

Hadrontherapy for cancer. An overview of HTA reports and ongoing studies

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Summary. Introduction. There is growing interest in the use of both proton beam therapy (PBT) and carbon ion radiation therapy (CIRT), which are types of hadrontherapy. Although neither are new technologies they have been subject to assessment by several Health Technology Assessment (HTA) agencies over the past years. The main claimed benefit of PBT and CIRT is a reduction in toxicity compared to conventional radiation therapy, resulting in fewer harms and a lower risk of induced secondary malignancies. Such an advantage would be particularly relevant to children and young adults. Sizeable hadrontherapy centres expansion is underway worldwide, while evidence supporting claims of superiority over conventional radiation therapy is thought to be currently insufficient. **Objectives.** This report is aimed at presenting the state of the art of clinical research in both PBT and CIRT, by summarising the evidence findings from most recent and up-to-date HTA reports and by providing a description of all currently ongoing clinical studies. **Methods.** The search for HTA reports was carried out on 3 databases to identify reports published between January 2011 and June 2019. The quality of the identified reports was assessed using the AMSTAR instrument. The search for ongoing studies was carried out on four public registers in July 2019. All identified ongoing studies were included. **Results.** The overview of available evidence for PBT is drawn from five HTA reports on a total of 16 oncology indications, including 295 primary studies of any study design. One HTA report also included eight guidelines. All included HTA reports concluded that the quality of research is low and that there is insufficient evidence to support the claimed benefits of PBT. Seventy-two non-comparative ongoing studies and 25 comparative ongoing studies were identified. Seventeen were randomized controlled studies comparing Proton Beam Therapy with current practice. The search for HTA reports assessing the use of CIRT in oncology identified five reports, two of which were up to date and of good quality reporting data from primary studies. The largest report identified 56 studies on 13 indications, but only 27 studies (including only one randomised trial) could be included in a qualitative synthesis, providing no evidence of differences in efficacy and safety of CIRT compared to photontherapy. The other report focused on the effects of CIRT on chordomas and chondrosarcomas, highlighting the heterogeneity and inconsistency of available data mostly coming from low-quality studies. Thirty-seven ongoing studies were identified, 5 of which were RCT versus conventional treatment and 32 were single-arm studies. Table A summarises the findings, by clinical indication, from the included HTA reports and from the overview of ongoing clinical research. The Table reports the current level of certainty on superiority of PBT or CIRT compared to pho-

Utilizzo di adroterapia nel cancro. Una rassegna dei rapporti di HTA e degli studi in corso.

Riassunto. Introduzione. Vi è un crescente interesse nell'utilizzo della terapia protonica (TP) e della terapia con ioni di carbonio (CIRT), particolari forme di adroterapia. Entrambe non sono tecnologie di recente introduzione e negli ultimi anni sono state oggetto di valutazione da parte di diverse agenzie di Health Technology Assessment (HTA). Il principale potenziale beneficio di TP e CIRT risiede nella riduzione della tossicità rispetto alla radioterapia convenzionale e risulterebbe in minori effetti collaterali e minore rischio di tumori secondari. Un tale vantaggio sarebbe particolarmente rilevante per i pazienti pediatrici e i giovani adulti. Vi è un considerevole aumento di centri di adroterapia in tutto il mondo, ma le prove a supporto della superiorità di questi trattamenti rispetto alla terapia con fotoni sono generalmente considerate a oggi insufficienti. **Obiettivi.** Questa analisi ha lo scopo di presentare lo stato dell'arte della ricerca clinica condotta su TP e CIRT, attraverso la sintesi dei risultati dei più recenti rapporti di HTA e la descrizione degli studi clinici attualmente in corso. **Metodi.** La ricerca per l'identificazione dei rapporti di HTA è stata condotta in tre banche dati considerando il periodo gennaio 2011-giugno 2019 come limite temporale. La qualità dei rapporti di HTA è stata valutata utilizzando lo strumento AMSTAR. La ricerca per gli studi in corso è stata condotta nel luglio 2019 su quattro registri pubblici e sono stati inclusi tutti gli studi identificati. **Risultati.** La sintesi delle prove disponibili per la TP si basa su cinque documenti di HTA che complessivamente comprendono 295 studi primari di qualsiasi disegno su un totale di 16 indicazioni oncologiche. Un rapporto di HTA ha incluso anche otto linee guida. Tutti i rapporti di HTA inclusi concludono che la qualità della ricerca clinica disponibile è bassa e che non vi sono evidenze sufficienti a supportare i potenziali benefici della TP. Sono stati identificati 72 studi non comparativi e 25 studi comparativi in corso (di cui 17 studi randomizzati che confrontano la protonterapia con un trattamento convenzionale). Per quanto riguarda la CIRT sono stati identificati 5 rapporti di HTA, due dei quali aggiornati e di buona qualità che riportano dati da studi primari. Il rapporto più ampio ha individuato 56 studi su 13 indicazioni cliniche; solo 27 di questi studi (di cui un solo RCT) sono risultati utilizzabili per una sintesi qualitativa che non ha evidenziato prove della differente efficacia e sicurezza di CIRT rispetto alla fototerapia. L'altro rapporto ha specificamente valutato gli effetti della CIRT su cordomi e condrosarcomi, sottolineando la necessità di cautela nell'interpretazione di risultati eterogenei e in parte contraddittori provenienti da studi di bassa qualità. Sono stati identificati 37 studi in corso, di cui 5 RCT verso trattamento convenzionale e 32 non comparativi. La Tabella A riassume i risultati dell'analisi

ton radiation therapy and the likelihood that future research results would resolve current uncertainty. **Conclusions.** Despite the growing number of studies being published and the growing number of PBT and/or CIRT centres opening or at a planning stage, there is persistent uncertainty on the added clinical benefit of hadrontherapy treatments over conventional radiation therapy. Clinical research currently underway may not contribute to solve this uncertainty. There is a lack of agreement on the appropriate study design to assess the effects of hadrontherapies and lack of coordination between centres in the production of joint research protocols to generate the necessary evidence. This has led to the production of numerous small, poorly designed and reported studies. These shortcomings might confine the use of PBT and CIRT to experimental treatments and require that patients willing to undergo PBT or CIRT be fully informed of the risks and uncertainties of the outcomes.

Key words. Carbon ion radiation therapy, hadrontherapy, proton beam therapy.

dei rapporti di HTA e degli studi clinici in corso, riportando il livello di certezza sulla superiorità della TP o della CIRT rispetto alla terapia con fotoni, e la probabilità che la ricerca futura possa risolvere la rimanente incertezza. **Conclusioni.** Nonostante il numero crescente di centri di adroterapia e di studi clinici pubblicati, vi è una persistente incertezza sul beneficio clinico aggiunto dei trattamenti con adroterapia rispetto alla radioterapia convenzionale, e la ricerca clinica attualmente in corso potrebbe non contribuire a risolvere questa incertezza. Vi è mancanza di consenso sul disegno di studio più appropriato alla valutazione degli effetti dell'adroterapia e mancanza di coordinamento tra i centri per la produzione delle evidenze cliniche necessarie ai decisori, inducendo la conduzione di numerosi piccoli studi di bassa qualità. Questi limiti potrebbero confinare la TP e la CIRT a un utilizzo sperimentale e richiedono che i pazienti che desiderano sottoporsi ai trattamenti siano pienamente informati dei rischi e dell'incertezza degli esiti.

Parole chiave. Adroterapia, terapia con ioni di carbonio, terapia protonica.

Table A. Available evidence and likelihood of generation of comparative evidence from ongoing studies on PBT/CIRT vs photon therapy.

Categories of service delivery	Superiority of PBT and CIRT versus photon therapy			
	Evidence of superiority from published studies		Likelihood that upcoming evidence could resolve uncertainty	
	TP	CIRT	TP	CIRT
1. Solid paediatric tumours	Uncertain	Not available	Likely	None*
2. Central nervous system tumours	Uncertain		Likely	
3. Sarcomas	Uncertain		Likely	
4. Chordomas	Uncertain		Unlikely	
5. Tumours of the head & neck region	Uncertain		Likely	
6. Cutaneous melanoma	Uncertain	Not available	Unlikely	None*
7. Lung malignancies	Uncertain		Unlikely	None*
8. Breast malignancies	Uncertain	Not available	Unlikely	None*
9. Thyroid malignancies	Not available		None*	
10. Pancreas malignancies	Uncertain	Not available	Unlikely	Likely
11. Colon and rectum malignancies	Uncertain		Unlikely	None*
12. Prostate malignancies	Uncertain		Unlikely	None*
13. Bladder malignancies	Uncertain		Unlikely	None*
14. Esophagus malignancies	Uncertain		Likely	None*
15. Urinary tract malignancies	Not available		None*	
16. Gastric malignancies	Uncertain		None*	
17. Uterine cervical malignancies	Not available		Unlikely	None*
18. Liver malignancies	Uncertain	Not available	Likely	None*
19. Recurrent tumours requiring repeat treatment in areas already exposed to radiotherapy	Uncertain	Not available	Unlikely	None*

*No ongoing studies were identified

Tabella A. Evidenze disponibili e probabilità di generazione di evidenze comparative da studi in corso sul confronto tra TP/CIRT e terapia con fotoni.

