités dans le sens latéral, mais pas dans les zones situées devant ou derrière la tumeur. Les faisceaux de protons et d'ions carbone sont bien délimités dans le sens latéral et n'irradient pratiquement pas la zone située derrière la tumeur.
2. Les faisceaux de protons et d'ions carbone sont excellents pour le traitement de haute précision. En comparaison avec l'irradiation par faisceaux de photons, les tissus sains reçoivent une dose de 2 à 10 fois moins forte.

Justification biologique pour l'utilisation d'ions carbone : Pas si mous, pas si durs !

1. Les faisceaux de photons et de protons déposent relativement peu de dose par mm de tissus traversé. Un tel dépôt de dose « mou » permet aux tissus normaux, mais aussi aux cancers de réparer substantiellement les dégâts d'irradiation.
2. Les faisceaux d'ions carbone ont une double nature biologique. Dans la première partie de leur trajectoire, devant la cible tumorale, ils ne sont pas aussi mous que les faisceaux de photons ou de protons, mais ils permettent néanmoins la réparation significative des dommages sous-létaux. Dans la deuxième partie de leur trajectoire, dans la tumeur même, ils ne permettent guère la réparation des lésions infligées. En revanche, ils ne sont pas aussi « durs » que les ions lourds tels les noyaux de néon ou d'argon dont l'« overkill » diminue l'efficacité de l'irradiation par unité de dose délivrée.
3. L'objectif principal de la protonthérapie est de réduire l'irradiation des tissus sains.
4. L'objectif principal de la thérapie par ions carbone est l'éradication des cancers radiorésistants.

Nombre de patients/an potentiels pour la thérapie par protons ou par ions carbone

1. Sur la base du Registre du Cancer Belge, le nombre de patients/an selon les indications standards, généralement reconnues et remboursées, est de 223 pour les adultes et de 34 pour les enfants.
2. La construction d'un centre belge pour ne traiter que des indications standards serait très coûteuse en raison même du nombre total faible de patients.
3. La recherche sur l'hadronthérapie dans les cancers communs est toute récente, car il a fallu attendre qu'un plus grand nombre d'installations soit disponible dans le monde entier. Les cancers du sein et de la prostate n'ont pas été étudiés parce que le résultat du traitement par photons a été jugé acceptable pour la majorité des patients. Pour les 7 entités de cancer les plus convaincantes (appelé indications modèles), 1,820 patients/ans belges ont été identifiés.
4. Le choix entre protons et ions carbone est fondé sur des données cliniques limitées et peut changer. Sur la base des données actuellement disponibles, les protons seraient le choix pour 32 enfants/an et les ions carbone pour 2 enfants/an. Chez les adultes, les indications entre protons ou ions carbone seraient moitié-moitié.

Choix techniques et technologiques

1. Trois concepts de centres ont été étudiés : un p-centre, n'utilisant que des protons, un (p + C)-centre utilisant les protons et les ions carbone et un C-centre, n'utilisant que les ions carbone. Seules les solutions technologiques disponibles sur le marché en 2012 ou connues pour faire partie de projets non académiques ont été prises en compte dans l'assemblage virtuel de chaque concept. Par conséquent, la distinction entre « technologie établie » et « technologie de centres pionniers » a été faite.
2. Seul un (p + C)-centre pourrait traiter, sans compromis, toutes les indications identifiées.
3. Aujourd'hui, la technologie établie permettrait des traitements « state of the art » pour toutes les indications standards et les 3 indications modèles qui partagent des caractéristiques clés avec les indications standards (récidive locale du cancer du rectum, tumeurs des glandes salivaires non adénoïdes kystiques et la réirradiation des cancers tête et cou). Le nombre total de patients éligibles est 545/an, qui est proche de la capacité au démarrage d'un (p + C)-centre à deux salles de traitement.

Coût de l'investissement et des opérations cliniques

1. Les calculs des coûts ont été réalisés pour les 3 concepts selon un scénario de 2 salles de traitement. Pour comparaison, un centre de proton à salle unique de traitement a également été étudié (tableau 1), car ce modèle devient de plus en plus populaire dans le monde entier.

Tableau 1. Coûts d'investissement et de remboursement requis pour les différents concepts.

	Deux salles de traitements			Salle unique
	(p+C)-centre	C-centre	p-Centre	p-Centre
Investissement	101,500,000 €	85,000,000 €	51,500,000 €	37,000,000 €
Patients/an	534	760	355	165
	Remboursement moyen nécessaire/patient pour le seuil de rentabilité			
Financement privé	51,150 €	32,400 €	51,200 €	70,600 €
Financement public	27,550 €	18,400 €	32,300 €	40,950 €

Légende: Patients/an: nombre de patients si occupation maximale de la configuration de démarrage. Dans le calcul avec un financement public, les coûts d'investissement complets ainsi que les frais de personnel au cours de la mise en service ont été soustraits du calcul du remboursement requis.

2. Les remboursements nécessaires pour couvrir les coûts moyens par patient sont calculés dans l'hypothèse d'une occupation maximale de chaque scénario (tableau 1). Les montants de 18,000 à 40,000 €/patient, généralement remboursés

pour les traitements par hadrons en Europe, sont suffisants si l'investissement se fait par des fonds publics, mais pas dans le cadre d'un financement privé.

3. En raison de traitements moins fractionnés, la thérapie par ions carbone est moins chère par patient que la protonthérapie. La protonthérapie dans un centre à salle unique de traitement engendre le coût le plus élevé par patient.
4. L'hadronthérapie évolue vers l'utilisation de moins de fractions par patient, ce qui pourrait diminuer le coût moyen/patient traité. En réduisant le nombre actuel de fractions par patient de 50 %, le remboursement de référence européen (18,000 à 40,000 €/patient) devient suffisant pour couvrir les coûts, même dans le cadre d'un financement privé.

Évaluations économiques

1. Le rapport coût-efficacité est moins certain pour les indications modèles que pour les indications standard. Trois indications modèles ont été sélectionnées pour l'évaluation coût-efficacité : le cancer du pancréas localement avancé (CPLA), le stade III du cancer du poumon non à petites cellules (CPNPC) et le carcinome hépatocellulaire (CHC) non résécable. Ensemble, ils représentent un nombre potentiel de 1,353 patients/an.
2. Par rapport à la photonthérapie + gemcitabine, la hadronthérapie par ions carbone + gemcitabine double l'espérance de vie médiane et réduit la toxicité au traitement chez les patients atteints d'un CPLA. Dans le cadre du financement public d'un (p + C)-centre, le coût par année de vie gagnée est de 23,000 à 25,000 € et par année de vie ajustée par sa qualité 33,000 - 38,000 €.
3. Par rapport à la chimiophotonthérapie, la chimioprotonthérapie améliore l'espérance de vie moyenne d'environ 6 mois et réduit la toxicité du traitement du stade III CPNPC. Dans le cadre du financement public d'une (p + C)-centre, le coût par année de vie gagnée est de 22,000 à 23,000 € et par année de vie ajustée par sa qualité 31,000 - 34,000 €.
4. Le financement privé d'une (p + C)-centre est associé à plus qu'un doublement des coûts par année de vie gagnée pour le CPLA et le stade III CPNPC.
5. Le CHC non résécable est une entité particulière. L'ablation par radiofréquence (RFA) reste le traitement de choix. Pour les patients où la RFA est actuellement le traitement standard, une alternative par hadronthérapie (protons ou ions carbone) se solderait par un bénéfice clinique limité, au prix de plus de 100,000 € par année de vie gagnée ou année de vie ajustée par sa qualité.
6. Pour les patients atteints de CHC non résécable qui ne sont pas éligibles pour une RFA, les options de traitement radical sont rares. Cependant, une hadronthérapie radicale est encore possible chez beaucoup de ces patients avec un stade intermédiaire ou avec envahissement ganglionnaire. Une étude plus approfondie est justifiée.

Recommandations

1. Construction en Belgique, sur le campus d'un grand hôpital général à même de fournir les services médicaux complémentaires, d'un seul et unique Centre d'hadronthérapie afin de centraliser l'expertise.
2. La mission de ce Centre en matière d'enseignement, de recherches et de développement requiert l'environnement que seul fournit un hôpital universitaire.
3. Une organisation et une gestion indépendantes sont recommandées pour faciliter la participation des parties prenantes de tout le pays. La collaboration avec le ou les hôpitaux qui offrent des services complémentaires peut être sécurisée par des accords d'obligations réciproques.
4. Nous recommandons le choix d'un (p + C)-centre avec une conception flexible permettant de traiter toutes les indications standards ainsi que les indications modèles les moins difficiles dès le début des opérations. La conception doit prévoir pour un stade ultérieur des possibilités d'expansions et de mises à niveau technologiques pour le traitement des indications modèles plus difficiles à aborder.
5. Nous recommandons de faire une description précise, avec les entreprises qui participent à des projets de (p + C)-centres (IBA, Mitsubishi, Toshiba, Sumitomo), de l'équipement qui serait nécessaire dans chaque salle de traitement. À partir des spécifications de l'équipement des chambres de traitements, chaque entreprise serait invitée à décrire le matériel (sources d'ions, accélérateur[s], lignes de faisceau) nécessaire à fournir les faisceaux de protons et ions carbone. Cette description permettra une estimation des coûts d'investissements pour réduire l'importante incertitude actuelle concernant l'investissement, l'exploitation et l'entretien d'un (p + C)-centre.
6. Le groupe à l'origine de l'étude de faisabilité a été naturellement limité dans sa capacité de répondre aux questions ouvertes concernant le site d'implantation, la structure organisationnelle, la structure financière, le remboursement, la recherche, la formation, le recrutement des patients et les collaborations souhaitables pour un futur centre belge d'hadronthérapie. Nous recommandons l'organisation d'un appel d'offres ouvert invitant les parties intéressées à rédiger une **Déclaration d'intention de dialoguer avec les Autorités publiques**. Le dialogue vise à répondre aux questions ouvertes et à choisir la meilleure association pour élaborer le MasterPlan d'un centre belge d'hadronthérapie.

SUMMARY

General context

1. Hadron therapy is a generic name for treatment with hadron beams. Hadrons are particles susceptible to nuclear forces (άδρός = strong), in practice protons, neutrons or atomic nuclei. Presently, protons and carbon ions receive most interest.
2. In 2012, Belgium hosted 25 radiotherapy centers and 11 satellites, which treat about 30,000 patients/year with external photon- or electron therapy. Hadron therapy is not available in Belgium.
3. Europe had 14 hadron (12 proton; 2 carbon ion and proton) therapy centers in operation. Charges/patient are in the 18,000-40,000 € range. USA is world leader for proton therapy. Charges/patient often exceed 100,000$. Japan is world leader in carbon ion therapy. Charges/patient are about 40,000 €; cost of logistic support included.
4. Very few Belgian patients are referred to foreign hadron centers because of waiting lists, language barriers, travel, lodging, social, logistic and financial issues.

Physical rationale: Little in front, almost nothing behind

1. Electron beams are not well delineated and therefore not suitable for high-precision therapy. Photon beams are well delineated in lateral direction but not in distance. Proton and carbon ion beams are well delineated in lateral and distal directions.
2. Proton and carbon ion beams are suitable for high precision cancer therapy and irradiate healthy tissues to 2-10 times less dose than photon beams.

Biological rationale for carbon ion therapy: Not so soft, not so hard

1. Photon and proton beams deposit little dose for each mm that they traverse in the patient. Such dose deposition allows normal tissues but also cancers to repair large amounts of the radiation damage. The radiation has a soft biological nature.
2. Carbon ion beams have a dual biological nature. In the first part of there trajectory they are not so soft as photon or proton beams but still allow substantial damage repair. In the second part of their trajectory they are not so hard as heavy ions like neon or argon nuclei, which cause ‘overkill’, associated with decreased efficiency per unit of radiation.
3. The primary aim of proton therapy is to reduce irradiation of healthy tissues.
4. The primary aim of carbon ion therapy is the eradication of radioresistant cancers.

Number of potential patients/year for proton or carbon ion therapy

1. Based on the Belgian Cancer Registry, the numbers of patients/year with generally accepted and reimbursed standard indications are 223 for adults and 34 for children.
2. Constructing a Belgian centre to treat only standard indications would be very expensive due to the fact that the total number of patients is small.
3. Research on hadron therapy in common cancers has been started recently, as more hadron beam capacity became available worldwide. Breast and prostate cancer were not studied because the outcome after photon therapy was considered acceptable for the majority of patients. For today's 7 most convincing cancer entities (called model indications), 1,820 Belgian patients/year were identified.
4. The choice between protons and carbon ions is based on limited clinical data and may be subject to shifts. Based on actually available data, protons would be the choice for 32 children/year and carbon ions for 2 children/year. In adults, the choice would be protons or carbon ions, each in about half of the patients.

Technical and technological choices

1. Three centre concepts were studied: a proton only (p-center); a combined proton-carbon ion ((p+C)-centre) and a carbon ion only (C-centre) concept. Only technological solutions that were commercially available in 2012 or that were known to be part of running non-academic projects were considered in the virtual assembly of each centre. Hence, a distinction between 'established' technology and technology of pioneering centers was made.
2. Only a (p+C)-centre could treat all eligible indications without compromises.
3. Today, established technology would enable state-of-the-art treatment for all standard indications and for 3 model indications that share key characteristics with standard indication (locally recurrent rectal cancer, non-adenoid cystic salivary gland tumours and re-irradiation for head and neck cancer). The total number of eligible patients (standard + 3 model indications) is 545/year, which is close to the capacity of a 2-room (p+C)-centre at start-up.

Cost of investment and clinical operations

1. Costs calculations were performed for the 3 concepts in a 2-room scenario and for a one-room proton centre (table 1), the latter becoming increasingly popular worldwide as add-on to existing large radiotherapy departments, to serve local needs.

Table 1. Investment and required reimbursement costs for different concepts.

	Two treatment rooms			Single room
	(p+C)-centre	C-centre	p-Centre	p-Centre
Investment	101,500,000 €	85,000,000 €	51,500,000 €	37,000,000 €
Patients/year	534	760	355	165
	Required average reimbursement/patient for break-even			
Private financing	51,150 €	32,400 €	51,200 €	70,600 €
Public financing	27,550 €	18,400 €	32,300 €	40,950 €

Legend: Patients/year: numbers at full occupancy of the start-up configuration. In the calculation with public financing, the full investment costs as well as the personnel costs during commissioning have been taken out of the calculation of required reimbursement.

2. The required average reimbursement costs/patient are calculated for full patient occupancy of each scenario (table 1). The 18,000 to 40,000 €/patient, commonly reimbursed for hadron treatments in Europe, is sufficient with public –but not private– financing of the investment costs.
3. Due to treatments with fewer fractions, carbon ion therapy is less expensive per patient treated than proton therapy. Proton therapy in a single room centre yields the highest cost/patient treated.
4. Proton and carbon ion therapy evolve towards the use of less fractions/patient, which decreases the average cost/patient treated. Halving the number of fractions/patient makes the European benchmark reimbursement of 18,000 to 40,000 € /patient sufficient to cover the costs even in a private scenario.

Health economic evaluations

1. The cost-effectiveness is less certain for model than for standard indications. Three model indications were selected for health economic evaluation: Locally advanced pancreatic cancer (LAPC), Stage III non-small cell lung cancer (NSCLC) and unresectable hepatocellular carcinoma (HCC). Together, they represent a potential number of 1,353 patients/year.
2. Compared to photon therapy + gemcitabine, carbon ion therapy + gemcitabine doubles median life expectancy and reduces treatment-toxicity in patients with LAPC. In public financing of a (p+C)-centre, the cost per life-year gained is 23,000 - 25,000 €, per quality-adjusted life-year 33,000 - 38,000 €.
3. Compared to chemo-photontherapy, chemo-protontherapy improves median life expectancy by about 6 months and reduces treatment-toxicity in stage III NSCLC. In public financing of a (p+C)-centre, the cost per life-year gained is 22,000 – 23,000 € and 31,000 - 34,000 € per quality-adjusted life-year.
4. Private financing of a (p+C)-centre is associated with more than doubling of the costs per life-year gained for LAPC and stage-III NSCLC.

5. Unresectable HCC is a peculiar cancer entity. Radiofrequency ablation (RFA) remains the treatment of choice in RFA-eligible patients since hadron alternatives (proton or C ion therapy) result in limited clinical gains at costs of more than 100,000 € per life-year, all or not adjusted for quality of life.
6. Radical treatment options are scarce in patients with unresectable HCC who are not eligible for RFA. However, radical hadron therapy is still possible in many of these patients with intermediate stage or node-positive HCC. Further study is warranted.

Recommendations

1. Building a single centre at a single site in Belgium, being the campus of a large general hospital that can provide the complementary medical services, is recommended to centralize expertise.
2. The centre's mission of education, research and development calls for the services of an academic hospital.
3. An independent organization and management structure is recommended to facilitate participation of stakeholders anywhere in the country. The collaboration with the hospital(s) that provide complementary services can be secured through service liability agreements.
4. We recommend the choice of a (p+C)-centre with flexible design that allows treating all standard indications as well as the least challenging model indications from the start of operations. The design must foresee the possibilities of expansions and technological upgrades for treating the more challenging model indications at a later stage.
5. We recommend making a precise description - together with the companies that participate in (p+C)-centre projects (IBA, Mitsubishi, Toshiba, Sumitomo) - of the equipment that would be needed in each treatment room. From the room specifications, each company derives what equipment (ion sources, accelerator(s), beam lines) they would need to install. A cost estimate should be asked to reduce the –presently large– uncertainty in the investment, operational and maintenance costs inherent to (p+C)-centers.
6. The group behind the Feasibility Study was inherently limited in its possibilities to answer open questions regarding implantation site, organization structure, financial structure, reimbursement, research, training, referral and collaboration of a future Belgian hadron therapy centre. We recommend organizing an open call asking interested parties to write a **Declaration of Intent to Dialogue with the Public Authorities**. The dialogue aims at answering the key questions and at selecting the best association to make a MasterPlan that must lead to a Belgian hadron therapy centre.

SAMENVATTING

Algemene context

1. Hadrontherapie is een generische naam voor de behandeling met hadron stralingsbundels. Hadrons zijn deeltjes die onderhevig zijn aan nucleaire krachten (άδρός = sterk), in de praktijk protonen, neutronen en atoomkernen. Op dit moment, krijgen protonen en koolstofionen de meeste aandacht.
2. In 2012, waren in België 25 radiotherapie-centra en 11 satellieten operationeel, die ongeveer 30,000 patiënten/jaar behandelden met externe foton- of elektron therapie. Hadrontherapie is niet beschikbaar in België.
3. Europa had 14 hadrontherapie (12 protonen, 2 koolstofionen en protonen) centra in werking. De kosten/patiënt variëren van 18,000-40,000 €. USA is wereldleider voor protontherapie. De kosten/patiënt zijn vaak hoger dan 100,000 $. Japan is wereldleider in koolstofionen therapie. De kosten/patiënt zijn ongeveer 40,000 €; kosten van logistieke ondersteuning inbegrepen.
4. Zeer weinig Belgische patiënten worden verwezen naar buitenlandse hadrontherapie centra omwille van wachtlijsten, taalbarrières, reiskosten, logies, sociale, logistieke en financiële kwesties.

Fysica rationale: Weinig voor, bijna niets achter

1. Elektronenbundels zijn niet goed begrensd en daarom ongeschikt voor zeer nauwkeurige therapie. Fotonenbundels zijn goed begrensd in zijdelingse richting, maar niet in de stralingsrichting. Proton- en koolstofionenbundels zijn goed afgebakend in zijdelingse en distale richtingen. De bestraling stopt net voorbij de tumor.
2. Proton- en koolstofionenbundels zijn geschikt voor hoge precisie kankertherapie en bestralen gezonde weefsels met tot 2-10 maal minder dosis dan fotonenbundels.

Biologische rationale voor koolstofionen therapie: niet zo zacht, niet zo hard

1. Foton- en protonbundels deponeren weinig dosis voor elke mm die ze doorkruisen. Dergelijke dosisdepositie laat normale weefsels maar ook kanker toe om grote hoeveelheden van de stralingsschade te herstellen. De straling heeft een relatief zacht biologische karakter.
2. Koolstofionenbundels hebben een dubbel biologisch karakter. In het eerste deel van hun traject zijn ze niet zo zacht als foton- of protonbundels maar laten toch nog toe om aanzienlijke schade te herstellen. In het tweede deel van hun traject zijn ze niet zo hard als zware ionenbundels, bijvoorbeeld neon- of argonkernbundels,

die 'overkill' veroorzaken waardoor de efficiëntie van de straling per dosiseenheid afneemt.
3. Het primaire doel van protontherapie is het verminderen van bestraling van gezonde weefsels.
4. Het primaire doel van koolstofionentherapie is de uitroeiing van radioresistente kanker.

Aantal potentiële patiënten/ jaar voor proton- of koolstofionentherapie

1. Op basis van het Belgisch Kankerregister zijn de aantallen patiënten/jaar met algemeen aanvaarde en terugbetaalde standaardindicaties 223 voor volwassenen en 34 voor kinderen.
2. Een Belgisch hadrontherapie centrum oprichten om alleen standaardindicaties te behandelen zou zeer duur zijn omdat het totale aantal patiënten/jaar beperkt is.
3. Onderzoek naar hadrontherapie in veel voorkomende vormen van kanker is onlangs gestart omdat er wereldwijd meer hadrontherapie capaciteit beschikbaar is gekomen. Borst-en prostaatkanker werden niet onderzocht omdat de uitkomst na fotontherapie aanvaardbaar geacht wordt voor de meeste patiënten. Voor de 7 meest belovende kankerentiteiten (de zogenaamde modelindicaties) werden 1,820 Belgische patiënten/jaar geïdentificeerd.
4. De keuze tussen protonen en koolstofionen is gebaseerd op beperkte klinische gegevens en is onderhevig aan verschuivingen. Op basis van actueel beschikbare gegevens, zou protontherapie de beste keuze voor 32 kinderen/jaar zijn en koolstofionentherapie voor 2 kinderen/jaar. Bij volwassenen zouden proton- of koolstofionentherapie de beste keuzes zijn; elk voor ongeveer de helft van de patiënten.

Technische en technologische keuzes

1. Drie centrum concepten werden onderzocht: een proton alleen (p-centrum), een gecombineerd proton-koolstofionen ((p + C)-centrum) en een koolstofionen alleen (C-centrum) concept. Alleen technologische oplossingen die in de handel verkrijgbaar waren in 2012 of die deel uitmaakten van niet-academische projecten werden beschouwd in de virtuele constructie van elk centrum. Daarom werd een onderscheid gemaakt tussen 'gevestigde' technologie en technologie van pioniercentra.
2. Van de 3 concepten kan alleen een (p + C)-centrum alle indicaties behandelen zonder compromissen.
3. De gevestigde technologie zou state-of-the-art behandeling toelaten voor alle standaardindicaties en voor de 3 modelindicaties (lokaal recidief van rectumcarcinoom, niet-adenoïd cystische speekselkliertumoren en herbestraling voor hoofd-en halstumoren) die specifieke kenmerken delen met standaardindicaties.

Het totale aantal patiënten (standaard- + 3 modelindicaties) is 545/year, hetgeen dicht bij de startcapaciteit van een 2-kamer (p + C)-centrum aanleunt.

Investeringskost en klinische operationele kost

1. De kostberekeningen werden uitgevoerd voor de 3 concepten in een 2-kamer-scenario alsook voor een één-kamer protoncentrum (tabel 1). Dit laatste concept wordt steeds populairder over de hele wereld als extensie van bestaande grote radiotherapie afdelingen om lokale behoeften te dienen.

Tabel 1. Investering en vereiste terugbetaling voor de verschillende concepten

	Twee behandelingskamers			Eén-kamer
	(p+C)-centrum	C-centrum	p-Centrum	p-Centrum
Investering	101,500,000 €	85,000,000 €	51,500,000 €	37,000,000 €
Patiënten/jaar	534	760	355	165
	Vereiste gemiddelde terugbetaling/patient voor evenwicht			
Private financiering	51,150 €	32,400 €	51,200 €	70,600 €
Publieke financiering	27,550 €	18,400 €	32,300 €	40,950 €

Legende: Patiënten/jaar: aantallen bij volle bezetting van de startconfiguratie. In de berekeningen onder publieke financiering werden geen investeringskosten noch personeelskosten gedurende de oplevering meegenomen.

2. De vereiste gemiddelde terugbetaling/patiënt werd berekend voor volle patiëntbezetting van elk concept (tabel 1). De 18,000 tot 40,000 €/patiënt, voor hadrontherapie in Europa, is voldoende bij publieke, maar niet bij private financiering van de investeringskosten.
3. Als gevolg van behandelingen met minder fracties is koolstofionentherapie minder duur per behandelde patiënt dan protontherapie. Protontherapie in een één-kamer centrum heeft de hoogste kosten/patiënt.
4. Proton- en koolstofionentherapie evolueren naar het gebruik van minder fracties/patiënt, waarbij de gemiddelde kost/patiënt voor beide afneemt. Halvering van het aantal fracties/patiënt maakt dat de Europese referentievergoeding van 18,000 tot 40,000 €/patiënt voldoende wordt om de kosten zelfs in een privaat financieringsmodel te dekken.

Gezondheidseconomische evaluaties

1. De kosten-effectiviteit is minder zeker voor model- dan voor standaardindicaties. Drie modelindicaties werden geselecteerd voor gezondheidseconomische evaluatie: Lokaal gevorderde pancreaskanker (LAPC), Stadium III niet-kleincellige long-

kanker (NSCLC) en niet-receseerbaar hepato-cellulair carcinoom (HCC). Samen vertegenwoordigen zij een potentieel aantal van 1,353 patiënten/jaar.

2. In vergelijking met fotontherapie + gemcitabine verdubbelt koolstofionentherapie + gemcitabine de gemiddelde levensverwachting en vermindert het de behandelingstoxiciteit bij patiënten met LAPC. In het publieke financieringsmodel van een (p + C)-centrum zijn de kosten per gewonnen levensjaar 23,000 tot 25,000 €, per levensjaar aangepast voor levenskwaliteit 33,000 - 38,000 €.
3. In vergelijking met chemo-fotontherapie verbetert chemo-protontherapie de mediane levensverwachting bij stadium III NSCLC met ongeveer 6 maanden en vermindert de behandelingstoxiciteit. In het publieke financieringsmodel van een (p + C)-centrum zijn de kosten per gewonnen levensjaar 22,000 tot 23,000 € en 31,000 - 34,000 € per levensjaar aangepast voor levenskwaliteit.
4. Private financiering van een (p + C)-centrum gaat gepaard met meer dan een verdubbeling van de kosten per gewonnen levensjaar voor LAPC en stadium-III NSCLC.
5. Niet-receseerbaar HCC is een interessante kankerentiteit. Radiofrequentie-ablatie (RFA) blijft de voorkeursbehandeling in patiënten die voor RFA in aanmerking komen omdat hadronalternatieven (proton of C ion therapie) slechts een beperkte klinische winst opleveren tegenover een kost van meer dan 100,000 € per gewonnen levensjaar, al dan niet aangepast voor levenskwaliteit.
6. Radicale behandelingsopties zijn schaars bij patienten met niet-reseceerbaar HCC die niet in aanmerking komen voor RFA. Radicale hadrontherapie is evenwel nog steeds mogelijk bij vele van deze patiënten met intermediair stadium of klierpositief HCC. Verder onderzoek is aangewezen.

Aanbevelingen

1. Het bouwen van één enkel centrum op een locatie in België, zijnde de campus van een groot algemeen ziekenhuis dat kan zorgen voor de complementaire medische diensten, wordt aanbevolen om kennis te centraliseren.
2. Het centrum heeft ook een missie van onderwijs, onderzoek en ontwikkeling. Dit vraagt om de diensten van een academisch ziekenhuis.
3. Een onafhankelijke organisatie- en managementstructuur wordt aanbevolen om de participatie van alle belanghebbenden te vergemakkelijken. De samenwerking met het ziekenhuis dat de complementaire diensten verleent kan worden verzekerd door middel van dienst-verplichting overeenkomsten.
4. We bevelen een (p + C)-centrum aan met flexibel ontwerp dat reeds bij de operationele start de behandeling van alle standaard- en de 3 modelindicaties kan verzekeren. Het ontwerp moet voorzien in de mogelijkheden van uitbreidingen en technologische verbeteringen voor de behandeling van meer uitdagende model indicaties in een later stadium.

5. Wij adviseren een nauwkeurig ontwerp - samen met de bedrijven die deelnemen aan (p + C)-centrum projecten (IBA, Mitsubishi, Toshiba, Sumitomo) - van de apparatuur die nodig zou zijn in elke behandelkamer. Vanuit de kamerspecificaties, kan elk bedrijf afleiden welke apparatuur (ionenbronnen, versneller (s), bundeltransportlijnen) ze zouden moeten installeren. Een kostenraming moet worden gevraagd om de grote onzekerheden betreffende operationele, investerings- en onderhoudskosten (p + C)-centra te verminderen.
6. De groep achter de haalbaarheidsstudie was inherent gelimiteerd in zijn mogelijkheden om open vragen te beantwoorden betreffende inplantatieplaats, organisatiestructuur, financiële structuur, terugbetaling, onderzoek, training, doorverwijzing en samenwerking voor een toekomstig Belgisch hadron therapie centrum. Wij adviseren tot organisatie van een open bevraging waarbij aan geïnteresseerde partijen gevraagd wordt om een **Intentieverklaring tot Dialoog met de Openbare Overheid** te schrijven. De dialoog beoogt antwoorden te bekomen op de open vragen en de selectie te maken van de beste associatie voor het maken van een MasterPlan dat moet leiden tot een Belgisch hadron therapie centrum.

I. Preface and background

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1. GENERAL CONTEXT

1.a. Participation and review by all Belgian University Hospitals

In March 2010, the 7 University Hospitals, SCK•CEN represented by their delegates in the Governing Board of the BHTC Foundation, and the University of Namur, confirmed their participation in a common feasibility project in the framework of the Cancer Plan Action 30 "feasibility study of a hadron therapy centre in Belgium". The representatives of the University Hospitals agreed, in a document signed on March 22 (see addendum 1), on managing the funds made available by the Federal Public Service of Health, Food Chain Safety and Environment for that purpose through the University Hospital Gent. This document has been signed for UZ Gent by Wilfried De Neve, for UZ Leuven by Karin Haustermans, for U Antwerpen by Danielle Van den Weyngaert, for UZ Brussel by Dirk Van den Berge, for HU Saint-Luc by Pierre Scalliet, for CHU Liège by Philippe Coucke and for Institut Jules Bordet by Paul Van Houtte. All 7 are members of the Board of Directors of the BHTC Foundation. Within the Board of Directors the members agreed on the task and resource repartition of the addendum 2. Not all of the institutes had the resources available for directly participating in the different submodules of this feasibility study and the degree of direct involvement in them is variable. Some of them even had to restrict their participation to reviewing the report made by others. As you can see, CHU Liège has not been actively involved in the preparatory study phase. HU Saint-Luc preferred to focus on their one-room proton therapy project, in collaboration with UCL, IBA and Région Wallonne and has delegated its participation in Action 30 to

Table 1: hadron therapy facilities in operation (incl. patient statistics):

Who, where	Country	Particle	S/C*, Max. Energy (MeV)	Beam Direction	Start of treat-ment	Total patients treated	Date of total
ITEP, Moscow	Russia	p	S 250	1 horiz.	1969	4246	Dec-10
St.Petersburg	Russia	p	S 1000	1 horiz.	1975	1372	Dec-11
Uppsala	Sweden	p	C 200	1 horiz.	1989	1185	Dec-11
Clatterbridge	England	p	C 62	1 horiz.	1989	2151	Dec-11
Loma Linda	CA.,USA	p	S 250	3 gantry, 1 horiz.	1990	15000	Jan-11
Nice	France	p	C 65	1 horiz.	1991	4417	Dec-11
Orsay	France	p*****	C 230	1 gantry, 2 horiz.	1991	5634	Dec-11
NRF - iThemba Labs	South Africa	p	C 200	1 horiz.	1993	521	Dec-11
UCSF	CA.,USA	p	C 60	1 horiz.	1994	1391	Dec-11
HIMAC, Chiba	Japan	C ion	S 800/u	horiz., vertical	1994	6569	Dec-11
TRIUMF, Vancouver	Canada	p	C 72	1 horiz.	1995	161	Dec-11
PSI, Villigen	Switzerland	p**	C 250	1 gantry, 1 horiz.	1996	1107	Dec-11
HZB (HMI), Berlin	Germany	p	C 72	1 horiz.	1998	1859	Dec-11
NCC, Kashiwa	Japan	p	C 235	2 gantry	1998	772	Dec-10
Dubna	Russia	p	C 200****	horiz.	1999	828	Dec-11
HIBMC,Hyogo	Japan	p	S 230	1 gantry	2001	3198	Dec-11
PMRC(2), Tsukuba	Japan	p	S 250	gantry	2001	2166	Dec-11
NPTC, MGH Boston	MA.,USA	p***	C 235	2 gantry, 1 horiz.	2001	5562	Oct-11
HIBMC,Hyogo	Japan	C ion	S 320/u	horiz.,vertical	2002	788	Dec-11
INFN-LNS, Catania	Italy	p	C 60	1 horiz.	2002	290	Dec-11
Shizuoka Cancer Center	Japan	p	S 235	3 gantry, 1 horiz.	2003	1175	Dec-11
IU Health PTC, Bloomington	IN.,USA	p	C 200	2 gantry, 1 horiz.	2004	1431	Dec-11
WPTC, Zibo	China	p	C 230	2 gantry, 1 horiz.	2004	1078	Dec-11
MD Anderson Cancer Center, Houston	TX.,USA	p***	S 250	3 gantry, 1 horiz.	2006	3400	Feb-12
UFPTI, Jacksonville	FL.,USA	p	C 230	3 gantry, 1 horiz.	2006	3461	Dec-11
IMP-CAS, Lanzhou	China	C ion	S 400/u	1 horiz.	2006	159	Dec-11
NCC, Ilsan	South Korea	p	C 230	2 gantry, 1 horiz.	2007	810	Dec-11
STPTC, Koriyama-City	Japan	p	S 235	2 gantry, 1 horiz.	2008	1378	Dec-11
RPTC, Munich	Germany	p**	C 250	4 gantry, 1 horiz.	2009	895	Dec-11
ProCure PTC, Oklahoma City	OK.,USA	p	C 230	1 gantry, 1 horiz., 2 horiz./60 deg.	2009	623	Dec-11
HIT, Heidelberg	Germany	p**	S 250	2 horiz.	2009	94	Dec-11
HIT, Heidelberg	Germany	C ion**	S 430/u	2 horiz.	2009	568	Dec-11
UPenn, Philadelphia	PA.,USA	p	C 230	4 gantry, 1 horiz.	2010	433	Dec-11
GHMC, Gunma	Japan	C ion	S 400/u	3 horiz., vertical	2010	271	Dec-11
CDH Proton Center, Warrenville	IL.,USA	p	C 230	1 gantry, 1 horiz., 2 horiz./60 deg.	2010	367	Dec-11
HUPTI, Hampton	VA., USA	p	C 230	4 gantry, 1 horiz.	2010	no data	start Aug-10
IFJ PAN, Krakow	Poland	p	C 60	1 horiz.	2011	11	Dec-11
Medipolis Medical Research Institute, Ibusuki	Japan	p	S 250	3 gantry	2011	180	Dec-11
CNAO, Pavia	Italy	C ion, p	S 430/u	3 horiz./1 vertical	2011	5	Dec-11
ProCure Proton Therapy Center, New Jersey	NY., USA	p	C 230	4 gantry	2012	15	Apr-12

Legend: * S/C = Synchrotron (S) or Cyclotron (C). ** with beam scanning at Gantry and passive beam at OPTIS2 (since Oct 2010). *** with passive beam and beam scanning. **** degraded beam. ***** new cyclotron and fixed beam operational since July 2010; the gantry is operational since Oct 2010. From PTCOG website: last update: 26-June-2012.

Prof. Stéphane Lucas of the University of Namur. The creation of a hadron therapy centre requires both clinical and basic scientific and technical knowledge. SCK•CEN and the Université de Namur perform supporting research to create fundamental physical and radiobiological know-how, specific to hadron therapy. References are available on http://bhtc.sckcen.be/en.

All 7 members have been asked to review the preliminary as well as the final reports. A first time the president of the BHTC Foundation has requested their input on September 12, 2012 after the intermediate report had been presented to the steering committee. A second and explicit request for their official review was repeated on November 29, 2012 concerning the draft of the interim report that was also submitted to the panel of international experts for discussion at the Expert Meeting on December 4-5, 2012. The 'Interim Report Revised Version – December 18th, 2012' which contained the review of the BHTC members was submitted to the members of the Steering Committee for discussion during the meeting of January 17, 2013. Remarks and answers to the questions of the Steering Committee and the updated versions of the cost-utility analysis regarding 3 potential indications were incorporated in the Report Version – April 9th, 2013.

1.b. Overview of hadron centers worldwide

Table 1 lists all hadron therapy facilities that were in operation worldwide in 2012 [1]. Europe had 14 hadron therapy centers in operation. Five centers (Clatterbridge, Nice, Berlin, Catania and Krakow) are limited to the treatment of eye diseases or superficial tumours. Nine centers have high-energy accelerators that produce beams for the treatment of deep-seated tumours. The three Russian centers have old installations (Moscow, St. Petersburg) or treat very few patients (Dubna). They are not candidate centers for referral of Belgian patients. The new clinical facility of Uppsala is under construction. The remaining 5 centers (Orsay (Paris), PSI (Villigen, Switzerland), Munich (Germany), Heidelberg (Germany) and Pavia (Italy)) are candidate centers for referral of Belgian patients. The new proton centre of Essen (Germany) is technically ready for operation but the clinical start-up is delayed for unclear reasons. Munich, Orsay and PSI treat with protons. Orsay and PSI have specialized teams and facilities for treating paediatric cancer. Heidelberg and Pavia have carbon ion and proton beams. Heidelberg is exploring the use of other ions like helium and oxygen. Pavia has a slow ramp-up of patients (Piero Fossati, communication at the 2nd expert meeting). Together, these 5 centers treated less than 2,000 patients in the year 2011. The capacity in European centers is expected to double in the next 3-5 years because operating centers increase capacity and some new centers like Essen, Trento, Uppsala, Marburg, Prague, Vienna and Krakow will start operations.

Table 2: Particle therapy facilities in a planning stage or under construction:

Who, where	Country	Particle	Max. clinical energy (MeV)	Beam direction	No. of treat-ment rooms	Start of treat-ment planned
PTC Czech s.r.o., Prague*	Czech Rep.	p	230 cyclotron	3 gantries, 1 horiz. fixed beam	4	2012
McLaren PTC, Flint, Michigan*	USA	p	250/330 synchrotron	3 gantries	3	2012
WPE, Essen*	Germany	p	230 cyclotron	3 gantries, 1 horiz. fixed beam	4	2012
Chang Gung Memorial Hospital, Taipei*	Taiwan	p	235 cyclotron	4 gantries, 1 experimental room	4	2012
Barnes Jewish St. Louis, MO*	USA	p	250 SC synchro-cyclotron	1 gantry	1	2012
PTC, Marburg*	Germany	p, C ion	430/u synchrotron	3 horiz. fixed beams 1 fixed beam 0 + 45 deg.	4	2012?
Northern Illinois PT Res.Institute, W. Chicago, IL*	USA	p	250 SC cyclotron	2 gantries, 2 horiz. fixed beams	4	2012?
PMHPTC, Protvino*	Russia	p	250 synchrotron	1 horiz. fixed beam	1	2012?
CCSR, Bratislava	Slovak Rep.	p	72 cyclotron	1 horiz. fixed beam	1	?
CMHPTC, Ruzomberok*	Slovak Rep.	p	250 synchrotron	1 horiz. fixed beam	1	?
SJFH, Beijing	China	p	230 cyclotron	1 gantry, 1 horiz. fixed beam	2	?
Skandion Clinic, Uppsala*	Sweden	p	230 cyclotron	2 gantries	2	2013
HITFil, Lanzhou*	China	C ion	400/u synchrotron	4 horiz.., vertical, oblique, fixed beams	4	2013
ATreP, Trento *	Italy	p	230 cyclotron	2 gantries 1 horiz. fixed beam	3	2013
Scripps Proton Therapy Center, San Diego, CA*	USA	p	250 SC cyclotron	3 gantries, 2 horiz. fixed beams	5	2013
SCCA Proton Therapy, a ProCure Center, Seattle, WA*	USA	p	230 cyclotron	4 gantries	4	2013
Robert Wood Johnson, New Brunswick*	USA	p	250 SC synchro-cyclotron	1 gantry	1	2013
Oklahoma University, Oklahoma City, OK*	USA	p	250 SC synchro-cyclotron	1 gantry	1	2013
MD Anderson, Orlando, FL*	USA	p	250 SC synchro-cyclotron	1 gantry	1	2013
First Coast Oncology, Jacksonville, FLI*	USA	p	250 SC synchro-cyclotron	1 gantry	1	2013
Fudan University Shanghai CC*	China	p, C ion	430/u synchrotron	3 fixed beams	3	2014
Samsung Proton Center, Seoul*	South Korea	p	230 cyclotron	2 gantries	2	2014
IFJ PAN, Krakow*	Poland	p	235 cyclotron	1 gantry	1	2014?
Med-AUSTRON, Wiener Neustadt*	Austria	p, C ion	430/u synchrotron	1 gantry (only for protons) 1 fixed beam, 1 fixed 0 + 90 deg.	3	2015
PTC Zürichobersee, Galgenen	Switzerland	p	230 cyclotron	4 gantries, 1 horiz. fixed beam	5	2016

* under construction. Last update: 04-August-2012. From PTCOG website.

Table 2 shows the centers that were planned or under construction in 2012 [1]. This list is heterogeneous and incomplete. Some centers are in the construction phase. Others are plans on paper with uncertain future. Five Japanese centers are not included: 2 will use carbon ions; 3 will use protons (Tadashi Kamada, communication at the 3rd expert meeting). The capacity of proton therapy is rapidly growing in the USA. Commercial exploitation is the standard. The low-end sales price of a proton treatment is around 100,000 US$. Japan is the world leader in carbon ion treatment. Foreign patients are accepted at approximately 40,000 US$ per treatment (Tadashi Kamada, communication at the 2nd expert meeting). Japanese centers should be seriously considered regarding referral of Belgian patients. Several vendors offer one-room proton centers. Mevion and IBA received orders for 18 and 22 one-room proton centers, respectively (communication of their representatives at the ESTRO Teaching Course on Proton and Light Ion Therapy, Pavia, Italy, March 9-14, 2013).

1.c. Problematic referral of Belgian patients abroad

Photon and electron beams are available in the 25 radiation oncology centers in Belgium while treatment with protons or carbon ions is not yet possible in the country. Hence, referral procedures must be initiated when a patient presents with an indication for hadron therapy.

I. Searching a hadron therapy center

European hadron therapy centers accept patients for a limited number of indications. For example, Heidelberg HIT runs 13 clinical protocols, mainly in adult patients. PSI at Villigen Switzerland and Orsay at the south of Paris accept paediatric patients as well as a restricted number of adult patients for specific indications. The first step is searching a hadron therapy centre which has the appropriate treatment program and has an open treatment slot within the required time window. Synchronization of hadron therapy with surgery and systemic therapy is often required. In paediatric patients, continuation of chemotherapy may have to be secured during the period of hadron therapy. In practice, the oncologic paediatricians affiliated to the hadron therapy centre are involved in the treatment.

II. Submission of the patient files to the hadron center

The second step involves preparation and eventually also translation of the patient files for submission to the hadron centre. The files are studied at the hadron centre and a recommendation for treatment, which may or may not involve hadron

therapy, is returned. At this point, the referring radiation oncologist knows if the patient will be accepted. European hadron therapy centers provide advisory services at no charge.

III. Organising travel and obtaining E112/S2

In case of acceptance, appointments have to be made. Travel and lodging have to be organized. The social services of our hospitals help the patients in obtaining the E112/S2 document. This document guarantees that the medical services offered to Belgian patients are reimbursed in other EU countries. European hadron therapy centers provide help for organising the patient's stay nearby their facilities. The patients must be able to (pre)finance a few thousand Euros for their travel and stay without guarantee that the full cost will be reimbursed. Hence, social equality does not exist in Belgium regarding access to hadron therapy. It is a substantial work for the Belgian referring doctor, the social services and the patient to file all the documents to the health insurance system, especially if an accompanying person is needed. In the past, travel and lodging were reimbursed by the Solidarity Fund but this was temporarily put on hold during the last years because a separate budget for treating patients with hadron therapy had been announced by the RIZIV/INAMI. Although reimbursement by the Solidarity Fund has restarted recently, substantial parts of the cost have not been reimbursed to the referred patients. The Foundation against Cancer has started complementary financial help for patients. Today (March 15, 2013) the administration services of the Foundation against Cancer and the referring centers have completed the files of 5 patients. The patients will receive 1,000 € each to reduce their own contribution in the cost of their hadron therapy.

IV. Organising follow-up

Most patients enter prospective clinical protocols at European hadron therapy centers. The referring Belgian doctor is asked to perform systematic follow-up according to the protocols of the foreign centers.

V. Conclusions and future directions

Substantial obstacles exist for Belgian patients as well as for the referring centre when an indication for hadron therapy is made. Referral to a European centre is facilitated by the E112/S2 document. Little experience exists with referring patients to Japan but considering their leading role in carbon ion therapy it is expected that the demand for treatment of Belgian patients will increase.

Following a government initiative which opens top-reference medical care in Japan to patients worldwide, a private company takes care of all logistic issues concerning referral of foreign patients for hadron therapy (http://www.medical-excellence-japan.org/en/). Table 3 is copied from the website.

Table 3: Examples of services provided by Medical Excellence JAPAN

Before your trip	• Responses to inquiries about healthcare in Japan • Contact with medical institutions in Japan, and proxy service for procedures necessary to receive treatment • Support with visa applications
During your stay	• Arrangement of airport pickup and transport • Medical interpretation and translation service • Comprehensive support throughout your stay in Japan, and for those accompanying you as well
After returning home	• Support for post-treatment follow-up examination at a medical institution

Foreign patient referral to NIRS is being organized by the services of Medical Excellence JAPAN. In their experience, the services of the company are highly valued by the patients and by the health care providers (Prof. Tadashi Kamada, 3rd Expert Meeting). The cost estimate is 3 million Yen (about 30,000 Euro; which is equal to the reimbursement rate in Japan) for the treatment with carbon ions at NIRS plus the cost of travel, lodging and the logistic services of Medical Excellence JAPAN. The global figure is around 40,000 Euro per patient as mentioned previously. American proton centers are commercialized and require up-front payment of the cost of treatment which is prohibitive for many Belgian patients.

Belgium lacks a centralized logistic and social support for the patients. In practice, hadron therapy is a possibility for Belgian patients if they can at least pre-finance travel and lodging to a European or Japanese centre. The whole initiative of referral to European centers is carried by the referring centre that must be capable to finance their part of the work themselves. In contrast, for referral to Japan, a large part of the logistic work is addressed by Medical Excellence JAPAN. Medical Excellence JAPAN could serve as a paradigm for organising logistic help for Belgian patients, for example, through a liaison office.

1.d. Networking for hadron therapy treatment

I. Organisation and management of a Belgian Hadron Therapy Center

During the presentation of the early versions of the interim report of the feasibility study on September 7 and October 23, 2012, members of the Steering Committee demanded to have already some idea on the future organisation and

management of such a centre.
As we still have to wait for the definitive report and -even more important- the intention of The Public Institution to fund or co-fund (in a Private-Public or other setting) this hadron therapy centre it is only possible and prudent to propose an outlay and a sequence, without time-frame of this organisation.
It is clear from the Interim Reports of the Feasibility Study that public funding of the initial investment cost is almost a necessity in the European context. This is consistent with the high interest shown by the Federal Government and the funding, by them, of the feasibility study.
Irrespective of the source(s) of funding, the scientific input and surveillance is the responsibility of the stakeholders, including the academic institutions and the experts in the field. The care for the routing of the treated patients is the responsibility of the referring physician according to the guidelines established by the experts and the professionals of the future hadron therapy centre. The experts and the professionals have also the duty of research and development regarding, not only patient treatment, but also the physics aspects of hadron therapy. The combination of clinical treatment with medical, translational and physics research is an organisational and management challenge. Our viewpoint, regarding a possible organisation model is proposed in appendix 1 at the end of this chapter. The general philosophy of the organisation and management model is one of control and policy making by all stakeholders, irrespective of the site of construction of the centre.

II. Referral/back-referral in Belgium

Providing hadron therapy as a treatment option is no standard practice in Belgian Oncological Care Programs. Standard Operating Procedures for referring patients abroad for hadron therapy are inexistent. The chance of referral to a hadron therapy centre depends entirely on local initiatives, even for standard indications like skull-base, paraspinal, salivary gland or paediatric cancers. Hadron therapy centers worldwide are involved in various types of local-regional, national and international networks. The most popular model seems one of unidirectional referral at the local-regional level and a system of referral and back-referral at the national and international level. In unidirectional referral the patients stays under the responsibility of the hadron therapy centre for treatment and follow-up. This system was favoured by most experts because it offers the best guarantee for careful follow-up of the patients and –hence– for high-quality data regarding the outcome of treatment. However, all experts recognize that unidirectional referral is difficult to accomplish, even at the local-regional level: referring doctors ‘loose’ their patients. In a system of referral/back-referral, the patient is send back after

the completion of treatment to the referring entity for follow-up. Standardisation of follow-up and integrity of follow-up data is more difficult to accomplish. A system of referral and back-referral would probably be the preferred system for a future Belgian hadron therapy centre.

III. Path of referral of patients to a future BHTC

1. Path of referral for adult patients

In Belgium, care for the cancer patient is organized at two levels. Oncological Care Programs are based at large hospitals that often have a radiotherapy department. All other Belgian hospitals have Programs of Basic Oncological Care that must be affiliated to one or more Oncological Care Programs. The disciplines involved in oncological patient care participate in Multidisciplinary Oncological Consulting (MOC) groups. The MOC groups, which are organized by the Oncological Care Programs or jointly between both program levels, play a decisive role in designing the path of care for the patient, either according to written guidelines or based on consensus. MOC groups are often disease-oriented according to the major oncological diseases. Radiation oncologists participate in all MOC groups and secure the path of care to and through the radiotherapy component of the treatment. This structure aims to provide access to optimal cancer care for all patients. Referral to the BHTC will be initiated at the MOC level for most of the Belgian patients. The radiation oncologist plays a crucial role in referral. He has the competence to assess if the patient is physically, mentally and socially able to follow treatment at a BHTC and to conduct the preparatory steps for referral (medical files, appointments for preparatory examinations and interventions, guidance).

2. Path of referral for paediatric patients

About 300 children annually are diagnosed with cancer in Belgium. Survival rates have markedly improved over the last decades with cure rates approaching 70-80% nowadays. Treatment of paediatric cancer is centralized. It was suggested during the meeting on March 9, 2012 with delegates of the Belgian Society of Paediatric Hematology and Oncology (minutes joined in addendum 5) that only hospitals with the recognized specialized paediatric hemato-oncological program as well as the main departments of radiotherapy (no satellites) could give an advice on need and referral of paediatric patients for hadron therapy. There are 4 such hospitals in this country: affiliated to university hospitals of UCL, ULB, KUL and UGent. A need for a liaison person between Belgian referral institutions, patients and their families and the hadron therapy centre was identified. The liaison

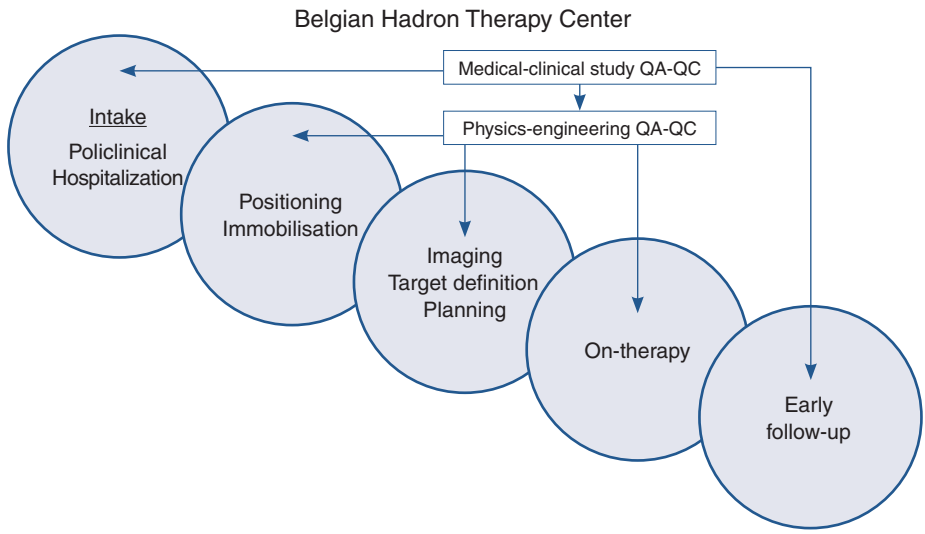
person would take charge of referral procedures. The vast majority of patients is treated according to international protocols which are also implemented at the European hadron therapy centers that treat children.

3. Path of care at a BHTC

Hadron therapy centers worldwide are vastly different in the quantity of services which they offer to the patients. On the one end, a hadron therapy centre may be limited to a therapy unit only. This is common in facilities that are located on the campus of physics research centers. Many of the preparatory services are provided through an affiliated radiation therapy department. On the other end, a hadron therapy centre may host such a wide variety of services, including diagnostic imaging, hospitalization, anaesthesia, day clinic that it can function largely independently. An example is NIRS in Chiba, Japan.

Modern, hospital-based centers host the technical facilities that are specifically needed for the treatment preparation and execution: immobilisation, CT-simulation, planning, verification, and quality-assurance. The centre relies on the nearby hospital for various support services like multimodality imaging, hospitalization, day clinic, anaesthesia, emergency medicine, hadron therapy-related surgery (markers, spacers), cardiac-respiratory monitoring, photon radiation and other. Different models were discussed at the second expert meeting (September 20-21, 2012) and the basic concept drawn in figure 1 found general agreement. This model hosts a polyclinic service to allow patient intake and limited follow-up independently

Figure 1: services provided by a (future) Belgian Hadron Therapy Center.



from the nearby hospital, services for treatment preparation (positioning, immobilisation, imaging, planning), services for treatment, a physics department and a clinical study unit. Service-liability agreements with the nearby hospital should secure hospitalization and other services. The BHTC would organize care from the moment of intake till the end of hadron treatment or of an early follow-up consultation, for example in case of hadron therapy-related toxicity. The future BHTC would provide patient care in a system of referral/back-referral. Back-referral passes through the referring entity which secures follow-up of the patient and communication of the follow-up data to the BHTC.

4. Post-hadron therapy follow-up

Due to the improved chances of cure, late complications of treatment are observed more frequently. Assessment of treatment toxicity in long-term survivors of childhood cancer indicates that at a mean age of 24 years, a severe burden of adverse effects was observed in 55% of patients who underwent radiotherapy [2]. Continuation of follow-up of childhood cancer patients beyond the age of 14-15 years is not generally secured in Belgium. Lifetime follow-up for all children who received hadron therapy should be organized.

1.e. UCL-IBA-Saint-Luc-Wallonnie proton therapy project

A project to build and operate a one-room proton therapy facility has been started in Belgium by a group involving IBA, Université Catholique de Louvain (UCL), Hôpital Universitaire Saint-Luc and Région Wallonne. From our contact with prof. Pierre Scalliet on October 25, 2012 we understood that:

1. The Walloon Government has approved the project after submittal to an international jury and to the regional competence poles Biowin and Mécatech, who will steer the project in the framework of the Walloon Marshall plan.
2. The financing structure has been finalized and the Walloon region will guarantee a bank loan. The signature of Minister Marcourt is awaited.
3. The project was developed for implantation in Ottignies at the site of a future general hospital.
4. In addenda 3 and 4 you can find a preliminary project description as well as a request for reimbursement.

2. INTERNATIONAL EXPERTS CONSULTANCY

Four advisory meetings, called Expert Meetings, with world-recognized experts in the field of hadron therapy were organized. The foreign expert group consisted of: professor A. Mazal, president, Particle Therapy Co-Operative Group (PTCOG), head of the Medical Physics Department, Proton Centre, Institut Curie, Orsay, France; professor T. Kamada, director, Research Centre for Charged Particle Therapy, the National Institute of Radiological Sciences (NIRS), Japan; professor J. Debus, director, Department of Radiation Oncology, Heidelberg Ion Beam Therapy Centre (HIT), Heidelberg University Hospital, Heidelberg, Germany; professor O. Jaekel, head of the Medical Physics Department, Heidelberg Ion Beam Therapy Centre (HIT), Heidelberg University Hospital, Heidelberg, Germany; professor A. Lomax, senior medical physicist, Centre for Proton Radiation Therapy, Paul Scherrer Institute (PSI), Villigen, Department of Physics, Swiss Institute of Technology (ETH), Zurich, Switzerland; professor P. Lambin, head of the Department for Radiation Oncology, University Hospital of Maastricht, Medical Director of the MAASTRO clinic, Maastricht, The Netherlands; dr. Stephanie Bolle, radiation oncologist, Proton Centre, Orsay, France; dr. P. Fossati, radiation oncologist, Italian National Centre for Oncological Hadron Therapy (CNAO), Pavia, Italy. The short CVs of the foreign experts can be found in appendix 2 at the end of this chapter.

3. HADRON THERAPY EXPLAINED

The name hadron is derived from the Greek ἁδρός, which means powerful. Hadrons are composed of the elementary particles (quarks) of the atomic nucleus and are subject of the nuclear forces. In radiation therapy, it is fashion to use the term hadron therapy for treatments using protons or neutrons and, by extension, also for treatment with nuclei of atoms like helium or carbon or with other particles of the nucleus like pi-mesons. In some literature, a distinction is made between light ions for treatment (helium, carbon, oxygen) and heavy ions (neon, argon). The feasibility study of a Belgian Hadron Therapy Centre (BHTC) focuses on proton and carbon ions. With these ions, a future BHTC can exploit most of the presently established advantages of hadron therapy.

3.a. Characteristics of proton, carbon and other therapeutic beams

Photon therapy, the irradiation with high-energy X-rays, is the present standard treatment in Belgian radiation therapy centers. To understand the reason for using

Figure 1.

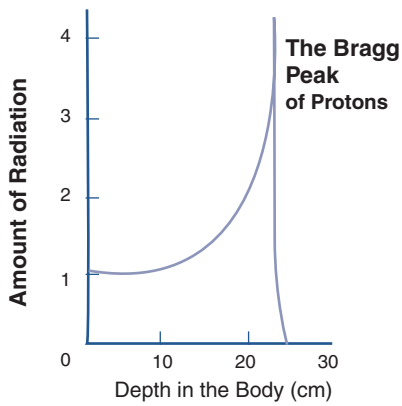
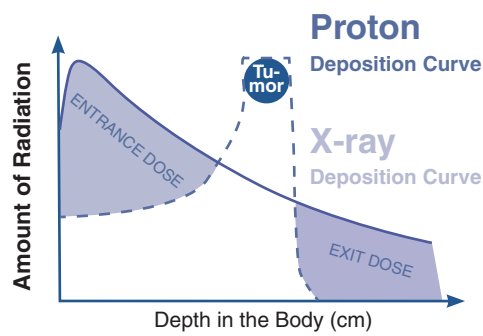


Figure 2.



protons instead of photons, it is useful to compare the dose deposition versus depth of photon and proton beams. This is illustrated in figures 1 and 2.

Fig.1 illustrates the energy deposited by a beam of mono-energetic protons in water. As the protons slow down and loose energy, the stopping power increases. Finally, the protons lose a major part of their energy in the final millimetres of their path. The dose versus depth plot exhibits the well known “Bragg” peak (named for William Henry Bragg who discovered it in 1903). The position in depth of the Bragg peak can be adjusted to sub-millimeter accuracy by adjusting the energy of the incoming proton beam.

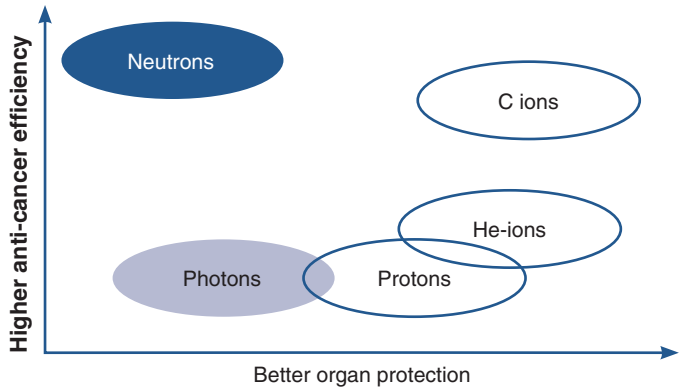
Actually, the Bragg peak of a normal proton beam is narrower than a typical tumour, so it is usual to superimpose several Bragg peaks made by proton beams of slightly different energy to obtain a “Spread-Out Bragg Peak” or SOBP. As shown in fig. 2, the depth/dose curve in a SOBP is very different from the depth/dose curve of the typical photon beam used in radiotherapy. With a proton SOBP, the dose reaches 100% of the requested level in the tumour zone only. Downstream from the tumour, the proton dose falls immediately to zero. Upstream, the proton dose is significantly lower than the photon dose that would give the same dose at the tumour.

When compared to photon therapy, and for a similar dose to the tumour, proton therapy provides a lower integral dose to the healthy organs surrounding the tumour. It is generally accepted that reduction of the dose to healthy organs reduces the probability of radiation induced complications and of secondary malignancies.

As shown in fig. 3, protons have about the same relative biological efficiency (RBE) as photons but offer the better protection of healthy organs. Helium (He)-ions have slightly higher RBE than photons or protons and offer a possibility to improve organ protection even over protons. He-ion treatment requires more

expensive equipment because higher energy for acceleration and stronger magnets for steering are needed than for protons to achieve equal therapeutic depth.

Figure 3.



A neutron beam is the reference for high RBE. It overcomes radioresistance by hypoxia or cell quiescence. Radioresistant tumours like adenoid cystic carcinomas were shown to be sensitive to neutron therapy. Neutron beams have physical dose-depth behaviour that is comparable to photon beams but are much more difficult to handle. Therefore, organ protection is more difficult to achieve than with photon beams. Normal tissues that cannot be protected are irradiated with high RBE neutrons. Severe, even life-threatening toxicity was observed several decades ago, when neutron therapy was clinically investigated. Moreover, the beam activates the equipment as well as the treatment room leading to irradiation of the personnel. For these reasons, neutron therapy became obsolete. Carbon (C)-ions combine the better of two worlds. In the SOBP, RBE is almost as high as for neutrons while organ protection is as good as for He-ions. C ions and He-ions are accelerated by the same type of equipment.

3.b. Rationale for hadron therapy

It is interesting to note that increased use of proton therapy is observed worldwide despite the fact that randomised studies demonstrating the clinical superiority of hadron therapy over the best photon therapy are not yet available today. However, in the history of radiotherapy, all major changes in technology, such as going from orthovoltage to cobalt, from cobalt to linear accelerators, from flat-beam radiotherapy to intensity-modulated radiation therapy (IMRT), from 2D dosimetry to 3D, from the use of body contours to CT for treatment planning, did take place before clinical evidence proving the undisputable superiority of the new technology was

available. In some special circumstances, a randomised trial may even jeopardise patient safety. For example, a randomised trial comparing the benefit of patient immobilisation for high-dose-high-precision radiation therapy to no immobilisation would be unethical. Radiotherapy can be modeled. Model-based predictions of decreased toxicity by reducing dose to healthy organs are reliable as are predictions of increased tumour eradication by increasing the biological dose in the tumour.
The KCE report 67A on hadrontherapy showed the absence of phase III randomised trials (http://www.kce.fgov.be/index_nl.aspx?SGREF=5272&CREF=10107).
A comparable but more recent Italian report "Agenas" (http://www.agenas.it/agenas_pdf/Hadrontherapy.pdf), building on the same constrained scope of hard medical evidence, evidently came to the similar conclusions. Hence, level I evidence demonstrating less toxicity by better organ protection or decreased mortality by higher anti-cancer efficiency is non-existent. Regarding the expected beneficial effects of hadron therapy over photon therapy, lower levels of evidence exist for a few cancers, including adenoid cystic carcinoma, mucosal melanomas and soft tissue sarcomas. At the question –may new photon technologies compete with hadron therapy?– the response is perhaps yes for some localisations (e.g. stereotactic radiotherapy for small lung cancers) but certainly not for radioresistant tumours close to vital organs or for recurrent tumours within an irradiated area.
Many centers for protons or carbon ions exist or are being constructed in Europe, Japan and the United States. In many countries, the radiation treatment with hadrons is supported by the health care system.

