Hadronentherapie bei Kindern

Evidenzsynthese zu 15 pädiatrischen Tumoren

Kontext zum belgischen HTA-Bericht

Ludwig Boltzmann Institut
Health Technology Assessment

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Hadron Therapy – an Update of the Scientific Evidence for Specific Paediatric Indications

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1 Einleitung

herkömmliche Strahlentherapie: Photonen

Die herkömmliche *Photonen*-Strahlentherapie hat sich in den letzten 1–2 Jahrzehnten stark weiterentwickelt hin zu schonenderen und nebenwirkungsärmeren Verfahren. Verantwortlich dafür sind nicht nur die zunehmende Präzision der Verfahren, sondern auch die Fraktionierung der Gesamtdosis in kleinere Dosen, bis hin zur Hyperfraktionierung (mehrmals tägliche Bestrahlung).

Partikeltherapie (Hadronentherapie): Protonen und C-Ionen

MedAustron seit 2015 in Betrieb

Seit den späten 90er Jahren haben einige Zentren weltweit eine Strahlentherapie begonnen, die *Partikeltherapie (Hadrontherapie)*, die mit *Protonen* und Kohlenstoff/*C-Ionen* arbeitet. Das Verfahren wird insbesondere bei PatientInnen angewandt, bei denen die herkömmliche Photonen-Bestrahlung nicht ausreichend genutzt werden kann, weil der Tumor entweder zu tief im Körper sitzt oder aber von empfindlichen Organen umgeben ist. Anfang 2015 ging auch das österreichische MedAustron in Betrieb.

Zusammenfassung von HTAs in LBI-HTA Bericht 2013

Evidenz zu klinischen Ergebnissen (Tumorkontrolle und Krebssterblichkeit) und zu Nebenwirkungen

Zahlreiche Assessments (zusammengefasst im LBI-HTA Bericht 2013, [1]) haben sich in den letzten Jahren damit befasst, die wissenschaftliche Evidenz aus klinischen Studien zur Hadronentherapie zusammenzufassen. Die PatientInnen-relevante Fragestellung zur Überprüfung des Nutzens jedweder Radiotherapie ist, welche der Strahlentherapien (Photonen, Hadronen) zu besseren klinischen Ergebnissen bei geringerem Nebenwirkungsprofil führt. Gemessen kann dies in vergleichenden Studien durch verbesserte Tumorkontrolle (validiert durch Reduktion der Krebssterblichkeit) bei gleichzeitig verringerten (Umfeld-) Normalgewebsschädigungen (und entsprechender Lebensqualität) sowie geringeren Langzeitschäden (gemessen an Reduktion der Radiotherapie-induzierten schwerwiegenden Nebenwirkungen und der sekundären Malignome) werden.

Belgisches HTA (2015): Evidenz zur Hadronentherapie bei pädiatrischen Tumoren eingebettet in österreichische Daten

Ein rezentes (Jänner 2015) belgisches Assessment [2, 3] befasste sich – als update des 2007 Berichts [4] – *nur* mit der Evidenz zur Hadronentherapie bei pädiatrischen Tumoren. Im Zuge verstärkter Europäischer Zusammenarbeit, wurde das LBI-HTA bereits in die Erstellung des belgischen Berichts einbezogen. Dieser vorliegende Bericht bettet die belgischen HTA-Ergebnisse in österreichische Daten zu Kindertumoren ein.

1.1 Krankheitslast: Malignome bei Kindern

Österreich: etwa 250 Krebs-Neuerkrankungen jährlich

In Österreich werden etwa 250 Krebs-Neuerkrankungen bei Kindern (0–14 Jahre) und Jugendlichen (15–19 Jahre) verzeichnet [5], insgesamt 2.598 Erkrankungen in den letzten 10 Jahren (2002–2011) [6].

Leukämie ist häufigste Krebserkrankung im Kindesalter

80–90 Kinder pro Jahr

wenige Schädelbestrahlungen

Leukämie ist die häufigste Krebsart im Kindesalter (28 %): etwa 80-90 Kinder erkranken jährlich an akuter Leukämie; insgesamt 719 (von 2.598) Erkrankungen in den letzten 10 Jahren (2002–2011) [6]. Leukämie bezeichnet eine Gruppe von bösartigen Erkrankungen des blutbildenden Systems. Die akute lymphoblastische Leukämie (ALL) betrifft etwa 80 % der an Leukämie erkrankten Kinder (im Alter von 2 bis 8 Jahren, ca 55–60 Kinder und Jugendliche pro Jahr). Die akute myeloische Leukämie (AML) betrifft etwa 20 % der Kinder (ca 20–25 Kinder pro Jahr). Chronische myeloische Leukämien (CML) spielen bei Kindern eine untergeordnete Bedeutung. Über 80 % aller ALL Kinder und etwa 60 % aller AML Kinder können geheilt werden. Nur wenige ALL-PatientInnen bedürfen – etwa bei einem manifesten Befall des ZNS/Zentralnervensystems – einer Schädelbestrahlung [7]. Die Strahlentherapie wird bei nicht-lymphatischer Leukämie (AML) meist als Vorbereitung für die Stammzelltransplantation durchgeführt [8].

Tabelle 1-1: Krebserkrankungen im Kindesalter (Österreich) 2002–2011, absolut

Alle	**2.598**
Leukämie	719
Lymphom	421
Zentralnervensystem	421
Tumor von Muskeln und Bindegewebe	173
Knochentumor	153
Keimzelltumor	143
Neuroblastom	140
Malignes Melanom	116
Nierentumor	101
Sonstiger Tumor	211

Sonstige Tumore *211*

Andere bösartige epitheliale Neoplasmen ohne Melanome	151
Andere unspezifizierte bösartige Neoplasmen	26
Nicht klassifizierte ICCC oder in situ	0
Retinoblastom	23
Lebertumor	11

Quelle: Statistik Austria [6]

Lymphome (Hodgkin und Non-Hodgkin Erkrankung)

33–40 Kinder pro Jahr

Strahlentherapie in Kombination mit Chemotherapie

Lymphome (Hodgkin und Non-Hodgkin Erkrankung) sind bösartige Tumore, die vom Lymphdrüsengewebe ausgehen und Lymphknoten bilden, die dicht an der Körperoberfläche und zu 80 % im Hals-Kopfbereich liegen. Lymphome sind die zweithäufigste Krebserkrankung im Kindesalter (16 %). Etwa 33–40 Neuerkrankungen pro Jahr und insgesamt 421 (von 2.598) Erkrankungen sind in den letzten 10 Jahren (2002–2011) [6] registriert. Hodgkin-Lymphome treten eher bei Jugendlichen (ca. 15 Neuerkrankungen pro Jahr), Non-Hodgkin-Lymphome (18–25 Neuerkrankungen pro Jahr) eher bei Kindern auf. Die Behandlung besteht immer aus einer Chemotherapie oder einer Kombination mit einer Strahlentherapie [9, 10]. 70–90 % der erkrankten Kinder und Jugendlichen können geheilt werden [5].

Tumore des ZNS/Hirntumore

niedrig- und hochgradige Gliome, Medulloblastome, Ependymome, Kraniopharyngeome

63 Kinder pro Jahr

oft auch Strahlentherapie, aber wegen zu erwartenden langfristigen Folgen oft verschoben oder auf kleinen Teil des Gehirns beschränkt

Tumore des ZNS/Zentralnervensystems, intrakraniale und intraspinale Tumore (niedriggradige Gliome wie Astrozytome, Gangliogliome und Oligodendrogliome, hochgradige Gliome wie anaplastisches Astrozytom und Glioblastom, Medulloblastome wie primitive neuroektodermale Tumoren/PNET sowie Ependymome und Kraniopharyngeome) treten bei Kindern und Jugendlichen in allen Altersstufen auf, insb. aber zwischen dem 5. und 10. Lebensjahr. Hirntumore sind – ebenso wie Lymphome – die zweithäufigste Krebserkrankung im Kindesalter (16 %). Etwa 15 % aller kindlichen Hirntumoren, ca. 10 pro Jahr, sind Medulloblastome [11] und ca 5–10 sind Ependymome [12]. Etwa 63 Hirntumor-Neuerkrankungen pro Jahr treten auf und insgesamt sind 421 (von 2.598) Erkrankungen in den letzten 10 Jahren (2002–2011) [6] registriert. Die Gefährlichkeit von Hirntumoren hängt wesentlich von Lage, Gewebeart und Ausdehnung ab. Heilungschancen liegen zwischen 20 % und 90 % [5]. Nach operativer Entfernung des Tumors besteht eine Behandlung meist aus Chemotherapie und Bestrahlung. Bei kleinen Kindern wird die Bestrahlung wegen der zu erwartenden langfristigen Folgen so lange wie möglich verschoben oder auf einen kleinen Teil des Gehirns beschränkt [13, 14].