Indicazione clinica	Superiorità della TP/CIRT sulla terapia con fotoni			
	Evidenze di superiorità dagli studi pubblicati		Probabilità che i risultati degli studi in corso risolvano le incertezze	
	TP	CIRT	TP	CIRT
1. Tumori solidi pediatrici	Incerte	Non disponibili	Probabile	Nessuna*
2. Tumori del sistema nervoso centrale	Incerte		Probabile	
3. Sarcomi	Incerte		Probabile	
4. Cordomi	Incerte		Improbabile	
5. Tumori testa-collo	Incerte		Probabile	
6. Melanoma cutaneo	Incerte	Non disponibili	Improbabile	Nessuna*
7. Tumore polmonare	Incerte		Improbabile	Nessuna*
8. Tumore della mammella	Incerte	Non disponibili	Improbabile	Nessuna*
9. Tumore tiroideo	Non disponibili		Nessuna*	
10. Tumore del pancreas	Incerte	Non disponibili	Improbabile	Probabile
11. Tumore del colon retto	Incerte		Improbabile	Nessuna*
12. Tumore prostatico	Incerte		Improbabile	Nessuna*
13. Tumore alla vescica	Incerte		Improbabile	Nessuna*
14. Tumore dell'esofago	Incerte		Probabile	Nessuna*
15. Tumori del tratto urinario	Non disponibili		Nessuna*	
16. Tumore gastrico	Incerte		Nessuna*	
17. Tumore della cervice uterina	Non disponibili		Improbabile	Nessuna*
18. Tumore epatico	Incerte	Non disponibili	Probabile	Nessuna*
19. Tumori ricorrenti in aree già esposte a radioterapia	Incerte	Non disponibili	Improbabile	Nessuna*

*Nessuno studio in corso

Introduction

There is a growing interest in the use of both proton beam therapy (PBT) and carbon ion radiation therapy (CIRT), although neither are new technologies. Approval of PBT by FDA dates back to 1980, but expansion of centres started nearly two decades later. A notable increase in hadrontherapy centres is underway worldwide. The website of the Particle Therapy Co-Operative Group (PTCOG), «an organisation for those interested in proton, light ion and heavy charged particle radiotherapy» reports a comprehensive list of facilities in operation in September 2019 (83 PBT and 13 CIRT)¹, under construction (39 PBT and 4 CIRT)² and planned worldwide (22 PBT and 2 CIRT)³. By 2023, Europe is expected to host up to 43 PBT centres.

However, it is debated whether such a growth has been accompanied by an equally large body of evidence: data on comparative effectiveness of PBT and CIRT showing superiority over conventional radiation therapy are claimed to still be lacking⁴.

As the main advantage of hadrontherapies is their precision and the consequent sparing of surrounding healthy tissues, their main claimed benefit is a reduction in toxicity compared to conventional radiation therapy, resulting in less side effects and lower risk of induced second malignancies. Such an advantage would be particularly relevant for children and young adults.

This report presents the state of the art of clinical research in both PBT and CIRT, by summarising the evidence findings from most recent and up-to-date Health Technology Assessment (HTA) reports and by listing all currently ongoing studies. The findings are synthesized for all clinical indications included by the HTA report and/or the ongoing studies.

As clinical research on efficacy and safety has started to develop in the last decade, an overview of ongoing research and forthcoming evidence was also necessary to integrate the information supporting decisions in clinical practice and investments.

Objectives

To report on the evidence base for comparative safety and effectiveness of PBT and CIRT versus conventional radiation therapy, by providing:

- an overview of the results from most up-to-date HTA reports of good methodological quality, reporting their synthesized evidence from included primary studies and their conclusions;
- a list and brief description of the currently ongoing studies;
- a summary on quality and quantity of clinical research carried out to date and expected to provide data in the near future.

Methods

HEALTH TECHNOLOGY ASSESSMENT REPORTS

The search for Health Technology Assessment reports was carried out by looking for research synthesis and HTA reports from 2011, in humans. The search was carried out on 30 June 2019 on the following databases: Medline, EMBASE and Cochrane Library. The search strategy, methods and the PRISMA flow chart are reported in Appendix (available online at www.recentiprogredi.it).

The search yielded 810 single items. After screening, we excluded 773 items and retained 37 synthesis documents (see diagram in Appendix). Given that the documents included mostly the same evidence with notable overlaps, only the 5 most up-to-date HTA documents of good methodological quality were included.

Readers should note that at least two additional HTA reports are in course of development and could not be included in this overview: Health Quality Ontario (HQO). Report on proton beam therapy⁵; Public Health England. Proton Beam Therapy for Children, Teenagers and Young Adults in the treatment of malignant and non-malignant tumours⁶.

The quality of HTA reports was assessed using A MeaSurement Tool to Assess systematic Reviews (AMSTAR) tool⁷. The number of AMSTAR assessable items relevant to our included HTA reports was 9 to 11. Assessment was carried out in double (by ALS and TJ).

The following data were extracted from each HTA report: objectives, date of evidence searches, number and design of included studies, results presented, and conclusions drawn by the authors.

ONGOING STUDIES

The search for ongoing studies was carried out in July 2019 using “proton beam therapy”, “proton beam radiotherapy” and “carbon ion therapy” as keyword and with time limits January 2010 to July 2019.

The following databases of ongoing trials were searched:

- Clinicaltrials.gov
- EU Clinical Trials Register
- ICTRP Search Portal - World Health Organization
- ISRCTN Registry
- Australian New Zealand Clinical Trials Registry (ANZCTR).

The inclusion criteria were any study design in which at least one intervention was treatment with proton beam radiotherapy or carbon ion therapy for patients with any cancer. Retrieved studies were classified as comparative or not comparative, where comparison was intended as any treatment other than hadrontherapies. Studies that compared PBT versus CIRT or different regimens or dosages of PBT or CIRT were

classified as not comparative, due to lack of comparator of interest. Single arms studies including different radiation therapy were excluded.

Modelling studies were also not included as – not being formal clinical studies – they are not registered in databases of ongoing clinical trials.

The following data were extracted from each ongoing study:

Registration number, registration year and reference; study design; enrolled population; and number of patients expected for recruitment; comparator (when available); main effectiveness and safety outcomes; length of follow-up; expected completion date; status.

QUALITY AND QUANTITY OF CLINICAL RESEARCH ON COMPARATIVE CLINICAL EFFECTIVENESS AND SAFETY

Available and upcoming evidence on comparative clinical effectiveness and safety of hadrontherapies retrieved from HTA reports and from ongoing studies, was analysed for the following potential clinical indications:

1. Solid paediatric tumours
2. Tumours of the central nervous system
3. Sarcomas
4. Chordomas
5. Tumours of the head and neck region
6. Primary cutaneous and uveal melanoma
7. Lung malignancies
8. Breast malignancies
9. Thyroid malignancies
10. Pancreas malignancies
11. Colon and rectum malignancies
12. Prostate malignancies
13. Bladder malignancies
14. Oesophagus malignancies
15. Urinary tract malignancies
16. Gastric malignancies
17. Uterine and cervical malignancies
18. Liver malignancies
19. Recurrences of any malignancies requiring repeat treatment in areas exposed to radiation therapy.

Conclusions on quality and quantity of available clinical research were drawn on the basis of the assessment and appraisal of the included HTA reports. The judgement on the quality and relevance of upcoming evidence was driven by the recommendations reported in the included HTA reports and by the type of evidence necessary to establish superiority of PBT and CIRT over other conventional treatments, namely randomized controlled trials assessing the following:

Clinical safety

- Acute adverse effect/toxicity
- Late adverse effect/toxicity
- Secondary malignancy

Clinical efficacy

- Primary outcomes: Overall survival; Disease specific survival; Quality of life.
- Secondary outcomes: Disease free survival; Progression free survival.
- Surrogate outcomes: Tumour response; Local control; Loco-regional control; Mass reduction.

Description of the technologies

INTRODUCTION

Radiation therapy (RT) involves high-energy particles or waves, such as gamma rays, electron beams, photon beams or proton beams to destroy or damage cancer cells, breaking the DNA of cancer cells and inhibiting their ability to proliferate. The radiation may also affect surrounding healthy tissues. Tumour types (and healthy tissues) vary with regard to their sensitivity to radiation. A goal of treatment planning is to damage cancer cells while minimizing damage to surrounding healthy cells including sensitive structures and organs at risk (OARs)⁸. Most often radiation is delivered using external beam radiation therapy (EBRT), a method of externally delivering radiation using a machine (eg. LINAC, cyclotron, synchrotron) to aim high-energy beams directly at the tumour from outside the body⁸.

RT may be classified by the type of beam or particle used (i.e. electron, photon or proton), with Photon RT being the most widely available and commonly used. RT may be used for a variety of reasons including to cure a radiosensitive tumour, to shrink a tumour pre-operatively, to prevent recurrence or spread post-operatively (adjuvant treatment), to treat a recurrent tumour or as a palliative treatment. It may be combined with other treatments such as chemotherapy.

Radiotherapy techniques have substantially improved in the last two decades. Advances in computer technology have enabled the possibility of transitioning from basic 2-dimensional treatment planning and delivery (2-D radiotherapy) to a more sophisticated approach with 3-dimensional conformal radiotherapy (3D CRT)⁹. Two of the most common applications are Intensity Modulated Radiation Therapy (IMRT) and Stereotactic Radiosurgery or Stereotactic Body Radiation Therapy (SBRT) (a further development of 3D CRT). IMRT employs the same image planning and distribution techniques above but goes a step further by altering the intensity (strength) of the beams being delivered, usually lessening the intensity of the beam near OARs. Stereotactic Radiosurgery and SBRT are similar to IMRT; however, the beams are delivered in fewer fractions (treatments) and at much higher doses than with IMRT. In addition to dose per fraction, the planning target volume margins are smaller with SBRT, requiring more rigid immobilization. Stereotactic radiosurgery, typically reserved

for tumours in the brain and spine, is usually completed in a single session. SBRT is completed in 3 to 5 sessions and is normally used to treat larger tumours in areas of the body other than the brain⁸.