3.c. Role of the Royal Academy of Medicine, the Foundation BHTC

The Royal Academy of Medicine shares the vision of the Foundation BHTC regarding the need to build a Belgian centre. The role of the BHTC Foundation is endorsed to develop a comprehensive and detailed business plan according to the 4 conditions expressed by minister Onkelinx: participation of all Belgian universities; a mission involving clinical research; dialogue with political representatives and non-exclusive consulting of Ion Beam Applications (IBA) for its know-how.
The Royal Academy of Medicine supports the development of criteria for the choice of the optimal location. Operational and financial independence from the host location is required to allow the BHTC to play its function as top-reference centre and to facilitate national and international collaboration. The Royal Academy of Medicine endorses the federal level of organisation.
The Royal Academy of Medicine takes note of important the financial aspects including the high cost of investment and operation and the need for support by the health insurance system.

The alternative, sending patients abroad for hadron therapy, does not seem to be less expensive and denies the country valuable opportunities for research, education, academic and industrial development.
The country offers also a unique opportunity due to its size, its communication network, the collaboration between institutions and its central location in Western Europe. There is a good expertise in radiotherapy and a strong know-how in medical imaging.

4. BRIEF DESCRIPTION OF THE STUDY, ITS DIFFERENT SUBMODULES AND ORGANISATION

The basic purpose of this study was to estimate the yearly number of patients for hadron (be it proton or carbon ions) therapy in Belgium. Additionally the costs for setting up a hadron centre and exploit it, had to be investigated in terms of feasibility in the Belgian context.

For this intent the study was originally divided in 6 submodules:

- Submodule 1: Drawing up the list of eligible indications for hadron therapy
- Submodule 2: Estimating the number of potential treatments and sessions for the different indications.
- Submodule 3: Defining the treatment chamber equipment requirements for these eligible indications.
- Submodule 4: Defining the accelerator performance parameters for these indications.
- Submodule 5: Modelling the costs for hadron treatment in comparison to conventional therapy.
- Submodule 6: Expected scientific output and spin-off effects.

During implementation, the different submodules –logical as they may have seemed at the start– impacted and interrelated substantially on one another and proved this division to be impractical. As a consequence of which a new grouping in more workable submodules had to be adopted. In this report we thus kept following submodule units apart:

- Submodule 1: Eligible indications for hadron therapy
- Submodule 2: Potential number for the different indications.
- Submodule 3: Treatment requirements in terms of technical specifications
- Submodule 4: Costs calculations, financing issues and economic considerations.

The original Submodules 3 and 4 were fused into a single new one (the new submodule 3). Furthermore the result of the work on the original submodule 6, “Expected scientific output and spin-off effects” was not considered sufficiently relevant in and compatible with this report. It can certainly be recovered as preparatory work for next step studies.

The BHTC Foundation together with UZ Gent organized the project management, the expert consultancy and general project logistics. Expert consultancy was mobilised from hadron facility experts worldwide, from specialists in health economic assessment, from the SCK·CEN and for a minor part also from legal consultants.
It is also the task of the BHTC Foundation to define the next module of the feasibility study on the request of the Steering Committee of the Cancer Plan, Action 30.

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6. APPENDIX 1: ORGANISATION AND MANAGEMENT OF THE BELGIAN HADRON THERAPY CENTRE (WIP)

The combination of medical and physics research lead us to the fact that the first step in the Organisation and Management of the Belgian Hadron Therapy Centre is the establishment of a 'Foundation', further called Belgian Hadron Foundation, were physicians and researchers in both fields join to organize these aspects of the future Centre. Therefore the Belgian Hadron Foundation could start soon, after the delivery of the final report, to continue the work of the actual working group but then in the context to move to the realization of the Belgian Hadron Therapy Centre, at least if the authority representatives agree with the project.

6.a. Aim

To start the definitive study to implement the physical and staffing outlay and the patient routing of the Belgian Hadron Therapy Centre as soon as the financing of the study has been allocated.

6.b. Organisational structure

The board consists of one representative of each member, the chairmen is the chairmen of the BHTC Foundation, the latter links all interested Belgian centers with the Foundation with the assurance for them that they will have the needed information, without the burden and the cost of being an active member of the Foundation.

The members will consist of large Radiotherapy Centers to allow a consistent patient load and clinical research, Academic Medical Centers (or University Hospital Scientific Centers) with a sufficient patient load and especially a research track in the field, Paediatric Hemato-Oncology Programs, Research Centers with well acknowledged research in the field. Depending on the funding (public or mixed) Industries will be allowed as affiliated (with no board access and not full disclosure of information) or full members. Fund raising organisations (Foundation against Cancer, Flemish League against Cancer, Kom op tegen Kanker, Télévie, …) and patient groups can be full members.

The members will have to pay an annual fee allowing the Foundation to have a director/CEO and secretarial assistance. The BHTC (or University Foundation or Academy of Medicine?) could serve as a host for this managing function.

The board needs also a scientific committee, comparable to the actual working group of the Feasibility Study.

The General Assembly consists of three representatives per member and will approve the Year Report.

6.c. Functioning

The board meets at least ten times a year, the scientific committee will meet at least 20+ times a year and the director/CEO will early on be full time. The scientific committee reports directly to the board, the director/CEO works on a continuous base together with the scientific committee but is nominated by the board who is the employer.
The General Assembly convenes once a year or at the special request of the board or 50+% of the members of the General Assembly.
Interim progress reports by the board can be distributed at their discretion to all members.

The time line for the Foundation depends on the access to capital.

It is clear that every patient with an established indication must have access to this treatment. Most of the referring physicians will be specialists in Radiotherapy, Oncology or Paediatric Hemato-Oncology. As already mentioned established protocols will be set up by the experts and their Societies. Part of this work has already been done by the protocols being established by INAMI/RIZIV to reimburse patients treated abroad. But this is a rather small fraction of the future patient population. At least the way how to proceed is shown.

As the Centre will combine patient treatment and research, it is logical that data on the follow-up will be included in the protocol. This information will have to be made available as research data. Therefore the consent of the patient and the collaboration of the referring physician are necessary. It is now too premature to write a detailed protocol, this has to be done by the Foundation with all mentioned parties. The follow-up of the protocols could be done by the Foundation with the help of the scientific societies and KCE.

6.d. Legal structure

Due to the initial funding, the reimbursement which probably will be outside the nomenclature, at least initially, and the participation of the Foundation which will be necessary to the follow-up and the research, a Public-Private structure (PPP) or a 'Vennootschap-Société' type structure will be most probable.
It is too early now to go into details; in any case there are enough examples in the

last decade, especially in the infrastructure area. KCE and PMV have published on PPP's and can also support the implementation.

In the initial phase the PPP will be very important for the construction of the site, afterwards, once patient flow and clinical research starts, the Foundation will have the most important task.
The consequence of this task change over time is that the board composition needs to have the flexibility to adapt to these changes. It would be logic to have as chairmen the chairmen of the BHTC.

6.e. Referral/back-referral in Belgium

Networking with the potential referring physicians remains a difficult topic. The recent example of the INAMI/RIZIV reimbursement for hadron therapy abroad has shown that only a very small fraction of the potential patients have been given the opportunity to be treated that way, due to lack of referral.
Absence of a liaison function was identified by the international experts as a threat to referral/back-referral of eligible patients for hadron therapy, irrespective of the locations of the centers, inside or outside the country. An interesting and flexible concept is Medical Excellence Japan which solves the logistic problem of referral/back-referral on the national and international levels.

7. APPENDIX 2: SHORT CURRICULUM VITAE OF THE FOREIGN EXPERTS

Stéphanie Bolle, MD

Position

Specialist in radiation oncology at the:
- Department of Radiation Oncology at the Institut Gustave Roussy, Villejuif
- Institut Curie - Centre de Protonthérapie d'Orsay (ICPO)

Educational background

- 1998 : Graduation in Medicine and M.D. degree, University of Liege – Belgium.
- 2003 : Specialization in Radiation Oncology, University of Liege – Belgium.
- 2004 : Inter-University Diploma of Paediatric Oncology, Paris XI – France.
- 2006 : University Diploma of Stereotactic Radiation Therapy, Paris VI – France.

Speciality and field of interest

Proton beam therapy, paediatric and skull base tumours.

Selected Publications

1. Aldhaban S, Marc S, Eshki M, Girod A, Boissonet H, Chapelier A, Carlotti A, Sastre-Garau X, Athanasiou A, Zemoura L, **Bolle S**, Wallach D, Avril MF. Giant basal cell carcinoma with regional lymph node and distant lung metastasis. Eur J Dermatol. 2011;21(6):972-5.

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Jürgen Debus, MSc, MD, PhD

Position

Director Dept. Radiation Oncology, Heidelberg.

Educational background

- 1988 : Graduation in Physics, University of Heidelberg.
- 1991 : Ph.D. in Physics, University of Heidelberg.
- 1992 : Graduation (Medicine) and M.D. degree, University of Heidelberg.
- 1991-1996 : Specialization in Radiation Oncology, Dep. Clinical Radiology, University Heidelberg.
- 1995 : Clinical Fellowship at the Harvard University, Boston USA, Massachusetts General Hospital, Department of Radiation Oncology.
- 1996 : Board certification in Radiation Oncology.
- 1997 : Habilitation (Radiology) at the University of Heidelberg,
- 1997-2003 : Chair of Clinical Cooperation Unit Radiotherapeutic Oncology German Cancer Research centre (DKFZ).
- Since 1997 : Chair of the German Heavy Ion Radiotherapy Project.
- 2001-2003 : Chairman of the Scientific Council (Wissenschaftlicher Rat) of the DKFZ.
- Since 2003 : Chair of Radiation Oncology at the University of Heidelberg.

Awards

Philipps Award (1992), Varian Award (1993); Award of the German Society of Ultrasound in Medicine (DEGUM), (1993), Young Investigator Award of the American Assocation of Medical Physicists (AAPM) (1995), Hermann Holthusen Award (1998), Erwin Schrödinger Award (1999), Nomination for the Future Award of the President of Germany (2000), First Innovation Award of the medical science association (AWMF, VUD) (2005).

Speciality and research field of interest

Precision Radiotherapy, ion beam radiotherapy, radiation biology, radiation oncology.

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1. Abdollahi A, Griggs DW, Zieher H, Roth A, Lipson KE, Saffrich R, Grone HJ,Hallahan DE, Reisfeld RA, Debus J, Niethammer AG, Huber PE (2005). Inhibition of alpha(v)beta3 integrin survival signaling enhances antiangiogenic and antitumour effects of radiotherapy. Clin Cancer Res 11, 6270-6279.

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10. **Debus J**, Wuendrich M, Pirzkall A, Hoess A, Schlegel W, Zuna I, Engenhart-Cabillic R, Wannenmacher M (2001). High efficacy of fractionated stereotactic radiotherapy of large base-of-skull meningiomas: long-term results. J Clin Oncol 19, 3547-3553.

Piero Fossati, Ir, MD

Position

European Institute of Oncology.
Member of radiation oncology department clinical staff.

University of Milan – Medicine and Surgery.
Full time employment as researcher.

Fondazione CNAO (Centro Nazionale di Adroterapia Oncologica): technology-translational research.

Particle Therapy Cancer Research Institute (PTCRi), Oxford Martin School, University of Oxford. Associate fellow.

Education

- 1991-1997 : "La Sapienza" University of Rome – Electronic Engineering, Rome, Italy.
- 1997-2002 : "La Sapienza" University of Rome – Medicine and Surgery, Rome, Italy.

Selected Publications

1. **Fossati P**, Molinelli S, Matsufuji N, Ciocca M, Mirandola A, Mairani A, Mizoe J, Hasegawa A, Imai R, Kamada T, Orecchia R, Tsujii H. Dose prescription in carbon ion radiotherapy: a planning study to compare NIRS and LEM approaches with a clinically-oriented strategy. Phys Med Biol. 2012 Oct 26;57(22):7543-7554 IF 2012: 2.829

2. Kessel KA, Bougatf N, Bohn C, Habermehl D, Oetzel D, Bendl R, Engelmann U, Orecchia R, **Fossati P**, Pötter R, Dosanjh M, Debus J, Combs SE. Connection of European particle therapy centers and generation of a common particle database system within the European ULICE-framework. Radiat Oncol. 2012 Jul 24;7:115. IF 2012 : 2.32

3. Combs SE, Kieser M, Habermehl D, Weitz J, Jäger D, **Fossati P**, Orrechia R, Engenhart-Cabillic R, Pötter R, Dosanjh M, Jäkel O, Büchler MW, Debus J. Phase I/II trial evaluating carbon ion radiotherapy for the treatment of recurrent rectal cancer: the PANDORA-01 trial. BMC Cancer. 2012 Apr 3;12:137. IF 2012 : 3.01

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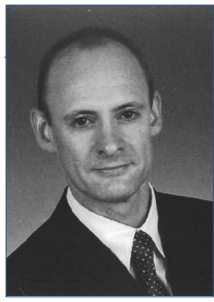


Oliver Jäkel, MSc, PhD

Position

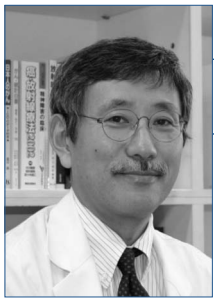
Medical Physics Director of the Heidelberger Ionenstrahl-Therapiezentrum at the Heidelberger University Clinics. Professor at the Medical Faculty of the Heidelberg University (http://www.klinikum.uni-heidelberg.de/Heidelberger-Ionenstrahl-Therapie-HIT.7591.0.html) and Leader of the Research Group “Heavy Ion Therapy” at the Department for Medical Physics in Radiation Oncology of the German Cancer Research Centre (DKFZ), Heidelberg (http://www.dkfz.de/en/medphys/heavy_ion_therapy/index.html).

Educational background

- Diploma in Experimental Physics and PhD in Theoretical Physics at the Friedrich-Alexander University of Erlangen, Germany
- Certification as Medical Physics Expert according to EU regulations
- Involved in Carbon Ion therapy since 1994, specifically at GSI and Heidelberg as Project Coordinator for Medical Physics

Speciality and research field of interest

Treatment planning, dosimetry and QA for scanned Ion beams (including protons).



Tadashi Kamada, MD, PhD

Position

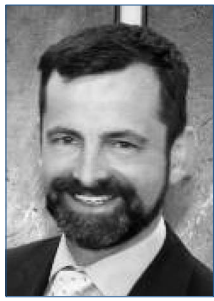
Director, Research Centre for Charged Particle Therapy, National Institute of Radiological Sciences, Chiba, Japan (2008-).
Professor, Chiba University, Chiba, Japan (2009-).
Professor, Niigata University, Niigata, Japan (2007-).

Educational background

Graduated with M.D, Hokkaido University, school of medicine (1979).

Speciality and research field of interest

Radiation oncology. Carbon ion radiotherapy. Bone and soft tissue sarcoma.



Philippe Lambin, MD, PhD

Position

Professor in Radiation Oncology, University of Maastricht
Head of the Department of Radiation Oncology "MAASTRO",
University Hospital of Maastricht.

Educational background

- Doctor of Medicine (MD, Université Catholique de Louvain).
- Doctor of Sciences (PhD).
- Specialist in Radiation-Oncology.

Speciality and research field of interest

Radiation Oncologist, pioneer in translational research with a focus on hypoxia and Decision Support Systems. His main areas of interest are directed towards translational research in Radiation Biology with a specific focus on tumour hypoxia, functional imaging (CT-PET), lung and head and neck cancer. He has a recent interest in the development of a "treatment decision support system" based on multiparametric databases containing clinical, imaging, biological and therapeutic information, and taking into account patient preferences (visit one of the websites he is managing: www.predictcancer.org).
Contact: MAASTRO, Dpt of Radiation Oncology, Dr. Tanslaan, 12, 6229 ET Maastricht, The Netherlands. Tel: + 31(0)88-44 55 666, fax: + 31(0)88 44 55 667. Email: philippe.lambin@maastro.nl. Website: www.maastro.nl, www.grow-unimaas.nl

Awards, Fellowships

- Postgraduate EC fellowship for Cancer Research Training (1990-1991).
- Fulbright-Hays Award for Research in the United States (1991).
- Postgraduate EC fellowship for Research in Radioprotection (1992).
- ESTRO travel grant (Annual meeting, 1992).
- Young scientist Award of the Radiation Research Society (Dallas 1993 and Chicago 1995).
- First price of the 'European Society for Therapeutic Radiology and Oncology' (ESTRO) Varian Award (Jerusalem, 1993).
- Fellowship of the Flemish Funds for Scientific Research (FWO-V, since 1996).

- Prize Albert van Dijck of the Royal Belgian Academy of Medicine (Brussel, 1996).
- Prize Dr. Raoul Biltris of the Royal Belgian Academy of Medicine (Brussel, 2002).
- Breur Award from the 'European Society for Therapeutic Radiology and Oncology' (ESTRO), Berlin, September 2009.
- Prof. Raymond Bush Award, University of Toronto, May 2010
- 'ESTRO ICTR 2012 lecture Award' » during the International Conference on Translational Research in Radiation Oncology (Geneva, 29 February 2012).

Grants

Principle investigator of more than 51 research grants (more than 32 million €).

Publications

279 published or in press peer-reviewed papers and more than 425 published conference contributions.

Patents

Seven officially granted, 5 submitted not yet officially filed.

Selected Publications (since 2000)

1. Predicting outcomes in radiation oncology-multifactorial decision support systems. **Philippe Lambin**, Ruud van Stiphout, Maud Starmans, Emmanuel Rios Velazquez, Georgi Nalbantov, Hugo Aerts, Erik Roelofs, Wouter van Elmpt, Paul Boutros, Pierluigi Granone, Vincenzo Valentini, Adrian Begg, Dirk De Ruysscher, and Andre Dekker. Nature Reviews Clinical Oncology. 2012 Nov 20.2012.196. [Epub ahead of print. Impact factor: 11.963

2. Nomograms for predicting local recurrence, distant metastases, and overall survival for patients with locally advanced rectal cancer on the basis of European randomised clinical trials. Valentini V, van Stiphout RG, Lammering G, Gambacorta MA, Barba MC, Bebenek M, Bonnetain F, Bosset JF, Bujko K, Cionini L, Gerard JP, Rödel C, Sainato A, Sauer R, Minsky BD, Collette L, **Lambin P**. J Clin Oncol. 2011 Aug 10;29(23):3163-72. Impact factor: 18.970

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6. Aerts HJ, Dubois L, Perk L, Vermaelen P, van Dongen GA, Wouters BG, **Lambin P**. Disparity between in vivo EGFR expression and 89Zr-labeled cetuximab uptake assessed with PET J Nucl Med. 2009 Jan;50(1):123-31. Impact factor: 6.662

7. Dubois L, Lieuwes NG, Maresca A, Thiry A, Supuran CT, Scozzafava A, Wouters BG, **Lambin P**. Imaging of CA IX with fluorescent labelled sulfonamides distinguishes hypoxic and (re)-oxygenated cells in a xenograft tumour model. Radiother Oncol. 2009 Sep;92(3):423-8. Impact factor: 5,580

8. Starmans MH, Krishnapuram B, Steck H, Horlings H, Nuyten DS, van de Vijver MJ, Seigneuric R, Buffa FM, Harris AL, Wouters BG, **Lambin P**. Robust prognostic value of a knowledge-based proliferation signature across large patient microarray studies spanning different cancer types. Br J Cancer. 2008 Dec 2;99(11):1884

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10. De Ruysscher D, Pijls-Johannesma M, Bentzen SM, Minken A, Wanders R, Lutgens L, Hochstenbag M, Boersma L, Wouters B, Lammering G, Vansteenkiste J, **Lambin P**. Time between the first day of chemotherapy and the last day of chest radiation is the most important predictor of survival in limited-disease small-cell lung cancer. J Clin Oncol. 2006 Mar 1;24(7):1057-63. Impact factor: 18.970

Tony Lomax, MSc, PhD

Position

Head of Medical Physics, Centre for Proton Radiation Therapy at Paul Scherrer Institute.

Titular professor, Physics Department, ETH, Zurich, Switzerland.

Educational background

BSc (Physics and physical electronics): Brighton Polytechnic, UK.
MSc/PhD (Medical physics): University of Aberdeen, Scotland.
1989 - 1992: Medical physicist (Nuclear medicine): Dryburn Hospital, Durham, UK.
1992 -: Medical physicist (Proton therapy): Paul Scherrer Institute, Switzerland.

Speciality and research field of interest

Medical physics aspects of proton therapy. Treatment planning. Optimisation and robustness analysis for treatment plans. Image-guided therapy and motion management.

Alejandro Mazal, MSc, PhD

Position

Since January 2008 head of medical physics at Institut Curie, Paris.

Educational background

Born in Argentina in 1958, close to Iguazu Falls, I first studied engineering followed by medical physics in Buenos Aires, where I have also worked at the National Academy of Medicine. In 1985 I moved to Paris. At the Universities of Toulouse and Paris I took a master and PhD degree in medical physics (dealing with stereotactic radiation therapy) and I then got a permanent position at Curie Institut under the direction of Jean Claude Rosenwald. In 1990 we started the proton therapy project in Orsay, where I was appointed as technical director covering the medical physics and engineering fields for about 8 years. I took some sabbaticals in US, at Indiana University Cyclotron Facility and at Massachusetts General Hospital & Harvard Medical School as invited scientist. In 2005 I have been in charge of the call for bids for the new proton therapy project in Orsay as the project director.

Speciality and research field of interest

My fields of interests are the state of the art on high precision radiation therapy integrating modalities (protons, tomotherapy, linacs, special implants, quality assurance, software, robotics) but also the daily work and logistics into a radiation therapy department, research, development and teaching (e.g. organising the first PTCOG training course in China), as well as keeping some activity on developing countries through Medical Physicist without borders (PMSF). I have a 17 years old son and a passionate life with friends all over the world.

II. Submodule 1

Eligible indications for hadron (proton & carbon ion) therapy

Authors:
I. Madani[1], W. De Neve[1,2,3], A. Gulyban[2], L. Veldeman[2], F. Duprez[2], P. Ost[2], K. Vandecasteele[2], D. Van den Berge[4], P. Van Houtte[5]

Reviewers:
panel of international experts, M. Mareel[1,2], P. Berkovic[2,]

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1. INTRODUCTION

1.a. Context and purpose

During the 1950s, physics research centers developed the technology that produced hadron beams which had sufficient energy, fluence and cross-sectional size to be used for medical purposes [1]. The physical and biological characteristics of these beams were studied in the numerous civil and military radiobiology laboratories that existed at those times. Physical and biological advantages of hadron beam as compared to photon beams were documented. During the following decades, many different types of hadron beams were clinically tested, with the largest numbers of patients being treated by neutrons, negative pi-mesons, protons, helium-, carbon-, oxygen- and neon-ions [2]. Neutron beams, which could be produced by relatively small installations, were used in Belgium at UCL and UGent until neutron therapy was abandoned worldwide because of alarming reports regarding its toxicity. The sad story of neutron therapy hampered further development of hadron therapy at large. However, research continued in a handful of physics research centers, with main focus on types of hadrons that had superb physical characteristics i.e. beams that had sharp lateral and distal edges. Recent clinical data are available for 2 types of beams: proton and carbon ion beams. Both types of beams require large installations that, until the mid 1990s, were

only available in physics research centers. Clinical treatments were performed as a side activity. In most centers the beam had to be shared between physics experiments and clinical treatment. Typically, medical treatments were grouped in periods of a few weeks 2-3 times per year. The medical activity focused on rare cancers that were very difficult to treat with conventional radiotherapy. The promising results attracted the interest of the specialists in the field of rare cancers, mainly paediatricians, paediatric surgeons, neurosurgeons and surgeons specialized in treating bone and soft-tissue tumours. These specialists joined the physicists, engineers and radiation oncologists who were treating the patients in the physics centers. Together, they formed highly specialized teams who further improved the therapeutic results and consolidated their top-reference position by centralizing treatment of these rare tumours. At HIT, Heidelberg University Hospital's carbon ion centre, more than 100 patients per year are treated for skull-base tumours. In contrast, each Belgian University Hospital treats a few patients with skull-base tumours per year. The Heidelberg multidisciplinary team was formed during the last 15 years when these treatments took place at the nuclear research centre GSI (Gesellschaft für Schwerionenforschung) in Darmstadt. Similar specialized teams originated worldwide for these and other rare tumours that were 'historically' treated at physics research laboratories. Given the absence of a physics research centre that was able to provide hadron beams for clinical use, Belgium has missed the opportunity to build expert teams that dispose of hadron beams.

Belgium has a population of 10.5 million people. The rough estimate of the number of patients with paediatric and other rare tumours that are accepted for treatment in hadron therapy centers is between 100 and 250 for a population of 10 million. The first goal of submodule 1 is to make an accurate estimate of the yearly number of patients for Belgium for these so-called 'standard indications'.

In the early 1990s, the first proton therapy centre that was dedicated to patient treatment started operations in Loma Linda, USA [3]. In the mid 1990s, the first centre that could continuously offer carbon ion treatment started in Chiba, Japan [4]. Since then, the worldwide capacity to treat with proton or carbon ion beams is steadily increasing. Many recently built centers are hospital-based. They treat patients during the whole year and operate independently from nuclear physics laboratories. This evolution offered the possibility to evaluate proton or carbon ion therapy in other than rare tumours. Subgroups of patients with common cancers were selected for phase I-II trials on the basis of 'model characteristics' of their disease, like an unfavourable anatomical location of the tumour for photon therapy or high resistance of the tumour against photon beams. Results of phase I-II trials strongly suggest the existence of 'model indications'. The second goal of submodule 1 is to identify 'model indications' and to estimate the yearly number of patients for Belgium, for each of the model indications.

1.b. Definition of standard and model indications

Uncommon cancers, which were often very difficult to treat in the past, mandated new investigations to improve the therapeutic outcome. The risk of negative outcome was of less concern as efficient treatment was essentially absent for these cancers. In case of positive outcome, the research centre would not be overwhelmed with patients demanding treatment because of the rarity of the disease. Excellent results obtained in some tumour types motivated the research centers to continue a small clinical activity for treating well-selected rare and challenging tumours. Although these treatments took place outside the normal clinical health insurance circuits, they were rapidly reimbursed in the countries hosting the research centre and gradually also by other countries.

Standard indications: definition

- Uncommon tumours that pose important therapeutic challenges.
- Hadron therapy started in nuclear physics research centers:
  - Relevant clinical results
  - Confirmation by independent treatment facilities.
- Dosimetrical and/or biological advantages over photon therapy still exist.
- No other treatment option offers similar or better outcome.
- Reimbursed in European countries.
- Endorsed by the teams of international experts.

At the time when physics research centers started clinical spin-off activities, only tumours that fulfilled several conditions could be treated with high precision: tumour location in anatomical sites that could be rigidly immobilized; no interference of respiratory motion or heartbeat; tumour sites that could be imaged by stereoscopic photon techniques. There is no reason why such tumours would remain the best indications for hadron therapy, considering the recent progress in imaging and radiotherapy technology. The anatomical and biological factors that determine the superior performance of hadron therapy over conventional radiation therapy are present in common as well as in rare tumours and the a-priori conditions for high-precision treatments some decades ago are no longer required. These considerations motivated testing hadron therapy for so-called model indications. Model indications result from identifying ‘model’ cancer entities for hadron therapy. Model cancer entities possess the anatomical and/or biological factors that were key factors of good outcome with hadron therapy in rare tumours. The adjective “model” is derived from the fact that, generally speaking, the clinical effects of radiotherapy can be predicted by models. Such models estimate the chances of cure or the risks of side effects from dose distributions in computer-simulated treatments. Those models are used on a daily basis in modern radiotherapy departments to select the best treatment from a variety of simulated treatments.

The number of model indications is potentially very large. This explains the fear, in Belgium and other countries, of a high cost increase for cancer care by allowing reimbursement of hadron therapy for model indications. It is a matter of debate if model indications should be accepted for reimbursement on the basis of the presently available phase I-II trials or if randomised controlled trials are still mandatory.

Model indications: definition

- Cancer entities for which severe clinical problems exist in terms of dismal cure rates and/or high toxicity rates with standard treatment options.
- The cancer entities pose specific anatomical challenges that favor the use of hadron therapy over conventional radiation therapy.
- The radiobiological characteristics of the tumour and/or the healthy tissues favor the use of hadron therapy over conventional radiotherapy.
- Phase I-II trials show promising results of hadron therapy as compared to standard treatment, including treatment options other than radiation therapy.

1.c. Paediatric and adult patients

Recent progress in photon therapy is beneficial mainly for adult cancer patients and far less for children. New high-precision photon techniques have resulted in less toxicity by their ability to distribute the unwanted dose outside the tumour in a better geometry so that lower grades of toxicity to the radiation sensitive organs were obtained. For most organs this is consistent with high doses being restricted to smaller sub-volumes while intermediate and low doses being given to larger sub-volumes of the organ. While the irradiation of larger sub-volumes at intermediate and low doses is relatively innocent in adults, it represents a major problem in children [5]. Growth and developmental disturbances, and as a consequence hypoplasia, asymmetry, intellectual and functional deficits, occur already at intermediate and low doses. Induction of secondary cancer by irradiation occurs at a wide range of doses, especially when delivered in fractionated irradiation [6,7]. The need to secure normal growth applies specifically to children. To avoid mutilation by growth arrest, radiotherapy has been omitted in European children's cancer protocols. Children included in European protocols had lower rates of tumour control and survival than children in North-American protocols, where investigators accepted more severe toxicity from using radiation therapy [8]. Cure rates are high in paediatric cancer and cured children have a long life expectancy. This puts them at long-term risk for developing second cancers induced by radiotherapy. The risk of cancer induction depends on many factors including dose, fractionation, irradiated volume and type of irradiation. If radiation is indicated to treat children, proton therapy offers the best compromise for the vast majority of paediatric cancers to obtain cure, avoid toxicity and to limit the risk of secondary cancer induction. Due to the rarity of paediatric cancers, all indications are listed as standard indication.

1.d. Rank-order of indications

The model indications were identified by literature search and by inside information of promising results in ongoing phase-I and II trials. The team of international experts mainly provided this inside information. Priority ranking of model indications was done during the Expert Meeting of September 20-21, 2012. Ranking was done as a function of the estimated gain in survival, disease-specific survival, local control or freedom from toxicity of hadron therapy as compared to standard treatment. Rank orders are snapshots in time and subject to change when new data emerge.

2. METHODS

2.a. Literature search of published clinical data

To obtain clinical data we performed systematic literature search using the key words (neoplasms OR tumour OR cancer OR carcinoma) AND ((hadron OR heavy-ion OR proton OR carbon ion) AND (radiotherapy OR radiation therapy OR beam therapy OR irradiation) AND (survival OR adverse effects OR secondary malignancies) as well as Medical Subject Heading Term (MeSH) and free-text queries structured using the PICO framework [9]. The following databases were searched for citations:

- MEDLINE® via PubMed (from inception to September 01, 2011);
- EMBASE® via OVID (from 1980 to September 01, 2011);
- Cochrane Library (Issue 4, 2011);
- Databases of the Centre for Reviews and Dissemination (National Health Service [NHS], UK) (to September 01, 2011);
- Web of Science® (from 1955 to September 01, 2011);
- System for Information on Grey Literature in Europe (SIGLE).

We also conducted hand search of abstracts of the American Society of Therapeutic Radiation Oncology (ASTRO) and European Society of Radiation Oncology (ESTRO) meetings as well as reading references of the retrieved articles, reviews and Health Technology Assessment (HTA) reports published in the period 2006-2011. Additionally search for ongoing clinical trials on hadron therapy was done in metaRegister of Controlled Trials [10], the National Institutes of Health (NIH) Clinical Trials database [11] and the Particle Therapy Co-operative Group (PTCOG) database of clinical protocols [12]. Titles and selected abstracts were scanned for further reviewing. Selected abstracts were entered onto a study register using a reference management software package. Selected abstracts were classified according to the tumour sites defined by the TNM classification of Malignant Tumours

(7th Edition, 2009). Although central nervous system (CNS) tumours are not a part of the TNM classification, we used CNS tumours to select abstracts and articles. We defined CNS tumours as any tumour arising from any part of the brain, cranial nerves, cranial nerve sheaths or cerebral meninges. Because hadron therapy for ophthalmic tumours requires a special beam line not usable in treatment for other tumour sites, ophthalmic tumours were excluded from literature search. We aimed at analysis of full-length articles in English on ≥50 patients comparing treatment outcome of different types of hadrons –carbon ions and protons - with each other or with photon radiotherapy or brachytherapy. That included RCTs or comparative case series (CCS). In absence of RCTs, CCS and case series reporting treatment outcome (survival, disease control, adverse effects and rates of secondary malignancies) after carbon ion and/or proton therapy were considered. If studies were on the same or overlapping patient population, only those with the largest patient number and/or the longest follow-up were included unless different clinical end-points were reported. All search queries were updated until June 01, 2012. Abstract scanning, selection and further reading of selected articles were done by at least two reviewers; disagreement was solved by consensus meetings.

2.b. Cross-checking by consulting expert knowledge

I. Belgian paediatric oncologists

There was a meeting with the steering committee of the Belgian Society of Paediatric Hematology & Oncology held in Ghent on March 09, 2012 (minutes enclosed: addendum 5).

II. International guidelines

We performed search of the following guidelines for evidence-based consensus-driven recommendations on the use of hadron therapy:

- National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®);
- American College of Radiology (ACR) Appropriateness Criteria;
- National Cancer Institute (NCI) Physician Data Query (PDQ®);
- National Institute for Health and Clinical Excellence (NICE);
- National Health Service (NHS) National Commissioning Group for Highly Specialized Services.

III. International experts

Four Expert Meetings were held in Brussels on March 20-21, 2012, August 01-02, 2012, September 20-21, 2012 and December 4-5, 2012 (minutes enclosed: addenda 6, 7, 8 and 9, respectively).

2.c. Reimbursement

Tumour types routinely treated with hadron therapy and fully reimbursed in countries with active hadron therapy centers were found at the PTCOG website where hadron therapy centers in operation are monitored [13]. The leading centers are located in the EU (carbon ion and proton therapy centers), Japan (carbon ion and proton therapy centers) and the US (proton therapy only). We considered a long-term clinical and reimbursement experience of European countries such as Germany (carbon ion and proton therapy), Switzerland (proton therapy), France (proton therapy) and Italy (carbon ion and proton therapy) as well as Japan (carbon ion and proton therapy). Because the Centers for Medicare and Medicaid Services (CMS) have yet to release a national coverage or non-coverage determination for proton therapy in the US [14], we excluded the US from the study as well as experience of other European countries – Sweden, the UK and Poland (all proton therapy centers) – and also Russia, China, South Korea, South Africa and Canada. We judged their experience to be: 1) non-contributing due to constraints on tumour types and number of patients resulting from outdated technology or limited capacity or 2) irrelevant to the European context.

3. RESULTS AND DISCUSSION

3.a. Paediatric indications

The proposal of indications that would be considered standard for paediatric patients was based on a) the list of paediatric tumour types routinely treated with hadron therapy and fully reimbursed in countries with active hadron therapy centers, b) ongoing trials on hadron therapy for paediatric tumours identified through search of clinical trials and protocols databases, c) expert's opinion and d) the Guidance for the Referral of Patients Abroad for NHS Protons Treatment, version 2.3 July 2011 (http://www.specialisedservices.nhs.uk/library/23/Guidance_for_referral_of_patients_abroad_for_NHS_Proton.pdf, last access October 16, 2012). Search was updated until June 01, 2012. The list of proposed standard indications was discussed at the meeting with the steering committee of the Belgian Society of Paediatric Hematology & Oncology on March 09, 2012 and at the Expert Meetings.

Table 1. List of standard indications for hadron therapy in paediatric patients

No.	Pathology	Type of hadron therapy
1	Skull base & spinal chordoma	Protons
2	Skull base chondrosarcoma	Protons
3	Spinal & paraspinal "adult" soft tissue sarcomas	Protons
4	Pelvic sarcoma	Protons
5	Rhabdomyosarcoma	Protons
6	Ewing's sarcoma	Protons
7	Retinoblastoma	Protons
8	Optic pathway & other selected low-grade gliomas	Protons
9	Ependymoma	Protons
10	Craniopharyngeoma	Protons
11	Pineal parenchymal tumours	Protons
12	Esthesioneuroblastoma	Protons
13	Medulloblastoma/primitive neuroectodermal tumours (PNET)	Protons
14	Central nervous system (CNS) germ-cell tumours	Protons
15	Unresectable osteosarcoma	Protons or carbon ions

Neuroblastoma was proposed as a model indication for proton therapy in paediatric patients during the Expert Meeting of December 4-5, 2012. It warrants further investigation during the 2nd phase of the feasibility study.

Standard indications (Table 1) – all but one for proton therapy - have been endorsed by both panels of experts and have been approved at a meeting of the Belgian Society of Paediatric Hematology & Oncology in 2012; indications will be updated every year.

Neuroblastoma was proposed as a model indication for proton therapy in paediatric patients during the Expert Meeting of December 4-5, 2012. It warrants further investigation during the 2nd phase of the feasibility study.

3.b. Complementary conditions for referral of children

In Belgium, oncological care for paediatric patients is centralized in 8 departments that fulfil the role of Peadiatrical Oncological Care Programs. The Belgian paediatric oncology departments work closely together amongst themselves and with international groups. Most children are treated according to multidisciplinary international protocols. The progress made in paediatric oncology is impressive. Cure rates have increased from about 30% in the late 1960s to over 80% now. The paediatric oncologists have achieved this result by carefully conducted clinical studies but without the use of randomised controlled trials. It is debatable if such rapid progress would have been possible by means of randomised controlled trials, considering the rarity of the paediatric cancers. With the increase of accessibility worldwide, most new protocols include the option of proton therapy. Two European centers are specialized in the treatment of children: Orsay in Paris, France and PSI in Villigen, Switzerland. Both centers accept patients from other Europe-

an countries using the E112 procedure. Using E112, the treatment is at no cost to the patients. However, the travel and stay, which may be substantial for paediatric patients and an accompanying person, usually a parent, is not covered by E112. The Solidarity Fund refuses to reimburse the cost of travel and lodging since the announcement, a few years ago, of a specific budget in RIZIV-INAMI. This means that patients had to cover these costs, typically several thousand Euros. As of the moment of writing (October 15, 2012) it seems that the Solidarity Fund has started reimbursing retrospectively travel and lodging cost, at least partially.

With only 2 operational centers, Europe faces a capacity problem for paediatric proton therapy. The multi-center enterprise ProCure, who operates 4 proton centers in the USA, has offered BHTC to treat Belgian children at a contractually guaranteed fee that would not exceed 100,000 US$ per patient (Eugen Hug, medical director of ProCure, personal communication). This is far less than what is presently charged at the Northeast Proton Centre, Boston, USA, the centre which has the largest experience in paediatric proton therapy worldwide and has probably treated most Belgian children until now. The main problem with referral of patients to the USA is the need to pay a large part of the cost up-front. The question if the patient (most often his/her family) is able to cover the cost poses ethical problems. In practice, only children who live in prosperous socio-economic conditions can be referred for proton therapy to the USA.

During the next decade, the European capacity will steadily increase when new centers like in Essen, Germany, Uppsala, Sweden, Trento, Italy, or PTC Holland, Delft, The Netherlands start operations.

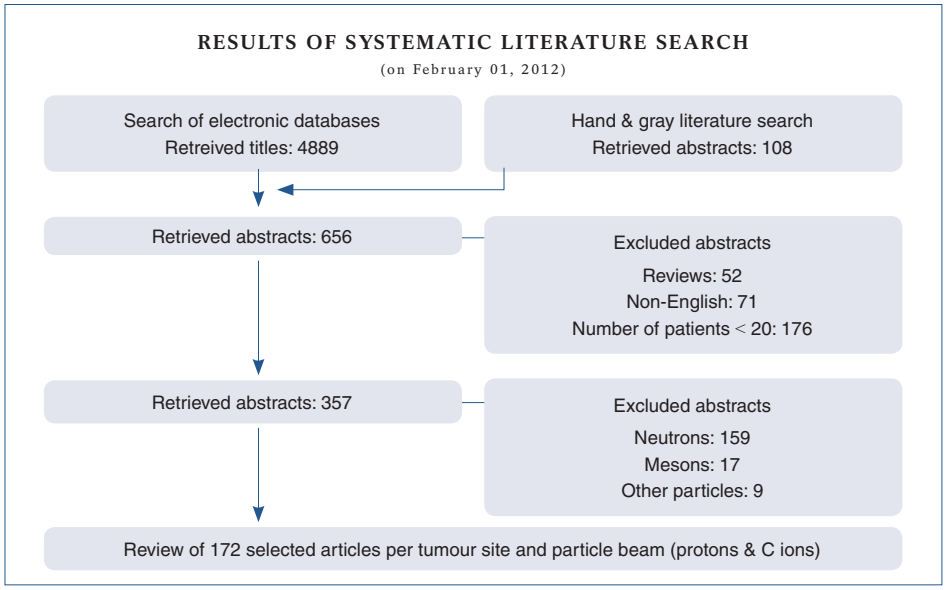
Still, considerable advantages of a Belgian centre exist apart from the distance from the patients' home. Proton therapy is part of a multimodality treatment for most paediatric cancers. Surgery and systemic therapy may be required immediately before or during the period of proton therapy. Nowadays, surgery, for example the placement of a spacer between tumour and sensitive normal tissues, is typically done in the foreign hospital affiliated to the proton centre. Children who need concurrent chemotherapy are treated at the affiliated oncological paediatric department. Timing and proper mutual adjustment of the different treatment modalities is important to obtain the optimal therapeutic result. It is self-evident that good synchronization of multimodality therapy is less challenging to accomplish in a Belgian centre than in a foreign country. The UCL-IBA-St.Luc-Région Wallonne aims at offering proton therapy for paediatric tumours (addenda 3 and 4).

3.c. Indications in adults

Results of a systematic literature search for clinical data are presented in figure 1. Of 4997 titles retrieved from searching electronic databases and from hand and

gray literature search, we selected 656 abstracts, of which 484 were excluded leaving 172 abstracts for studying full-length articles (Figure 1).

Figure 1. Results of systematic literature search (on February 01, 2012).



I. Standard indications

Standard indications for hadron therapy in adult patients are listed in table 2. Selection of standard indications in accordance with our definition was based on systematic literature search, data of full reimbursement of hadron therapy in Europe, international guidelines and endorsement by the panel of international experts. Given rarity of tumours leading to slow patient accrual and a limited access to hadron therapy at physics research centers in the past, only two randomised controlled trials (RCTs) were initiated but not published as full-length articles: 1) a RCT PROG 85-26 on skull base chordoma and chondrosarcoma investigating dose escalation delivered with combination of protons and photons or helium ions; 2) a RCT PROG 92-13 on recurrent or incompletely excised benign intracranial meningioma investigating dose escalation with combined protons and photons. Clinical evidence supporting consensus that hadron (carbon ion or proton) therapy is appropriate for standard indications has come from prospective clinical phase I/II or II trials mainly on carbon ion therapy, prospective and retrospective comparative case series and retrospective case series were found during systematic literature search.

Data on full reimbursement of hadron therapy in Europe and Japan are presented

Table 2. Standard indications for hadron therapy in adult patients.

No.	TNM classification	Pathology	Condition	Type of hadron therapy	Country of full reimbursement of hadron therapy	International guidelines
1	Bone & soft tissue tumours	Chordoma & chondrosarcoma	Skull base	Carbon ions	Germany	-
				Protons	Switzerland, France	NCCN (v.2 2012), NHS
2	Bone & soft tissue tumours	Chordoma & chondrosarcoma	Sacral or coccygeal Primary & recurrent	Carbon ions	Germany	-
				Protons	Switzerland, France	
3	Bone & soft tissue tumours	Chordoma & chondrosarcoma	Paraspinal Primary & recurrent	Protons	Switzerland, France	NCCN (v.2 2012)
4	Bone & soft tissue tumours	Sarcoma	Bone & soft-tissue Skull base, paraspinal, retroperitoneal, sacral & coccygeal	Carbon ions*	Germany†, Japan‡	-
				Protons§	Switzerland, Italy, France	NCCN (v.2 2012), NHS
5	Head & neck tumours	Malignant melanoma of the upper aerodigestive tract	Primary & recurrent	Carbon ions	Germany, Japan (private)	-
6	Head & neck tumours	Adenoid cystic carcinoma (salivary glands)	Primary & recurrent R ≥1 or inoperable or perineural invasion	Carbon ions	Germany	-
7	Head & neck cancer	Non-squamous cell carcinoma of head & neck including paranasal sinus tumours	Primary & recurrent Post-operative & inoperable	Protons	Switzerland, France	-
8	Brain tumours	Meningioma	Benign & malignant	Protons	Switzerland, France	-
9	Brain tumours	Glioma	Low-grade (grade 1 & 2)	Protons	Switzerland, France	-

*unresectable tumours; †patients treated within clinical study protocols; ‡to be approved; §partially resected tumours, micro- or macroscopic residual disease after surgery; ¶R≥1: micro- or macroscopic residual disease after surgery.

in table 2. Despite difference in reimbursement systems varying from country to country, there is consistency in selection of tumours as standard hadron therapy indications receiving reimbursement. NHS ensures reimbursement of British patients referred for proton therapy abroad, although the list of indications for adult patients is limited to skull base chordoma and chondrosarcoma as well as spinal and paraspinal bone and soft-tissue (not Ewing's) sarcoma (http://www.specialisedservices.nhs.uk/library/23/Guidance_for_referral_of_patients_abroad_for_NHS_Proton.pdf; last access October 16, 2012).

NCCN Guidelines® recommend the use of proton therapy alone or in combination with photon radiotherapy for bone sarcomas including chordoma, chondrosarcoma and osteosarcoma in patients with advanced or unresectable tumours. These recommendations were clarified by the panel of international experts: 1) skull base chordoma and chondrosarcoma: a HIT RCT investigating carbon ions versus protons will provide high-level evidence which type of hadron therapy - whether proton or carbon ion therapy - has superiority in treatment for those tumours; 2) sacral and coccygeal chordoma and chondrosarcoma: proton therapy can be recommended in adjuvant settings, while carbon ion therapy can be used for resectable and unresectable tumours; 3) osteosarcoma: proton therapy is recommended in patients undergoing surgery, who received partial resection with micro- or macroscopic residual disease after surgery, while carbon ion therapy is recommended in patients with large unresectable tumours, particularly of the trunk. No other recommendations regarding standard indications for hadron therapy were found. Neither ACR Appropriateness Criteria, nor NCI PDQ®, NICE provided any guidelines on the use of hadron therapy.

II. Considerations regarding specialized teams

Standard indications involve rare tumours for which hadron therapy is part of a multi-modality approach, for most indications being a combination of surgery and radiotherapy. During decades of focus on these rare tumours, hadron therapy centers have built multi-disciplinary expert teams. They are attraction poles for national and international referral. Hence, they have sufficient numbers of patients to maintain their skills and to improve the treatment of these rare cancers. For example, the team of HIT, Heidelberg treats more than 100 skull base chordomas and chondrosarcomas per year while most –if not all - Belgian university hospital departments treat less than 5 per year, each. Paediatric 'foreign' expert, Dr. Stéphanie Bolle is in charge of radiotherapy for about 120 children yearly, which is far more than the total number of children that are treated yearly by all Belgian radiotherapy departments, together. Building and maintaining specialized teams requires sufficient patient throughput. This will be an issue of concern for treating standard indications at a future Belgian hadron therapy centre.

III. Model indications

Model indications for hadron therapy in adult patients are listed in table 3. Selection of model indications was based on the systematic literature search shown in figure 1 and on data of ongoing trials known by the panel of international experts. During the Expert Meeting of September 20 and 21, 2012 suggestions

were made to rank the model indications according to clinical relevance of the results obtained thus far. This rank order is embedded in table 3.

This list of model indications is a snapshot in time. The expectation of the expert panel is that the number of model indications will increase year by year. Part of this increase will be a shift from photon therapy to hadron therapy. Another part will result from cancer entities that are not candidates for photon therapy because of unacceptable dose to surrounding tissues or radioresistance. The larger the tumour, the more the physical advantage (for proton and C ions) and the biological advantage (for C ions) is important. The same reasoning is valid regarding co-morbidity or iatrogenic damage: the higher the expected co-morbidity with photon therapy, the more advantage for hadron therapy. Re-irradiation is a situation where one must deal with iatrogenic co-morbidity. Therefore, we expect that re-irradiation using hadron therapy after failure to photon therapy will gain importance during the next decade. Oligo-metastatic disease, a hot topic in the field of photon stereotactic body radiotherapy, is expected to be a future direction for hadron therapy.

In the next section a structured summary of clinical results is presented for each model indication. Each summary contains 5 paragraphs. The first paragraph

Table 3. Model indications for hadron therapy in adult patients

No.	TNM classification	Pathology	Cancer entity	Type of hadron therapy
1	Digestive tract tumours	Pancreatic cancer	Locally advanced	Carbon ions
2	Digestive tract tumours	Rectal cancer	Locally recurrent	Carbon ions
3	Lung & pleural tumours	Non-small cell lung cancer (NSCLC)	Stage III Inoperable	Protons
4	Head & neck tumours	Major salivary glands tumours other than adenoid cystic carcinoma	Primary & recurrent R >1* or inoperable Perineural invasion	Carbon ions
5	Head & neck tumours	Any	Re-irradiation	Protons Carbon ions
6	Lung & pleural tumours	Non-small cell lung cancer (NSCLC)	Stage I Medically inoperable/refusal	Carbon ions Protons
7	Digestive tract tumours	Hepatocellular carcinoma	Primary & recurrent (Child-Pugh grade A or B) Size of < 3 cm: adjacent to vessels or bile ducts or the gastrointestinal tract Size of > 3cm	Carbon ions Protons

Abbreviations: *R>1: R>1: macroscopic residual disease after surgery. In case of evidence in favor of both hadron modalities, the one for which the strongest evidence exist is written on top.

describes the clinical problem with emphasis on hurdles to improve the results of treatment. The second and third paragraphs describe with the anatomical and biological challenges, respectively, that can be better addressed by hadron therapy than by photon therapy. In the fourth paragraph the best results published thus far by modern non-hadron treatment approaches are compared with the results obtained by hadron therapy or by multimodality treatment that included hadron therapy. These non-hadron treatment approaches include advanced forms of photon therapy or the best other treatment modalities for disease entities in which photon therapy is not a candidate treatment. The fifth paragraph lists pertinent conclusions.

IV. Summaries of clinical results for model indicationp

1. Locally advanced unresectable pancreatic cancer

Clinical problem

Patients with locally advanced non-metastatic pancreatic cancer have tumours that are technically unresectable because of local vessel impingement or invasion by the tumour. Most of these patients, who represent one-third of all patients diagnosed with pancreatic cancer [15,16], are incurable at the time of diagnosis. Standard therapy for those patients focuses on palliation of biliary obstruction by endoscopic, surgical, or radiological means [17] or palliation by (radio)chemotherapy [15,18] without any significant impact on survival. Two-year overall survival does not exceed ~10% at a median survival less than 12 months [19]. Locally advanced non-metastatic disease appears to have a natural history different from that of metastatic disease: an autopsy series demonstrated that 30% of patients presenting locally advanced disease died without evidence of distant metastases [20]. This observation supported investigating hadron therapy.

Anatomical challenges

The pancreas and, hence, pancreatic tumours are located at one of the most challenging locations for photon radiotherapy in the human body. Locally advanced pancreatic cancer is encased by highly radiation-sensitive organs such as the bowel, stomach, kidneys, liver which lay in the entrance or exit paths of all possible beam directions. Posterior beam directions are good choices for beams that have no exit paths i.e. stop at the distal edge of the tumour like hadron beams.

Biological challenges

Severe radioresistance of pancreatic adenocarcinoma to photon radiotherapy is

well-known since decades. This knowledge supported the inclusion of patients with locally advanced unresectable pancreatic cancer in trials that tested high-LET radiation using neutrons [21,22] or negative pi-mesons [23,24]. These trials, conducted before the CT-scan era showed superiority of high-LET irradiation over photon radiotherapy in parameters that reflected local disease control like duration of palliation or disappearance of the tumour in the irradiated territory at autopsy [21-24]. The inability to avoid life-threatening toxicity caused by the bombardment of high normal tissue volumes with high-LET irradiation terminated the use of neutron and pi-meson therapy. However, it was demonstrated that pancreatic cancer is sensitive to high-LET irradiation. This observation supported testing high-LET carbon ion therapy in treatment for locally advanced unresectable pancreatic cancer. The possibility offered by carbon ion therapy to deliver high-LET irradiation to the tumour and low-LET to normal tissues is the biological rationale for its choice.

Comparative clinical data

Most randomised controlled trials comparing photon radio chemotherapy with chemotherapy alone showed modestly (at best) improved survival for the combined treatment with a few exceptions (Table 4)..

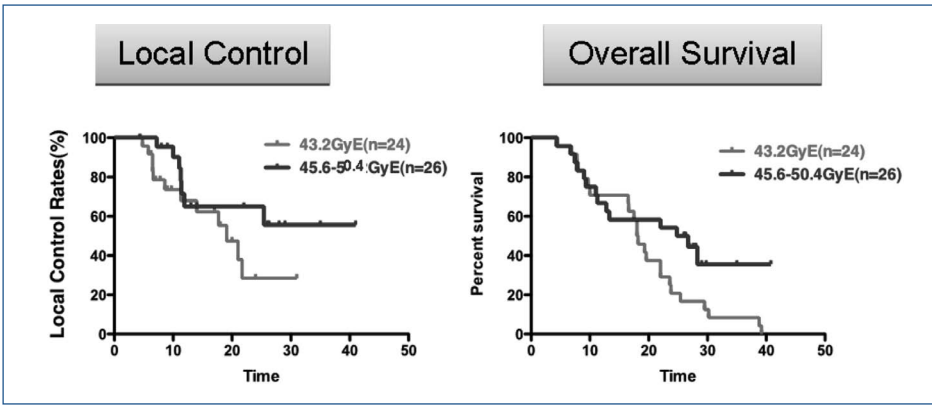
Table 4. Selected key randomised controlled trials for locally advanced pancreatic cancer.

Study	No. of patients	Median survival (months)	Overall survival, (months)	Toxicity
ECOG Klaassen 1985 [25]				Grade:
Fluorouracil alone	44	8.2†	21% (18)	27%
RT (40 Gy) + fluorouracil	47	8.3†	11% (18)	51%
GITSG 1988 [26]				Grade ≥ 3:
SMF only	21	8*	0% (18)*	NR
RT (54 Gy) + fluorouracil and SMF	22	10.5*	18% (18) *	50%
FFCD/SFRO Chauffert 2008 [27]				Grade 3-4:
Gemcitabine alone	60	13*	53% (12)*	40%‡
RT (60 Gy) + fluorouracil + cisplatin	59	8.6*	32% (12)*	65.5%‡
ECOG Loehrer 2011 [28]				Grade 4-5:
Gemcitabine alone	37	9.2*	5% (24)*	9%
RT (50.4 Gy) + gemcitabine	34	11.1*	12% (24)*	41%

Abbreviations: ECOG: Eastern Cooperative Oncology Group; RT: photon radiotherapy; NR: not reported; GITSG: Gastro-Intestinal Tumour Study Group; SMF: streptozocin, mitomycin and fluorouracil chemotherapy; MMC: mitomycin-C; FFCD-SFRO: Federation Francophone de Cancerologie Digestive and Societe Francaise de Radiotherapie Oncologique. *statistically significant; †not statistically significant; ‡during induction phase of treatment.

The best arms of these trials reported a median survival of 8.2-13 months at 40-65% rates of high-grade treatment-induced toxicity observed in the radio chemotherapy arms. The latter was due to using chemotherapy agents exhibiting radiosensitising properties, e.g., gemcitabine that is now employed by most standard radio chemotherapy schedules [18]. In comparison, a total of 60 patients with locally advanced unresectable cancer were treated with carbon ion therapy over five dose levels (43,2 –52.8 GyE/12 fractions/3 weeks) and concurrent weekly gemcitabine over three dose levels (400–1000 mg/m^2) [29]. Median survival for the whole group was 19.3 months at 2-year overall survival and local control of 32% and 26%, respectively. The local control and overall survival rates increased along with the dose escalation with carbon ions. In the high-dose group, for whom the total dose of ≥45.6 GyE/12 fractions with the concomitant use of gemcitabine (1000 mg/m^2) was given, the 2-year local control was 65% and median overall survival rate was 24 months (Figure 2, from T. Kamada at the 4th Expert Meeting). Concomitant administration of high-dose gemcitabine (1000 mg/m2) did not increase incidence of toxicity: only 3 cases (5%) of grade ≥4 toxicity were observed versus 40-65% grade 3-5 toxicity reported after gemcitabine-based photon radio chemotherapy (Table 4).

Figure 2: carbon ion therapy + gemcitabine for locally advanced pancreatic cancer



Thanks to Tadashi Kamada, NIRS, Japan.

Conclusions

1. The median survival of patients with locally advanced pancreatic cancer is typically less than one year after photon therapy combined with gemcitabine. After carbon ion radiotherapy combined with gemcitabine the median survival is 19.3 months for the whole group of patients treated at NIRS, Japan and 24 months for the high-dose treated group.

2. Carbon ion therapy could be combined with concurrent gemcitabine at 1000 mg/m^2/week. Even at such doses, treatment-induced toxicity appeared lower than for photon-gemcitabine combinations.
3. The results are consistent with expectations from modeling studies: better anti-tumour efficacy of carbon ion than photon radiotherapy; less irradiation of surrounding tissues leading to less toxicity for carbon ions; increased window of safety for dose escalation and combination with gemcitabine.
4. The results of carbon ion therapy combined with gemcitabine for locally advanced pancreatic cancer are the best reported, thus far.

2. Locally recurrent rectal cancer

Clinical problem

Improvements in surgical (implementation of total mesorectal excision) and (neo-) adjuvant management for primary rectal cancer decreased the incidence of locally recurrent rectal cancer (LRRC) from 50% to approximately 10% [30]. Because of disabling symptoms, severity of compromised quality of life and a limited choice of treatment options, LRRC presents an important clinical problem. Without treatment, patients presenting LRRC have a median survival 3-8 months [31]. Surgical resection is the first treatment choice, although highly invasive, debilitating procedures like pelvic exenteration or abdomino-sacral resection are often required. About 40-50% of all patients with LRRC could be expected to undergo surgery with a curative intent and of those 30-45% would have microscopically complete (R0) resection [32]. Thus, only 20-30% of all patients with LRRC would have a potentially curative surgery. The postoperative complication rates varied between 15 and 68% with 3-5% post-operative mortality. The rates of re-recurrence varied from 4 to 54% after curative surgery. The 5-year overall survival rates were 9-39% at a median survival 21-55 months [32]. Photon therapy is mainly used with palliative intent in patients in whom the disease cannot be cured or controlled by surgery. Providing temporal symptomatic relief, photon therapy alone or in combination with chemotherapy resulted in 5-year overall survival of less than 5% with a median survival of 14 months [33]. Given a role of photon therapy as a primarily palliative treatment for unresectable LRRC, search for alternative curative radiotherapy modalities is warranted.

Anatomical challenges

The main anatomical challenge of the locally recurrent tumour resides in close vicinity of the small bowel mostly anteriorly to the tumour. The small bowel is a very radiosensitive and thus dose-limiting organ. Its overdosage leads to stric-

tures or perforation which may be life-threatening. Lateral hadron beams are often used to spare the small bowel. At the Research Centre for Charged Particles, National Institute of Radiological Sciences (NIRS), Japan, a 5 mm gap between the recurrent tumour and small bowel achieved by spacer placement was found sufficient to avoid bowel (gastrointestinal) toxicity [34]. With photon therapy, multiple beam directions are required which limit the steepness of dose gradients generated between the recurrence and small bowel. In patients who received photon therapy as part of their primary treatment, the nerves, bone, bladder and vessels become additional dose-limiting structures for re-irradiation.

Biological challenges

The results of using photon therapy with curative intent in patients with unresectable LRRC were poor with only few patients reaching 5-year survival (Table 5).

Table 5. Treatment outcome of Photon therapy for locally recurrent rectal cancer.

Study	No. of patients	Total dose	Overall survival (year)	Local control (year)
O'Connel 1982 [35]	17	50 Gy	0% (5)	24% (2)
Wong 1991 [36]	22	40–50 Gy	16% (5)	9% (5)
Lybeert 1992 [37]	76	6–66 Gy	3% (5)	28% (3)

Neutron therapy has been tested to overcome intrinsic and hypoxia-related radioresistance of rectal cancer. Over 350 patients with locally advanced unresectable primary or recurrent rectal cancer were entered in studies comparing neutrons used alone and neutrons used in a mixed-beam treatment schedule [38,39]. Local control and pain improvement was better with neutrons than with photons. However, the inability to deliver highly focused irradiation has led to life-threatening complications and dismal survival rates. With the advent of carbon ion therapy, the biological effect of neutron therapy on the tumour can be mimicked while the detrimental effects on normal tissue can be limited. This has become the basic hypothesis behind the trials on LRRC at the Research Centre for Charged Particles, NIRS, Japan [34], at Heidelberg Ion Beam Therapy Centre (HIT), Heidelberg University Hospital, Germany and at the Italian National Centre for Oncological Hadron Therapy (CNAO), Pavia, Italy [40].

Comparative clinical data

Since the 90^{s}, major efforts have been focused on improving the resectability rates of LRRC by multimodality treatment, mainly pre-operative radio(chemo) therapy. To improve treatment outcome for LRRC, a variety of therapeutic approaches have been investigated including photon external beam and electron

intra-operative radiotherapy, brachytherapy, hyperthermia, systemic or intra-arterial chemotherapy or combinations hereof. Results obtained in selected studies on the use of pre-operative photon external beam or intra-operative radio(chemo) therapy are presented in Table 6.

A meta-analysis of survival based on resection margin status following surgery for recurrent rectal cancer demonstrated that R0, i.e., complete microscopic resection is required to obtain better long-term disease control and survival [45]. In 1460 patients undergoing surgery for LRRC the ranges of median survival as function of the resection margins were for R0 (free resection margins at pathological examination): 28-92 months; for R1 (microscopic residual disease after resection): 12-50 months and for R2 (macroscopic residual disease after resection): 6-17 months. However, as it is seen from Table 5, approximately 50% of patients who underwent multimodality treatment still had R1-2 resection after pre-operative or intra-operative low or intermediate dose irradiation that reduced their chance for disease control and survival.

Table 6. Treatment outcome of multimodality treatment for locally recurrent rectal cancer.

Study	No. of patients	Pre-operative treatment	R1-2 resection, %	Overall survival (year)	Local control (year)	Toxicity
Valentini 2006 [41]	59	EBRT (40.8 Gy)* ± CHT	30.5%	22.3% (5)†	38.8% (5)	Acute grade ≥3: 5.1%
Dresen 2008 [42]	147	EBRT (30.6-50.4 Gy) ± CHT ± IORT (10-17.5 Gy)	42.8%	43.8% (3)	57% (3)	NR
Das 2010 [43]	50	EBRT (39 Gy) ‡ ± CHT ± IORT (10-15 Gy)	NR	27% (3)	21% (3)§	Acute grade 3: 4% Late grade 3-4: 26%
Haddock 2011 [44]	607	EBRT (45.5 Gy) ± CHT + IORT (15 Gy)	63%	16-27% (5)¶	26% (3)¶	Grade 3 neuropathy: 3% Grade 5: 1%

Abbreviations: R1: microscopic residual disease after resection; R2: macroscopic residual disease after resection; EBRT: Photon external beam radiotherapy; CHT: chemotherapy; IORT: electron intra-operative radiotherapy. NR, not reported.

*re-irradiation; † in patients treated without surgery or after R2 surgery;‡ hyperfractionated accelerated EBRT §in patients without surgery; ¶in patients after R1-R2 surgery.

A dose-escalation study using carbon ion therapy for LRRC patients who were not previously irradiated showed that the local control and survival rates were dependent upon total doses delivered [34]. The 5-year survival rates were 24% for patients treated with 67.2 GyE/16 fractions (10 patients), 27.5% for patients

treated with 70.4 GyE/16 fractions (19 patients) and 42.3% for those treated with 73.6 GyE/16 fractions (111 patients). The 5-year local control rate in the 73.6 GyE treated patients was 95.2%. No acute grade≥3 gastro-intestinal or urinary toxicity have been observed. Late toxicity (defined as those occurring no earlier than 3 months after the start of therapy) were observed in 4 patients (3%), who developed a pelvic abscess after tumour necrosis. Patient accrual has been continuing at the 73.6 GyE dose level.

Patients who suffer from LRRC after prior pelvic irradiation pose additional challenges. Apart from the small bowel other tissues, mainly the bladder, nerves, bone and blood vessels, become of more concern since their tolerance levels have been reduced by previous irradiation. In these patients re-irradiation would be expected to be associated with a higher risk of acute and late toxicity at these organs than primary irradiation. At the Research Centre for Charged Particles, NIRS, Japan, carbon ion therapy was performed as re-irradiation in 23 patients with LRRC [34]. Nine relapses originated in the pre-sacral region, 8 in the pelvic sidewalls and 6 in the perineal region. The total dose of 70.4 GyE was administered in 16 fixed fractions over 4 weeks (4.4 GyE/fraction). All patients completed the scheduled treatment course. No acute grade ≥3 toxicity was observed. Grade 3 peripheral neuropathy or infection occurred in 6 patients (26%). The 1-year and 3-year overall survival rates were 83% and 65%, respectively. The 1-year and 3-year disease-free survival rates were 71% and 51%, respectively. Furthermore, carbon ion therapy for LRRC appears to be more cost-effective treatment as compared to conventional multimodality treatment including surgery, photon therapy, chemotherapy and hyperthermia [46].

