agena.s. AGENZIA NAZIONALE PER I SERVIZI SANITARI REGIONALI

RIHTA Rete Italiana Health Technology Assessment

Hadrontherapy for cancer treatment: overview of the evidence on safety and effectiveness

Agenzia nazionale per i servizi sanitari regionali
Via Puglie, 23 - 00187 Roma
Tel. 06-427491
Fax: 06-42749488
www.agenas.it

Hadrontherapy for cancer treatment: overview of the evidence on safety and effectiveness

Agenzia nazionale per i servizi sanitari regionali
Via Puglie, 23 - 00187 Roma
Tel. 06-427491
Fax: 06-42749488
www.agenas.it

Introduzione

Questo documento è frutto di un'esperienza di collaborazione scientifica interregionale nell'ambito della Rete Italiana per l'Health Technology Assessment-RIHTA, maturata nel corso di un'iniziativa formativa realizzata da Agenas nel 2011.

Si tratta quindi anche di una prima esperienza strutturata di condivisione di linguaggio, di metodi, di carico di lavoro in rete interregionale, resa possibile dallo sforzo collaborativo di professionisti di diverse discipline e provenienti da diversi contesti.

IL DIRETTORE AGENAS

Fulvio Moirano

Abstract

Background

I tumori sono fra le principali cause di morte nel mondo. Le terapie per il trattamento dei tumori includono la chirurgia, la chemioterapia ed i trattamenti radioterapici (RT). L'adroterapia (HT) è una forma di radioterapia (RT) che utilizza fasci di protoni e/o fasci di ioni di carbonio. L'HT potrebbe migliorare il trattamento delle lesioni tumorali grazie alla natura di protoni e ioni di carbonio che teoricamente aumentano la precisione rispetto alla radioterapia convenzionale poiché risparmiano i tessuti sani circostanti. I tumori per i quali l'HT potrebbe fornire risultati migliori rispetto ad altre forme di radioterapia sono quelli circondati da tessuti vitali sensibili alle radiazioni, come i tumori della testa e del collo, dell'occhio, del fegato, del polmone (tumore non a piccole cellule del polmone, NSCLC), della prostata, del pancreas, dei tessuti moscolo-scheletrici, del sistema gastrointestinale e del bacino. In Italia, tutti questi tumori sono responsabili di circa 80.000 nuovi casi ogni anno.

Obiettivi

L'obiettivo dell'analisi è quello di fornire una panoramica delle informazioni disponibili inerenti la sicurezza (diminuzione degli effetti collaterali) ed l'efficacia (miglioramento del controllo della massa tumorale a livello localizzato e sopravvivenza generale) dell'HT per il trattamento dei tumori rispetto ad altre tecniche di RT. In particolare, il quesito di ricerca è stato sviluppato come segue:

- Popolazione: pazienti affetti da qualsiasi neoplasia trattati con radioterapia
- Intervento: adroterapia
- Comparatore: qualsiasi altra tecnica di radioterapia
- Outcome: sicurezza (diminuzione degli effetti collaterali acuti e tardivi) ed efficacia (controllo della massa localizzata e sopravvivenza generale).

Metodologia di ricerca

Al fine di ricercare report HTA e/o revisioni sistematiche inerenti la valutazione di efficacia dell'HT per il trattamento dei tumori sono state consultate le seguenti banche dati e siti web: Database of Abstracts of Reviews of Effects (DARE); Health Technology Assessment (HTA) database; NHS Economic Evaluation Database (NHS EED); TripDatabase; siti web INAHTA e AHRQ.

La ricerca della letteratura primaria è stata consultata allo scopo di aggiornare la ricerca secondaria letteratura esistente, pertanto sono state consultate le seguenti banche dati e siti web: Pubmed; Clinicaltrials.gov; Controlled-trials.com, Cochrane Central Register of Controlled Trials. Soltanto gli studi controllati randomizzati (RCT) sono stati inclusi nella ricerca della letteratura primaria.

Criterio di selezione

Sono stati inclusi tutti i report di HTA e revisioni sistematiche di valutazione di sicurezza ed efficacia dell'HT rispetto alla pratica convenzionale nel trattamento di pazienti affetti da tumore.

Si sono ricercati tutti studi clinici randomizzati, inerenti la valutazione dell'HT, pubblicati negli ultimi cinque anni, al fine di verificare la validità delle conclusioni riportate nella letteratura secondaria esistente.

Non è stata condotta una specifica ricerca della letteratura di valutazione economica dal momento che questo non è un obiettivo specifico della presente revisione, anche se è stata fornita comunque una sintesi degli aspetti economici dell'HT.

Raccolta e analisi dei dati

Gli studi primari e secondari trovati in letteratura sono stati assegnati a coppie di autori. Ogni autore, in modo indipendente, ha poi raccolto, valutato, analizzato e sintetizzato i dati ivi contenuti.

Principali risultati

La ricerca in letteratura di report HTA e revisioni sistematiche ha prodotto 33 risultati, di questi, solo 15 documenti rispettano i criteri di inclusione. Dalla ricerca della letteratura primaria, 11 pubblicazioni sono state individuate, ma nessun documento rispetta i criteri.

I report HTA e le revisioni sistematiche inclusi che hanno valutato l'uso dell'HT nel trattamento di vari tumori concludono che:

Tumori della base cranica e della testa-collo: non ci sono prove a favore di una migliore efficacia dell'HT rispetto ai trattamenti convenzionali. In assenza di studi clinici ben disegnati non è possibile trarre conclusioni definitive.

Tumori dell'occhio: gli studi secondari differiscono nella tipologia della patologia considerata, nel tipo di tecnologia utilizzata per l'HT e nel disegno degli studi primari inclusi; pertanto, non è possibile trarre conclusioni. Ci sono limitate evidenze inerenti l'efficacia e la sicurezza dell'HT per i tumori oculari a causa della mancanza di studi correttamente disegnati e descritti. Un numero limitato di studi disponibili suggerisce un risultato potenzialmente migliore con radioterapia con protoni per il trattamento locale del melanoma uveale se è vicino al disco ottico o della fovea o se il suo spessore è superiore a 5 mm.

Tumore del polmone: è stato selezionato uno studio di meta-analisi per il trattamento di pazienti con NSCLC in stadio I che però include 8 studi primari di bassa qualità**.** La meta-analisi riporta che i tassi di sopravvivenza per la terapia con particelle sono superiori a quelli con radioterapia convenzionale ma simili a quelli ottenuti con la radioterapia stereotassica. Non ci sono conclusioni definitive in merito ad eventi avversi. In generale, gli autori di tutti i documenti analizzati sottolineato che gli studi sulla efficacia sono di tipo non-comparativo ed hanno una bassa qualità metodologica e concludono che l'efficacia dell'uso di HT per questi pazienti non è chiara.

Tumori gastrointestinali: negli studi attualmente disponibili è presente un numero esiguo di pazienti che preclude ogni conclusione certa e pertanto il ruolo dell'HT per il trattamento nei tumori gastrointestinali rimane poco chiaro.

Tumori pelvici: a causa dell'esiguo numero di pazienti con tumori pelvici trattati con HT non è possibile trarre conclusioni definitive.

Tumore della prostata: tutti gli studi selezionati concordano sul fatto che le prove disponibili non sono sufficienti per dimostrare la superiorità del trattamento con l'HT rispetto alle alternative.

Tumori muscolo scheletrici: a causa della mancanza di dati comparativi, non è possibile trarre conclusioni su una migliore performance dell'HT in termini di efficacia e sicurezza rispetto agli altri trattamenti disponibili per questi tipi di tumori.

Limiti

L'HT è caratterizzata da una continua evoluzione hardware e software che introduce modifiche nell'utilizzo dell'HT che potrebbero condizionare gli outcome.

La qualità delle revisioni sistematiche incluse è stata valutata utilizzando la checklist AMSTAR e poi discussa tra gli autori, ma questa valutazione non è stata formalmente esplicitata.

Conclusioni

La mancanza di studi comparativi tra l'HT e gli altri trattamenti attualmente disponibili (altre tecniche radioterapiche RT e/o chemioterapia) non permette di trarre conclusioni definitive sugli effetti dell'HT nel trattamento dei tumori. In circostanze specifiche, studi clinici suggeriscono dei miglioramenti in termini di sicurezza ed efficacia utilizzando l'HT in luogo della convenzionale RT per alcuni tipi di tumori (in particolare melanoma uveale, cordomi della regione testa-collo, e NSCLC). Tuttavia, vi è incertezza per quanto riguarda queste stime, a causa di debolezze metodologici e del disegno degli studi disponibili. Pertanto le evidenze attualmente disponibili non sono sufficienti a supportare l'uso clinico dell'HT nella routine.

In Italia gli Istituti che hanno introdotto l'HT dovrebbero dare la priorità ad un uso sperimentale volto a produrre, in futuro, evidenze con un alto grado di affidabilità, avvalendosi della collaborazione internazionale per la predisposizione di studi comparativi adeguati sia nel metodo che nel disegno. All'interno di studi clinici dovrebbero essere incoraggiati follow-up (15-20 anni) per la valutazione degli effetti a lungo termine del trattamento con HT.

Prima di pianificare ulteriori installazioni HT, devono essere fornite prove di efficacia più robuste, affidabili e correttamente valutate.

Abstract

Background

Cancer is one of the leading causes of death worldwide. Therapies for cancer include surgery, chemotherapy and radiation therapy (RT). Hadrontherapy (HT) is a form of RT that relies on protons and/or carbon ion beams. Because of the nature of protons and carbon ions, the accuracy of HT is theoretically much higher than that of conventional radiotherapy and the technology might improve tumour control due to greater precision in radiation dose delivered to the tumour. HT may reduce adverse effects due to reduced radiation dose to surrounding normal tissues. Tumours for which HT could provide better results compared with other forms of radiotherapy are those surrounded by vital and radiation sensitive tissues, such as tumours of head and neck, eye, liver, lung (Non-Small Cell Lung Cancer, NSCLC), prostate, pancreas, soft tissue, skeletal system, gastrointestinal system and pelvis, which all together are responsible for approximately 80,000 new cases per year in Italy.

Objectives

The objective of the analysis is to provide an overview of available evidence on safety (decrease in adverse effects) and effectiveness (improvement in local control and overall survival) of HT for the treatment of cancer compared to other RT techniques. In particular, the research question was developed as follows:

- Participants: patients affected by any neoplasm treated with radiotherapy
- Intervention: hadrontherapy
- Comparator: any type of radiotherapy
- Outcomes: safety (decrease in acute and late adverse effects) and effectiveness (local control and overall survival).

Search Methods

The following databases and web sites were searched for HTA and/or systematic reviews evaluating HT in cancer: The Cochrane Database of Systematic Reviews; Database of Abstracts of Reviews of Effects (DARE); Health Technology Assessment (HTA) database; NHS Economic Evaluation Database (NHS EED); TripDatabase; INAHTA and AHRQ web sites.

The following databases and web sites were searched for primary literature in order to update the secondary literature search through RCTs: Pubmed; Clinicaltrials.gov; Controlled-trials.com; Cochrane Central Register of Controlled Trials. Only Randomized Controlled Trials (RCTs) were included in the primary literature search.

Selection criteria

HTA reports and systematic reviews evaluating safety and efficacy of hadrontherapy when compared to current practice in the treatment of patients with cancer were included.

Randomized Clinical Trials evaluating hadrontherapy, published in the last five years were also searched to establish whether more recent evidence could challenge conclusions of existing secondary literature.

A specific literature search was not undertaken for economic evaluation since this was not an objective of this review but a summary of economic aspects of HT was provided.

Data collection and analysis

Papers were assigned to couples of authors and each author independently collected evaluated, analyzed and summarised data from both secondary and primary literature.

Main results

The literature search of HTA and systematic reviews retrieved 33 publications but only 15 documents met the inclusion criteria and were thus included.

From the primary literature search, 11 publications were retrieved; however no documents met the inclusion criteria and were thus excluded.

HTA and systematic reviews included studies investigating the use of HT in the treatment of the following cancers concluding that:

Skull base tumours and others head and neck tumours: there is no evidence in favour of a better efficacy of HT versus standard treatments. In the absence of well-designed trials no definitive conclusions can be drawn.

Ocular tumours: secondary studies differed in disease, type of HT and design of primary studies included and no conclusions could be drawn. There is limited evidence on the effectiveness and safety of HT for ocular tumours due to the lack of well-designed and well-reported studies. A limited number of available studies suggests a potential improvement in local control with proton radiotherapy for uveal melanoma if it is close to optic disk or fovea or if its thickness is superior to 5 mm.

Lung cancer: A good quality meta-analysis for the treatment of stage I NSCLC patients included 8 low-quality primary studies. The meta-analysis reports that survival rates for particle therapy are higher than those for conventional radiotherapy but similar to those achieved with stereotactic radiotherapy. No firm conclusions could be drawn concerning adverse events. In general the authors of all the retrieved documents underlined that studies on efficacy are non-comparative and have low methodological quality concluding that the effectiveness of the use of HT for these patients remains unclear.

Gastrointestinal tumours: The small number of patients enrolled in the presently available studies precludes any firm conclusion so that the role of HT in GI cancers remains unclear.

Pelvic tumours: Due to the small number of patients with pelvic tumours treated with HT no firm conclusions can be drawn.

Prostate cancer: All the retrieved documents agree that the available evidence is insufficient to demonstrate improved outcomes for HT when compared to alternative treatments.