PHYSICAL PROPERTIES OF PBT

PBT and CIRT are forms of charged particle beam radiotherapy, also called hadron therapy. Charged particles used may include accelerated protons or heavy ions such as carbon, helium, neon, or silicon ions¹⁰. Accelerated protons emit a small, steady dose as they lose kinetic energy. Tissues along the path receive a small dose, called the “entrance dose”, as the protons move through the body to the target tumour. Protons lose their kinetic energy and stop in the body due to a combination of their mass, charge, and interaction with surrounding tissues. The distance protons travel in the body depends on their speed, which must be carefully calibrated to stop the protons at a tissue depth that is within the tumour target. Once stopped, protons release most of their energy as a radiation dose, called the Bragg peak, to a small radius of surrounding tissue (figure 1)¹¹.

Beyond this point, there is “no exit dose” (figure 2) because the protons have stopped moving, as tissue beyond the point of peak energy deposition receives little or no radiation. In contrast, photons are characterized by a high deposit of energy near to the body surface with an exponential decrease of energy release as a function of depth¹⁰.

Radiation therapies are compared using their relative biological effectiveness (RBE), defined as the ratio of the radiation dose required to produce a specific biological effect (i.e., tumour cell destruction) with Cobalt-60 photons (the reference radiation), to the dose of charged particles required to achieve the

same biological effect. Protons have an RBE of approximately 1.1. Thus, PBRT is intended to deliver a larger radiation dose to a tumour target with less radiation exposure to surrounding tissues than with photon beam radiotherapy¹⁰. Recent studies have shown that the Relative Biological Effectiveness (RBE) of protons in relation to photons are not known with absolute certainty for all types of tissues and fractionation schemes, particularly in adult tumours¹². However, RBE is dependent on several factors such as dose per fraction, Linear Energy Transfer (LET), tissue radio-sensitivity, particle speed, tissue type, and local microenvironments such as oxygen level. One study identified situations in which RBE was found to be both larger and smaller than 1.1 and another found that ignoring possible variations in RBE could lead to suboptimal PBT treatment plans. The concern with assuming a 1.1 RBE for all tumour types treated with PBT is that it may result in treatment plans that deliver a lower biological dose to the target and a higher biological dose to the normal tissue. Another concern is the effects of neutrons, which are produced by passively scattered proton beams and result in additional radiation dose to the patient. The location of neutron production in a PBT patient and its biologic significance is currently a topic of significant debate⁸.

PROTON THERAPY CENTERS

The major facilities of a proton center are: cyclotron, gantry, beam line elements, patient positioning system, and control system¹³. Moreover there are many types of proton treatment delivery systems that can provide scattered or scanned proton beams operating in single or multiroom facilities (up to 5 gantries).

Several approaches to reduce the costs of delivering PBT are being explored, such as the construction of compact, single-gantry proton facilities⁸. Space requirements limit the siting of PBRT centers, particularly in urban areas. A traditional multiroom center is typically 7,000 to 9,500 square meter on 2 hectare of land including all spaces for facilities and equipment¹⁴. Major facilities are placed in bunkers with wall of over 1 meter depth.

In a feasibility study for the proton therapy center in the IRCCS Istituto Tumori “Giovanni Paolo II” in Bari, the width of the necessary surface was estimated to be over 7,000 square meters (DGR Regione Puglia 428/2018)¹⁵.

These structures can hardly be reused for other purposes or re-adapted in the future.

Smaller PBRT systems can be accommodated in 360 square meter but could require extra shielding because of the closer proximity of the accelerator to treatment rooms¹⁴. The smallest systems house the accelerator and treatment gantry in a single room, which lowers initial costs but limits patient capacity.

In the next future the cyclotron miniaturization and new gantry design will require much smaller spaces and probably also the costs will be drastical-

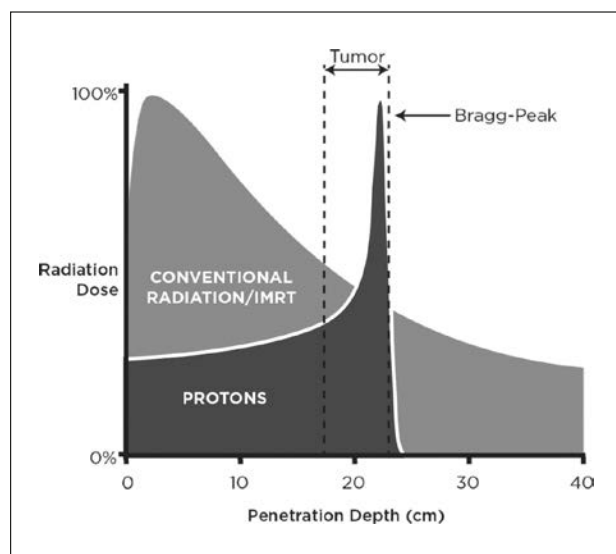


Figure 1. Comparison of dose between conventional radiation and protons. Available from: <https://www.kisspng.com/png-proton-therapy-bragg-peak-radiation-therapy-x-ray-2430152/> (free image)¹¹.

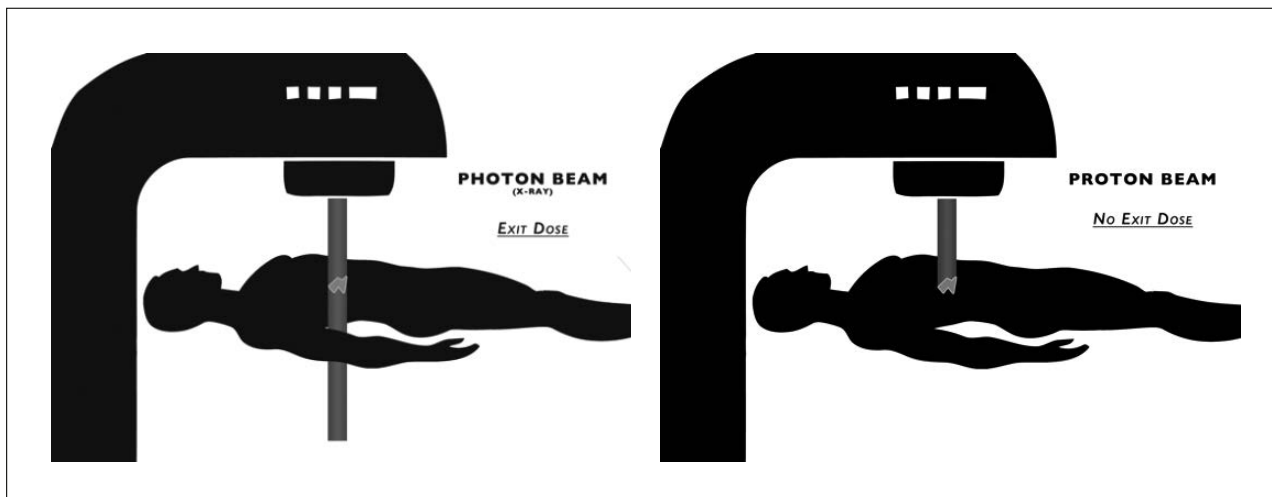


Figure 2. Proton beam stop in target and don't exit from the body (credit: Sergio Sassano).

ly reduced. Producers are designing or have ready to market more compact size cyclotrons and gantries. For example, CERN Geneva is working on a new compact non-rotating gantry design that would enable the treatment of tumours from different angles using superconducting toroidal magnets sparing even more of the surrounding tissue and considerably reducing the size and weight of the gantry¹⁶.

Currently different configuration and systems for photon therapy are available on the market.

Three systems are registered within the Italian National medical device database (BD/RDM) held by the Italian Ministry of Health and are reported in the Table 1.

PHYSICAL PROPERTIES OF CIRT

A Carbon delivery system is a complex facility and generally consists of an accelerator system, a high-energy beam transport system and an irradiation system. The dose is delivered to the patient with either a narrow beam extracted from the accelerator (pencil beam scanning method) or a broadened beam (broad beam method)¹⁷. When carbon ion beams pass through or hit these beam line structures, secondary radiations including neutrons are produced, and some of the particles in the structures can become radioactive and form an autoradioactive component of the beam. In most cases, synchrotron, cyclotron or synchrocyclotron is used to accelerate particles and are installed in a building with appropriate shielding (bunker).

Carbon ions are heavier than protons and they offer additional physical advantages over protons. Due to their increased mass, carbon ions have limited lateral scattering and maintain their direction when aimed at a tumor. This results in sharp lateral dose deposition edges. Their physical range uncertainty mostly stems from patient imaging uncertainties and therefore is similar to that of protons; carbon ions ex-

hibit a much sharper dose fall off than protons in the longitudinal direction¹⁸.

Carbon ions have higher RBE values than protons but the variation with depth in tissue and energy is not well defined¹⁰. Carbon ions (and heavy ions in general) differ from protons in their radiobiological properties; the enhanced RBE is a result of the much higher ionization density (high LET). These differences constitute a two-edged sword: some may be advantageous while other may be disadvantageous.

CARBON ION THERAPY CENTRES

According to PTOGC to date, 13 cancer therapy centres worldwide offer CIRT, most of them are located in Asia (3 in China, 6 in Japan) and few in Europe (2 in Germany, 1 in Italy and 1 in Austria). In the next few years (2019-2023) 5 CIRT, 4 in Asia and 1 in France, are expected to come into operation.