Conclusions

1. With photon therapy, 5-year survival of patients with incompletely resected or unresectable local recurrence of rectal cancer does not reach 20%.
2. Survival after modern multimodality treatment depends on resection margin status after surgery. Despite combination of surgery with advanced photon/electron radiotherapy techniques and chemotherapy, residual disease can still be observed in approximately 50% of patients. Five-year overall survival rates of 16-27% are obtained at the cost of high toxicity and morbidity.
3. Using carbon ion therapy, 5-year survival rates of 42.3% (high-dose) and 24% (low dose) were reported. The high-dose schedule yields high ability to eradicate the disease locally - 5-year local control of 95.2% - and is associated with less than 5% severe toxicity.
4. Twenty-three prognostically worse patients who had been irradiated

previously were re-irradiated with high-dose carbon ion therapy. Three-year survival was 65%. Grade 3 late toxicity (neuropathy or infection) occurred in 6 patients (26%).

3. Inoperable stage III non-small cell lung cancer (NSCLC)

Clinical problem

In Belgium, lung cancer, more than 85% of which accounts for non-small cell lung cancer (NSCLC), is the major cause of cancer death in males (about one third of all male cancer deaths) and the second most important cause of cancer death in females [47]. Approximately 30-35% of patients present locally or loco-regionally advanced disease (stage III) at the time of diagnosis. The 5-year overall survival rates of stage III NSCLC is about 10% while the median survival does not exceed 20 months. Local control rates of ~50% are reported after photon(chemo)therapy [48]. Although surgery provides the best chance for cure, only a small number of patients with stage III NSCLC have resectable disease. The majority of patients are treated with sequential or concurrent chemoradiotherapy or radiotherapy alone [48]. Concurrent chemoradiotherapy significantly improves overall survival as compared to radiotherapy and is considered standard treatment for stage III NSCLC. However, it is associated with increased frequency, severity and duration of toxicity as well as increase in treatment-related death [49]. Up to 50% of patients receiving concurrent chemoradiotherapy develop severe grade $\geq$3 acute toxicity, while 10-15% of patients suffer from severe grade $\geq$3 late toxicity [50,51]. Commonly prescribed doses for curative photon radiotherapy (50-70 Gy) are not high enough to achieve sustainable disease control, given a clear radiation dose-response relationship [52-54]. Emergence of new radiotherapy technology such as intensity-modulated photon radiotherapy (IMRT) and hadron therapy can allow dose escalation in large, locally advanced tumours. However, the potential gains by IMRT could be limited due to large volumes of surrounding tissues irradiated to low-to-intermediate doses e.g., the lungs, esophagus, spinal cord, heart [55] that leaves hadron therapy as the primary treatment candidate to improve treatment outcome.

Anatomical challenges

Most stage III NSCLC present as tumours surrounded by radiation-sensitive organs and tissues. In photon radiotherapy, good beam directions are scarce. Entrance and exit paths of photon beams traversing large volumes of the lungs, heart, esophagus, lung or main airways can almost never be avoided. Toxicity to

the lung or esophagus expressed as radiation pneumonitis and esophagitis are the main radiation dose-limiting toxicities encountered in modern photon-chemotherapy protocols. It is self-evident that the possibility to limit irradiation by exit paths beyond the tumour is a major advantage of proton or carbon ion therapy in the treatment of stage III NSCLC.

Biological challenges

Radiation-induced pulmonary toxicity depends on various patient, tumour, biological and treatment factors, among the latter the mean radiation dose to the lung and the relative volume of healthy lung exposed above threshold doses as low as 5 Gy (V5) [56,57]. Esophagitis is also primarily related to dosimetric factors including the length or the circumference of the esophagus irradiated above a threshold dose [58]. Proton therapy in computer model comparisons has consistently

Table 7. Selected meta-analyses on chemo- or radiotherapy for stage III NSCLC.

Study	No. of patients	Overall survival (year)	Local control (year)	Toxicity
O'Rourke 2010 [49] Concurrent chemoradiotherapy Radiotherapy alone	19 RCTs, 2728	HR 0.71, 95%CI 0.64-0.80; I^2 0%*	HR 0.69, 95% CI 0.58-0.81; I^2 45%*†	Grade ≥3 esophagitis/ pneumonitis 0-48%‡/1-16%§ 0-33%‡/0-12%§
Aupérin 2010 [62]	6 RCTs, 1205		HR, 0.77; 95% CI, 0.62-0.95*	Acute grade 3-4 esophagitis
Concurrent chemoradiotherapy		15.1% (5) ‡		18%
Sequential chemoradiotherapy		10.6% (5) ‡		4%
Liang, 2010 [63]	10 RCTs, 2043		OR 0.68; 95%CI, 0.52–0.87*	Grade ≥3 esophagitis/ pneumonitis
Concurrent chemoradiotherapy		5.1-16.5% (5) ‡		16.3%‡/6.4%§
Sequential chemoradiotherapy		6.2-8.9% (5) ‡		6.4%‡/6%§
Mauguen, 2012 [64]	10 RCTs, 2000		NS	Acute grade 3 esophagitis
Hyper- or accelerated fractionation		10.8% (5) ‡		19%‡
Conventional fractionation		8.3% (5) ‡		9%‡

Abbreviations: RCT: randomised controlled trial; HR: hazard ratio; CI: confidence interval; I^2: presence and degree of heterogeneity; OR: odd ratio; NS: statistically non-significant.

*in favor of concurrent chemoradiotherapy; †overall progression-free survival in favor of concurrent chemoradiotherapy; ‡statistically significant; §statistically non-significant.

demonstrated the ability to reduce the dose delivered to normal tissues in the low-to-moderate dose range. The ample evidence that proton therapy can significantly reduce the volume of lung receiving between 5 Gy and 30 Gy was confirmed in two recently published in-silico trials that compared the best photon radiotherapy with proton therapy. In the first study, protons resulted in the lowest dose to the organs-at-risk, while keeping the dose to the target at 70 Gy [59]. The mean lung dose was reduced from 16.4 Gy for IMRT to 13.5 Gy for proton therapy. The mean lung dose was 40% higher for photons than for protons [59]. In the second study proton therapy spared more lung, heart, spinal cord, and esophagus than IMRT, even with dose escalation from 63 Gy to 83.5 Gy [60]. The advantage of proton therapy over IMRT was highest in patients with complicated tumour anatomies.
Many biological characteristics of NSCLC (tumour radioresistance, rapid growth, hypoxia, propensity to develop distant metastasis) determining poor disease control and survival suggest a role for hypofractionated carbon ion therapy.

Comparative clinical data

Chemoradiotherapy is standard treatment for unresectable stage III NSCLC. Numerous randomised controlled trials and meta-analyses (Table 7) have shown superiority of concurrent chemoradiotherapy over sequential chemoradiotherapy or radiotherapy alone [49, 61-64].

Concurrent chemoradiotherapy provides absolute survival benefit of 8% and 10% at 2 years as compared to radiotherapy alone or sequential chemoradiotherapy, respectively [49]. Improvement of overall survival appears to be due to decrease of locoregional failure - an absolute decrease of 6.0% and 6.5% at 3 and 5 years, respectively, was achieved by concurrent chemotherapy as compared to sequential chemotherapy [61]. However, improved disease control and survival is associated with increased rates of severe hematological and non-hematological toxicity: all studies consistently report significantly higher rates of severe acute esophagitis in the concurrent chemotherapy arm, while the incidence of pneumonitis is non-significantly higher. To limit treatment-induced toxicity most randomised trials used reduced radiation doses or chemotherapy doses. Accelerated or hyperfractionated radiotherapy alone was explored as an alternative treatment. A meta-analysis showed improved overall survival with modified fractionation at the cost of increased severe toxicity [64].
Case series comparing proton therapy with best photon therapy – IMRT and three-dimensional radiotherapy (3DCRT) - demonstrated a significant reduction of acute grade $\geq$3 pneumonitis and esophagitis after high-dose proton therapy concomitant with chemotherapy ($p<0.001$) [65,66] that was consistent with results of in-silico trials (Table 8). These data were supported by case series reporting

the incidence of acute grade 3-4 esophagitis in range of 0-11.4%, though 11.4% was observed in the trial where half of patients received induction chemotherapy prior to concurrent chemotherapy and proton therapy [68]. In most studies acute grade ≥3 toxicity was limited to a few patients with no patients developing late grade ≥4 toxicity. Employing proton therapy allowed increasing total dose above 70 GyE resulting in a median survival rate of almost 30 months [69]. The promising results are currently being investigated in a randomised controlled trial comparing proton therapy versus photon IMRT, both to 74 Gy with concurrent chemotherapy, for stage III NSCLC (clinicaltrials.gov identifier NCT00495040).

Table 8. Comparative and case series on hadron therapy for inoperable stage III NSCLC.

Study	No. of patients	Total dose	Overall survival (year)	Local control (year)	Toxicity
Sejpal 2011 [65]					Acute grade 3-4 esophagitis/ pneumonitis
Protons + cCHT	62	74 GyE	NR	NR	5%/2%*
IMRT+ cCHT	66	63 Gy			44%/9%*
3DCRT+ cCHT	74	63 Gy			17.5%/30%*
Gomez 2012 [66]					Acute grade ≥3 esophagitis
Protons + cCHT	108	74 GyE	NR	NR	6%*
IMRT + cCHT	139	63 Gy			28%*
3DCRT + cCHT	405	63 Gy			8%*
Shioyama 2003 [67] Protons ± photons	51	76-78 GyE	29% (5)	57% (5)	Acute grade ≥3 pneumonitis 2%
Chang 2011 [68] Protons + cCHT†	44	74 GyE	86% (1)	NR	Acute grade 3 esophagitis/ pneumonitis 11.4%/2.3%
Xiang 2012 [69] Protons + cCHT	84	74 GyE	37.2% (3)	83.3% (2)	NR
Oshiro 2012 [70] Protons	57	74 GyE	39.4% (2)	64.1% (2)	Acute grade 3-4 esophagitis/ pneumonitis 0%/5% Late grade 3-4 esophagitis/ pneumonitis 0%/0%

Abbreviations: IMRT: intensity-modulated photon radiotherapy; cCHT: concurrent chemotherapy; 3DCRT: three-dimensional photon conformal radiotherapy; NR: not reported. *statistically significant; †in combination with induction chemotherapy.

Conclusions

1. Concurrent photon-chemotherapy for inoperable stage III NSCLC results in ≤ 20 months median survival and 5-year overall survival and local control rates of ~15% and ~50%, respectively.
2. Between ~20 and ~50% of patients undergoing concurrent photon-chemotherapy develop severe acute grade ≥3 esophagitis. Late grade ≥3 toxicity is reported in 10-15% of patients.
3. Concurrent photon-chemotherapy is significantly associated with increase rates of treatment-related death as compared to photon therapy alone.
4. Median survival exceeds 24 months after combined chemo- and proton therapy.
5. Concurrent proton therapy and chemotherapy appears to be a safe treatment combination - no grade 4-5 toxicity - and acute grade 3 esophagitis and pneumonitis is limited to only a few cases.

4. Non-adenoid cystic carcinoma of the salivary glands

Clinical problem

Salivary gland tumours can arise in the parotid, submandibular, sublingual and minor salivary glands. The former are called the “major” salivary glands, in contrast with the “minor” salivary glands that are located in the oral cavity, sinuses, pharynx and larynx.

In Belgium in 2009, 3.6% of all registered malignant primary head-and-neck tumours were located in the salivary glands [71]. In the United States, the incidence is as high as 8.1% of all malignant head-and-neck tumours [72]. About 64-80% were located in the parotid glands and mostly in the superficial lobe. Most of the other malignant salivary gland tumours are located in the minor salivary glands or the submandibular glands [73]. The 5-year survival of all salivary gland malignancies is 65%. Salivary gland malignancies are mostly surgically resected. However, in most cases, resection is incomplete aimed at sparing the facial nerve. Incomplete resection has been shown to correlate strongly with worse disease control [74, 75]. In all cases of locoregionally advanced parotid malignancies and in most cases of less advanced stage disease, adjuvant radiotherapy to the tumour bed and elective nodal regions is advocated [76, 77]. Locally very advanced stage disease is often unresectable and then primarily irradiated, resulting in complete response in up to 65% [78].

Adding agents targeting the epidermal growth factor receptor (EGFR) might increase survival as EGFR-overexpression, seen in 35% of all salivary gland malignancies (especially in squamous cell and mucoepidermoid carcinoma) is independently correlated with worse survival [79]. Adding targeted agents to radiotherapy in salivary gland malignancies is still investigational.

Anatomical challenges

Tumours in the head-and-neck region are in close vicinity of structures as:

a. Mandibular bone prone to osteoradionecrosis [80, 81].
b. High dental and paradontal doses leading to late dental decay, caries, apical periodontitis (> 40 Gy), dental loss and thereby increased risk for mandibular necrosis (> 60 Gy) [81-85]. The incidence of dental decay is especially enhanced by the post-surgical and –radiotherapeutical xerostomia.
c. The ear, leading to otitis media and externa, and consequently hearing loss.
d. The facial nerve.
e. The oral cavity, in which the photon exit paths can lead to acute mucositis and taste alteration, despite the fact that it is not a part of the target volume [81].
f. The ipsilateral temporo-mandibular joint: high doses on this organ-at-risk can lead to life-long complaints of debilitating trismus [81].
g. The skin, possibly leading to severe acute dermatitis and late skin toxicity, e.g. telangiectasia.

On the other hand, the target volume in parotid tumours is typically superficially located, around the ear, which makes it difficult to obtain the desired dose distributions. Underdosage in the target or overdosage near to the skin in the target volume is frequently seen, leading to lower chances of local control or telangiectasia, respectively.

Beams that have no exit paths, i.e. stop at the distal edge of the tumour like proton or carbon ion beams enable better dose distributions to target volume and lower doses to the non-involved tissue in the direct vicinity, except for the skin.

Biological challenges

Clinical trials, which have been completed in the United States and England, indicate that fast neutron-beam radiation therapy improves disease-free survival

Table 9. Local control rate according to histology by neutron therapy for salivary gland tumours (from [89])

	$N_{controlled}$ / $N_{treated}$	Local control (%)
Adenoid cystic carcinoma	111/155	72
Muco-epidermoid carcinoma	36/59	61
Adenocarcinoma	32/41	80
Malignant mixed tumours	11/17	65
Squamous cell carcinoma	4/8	50
Acinic cell carcinoma	6/6	100
Other histologies	13/17	76

Abbreviations: $N_{controlled}$: number of patients with their tumours locally controlled.
$N_{treated}$: number of patient treated.

and overall survival in patients with advanced, unresectable or recurrent salivary gland tumours [86-88]. The most common histologies were adenoid cystic carcinoma, muco-epidermoid carcinoma and malignant mixed tumours. Superiority of neutron therapy over photon therapy is best documented for adenoid cystic carcinoma [87,88] but similarly high local control rates were also observed for other histologies (Table 9 [89]), except for squamous cell carcinoma which is a common observation with neutron therapy. Hence, a biological rationale for treating non-adenoid cystic carcinoma of the salivary gland with the neutron-mimicking high-LET part of carbon ion beam trajectories exists.

Comparative clinical data

Most studies are retrospective patient cohorts consisting of different histologies and sites of salivary gland malignancies. To our knowledge comparative clinical data including carbon ion therapy do not exist for advanced or unresectable non-adenoid cystic carcinoma. An extensive review on fast neutron or photon irradiation for inoperable, unresectable, or recurrent malignant salivary gland neoplasms showed a locoregional control rate of 67% for fast neutrons versus 25% for photons and/or electrons [90].

Conclusions

1. Locoregional control and survival after primary and adjuvant photon radiotherapy is average for unresectable salivary gland malignancies.
2. Late toxicity can be severe. Based on the reports in literature, the occurrence is not very high. However, the retrospective nature of all studies might underestimate severe late toxicity. The physical characteristics of proton or carbon ion therapy bear the potential to lower doses to the surrounding organs-at-risk, thereby minimizing in each case the chance for severe late toxicity.
3. The anatomical and biological rationale for the use of carbon ion therapy is strong.

5. Re-irradiation of head-and-neck cancer

Clinical problem

Despite intensification of single or combined modality treatment more than half of patients with locally advanced head-and-neck cancer develop locoregional recurrence [91-93]. For those who did not develop locoregional or distant recurrence, there is still a risk of 25% at 5 years and 40% at 10 years to develop a second primary head-and-neck cancer [94,95]. Salvage surgery is not feasible in most of patients presenting recurrences at the advanced stage. The use of

brachytherapy is restricted by tumour location and size that makes it possible only in a few patients. In patients with unresectable tumours chemotherapy alone is considered the standard despite extremely poor outcome – response rates are only 10-40% and median survival is in the range of 6-11 months [96]. External photon high-dose re-irradiation offers a chance for cure – 5-year overall survival of 20% and locoregional control of 40% in the best retrospective series [97] - at the cost of severe late toxicity in ~50% of patients due to higher cumulative dose in the previously irradiated large volumes of normal organs and tissues, among which fatal arterial bleedings present the most dangerous events [97-103]. However, delivery of high radiation doses needed for improvement of overall survival [104] was found feasible only when the irradiated volume was small making a case for stereotactic body radiotherapy [99,103,105]. For large, advanced recurrences conformal photon therapy or intensity-modulated radiotherapy (IMRT) are still associated with often excessive severe toxicity [97,98,101,106]. These observations support investigation of other re-irradiation modalities such as hadron therapy that could still deliver higher radiation doses to the recurrent tumour while minimizing severe toxicity.

Anatomical challenges

Head-and-neck tumours are surrounded by multiple normal organs and tissues critical for toxicity development:

a. The spinal cord, brain stem and plexus brachialis have limited tolerance to ionizing radiation that might be already reached during primary radiotherapy. The brain is at higher risk of radiation-induced injury including brain necrosis after re-irradiation.
b. Over-irradiation of large arterial vessels, e.g., the carotid arteries, could cause carotid hemorrhage and death of patients.
c. Osteoradionecrosis of the mandible or skull base bones is not a rare event (0.4-56%) even after primary photon therapy [107]; after re-irradiation osteoradionecrosis was reported in 8% of patients [108].
d. Esophageal stenosis and mucosal necrosis present the most common late toxicities, the latter being observed in 21% of re-irradiated patients [108].
e. Previously irradiated fibrous subcutaneous tissues are prone to necrosis and fistula formation.
f. Cartilages are at higher risk of chondronecrosis after re-irradiation; although laryngeal necrosis is a rare complication - ~1% after primary radiotherapy – some studies reported the incidence up to 15% [109].

Higher doses to the tumour increase the probability of better overall survival [104]. However, increased toxicity rates depending on dose and re-irradiated volumes of normal organs and tissues may compromise the chance for cure or disease

control if photon re-irradiation is performed. Re-irradiating volumes as small as possible is the present paradigm. This can be better achieved with hadron beams characterized by steeper dose gradients than photon beams and by the absence of exit beam paths.

Biological challenges

Head-and-neck locoregional recurrence has been shown to be more radioresistant than the initial tumour [110-112]. Early trials on re-irradiation of head-and-neck cancer using fast neutrons showed promising results regarding local control, though toxicity rates discouraged further use of neutron therapy [113-114]. However, it demonstrated that high-LET irradiation might have superiority over photons in terms of disease control. Carbon ions lacking drawbacks of fast neutrons appear to increase biological effectiveness of re-irradiation: suppression of oxygenation effect and reduction of cell cycle dependence of radiosensitivity were described for carbon ions [112]. All these observations underlie the proposal of using hadron therapy for head-and-neck re-irradiation.

Comparative clinical data

There is only randomised controlled trial that compared re-irradiation concurrent with chemotherapy with chemotherapy alone was discontinued prematurely. The clinical evidence is based on single arm studies (Table 10).

Despite combination of photon re-irradiation with chemotherapy or targeted drugs treatment outcome was still dismal in the best prospective studies: 3-year overall survival and local control are 22% and 31%, respectively. The results might be explained by lower radiation doses in range between 18 and 60 Gy that appeared not to have a sparing effect on normal organs and tissues: approximately two third of all patients developed severe late toxicity, some of which resulting in patient death (grade 5 toxicity). The rates of acute toxicity varied from study to study: RTOG 9610 trial combining re-irradiation with chemotherapy reported toxicity-related death in 7.6% of patients, while combining IMRT with cetuximab resulted in grade 3 toxicity in 78% of patients.

In contrast to photon re-irradiation hadron (carbon ion and proton) therapy to 36-72.7 GyE did not produce any severe acute toxicity: of 16 patients, toxicity was limited to grade 2 toxicity in 5 patients (31%), while the rest of patients did not have any or grade 1 [115]. Overall response rates were 53.3% at 8 weeks. Proton re-irradiation of 39 patients with recurrent nasopharyngeal carcinoma to 59.4-70.2 GyE resulted in 49% overall and 70% locoregional progression-free survival at 2 years, respectively [120]. Locoregional control was higher at doses >61 GyE reaching 77% at 2 years. Late grade 3-4 toxicity was observed in 23% of patients.

Table 10. Selected prospective studies on photon re-irradiation for recurrent and second primary head-and-neck cancer.

Study	No. of patients	Total dose	Overall survival (year)	Local control (year)	Toxicity
GORTEC 98-03 [116] 2DRT/3DCRT + fluorouracil + hydroxyurea Methotrexate	 30 27	 60 Gy	 23% (1)* 22% (1)*	 NR	 Late grade 3-4 37% 19%
RTOG 9610 [101] 3DCRT + CHT	79	60 Gy	3.8% (5)		Acute grade 5: 7.6% Late grade 3-5: 49%
Hehr 2005 [117] 3DCRT + CHT	27	40 Gy	18% (3)	31% (3)	Acute grade 3-5: 78%†
Langendijk 2006 [99] 3DCRT	34	60 Gy	22% (3)	27% (2) ‡	Late grade 3-4: 66%
Balermpas 2012 [118] IMRT + cetuximab	18	50.4 Gy	44% (1)	33% (1)	Acute grade 3: 78%
Comet 2012 [119] SRS ± cetuximab or CHT	40	36 Gy	24% (2)	NR	Late grade 3: 15%

Abbreviations: 2DRT: two-dimensional radiotherapy; 3DCRT: three-dimensional conformal radiotherapy; CHT: chemotherapy; NR: not reported; SRS: stereotactic radiosurgery. *not statistically significant; †non-hematological toxicity; ‡locoregional control.

Initial results of hadron therapy hold the promise of minimizing frequency and severity of acute and late toxicity that warrants further investigation in prospective trials, e.g., the ongoing study of the Abramson Cancer Centre of the University of Pennsylvania “Proton Therapy for Recurrent Tumours” (ClinicalTrials.gov Identifier: NCT01126476). A trial using proton therapy has also been initiated at CNAO, Italy (Piero Fossati, Expert Meeting, December 4-5, 2012).

Conclusions

1. Chemotherapy remains the standard treatment for most patients with unresectable recurrent head-and-neck cancer with a median survival of 6-11 months.
2. Photon re-irradiation alone or in combination with chemotherapy improves disease control and survival - 3-year overall survival and local control of ~20% and ~30%, respectively – at higher rates of severe, life-threatening toxicity occurring in between 2/3 and 3/4 of re-irradiated patients.
3. Hadron therapy has the potential to substantially reduce severe and late toxicity. It may also open the window for dose escalation and safer combinations with chemo- and targeted therapies.

6. NSCLC: stage I medically inoperable

Clinical problem

For patients diagnosed with early stage NSCLC, lobectomy (including systematic lymph node dissection) remains the cornerstone treatment with 5-year overall survival approaching 60% [121]. For those patients who are not candidates for surgery due to medical co-morbidities or refusing surgery, radiotherapy is a reasonable alternative treatment option. Local control is high with treatment by photons, protons or carbon ions. Stereotactic body radiotherapy (SBRT) is being extensively employed even in the fit elderly (>75 years old) [122]. Using SBRT in medically inoperable patients, higher 5-year local control and overall survival rates of ~70% and 42%, respectively, have been reported [123]. Dose-escalation in the tumour increases the probability of disease control and survival [124]. However, increasing radiation dose is hampered by tolerance of surrounding healthy tissues such as the bone, normal lung tissue, heart, spinal cord and oesophagus) [122].

Anatomical challenges

Anatomical challenges include, but are not limited to those described above for stage III NSCLC. Because very large fraction sizes are used in the modern treatment of stage I NSCLC, large airway passages, blood vessels, plexus brachialis and intercostal nerves, soft tissues of the thoracic wall and ribs are of additional concern. The key challenge is the creation of sufficiently large dose gradients between the edge of the tumour and the critical structures. Large fraction size has a dual character. On the one hand it is the enemy of the tumour: the larger the fraction size, the higher the tumour control rate for equal total dose. On the other hand, large fraction size is also the enemy of the healthy tissues. By large dose gradients, fraction size in healthy tissues must be constrained to levels below tolerance. Exceeding tolerance may result in severe and even life-threatening complications. These include stricture of large bronchi, profuse bleeding of large vessels, palsies or severe pain by nerve toxicity, rib fractures, disabling fibrosis or ulceration of the thoracic wall. At close distance from the tumour edge ($\leq$ 0.5 cm), dose gradients achieved in proton or carbon ion therapy are equal to those achieved in photon therapy. Beyond 0.5 cm from the tumour edge, dose fall-off is much better for proton or carbon ion therapy than for photon therapy.

Biological challenges

Biological challenges include, but are not limited to those described above for stage III NSCLC. For larger tumours, proton and carbon ion therapy offer a dual advantage over photon therapy. All radiotherapy modalities create an anisotropic

halo of dose fall-off around the tumour. This halo of high, intermediate and low doses is proportional to the size of the tumour but is much narrower for proton and carbon ions than for photon therapy. The total energy of dose deposited in the halo is strongly correlated with the risk of radiation pneumonitis and is typically 3- and more-fold less for proton or carbon ion therapy than for photon therapy. This risk is rapidly dose- and fraction dose-limiting for large tumours treated with photon therapy. This mechanism explains the specific advantage of hadron therapy in large tumours, which can be treated with larger fraction sizes of hadron therapy than of photon therapy. Carbon ion therapy may offer an additional advantage in hypoxic or slowly proliferating tumours and for non-squamous cell histology.

Comparative clinical data

Treatment outcome of radiotherapy for medically inoperable stage I NSCLC is presented in Table 11. No randomised controlled trials comparing conventional radiotherapy against SBRT are reported. Conventional radiotherapy results in poor 2-year overall survival varying between 24% and 72% [123,126]. SBRT using hypofractionation (typically 8 to 3 fractions of 7.5-20 Gy per fraction) seems

Table 11. Selected meta-analyses on radiotherapy for medically inoperable stage I NSCLC.

Study	No. of patients	Total dose	Overall survival (year)	Local control (year)	Toxicity
Grutters et al. 2010 [123]		NR		NR	Grade 3-5 pneumonitis†:
CRT	11 studies, 1326		19% (5)*		0.0023
SBRT	11 studies, 895		42% (5)*		0.02
Protons	5 studies, 180		40% (5)*		0.0079
Carbon ions	3 studies, 201		42% (5)*		0.0143
Zhang et al. 2011 [126]	34 studies, 2587				Grade 3-5 toxicity†:
SBRT					
Low-BED		<83.2 Gy	62.3% (2)*	96% (1)	0.053
Medium BED		83.2-106 Gy	76.1% (2)	97% (1)	0.073
Medium-high BED		106-146 Gy	68.3% (2)	NR	0.078
High BED		>146 Gy	55.9% (2)*	98% (1)	0.093
Rowell et al. 2001 [125]				NR	Grade 3 pneumonitis:
CHART	1 RCT, 169	60 Gy	37% (2)		NR
CRT	26 studies, 2003	>40 Gy	24% (2)		~3%

Abbreviations: CRT: conventional radiotherapy; NR: not reported; SBRT: stereotactic body radiotherapy; BED: Biological equivalent dose. *statistically significant; †proportion of treated patients suffering from toxicity.

to improve treatment outcome with 2-year overall survival of 70% (63%-77%) at similar incidence of severe toxicity [123,126].

As it is generally applied to all cases of NSCLC, results of SBRT are dose-dependant: significant higher overall and cancer-specific survival is reported at biological equivalent doses >83.2Gy [126]. However, biological equivalent doses >146 Gy lead to increase in the toxicity rates and even treatment-related death as compared to conventional radiotherapy [126].

A comparative case series comparing results of 23 patients treated with 4 fractions of carbon ions and 57 patients treated with 10 or 20 fractions of protons did not find a significant difference in overall survival and local control rates between the two types of hadrons, although incidence of severe toxicity was less in the carbon ion group [127] (Table 12). Carbon ion therapy for stage I NSCLC was investigated in prospective phase I/II and phase II studies. Increase in fraction dose from 3.3 to 46 GyE and respective reduction of treatment fractions from 18 to 1, positively affected 5-year overall and cause-specific survival reaching 52.6% and 71.5% after single-fraction treatment [129], respectively. Local control at 5 years was highest for T1 tumours - 98% as compared with 80% for T2-tumours [128]. Proton therapy also employed hypofractionation: overall survival and local control at 3 years was 44% and 74% [130]. In all studies acute grade ≥3 toxicity was limited to a few patients and no patients developing late grade ≥4 toxicity.

Table 12. Comparative and case series on hadron therapy for stage I NSCLC.

Study	No. of patients	Total dose	Overall survival (year)	Local control (year)	Toxicity
Iwata 2010 [127] Carbon ions Protons	 23 57	 52.8 GyE 60-80 GyE	 86% (3)* 61-90% (3)*	 86% (3)* 81-83% (3)*	Late grade 3 pneumonitis: 0% 2%
Miyamoto 2007 [128] Carbon ions	79	52.8-60 GyE	45% (5)	90% (5)	Acute grade 2 pneumonitis: 1% Late grade 2 pneumonitis: 1%
Yamamoto 2011 [129] Carbon ions	131	36-46 GyE	45.3% (5)	91.5% (5)	Acute grade 3 pneumonitis: 0% Acute grade 2 pneumonitis: 1% Late grade 1-2 pneumonitis: 100%
Bush 2004 [130] Protons	68	51-60 GyE	44% (3)	74% (3)	Acute and late grade 0-4 esophageal and heart toxicity: 0%
Nakayama 2010 [131] Protons	55	66-72.6 GyE	97.8% (2)	97% (2)	Acute grade 3 pneumonitis: 4%

*statistically significant.

Conclusions

1. In patients with stage I NSCLC medically inoperable or refusing surgery, photon conventional radiotherapy results in 2-year overall survival of 30-50%. Higher rates of severe toxicity do not allow dose escalation needed for improvement of treatment outcome.
2. Photon SBRT results in high local control rates. For T1 tumours, photon SBRT, proton and carbon ion therapy report similar local control rates. Rates of toxicity increase rapidly with increasing dose, tumour size and more central locations for photon therapy.
3. Hadron therapy appears to be well tolerated with minimal acute and late severe (grade 3) toxicity <4%. No grade 4-5 toxicity was reported.
4. Peculiar types of toxicity were reported for photon SBRT: brachial plexopathy in apical tumours and rib fractures in lesions very close to the thoracic wall.
5. Although carbon ion and proton therapy use reduced number of fractions, carbon ions may have advantages by delivering treatment in a single fraction.
6. For all radiation modalities, the functional status at 10 or more years is not known.

7. Hepatocellular carcinoma: Primary & recurrent; < 3 cm *(adjacent to vessels, bile ducts, gastrointestinal tract)*; > 3 cm

Clinical problem

Liver cancer is the 3rd cause of cancer-related death with hepatocellular carcinoma (HCC) accounting for 90% of all liver cancers [132]. Resection and liver transplantation are the first-line treatments for patients with early stage HCC resulting in 5-years survival of 60-80% and 65-78%, respectively [132]. Peri-operative mortality of ~3% is similar for both treatment modalities. However, the strict criteria for resection and transplantation limit its applicability - approximately only 20% of patients with HCC are suitable for surgery or liver transplantation [133]. Percutaneous ethanol injection (PEI) and radio frequency ablation (RFA) for early or intermediate disease are considered standard of care for patients not suitable for surgery [132]. Chemoembolization (TACE) is the recommended first line-therapy for patients with intermediate stage HCC [132]. For inoperable patients, RFA has reported 5-year overall survival rates of 40-70% and is superior to PEI for survival and local recurrence with tumours >2cm [134,135,136]. The main drawback of RFA is its higher rates of major complications (4%; 95% CI, 1.8–6.4%) compared

to PEI (2.7%; 95% CI, 0.4–5.1%) [134,137]. Treatment of patients with larger tumours (3–5 cm), multiple tumours (2-3 nodules <3 cm) and advanced liver failure (Child–Pugh B) with these techniques results in higher recurrence rates and toxicity. For intermediate HCC, the median overall survival is about 20 months with TACE, which does not significantly differ from control treatments [136]. However, due to the limitations of these modalities described above, not all unresectable lesions are eligible for these local ablative treatments and these individuals have a median overall survival in the range of 6 to 7 months [138]. However, these local treatments also have important limitations including size of the lesion (RFA: <5cm, PEI <2cm), vicinity of large vessels, location at the subcapsular region. When not respected, the tumour recurrence rate rises dramatically or toxicity becomes unacceptable [132]. These observations support investigating alternative local treatments, such as external beam radiotherapy, less restricted by these specific limitations.

Anatomical challenges

The liver is a parallel organ with low radiation dose tolerance per millilitre of tissue and toxicity is volume dependent. In the early experiences with radiotherapy for HCC, large volume or whole liver photon radiotherapy was used to treat large HCC resulting in high rates of radiation-induced liver disease (RILD) and poor tumour response rates. The incidence of RILD is approximately 5% at 30-33 Gy delivered to the whole liver. Moreover, the dose that can be safely delivered to the liver is even more reduced for patients with liver cirrhosis (60-80% of HCC cases) and hepatitis virus B carrier status [139]. Radiation tolerance of nearby organs-at-risk such as the spinal cord, kidney, heart, esophagus, small intestine and stomach adds to the challenges of conventional photon radiotherapy [140], though the vicinity and tolerance of the large vessels is less an issue with radiotherapy. Improvements in diagnostic imaging, radiotherapy planning techniques (to produce three-dimensional conformal radiotherapy plans, minimizing dose to surrounding tissues), image-guided radiotherapy (to localize tumour at time of treatment), tumour immobilisation (to account for respiratory-related organ motion) in combination with improved knowledge of partial volume liver tolerance has facilitated the delivery of tumouricidal photon doses to focal HCC. However, despite these advances in photon radiotherapy, significant volumes of liver still receive low doses of radiation that can preclude dose escalation, particularly in patients with limited functional liver reserves. By exploiting the lack of exit dose along the beam path beyond the tumour and higher biological effectiveness, hadron therapy offers the promise of maximizing tumour control via dose escalation without excessive liver toxicity.

Biological challenges

HCC is traditionally considered a radioresistant tumour with substantial toxicity even at low doses, leading to a waning interest in the use of radiotherapy as a treatment modality. Although the radiosensitivity data for HCC are rather scarce, the α/β values and the fraction of cells surviving radiotherapy doses of 2 Gy are in the range with other non-HCC tumours, which are frequently treated with radiotherapy [141]. The general misconception of radioresistance is mainly driven by the initial poor results due to insufficient doses to the tumour. Dose-escalation offers better tumour response and local control, but its use is hampered by anatomical challenges [142,143].

Comparative clinical data

Results of selected prospective studies investigating the role of external beam photon radiotherapy for unresectable HCC are presented in Table 13.
Higher rates of severe toxicity including RILD discouraged the use of high-dose conventional photon radiotherapy that is currently being replaced by stereotactic body radiotherapy. Stereotactic body radiotherapy employing hypofractionation (3-10 fractions of 5-12.5 Gy depending on tumour size and location) provided better 1-year local control rates of 65-100% at a median survival of ~16 months; 1-year overall survival varies between 48 and 75%.

Table 13. Selected prospective studies on photon radiotherapy for unresectable HCC.

Study	No. of patients	Total dose	Overall survival (year)	Local control (year)	Toxicity
Mornex 2006 [144] 3DCRT	27	66 Gy	NR	NR	Acute grade 3 toxicity: 44% Acute grade 4 toxicity: 11% Late grade 3 toxicity: 26% Late grade 4 toxicity: 0%
Mendez 2006 [145] SBRT	25	25-37.5 Gy	40% (2)	75% (1)	Acute grade 1-2 liver toxicity: 96% Grade 5 toxicity: 4% Late toxicity: 0%
Tse 2008 [146] SBRT	41	24-54 Gy	48% (1)	65% (1)	RILD: 0% Grade 3 liver enzyme toxicity: 20%
Iwata 2010 [147] SBRT	18	50-55 Gy	94% (1)	86% (1)	RILD: 0%
Cardenes 2010 [148] SBRT	17	36 Gy	60% (2)	NR	Grade 4 toxicity: 5.9% RILD: 18%

Abbreviations: 3DCRT: three-dimensional conformal radiotherapy; NR: not reported; SBRT: stereotactic body radiotherapy; RILD: radiation-induced liver disease.

A comparative case series compared treatment outcome of 343 patients with unresectable HCC with macroscopic vascular invasion receiving either carbon ion (101 patients) or proton (242 patients) therapy [149] (Table 14). There was no difference between the two treatments in 5-year overall survival and local control: 36.3% vs. 38% and 93% vs. 90.2%, respectively. Rates of late toxicity were similar too: grade ≥3 toxicity was observed in 4 patients after carbon ion therapy vs. 8 after proton therapy. The rates of survival and disease control after carbon ion therapy appeared to be dose-dependent reaching 72% and 95% at 3 years, respectively [150]. Studies employing protons reported treatment outcome similar to that after carbon ion therapy. Overall survival and local control at 5 years was in the range 23.5-48% and 81-87.8%, respectively. Proton therapy was well-tolerated with mild toxicity.

Table 14. Selected studies on hadron therapy for unresectable HCC.

Study	No. of patients	Total dose	Overall survival (year)	Local control (year)	Toxicity
Komatsu 2011 [149] Carbon ions Protons	 101 242	 52.8-76 GyE 52.8-84 GyE	 36.3% (5) 38% (5)	 93% (5) 90.2% (5)	Late grade 3-4 toxicity 1% 3%
Imada 2011 [150] Carbon ions	83	32-45 GyE	54-72% (3)*	74-95% (3)*	Late grade 4 liver toxicity: 0%
Chiba 2005 [151] Protons	162	72 GyE	23.5% (5)	86.9% (5)	All late toxicity: 3%
Fukumitsu 2009 [152] Protons	51	66 GyE	38.5% (5)	87.8% (5)	Late grade 3-4 toxicity: 2% Late grade 1-3 bone toxicity: 6%
Mizumoto 2011 [153] Protons	266	66-77 GyE	48% (5)	81% (5)	Acute grade 3 skin toxicity: <1% Late grade 4 skin toxicity: <1% Late grade 4 GI toxicity: 1%

*patients received <45.6 GyE and ≥45.6 GyE.

Conclusions

1. Approximately 80% of patients with HCC are not operable due to tumour multifocality, inadequate liver function, and/or involvement of neighbouring structures.
2. Locally ablative treatments can be performed in highly selected patients.
3. The use of conventional photon radiotherapy is limited by its inability to deliver doses high enough for disease control without increase in severe toxicity. Stereotactic body radiotherapy allowing dose escalation in selected patients. It is associated with still high rates of grade 4-5 toxicity varying

between 0 and 6% and RILD up to 18%. One-year local control varies between 65-100%.

4. Hadron therapy for unresectable HCC minimizes acute and late severe toxicity to <3%. Overall survival and local control are similar for proton and carbon ion therapy: 36.3-48% and 81-93%, respectively. However, hypofractionation used in carbon ion therapy – 2-4 fractions against normofractionation with proton therapy – may favour carbon ions.

4. CONCLUSIONS

1. Hadron therapy started as a side activity in physics research centers. Their clinical activity focused on rare tumours that were difficult to treat because of a challenging tumour location, often nearby the central nervous system, or because of resistance to the standard available photon or electron radiation beams.
2. Many types of hadron therapy have been used in the past. Nowadays, proton and carbon ions are the most frequently used types of hadron therapy.
3. In a variety of paediatric cancers, proton therapy is first choice treatment due to its ability to avoid growth and developmental disturbances while carbon ion therapy is experimentally used to avoid mutilating surgery in children with osteosarcoma. Paediatric standard indications are reimbursed in many countries worldwide.
4. Standard indications in adult patients are restricted to very rare tumours that were the historical niche of clinical activity in physics research centers. Multidisciplinary teams, which were built around the niche, consolidated the excellent results and attracted wide-range referral of patients. This centralization in specialized centers provided the teams with sufficient numbers of patients to conduct clinical research which allowed them to improve further the therapeutic results.
5. The first proton and carbon ion centers, which had patient treatment as their main objective, were built in the 1990s. During the last decade, many clinical hadron therapy projects have been launched and the worldwide treatment capacity has rapidly increased.
6. Thanks to progress in medical imaging and computer technology, virtual modeling studies involving hadron therapy were possible since the 1980s. By increased capacity, it became realistic to conduct case studies to test hadron therapy in more common cancers that were identified as good candidates by modeling studies.

7. Case studies typically focused on subgroups of cancer patients in whom conventional treatment showed disappointing results and for whom new photon radiotherapy modalities were unlikely to significantly improve local control or toxicity rates.
8. Patients with locally advanced unresectable pancreatic cancer treated by high-dose carbon ion radiotherapy + gemcitabine had a median survival of 24 months. Median survival is <12 months after photon radiotherapy + gemcitabine. Treatment-induced toxicity appeared lower for carbon ion therapy + gemcitabine although higher therapeutic doses of both modalities were given than in photon-gemcitabine protocols.
9. Patients with unresectable locally recurrent rectal cancer who receive photon radiotherapy ± chemotherapy have a 5-year survival rate of 16-27% in the best series. The best carbon ion schedule yielded a 42% 5-year survival rate and was associated with <5% severe toxicity, which is less than expected from photon radiotherapy ± chemotherapy.
10. In stage III NSCLC, proton therapy 70 GyE + chemotherapy resulted in a median survival > 24 months as compared to ~20 months after photon chemoradiotherapy in the best series and appears to be a less toxic treatment as well.
11. At least 5 other cancer entities with good anatomical and biological model characteristics are being studied in the hadron therapy centers of our expert panel: salivary gland tumours with other than adenoid cystic histology; recurrent head and neck cancer; stage I NSCLC, unresectable hepatocellular carcinoma and poor-prognosis locally advanced prostate cancer.
12. At present, studies of hadron therapy in common cancers do not 'cannibalize' photon radiotherapy, mainly because of a lack of capacity worldwide. This might change in the future with increased capacity. Hadron therapy is ready for new directions, like the treatment of oligometastatic disease, which are now explored by advanced photon therapy techniques. The number of model indications is likely to increase in the next years and may finally lead to replacement of photon radiotherapy for a significant proportion of our patients.

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III. Submodule 2

Number of potential patients and sessions for the different indications for hadron (proton & carbon ion) therapy

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1. OBJECTIVES

The objectives of Submodule 2 were defined as *1)* estimating number of treatment sessions per indication and *2)* estimating number of patients per eligible indication as determined by Submodule 1.

2. METHODS

The number of treatment sessions per standard and model indication for paediatric and adult patients is based on the treatment protocols of the International Society of Paediatric Oncology (SIOP), data of systematic literature search, standard treatment and clinical study protocols applied in proton and carbon ion centers, and experts' knowledge.

For carbon ion treatments, the number of treatment sessions is based on the clinical practice in 2 centers: NIRS, Chiba, Japan and HIT, Heidelberg, Germany. The centers follow a different strategy. In NIRS, the whole radiation treatment is delivered by carbon ions. In HIT, some protocols use carbon ions as a boost. Hence, part of the treatment is delivered by advanced photon techniques and part by carbon ions. The calculation of the number of sessions takes only into account

those delivered by carbon ions. The treatment sessions delivered by photons do not contribute to the workload of the hadron therapy installation. Other protocols at HIT (skull base chordoma and chondrosarcoma, locally advanced HCC, locally recurrent rectal cancer) use carbon ions for the whole treatment. The clinical practice of NIRS evolves towards extreme hypofractionation (very low numbers of fractions and high dose per fraction), while HIT uses moderate hypofractionation. For proton therapy -given almost no difference in radiobiological effects produced by protons and photons- the panel of international experts recommended to use the same number of treatment sessions as for conventionally fractionated photon radiotherapy.

The number of paediatric patients per standard indication is based on data of the Belgian Cancer Registry registered in 2004-2009. The numbers of paediatric patients with esthesioneuroblastoma and primitive neuroectodermal tumours (PNET) are not in the report of the Belgian Cancer Registry; central nervous system (CNS) germ-cell tumours were not distinguished from all germ-cell tumours, though we presume that esthesioneuroblastoma, PNET and CNS germ-cell tumours were reported under “other central nervous system tumours than those mentioned above”.

Numbers of adult patients per standard and model indication were determined by a 2-step process. The first step was based on data of the Belgian Cancer Registry registered in 2009. This step provided the total number of patients that was registered in 2009 with a cancer that could fit a standard or a model indication. For some cancers the registered data allowed to identify the total number of eligible patients directly. In most instances, this was not possible because the variables needed to identify the subgroup were not registered. In this case, a second step, based on various sources of complementary information was used as described in the results section.

3. RESULTS

3.a. Number of treatment sessions per indication

I. Paediatric indications

The number of treatment sessions used in SIOP protocols for photon radiotherapy was taken as reference with an average number of 30 fractions (table 1). In case of unresectable osteosarcoma, the only paediatric indication for carbon ion treatment (the HIT protocol, registration number ClinicalTrials.gov: NCT01005043), less treatment sessions are foreseen - 20-23 treatment sessions are used.

Table 1. Number of treatment sessions per paediatric standard indication.

No.	Pathology	Type of hadron therapy	Average number of fractions (range)
1	Skull base & spinal chordoma	Protons	39
2	Skull base chondrosarcoma	Protons	39
3	Spinal & paraspinal "adult" soft tissue sarcomas	Protons	(28-33)
4	Pelvic sarcoma	Protons	According to histology
5	Rhabdomyosarcoma	Protons	(20-30)
6	Ewing's sarcoma	Protons	(22-35)
7	Retinoblastoma	Protons	(45-46)
8	Optic pathway & other selected low-grade gliomas	Protons	(28-30)
9	Ependymoma	Protons	(30-32)
10	Craniopharyngeoma	Protons	29-30
11	Pineal parenchymal tumours	Protons	According to histology
12	Esthesioneuroblastoma	Protons	30
13	Medulloblastoma/primitive neuroectodermal tumours (PNET)	Protons	(28-30)
14	Central nervous system (CNS) germ-cell tumours	Protons	30
15	Unresectable osteosarcoma	Carbon ions	(20-23)

II. Indications in adults

Numbers of treatment fractions for adult standard indications are presented in table 2. The number of carbon ion treatment sessions per standard indication varies between 16 and 21 if the whole treatment consists of carbon ion therapy and between 6 and 8 if the treatment consists of photon radiotherapy plus a carbon ion boost. The fraction size is typically ≥3 GyE (hypofractionation) in carbon ion therapy. The overall average of 15 treatment sessions is further taken as baseline for cost calculations. The number of treatment sessions per standard indication for proton radiotherapy is in the range of 30-37 with the average of 32 fractions (normofractionation).

The number of carbon ion treatment sessions per model indication is in the range of 1-24 at the average of 12 fractions depending on the tumour type with the lowest for stage I NSCLC and hepatocellular carcinoma – 1 and 2 fractions, respectively (table 3). There is a trend of reducing of the number of fractions further. The number of proton treatment sessions per model indication currently remains in the range

Table 2. Number of treatment sessions per standard indication in adults

No.	TNM classification	Pathology	Type of hadron therapy	Average number of fractions (range)
1	Bone & soft tissue tumours	Chordoma: skull base	Carbon ions Protons	21 (16-21) 36 (34-37)
2	Bone & soft tissue tumours	Chondrosarcoma: skull base	Carbon ions Protons	20 (16-20) 35 (34-36)
3	Bone & soft tissue tumours	Chordoma & chondrosarcoma: Sacral or coccygeal	Carbon ions Protons	16 30
4	Bone & soft tissue tumours	Chordoma & chondrosarcoma: paraspinal	Protons	36 (34-37)
5	Bone & soft tissue tumours	Bone & soft-tissue sarcoma: skull base, paraspinal, retroperitoneal, sacral & coccygeal	Carbon ions Protons	16 30
6	Head & neck tumours	Malignant melanoma of the upper aerodigestive tract	Carbon ions	16
7	Head & neck tumours	Adenoid cystic carcinoma	Carbon ions	16 or 6 (6-8)*
8	Head & neck cancer	Paranasal tumours	Protons	30
9	Brain tumours	Benign & malignant meningioma	Protons	30
10	Brain tumours	Low-grade (Grade 1 & 2) glioma	Protons	30

*delivered as a boost.

Table 3. Number of treatment sessions per model indication in adults

No.	TNM classification	Pathology	Type of hadron therapy	Average number of fractions (range)
1	Digestive tract tumours	Pancreatic cancer	Carbon ions	12 (8-16)
2	Digestive tract tumours	Rectal cancer	Carbon ions	16 (12-18)
3	Lung & pleural tumours	Stage III NSCLC	Protons	30 (30-37)
4	Head & neck tumours	Major salivary gland tumours other than adenoid cystic carcinoma	Carbon ions	16 or 6-8 (boost)
5	Head & neck tumours	Any (re-irradiation)	Protons	35 (30-35)
6	Gynecological tumours	Non-SCC cervical cancer	Carbon ions	20 (20-24)
7	Lung & pleural tumours	Stage I NSCLC	Carbon ions	4 (1-9)
8	Digestive tract tumours	Hepatocellular carcinoma	Carbon ions	4 (2-15)

Abbreviations: NSCLC: non-small cell lung cancer; SCC: squamous cell carcinoma.

of 25-37 at the average of 30 fractions per indication (table 3). The panel of international experts does not exclude the possibility of implementing hypofractionation in proton therapy in the mid- to long-term future. The reluctance of the proton therapy centers to follow the trend that is nowadays observed in advanced types of photon radiotherapy is surprising considering the physical superiority of proton therapy over photon radiotherapy.

3.b. Number of patients per eligible indication

I. Paediatric patients

Eight hundred thirty-three paediatric patients with standard indications for hadron therapy have been registered in Belgium in 2004-2009, on the average 139 patients per year, a quarter of whom (34 patients/year) have been treated with radiotherapy. Thus, at least paediatric 34 patients can be considered eligible for hadron

Table 4. Number of paediatric patients with standard indications for hadron therapy registered in Belgium in 2004-2009 (data of the Belgian Cancer Registry).

No.	Pathology	No. of patients	Treatment known (*n*)	Treated with RT (*n*)	Treated with RT (%)
1	Skull base & paraspinal chordoma	2	0	0	0
2	Skull base chondrosarcoma	3	2	0	0
3	(Para)-spinal adult type sarcoma	11	9	3	33
4	Pelvic sarcoma	33	28	10	36
5	Rhabdomyosarcoma	50	44	21	48
6	Ewing's sarcoma	53	47	18	38
7	Retinoblastoma	64	56	5	9
8	Low-grade glioma	265	193	40	21
9	Optic pathway low-grade glioma	38	31	6	19
10	Ependymoma	58	45	18	40
11	Craniopharyngeoma	22	16	7	44
12	Pineal parenchymal tumours (not pineoblastoma)	0	0	0	0
13	Medulloblastoma	52	48	38	79
14	Germ-cell tumours	59	49	11	22
15	Other central nervous system tumours than those mentioned above	78	59	27	46
16	Non-resectable osteosarcoma	45	42	2	5
	TOTAL (2004-2009)	**833**	**669**	**206**	**31**
	TOTAL per year (average)	**139**	**112**	**34**	**31**

Abbreviations: n: number of patients; RT; radiotherapy.

therapy annually. In 164 patients, the treatment was not recorded. Supposing the same utilization rate in these patients as in the patients for whom treatment was known (31%) the yearly number of eligible paediatric patients would be 43.

II. Adult patients

Numbers of adult patients per standard and model indication were based on data of the Belgian Cancer Registry registered in 2009 (table 5). Because of limitations of query selection criteria, adult patient data provided by the Belgian Cancer Registry lack tumour conditions needed for characterization of the indication, e.g., tumour stage, location or resectability. To obtain estimates of the number of patients eligible for hadron therapy, we had to draw inference from existing literature data whenever the data were missing (table 6). When the data on tumour conditions were found sufficient, we considered the number of patients treated with photon radiotherapy as eligible for hadron therapy; that included bone & soft-tissue sarcoma, malignant melanoma of the upper aerodigestive tract, adenoid cystic carcinoma of head & neck, paranasal tumours, benign & malignant meningioma, low-grade glioma, stage III NSCLC, major salivary gland tumours other than adenoid cystic carcinoma, stage I NSCLC (table 6).

Of 6 and 7 patients with chordoma and chondrosarcoma, respectively, registered in 2009, only 2 received radiotherapy most probably due to physical and biological limitations of photon radiotherapy. We presume that all 13 patients with this pathology are eligible for hadron therapy. At least 25-35% of all chordoma originate from the skull base, 50-60% from the sacrum and the rest from the true vertebrae [1]. At least 2% of all chondrosarcoma occur in the head and neck region, i.e., skull base and cervical, while 25% are pelvic, i.e., sacral or coccygeal [2]. Skull base and sacral or coccygeal chordoma and chondrosarcoma are standard indications for hadron therapy, preferably carbon ions due to a fewer number of treatment sessions as compared to proton therapy. Therefore we considered 8 patients with those tumour locations eligible for carbon ion therapy, leaving 2 patients eligible for proton therapy.
Criteria of locally advanced unresectable pancreatic cancer [3] are not defined by the TNM classification, though at the time of diagnosis 30% of patients fit those criteria [4]. Of 1,338 registered patients, at least 401 patients (30%) would have locally advanced cancer making them eligible for hadron (carbon ion) therapy.
Approximately 10% of patients with rectal cancer relapse locally after curative treatment, of which 50% would undergo surgery with 70% of micro- or macroscopic residual disease after surgery [5]. The latter are candidates for hadron (carbon ion) therapy: of 2347 patients with all stages rectal cancer, 235 patients

Table 5. Data of the Belgian Cancer Registry for 2009 which served as basis for calculation of the numbers of standard and model indications in adults

No.	Pathology	No. of patients	Treatment known (*n*)	Treated with RT (*n*)	Treated with RT (%)
Standard indications					
1	Chordoma (all stages of the skull base, paraspinal, sacral & coccygeal)	6	2	1	50
2	Chondrosarcoma (all stages of the skull base, paraspinal, sacral & coccygeal)	7	3	1	33
3	Bone and soft-tissue sarcoma (all stages of skull base, paraspinal, sacral & coccygeal)	98	67	24	36
4	Malignant melanoma of the upper aerodigestive tract	18	16	8	50
5	Adenoid cystic carcinoma of head & neck (all stages)	30	25	21	84
6	Paranasal tumours (all stages)	110	87	65	75
7	Meningioma benign and malignant	572	325	24	7
8	Low-grade glioma (grade 1 & 2)	236	191	71	37
		1,077	**716**	**215**	**30**
Model indications					
9	Pancreatic cancer (all stages)	1,338	1,077	78	7
10	Rectal cancer (all stages primary & recurrent)	2,347	1,956	1,076	55
11	NSCLC (stage III)	1,229	1,185	588	50
12	Major salivary gland tumours other than adenoid cystic carcinoma (all stages)	107	81	50	62
13	Head & neck cancer (primary and recurrent)	2,574	2,101	1,560	74
14	NSCLC (stage I)	1,054	907	179	20
15	Hepatocellular carcinoma (all stages)	455	353	16	5
		9,104	7,660	3,547	46
	TOTAL (all indications)	**10,181**	**8,376**	**3,762**	**45**

Abbreviations: n: number of patients; NSCLC: non-small cell lung cancer.

(10%) would be at risk of local recurrence and 82 patients out of 235 would be eligible for hadron therapy.

Our estimation of the number of head and neck cancer requiring re-irradiation is based on the data of the head & neck cancer database, department of radiotherapy, Ghent University Hospital that treats the highest number of patients with recurrences in the previously irradiated head and neck region in Belgium. At least 10% of 2,574 registered patients could be eligible for re-irradiation with protons.

Data of the Belgian Cancer Registry on hepatocellular carcinoma lack a tumour size, number of tumour lesions, liver function and tumour relation to the neighbouring

Table 6. Estimates of adult patients with standard or model indications eligible for hadron therapy in Belgium per annum.

No.	Indication	No. of patients	Treated with RT (*n*)**	Type of hadron therapy	Estimates of eligible patients (*n*)
Standard indications					
1	Chordoma (all stages & sites)	6	1		
	Skull base			Carbon ions Protons	2
	Sacral & coccygeal			Carbon ions Protons	3
	Paraspinal			Protons	1
2	Chondrosarcoma (all stages & sites)	7	1		
	Skull base			Carbon ions Protons	1
	Sacral & coccygeal			Carbon ions Protons	2
	Paraspinal			Protons	1
3	Bone & soft-tissue sarcoma (all stages of skull base, paraspinal, sacral & coccygeal)	98	24	Carbon ions Protons	24
4	Malignant melanoma of the upper aerodigestive tract	18	8	Carbon ions	8
5	Adenoid cystic carcinoma of head & neck (all stages)	30	21	Carbon ions	21
6	Paranasal tumours (all stages)	110	65	Protons	65
7	Meningioma benign and malignant	572	24	Protons	24
8	Low-grade glioma (grade 1 & 2)	236	71	Protons	71
				Carbon ions	**61**
				Protons	**162**
Model indications					
9	Pancreatic cancer (all stages)	1,338	78		
	Locally advanced inoperable			Carbon ions	401
10	Rectal cancer (primary & recurrent)	2,347	1,956		
	Local recurrence			Carbon ions	82
11	NSCLC (stage III)	1,229	588	Protons	588
12	Major salivary gland tumours other than adenoid cystic carcinoma (all stages)	107	50	Carbon ions	50
13	Head & neck cancer (primary & recurrent)	2,574	1,560		
	Re-irradiation			Protons	156
14	NSCLC (stage I)	1,054	179	Carbon ions	179
15	Hepatocellular carcinoma (all stages) Primary & recurrent size <3 cm: adjacent to vessels or bile ducts or the gastrointestinal tract; Primary & recurrent size >3 cm	455	16	Carbon ions	364
				Carbon ions	**1,076**
				Protons	**744**
TOTAL (all indications)				**Carbon ions**	**1,137**
				Protons	**906**

structures. Knowing that 80% of patients with hepatocellular carcinoma are not suitable for surgery due to cancer multifocality, inadequate liver function, and/or involvement of vascular or biliary structures [6], we inferred that at least 364 patients can be eligible for hadron therapy, preferably with hypofractionated carbon ion therapy, that may be combined with any other non-surgical treatment [7]. Thus, the number of adult patients eligible for hadron therapy is 2,043, of whom 223 with standard indications (61 with carbon ions and 162 with protons) and 1,820 with model indications (1,076 with carbon ions and 744 with protons).

4. DISCUSSION AND CONCLUSIONS

Standard indications for hadron therapy were identified in 34-43 children yearly. This is a substantially lower number than predicted by the hand-rule of 10 paediatric hadron therapy indications per million population.

Standard indications for hadron therapy were identified in 223 adult patients yearly. Three cancer entities - paranasal tumours, meningeomas and gliomas - contribute to more than two-thirds of the standard indications. It has been debated at the experts' meetings if these cancer entities belong to standard or model indications. Without these, the number of standard indications would be about 60/year for adult patients.

Subgroups of patients with common cancers are increasingly studied in proton and carbon ion therapy centers worldwide. Over the last years, promising results were reported. Today, early 2013, model indications were identified in 1,820 patients yearly in Belgium. Some model indications, for example stage III NSCLC, call for a shift from photon therapy to hadron therapy and would 'cannibalize' conventional radiation treatment. Other model indications, for example, hepatocellular carcinoma, would represent new indications for radiation therapy.

The selection of the best hadron for each indication is a research topic. Results better than expected with the present standard therapy were reported with protons as well as with carbon ions for many indications. The rapid evolution towards the use of few treatment sessions is a strong argument in favour of carbon ion therapy for those indications where proton and carbon ion studies report similar clinical outcome.

Arguably, a Belgian hadron therapy centre should focus on one or a few model indications during the start-up period. Selection criteria for start-up could include the technical challenges of the model indications and its incidence. It was argued by prof. T. Kamada and other experts that patients with unfavourable prostate cancer could be considered model indications which would be suitable for start-up: low technical challenge and high patient numbers. This patient group will be studied further.

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IV. Submodule 3

Treatment requirements in terms of technical specifications

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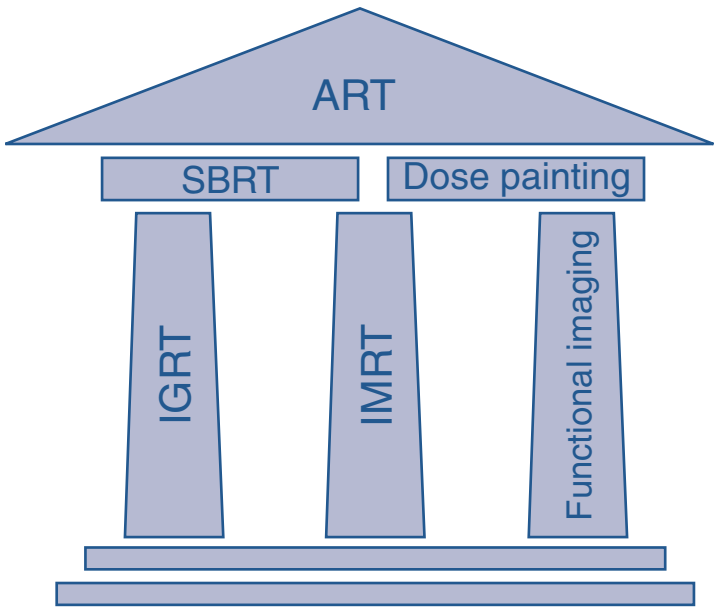
1. HADRON THERAPY RELATED TO NEW DEVELOPMENTS IN PHOTON THERAPY

Over the last 2 decades, the practice of radiation therapy has been thoroughly changed. Integration of two- and three-dimensional (3D) imaging techniques with the treatment machines in the late 1980s formed the basis of image-guided patient positioning which matured to various forms of image-guided radiation therapy (**IGRT**) [1]. Practical devices to define the shape and modulate the intensity profiles of photon beams were developed since the early 1990s and formed the basis for intensity-modulated radiation therapy (**IMRT**) [2]. The concept of radiation therapy planning based on **functional imaging**, which gives information of radioresistance inside tumours and tissues, was launched in the early 2000s [3]. IGRT, IMRT and functional imaging formed the foundations for further developments (figure 1). Stereotactic body radiation therapy (**SBRT**), the irradiation of targets anywhere in the body with stereotactic precision, became possible by combining IGRT and IMRT techniques [4]. SBRT opened the possibility to deliver high doses in a single or a few radiation sessions safely with IGRT and IMRT techniques securing precise dose delivery and tightly shaped dose distributions, respectively. **Dose painting**, the delivery of dose distributions which are tailored to intra-tumour variations of radioresistance, was made possible by combining functional imaging

with IMRT techniques [2, 5, 6]. Contemporary research aims at adapting the daily treatment to changes in anatomy and biology, which occur during the course of radiotherapy. This approach is called adaptive radiation therapy (**ART**) [7]. ART involves the recursive use of IGRT, IMRT and functional imaging techniques.
The recent innovations in conventional radiation have offered new possibilities for reducing toxicity and increasing cure rates. But do they narrow the gap with hadron therapy or does hadron therapy evolve in a similar way? These are the questions that will be addressed in the next paragraphs for each of the recent innovations.

Figure 1. Innovations in photon radiation therapy



Legend: In the 1990s, IGRT, IGRT and functional imaging evolved to an assembly of techniques which are routinely used in radiotherapy departments. Cross-combinations of these techniques resulted in SBRT, dose painting and ART, which are hot topics of contemporary radiation research.

1.a. Image-Guided Radiation Therapy (IGRT)

IGRT uses imaging of the tumour and its surroundings in the treatment position. The coordinates of all relevant anatomical structures are compared with their reference coordinates, which were defined during the preparatory phase of the treatment. Radiation is started if differences between the actual and the reference coordinates are within tolerance levels. Otherwise, adjustments in patient

position or treatment machine are made before the treatment is started. Modern IGRT takes the precision of radiation therapy to the mm and in some tumour locations even to the sub-mm level.