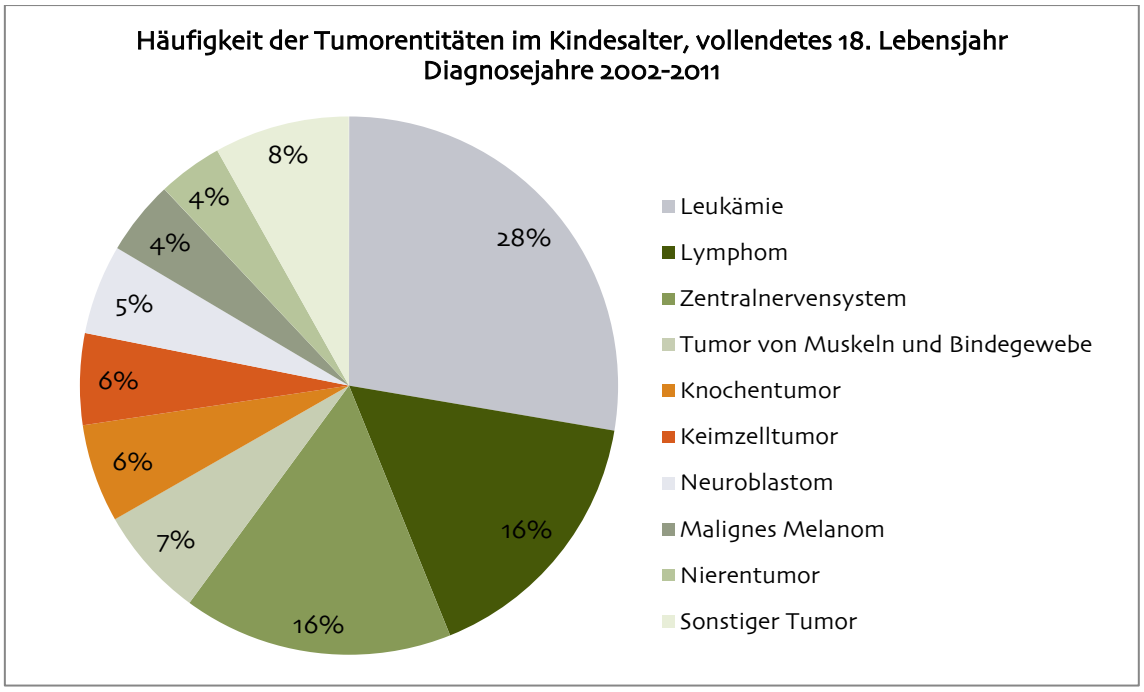

Abbildung 1-1: Krebserkrankungen im Kindesalter (Österreich) 2002–2011, relativ, Quelle: Statistik Austria [6]

Weichteiltumore

Rhabdomyosarkom
15 Kinder pro Jahr

manchmal
Strahlentherapie

Tumore von Muskeln und Bindegewebe werden auch Weichteiltumore genannt. Das häufigste – das Rhabdomyosarkom – ist ein Tumor, der im quergestreiften Muskelgewebe entsteht. Andere Weichteiltumore werden im glatten Muskelgewebe (Leiomyo-), im Bindegewebe (Fibro und Desmoid-), in den Blutgefäßen (Angio- oder Hämangio-), in der Schleimhaut der Gelenkskapsel (Synovial-) oder im Fettgewebe (Lipo-)gebildet [15]). Jedes Jahr erkranken in Österreich ca. 15 Kinder an einem Weichteiltumor. Ingesamt sind 173 Erkrankungen (7 % von 2.598) in den letzten 10 Jahren (2002–2011) [6] registriert. Die Behandlung eines Rhabdomyosarkoms setzt sich aus einer Chemotherapie, einer Operation und manchmal auch einer Strahlentherapie zusammen. Es überleben 80 % der erkrankten Kinder länger als 2 Jahre. Geheilt können etwa 50 % werden [5].

Knochentumore

Osteosarkome,
Ewing-Tumore,
Chondrosarkome

8–15 Kinder pro Jahr

manchmal
Strahlentherapie

Osteosarkome entstehen im Knochengewebe, Ewing-Tumoren in den Nervenzellen der Knochen und des Knochenmarks sowie manchmal auch außerhalb des Knochens, während Chondrosarkome im Knorpelgewebe vorkommen [16]. Jedes Jahr erkranken in Österreich ungefähr 8 bis 15 Kinder und Jugendliche an einem Knochentumor; Ingesamt sind 153 Erkrankungen (6 % von 2.598) in den letzten 10 Jahren (2002–2011) [6] registriert. Osteosarkome und Ewing-Tumore treten öfter auf als die sehr seltenen Chondrosarkome. Nach einer Operation und Chemotherapie folgt zur Behandlung manchmal auch eine Strahlentherapie. Die Heilungschancen von Kindern und Jugendlichen mit Knochentumoren liegen zwischen 60–70 % und hängen vom Ort ab, an dem sich der Tumor befindet.

Keimzelltumore

5–8 Kinder pro Jahr

Strahlentherapie ev.
bei Metastasierung

Keimzelltumore sind sehr seltene Erkrankungen, die in den Hoden und Eierstöcken, aber auch in anderen Geweben ihren Ursprung haben. Jedes Jahr wird in Österreich bei ungefähr 5 bis 8 Kindern ein Keimzelltumor entdeckt [17]. Ingesamt sind 143 Erkrankungen (6 % von 2.598) in den letzten 10 Jahren (2002–2011) [6] registriert. 80 % der Kinder können geheilt werden. Kann der Keimzelltumor nicht vollständig entfernt werden oder kommt es zu Metastasierungen, bekommt das Kind in jedem Fall eine Chemotherapie und/ oder Strahlentherapie.

Neuroblastom

25 Kinder pro Jahr

Strahlentherapie
nur bei
metastasierenden
Tumoren

Das Neuroblastom ist eine bösartige Erkrankung des sympathischen Nervensystems: Neuroblastome treten im Bauch-, Becken-, Brust- oder Halsbereich auf. Es werden etwa 25 Neuerkrankungen pro Jahr entdeckt [18] und 140 Erkrankungen (5 % von 2.598) sind in den letzten 10 Jahren (2002-2011) [6] registriert. Betroffen sind Kinder bis zum 8. Lebensjahr [5]. In einem Viertel aller Fälle treten erste Anzeichen (Knoten, Schwellungen etc.) bereits innerhalb der ersten 12 Monate auf. Tritt ein Neuroblastom im Babyalter auf, kann es zumeist geheilt werden. Bei metastasierenden Tumoren (Stadium 4) kann bei ausgewählten Tumorlokalisationen zusätzlich zur Operation und Chemotherapie eine Strahlentherapie angewandt werden.

Malignes Melanom

10–12 Kinder pro Jahr

Das maligne Melanom, Hautkrebs ist eine seltene Krebserkrankung im Kindesalter. Jedes Jahr erkranken in Österreich ungefähr 10–12 Kinder an einem Hautkrebs. 116 (4 % von 2.598) Neuerkrankungen sind in den letzten 10 Jahren (2002-2011) [6] registriert.

Nephroblastom,
Wilms-Tumor
10-12 Kinder pro Jahr
manchmal
Strahlentherapie

Der Wilmstumor oder Nephroblastom ist ein bösartiges Geschwulst der Niere, das in 50 % der Fälle bis zum 3. Lebensjahr auftritt. Jedes Jahr erkranken in Österreich ungefähr 10–12 Kinder an einem Nephroblastom; insgesamt sind 101 (4 % von 2.598) in den letzten 10 Jahren (2002–2011) [6] registriert. Die Heilung liegt bei 80-90 % der Kinder. Eine Strahlentherapie kann manchmal, neben der Chemotherapie notwendig sein [19].

Retinoblastom
4 Kinder pro Jahr
Strahlentherapie selten

Das Retinoblastom ist eine sehr seltene Erkrankung von Zellen der Netzhaut. Betroffen sind vor allem Säuglinge und Kleinkinder bis 5 Jahre [5]. In 25-30 % der Fälle sind beide Augen betroffen. Jedes Jahr erkranken in Österreich ungefähr 4 Kinder an einem Retinoblastom. insgesamt sind 23 (1 % von 2.598) in den letzten 10 Jahren (2002–2011) [6] registriert. Kinder mit einem Retinoblastom haben Heilungschancen von über 90 %, wobei allerdings die Größe und die Ausbreitung des Tumors eine Rolle spielt [20]. Nur in wenigen Fällen kommt eine Strahlentherapie zu Anwendung.

Hepatozelluläre Karzinome
1 Kind pro Jahr

Hepatozelluläre Karzinome sind bei Kinder und Jugendlichen sehr selten (0,4 %, 11 in 10 Jahren, 2002–2011) [6]. Chirurgische Entfernung des Tumors, gefolgt von Chemotherapie sind die und Behandlungen der Wahl. Die Heilungschancen liegen bei 50 % [5].

Tabelle 1-2: Krebserkrankungen im Kindesalter (Österreich) 2002–2011, nach Alter der Erkrankung

International Classification of Childhood Cancer	Alle 2002-2011	Alter				
		0<1	1<5	5<15	15<18	18<19
	N	N	N	N	N	N
Alle	2.598	166	561	1.077	585	209
I Leukemias, myeloproliferative diseases, and myelodysplastic diseases	719	30	254	307	99	29
II Lymphomas and reticuloendothelial neoplasms	421	4	19	193	156	49
III CNS and miscellaneous intracranial and intraspinal neoplasms	421	22	94	224	70	11
IV Neuroblastoma and other peripheral nervous cell tumors	140	51	65	21	3	0
V Retinoblastoma	23	10	12	1	0	0
VI Renal tumors	101	19	58	22	1	1
VII Hepatic tumors	11	3	4	3	1	0
VIII Malignant bone tumors	153	0	7	97	37	12
IX Soft tissue and other extraosseous sarcomas	173	14	33	75	38	13
X Germ cell tumors, trophoblastic tumors, and neoplasms of gonads	143	8	8	41	56	30
XI Other malignant epithelial neoplasms, without malignant melanomas	151	0	2	47	55	47
XI Other malignant epithelial neoplasms, only malignant melanomas	116	1	1	40	58	16
XII Other and unspecified malignant neoplasms	26	4	4	6	11	1

Quelle: Statistik Austria [6]

1.2 Krankheitslast: Spätfolgen

hohe Überlebensraten

ABER: Balance zwischen Heilung und langfristigen Folgen für Gesundheit Survivorship-Pass

Aufgrund therapeutischer Verbesserungen sind die Überlebensraten unter krebskranken Kindern und Jugendlichen groß. Die Herausforderung in der Krebstherapie stellt aber – neben dem Überleben – die Balance zwischen Heilung und langfristiger Morbidität der Überlebenden dar. Im österreichischen Krebsrahmenprogramm ist als *ein* vorrangiges Ziel, die Einführung eines Survivorship-Passes [21], in dem auch langfristig die Daten der KrebspatientInnen dokumentiert werden, geplant.