According to the LBI HTA report, by the end of 2016, approximately 21,580 patients were recorded to have been treated with CIRT, with the majority of patients treated at HIMAC, in Chiba, Japan (10,692) followed by HIT, in Heidelberg, Germany (2,430) and HIBMC, in Hyogo, Japan (2,527). To date 2,200 patients have been treated in Italy (CNAO Pavia), most of them were funded by the Italian NHS and two thirds were treated with CIRT¹⁹.

Results

PROTON BEAM THERAPY HEALTH TECHNOLOGY ASSESSMENT REPORTS

The following five HTA reports were included in this overview:

1. Institut National d'Excellence en Santé et en Services Sociaux (INESSS). Mise à jour des indi-

Table 1. Manufacture and models registered on BD/RDM (last query on 27.08.2019).

Manufacturer	Model	CND	RDM/BD code
MEVION MEDICAL SYSTEMS, INC	S250I	Z119080 - STRUMENTAZIONE VARIA PER BIOIMMAGINI E RADIOTERAPIA - COMPONENTI ACCESSORI HARDWARE	1740146
VARIAN MEDICAL SYSTEMS PARTICLE THERAPY GMBH	Varian Proton Therapy Delivery System	Z11019099 - STRUMENTAZIONE VARIA PER RADIOTERAPIA NON ALTRIMENTI CLASSIFICATA	365270
ION BEAM APPLICATIONS S.A.	PROTEUS 235 (ProteusPLUS)	Z11019099 - STRUMENTAZIONE VARIA PER RADIOTERAPIA E RADIOCHIRURGIA NON ALTRIMENTI CLASSIFICATI	489091

cations de la protonthérapie en oncologie. Note informative rédigée par Nina N. Mombo. Québec, Qc: INESSS; 2017²⁰.

2. ECRI Institute. Proton Beam Therapy for Pediatric Craniospinal Tumors 2019. (available on subscription)²².
3. CADTH 2017. Proton beam therapy for the treatment of cancer in children and adults: a health technology assessment. Ottawa: CADTH; 2017 Aug. (CADTH health technology assessment; no.145)²².
4. Vlayen J, García Fernández LI, Boterberg T, San Miguel L. Proton beam therapy in adults – a systematic review. Health Technology Assessment (HTA) Brussels: Belgian Health Care Knowledge Centre (KCE). 2019. KCE Reports 307. D/2019/10.273/10²³.
5. Washington State Health Care Authority. Proton beam therapy re-review: evidence report. 15 April 2019⁸.

For the overview of paediatric solid tumours the following KCE report published in 2015 was also included, as it focused only on children and was extensively cited by the 2019 KCE report.

- Leroy R, Benahmed N, Hulstaert F, Mambourg F, Fairon N, Van Eycken E, De Ruyscher D. Hadron therapy in children – An update of the scientific evidence for 15 paediatric cancers. KCE reports 235. Bruxelles, Belgique: Centre fédéral d'expertise des soins de santé (KCE); 2015²⁴.

Information from HTA reports was available for most listed pathologies, except for primary cutaneous melanoma; acoustic neurinoma; urinary tract malignancies and uterine cervical malignancies.

ONGOING STUDIES

After removing doubles, the search yielded 132 records, and 23 were excluded as not pertinent, leaving a total of 109 records.

Overall, 72 non-comparative studies and 25 comparative studies were identified of which 17 were ran-

domized controlled studies comparing Proton Beam Therapy with a relevant comparator.

QUALITY AND QUANTITY OF CLINICAL RESEARCH ON COMPARATIVE EFFECTIVENESS AND SAFETY

Results by pathology or groups of pathologies are reported in narrative form in the main text and in tabular form in the Appendix. Tables A1 to A19 report results extracted from the five HTA reports included in this overview, while Table A1i to A19i summarise the information on the ongoing studies. Due to some overlap between given indications, information is at time repeated in Tables. Ongoing studies recruiting patients with any type of disease are reported in Table A20.

Coverage by the included five HTA reports and number of ongoing trials for each indication are reported in Table 2.

Summary of findings

1. SOLID PAEDIATRIC TUMOURS [SEE APPENDIX - TABLE A1 AND A1i]

All included HTA reports provided information on these tumours. Evidence on solid paediatric tumours was included in 3 HTA reports^{8,21,22}. Most of the available data related to children comes from studies that include mixed adults and children population and a range of diseases. Included studies overlap across HTA reports, mostly are case series with additional 1 prospective and 9 retrospective comparative cohort studies. The evidence, suggesting comparable effectiveness in terms of survival but potential better quality of life and safety in terms of acute and late toxicity and adverse events, has been judged by all reports as of low or very low quality. More studies of better quality with long term follow-up to assess secondary malignancies are deemed necessary by the included HTA reports.

Overall, 14 ongoing studies have been identified. One comparative study, expected to end in 2027, is recruiting 140 children with craniopharyngioma to re-

Table 2. Availability of information in included HTA reports on PBT and N. of ongoing non-comparative and comparative studies by clinical indications^{8,20-23*}.

Indication	KCE 2019	INESSS 2017	CADTH 2017	ECRI 2019	WSHA 2019	N. ongoing non comparative studies	N. ongoing comparative studies
1. Solid paediatric tumours	X	X	X	X	X	13	1
2. Central nervous system tumours	X		X	X	X	11	4
3. Sarcomas	X		X	X	X	4	2
4. Chordomas				X	X	3	0
5. Tumours of the head & neck region	X	X	X	X	X	6	7
6. Cutaneous and uveal melanoma	X	X	X		X	1	2
7. Lung malignancies			X		X	7	3
8. Breast malignancies	X		X		X	7	2
9. Thyroid malignancies						0	0
10. Pancreas malignancies					X	2	0
11. Colon and rectum malignancies					X	4	0
12. Prostate malignancies at high metastathases risk		X	X	X	X	12	1
13. Bladder malignancies					X	0	1
14. Esophagus malignancies					X	3	2
15. Urinary tract malignancies						0	0
16. Gastric malignancies					X	0	0
17. Uterine cervical malignancies						1	0
18. Liver malignancies	X		X		X	4	4
19. Recurrent tumours requiring repeat treatment in areas already exposed to radiotherapy					X	2	0

Key: N.= number; *some studies may be repeated as they may be pertinent to different tumours.

ceive PTB or surgery and will assess overall survival at 3 years, progression free survival, adverse events and quality of life. Six non-comparative studies include children with cranionpharyngioma (two studies: 33 and 112 young patients respectively), grade IV glioma (43 patients), primary CNS tumour (80 patients), ganglio/neuroblastoma (30 patients) and Central Nervous System Germ Cell Tumor (45 patients 3-25 years old). Relevant data - once published - is expected to come from the ongoing 5 Registries started between 2012 and 2016 and from two large cohort studies, expected to be recruiting for 10 years or over. Three of the registries are recruiting both adults and

children with any disease and do not report measured outcomes. The remaining two registries and the cohort studies are recruiting only children with any disease and will assess toxicity, tumour control, adverse events and quality of life. One cohort study expected to recruit 1000 children will assess mortality and secondary malignancies at 5 and 10 years. Completion of this study, started in 2017, is expected in 2037. Another cohort study expected to recruit 400 children planned to be treated with proton therapy will assess toxicity, mortality and secondary malignancies and is expected to provide results by 2025 after a follow-up of 10 years.

Conclusions

Assessing evidence of comparative effectiveness and safety of PBT in children is challenging as data are dispersed across mixed population studies. There are comparative studies suggesting comparable effectiveness and higher safety of PBT compared to other types of radiation therapy, but studies of higher quality and with longer follow-up are needed to confirm such findings. There are several ongoing registries recruiting children undergoing treatment with PBT, which will assess acute and late toxicity and one cohort study of 1000 children expected to provide data deemed necessary by the included HTA reports, namely data on mortality and secondary malignancies.

2. TUMOURS OF THE CENTRAL NERVOUS SYSTEM [SEE APPENDIX - TABLE A2 AND A2I]

Four of the five HTA reports assessed comparative safety and effectiveness of PBT in Tumours of the Central Nervous System^{8,21-23}. Only few small retrospective comparative studies have been retrieved, judged of low to very low quality, reporting data on safety and/or effectiveness and mostly not showing statistically significant or clinically relevant differences between PBT and other types of radiation therapy. Available studies are quite heterogeneous in terms of morphology and tumour behaviour.

There are three ongoing RCTs comparing PBT with photon radiotherapy; one of these studies also compares proton and carbon-ion therapies. The first RCT, enrolling 606 grade IV glioma patients, is a four-arm trial comparing standard and dose escalation treatments with PBT and photon therapy. Results on 5 years overall survival, progression free survival and toxicity are expected in 2026. A second RCT enrolling 120 patients with grade II/III astrocytoma, oligodendroglioma or oligoastrocytoma (excluding grade IV disease) compares PBT with IMRT and results on 10 years local control, overall survival, progression free survival, toxicity and quality of life are expected in 2025. The third RCT, enrolling 80 patients with skull base meningioma, compares PBT with carbon-ion therapy, hypofractionated photon therapy and conventional photon radiotherapy. 3-years results on toxicity, overall survival, progression free survival and quality of life are expected by 2022. These studies enrol patients with discrete or good performance status, and exclude those with metastases, distant disease, co-morbidities or previously treated with chemotherapy or radiotherapy. There is also one comparative study vs surgery, which is intended to recruit 140 craniopharyngioma patients up to 21 years old and will be completed by 2027.