Skeleton and soft tissues tumours: Due to the lack of comparative data, it is not possible to draw any conclusions on a better performance of HT in terms of efficacy and safety compared to other available treatments for these types of cancers.

Limitations

HT has been characterised by continuous hardware and software evolutions, leading to variations in HT practice. It is not clear how these can impact on clinical outcomes.

The quality of the included systematic reviews was assessed using the Amstar checklist and then discussed among authors but this assessment was not formally reported.

Conclusions

The lack of comparative studies comparing HT with other currently available treatments (other RT techniques and/or chemotherapy) does not allow drawing firm conclusions about the effects of HT in cancer treatment. In specific circumstances, clinical studies suggested improvements in safety and effectiveness by using HT instead of traditional RT for some types of tumours (in particular uveal melanoma, skull and neck chordomas, and NSCLC). Nonetheless, there is uncertainty regarding these estimates, due to methodological and design flaws of available studies. Therefore presently available evidence is not sufficient to support routine clinical use of HT.

Italian centres which introduced HT should give priority to experimental use of HT aimed at producing in future high quality evidence setting up comparative studies, adequate in design and methods with international collaboration. Long term follow-up (15-20 years) within clinical studies should be encouraged for the assessment of very late effects of HT.

Prior to planning further use of HT, it is important that high quality evidence is provided and properly assessed.

Contributions

Authors:

(in alphabetical order) Fedele Bonifazi, Laura Camilloni, Angelo Capizzi, Francesco Cardinale, Anna Cavazzana, Elisa Giani, Susanna Maltoni, Giovanni Mastrandrea, Horand Meier, Massimiliano Orso, Nicola Pace, Valeria Romano, Sergio Sassano

RIHTA – Rete Italiana HTA

External reviewers:

Leslie Levin, MB MD FRCP (Lon) FRCPC

Head, Medical Advisory Secretariat

Health Quality Ontario

Bleddyn Jones, MD
Gray Institute for Radiation Oncology & Biology
University of Oxford
Oxford – UK

Madelon Pijls-Johannesma
Head data centre/Epidemiologist
MAASTRO clinic
Dr. Tanslaan 12,
6229 ET Maastricht, The Netherlands
P.O. Box 1588, 6201 BN **Maastricht**, The Netherlands

Competing interests declaration

The authors declare that they will not receive either benefits or harms from the publication of this report. None of the authors have or have held shares, consultancies or personal relationships with any of the producers of the devices assessed in this document.

Acknowledgments

Authors would like to thank Chiara Bassi for support in designing the literature search strategy and Marina Cerbo, Tom Jefferson and Luciana Ballini for valuable comments on the draft of this overview. Authors would also like to thank Giacomo Cuttone (Director of LNS–INFN) for context analysis, and Carlo Alberto Perucci for continuous help with the stimulus, and Emilio Chiarolla for collaboration.

Contents

List of Acronyms and abbreviation

ACC: Adenoid Cystic Carcinoma
Age.Na.S.: Agenzia Nazionale per i Servizi Sanitari Regionali (Italian National Agency for Regional Health Care Services)
AHRQ: Agency for Healthcare Research and Quality
AMD: Age-related Macular Degeneration
ANZHSN: Australian and New Zealand Horizon Scanning Network
CCT: Case Control Trial
CGE: Cobalt Gray Equivalent
CNVM: Subfoveal Choroidal Neovascular Membranes
CRD: Centre for Reviews and Dissemination
DARE: Database of Abstracts of Reviews of Effects
EBRT: External Beam Radiation Therapy
HAS: Haute Autorité de Santé
HT: Hadrontherapy
HTA: Health Technology Assessment
ICER: Institute for Clinical and Economic Review
IMRT: Intensity Modulated Radiation Therapy
INAHTA: International Network of Agencies for Health Technology Assessment
IR: Ionizing Radiation
KCE: Federaal Kenniscentrum voor de Gezondheidszorg
LC: Local Cancer control rate
NHS EED: NHS Economic Evaluation Database
NSCLC: Non-Small Cell Lung Cancer
OS: Overall Survival
PBT: Proton Beam Therapy
QALY: Quality Adjusted Life Years
RCT: Randomized Control Trial
RIHTA: Rete Italiana per l'Health Technology Assessment (Italian Network for Health Technology Assessment)
RT: Radiation Therapy
SR: Systematic Review
STR: Stereotactic Radiotherapy
TTT: Transpupillary Thermotherapy
VATAP: Veterans Health Administration Office of Patient Care Services Technology Assessment Program

Abstract

Background

Cancer is one of the leading causes of death worldwide. Therapies for cancer include surgery, chemotherapy and radiation therapy (RT). Hadrontherapy (HT) is a form of RT that relies on protons and/or carbon ion beams. Because of the nature of protons and carbon ions, the accuracy of HT is theoretically much higher than that of traditional radiotherapy and the technology might improve tumour control due to greater precision in radiation dose delivered to the tumour. HT may reduce adverse effects due to reduced radiation dose to surrounding normal tissues. Tumours for which HT could provide better results compared with other forms of radiotherapy are those surrounded by vital and radiation sensitive tissues, such as tumours of head and neck, eye, liver, lung (Non-Small Cell Lung Cancer, NSCLC), prostate, pancreas, soft tissue, skeletal system, gastrointestinal system and pelvis, which all together are responsible for approximately 80,000 new cases per year in Italy.

Objectives

The objective of the analysis is to provide an overview of available evidence on safety (decrease in adverse effects) and effectiveness (improvement in local control and overall survival) of HT for the treatment of cancer compared to other RT techniques. In particular, the research question was developed as follows:

- Participants: patients affected by any neoplasm treated with radiotherapy
- Intervention: hadrontherapy
- Comparator: any type of radiotherapy
- Outcomes: safety (decrease in acute and late adverse effects) and effectiveness (local control and overall survival).

Search Methods

The following databases and web sites were searched for HTA and/or systematic reviews evaluating HT in cancer: The Cochrane Database of Systematic Reviews; Database of Abstracts of Reviews of Effects (DARE); Health Technology Assessment (HTA) database; NHS Economic Evaluation Database (NHS EED); TripDatabase; INAHTA and AHRQ web sites.

The following databases and web sites were searched for primary literature in order to update the secondary literature search through RCTs: Pubmed; Clinicaltrials.gov; Controlled-trials.com; Cochrane Central Register of Controlled Trials. Only Randomized Controlled Trials (RCTs) were included in the primary literature search.

Selection criteria

HTA reports and systematic reviews evaluating safety and efficacy of hadrontherapy when compared to current practice in the treatment of patients with cancer were included.

Randomized Clinical Trials evaluating hadrontherapy, published in the last five years were also searched to establish whether more recent evidence could challenge conclusions of existing secondary literature.

A specific literature search was not undertaken for economic evaluation since this was not an objective of this review but a summary of economic aspects of HT was provided.

Data collection and analysis

Papers were assigned to couples of authors and each author independently collected evaluated, analyzed and summarised data from both secondary and primary literature.

Main results

The literature search of HTA and systematic reviews retrieved 33 publications but only 15 documents met the inclusion criteria and were thus included.

From the primary literature search, 11 publications were retrieved; however no documents met the inclusion criteria and were thus excluded.

HTA and systematic reviews included studies investigating the use of HT in the treatment of the following cancers concluding that:

Skull base tumours and others head and neck tumours: there is no evidence in favour of a better efficacy of HT versus standard treatments. In the absence of well-designed trials no definitive conclusions can be drawn.

Ocular tumours: secondary studies differed in disease, type of HT and design of primary studies included and no conclusions could be drawn. There is limited evidence on the effectiveness and safety of HT for ocular tumours due to the lack of well-designed and well-reported studies. A limited number of available studies suggests a potential improvement in local control with proton radiotherapy for uveal melanoma if it is close to optic disk or fovea or if its thickness is superior to 5 mm.

Lung cancer: A good quality meta-analysis for the treatment of stage I NSCLC patients included 8 low-quality primary studies. The meta-analysis reports that survival rates for particle therapy are higher than those for conventional radiotherapy but similar to those achieved with stereotactic radiotherapy. No firm conclusions could be drawn concerning adverse events. In general the authors of all the retrieved documents underlined that studies on efficacy are non-comparative and have low methodological quality concluding that the effectiveness of the use of HT for these patients remains unclear.

Gastrointestinal tumours: The small number of patients enrolled in the presently available studies precludes any firm conclusion so that the role of HT in GI cancers remains unclear.

Pelvic tumours: Due to the small number of patients with pelvic tumours treated with HT no firm conclusions can be drawn.

Prostate cancer: All the retrieved documents agree that the available evidence is insufficient to demonstrate improved outcomes for HT when compared to alternative treatments.

Skeleton and soft tissues tumours: Due to the lack of comparative data, it is not possible to draw any conclusions on a better performance of HT in terms of efficacy and safety compared to other available treatments for these types of cancers.

Limitations

HT has been characterised by continuous hardware and software evolutions, leading to variations in HT practice. It is not clear how these can impact on clinical outcomes.

The quality of the included systematic reviews was assessed using the Amstar checklist and then discussed among authors but this assessment was not formally reported.

Conclusions

The lack of comparative studies comparing HT with other currently available treatments (other RT techniques and/or chemotherapy) does not allow drawing firm conclusions about the effects of HT in cancer treatment. In specific circumstances, clinical studies suggested improvements in safety and effectiveness by using HT instead of traditional RT for some types of tumours (in particular uveal melanoma, skull and neck chordomas, and NSCLC). Nonetheless, there is uncertainty regarding these estimates, due to methodological and design flaws of available studies. Therefore presently available evidence is not sufficient to support routine clinical use of HT.

Italian facilities which introduced HT should give priority to experimental use of HT aimed at producing in future high quality evidence setting up comparative studies, adequate in design and methods with international collaboration. Long term follow-up (15-20 years) within clinical studies should be encouraged for the assessment of very late effects of HT.

Prior to planning further use of HT, it is important that high quality evidence is provided and properly assessed.

Background

Cancer is one of the major causes of death worldwide. In 2008, it accounted for 13% of all deaths (WHO 2011). The incidence of cancer was 11.3 million in 2007 and is expected to increase to 15.5 millions by 2030 (WHO 2011). In Italy, cancer accounts for approx. 122,000 deaths per year, with 250,000 new cases per year (AIRTUM 2009).

Therapies for cancer include surgery, chemotherapy, radiation therapy (RT), or a combination of these, according to tumour type, stage and location. RT is defined as the medical use of ionizing radiation (IR) for cancer treatment. Target tissue is exposed to a certain IR dose to kill malignant cells and increase local cancer control rate (LC), eventually improving overall survival (OS).

Particles traditionally used in RT include photons, electrons, and gamma rays: due to the nature of their interaction with tissue, to deliver a certain amount of dose to the tumour, part of the radiation dose will be absorbed by the healthy tissues surrounding the target volume. In most of the RT treatments, the total radiation dose to be delivered to the pathologic tissue is fractionated (spread out over time). Fractionation allows normal cells time to recover, while tumor cells are generally less efficient in repair between fractions. Anyway in some cancer types, prolongation of the fraction schedule over too long can allow for the tumor to begin repopulating, and for these tumor types radiation treatment is preferably completed within a certain amount of time. Depending on the type of radiation, the treatment, and the pathology, the fractionation can entail large doses delivered less than once a day (hypofractionation) and smaller doses delivered more than once in a day (hyperfractionation).

Although advanced techniques are used for dose planning and delivering to minimize radiation exposure of non-malignant tissues, adverse effects related to radiation exposure are common. According to the part of the body which is irradiated, acute side effects of RT include local necrosis, diarrhoea, fatigue, hair loss, nausea and vomiting, mucosal inflammation, vascular and cardiac pathologies, changes in sexuality and fertility activities, and damage to skin, throat, urinary tract and bladder. Late harms include infertility, lymphoedema, changes in the brain causing cognitive dysfunction, and changes in the joints and mouth, in addition to an increased risk of developing secondary cancer (NCI 2011). Such adverse effects may lead to dramatic consequences, especially when the damaged non-malignant tissue represents a critical part of the body such as nerves, brain, glands and eyes. In particular, secondary tumours due to RT exposure are of great concern as they are thought to significantly decrease life expectancy of primary cancer survivors.

In the last decades a new form of RT (Hadrontherapy - HT), has been introduced. HT relies on the use of protons or heavy ions (mostly carbon ions) instead of other particles. The particular interaction of protons and carbon ions with matter makes it possible to concentrate the delivered dose to the target tissue with greater precision while decreasing the dose to surrounding tissues, therefore theoretically increasing the effectiveness on malignant tissue and reducing harms (including short- and long-term damages to surrounding organs). Such an increase in precision is particularly important when target tumours are surrounded by vital and radiation-sensitive healthy tissues. This is why HT is claimed to be the elective therapeutic strategy for some kinds of ocular, head and neck, and prostate cancers, especially in the early stages. Although particle physics principles clearly advantage HT over other RT techniques, there are a series of technical difficulties in translating such theoretical superiority into practice. Difficulties in patient positioning, intra-fractional organ motion, inter-fractional changes in anatomy and tumour size, precision of the imaging technique used for treatment planning are all factors that pose a threat to HT accuracy. Since the first phases of its clinical use, HT has experienced a continuous technical development to overcome such limitations. This makes HT a rapidly evolving and non-mature technology, limiting the generalization and the extent of any conclusion that can be drawn from published studies.