30 Jahre nach Krebs im Kinder-und Jugendalter

73 % chronische Gesundheitsprobleme

42 % schwerwiegende Gesundheitsprobleme: Sekundäre Tumore, Nebenwirkungen der Therapien

Tatsächlich ist die Krankheitslast durch chronische Erkrankungen groß: 30 Jahre nach der Diagnose Krebs im Kinder-und Jugendalter beträgt die kumulative Inzidenz von chronischen Gesundheitsproblemen 73,4 % (95 % CI; 69,0–77,9), mit einer kumulativen Inzidenz von schwerwiegenden und lebensbedrohlichen Gesundheitszuständen von 42 % (95 % CI; 33,7–51,2) [22]. Die Risiken der Überlebenden nach Krebs sind – bedingt ebenso durch Rezidive wie durch die langfristigen Nebenwirkungen von Behandlungen des Primärtumors – späte Mortalität, sekundäre Neoplasmen, aber auch kardio-vaskuläre Erkrankungen, Organdysfunktionen oder Wachstumsverzögerung [22-25].

Spätfolgen von Strahlentherapie am Kopf:

neurokognitive Defizit, endokrine Störungen, Wachstumsverzögerung, etc.

Strahlentherapie ist eine wesentliche Komponente im Behandlungsspektrum von Neoplasmen im Kindes- und Jugendalter. Unglücklicherweise sind Kinder- und Jugendliche nicht nur sehr empfänglich im Ansprechen auf Strahlentherapie, sondern reagieren auch sehr empfindlich auf die Exposition durch radiotherapeutische Strahlenbelastung, was zu späten schweren Nebenwirkungen auch bei geringen Strahlendosen führen kann. Die Strahlenexposition des Gehirns ist mit neurokognitiven Defiziten, endokrinen Dysfunktionen bis zu Hörverlust assoziiert. Insb. Kinder unter 7 Jahren sind hier stärker betroffen [26, 27], weswegen im Behandlungsplan Radiotherapie häufig verschoben oder ersetzt wird. Diese Nebenwirkungen können aber auch durch die Erkrankung selbst (Gehirntumor) oder andere Therapien wie Chemotherapie oder chirurgische Exzision des Tumors, verursacht werden. Weiters kann kraniospinale Bestrahlung zu Schilddrüsendysfunktion und zu spinaler Wachstumsbeeinträchtigung und zu Schädigungen der Lunge, am Herz und bei intestinale Funktionen führen [27, 28].

sekundäre Malignome frühestens 5–19 Jahre nach der Bestrahlung

6-fach erhöhtes Risiko

schlechte Datenlage wegen langer Nachbeobachtungszeit

Sekundäre Tumore sind die häufigste Todesursache unter Überlebenden. Die Childhood Cancer Survivor Study (mit einer Kohorte von 14.000 PatientInnen) zeigt eine 30-Jahres kumulative Inzidenz von 7,9 % (95 % CI; 7,2–8,5) für sekundäre Neoplasmen, was einem 6-fach erhöhtem Risiko – im Vergleich zur allgemeinen Bevölkerung – entspricht [29-31]. Die Tumore treten frühestens 5–19 Jahre nach der Bestrahlung auf. Radiotherapie-induzierte Malignome können sowohl in den benachbarten Regionen oder auch in entfernten Körperregionen zu Karzinomen führen. Sarkome treten dagegen an derselben Stelle oder in unmittelbarer Nähe zur bestrahlten Region auf [32]. Eine Untersuchung von 115 Sekundärmalignomen zeigte, dass 66 % der Tumore in der benachbarten Region, 22 % mehr als 5 cm entfernt und nur 12 % im Zentrum der ehedem bestrahlten Region lagen [33]. Die Daten zu Strahlentherapie-induzierten sekundären Malignomen sind aber wegen der langen Nachbeobachtungszeit von 25–30 Jahren und in Ermangelung von Kontrollgruppen beschränkt: die Childhood Cancer Survivor Study zeigt auch, dass das Risiko zu Sekundärtumoren über die Jahre steigt und kein Plateau – auch 30 Jahre nach Behandlung – aufweist [34].

Zusammenfassend ist zu sagen, dass das Ziel der Behandlung von Tumoren im Kinder- und Jugendalter nicht nur deren Heilung, sondern auch die Vermeidung von langfristigen schwerwiegenden Nebenwirkungen sowie die Vermeidung von sekundären Malignomen ist. Es wird angenommen, dass die Reduktion der Bestrahlung von – dem Tumor – benachbartem Gewebe auch zu einer Reduktion von langfristigen Nebenwirkungen und Folgemalignomen führt. Die Anwendung von Protonentherapie kann die integrale Strahlendosis um einen Faktor 2–3 im Vergleich zur konventionellen Photonentherapie oder zur IMRT/Intensity modulated photon therapy reduzieren [35]. Deshalb wird angenommen, dass die Protonentherapie auch geringere langfristige Nebenwirkungen hat.

Ziel der Behandlung von Tumoren im Kinder- und Jugendalter: Heilung UND Vermeidung von langfristigen schwerwiegenden Nebenwirkungen

2 Zusammenfassung der Ergebnisse des KCE-Reviews

Update zu 2007 Bericht

Der belgische HTA-Bericht „Hadron Therapy in Children – an update of the scientific evidence for 15 paediatric cancers“ [2, 3] setzte auf den ersten, bereits 2007 veröffentlichten Bericht [4] auf und wertete die klinische Evidenz zur Wirksamkeit der Hadronentherapie in 15 Indikationen aus. Es konnten insgesamt 21 klinische Studien zu den Indikationen gefunden werden. Eine systematische Suche nach relevanten Publikationen wurde in drei Datenbanken (Medline via OVID, EMBASE, Cochrane Library) durchgeführt. Systematische Reviews und Primärstudien zur Protonentherapie und/oder Kohlenstoffionentherapie veröffentlicht zwischen 2007 bis März 2014 wurden gesucht (ein letztes Update der Suche erfolgte im September 2014).

systematische Suche in 3 Datenbanken

21 klinische Studien

Qualitätsbeurteilung der vorliegenden Evidenz mit GRADE

Abseits der Studiendesigns (nicht-randomisiert, nicht-kontrolliert und retrospektiv) der Studien – mit den für diese Art von charakteristischen Einschränkungen (z. B. Selektionsbias, Recall-Bias) –, zeigten alle Studien schwere methodische Mängel (u. a. kleine Stichproben, lange Zeiträume beim Einschluss der PatientInnen, unterschiedliche Behandlungsschemata, kurze Follow-ups, Berichterstattung oder Dokumentation von Komplikationen nur bei einem Teil der PatientInnen). Unter Anwendung von GRADE war die wissenschaftliche Evidenzlage für alle Ergebnisse in allen Indikationen war sehr gering.

sehr niedrige Qualität der Evidenz

Ergebnisse: in 13 von 15 Indikationen: Evidenz unzureichend, keine Aussage möglich in 2 Indikationen: niedrige Evidenz

Die Ergebnisse sind in Tabelle 2-1 zusammengefasst und sagen aus, dass in 13 von 15 Indikationen die Evidenz unzureichend ist, um Aussagen zugunsten oder gegen Hadronentherapie zu machen. In 2 Indikationen liegt sehr niedrige Evidenz, die für Gleichwertigkeit zwischen Protonentherapie und IMRT/ Intensitätsmodulierte Strahlentherapie beim Craniopharyngioma, resp. einem geringeren Risiko für Sekundärtumore beim Retinoblastom spricht.

Schlussfolgerung: es fehlt weiterhin an klinischen Daten zur Protonentherapie

Hoffnung vs. Belege

Die Schlussfolgerung lautet dementsprechend, dass weiterhin klinische Daten zur Protonentherapie in allen untersuchten pädiatrischen Krebserkrankungen zur langfristigen Wirksamkeit und zu Nebenwirkungen fehlen. Nur bei sehr wenigen Tumoren ist die Protonentherapie wegen der in hohem Maße vorhersehbaren ernsthaften Schäden bei anderen Formen der Strahlentherapie als einzige Behandlungsmethode möglich. In den meisten Fällen gibt es eine Wahl. Die Hoffnungen auf bessere klinische Ergebnisse mit Protonentherapie sind nicht belegt.

Empfehlungen: PatientInnen-Informationen zum Mangel an Belegen

Folgende Empfehlungen werden ausgesprochen:

- PatientInnen (oder ihre Eltern und Angehörigen) sollte umfassend informiert werden, dass trotz der physischen Untermauerung der Protonentherapie, die klinische Wirksamkeit in den untersuchten Indikationen noch nicht in klinischen Studien bestätigt wurde.

Behandlung nur in Zentren mit Erfahrung mit Kindern, nur im Rahmen klinischer Studien

- Kinder sollten nur Protonen-Zentren mit dem notwendigen Know-how in der Behandlung von Kindern mit der spezifischen Pathologie und im Rahmen klinischer Studien mit Langzeit-Follow-up einbezogen werden.

Langzeit-Dokumentation

- Die genaue Dokumentation der Therapien zur langfristigen Nachbeobachtung etwa beim Auftreten von sekundären ist zu empfehlen.

- Es besteht die dringende Notwendigkeit für Forschung nicht nur zur klinischer Wirksamkeit, Nebenwirkungen und Schäden, aber auch den ökonomischen Auswirkungen, sowie zu den physikalischen und biologischen Mechanismen. Die klinische Forschung sollte international koordiniert durchgeführt werden.

international koordinierte Forschung

- Der Aufbau eines europäischen Hadronen-Therapie Registers ist zu empfehlen.