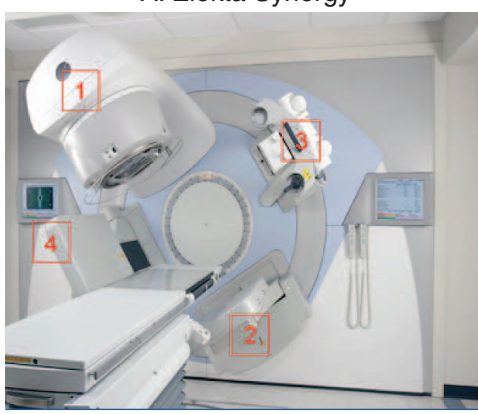
Academic institutions and commercial vendors are promoting an ever-increasing array of novel IGRT technologies spanning numerous imaging modalities: X-ray, ultrasound, magnetic resonance, nuclear medicine techniques and even imaging based on hadron beams. For answering the question 'does IGRT provide a differential benefit between photon and hadron therapy?' it is important to distinguish between planar and volumetric IGRT techniques.

The main example of planar IGRT is stereoscopic X-ray imaging. With the patient in treatment position 2 planar X-rays are taken in different –often orthogonal– directions. The coordinates of landmarks are calculated from their projections in the images. Hadron therapy centers played a pioneering role in the introduction of X-ray stereoscopic imaging in clinical practice. In conjunction with sophisticated patient immobilisation and positioning devices, –development of such devices is also a field of expertise of hadron therapy centers– mm-precision was achieved in hadron therapy. The availability of radio-opaque landmarks is a key factor in X-ray stereoscopy. Such landmarks like the bone, air or implanted markers are not available for many tumour sites. Hence, the use of X-ray stereoscopy is restricted to selected tumour sites, in which landmarks exist that accurately report the anatomical position of the tumour and organs-at-risk. This is typically the case for standard indications.

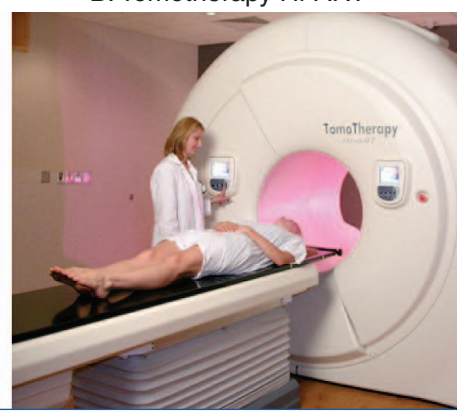
The construction of treatment rooms that host volumetric imaging devices which

Figure 2.: Volumetric IGRT devices of linear accelerators.

A: Elekta Synergy



B: Tomotherapy Hi-ART



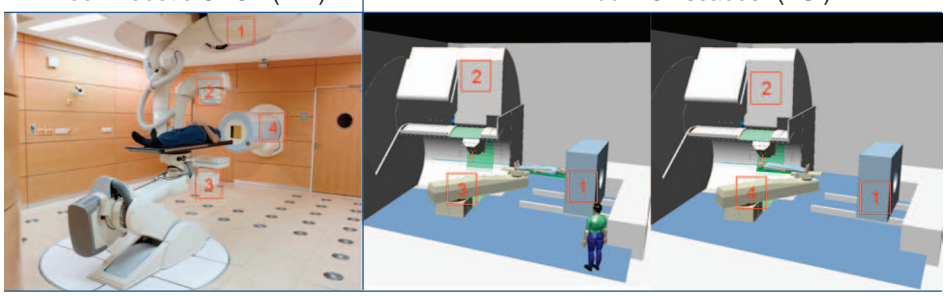
Legend: A: treatment unit combining a linear accelerator with a cone-beam CT device: 1: head of the linear accelerator; 2: detector for constructing planar megavoltage photon images; 3: kilovoltage X-ray source for cone-beam CT, 4: detector plate for cone-beam CT. B: Tomotherapy unit, which uses a 5 MV linear accelerator for treatment and imaging in helical mode of operation. Various components of the Tomotherapy unit originate from 'bomb scanners' used at airports.

used the same coordinate system as the treatment machine, extends the domain of IGRT application to virtually all tumour sites. Volumetric IGRT is commercially available in photon therapy from various vendors including Elekta, Varian, Tomotherapy. Figure 2 shows the Elekta Synergy and the Tomotherapy treatment machines, which are representative of most popular volumetric IGRT approaches: therapeutic X-rays combined with cone-beam or helical CT-scanning, respectively.

Volumetric IGRT is not yet commercially available for hadron therapy but exists in research centers. Figure 3A shows the installation at HIT, Heidelberg, where a robotic arm moves an X-ray source and a detector plate. By moving this assembly around the patient, volumetric cone-beam CT can be acquired in treatment positions, just like it is done at the Elekta Synergy device shown in figure 2.

Figure 3. Volumetric IGRT devices at HIT, Heidelberg and PSI, Villigen.

A: in-room robotic CBCT (HIT) | B: in-room CT-scabber (PSI)



Legend: A: robotic cone-beam CT (CBCT) device in the horizontal beam treatment rooms at HIT, Heidelberg. 1: robotic arm fixed at the ceiling of the room; 2: x-ray source; 3: detector plate; 4: treatment device carrying horizontal beam line. B: drawing of the volumetric IGRT device being installed at PSI. 1: CT-scanner installed in the treatment room; 2: head of proton Gantry-2; 3: patient support system in imaging position; 4: patient support system in treatment position.

The foreign expert panel identified the absence of volumetric IGRT as a major weakness of contemporary hadron therapy installation. This situation mainly hampers hadron therapy for model indications.

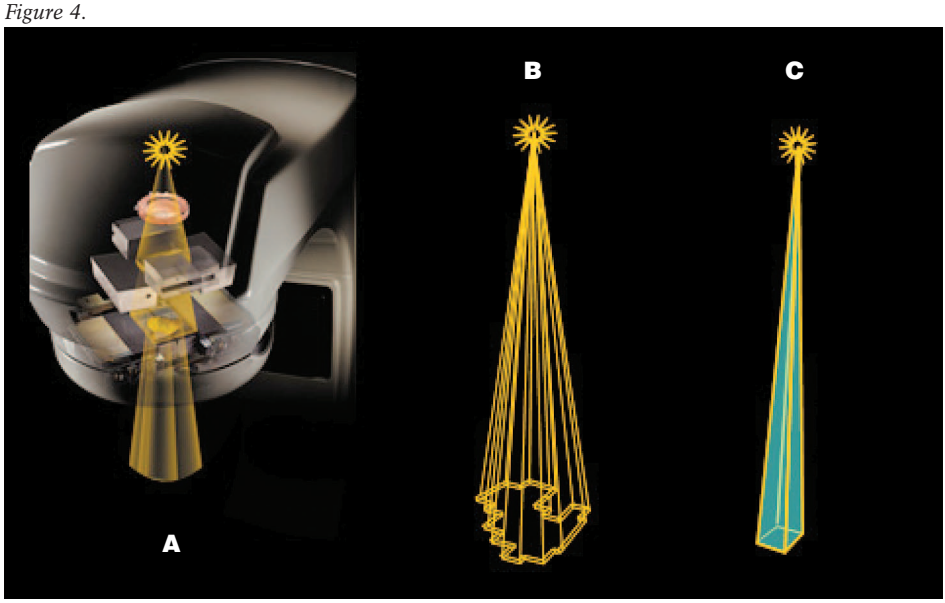
Safety margins around tumours and organs-at-risk can be narrowed with the use of IGRT [1]. Narrower safety margins result in smaller volumes irradiated at therapeutic dose and less integral dose. In tumour sites where volumetric IGRT is prerequisite for smaller safety margins, photon IGRT might have decreased the advantage of hadron therapy. For tumours that can now be treated with high cure rates and low toxicity by photon IGRT, the window for improvement by hadron therapy may be futile. Loss of advantage of hadron therapy, persisting even when volumetric hadron IGRT has become routine treatment, can be expected for patients with small tumours, which are not the majority of patients

in radiotherapy departments. For most tumours the advantage of hadron therapy over photon IGRT is expected to increase once volumetric hadron IGRT becomes widely available. New hadron therapy centers should not be limited to the presently available commercial IGRT technology. Our foreign experts advised us to have no hesitation in requesting volumetric IGRT technology from the start of clinical operations, which is at least 5 years from now.

1.b. Intensity-Modulated Radiation Therapy (IMRT)

Until the 90s, radiation oncologists employed beams with aperture shapes that encompassed the whole tumour. In the mid-90s a handful of research centers, including UGent and UZ Brussel explored a technique of narrower beams (beamlets) that irradiated only a part of the tumour each (figure 4). Very many beamlets were needed to irradiate the entire tumour [2]. The radio-sensitive normal tissues received lower dose by a good choice of directions from which radiation was delivered and by computer optimization techniques to tune the intensity of each beamlet separately. This approach, called intensity-modulated radiation therapy (IMRT), resulted in a new paradigm [2]. Instead of beams with equal intensity across their aperture, the new beams had modulated intensity across their aperture by juxtaposition of beamlets with individually optimised intensity.

Figure 4.



Legend: A: head of a photon radiation therapy machine with the beam in yellow leaving the machine downwards. B: schematic representation of a beam with a shaped aperture to encompass the whole tumour. C: beamlet that irradiates only a part of the tumour.

Because IMRT had the ability to generate concave dose distributions, radiotherapy could be tailored to fit complex targets that extend nearby or even surround healthy critical structures. Before IMRT, such dose distributions were employed in hadron therapy. Hence, IMRT bridged somewhat the gap between photon and hadron therapy. However, IMRT does not reduce integral dose or addresses the yet unresolved problem in photon radiation: creation of sharp dome-like convex dose distributions.

Initially, IMRT was not well accepted by the radiation oncology community since its basic paradigm challenged the existing dogma that beam apertures should encompass the whole target. Until the late-90s few research teams investigated the hypothesis that IMRT could decrease radiotherapy-induced toxicity as compared to non-IMRT techniques. A decade later, results of clinical studies confirmed this hypothesis [8, 9] and explain the widespread adoption of IMRT and several IMRT-derived techniques (IMAT, VMAT, RapidArc, further also called IMRT). In modern radiation oncology centers worldwide IMRT has replaced non-IMRT techniques for the treatment of more than 50% of the patients including almost all patients treated with curative intent.

The pioneering work of PSI and Darmstadt-Heidelberg teams in development of pencil beam scanning for proton and carbon ion beams paved the way to intensity modulation in hadron therapy [10, 11] coined intensity-modulated proton therapy (IMPT) by Lomax or intensity modulated particle therapy by Jäkel. Comparative in-silico studies between IMRT and IMPT typically result in similar dose distributions inside the target volume but far better sparing of the surrounding tissues by IMPT.

1.c. Stereotactic Body Radiation Therapy (SBRT)

SBRT follows the paradigm set by the stereotactic radiosurgery or radiotherapy approach in the central nervous system (CNS), except that it deals with tumours outside of the CNS. The paradigm combines high precision, high dose per fraction, a small high-dose volume, steep dose fall-off and delivery of the total treatment in one or a few fractions. When we consider the techniques mostly used, SBRT is a misnomer. The name stereotactic refers to the use of a frame that has a stereotactic coordinate system and is rigidly fixed to the skull of the patient. The imaging and treatment procedure, uses the coordinate system of the frame. This is a high precision procedure because CNS-targets move little in relation to the skull and frame assembly. Outside the skull, IGRT instead of a stereotactic frame is used to achieve the high-precision requirements. IMRT-like optimization techniques are used to achieve the intended dose distributions. Photon SBRT demonstrated high eradication rates for small tumours and metastases. The present domain of

application includes primary lung, pancreatic, bile duct, liver, kidney, prostate and other pelvic tumours, sarcomas and a condition called oligometastatic disease (low number of metastases with the primary tumour controlled).
SBRT is used in photon and in hadron therapy. For small tumours, photon and hadron therapy seem to perform equally well but with increasing tumour size, efficacy of photon SBRT decreases [12-14]. Larger tumour size turns into larger integral dose and increased toxicity [15, 16]. The physical and biological advantages of hadron therapy (steeper dose fall-off, biological advantages) are expected to translate to lower toxicity and better eradication rates for larger tumours. In treatment of oligometastatic disease, the number of syn- or metachronic treatments that can be safely delivered is expected to be larger for hadron therapy than for photon therapy due to difference in integral dose in favour of hadron therapy. Hadron and photon SBRT may have a complementary role. With a risk of oversimplification we could state that hadron beams extend the domain of SBRT application beyond what is possible with photons: larger and more radioresistant tumours, better cure/toxicity ratio and higher repeatability of treatment.

1.d. Functional imaging and dose painting

There is currently a wide interest in integrating biological information in radiotherapy treatment planning with the primary aim of targeting radioresistant tumour regions on the one hand or avoiding functional damage to radiosensitive organs on the other hand. Biological conformality is pursued by creating a heterogeneous dose pattern reflecting intra-tumour, intra- and inter-organ variation in biological factors of importance for radiation sensitivity, the concept has been designated ‘dose painting’. “Functional (also called biological) imaging” mainly PET, f-MRI and MRS is used to construct 3D maps of values that reflect various aspects of radioresistance. Dose painting is based on the integration of functional imaging and IMRT. Dedicated IMRT optimization techniques turn the biological imaging information into dose intensification or dose reduction to radioresistant or radiosensitive regions, respectively [18, 19]. The resulting treatment is now called dose-painting-by-numbers. In dose-painting-by-numbers, the dose level in each sub-volume of the tumour is a function of the signal-intensity number of the corresponding volume in the co-registered biological image. The procedure resembles the ‘paint by numbers’ method (figure 5), in which artwork is created by painting regions with the colour indicated by a number in the colour list.

Figure 5. Paint by numbers.

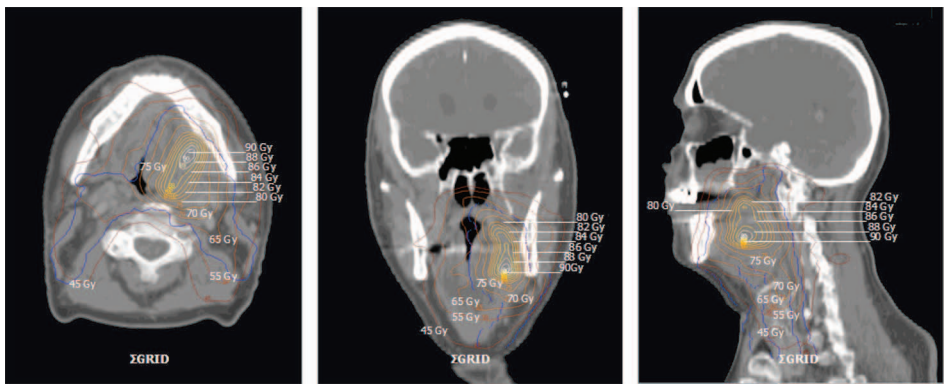
Andy Warhol. Do It Yourself Flowers). 1962. Elizabeth De Vaal (2006)

Legend: Left panel: contour-based. A mosaic of regions is drawn. Each region has a number. Each number has a corresponding color. The painter fills the region with the corresponding color. Right panel: 'voxel-based' painting by numbers. Each individual building block (voxel) of the hand is painted separately.

Two methods of dose-painting-by-numbers are being used in clinical applications [5, 20]. The first is contour-based and is identical to the procedure drawn at the left side of figure 5. The radiation oncologist delineates sub-volumes of the tumour and calculates a representative signal-intensity number for each sub-volume using the biological image. The contour dose painting program secures that each sub-volume receives the dose level that is indicated by the signal-intensity number. Higher radioresistance corresponds to a signal-intensity number that indicates a higher dose. The second dose painting program is voxel-based [18, 19]. Voxels (VOlume piXEL) are the building blocks of medical images. The painting at the right side of figure 5 is suitable to illustrate voxel-based dose painting. The 'voxels' of the hand appear as 'tiles', which have been individually painted. The voxel dose painting program secures that each voxel of the tumour receives the dose that is indicated by the signal-intensity number of the corresponding voxel in the biological image. An example of voxel dose painting is shown in figure 6. Voxel dose painting is more powerful than contour dose painting since it paints at the maximum possible resolution, namely

resolution of the elementary building blocks of the medical images. It is also more efficient since there is no need to delineate sub-volumes. Photon techniques allow dose painting at resolution of contemporary PET or SPECT images. The resolution of state-of-art CT- and MRI scanners exceeds that of contemporary photon delivery techniques. The few available data suggest that dose painting patterns of proton and photon inside tumours are similar but that protons are superior to spare healthy tissues outside the tumour [21, 22].

Figure 6.



Voxel-based dose painting for head-and-neck cancer. Dose peaks at regions of high signal-intensity in functional imaging.

The distal part of the Bragg peak of a beam of charged particles such as carbon ions has a region of high linear energy transfer (LET). Tumour cells which are resistant to low-LET radiation beams, such as photon beams, because of hypoxia or cell quiescence, are equally sensitive to oxygenated cells when high-LET irradiation is used. Spread out Bragg peaks (SOBP) are used to cover the tumour (see *Preface and Background*) with dose. The spatial pattern SOBP results from optimising the distribution of dose, which results in a dilution towards average LET in the tumour volume. The concept of LET-painting was recently proposed [23]. LET-painting aims at optimising the distribution of LET in order to maximize LET in resistant regions of the tumour. LET-painting may be a safer and more efficient strategy to overcome hypoxia than physical dose escalation. LET-painting is impossible with photon beams.

1.e. Adaptive radiation therapy (ART)

Throughout fractionated radiation therapy, which may last several weeks, tumour response, alterations in non-tumour anatomy and treatment-induced toxicity, e.g., weight loss or edema, are causing a mismatch between dose distributions on the

one hand and the shapes of tumour and vulnerable organs on the other hand. Such mismatches are disregarded in standard radiotherapy schedules that base the whole treatment on a pre-treatment imaging snapshot. Many tumours regress in response to radiotherapy. For example, head-and-neck tumours become on the average 40% smaller after 2 weeks, which is less than 1/3th of the total duration of a typical radiation therapy. In standard radiotherapy schedules the high-dose volume becomes over-dimensioned with regard to the tumour and gradually encompasses more normal tissues. By regularly adapting the treatment to changing anatomy, avoidance of vulnerable organs is maintained during the whole treatment. In adaptive radiation therapy (ART) updating dose-distributions for optimal targeting of the tumour and avoidance of vulnerable organs are regularly re-assured.

ART has its price. It comes with the cost of several imaging examinations and is labor-intensive: re-contouring, re-planning and summation of consecutive treatment phases. Based on human effort only, multiple adaptations during a treatment course are rapidly impracticable. Technology developments aim at automation of all error-prone and labor-intensive tasks [24]. At present, we are at the level of semi-automation for re-contouring and re-planning. The burden and cost of ART are proportional to the number of adaptations during fractionated treatment and, hence, hypofractionation is a strategy to reduce cost. Hypofractionation is a topic of intense research in carbon ion therapy. Schedules with very few or even a single fraction are under investigation. Single-fraction treatments make ART obsolete.

2. SOURCES OF INFORMATION

Sources of information were meetings on hadron therapy and visits to the centers in Darmstadt, Heidelberg, Germany and Orsay, France, participation in European hadron projects (Trento, Italy; PTC Holland, Netherlands; FranceHadron, France; Archade, France) and participation in ESTRO hadron teaching courses.

The first proposal for technical specifications was discussed at the BHTC meeting on Submodule 1.3, Brussels, December 6, 2011. The proposal was adapted following the discussion with the foreign experts during the Expert Meetings on March 20-21 (addendum 6) and September 20-21, 2012 (addendum 8) and December 4-5, 2012 (addendum 9). A brief discussion with company representatives (IBA, Belgium; Still River, US; Varian, US; Sumitomo, Japan) took place at the ESTRO Hadron Therapy Teaching Course, Uppsala, Sweden, March 25-29, 2012. Discussion with professor Tadashi Kamada (NIRS, Chiba, Japan) took place at the ESTRO Hadron Therapy Teaching Course, Uppsala, Sweden, March 25-29, 2012 and at a meeting in Brussels on August 1-2 (addendum 7).

3. GENERAL CONCEPT

The general concept is a facility of a minimum size at start-up offering the possibility to treat Belgian patients that are eligible for hadron therapy according to priority ranking. Proton therapy is most available worldwide and is in rapid expansion. Carbon ion (C ion) therapy is mainly performed in Japan and Germany. The choice for protons, C ions or both is not clear. For the feasibility study of the project the experts advised to consider 3 types of facilities: combined proton and C ion; proton only; C ion only. The experts proposed to install at least 2 treatment rooms from the start of clinical operations to allow continuity of clinical operations during maintenance or upgrades. The concept foresees the possibility of later expansions of the facility with more C ion rooms and/or proton rooms by connecting a dead end branch to the beam line(s). A temporary room for quality assurance (QA) and research is planned at the dead end of the beam lines. The QA and research room can be replaced by a treatment room when expansion is needed. All treatment rooms must be equipped with 3D-set-up imaging devices from the start of clinical operation i.e. the possibility to perform volumetric IGRT should be secured from the start of operations.

A project to build and operate a one-room proton therapy facility has been started in Belgium by a group involving IBA, Université Catholique de Louvain (UCL), Hôpital Universitaire Saint-Luc and Région Wallonne. The one-room facility is a new trend in proton therapy proposed by the main vendors of equipment. The trend is mainly driven by commercial considerations such as bringing proton therapy within the budgetary range of radiation therapy centers in the US and elsewhere. The main argument against a one-room facility is the difficulty to provide a continuous clinical operation. Maintenance and upgrades in the treatment room carry risk of halting clinical operations. The one-room facility may become rapidly outdated, if the management chooses to keep the facility unchanged to pursue continuity of clinical operations. Hadron therapy is in fast evolution; IGRT, gating, tracking, IMPT, dose painting, adaptive procedures is under investigation in many centers worldwide. Many of the new evolutions impose in-room modifications. With 2 rooms operations can continue, while they would be interrupted in a one-room centre. In the section on cost calculation, a one-room proton facility has been studied in addition to the 3 types of 2-room centers to compare economic parameters.

The BHTC should be hospital-based. The reluctance towards a stand-alone centre is based on the experience of the expert group in Orsay, France, Paul Scherrer Institute, PSI, Switzerland or GSI Helmholtzzentrum für Schwerionenforschung

GmbH, Germany. The competence of the hospital is needed for anaesthesia, surgery, imaging and general patient care in order to concentrate on acquiring hadron treatment experience that is not present in Belgium, today.

With a population of 10.5 million people, this country is relatively small. Belgium has a world-leading commercial vendor of proton therapy, IBA. A substantial fraction of the invested money might remain in the country if IBA is involved in a future Belgian hadron therapy project. Belgium cannot build a clinical demonstration project from a nuclear physics research facility as it was the case in many other countries that now have operational hadron facilities. Belgium will heavily depend on the commercial sector. Arguments in favour of a single centre in Belgium are numerous. The knowledge should be concentrated for technological and clinical reasons. A hadron centre needs a minimum critical mass in different domains: physics, engineering, biology and oncology. The clinical part, being 3rd- and 4th-line referral, needs sufficient patient throughput to support building and maintaining comprehensive medical expert teams. This will be difficult to achieve in Belgium in more than one centre.

The statement 'start with protons, add C ions later' has been discussed at the Expert Meetings. It was argued that a 2-phase approach was more realistic for the inexperienced group represented by the BHTC Foundation. The subject was discussed at the 2012 ESTRO hadron therapy teaching course. Conceptually, the installation should be designed to treat with protons and C ions from the start, if the choice is made to treat also with ions heavier than protons. Upgrading a typical proton installation for C ion treatment is hardly possible. It would also require a shutdown of clinical activities. Realistic is a 2-phase approach of clinical operations on an installation that allows treating with protons and C ions. Such an approach is followed in CNAO, Pavia, Italy. CNAO had started initially with proton therapy and added carbon ion treatments end 2012. The expert group had a split-opinion on delivering proton and carbon ion therapy with the same equipment. Prof. Kamada is strongly against. The technological complexity of a combined centre is high. There is however consensus that, if a combined centre is chosen, it is preferentially built as an assembly of 2 dedicated facilities (one proton, one carbon ion) at the same implantation site (Expert Meeting 4-5 December 2012).

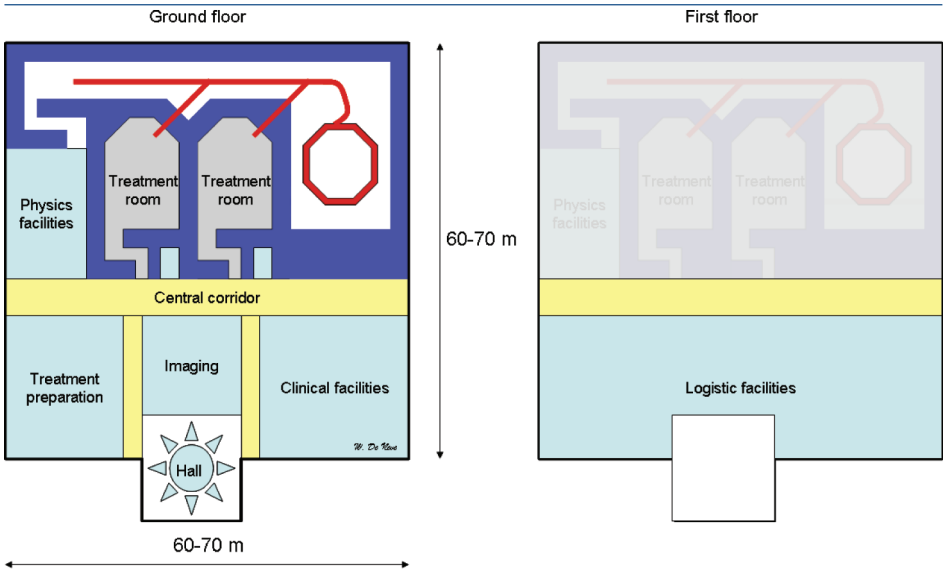
Four commercial vendors (IBA, Varian, Still River (MevIon) and Sumitomo) participated in a vendor discussion session at the 2012 ESTRO hadron therapy teaching course (Uppsala, March 25-29, 2012). Varian and Still River restrict themselves to proton therapy. IBA and Sumitomo would accept to compete in light-ion projects. Other Japanese companies might also compete in light-ion

projects. Professor T. Kamada (NIRS, Chiba, Japan) explained (Uppsala, March 25, 2012) that Sumitomo and Hitachi have build proton therapy facilities. Toshiba builds C ion therapy facilities. Mitsubishi builds facilities for treatment with both ions. Professor T. Kamada thinks that all 4 would eventually be capable to build any type of facility (proton, light-ion or both) because all 4 have the technology. The charged-particle cancer therapy HIMAC project (NIRS, Japan) was a joint venture of the 4 companies.

The implantation site, type of centre, and vendor are presently unknown. The lay-out must allow operations similar to a photon radiotherapy centre. The question of size-reduction by focusing on new accelerator, beam-line and gantry technology was raised. Numerous projects are running: superconductive magnet technology, synchro-cyclotron, compact synchrotron, dielectric wall accelerator, half-rotation gantry. Not all experts consider physical size of the equipment to be of concern except if it translates to increased operational cost. The experts suggest asking the vendors to propose smaller-size alternatives of their ad-hoc standard equipment. The smaller-size alternatives should be chosen only if they offer at least the same quality of treatment as standard technology, and are as reliable, available from the start of operations.

Drawing detailed architectural plans is expensive and is not a part of the first phase of the feasibility study. Figure 7 shows a general lay-out at the level of the treatment floor. The lay-out of the non-block-house part should support a central income hall with separate flows for *i)* patient intake and post-treatment follow-up (clinical facilities); *ii)* treatment preparation: patient positioning, immobilisation, virtual simulation and planning; *iii)* patient treatment (treatment rooms). The imaging facility positioned centrally in-between the 3 entities hosts simulation-CT, PET-CT, ultrasound and MRI equipment. The central location of the imaging facility secures short distances to facilitate set-up outside the treatment room. The physics facilities host a laboratory and physics equipment for QA and quality control. The block-house part spans several levels. Outside the block-house footprint, above the treatment preparation, imaging and clinical facilities, a floor of offices is planned (not shown in Fig. 7). No offices are planned above the physics facilities. In a scenario of expansion a third treatment room would be built at the site of physics facility. Below the treatment preparation, imaging and clinical facilities, a multi-functional cave is planned (not shown on Fig. 7). The footprint, preliminarily drawn as 60-70 x 60-70 m², will ultimately depend on choices, which are not yet made: a scenario, a gantry or fixed beam, a type of accelerator, one or 2 accelerators in case of a combined proton-C ions facility.

Figure 7.



Legend: General lay-out of a two treatment room hadron therapy facility at the level of the treatment floor.

Building cost estimations ware made as follows. The proton only scenario, hosting 2 gantries, was estimated to have a 60 x 60 m² footprint at a cost of 4,000 Euro per square meter which results in a building cost of 14.4 million Euros. This was rounded to 15 million Euros. The C ions only scenario, hosting 2 horizontal fixed beam rooms, was estimated to have a 64 x 64 m² footprint at a cost of 6,000 Euros per square meter which results in a building cost of 24,576 million Euros. This was rounded to 25 million Euros. The combined proton C ion scenario, hosting a proton gantry and a horizontal fixed beam, was estimated to have a 70 x 70 m² footprint at a cost of 6,000 Euro per square meter, which results in a building cost of 29.4 million Euros. This was rounded to 30 million Euros. The (expandable) one-room proton reference scenario, hosting a proton gantry, was estimated to have a 50 x 50 m² footprint at a cost of 4,000 Euros per square meter, which results in a building cost of 10.0 million Euros.

4. CLINICAL INFORMATICS, INTERFACES AND NETWORKING

A strong development takes place in the domain of Record and Verify (R&V) systems in photon radiotherapy. Systems like MOSAIQ (Elekta) or ARIA (Varian Medical Systems) have evolved to become the operating systems of photon radiotherapy centers that support the clinical management and intend providing the interfaces with hospital information systems as well as the networking between

the equipment used in treatment preparation, treatment delivery and quality control. Interfacing with hospital information systems is still a challenge at the present stage of development. R&V systems of hadron facilities seem far less developed. Difficulties in developing R&V systems for hadron therapy have jeopardised the start-up of operations in newly constructed centers. The major hadron therapy vendors adapt photon R&V systems for use in hadron therapy facilities. The experts (expert meeting March 20-21, 2012) advice using photon R&V systems as a paradigm for defining specifications of R&V systems in a future hadron therapy centre. Defining minimum specifications requires participation of vendors and is a part of a later phase of the feasibility study or, ultimately, the comprehensive business plan. The investment cost of a clinical information support system is estimated at 500,000 Euros. It can be expected that a substantial participation of BHTC personnel will be needed to customize the system. The cost of logistic facilities and offices is estimated at 2.5 million Euros for the 2-room scenarios and at 1.0 million Euros for the 1-room scenario.

5. BEAM AVAILABILITY AND UPTIME

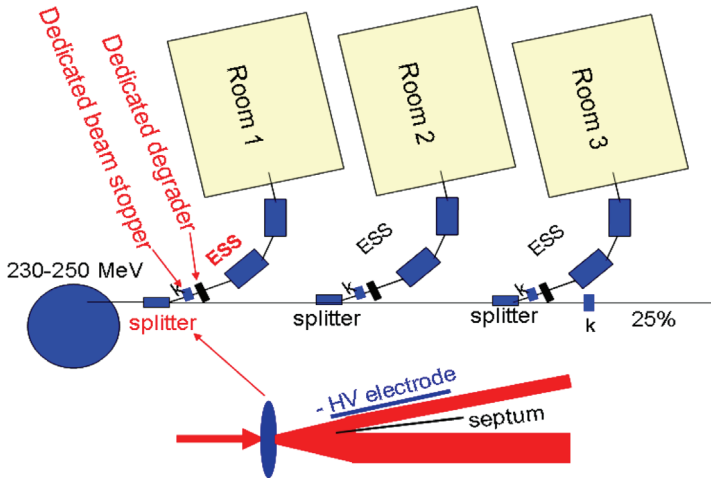
Beam availability for clinical treatment determines the operating schedule of the facility and is a main factor in efficiency during clinical operation. Clinical operation of 16 hours/day, 6 days/week is feasible in proton therapy centers. Long week-ends are typically allowed for maintenance. Proton therapy installations are very reliable. Uptime figures >97% are typical. Loma Linda did run for 20 years at nearly 100% uptime (Dr. Carl Rossi, Loma Linda Proton Centre, US, personal communication). Full maintenance by the company plus a local crew that can perform urgent interventions seems a good choice for the BHTC.

Heidelberg Ion-Beam Therapy Centre (HIT) presently works at a throughput of >700 patients per year, the vast majority being treated with C ions, in two treatment rooms, 12 hours/day, 6 days/week. They treat patients on a standard basis also on Saturday, because they cannot get maintenance personnel on that day. The installation is shut down on Sundays. Every 2 weeks a shutdown from Saturday noon till Monday noon is organized to do maintenance on Monday morning. Three times per year a 3-day shutdown is organized. Every year, during the Christmas and New Year's period a 14-day shutdown is organized. HIT runs at 98% uptime.

Hadron therapy installations usually have a single accelerator. When the beam is directed to one room, another room may have to wait for beam. Such interplay between different treatment rooms to obtain beam does not occur in photon radiotherapy where each room hosts its own accelerator and works independently.

Beam splitting may become available in the near future (Fig. 8). Beam splitting will make simultaneous irradiation possible in different rooms. Presently, treatment slots are relatively long for hadron therapy as compared to photon radiotherapy, typically between 20 and 30 minutes.

Figure 8.



Concept of beam splitting. The radiation beam will be simultaneously available in the treatment rooms (Thanks to Marco Schippers, Paul Sherrer Institute, Villigen, Switzerland).

6. BEAM DIRECTION SPECIFICATIONS

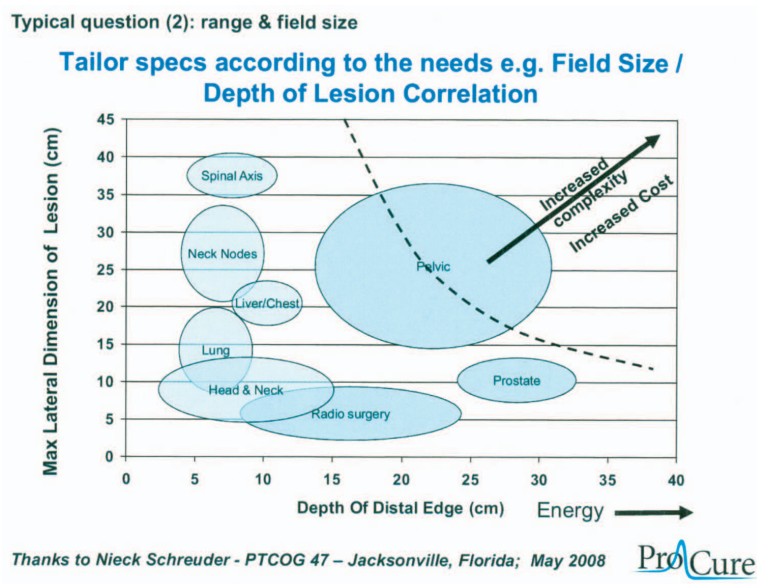
Standardisation in proton therapy involves the use of a gantry and a treatment couch with 4 to 6 degrees of motion. On November 26, 2012, no commercial vendor offers a gantry for C ions. Clinical operation of the HIT gantry at Heidelberg, the first C ion gantry worldwide, is expected to start during Q4 2012. The NIRS gantry at Chiba, Japan has a diameter of about 15 m and a length of 15 m with a weight of 350 tons. It is smaller than the HIT gantry. Design studies in Japan and elsewhere foresee a further size reduction of 1/3th in length and diameter with a weight under 200 tons. A gantry is a standard equipment in proton therapy rooms (unanimous experts' opinion, Expert Meeting March 20-21, 2012). The experts differ in opinion regarding a gantry for C ions. The experts from Heidelberg argue in favour of a gantry. Other experts are more hesitant. Concerning the gantry for C ions, all experts agree that, if the objective is mainly clinical treatment and less research, it is acceptable to leave out the gantry. Regarding other than horizontal fixed beam directions, the experts prefer oblique beam directions over a vertical beam. The inclination should be about 60°-75°.

A variety of couch designs are used in hadron therapy. A key request for modern couches is compatibility with 3D-set-up imaging, preferentially with the patient at the location of treatment. Photon experience shows that 3D-set-up imaging is expensive by increasing the duration of a treatment slot by several minutes. Efficiency of 3D-set-up imaging is a serious concern for hadron therapy. Patient positioners must have the operational characteristics of a modern photon couch. Considering the limitations of fixed beams, the ideal positioner design needs further investigation. Cost calculations are based on the assumption of 2 horizontal fixed beams for the C ions scenario, 2 gantries for the proton only scenario, one proton gantry and a horizontal fixed beam offering C ions and protons for the combined scenario. The reference one-room scenario hosts a gantry.

7. BEAM CHARACTERISTICS

The maximum cross-sectional size of the planning target volume (PTV), measured perpendicular to the beam direction, the depth of the distal edge of the PTV that must be reached and the range of depths that must be covered are important parameters to specify the cross-sectional beam size and the energy range. Size and depth of the PTV are tumour-site dependent (Figure 9).

Figure 9.



Field size and range requirements for various tumour sites.

The cost of the installation is a function of the field size and range (energy) specifications. Setting smaller field size specifications puts a relative constraint on the cancer sites that can be treated (field patching). Setting lower energy specifications will render a tumour untreatable, if the tumour or regions thereof cannot be reached anymore from any of the beam directions that are available. For C ions, the minimum specifications for protons will be used as a reference for negotiations with the vendors. Pencil beam scanning will be requested. Fast re-scanning is requested. The accelerator, beam lines and all treatment devices must be configured in order to treat with up to ≥230 MeV protons or with up to ≥400 MeV/nu helium, carbon, nitrogen or oxygen ions.

8. TREATMENT PREPARATION, SET-UP IMAGING AND CORRECTION

This section involves immobilisation and set-up techniques, imaging for planning, planning, plan verification, set-up imaging in-room and remote, set-up correction, per-treatment monitoring. It is part of a later phase of the feasibility study.

9. CONCLUSIONS ON TREATMENT REQUIREMENTS IN TERMS OF TECHNICAL SPECIFICATIONS

1. Recent innovative developments in photon radiotherapy have improved efficacy and reduced toxicity as compared to conventional techniques. Each of these developments is applicable to hadron therapy and is being implemented, however, at a slower pace.
2. The preferred choice for Belgium is a single hadron therapy centre in order to concentrate the wide clinical and technological knowledge infrastructure in one single place, nearby an existing hospital. The campus of an academic hospital is preferred since research and development is part of the mission of a hadron therapy centre.
3. The general concept is a centre with 2 treatment rooms. The centre should be expandable at a later time. In a proton scenario, each room should have a gantry. In a carbon ion scenario, fixed beams are standard. However, a gantry would facilitate the treatment, especially for the group of patients with model indications.
4. A combined (proton and carbon ion beam lines) is the most versatile solution. However, it is the most challenging scenario. Internal separation of proton and carbon ion treatments by installing dedicated accelerators, beam lines and treatment rooms for each ion is the preferred design.

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V. *Submodule 4*

Costs calculations, financing issues and health economic evaluation

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1. COST CALCULATION AND FINANCING ISSUES

1.a. Context and general introduction to the costing models.

Reimbursements of approximately 18,000 to 40,000 €/patient are commonly charged for hadron treatments in European and Japanese centers. Our first calculations revealed that these amounts are not sufficient to cover the full costs. This observation led to the hypothesis that European and Japanese centers have other financial resources than patient reimbursement at their disposal. Discussions with the expert team confirmed that and made the BHTC team realise that the majority of the projects in surrounding countries, to which a potential Belgian centre would have to benchmark, were started as research and development projects both in the field of clinical and technological development. Public means were often devoted to these projects as an up-front investment, hence not accounted for in the reimbursement of the - purely operational - treatment costs. A succinct overview of how some of the European centers are or have been financially supported is given in the appendix.
In contrast to this, the context and approach in the USA is very different. American centers are typically set on a commercial basis and have to take the full range of capital and risks into account for their reimbursement setting [1]. It is therefore not surprising that some of these centers are known to charge 100,000$ per patient or more.

These very distinct backgrounds and approaches made us decide to perform the cost calculation for this project in different ways (business model vs. Activity-Based Costing model) and to consider different financing models (private, public and mixed financing). Because of the close interaction with the development of the business model, the different financing models will be explained in more detail in section 4.1.4. of the business model.

The **business model** analyses the financial implications of setting up a facility over time. In such a longitudinal ("horizontal") approach, information is provided about the costs incurred from the phase of preparation, first investment and commissioning, over the years where the centre starts to accrue patients (ramp-up period) until operation at full capacity and beyond.
Different financing models (private, public and mixed, see further) are presented with suggestion of the most optimal approach, based on the reimbursement required to make the centre sustainable.
Sensitivity analyses provide insight in the consequences of longer commissioning periods, of different interest rates, higher investment costs and lower personnel requirements. The latter two have been instigated by the comments of the experts who felt that in our literature-based input parameters the investment costs might be underestimated and the personnel requirements rather overestimated.

The **Activity-Based Costing (ABC) model** analyses the departmental and treatment costs in a "vertical" way, that is, for a centre in a specific year corresponding to "steady state operation".
Annual operational costs and average cost per patient are bench marked to the data obtained in the business model for centers in full operation.
The ABC model is specifically useful for computing treatment-specific costs per type of indication. This was done for private as well as public financing. Sensitivity analyses focused on the impact of variable investment costs, different product mixes and the impact of fractionation on the treatment cost. Furthermore, the ABC-model was used to evaluate the productivity of different personnel categories, all or not taking research and development into account. These calculations were all performed using the public financing model.

1.b. Technical alternatives

I. Combined centre

The basic technical solution will be called the **combined centre** hereafter. Its layout is the fruit of our discussions with the expert team (see submodule 3) and is

based on a minimal but necessary equipment for both proton and carbon therapy. The centre consists of one accelerator (if the vendor can supply a combined accelerator for proton an carbon) or two accelerators (if vendor chooses for separate accelerators), two treatment rooms (one gantry room for proton treatment and one fixed beam room for carbon treatment) and the ancillary equipment consisting mainly of imaging, simulation, planning, record & verify and anaesthesia equipment.

II. Two-room carbon ion centre

A **two-room carbon ion centre** is also considered in view of the fact that the number of paediatric patients in Belgium seems to be limited to <50 patients per year, which ultimately cannot justify the proton facility investment – even not when there would be rather 100 instead of 50 patients per year according to a hand-rule calculation of 10 patients/year per million population. The number of adult patients that might profit from carbon ion therapy on the contrary is potentially very large, so that a two-room carbon ion centre is a promising alternative to the combined centre. Another argument in favour of this approach is that the shorter fractionation schedules may result in a higher throughput, hence potentially result in quite competitive treatment costs.

The pure carbon ion centre consists of one accelerator, two fixed beam treatment rooms and the ancillary equipment, consisting of imaging, simulation, planning and record & verify. The anaesthesia facilities can be omitted, as no paediatric patients will be treated.

III. Two-room proton centre

A **two-room proton centre** would be today's technically least challenging solution. Specific for this alternative is the fact that – apart of the <50 paediatric patients – the most suited adult cancers for proton treatment are brain, skull-base, paraspinal, hepatocellular and lung cancers. Because the number of required fractions in proton treatment is high, the total number of patients that can be treated in this centre is restricted to approximately 350 per year, which in turn has its impact on the treatment costs.

This pure proton centre would be equipped with one accelerator and would have 2 treatment rooms, both with complete gantry equipment. Furthermore, there would be a similar set-up of the ancillary equipment as in the first alternative.

IV. One-room Proton centre

Contrary to the above alternative, the **one-room proton centre** is a solution that has been reduced to the bare minimum that might still fit the Belgian stand-alone hospital in terms of bearable investment costs.
In line with some market developments in the USA, only a single treatment room would be provided, together with its accelerator. The investment of the ancillary equipment can be reduced due to the insertion of the proton centre into an established photon radiotherapy department.

1.c. Input parameters

The input parameters include building and equipment investment and financing costs amortization, personnel costs, maintenance costs, energy costs, facility management costs, medical consumable costs and insurances. The following costs have been omitted from the model: costs for the lands (considered to be made available by the hospital from the hospital site where the hadron centre is operational) and demolition costs of the equipment and building at their life end. All cost simulations however provide for sufficient cash flow at the end of the amortization period (years 16 to 20 after start-up).

For the baseline parameters used in the modelling, the KCE report vol. 67A, published in 2007, was taken as starting point and reference [2]. They were however adapted to conform to the actual state of the art based on discussions with the experts and literature review [3-13]. Most important adaptations were made in:

- Investment costs: these were actualised to more recent knowledge and sized down to 2 instead of 3 treatment rooms. The ancillary equipment has been made more expensive in view of the fact that this is an area where the most significant future development is to be expected.
- Personnel: for the basic technical solution (combined centre), a number of 64 FTE has been defined for the 2 rooms. The data have been crosschecked with available literature [13-20] and the model from the ENLIGHT project (European Network for LIGht Ion Hadron Therapy, ESTRO-project supported by the European Commission, QLG1-CT-2002-01574) [5].
- The yearly building's maintenance costs have been reduced from 3 to 1% of the investment costs because it largely consists of a basic concrete structure.

I. Investment costs

In-depth discussions with vendors on the investment costs have not been possible in the limited scope of this feasibility study. It was judged that there was neither time available for that, nor that the credibility of a final project was sufficiently high to tempt vendors to spend more than a couple days of time or to invest much money on this study. The investment costs are therefore not defined per unit of equipment but rather lumped together in large cost entities. These figures, used in our baseline calculations, are estimates derived from our first exploratory contacts with the vendors (see submodule 3).
Table 1 gives an overview of the estimated investments for the different technical solutions, VAT not included.

Building and equipment investment costs

In the basic technical solution of a combined centre, the investment costs for carbon ion therapy (building as well as equipment) have been estimated to be twice as high as those required for proton therapy.
For the two-room carbon ion centre, the building and the carbon equipment investment costs have been assumed to be 25 % higher than the carbon ion part in the combined centre.
In the two-room proton centre, building and equipment investments have both been increased with 5 Mio € compared to the proton investments in the combined centre.
In the one-room proton centre, the building and proton equipment investment costs have been taken the same as in the combined centre.

Ancillary equipment

The investment costs of the ancillary equipment have been estimated to be the same in the combined and the two-room proton centre. In the two-room carbon ion centre, anaesthesia facilities are not required. In the one-room proton centre, the ancillary equipment for imaging, simulation and planning have been sized down to a one-room set-up.

All investment costs are amortized over 20 years, except for IT equipment (planning equipment and record & verify), which is amortized over and replaced every 5 years.

Table 1. Investment costs for the different technical solutions, VAT not included

	Investment costs in different technical solutions.			
Type of investment	Combined centre	Two-room carbon ion centre	Two-room proton centre	One-room proton centre
Building carbon ion equipment	20 Mio €	25 Mio €	-	-
Building proton equipment	10 Mio €	-	15 Mio €	10 Mio €
Carbon ion beam equipment	40 Mio €	50 Mio €	-	-
Proton beam equipment	20 Mio €	-	25 Mio €	20 Mio €
Imaging equipment in each room	4 Mio €	4 Mio €	4 Mio €	2 Mio €
Simulation equipment	2 Mio €	2 Mio €	2 Mio €	1 Mio €
Planning equipment + record & verify	1.5 Mio €	1.5 Mio €	1.5 Mio €	1.5 Mio €
Anaesthesia facilities	1.5 Mio €	-	1.5 Mio €	1.5 Mio €
Other facilities	2.5 Mio €	2.5 Mio €	2.5 Mio €	1 Mio €
Total investment	**101.5 Mio** €	**85 Mio** €	**51.5 Mio** €	**37 Mio** €

II. Operational costs

Personnel costs were based on the KCE report vol. 67A [2], but adapted to current standards. No distinction has been made between senior and junior personnel types for administration, radiographers and therapists. For each of these professions, the cost/FTE/year corresponds to the cost of a senior staff member. Data managers, trajectory nurses and IT/maintenance engineers have been added as staff categories. Their yearly personnel costs correspond to the costs of junior administrative staff members, junior therapists and chief physicists, respectively. The personnel cost for engineers has been assumed to be relatively high because their working schedule includes nights, weekends and holidays.
All personnel costs have been assumed to be subject to a yearly inflation of 2%.
Table 2 gives an overview of the personnel requirements in the different technical solutions.

Yearly **maintenance costs** have been set as a fixed percentage of the investment costs (see table 1): 1% for building; 5% for proton or carbon beam equipment; 10% for planning equipment and record & verify systems; and 7% for imaging and simulation equipment, anaesthesia and other facilities. Maintenance costs have been assumed to be subject to a yearly inflation of 2%.
The **energy costs** for the combined centre, for the carbon-only and for the two-room proton centre have been assumed to be identical and have been set to 677.754 € per year excluding VAT. For the one-room proton centre, the energy

Table 2. Personnel requirements and yearly costs for the different technical solutions

		Number of FTE in different technical solutions			
Personnel type	**Cost/FTE/year**	Combined centre	Two-room carbon ion centre	Two-room proton centre	One-room proton centre
General manager	180,000 €	1	1	1	1
Chief physicist	140,000 €	1	1	1	1
Chief medical Doctor	180,000 €	1	1	1	1
Administration	55,000 €	5	5	5	2
Data manager	46,000 €	2	2	2	1
Radiation oncologists	180,000 €	6	6	6	3
Radiographer	56,000 €	3	3	3	1
Therapists	56,000 €	18	18	18	9
Trajectory	50,000 €	4	4	4	2
Dosimetrists	93,000 €	6	6	6	3
Physicists	93,000 €	6	6	6	3
IT engineers and technicians	140,000 €	4	4	4	2
Maintenance engineers and technicians	140,000 €	7	7	5	3
Total number of FTE		**64**	**64**	**62**	**32**
Total cost/year		**5,979,000** €	**5,979,000** €	**5,699,000** €	**3,114,000** €

costs have been reduced by 50% to 338,877 € per year excluding VAT. Energy costs have been assumed to be subject to a yearly inflation of 2.5%.

Like the energy costs, the yearly **facility maintenance costs** have also been assumed to be the same for all technical solutions that include 2 treatment rooms (382,667 € per year excluding VAT), and have been halved for the one-room proton centre (191,333 € per year excluding VAT). Facility management costs have been assumed to be subject to a yearly inflation of 2%.

The costs necessary for **insurances** have been set to 20,000 € per year excluding VAT for the two-room technical solutions, and to 10,000 € per year excluding VAT for the one-room proton centre, also subject to a yearly inflation of 2%.

For each patient a cost of 750 € excluding VAT for **medical consumables** has been assumed, subject to a yearly inflation of 2%. Although the expert team has pointed out that the 750 €/patient is far too little when scattered beam technology

would be used, we have not adapted our cost modelling for that, in view of the minor impact of this costs on the final results of the study. The scanning beam technology, though still under development and does not generate a per patient consumables cost, seems the most promising tech-nology anyhow.

III. Patient population, fractionation schedules and time slots

The department is assumed to operate from 07:30 till 20:00, in a 5-day workweek during 48 weeks per year (a yearly 4-weeks break is foreseen for maintenance and quality assurance).

For all **proton** indications (paediatric as well as adult indications) we assumed that treatments are delivered in 30 fractions. As it has been assumed that children will require anaesthesia, time slots of 45 minutes per fraction have been allotted in contrast to adults who only require 30 minutes per fraction.

It has been assumed that only adults will be treated in the carbon ion machine. An average of 15 fractions is assumed per **carbon ion** treatment, all delivered in time slots of 30 minutes, was taken as baseline for the calculations. In the sensitivity analyses, the fractionation schemes have been adapted to the type of indication – varying between 4 and 20 fractions – all with the same time slots of 30 minutes.

Based on these parameters, the maximal number of patients that can be treated in the different technical solutions could be calculated. The resulting population mixes used in the different technical solutions are shown in table 3.

Table 3. Population mixes used in the different technical solutions

	Population mixes in different technical solutions			
Type of treatment	Combined centre	Two-room carbon ion centre	Two-room proton centre	One-room proton centre
Paediatric	50	---	50	50
Adult proton	115	---	305	115
Adult carbon ion	369	760	---	---
TOTAL	534	760	355	165

1.d Business model

I. Description of the model

In the business model, the treatment costs have been modelled in spread sheets (Excel®). A separate set of spread sheets has been created for the combined, two-room carbon ion and both double and one-room proton centers. Each set includes an overview of the investments, operational characteristics, exploitation costs, reimbursement rates, annuities and cash flow for a certain model.

Investments have been spread over a project preparation and commissioning period of 4 years. We assumed that the full building costs are financed in the first year. Proton and carbon equipment investment expenditures have been spread over the second (33%) and third (67%) year, whereas imaging and simulation equipment costs have been spread over the third (33%) and fourth (76%) year. The other investments have been supposed to be made during the fourth year. During this period, a fraction of the personnel has already been assumed to be required for preparation and commissioning. These personnel costs have been modelled as a fraction of the total personnel cost of the centre operating at full capacity, namely 10% (year 1), 20% (year 2), 25% (year 3), 30% (year 4). Yearly interim interests of 5% have been assumed to be required on both the investments and personnel costs during the preparation and commissioning period.

The operational model describes the yearly organisation and work schedule, staffing costs and number of patients of the centre operating at full capacity. We assumed to operate all technical alternatives at full capacity 4 years after commissioning, which is 8 years after initial project start. During the first 4 years after start-up, the personnel costs have been assumed to be 40% (year 1 after start-up), 65% (year 2), 90% (year 3) and 100% (year 4) of the costs at full capacity, while patient numbers have been assumed to increase steadily from 25% (year 1 after start-up) over 50% (year 2) and 75% (year 3) to 100% (year 4) of the total number of patients at full capacity.
All staffing and exploitation costs have been assumed to be subject to a yearly inflation of 2%, except for the energy costs, for which the inflation has been assumed to amount to 2.5%.

An average and fixed reimbursement rate per patient has been determined for each centre at full capacity (year 4) and subject to a yearly indexation of 2%. In all technical alternatives the reimbursement rate has been fixed at a level where positive cumulated net cash flow is generated 16 years after the start-up. At that time, the accumulated reimbursements have become large enough to balance the total cash out flow, including investment and operational expenditures, bank repayments including interest payments and short-term loans and their interests. A yearly interest rate of 5% on both long- and short-term loans has been assumed. A private, a public and a mixed model have been considered with regard to the financing of the investments, commissioning and operational costs, see hereafter.

II. Financing methods

The **private financing** approach assumes that the entire cost coverage for setting up the centre has been obtained through private financing. The consequence of this approach is that, apart from the basic investment costs, both the personnel expenses during commissioning (taken to be 4 years from start of the building up to the first treatment) and the interim interests on the investment capital required during this period have been considered to be part of the initial capital that has to be financed privately (inclusive VAT).
After start-up another 4 years have been planned to ramp-up to full patient treatment throughput. With the assumption that the RIZIV-INAMI only reimburses in proportion to the number of patients, a cash drain has to be financed separately during this ramp-up period and thereafter, with short or medium term private loans. The required reimbursement rate per patient has thus been defined at a level such that the Net Cash Flow situation becomes positive in a reasonable period of time. In the modelling this supposed to happen at year 16 after starting the treatment of the first patient (and thus shortly before the end of the amortization period of 20 years).

In the **mixed financing** model it has been assumed that 40% of the funding comes from private loans and that the remaining 60% has been covered by public funding. Hence, the same assumptions hold here as for private financing, except that public financing has been supposed to take 60% of the investment costs out of the project and thereby reduce the annuities by 60%.

In the calculation with **public financing**, the full investment costs as well as the personnel costs during commissioning have been taken out of the project. Hence, the calculation has been based purely on the operational costs, which are the same as for the other financing solutions (e.g. the maintenance costs are of course independent from the source of the investment financing). Apart from that, modelling remains identical as in the previous financing methods.

Some general remarks on **private financing**:

- In the case of private or mixed financing, the investments have been supposed to be amortized by fixed annuity payments over 20 years time at an interest rate of 5 %, except for the planning and record & verify equipment, where 5 years have been considered to be more realistic. This means that for every 10 Mio € invested, a yearly annuity of 802,426 € is due over 20 years. It should be acknowledged that at the present time this interest rate of 5 % is probably too low for a private financing of this type of risk investment.

- In case of private financing of this size of investments, where time spend and money expenditure from the start of the project up to the final commissioning can be considerable, it is common practice to include these costs in the financing costs of the project. These costs consist of operational costs as well as intercalary interests to be paid on the capital before the effective start of the installation, at which time only amortization really starts.

III. Results

Operational costs

The yearly operational costs of the 4 technical solutions with the 3 financing models are given in table 4 (including inflation, *without inflation in italic*).

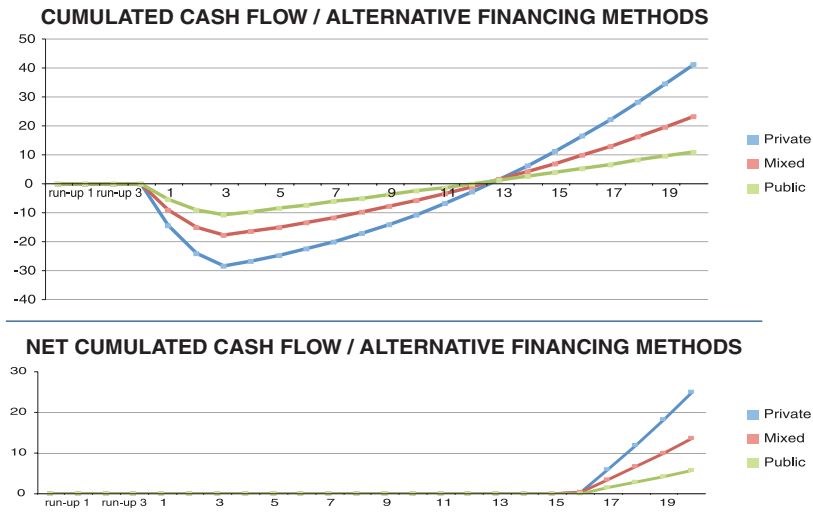
Table 4. Annual operational costs (in €) of the different technical solutions and financing models in year 4 after start-up, i.e. at full operation, with and *without* 2% inflation.

	Operational costs in different technical solutions			
Type of financing	Combined centre	Two-room carbon ion centre	Two-room proton centre	One-room proton centre
Private financing	25,596,686 *24,800,826*	23,141,965 *22,382,063*	17,079,149 *16,451,459*	10,954,312 *10,587,015*
Mixed financing	18,391,638 *17,595,779*	17,035,703 *16,275,801*	13,235,227 *12,607,536*	8,139,548 *7,772,251*
Public financing	13,588,273 *12,792,414*	12,964,861 *12,204,959*	10,672,612 *10,044,922*	6,263,039 *5,895,742*

Cumulated Cash Flow

Figure 1 shows how the Cumulated Cash Flow (CCF) develops for the combined centre with the 3 different modes of financing during the 20 years after start-up. The top part demonstrates the peak in Cash Drain at year 3 and its recovery beginning at year 4. In private financing the Cumulated Cash Drain peaks to the highest level of -30 Mio € because of the fact that in the first 3 years after start-up not all operational costs and the amortization of the invested capital can be covered by reimbursement. Full patient throughput is only attained at year 4. In the case of mixed and public financing the maximum Cumulated Cash Drain is limited to approximately -20 and -10 Mio €.
The bottom part curves show the net Cash Flow after short-term private loans to compensate this drain. It takes up to the 16th year before Net Cumulated Cash Flow (NCCF) is generated.

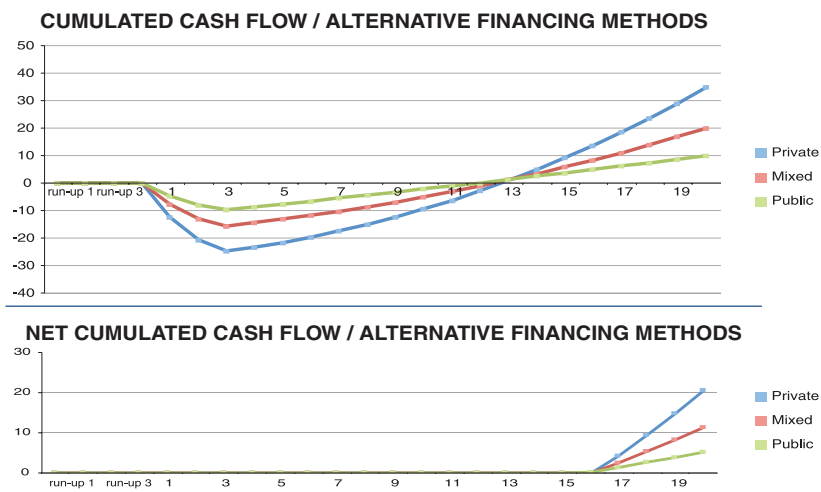
Figure 1. CCF and NCCF for a combined centre (in million €).



Similar curves are drawn for the technical alternatives of the two-room carbon ion centre as shown in figure 2 below.

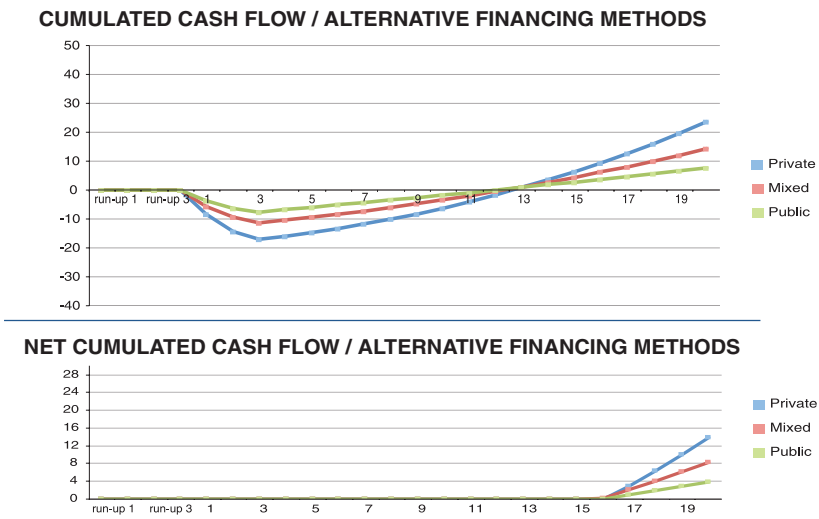
The curves are very comparable to those of the combined centre, be it slightly less pronounced due to the lower level of annuities on the invested capital.

Figure 2. CCF and NCCF for a two-room carbon ion centre (in million €).



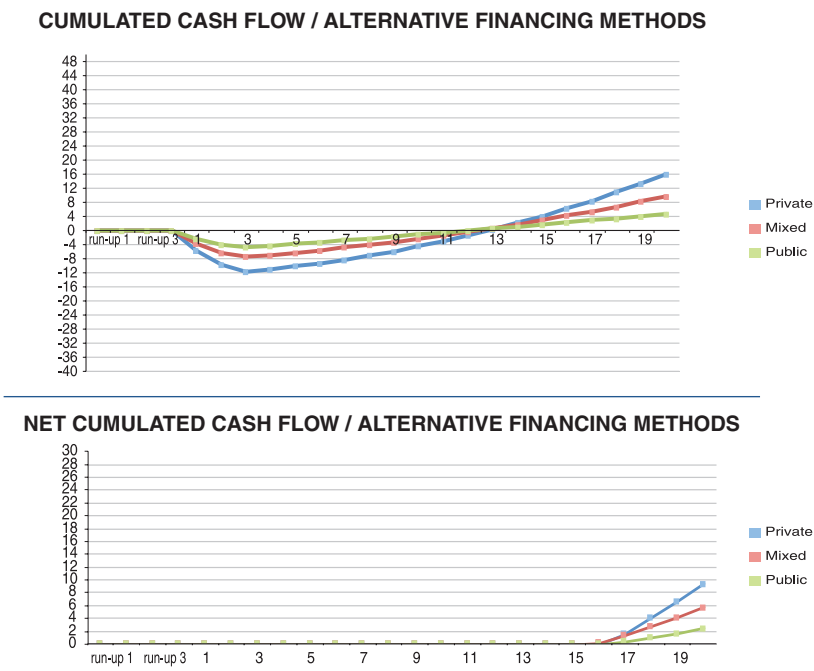
The third technical variant of a two-room proton centre shows similar tendencies as can be seen in figure 3. In this scenario the Cumulated Cash Flow drops to -18 Mio € only for the case of private financing. One should remember however that the investment is about half the one of the combined centre.

Figure 3. CCF and NCCF for a two-room proton centre (in million €).



We finally also show the case of the single-room proton centre in figure 4. The curves are evidently getting much flatter, the investments being limited to 37 Mio €.

Figure 4. CCF and NCCF for a one-room proton centre (in million €).



Required reimbursement

Table 5 shows the average reimbursement levels that have to be foreseen in order to make the centers sustainable for 4 technical solutions and 3 financing methods.