Lately, HT has been suggested for the treatment of some cases of cancers of lung, liver, pancreas, gastrointestinal system, and pelvis. All together, the pathologies for which HT is advocated to be a better treatment option account for almost 110,000 new cases of tumour per year (see details in Appendix 1). It is thus of primary importance to evaluate the safety, the effectiveness and the appropriateness of HT to drive its possible implementation and diffusion in Italy.

In addition new promising forms of RT (such as Intensity Modulated Radiation Therapy – IMRT, Brachytherapy and Radiosurgery) associated with a higher therapeutic index are claiming to show increased advantages over traditional RT.

For these reasons a comparison of HT with other innovative RT options is necessary.

Currently (December 2011), there are 38 HT facilities operating worldwide (Particle Therapy Co-Operative Group, 2011). Presently in Italy there is one operating centre in Catania (Sicily, Southern Italy) where only ocular tumours can be treated due to the low energy of the protons produced. Another centre is in the start-up phase (in Pavia, Northern Italy), and a third centre (in Trento, Northern Italy) is under construction. The low uptake of HT worldwide may be a combination of factors including uncertainty of effectiveness compared to other RT approaches and the high costs of HT facilities. The disproportionate increase in HT facilities across Italy relative to worldwide uptake adds importance to this assessment of effectiveness and safety.

Objective

The objective of this analysis is to provide an overview of published literature evaluating safety (decrease in adverse effects) and effectiveness (local control and overall survival) of HT (proton, ion and neutron beam therapy) in comparison with no treatment or other RT techniques (conventional RT, IMRT, stereotactic surgery, brachytherapy) for the treatment of cancer. A comprehensive economic analysis was beyond the objectives of the present document, although a summary of (cost)-effectiveness results retrieved from the included studies is added at the end of the overview.

Methods

The project was developed by the Italian network for HTA (RIHTA) and co-ordinated by the Italian National Agency for Regional Health Care Services (Agenzia Nazionale per i Servizi Sanitari Regionali – Age.Na.S). The RIHTA Network identified a multi-regional team of contributors with different expertise for producing this overview.

The research question for this report was: what is the available literature on the use of HT for the treatment of cancer?

Criteria for considering studies for this review

First of all the working group decided to perform a search for secondary literature (HTA reports and Systematic Reviews) in order to collect available evidence on HT. In addition, the team decided to update the evidence, performing a literature search for primary literature, limited to randomised controlled trials (RCTs), to assess whether recent evidence could change the conclusions derived from the secondary literature review.

Types of studies

HTA reports only if including a systematic review, systematic reviews and RCTs.

Types of participants

Inclusion criteria: patients with any type of cancer.

Exclusion criteria: patients with disease other than cancers.

Types of interventions

- Intervention: HT (proton, ion and neutron beam therapy)
- Control: current practice including other RT techniques (conventional RT, IMRT, stereotactic surgery, brachytherapy) or no treatment.

Types of outcome measures

- Safety: decrease in short-term and long-term adverse effects
- Effectiveness: local control and overall survival

Search methods for identification of studies

Electronic searches

The following databases and web sites were searched for secondary literature (HTA reports and systematic reviews):

- The Cochrane Database of Systematic Reviews;
- Database of Abstracts of Reviews of Effects (DARE);
- Health Technology Assessment (HTA) database;
- NHS Economic Evaluation Database (NHS EED);
- TripDatabase;
- INAHTA and AHRQ web sites.

The following search terms were included in all searches: "hadron therapy" OR Hadrontherapy OR "proton beam" OR "charged particles" OR "proton therapy" OR "heavy ions therapy" OR "charged particles" OR “protontherapy”. Last search was performed on 27th October 2011. Limits were applied for publication year: from 2007 to present (a time frame limited to the last five years was considered appropriate considering the rapid evolution of HT). Duplicates were excluded. Only English, Italian, French and German language papers were included.

To update the secondary literature search through RCTs, the following databases and web sites were searched for primary literature:

- Pubmed;
- Clinicaltrials.gov;
- Controlled-trials.com;
- Cochrane Central Register of Controlled Trials.

The search terms included were the same used for the secondary literature search. The last search was performed on 29th November 2011. Limits were applied for the publication year: from 2007 to present (a time frame limited to the last five years was considered appropriate considering the rapid evolution of HT). Duplicates were removed. Only English, Italian, French and German languages were considered.

Data extraction and management

Four authors (AC, FB, NP and SM) independently screened abstracts and titles and included HTA reports and systematic reviews focusing on clinical effectiveness and/or adverse events for one or more diseases.

Two researchers (AC and MO) independently screened RCTs retrieved by the primary literature search and included them on the basis of clinical effectiveness/efficacy and/or adverse events for one or more types of cancer.

Relevant HTA reports and systematic reviews were shared in the working group in order to extract data and evaluate the methodological quality of the systematic reviews using criteria from the AMSTAR checklist (Shea 2009). Each document was read by at least two researchers and disagreements on data extraction and/or quality appraisal were discussed to reach a consensus.

The quantity and quality of the available evidence (secondary and primary) on the risk/benefit profile of HT in cancer treatment was summarised.

Teamwork and roles

All the authors conceived and wrote the protocol and the drafts and approved the final version of the paper.

In addition:

- Valeria Romano (VR): designed and performed the search strategies;
- Fedele Bonifazi (FB): analysed and extracted data from HTA reports and SRs reporting on studies evaluating safety and efficacy of HT for gastro-intestinal, pelvic and prostate tumours, wrote the draft of the report, made corrections according to peer-reviewers' comments and approved the final version;
- Laura Camilloni (LC): analysed and extracted data from HTA reports and SRs reporting on studies evaluating safety and efficacy of HT for tumours of the base of the skull and others head and neck tumours, wrote the draft of the report, made corrections according to peer-reviewers' comments and approved the final version.
- Angelo Capizzi (ACZ): analysed and extracted data from HTA reports and SRs reporting on studies evaluating safety and efficacy of HT for skeleton and soft tissues tumours, and those addressing economic aspects; wrote the draft of the report, made corrections according to peer-reviewers' comments and approved the final version;
- Francesco Cardinale (FC): epidemiological assessment

- Anna Cavazzana (AC): analysed and extracted data from HTA reports and SRs reporting on studies evaluating safety and efficacy of HT for lung tumours, screened RCTs retrieved by the primary literature search, wrote the draft of the report, made corrections according to peer-reviewers' comments and approved the final version;

- Elisa Giani (EG): collaboration to literature research; quality assessment and data extraction from HTA reports about different pathology, made corrections according to peer-reviewers' comments and approved the final version.

- Susanna Maltoni (SM): analysed and extracted data from HTA reports and SRs reporting on studies evaluating safety and efficacy of HT for tumours of the base of the skull and others head and neck tumours, wrote the draft of the report, made corrections according to peer-reviewers' comments and approved the final version.

- Giovanni Mastrandrea (GM): analysed and extracted data from HTA reports and SRs reporting on studies evaluating safety and efficacy of HT for gastro-intestinal, pelvic and prostate tumours, wrote the draft of the report, made corrections according to peer-reviewers' comments and approved the final version;

- Massimiliano Orso (MO): analysed and extracted data from HTA reports and SRs reporting on studies evaluating safety and efficacy of HT for ocular tumours, screened RCTs retrieved by the primary literature search, wrote the draft of the report, made corrections according to peer-reviewers' comments and approved the final version.

- Nicola Pace (NP): wrote the background section, screened secondary studies retrieved by the secondary literature search, wrote the draft of the report, made corrections according to peer-reviewers' comments and approved the final version.

- Sergio Sassano (SS): analysed and extracted data from HTA reports and SRs reporting on studies evaluating safety and efficacy of HT for gastro-intestinal, pelvic and prostate tumours, wrote the draft of the report, made corrections according to peer-reviewers' comments and approved the final version.

The project was managed by Horand Meier (HM). Overall supervision was provided by Tom Jefferson.

Results

Results of the secondary literature search

The secondary literature search identified 33 publications: only 15/33 documents met the inclusion criteria and were included.

Results for secondary literature search (systematic reviews or HTA reports including a systematic review):

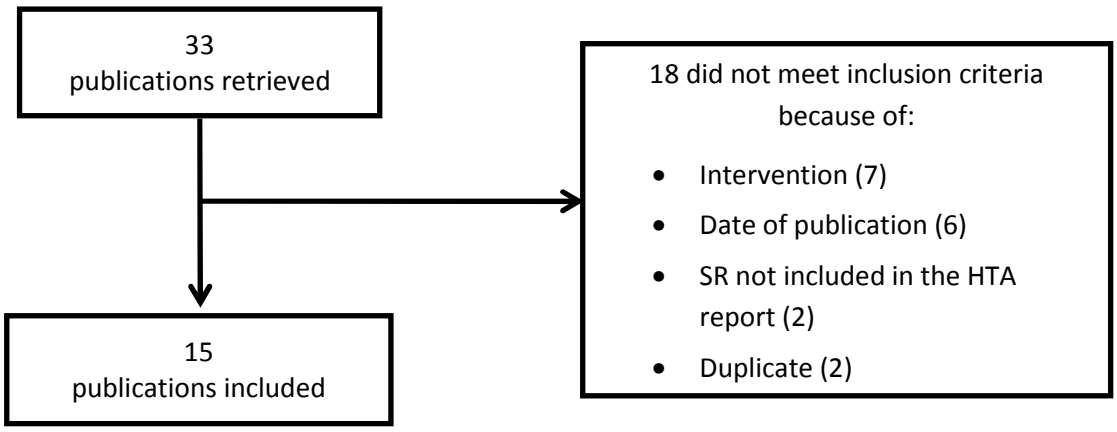


Table 1 lists the characteristics of included studies (complete references can be found in Appendix 2); the list of excluded studies is reported in Appendix 3 together with the reasons for their exclusion.

Table 1. Secondary literature search, included studies:

1st Author, year	Agency	Title	Content	Language
Amichetti 2009		Proton therapy in chordoma of the base of the skull: a systematic review	Cancer: - Skull base	English
Bannuru 2011		Comparative Evaluation of Radiation Treatments for Clinically Localized Prostate Cancer: An Updated Systematic Review	Cancers: - Prostate	English
Bekkering 2009		The effectiveness and safety of proton radiation therapy for indications of the eye: a systematic review	Cancers: - Ocular	English
Blanchard 2010	Haute Autorité de Santé (HAS), France http://www.has-sante.fr	Carbon ion radiotherapy (Hadrontherapy)	Cancers: - Ocular - Head and neck - Skull base - Prostate - GI - Lung - Pelvic - Soft tissue sarcoma	French
Flynn 2010	Veterans Health Administration Office of Patient Care Services Technology Assessment Program (VATAP), US www.va.gov/vatap	Proton beam therapy for cancer	Cancers: - Ocular - Head and neck - Skull base - Prostate - GI - Lung	English
Grutters 2010		Comparison of the effectiveness of radiotherapy with photons, protons and carbon-ions for non-small cell lung cancer: a meta-analysis	Cancers: - Lung	English
Huybrechts 2007	Federaal Kenniscentrum voor de Gezondheidszorg (KCE), Belgium http://www.kce.fgov.be	Hadrontherapy	Cancers: - Ocular - Head and neck - Skull base - Prostate - GI - Lung	English

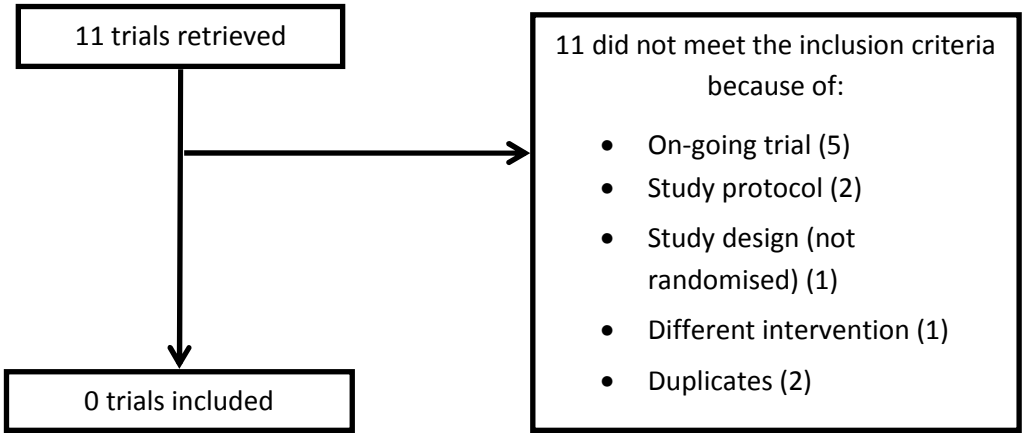
1st Author, year	Agency	Title	Content	Language
			- Pelvic - Soft tissue sarcoma	
Lee 2007a	Australian and New Zealand Horizon Scanning Network (ANZHSN), Australia http://www.horizonscanning.gov.au	Proton beam therapy for the treatment of neoplasms involving (or adjacent to) cranial structures	Cancers: - Head and neck - Skull base	English
Lee 2007b	Australian and New Zealand Horizon Scanning Network (ANZHSN), Australia http://www.horizonscanning.gov.au	Proton beam therapy for the treatment of uveal melanoma	Cancers: - Ocular	English
Lodge 2007		A systematic literature review of the clinical and cost-effectiveness of hadron therapy in cancer	Cancers: - Ocular - Head and neck - Skull base - Prostate - GI - Lung - Pelvic	English
Ollendorf 2008		Brachytherapy/proton beam therapy for clinically localized, low-risk prostate cancer	Cancers: - Prostate	English
Samson 2011a	Blue Cross and Blue Shield Association, US www.bcbs.com/tec	Proton beam therapy for non-small-cell lung cancer	Cancers: - Lung	English
Samson 2011b	Blue Cross and Blue Shield Association, US www.bcbs.com/tec	Proton beam therapy for prostate cancer	Cancers: - Prostate	English
Trikalinos 2009	Agency for Healthcare Research and Quality (AHRQ), US www.ahrq.gov	Particle Beam Radiation Therapies for Cancer	Cancers: - Ocular - Head and neck - Skull base - Prostate - GI - Pelvic	English
Wilt 2008		Comparative effectiveness of therapies for clinically localized prostate cancer	Cancers: - Prostate	English

Quality assessment of included HTA reports and/or systematic reviews was assessed through AMSTAR checklist (Shea 2009) and results are reported in Appendix 4.