Aufbau eines europäischen Hadronen-Therapie Registers

Tabelle 2-1: Zusammenfassung der Ergebnisse und Konklusion

PROTONTHERAPY	
Skull base chondrosarcoma	1 retrospective Fallserie (n=7): insufficient scientific evidence to support or to refute
Skull base & (para)spinal chordoma	2 retrospective case series (n=41): At present insufficient scientific evidence to support or to refute
Craniopharyngioma	1 retrospective comparative study & 2 retrospective case series (n=74): At present very low level scientific evidence that PBT compared with IMRT does not result in significant differences in 3-yr OS, 3-yr CFFS, 3-yr NFFS, toxicity or cyst dynamics.
Ependymoma	1 prospective case series & 1 retrospective case series (n=78): At present insufficient scientific evidence to support or to refute
Esthesioneuroblastoma	1 retrospective case series (n=22): At present insufficient scientific evidence to support or to refute
Ewing sarcoma	1 retrospective case series (n=30): At present insufficient scientific evidence to support or to refute
CNS germinoma	1 retrospective case series (n=22): At present insufficient scientific evidence to support or to refute
Low-grade glioma (incl. optic pathway)	2 retrospective case series (n=38): At present insufficient scientific evidence to support or to refute
Medulloblastoma/ primitive neuroectodermal tumours (PNET)	None: At present insufficient scientific evidence to support or to refute
Non-resectable osteosarcoma	1 retrospective case series (n=55): At present insufficient scientific evidence to support or to refute
Pelvic sarcoma	None: At present no scientific evidence to support or to refute
Pineal parenchymal tumours („not pineoblastoma")	None: At present no scientific evidence to support or to refute
Retinoblastoma	1 retrospective comparative study (n=55): At present there is very low level scientific evidence that PBT results in lower risk of developing RT-induced in-field secondary malignancies. However, since radiation-induced solid malignancies need at least 5 to 10 years to develop and for some children in the study the follow-up was short, the results should be interpreted with caution.
Rhabdomyosarcoma	3 retrospective case series (n=36): At present insufficient scientific evidence to support or to refute
(Para)spinal 'adult type' soft tissue sarcoma	None: At present no scientific evidence to support or to refute
CARBON ION RADIOTHERAPY	
Non-resectable or incompletely resected high-grade osteosarcoma with or without metastases	1 retrospective case series (n=78): At present insufficient scientific evidence to support or to refute

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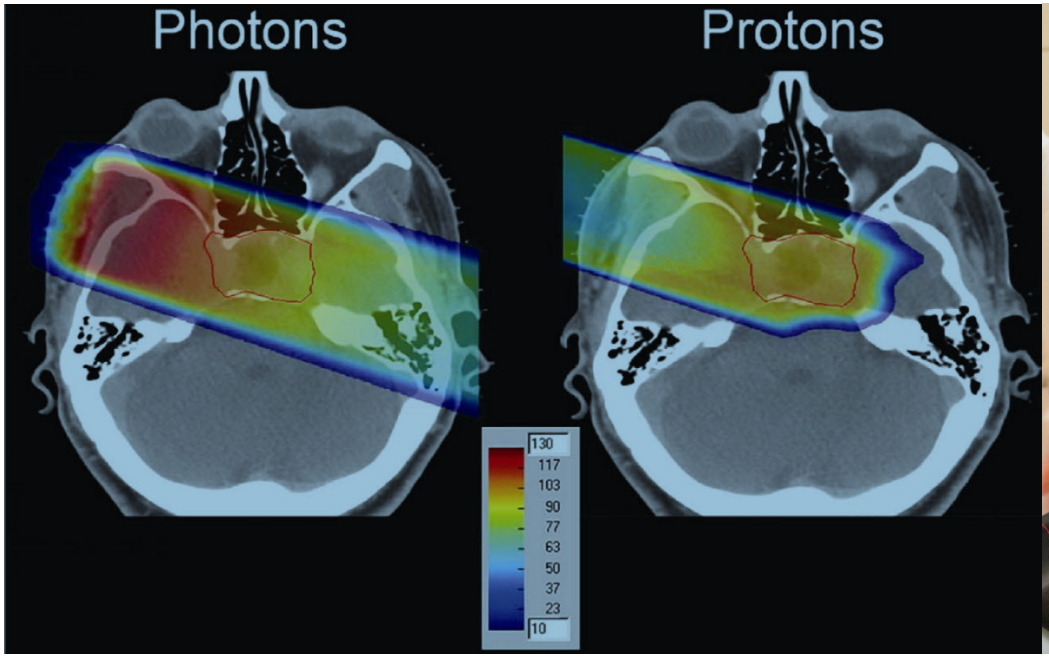
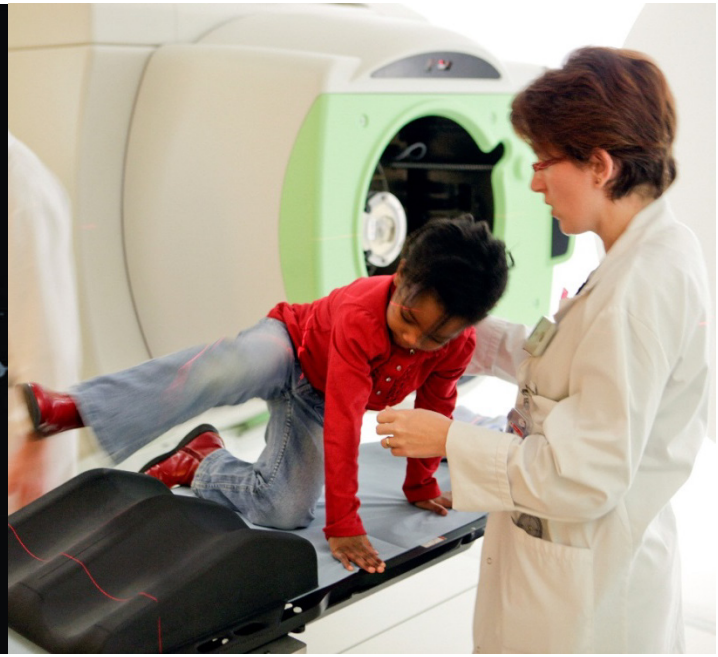
SYNTHESIS

HADRON THERAPY IN CHILDREN

AN UPDATE OF THE SCIENTIFIC EVIDENCE FOR 15 PAEDIATRIC CANCERS





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Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

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SYNTHESIS

HADRON THERAPY IN CHILDREN

AN UPDATE OF THE SCIENTIFIC EVIDENCE FOR 15 PAEDIATRIC CANCERS

ROOS LEROY, NADIA BENAHMED, FRANK HULSTAERT, FRANÇOISE MAMBOURG, NICOLAS FAIRON, LIESBET VAN EYCKEN, DIRK DE RUYSSCHER

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COLOPHON

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FOREWORD

If there is one area in health care that is emotionally difficult, it is paediatric oncology. The sight of a child suffering - of a dying child - is not only unbearable, it also evokes a feeling of rebelliousness, an appeal to do everything within our capabilities to save this child. And then there is this high-tech radiation technique, which promises to offer just that little bit extra. A form of radiation that is at least equally effective against the tumour, but clearly causes less collateral damage to the surrounding tissues and therefore should also cause fewer secondary tumours induced by the radiation itself. The physical models are convincing, the simulations are promising and the clinical experience appears to be positive.

The stakes are high in every respect, not only because this is about children with cancer. The price tag for a new proton centre can easily exceed 30 million Euros and the running costs are similarly high. Understandably, those who have set out on this path defend their case through thick and thin; and they are determined to conquer a place for this innovative technique in the health care landscape. From experience we know that this type of hi-tech innovations cannot be stopped anyway, and recent history seems to confirm this also for hadron centres.

It is a downright shame that - even after enormous global investments and at least 120,000 patients treated - there is still virtually no conclusive evidence to support the superiority of this technique in children. Whilst good international, multi-centre studies could quickly provide the required insights for a fraction of the investment costs, the centres and their protagonists mainly continue to act as rival SMEs who compete for patients. And one does not need to look to the suppliers of this heavy infrastructure for support for this type of studies.

So, in response to the question posed to us by the National Institute of Health and Disability Insurance (RIZIV – INAMI) whether there is now more evidence to support the reimbursed paediatric indications - the answer sadly remains “no”. Whilst awaiting the results of the few studies that are ongoing, there is probably little choice other than to give these young patients the benefit of the doubt, but without any guarantee that the result will eventually be positive. This is and remains too little, too late.

Christian LÉONARD
Deputy general director

Raf MERTENS
General director

SUMMARY

1 INTRODUCTION

Anno 2014 there are no hadron facilities in Belgium; Belgian citizens eligible for hadron therapy (i.e. proton beam therapy (PBT) or carbon ion radiotherapy (CIRT)) are sent abroad. From September 2014 on (and until the end of September 2017), the costs related to hadron therapy (i.e. the treatment, transport and accommodation) are reimbursed if the diagnosis is on the list of eligible indicationsa and if the "Agreement Council for Hadron Therapy" (akkoordraad/ conseil d'accord) approves the application.

The objective of this study was to evaluate the clinical effectiveness of proton beam (or carbon ion) therapy in those indications in children currently reimbursed by the National Institute for Health and Disability Insurance (RIZIV – INAMI). It concerns the following 16 indications:

Proton beam therapy
Skull base chondrosarcoma
Skull base & (para)spinal chordoma
Craniopharyngioma
Ependymoma
Esthesioneuroblastoma
Ewing sarcoma
CNS germinoma
Low-grade glioma (incl. optic pathway)
Medulloblastoma / primitive neuroectodermal tumours (PNET)
Non-resectable osteosarcoma
Pelvic sarcoma
Pineal parenchymal tumours (not pineoblastoma)
Retinoblastoma
Rhabdomyosarcoma
(Para)spinal 'adult type' soft tissue sarcoma

a http://www.riziv.fgov.be/nl/professionals/verzorgingsinstellingen/ziekenhuizen/zorg/Paginas/Hadron-english.aspx; for osteosarcoma PBT & CIRT are considered, leading to 16 indications in 15 cancers.