Eleven non-comparative studies have been identified assessing PBT in tumours of the Central Nervous System measuring effectiveness and/or safety outcomes: two are intended to recruit a total of 200 pa-

tients with benign or malignant tumours of the brain or at the base of the skull (one of them ending in 2024, in the other one the end date is not reported); two are intended to recruit a total of 76 patients with glioma (grade IV in both studies and also low grade/grade III in one study) and will be completed by 2020/2021; one is intended to recruit 112 patients 0-21 years old with craniopharyngioma, and will be completed by 2021; one is intended to recruit 80 patients 4 to 21 years old with primary CNS tumor or diagnosis of metastatic disease to the CNS, and will be completed by 2025; one is intended to recruit 45 patients 3-25 years old with central nervous system germ cell tumour, and will be completed by 2020; one is intended to recruit 30 patients 6 months to 25 years old with neuroblastoma or ganglioneuroblastoma, and will be completed by 2028; one is intended to recruit 30 adults with vestibular schwannoma or acoustic neuroma and will be completed in 2021; one is an RCT not comparing hadrontherapies vs photontherapy but PBT or carbon-ion therapy, therefore considered as single-arm study; it was intended to recruit 150 patients with unifocal, supratentorial primary glioblastoma and expected to provide results on toxicity, overall survival and progression free survival by 2014, but its status is unknown. One single arm study on malignant peripheral nerve sheath tumours has been withdrawn for feasibility issues.

Conclusions

All Health Technology Assessment reports included in this analysis conclude that there is insufficient evidence to establish whether treatment of tumours of the central nervous system with proton beam therapy is more or less effective and more or less safe than treatment with photon therapy. Two ongoing randomized controlled trials are expected to provide data on comparative effectiveness and safety vs photon therapy for patients with grade IV glioma and grade II/III astrocytoma, oligodendroglioma or oligoastrocytoma and results should be available by 2026.

No currently available evidence was found on the effects of PBT on peripheral nerve sheath cancers. Only one small single arm ongoing study on acoustic neuromas was retrieved.

3. SARCOMAS [SEE APPENDIX - TABLE A3 AND A3I]

Sarcomas or malignant cancers of soft tissues are distributed across several different categories within the HTA documents, reflecting the ubiquitous nature of soft tissues. No evidence of superiority of PBT over photon or other therapy was identified in the reports.

Two ongoing comparative studies (one RCT and one non-randomised trial) were identified. The RCT compares proton therapy vs radical radiotherapy by Xrays and/or carbon-ion therapy and is intended to include 250 patients with soft tissue sarcoma, rhabdo-

myosarcoma, retroperitoneal sarcoma, osteosarcoma (Ewing excluded), chondrosarcoma (except of skull base), angiosarcoma and without metastatic disease. The non-randomised trial, comparing PBT with IMRT and ending in Dec 2019, is intended to enroll 80 patients with soft tissue sarcoma of the retroperitoneum and to provide data on overall survival and progression free survival.

One RCT provides non comparative data versus conventional treatments as it compares PBT vs CIRT; it is intended to include 154 patients with low-intermediate grade chondrosarcoma and will provide five-years data on overall survival, progression free survival, toxicity and quality of life by 2022. Three ongoing non-comparative studies are expected to enrol a total of 109 patients with soft tissue sarcoma (2 studies with a total of 84 patients, one of which ending in 2018 with no data available) and with sarcoma of the kidney (1 study with 25 patients). Data on acute and/or late toxicity are expected by 2023-2026. A fourth non-comparative study on patients with sarcoma of the Peripheral Nerve Sheath (MPNST) has been withdrawn for feasibility issues.

Conclusions

All Health Technology Assessment reports included in this analysis conclude that there is insufficient evidence to establish whether treatment of sarcomas with proton beam therapy is more or less effective and more or less safe than treatment with photon therapy. Two ongoing RCTs vs carbon ion may provide comparative efficacy and safety data on these two hadrontherapies by 2023. One non-randomised comparative study vs IMRT, ending in 2019, may provide some data on overall survival and progression free survival.

4. CHORDOMAS [SEE APPENDIX - TABLE A4 AND A4I]

Two of the five HTA reports assessed comparative safety and effectiveness of PBT in a number of diseases referable to chordomas^{8,22}. Only retrospective case series have been retrieved, enrolling miscellaneous and highly heterogeneous population. Authors of both documents reported that the low quality of available evidence made results not interpretable.

Three ongoing studies have been identified, none of them comparing PTB with photon therapy. Two RCTs comparing PTB versus carbon ion radiotherapy are expected to enrol 419 patients including people with chordoma, chondroid chordoma, sacrococcygeal chordoma or skull base tumour. Results on overall survival, progression free survival and toxicity are expected by 2022-2023. The other ongoing study will provide non-comparative efficacy and safety data on 64 patients that will be available around 2022. All these studies exclude patients with previous radiation therapy.

Conclusions

HTA reports included in this analysis conclude that there is insufficient evidence to establish whether treatment of chordomas with proton beam therapy is more or less effective and more or less safe than treatment with photon therapy. Results from ongoing non-comparative studies are not expected to provide adequate clinical data to solve this uncertainty. RCTs will only compare two different types of hadrontherapies, not providing data versus standard radiotherapies

5. TUMOURS OF THE HEAD & NECK REGION [SEE APPENDIX - TABLE A5 AND A5I]

All five HTA reports assessed comparative safety and effectiveness of PBT in malignancies occurring in the head and neck district. Available studies are mostly non-comparative and retrospective, providing inconclusive evidence on differences between PBT and alternatives. Only one HTA (INESS) reported statistically significant results in favour of PBT versus Photon Therapy, based on a review of non-comparative studies, for overall survival and progression free survival rate at 5 years and for long-term locoregional control in patients with nasal cavity and paranasal sinus cancer. However, the authors state that biases inherent in retrospective and non-controlled prospective studies limit the scope of the conclusions.

Only one HTA report assessed comparative safety and effectiveness of PBT in salivary glands adenocarcinoma, identifying one retrospective and one prospective case series with few patients⁸. The data were judged as sparse.

Four included HTA reports assessed comparative safety and effectiveness of PBT in orbital and peri-orbital cancers^{8,20,21,23}. Three retrospective case series and a review of 41 non-comparative studies using different types of radiation therapies on patients with sinonasal cancer were included. The indirect comparison performed by the review's authors showed no difference in safety and effectiveness between PBT and comparators. Characteristics of the included population are heterogeneous and all four HTA Reports judged the quality of the evidence as very low and inconclusive.

Thirteen ongoing studies were identified. Four ongoing randomized controlled studies will assess acute and/or late toxicity as primary outcomes of PBT versus RT recruiting patients with Squamous cell carcinoma of the oropharynx (360 patients) of the tonsil (100 patients), with recurrent head and neck cancer (100 patients), and of salivary glands (132 patients). One more RCT will compare PBT with radical radiotherapy by Xrays and/or carbon-ion therapy in 250 patients with radioresistant adenoid cystic carcinoma of head and neck (larynx and trachea excluded). One of the five studies will assess effectiveness as primary outcome, two as secondary outcomes. Results are expected between 2021 and 2028.

The trial including patients with resectable salivary gland cancer and no prior irradiation is currently enrolling and will assess safety outcomes (complications and toxicity) at 1 year and “specific global survival” at 60 months.

One ongoing comparative, non-randomized study will compare safety and effectiveness of PBT versus RT in 90 patients with previously untreated cancers of different histology types in head and neck region. Results are expected by 2021.

Seven non-comparative studies on patients with head and neck cancers are planned assessing toxicity and/or effectiveness. Except for one study expected to recruit a cohort of 450 patients by 2026, six are all small studies (min. 20-max. 67 patients) with results expected to be available between 2020 and 2025. One study has been completed but no results were posted. Most studies exclude previously irradiated patients.

No ongoing studies explicitly including non-melanoma ocular malignancies were found.

Conclusions

All HTA reports included in this analysis conclude that there is insufficient evidence to establish whether treatment for head and neck and periorbital cancers with proton beam therapy is more or less effective and more or less safe than treatment with photon therapy. There is no data to assess comparative effectiveness and safety of PBT in salivary glands cancer.

There are 5 ongoing prospective comparative studies (4 randomized and 1 non-randomized) with follow-up periods that range between 2 and 5 years, which should provide data on comparative effectiveness and safety and are expected to be completed between 2020 and 2028.

In particular, results from one ongoing small RCT should provide some data on comparative safety of PBT versus IMRT in patients with resectable salivary glands adenocarcinoma.

6. PRIMARY MELANOMA

[INCLUDING CUTANEOUS AND UVEAL MELANOMA]
[SEE APPENDIX - TABLE A6 AND A6I]

None of the included HTA reports assessed comparative effectiveness and safety of PBT in cutaneous melanoma.

Three included HTA reports assessed comparative safety and effectiveness of PBT in ocular melanoma^{8,20,21}. Specifically, three systematic reviews report lower recurrence rates with hadrontherapies vs brachytherapy, although the need for caution in the interpretation of results is highlighted given the low quality of the included primary studies.

One ongoing randomized controlled study, enrolling 132 patients with various diseases, including skin cancer and melanoma comparing PBT versus IMRT is expected to be completed in 2021, providing data only on acute mucositis.

One comparative, non-randomised study vs IM-RT collects evidence on effectiveness and safety on 90 patients with cancers of different histology, including melanoma. Results are expected by 2021.