Results of the primary literature search

From the **primary literature search**, 11 publications were retrieved but none met the inclusion criteria. The list of excluded studies and the reasons for exclusion are reported in Appendix 5.

Search for primary studies:



Results on safety and effectiveness

Safety (decrease in adverse effects) and effectiveness (local control and overall survival) of HT in comparison to current practise (conventional RT, IMRT, stereotactic surgery, brachytherapy, no treatment) were assessed in cancers affecting:

A. Skull base and head and neck;

B. Eye;

C. Lung;

D. Gastrointestinal system;

E. Pelvis;

F. Prostate;

G. Skeleton and soft tissues.

A summary of results and conclusions of included HTA reports and systematic reviews are reported in Table 2, while details for findings of included HTA and systematic reviews are provided below.

Table 2. Conclusions from HTA reports and systematic reviews on HT in cancer treatment

Anatomic sites	Studies	Overall result
Tumours of the skull base	Blanchard 2010 Flynn 2010 Amichetti 2009 Trikalinos 2009 Lee 2007a Huybrechts 2007 Lodge 2007	Available literature suggests a better efficacy of HT if compared to traditional radiotherapy in patients with skull base chordomas but all identified documents (HTA or SRs) highlight the methodological flaws affecting the presently available literature, claim for well-designed randomised controlled trials and state that presently available literature is not sufficient to draw any conclusion.
Head and neck	Blanchard 2010 Flynn 2010 Trikalinos 2009 Lee 2007a Huybrechts 2007 Lodge 2007	Available literature suggests a better efficacy of HT if compared to traditional radiotherapy in patients with adenoid cystic carcinoma of the head and neck but all the retrieved documents (HTA or SRs) highlight the methodological flaws affecting the presently available literature, claim for well-designed randomised controlled trials and state that presently available literature is not sufficient to draw any conclusion.
Eye	Blanchard 2010 Flynn 2010 Bekkering 2009 Trikalinos 2009 Lee 2007b Huybrechts 2007 Lodge 2007	The secondary publications retrieved do not provide an exhaustive evidence of effectiveness and safety for the treatment of ocular tumours with HT. The lack of comparative studies severely limits the conclusions that can be drawn from the available evidence; in general, the majority of studies included were of low quality.
Lung	Samson 2011a Blanchard 2010 Flynn 2010 Grutters 2010 Huybrechts 2007 Lodge 2007	All the reviews indicate that studies concerning efficacy are mainly non comparative and have low methodological quality. No randomized controlled trials and high quality comparative studies relating to HT for the treatment of non-small-cell lung cancer are available, thus the efficacy of this technology for these patients remains unclear.
Gastrointestinal system	Blanchard 2010 Flynn 2010 Trikalinos 2009 Huybrechts 2007 Lodge 2007	In all considered studies, the various authors agree on the need for further studies and for all gastrointestinal tumours, the results obtained did not allow a conclusion on the use of these technologies
Pelvis	Blanchard 2010 Trikalinos 2009 Huybrechts 2007 Lodge 2007	The results of the examined studies were that in the absence of additional data, particularly comparative data, the value of technology is not defined
Prostate	Bannuru 2011 Samson 2011b Blanchard 2010 Flynn 2010 Trikalinos 2009 Wilt 2009 Ollendorf 2008 Huybrechts 2007 Lodge 2007	All analyses and reviews agree that currently available evidence is insufficient to demonstrate that charged particles therapies are better than alternative treatments for prostate cancer
Skeleton and soft tissues	Blanchard 2010 Huybrechts 2007	The documents remarked that there is no evidence in favour of hadron therapy for lack of comparative studies, and because the observed studies are heterogeneous with regard to the included population and results

A. Tumours of the base of the skull and other head and neck tumours

The secondary literature search identified seven publications (VATAP overview: Flynn 2010; HTA-HAS: Blanchard 2010; AHRQ: Trikalinos 2009; KCE-REPORT: Huybrechts 2007; Lodge 2007; Amichetti 2009; ANZHSN: Lee 2007a). All except one (Amichetti 2009) include both studies on the use of HT for base of the skull tumours and for head and neck tumours; the systematic review by Amichetti focused exclusively on base of the skull tumours. Three documents (Flynn 2010; Lee 2007b; Amichetti 2009) considered only proton therapy and one (Blanchard 2010) C-ion beam radiotherapy only. Four documents are HTA-reports (HTA-VATAP: Flynn 2010; HTA-HAS: Blanchard 2010; AHRQ: Trikalinos 2009; KCE-REPORT: Huybrechts 2007), two are systematic reviews (Lodge 2007; Amichetti 2009) and one is a horizon scanning analysis (ANZHSN: Lee 2007a).

Four documents (AHRQ report: Trikalinos 2009; KCE report: Huybrechts 2007; ANZHSN report: Lee 2007a; Amichetti 2009) also include paediatric patients.

The large majority of documents analysed the same primary studies and highlighted the same methodological flaws that affect the body of literature on HT.

When possible, summary of findings of the retrieved documents will be reported separately for head and neck, base of the skull and central nervous system tumours.

Results

Flynn *2010 "Brief overview: proton therapy for cancer" (VATAP - Veterans Health Administration Office of Patient Care Services Technology Assessment Program)*

The **VATAP** report provides an overview of secondary literature on proton therapy including systematic reviews, technology assessments or economic evaluations and an update by a literature search of primary studies published after included secondary documents. The VATAP report includes six publications on HT use for base of the skull tumours: three are systematic reviews, one is an horizon scanning report, one a cross-sectional study and one a case series study. In general, the quality of the available evidence is considered poor: "available reviews generally reflect the state of the literature in that they attempt to cover so much territory (multiple tumours or types of radiation) that the reviews themselves are cumbersome to read, poorly organized, correspondingly difficult to abstract, and provide only diffuse or equivocal conclusions by individual diagnoses. Several reviews attempt ill-advised or inadequately reported statistical combination of results from multiple poor-quality observational studies, further clouding credibility of results from primary studies". No comprehensive summary of the results was reported by Authors but, in general, conclusions on all the considered cancer indications (thus including also base of the skull and head and neck neoplasm), state that "the literature reflects the early clinical investigation status for effectiveness of proton therapy" and conclude that "there are no indications for which proton therapy has been shown unequivocally to be effective, or more effective than its alternatives.".

Blanchard *2010 "Hadrontherapie par ions carbone - rapport préliminaire" (Haute Autorité de Santé - HAS)*

The **HAS** report focuses on carbon-ion HT only and overall includes 18 documents: 3 recommendations, 1 systematic review (the one published by Lodge et al, see details below), 1 meta-analysis (on 11 indications and including 22 prospective or retrospective studies) and 13 other publications or scientific

communications. The HAS report provides a summary of both the systematic review by Lodge (Lodge 2007) and the French recommendations on the irradiation of adult patients and for each indication provides a summary of the results drawn by secondary and primary literature.

The HAS report analyses separately different types of tumours localised in head and/or neck: adenoid cystic carcinoma (ACC), tumours of salivary glands, tumours of the sinus/nasal cavity, mucous melanoma, base of the skull chordomas and chondrosarcomas.

Adenoid cystic carcinoma (ACC): the HAS report cited two studies on patients with ACC (1 prospective study on 29 patients with locally advanced ACC, included also by the review of Lodge and another study on 107 patients) reporting a better local tumour control rate than photon-based radiotherapy (approximately 75% versus 50%).

Tumours of salivary glands and of the sinus: the HAS report includes one phase II study on patients with tumours of salivary glands (N=31) or of the sinus/nasal cavity (N=117).

- In patients with salivary gland tumours HT with C-ion seems to perform better that RT with photons in terms of 5-year local control rate (80.4% versus 50-70%)

- In patients with tumours of the sinus results for HT are comparable to that of IM-RT (local control rate at 5 years: 63-75.7% vs 58-70.7% and 5-year survival rates: 58.5-65% vs 25.8-44.8%).

For mucosus melanoma the HAS report cites two studies on a total of 247 patients with mucous melanoma treated with C-ion HT reporting 5-year local control rates ranging from 74 to 85% and a 5-year overall survival ranging from 27 to 68% (somehow better than RT with photon).

For base of the skull chordomas and chondrosarcomas the HAS report is essentially based on data retrieved by the systematic review of Lodge (Lodge 2007) leading to the conclusion that C-ion HT could be comparable to partial surgery associated to proton therapy or stereotactic RT. A grade 2 and 3 late toxicity was reported.

HAS report, after underlining severe limitations of available literature (non-comparative studies, phase I or II studies, small and mixed populations of patients in terms of type and stage of tumours) concludes that "Keeping in mind all the limitations of available literature, results suggest that:

- for adenoid cystic carcinoma of the head and neck, for neoplasms of salivary glands not completely resectable and for skull-base chordomas and chondrosarcomas, carbon-ion hadrontherapy seems to perform better than conventional radiotherapy;
- for skull-base chordomas and chondrosarcomas and for head and neck cancers, carbon-ion hadrontherapy seems to be equivalent to other high-technology radiotherapy techniques (for example stereotactic radiotherapy);
- late toxicity is reported especially for skull-base chordomas and chondrosarcomas."

The report goes on to state that, in general, there are no sufficient data to draw definitive conclusions on the relative merits of HT.

Trikalinos *2009 "Particle Beam Radiation Therapies for Cancer. Technical Brief No. 1." (Agency for Healthcare Research and Quality - AHRQ)*

The AHRQ report overall includes 243 papers of which 56 investigated the use of HT in cancers of the head and neck or of the central nervous system. Among these studies 53 are single-harm, 1 is non-randomized comparative study and 2 are RCT (on a total of only 8 RCTs retrieved for all the tumours considered by the systematic review). The report provides both a figure summarizing the type, number, population of studies on different tumours and a summary table where the characteristics but not the results of the available literature are analysed.

AHRQ report highlights that despite "there are many publications on particle (mainly proton) beam therapy for the treatment of cancer" the presently available literature is far from to be sufficient to "provide definitive answers on the effectiveness and safety of particle beam therapy compared to other interventions for most if not all cancer categories", as the studies suffer from major methodological flaws.

Huybrechts *2007 "Hadrontherapie" (Federaal Kenniscentrum voor de Gezondheidszorg - KCE)*

The KCE report overviewed 45 documents about the use of proton or carbon ion therapy, with the following results:

Base of the skull chordomas: a case series with proton beam therapy showed high rates of 5-year local progression-free survival (beyond 60%) and 5-year overall survival (81%, according to the systematic review by Lodge 2007). The safety seemed acceptable, even if there are insufficient data to compare toxicity induced by photon or proton beam therapy. Case series with carbon ion irradiation also show good results in chordomas of the base of the skull without serious toxic reactions. However, there is currently no clear clinical evidence from comparative studies to assess the clinical superiority in efficacy between proton or carbon ion and traditional or high precision photon therapies (or their combination).

Base of the skull chondrosarcoma: from the available literature, no differences between photon and proton irradiation in local control and overall survival rates of chondrosarcomas of the base of the skull are shown whilst carbon ion therapy seems to be less effective than existing treatments. The included studies are small, heterogeneous, non-comparative case series reflecting low quality of evidence.

Other intracranial tumours: the KCE report failed to identify any evidence on the use of proton or carbon ion therapy in the other malignant or not malignant intracranial tumours, however a better local control (but no significant difference in survival) with carbon ion and photons than with photons alone in patients with cystic adenoid carcinoma was reported. […]".

Paediatric cranial tumours: Proton radiation therapy seems to be safe and well tolerated by children suffering from central nervous system tumours (no RCTs available, sparse retrospective evidence) but there is currently not enough evidence to support the use of proton therapy as first line treatment in central nervous system tumours in children.

For salivary gland tumours one randomized controlled trial showed a significantly better local control rate - but no difference in survival rates - with neutrons versus conventional photons therapy (10-year local control rate: 56 vs 17%, 10-year survival rate: 15 versus 25%) in inoperable, unresectable or recurrent malignant salivary gland tumours. A comparative case series also found better local control (without any significant difference in survival rates) with carbon ion and photons than with photons alone in patients with cystic adenoid carcinoma.

***Lee** 2007 "Proton beam therapy for the treatment of neoplasms involving (or adjacent to) cranial structures" (Australian and New Zealand Horizon Scanning Network – ANZHSN)*

The ANZHSN horizon scanning document focused exclusively on proton beam therapy for the treatment of neoplasms involving (or adjacent to) cranial structures. The HS reviewed a total of 24 case series reporting data on safety and efficacy on the use of proton beam therapy for the treatment of adult and paediatric patients with various head and neck tumours. Four comparative treatment planning (modelling) studies were also included. Most of the included studies report local tumour control rates which are similar to conventional photon radiotherapy; the prevalence of proton radiation-induced side effects in the included studies appears to be within the range expected for conventional photon therapy, with some studies inferring that proton therapy is substantially safer. However the lack of consistency across studies and the lack of direct comparative studies severely limit the validity of these conclusions.