Carbon ion radiotherapy

Non-resectable or incompletely resected high-grade osteosarcoma with or without metastases

2 METHODS

A systematic search for relevant publications was carried out in Medline, EMBASE, and the Cochrane Library. Reviews and primary studies on proton beam therapy and/or carbon ion therapy published between 2007 (i.e. end date of search strategy of previous KCE Hadron HTA[1]) up to March 2014 were searched. An overview of the inclusion and exclusion criteria, the search strategy and the flow chart of the selection process are provided in the Supplement. A final update of the search (restricted to Medline) was performed on September 11, 2014.

3 RESULTS

After selection, we retrieved 21 primary studies on the 16 potential indications under study. On top of the non-randomized, non-controlled and retrospective nature of the majority of retrieved studies - with the limitations characteristic of these types of studies (e.g. selection bias, recall bias) - all studies suffered from very serious methodological limitations (among others small sample size, long enrolment period, no clear inclusion nor exclusion criteria, variable treatment schemes, short follow-up, no information on the methods and intervals of follow-up, complications only assessed in a subset of patients) and hence when GRADE[2] was applied, the level of scientific evidence for all outcomes in all indications was very low.

- For retinoblastoma there is very low level scientific evidence that PBT results in a lower risk of developing RT-induced in-field secondary malignancies. However, since radiation-induced solid malignancies need at least five to ten years to develop and for some children in the study the follow-up was short, the results should be interpreted with caution.
- For craniopharyngioma there is very low level scientific evidence that PBT compared with intensity modulated radiotherapy (IMRT) did not result in significant differences in overall survival, cystic failure-free survival, nodular failure-free survival, toxicity or cyst dynamics.
- For chondrosarcoma, chordoma, ependymoma, esthesioneuroblastoma, Ewing sarcoma, CNS germinoma, glioma, medulloblastoma, non-resectable osteosarcoma (for PBT as well as CIRT) and rhabdomyosarcoma there is insufficient scientific evidence to support or to refute the use of PBT (or CIRT) in children.
- For pelvic sarcoma, pineal parenchymal tumour, PNET and (para-)spinal “adult type” soft tissue sarcoma there is no scientific evidence to support or to refute the use of PBT in children.

Based on the 2004-2011 data provided by the Belgian Cancer Registry, it can be estimated that in Belgium 37 children (0-14 y.o.) and 14 adolescents (15-19 y.o.) may be eligible for radiotherapy/proton beam therapy on a yearly basis.

4 CONCLUSIONS

Although there is no doubt that proton therapy reduces the radiation dose to normal tissues and organs, to date clinical data on PBT in all paediatric cancers under study is lacking critical information on measures of long-term effectiveness and harm. Prospective comparative clinical trials in the field are urgently needed.

SYNTHESIS

LIST OF FIGURES

LIST OF ABBREVIATIONS & ACRONYMS

ABBREVIATION	DEFINITION
BCR	Belgian cancer registry
CFFS	Cystic failure-free survival
CIRT	Carbon ion radiotherapy
CNS	Central Nervous System
CSI	Craniospinal irradiation
DNA	Deoxyribonucleic acid
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HTA	Health technology assessment
IMRT	Intensity modulated radiotherapy
Incl.	Including
KCE	Belgian Health Care Knowledge Centre
MOC/COM	Multidisciplinary oncological consultation
NFFS	Nodular failure-free survival
OAR	Organs at risk
OS	Overall survival
PBT	Proton beam therapy
PNET	Primitive neuroectodermal tumours
RBE	Relative biological effectiveness
RIZIV-INAMI	National Institute for Health and Disability Insurance (Rijksinstituut voor Ziekte- en Invaliditeitsverzekering - Institut National d'Assurance Maladie-Invalidité)
RT	Radiotherapy
SEER	Surveillance, Epidemiology and End Results (database)
SOBP	Spread Out Bragg peak
STS	Soft tissue sarcomas
y.o.	Years old

1 INTRODUCTION

1.1 Rationale & research questions

Anno 2014 there are no hadron facilities in Belgium; Belgian citizens eligible for hadron therapy are sent abroad. From September 2014 on (and until the end of September 2017), the costs related to hadron therapy (i.e. the treatment, transport and accommodation) are reimbursed through a specially earmarked budget of € 3.6 million per year (an amount that is index-linked). A list of eligible indications for children (and adults) has been defined[b]; this list was based on the Feasibility study of a Hadron Therapy Centre in Belgium (2013)[3]. The "Agreement Council for Hadron Therapy" (Akkoordraad voor de begeleiding van hadrontherapie/Conseil d'accord pour l'accompagnement de l'hadronthérapie) evaluates every application and decides whether the treatment is reimbursed.

The objective of this study was to evaluate the clinical effectiveness of proton beam (or carbon ion) therapy in the 16 indications in children currently reimbursed by the National Institute for Health and Disability Insurance (RIZIV – INAMI). It concerns the following indications:

Proton beam therapy

- Skull base chondrosarcoma
- Skull base & (para)spinal chordoma
- Craniopharyngioma
- Ependymoma
- Esthesioneuroblastoma
- Ewing sarcoma
- CNS germinoma
- Low-grade glioma (incl. optic pathway)
- Medulloblastoma / Primitive neuroectodermal tumours (PNET)
- Non-resectable osteosarcoma
- Pelvic sarcoma
- Pineal parenchymal tumours (not pineoblastoma)
- Retinoblastoma
- Rhabdomyosarcoma
- (Para)spinal 'adult type' soft tissue sarcoma

Carbon ion radiotherapy

- Non-resectable or incompletely resected high-grade osteosarcoma with or without metastases

[b] http://www.riziv.fgov.be/nl/professionals/verzorgingsinstellingen/ziekenhuizen/zorg/Paginas/Hadron-english.aspx; for osteosarcoma PBT & CIRT are considered, leading to 16 indications in 15 cancers.

1. 2 What is hadron therapy?

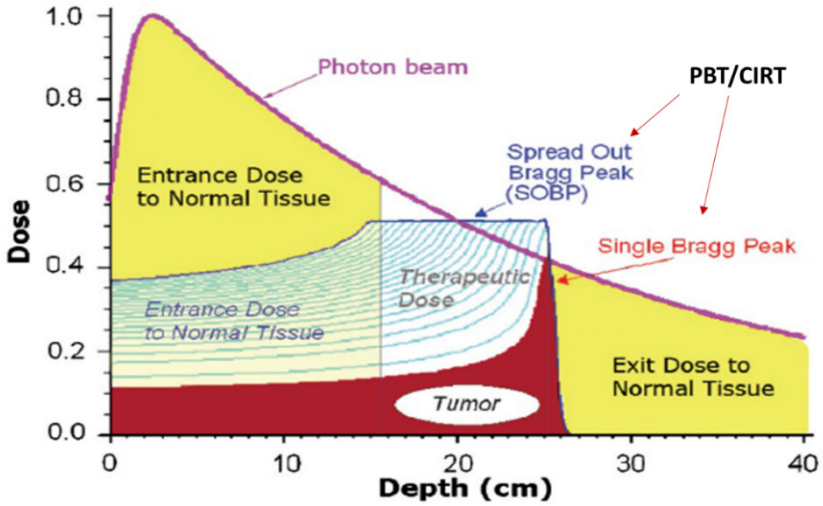
2. Hadron therapy or charged particle radiation therapy uses beams of protons or other charged particles, such as carbon, helium, neon, or silicon. At present **only protons and carbon ions** are in clinical use[4]. Worldwide, more than 120 000 patients have been treated with particle therapy since 1954: more than 13 000 with carbon ions and more than 105 000 with proton therapy[4]. Proton beam therapy in children has only been introduced a couple of decades ago; in the US, paediatric patients comprised 13% of all patients treated with PBT in 2012[5].

Photon radiation (i.e. conventional radiotherapy) deposits most of its energy below the skin surface and in normal tissue going in ('proximal dose'), hits the target site (the tumour) and still deposits energy and thus affects normal tissues when coming out past the target ('distal dose') (**Figure 1**). In contrast, charged particles deposit a low dose near the surface and a large fraction of their energy at or around the target, at the end of the range of beam penetration. Tissues beyond the tumour location receive very little of the dose. This peak energy delivery is known as the **Bragg Peak** (**Figure 1**)[6]. The absence of radiation distal to the target is one of the major advantages of proton radiotherapy, allowing for substantial tissue sparing.

By adjusting the energy of the charged particles and the intensity of the beam, one can deliver pre-specified doses anywhere in the body with high precision[7]. In this way the proton beam can be adjusted to match the depth and extent of the target volume and excellent conformity can be achieved. Because the Bragg peak of a mono-energetic proton beam is narrow, several beams with closely spaced penetration depths are used to treat the entirety of the tumour. This area of uniform dose over the entirety of the tumour is termed a **Spread Out Bragg Peak** (SOBP) (**Figure 1**). While the SOBP does increase dose deposition proximal to the tumour, the entrance dose usually remains substantially lower than that of photon radiotherapy[8].