One ongoing randomized trial comparing different regimens of PTB has been identified recruiting 32 patients with large choroidal melanoma. Results expected in 2021 will not provide data on comparative effectiveness and safety of PTB versus conventional radiation therapy.

Conclusions

Comparative effectiveness and safety evidence of PBT versus photon therapy in cutaneous melanoma has not been assessed in the included HTA reports.

Health Technology Assessment reports included in this analysis conclude that there is insufficient evidence to establish whether treatment with proton beam therapy is more or less effective and more or less safe than treatment with photon therapy in treating orbital melanoma.

One ongoing randomized controlled trial and one comparative non-randomised study are assessing evidence on safety (and effectiveness in the latter) on mixed patients, including some patients with skin cancer or melanoma. Effects on ocular melanoma are assessed in a study not comparing PBT versus conventional radiation therapy.

Data from these studies are not expected to provide conclusive information on comparative effectiveness and safety of PBT in cutaneous and ocular melanoma.

7. LUNG MALIGNANCIES

[SEE APPENDIX - TABLE A7 AND A7I]

Two of the five HTA reports assessed comparative effectiveness and safety of PBT in primary lung malignancies^{8,21}. Retrieved studies assessing both benefits and harms include several case series, 4 retrospective cohorts, 1 cohort with historical control and 1 RCT. Quality of evidence was judged to be fair for the one RCT and low for the remaining studies. Consistent findings suggest PBT to be comparable to other types of radiation therapy in terms of overall survival and toxicity. Most enrolled patients were adults with advanced NSCLC.

Eleven ongoing studies were identified. All are enrolling patients with Non-Small Cell Lung Cancer, with good to fair performance status. Most studies exclude previously irradiated patients. Seven of the 12 studies are non-comparative, two of which are completed but with no results and one was terminated due to low accrual. Of the four ongoing comparative studies, one randomized trial was terminated for low accrual, while two, comparing PBT versus photon therapy are still recruiting 330 and 98 patients respectively. The smaller trial, to be completed in 2024, assesses only acute and late toxicity at 6 months, while

the larger trial evaluates also effectiveness outcomes and cost-effectiveness: overall survival at 7 years, progression free survival and quality of life. This study is expected to be completed in 2020. A fourth randomized controlled study comparing PBT versus IMRT is a dose finding study expected to be completed in 2019.

Conclusions

The HTA reports included in this analysis conclude that currently there is insufficient evidence to establish whether treatment of primary lung cancer with PBT is more or less effective and more or less safe than treatment with photon therapy. Upcoming results from the larger ongoing randomized controlled trial comparing effectiveness and safety of PBT versus photon therapy will be relevant to support or confute data from the previously published RCT.

8. BREAST MALIGNANCIES [SEE APPENDIX - TABLE A8 AND A8I]

Three of the five HTA reports assessed comparative effectiveness and safety of PBT in breast malignancies^{8,21,23}. Retrieved studies assessing both benefits and harms include 2 comparative studies (1 prospective and 1 retrospective) and 3 retrospective case series. Findings suggest that PBT presents comparable effectiveness to other types of radiation therapy but higher skin toxicity. Quality of evidence was judged by the reports' authors to be low.

Nine ongoing studies were identified, seven of which are non-comparative. Five are small studies with short follow-up assessing mainly short-term adverse event, while the remaining two are recruiting 150 and 132 patients respectively, and measure rate of recurrence as well as acute and late toxicity. Two small comparative non-randomized trials were identified. One is completed with all 18 recruited patients ending with being treated with photon and no results are posted. The other comparative ongoing trial is expected to be completed in 2021 and provide results on toxicity and overall survival on 55 patients. All ongoing studies excluded previously irradiated patients.

Conclusions

The three HTA reports included in this analysis conclude that there is insufficient evidence to establish whether treatment of breast cancer with PBT is more or less effective and more or less safe than treatment with photon therapy. There are several non-comparative studies and one small comparative non-randomized study ongoing. Due to the design and size of the trials, results, which will become available between 2021 and 2033, are not expected to resolve the current uncertainty on comparative effectiveness and safety.

9. THYROID MALIGNANCIES [SEE APPENDIX - TABLE A9]

None of the included HTA reports assessed comparative effectiveness and safety of PBT in thyroid malignancies and no ongoing studies were identified.

Conclusions

There is no clinical evidence, available or upcoming, to establish whether treatment with proton beam therapy is more or less effective and more or less safe than treatment with photon therapy in thyroid malignancies.

10. PANCREATIC MALIGNANCIES [SEE APPENDIX - TABLE A10 AND A10I]

Only one of the HTA reports included in this analysis assessed comparative effectiveness and safety of PBT in pancreatic malignancies⁸. The included case series provide limited information to evaluate radiation safety or effectiveness of PBT in pancreas cancer, while the only comparative study, small and retrospective provided no statistically significant differences. The quality of the evidence was judged to be very low.

Two very small ongoing studies were identified. Neither compared PBT with photon therapy.

Conclusions

The only report assessing PBT in cancer of the pancreas concludes that there is insufficient evidence to establish comparative effectiveness and safety of PBT. Data from currently ongoing studies will not provide adequate additional information.

11. COLON AND RECTUM MALIGNANCIES [SEE APPENDIX - TABLE A11 AND A11I]

Only one of the included HTA reports assessed comparative effectiveness and safety of PBT in colorectal malignancies⁸. Only few and small non-comparative case series were included, which do not provide information on safety or effectiveness of PBT in colorectal cancer.

Four non-comparative ongoing studies have been retrieved. Two small-sampled studies recruited colorectal cancer patients with lung or liver metastasis, while two equally small studies recruited patients with non-metastatic squamous cell carcinoma or basaloid carcinoma of the anal canal.

Conclusions

The only report assessing PBT in colorectal cancer concludes that there is no evidence to establish com-

parative effectiveness and safety of PBT, while the currently ongoing studies will not provide adequate data for future re-assessment.

12. PROSTATE MALIGNANCIES AT HIGH RISK OF METASTASES [SEE APPENDIX - TABLE A12 AND A12I]

Of the five included HTA reports, one²³ did not assess PBT in prostate cancer and one reported only negative results from a systematic review of cost-effectiveness studies²². The remaining three reports include systematic reviews of comparative prospective and retrospective studies, primary comparative studies and primary non-comparative studies^{8,20,21}. Most studies assessed toxicity and quality of life, while few studies reported also on overall survival, disease free survival or tumour control. All three HTA reports judge the quality of the available evidence as low or very low.

Fifteen ongoing studies were identified, two of which were suspended or halted, two completed but not published, while results from the remaining 11 studies are expected between 2019 and 2033. Included patients range from having low to high-risk disease and nearly all studies exclude patients previously treated with chemotherapy, radiotherapy or surgery. Only one ongoing randomized controlled study versus IMRT has been identified assessing EP-IC bowel scores and/or quality of life. The remaining studies are non-comparative measuring mainly safety and quality of life. Among these, one RCT comparing two hadrontherapies (PBT vs CIRT, not vs photon) has been completed in 2015 but no results are currently available. Only five non-comparative studies measure effectiveness outcomes (overall survival or disease-free survival).

Conclusions

All Health Technology Assessment reports included in this analysis conclude that there is insufficient evidence to establish whether treatment with proton beam therapy is more or less effective and more or less safe than treatment with photon therapy in prostate cancer.

Results from ongoing studies (all non-comparative except one assessing only early toxicity and quality of life) are not expected to provide adequate clinical data to solve the uncertainty on comparative long-term safety and effectiveness of PBT in prostate cancer.

13. BLADDER MALIGNANCIES [SEE APPENDIX - TABLE A13 AND A13I]

Only one of the included HTA report assessed comparative effectiveness and safety of PBT in bladder malignancies⁸. One retrospective non-comparative

case series was included, which does not report information on safety or effectiveness of PBT in bladder cancer.

Only one ongoing comparative non-randomized trial comparing PBT with IMRT on 30 patients with urothelial carcinoma has been retrieved. The study, expected to be completed in 2013 with data on acute and late toxicity, appears not to be recruiting.

Conclusions

The only report assessing PBT in bladder cancer concludes that there is insufficient evidence to establish comparative effectiveness and safety of PBT. No significant results from ongoing research are expected in the near future.

14. OESOPHAGUS MALIGNANCIES [SEE APPENDIX - TABLE A14 AND A14I]

Only one of the included HTA reports assessed comparative effectiveness and safety of PBT in esophageal cancer⁸. It included five retrospective comparative cohorts reporting data on effectiveness (overall survival, mortality and progression/disease free survival) and safety (toxicity and adverse events). Quality of the evidence was judged to be very low.

There are two randomized controlled trials ongoing comparing PBT with IMRT (180 and 300 patients respectively) and one comparative non-randomized trial withdrawn after enrolling 0 patients. Results on 5 and 8 years overall survival, progression free survival, adverse effects and quality of life are expected between 2020 and 2032. Both RCTs enrol patients with oesophageal adenocarcinoma and squamous-cell carcinoma, with good performance status, and exclude those with metastases, distant disease, co-morbidities or previously treated with chemotherapy or radiotherapy.

One single arm study recruiting 3 patients and completed in 2015 has posted no results. Three non-comparative studies recruiting a total of 118 patients with esophageal cancer (adenocarcinoma or squamous cell carcinoma of the cervical or thoracic esophagus, gastroesophageal junction or cardia) and good performance status (excluding previous cancers and severe comorbidities) measuring survival, toxicity and quality of life will be completed by 2022/2026. Two of them excluded previous radiation therapy.