The report concludes that "The evidence for proton beam therapy in neoplasms involving or adjacent to, cranial structures remains inconclusive. Further studies are required to determine if proton therapy is indeed substantially better compared to conventional radiotherapy, as inferred by numerous model/treatment-planning studies".

***Lodge** 2007 "A systematic literature review of the clinical and cost-effectiveness of hadron therapy in cancer"*

The systematic review by Lodge retrieved several studies focussing on the use of HT in head and neck, central nervous system neoplasms and base of the skull chordomas and chondrosarcomas.

For head and neck tumours the systematic review identified two small retrospective low quality studies on protons, and two prospective studies on C-ions. When (indirectly) compared to photon RT in patients with squamous cell carcinomas, HT with protons or C-ions performed similarly in terms of efficacy (5-year local tumour control rates of: 50-70% with photons, 74-84% with protons and 75% with C-ions and 5-year overall survival of: 70-93% with photons, 44-65% with protons); however in patients with ACC C-ions seems to be associated to a better local control in respect to photons (4-year local tumour control: 24.6 versus 77.5%, respectively) but not to a better 4-year overall survival (77.9 versus 75.8%) (indirect comparison).

For tumours of the central nervous system (high or low-grade gliomas, benign meningiomas etc) 8 studies on protons and 2 studies on C-ions were identified but no clear results are reported.

Base of the skull chordomas: the retrieved (small) studies in patients with (6 studies on photons, 3 on protons and 2 on C-ions) seem to suggest a better local tumour control and overall survival at 5 years for protons (63% and 81%, respectively) and C-ions 2-year local tumour control: 72% and 5-y overall survival: 83%) when (indirectly) compared to photon RT (local tumour control: 25% and 5-year overall survival: 44%).

Base of the skull chondrosarcomas: the retrieved studies (2 for each interventions, photons, protons and C-ions) suggest a similar efficacy of the three interventions in terms of 5-year local tumour control and 5-year overall survival rates (photon RT and proton therapy performing slightly better than C-ions HT).

Considering the methodological flaws of the available literature, as other researchers, the Authors of the review concluded that: "In the absence of well-designed trials clearly demonstrating the superiority of protons and C-ions over the best photon techniques, no definitive conclusions on the relative merits of photons, protons and ions can be drawn for head and neck cancer".

***Amichetti** 2009 "Proton therapy in chordoma of the base of the skull: a systematic review"*

Amichetti et al. conducted a systematic review specifically on the treatment of base of the skull chordomas with proton therapy compared to other radiation techniques (conventional radiation therapy, ion therapy, fractionated stereotactic radiation therapy, and radiosurgery). No prospective trials (randomized or nonrandomized) were found and the review consisted of seven uncontrolled single-arm studies, providing clinical outcomes for a total of 416 patients: five studies enrolled adult and paediatric patients and two paediatric patients only. These reports were mainly based on advanced inoperable or incompletely resected tumours. The use of protons showed better results in terms of efficacy and safety if compared to traditional photon irradiation, resulting in the best long-term (10 years) outcome with relatively few significant complications considering the high doses delivered.

The Authors concluded that "on the basis of the available literature, superiority in terms of local control of protons has been demonstrated only versus conventional photon radiotherapy and in terms of treatment planning and delivery with respect to other modalities mainly in larger lesions in proximity to normal critical structures and in irregularly shaped tumours. Data on stereotactic radiotherapy are scarce and data on IMRT are still lacking. There is a need to compare proton therapy with photon-based treatments delivered at the best of conformal technologies available".

Conclusions on the base of the skull tumours and other head and neck tumours

Some of the retrieved reports provide a conclusion on the assessment of efficacy and safety of HT specifically in base of the skull and head and neck cancers (HAS 2010, Lodge 2007, KCE 2007, Amichetti 2009, ANZHSN 2007); others (VATAP 2010, AHRQ 2009) provide only a general conclusion on its benefit-risk profile for all possible indications in cancer. Only for base of the skull chordomas and for adenoid cystic carcinoma of the head and neck the superiority of HT compared to conventional RT seems to be suggested by available studies. However all the documents highlight the methodological flaws affecting the presently available literature in terms of study design (RCT or controlled studies are extremely scarce), patients' selection (studies almost always enrolled mixed population of patients) and reporting of results. All the documents demand for well-designed randomised controlled trials providing reliable conclusions on efficacy and safety of HT in comparison to other currently available treatments.

B. Ocular neoplasms

Seven publications on HT for the treatment of ocular diseases were found by secondary literature search. Four of these are HTA-reports (HTA-VATAP: Flynn 2010; HTA-HAS: Blanchard 2010; AHRQ: Trikalinos 2009; KCE-Report: Huybrechts 2007), two are systematic reviews (Bekkering 2008; Lodge 2007) and one is a horizon scanning report (ANZHSN: Lee 2007b). The systematic review by Bekkering et al. and the horizon scanning report by Lee et al. considered only the efficacy of HT in ocular diseases while the HTA reports studied the application of this technology also in other types of tumours.

Results

Trikalinos 2009 "Particle Beam Radiation Therapies for Cancer" (*Tufts Medical Center Evidence-based Practice Center - AHRQ*)

For uveal melanoma, particle beam therapy was used for a wide range of melanoma locations (i.e., choroid plexus, ciliary body, or iris) and sizes; the outcomes of interest were overall survival, cancer specific

survival, outcomes specific for these types of tumours (eye retention rate, vision retention, visual acuity and changes in tumours size), adverse events, outcomes relevant to the quality of life.

Three RCTs were included and reported comparing lower vs. higher doses of particle beam therapy, particle beam therapy vs. other radiotherapy (brachytherapy), particle beam therapy vs. particle beam therapy plus laser transpupillary thermotherapy, respectively. These studies are shown in Table 3. No trial reported significant differences in overall or cancer-specific survival or in incidence of total serious adverse events.

Table 3. Comparators assessed in the randomized controlled trials (Uveal melanoma)

Centre, reference	Comparison	N	Survival (overall/ specific)
MGH (USA), Gragoudas 2000	Higher vs. Lower dose proton RT	188	No/No
UCSF (USA), Char 1993	Helium RT vs. I^{125} Brachytherapy	320	Yes/Yes
CPO (France) , Desjardins 2006	Proton RT vs. Proton RT + laser TTT	151	Yes/Yes

CPO=Centre de protonthérapie d'Orsay; MGH=Massachusetts General Hospital; N=number of enrolled patients; RT=radiotherapy; TTT=transpupillary thermotherapy; UCSF=University of California San Francisco. Yes=overall/specific survival reported; No=overall/specific survival not reported.

The same authors found seven observational studies comparing particle beam radiotherapy with brachytherapy, conventional photon radiation or surgery. These are shown in Table 4

Table 4. Observational studies (uveal melanoma)

Centre, reference, type of study	Comparison	N	Survival (overall/ specific)
CPO (France), Desjardins 2003 (retrospective cohort study)	Proton RT vs. I^{125} brachytherapy	1272	Yes/No
UCSF (USA) , Harbour 1997 (case control study)	Helium RT vs. I^{125} brachytherapy	766	No/No
MGH (USA), Seddon 1990 (case control study)	Proton RT vs. enucleation	556	Yes/Yes
UCSF (USA) , Char 1996 (case control study)	Helium RT vs. I^{125} brachytherapy	426	No/No
CCO (UK), Wilson 1999 (retrospective cohort study)	Proton RT vs. I^{125} brachytherapy vs. Ru-106 brachytherapy	267	Yes/No
MGH (USA), Seddon 1985 (retrospective cohort study)	Proton RT vs. enucleation	120	Yes/Yes
UCSF (USA) , Char 2003 (case control Study)	Proton RT vs. proton RT + laser TTT	56	No/No

CCO=Clatterbridge Centre for Oncology; CPO=Centre de protonthérapie d'Orsay; GI=gastrointestinal; GSI=Gesellschaft fuer; IMRT=intensity-modulated radiotherapy; LLU=Loma Linda University; MGH=Massachusetts General Hospital; N=number of included patients; NIRS=National Institute of Radiological Sciences; RT=radiotherapy; SFRT=stereotactic fractionated radiotherapy; TTT=transpupillary thermotherapy; UCSF=University of California San Francisco. Yes=overall/specific survival reported; No=overall/specific survival not reported.

A summary of the results for all the included trials was not provided. Authors conclude that "Overall, no study found that charged particle radiotherapy is significantly better than alternative treatments with respect to patient-relevant clinical outcomes. However, this Technical Brief did not intend to assess outcomes or evaluate the validity of claims on the safety and effectiveness of particle beam radiotherapy".

***Lee** 2007b "Proton beam therapy for the treatment of uveal melanoma" (Australian and New Zealand Horizon Scanning Network – ANZHSN)*

The horizon scanning report included 2 small RCTs, 1 comparative observational study and 22 peer reviewed case series studies and reported safety and effectiveness of proton beam therapy for the treatment of patients with uveal melanoma.

One RCT (Gragoudas 2000) showed that patients treated with a higher dose of proton beam therapy [70 Cobalt Gray Equivalent (CGE)] had similar rates of rubeosis iridis/neovascular glaucoma (safety) compared to patients receiving a lower radiation dose (50 CGE) (7%, 7/94 patients and 10%, 9/94 patients, respectively. Comparisons between the patients randomised to 70 CGE or 50 CGE doses revealed that the incidence of posterior subcapsular opacity was twice as high in patients who received the lower dose of 50 CGE, but this difference was not statistically significant. In patients with tumours less than 4 DD to the optic disc and/or the macula, there were no statistically significant differences in retention of visual acuity between patients treated with 70 CGE or 50 CGE proton beam therapy at 12 months and 60 months post-treatment. Patients treated with the lower dose experienced significantly less visual field loss: mean increase at 24 months from baseline in average defect (Octopus perimeter) was 2.3 times higher in 70 CGE group (95%, 1.1-8.2) than in the lower- dose group.

Reduction of the total dose in ocular melanomas from 70 CGE to 50 CGE does not appear to reduce the complication rate. Such a finding indicates that even the 50 CGE dose is at the upper end of the dose response curve. Further reductions in dose per treatment or an increase in the number of lower dose per treatment may indeed reduce side effects due to radiation rather than those conditions that are related to tumour size.

There was no difference in local tumour control rates (effectiveness) in patients treated with 70 CGE or 50 CGE proton beam therapy. Given the low event rate, the lack of statistical significance for these observations may have been attributed to a low power study design and do not necessarily exclude real differences.

The RCT by Desjardins (2006) in an effort to decrease the risk of exudates and glaucoma, examined if the systematic addition of transpupillary thermotherapy (TTT) after proton beam therapy had a beneficial effect on these ocular complications. No significant difference in the reduction in the incidence of glaucoma was noted between the two treatment groups. Patients who received TTT had less severe glaucoma, with intraocular pressure that tended to return to normal after several months of treatment. In addition, patients treated with TTT had significantly lower secondary enucleation rates ($p = 0.02$).

The majority of studies included in Lee 2007b were of a low quality. The key measures of the effectiveness of proton beam therapy for the treatment of uveal melanoma were local tumour control, survival and retention of the treated eye which differed from the key complications assessed following proton beam therapy, these being the incidence of rubeosis iridis, neovascular glaucoma, cataracts and vision loss. The utilisation of proton beam therapy for the treatment of uveal melanomas appears to be associated with substantial complications that are highly dependent on tumour characteristics (size, location) as well as pre-treatment patients' characteristics (e.g. pre-treatment visual acuity, glaucoma etc.). The lack of comparative studies severely limits the conclusions that can be drawn from the available evidence. Local tumour control rates achieved with proton beam therapy was approximately 95%, indicating that this treatment is capable of preventing recurrence in most patients. The incidence of metastases appears to be comparable to other treatment modalities, with 5-year metastases-free survival ranging from 73% to 80%. Overall patient survival after proton beam therapy ranged from 78% to 85% at 5-years post-treatment, which appears to be similar to patients treated with brachytherapy.

Authors concluded that "The evidence on the safety and effectiveness of proton beam therapy for the treatment of uveal melanomas is mixed. The local tumour control rates achieved are remarkably consistent across studies despite the heterogeneity across study cohorts and methodology, and at the very least appears to be comparable to brachytherapy. Meanwhile, the incidence of metastasis and overall patient survival is comparable to brachytherapy as well. However, it is unclear if proton beam therapy results in a substantial improvement of eye preservation rates and the ocular complications observed post-treatment are of concern. Further studies are required to address the limitations of previous studies and to compare proton beam therapy to existing techniques. It is important to note that due to the heterogeneity between the included studies, it may be impossible to compare results in a meaningful manner. A large proportion of existing studies on proton beam therapy for uveal melanoma are quasi-anecdotal due to the fact that treatment parameters and patient selection are so variable".

Flynn *2010 "Brief overview: proton therapy for cancer" (VATAP - Veterans Health Administration Office of Patient Care Services Technology Assessment Program)*

The HTA report included 4 publications on ocular diseases: Brada 2009, Trikalinos 2009, Bekkering 2008, ANZHSN (2007b).