Table 5: Required reimbursement rate (in € per patient) in the different technical solutions for various financing models

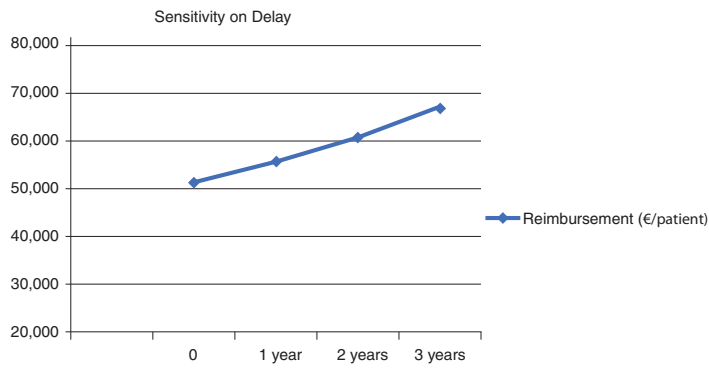
	Required reimbursement in different technical solutions			
Type of financing	Combined centre	Two-room carbon ion centre	Two-room proton centre	One-room proton centre
Patients treated / year	534	760	355	165
Private financing	51,150	32,400	51,200	70,600
Mixed financing	37,000	24,000	39,900	52,900
Public financing	27,550	18,400	32,300	40,950

IV. Sensitivity analysis

Delay in commissioning or ramp-up

Figure 5 shows the very high sensitivity of the required reimbursement rate on delays in commissioning and ramp-up in the case of a private financing of a combined centre. Every year of delay roughly adds 5,000 €/patient to the required reimbursement rate. In the case of mixed financing, this effect is about two-thirds of it. This same effect of course becomes almost negligible in public financing because the initial debts at start are inexistent. The risk of delayed start-up highlights the need for public financing.

Figure 5. Impact of commissioning delay on required reimbursement (combined centre/private financing).

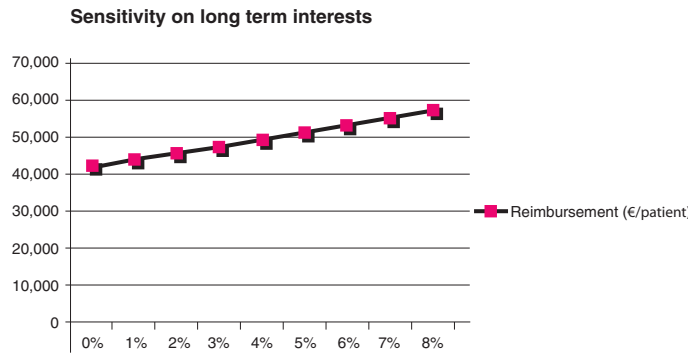


In this example of a combined centre with private financing, one could also express it differently: losing a full year of patient treatment (for example because of slower ramp-up) roughly corresponds to a year of lost reimbursements at full throughput capacity or a loss of approximately 27 Mio € Cash Flow (51,150 € times 534 patients). This loss will again have to be covered by short-term bank loan and interests will have to be paid on them.

Long-term interests

Figure 6 shows that every extra 2% long-term interest on the privately financed capital adds about 4000 €/patient to the required reimbursement. In the case of mixed financing, this effect is about half of that. This effect evidently disappears with public financing.

Figure 6. Impact of long-term interest on required reimbursement (combined centre/private financing).



Investment costs

When a project is privately financed, investments costs evidently have an important influence on the treatment costs whatever choice is made for the technical solution.

In the discussions with the experts, no firm data could be gathered on investment costs. Instead their advice has been to start contacting the vendor in a further stage of the feasibility study. Although no hard figures could be obtained from the experts so far, large uncertainty with important variations seemed to prevail. Some of the experts cited investment costs in hadron projects (especially for carbon equipment) that were twice as high as our estimation; whereas other stated that

(part of) our estimates were too high. Taking this uncertainty into consideration, it was therefore decided to perform a sensitivity analysis on investment costs from – 25% to + 100% (Table 6).

Table 6. Treatment costs (in € per patient) in the different technical solutions for various financing models when corrected for – 25% up to +100% investment costs.

	Required reimbursement in function of varying investment cost.					
Type of technical solution and financing	-25%	**baseline**	+25%	+50%	+75%	+100%
Combined centre						
Private financing	42,800	**51,150**	59,500	67,850	76,200	84,550
Mixed financing	32,000	**37,000**	42,000	47,000	52,000	57,000
Public financing	24,750	**27,550**	30,350	33,150	35,950	38,750
Two-room carbon ion centre						
Private financing	27,400	**32,400**	37,400	42,400	47,400	52,400
Mixed financing	21,000	**24,000**	27,000	30,000	33,000	36,000
Public financing	16,750	**18,400**	20,050	21,700	23,350	25,000
Two-room proton centre						
Private financing	44,400	**51,200**	58,000	64,800	71,600	78,400
Mixed financing	35,900	**39,900**	43,900	47,900	51,900	55,900
Public financing	30,000	**32,300**	34,600	36,900	39,200	41,500
One-room proton centre						
Private financing	60,000	**70,600**	81,200	91,800	102,400	113,000
Mixed financing	46,600	**52,900**	59,200	65,500	71,800	78,100
Public financing	37,350	**40,950**	44,550	48,150	51,750	55,350

This table will not basically alter our conclusions on the choice of the technical solution or the financing method drawn from table 5 (see further). Increase of investment costs, whether 25%, 50%, 75% or even 100% only reinforce the necessity of public funding.

Personnel requirements

The expert team felt that, especially for the proton centers, the personnel numbers seemed to be overestimated. It is true that we only adjusted the personnel numbers on the basis of the number of machines and not on the number of patients. Furthermore, it is well known that different types of personnel may cover for different activities in the radiotherapy process and that this varies considerably amongst countries. This was confirmed in our discussion with the experts.

Finally, the experts admitted that not all personnel working on research and development in their home facilities were taken as part of the operational team. Due to all these uncertainties we decided to restrict ourselves to a rough sensitivity analysis in which a personnel reduction of 30% was assumed.
The table 7 below demonstrates the result of this sensitivity calculus.

Table 7. Treatment cost (in € per patient).

	Required reimbursement per technical solution - baseline				**Required reimbursement per technical solution – personnel reduction 30%**			
Type of financing	Combined centre	Two-room carbon ion centre	Two-room proton centre	One-room proton centre	Combined centre	Two-room carbon ion centre	Two-room proton centre	One-room proton centre
Private financing	51,150	32,400	51,200	70,600	47,791	30,040	46,384	64,938
Mixed financing	37,000	24,000	39,900	52,900	33,641	21,640	35,084	47,238
Public financing	27,550	18,400	32,300	40,900	24,191	16,040	22,484	35,238

A decrease of 30% of the personnel requirements impacts on treatment costs for 7 to 9% in case of private financing; for 9 to 12% for mixed financing; and 12 to 25% in case of public financing. This should not come as a surprise because of the higher part of personnel costs in the treatment costs as public financing increases. The impact of a personnel decrease is evidently highest for the two-room and one-room proton centers for exactly the same reason.
Although this impact is certainly not to be neglected, it however does not affect the major conclusions of this study.

In the recent KCE report on medical personnel costs [21], the costs of the radiation oncologists were substantially higher than the salary scales used in our model. That the costs of the medical doctors in reality may be higher than we assumed, may in part counterbalance the above mentioned overestimation of numbers of personnel in our baseline calculations. The impact of using the salaries from the KCE Report 178A [21] is looked at into more detail in the ABC-analysis.

1.e. Activity-Based Costing

I. Description of the ABC model

Activity-Based Costing (ABC) is an advanced cost calculation method that allocates resource costs to products in a stepwise fashion through the intermediary of activity consumption. Hence, the treatment that a patient receives is made up of a series of services (activities) each of which the cost is estimated, typically on the basis of time consumption. By doing so, ABC provides a more accurate calculation of the treatment costs and gives a better insight in the (cost-)structure of a radiotherapy department as a whole, which makes it suitable for evaluating the budgetary impact of new technologies and process changes.
In this project ABC was used in addition to the business model as it allowed to make distinction between the costs of different treatment types (proton vs. carbon ion, paediatric vs. adult) and to model the impact of different operational models and population mixes, with different numbers of paediatric patients and varying fractionation schedules in the carbon ion treatments.

The **resource costs** used in the model are the ones described above: personnel costs, equipment, and building costs, material costs (i.e. medical consumables). Overhead costs have been defined as care-related (e.g. energy costs) or non care related activities (e.g. facility maintenance costs).
Only those personnel costs consumed in the actual treatment process (e.g. wages of radiation oncologists, therapists/nurses, physicists, etc.) were allocated to the treatments using the stepwise ABC methodology. In contrast, the wage costs of maintenance engineers, for example, were reallocated to equipment/building whereas others (general manager, chief physicist, chief medical doctor) were allocated to overhead.
All building and equipment costs were allocated to the treatments using the ABC-methodology. The yearly building and equipment costs were defined differently in accordance with the financing model. In case of public financing only the yearly maintenance costs were used, whereas in private financing an equivalent annual cost was added per type of equipment and building.
The fixed medical consumable cost (as defined in the input parameters section) was directly allocated per patient. Overhead costs, conversely, have been allocated to the products on the basis of the number of fractions.

The different **treatment-related activities** performed within the radiotherapy treatment process have been defined on the basis of literature [3-7, 12, 13] - mainly the ABC model from Leuven for photon therapy [3,4] and the ENLIGHT model for

hadron therapy [5] - and discussions with the expert team on the technical lay-out of the centre (see submodules 1.3 and 1.4).
Six major activity-groups (first patient contact, simulation, target delineation, dose calculation, treatment delivery and end of treatment) have been defined. Each activity-group is further composed by one or more sub-activities.
For each sub-activity the time spent per type of personnel has been defined based on the available data in the literature, supplemented with expert input (table 8).

The number of times the cost of a sub-activity was allocated to the treatment depends on its use in the treatment process. The cost of the activity of treatment delivery ("treatment slot") was allocated to the treatment in line with the number of fractions, that is, each time a fraction is delivered. The cost of activities as "weekly follow-up" or "chart round", on the contrary, was added on a weekly basis, that is, for every five fractions delivered. All other activity costs have been added only once. As it was assumed that general anaesthesia is only used in children, this activity was only added in paediatric patients.

The treatment-related activities used in the model are presented as a clinical workflow in figure 7.

Figure 7: Treatment-related activities within the ABC-model

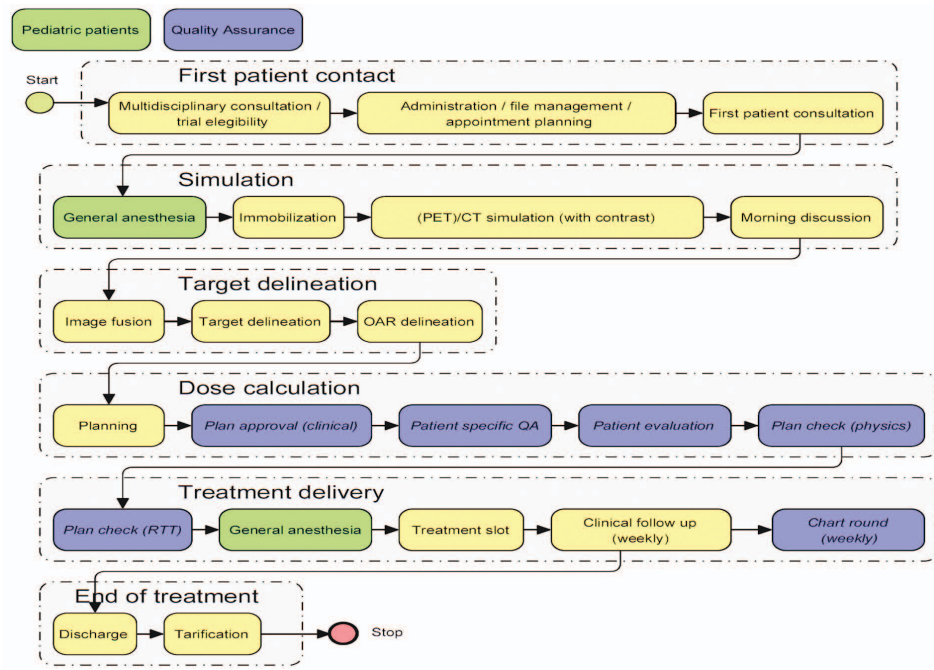


Table 8. Number of personnel (N) and time spent (in minutes) per type of personnel for each sub-activity in the ABC-model.

Activity	Sub activity	Rad Oncol		Radio-grapher		Thera-pists Nurses		Data mana-ger		Physi-cists		Dosi-metrist		Admini-stration		Main-tenance		IT engineers		Traject Nurses	
		N	time	N	time	N	time	N	time	N	time	N	time	N	time	N	time	N	time	N	time
First patient contact																					
	Consult Multidispl.	3	60					1	60	1	60									1	60
	Administration													1	60			1	60		
	Fist patient Consultation	1	60									1	15							1	60
Simulation																					
	Immobilisation	1	20	2	20															1	20
	Simulation	1	30	2	30															1	20
	Anesthesia																			1	30
	Morning	3	15	2	15	2	15			2	15	2	15								
Target delineation																					
	Image fusion									1	10	1	30								
	Target delineation	1	90																		
	OAR delineation	1	30									1	60								
Planning																					
	Planning									1	180	1	180								
	Plan approve	1	30																		
	Patient specific QA									1	30	1	30								
	Evaluation patient									1	120										
	Plan approve									1	30										
Treatment delivery																					
	Plan check RTT					1	15														
	Anesthesia																			1	15
	Treatment slot					3	30/ 45														
	Weekly fup	1	30																	1	30
	Weekly chart	3	15			2	15	2	15	1	15									4	15
End of treatment																					
	Discharge	1	30					1	120					1	30					1	30
	Tarification													1	15						

Apart from the treatment-related activities, **departmental supporting activities** were defined as non-product specific activities performed by personnel of the RT department. They were further subdivided into care-related support (e.g. personnel devoted to management) and non–care-related support (e.g. facility maintenance cost, research), in analogy with the previously published ABC-model for photon therapy [4].
In the basic calculations, the type of equipment (proton vs. carbon ion) and the type of patient (paediatric vs. adult) define the **products**, i.e. the delivered treatments. In the sensitivity analyses, the specificity of the treatment is further defined by the number of fractions and the tumour type.

II. Results

Operational costs and average cost per patient

A formal comparison between the ABC-model and the business model has been made for all technical solutions with two machines, i.e. the combined centre, the two-room carbon ion centre and the two-room proton centre. As demonstrated in table 9, the yearly **operational costs** of both models are perfectly in line with those obtained in the business model (cf. table 4), when for the latter a centre in full operation is assumed and the yearly inflation is disregarded.
The table also shows the **average cost per patient** calculated with ABC. As the yearly inflation is not taken into account in the ABC approach, the average costs are slightly lower than the cost levels per patient calculated in the business model.

Table 9: Yearly operational cost and cost per patient (in €).

	Different technical solutions and types of financing					
	Combined centre		**Two-room carbon ion centre**		**Two-room proton centre**	
	Private	***Public***	***Private***	***Public***	***Private***	***Public***
Patients treated/year	534		760		355	
Yearly operational Cost	24,800,826	12,792,414	22,382,063	12,204,959	16,451,459	10,044,922
Average cost/patient	46,443	23,956	29,450	16,059	46,342	28,296

Given that the calculated operational costs were found the same, as well for the private as for the public approach in all two-room technical solutions, it was concluded that the ABC-model is valid and can be used to calculate the average cost per patient, to further refine the cost per type of treatment and to perform sensitivity analyses.

Cost per patient and per fraction

The **cost per type of treatment and per fraction** is further calculated for the same three technical solutions, in private and public financing, based on the patient numbers defined in the input section (Table 10).

These data demonstrate how the lower fraction numbers in carbon ion treatments compensate for the higher investment costs. Moreover, in line with literature data [12], it is shown that hadron treatments delivered in a combined centre are more expensive than in centers dedicated to protons or carbon ions, especially in case of private financing. This is because economies of scale come into play with higher patient throughput and because lower incremental investment costs are required for a second treatment room similar to the first. Due to the omission of the investment costs, this impact is less pronounced in the public scenarios.

Table 10. Cost per type of treatment and per fraction (in €).

	Different technical solutions and types of financing					
	Combined centre		**Two-room carbon ion centre**		**Two-room proton centre**	
	Private	***Public***	***Private***	***Public***	***Private***	***Public***
Patients treated / year	534		760		355	
Number of fractions	10,485		11,400		10,650	
Cost per patient						
Paediatric (30 fr)	69,701	35,579	NA	NA	61,591	34,878
Adult proton (30 fr)	48,185	26,791	NA	NA	43,842	27,217
Adult c ion (15 fr)	42,749	21,507	29,450	16,059	NA	NA
Cost per fraction						
Paediatric	2,323	1,186	NA	NA	2,053	1,163
Adult proton	1,606	892	NA	NA	1,461	907
Adult c ion	2,850	1,434	1,963	1,071	NA	NA

In comparison with data from literature, the figures for cost per fraction shown in table 10 are relatively high, especially for carbon ion treatments. For a combined centre, an average cost of 1,128 € per fraction has been reported [12]. For carbon ion only centers, treatment costs of 1,028 € and 1,130 € have been calculated [5, 7]. The observed differences can be explained by different parameters used in the models: the use of shorter treatment time per fraction all or not along with a higher utilization of the treatment facility (i.e. more daily working hours). We have however based our assumptions on treatment time slots and patient throughput on the actual operation in the centers of our experts. Moreover, the literature highlights the impact of fractionation schedules [12], which we will analyse in the sensitivity analyses below.

III. Sensitivity analyses

All sensitivity analyses performed with ABC have been carried out for the basic technical solution, i.e. the combined centre with public financing, except for the analysis on personnel productivity.

Operating scenarios and product mix

A first approach was to look at different operating scenarios and product mixes. Following scenarios have been analysed (table 11):

A. A 6-days workweek instead of 5. This scenario results in an increase of 2,250 sessions per year, i.e. 23 additional adult patients on the proton facility (138 patients instead of 115) and 74 extra patients on the carbon ion facility (443 instead of 369) or 97 patients in total.
B. 100 instead of 50 paediatric patients treated on the proton facility. Due to the longer treatment time required for a paediatric patient, fewer adults (40 instead of 115) can be treated on the proton facility, which results in a total decrease of 25 patients per year.
C. Mixed carbon ion patient population (i.e. mixed number of fractions instead of the baseline average of 15 fractions) on the carbon ion facility. The population mix was defined on the basis of the 2008 Cancer Registry data on cancer incidence and delivered radiotherapy treatments. Because in this scenario a lot of patients can be treated with less than 15 fractions, the number of patients at the carbon ion facility increases from 369 to 700 patients a year, or a total increase of 331 patients.

The difference in the yearly operational costs for the different scenarios is related to the fact that a fixed price is added per patient for treatment specific materials.

As can be expected, the average cost per patient comes down in parallel with the increase in number of patients treated on annual basis.
Furthermore, it is well-recognized that machine time – i.e. overall treatment time expressed in daily treatment time multiplied by the number of fractions – is the most important determinant of radiotherapy treatment cost. Our calculations confirm the impact of daily treatment time in the analysis of proton treatments for paediatric patients compared to adult patients, where the shorter time slots in the latter translate into a lower cost per fraction and lower cost per patient.
The impact of fractionation on treatment cost is highlighted in the sensitivity analysis on the number of fractions per carbon ion treatment. Because the

Table 11: Number of patients and cost per patient and fraction (in €).

	Different operational and product mix scenarios			
	Baseline	**Scenario A: 6 days/week**	**Scenario B: 100 paediatric**	**Scenario C: 50 paediatric + mixed carbon**
	Number of patients treated per year			
Paediatric (proton)	50	50	100	50
Adults (proton)	115	138	40	115
Adults (carbon ion)	369	443	369	
Adults 20 fr carbon				20
Adults 16 fr carbon				100
Adults 12 fr carbon				100
Adults 6 fr carbon				30
Adults 4 fr carbon				450
Total	**534**	**631**	**509**	**865**
	Cost per patient			
Paediatric (proton)	35,579	31,394	35,496	33,036
Adults (proton)	26,791	23,310	27,627	24,304
Adults (carbon ion)	21,507	18,271	22,073	
Adults 20 fr carbon				23,733
Adults 16 fr carbon				20,066
Adults 12 fr carbon				16,399
Adults 6 fr carbon				11,026
Adults 4 fr carbon				9,320
Average cost/ patient	**23,956**	**20,413**	**25,088**	**15,136**
	Cost per fraction			
Paediatric (proton)	1,186	1,046	1,173	1,101
Adults (proton)	892	777	921	810
Adults (carbon ion)	1,434	1,218	1,472	
Adults 20 fr carbon				1,187
Adults 16 fr carbon				1,254
Adults 12 fr carbon				1,367
Adults 6 fr carbon				1,838
Adults 4 fr carbon				2,330
Average cost per fraction	**1,220**	**1,048**	**1,312**	**1,292**
Total yearly operational cost	**12,792,414**	**12,880,442**	**12,769,727**	**13,092,797**

preparation cost remains the same regardless of the number of fractions, its relative impact on the cost per fraction increases non-linearly for more hypofractionated schedules. This is in contrast to calculations performed with non-ABC cost-accounting models, which mostly rely on the poor approximation that treatment cost scales linearly with the number of fractions [12]. The gradual increase in cost per fraction in our model however does not preclude the positive effect of lower fraction numbers on the total treatment cost. The potential of hypofractionation, as well in terms of patient convenience as from a financial perspective, is supported by our calculations. Similar conclusions have been drawn in other literature reports on the cost of Hadron therapy [5, 12].

Personnel requirements and impact on treatment cost

The number of personnel used in our baseline calculations were derived from the KCE report vol. 67A [2], but adapted to the number of equipment and crosschecked with literature data and input from the experts. As mentioned before, considerable uncertainty exists in the required number of personnel as well as in their relative involvement in different activities in the radiotherapy process. It is moreover customary in such high-tech environments that part of the staff is specifically hired to perform research. Other funding than the standard reimbursement may therefore cover their salary cost. Finally, different salary scales may also have an impact on the treatment cost.
In the following we have tried to analyse these uncertainties.

Table 12. Impact of different salary scales (in €).

	Different salary scales	
	Baseline (cf. KCE report 67A [2])	**KCE manual (cf. KCE report 178A [21])**
Cost per patient		
Paediatric (proton)	35,579	34,940
Adults (proton)	26,791	26,407
Adults (carbon ion)	21,507	20,795
Average cost/patient	**23,956**	**23,328**
Cost per fraction		
Paediatric (proton)	1,186	1,165
Adults (proton)	892	880
Adults (carbon ion)	1,434	1,386
Average cost/fraction	**1,220**	**1,188**
Total yearly operational cost	**12,792,414**	**12,457,739**

Due to the recent publication of a KCE report on medical personnel costs [21], in which the salary costs of radiation oncologists were substantially higher than those used in our model, whereas those of physicists and dosimetrists were lower, we performed a sensitivity analysis on the impact of different salary scales (table 12).

The impact of the different salary scales is negligible and in the order of magnitude of 2.6% of the yearly operational cost.

Another important question is whether the number of personnel used in our calculations is adequate. As this is a very difficult question to answer based on literature and even in the benchmark with operational departments, we used the ABC-model to give us a hint of the productivity of the personnel in the different technical solutions. More precisely, we evaluated the percentile time consumption of the different types of personnel, based on the activities they perform and on the estimated time per activity (Table 13).

Table 13. Personnel productivity for different technical solutions, operational scenarios and product mixes.

	Different technical solutions, operational scenarios and product mixes					
	Combined centre	**Two-room carbon ion centre**	**Two-room proton centre**	**6 days/ week**	**100 paediatric**	**50 paediatric + mixed carbon**
	Patients per year					
	534	760	355	631	509	865
	Productivity					
Radiation Oncologists (6)	70%	91%	56%	83%	66%	97%
Radiographers (3)	23%	32%	15%	27%	21%	37%
Physicists (6)	45%	62%	32%	53%	43%	70%
Dosimetrists (6)	30%	43%	20%	35%	29%	48%
IT Engineers (4)	106%	109%	103%	107%	106%	111%
Data Managers (2)	78%	100%	62%	91%	73%	106%
Therapists/ Nurses (18)	59%	61%	60%	69%	59%	58%
Administration (5)	11%	16%	7%	13%	10%	18%
Maintenance Engineers (5-7)	98%	98%	98%	98%	98%	98%
Trajectory (4)	77%	85%	69%	89%	78%	91%

° number of FTE used in the model is given between brackets.

The above figures show that, based on the assumptions taken in the ABC model on the activities performed by the different personnel categories and the assumed times per activity (table 8), there is an underutilization of the majority of the personnel. Obviously, the more patients treated in the different scenario's, the more optimal the personnel will be utilized.

One should however take into account that this way of calculating the productivity assumes that each activity can follow immediately after the other, in other words, that there is no idle time between activities. This is of course not realistic and an idealization of the production process. Hence, the figures should be interpreted with caution and not in absolute terms, as they rather give us an idea of which personnel categories could be reduced in numbers without negative impact on the departmental operation. In function of the final organisation and management model of a future centre, these activities will have to be reassessed.

A last analysis was performed to look at the impact on treatment cost of personnel being financed by other sources than the formal reimbursement.
For that, we assumed that radiation oncologists and physicists would devote 50% of their time to research; trajectory, study and data nurses 30%; dosimetrists 20% and radiographers and radiation therapists 10%. If we then assume that this part of the wage costs would be covered for by additional funding, the average cost per patient (for the base case of a combined centre with public financing) would decrease from 23,956 € to 21,818 €. For the different situations of a paediatric patient, an adult patient treated with protons and one treated with carbons, the cost would be 32,854 € (instead of 36,143 €), 24,252 € (instead of 27,541 €) and 19,563 € (instead of 21,187 €) respectively. This represents an impact of on average 10% (8 to 14%).

The assumption of dedicated research time for the personnel moreover means that we move from the first assumption of a centre that is entirely focused on patient care towards an environment where clinical research is accepted as a standard part of the activity. The latter is obviously more in line with the reality of a high-tech environment as a hadron centre. Finally, the assumption of dedicated research time will also alter the calculations on productivity that we presented above.

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2. HEALTH ECONOMIC EVALUATION

2.a. General introduction

As shown in the former paragraphs, radiation treatments delivering protons or carbon ions are more expensive than photon treatments. It is therefore not surprising that, in this tight budgetary climate where novel health care expenses are scrutinized, the question is raised whether the expected improvement in clinical outcome justifies the higher capital and operating costs. Health economic evaluation is a commonly accepted method to examine this trade-off between costs and effects of comparative treatments. Although this approach is slowly gaining acceptance in the field of radiotherapy, literature on the cost-effectiveness of hadron therapy compared to conventional radiotherapy to date is scarce.

This is at least partially related to the limited availability of accurate cost data along with the paucity in long-term outcome data. Yet, there is a need to estimate the cost-effectiveness of hadron therapy over a sufficiently long time-horizon. Indeed, in contrast to the higher costs that are made immediately, the clinical advantages typically only become apparent with time: improved local control is expected to translate in better survival, decreased late toxicity in improved quality of life. If these long-term outcomes are not accurately captured, the incremental benefit of the new treatment strategy – along with the potential cost savings related to the decreased late side effects – will be underestimated.

The most extreme example of this is described for proton treatments of paediatric malignancies, where the typical vulnerability to late side effects together with the long life expectancy of children leads to a double advantage of not only improved survival but also decreased life-long side effects and associated costs, which easily compensate for the higher up-front costs [1].

I. Choice of the clinical indications

Because of the reported favourable balance between costs and outcome of proton treatment in childhood cancer, we decided not to focus on this clinical example in our health economic evaluations. Similarly, we also agreed not to calculate the cost-effectiveness of the other indications 'defined as standard' [2]. It indeed seemed more worthwhile to focus on the 'model' indications. Not only do they represent the vast majority of the population mix of a potential hadron centre, their value for money is also the most uncertain as well as critically related to the balance between expected gain in outcome and patient selection [3-5].

On the basis of the model indications defined in submodule 1, it was decided to select the following target populations for cost-effectiveness analysis of hadron

therapy compared to the current standards of care, all or not including photon radiotherapy:

1. patients with locally advanced pancreatic cancer (carbon ion)
2. patients with locally advanced non-small cell lung cancer (proton)
3. patients with unresectable hepatocellular carcinoma (proton, carbon ion)

The reason for this selection was motivated by the fact that it not only allowed us to evaluate proton as well as carbon ion model indications, but also to investigate the additional impact of the cost on the ranking from high to low as classified in submodule 2 on clinical grounds and expert opinion.

II. Health economic evaluations

Evaluation studies assessing the effectiveness of new treatment options for several types of cancers are important to obtain knowledge on which of those treatment options work best and are thus most effective. Evidence on the effectiveness alone of a treatment is yet insufficient for policy making. There is growing need on health economic research in health care. This is largely caused by increasing budget constraints and rising demands for evidence-based health care spending [6]. Policy makers are facing the problem how to set priorities in the allocation of health care resources to medical or public health interventions [7]. Knowledge on this can be obtained by performing health economic evaluations of treatments or health care interventions providing payers and governments with better insights how to spend the available resources in the most efficient way. Health economic evaluations, performed with the aim to examine the value for money of new interventions compared to standard treatment, measure the extra costs consumed by the new intervention compared to the actual standard, for the additional gain in clinical effect.

In a **cost-effectiveness analysis,** the clinical consequences of a treatment or intervention are ideally measured in terms of “life years (LY) gained”.

In a **cost-utility analysis,** the health effects are expressed in quality-adjusted life years (QALYs) gained. QALYs are calculated by multiplying the utility level for a given disease status (a health-related quality of life weight that ranges between 0 and 1) with the number of years an individual lives with a particular disease. A utility of 1 is equal to full or perfect health, while 0 stands for death [6].

Any treatment option in the comparative analysis is associated with a difference in cost as compared to another treatment option, as well as a difference in LY gained or QALY. When dividing the difference in costs (= incremental costs) of a treatment option versus another one by the difference in LY gained (= incremental LY gained) or QALYs (= incremental QALYs) a ratio is obtained which is called the “incremental cost-effectiveness ratio” (ICER), calculated as:

$$ICER = \frac{COST_I - COST_C}{LY\ gained_I - LY\ gained_C}$$

$$ICER = \frac{COST_I - COST_C}{QALY_I - QALY_C}$$

Where subscript "I" stands for the new treatment (here hadron radiotherapy) and "C" for the current treatment standard. Note that the term "ICER" is used both for cost-effectiveness as cost-utility studies.

A report of the Belgian Health Care Knowledge Centre (KCE) found that, depending on the country, a variety of ICER thresholds exist. In some countries, an "acceptable" ICER range is used, while in other countries no specific threshold is used. In Belgium, a treatment or intervention is generally considered cost-effective if the ICER is below a threshold of +/- 30,000-40,000 €/QALY [8].

With regard to the cost dimension, all current and future costs are taken into account in the analysis: the treatment costs, the costs of disease (either controlled or with progression) and adverse events of radiation treatment.

III. Markov modelling

In order to overcome the described problem of scant long-term clinical trial data, the use of modelling – which allows real-life situations to be represented in a mathematical or a statistical manner – has gained wide acceptance in the field of health economic evaluation. The most frequent approach is Markov modelling, in which data from different sources can be combined and projections of the results over time can be made. In practice this means that differences in effects (in terms of long-term tumour control and/or late side-effects) between hadron therapy and the current standard practice can be collected from different trials and combined with cost data in order to compute the cost-effectiveness of hadron therapy compared to its best comparator.

Markov models are based on a series of *'health states'* that a patient can occupy at a given point in time. The time periods patients remain in these states are called *cycles*. The length of these cycles *(cycle times)* will depend on the nature of the disease and the interventions being evaluated. The speed with which patients move between the health states in the model is determined by a set of *transition probabilities*.

Each state in the model has a cost associated with it and, for cost-utility analysis, a utility value. The time during which the average patient occupies the various states in the model will, when weighted by the relevant cost or utility, be used to calculate the expected costs and outcomes.

The total time a model is allowed to run is called the *time horizon,* which can be a defined as a number of years or as a lifetime time horizon, in which case the Markov process ends when all patients have deceased.

Figure 8 gives a schematic representation of how patients migrate through a Markov model.
In this example, all patients start in full health and migrate to the "illness" and "death" states, represented by the ovals. Each row represents one cycle of a predefined time period. Transitions between the states are represented as arrows between the ovals, and transition probabilities appear beside the arrows on first appearance. The proportion of patients in each state at the beginning of the cycle is shown in the box below the ovals.
At the end of the model, all patients have transited from the "full health" to "death".

IV. Uncertainty in health economic evaluations

Health economic evaluations are characterized by some degree of uncertainty, imprecision, or methodological considerations. Several methods exist to handle uncertainty such as probabilistic sensitivity analysis, one-way sensitivity analysis and scenario analysis [6]. In the current study, one-way sensitivity analysis and scenario analysis were applied. Using one-way sensitivity analysis makes it possible to assess the effects of key parameters on the ICER, by varying them separately. In scenario analysis, a series of scenarios is constructed to evaluate their impact on the cost-effectiveness results.

V. Structure of the performed health economic evaluations

Three health economic evaluations compare hadron therapy to the actual standards of care in patients with locally advanced pancreatic cancer, locally advanced non-small cell lung cancer and unresectable hepatocellular carcinoma. They all follow the same structure:

- Aim of the study:
  - to compare the costs and effects of hadron therapy with currently relevant treatment strategies
- Description of the Markov decision-analytic model:
  - description of the model with graphic representation, and definition of the health states, time cycles, transitions and time horizon
- Input data:
  - clinical data: description of the literature data sources and definition of the transition probabilities in the compared treatment strategies

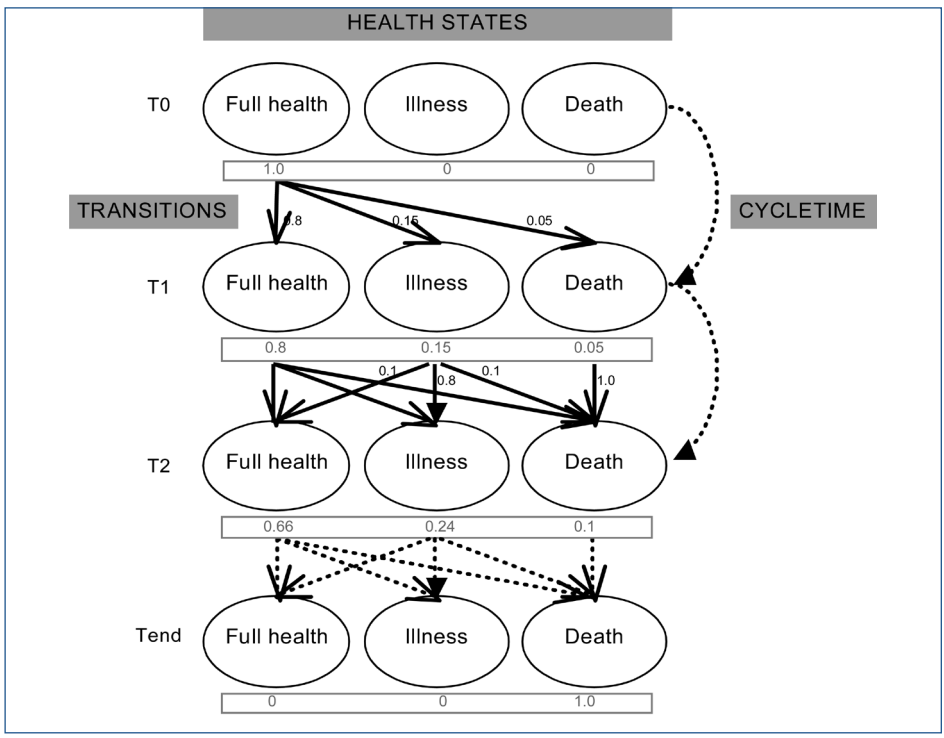
- treatment-related toxicity: definition of the treatment-related toxicity of the compared treatment strategies, based on literature data
- quality of life: definition of the utilities in the different health states, based on literature data
- costs: treatment costs, toxicity costs and follow-up costs of controlled disease, costs at progression, based on submodule 4.1 and literature data

▸ Results:

- overall survival
- incremental cost-effectiveness ratios
- scenario analysis
- one-way sensitivity analysis

A general conclusion, compiling the results of all three health economic evaluations, will be formulated at the end of this chapter.

Figure 8: schematic representation of migration through a Markov model.



2.b. Health economic evaluation of C ion therapy in the treatment of locally advanced pancreatic cancer (LAPC)

I. Aim of the study

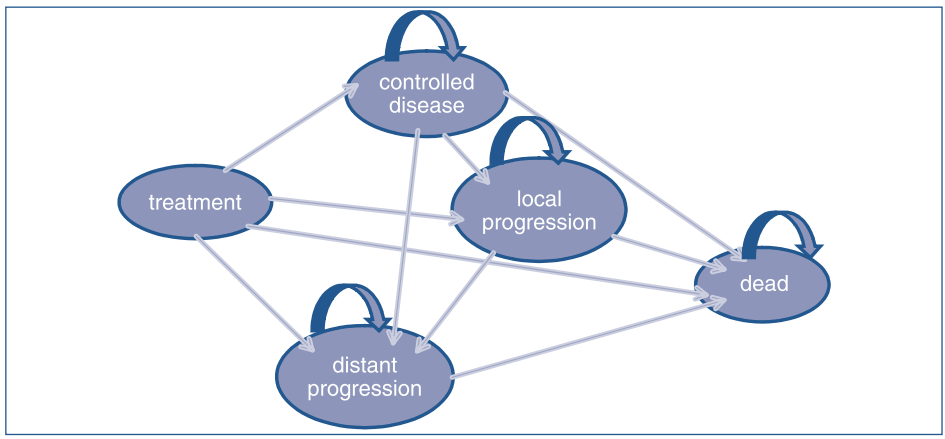
The aim of this study is to assess the potential cost-effectiveness of carbon ion (C ion) radiotherapy for locally advanced pancreatic cancer (LAPC), delivered concurrently with gemcitabine chemotherapy compared to concurrent chemo-radiotherapy with photon radiotherapy – either 3D conformal radiotherapy (3D-CRT), intensity-modulated radiotherapy (IMRT) or stereotactic body radiotherapy (SBRT) – and to the approach with gemcitabine chemotherapy alone.
Hence, the following strategies were compared:

- C ion radiotherapy + gemcitabine versus gemcitabine as single treatment;
- C ion radiotherapy + gemcitabine versus gemcitabine + 3D-CRT;
- C ion radiotherapy + gemcitabine versus gemcitabine + IMRT;
- C ion radiotherapy + gemcitabine versus gemcitabine + SBRT.

II. Description of the Markov decision-analytic model

The Markov decision-analytic model utilized in this study is based on a model published by Murphy et al. [9] and further developed using Microsoft® Excel 2007 (Microsoft Corporation, Redmond, WA, US) to account for the specific context of our study.
Five possible health states were included into the model (Figure 9): treatment, controlled disease, local progression, distant progression, and dead.

Figure 9: Markov model for LAPC.



The time horizon of the model is five years divided in 20 three-month periods ("cycles"). All patients start in the "treatment" state. As the total time of radiotherapy does not exceed a three-month period, it was assumed that all patients could stay in the "treatment" state for a maximum of one three-month cycle. After the first cycle, all patients move to either the states "controlled disease", "local progression", "distant progression", or "dead". Patients in the "controlled disease" state can every cycle either stay in that state or move to one of the two progression states or to the "dead" state. Patients in the "local progression" state can every cycle stay in that state or move to "distant progression" or "dead". Finally, patients in the "distant progression" state can every cycle either stay in that state or die.

III. Clinical data inputs

Standard treatments

The risk of developing local or distant progression or of dying is specified with transition probabilities. The transition probabilities were derived from the literature or based on assumptions when evidence on a certain transition probability was absent. For all four standard treatments (gemcitabine or gemcitabine combined with photon therapy, be it 3D-CRT, SBRT, or IMRT) the transition probabilities from the "treatment" and "controlled disease" states to the "local progression" and "distant progression" could be derived from the literature.

In Loehrer et al. [10] , 74 patients with localized unresectable adenocarcinoma of the pancreas were randomly assigned to receive gemcitabine alone (at 1000 mg/m²/week for weeks 1 to 6, followed by 1 week rest, then again 1000 mg/m²/week for 3 weeks) or gemcitabine (600 mg/m²/week for weeks 1 to 5, then 4 weeks later 1000 mg/m²/week for 3 or 4 weeks) plus 3D-CRT (starting on day 1, total prescribed dose of 50.4 Gy in 1.8 Gy per fraction). No significant differences between the two groups existed with respect to mean age (gemcitabine: 67 years vs. gemcitabine + 3D-CRT: 65.3 years, p=0.48) and sex (p=0.54). The primary endpoint was survival, which was 9.2 months (95% CI, 7.9 to 11.4 months) and 11.1 months (95% CI, 7.6 to 15.5 months) for the mono and combination arm respectively (p=0.017).

In their Markov model, Murphy et al. [9] applied the same transitions for IMRT as for 3D-CRT, which we also did in our model. SBRT data were obtained from a small (n=20) observational study from Goyal et al. [11], hence should be interpreted with caution. The calculated transition probability from "treatment" to "distant progression" is yet comparable with data derived from a study by Mahadevan et al. [12]. In that study, 47 patients were planned to receive gemcitabine and SBRT. SBRT was however sequentially offered to the patients. Mean age of the patients was

younger than that from the participants in the study of Goyal et al. (67 vs. 74 years). The transition probability from "local progression" to "distant progression" could not be obtained directly from the literature. It is clear however from several studies [11,13] that patients, once in local progression, move very fast to metastatic disease. Therefore, we used the following approach for defining the transition probability:

The transition probability from "local progression" to "distant progression" = the transition probability from "controlled disease" to "distant progression" times a "multiplication factor".

This factor was estimated via traditional model calibration techniques in order to obtain a realistic distant metastasis free and overall survival curve (see also further). The probabilities from the "treatment" and "controlled disease" states to the "dead" state (death from other cause than gastro-intestinal cancer) were derived from nationally available data [14], multiplied with a factor accounting for the mortality related to the co-morbidities of the considered patient population. It was assumed that, once a patient entered the "local progression" or "distant progression" state, the risk of dying was independent of the treatment previously received. The mortality probability from "local progression" to "dead" was calculated (weighted average) as the overall mortality probabilities in the case of treatment with gemcitabine, 3D-CRT, IMRT and SBRT minus the mortality probability from "treatment" to "dead" (dead from another cause than gastro-intestinal cancer). The mortality probability from the "distant progression" state to "dead" was derived from a paper by Milano et al. [13] as in that paper the mortality due to metastatic disease was reported. The latter may be overestimated due to the rather old data. Data were calibrated to ensure survival curves mimic the observed and reported survival data in the literature (see further).

An overview of the transition probabilities for the standard treatments can be found in table 14a-d.

Table 14a: Gemcitabine alone, transition probabilities per 3-monthly cycle.

Transition	Probability	Reference
Treatment to local progression	0.266800	Murphy et al. (2007) [15]
Treatment to distant progression	0.266800	Murphy et al. (2007) [15]
Treatment to dead	0.150000	Murphy et al. (2007) [15]
Controlled disease to local progression	0.266800	Murphy et al. (2007) [15]
Controlled disease to distant progression	0.266800	Murphy et al. (2007) [15]
Controlled disease to dead	0.014175	Assumption – NIS (2010) [14]
Local progression to distant progression	0.533641	Calculation of weighted average - adjusted
Local progression to dead	0.360000	Calculation of weighted average - adjusted
Distant progression to dead	0.360000	Milano et al. (2004) [13] – adjusted

Table 14b: Gemcitabine + 3D-CRT, transition probabilities per 3-monthly cycle.

Transition	Probability	Reference
Treatment to local progression	0.195262	Murphy et al. (2007) [15]
Treatment to distant progression	0.097631	Murphy et al. (2007) [15]
Treatment to dead	0.150000	Murphy et al. (2007) [15]
Controlled disease to local progression	0.195262	Murphy et al. (2007) [15]
Controlled disease to distant progression	0.097631	Murphy et al. (2007) [15]
Controlled disease to dead	0.014175	assumption – NIS (2010) [14]
Local progression to distant progression	0.195262	Calculation of weighted average - adjusted
Local progression to dead	0.360000	Calculation of weighted average - adjusted
Distant progression to dead	0.360000	Milano et al. (2004) [13] – adjusted

Table 14c: Gemcitabine + IMRT, transition probabilities per 3-monthly cycle.

Transition	Probability	Reference
Treatment to local progression	0.195262	Murphy et al. (2007) [15]
Treatment to distant progression	0.097631	Murphy et al. (2007) [15]
Treatment to dead	0.150000	Murphy et al. (2007) [15]
Controlled disease to local progression	0.195262	Murphy et al. (2007) [15]
Controlled disease to distant progression	0.097631	Murphy et al. (2007) [15]
Controlled disease to dead	0.014175	Assumption – NIS (2010) [14]
Local progression to distant progression	0.195262	Calculation of weighted average - adjusted
Local progression to dead	0.360000	Calculation of weighted average - adjusted
Distant progression to dead	0.360000	Milano et al. (2004) [13] – adjusted

Table 14d: Gemcitabine + SBRT, transition probabilities per 3-monthly cycle.

Transition	Probability	Reference
Treatment to local progression	0.166738	Goyal et al. (2012) [11]
Treatment to distant progression	0.083369	Goyal et al. (2012) [11]
Treatment to dead	0.100000	Goyal et al. (2012) [11]
Controlled disease to local progression	0.166738	Goyal et al. (2012) [11]
Controlled disease to distant progression	0.083369	Goyal et al. (2012) [11]
Controlled disease to dead	0.014175	Assumption – NIS (2010) [14]
Local progression to distant progression	0.166738	Calculation of weighted average - adjusted
Local progression to dead	0.360000	Calculation of weighted average - adjusted
Distant progression to dead	0.360000	Milano et al. (2004) [13] –adjusted

New treatment: carbon ion radiotherapy

Only limited data was found in the literature regarding the effectiveness of C ion radiotherapy in patients with LAPC. In two papers [16,17], local control rates in patients with LAPC after C ion radiotherapy were reported.

In the review by Okada et al. [16] only 19% loco-regional recurrence was observed after 12 months. There was no evidence that distant recurrence was better than with SBRT. A recent review by Tsjujii & Kamada [17] shows better results for C ion therapy, but for conservative reasons the earlier data were applied in the base case analysis. In the sensitivity analysis (see further) the better effect for C ion radiation therapy, in line with the more up-to-date results of Tsjujii & Kamada were simulated.

For mortality, the same assumptions were applied as with the standard therapies. There are no head to head studies comparing C ions with the other alternatives available. Therefore, some selection bias cannot be ruled out in the current model. It should however be noted that the patients amenable to SBRT treatment are typically those with smaller tumour sizes.

An overview of the transition probabilities for C ion radiation therapy can be found in table 15.

Table 15: Gemcitabine + C ion therapy, transition probabilities per 3-monthly cycle.

Transition	Probability	Reference
Treatment to local progression	0.051317	Okada et al. (2010) [16]
Treatment to distant progression	0.083369	Okada et al. (2010) [16]
Treatment to dead	0.050000	NIS (2010) [14]
Controlled disease to local progression	0.051317	Okada et al.(2010) [16]
Controlled disease to distant progression	0.083369	Okada et al. (2010) [16]
Controlled disease to dead	0.014175	Assumption – NIS (2010) [14]
Local progression to distant progression	0.166738	Calculation of weighted average - adjusted
Local progression to dead	0.360000	Calculation of weighted average
Distant progression to dead	0.360000	Milano et al. (2004) [13]- adjusted

IV. Incidence of treatment-related toxicity

For this model, the occurrence of ≥ grade 3 gastrointestinal toxicity i.e. nausea and vomiting, diarrhoea, and gastrointestinal ulcer were included. The incidences of these toxicities were derived from the literature or based on assumptions when evidence on treatment-related toxicity was absent.

Loehrer et al. [10] reported a 17.1% nausea and vomiting incidence and 2.9% diarrhoea in patients treated with gemcitabine. Murphy et al. [15] found an incidence

of 7% ≥grade 3 nausea and vomiting, and diarrhoea in patients treated with 3D-CRT. Gastrointestinal ulcer was observed in 8% of the patients. The same authors also suggested a strong reduction (-62%) of GI adverse events with IMRT as compared to 3D-CRT. However, since this would lead to very low nausea rates, the reduction for that AE was applied to the gemcitabine rates. Incidence of treatment-related adverse events in patients treated with SBRT was derived from an abstract presented at the "2012 ASCO Annual Meeting" [18]. In that study, an incidence of 15% nausea and 9% gastrointestinal toxicity was found in patients treated with SBRT and gemcitabine. For C ion therapy we assumed a slightly improved toxicity as compared to IMRT.

An overview of the toxicity rates can be found in table 16.

Table 16: Treatment-related toxicity occurrence (≥grade 3)

Treatment	Nausea & vomiting	Diarrhea	GI ulcer	Source
Gemcitabine	17.1%	2.9%		Loehrer et al. (2011) [10]
3D-CRT + gem.	7.0%	7.0%	8.0%	Murphy et al. (2007) [15]
IMRT + gem.	8.8%	2.6%	2.1%	Murphy et al. (2007) [15]
SBRT + gem.	15.0%	3.9%	9.0%	Herman et al. (2012) [18] – assumption
C ion + gem.	8.0%	2.6%	2.0%	Assumptions

GI ulcer: gastrointestinal ulcer; gem.: gemcitabine

V. Quality of life data

Data on health-related quality of life were derived from the paper by Murphy et al. [9]. In that paper, a utility of 0.68 was reported for the "controlled disease" state. A utility decrement of 0.12 was assumed for patients in the "treatment" phase. Utilities for "local progression" and "distant progression" could also be derived from that paper. No utility penalties for adverse events were applied since these could not be found in the literature.

In table 17, an overview of the health utilities used in the model are listed.

Table 17: Overview of health utilities used in the Markov model.

Transition state	**Utility**	**Reference**
Treatment	0.56	Murphy et al. (2012) [9]
Controlled disease	0.68	Murphy et al. (2012) [9]
Local progression	0.62	Murphy et al. (2012) [9]
Distant progression	0.56	Murphy et al. (2012) [9]
Dead	0	Murphy et al. (2012) [9]

VI. Costs

Treatment costs

The treatment costs of the standard treatments 3D-CRT, IMRT and SBRT were obtained from the KCE-report "Innovative radiotherapy techniques, a cost calculation" [19] . In this study, a cost calculation was performed in 10 Belgian radiotherapy institutes using the Activity-Based Costing methodology. The cost of innovative radiotherapy techniques, being introduced in Belgium, was computed, along with that of standard radiotherapy treatments. For LAPC, the average cost of 3D-CRT and IMRT was 4,927 €, for SBRT the calculated cost was 5,341 €.
The cost of C ion radiotherapy was derived from the Activity-Based Costing exercise described in submodule 4.1 of this report. For the base case analysis, the cost of a C ion treatment, delivered in a combined centre with public financing, was used (21,507 €).
As we compared C ion radiotherapy concurrently with chemotherapy to standard radiotherapy techniques concurrently with chemotherapy as well as to chemotherapy alone, the cost of gemcitabine was taken into account for all radiotherapy treatments. It was derived from a report on the cost of gemcitabine in LAPC [20].

This cost was actualized to account for the year 2011 Euros.

Toxicity costs

The literature was searched to retrieve data on the radiation treatment-related toxicity costs included in the Markov model. Annemans et al. [21] found a mean cost of 28.38 € for chemotherapy-induced nausea. The cost of treatment-related diarrhoea was derived from a study by Dranitsaris et al. [22]. In this cost of illness study, a mean cost of 2,559 Can $ for chemotherapy-induced diarrhoea was found in a sample of patients with colorectal cancer. As this cost was reported in Can $, it was first converted into the year 2004 Euros.
No toxicity cost for radiation treatment-related gastrointestinal ulcer was found in the literature. We however did find a mean cost of gastrointestinal ulcer in patients taking NSAIDs. In that paper, a mean cost of 8,375 € was found [23].
It was assumed that acute gastrointestinal toxicity including nausea and vomiting, and diarrhoea only occurred during and shortly after radiation treatment. For this reason, the toxicity cost of these adverse events was only accounted for in the cycles 0 and 1 in the Markov model. Gastrointestinal ulcer is a late treatment-related toxicity event and is accounted for in the Markov model from cycle 2.
Table 18 gives an overview of the costs retrieved from the literature.

Table 18: Overview of the toxicity costs retrieved from the literature.

Toxicity (grade ≥3)	Published costs (€)	Reference
Radiation nausea & vomiting	28.4 (year 2005)	Annemans et al. (2008) [21]
Radiation diarrhea	1,583.0 (year 2004)	Dranitsaris et al. (2005) [22]
Radiation GI ulcer	8,375.0 (year 2003)	Vonkeman et al. (2007) [23]

Next, the costs listed in table 19 were actualized to account for the year 2011 Euros.

Table 19: Overview of the toxicity costs for the Markov model.

Toxicity (grade ≥3)	Costs (€) used in the Markov model
Radiation nausea & vomiting	32.3
Radiation diarrhea	1,840.0
Radiation GI ulcer	9,893.0

Finally, these costs were multiplied by the percentage of patients suffering from the particular toxicity as listed in table 19.

Follow up costs controlled disease

A follow up cost of a CT scan and physician consultation every three months in patients with controlled disease is accounted for in the model. These costs were retrieved from the National Institute for Health and Disability Insurance (NIHDI) (https://www.riziv.fgov.be/webprd/appl/pnomen/Search.aspx?lg=N).

Cost of progression

Costs related to both local and distant progression were derived from the literature. Tingstedt et al. [24] found a mean cost of 5,586 € and 10,154 € in patients with respectively local and distant progression. As this consisted of a cost/month, we tripled this cost to account for the three-month cycles of the Markov model. Next, this cost was actualized to account for the year 2011 Euros.
In table 20a, an overview of the treatment costs, controlled disease costs and costs of disease progression included into the Markov model is provided while table 20b lists the toxicity costs included in the model.

VII. Results

Based on the data inputs, a n overall survival curve was constructed and the cost/QALY and cost/LY gained for gemcitabine + C ion radiotherapy versus the standard treatments (gemcitabine, gemcitabine + 3D-CRT, gemcitabine + IMRT, and

Table 20a: Costs of treatment, controlled disease and progressive disease included into the Markov model.

Cost data input	Cost chemo-therapy (€)	Cost radio-therapy (€)	Total cost/ cycle (€)	Source
Treatment cost				
Gemcitabine + C ion	3,746.0	21,507.0	25,253.0	Van Bochove et al. [20] + Hadron report
Gemcitabine	3,746.0	/	3,746.0	Van Bochove et al. [20]
Gemcitabine + 3D-CRT	3,746.0	4,927.0	8,673.0	Van Bochove et al. [20]+ KCE-report [19]
Gemcitabine + IMRT	3,746.0	4,927.0	8,673.0	Van Bochove et al. [20]+ KCE-report [19]
Gemcitabine + SBRT	3,746.0	5,341.0	5,341.0	Van Bochove et al. [20] + KCE-report [19]
Follow up cost/cycle				
CT-scan			129.6	RIZIV
Consult physician			54.0	RIZIV
Progression cost/cycle				
Local progression			17,559.0	Tingstedt et al. (2011) [24]
				Tingstedt et al. (2011) [24]
Distant progression			31,918.0	

Table 20b: Treatment-related toxicity costs included into the Markov model.

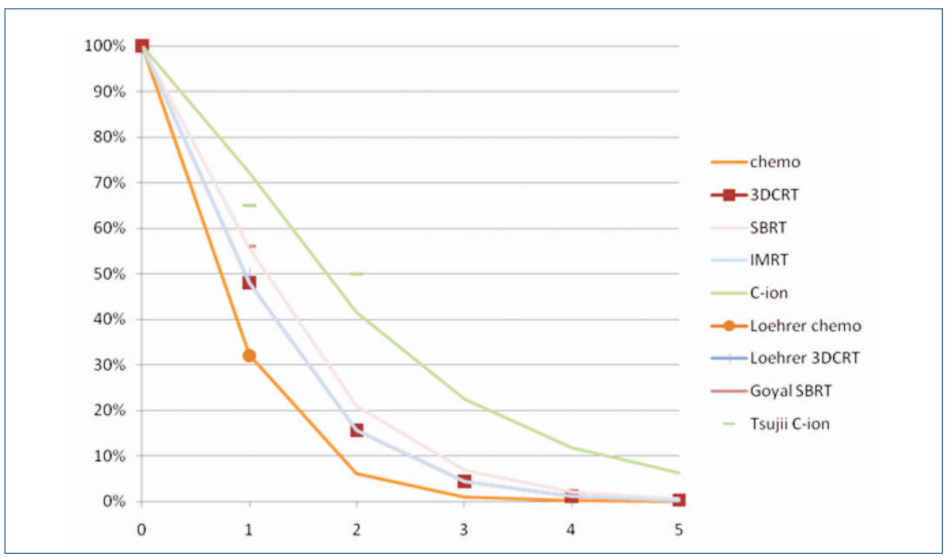
Cost data input	Cost/cycle (€)	Source
Nausea and vomiting		
Gemcitabine	5.5	Annemans et al. (2008) [21], Loehrer et al. (2011) [10]
Gemcitabine + 3D-CRT	2.3	Annemans et al. (2008) [21], Murphy et al. (2007) [15]
Gemcitabine + IMRT	2.9	Annemans et al. (2008) [21], assumption
Gemcitabine + SBRT	4.9	Annemans et al. (2008) [21], Herman et al. (2012) [18]
Gemcitabine + C ion	2.6	Annemans et al. (2008) [21], assumption
Diarrhea		
Gemcitabine	53.4	Dranitsaris et al. (2005) [22], Loehrer et al. (2011) [10]
Gemcitabine + 3D-CRT	128.8	Dranitsaris et al. (2005) [22], Murphy et al.(2007) [15]
Gemcitabine + IMRT	48.3	Dranitsaris et al. (2005) [22], assumption
Gemcitabine + SBRT	72.4	Dranitsaris et al. (2005) [22], assumption
Gemcitabine + C ion	48.3	Dranitsaris et al. (2005) [22], assumption
Gastrointestinal ulcer		
Gemcitabine	-	
Gemcitabine + 3D-CRT	791.5	Murphy et al.(2007) [15], Vonkeman et al. (2007) [23]
Gemcitabine + IMRT	206.1	Vonkeman et al. (2007) [23], assumption
Gemcitabine + SBRT	890.4	Herman et al. (2012) [18], Vonkeman et al. (2007) [23]
Gemcitabine + C ion	197.9	Vonkeman et al. (2007) [23], assumption

gemcitabine + SBRT) was calculated. Scenario analysis and one-way sensitivity analysis was performed to capture the uncertainty associated with some parameters used in the model.

Overall survival

We compared the predicted survival data from the model with the observed and reported survival from the literature [10,11,13,17], as shown in Figure 10.
Loehrer et al. [10] published a one year survival probability of 32% and 50% for chemotherapy and chemotherapy + 3D-CRT respectively. We assumed a same survival for IMRT.
In Goyal et al. [11], the probability of overall survival at 6 and 12 months with SBRT were 89% and 56%.
Tsujii and Kamada [17] reported high survival rates in the high-dose group of C ion therapy, for whom the total dose of 45.6 GyE/12 fractions with the concomitant use of gemcitabine (1000 mg/m²) was given, namely 65% at 1 year and 50% at 2 years. Earlier reports referring to lower doses however did not report better outcomes as compared to SBRT. Because of the uncertainty in survival between different C ion series and because there seems to be a negative selection in C ion series with larger tumour sizes, especially in comparison to SBRT-series that focus on a more favourable patient population with smaller tumours at distance from the critical structures, we believe that the survival curves as presented in figure 10 are a reasonable reflection of the reality.

Figure 10: Overall survival compared to literature data.



Incremental cost-effectiveness ratio results

The tables below give an overview of the ICERs of C ion radiotherapy compared to the existing alternatives for patients with LAPC, in terms of costs/QALY (table 21a) and costs/LY gained (table 21b).

Table 21a: Overview of the Markov model outputs expressed in cost/QALY.

Gemcitabine alone		**C ion + Gemcitabine**			
QALYs	**Cost (€)**	**QALYs**	**Cost (€)**	**delta QALY**	**delta cost (€)**
0.55	65,111	1.26	79,300	0.70	14,189
ICER					**20,189**
Gemcitabine + 3DCRT		**C ion + Gemcitabine**			
QALYs	**Cost (€)**	**QALYs**	**Cost (€)**	**delta QALY**	**delta cost (€)**
0.75	62,243	1.26	79,300	0.51	17,057
ICER					**33,411**
Gemcitabine + IMRT		**C ion + Gemcitabine**			
QALYs	**Cost (€)**	**QALYs**	**Cost (€)**	**delta QALY**	**delta cost (€)**
0.75	60,449	1.26	79,300	0.51	18,851
ICER					**36,926**
Gemcitabine + SBRT		**C ion + Gemcitabine**			
QALYs	**Cost (€)**	**QALYs**	**Cost (€)**	**delta QALY**	**delta cost (€)**
0.86	64,336	1.26	79,300	0.40	14,964
ICER					**37,713**

Table 21b: Overview of the Markov model outputs expressed in cost/LY gained

Gemcitabine alone		**C ion + Gemcitabine**			
LYs	**Cost (€)**	**LYs**	**Cost (€)**	**delta LY**	**delta cost (€)**
0.82	65,111	1.85	79,300	1.02	14,189
ICER					13,855
Gemcitabine + 3DCRT		**C ion + Gemcitabine**			
LYs	**Cost (€)**	**LYs**	**Cost (€)**	**delta LY**	**delta cost (€)**
1.09	62,243	1.85	79,300	0.76	17,057
ICER					**22,562**
Gemcitabine + IMRT		**C ion + Gemcitabine**			
LYs	**Cost (€)**	**LYs**	**Cost (€)**	**delta LY**	**delta cost (€)**
1.09	60,449	1.85	79,300	0.76	18,851
ICER					**24,936**
Gemcitabine + SBRT		**C ion + Gemcitabine**			
LYs	**Cost (€)**	**LYs**	**Cost (€)**	**delta LY**	**delta cost (€)**
1.26	64,336	1.85	79,300	0.59	14,964
ICER					**25,489**

The Markov model outputs expressed in cost/QALY show that C ion radiotherapy is cost-effective compared with the use of gemcitabine as single treatment and borderline cost-effective compared with 3D-CRT, IMRT and SBRT.
When the results are expressed in LYs gained, the outcome is overall better for C ion therapy. This is explained by the fact that the additional survival with C ion therapy is not adjusted downwards for the quality level of the remaining months alive.
The above presented results should be interpreted with caution because of several uncertainties in terms of cost and outcome and possible selection bias e.g. between C ion and SBRT populations. Scenario and sensitivity analysis are therefore required to estimate the impact of different input variables on the final outcomes.

Scenario analysis

As described under the section “Costs”, a C ion cost of 21,507 € was used as base case. This represents the cost of C ion in a combined centre with public funding. Scenario analysis was applied to assess the effect on the ICER if C ion should be provided under other conditions (table 22).
The scenarios tested were the delivery in a combined centre with private financing (42,749 €) and in a C ion only facility, all or not with public or private funding (16,059 € res. 29,450 €). Moreover, the influence of a lower cost due to shorter fractionation schedules, now being tested in prospective trials in Japan, was analysed for the combined public scenario. A decrease in factions from 15 in the base case to 12, 6 and res. 4 decrease the treatment cost to 16,399 €, 11,026 € and res. 9,320 €.

Table 22: Scenario analysis: effects of C ion cost on the ICER (expressed as €/QALY and €/LY).

Variable	C ion vs. Gem.		C ion vs. 3D-CRT		C ion vs. SBRT		C ion vs. IMRT	
	Cost/ QALY	Cost/ LY	Cost/ QALY	Cost/LY	Cost/ QALY	Cost/ LY	Cost/ QALY	Cost/ LY
Combined public (BC)	20,189	13,855	33,411	22,562	37,713	25,489	36,926	24,936
Combined private	50,414	34,597	75,019	50,661	91,250	61,673	78,534	53,034
2-room C ion public	12,437	8,535	22,739	15,356	23,983	16,209	26,254	17,730
2-room C ion private	31,491	21,611	48,969	33,069	57,732	39,020	52,484	35,443
15 fractions (BC)	20,189	13,855	33,411	22,562	37,713	25,489	36,926	24,936
12 fractions	12,921	8,867	23,405	15,806	24,839	16,788	26,920	18,179
6 fractions	5,276	3,621	12,881	8,698	11,298	7,636	16,396	11,072
4 fractions	2,849	1,955	9,539	6,442	6,998	4,730	13,054	8,815

BC = base case

The scenario in which C ion radiotherapy is offered in a combined centre with private funding (which is the correct scenario in a full societal perspective) is obviously not cost-effective (except for the comparator gemcitabine only where a borderline cost-effective result is found if the ICER is expressed as cost/LY). As the cost of C ion therapy delivered in a C ion only centre is lower than in a combined centre, the ICER is somewhat more positive, though remaining not cost-effective in the majority of the cases,

Lowering the number of fractions from 15 to 12, 6 or 4 results in a cost-effective treatment for all four comparators if the ICER is expressed as cost/QALY. If expressed in cost/LY a cost-effective result for all four comparators was already demonstrated for the base case scenario (15 fractions). As a matter of fact, the current standard C ion treatment at NIRS is delivered in 12 fractions, resulting in an overall cost-effective approach.