Because charged particles damage cell DNA in qualitatively different ways than photons, the same amount of physical radiation can have much more pronounced biological effects, resulting in larger cellular damage[7]. The **relative biological effectiveness** (RBE) is defined as the ratio of a dose of photons to a dose of any particle to produce the same biological effect. The RBE of protons is approximately 1.1, indicating that protons result in approximately 10% more biological damage per unit dose than photons[7]. Carbon ions have a similar RBE to protons along the particle path but have a markedly increased RBE (estimated at 3-4) at their maximum depth of penetration. As a result, the deleterious effects on normal tissues proximal to the tumour are expected to be similar to proton radiotherapy, while tumour killing is enhanced at maximum depth[8].

Figure 1 – Radiation dose profiles: photons vs. protons



[Figure – Source: Cotter et al., 2012 p269[8] - traduction]

1.2.1 Proton beam therapy

The protons emerging from a cyclotron or synchrotron form a narrow pencil beam; in order to cover a treatment field of the size of a tumour and hence produce a Spread Out Bragg Peak, the pencil beam either scans the target or is scattered by a foil. Currently, both passive scattering and active scanning beam delivery systems are in use.

Passive scattering technique (or scatter foil technique)

Passive scattering is currently the most common proton beam technique employed[8, 9]. A proton beam hits the scatter foil and is spread laterally (**Figure 2**). The beam is further shaped via brass apertures and compensators to conform to the distal edge of the tumour[8]. There are several *disadvantages* associated with the passive scattering technique; the most important is the production of **secondary neutrons**, which may induce secondary malignancies[9-11]. It is estimated that these external neutrons deliver a total-body equivalent dose that is even larger than the leakage radiation from conventional linear accelerators[12]. Yet, the passive scattering technique may be indicated in those cases where the target has a regular, not too complex shape (G.Goitein, personal communication).

Active scanning technique

There are two types:

Spot-scanning or pencil beam scanning

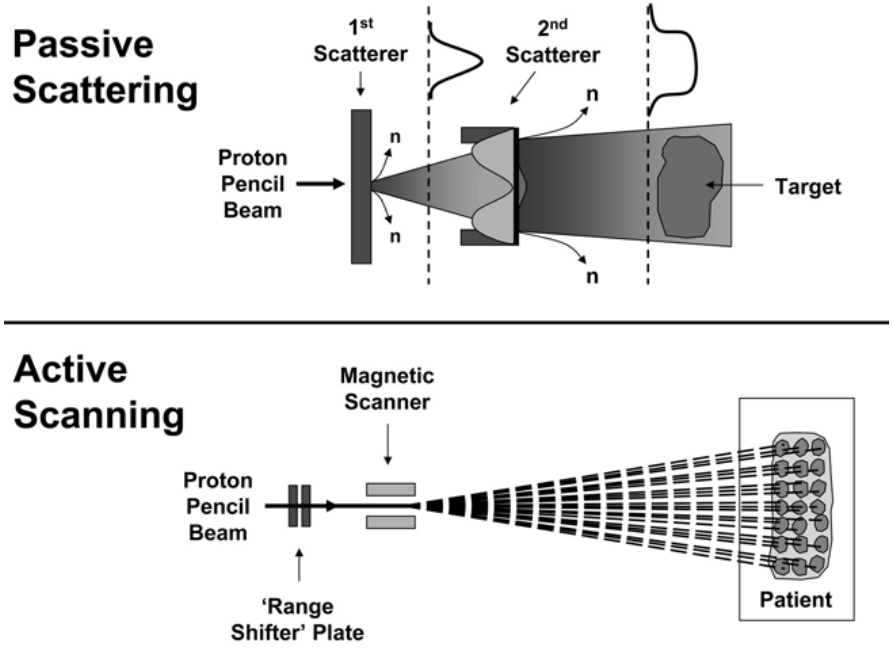
Only a couple of centres worldwide use this technique where magnets steer a small pencil beam of protons to specific positions within a tumour target without the need for brass apertures or compensators (**Figure 2**)[8]. The pencil beam technology has two main *advantages* over the passive scattering technique. First, it allows for decreasing the entry dose while avoiding an exit dose. Second, the neutron scatter is reduced significantly, an advantage that is particularly important for the paediatric patient[8, 9]. Yet, pencil beam is *more sensitive* to any misalignment or density change.

Uniform beam scanning

This technique uses a range modulator, patient collimator and range compensator similar to the passive scattering technique, but it utilizes magnets instead of scattering foils to spread the beam laterally[13]. With this system,

the beams are scanned in a fixed pattern with a uniform intensity for each layer, while in the pencil beam scanning system, beams are scanned with variable intensity and pattern[14]. Overall, the uniform scanning system uses less material in the beam path compared to the passive delivery system and therefore is supposed to produce fewer neutrons[13].

Figure 2 – Passive scattering vs. pencil beam (active) scanning



[Figure – Source: Hall 2006 p6[12]]

1.2.2 Carbon ion radiotherapy

As carbon ion radiotherapy is hardly used in children and there was only one research question on carbon ion radiotherapy, the interested reader is referred to the Scientific Report for more background information.

1.3 Why proton beam therapy in children?

In paediatric radiation oncology, the ultimate goal is to treat the disease while limiting as much as possible the (acute and late) effects of radiation on growth and development, cognition, neuroendocrine function and last but certainly not least the induction of secondary tumours. The age of the paediatric patient plays a major role in the design of the treatment plan. New developments aim at avoiding and/or postponing radiotherapy in children, e.g. by altering the chemotherapy regimen. Reducing the exposure of normal tissues to therapeutic radiation would presumably decrease the risk of subsequent malignancies and other radiation-induced side effects[15]. Here, the option of hadron therapy, particularly proton beam therapy, comes in.

Essentially, there are two rationales for using proton beam therapy: the dose to organs at risk can be reduced and/ or the risk for second malignancies can be lowered, and second, the dose to the tumour can be increased without putting the organs at risk to a higher dose (dose escalation). Although the latter is appealing, dose-escalation and hypofractionation are experimental approaches that should be restricted to clinical trials.

1.4 Proton beam therapy – the Holy Grail in paediatric radiation oncology?

Despite the thorough physical underpinning of proton beam therapy showing a **reduction of the radiation dose** to normal tissues and organs, several systematic reviews on the clinical effectiveness of PBT clearly stated that for most clinical indications, it still **cannot be concluded that proton beams are clinically truly superior** to photon therapy[1, 16-19]. It remains unproven in the clinic whether protons are more suitable when OAR dose constraints limit the delivery of the most appropriate tumour X-ray radiotherapy doses[19]. Nor is it known whether proton therapy allows radiation dose escalation without increasing side effects[19].

What's more, the clinical application of proton beams still suffers from **several technical limitations and disadvantages**, which are elaborated in the Scientific Report. One of the most critical concerns is the production of **secondary neutrons** with the passive scattering technique as even low neutron doses have a high potential for carcinogenesis[20]. This is extremely important, in particular because the reduction of secondary cancer risk is in fact one of the principal reasons for the move from photon towards proton beam therapy in children.

2 SYSTEMATIC LITERATURE REVIEW

A systematic search for relevant publications was done in Medline (through OVID), EMBASE, and the Cochrane Library. Reviews and primary studies on proton beam therapy and/or carbon ion therapy published between 2007 (i.e. end date of the search strategy of the previous KCE Hadron HTA[1]) up to March 2014 were searched. An overview of the inclusion and exclusion criteria, the search strategy and the flow chart of the selection process are given in the Supplement. A final update of the search (restricted to Medline through OVID) was performed on September 11, 2014.

After selection, we retrieved **21 primary studies** on the 16 potential indications under study. On top of the non-randomized, non-controlled and retrospective nature of the majority of retrieved studies - with the limitations characteristic of these types of studies (e.g. selection bias, recall bias) - all studies suffered from very serious methodological limitations (among others small sample size, long enrolment period, variable treatment schemes, short follow-up, complications only assessed in a subset of patients) and hence when GRADE[2] was applied, the **level of scientific evidence for all outcomes in all indications** was **very low**.

2.1 Clinical effectiveness of proton beam therapy and eligibility for radiotherapy/proton beam therapy by tumour type

In the subsequent sections, eligibility for radiotherapy/proton beam therapy (RT/PBT) is based on the report of the multidisciplinary oncological consultation where the treatment plan for newly diagnosed cancers is discussed and decided (MOC/COM report).

2.1.1 Skull base chondrosarcoma

Chondrosarcomas are uncommon malignant neoplasms of the cartilage; only 1% of chondrosarcomas arise in the skull base[21]. Chondrosarcomas are rare in children; when they occur, they tend to be aggressive[22]. The complete surgical resection of these tumours is most often prevented by their deep location; consequently, a combination of surgery and irradiation has become the mainstay of treatment[23].

Incidence in Belgium (2004-11)[c]	**Children (0-14 y.o.): <1/year**
Eligible for RT/PBT (estimate)[d]	Children (0-14 y.o.): 0
Evidence base PBT	1 retrospective case series (n=7)
Conclusion	At present **insufficient scientific evidence** to support or to refute

[c] Data provided by the Belgian Cancer Registry. Cave: for some tumour types the indications under study were slightly redefined. Second, some selection criteria were overlapping, resulting in double recordings of some patients. For more details the reader is referred to the Scientific Report.

[d] Data provided by the Belgian Cancer Registry.

2.1.2 Skull base & (para)spinal chordoma

Chordomas are extra-axial tumours that originate from the remnants of the notochord. Chordomas rarely affect children and adolescents[24]. In children and adolescents surgery is rarely curative because of the difficulty to obtain clear margins and the likelihood of chordomas to arise in the skull base, where they are relatively inaccessible to complete surgical excision[25]. Tumour tissue that remains after surgery, particularly when small in volume, can be managed effectively with radiotherapy[24].