Conclusions

The only HTA report assessing comparative effectiveness and safety of PBT in esophageal cancer concluded that due to the limited information available from case series, there is insufficient information to evaluate radiation safety or effectiveness of PBT. Two ongoing randomized controlled trials are expected to

provide data on comparative effectiveness and safety for patients with oesophageal cancer and results should be available by 2020 and 2032.

15. URINARY TRACT MALIGNANCIES [SEE APPENDIX - TABLE A15]

None of the included HTA reports assessed comparative effectiveness and safety of PBT in urinary tract malignancies and no relevant ongoing studies were identified.

16. GASTRIC MALIGNANCIES [SEE APPENDIX - TABLE A16]

One of the included HTA reports assessed comparative effectiveness and safety of PBT in gastric cancer, retrieving only one prospective case series with mixed patients. Quality of the evidence provided from a case series was judged to be very low. No ongoing studies were identified.

Conclusions

The only HTA report assessing comparative effectiveness and safety of PBT in gastric cancer did not find sufficient information to evaluate radiation safety or effectiveness of PBT, while no data from upcoming research is expected.

17. UTERINE CERVICAL MALIGNANCIES [SEE APPENDIX - TABLE A17]

None of the HTA reports included assessed comparative effectiveness and safety of PBT in uterine cervical malignancies, while one report mentioned it as an experimental treatment⁸. Only one ongoing small non-comparative trial was identified. There is no clinical evidence, available or upcoming, to establish whether treatment with proton beam therapy is more or less effective and more or less safe than treatment with photon therapy in uterine or cervical malignancies.

18. LIVER MALIGNANCIES [SEE APPENDIX - TABLE A18 AND A18i]

Three of the five included HTA reports assessed comparative effectiveness and safety of PBT in liver cancer^{8,21,23}. Two systematic reviews of poor-quality studies and additional retrospective and prospective case series were included, as well as a randomized controlled trial comparing PBT with TACE. The overall quality of the evidence was judged to be low and the only RCT reported not significant differences between treatments, though progression free survival

(PFS) and local control tended to be greater following PBT.

There are three ongoing randomized controlled trials comparing PBT with radiofrequency ablation (166 patients), with photon radiotherapy (186 patients) and with transarterial chemoembolization (200 patients) in unresectable hepatocellular cancer (HCC), respectively. A fourth comparative, non-randomized study compares PBT with hepatectomy, recruiting 290 patients with resectable HCC. These studies include only patients with a good performance status and exclude those with metastatic disease and previous chemotherapy or radiotherapy for HCC. The three comparative studies collect data on overall survival, disease free and progression free survival, safety and quality of life with a follow-up length up to five years. The first RCT declared the end date in December 2018 but no recent data are published, and the recruitment is reported as ongoing. Data from the second RCT will be available in 2022, while results from the non-randomised comparative study are expected in 2029.

Four further non-comparative studies are ongoing, two of which recruiting a total of 246 patients with unresectable HCC and one including 66 HCC patients. Data on overall survival, progression free survival and toxicity collected from a follow-up of 1 up to 3 years will be available between the end of 2019 and 2024. Only two of these studies collect data on quality of life. The fourth non-comparative study enrolls 35 patients with non-lymphoma liver metastases, rather than primary liver malignancies, collecting data on local control and toxicity with a follow-up of 2 years; data are expected in 2026. All studies exclude previously irradiated patients.

Conclusions

All three HTA reports conclude that there is insufficient evidence to establish whether PTB is more or less effective and more or less safe than other treatments for patients with liver cancer. Two ongoing randomized controlled trials are expected to provide data on comparative effectiveness and safety for patients with unresectable hepatocellular cancer and results should be available by 2022.

19. RECURRENCES REQUIRING REPEAT TREATMENT IN AREAS ALREADY EXPOSED TO RADIOTHERAPY [SEE APPENDIX - TABLE A19 AND A19i]

Four of the five included HTA reports considered use of PBT in reirradiation of recurrences^{8,20,21,23}, three of which concluding that there is no evidence in support of such treatment. One report included 3 retrospective case series, which provide insufficient data⁸.

Two non-comparative studies on repeat treatment in areas already exposed to radiotherapy were identified from the databases of ongoing studies. One

study of 49 patients with Non-Small Cell Lung Cancer, completed in 2016, has no results posted, while for the other study, an RCT comparing safety of two types of PTB and expected to be completed in 2017, the status is unknown.

Conclusions

All four HTA reports included in this analysis conclude that there is insufficient evidence to assess comparative effectiveness and safety of PBT in recurrences requiring repeat treatment in areas already exposed to radiotherapy. No relevant data are expected to become available in the near future. The great majority of ongoing studies included in this report, specified previous radiation treatment as an exclusion criteria for patients' enrolment.

There is no clinical evidence, available or upcoming, to establish whether treatment with proton beam therapy is more or less effective and more or less safe than treatment with photon therapy in people with increased radiosensitivity.

20. ALL MALIGNANCIES

[SEE APPENDIX - TABLE A20]

Six ongoing studies recruiting all patients receiving PBT were identified and retrieved. Three are small sized single arm studies, with a short follow-up (2 months to 2 years) measuring adverse events, progression free and overall survival. The other three studies are register series expected to recruit a minimum of 300 and a maximum of 3200 patients and supposed to run for at least 10 years and up to 25 years. No pre-specified measurement of outcomes is provided by any of the three studies. Two more studies failed recruiting targets and were terminated.

Results: Carbon-ion radiation therapy

HEALTH TECHNOLOGY ASSESSMENT REPORTS

Our searches identified five HTA reports:

1. Goetz, G, Mitic, M. Carbon ion beam radiotherapy (CIRT) for cancer treatment: a systematic review of effectiveness and safety for 12 oncologic indications. HTAProject Report No. 101; 2018. Vienna: Ludwig Boltzmann Institute for Health Technology Assessment¹⁹.
2. Carbon ion beam therapy for chordoma: a review of clinical effectiveness, cost-effectiveness, and guidelines. Ottawa: CADTH; 2018 Oct (CADTH rapid response report: summary with critical appraisal). ISSN: 1922-8147²⁵.
3. Morrison, A. Carbon Ion Radiation Therapy [Environmental Scan issue 3]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009²⁶.

4. Hassed P, Mundy L. Proton and Heavy Ion Therapy: An overview: January 2017. Health Policy Advisory Committee on Technology (HealthPACT)²⁷.
5. Proton beam, neutron beam, and carbon ion radiotherapy (Aetna Clinical policy bulletin, no. 0270, July 2019)²⁸.

Of these only two^{19,25} reported data from primary studies. One report was an environmental scan carried out in 2009²⁶ which was retained for its useful baseline description of the evidence situation a decade ago. The other reports contained description of the Australian situation with a detailed analysis of start up and operating costs of the structures²⁷ and an AETNA report re-analysing and updating the LBI report²⁸. These last three reports add depth and detail to a thin evidence base (Table A21).

QUALITY AND QUANTITY OF CLINICAL RESEARCH ON COMPARATIVE EFFECTIVENESS AND SAFETY

Due to the paucity of available clinical research, results for carbon-ion radiotherapy have been reported in an aggregate way. To allow comparison with state of the art of CIRT clinical research, Table 3 reports coverage by the included HTA reports and retrieved ongoing studies of the main indications considered in the present report. Results extracted from the included HTA are reported in Table A21, while Table A21i summarises the information on the ongoing studies. Information is at times repeated in Tables, when overlaps of indications occur in the same study or report.

Summary of findings

The largest HTA report looked for evidence on 54 specific indications¹⁹. The report found only one randomised trial described as a "feasibility study" and 26 non-randomised studies of which only 6 were comparative and 20 were case series. The authors did not identify any evidence for 41 indications. For the remaining 13 indications the evidence was insufficient in 7 regions: skull base, brain, nasal and paranasal cavities and salivary glands, soft tissues, lung, prostate and gastrointestinal tumours including rectal cancers. The observational studies were assessed as at moderate risk of bias. The authors concluded that CIRT should be considered an experimental treatment due to the low quality evidence of its effects.

The other HTA report assessed the effects of CIRT specifically on chordomas and chondrosarcomas²⁵. The authors identified a systematic review described as "a meta-analysis" of 25 case series comprising 996 patients all in China. This "meta-analysis" had been conducted by some of the authors of the single studies. Included in the "meta-analysis" were also four studies from the same centre with overlapping au-

Table 3. Availability of information in included HTA reports on CIRT and N. of ongoing non-comparative and comparative studies by clinical indications^{19,25-28*}.

Indication	LBI 2018	CADTH 2018	CADTH 2009	HeaLth PACT 2017	AETNA 2019	N. ongoing non comparative studies	N. ongoing comparative studies
1. Solid paediatric tumours						0	0
2. Central nervous system tumours	X					1	4
3. Sarcomas	X	X				0	2*
4. Chordomas	X	X				3	1*
5. Tumours of the head & neck region	X					6	1*
6. Cutaneous and uveal melanoma						0	0
7. Lung malignancies	X					0	0
8. Breast malignancies						0	0
9. Thyroid malignancies						0	0
10. Pancreas malignancies	X					6	1
11. Colon and rectum malignancies	X					1	0
12. Prostate malignancies at high metastathases risk	X					7	0
13. Bladder malignancies						0	0
14. Esophagus malignancies	X					0	0
15. Urinary tract malignancies						0	0
16. Gastric malignancies						0	0
17. Uterine cervical malignancies						0	0
18. Liver malignancies						7	0
19. Recurrent tumours requiring repeat treatment in areas already exposed to radiotherapy						0	0

Key: N.= number; *some studies may be repeated as they may be pertinent to different tumours

thors, two of which were modelling studies. The comparators were miscellaneous interventions including surgery and other forms of radiotherapy. The authors urge caution in interpreting the results, which are heterogeneous and partly contradictory, given the low quality of the studies.