One-way sensitivity analysis

In order to capture the uncertainty associated with some of the parameters used in the model, one-way sensitivity analysis was performed. This made it possible to assess the effect of each parameter on the ICER (cost/QALY), by varying them separately. One-way sensitivity analyses were performed separately for C ion radiotherapy versus gemcitabine, gemcitabine + 3D-CRT, gemcitabine + IMRT, and gemcitabine + SBRT for the variables “treatment cost”, “progression cost”, “utilities”, and “transition probabilities”.

Table 23a-d give an overview of the one-way sensitivity analyses for C ion radiotherapy versus gemcitabine (table 23a), gemcitabine + 3D-CRT (table 23b), gemcitabine + IMRT (table 23c), and gemcitabine + SBRT (table 23d).

Table 23a: One-way sensitivity analysis: effects on cost/QALY (in €/QALY), gemcitabine vs. C ion therapy + gemcitabine.

Variable	ICER vs. Gemcitabine lower	higher
C ion local progression (70-130%)	17,368	23,078
C ion distant progression (70-130%)	9,852	31,189
Progression dead (26-46%)	14,222	23,289
Cost gemcitabine (130-70%)	18,590	21,788
Cost local progression (70-130%)	19,802	20,576
Cost distant progression (130-70%)	15,921	24,458
Utility controlled disease (130-70%)	15,416	29,243
Utility local progression (130-70%)	20,073	20,307
Utility distant progression (70-130%)	19,883	20,505

Table 23b: One-way sensitivity analysis: effects on cost/QALY (in €/QALY), 3D-CRT + gemcitabine vs. C ion therapy + gemcitabine.

Variable	ICER vs. Gem. + 3D-CRT lower	higher
C ion local progression (70-130%)	27,931	39,558
C ion distant progression (70-130%)	17,211	53,273
Progression dead (26-46%)	31,021	34,200
Cost gem. + 3D-CRT (130-70%)	28,314	38,507
Cost local progression (130-70%)	29,429	37,392
Cost distant progression (70-130%)	28,685	38,136
Utility controlled disease (130-70%)	25,511	48,396
Utility local progression (70-130%)	32,270	34,634
Utility distant progression (130-70%)	32,574	34,292

Table 23c: One-way sensitivity analysis: effects on cost/QALY (in €/QALY), IMRT + gemcitabine vs. C ion therapy + gemcitabine

Variable	ICER vs. Gem. + IMRT lower	higher
C ion local progression (70-130%)	30,985	43,606
C ion distant progression (70-130%)	19,985	57,743
Progression dead (26-46%)	35,391	37,226
Cost gem. + IMRT (130-70%)	31,829	42,022
Cost local progression (130-70%)	32,944	40,907
Cost distant progression (70-130%)	32,200	41,651
Utility controlled disease (130-70%)	28,195	53,488
Utility local progression (70-130%)	35,665	38,278
Utility distant progression (130-70%)	36,001	37,899

Table 23d: One-way sensitivity analysis: effects on cost/QALY (in €/QALY), SBRT + gemcitabine vs. C ion therapy + gemcitabine

Variable	ICER vs. Gem. + SBRT lower	higher
C ion local progression (70-130%)	30,219	46,861
C ion distant progression (70-130%)	16,957	67,061
Progression dead (26-46%)	34,437	38,890
Cost gem. + SBRT (130-70%)	30,843	44,584
Cost local progression (130-70%)	31,599	43,827
Cost distant progression (70-130%)	31,315	44,112
Utility controlled disease (130-70%)	28,527	55,626
Utility local progression (70-130%)	35,722	39,939
Utility distant progression (130-70%)	36,483	39,029

The results of the one-way sensitivity analysis are also shown as Tornado diagrams (Figure 11a-b), as this is useful to point out the critical input parameters to the Markov model.

Figure 11a: One-way sensitivity analysis: effects on cost/QALY, gemcitabine vs. C ion therapy + gemcitabine.

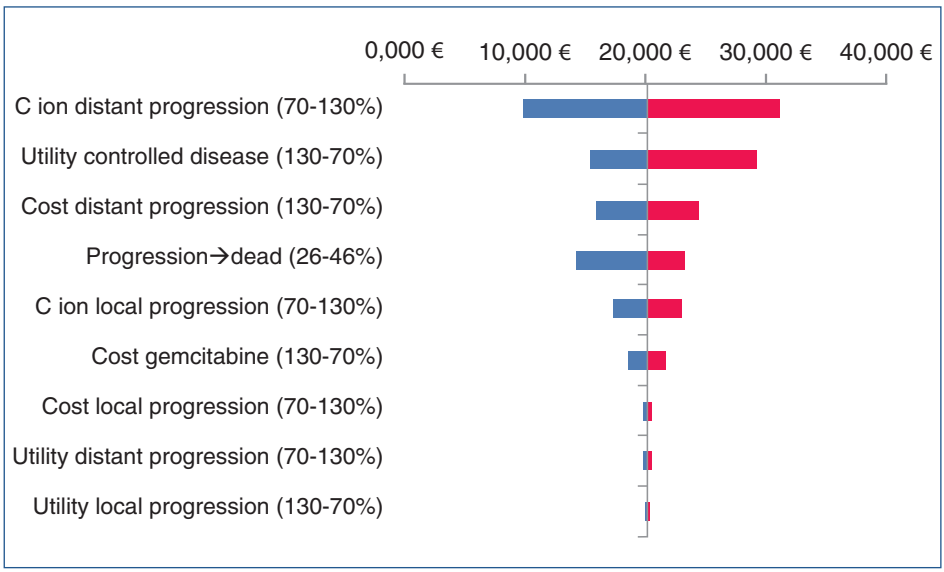


Figure 11b: One-way sensitivity analysis: effects on cost/QALY, 3D-CRT + gemcitabine vs. C ion therapy + gemcitabine.

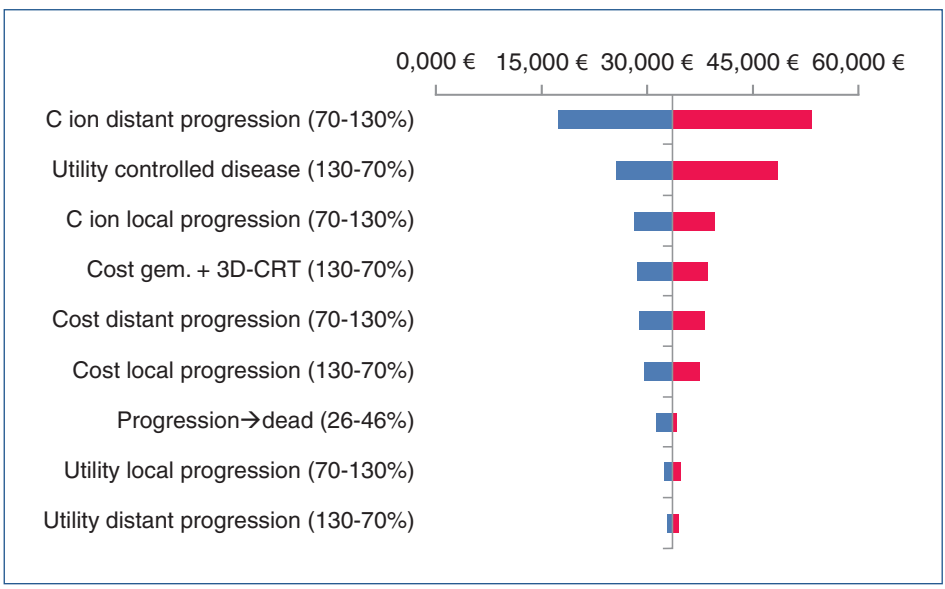


Figure 11c: One-way sensitivity analysis: effects on cost/QALY, IMRT + gemcitabine vs. C ion therapy + gemcitabine.

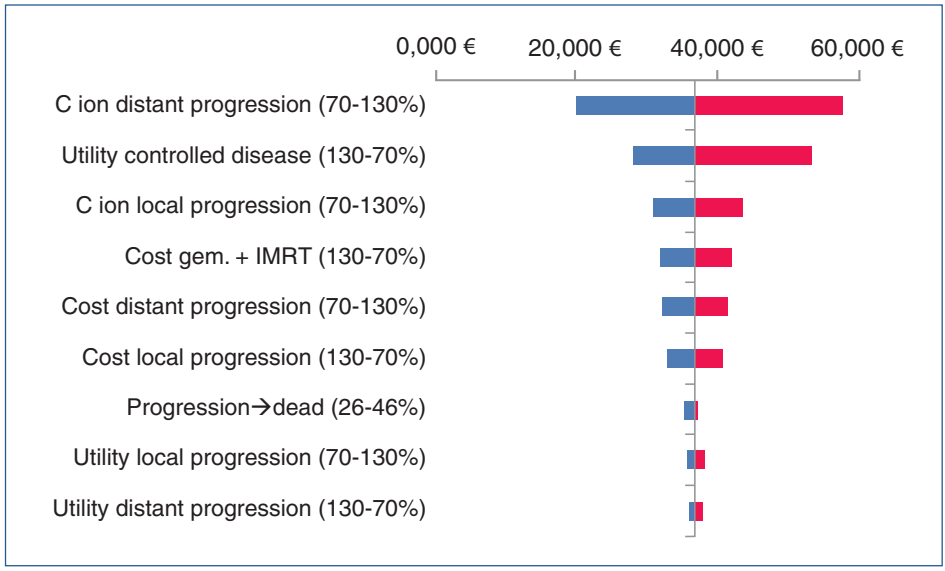
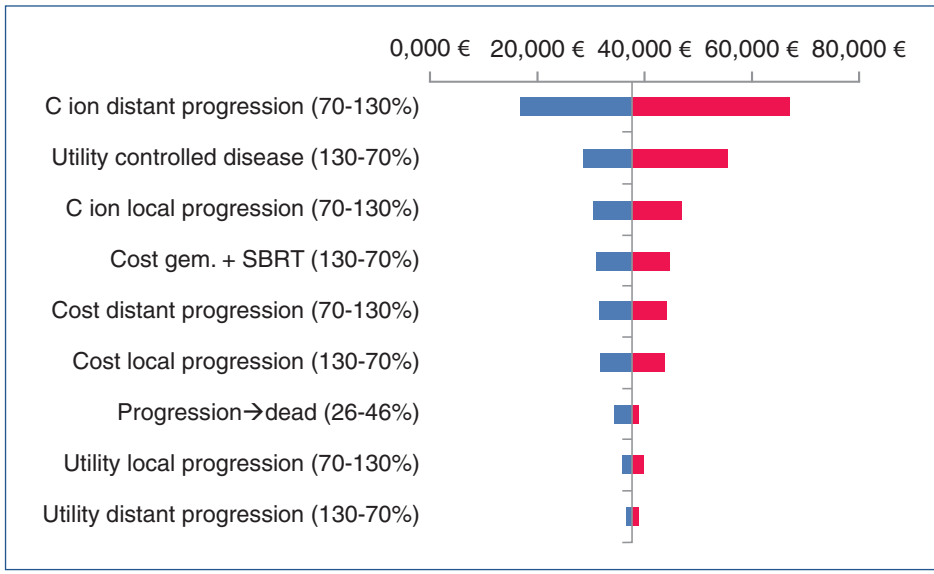


Figure 11d: One-way sensitivity analysis: effects on cost/QALY, SBRT + gemcitabine vs. C ion therapy + gemcitabine.



The results of the one-way sensitivity analyses reveal that the model is most sensitive to the effect of C ion therapy on distant disease control, as well as to the utility (quality of life) of controlled disease. Varying the other input parameters of the model has less influence on the results.

2.c. Health economic evaluation of proton radiotherapy in the treatment of locally advanced non-small cell lung cancer (LA-NSCLC)

I. Aim of the study

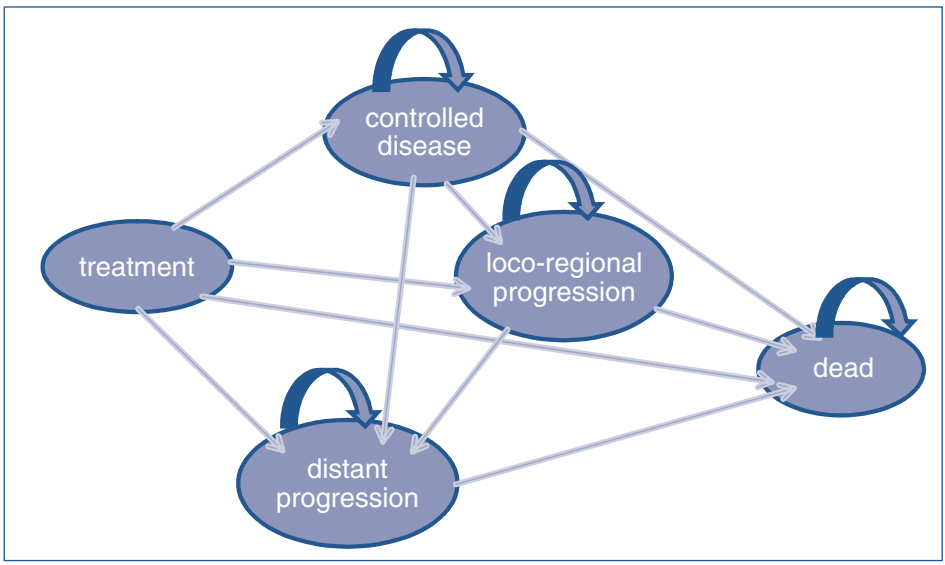
The aim of this study is to assess the potential cost-effectiveness of proton radiotherapy for locally advanced non-small cell lung cancer (LA-NSCLC), delivered concurrently with chemotherapy compared to concurrent chemoradiotherapy delivered with photon radiotherapy.
Hence, the following strategies were compared:

- Chemotherapy + proton radiotherapy vs.
- Chemotherapy + 3D conformal radiation therapy (3D-CRT) and vs.
- Chemotherapy + intensity-modulated radiation therapy (IMRT).

II. Description of the Markov decision-analytic model

The applied Markov decision-analytic model was based on a model published by Sher et al. [25] and further developed using Microsoft® Excel 2007 (Microsoft Corporation, Redmond, WA, US) to account for the specific context of our study. Five possible health states were included into the model (Figure 12): treatment, controlled disease, loco-regional progression, distant progression, and dead.

Figure 12: Markov model for LA-NSCLC.



The time horizon of the model is ten years divided in 40 three-month periods ("cycles"). All patients start in the "treatment" state. As the total time of radiotherapy does not exceed a three-month period, it was assumed that all patients could stay in the "treatment" state for a maximum of one three-month cycle. After the first cycle, all patients move to either of the states "controlled disease", "loco regional progression", "distant progression", or "dead". Patients in the "controlled disease" state can every cycle either stay in that state or move to one of the two progression states or to the "dead" state. Patients in the "loco regional progression" state can every cycle stay in that state or move to "distant progression" or "dead". Finally, patients in the "distant progression" state can every cycle either stay in that state or die.

III. Clinical data inputs

Standard treatments

The risk of loco-regional or distant progression or mortality is specified with transition probabilities. The transition probabilities were derived from the literature or based on assumptions when evidence on a certain transition probability was absent.

For the two standard treatments (3D-CRT and IMRT) the transition probabilities from the "treatment" and "controlled" states to the "loco-regional progression" and "distant progression" state were derived from the literature [26]. In Liao et al., results for a total of 409 NSCLC patients treated at M.D. Anderson Centre in the US were reported. Among these, 318 were treated with 3D-CRT and 91 with IMRT. No differences between the two groups existed concerning sex, chemotherapy agents, nodal stage, mean gross tumour volume, and Karnofsky performance status. Patients in the IMRT-group were older, although not significant (64.4 vs. 62.4 years, $p=0.056$). A higher proportion of patients in the IMRT-group had pre-treatment PET compared with those in the 3D-CRT group (82 vs. 49%, $p<0.0005$). Both groups received a median dose of 63 Gy. Mean follow time was 1.3 years for IMRT and 2.1 years for 3D-CRT. IMRT was tolerated better, but no significant differences were found between 3D-CRT and IMRT for the transition probabilities from "treatment" to "loco-regional progression" nor from "treatment" to "distant progression". However, a better median survival was observed for IMRT (1.4 vs. 0.85 years, $p=0.039$) bearing in mind that the follow-up time for the IMRT group was shorter than that for the 3D-CRT group. It is hypothesized that this difference in survival is related to the decrease in pulmonary toxicity.

The transition probability from "loco-regional progression" to "distant progression" could not be found in the literature. It is clear however from Liao et al. and other

literature that patients with this condition move very fast to metastatic disease. Therefore, we used the following approach:

Transition probability from "loco-regional progression" to "distant progression" = transition probability from "treatment" to "distant progression" times a "multiplication factor".

This factor was estimated via traditional model calibration techniques in order to obtain a realistic distant metastasis free and overall survival curve (see also further).

The probabilities from the "treatment" and "controlled disease" states to the "dead" state (death from other cause than respiratory cancer) were derived from national available data [14], multiplied with a factor accounting for the mortality related to the co-morbidities of the considered patient population. It was assumed that, once a patient entered the "loco-regional progression" or "distant progression" state, the risk of dying was independent of the previous treatment received. The transition probability from "loco-regional progression" to "dead" and from "distant progression" to "dead" was derived from the paper of Sher et al. [25]. An overview of the transition probabilities and sources can be found in tables 24 and 25.

Table 24: Chemotherapy + 3D-CRT, transition probabilities per 3-month Markov cycle.

Transition	Probability	Reference
Treatment to loco-regional progression	0.057058	Liao et al. (2010) [26]
Treatment to distant progression	0.105464	Liao et al. (2010) [26]
Treatment to dead	0.050991	Adjusted from NIS [14], Hoang et al. [27], Liao et al. [26]
Controlled disease to loco-regional progression	0.057058	Liao et al. (2010) [26]
Controlled disease to distant progression	0.105464	Liao et al. (2010) [26]
Controlled disease to dead	0.016572	Adjusted from NIS (2010) [14]
Loco-regional progression to distant progression	0.210927	Adjusted for model calibration
Loco-regional progression to dead	0.259917	Sher et al. (2011) [25]
Distant progression to dead	0.259917	Sher et al. (2011) [25]

Table 25: Chemotherapy + IMRT, transition probabilities per 3-month Markov cycle.

Transition	Probability	Reference
Treatment to loco-regional progression	0.057058	Liao et al. (2010) [26]
Treatment to distant progression	0.105464	Liao et al. (2010) [26]
Treatment to dead	0.050991	Adjusted from NIS [14], Hoang et al. [27], Liao et al. [26]
Controlled disease to loco-regional progression	0.057058	Liao et al. (2010) [26]
Controlled disease to distant progression	0.105464	Liao et al. (2010) [26]
Controlled disease to dead	0.013895	Adjusted from NIS (2010) [14]
Loco-regional progression to distant progression	0.210927	Adjusted for model calibration
Loco-regional progression to dead	0.217931	Adjusted Sher et al. (2011) [25]
Distant progression to dead	0.217931	Adjusted Sher et al. (2011) [25]

Note that the mortality probabilities with IMRT were adjusted downwards to reflect the better survival reported by Liao et al. [26]. This was performed by accounting for the differences in toxicity, as reported further below.

New treatment: proton radiotherapy.

For proton radiotherapy, the transition probabilities from the "treatment" state and the "controlled disease" state to the two "progression" states were derived from Xiang et al. [28]. In this study, 84 unresectable stage III NSCLC patients were treated prospectively with 74 Gy (RBE) proton therapy and concurrent chemotherapy. Median age was 70 and median Karnofsky performance status was 90%. Table 26 shows the patient-, tumour-, and treatment-related variables of the 3 patients groups. Whereas the proton therapy group is an older patient population, with more current smokers and more males, all negative prognostic factors, it treated smaller target volumes on average. Whether this may be related to the more frequent use of PET-scan for treatment planning and may have resulted in the higher delivered median dose, cannot be concluded on the basis of this comparison.

Table 26: patient-, tumour-, and treatment-related variables in the 3D-CRT, IMRT and proton therapy populations.

		Liao		Xiang
		3D-CRT	**IMRT**	**proton**
Number of patients		318	91	84
Male sex		52%	59%	65%
Median age		62.4	64.4	70
KPS	>70%	88%	78%	
	median (range)			90 (70-100)
Current smoker		25%	37%	77%
Histology	Adeno	33	44	34
	squamous	30	26	38
	unspecified	37	30	12
Mean GTV cc ± 1SD		200±188	199±165	
Median GTV cc (range)				96.6 (4-753)
Pre-radiotherapy PETscan		49%	82%	100%
Median radiation dose (range)		63 Gy (50-73)	63 Gy (50-72)	74 Gy(RBE)

The transition probability from "loco-regional progression" to "distant progression" was again based on the earlier explained calibration approach, however this time adjusted proportionally to the lower transition to "distant disease" from Xiang et al. as compared to Liao et al. The probabilities of dying from "loco-regional" or "distant progression" were set equal as those for IMRT.

An overview of the transition probabilities can be found in table 27.

Table 27: Chemotherapy + proton radiotherapy, transition probabilities per 3-month Markov cycle.

Transition	Probability	Reference
Treatment to loco-regional progression	0.012944	Xiang et al. (2012) [28]
Treatment to distant progression	0.074327	Xiang et al. (2012) [28]
Treatment to dead	0.050991	NIS (2010)[14]
Controlled disease to loco-regional progression	0.012944	Xiang et al. (2012) [28]
Controlled disease to distant progression	0.074327	Xiang et al. (2012) [28]
Controlled disease to dead	0.013003	Adjusted from NIS (2010) [14]
Loco-regional progression to distant progression	0.148653	Adjusted for model calibration
Loco-regional progression to dead	0.217931	Adjusted Sher et al. (2011) [25]
Distant progression to dead	0.217931	Adjusted Sher et al. (2011) [25]

A final adaptation of the data above was made to reflect the typically observed phenomenon in LA-NSCLC patients, whereby after 2-3 years the survival curve seems to follow another shape, which has been explained by the fact that a proportion of patients (+/- 15%) do not seem to progress to local or distant lesions. We accounted for this by adjusting the probabilities for progression downwards as from the 9th cycle in the model as to better reflect the observed survival curves in Liao et al. [26], Hoang et al. [27] (both papers reflecting photon therapy) and Xiang et al. [28] (the latter representing proton therapy).

IV. Incidence of treatment-related toxicity

For this model, the occurrence of ≥grade 3 radiation pneumonitis, radiation esophagitis/dysphagia and pulmonary radiation fibrosis was accounted for. The incidences of these toxicities were derived from the literature. Sejpal et al. [29] reported on radiation esophagitis and radiation pneumonitis in a comparative study of the three treatment alternatives in our model. The authors found strongly reduced rates for proton beam therapy. Surprisingly IMRT scored higher than 3D-CRT, which is in contradiction to earlier reports. After discussion with experts, it seemed that the 3D-CRT related incidence of esophagitis was underestimated. The same authors [29] showed an overview of previously reported data, which was applied in our analysis, using a same rate of radiation esophagitis for IMRT and 3D-CRT.
Mazeron et al. [30] found an incidence of late radiation grade III pulmonary fibrosis of 8.3% with 3D-CRT. Jiang et al. [31] reported pulmonary fibrosis with IMRT and Chang et al. [32] with proton therapy. An overview of the toxicity rates can be found in table 28.

Table 28: Treatment-related toxicity occurrence (≥grade 3).

Treatment	Esophagitis	Pneumonitis	Fibrosis	Source
3D-CRT	31.6%	30%	8.3%	Mazeron et al. (2010) [30], Sejpal et al. (2011) [29]
IMRT	31.6%	9%	7.6%	Jiang et al. (2012) [31], Sejpal et al. (2011) [29]
Proton	5%	2%	4.5%	Chang et al. (2011) [32], Sejpal et al. (2011) [29]

V. Quality of life data

Data on health-related quality of life were derived from the literature. Utilities for the transition states "treatment" and "controlled disease" were derived from a cost-utility study in NSCLC patients treated with chemotherapy alone or in combination with Bevacizumab [33]. A utility of 0.46 for the two "progression disease" states was derived from the paper of Sher et al. [25]. Grutters et al. [3] reported utilities for the treatment-related toxicities in stage I NSCLC patients. For all three toxicities included in our model, a utility of 0.46 was observed. Note that these toxicity-related utilities are equal to those of progressive disease. In table 29, an overview of the so-called health utilities used in the Markov model are listed.

Table 29: Overview of health utilities used in the Markov model.

Transition state	Utility	Reference
Treatment	0.58	Goulart & Ramsey (2011) [33]
Controlled disease	0.63	Goulart & Ramsey (2011) [33]
Loco regional progression	0.46	Sher et al. (2011) [25]
Distant progression	0.46	Sher et al. (2011) [25]
Acute pneumonitis ≥grade 3	0.46	Grutters et al. (2010) [3]
Acute esophagitis ≥grade 3	0.46	Grutters et al. (2010) [3]
Irreversible dyspnea ≥grade 3	0.46	Grutters et al. (2010) [3]
Dead	0	

VI. Costs

Treatment costs

The treatment costs of the standard treatments 3D-CRT and IMRT were obtained from the KCE-report "Innovative radiotherapy techniques, a cost calculation" [19]. In this study, a cost calculation was performed in 10 Belgian radiotherapy institutes using the Activity-Based Costing methodology. The cost of innovative radiotherapy techniques, being introduced in Belgium, was computed, along with that of standard radiotherapy treatments. For LA- NSCLC, an average cost of 5,920 € for 3D-CRT and 7,379 € was found.

The cost of proton radiotherapy was derived from the Activity-Based Costing exercise described in submodule 4.1 of this report. For the base case analysis, the cost of a proton treatment, delivered in a combined centre with public financing, was used (26,791 €).
The cost of concurrent chemotherapy was not taken into account as – being the same in all treatments – it becomes irrelevant in the incremental approach.

Toxicity costs

For this model, the costs of grade 3 and 4 radiation pneumonitis, radiation esophagitis and radiation pulmonary fibrosis were included. The toxicity costs were obtained from the literature and from national available data. Most of the data concerning the toxicity costs were retrieved from the paper by Grutters et al. [3].
The cost of radiation pneumonitis included a hospitalization and medication cost. A hospitalization cost/day of 392.23 € was obtained from the National Institute for Health and Disability Insurance (http://www.riziv.fgov.be/care/nl/hospitals/specific-information/prices-day/index.htm). We multiplied this with a mean number of 11 days of hospital stay for patients with acute pneumonitis ≥grade 3 reported by Grutters et al. [3]. The medication cost was also derived from the paper of Grutters et al. [3]. They reported a medication cost/month of 19 €. This cost was multiplied with 1.5 months of medication for pneumonitis. The medication cost was actualized to account for the year 2011 Euros.
The cost of radiation esophagitis included hospitalization, medication and tube feeding costs. The hospitalization cost was calculated by multiplying the hospitalization cost/day (392.23 €, RIZIV) with the number of hospitalization days (n=2) with acute esophagitis [3]. A medication cost/month of 30 € (treatment duration: 1 month) and tube feeding costs (placing/removing the tube: 100 €, 21 days of tube feeding with a daily cost of 18 €) were derived from Grutters et al. [3]. The medication and tube feeding cost were actualized to account for the year 2011 Euros.
Finally, Grutters et al. [3] also reported an annual cost associated with irreversible dyspnoea ≥grade 3 of 1,045 €. This cost was actualized to account for the year 2011 Euros and divided by 4 as the Markov model consisted of three-month cycles. It was assumed that radiation esophagitis and radiation pneumonitis only occurred during and shortly after treatment. For this reason, the toxicity cost for esophagitis was only accounted for in the first cycle (treatment phase) of the Markov model. The toxicity cost of pneumonitis was accounted for in the model in the cycles 0 and 1. Radiation pulmonary fibrosis is a late treatment-related toxicity event and was accounted for in the Markov model from cycle 2.
In table 30, an overview of the retrieved costs from the literature is provided.

Table 30: Overview of the toxicity costs retrieved from the literature.

Toxicity (grade ≥3)	Published costs (year 2007 Euros)	Reference
Radiation esophagitis	1,220	Grutters et al. (2010) [3]
Radiation pneumonitis	3,945	Grutters et al. (2010) [3]
Radiation pulmonary fibrosis	1,045	Grutters et al. (2010) [3]

In table 31, an overview can be found of the costs/toxicity used in the Markov model. These are the costs obtained after replacing the hospital admission cost/day used by Grutters et al. [3] (study conducted in the Netherlands) by a mean hospital admission cost/day for Belgium and after actualizing the costs to account for the year 2011.

Table 31: Overview of the toxicity costs for the Markov model.

Toxicity (grade ≥3)	Costs (€) used in the Markov model
Radiation esophagitis	1,343
Radiation pneumonitis	4,346
Radiation pulmonary fibrosis	287

Finally, these costs were multiplied by the percentage of patients suffering from the particular toxicity (table 32).

Follow up costs controlled disease

A follow up cost of a CT scan and physician consultation every three months in patients with controlled disease is accounted for in the model. These costs were retrieved from the National Institute for Health and Disability Insurance (NIHDI) (https://www.riziv.fgov.be/webprd/appl/pnomen/Search.aspx?lg=N).

Cost of progression

Costs related to disease progression (both loco-regional and distant) were derived from a cost analysis of concurrent versus sequential radio chemotherapy in patients with stage III unresectable NSCLC in France [34].
The following costs were taken into account: (i) protocol costs, (ii) early relapse and follow up costs, (iii) relapse after follow up, and (iv) terminal care costs. An average overall cost per patient of 15,245 € (expressed in 2003 Euros) was found in patients receiving concurrent chemotherapy and radiotherapy.
For our model, the overall cost minus the protocol cost (6,981 €) was used as this cost was already accounted for in the "treatment costs". This resulted in a cost/patient of 8,264 €. Next, this cost was actualized to account for the year 2011 Euros.

The cost is likely an underestimation given the recent use of targeted therapy such as erlotinib.
In table 32, an overview of the costs included in the Markov model is provided.

Table 32: Costs included in the model.

Cost data input	Cost (€)	Source
Treatment cost		
Proton	26,791.0	Interim report Hadron (2012)
3D-CRT	5,920.0	KCE report [19]
IMRT	7,379.0	KCE report [19]
Toxicity cost (cost/cycle)		Grutters et al. (2010) [3] / RIZIV[1]
Esophagitis		
Proton	67.1	
IMRT	424.0	
3D-CRT	424.0	
Pneumonitis		
Proton	86.9	
IMRT	391.0	
3D-CRT	1,304.0	
Fibrosis		
Proton	12.9	
IMRT	21.8	
3D-CRT	23.8	
Follow up cost/cycle		
CT-scan	129.6	RIZIV
Consult physician	54.0	RIZIV
Progression cost /cycle	9,762.0	Vergnenegre et al. (2006) [34]

[1]http://www.riziv.fgov.be/care/nl/hospitals/specific-information/prices-day/index.htm

VII. Results

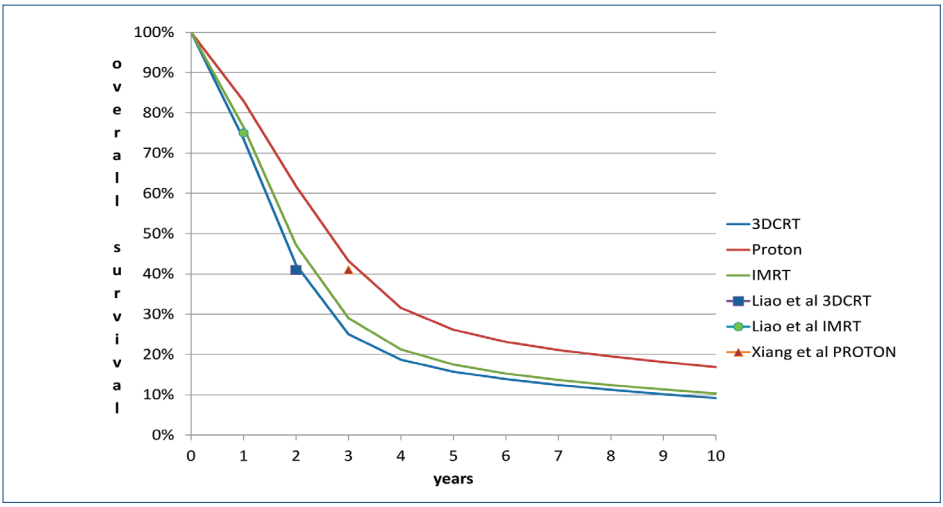
Based on the data inputs, an overall survival curve was constructed and the cost/QALY and cost/LY gained for respectively proton vs. 3D-CRT and proton vs. IMRT was calculated. Scenario analysis and one-way sensitivity analysis was performed to capture the uncertainty associated with some parameters used in the model.

Overall survival

First, the survival curves generated by the model were compared to the literature data in order to ascertain the validity of the constructed model.
In figure 13, the predicted survival curves from the model are compared with

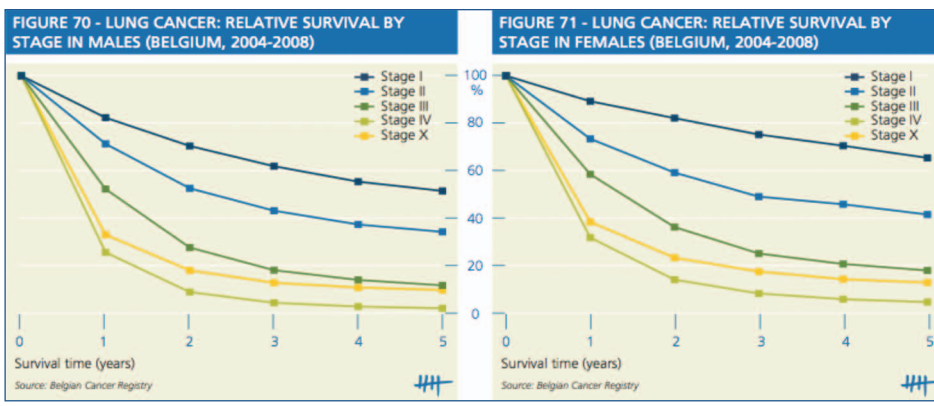
the observed survival data from respectively Liao et al. [26] and Xiang et al. [28]. From the graph, it can be seen that the predicted survival fits well with the published data.

Figure 13a: Overall survival compared to literature data.



Additionally, the curves were also compared to lung cancer survival data from the Belgian Cancer registry, and again, the calculated survival graphs are in line with the Cancer registry data (figure 14).

Figure 14: Relative survival by lung cancer stage in males and females (Belgium, 2004-2008).



Incremental cost-effectiveness ratio results

The tables below give an overview of the ICERs of proton radiotherapy compared to the existing radiotherapy alternatives for patients with LA-NSCLC, in terms of costs/QALY (table 33a) and costs/LY gained (table 33b).

Table 33a: Overview of the Markov model outputs expressed in cost/QALY.

chemotherapy + 3D-CRT		chemotherapy + proton			
QALYs	**Cost (€)**	**QALYs**	**Cost (€)**	**delta QALY**	**delta cost (€)**
1,408	31,200	1,957	50,075	0.549	18,875
ICER					**34,396**
chemotherapy + IMRT		**chemotherapy + proton**			
QALYs	**Cost (€)**	**QALYs**	**Cost (€)**	**delta QALY**	**delta cost (€)**
1,505	35,818	1,957	50,075	0.452	14,257
ICER					**31,541**

Table 33b: Overview of the Markov model outputs expressed in cost/LY gained.

chemotherapy + 3D-CRT		chemotherapy + proton			
LY	**Cost (€)**	**LY**	**Cost (€)**	**delta LY**	**delta cost (€)**
2,363	31,200	3,200	50,075	0.837	18,875
ICER					**22,543**
chemotherapy + IMRT		**chemotherapy + proton**			
LY	**Cost (€)**	**LY**	**Cost (€)**	**delta LY**	**delta cost (€)**
2,536	35,818	3,200	50,075	0.664	14,257
ICER					**21,469**

The Markov model outputs expressed in cost/QALY show that proton therapy is borderline cost-effective versus the current alternatives. When the results are expressed in LY gained, the outcome is overall better for proton therapy showing a cost-effective result versus the standard treatments 3D-CRT and IMRT.

Scenario analysis

As described under the section “costs”, a proton treatment cost of 26,791 € was used as base case. This represents the cost of proton in a combined centre with public funding.

Scenario analysis (table 34) was applied to assess the effect on the ICER if the proton treatment would be provided in a combined centre with private funding (proton treatment cost: 48,185 €) or in a 2-room proton centre with either public or private funding (proton treatment cost 27,217 € and 43,842 € res.).

Table 34: Scenario analysis: effects of proton cost on the ICER (expressed as cost/QALY and cost/LY, both in €).

Variable	Proton vs. 3D-CRT		Proton vs. IMRT	
	Cost/QALY	Cost/LY	Cost/QALY	Cost/LY
Combined centre public	34,396	22,543	31,541	21,469
Combined centre private	73,382	48,095	78,873	53,685
2-room proton centre public	35,172	23,052	32,484	22,110
2-room proton centre private	65,468	42,908	69,265	47,145

The scenarios in which proton radiotherapy is offered with private funding, be it in a combined or in a 2-room proton centre, are clearly not cost-effective. It can thus be concluded that the cost of proton therapy has an important impact on its cost-effectiveness.

One-way sensitivity analysis

In order to capture the uncertainties associated with some of the parameters used in the model, one-way sensitivity analysis was performed. This made it possible to assess the effect of each parameter on the ICER, by varying them separately. One-way sensitivity analyses were separately performed for 3D-CRT (table 35a) and IMRT (table 35b) for the variables of treatment cost, progressive disease cost, toxicity cost, utilities, and transition probabilities.

Table 35a: One-way sensitivity analysis: effects on cost/QALY (in €/QALY), 3D-CRT vs. proton therapy.

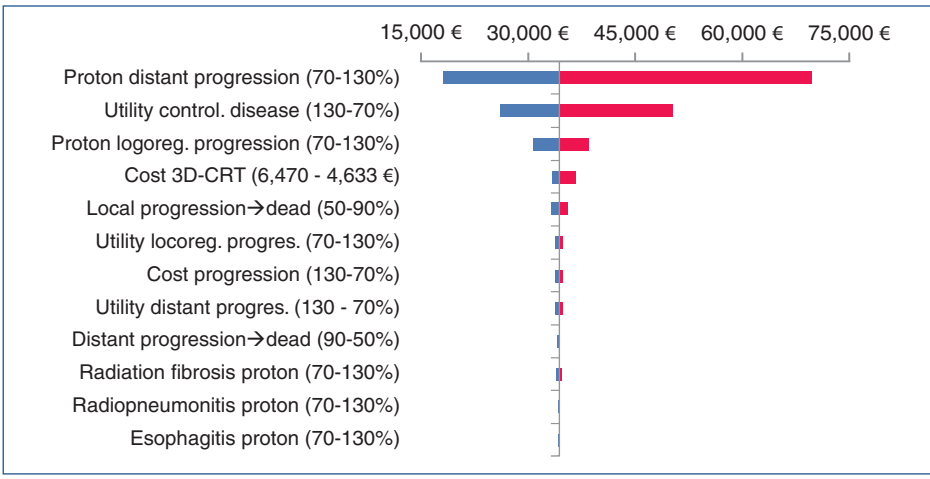
Variable	ICER vs. 3D-CRT	
	lower	higher
Proton loco-regional progression (70-130%)	30,743	38,555
Proton distant progression (70-130%)	18,165	69,746
Local progression dead (50-90%)	33,225	35,584
Distant progression dead (90-50%)	34,118	34,474
Utility controlled disease (130-70%)	26,151	50,235
Utility loco-regional progression (70-130%)	33,807	35,006
Utility distant progression (130-70%)	33,873	34,936
Radiation fibrosis proton (70-130%)	34,011	34,788
Radiopneumonitis proton (70-130%)	34,252	34,541
Esophagitis proton (70-130%)	34,331	34,461
Cost 3D-CRT (6470-4633 €)	33,394	36,741
Cost progression (130-70%)	33,861	34,932

Table 35b: One-way sensitivity analysis: effects on cost/QALY (in €/QALY), IMRT vs. proton therapy.

Variable	ICER vs. IMRT lower	higher
Proton loco-regional progression (70-130%)	27,455	36,368
Proton distant progression (70-130%)	14,382	79,805
Local progression dead (50-90%)	29,893	33,293
Distant progression dead (50-90%)	30,091	32,577
Utility controlled disease (130-70%)	23,525	47,846
Utility loco-regional progression (130-70%)	31,135	31,958
Utility distant progression (70-130%)	29,987	33,266
Radiation fibrosis proton (70-130%)	31,107	31,986
Radiopneumonitis proton (70-130%)	31,378	31,705
Esophagitis proton (70-130%)	31,465	31,617
Cost IMRT (8297-5020 €)	29,510	36,760
Cost progression (130-70%)	28,254	34,828

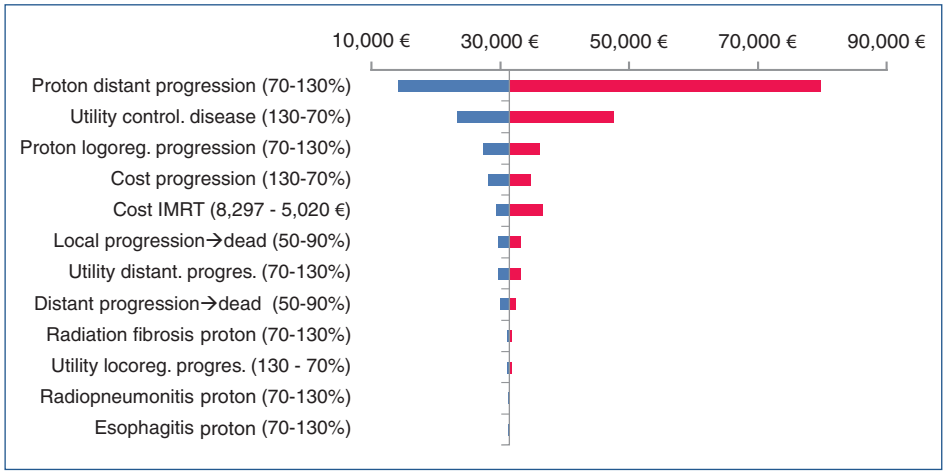
The results of the one-way sensitivity analysis are also shown as Tornado diagrams (Figure 15a-b), as this is useful to point out the critical input parameters to the Markov model.

Figure 15a: One-way sensitivity analysis: effects on cost/QALY, 3D-CRT vs. proton therapy.



The results of the one-way sensitivity analysis reveal that the model is most sensitive to the effect of proton therapy on disease control, loco-regionally as well as at distance, and to the utility (quality of life) of controlled disease. Varying the other input parameters of the model has minor influence on the results.

Figure 15b: One-way sensitivity analysis: effects on cost/QALY, IMRT vs. proton therapy.



2.d. Health economic evaluation of hadron therapy in the treatment of unresectable hepatocellular carcinoma (HCC)

I. Aim of the study

The aim of this study is to assess the potential cost-effectiveness of hadron therapy – C ion as well as proton therapy – in patients with unresectable hepatocellular carcinoma (HCC), compared to percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA).

Possibly, a comparison with other comparators (chemo-embolisation, systemic treatment) would have been a better option, since RFA and PEI are more reserved for smaller and more localized tumours. Yet, this insight was obtained at a later stage in the iterative process with the clinical experts. We were, therefore, not anymore in the possibility to collect relevant input data for these other strategies. Hence, the following strategies were compared:

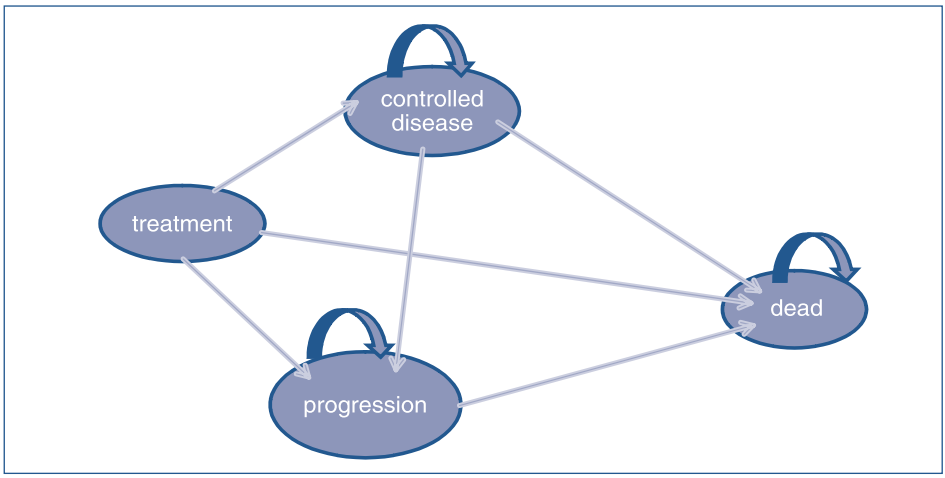
- Percutaneous ethanol injection versus C ion radiotherapy;
- Percutaneous ethanol injection versus proton radiotherapy;
- Radiofrequency ablation versus C ion radiotherapy;
- Radiofrequency ablation versus proton radiotherapy.

II. Description of the Markov decision-analytic model

The applied Markov decision-analytic model was developed based on the findings of published studies assessing the use of PEI and RFA [35], C ion radiotherapy

[36] and proton radiotherapy [37] in patients with HCC. The model was developed using Microsoft® Excel 2007 (Microsoft Corporation, Redmond, WA, US).
Four possible health states were included into the model (Figure 16): treatment, controlled disease, progressive disease and dead.

Figure 16: Markov model for HCC.



The time horizon of the model is ten years divided in 40 three-month periods ("cycles"). All patients start in the "treatment" state. As the total treatment time of PEI, RFA [35,38,39], and hadron therapy [37] did not exceed a three-month period, it was assumed that all patients could stay in the "treatment" state for a maximum of one three-month cycle. After the first cycle, all patients move to the "controlled disease" state, the "progressive disease" state or to the "dead" state. Patients staying in the "controlled disease" state can every cycle either stay in that state or move to the "progressive disease" state or to the "dead" state. Finally, patients in the "progressive disease" state can every cycle stay in that state or move to the "dead" state. Once a patient enters into the "dead" state, no further transitions are possible, as this is the final state.

III. Clinical data inputs

Standard treatments

The risk of developing progressive disease or dying is specified with transition probabilities. The transition probabilities were derived from the literature or based on assumptions when evidence on a certain transition probability was absent.
For the two standard treatments (PEI and RFA), the transition probability from the "treatment" state to the "progressive disease" state could be derived from the

literature [35]. In Shiina et al (2005), 232 patients with Child-Pugh class A or B HCC were randomly assigned to receive PEI (n=114) or RFA (n=118). No significant differences between the two groups existed with respect to the percentage patients aged ≤65/>65 years, sex and tumour characteristics (tumour number, tumour size…). Patients were included with up to 4 lesions, all 3 cm or smaller in size. Median follow up was 3.1 years and 2.9 years in respectively the RFA and PEI group. Overall survival was significantly higher in the RFA group than in the PEI group (p= .01, log-rank test). The 4-year survival in the RFA group was 74% (95% CI: 65%-84%) compared with 57% (95% CI: 45%-71%) in the PEI group. The transition probability from "controlled disease" to "progressive disease" was assumed to be equal to the transition probability from "treatment" to "progressive disease".
The probabilities from the "treatment" and "controlled disease" state to the "dead" state (= death from other cause than gastro-intestinal cancer) were derived from nationally available data [14].
It was assumed that, once a patient entered the "progressive disease" state, the risk of dying was independent of the previous treatment received. The transition probability from the "progressive disease" state to the "dead" state was derived from the literature [40]. In that study, 207 patients treated with RFA were followed up for a median period of 26 months. Mortality rates due to intrahepatic recurrence, local and distant progression were reported and an overall transition probability was calculated (weighted average of the number of patients dying from intrahepatic recurrence, local and distant progression).
An overview of the transition probabilities and sources for the standard treatments can be found in table 36a (PEI) and table 36b (RFA).

Table 36a: Percutaneous ethanol injection, transition probabilities per 3-month Markov cycle.

Transition	Probability	Reference
Treatment to local progression	0.111810	Shiina et al. (2005) [35]
Controlled disease to progression	0.111810	Shiina et al. (2005) [35]
Treatment to dead	0.011033	NIS (2010) [14]
Controlled disease to dead	0.011033	NIS (2010) [14]
Progressive disease to dead	0.112644	Ng et al. (2008) [40]

Table 36b: Radiofrequency ablation, transition probabilities per 3-month Markov cycle.

Transition	Probability	Reference
Treatment to local progression	0.072487	Shiina et al. (2005) [35]
Controlled disease to progression	0.072487	Shiina et al. (2005) [35]
Treatment to dead	0.011033	NIS (2010) [14]
Controlled disease to dead	0.011033	NIS (2010) [14]
Progressive disease to dead	0.112644	Ng et al; (2008) [40]

New treatment: proton and C ion radiotherapy

The transition probability from the "treatment" state to the "progressive disease state" was derived from the literature. In two studies [36,37], data on progression in patients with HCC treated with C ion or proton radiotherapy were reported. In Komatsu et al. [36], a five year overall survival of 36% and 38% was observed in patients treated with C ion therapy and proton therapy respectively.

As for PEI and RFA, the transition probability from "controlled disease" to "progressive disease" was assumed to be equal to the transition probability from "treatment" to "progressive disease".

The same mortality assumptions were applied as with the standard therapies.

Note that no head to head studies comparing C ion and proton radiotherapy with the other alternatives are available. Therefore, selection bias in the patient population cannot be ruled out in the current model. It is known, for example, that patients amenable to PEI typically have tumours smaller than 2cm, and those treated with RFA have tumour sizes below 5 cm, whereas HCCs treated with proton or C ion therapy have a wide variation in size (range between 1 and 12cm).

An overview of the transition probabilities can be found in table 37a (C ion) and in table 37b (Proton).

Table 37a: C ion therapy, transition probabilities per 3-month Markov cycle.

Transition	Probability	Reference
Treatment to local progression	0.061322	Komatsu et al. (2011) [36]
Controlled disease to progression	0.061322	Komatsu et al. (2011) [36]
Treatment to dead	0.011033	NIS (2010) [14]
Controlled disease to dead	0.011033	NIS (2010) [14]
Progressive disease to dead	0.112644	Ng et al. (2008) [40]

Table 37b: proton therapy, transition probabilities per 3-month Markov cycle.

Transition	Probability	Reference
Treatment to local progression	0.058146	Chiba et al. (2005) [37]
Controlled disease to progression	0.058146	Chiba et al. (2005) [37]
Treatment to dead	0.011033	NIS (2010) [14]
Controlled disease to dead	0.011033	NIS (2010) [14]
Progressive disease to dead	0.112644	Ng et al. (2008) [40]

IV. Incidence of treatment-related toxicity

Due to the very limited literature evidence and the low incidence of toxicity, along with the difficult comparability of patient populations amongst different treatment

strategies, and the fact that tumour size and/or location may be an important determinant of toxicity, toxicity data were not included in the model.

V. Quality of life data

Only limited data on health-related quality of life in patients with HCC was found in the literature. The utility for the "controlled disease" state was derived from the paper by Tengs and Wallace [41].

For the "treatment" and "progressive disease" state, the utilities were calculated, as these could not be retrieved from the literature: the utilities used in the Markov NSCLC-model were used as basis to calculate the "treatment" and "progressive disease" utilities for the HCC-model. First, the percentage decline in health-related quality of life between the "controlled disease" state and the "treatment" state (decline: 8%) and between the "controlled disease" state and the "progressive disease" state (decline: 27%) in patients with NSCLC was calculated. Next, the "treatment" and "progressive disease" utilities for the HCC-model were calculated using the percentage decline as calculated for NSCLC.

We are aware that this method may have led to an underestimation or overestimation of the utilities used in the model. For this reason, also calculating the ICER expressed in cost/LY gained was considered as of considerable importance. In table 38, an overview of the health utilities used in the Markov model are listed.

Table 38: Overview of health utilities used in the Markov model.

Transition state	Utility	Source
Treatment	0.45	Assumption
Controlled disease	0.49	Tengs & Wallace (2000) [41]
Progressive disease	0.36	Assumption
Dead	0	

VI. Costs

Treatment costs

The treatment costs of the standard treatments PEI and RFA were derived from the published literature. Data on hospitalization was obtained from the study by Shiina et al. [35]. In that study, the patients (n=118) treated with RFA received on average 2.1 sessions, while those treated with PEI (n=114) received on average 6.4 sessions. We assumed a hospital stay of one day per treatment session as indicated in the paper of Seror et al. [42] resulting in 6 days for PEI and 2 for RFA. These hospitalization days were charged at a mean hospitalization cost/day of 392 € (RIZIV-INAMI).

Treatment costs for RFA and PEI including medical imaging, intervention and materials were, as far as available, retrieved from national data (RIZIV) and from the literature [42]. The treatment costs were retrieved from several sources which may probably have led to an underestimation of the treatment cost. For this reason, the input parameters "RFA cost" and "PEI cost" were considered as key variables to be included in the one-way sensitivity analysis.
An overview of the treatment costs of PEI and RFA can be found in table 39.

Table 39: Overview of PEI and RFA treatment costs.

Cost data input	Unit cost (€)	Cost/cycle (€)	Source
PEI			
Hospitalization	392.2	2,354	RIZIV
Medical imaging	451.7	2,891	RIZIV
Embolization catheter	692.9	4,435	RIZIV
RFA			
Hospitalization	392.2	784	RIZIV
Medical imaging	129.6	272	RIZIV
Medical imaging	451.7	949	RIZIV
Material	404.5	1,018	Seror et al. (2006) [42]

The cost of C ion and proton radiotherapy was derived from the Activity-Based Costing exercise described in submodule 4.1 of this report. A C ion cost of 21,507 € and a proton cost of 26,791 €, applicable for a combined centre with public funding was used as base case.

Follow up costs controlled disease

According to the guidelines of the European Association for the Study of the Liver (EASL) and the European Organisation for Research and Treatment of Cancer (EORTC), follow up strategies for detection of recurrence should include imaging every three months during the first year, and every six months thereafter to complete at least two years. Afterwards, regular ultrasound is recommended every six months [43]. A cost of medical imaging (CT-scan and ultrasound examination) and physician consultation was included as follow up cost into the Markov model.

Cost of progression

The costs of progressive disease were derived from a study comparing the annual costs of hepatitis B and HCC in a selection of four European countries. An annual cost of HCC for France of 9,352 € (year 2001) was used to calculate the cost of progression to be included in our model. The cost was actualized to account for

the year 2011 Euros and divided by four as the cycle-length in the Markov model consisted of three-month periods.
Table 40 gives an overview of the treatment costs, controlled disease costs and costs of disease progression included into the Markov decision-analytic model.

Table 40: Costs included in the model.

Cost data input	Cost (€)	Source
Treatment cost		
C ion	21,507	Interim report Hadron (2012)
Proton	26,791	Interim report Hadron (2012)
PEI	9,679	Shiina et al. (2005) [35], Seror et al. (2006) [42], RIZIV
RFA	3,023	Shiina et al. (2005) [35], Seror et al. (2006) [42], RIZIV
Follow up cost	229	RIZIV
Progressive disease cost	2,852	Brown et al. (2004) [44]

Note that from cycle 4 on, the follow up cost was divided by two as the EASL-EORTC guidelines [43] recommend follow up every six months after the first year following the treatment.

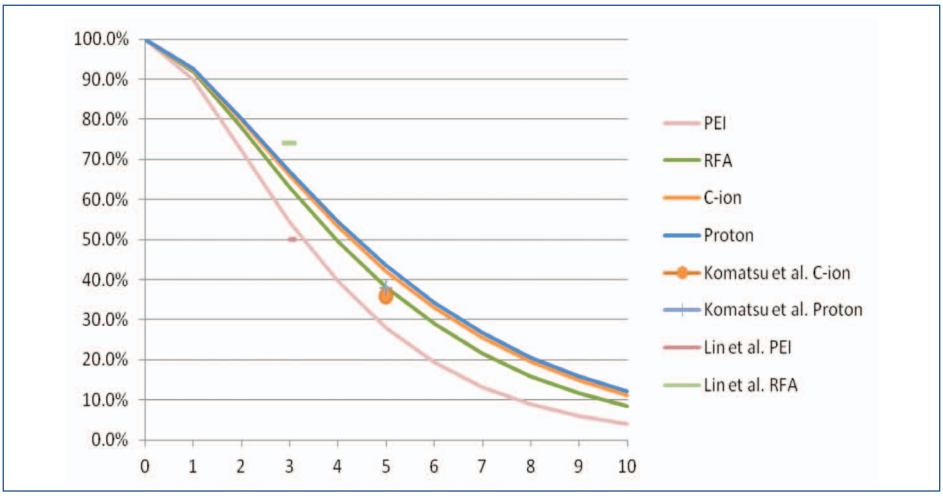
VII. Results

Based on the current data inputs, overall survival curves were constructed and the cost/QALY and cost/LY gained for C ion respectively proton radiotherapy vs. the standard treatments PEI and RFA were calculated. Scenario analysis and one-way sensitivity analysis was performed to capture the uncertainty associated with parameters used in the model.

Overall survival

We compared the predicted survival data from the model with the observed and reported survival from the literature [36,45]. Lin et al. [45] reported a 3-year overall survival of 74% in patients treated with RFA and 50% in those treated with PEI. In Komatsu et al. [36], overall survival at five years was 36% and 38% in patients treated with C ion and proton radiotherapy respectively. If we compare those data with the overall survival data from the model (Figure 17), we believe that these survival curves are a reasonable reflection of the reality.
However, the reconstructed survival curves show how difficult it is to develop a reliable model, based on the limited available literature data. Additionally one should bear in mind the large uncertainty with respect to patient population treated and to the exact tumour characteristics. This underscores that results have to be viewed with extreme caution.

Figure 17: Overall survival compared to literature data.



Incremental cost-effectiveness ratio results

The tables below give an overview of the ICERs of C ion and proton radiotherapy compared to the existing alternatives for patients with unresectable HCC, in terms of costs/QALY (table 41a) and costs/LY gained (table 41b).

Table 41a: Overview of the Markov model outputs expressed in cost/QALY.

PEI		C ion			
QALYs	**Cost (€)**	**QALYs**	**Cost (€)**	**delta QALY**	**delta cost (€)**
1.45	25,443	1.84	34,619	0.39	9,177
ICER					**23,611**
PEI		**Proton**			
QALYs	**Cost (€)**	**QALYs**	**Cost (€)**	**delta QALY**	**delta cost (€)**
1.45	25,443	1.88	39,640	0.43	14,198
ICER					**33,405**
RFA		**C ion**			
QALYs	**Cost (€)**	**QALYs**	**Cost (€)**	**delta QALY**	**delta cost (€)**
1.73	16,940	1.84	34,619	0.11	17,679
ICER					**155,766**
RFA		**Proton**			
QALYs	**Cost (€)**	**QALYs**	**Cost (€)**	**delta QALY**	**delta cost (€)**
1.73	16,940	1.88	39,640	0.15	22,700
ICER					**151,491**

Table 41b: Overview of the Markov model outputs expressed in cost/LY.

PEI		C ion			
LY gained	**Cost (€)**	**LY gained**	**Cost (€)**	**delta LY gained**	**delta cost (€)**
1.67	25,443	2.20	34,619	0.52	9,177
ICER					**17,586**
PEI		**Proton**			
LY gained	**Cost (€)**	**LY gained**	**Cost (€)**	**delta LY gained**	**delta cost (€)**
1.67	25,443	2.25	39,640	0.57	14,198
ICER					**24,822**
RFA		**C ion**			
LY gained	**Cost (€)**	**LY gained**	**Cost (€)**	**delta LY gained**	**delta cost (€)**
2.04	16,940	2.20	34,619	0.16	17,679
ICER					**113,843**
RFA		**Proton**			
LY gained	**Cost (€)**	**LY gained**	**Cost (€)**	**delta LY gained**	**delta cost (€)**
2.04	16,940	2.25	39,640	0.21	22,700
ICER					**110,492**

The Markov model outputs expressed as cost/QALY show that C ion and proton radiotherapy is borderline cost-effective compared with PEI, but not at all cost-effective compared with RFA. When the results are expressed in cost/LY, the outcome is overall better for C ion and proton radiotherapy. Nevertheless, comparing C ion and proton therapy with RFA shows that it remains not cost-effective.
The results presented above need to be interpreted with caution because of several uncertainties, and possible selection bias. Scenario and sensitivity analyses are therefore required in order to estimate the impact of different input variables on the outcomes.

Scenario analysis

As described under the section “Costs”, a C ion cost of 21,507 € and a proton cost of 26,791 € was used as base case. This represents the cost of C ion and proton radiotherapy provided in a combined centre with public funding.
Scenario analysis was applied to assess the effects on the ICER if these therapies would be provided in a combined centre with private funding (42,749 € for C ion and 48,185 € for proton radiotherapy). Alternatively, the costs in the 2-room technical scenarios were analysed: for C ion this results in a cost of 16,059 € and 29,450 € for the public approach vs. the private approach; for proton therapy the costs are 27,217 € and 43,842 € res. (table 42 and 43).

Table 42: Scenario analysis: effects of C ion radiotherapy cost on the ICER (expressed as cost/QALY and cost/LY, both in €).

Variable	C ion vs. PEI		C ion vs. RFA	
	cost/QALY	cost/LY	cost/QALY	cost/LY
combined-public (BC)	23,611	17,586	155,766	113,843
combined-private C ion (42,749 €)	78,264	58,293	342,923	250,628
2-room C ion public (16,059 €)	9,594	7,145	107,765	78,761
2-room C ion private (29,450 €)	44,047	32,807	225,750	164,991

Table 43: Scenario analysis: effects of proton therapy cost on the ICER (expressed as cost/QALY and cost/LY, both in €).

Variable	1,2 mm		Proton vs. RFA	
	cost/QALY	cost/LY	cost/QALY	cost/LY
combined-public (BC)	33,405	24,822	151,491	110,492
combined-private proton (48,185 €)	83,743	62,226	294,266	214,626
2-room proton public (27,217 €)	34,408	25,567	154,334	112,565
2-room proton private (43,842 €)	73,524	54,633	265,282	193,487

As could be expected, scenario analysis of RFA versus C ion and proton radiotherapy did not result in cost-effective outcomes. In comparison with PEI, the scenario in which C ion and proton is offered in a combined centre with private funding is not cost-effective. Contrary, a 2-room C ion centre with public funding is cost-effective vs PEI, while a 2-room proton centre with public funding can be considered as borderline cost-effective.

One-way sensitivity analysis

In order to capture the uncertainty associated with the parameters used in the model, one-way sensitivity analysis was performed. This made it possible to assess the effect of each parameter on the ICER (cost/QALY), by varying them separately (table 44a and b). Only the comparison of both hadron approaches compared to PEI were analysed, as the results of the base case analyses for RFA made it extremely improbable that by varying the parameters a cost-effective result can be expected.

Table 44a: One-way sensitivity analysis, effects on cost/QALY (in €/QALY), C ion vs. PEI.

Variable	ICER C ion vs. PEI	
	lower	higher
C ion progression (70-130%)	11,716	49,191
Progressive disease dead (28-48%)	23,386	23,825
Utility controlled disease (130-70%)	18,162	33,730
Utility progressive disease (70-130%)	21,929	25,572
Cost PEI (130-70%)	16,140	31,082
Cost progressive disease (130-70%)	21,260	25,962

Table 44b: One-way sensitivity analysis, effects on cost/QALY (in €/QALY), proton vs. PEI.

Variable	ICER proton vs. PEI	
	lower	higher
Proton progression (70-130%)	18,641	62,566
Progressive disease dead (48-28%)	33,022	34,268
Utility controlled disease (130-70%)	25,696	47,722
Utility progressive disease (70-130%)	31,001	36,213
Cost PEI (130-70%)	26,573	40,237
Cost progressive disease (130-70%)	31,044	35,766

The results of the one-way sensitivity analysis are also shown as Tornado diagrams (Figure 18a-b), as this is useful to point out the critical input parameters to the Markov model.

Figure 18a: One-way sensitivity analysis: effects on cost/QALY, C ion vs. PEI.