Incidence in Belgium (2004-11)[c]	**Children (0-14 y.o.): <1/year**
Eligible for RT/PBT (estimate)[d]	Children (0-14 y.o.): NA
Evidence base PBT	2 retrospective case series (n=41)
Conclusion	At present **insufficient scientific evidence** to support or to refute

2.1.3 Craniopharyngioma

Craniopharyngiomas are relatively rare intracranial tumours, with a peak incidence occurring at 5-14 years of age[26]. Despite their histologically benign nature, craniopharyngiomas frequently cause profound disabilities due to their proximity to critical structures such as the optic pathway, cerebral arteries, the hypothalamus, the pituitary gland, cranial nerves and the brain parenchyma[26-28,29]. There is no consensus on the optimal treatment of newly diagnosed craniopharyngiomas, but surgery and radiotherapy are the cornerstones in their management[30]. Regardless of the treatment modality, 5- and 10-year overall survival rates in children are greater than 90%[31].

Incidence in Belgium (2004-11)[c]	**Children (0-14 y.o.): 3/year**
Eligible for RT/PBT (estimate)[d]	Children (0-14 y.o.): 1/year
Evidence base PBT	1 retrospective comparative study & 2 retrospective case series (n=74)
Conclusion	At present **very low level scientific evidence** that PBT compared with IMRT **does not result in significant differences** in 3-yr OS, 3-yr CFFS, 3-yr NFFS, toxicity or cyst dynamics.

OS: overall survival; CFFS: cystic failure-free survival; NFFS: nodular failure-free survival

2.1.4 Ependymoma

Ependymomas are one of the three types of gliomas, tumours of the supporting tissue of the brain. In children, most ependymomas arise in or around the fourth ventricle[32]. One third of cases are diagnosed under the age of three years and the vast majority by age six years[8]. Standard treatment for all grades and ages includes maximal surgical resection and adjuvant radiotherapy[33]. For children aged 0-19 years with ependymoma, the overall 5-year relative survival rate is 72.1%[34].

Incidence in Belgium (2004-11)[c]	**Children (0-14 y.o.): 6/year**
Eligible for RT/PBT (estimate)[d]	Children (0-14 y.o.): 4/year
Evidence base PBT	1 prospective case series & 1 retrospective case series (n=78)
Conclusion	At present **insufficient scientific evidence** to support or to refute

2.1.5 Esthesioneuroblastoma

Esthesioneuroblastoma, also known as olfactory neuroblastoma, is an uncommon malignancy of neural crest origin[35, 36]. The behaviour of the tumour varies from an indolent slow-growing neoplasm to that of a highly aggressive and locally invasive malignancy with a capacity for regional and distant metastases[37]. Approximately 7% to 20% of patients present at the age of 10 to 24 y.o.[35]. Surgery and adjuvant radiation therapy have been the mainstay of treatment. Chemotherapy has also been used in combination with surgery and radiation therapy[37]. Estimated 5-year overall survival rates are 73% for surgery and radiotherapy, 68% for surgery only, 35% for radiotherapy only, and 26% for neither surgery nor radiotherapy[38].

Incidence in Belgium (2004-11)[c]	**Children (0-14 y.o.): <1/year**
Eligible for RT/PBT (estimate)[d]	Children (0-14 y.o.): <1/year
Evidence base PBT	1 retrospective case series (n=22[e])
Conclusion	At present **insufficient scientific evidence** to support or to refute

[e] Mixture of children and adults

2.1.6 Ewing sarcoma

Ewing sarcomas are derived from primordial bone marrow–derived mesenchymal stem cells. They arise mainly in bone and infrequently in soft tissues[39]. The median age of patients with Ewing sarcoma is 15 years[39]. Current treatment consists of a multimodal approach combining surgery, radiotherapy and chemotherapy[40, 41]. Between 1975 and 2002, the 5-year overall survival rate has increased from 59% to 76% for children (<15 y.o.) and from 20% to 49% for adolescents (15-19 y.o.)[39]. Patients with metastatic disease (i.e. 1 out of 4) achieve a 6-year event-free survival of approximately 28% and an overall survival of approximately 30%[39].

Incidence in Belgium (2004-11)[c]	**Children (0-14 y.o.): 8/year**
Eligible for RT/PBT (estimate)[d]	Children (0-14 y.o.): 3/year
Evidence base PBT	1 retrospective case series (n=30)
Conclusion	At present **insufficient scientific evidence** to support or to refute

2.1.7 CNS germinoma

Central nervous system (CNS) germ cell tumours generally affect adolescents[42]. Two types have been identified: germinomas, which are the most common and carry the most favourable prognosis, and mixed malignant germ cell tumours (also termed non-germinomatous germ cell tumours), which are relatively resistant to therapy[43]. Germinomas are highly radiosensitive and have been traditionally treated with radiation therapy alone. Craniospinal irradiation with a boost to the region of the primary tumour has resulted in 5-year overall survival rates greater than 90%[44].

Incidence in Belgium (2004-11)[c]	**Children (0-14 y.o.): 2/year**
Eligible for RT/PBT (estimate)[d]	Children (0-14 y.o.): 2/year
Evidence base PBT	1 retrospective case series (n=22)
Conclusion	At present **insufficient scientific evidence** to support or to refute

2.1.8 Low-grade glioma (incl. optic pathway)

Any tumour that arises from glial cells is a glioma. Low-grade gliomas are the most common paediatric brain tumour, representing over 30% of all childhood primary brain tumours[45]. Low-grade gliomas are frequently amenable to surgical resection[46]. Yet, when the risk of post-surgical morbidity is considered too high chemotherapy may be the first line of treatment for children under 7-10 years of age. Radiation therapy is used when tumours progress after chemotherapy or in older children[46].

Incidence in Belgium (2004-11)[c]	**Children (0-14 y.o.): 47/year**
Eligible for RT/PBT (estimate)[d]	Children (0-14 y.o.): 9/year
Evidence base PBT	2 retrospective case series (n=38)
Conclusion	At present **insufficient scientific evidence** to support or to refute

2.1.9 Medulloblastoma / primitive neuroectodermal tumours

Medulloblastomas and primitive neuroectodermal tumours (PNET) are embryonal tumours, which share the tendency to disseminate throughout the nervous system [47]. They occur throughout the paediatric age spectrum, but tend to cluster early in life[47]. Surgical resection is the mainstay of therapy for all medulloblastoma/PNET. Due to the high metastatic tendency within the CNS, all patients receive "prophylactic" craniospinal irradiation (CSI) for elimination of invisible micrometastases. The 5-year overall survival for children with standard risk medulloblastoma is 75 – 85%[48]. In the subset of children younger than 5 y.o. long-term disease control is far worse (e.g. ranging from 14% to 55% depending on tumour histology[49]), although others reported five-year progression-free and overall survival rates of 85±8% and 95±5%, respectively, in children younger than 3 y.o. with desmoplastic medulloblastoma[50]. Paediatric PNETs carry an even more dismal prognosis: the 5-year overall survival ranges between 30 and 40%[49].

Incidence in Belgium (2004-11)[c]	**Children (0-14 y.o.): 12/year**
Eligible for RT/PBT (estimate)[d]	Children (0-14 y.o.): 9/year
Evidence base PBT medulloblastoma	1 prospective case series & 2 retrospective case series (n=147[f])
Evidence base PBT PNET	None
Conclusion medulloblastoma	At present **insufficient scientific evidence** to support or to refute
Conclusion PNET	At present **no scientific evidence** to support or to refute

[f] This is an overestimation as some cases may have been reported in 2 publications.

2.1.10 Non-resectable osteosarcoma

Osteosarcoma is an aggressive, malignant bone-forming mesenchymal tumour, predominantly affecting the long bones of adolescents and young adults. Aggressive local growth and rapid haematogenous systemic dissemination are typical features. Successful treatment generally requires the combination of effective systemic chemotherapy and complete resection of all clinically detectable disease. Osteosarcomas are generally considered to be radioresistant[51], but when complete surgical resection is not possible radiotherapy may be an option to try to extend the progression-free interval[52]. Local control of the tumour is absolutely critical, because the chances of long term survival are <10% if a complete surgical resection of the tumour is not possible[53].

Incidence in Belgium (2004-11)[c]	**Children (0-14 y.o.): 9/year**
Eligible for RT/PBT (estimate)[d]	Children (0-14 y.o.): <1/year
Evidence base PBT	1 retrospective case series (n=55[e])
Conclusion	At present **insufficient scientific evidence** to support or to refute

2.1.11 Pelvic sarcomas

Treatment of malignant sarcomas of the pelvis poses a challenge for local disease control and oncologic outcome[54]. Surgical resection is difficult because of the anatomic proximity to many neurovascular structures and the urinary and intestinal tracts and because extensive resection of pelvic sarcomas often necessitates reconstruction to avoid severe functional disabilities from the impairment of the load-bearing axis[55]. At present, there is no consensus yet whether a uniform treatment strategy should be applied to all patients regardless of the histopathology[54]. Evaluation of the SEER[g] database revealed a 5-year overall survival of 47% with osteosarcoma having the worst 5-year survival at 19% and patients with chordoma having the best 5-year survival at 60%[54].

Incidence in Belgium (2004-11)[c]	**Children (0-14 y.o.): 6/year**
Eligible for RT/PBT (estimate)[d]	Children (0-14 y.o.): 2/year
Evidence base PBT	None
Conclusion	At present **no scientific evidence** to support or to refute

[g] The Surveillance, Epidemiology and End Results (SEER) database provides population-based incidence and survival data for primary malignant tumours collected from 17 registries in the United States.

2.1.12 Pineal parenchymal tumours

Tumours originating from the pineal region are very rare; they account for less than 1% of all primary central nervous system tumours[56]. Pineal parenchymal tumours represent about 10-30% of all tumours in the pineal region[57]. Treatment may consist of surgery, radiotherapy and/or chemotherapy. In general, survival of patients with pineal parenchymal tumours is considered much more doubtful compared to that of patients with other pineal region tumours. Evaluation of the SEER[g] database revealed a 5-year overall survival of 47.2% and a median survival of 4.5 years[56].