Brada (2009): This was a quantitative summary of low quality highly variable (for diagnosis, interventions, follow up) observational primary studies and was not included in the report.

Trikalinos (2009): This HTA report was based on single-arm studies, case series or cohort studies, (220, of which 80 on ocular cancers), RCTs (10, 4 on ocular cancers), CCTs (13, 7 on ocular cancers). RCTs and CCTs compared treatment with and without charged particles; no reports of statistically significant or important differences in survival or adverse events were found.

Bekkering (2008): This systematic review highlighted how methodological quality of the available studies is low and affected by large variations in intervention techniques and patient characteristics within and between studies. Results for uveal and choroidal melanoma suggest survival benefit but with significant side effects, including choroidal hemangioma and AMD. No benefit for HT was reported .

ANZHSN (2007b): This horizon scanning points out how proton beam, like other radiation therapy for uveal melanoma, is associated with considerable complication rates (rubeosis, neovascular glaucoma, cataract,

vision loss) and approximately comparable tumours' control rates and patient survival (≈95%) when compared to brachytherapy. One comparative study showed that enucleation rates for proton therapy were comparable to brachytherapy.

Considering all the studied indications in oncology for HT (thus including also ocular neoplasms), Authors conclude that "Available reviews for proton therapy generally concur on the state of the literature as consisting primarily of observational studies from which conclusions about the effectiveness of proton therapy versus alternatives cannot validly be made. Available reviews generally reflect the state of the literature in that they attempt to cover so much territory (multiple tumours or types of radiation) that the reviews themselves are cumbersome to read, poorly organized, correspondingly difficult to abstract, and provide only diffuse or equivocal conclusions by individual diagnoses. Several reviews attempt ill-advised or inadequately reported statistical combination of results from multiple poor-quality observational studies, further clouding credibility of results from primary studies. In other words, the literature reflects the early clinical investigation status for effectiveness of proton therapy, where observational studies are framed in terms of potential benefits, reasoning from pathophysiology, dose-finding, refinement of treatment protocols, and baseline safety of the entire approach. Only prostate cancer and uveal melanoma are represented by CCTs: in both cases with other significant methods weaknesses. There are no indications for which proton therapy has been shown unequivocally to be effective, or more effective than its alternatives. No research published subsequent to the searches conducted for available systematic reviews has changed the conclusions of those reviews".

Blanchard *2010 "Hadrontherapie par ions carbone - rapport préliminaire" (Haute Autorité de Santé - HAS)*

Results are based on the systematic review of HT performed by Lodge (2007) whose results are described below. Anyhow, Authors conclude that "Two studies on choroid melanoma and ocular tumours, with imperfect specified treatment modalities administration of carbon ion, have shown the occurrence of neovascular glaucoma in more than 40% of patients. These studies were included in the systematic review of Lodge (2007) that considered similar the different radiation therapy, but there is the finding of a higher rate of neovascular glaucoma with carbon ion therapy. However, in the absence of comparative data, no definitive conclusion is possible".

Huybrechts *2007 "Hadrontherapie" (Federaal Kenniscentrum voor de Gezondheidszorg - KCE)*

Proton Therapy is considered in one HTA report (ANZHSN 2006) and in three systematic reviews (Brada 2007, Lodge 2007, Olsen 2007). The comparative studies included were 1 RCT that compared doses of proton therapy, one cohort study comparing groups with proton therapy and groups with enucleation as treatment and one comparative study between proton beam radiation versus ^{125}I and ^{106}Ru episcleral radiation therapy (brachytherapy).The RCT of Gragoudas assessed the clinical effects of two doses of either 50 or 70 CGE in 188 patients with small or medium size melanomas (< 15 mm in diameter and < 5 mm in height) near the optic disc or macula. Local and distant tumour recurrence and cancer specific death rates were similar. Visual acuity loss was similar. The lower-dose group did experience significantly less visual field loss. The trial was underpowered to conclude whether there were differences in cancer control rates.

In the systematic review by Olsen 2007 was analyzed one study (two publications: Seddon 1985, Seddon 1990) in patients with uveal melanomas that compared cancer control rates following proton therapy versus enucleation. Patients treated with proton therapy were younger, had smaller tumours and different locations compared with controls treated by surgery. Five year overall survival was 81% in the proton

therapy group and 68% in the enucleation group. Cox regression analysis adjusted for prognostic variables found no difference in overall survival, RR 1.2 (95% CI 0.9–1.2), or disease free survival, RR 1.0 (95% CI 0.7–1.4).

One retrospective comparative case series (Wilson 1999) studied 597 patients with choroidal melanomas treated either with proton beam irradiation or with episcleral (^{106}Ru and ^{125}I) brachytherapy. Local recurrence rates were better with proton therapy but with a higher mortality rate. The model was not appropriately adjusted for possible confounders.

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

Carbon and Helium Ion Therapy: This topic is considered only in one systematic review included in the KCE report, the one by Lodge (Lodge 2007). In the SR by Lodge et al, two studies dealt with Helium ion therapy. The two other studies (Tsuji, 2007 and Hirasawa, 2007) were prospective phase I/II clinical trials in which eye retention rates and severe side effects such as neovascular glaucoma were analyzed. The rates with carbon ion (84% eye retention and neovascular glaucoma > 40%) seems to be inferior to proton or photon therapy rates.

The authors conclude that “Several treatments are possible for eye melanomas. Proton therapy is a possible alternative to photon therapy when brachytherapy is inappropriate, for example when the posterior margin extends close to the optic disc or to the fovea, or when the thickness exceeds 5.5mm. Convincing arguments are currently lacking to allow a choice between proton and photon therapy since local control, eye retention after radiation and survival were equivalent in the non-comparative cases series (the limited studies done indicate a potential improvement in local control with proton radiotherapy for uveal melanoma if close to optic disk or fovea or thickness >5 mm). There were no differences in visual acuity loss and visual field loss. Occurrence of neo vascular glaucoma was slightly less frequent with proton therapy. Carbon ion therapy seems less interesting than proton or photon therapy for ocular melanomas”.

Bekkering *2008 “The Effectiveness and Safety of Proton Radiation Therapy for Indications of the Eye”*

This systematic review focuses on results of studies on uveal melanoma and choroidal hemangioma.

Methodological quality of the included studies was low. None of the controlled trials reported concealment of allocation and only two studies used blind randomisation techniques.

Uveal Melanoma: 1 RCT (Gragoudas 2000) and 12 case series were found. The RCT including 188 patients was designed to determine whether a reduction in proton radiation dose would decrease radiation-induced complications for patients with uveal melanoma and at high risk of these complications. All tumours were located within four disk diameters of the optic disk and/or the macula. The study showed no reduction in visual loss when reducing the radiation dose from 70 to 50 CGE.

Choroidal Hemangioma: no RCTs were identified: there was one observational study with historical controls and two case series. The observational study (Hocht 2006) showed that proton as well as photon radiation

was effective in resolving retinal detachment. Proton therapy, however, appeared to be associated with more side effects. Adverse effects reported (experimental vs. comparison intervention): grade 4 retinopathy 1 vs. 0; grade 3 adverse effects on lens 0 vs. 1; grade 3 lacrimation 1 vs. 1; any grade retinopathy 40% vs. 15.7%. The results of the 2 case series suggested that vision improved in the majority of patients.

The authors conclude that "There is limited evidence on the effectiveness and safety of proton radiation due to the lack of well-designed and well-reported studies. There is a need to lift evidence on proton therapy to a higher level by performing dose-finding RCTs, comparative studies of proton radiation versus standard given alternatives and prospective case studies enrolling only patients treated with up-to-date techniques, allowing extrapolation of results to similar patient groups".

Lodge *2007 "A systematic literature review of the clinical and cost effectiveness of hadron therapy in cancer"*

For proton therapy, two prospective phase I/II dose escalation studies and eight retrospective studies were identified. Authors have calculated weighted means for the following outcomes: 5 years local tumour control, 5 years overall survival, 5 years cause specific survival, eye retention and neovascular glaucoma. Weighted means for local tumour control and 5 year overall/cause specific survival were 97% and 85% / 85%, respectively. The weighted mean for eye retention was 90%, and neovascular glaucoma occurred in 12% of patients. However, not all studies reported all the outcomes, they had a different study design and were of low quality.

For ion therapy, six studies were identified which were performed in two institutions (Berkeley, US and Chiba, Japan). In Berkeley, two retrospective case studies (Castro 1997, Char 2002) (He-ions, n = 1343) and one phase III study (Char 1993) were performed (helium ions vs. brachytherapy, n = 184; ion arm n = 86). In the only phase III trial that met the inclusion criteria, 184 patients with uveal melanoma were randomised between helium ions and ^{125}I brachytherapy. There were significantly more tumour recurrences in the brachytherapy than in the He arm (13.3% vs. 0%, $p < 0.001$). Reported complication rates of dry eye, epiphora and neovascular glaucoma were more frequent in the helium-ion treated than in the brachytherapy group (27.9% vs. 8.2%, 20.9% vs. 3.1%, 29.1% vs. 11.2%; p values not given in the article, but according to the 95% confidence intervals all differences were statistically significantly different). There was no significant difference in the rate of enucleation between both groups (He: 9.3%, brachytherapy (^{125}I): 17.3%) and similarly the incidence of distant recurrences and mortality rates were not different between both groups (He: 9.3% vs. ^{125}I: 8.2% and He: 16.2% and vs. ^{125}I 19.4%, respectively). In both groups, approximately 66% of the patients retained at least 20/50 visual acuity 3 years after treatment.

Two prospective phase I/II trials for carbon ion therapy were performed at Chiba (Hirasawa 2007, Tsuji 2007). Eye retention rates and severe side effects such as neovascular glaucoma were specifically investigated. Both outcomes, i.e. eye retention rate 84% and neovascular glaucoma >40%, appeared to be inferior to proton or photon therapy.

The authors conclude that "In ocular tumours, eye preservation rates >90%, with useful vision in approximately 50% after 5 years were reported with protons. In larger tumours and in some specific anatomical localisations in the eye, probably the best results, compared to other treatment modalities, were achieved with protons. In smaller lesions (e.g. <4 mm) the superiority of protons compared to other

modalities was less clear-cut. Although tumour control rates achieved with carbon ions were similar to those achieved with protons, more toxicity was observed".

Conclusions on ocular neoplasms

The secondary publications identified do not provide an exhaustive evidence of effectiveness and safety for the treatment of ocular tumors with HT. The lack of comparative studies severely limits the conclusions that can be drawn from the available evidence; in general, the majority of studies included were of low quality.

C. Non-small cell lung cancer (NSCLC)

Six documents focusing on the treatment of lung tumours were found by secondary literature search. Four of these are HTA-reports (HTA-VATAP: Flynn Karen, 2010, HTA-HAS: Blanchard, 2010, Blue Cross and Blue Shield Association TEC: Samson, 2011, KCE-REPORT: Huybrechts, 2007), one is a systematic review (Lodge, 2007) and one is a meta-analysis (Grutters, 2010).

The meta-analysis by Grutters and the HTA report by Samson analysed the effectiveness of HT only in lung cancer while other documents studied the application of this technology in more types of tumours.

Results

Samson *2011 "Proton beam therapy for non-small-cell lung cancer" (Technology Evaluation Center, Blue Cross and Blue Shield Association)*

The included studies compared proton beam therapy to stereotactic body radiotherapy. All included studies were case series and only one was a phase I/II study. None of the included primary studies were randomized controlled trials. The outcomes considered by the Blue cross Blue Shield Association were: overall survival, disease-specific survival, local tumour control, disease-free survival, adverse events at two and five year follow up. 301 patients had stage I NSCLC, and a few patients had stages II to IV or recurrent disease (13 patients stage II, 20 patients stage III, 1 patients stage IV and 5 with recurrent disease). Results were only reported for patients with stage I NSCLC. All outcomes showed no statistical differences between proton beam therapy and stereotactic body radiotherapy. Authors reported that patients had heterogeneous characteristics and treatments and results were highly variable.

Grutters *2010 "Comparison of the effectiveness of radiotherapy with photons, protons and carbon-ions for non-small cell lung cancer: a meta-analysis"*

The meta-analysis compared radiotherapy with photons, conventional radiotherapy (CRT) and stereotactic radiotherapy (SBRT) to radiotherapy with protons and carbon ions for the treatment of stage I NSCLC. Five studies assessed the use of proton therapy (two prospective, two retrospective and one phase II) and three the use of C-ion therapy (two phase I/II and one phase II). None of the included primary studies was a randomized controlled trial. The outcomes considered were: survival after 2 and 5 years, disease-specific survival after 2 and 5 years and adverse events. Data analysis focused on 1,326 patients treated with C-ion therapy, 895 patients treated with SBRT, 180 patients treated with proton therapy and 210 treated with C-ion therapy. Statistically significant differences in overall survival at 5 years were found comparing proton and C-ion therapy to CRT (40%, p=0.014; 42%, p‹0.001 and 19% respectively) while five year disease-specific survival for CRT (43%) was statistically significantly lower than that for SBRT (63%; p=0.045). Overall

survival and disease free survival of proton and C-ion therapy were not statistically different from SBRT. Severe adverse events were infrequent in all types of radiotherapy analysed. The studies for SBRT reported more adverse events expressed as incidence per thousand patients at risk for dyspnoea (compared to CRT, SBRT, proton and C-ion therapy: 5.1; 7.8; 0.0 and 0.0 respectively), esophagitis (compared to CRT, SBRT and proton therapy: 1.2; 2.4 and 0.0 respectively; while no data were reported for C-ion therapy), treatment-related deaths (compared to CRT, SBRT, proton and C-ion therapy: 1.0; 6.9; 0.0 and 0.0 respectively) and pneumonitis grade 3/4 (compared to CRT, SBRT, proton and C-ion therapy: 2.3; 20.0; 7.9 and 14.3 respectively).