ONGOING STUDIES

A total of 37 ongoing studies were retrieved (Table A21i). Of these 32 ongoing studies will provide non comparative data on efficacy and safety outcomes of CIRT – mostly in subjects not previously

exposed to radiotherapies – in a variety of clinical areas, more specifically: 7 studies are intended to include a total of 1244 patients with prostate cancer and are expected to end by 2027 (one has preliminary results already published); 7 studies on a total of 385 patients with liver malignancies are expected to end by 2021 (three of them should have already been completed but no results have been published); 5 studies on a total of 252 patients with nasopharyngeal cancer are expected to end by 2022; 6 studies on a total of 149 patients with pancreatic cancer are expected to end by 2021 (one of them should have already been completed but no results have been published); one study on

49 patients with head & neck cancer (adenoid cystic carcinoma) was expected to end by 2017 (unknown status); one study on 40 patients with atypical meningioma (already exposed to prior photon therapy) is expected to end by 2020; one study on 14 patients with rectal cancer has been completed in 2018 (unknown status).

Five randomised controlled trials were identified, including 3 completed trials with unpublished data on Tumours of the Central Nervous System (2 on glioma and one on glioblastoma) ended between 2014 and 2016. The remaining 2 ongoing RCTs will be concluded in 2023 and will provide data on toxicity, overall survival, progression free survival and quality of life, excluding patients with prior radiotherapy. More specifically: one RCT will include chordoma patients (except of skull base) in a mixed population including a total of 250 patients with adenoid cystic carcinoma of head and neck (larynx and trachea excluded), soft tissue, retroperitoneal or rhabdomyosarcoma, osteosarcoma (Ewing's sarcoma is excluded), chondrosarcoma (except of skull base), or angiosarcoma; this trial will compare CIRT with PBT and x-ray radiotherapy with a follow-up of 5 years; the other RCT will compare CIRT with x-ray chemoradiotherapy on 110 patients with unresectable pancreatic cancer, with a follow-up of 2 years.

Finally, four RCTs will compare CIRT vs PBT, thus not providing comparative data vs other treatments: two of them will focus on chordoma aiming to include 419 patients not previously exposed to radiotherapy, with up to 8-years follow-up; one is aimed to recruit 154 patients with chondrosarcoma, with a follow-up of 5 years; one is aimed to recruit 80 patients with meningioma, with a follow-up of 3 years.

Data from these RCTs, if published, may provide some insight on the comparative effectiveness and safety of CIRT vs PBT in the clinical areas listed above. However, it is not clear whether sufficient statistical power will be available to establish possible differences between the two hadrontherapies. As for CIRT vs conventional radiotherapies, very little data are expected on their comparative efficacy and safety from ongoing studies.

It should be noted that our research in clinical trial registers retrieved 3 more studies that were withdrawn for problems of recruitment (2 studies, one on liver cancer and one on head and neck cancer) and for administrative barriers (1 study on pancreatic cancer).

Overall findings

Table 4 summarises the findings, by clinical indication, from the included HTA reports and from the overview of ongoing clinical research. The Table reports the current level of certainty on superiority of PBT or CIRT compared to photon radiation therapy and the likelihood that future research results would resolve current uncertainty.

Discussion

We carried out an overview of the evidence included in six high quality up-to-date HTA reports assessing PBT and two HTA reports assessing CIRT. These comprised a large number of systematic reviews, comparative and non-comparative studies on the effects of hadrontherapies in a wide variety of cancers, stages, populations and clinical settings^{8,19-25}.

We also identified 72 ongoing non-comparative studies and 25 comparative studies on PBT – of which 17 were randomized controlled trials – and 37 ongoing studies on CIRT, of which 5 were RCTs.

The HTA documents on which our overview is based, are of good quality, up-to-date and from publicly funded bodies, except for the ECRI institute, which is a not-for-profit independent body. They all reach consistent conclusions, namely that the use of PBT and CIRT does not at present appear to be supported by clear or sufficient evidence. Specifically there is no clear evidence of superiority of PBT or CIRT versus other currently used types of radiotherapy in terms of both effectiveness (survival and disease progression), quality of life and safety (acute and late toxicity). A small number of ongoing studies may in time provide evidence for specific indications but the great majority of identified ongoing studies will not be able to resolve the uncertainty for decision makers because of inappropriate study design, small sample size, lack of clinically important outcomes and inadequate follow-up.

Hadrontherapies are not without toxicity, occurring when healthy tissues in the path of the radiation beam are damaged. However, such effects have not been adequately investigated to date and few future studies might provide limited evidence on toxicity of PBT and CIRT. Long-term consequences of PBT are also understudied, although probably rare. Secondary cancers may occur in long-term cancer survivors and this is of particular concern in patients receiving radiation at younger ages, as well as effects on neurocognitive development, especially when administered to children under 3 years of age.

Based on the HTA authors' consistent comments on the low quality of available studies one could consider PBT and CIRT as technologies which have not fulfilled their theoretical potential, despite their long-standing availability. However, this could be a potentially wrong interpretation, as absence of evidence of effect must not be considered as evidence of no effect. PBT and CIRT do not appear to have been robustly tested using large multicentre randomised comparisons with phototherapy for specific conditions. Similarly to other oncotherapeutics, there could be specific subpopulations of cancer patients who could benefit from hadrontherapies. Research resources need to be employed in identifying such categories and specific indications using robust methods.

Table 4. Available evidence and likelihood of generation of comparative evidence from ongoing studies on PBT/CIRT vs photon therapy.

Categories of service delivery	Superiority of PBT and CIRT versus photon therapy			
	Evidence of superiority from published studies		Likelihood that upcoming evidence could resolve uncertainty	
	TP	CIRT	TP	CIRT
1. Solid paediatric tumours	Uncertain	Not available	Likely	None*
2. Central nervous system tumours	Uncertain		Likely	
3. Sarcomas	Uncertain		Likely	
4. Chordomas	Uncertain		Unlikely	
5. Tumours of the head & neck region	Uncertain		Likely	
6. Cutaneous melanoma	Uncertain	Not available	Unlikely	None*
7. Lung malignancies	Uncertain		Unlikely	None*
8. Breast malignancies	Uncertain	Not available	Unlikely	None*
9. Thyroid malignancies	Not available		None*	
10. Pancreas malignancies	Uncertain	Not available	Unlikely	Likely
11. Colon and rectum malignancies	Uncertain		Unlikely	None*
12. Prostate malignancies	Uncertain		Unlikely	None*
13. Bladder malignancies	Uncertain		Unlikely	None*
14. Esophagus malignancies	Uncertain		Likely	None*
15. Urinary tract malignancies	Not available		None*	
16. Gastric malignancies	Uncertain		None*	
17. Uterine cervical malignancies	Not available		Unlikely	None*
18. Liver malignancies	Uncertain	Not available	Likely	None*
19. Recurrent tumours requiring repeat treatment in areas already exposed to radiotherapy	Uncertain	Not available	Unlikely	None*

*No ongoing studies were identified

While the quality of currently available evidence was assessed as uniformly low by the HTA documents analysed, it is not clear whether ongoing studies will be able to shed much light on the effects of PBT or CIRT compared to other forms of phototherapy, since no detailed information is available on their methodological quality. It should be noted that RCTs are underway assessing PBT and/or CIRT in tumours of the central nervous system, sarcomas, head & neck, lung, esophageal and liver malignancies, chordoma, meningioma and pancreatic cancer.

There is a current discussion among the radiotherapy community on how to best test the effects of hadrontherapies. The proposed types of studies are classic randomised controlled trials and trials nested within large multicentre patient registers²⁹. Model based treatment plans, in which the risk of radiation-induced toxicity can be predicted with probabi-

listic models, are also suggested, although they would mainly serve as proof of concept studies

A recurring comment made in the HTA documents included in this overview is the lack of comparability of the effects of hadrontherapies with phototherapy due to heterogeneity of participants in terms of age, comorbidities, tumor types and stages, and concurrent medications. This type of problem is best addressed through randomization of participants and better international coordination among research centres.

Limitations

A limitation of our analysis lies in the potential repetition and overlap of the evidence across studies, tumour types and HTA source documents, especial-

ly in relation to malignancies of soft and connective tissues, which are ubiquitous in the human body. However, since we have not carried out quantitative aggregation and analysis of the data, and given the consistent views of all HTA report authors, we think this has not affected our conclusions.

Conclusions

Despite the growing number of studies being published and the growing number of PBT and/or CIRT centres opening or at a planning stage, there is persistent uncertainty on the added clinical benefit of hadrontherapy treatments over conventional radiation therapy. Research currently underway may not contribute to solve this uncertainty. There is a lack of agreement on appropriate study designs to assess the effects of hadrontherapies and lack of coordination between centres in the production of joint research protocols to generate the evidence necessary for decision-makers. This leads to the production of numerous small and poorly designed and reported studies. These shortcomings might confine the use of PBT and CIRT to experimental treatments and require that patients willing to undergo PBT or CIRT be fully informed of the risks and uncertainties of the outcomes.

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