Incidence in Belgium (2004-11)[c]	**Children (0-14 y.o.): <1/year**
Eligible for RT/PBT (estimate)[d]	Children (0-14 y.o.): 0/year
Evidence base PBT	None
Conclusion	At present **no scientific evidence** to support or to refute

2.1.13 Retinoblastoma

Retinoblastoma is a relatively uncommon tumour of childhood that arises in the retina; 95% of cases are diagnosed before age 5 years, and two-thirds of these cases occur before age 2 years. Due to the radiosensitive nature of retinoblastomas, external beam radiation therapy (EBRT) has been thought to be the first line and major treatment method for retinoblastoma[58]. However, EBRT may result in orbital bone growth retardation and consequent cosmetic problems, particularly in younger children. Therefore, treatment modalities were shifted toward primary systemic chemotherapy for reducing tumour volume initially (chemo reduction) and additional focal treatment such as cryotherapy, thermotherapy, or brachytherapy[58]. According to estimates based on the SEER[g] database current 5-year survival rate may be as high as 96.5% (1995–2004)[59].

Incidence in Belgium (2004-11)[c]	**Children (0-14 y.o.): 12/year**
Eligible for RT/PBT (estimate)[d]	Children (0-14 y.o.): 1/year
Evidence base PBT	1 retrospective comparative study (n=55)
Conclusion	At present there is **very low level scientific evidence** that PBT results in lower risk of developing RT-induced in-field secondary malignancies. However, since radiation-induced solid malignancies need at least 5 to 10 years to develop and for some children in the study the follow-up was short, the results should be **interpreted with caution**.

2.1.14 Rhabdomyosarcoma

Rhabdomyosarcomas are malignancies of mesenchymal cell origin that arise primarily in striated muscle tissues[8, 60]. In children, the most common primary sites are the orbit (i.e. 35-45% of all childhood rhabdomyosarcoma)[61] and the genito-urinary tract[62]. There is a bimodal incidence distribution with a first peak at 6 y.o. and a second peak at adolescence[8]. Rhabdomyosarcomas require a multidisciplinary approach including surgery, chemotherapy and radiotherapy[63]. Prognosis depends on the histologic type and the tumour site[63]. The overall impression is that survival for most patient subsets is superior with the use of early local therapy, including RT[62].

Incidence in Belgium (2004-11)[c]	**Children (0-14 y.o.): 9/year**
Eligible for RT/PBT (estimate)[d]	Children (0-14 y.o.): 4/year
Evidence base PBT	3 retrospective case series (n=36)
Conclusion	At present **insufficient scientific evidence** to support or to refute

2.1.15 (Para-)spinal 'adult type' soft tissue sarcoma (STS)

The most common STS in children younger than 15 y.o. is rhabdomyosarcoma; the remaining soft tissue sarcomas are commonly referred to as non-rhabdomyosarcomatous STS and account for about 3% of all childhood tumours. The latter are characterized by local aggressiveness and a propensity to metastasize that is correlated to their grade of malignancy[64]. Radiotherapy plays a dominant role in those tumours which cannot be surgically removed without leading to major impairment, yet, it may cause severe late side effects. Five year overall survival in children and adolescents with non-rhabdomyosarcomatous STS may be as high as 89% in patients who underwent complete resection at diagnosis, 79% in patients with marginal resection, 52% in initially unresected patients and 17% in patients with metastases at onset[64].

Incidence in Belgium (2004-11)[c]	**Children (0-14 y.o.): <1/year**
Eligible for RT/PBT (estimate)[d]	Children (0-14 y.o.): <1/year
Evidence base PBT	None
Conclusion	At present **no scientific evidence** to support or to refute

2.2 Clinical effectiveness of carbon ion radiotherapy and eligibility for radiotherapy/carbon ion radiotherapy

Non-resectable osteosarcoma

(For the pathology description, the reader is referred to paragraph 0)

Incidence in Belgium (2004-11)[c]	**Children (0-14 y.o.): 9/year**
Eligible for RT/CIRT (estimate)[d]	Children (0-14 y.o.): <1/year
Evidence base CIRT	1 retrospective case series (n=78[e])
Conclusion	At present **insufficient scientific evidence** to support or to refute

3 DISCUSSION

Due to its physical properties, proton therapy spares more normal tissues and organs at risk than conventional radiotherapy. Because a reduction of radiation dose to the healthy tissue is the goal of radioprotection, it is conceivable that a decrease of radiation dose to vulnerable tissues by using protons will decrease important side effects and radiation-induced cancers as well.

Worldwide a growing number of children is being treated with proton beam therapy (PBT). Yet, we have no Belgian data and a European registry has not been installed yet. A survey among all American proton centres showed that in 2012 a total of 694 paediatric patients were treated[5]. The six most common tumour types treated were ependymoma, medulloblastoma, low-grade glioma, rhabdomyosarcoma, Ewing sarcoma, and craniopharyngioma[5]; indications for which we found either no or insufficient scientific evidence to support or to refute proton beam therapy.

It is appalling that **only a fraction of children treated with PBT** are **enrolled in clinical trials**[65]. There may be several reasons for that, including the fact that many clinicians are convinced that the superior dose distribution and lower integral dose makes proton beam therapy the preferred treatment option, and thus making them reluctant to randomize patients. Furthermore, long-term follow-up, crucial to assess late side effects as well as secondary cancer risk, may be difficult when patients come from large distances or from abroad and will take over a decade.

While multicentre studies are definitely the only possible way to get more data on the clinical effectiveness of proton beam therapy, the (international) collaboration between centres is not going without a hitch. In fact, there seems to be some competition between them and funding for this type of research is also lacking.

In the medical literature animated debates have been held on the necessity or ethical justification of randomized controlled trials to test proton beam therapy[66-69]. Given the fact that systematic reviews fail to demonstrate clear evidence of a clinical superiority for protons, it is difficult to understand why it would be unethical to perform randomized trials[67, 69], except in those cases where there are manifest anatomical and physical reasons against the use of photons (e.g. low-grade glioma, craniopharyngioma, skull base chordoma and skull base osteosarcoma). Most certainly, for prevalent indications (e.g. in adults), there should be no discussion on the

necessity of proving PBT's superiority and cost-effectiveness through randomized clinical trials.

For children (and for adults with rare cancers), some mitigating factors may apply: in addition to the factors mentioned before, the number of children with cancer requiring radiotherapy as part of their treatment is so small that it is unlikely that prospective randomized trials can be conducted to test if different dose distributions indeed make a clinical difference[70].

Furthermore, as was pointed out earlier, the clinical application of proton beam therapy still has to contend with **serious technical limitations and disadvantages**: the magnitude of the lateral penumbra, the uncertainty about the distal edge degradation, range inaccuracies, patient-position related uncertainties, operational difficulties and last but not least cost-effectiveness issues. With an extra cost of 70% to 150%[71, 72], the payer - whether public or private - deserves to know how much better the outcomes are.

As the treatment of children demands **specific skills and precautions** (e.g. anaesthesia is required in nearly half of the children[5]), the concentration of children in a restricted number of centres should be mandatory. **Quality assurance** is another important aspect not to be neglected. Yet, high quality can only be delivered if the operators have sufficient time; economic pressure to increase the throughput of the machine should never prevail. The protocols being developed by the Particle Therapy Co-Operative Group (PTCOG)[h] are an important initiative in that respect.

Prospective comparative clinical trials in the field are urgently needed. In addition, the establishment of a **European Hadron Therapy Registry** (EHTR), which holds (anonymised) data on patients treated by European hadron centres would provide a simple but effective solution to the current lack of coherent published data[73]. In the US the Pediatric Proton Consortium Registry (PPCR) was recently installed for that purpose[74].

[h] http://www.ptcog.ch/index.php/clinical-protocols

4 KEY MESSAGES

- **Based on the 2004-2011 incidence data, it can be estimated that in Belgium 37 children (0-14 y.o.) and 14 adolescents (15-19 y.o.) may be eligible for RT/PBT on a yearly basis.**
- **The use of PBT in children is supported by physical data showing an important reduction of the radiation dose to normal tissues. Yet, to date clinical data on PBT in all paediatric cancers under study is lacking critical information on measures of long-term effectiveness and harm.**

RECOMMENDATIONS[i]

To the clinicians:

- Patients (or their parents or representatives) should be fully informed that despite the physical underpinning of proton beam therapy, its clinical efficacy for the indications considered in this report has not yet been confirmed in clinical studies.
- Children should be referred to proton beam centres with the necessary expertise in treating children with that specific pathology and involved in clinical studies with long-term follow-up (if recruiting in Europe).
- The registration in the Belgian Cancer Registry (BCR) database of the chemotherapy regimen and radiotherapy schedule (including hadron therapy) administered in children is recommended. This registration can allow, amongst others, the monitoring of secondary malignancies occurrence.
- *To the Technical Medical Council & the Insurance Committee of the RIZIV - INAMI:*
- The current reimbursement for PBT should be reevaluated periodically as new scientific evidence on effectiveness and safety becomes available. Meanwhile, the 15-year age limit should be reconsidered for certain indications.
- The amount reimbursed for radiotherapy in children should take into account the complexity of treatment administration, including the potential need for anaesthesia. The reimbursement should be made conditional to the registration into the BCR database.
- *To the RIZIV - INAMI, BCR & FANC - AFCN and scientific/professional associations:*
- Our country should actively promote the set-up of a European Hadron Therapy Registry.

Research agenda:

- There is an urgent need for more research, not only on the clinical efficacy, side effects, and harms, but also on the economical aspects, and on the physics and biology. Clinical research should preferentially be conducted in an internationally coordinated way.

[i] The KCE has sole responsibility for the recommendations.

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