Flynn *2010 "Brief overview: proton therapy for cancer" (VATAP - Veterans Health Administration Office of Patient Care Services Technology Assessment Program)*

The VATAP report analysed the efficacy of HT for lung and other cancers. Concerning lung cancer the report focused on the systematic review by Pijls-Johannesma et al (2010) which consists of an update of another systematic review (Lodge, 2007 reported below). The selected studies included five focusing on protons (214 patients) and six which investigated C-ions (210 patients). No RCT on lung cancer was included in this SR.

Reported results:

- proton therapy: local control rates, 57-87%; 2-year cause-specific survival, 58-86%; 5-year cause-specific survival, 46%; radiation-induced pneumonitis, 10%;
- carbon ions therapy: overall local tumour control, 77%; 95% with hyperfractionation; 5-year overall survival, 42%; cause-specific survival, 60%;
- pooled estimates for combined outcomes from multiple studies were not reported.

Blanchard *2010 "Hadrontherapie par ions carbone - rapport préliminaire" (Haute Autorité de Santé - HAS)*

The HAS report included two papers that analyzed the effect of carbon ion therapy in lung cancer: a meta-analysis with 210 patients treated with carbon ion therapy reported as "a preprint on line by Grutters, 2009", later published in 2010, (see previous reference) and a phase I/II study reported by Sugane in 2009 with a sample size of 18 patients. No randomized controlled trials were included and no pooled estimates were presented. The outcomes considered were: overall survival, adverse events and local tumour control. Results concerning overall survival were reported for C-ion and proton therapy and SBRT without significant differences at 2 years (74%, 61% and 70% respectively) and at 5 years (42%, 40% and 40% respectively) while adverse events were only reported for C-ion therapy: 1,4% pneumonitis grade 3-4, 0% dyspnoea grade 3-4 and 0% of treatment-related deaths (data extracted by the meta-analysis of Grutters). Data extracted by Sugane reported 95.8% of local tumour control and 30.7% of overall survival at 5 years while 0% of adverse events were reported for C-ion therapy. No comparative data were reported.

Huybrechts *2007 "Hadrontherapie" (Federaal Kenniscentrum voor de Gezondheidszorg - KCE)*

The aim of the KCE report was to evaluate the clinical effectiveness (local tumour control, disease free survival, overall survival and adverse events) of both proton and carbon ion therapy. The six studies on lung cancer included 3 prospective and 3 retrospective studies. The sample size for each study varied from 37 to 82 patients. No aggregated results were presented and no RCTs were included. Local tumour control rates

at 2 years ranged from 80 to 87%, at 3 years 74%, at 3.5 years 77% and at 5 years 89% (stage IA) and 39% (stage IB). Survival rates at 3 years ranged from 72 to 84%. Survival rates at 5 years reported in a prospective study were 63% in the entire group and 86% in stage I patients. Survival rates at 5 years reported in a retrospective study were 29% for all patients, 70% for stage IA patients and 16% for stage IB patients. Finally severity of pulmonary reactions correlated with dose-volume factors was reported in another prospective study. No data on CRT were reported.

Lodge *2007 "A systematic literature review of the clinical and cost-effectiveness of hadron therapy in cancer"*

The efficacy in terms of local tumour control, overall survival, cause specific survival and adverse events (pneumonitis ≥ grade 2) of proton therapy and carbon ion therapy compared to stereotactic radiotherapy was investigated by the systematic review by Lodge et al, for the treatment of stage I/II lung cancer. No RCTs were included in the analysis. For proton therapy, one prospective study (n = 68) and two retrospective case studies (n = 88) were identified, mainly in stage I patients. Weighted means of 2/5 year local tumour control rates varied between 68% and 84%. The weighted means for 2 year/5 year overall survival and 2/5 year cause-specific survival were 53%/23% and 66%/46%, respectively. Radiation induced pneumonitis was observed in about 10% of the patients. For carbon ion therapy, results of three prospective phase I/II dose escalation studies in stage I patients (n = 82) were reported, all performed in Chiba, Japan. Local tumour control rate was 77% and the 5-year overall survival and cause specific survival rates were 42% and 60%, respectively. Similar outcomes were achieved using stereotactic radiotherapy.

Conclusions on NSCLC

All the reviews indicate that studies concerning efficacy are mainly non comparative and have low methodological quality. No randomized control trials and high quality comparative studies relating to HT for the treatment of non-small-cell lung cancer are available, thus the efficacy of this technology for these patients remains unclear. Lodge and colleagues were not able to report clear conclusions for the efficacy of protons and carbon ions in the treatment of non-small cell lung cancer. The VATAP report defines HT as promising but adds that more evidence of effectiveness and cost-effectiveness is needed: they conclude that until these results are not available for lung cancer, HT should be considered experimental. Both the KCE report and the HAS report concluded that outcomes observed with C-ions for lung cancer are similar to those achieved by conventional radiotherapy. The HAS report also reported that no data of efficacy of C-ions compared to proton therapy or stereotactic radiotherapy were available. The meta-analysis by Grutters et al showed survival rates for particle therapy higher than those for conventional radiotherapy, but similar to stereotactic body radiotherapy in stage I inoperable non-small-cell lung cancer. In addition the meta-analysis suggests that particle therapy and conventional radiotherapy appear to result in less adverse events than stereotactic body radiotherapy, but these were difficult to compare due to poor or incongruous reporting. However the lack of 15-20 year follow up clinical studies prevents drawing conclusions on very late effects of HT compared to conventional and stereotactic body radiotherapy. Finally the Blue Cross and Blue Shield Association TEC report concludes that evidence is insufficient to derive conclusions on the efficacy of proton therapy in comparison to stereotactic body radiotherapy: survival rates are highly variable and heterogeneity in patient and treatment characteristics may be confounding. The authors also underline that there is even less clarity regarding adverse event rates. Thus it is unclear if benefits of proton beam therapy outweigh harms. For all these reasons proton beam therapy for the

treatment of non-small-cell lung cancer or for recurrent non-small-cell lung cancer did not meet the criteria of the Blue Cross and Blue Shield Association Technology Evaluation Center.

D. Gastrointestinal cancer

Five documents discussing the use HT for gastrointestinal cancers (including liver, oesophageal, pancreatic, and bile duct tumours) were found through a secondary literature search. Four of these are HTA-reports (VATAP: Flynn 2010; HAS: Blanchard 2010; AHRQ: Trikalinos 2009; KCE-REPORT: Huybrechts 2007) and one is a systematic review (Lodge 2007).Results

Flynn *2010 "Brief overview: proton therapy for cancer" (VATAP - Veterans Health Administration Office of Patient Care Services Technology Assessment Program)*

VATAP first identified available systematic reviews, technology assessments, and economic evaluations (12 reports) and then updated the search to confirm the presence or absence of subsequently published primary studies that could change conclusions reached by these reviews. One case series consisting of gastrointestinal cancer patients was found (Fukumitsu, 2009: 51 patients; overall survival: 3 yrs, 49.2%; 5 yrs, 38.7%; local control: 3 yrs, 94.5%; 5 yrs, 87.8%; post-treatment α–feto-protein reduced from pre-treatment ($p<0.0001$); minor acute adverse reactions (≤ grade 1); 3 patients had late adverse reactions (≥grade 2); no treatment-related deaths; "hypofractionated proton beam therapy is safe and well-tolerated by patients with hepatocellular (liver) cancer located greater than 2 cm away from the porta hepatis or G tract and may be an effective alternative to other modalities"). The authors concluded that, for all its potential indications, "available reviews for proton therapy generally concur on the state of the literature as consisting primarily of observational studies from which conclusions about the effectiveness of proton therapy versus alternatives cannot validly be made […] Weaknesses of currently available economic studies precluded their inclusion here […] There are no indications for which proton therapy has been shown unequivocally to be effective, or more effective than its alternatives. No research published subsequent to the searches conducted for available systematic reviews has changed the conclusions".

Blanchard *2010 "Hadrontherapie par ions carbone - rapport préliminaire" (Haute Autorité de Santé - HAS)*

The objective of this preliminary report was to assess the potential value of carbon ion therapy. Only one systematic review was found and discussed (Lodge 2007) concluding that, for gastrointestinal tumours, the reported results did not allow a final conclusion on the role of protons or C-ions therapy.

Trikalinos *2009 "Particle Beam Radiation Therapies for Cancer. Technical Brief No. 1." (Agency for Healthcare Research and Quality - AHRQ)*

The Agency for Healthcare Research and Quality (AHRQ) required a Technical Brief on the role of particle beam radiotherapy for the treatment of cancer conditions using several key questions focused on different particle beam radiation therapies and on the theoretical advantages and disadvantages of these therapies compared to other radiation therapies that are currently used for cancer treatment (eg. helium RT vs. photon RT, proton RT vs. photon RT, surgery + photon RT vs. Surgery + proton RT). A total of 3 studies on patients with gastrointestinal tumours were included in the review: 1 was a randomized controlled trial and 2 were nonrandomized comparative studies. The outcomes considered by the authors were overall survival and specific survival, effectiveness and safety. One RCT (Linstadt 1988) compared helium RT photon RT.

The Authors anticipated that the systematic review would not be able to provide definitive answers on the effectiveness and safety of particle beam therapy compared to other interventions for most (if not all) cancer categories.

***Huybrechts** 2007 "Hadrontherapie" (Federaal Kenniscentrum voor de Gezondheidszorg - KCE)*

In this HTA report the Authors present the rationale behind the use of ions in the treatment of cancer, reviewing the scientific evidence with regard to the efficacy and safety of HT, calculating the number of patients who could reasonably benefit from this treatment for indications considered. Three SRs on the use of HT for the treatment of patients with gastrointestinal tumours were evaluated in this study (Olsen 2007, Brada 2007 and Lodge 2007). Their conclusions were that results reported for protons or carbon ions are similar to those achieved by RT and that the small number of patients studied precludes any firm conclusions.

***Lodge** 2007 "A systematic literature review of the clinical and cost-effectiveness of hadron therapy in cancer"*

In view of the continued increase in the number of centres for hadron (i.e. neutron, proton and light or heavy ion) therapy (HT) the Authors performed a systematic literature review to identify reports on the efficacy of HT. The outcomes considered were overall survival (2 and 5 year), local tumour control and toxicity. A total of 7 studies were included: 4 were retrospective studies (Choi 2006, Hata 2006, Sugahara 2005, Kato 2004), 2 were prospective studies (Kawashima 2005, Bush 2003) and 1 was an RCT (Linstadt 1988), the latter being the only RCT on pancreatic cancer comparing Helium RT vs. photon RT. Local control rates were slightly higher in the helium-treated patients (10% vs. 5%) but the small number of patients (n=49) precluded any conclusions. No RCTs were found for oesophageal or hepatocellular cancers. "*In summary, for gastrointestinal cancers, the role of protons or C-ions remains unclear*".

Conclusions on gastrointestinal cancer

In all considered studies (HTA reports and systematic reviews), the Authors agree on the need for further studies as for all gastrointestinal tumours (likewise other tumours), the results obtained did not allow any conclusion on the use of these treatments.

E. Pelvic cancer

Four documents discussing the use of HT for pelvic cancers (including cervix and bladder tumours) were found through a secondary literature search. Three of these are HTA-reports (HTA-HAS: Blanchard 2010 AHRQ: Trikalinos 2009; KCE-REPORT: Huybrechts 2007) and one is a systematic review (Lodge 2007).

Results

***Blanchard** 2010 "Hadrontherapie par ions carbone - rapport préliminaire" (Haute Autorité de Santé - HAS)*

The objective of this preliminary report was to assess the potential value of carbon ion therapy. Only one systematic review was found and discussed (Lodge 2007) concluding that - in the absence of additional, particularly comparative, data - the value of the technology for pelvic tumours remains undefined.

***Trikalinos** 2009 "Particle Beam Radiation Therapies for Cancer. Technical Brief No. 1." (Agency for Healthcare Research and Quality - AHRQ)*

The Agency for Healthcare Research and Quality (AHRQ) required a Technical Brief on the role of particle beam radiotherapy for the treatment of cancer conditions focussing on different particle beam radiation therapies and on the theoretical advantages and disadvantages of these therapies when compared to other currently used radiation therapies (e.g. carbon RT vs. photon RT + brachytherapy, proton RT vs. photon RT, surgery + photon RT vs. surgery + proton RT). The key questions were defined by AHRQ after discussions with the Tufts Medical Center EPC. No RCTs on patients with pelvic tumours were retrieved and included in the HTA report, but 7 non comparative studies were found and included. The Authors concluded that systematic reviews of the current literature do not provide answers on the effectiveness and safety of particle beam therapy compared to other interventions for most if not all cancer categories including pelvic tumours.

***Huybrechts** 2007 "Hadrontherapie" (Federaal Kenniscentrum voor de Gezondheidszorg – KCE)*

In this HTA report the Authors present the rationale behind the use of ions in the treatment of cancer, reviewing the scientific evidence with regard to the efficacy and safety of HT, calculating the number of patients who could reasonably beneficiate for the relevant indications considered. Only one systematic review evaluating the use of HT in patients affected by pelvic tumours was included (Lodge 2007) and the result of the evaluation was that further comparative studies enrolling more patients will be required to address these issues.