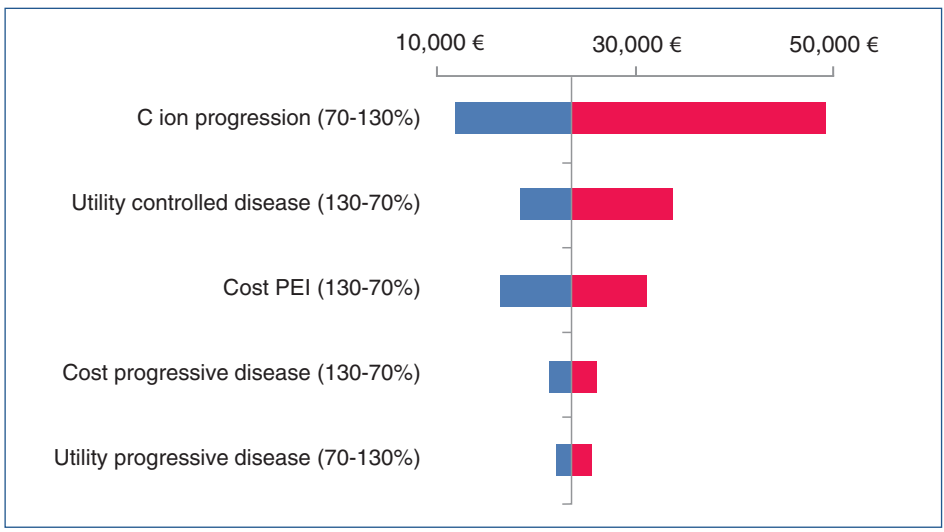
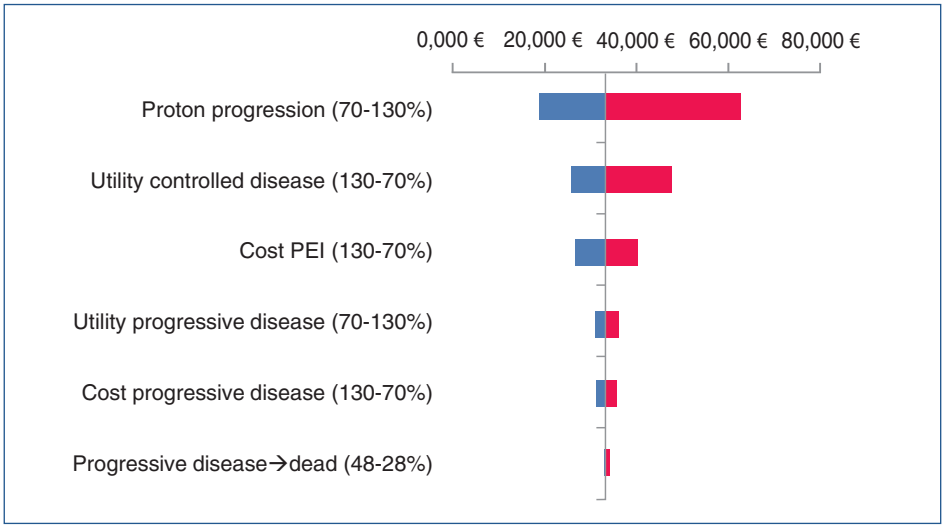


Figure 18b: One-way sensitivity analysis: effects on cost/QALY, proton vs. PEI.



The results of the one-way sensitivity analysis show that the model is most sensitive to the effect of hadron therapy on disease control and to the utility (quality of life) of controlled disease. Varying the other input parameters of the model are having only minor influence on the results.

2.e. Discussion of the health economic evaluations

The decision to select model indications for the health economic evaluation of hadron therapy compared to current standard practice has been motivated by the fact that they represent the vast majority of the population mix of a potential hadron centre and that their value for money is even more uncertain than that of standard indications.

Based on the clinical ranking made in submodule 1, indications being more or less promising for adoption of hadron therapy in standard care were selected: carbon ion therapy for locally advanced pancreatic cancer (LAPC), proton therapy in stage III NSCLC and hadron therapy, proton and C ion, for inoperable hepatocellular carcinoma. This selection not only allowed us to evaluate proton as well as carbon ion model indications, but also to investigate the additional impact of the cost on the ranking from high to low potential which was defined on clinical grounds and expert opinion. So far, the ICERs seem to support the clinical ranking.

In the *base case calculations* with an ICER expressed in *cost/QALY*, all indications are borderline cost-effective, that is around 30,000 €/QALY. This result compares favourably to the average result of novel cancer drugs that have been reimbursed during the last 5 years by the RIZIV-INAMI (45). Exception to this borderline

cost-effectiveness is seen for LAPC, where C ion therapy is clearly cost-effective compared to gemcitabine as single treatment modality, and for unresectable hepatocellular carcinoma, where nor C ion nor proton therapy was found cost-effective compared to radiofrequency ablation, in RFA eligible patients. For all indications a gain in QALYs was found, be it at increased costs.

When the results are expressed in *cost/LY*, the outcome becomes better for all indications. This is explained by the fact that the additional survival with hadron therapy is not adjusted downwards for the quality level of the remaining months alive. In this situation, all analysed comparisons become cost-effective (in the order of magnitude of 20,000 €/LY gained), except for hadron therapy in HCC that remains inferior to RFA in terms of value for money.

The base case analyses have all been performed with the hadron therapy cost obtained from ABC in a combined centre with public financing. As it was found that the results of the health economic evaluations were critically dependent of the hadron treatment cost, *scenario analyses* were performed to evaluate the impact of the initial hadron cost. From these analyses it became clear that, for all three clinical indications, hadron therapy in the extreme financial setting of a private environment exceeds the commonly used Belgian threshold for cost-effective care.

As could be expected, the scenario analysis that tested the impact of hypofractionation in C ion treatment for LAPC confirmed the positive effect on the treatment cost, hence on the ICER, of shortening the total treatment time.

In order to capture the uncertainty associated with the other model parameters, *one-way sensitivity analysis* was performed. By varying the parameters used in the model separately, it is made possible to assess their individual effect on the ICER. In all three tested clinical situations the models were found to be most sensitive to the effect of hadron therapy on disease control, locally and/or at distance, as well as to the utility (quality of life) of controlled disease. This underscores the need for further clinical evaluation of hadron therapy with regard to its impact on controlling the disease while reducing late side effects and maintaining a good quality of life.

Although the analyses performed give a first hint into the potential cost-effectiveness of hadron therapy, they equally highlight the weaknesses of these models that are but as trustful as the data that are used to feed them. It therefore becomes clear how important it is to further refine these data, costs as well as outcomes, before we can draw firm conclusions about the cost-effectiveness of C ion or proton therapy compared to the actual standard treatments.

In this context some weaknesses of the models deserve attention. First of all, we calculated the cost of hadron therapy in the preferred technical scenario – a combined centre – in the assumption that public financing would be applied.

The latter was motivated by the fact that the cost calculations withheld public financing as the only viable solution in the European context. Although we do believe that financing a highly research-driven environment should not necessarily follow the same rules as standard patient care, from a methodological point of view it would be more correct to use similar cost inputs for hadron treatments as for the comparator photon treatments. There are inherent differences in cost allocation procedures between the ABC model in this project and the KCE reports 198C [19], but based on an analysis of the KCE (personal communication during the last meeting of the Steering Committee), the best comparator for the photon KCE costs is assumed to be the hadron costs in a mixed financing environment. This issue will have to be addressed in future analyses.

For *some transition states* in the models no data could be derived from the literature. For these transition probabilities assumptions had to be applied. It is thus possible that this may have led to an underestimation or overestimation of these transition probabilities. The problem was especially seen in the HCC model, where survival curves reconstructed through the model could not completely mimic reality.

In none of the analysed indications, *head to head comparisons* of the treatment alternatives are available in the literature. Hence, data in the models were derived from different studies, often performed in other countries, health care systems and populations. At best, as shown in the LA-NSCLC model, data could be obtained from one large centre providing data about all treatment strategies used in the comparison. Even then it became clear that differences in tumour-, patient-, and treatment-related characteristics may have an impact on the result.

This problem of the *heterogeneity of patient populations* amongst different treatments, and also of patients treated with hadron therapy, became all the more prominent in the LAPC and HCC models. In LAPC, literature data suggest a negative patient selection in C ion series treating larger tumour sizes, in comparison to SBRT-series that focus on a more favourable patient population with smaller tumours at distance from critical structures. Similarly, for HCC it was found extremely challenging to select the appropriate comparator for proton or C ion therapy. In analogy with the above, only smaller tumours seem to be amenable for the comparator treatments defined in the model (PEI and RFA), whereas hadron therapy treats a much wider range of tumour sizes. Because of these inconsistencies in compared patient subgroups, the results of the analyses should be interpreted with caution.

Hence, apart from fine-tuning the cost and outcome parameters in the models, especially the gastro-intestinal models urge for a better definition of the comparators and their standard treatments. Further work will therefore have to focus on separating out patients subsets treated with different standard treatment modalities in order to compare these with the clinical outcome of hadron therapy in those specific patient subgroups.

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3. CONCLUSIONS

3.a. cost calculations and the financial analysis

I. Concerning the financing model

Private financing requires high reimbursement rates in order to make the centre sustainable. These proved to be very high in a European or Japanese context, where hadron treatments are typically reimbursed at approximately 18,000 to 40,000 €/patient, which is the direct consequence of the fact that all of these European projects have been publicly financed. The most dominant factors for the cost of a patient treatment appear to be the annuities on the initial investment capital on the one hand and sum of personnel and maintenance costs on the other. Both are at approximately the same level and together make up more than 90 % of the total treatment costs. The fact that in Europe and Japan the initial investment costs are often taken out of the calculation of treatment costs explains why reimbursement rates are about half of what we calculated as full costs.
Moreover, changes in the assumptions in terms of commissioning period and available interest rate can have a major impact on the results, as has been demonstrated in the sensitivity analysis. They reinforce the belief that public financing is an essential requirement.

On the basis of these data it seems unlikely that private or even mixed financing will turn out feasible, with **public financing** seemingly the only viable solution in the Belgian context. Hence, this approach has been used as the base case for the further calculations in the ABC-model.

II. Concerning viable technical solutions with public financing perspectives

A one-room proton centre, even when publically financed, still necessitates high reimbursement rates compared to the other technical alternatives. This is due to the fact that this type of centre has a large proportion of paediatric patients that demand high number of fractions and longer treatment times than adult patients. Hence, fewer patients can be treated and the costs of investment, personnel, energy and maintenance have to be shared among fewer treatments.
In a combined centre with public financing treatment costs come into the range of the European reimbursement rates.
The two-room carbon ion centre turns out even more attractive since the potentially high number of adult patients brings the reimbursement rates further down. The drawback is that no paediatric patients will be treated in such a centre. It could however be an opportunistic - yet economically sound - alternative to send the Belgian paediatric patients abroad and treat only adults locally.
The treatment costs for a two-room proton centre are slightly higher than those of a combined centre when privately financed. Nevertheless it should be born in mind that this is a solution where the potential patient population remains restricted to paediatric indications and very specific adult cancer treatments. The potential field of its application is more limited in comparison to carbon treatments. This is not the most recommended technical solution because probably not the option with the most promising long term potential.

3.b. Health economic evaluation

The choice of indications for economic evaluation was motivated by the fact that they represent the vast majority of the population mix of a potential hadron centre and that their value for money is more uncertain than that of standard indications. From 7 model indications eligible for hadron therapy (see II) the following three were selected as representative for a further cost effectiveness analysis: locally advanced pancreatic cancer; locally advanced non-small cell lung cancers and unresectable hepatocellular carcinoma.
For details on the data, on the methodology and the outcome of this cost effectiveness study, we refer to the main report. Here we will only sketch the general

results of the efforts made and the further steps to be taken.

Overall the health economic evaluations show that hadron therapy is borderline cost-effective compared to the best available treatments, with a cost-effectiveness ratio of around 30,000 € to gain one Quality Adjusted Life Year (QALY) in most indications. In terms of cost per Life Year (LY) gained calculations show outcomes of approximately 20,000 € per year gained by hadron therapy.

The above results were obtained in the context of public financing. The scenario analyses exposed that with private financing the costs of hadron therapy would exceed a cost-effectiveness threshold of 30,000 €-40,000 €/QALY, which is often referred to, be it not officially, in Belgium.

Due to different reasons no decisive conclusions can be drawn from these economic evaluations.

Analyses showed high sensitivity of the results to the costs and to the effect of hadron therapy on disease control and quality of life. Fine-tuning these cost and outcome parameters requires more details of the technical scenario and related investment costs as well as further clinical research.

Furthermore, a major obstacle in the performed cost-effectiveness analyses was related to the heterogeneity of patient populations treated with hadron therapy and its comparators, and to the ensuing difficulty to define the correct therapeutic comparator.

Last but not least, the recently formulated conclusions and recommendations (see later) for a first phase technological choice of a Belgian centre seem to make the 3 model indications less relevant for this first phase feasibility study. This observation is an unavoidable consequence of the parallel progress both in investigating the technological feasibility of commercially available equipment on the one hand and in the decision on economic cost effectiveness assessments of the early study list of eligible indications on the other hand.

However, due to the rapidly evolving technological landscape, it is expected that the required technical specificities will be standard by the time of an operating hadron centre in Belgium.

In conclusion, our first results point to a borderline cost-effectiveness of hadron therapy, with a result that is highly sensitive to the cost of the therapy to society. Further in-depth clinical studies and economic calculations are required to allow more stable and reliable cost effectiveness statements relevant to the project.

4. APPENDIX: FINANCING IN EXISTING CENTERS

Our hypothesis that existing centers had to dispose of other financing means than their reimbursements (some 18,000 to 40,000 €/patient) income from the health insurance institutes throughout Europe and Japan could be confirmed by the following examples. Unfortunately we could collect only very limited data in the scope of this study. Many centers do not have a clear overview of the global financing flows, since basically all of them were founded within research environments.

Italy: CNAO project at Pavia

The CNAO Foundation was financed as a research investment by the Italian state. The funds have not been made available all at once but rather over the 5 years of its construction. Some delay in the payment by the government has been bridged by a loan from the European Bank of Investment and guaranteed by the Italian Government commitment to finance the centre.
There are also some hidden costs: the land has been donated for free by PAVIA town and also the interconnection into the electric network has been partially paid by the PAVIA town.
CNAO also has profited of advantageous tax policies, like the potential to delay tax payment without fees and tax relaxation on the salary of foreign experts, as commonly practiced for research institutions in Italy.
Basically the investment costs are not charged on the project and the reimbursement for patient treatment is not covering them.

Japan

The NIRS (National Institute for Radiological Research) research project, called HIMAC (Heavy Ion Medical Accelerator in Chiba) was funded for 100% on government budgets (mainly by the National Ministry of Industry). Investment costs are not being charged on the institute that takes care of the patient treatment with carbon ion beam irradiation.
Other Japanese carbon facilities had their initial investments similarly subsidized: At Hyogo the financing was 100% local government funded. At Gunma: 10% local government and 90% national government funding.

VI. Centre of preference: rational choice

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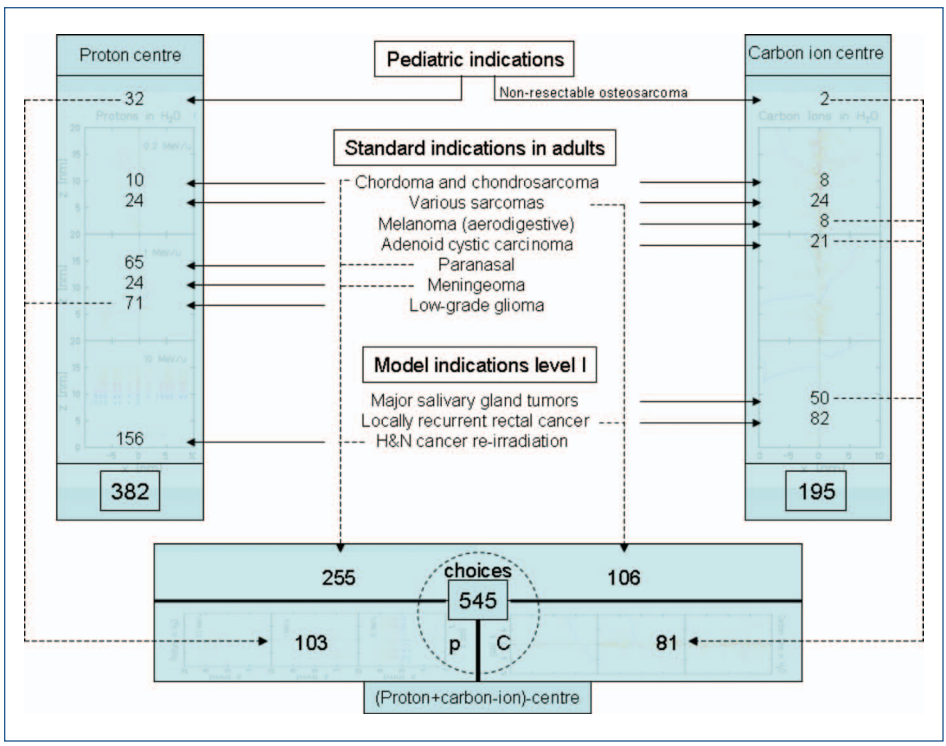
1. CHOICE OF THE START-UP PLATFORM

Considering the absence of a physics research centre with a track record of hadron therapy, Belgium will have to rely on commercially available equipment as a start-up platform for hadron therapy. Companies sell established equipment and make research agreements with their customers to develop emerging technology to the equipment of the future.

1. The candidate patients for treatment with established technology belong to 3 groups: children, adults with standard indications and adults with model indications which do not pose challenges beyond what can be addressed by these installations (called model indications level I). The pathologies involved are shown in the middle of figure 1.
2. Boxes at the left, bottom and right side of figure 1 represent the 3 competitive scenarios for a future Belgian hadron therapy centre: a proton only centre, a combined proton+carbon ion centre and a carbon ion centre, respectively.
3. Solid arrows show the preferred allocation of patients (based on tables 4 (children) and 6 (adults), Submodule 1) between a proton centre and a carbon ion centre. For chordoma, chondrosarcoma and various sarcomas (numbers 1, 2 and 3 in table 6 of Submodule 1) both hadron modalities are supported by clinical data. The solid arrows point to the number of patients/year for each indication.
4. The case-mix for a proton centre yields a total number of 382 patients/year; 32 children and 350 adults. This number of patients would use approximately the full capacity of a 2-room proton centre, which was calculated to be 355 patients (50 children and 305 adults) in table 3 of Submodule 4.

5. The case-mix of a carbon ion centre yields a total number of 195 patients/year. This number of patients would use less than 1/3th of the capacity of a 2-room carbon ion centre which was calculated to be 760 patients/year (table 3, Submodule 4).
6. Serious drawbacks of the proton-only and carbon ion only scenarios are the incomplete coverage of indications with the hadron of preference. The drawbacks are resolved by a combined (proton+carbon ion) centre.
7. The case-mix of a combined (proton+carbon ion) centre yields a total number of 545 patients/year. This number of patients is almost in perfect agreement with the capacity of a 2-room combined centre which was calculated to be 534 patients/year (proton: 50 children + 115 adults; carbon ions: 369 adults. Table 3, Submodule 4).
    a. Indications with a strong preference for protons (yearly 32 children and 71 adult patients with low grade glioma) or carbon ions (yearly 2 children and 79 adult patients with

Figure 1: case-mix for different scenarios: installations limited to commercially available technology



Abbreviations: p = proton therapy; C = carbon ion therapy; choices: either proton or carbon ion therapy may be the hadron of choice, which may, for example, depend on randomization in a trial.

aerodigestive melanoma, adenoid cystic carcinoma or other major salivary gland tumours) could directly be allocated to the hadron of preference.

b. The other pathologies for which the best choice is much more debatable could be entered in comparative trials. It is of interest that randomised trials comparing proton with carbon ion therapy are planned at HIT, Heidelberg.

8. Points 1-7 lead to the conclusion that the combined (proton+carbon ion) centre is the first choice as start-up platform.

2. EVOLUTION OF THE PLATFORM

The remaining model indications (locally advanced inoperable pancreatic cancer, stage III non-small cell lung cancer (NSCLC), stage I NSCLC and various stages of hepatocellular carcinoma: further called model indications level II) represent 1,532 patients/year. Extension of the clinical activity to model indications level II requires additional investments to cover upgrades of the installation and a research, development and implementation program, irrespective of the choice of type of centre as initial platform.

1. Expansion (adding treatment rooms) of a start-up proton or combined platform (adding treatment rooms) would be needed to treat one or more of the model indications because full capacity is used by standard and model indications level I.
2. New developments (beam splitters, fast beam switching between rooms, patient set-up outside the treatment rooms) aim at increasing capacity. Proton centers (mainly in Japan) are studying hypofractionation. The implementation of more efficient technology and hypofractionation will delay the need for expansion.
3. A start-up carbon ion platform has spare capacity. Hence, it is the most interesting platform for extension of clinical activity to model indications level II.

VII. Overall conclusions and recommendations

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1. CONCLUSIONS

The term hadron therapy is a generic name for radiotherapy with atomic nuclei or nuclear particles. Most hadron therapy centers use the nuclei of hydrogen (protons) or carbon (carbon ions). Treatment with other nuclei (helium, lithium, oxygen, nitrogen) is a research topic. Hadron therapy using atomic nuclei has superb characteristics for high-precision radiation therapy. Proton therapy seems particularly suitable to treat childhood cancer as there is a potential to reduce side effects like developmental retardation and secondary cancers. Heavier nuclei than protons have the same or even slightly better characteristics than protons for high-precision radiation therapy. Treatment with heavier nuclei like carbon ions is rarely used in children. Its main domain of application is in adult patients to cure cancers that are resistant to conventional and proton radiotherapy. The main obstacles for hadron therapy are the technological challenges and the cost of the installations. Significant technological progress has been made during the last decade.

1.a. Context of a Belgian hadron therapy project

1. Belgium hosts 25 radiotherapy centers and 11 satellites, which treat about 30,000 patients/year with external photon- or electrontherapy. On a European scale Belgian centers are small or medium in size. Hadron therapy is not available in Belgium.
2. In 2012, Europe had 14 hadron therapy centers in operation. Five of these are candidate centers for referral of Belgian patients: Orsay (Paris), PSI (Villigen, Switzerland), Munich (Germany), Heidelberg (Germany) and Pavia (Italy). Prices per treatment in European centers are in the 18,000-40,000 Euro range.
3. The capacity in European centers is expected to double in the next 3-5 years because operating centers increase capacity and some new centers like Essen, Trento, Uppsala, Marburg, Prague, Vienna and Krakow will start operations.

4. The capacity of proton therapy is rapidly growing in the USA where commercial exploitation is the standard. The low-end sales price of a proton treatment is around 100,000 US$.
5. Japan is the world leader in carbon ion treatment. Referral of foreign patients is facilitated through a logistic service company, Medical Excellence JAPAN. Total expenditure for treating a Belgian patient is estimated at 40,000 Euros per treatment. Reimbursement for carbon ion therapy at HIT Heidelberg is 18,000 Euros/treatment.
6. Although European centers are hospitable, substantial obstacles exist for Belgian patients as well as for the referring centre. Waiting lists, language barriers, travel, lodging, social, logistic and financial issues make referral difficult. For these reasons, Belgian radiation oncologists remain reluctant to propose hadron therapy, even for their paediatric patients. The absence of centralized logistic and social support for the Belgian patients is a hurdle for referral abroad and will also be a hurdle for referral to a future Belgian hadron therapy centre.
7. Cross-referral between radiotherapy centers is almost inexistent in Belgium. Non-referral of eligible patients is a threat for a future Belgian hadron therapy centre. A system of referral, back-referral and registration should be established in Belgium.
8. A project to build and operate a one-room proton therapy facility in Ottignies has been started by a group involving IBA, Université Catholique de Louvain (UCL), Hôpital Universitaire Saint-Luc and Région Wallonne. The signature of Minister Marcourt is awaited to continue the project.

1.b. Number of potential Belgian patients

1. According to conservative estimations based on the Belgian Cancer Registry, the numbers of patients/year with generally accepted standard indications are 223 for adults and 34 for children.
2. Constructing a Belgian centre to treat only standard indications would be very expensive due to the fact that the total number of patients is small.
3. Research on treating more common cancers, has only been started recently, as more hadron beam capacity became available worldwide. Breast and prostate cancer were not studied because the outcome after photon therapy was considered acceptable for the majority of patients. For today's 7 most convincing model indications, 1,820 Belgian patients/year were identified.
4. The choice for protons versus carbon ions is based on limited clinical data and may change in the near future. Based on actual data, the hadron therapy modality of preference would be protons for 32 children/year and carbon ions

for 2 children/year. Taking all indications in adults together, the preferred treatment would be protons in about half of the patients and carbon ions in the other half.

1.c. Technical solutions and technological feasibility

1. Recent innovative developments in photon radiotherapy have shown improved efficacy and reduced toxicity as compared to conventional techniques. Each of these developments is applicable to hadron therapy and is under development, however at a slower pace than in photon therapy. There is no risk that hadron therapy will definitively loose its advantages over further evolving photon therapy.
2. Budgetary leanness was assumed in the study by opting for a minimal size facility (2 treatment rooms) at the start-up and is designed to allow further expansion and upgrade.
3. When gathering information on the equipment, the choice for proton or carbon ions was still left open. Three alternative facilities were investigated: 1) A combined centre for irradiation with both proton and carbon ion beams in which one room is equipped with a proton gantry and the other with a fixed carbon beam, 2) A two room carbon centre with two fixed beam treatment rooms and 3) A two room proton centre with gantry equipment in both rooms. For comparison, a stand-alone one-room proton centre was added as a fourth technical alternative.
4. The ancillary equipment in all 4 technical alternatives consists of imaging, simulation, planning, record & verify and anaesthesia equipment (necessary only for proton beam treatment of paediatric patients). Contrary to photon therapy, where this ancillary equipment is already well integrated with the basic irradiation facility, the integration is still very much an on-going development in hadron therapy.
5. A combined (proton and carbon ion beam lines) centre is the only solution that is conceptually capable of treating all indications. However, it is the most challenging scenario. Internal separation of proton and carbon ion treatments by installing dedicated accelerators, beam lines and treatment rooms for each ion is the preferred design.
6. It is important to make a distinction between established and research technology. Established technology is commercially available. Research technology is being developed through research&development programs in pioneering hadron therapy centers. Established technology allows for state-of-the-art treatment of standard indications but not for all model indications.
7. The technical considerations, estimations of investment cost, operational procedures and patient throughput figures of each of the 4 scenarios were based

on established technology: Fixed beams for carbon ion therapy rooms and gantries for proton therapy rooms.

8. Today, established technology would enable state-of-the-art treatment for the 3 model indications that share key characteristics with standard indication. Non-moving tumour sites that can be precisely positioned with rigid immobilisation devices or have fiducial (anatomic or implanted) landmarks for X-ray stereoscopic imaging. These model indications are locally recurrent rectal cancer, non-adenoid cystic major salivary gland tumours and re-irradiation for head and neck cancer.
9. The other model indications require additional technology for state-of-the-art treatment. Additional requirements include technology to treat moving tumour sites and three-dimensional imaging for precise positioning and monitoring. Companies make large efforts to turn the technological developments of the pioneering centers into commercial products but the timescale of availability and the cost of the products are highly uncertain.

1.d. Financing model and reimbursement

1. The financial context of hadron centers in Europe and Japan is completely different from the situation in the USA. Whereas in the former countries all – or at least part of – the investment costs are covered by public money, centers in the USA are typically set on a commercial basis where they have to take the full range of capital and risks into account for their reimbursement setting. That explains the large differences in reimbursement in Europe and Japan (roughly 18,000-40,000€) as opposed to figures exceeding 100,000$ in the USA.
2. For our financial analysis we used 2 types of calculations and 3 types of financing models. For the cost calculation we compared a business model that analyses the financial consequences of a centre over time and estimates the required reimbursement to make a centre sustainable, with an Activity-Based Costing model analysing the costs of a centre in steady state at full operation. These models were tested for a private, a public and a mixed financing approach.
3. The benchmark of approximately 18,000 to 40,000 €/patient, commonly charged for hadron treatments in European and Japanese centers, is mostly insufficient to cover the calculated full costs.
4. Our calculations suggest that of the 4 presented technical solutions, a two-room carbon ion centre is financially the most attractive in terms of cost per treatment, consequence of the lower number of fractions delivered per treatment. The clinical potential of even more extreme hypofractionation is expected to have a further positive impact on the costs.

5. Proton treatments are more costly because the protocols prescribe a higher number of fractions than carbon ion protocols and because most paediatric patients, which require more daily treatment time, are treated with protons. Cost wise, the most extreme situation is found in single-room proton centers.
6. Treatments delivered in combined centers are more expensive than in dedicated proton or carbon ion centers of the same size.
7. Public financing seems to be the viable financial option, as private financing would require too high reimbursements.
8. Prolongation of the commissioning period and higher interest rates may have a tremendous negative impact on the required reimbursement in a private or mixed financing approach.
9. Uncertainties in investment cost have a far greater impact on the treatment cost and the required reimbursement than changes in personnel costs.
10. All factors that allow reducing the total treatment time (i.e. the daily treatment time multiplied by the number of fractions), positively influence the ultimate cost. It will therefore be of utmost importance to optimise the operational procedures and to pursue the clinical research in hypofractionation.
11. Personnel requirements are not yet well established and need further refinement depending on the technical solution and the associated patient through-put.
12. In line with the reality of a high-tech environment as a hadron centre, clinical research should be an integrated part of the activity. The financial impact of dedicated research time for part of the personnel is limited to roughly 10% in the cost picture.

1.e. Cost-effectiveness and cost-utility analyses

1. Cost-effectiveness and cost-utility analyses examine the trade-off between costs and effects of different treatment strategies, the results being expressed in cost per life-year or quality-adjusted life-year gained.
2. In order to deliver value for money, the higher initial treatment cost of hadron therapy has to be counterbalanced by the clinical advantages of improved local control and decreased toxicity, of which it is expected that they will further translate into better long-term survival and quality-of-life
3. For childhood malignancies, this balance was shown to be clearly in favour of proton therapy due to the double advantage of improved survival along with decreased side effects and their associated long-term costs. Hence paediatric malignancies do not call for a further economic evaluation. For similar reasons economic calculations have also been omitted for the other standard indications.
4. The cost-effectiveness is less certain for model than for standard indications. Three model indications were selected for health economic evaluation:

Locally advanced pancreatic cancer (LAPC), Stage III non-small cell lung cancer (NSCLC) and unresectable hepatocellular carcinoma (HCC). Together, they represent a potential number of 1,353 patients/year.

a. Compared to photon therapy + gemcitabine, carbon ion therapy + gemcitabine doubles median life expectancy and reduces treatment-toxicity in patients with LAPC. In public financing of a combined (proton + carbon ion) centre, the cost per life-year gained is 23,000 – 25,000 € or 33,000 – 38,000 € when expressed in cost per quality-adjusted life-year gained.
b. Compared to chemo-**photon**therapy, chemo-**proton**therapy improves median life expectancy by about 6 months and reduces treatment-toxicity in stage III NSCLC. In public financing of a combined centre, the cost per life-year gained is 22,000 – 23,000 € or 32,000-34,000 € when expressed in cost per quality-adjusted life-year gained.
c. Private financing of a combined centre is associated with more than doubling of the costs per life-year gained for LAPC and stage-III NSCLC.
d. Unresectable HCC is a peculiar cancer entity. Radiofrequency ablation (RFA) remains the treatment of choice in RFA-eligible patients since hadron alternatives (proton or C ion therapy) result in limited clinical gains at costs of more than 100,000 € per (quality-adjusted) life-year gained.
e. Belgian patients with unresectable HCC who are not eligible for RFA have little or no access to radical treatment options. However, radical hadron therapy is still possible in many of these patients with intermediate stage or node-positive HCC. Further study is warranted.

5. Economic evaluations of model indications show that hadron therapy may be cost-effective compared to standard therapeutic options, but the sensitivity to the actual treatment costs and outcome data underscore the need for further clinical and economic evaluation.

1.f. Limitations of the feasibility study

1. The feasibility study answered fundamental questions on the number of eligible patients in Belgium, on cost, on cost-effectiveness and on alternatives for hadron therapy in the rapidly evolving oncological scene.
2. With more arguments in favor of a Belgian hadron therapy center, additional questions have been raised during the meetings of the Steering Committee, concerning:
    a. Implantation site
    b. Organization structure
    c. Financial structure-reimbursement

   d. Scope including research
   e. Training of staff
   f. Organizing of referral
   g. Collaboration with the planned UCL-IBA-St.-Luc-Région Wallonne one-room proton centre
3. The group behind the Feasibility Study was limited in its possibilities to answer these questions. The answer to these questions will depend on the entity that will finally build and exploit the Belgian hadron therapy centre. Therefore the group behind the Feasibility Study can only give a recommendation on how to address these key questions (see below: section 2.c. Declaration of Intent to Dialogue with the Public Authorities).

2. RECOMMENDATIONS

2.a. Regarding a Belgian hadron therapy centre

The location, organisation and management

1. We recommend building a single centre at a single site being the campus of a large general hospital that can provide the complementary medical services: medical imaging, oncologic care services for children and adults, day clinic, hospitalization, surgery, emergency medicine and anaesthesia. Due to the fact that hadron therapy implies a strong research program (medical, technology and biology) an academic hospital should be preferred to a non-academic hospital.
2. We recommend an independent organisation and management structure for the future Belgian hadron therapy centre. The collaboration with the hospital(s) that provide complementary services can be secured through service liability agreements.

The technical aspects

1. Only a centre that offers proton and carbon ion therapy could cover all clinical indications. We therefore recommend reducing the 4 scenarios of the feasibility study to a single one: a combined centre that allows treating with protons and carbon ions.
2. We recommend a flexible design for the future combined centre that allows treating all standard indications as well as the least challenging model indications from the start of operations. The design must foresee the possibilities of expansions and technological upgrades for treating the more challenging model indications at a later stage.

3. A strong disagreement exists between the Japanese and European experts regarding the technological concept of a combined centre. The Japanese experts argue strongly against using the same equipment (accelerator, beam lines) for proton and carbon ion treatments (which is done at European centers in Heidelberg and Pavia). The European experts admit that the concept may not be ideal but argue that it is relatively inexpensive to add the capability to treat with protons on equipment designed to treat with carbon ions. Following the advice of the Japanese experts would lead to the more expensive solution of two accelerators and separate beam transport and delivery systems. We recommend a pragmatic approach of accepting the solution that is favoured by the ultimately selected equipment company/companies.
4. The challenging model indications (representing ¾ of the indications) pose higher technological challenges like a larger variety of beam directions (or gantry) for carbon ions, in-room volumetric imaging, fast rescanning, gating or tracking. We recommend a limited exploratory consultation of the potential hadron therapy companies to i) obtain information on the status of these technologies, ii) identify opportunities for participation in their research and development and iii) assess the cost involved. Based on experience in building combined centers or projects in that direction, we identified the following companies that should be included in the consultation: IBA, Mitsubishi, Toshiba and Sumitomo.
5. Based on the clinical objectives regarding the coverage of standard and model indications, we recommend making a precise description - together with each company - of the equipment that would be needed in each treatment room. From the equipment specifications, each company can derive what equipment (ion sources, accelerator(s), beam lines) they would need to install inside the machine rooms of the facility. Treatment- and machine-room equipment determine the characteristics of the housing and allow designing plans of the facility with limited detail. We recommend gathering this information on equipment and building for the combined centre scenario. A good occasion would be the 2013 PTCOG meeting on June 2-8 in Essen, Germany, where each of the 4 above mentioned companies will be represented. On the basis of such information a more precise investment cost estimate can be made which would reduce the uncertainty range that has been applied in the sensitivity analyses of cost- and cost-utility studies during phase-I of the feasibility study.

2.b. Regarding access for Belgian patients to hadron therapy

As part of the Cancer Plan initiative in 2009, a yearly recurrent budget of more than 3.5 million Euros was announced to secure that Belgian patients would have

access to hadron therapy in foreign countries. The rationale for this budget and its value for the Belgian cancer patient were clear. The budget could cover the most urgent needs for hadron therapy of Belgian patients while, in the mean time, Action 30 would investigate the feasibility of a future Belgian hadron therapy facility. Paradoxically, this noble initiative turned into a sad story. In almost 4 years, not a single Euro of these announced budgets could be used. The reality is even more disappointing. In spite of a visionary political decision and the reservation of a significant budget, the situation for the patients who need hadron therapy has deteriorated. Uncertainties in reimbursement and unreasonable delays in refunding the costs of travel and lodging during treatment have turned hadron therapy into a therapeutic option for patients from the higher socio-economic classes only. We are convinced that this reality is the opposite of what the Cancer Plan intended.

1. We therefore recommend that the budget should be made immediately accessible for referring patients. Considering the number of standard and model indications (Submodule 1), we realize that the demand may rapidly outgrow the budget. Therefore priority ranking will be needed.
2. We recommend the following priority ranking: 1. Paediatric standard indications; 2. Standard indications in adults; 3. Model indications according to the table (priority ranked top to bottom) in Submodule 1.
3. We recommend that 95% of the yearly reserved budget will be used for covering the direct patient-related cost and 5% to cover the cost of a Central Liaison Office. The Central Liaison Office supports logistics and organizes travel, lodging and follow-up for eligible patients. Its key philosophy is to help the patient in bridging the gap between the Belgian care providers and the foreign hadron therapy centre. This gap has many dimensions -distance, language, financial, lodging, psychosocial, medical- which have to be assessed and remediated individually.
    - Belgium has organisations, like for example, the Foundation against Cancer, that have a long track-record of covering the multi-dimensional aspects of helping cancer patients. These organisations have the competence and the people to install a Central Liaison Office in a very short time.
    - Phase-I of the Feasibility Study has accomplished preparatory work for a Central Liaison Office. Submodules 1 and 2 have identified the contemporary status of standard and model indications. Privileged relations with hadron therapy centers in Europe and Japan have been established through the foreign experts (Addendum 2 of Preface and Background). Their centers are willing to accept all Belgian patients with paediatric and adult standard indications. These are also the pioneering centers for all model indications except stage III NSCLC for which MD Anderson Proton

Therapy Centre, Houston, USA is the centre that generated the clinical data. If needed, the Feasibility Study-team will reach out to this centre, attempting access for Belgian patients regarding the missing model indication.

4. The Central Liaison Office may also facilitate the integration of a future Belgian hadron therapy centre in the existing network of centers. Like other facilities worldwide, the future Belgian centre would have to focus on a limited number of indications. For these indications, the Central Liaison Office could then organize the path of care through the Belgian centre while for other indications it would still pass through foreign centers. Hence, we recommend continuing the financing of the Central Liaison Office after a Belgian hadron therapy centre has started clinical operations.

2.c. Declaration of Intent to Dialogue with the Public Authorities

1. To find answers to the open questions which are of direct importance for building a Belgian centre, we recommend the public authorities to organize an open call to dialogue with parties which have interest to develop a MasterPlan that must lead to a Belgian hadron therapy centre. This report, the final of phase-I of the feasibility study, is the 'cahier de charges' regarding the type of centre and the services that the centre should provide to society. The open call invites interested parties to write a Declaration of Intent to Dialogue with the Public Authorities.
2. The Declaration of Intent should contain following topics:
    a. Description of the interested party
    a. Proposal regarding the implantation site (only one allowed)
    a. Vision regarding organization and financial structure
    a. Vision regarding research and training of staff
    a. Vision regarding referral and collaboration
        i. At the local, regional, national and international levels
        ii. With possible other hadron therapy initiatives in Belgium
3. The Declaration of Intent should be a brief document (maximum 10 pages).
4. The Steering Committee could play a role in the dialogue and help identifying the party(ies) which is (are) eligible to develop a MasterPlan.

Addendum 1: Letter of agreement between the University Hospitals

22 maart 2010

Ter attentie van Dr. S. Van den Bogaert
FPS Health, Food Chain Security and Environment
Directorate-General for the Organisation of Health Care Establishments
Eurostation II - 01D228
Pl. Victor Horta 40B10
BE-1060 Brussel

Betreft: financiering van de haalbaarheidstudie BHTC

Geachte Mevr. Van den Bogaert,

Ondergetekenden, vertegenwoordigers van de diensten radiotherapie van de universitaire ziekenhuizen in België bij de Stichting BHTC en alle 7 leden ervan, verzekeren hierbij hun medewerking aan het gezamenlijk project "Uitvoeren van een haalbaarheidstudie voor de mogelijke oprichting van een Belgisch Hadron Therapie Centrum" in het kader van actie nr. 30 "Toepassing van Hadron Therapie in België" van het Nationaal Kankerplan.

Zij verklaren zich gezamenlijk akkoord om alle financiële middelen, die het FOD Volksgezondheid ten behoeve van deze studie beschikbaar maakt, integraal via het Universitair Ziekenhuis Gent te laten beheren.

Hoogachtend,

Wilfried De Neve
Universitair Ziekenhuis Gent

Karin Haustermans
Universitair Ziekenhuis Leuven

Danielle Van den Weyngaert
Universitair Ziekenhuis Antwerpen

Dirk Van Den Berge
Universitair Ziekenhuis Brussel

Pierre Scalliet
Cliniques Universitaires St-Luc

Philippe Coucke
Centre Hospitalier Universitaire de Liège

Paul Vanhoutte
Institut Jules Bordet

Addendum 2: Planned FTE contribution of the University Hospitals

Attachment 2

Resources allocation feasibility study for a hadron therapy centre

Academic Hospital	Original Submodule	Name and affiliation	Estimated resources months	Estimated resources months Total
AH Gent				
	1	M. Coghe (MSc, UG)	0	
	1	G. De Meerleer (UG)	0	
	3	W. De Neve	2	
	4	W. De Neve (UG)	1	
	1	F. Duprez (resident, UG)	0,5	
	1	V. Fonteyne (resident, UG)	0	
	5	Y. Lievens (UG)	2	
	1	I. Madani (Post-doc, UG)	4,5	
	4	I. Madani (post-doc, UG)	0	
	6	I. Madani (UG)	0,5	
	3	B. Speleers (UG)	1,5	
	1	C. Vandenabeele (MSc, UG)	1	
	5	B. Vanderstraeten (UG)	6	
	3	L. Veldeman (Postdoc, UG)	0	
	Total	Total		19
AH Leuven				
	4	M. De Rydt (KUL)	0,5	
	3	H. Devrieze (KUL)	0,5	
	6	K. Haustermans (KUL)	0,5	
	1	J. Menten (KUL)	0,5	
	2	S. Nuyts (KUL)	0,5	
	3	F. Van den Heuvel (KUL)	0,2	
	4	F. Van den Heuvel (KUL)	0,3	
	5	J. Verstraete (KUL)	6	
	Total			9
AH Brussels				
	1	M. De Ridder (VUB)	0	
	2	M. De Ridder (VUB)	0,4	
	1	D. Vandenberge (VUB)	1,5	
	Total			1,9
AH Bordet				
	1	M. Roelandt (ULB)	3	
	2	M. Roelandt (ULB)	0	
	1	P. Van Houtte (ULB)	1	
	Total			4
AH Saint-Luc				
	6	A-C Heuskin (FUNDP)	6	
	6	S. Lucas (FUNDP)	0	
	Total			6

Addendum 3: Un centre de proton-thérapie de recherche UCL-IBA en Wallonie:Pourquoi et Comment?

Vincent Grégoire*, Pierre Scalliet* et Yves Jongen**

* Service de Radiothérapie oncologique et Laboratoire d'Imagerie Moléculaire et de Radiothérapie Expérimentale (IMRE), Cliniques Universitaires St. Luc et Université Catholique de Louvain

** Ion Beam Applications sa (IBA)

Sommaire

L'UCL et la société IBA proposent de s'associer pour créer un centre de recherche en protonthérapie en Wallonie. L'objet de ce centre serait de faire des recherches cliniques en proton thérapie, c'est-à-dire de traiter des patients dans le cadre de protocoles de recherche, mais aussi d'effectuer des recherches scientifiques et technologiques permettant d'optimiser cette nouvelle forme de traitement du cancer. Le centre serait aussi utilisé par IBA pour valider ses nouveaux concepts dans le domaine de la proton thérapie.

Le succès de ce projet de recherche en protonthérapie requiert un environnement clinique et de recherche fort et de haut niveau. Dans l'histoire de la radiothérapie dans le monde, on trouve plusieurs exemples où des programmes de recherche originaux et prometteurs ne se sont pas traduits en succès cliniques par défaut d'un environnement permettant un transfert harmonieux de la recherche à la pratique clinique. C'est pourquoi le traitement de patients dans ce centre est une dimension essentielle. Ces traitements devraient également jouer un rôle important en formation. Le nouveau centre de protonthérapie pourrait être adjoint au service de radiothérapie de la clinique St Pierre à Ottignies.

Ce centre serait géré par le Service de Radiothérapie oncologique des Cliniques universitaires St-Luc pour les aspects cliniques et pour ce qui concerne les aspects scientifiques, conjointement par l'UCL et IBA. Il jouerait le rôle de plateforme technologique dans l'esprit du plan Marshall wallon, et serait accessible aux chercheurs d'autres universités wallonnes, belges et européennes, et d'autres sociétés développant des produits ou des logiciels adossés à la protonthérapie. Un comité scientifique international décidera de l'attribution du temps de

faisceau destiné à la recherche en se basant exclusivement sur la valeur scientifique des projets de recherche proposés.
A côté des maitrises et des thèses découlant des programmes de recherche, le centre de recherche en protonthérapie de l'UCL développera un programme d'enseignement et d'éducation spécifique aux domaines de la physique médicale et de la radiothérapie utilisant des faisceaux de protons. Ce programme sera intégré dans les programmes post-graduat de l'Académie Louvain.

L'investissement requis serait de 25 M Euros environ, et devrait être financé par les pouvoirs publics wallons, par exemple par la SRIW et/ou la Sofipôle. Le remboursement de l'emprunt et les frais de fonctionnement du centre pourraient être assurés par l'achat d'heures de faisceau par les chercheurs utilisateurs (dont IBA), et par le remboursement des traitements de malades.

I. La Protonthérapie : un enjeu de santé publique

En Belgique (comme dans les autres pays occidentaux), le cancer est devenu la principale cause de décès, et son incidence va probablement augmenter a cause du vieillissement de la population. En 2015, environ 70,000 nouveaux cas de cancer seront détectés en Belgique. La radiothérapie avec des photons (ou rayons X) est une des méthodes principales de thérapie du cancer. Les études épidémiologiques montrent que la radiothérapie, utilisée seule ou combinée à d'autres modalités est aujourd'hui créditée de la guérison de la moitié des patients atteints du cancer. De plus, la radiothérapie offre une solution économiquement très abordable pour les soins palliatifs dans le cadre du cancer, et de ce fait contribue grandement à améliorer la qualité de vie des patients incurables.
En dépit de progrès techniques considérables au cours des dernières décades (Intensity-modulated radiation therapy (IMRT) ou Image Guided Radiation Therapy (IGRT)), et en dépit de progrès significatifs dans la compréhension des mécanismes d'action des rayonnements ionisants, amenant à une meilleure prescription de la dose, trop de patients souffrent encore de récurrence de leur tumeur ou de dommages collatéraux du traitement impactant leur qualité de vie. Ceci explique qu'il est nécessaire de continuer à améliorer les méthodes permettant de concentrer la dose de radiation dans la tumeur et d'épargner les tissus sains autour de la tumeur.
Dans ce cadre, la protonthérapie offre une opportunité unique d'améliorer la distribution de la dose dans le patient. En effet, les protons ont une façon très différente de déposer la dose dans la matière. Le proton s'arrête dans la matière à une profondeur qui dépend précisément de son énergie, et l'essentiel de la dose est déposé dans les derniers millimètres de la trajectoire, près de l'endroit où le proton s'arrête. La répartition de la dose en fonction de la profondeur montre un

pic étroit en fin de trajectoire. C'est le pic de Bragg.
Grace à cette spécificité des protons, la radiothérapie par faisceaux de protons, ou protonthérapie, permet d'augmenter la dose dans la tumeur (améliorant ainsi le contrôle local) et de diminuer la dose dans les tissus sains avoisinants, réduisant ainsi les dégâts collatéraux causés par le traitement. De tels progrès cliniques ont étés observés dans les centres qui aujourd'hui utilisent les faisceaux de protons pour le traitement du cancer.

Ceci dit, malgré les progrès cliniques importants que la protonthérapie permet d'attendre, de nombreuses questions restent ouvertes. Dans ce contexte, le présent projet vise à établir un centre de recherche en protonthérapie partagé entre l'UCL et IBA. La finalité du nouveau centre sera la recherche clinique en protonthérapie, le développement de la technologie de la protonthérapie et l'éducation.

II. La protonthérapie et IBA : un enjeu économique Wallon

La protonthérapie s'était développée initialement autour d'accélérateurs de protons développés pour la recherche fondamentale en physique nucléaire. Mais depuis une quinzaine d'années, le développement de la protonthérapie s'est fait sur des systèmes de protonthérapie industriels, fabriqués par des sociétés spécialisées et installés dans des hôpitaux et non dans des centres de recherche en physique.
La société IBA, spin-out de l'UCL située à Louvain-la-Neuve est aujourd'hui le leader mondial dans ce marché. Aujourd'hui, 39 systèmes de protonthérapie ont été commandés à l'industrie, dont 21 à IBA. Un centre de protonthérapie tel que vendu par IBA représente une commande d'équipement dont le montant varie entre 30 et 70 M Euros. Chaque contrat de protonthérapie représente près d'une centaine d'années-homme de travail chez IBA, et probablement autant ou plus chez les sous-traitants d'IBA en Wallonie.
De plus, autour de l'activité d'IBA en protonthérapie, on a observé récemment le développement de sociétés proposant des matériels, des services ou des logiciels nouveaux et innovants s'appuyant sur l'activité économique d'IBA. Citons par exemples des sociétés telles que Jema-Elec, ALM, Nomics, Q-Spin, Palantiris)
Paradoxalement, alors que l'on trouve des centres de protonthérapie IBA en construction ou traitant des patients dans plusieurs pays d'Europe (France, Allemagne, Italie, Tchéquie, Suède, Russie), aux USA (6 centres IBA traitants des patients et 4 en construction) et en Asie (Japon, Chine, Corée), on ne trouve pas de centre de protonthérapie en Belgique. Si un consensus se dégage entre les partenaires académiques belges, sur l'utilité clinique d'un grand centre de

protonthérapie, ou d'hadron thérapie (thérapie par faisceaux de protons ou de carbone), comme IBA en installe d'habitude, un accord final ne s'est pas encore dégagé. Et pourtant, les responsables des services de radiothérapie des grands hôpitaux universitaires ont constitué, avec la Fondation Belge contre le Cancer et le SCK-CEN le « Belgian Hadron Therapy Consortium ». Toutefois, s'il a été facile de dégager un accord sur le besoin d'un centre de hadronthérapie en Belgique, un accord ne c'est pas encore matérialisé sur la localisation de ce centre et les modalités de son financement et de son fonctionnement. Les questions qui se posent aujourd'hui sur le statut d'institutions à caractère national ont tout à fait gelé le dossier.

L'absence d'un centre de protonthérapie en Belgique est bien sur pour IBA un important handicap commercial. Il est plus difficile de convaincre des institutions étrangères quand on n'a pas été capable de convaincre les institutions de son pays. Mais aussi, et plus fondamentalement, c'est un obstacle important aux développements scientifiques et techniques d'IBA en proton thérapie. En effet, le développement de concepts nouveaux dans le domaine de la protonthérapie exige l'accès à des faisceaux de protons ayant les qualités cliniques requises. Mais le coût d'un équipement de protonthérapie est tel qu'IBA ne peut envisager d'investir seul le montant requis pour installer un centre de protonthérapie pour la recherche et le développement de l'équipement. Pour résoudre cette difficulté, IBA doit obtenir à grand peine des heures de faisceau disponibles la nuit ou le week-end sur des centres de proton thérapie qui traitent des patients de jour. Beaucoup de développements importants se sont par exemple faits sur le centre de protonthérapie IBA installé à Jacksonville en Floride.

Aujourd'hui, les développements techniques d'IBA requièrent l'accès à un grand nombre d'heures de faisceau de protons chaque année. Si un centre de recherche en protonthérapie était établi en Wallonie, IBA pourrait acheter pour ses propres besoins en recherche une partie du temps de faisceau de centre, ou, alternativement, participer au financement de ce centre.

III. Une opportunité : le développement du « Proteus One »

L'équipement d'un centre de protonthérapie classique coûte de 50 à 60 M Euros. Le bâtiment nécessaire pour héberger un tel centre coûte de 25 à 35 M Euros. En ajoutant les intérêts capitalisés, et le capital requis pour le lancement des activités, on voit que le besoin de financement s'établit à un niveau proche de ou supérieur à 120 M Euros. Un tel projet est difficilement pensable en Wallonie. Toutefois, IBA a identifié un nouveau segment de marché pour la proton thérapie. C'est le segment des hôpitaux de plus petite taille qui pratiquent déjà la radiothérapie conventionnelle, et voudraient ajouter à leur installation un système de

protonthérapie moins coûteux, avec une seule salle de traitement.
Pour répondre aux besoins de ce segment de marché, IBA est en train de développer un tout nouveau système de protonthérapie, de prix et de dimensions réduites. Ce système, dont le développement est en cours mais qui n'est pas encore commercialisé aujourd'hui, aurait un prix de vente de 20 M Euros environ, et le bâtiment nécessaire pour l'abriter serait une extension d'un service de radiothérapie existant. Le prix d'une telle extension serait de 5 M Euros environ. Le montant à financer pour la réalisation d'un tel centre serait donc de 25 M Euros environ.
Un tel centre, s'il était consacré exclusivement à la protonthérapie clinique aurait une capacité de traitement de 400 patients par an environ. Par contre, dans le projet proposé ici, le temps du centre serait partagé entre des traitements en protonthérapie (dans le cadre de protocoles de recherches cliniques), des recherches de nature plus fondamentale sur les effets des faisceaux de protons, des recherches à caractère plus technologique, dont le but est d'améliorer les performances des systèmes de protonthérapie et des systèmes associés, et enfin le temps demandé par IBA pour la mise au point de ses nouvelles fonctionnalités en protonthérapie. Dans ce cadre, on peut estimer la capacité de traitement à 150-200 malades par an, environ.

IV. Localisation du projet

Le succès de ce projet de recherche en protonthérapie requiert un environnement clinique et de recherche fort et de haut niveau. Dans l'histoire de la radiothérapie dans le monde (en ce compris l'histoire des développements en neutron thérapie à l'UCL), on trouve plusieurs exemples où des programme de recherche originaux et prometteurs ne se sont pas traduits en succès cliniques par défaut d'un environnement permettant un transfert harmonieux de la recherche à la pratique clinique. La proximité d'IBA est aussi un paramètre important à considérer. Dans ce contexte, il y a des arguments forts pour placer ce système de protonthérapie dans le service de radiothérapie de la clinique St Pierre à Ottignies. Ce service fait partie du département de radiothérapie des Cliniques Universitaires St Luc de l'UCL à Woluwe. Le système ne serait qu'à quelques kilomètres du campus principal de l'UCL à LLN et du siège d'IBA, et serait à moins de 30 km des Cliniques Universitaires St Luc.
D'autres sites possibles ont étés examinés, mais ces autres sites ne semblent pas avoir les mêmes atouts que le service de radiothérapie de la clinique St Pierre à Ottignies.

V. Le programme de recherches cliniques

Même s'il est vrai qu'en principe chaque patient pourrait bénéficier de la distribution de dose supérieure que permettent les faisceaux de protons, d'un point de vue clinique cette supériorité ne représente un avantage vraiment substantiel que pour des patients sélectionnés. Parmi ceux-ci, il existe des arguments très forts pour suggérer que les patients pédiatriques sont le plus à même de bénéficier des avantages de la protonthérapie. En effet, pour de jeunes enfants, minimiser la dose de radiation aux tissus sains entourant la tumeur permet de réduire des complications comme les déficits de croissance ou les cancers secondaires induits par l'irradiation. Ce dernier point est particulièrement important pour des patients qui ont une longue espérance de vie après le traitement. Selon le registre belge du cancer, 350 tumeurs pédiatriques ont été observées en 2005. Parmi ces patients, 20 à 30% ont étés traités par radiothérapie. Tous ces patients pédiatriques auraient été de bons candidats pour un traitement par protonthérapie. D'autres tumeurs assez rares des adultes, tels les chordomes ou les chondrosarcomes de la base du crane, de même que les sarcomes rétripéritonéens sont aussi de bons candidats pour la protonthérapie. Cela ne représentera que quelques dizaines de cas par ans.
Avec seulement ces indications clairement reconnues, le programme de protonthérapie de l'UCL pourrait traiter 100 à 120 patients par an, laissant un partie importante du temps pour les autres programmes de recherche. En effet, le centre de protonthérapie de l'UCL aura aussi pour mission de valider d'autres indications pour la protonthérapie, comme de petites tumeurs pulmonaires ou hépatiques. Ces indications seront envisagées dans le cadre de protocole de recherche clinique (étude randomisées) en collaboration avec les autres centres de protonthérapie internationaux et en comparaison aux traitements actuellement validés. Ce programme clinique en protonthérapie sera renforcée et élargie par une collaboration qui existe de longue date entre le service de radiothérapie et l'unité de recherche IMRE de l'UCL et d'autres centres académiques : le département de radiothérapie de la KUL (Professeur K. Haustermans) et le département de radiothérapie du centre Oscar Lambret à Lille et de l'université de Lille 2 (Professeur E. Lartiguau). Mais des propositions de recherches cliniques venant d'autres institutions pourront être proposées et seront examinées par le comité de pilotage international sur base de leur valeur scientifique.

VI. Le programme de recherche du nouveau centre

Bien que la protonthérapie soit utilisée depuis plus de 30 ans pour traiter des patients atteints du cancer, de nombreuses questions restent encore sans

réponse dans le domaine de la physique, de l'ingénierie et de la radiobiologie. Grace à ce nouvel outil de recherche, le programme du centre de recherche en protonthérapie inclura une dimension essentielle de recherche et de développements. Ces recherches pourraient, par exemple, couvrir les aspects suivants (liste non limitative) :

a. Amélioration des techniques de délivrance du faisceau de proton par balayage de la tumeur
b. Dosimétrie des protons et détecteurs optimisés
c. Logiciels de plans de traitement spécifiques aux protons et algorithmes associés de calcul de la dose
d. Traitements guidés par l'image (IGPT), ceci incluant la problématique de coregistration d'images d'origine différente, et traitements adaptatifs
e. Monitoring de la dose in-situ
f. Etude des interactions entre le balayage du faisceau et les mouvements d'organes
g. Etudes cliniques d'efficacité et de toxicité des protons, augmentation graduelle des doses
h. Etudes économétriques sur l'efficacité et le coût de la protonthérapie dans le cadre d'une politique de santé publique

Ce programme de recherche sera mené par de nombreux chercheurs venant d'horizons différents, incluant la faculté de médecine, l'école polytechnique et la faculté des sciences de l'UCL, ainsi que nos partenaires de la KUL et de Lille2 Ce programme de recherche devrait donner lieu à l'attribution de maitrises et de doctorats.

Mais le centre de recherche sera ouvert aussi à des propositions d'expériences émanant d'autres institutions que celle mentionnées ci-dessus comme l'Académie Louvain. Ces propositions seront examinées par le comité de pilotage international sur base de leur valeur scientifique.

VII. Le comité de pilotage international

Même si la majorité des projets de recherche effectués dans le centre seront proposés par des chercheurs de l'UCL, on encouragera la proposition de projets de recherche par des groupes extérieurs à l'UCL, ou par des groupes de recherche mixtes formés de chercheurs de l'UCL et de chercheurs d'autres institutions de recherche.

La sélection des projets de recherche, et le partage du temps de faisceau disponible entre les différents projets de recherche sera effectué par un comité de pilotage. Le comité de pilotage sera formé de chercheurs de l'UCL et d'autres institutions, choisis en fonction de leur expertise dans les domaines de recherche

considérés. Un tiers au moins des membres de ce comité seront choisis dans des institutions non belges.

VIII. Enseignement et éducation

Aujourd'hui, un des freins les plus importants au développement de la proton-thérapie dans le monde est le manque de médecins radiothérapeutes et de physiciens médicaux éduqués à la protonthérapie. A côté des maitrises et des thèses découlant des programmes de recherche décrits ci-dessus, le centre de recherche en protonthérapie de l'UCL développera un programme d'enseignement et d'éducation spécifique aux domaines de la physique médicale et de la radiothérapie utilisant des faisceaux de protons. Ce programme sera intégré dans les programmes post-graduat de l'Académie Louvain.
L'existence de ce programme de formation en protonthérapie de niveau post-gradué à l'UCL sera une aide précieuse pour les nouveaux clients d'IBA dans le monde, et sera pour IBA un avantage compétitif important.
Des programmes de formations spécialisés dans les domaines de compétence couverts par le centre pourront également être organisés dans le cadre des initiatives d'éducation prises dans le cadre des pôles Biowin et Mécatech.

IX. Les recherches et développements d'IBA

IBA consacre aujourd'hui près de 15 M Euros à la recherche et au développement en protonthérapie. Plus d'une centaine de chercheurs, d'ingénieurs et de techniciens contribuent à cet effort. Mais pour pouvoir valider beaucoup des nouveaux développements en protonthérapie, il faut pouvoir disposer d'un accès à un système de protonthérapie. Pour répondre à ce besoin, IBA déploie des efforts considérables pour obtenir des heures de faisceau de nuit ou durant les week-ends sur des centres de protonthérapie IBA qui traitent des patients de jour. Certains de ces centres sont très loin : aux USA ou en Corée.
En échange d'une participation financière stable et garantie au budget du centre de recherche, IBA aura accès à 30%- 40% des heures de faisceau du centre de recherche pour ses recherches et développements. Pour ne pas perturber les traitements de patients, qui se font normalement durant la journée en semaine, les week-ends seront réservés pour les recherches d'IBA. Les autres recherches ainsi que la maintenance du système seront effectuées durant les heures de soirée et de nuit en semaine.

X. Financement de l'investissement et du fonctionnement

L'infrastructure proposée jouera le rôle de plateforme technologique dans l'esprit du plan Marshall wallon. Le montant à financer pour acheter un système de protonthérapie Proteus One à IBA, et pour financer le bâtiment destiné à héberger le système s'élève à 25 M Euros environ. Ce montant devrait être financé par les pouvoirs publics, soit par subside, soit par prêt soit par une combinaison des deux. Une certaine contribution de mécénat sera aussi envisagée.

Une fois construit, le financement de l'opération du centre de recherche et du service de la dette serait assuré par la contribution d'IBA (et éventuellement d'autres partenaires industriels) et par la vente du temps de faisceau aux chercheurs belges et étrangers. Une partie de ces recherches pourront prendre le caractère de PPP entre l'UCL, un partenaire industriel comme IBA et la RW. D'autres projets de recherche pourraient voir le jour dans le cadres des pôles Biowin et Mécatech.

Une partie du financement viendra enfin du remboursement par la sécurité sociale des traitements de protonthérapie administrés aux patients. Nous faisons ici l'hypothèse que les traitements de protonthérapie seraient remboursés initialement au plus haut barème des traitements en radiothérapie classique, mais pas à un taux de remboursement plus élevé spécifique à la protonthérapie, comme c'est le cas dans les pays voisins.

A ce stade préliminaire du projet, un plan financier détaillé n'a pas encore été élaboré. Dans une première étape, les grosses masses peuvent être esquissées afin d'envisager les structures possibles de montage de l'opération. Ensuite on construirait un business plan détaillé.

Addendum 4: Request for RIZIV-INAMI reimbursement

Request for a reimbursement of protontherapy treatments delivered in Belgium

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0. Executive summary

Protontherapy permits a more conformed dose distribution in irradiated matter, leading to a potential decrease in late treatment toxicity and/or an increase in tumor cure. A potential benefit of protontherapy is expected for pediatric tumors, chordoma and sarcoma of the base of skull and spine, retroperitoneal sarcoma, and stage I non-small cell lung carcinoma. In this framework, a joint consortium between the "Cliniques universitaires St-Luc", UCL, IBA and the Walloon Region has been created to build and operate a hospital-based research protontherapy centers in Louvain-la-Neuve aiming at treating a maximum of 200 patients per year. The Scientific Committee for hadrontherapy of the INAMI/RIZIV will have previously validated the indications mentioned above. The facility will be equipped with a newly designed compact system developed by IBA. The center will be open for collaboration with the Belgian academic hospitals, and with the "Centre Oscar Lambret" in Lille (France). The business plan foresees an initial investment of 24M € (building, equipment, and other expenses such as working capital, start-up expenses, and bank interests) that will be provided by the consortium (8M €), a bank loan (13M €), grants and donations (3M €). The yearly budget for personal (0.7M €), consumable (0.1M €), maintenance of the equipment (1.2M €), and back payment (1M €) is estimated to 3M €. According to this business plan, a reimbursement of **20.000 €** per treatment is requested to make the protontherapy center sustainable.

1. Introduction: why protons?

In Belgium (as in the other western countries) cancer is the leading cause of death, and its incidence is likely to increase in the coming years due to the aging of the population. In 2008, 60.000 new cancers were registered in Belgium; in 2015, around 70.000 new cases of cancer are expected. Radiotherapy with photons (or X-rays) is a mainstay of modern cancer treatment. Epidemiological studies estimate that radiotherapy is currently the sole or a major component in the cure of roughly half the cancer population. In addition, radiotherapy offers very cost-effective palliation of symptoms caused by cancer, thus improving the quality of life of patients.

Despite strategies to improve radiotherapy efficacy with drugs and targeted agents, as well as refinement in dose delivery (e.g. IMRT), too many patients still suffer from loco-regional

tumor recurrence or permanent side effects directly impacting on their quality of life. This calls for both further improvements in combined modality treatments and in radiation delivery.

Protons are charged particles with a limited course in patients, and they deposit their dose abruptly at the end of their trajectory, i.e. the Bragg peak. The penetration of the beam depends on the initial proton energy, so that the dose deposition can be adjusted to the depth of the tumor by varying the incident energy, and can be conformed to its shape. Consequently, a higher dose can be delivered to the tumor compared to the upstream normal tissues, and no dose will be delivered behind the Bragg peak.

When several beam angles are used, each with a modulation of their intensity (i.e. proton IMRT), a significant dose reduction in the surrounding normal tissues can be observed in comparison with photon IMRT, i.e. a significant reduction in the "integral dose" (Fig. 1). In clinical situations where the tolerance of the surrounding normal tissues to radiation is low, the use of protons might allow a substantial reduction in the treatment side effects. In clinical situations where a higher dose needs to be delivered to the tumor, the use of protons may increase the local tumor cure without consequential increase in side effect. Such clinical improvements have been observed in the few centers, which did pioneer the use of proton for treatment of eye melanoma, and sarcoma of the base of skull and spine.

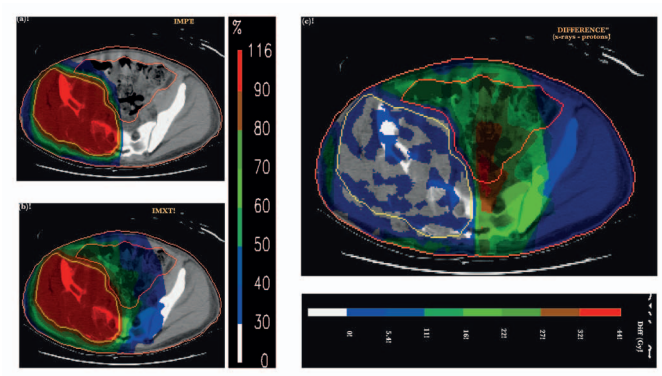

Figure 1: comparison between dose distribution obtained with a photon IMRT treatment (lower left panel) and a proton IMRT treatment (upper left) for a pelvic Ewing sarcoma. The differential dose display (right panel) shows that the main difference between the 2 treatments resides in the lower dose outside the tumor volume (outlined in yellow) with protons (from Goiten 2007).

Despite the high promises of protontherapy, many clinical questions remain to be answered. In this context, the "Cliniques universitaires St-Luc" decided to set up a **research protontherapy facility** in collaboration with the "Université catholique de Louvain (UCL)" and Ion Beam Application (IBA), the worldwide leader in protontherapy equipment. In addition to the clinical program, this facility will also include strong research (e.g. new technological development, dosimetry, on-line imaging) and educative (e.g. training in medical physics and radiation oncology applied to protons) components. This facility will be open to scientific and clinical collaborations with academic partners in Belgium and in Europe. For the later, the Radiation Oncology department of the "Centre Oscar Lambret (COL)" (Lille, France) and the "Université Lille 2" (Prof. E. Lartigau) have agreed to collaborate to this project. For rare tumors, the "COL" has a catching area of 6M people.

2. A protontherapy facility in Belgium

Typically, existing clinical protontherapy centers consist of large facilities equipped with a synchrotron or a cyclotron coupled to rotating gantry(ies) and/or fixed vertical or horizontal beam lines. These facilities require an investment of around 120 millions Euros, and aim at treating more than 1.000 patients a year. Such scenario is not adapted to the Belgian situation both from health care and patient management points of view.

In the context of smaller market size, IBA has been developing a compact protontherapy equipment (the so-called "Proteus One") aiming at treating around 300-400 patients a year. "Proteus One" consists of a smaller supraconducting cyclotron (2.5 m in diameter) coupled to a rotating gantry (220°) and a robotic patient positioner that can fit into a space not larger than the size of two linear accelerator bunkers. The treatment room will be equipped with stereoscopic x-ray and cone beam CT for daily repositioning, and with on-line dose monitoring for real-time in vivo dosimetry and adaptive treatment. In comparison with existing IBA protontherapy facilities in operation (e.g. Boston, Philadelphia, Jacksonville, Seoul, Wanjie, Essen) or in construction (e.g. Krakow, Prague, Uppsala), "Proteus One" can easily fit into a hospital-based existing radiotherapy department.

In this new environment, the "Cliniques universitaires St-Luc" in Brussels, UCL and IBA have decided to join forces for establishing a **joint research protontherapy facility** in Belgium (Fig. 2). This facility will be installed on the outskirt of the UCL campus in

Louvain-la-Neuve for several reasons. First, this protontherapy center will be part of the new Brabant hospital ("grand hôpital du Brabant") that is foreseen for the early 2020s in Louvain-la-Neuve as a partnership between several shareholders including the "Cliniques universitaires St-Luc"; second, as this project will have a strong industrial, research and education components, it seemed logical to install the facility close to the industrial partner IBA and several university research units; third, Louvain-la-Neuve is centrally located in Belgium and easily accessible by route or air from all majors academic centers in Belgium and in the neighboring countries.

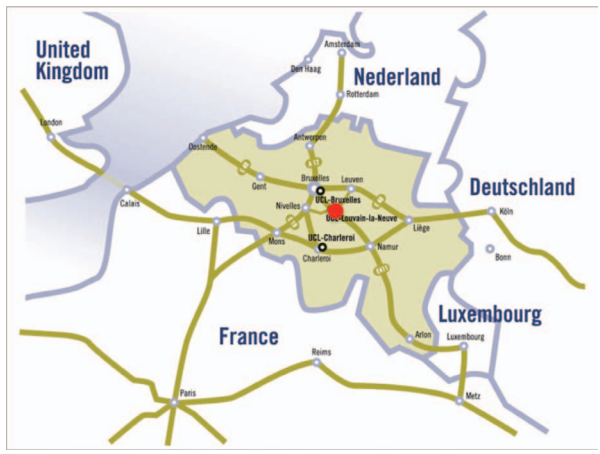

Figure 2: location of the protontherapy facility in Louvain-la-Neuve, a centrally located situation easily accessible from Belgium and the neighboring countries.

3. Clinical indications for protontherapy

No randomized study aiming at positioning protontherapy has ever been conducted. Indications for protontherapy can thus only be inferred from theoretical considerations on the relative dose distribution in target volumes and surrounding normal tissues, and from retrospective clinical studies. A recent overview on the treatment of pediatric brain tumors has

been recently submitted to *Radiotherapy & Oncology*, the official scientific journal of the European Association for *Radiotherapy & oncology*[1].

From a theoretical point of view, any method that contributes to reduce the irradiation dose in normal tissues outside the target volume is of potential interest. Indeed, on one side it may reduce both the acute and late toxicity, and on the other side, it may allow for dose intensification within the target volume, thus potentially leading to higher tumor control probability.

From a practical point of view however, the intrinsic advantage of a better dose distribution needs to be considered in light of the clinical situation, and protontherapy might only translate into a significant clinical advantage for selected patients.
Patients requiring palliative radiotherapy (e.g. patients with a life expectancy of a few weeks or months), patients who are already cured by photon radiotherapy without major toxicity (e.g. early stage prostate, laryngeal or cervix cancers), or patients with extremely radioresistant tumors not responding to increased dose (e.g. glioblastoma) may have little or no benefit from protontherapy.
On the other hand, patients who are cured by radiotherapy but at the expenses of late toxicity (e.g. pediatric cancer patients) or patients to whom dose delivery to the target volume is limited by the sensitive surrounding normal tissues (e.g. chordoma and sarcoma of the spine and base of skull) are potential candidates for protontherapy.

In this framework, the present research project aims at restricting the indications for protontherapy to specific diseases for which there are convergent arguments to suggest an improved therapeutic ratio. The present project will not consider palliative indications, indications for which there are ample evidences on the efficacy of IMRT treatments with photons, or indications for which there are doubtful arguments in favor of a dose-response relationship. Altogether, the objective of the Belgian research protontherapy center is to treat a maximum of 200 patients per year; these patients will come from Belgium and the neighboring countries.

There are strong arguments to suggest that pediatric cancer patients treated with curative intend for solid tumors may benefit the most from protontherapy. Indeed in children,

[1] A. Laprie et al. Proton and carbon-ion radiotherapy for the treatment of pediatric brain tumors: workshop report and treatment recommendations from the French Children Cancer Society (SFCE) committee on brain tumors and radiotherapy. Submitted to Radiotherapy & Oncology.

extremely conformed dose distribution is likely to reduce late toxicity in normal tissues, such as growth retardation, cardiac and pulmonary dysfunction, hypothyroidism, infertility, and IQ. It is also likely to reduce the probability of radiation-induced cancer. The latest is particularly important for patients with long life expectancy. According to the Belgian cancer registry, 240 pediatric solid tumors (109 in girls; 131 in boys) were diagnosed in 2008, and among those around 20 to 30% did receive radiotherapy. Those patients could have been good candidate for a protontherapy treatment.

Other quite rare tumors in adults such as cordoma and chondrosarcoma of the base of skull and spine, and retroperitoneal sarcoma could also be candidate for protontherapy. According to epidemiological data, around 25 of these tumors were observed in Belgium in 2008. Assuming that 50% of these patients may benefit from radiotherapy, another 10-15 patients could be offered protontherapy.

Anatomic region	Tumor type	Absolute number[1]
Pediatric tumor		60
Base of skull & spine	Chordomas / Chondrosarcomas	10
Chest and abdomen	Inoperable NSCLC Inoperable hepatocarcinoma Retroperitoneal sarcoma	40 non available 5
Pelvis	Chordomas / Chondrosarcomas	5
Total		**120**

[1]conservative estimation for Belgium only

Table 1: number of clinical indications for the Belgian protontherapy facility

Last, as a research center, the protontherapy facility may launch randomized studies to position protons in indications such as inoperable early non-small cell lung tumors (NSCLC) and inoperable localized hepatocarcinomas. For stage I NSCLC (≈ 20% of all NSCLC), according to standards of care, 25% of patients could benefit from hypofractionation radiotherapy for such an indication. In a randomized setting, half of these patients would be

treated by photon IMRT. There are no data available for inoperable localized hepatocarcinoma, but it should only represent few patients per year.

The appropriate indications for protontherapy discussed above are in agreement with the conclusion of a report on hadrontherapy published by the KCE (report 67B) in 2007[2]. This report also strongly recommended the inclusion of patients into prospective clinical studies (phase II and III) aiming at further positioning protontherapy in our armamentarium.

4. Procedure for patient referral

The procedure for patient referral to the protontherapy center is outlined in Figure 3. The general philosophy can be summarized as followed:

- Patients will be work-up in their referring academic institution. If necessary, guidelines will be proposed to help harmonizing the work-up. Expert pathologists at the protontherapy facility will review all pathology material centrally.
- Only patients presenting with one of the indications outlined in Table 2 will be considered for a protontherapy treatment. The Scientific Committee for hadrontherapy of the INAMI/RIZIV will have previously validated these indications. For each indication, the ICDO code, the pathologic diagnosis and the TNM stage (or equivalent if more appropriate) will be recorded for central review. A working procedure (e.g. monthly retrospective review of the cases already validated at the protontherapy center) will have to be agreed upon with the members of the committee to allow a swift follow-up of every request without delaying the treatment start. To ease the submission procedure, an on-line form could be developed, allowing for referring physicians to immediately verify whether the case under consideration fits in the treatment protocols.
- When the indication is confirmed, patients will be taken care off by the protontherapy team (i.e. radiation oncologist, medical physicist, radiographer or any other expert if felt necessary), which will be responsible for the treatment preparation (e.g. immobilization device), the treatment planning, the QA-RT, the treatment delivery, on-treatment follow-up visits, and treatment evaluation.

[2] Huybrechts M, Obyn C, Gailly J, Mambourg F, Vinck I, Ramaekers D. Hadronthérapie. Health Technology Assessment (HTA). Bruxelles: Centre fédéral d'expertise des soins de santé (KCE); 2007. KCE reports 67B (D/2007/10.273/51)

- The follow-up will be performed alternately by the referring physician, if any, and by the radiation oncologist of the protontherapy center according to a well-defined agenda. Clinical examination and/or imaging studies will be performed according to well-defined protocols.

All Belgian patients referred to the protontherapy facility will be addressed in their native language (French or Flemish). As the center is expected to welcome research fellows from all over the world, English will however be the usual scientific language and will be used in any medical correspondence with the referring physicians.

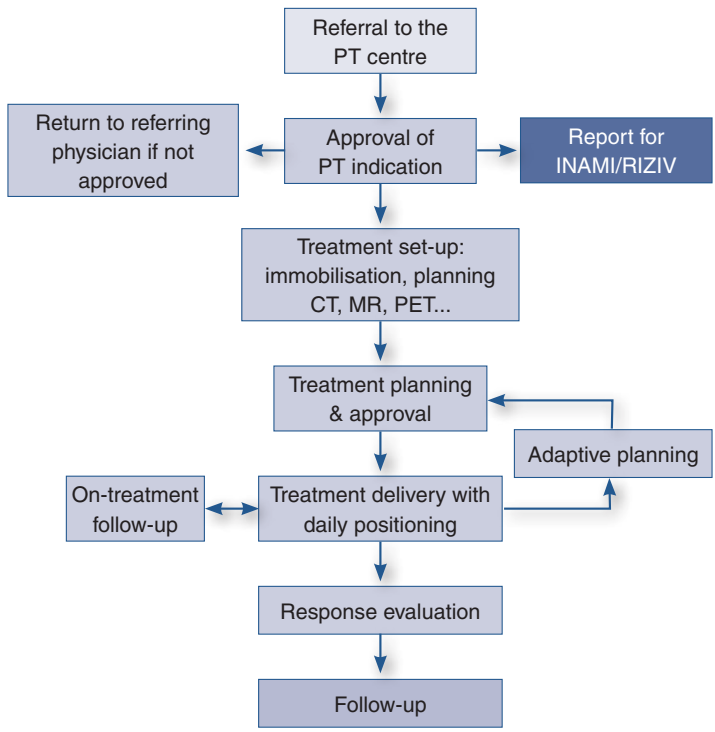

Figure 3: work-flow for patient referral, treatment and follow-up at the protontherapy center.

The procedure outlined above appears as a good compromise to harmonize both a local management (i.e. work-up performed by the referring specialist) and centralized cares at the protontherapy center. It aims at guaranteeing the highest level and homogeneity of treatment and an optimal academic output, while maintaining convenience for patients.

5. Business plan and treatment reimbursement

The total investment for the protontherapy facility including the building, the cyclotron, the gantry, other equipments (planning station, cone-beam CT, …) and other expenses (working capital, start-up expenses, bank interests) has been estimated to **24M €**.

To cover this investment, a partnership has been established between the "Cliniques universitaires St-Luc", UCL, IBA and the Walloon Region ("Région wallonne"), which together have agreed to invest in the facility up to a limit of 8M €. A bank loan will cover for 13M €, while the remaining 3M € will be covered by subsidies and research grants from the Walloon Region, and donations.

The running cost has been estimated to **3M €** a year. It includes the human resource (1 physician, 3 nurses/RTT, 1 physicist, 1 engineer, 1 administrative staff) estimated to 0.7M € per year, the maintenance of the building and the equipment (1.2M € per year), the consumables (0.1M € per year), and the reimbursement of the bank (1M € per year).

With an average of 175 treatments per year, the clinical protontherapy facility could be operated with a reimbursement of **20.000 €** per treatment. Each treatment would typically include around 25 to 30 fractions. With such a level of reimbursement, a small profit of 0.5M € per year would be generated. It will be used to cover for unforeseen expenses and to reimburse the partner's contribution. This reimbursement of 20.000 € is at the lower end of what is granted or foreseen in the other protontherapy facilities in Europe and in the world. (Table 2).

Assuming that one third of the patients referred to the protontherapy center will come from neighboring countries (mainly from Lille), the total annual budget for the INAMI/RIZIV would reach **2.3M €**. This budget is lower than the amount of money of 3.4 M € allocated to refer patients to hadrontherapy facilities outside of Belgium.

Country	Billing rate
France	39.000 € (for 30 fractions)
Germany	16.500 € (eye); 18.500 € (other indication)
Italy	24.000 €[1]
Sweden	24.000 € (for 30 fractions)[1]
USA	30.750-40.500 US$ (for 30 fractions)
Quatar	95.000 US$[1]

[1] anticipated reimbursement

Table 2: comparison of protontherapy billing rates

Addendum 5: Minutes of the Belgian expert meeting in paediatric hemato-oncology

Date: March 09, 2012.
Time: 15:00 – 17:00
Location: Vakgroeplokaal, 1P7, Department of Radiotherapy, UZ Gent.

Meeting called by: BHTC and experts of the Belgian Society of Paediatric Hematology and Oncology.

Present:

Yves Benoit, head, department of paediatric hematology-oncology and stem cell transplantation, UZ Gent;
Christophe Chantrain, medical oncologist, department of paediatric hematology-oncology, UCL St-Luc University Hospital;
Eric Sariban, medical oncologist, department of paediatric hematology-oncology, ULB;
Laurette Renard, radiation oncologist, department of radiation oncology, UCL St-Luc University Hospital;
*Dirk Van den Berg*e, radiation oncologist, department of radiotherapy, UZ Brussel;
Wilfried De Neve, head of research, department of radiotherapy, UZ Gent;
Tom Boterberg, radiation oncologist, department of radiotherapy, UZ Gent;
Indira Madani, radiation oncologist, department of radiotherapy, UZ Gent.

Absent:
Stefaan Van Gool, head, laboratory of paediatric immunology, KUL.
Topic: **Defining the list of eligible paediatric indications for hadron therapy.**

1. INAMI-RIZIV allocated budget: paediatric and adult patients.
Presenter: Wilfried De Neve.

INAMI-RIZIV was willing to allocate 3,548,000 EUR/year for referral of paediatric and adult patients for hadron therapy abroad (as indicated in the draft of the Royal Decree (CGV2011/420, Brussels, Dec 09, 2011). The draft was also defining the indications eligible for hadron therapy that BHTC found not acceptable as indications were being constantly changed. Moreover, indications should be considered separately for children and adults. Costs of referral and hadron therapy abroad in the range of 18,000 - 40,000 EUR in Europe could be reimbursed by

using the E112 form accepted by any European health care institution including hadron therapy centers. Using E112 would make referral easier and traceable as problems imposed by a direct contract between the Belgian insurance companies and a treating hospital would be eliminated. The experts agreed to endorse the use of the E112 form in referral of paediatric patients for hadron therapy abroad. RIZIV was also prepared to reimburse hadron therapy expert advice irrespectively whether it would be followed by treatment. There was a need in a liaison person between Belgian referral institutions, patients and their families and the hadron therapy centre. The experts completely supported the idea of the liaison person in charge of referral procedures. The question of Belgian referral institutions was raised. It was suggested that only hospitals with the recognized specialized paediatric hemato-oncological program as well as recognized departments of radiotherapy (no satellites) could give an advice on need and referral of paediatric patients for hadron therapy. There are 4 such hospitals in this country: UCL, ULB, KUL and UZ Gent. That would be a centralized advice on referral, while RIZIV would provide a logistics support.

2. "Feasibility study of a Hadron Therapy Centre in Belgium: Definition of the medical concept in terms of patient population and of clinical research" in the frame of the National Cancer Plan NKP-30.
Presenter: Wilfried De Neve.

The positive decision of the federal government on financing the feasibility study (Module 1) was made last year. Of 6 submodules, Submodule 1.1 of the study must define the list of indications eligible for hadron therapy. Paediatric malignancies requiring radiotherapy were worldwide recognized as indications for hadron therapy. The Guidance for the referral of patients abroad for NHS proton treatment (version 2.3, July 2011) was proposed as a basis of the paediatric eligible indications and additionally CNS tumours requiring craniospinal or whole-ventricle irradiation, inoperable osteosarcoma and germ cell tumours form the running protocols of hadron therapy centers. The experts agreed with the proposal that would be approved by the Belgian Society of Paediatric Hematology and Oncology in June 2012. The indications will be revised every 6 months.

Addendum 6: Minutes of the first Expert Meeting

FIRST BHTC EXPERT MEETING FOR THE NATIONAL CANCER PLAN, ACTION 30

Date: March 20-21, 2012.
March 20, 2012: time 10:30–18:30.
March 21, 2012: time 09:00–13:30.
Location: Gomasio meeting room, Le Méridien, Brussels.

Meeting called by: BHTC.

Present:

FOD

- *Lieve Jorens*.

BHTC

- *Roger De Croock,* BHTC project manager;
- *Frank Deconinck,* director, BHTC;
- *Wilfried De Neve,* head of research, department of radiotherapy, UZ Gent;
- *Paul Van Houtte,* head, department of radiotherapy, Institut Bordet;
- *Dirk Van den Berge,* radiation oncologist, department of radiotherapy, UZ Brussel;
- *Yolande Lievens,* head, department of radiotherapy, UZ Gent;
- *Indira Madani,* radiation oncologist, department of radiotherapy, UZ Gent.

Hadron therapy experts

- *Alejandro Mazal,* head, medical physics department, Proton Therapy Centre, Orsay, France; president, Particle Therapy Co-operative Group (PTCOG);
- *Stephanie Bolle,* radiation oncologist, Proton Therapy Centre, Orsay, France;
- *Oliver Jaekel,* head, medical physics department, Heidelberg Ion Beam Therapy Centre, Heidelberg, Germany;
- *Jurgen Debus,* director, department of radiation oncology, Heidelberg Ion Beam Therapy Centre, Heidelberg University Hospital, Heidelberg, Germany;
- *Antony Lomax,* medical physicist, Paul Scherrer Institut Centre for Proton Radiation Therapy, Villigen, Switzerland;
- *Piero Fossati,* radiation oncologist, Italian National Centre for Oncological Hadron Therapy (CNAO), Pavia, Italy;
- *Philippe Lambin,* head, department for radiation oncology, University Hospital of Maastricht; medical Director, MAASTRO clinic, Maastricht, Netherlands.

Topic: **International expertise of the study "Feasibility study of a Hadron Therapy Centre in Belgium: Definition of the medical concept in terms of patient population and of clinical research".**

1. **Practical arrangements.**
   Presenter: Roger De Croock.

Consultancy contracts were prepared to be signed by experts on the voluntary basis; the contracts provided refunding of travel expenses and consultancy fees. One of the 2 copies of the contract should be returned by mail to Wendy Schelfhout, BHTC project secretary. A new hadron experts' group meeting would follow the first one. A number of dates were suggested, tentatively the 2nd meeting would be held on June 25-26, 2012; to be confirmed. The experts agreed to review and approve the final report of "Feasibility study of a Hadron Therapy Centre in Belgium: Definition of the medical concept in terms of patient population and of clinical research" as to be submitted to FOD. Explanations about the role of the BHTC in execution of the project were given.

2. **Presenting the National Cancer Plan NKP-30 and the structure of the project "Feasibility study of a Hadron Therapy Centre in Belgium: Definition of the medical concept in terms of patient population and of clinical research" in the frame of this initiative.**
   Presenter: Lieve Jorens.

The experts were introduced to the National Cancer Plan NKP-30 - its objectives, structure, expecting deliverables and financing. The mandatory external expertise of the project was addressed. Alejandro Mazal requested the copy of Mrs Joren's presentation. He also asked about the participants of the project and its time frame. Frank Deconinck and Wilfried De Neve explained that all (seven) Belgian university hospital departments of radiotherapy were the members of the project but not all of them were participating in its execution. The duration of the project would be one year ending on September 2012. W. De Neve clarified the scope of the Belgian hadron therapy as clinical excluding clinical research due to reimbursement issues and the government request and the facility would be hospital-based.

3. Presenting the results of Submodule 1.1. as input for Submodule 1.2.
Presenter: I. Madani.

Defining the list of eligible indications for hadron therapy was the objective of Submodule 1.1. All indications were split into paediatric and adult. The list of paediatric malignancies, standard indications for hadron therapy, had been accepted by the Steering committee of the Belgian Society of Paediatric Hematology and Oncology on March 09, 2012 and would be approved by the general meeting of the society in June 2012. The list of indications would be reviewed every 6 months. The "liason" person coordinating referral of paediatric patients for treatment abroad will be hired by the society. The request on incidence of particular type of paediatric malignancies had been done to the Belgian Cancer Registry. The experts supported the list of paediatric indications and provided the data on number of treatments, sessions and fraction size per treatment of skull base chordoma and chondrosarcoma, spinal and paraspinal "adult" type bone and soft-tissue sarcomas and pelvic sarcoma. As for treatment details of other paediatric indications, the experts's advice was to consult the SIOP protocols and use their prescriptions (number of sessions and fraction size per treatment) as they are used in photon radiotherapy. The experts would approve the final report on paediatric indications. Execution of Submodule 1.1 and 1.2 on paediatric indications was planned to be finished by the end of April 2012.

To identify adult eligible indications for hadron therapy results of systematic literature search were presented. All indications were divided between standard, model and potential. Experts made suggestions on what to be included into standard and model indications for hadron therapy (either proton or carbon ion, and individually for carbon ion and proton radiotherapy). They also ranked model indications (top three and bottom three) and provided data on number of treatments, sessions and fraction size per standard and model indication. Potential indications were not discussed. Alejandro Mazal suggested re-considering ophthalmic tumours as standard indications despite widespread availability of dedicated eye beam lines in Europe. Philippe Lambin suggested putting more emphasis on re-irradiation, so selected indications on re-irradiation were in the list of model indications for proton radiotherapy. The request on incidence of standard and model indications for hadron therapy will be sent to the Belgian Cancer Registry. The final report on Submodule 1.1 and 1.2 will be sent to the experts for their approval.

In absence of clinical data in-silico trials were planned in Submodule 1.1. Given the short time frame and lack of expertise, the experts recommended omitting any in-silico trials and limiting the work only to the systematic review of literature on in-silico trials. Piero Fossati expressed interest in conducting analysis of comparative

effectiveness of hadron therapy and photon radiotherapy for head and neck cancer. I. Madani agreed to collaborate with him and provide all necessary data.

4. Presenting the results of Submodule 1.3 and 1.4.
Presenter: W. De Neve.

The structure of Submodule 1.3 and 1.4 was presented and working packages of both submodules were explained. The experts suggested the three possible design scenarios of the Belgian Hadron Therapy Centre as a national, hospital-based centre with objectives of clinical research that needed further exploration, where the first step would be contacting vendors. Experts agreed to draft a letter to vendors within 1-2 weeks. The common principle is a start with 2 treatment rooms using a later-expandable design. The three scenario's are: 1. a single accelerator powers one room hosting a fixed beam device for proton and carbon ion treatment and one hosting a gantry for proton therapy. 2. The same as 1. but each room is powered by its own accelerator. 3. A proton-only scenario with a gantry in both rooms. W. De Neve and D. Van den Berge would elaborate working packages of Submodule 1.3 and 1.4 in accordance with experts' recommendations.

5. Presenting methodology of Submodule 1.5.
Presenter: Y.Lievens

Methodology of cost computations was presented and discussed as applied to hadron therapy. Standard and model indications for hadron therapy as approved by the experts would be used in cost computations. Alejandro Mazal offered using some data of PTCOG on costs of upgrading/maintenance of the equipment as well as requiring personnel. He also advised to compile indications for proton and carbon ion radiotherapy in cost computations. Frank Deconinck suggested including costs of dismantling into cost computations.

6. Experts' opinion.
Presenter on behalf of all present experts: A. Mazal.

From what was presented to the experts and changes in the landscape of hadron therapy in Europe and worldwide, it appeared that a hadron therapy centre might be feasible in Belgium if it was a national, hospital-based cancer centre with the scope of clinical research. Reimbursement demands should be compared with the ones of European countries where hadron therapy is standard treatment. Progress of work on details of the project would be addressed at the next experts' meeting in June 2012. A. Mazal will draft a 10-point recommendation report.

Detailed expert advises, opinions and remarks recorded during the presentation of the work packages (WP)

WP 1.

- The centre should by all means be hospital based. Do not start on the green field, because all the hospital experience should be given in order to concentrate on the hadron treatment experience that is to be gained
- When looking at the list of suppliers, do not leave Mitsubishi and Hitachi out: The Japanese have made an offer for the Lyon plant.
- (Lomax) In the UK the number of patients considered is about 1700/year, which would be treated in 2 centers. Sizing this to Belgian population, this would be about 300 to 400 patients/year.
- On gantry/fixed beam choice for Carbon treatment, M. J. Debus was confronted with the question what would be the HTI choice if extension would be required. His answer was that today the extension issue is already being considered in 3 years from now. They are considering a proton facility or carbon extension. For the carbon the issue of fixed beam or gantry is not settled yet. The experience with fixed beam treatment is not negative. It is true that one has to learn living with this restriction and that not all potential patients can be treated with fixed beams.
- The Belgian context is being discussed:
    - The very sophisticated hadron therapy knowledge should be concentrated in one single centre.
    - There is no extensive technology know-how in the public domain on accelerator, beam selection or beam delivery available in Belgium. This implies that the choice of centre should be limited to commercial turn-key solutions.
- In view of the above, 3 alternative installation set-ups should be considered, by checking the market availability on turn-key solutions for these alternatives.
    - Alt. 1: one accelerator for proton, 2 treatment rooms, 2 gantries.
    - Alt. 2: two accelerators, one for proton and one for carbon, 2 treatment rooms, one with gantry for proton and one with fixed beam for carbon.
    - Alt. 3: One combined proton/carbon accelerator, 2 treatment rooms, one with gantry for proton and one with fixed beam for carbon.

WP 3.
Was considered being not relevant at this moment.

WP 4.

- Mosaiq integrates fairly well into proton and carbon.
  Hitachi has done projects with Mosaiq.
- The costs for interfacing the treatment room into the system may well run up to 500,000€ per treatment room (Lomax).
- In the price inquiry letter mention the interfaces according to photon standards.
- The developments are going very fast, so do not specify too explicitly.
- It is worthwhile mentioning that planning is going to develop step by step and that re-planning should be done easily.

WP 5.

- On time partitioning for Villingen (proton) M. Jackel stressed the point that longer maintenance periods do lead to important loss of potential patients, because of the build up and build down periods required to spread fractionation. The suppliers should be pushed for more but shorter maintenance periods. In Villingen typically 3 days every 2 months. At HTI there are 5 3 day stoppages and one 10 day stoppage in the Christmas period.

Experts' conclusions and recommendations and questions at the end of the meeting.

- How does the action plan 30 fit into the complete Belgian National Cancer Plan?
- There should be enough patients in Belgium to justify a centre. Do bear in mind however that the health insurance should be convinced to also incorporate some clinical research in the project.
- The centralised approach of one Belgian Centre on a hospital site is a very necessary approach.
- Address the question of a Belgian project alone or with foreign participation. Networking is going to be of great importance in commissioning the plant.
- Narrow the scope of the project from doing nothing to doing all to a realistic project. Provide for plan B if a single Belgian centre would not be feasible.
- Get a better view on the BHTC positioning towards a IBA realisation.
- How to proceed further?
  - The experts will only advise on scientific and technological issues, not on political ones.
  - Be aware of the restrictions of the 3 level indication approach (standard, model and potential indications). In practice … ??

- Technical choices have to be made: is there going to be a gantry with carbon or not? IGRT?, Scanning or scattering beam? Etc.
- In choosing, consider that the equipment should be competitive for the next 10 year and beyond.
- How to address the feasibility question? What is different to 2007 to convince the authorities?
    - Lower costs of investments?
    - More allowance for clinical research?
    - Political people changed?
    - Patients sending abroad unrealistic in practice?

WP 6.

- On a proton facility a gantry is the standard and a must.
- The developments of gantries with 180° rotation (starting from the vertical direction of the beam, right through to vertical again) has been driven by considerations for more place availability around the gantry, rather than by efforts of cost reduction. Integration of CT may indeed become an important advantage. Still River has adopted such a gantry. There is no single opinion on the matter however.
- When adopting the scanning beam, 4D and even 5D (fourth axis: biology) become prerequisite and space around the gantry even more critical. Ask the vendors about their developments.
- Also the IBA compact solution is with a 180° gantry. We should contact Madrillion in Nice for their opinion (A. Mazal will provide the coordinates).
- For Carbon beams there is no gantry available on the market, and fixed beam remains the only option at present.
- Of all the fixed beams, the vertical beam has the least advantages. The technical problems with the vertical beam kept Siemens from commissioning it in Kiel.
- Horizontal beam are standard, but oblique beams are also being developed because they have less limitations than the horizontal ones. In the category of oblique beams the angle should be steeper than the 45°. For instance 70°could be optimal. It could be interesting to contact Procure for this matter.
- The Japanese are reported to frequently include patient tilting (up to 10°) in the treatment chamber.
- Also ask the vendors for an additional patient chair solution in the treatment chamber.
- Does the BHTC project also provide in radio-surgery? (In paediatrics?) .
- Why avoid ophthalmological treatments? Why restrict oneself technologi-

cally in such an important investment?

- Side consideration: why not send more patients abroad? Think of registering the patients also that cannot be send abroad. This will put the necessity of a BHTC more in evidence.
- Couch issue: everybody is going for robot couches. Bear in mind that the robots often are not as accurate as the vendors specify them to be. The robots are basically robots from the automotive industry that are being limited in their movements for medical applications.
- The question of the set-up inside or outside the treatment room is another question with no single solution, for some set-ups can be done very fast in-room, where others require cumbersome preparation. Also consider that set-up outside the room does not necessarily mean that CT scanning should also be done outside. The choice is a big decision because of the cost impact.

WP 7.

- Beam characterisation with respect to cross section and energy range is pretty standard. Low-level energy issues are not important at this stage of the project except when ophthalmologic treatments are to be provided for.
- Both dynamic and passive scanning should preferably be provided. If a single choice has to be made: go for active scanning. Some vendors can supply scanning-beam emulation by “wobbling”.
- The debate on scanning is still going on: for some cases scattering can be advantageous. When multiple rooms are available, a dedicated room with scattering beam may be a good compromise.
- Repainting is also still a very much-unsettled issue.

Module 1.5

- Check whether there is enough MRI capacity available (at Orsay, HTI, CNAO … this is a problem) on the site.
- Make provision for dismantling in estimating the investment costs.
- If there is no public participating in the investment costs and the treatment cost also has to cover investment depreciation and financial costs, the level of reimbursement may become unacceptable to health insurance.
- There is an older study on operational costs (done on PTCOG level?) that still could be valuable for the BHTC feasibility study (Mazal).

Addendum 7: Minutes of the second Expert Meeting (prof. T. Kamada)

SECOND BHTC EXPERT MEETING FOR THE NATIONAL CANCER PLAN, ACTION 30 MEETING WITH PROF. T. KAMADA

On 1st and 2nd August 2012
Le Méridien Brussels

Present: *T. Kamada, Yolande Lievens, Indira Madani, T. Jacob, Paul Van Houtte, J. Verstraete, W. De Neve, R. De Croock, H. De Croo* (partly: on 2/8/2012)

Submodule 1.1 Eligible indications

Paediatric malignancies: standard indications (Slides I. Madani)

- In Japan about 100 paediatric patients per year are presently treated with Carbon. The main objective being to make Carbon treatment also acceptable for a larger spectrum of paediatric malignancies within the next 10 to 20 years. This seems not to be their priority.
- Proton is not often applied for paediatric cancer treatment. Although 6 to 7 facilities are equipped with proton beam, passive proton beams seem to result in much worse neutron contamination than is the case for the Carbon beam. With pencil beam development proton may again increase the potential of paediatric proto treatment.
- One of the important – but rarely mentioned - draw-backs of the HIT scanning beam is supposed to be that it is much too slow for beam gating applications such as required for lung cancer for instance. Japan is now in the process of developing a fast scanning beam (100 times faster than the German one). These problems encountered with scanning beam may be one of the reasons why Siemens drew out of the business.
- Concerning proton “Paediatric malignancies: standard indications” in the table of Indira Madani: To Mr Kamada No 1 & 2 seem to be useless efforts of HTI. Good phase 2 studies are required here. In general phase 3 trials are not feasible here.
- Concerning Randomised Clinical Studies in general Kamada is of the opinion that RCS only make sense in the case of common cancers where Carbon hypo-fractionation is possible and such studies could be organised on the long run.

- For no 4 indications Japan gets 50% survival on 5 years with Carbon instead of proton.
- For no 5 “Mucosa” has to be added. When combined with chemo treatment Japan gets good results with Carbon.
- No 6 Carbon also gives good response. Local recurrence > 5 years. Dose to be increased from 51 to 64 Gray in 16 fractions (?).
- No 7 may also be candidate for Carbon treatment although proton gives good results.
- For no 8 about 50 patients/y are treated with Carbon in Japan with 50% survival after 5 years.
- The no 9 proton treatments in Europe are mostly postoperative results. For non-operative cases Carbon may also be a good alternative. One should also take into account that proton therapy is often combined with photon therapy and that it is difficult to discern the results of the first and the later.
- On no 10 to 15??

Adult malignancies: standard indications (slide I. Madani)

- No 1 to 11: OK, no comments

Adult malignancies: model indications:

- No 1 to 5: OK.
- Other candidates: kidney, re-irradiations of metastasis, but its priority is not high since the long-term survival is not very good.

Submodule 1.2.

a) Number of fractions (slide I. Madani)

Number of treatment sessions: paediatric standard indications.

- In Japan, since paediatric patients are also treated with Carbon, the # of fractions for children is the same as for adults (mostly16 fractions).

Number of treatment sessions: adult standard indications.

- As general remark Kamada states that in Japan mixed Carbon/Proton is not applied. One should choose of either the one or the other. Otherwise treatment becomes both too time consuming and too complicated.
- Number of fractions for No 1: 12 fractions; No 2: 4 fractions; No 3: 20 fractions.
- For stage 1 lung cancers and metastatic liver cancer: a single 50 Gy fraction.

- Kamada promotes the Carbon treatment of prostate cancers because of its ease of treatment. Japan is diminishing the number of fractions for this treatment step by step from 16 to 12.
- One should also consider treating Eye Melanoma with Carbon. Only a special snout is required for them.

Number of treatment sessions: adult model indications.

- On no 3 Kamada reports that although this disease is indeed a good candidate for Carbon treatment, Brachi-therapy has such a dominant history in Japan that it will not easily be stopped overnight to switch to Carbon therapy.

b) Number of patients

- At large Japan estimates the potential candidates for hadron therapy at 5% of all new cancer patients. Our estimation of 2000 eligible candidates per year corresponds to 3% (of the 60,000 new patients per year) and is considered on the safe side. Of its potential Japan has been treating an increasing number: in the 1990's about 300 per year, today above 2400 patients per year. The number of hadron centers in 2011 amounts to 10 facilities. Several others are now under construction or in planning. (Slides of Mr Kamada).
- The Kyogo centre was recently started and has been treating 78 patients for head-and-neck tumours, 60 for lung cancers, #? with pancreas cancer and 100 patients for liver malignancies.
- One of the mayor obstacles for treating moving targets remains the scanning speed. Japan counts on the next 3 to 5 years to develop this technique.

Submodule 1.3 and 1.4. (slides of W. De Neve)

- Comments on the slide "Size of centre and scenarios": Keep it simple and stick to either proton or carbon. If only Carbon treatment would be the choice such as is highly recommended, there is only one available technical solution available commercially, namely the large-size synchrotron accelerator. If the time perspective for a Belgian centre would be rather 10 years from now, maybe also a cyclotron could be an alternative choice.
- The synchrotrons of today measure about 20 m in diameter. The Japanese ministry is now freeing money for the development of a compact synchrotron (about 6 to 7 m in diameter). The development time is estimated at 15 years.

- Comment 1 on the hospital based centre: also take into account the power of the local hospital in competing treatment philosophy. For instance the department for neuro-oncology could be very strong and powerful and put a brake on hadron development!
- Comment 2 on the hospital based centre: take into account that you may need sufficient beds available for your patients. In Japan the insurance companies only reimburse for treatments with hospitalisation. The consequence is that patients request hospitalisation also for instance for prostate cancer irradiation, although not absolutely necessary.
- Comment 3 on the hospital based centre: it may in some cases be necessary to provide in the hadron centre's own MRI, PET etc. equipment in order to be assured at all time of a reliable service.
- Comment 1 on layout: although outside-treatment-room set-up may be a good thing, Kamada does not know of any reliable solution yet.
- Comment 2 on layout: one room with horizontal and one with vertical beam is recommended in combination with a rolling table for the patients (+/- 15°) as utilised in Japan. Kamada feels that a 45° beam will make treatment planning and execution too complicated to handle.
- Concerning commercial vendors on the market: for Carbon beam only the Japanese vendors can offer a viable system. Apart from proton equipment, Sumitomo will also be able to offer a carbon facilities in the future.
- Building costs estimates: a solution with 2 horizontal beams is not OK. Neither is a combined Carbon/proton a realistic alternative in view of its complexity. Carbon alone or proton alone are more pragmatic approaches.
- As far as the most efficient choice is concerned, the optimal number of treatment rooms would be 3.
- The development of a gantry solution for Carbon with acceptable size – about the size of today's proton gantries – is now started in Japan. It may take some 10 to 15 years to become commercially ripe.
- Fixed beam treatment with both passive and slow scanning beam is now a reliable solution. The Japanese development of a fast scanning beam may take another 2 to 3 years, maybe 5 before commercialisation.
- Comments 1 on WP 5: in Japan more machine breaks for updating and improvement of the equipment are provided. One should also know however that the government (another ministry than the one providing the investment resources) now puts limitations on the personnel made available for the exploitation of the centers. In this way capacity is not fully used.
- Comment 2 on WP 5: in Japan all the in-room CT scans have been taken out. Only X-rays stayed inside. To Kamada CT scans provide too much information, making image matching very difficult.

- Comment 1 on WP 6: a gantry for Carbon will make life much more easy and will extend he treatment potentials. That is why the ministry of industry now decided to develop a compact gantry for Carbon.
- Comment 2 on WP 6: experience shows that for fixed rooms about 1/3 of the time vertical beam is required. For 2/3 of the time horizontal beam treatment is necessary. In a constellation with 3 rooms, 2 would be horizontal and 1 vertical. The combination of vertical and horizontal would also be an advantage.
- Comment on WP 7: in Japan eye melanomas are Carbon treated (about 2 cm depth range is required.
- Our investment costs assumptions for carbon equipment are probably 30 to 50 % underestimated. The 50 Mio € estimate for Carbon Only specific equipment should rather be 75 Mio. Accordingly investment costs for a mixed centre are to be adjusted.
- The pilot plants for Lyon and Saudi Arabia will cost 2 to 2.5 times our estimates. No clear explanation was given to motivate this large discrepancy.

Tijdens de presentaties van submodule 1.5 nam ik zelf geen nota.

Submodule 1.5

- Recently completed facilities in Japan
    - Hyogo centre: 200 million Euro: Carbon ions and protons
- Gunma centre: 100 million Euro: C ions only in 3 rooms. Mitsubishi was the constructorIf the Japanese companies have to build outside Japan, the cost seems to be 2-2.5 times higher. Examples are ETOILE: Mitsubishi and the French company ALEBA have a cost estmate of 2.5 times the typical Japanese price. A similar joint venture between a Japanese company and Saudi Arabian authorities for a centre that accelerates heavy ions, conducts research and handles nuclear disasters is estimated at 250 million Euro. Part of the explanation is the recent exchange rate drop of the Euro against the Yen.
- Two technical developments are priority
    - Scanning beam (next year at NIRS)
    - Gantry: planned for 2016 by Toshiba
- Facility building in Japan takes about 3 years
- Different companies have specific skills
    - Mitsubishi: accelerator
    - Toshiba: medical applications
    - Hitachi: proton centers
    - Sumitomo: (compact) proton centers but will add carbon ions

- Starting a centre: 200 patients is the maximum for the first year.
- Passive beams: collimator and compensator construction is very expensive: about 1,000 Euro per beam. On the average, 3 beams/patient are used.
- Moving targets remain a major problem as long as fast scanning is not available. Kamada says that a realistic estimate for the near future (5-10 years) would be treating half of the patient population with passive beams and the other half with scanning.
- We have underestimated maintenance cost.
- A 4-year start-up is too ambitious considering the challenging patient population, that includes moving targets.
- Kamada insist on considering a large-volume easy treatment like prostate cancer to secure revenue.
- CT-based set-up verification and correction is very challenging. Consider simpler solutions.

The Japanese task force on hadron therapy

- Loss of world-wide competitivity in medical products
- Change of policy
- Hadron therapy task force is model
    - Ministery of education
    - Ministery of science and technology
    - Ministery of health
    - Joint venture of 4 companies
        - Mitsubishi
        - Toshiba
        - Sumitomo
        - Hitachi

Addendum 8: Minutes of the third Expert Meeting

THIRD BHTC EXPERT MEETING FOR THE NATIONAL CANCER PLAN, ACTION 30

Le Méridien, Brussels
September 20-21, 2012

Participants:

Minister of State *Herman De Croo*
Experts: *Piero Fossati, Oliver Jäkel, Tony Lomax, Alejandro Mazal, Tadashi Kamada*
BHTC: *R. De Croock W., De Neve, Y. Lievens, I. Madani, J. Verstraete, D. Van den Berge, B. Vanderstraeten*

General remarks on the interim report (related to a series of questions by the BHTC Steering Committee).

- The experts perceive interim report is as quite thorough and think that it addresses the key issues.
- Suggestions for improvement
  - The literature search has been done very extensively, but some of the it should be distilled from it and brought to the core of the report. The problem of indications is not sufficiently addressed (P. Fossati). Levels of evidence have been defined for pharmaceutical products. The ranking low to high is not necessarily the same for radiotherapy. Emphasize importance of modelling in radiotherapy.
  - The clinical potentials of combined photon / hadron treatment, although very convincing, is lacking in the report.
  - It is recommended to give the different sub-title levels a consistant level of importance.
  - Mistakes in the submodule 1.3 regarding HIT were corrected by Dr. O. Jaekel.
  - Unfortunately two important publications from Astro and from Boston are in the pipeline, but not yet published.
- Suggestions for additional issue to be included.
  - State what have been the contacts with vendors.
  - Stress that clinical trials are going to require a research environment.
  - Point out that Networking is an important issue both at local and at national level.

- Describe the referral system in Belgium and make suggestions for making it work better.
- Advise to put in place a central Belgian organisation for referral abroad.
- The model of a single centre in Belgium inside a network of European centers is favoured. The Belgian centre itself should be part of a national network. The model of Uppsala was discussed. This model was not felt feasible because the tasks are too distributed. Participation of the network centers in patient selection and follow-up exists in Switserland, Paris (local network) and Germany. In Germany, referring centers may execute the photon part in photon-hadron protocols but O. Jaekel said that this care path regularly causes trouble.
- The argument of lack of capacity for paediatric tumours is not convincing. The lack of capacity will be resolved in the near future.
- Provide a separate paragraph on the carbon gantry developments.
- Add a paragraph o quality control. And on the available beam techniques (passive and dynamic).

- Specific for the HIT comments in the report.
  - Personnel failing because they are too expensive in the WE, not because they are not available.
  - No shutdown on Sunday, but availability for maintenance and repair.
  - Shutdown: from Sunday midnight to Monday noon.

On the demonstration of the effects and advantages of hadron therapy (related to a series of questions from the BHTC Steering Committee).

- On the original rationale for the existing centers.
  - For Italian CNAO, the German HTI and the Japanese centers, the projects are research program both in clinical and technological research and development. The advantages for health care simply where not scrutinised. As a consequence of that there is little documentation available in their project motivations.
  - The Swiss PSI project is in the middle of a research environment.
  - In French Orsay the project was of smaller size. The first machine was available anyway and the second one has been purchased based of the existing experience and the promising potential for paediatric patients..
- Eligible indications and their health care advantages:
  - It is important to explain – in a preamble - that radiotherapy has a particular history in oncological treatment in general. From the start radiotherapy has been driven by dose distribution improvement and

toxicity avoidance throughout its history, rather than by randomised comparative studies. This is a very central issue!

- Modelling is the paradigm in radiotherapy because of the very high predictive quality of the radiotherapy beams, be it photon, proton or carbon beams.
- The main targets for carbon therapy are not real candidates for photon therapy. The larger the tumour, the more the physical advantage (for proton and C ions). Also the biological advantage (for C ions) is important. The same reasoning is valid regarding comorbidity or iatrogenic damage. The more co-morbidity, the more advantage for hadron therapy. Dr. Kamada mentioned re-irradiation as a situation where one must deal with iatrogenic co-morbidity. Phase 2 studies are no candidate for photon therapy.
- A reason why comparative studies are rare is the fact that in the different hadron centers worldwide the treatment delivery is far from being standardised and every centre has still its own recipe that is related to its specific beam delivery set-up.
- Some comparative modelling studies were performed in the late 90's. But any comparative study remains very difficult to perform and the existing centers do not continue investing in them. "There is certainly no necessity felt to redo them!"
- Suggestions were given to re-order the standard indications. Indira re-ordered these as suggested by the experts.

On Model indications:

- The experts agree on the priority list of 7 model indications.
- In the ranking of priority, Hepatocellular carcinoma should be moved down the list.
- Some of the experts also believe that some of the indications that were chosen for carbon treatment exclusively may also be candidates for proton therapy. The list was adapted during the meeting.
- Methods have been proposed and discussed with the expert team to make the necessity of these indications more evident for outsiders, in cases where RCT (Randomised Clinical Trials) are not available or cannot be made available.
- The BHTC team could find no real modelling reports for pancreatic cancer.
- A trade-off between level of evidence on the one hand and level of expected end-points (health care benefit) on the other hand should be made. The decreasing levels of evidence are: RCT, NRCT (Non-RCT), Case Series (CS) and BCS (Best CS). The increasing levels of expected end-point:

Direct Surrogates, Toxicity Improvement, Improvement of Quality of Life, Disease Specific Survival and Overall Survival. Lower levels of evidence should be compensated by higher endpoint results. Also the number of patients in the documented clinical reports could be a factor for choosing or omitting an eligible model indication.

- From the list of 7 model indications W. De Neve has been able - for locally advanced pancreatic cancer - to trace sufficient clinical evidence to compare the best classical treatment with particle treatment. The endpoint results for this case seems so overwhelmingly promising in terms of expected survival rate, that the first results from Japan already suffice to select this indication as model indication.
- Further attempts will now be made to gather sufficient clinic results to document the other 6 indications.
- The experts also remark that there are specific cases in the many other indications where particle therapy is the only way out (some comorbidity cases for instance?).
- Oligometastatic disease will become an application domain for hadron therapy.

On standard indications

- The different criteria for selecting standard indications are confirmed.
- An overview table where all these criteria are being judged for the different standard indications is felt to be sufficiently self-explaining.
- Here also some experts believe that some of the carbon specific indications could also become candidate for proton treatment, the exemptions being adenoid cystic carcinoma and mucosal melanoma.
- The USA Medicare list of commonly accepted indications largely overlaps the list presented by the BHTC team.
- On the column for reimbursement the experts comment that in the USA 4 levels of reimbursement exist. In France all indications for proton treatment are reimbursed. Selection of acceptable indication still takes places in a case-by-case and critical acceptance procedure by the authorities.

On cost effectiveness:

- In general the experts believe that it is extremely difficult and complicated to evaluate and compare hadron treatment costs with those for standard treatments.
- Hospital costing is difficult and very different from country to country. At present there are no known hadron centers where reliable real overall treatment costs data are accessible. This is not specific for hadron therapy

however, but probably characteristic of all complicated clinical treatments in general.

- In the Netherlands cost effectiveness has been put in perspective on a high level of health care budget considerations. For more detailed calculations you actually need a facility. Major consideration is that the introduction of new techniques should be cost-neutral. Costs have to be compensated by savings in other therapies. A Qaly can cost maximum 80,000 €/year in the Netherlands.
- Generally spoken, within a perspective of research centers, cost effectiveness calculations are not top priority yet.
- On should stress that hypo-fractionation is the important potential for bringing down the costs per treatment. Japan is resolutely choosing this strategy. In Europe it is felt that development should go in two steps: first establish sufficient clinical evidence, starting from the known reference of photon therapy, trying out hypo-fractionation only at a later stage.
- Dr. Kamada argues that the reference treatment is not necessarily radiotherapy but maybe surgery or other treatments, for example HCC.

On cost calculation and financing.

- The cost of upgrading the equipment on a regular basis should be separated from the maintenance costs.
- Cope for sending people abroad even before the start of building the facility. One should calculate with 5 staff members during 2 years. If they are included in the personnel that provided for commissioning, make it transparent.
- The opinions on required personnel were too diverse to come to clear recommendations.
- Idem ditto for the investment costs. It was concluded to make a sensitivity study for investment costs (lower as well as higher).
- On commissioning and run-up there should be differentiated for the different technical solutions. A proton centre can be planned to start faster than a carbon centre.
- Why was land not included in the cost calculation? The BHTC team takes it for granted that the receiving academic hospital would provide it for free.
- Cost for upgrades should be separated from maintenance. For yearly upgrades, 3-5% of the equipment investment cost was proposed by the experts
- The cost of the HIT building was 32 million Euro. Our building cost estimates may be high.
- Decommissioning is an issue that is to be incorporated in the life cycle of

the equipment. Its costs are estimated at between 2 and 10 Mio €. The cash flow at the end of the life cycle in our linear cost modelling could be used for it.

- Financial sources of European projects.
  - Orsay: difficult to trace
  - CNAO: 100% public
  - HIT: 50 million from federal research sources; 60 million from banks. Heidelberg University owns the project. About 50% of the income of HIT comes from reimbursement of treatments

Recommendations of the expert on module 2.

- P. Fossati raised the idea of sending a cohort of patients with locally advanced pancreatic cancer for carbon treatment to Japan in the framework of a RCT with conventional Belgian treatment as standard arm. This could be part of Belgian's contribution to a comparative study for a very promising treatment alternative to today's standard treatment with a poor outcome indeed. Dr. Kamada proposed to send simultaneously Belgian personnel to NIRS to assist in treating the patients and receive training. A comparable initiative was launched by NIH to send American patients to C ion centers for the treatment of high-grade gliomas in the framework of a controlled trial
- Dr. A. Mazal proposed to start a call for bids to the companies. Start contacting the vendors to get a better view on what is presently available on the market and on the expected developments in that field. What would be the corresponding investment costs, presently and in the future? Dr. Mazal thinks that the companies should be paid for their effort since we have no project. Architectural plans have to be paid anyhow.
- Dr. Kamada proposed to expand the feasibility study to the investigation of other ions, especially the heavier ones than carbon.
- Dr. O. Jaekel proposed to purchase planning equipment for training and comparative modelling studies. He also proposed to invest in 2-3 PhD students who would perform their research in operating hadron therapy centers and would simultaneously receive training.
- Time spend with the experts unfortunately was too short to organise a session where the experts could meet alone.
- Are there people around the table that are 'juge et partie'? The BHTC group may not be the best choice in an advisory role for the minister in such case. The BHTC refuted this argument and stated that here is neither a decision on the necessity of a Hadron Centre in Belgium nor on its location, so that there cannot be a "partie" yet.

- The consensus, even in the smaller group meeting the experts, seemed absent for some matters such as cost effectiveness. Dr. Mazal advised that those who communicate with the government should first have consensus amongst themselves. The BHTC team agreed that there were still certain issues where time has been failing to finalise the internal team discussions. Reporting to the steering committee evidently only takes place after internal project team consensus has been reached.

Addendum 9: Minutes of the fourth Expert Meeting

FOURTH BHTC EXPERT MEETING FOR THE CANCER PLAN, ACTION 30

Le Méridien, Brussels
December 04-05, 2012

Participants:

Experts: *Stéphanie Bolle, Piero Fossati, Tony Lomax, Alejandro Mazal, Tadashi Kamada*
BHTC: *F. Deconinck, W. De Neve, Y. Lievens, D. Van den Berge*

First draft: W. De Neve, December 10, 2012
Reviewing:
Final draft:

December 04

The first day of 4th expert meeting was dedicated to the review of the version of the interim report, which was mailed to the Cell Cancer Plan and the experts on November 27 2012. On November 29, 2012, it was also mailed to the members of the board of the BHTC Foundation, by the President, for review in their institutions.

The participants studied the documents systematically:

General

Experts found the general pace of the study too slow, partly caused by the request of conducting numerous side-studies e.g. on conventional radiation therapy, referral, organisation. It is due time to increase focus.

Preface and background

Was considered the weakest part, written at a scientifically lower level than the other chapters of the interim report.

1. The part on Organisation and Management was difficult to understand by foreign people, not knowing what Belgian Foundations are. It was suggested to put a paragraph in the text and to move the bulk of the text to an appendix.

2. A similar change was suggested regarding the short CVs of the foreign experts: to write a paragraph and move the move the short CVs to an appendix.
3. p 11 l7-8. The aim to conduct lifetime follow-up for paediatric patients at BHTC is too ambitious. Organising lifetime follow-up is accomplished in The Netherlands, France, UK. Ask the Belgian Government to make an initiative.
4. p12. Redundant. Remove repeats.
5. p5-6. Most of the hurdles for referral will also exist for a Belgian centre. Considerations of the experts were the numerous small Belgian radiotherapy centers, some of whom have even dispersed their activities in satellites. Many need each patient to survive or fulfil the legal criteria. Referral to a hadron centre will need supportive measures for the referring department or obligatory conditions.
6. The consequences of the UCL project should be considered. The UCL project can be complementary to the BHTC project but cannot replace it. The UCL project is too narrow in scope. The experts disagree with statements in the interim report to deviate standard indications to the UCL project or –in absence- to foreign centers.
7. The paths of referral for adult patients are too narrowly focused on radiation oncologists. Considering their battle for the patient in Belgium it seems unlikely that many of them will refer other than their problematic patients. Different oncological disciplines should be directly involved, not indirectly though the Care Programs, especially the oncologic surgeons.
8. The list of planned centers is unreliable: incomplete; uncertain future for many of them. Remove the list or put a warning against firm conclusions using the list: to the best of our knowledge ....
9. Medical Excellence Japan, although a private company, is a Japanese Government initiative. It takes care of the logistics of worldwide referral to Japan for hadron therapy and other top-reference medical procedures. The experience of Prof. Kamada regarding the services of Medical Excellence Japan is very good. He expects that referral of Belgian patients to Japan will go flawless through using the services of Medical Excellence Japan. Medical Excellence Japan can be considered as a paradigm for Belgium to deal with the logistic problems of referral/back-referral. (http://www.medical-excellence-japan.org/en/

Submodule 1

1. The methodology of the search was highly valued.
2. p8 l4 No model paediatric indications. Neuroblastoma deserves to be studied as potential model indication.
3. Present capacity in Orsay and Villigen is high enough to treat 40 Belgian children/year. However, capacity is increasingly filled up with referrals from outside Europe and from other European countries.
4. Constructing a BHTC but still referring paediatric patients abroad is not sustainable. Negative PR?
5. The low number of 40 children with standard indications treated yearly in Belgium is surprising. Dr. S. Bolle is in charge of the treatment of 120 children/year at Institut Gustave Roussy, Paris. The team at Institut Curie, Paris treats an equal number/year.
6. Standard indications in adults were intensively discussed. Choroidal melanoma should be added for completeness even though there is no intention to invest in an eye-line at a future BHTC.
7. Table 2:
    a. Italy does not have reimbursement although it is expected to be the case soon.
    b. Grade 2 glioma is not reimbursed in France.
    c. Reimbursement of benign meningeoma should be checked. Is it reimbursed anywhere?
    d. Replace 'paranasal sinus tumours' by 'non-squamous cell head and neck cancer including paranasal sinus tumours'.
    e. Sacral and coccygeal chordoma/chondrosarcoma: replace 'neo-adjuvant' by 'adjuvant'.
8. Table 3:
    a. Investigate locally advanced high-grade prostate cancer.
    b. Nr. 5 H&N tumours add carbon.
    c. Stage I lung and pleural: add proton (trials in USA).
    d. HCC add proton.
9. Cholangiocharcinoma cause challenging targets because of tree-like spread along the biliary tracts and its vicinity to duodenum. Intra-hepatic cholangiocarcinoma is accepted at NIRS.
10. p22 end of 1st paragraph. Skin is a critical organ for particle therapy unless the superficial part of the parotid is not target. Then scanning techniques allow for some skin sparing.
11. Most model indications are supported by single-institution clinical studies: NIRS, Japan.

12. Most model indications are technically challenging. A horizontal beam is not sufficient. Many model indications call for a gantry. Techniques to treat moving targets are needed for some model indications.
13. Standard indications are technically less challenging. Most can be treated with a horizontal beam. It is not logical to send these indications abroad. If a future BHTC can master pancreas, lung or HCC, why send the 'easy' standard indications abroad?

Submodule 2

Number of fractions per patient is a snapshot. It tends to decrease, hence increasing capacity of the centre.

Submodule 3

1. Commonly used indices of capacity should be added to the tables:
    a. Number of fractions/day
    b. Number of fractions/year
2. Too much credit is given to the opinion of experts. The BHTC working group should take more responsibility and make choices.
3. The main problems of European carbon ion installations are speed and intensity. The European technology is slow as compared to the Japanese. This affects throughput, negatively.
4. Result of a long discussion: DO NOT COMBINE PROTONS AND CARBON IONS ON THE SAME INSTALLATION. If Belgium evolves to a single centre and needs both modalities install separate equipment for proton and carbon at the same site. Cfr. the idea at Heidelberg to build a one-room proton centre next to HIT.

Submodule 4

The methodology of the cost calculations was highly valued. The business and ABC modeling were performed in an unbiased philosophy. No sign of hidden costs. The patient numbers are realistically achievable with today's technology. No tendency to claim the treatment of enormous numbers of patients to make cost figures more acceptable. No tendency to underestimate personnel needs; rather the contrary. Maintenance and energy cost seem realistic.

1. The investment estimates for the carbon-only and the mixed scenarios were considered as the weakest points.
    a. Since these are the major determinants of cost the uncertain investment cost estimates cast doubt on the results of the outcome of the 3 approaches
        I. Business model
        II. ABC model
        III. Cost-utility analysis
    b. It was advised to perform an investment cost estimate through the vendors
        I. The number of scenarios should be reduced to 1-2.
        II. Short specifications should be written for the scenario(s):
            1. the team of one of the experts could be asked to make a first draft.
            2. Organize a committee meeting to fine-tune the specifications.
        III. Ask the vendors to provide a cost estimate for equipment and building.
        IV. Paying the companies for their work seems mandatory because the Belgian hadron project has not gained enough credibility regarding its realization.
        V. A juridical support is needed. Cave the problems that pre-negotiations caused at Uppsala.
    c. A fast round on investment cost through the European projects which have passed a tendering effort is suggested
        I. Med-Austron, Vienna, Austria
        II. Etoile, Lyon, France
        III. Archade, Caen, France?
3. The personnel estimates need further refinement with the remaining scenario(s).
4. Prof Y. Lievens presented the preliminary results of the cost-utility analysis for locally advanced pancreatic cancer (model indication 1).
    a. Highly appreciated by the expert team.
    b. Cost-utility analysis seems performed in an unbiased philosophy. No tendency to 'favor' hadron therapy over conventional radiation therapy.
    c. The investment cost for a carbon ion facility may have been underestimated. The comparison between carbon ion and proton may be biased in favor of carbon ion if the investment cost is underestimated for carbon ion.

December 5

The second day of 4th expert meeting was dedicated to deriving overall conclusions from the feasibility study and defining the subject to be studied during the second phase of the study.

1. Overall conclusions
    a. Paediatric and adult indications should be treated in Belgium
    b. Model indications should be treated to secure sustainable operations
        I. This implies that research must be added to the scope
        II. A gantry seems a necessity also for carbon ion treatments
        III. Scanning is preferred
    c. Public or mixed funding of investment cost is a necessity in Europe
    d. Reducing the number of scenarios to
        I. Carbon ion only centre
        II. Mixed proton-carbon ion centre which is the same as i. plus a 1- or 2-room proton therapy unit at the same implantation site. The latter will come at reduced cost as compared to the estimates in submodules 3 and 4 since it uses the auxiliary support functions of the carbon ion centre.
    e. Carbon ion only centre could be the preferred option for BHTC if the UCL-IBA-HU St.Luc-Walloon_Region project is realized.

2. Subject of the second phase of the feasibility study: towards a business plan
    a. Organisation model
    b. Limited call for bids. Companies are expected to provide valuable information for a future comprehensive technical description (what we (wrongly?) called comprehensive business plan)
        I. Carbon only scenario
        II. Twin scenario: carbon only + proton only
        III. Suggested companies: Mitsubishi, Toshiba, IBA
        IV. Juridical coverage of the procedure
    c. Cost-utility analysis of all model indications to determine priority ranking
    d. Analyzing candidate model indications

I. Neuroblastoma
II. Locally advanced high-grade prostate cancer

d. Identifying research topics
I. Based on research strengths in Belgium
II. Uneven distribution of effort between the partners conducting the feasibility study. Will it be more balanced once research is added to the scope?

e. Identify who will perform the PR
I. Symposium together with NIRS and European partners?
II. Contact other disciplines than radiation oncology
III. Future stakeholders
IV. Public