***Lodge** 2007 "A systematic literature review of the clinical and cost-effectiveness of hadron therapy in cancer"*

The Authors performed a systematic literature review to identify reports on the efficacy of HT in pelvic tumours. Seven studies were included: 3 were retrospective (Hata 2006, Kagei 2003 and Tsujii 1994) and 4 prospective (Kato 2006, Nakano 2006, Molla 2005, Shipley 2005). The outcomes considered were 5-year overall survival, local tumour control, toxicity and bladder preservation. For cervical cancer (1 retrospective and 3 prospective studies) no firm conclusions could be drawn due to the small number of patients, and for bladder cancer (2 retrospective and 1 prospective studies) the results were similar to the reported outcomes for combined modality therapy including photon RT, though a higher bladder preservation rate was reported for proton therapy. In general there were no definitive conclusions on the relative advantages of photons, protons and ions for pelvic tumours.

Conclusions on pelvic cancer

The results of the examined studies were that in the absence of additional data, particularly comparative data, the value of technology is not defined.

F. Prostate cancer

Several documents on the use of charged particle (proton, ion, neutron) beam radiotherapy - used alone or in combination with other interventions - in patients with prostate cancers were found through a secondary literature search. Four of these are HTA-reports (HTA-VATAP: Flynn 2010; HTA-HAS: Blanchard 2010; AHRQ: Trikalinos 2009; KCE-REPORT: Huybrechts 2007) and five are systematic reviews (Bannuru 2011; Samson 2011; ICER: Ollendorf 2008; Wilt 2008; Lodge 2007). Bannuru 2011, Samson 2011, Ollendorf 2008 and Wilt 2008 investigated the use of HT in prostate cancer only, while the other Authors included also other types of cancers. Bannuru 2011, Samson 2011, Flynn 2010, Ollendorf 2008 and Wilt 2008 focused their attention on proton beam therapy only, HAS 2010 on carbon ion only, Huybrechts 2007 and

Lodge 2007 on both proton and carbon ion and Trikalinos 2009 studied all charged particles (proton, ion and neutron). Ollendorf 2008 designed an economic model to assess the incremental cost-effectiveness of using brachytherapy or proton beam therapy (PBT) vs. image-guided Radiation Therapy (IMRT) to treat patients with low risk, clinically localised prostate cancer.

Results

***Bannuru** 2011 "Comparative Evaluation of Radiation Treatments for Clinically Localized Prostate Cancer: An Updated Systematic Review"*

The authors analysed 75 studies involving patients with localized prostate cancer who either had first line radiation therapy or received no initial treatment. Comparators of interest were no treatment or no initial treatment or different forms of radiation therapy. Ten of these studies were RCTs and one trial (Zietman 2005 and 2010) which was rated as "susceptible to some bias but not sufficient to invalidate results" used a proton therapy boost after initial photon therapy and found a Risk Difference of 0.16 (0.07 to 0.24, 95% CI) in favour of the treatment using high-dose over conventional-dose conformal radiation based on freedom from biochemical failure. The considered outcomes were overall survival, prostate cancer–specific survival, metastases- and/or clinical progression–free survival, biochemical failure, health status, and quality of life. All studies reported that higher-dose External Beam Radiation Therapy (EBRT) was associated with increased rates of freedom from biochemical failure at 5 to 10 years compared with lower-dose EBRT. "No differences in urinary or bowel toxicities between higher- and lower-dose EBRT were found". The authors concluded that currently available evidence was "insufficient to draw definitive conclusions about the effectiveness of radiation treatments for localized prostate cancer compared with no treatment or no initial treatment".

***Samson** 2011b "Proton Beam Therapy for Prostate Cancer" (Technology Evaluation Center, Blue Cross and Blue Shield Association)*

The objective of the HTA report was to compare the effects of proton beam therapy, with or without external-beam radiotherapy, against alternative RT modalities (3D conformal radiotherapy, intensity modulated radiotherapy and image-guided radiotherapy; earlier 2D methods are now considered outmoded) and other treatments for prostate cancer (watchful waiting, radical prostatectomy, and brachytherapy). A total of 9 studies were included in the review: 4 were comparative and 5 were non-comparative. The outcomes considered were overall survival, disease-specific survival, biochemical failure, quality of life or symptom status and genitourinary and gastrointestinal toxicities. Of two RCTs found, one (Shipley 1995, rated as "good in quality") used external beam RT methods that are no longer relevant to clinical practice, precluding conclusions about the comparative effects of external-beam radiotherapy plus either an x-ray boost or a proton beam boost. The other RCT (Zietman 2010, rated as "good in quality") compared high dose to low dose proton beam boost and showed a significantly improved intermediate outcome favouring high-dose proton beam boost over conventional-dose proton beam boost with Local Failure/Control Hazard Ratio 0.57 (95% CI 0.43 to 0.74, p<0,0001). However, there was no difference in long-term health outcomes (Overall Survival 83.4% vs. 78.4, p=0.41). Currently available randomized trials were found to be insufficient to clearly answer the Authors' research questions: whether proton beam therapy improves outcomes in any setting in prostate cancer has not yet been established.

***Flynn** 2010 "Brief overview: proton therapy for cancer" (VATAP - Veterans Health Administration Office of Patient Care Services Technology Assessment Program)*

VATAP first identified available systematic reviews, technology assessments, and economic evaluations (12 reports) and then updated the search to confirm the presence or absence of subsequently published primary studies that could change conclusions reached by these reviews. There were 5 primary non-RCT studies on effectiveness or adverse effects, and 1 case series consisting of prostate cancer patients. Some controlled clinical trials on prostate cancer (and uveal melanoma) were included in the retrieved reviews, but significant methodological weaknesses were identified. The authors concluded that, in general, "available reviews for proton therapy generally concur on the state of the literature as consisting primarily of observational studies from which conclusions about the effectiveness of proton therapy versus alternatives cannot validly be made … Weaknesses of currently available economic studies precluded their inclusion here … There are no indications for which proton therapy has been shown unequivocally to be effective, or more effective than its alternatives. No research published subsequent to the searches conducted for available systematic reviews has changed the conclusions of those reviews".

Blanchard *2010 "Hadrontherapie par ions carbone - rapport préliminaire" (Haute Autorité de Santé - HAS)*

The objective of this preliminary report was to assess the effectiveness of carbon ion therapy. This report evaluated the systematic review of Lodge 2007 reporting on two RCTs (Zietman 2005 and Shipley 1995). The results obtained did not allow the authors to reach any conclusions regarding the efficacy and safety of carbon ion treatment for prostate cancer.

Trikalinos *2009 "Particle Beam Radiation Therapies for Cancer. Technical Brief No. 1." (Agency for Healthcare Research and Quality - AHRQ)*

The authors retrieved 243 papers (10 RCTs, 13 nRCTs and 220 single arm studies) discussing charged particle beam RT used alone or in combination with other interventions for both common cancers (e.g., lung, prostate, breast) and uncommon cancers (e.g., skull base tumours, uveal melanomas). A total of 19 studies on prostate cancer were analysed (of which 3 RCTs and 2 non-randomised comparative studies); among these, Zietman 2005 compared Photon RT + standard dose proton vs. Photon RT + high dose proton and both Benk 1993 and Shipley 1995 Photon RT + local photon boost vs. Photon RT + local proton boost. All 3 RCTs investigated overall survival and cancer-specific survival. The report concluded that a large number of scientific papers on charged particle radiotherapy for the treatment of cancer currently exist; however, these studies do not document the circumstances in contemporary treatment strategies in which RT with charged particles is superior to other modalities. The Authors concluded that comparative studies in general, and RCTs in particular (when feasible), are needed to document the theoretical advantages of charged particle radiotherapy to specific clinical situations.

Ollendorf *2008 "Brachytherapy & proton beam therapy for treatment of clinically-localized, low-risk prostate cancer, final appraisal document" (Institute for Clinical and Economic Review - ICER)*

The objective of the report was to assess the comparative clinical effectiveness and comparative value of brachytherapy (BT), image-guided Radio Therapy (IMRT), and proton beam therapy (PBT) for men with clinically-localized, low-risk prostate cancer: a total of 166 studies matching the entry criteria were found. There were no RCTs comparing measures of benefit and/or harm between BT, proton therapy, IMRT, and active surveillance; information on PBT is limited to case-series from a single institution. Data on overall and disease-specific survival from studies that met Institute for Clinical and Economic Review eligibility criteria were only available for brachytherapy and active surveillance. Considering a follow up period between 1.5 and 6 years, rates of freedom from biochemical failure for all PBT (n=6) and IMRT (n=7) studies

that report such outcomes are in the range 79%-95% and 69%-99% for PBT and IMRT respectively. Potential harms related to PBT are: hypothetical greater incidence of hip fracture (based on experts opinion, no published studies on this issue), radiation-induced malignancies (with a lifetime attributable risk of 1% for PBT and IMRT and 0.5% for BT), and acute/late radiation toxicity (assessed with a random-effects meta-analysis: the rate of late GI toxicity appears to be higher for PBT, 16.7%, than for either IMRT, 6.6%, or brachytherapy, 4.0%; however wide confidence intervals were observed). Finally, using an economic model, BT was found to be cost-saving and more effective than IMRT, while PBT was more expensive and less effective than IMRT for a base case of a 65 year-old man with clinically localized prostate cancer and a low risk of cancer recurrence (a similar result was found for a model based on men 58 years of age).

***Wilt** 2008 "Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer" (Agency for Healthcare Research and Quality - AHRQ)*

This report was prepared to address questions regarding the comparative risks, benefits, short- and long-term outcomes of the alternative therapies (including radical prostatectomy, external beam radiotherapy, 3D conformal radiation therapy, Intensity Modulated Radiation Therapy, Interstitial brachytherapy, watchful waiting, hormonal therapy) for clinically localized prostate cancer, the relationships between patients', provider/hospital's and tumour's characteristics and outcomes. Moreover the report investigated on potential gaps of knowledge to be filled to allow patients to better understand treatment options. No RCTs comparing the effectiveness of proton vs. photon therapy were found. One RCT (Shipley 1995) assessed prostate cancer control of high dose irradiation followed by a boost with conformal protons compared with conventional dose irradiation using photons alone for advanced prostate cancer. At 8 year follow-up, combination therapy was better than conformal therapy alone: OR 1.88, 95% CI 1.04-3.41). Overall survival did not differ between groups in an RCT (Zietman 2005) of 393 men with localized prostate cancer and PSA <15 ng/ml treated with a combination of conformal photon and proton beams. Absolute rates of outcomes after proton radiation appear similar to other treatments, but there is no direct evidence that proton radiation is better than other treatments (non randomized clinical trials, phase II: Yonemoto 1997 and Nihei 2005; case series: Slater 1999, Slater 2004, Rossi 2004). The authors concluded that while emerging technologies (including proton beam therapy) are becoming popular despite their increasing use, no RCTs have been conducted. They went on to indicate that these technologies need to be studied in large RCTs to assess long-term tumour control, complications, costs, and survival.

***Huybrechts** 2007 "Hadrontherapie KCE reports vol. 67A" (Federaal Kenniscentrum voor de Gezondheidszorg – KCE)*

This report was prepared to investigate the efficacy of HT compared to current treatments in terms of improving local tumour control, disease free survival and/or overall survival, whether HT has less side effect than other treatments. The Authors were also interested in both the assessment of HT current use and of its possible use in diseases other than cancer. Forty six reports and studies were selected. The Authors concluded that "globally, the HTA reports favour a limited use of HT for selected groups of patients". Their conclusions are based on low quality evidence and further research is necessary. Proton beam therapy can be considered for rare tumours with specific indications where conventional therapy presents a significant risk to adjacent important structures. Carbon ion therapy is regarded as "an appealing but still experimental approach". Focusing on prostate cancer (proton: RCTs: Shipley 1995 and Zietman 2005; case series: Slater 2004. Carbon ion, case series: Akakura 2005, Ishikawa 2006 and Tsuji 2005) the authors reported that "1. the value of proton and carbon-ions therapy in prostate cancer remains unclear; 2. high dose RT combining

photons and protons has shown a significant (P<0.001) reduction in the risk of biochemical failure (PSA level) but no significant difference in overall survival rates; 3. it is necessary to compare high dose RT combining photons and protons with conventional and emerging treatments".

Lodge *2007 "A systematic literature review of the clinical and cost-effectiveness of hadron therapy in cancer"*

The findings from 40 relevant studies on proton therapy and 22 on ion therapy were reported in the paper. Shipley 1995 (inadequate photon doses and techniques according to today's standards) and Zietman 2005 were the 2 RCTs found and used to discuss prostate cancer with one large retrospective study (Slater 2004). Ion therapy relevant studies were 4 prospective phase I/II studies (Akakura 2004, Ishikawa 2006a, Ishikawa 2006b, Tsuji 2005). Proton therapy was found to have similar outcomes compared to conventional therapies while "no firm conclusion" was possible for ion therapy. The weighted estimates for local tumour control, 5 year overall survival and late gastrointestinal and genitourinary toxicity are 74%, 89%, 15%, 7% and 100%, 89%, 6%, <5% respectively for protons and ions. The results with high dose photon therapy are similar: 83%, 66%, 29%, 28%. The Authors concluded that "in locally advanced prostate cancer (T3–T4, N0–N2, M0), no clear superiority of protons or photons could be demonstrated. The two RCTs were dose-escalation studies of which one used protons and photons in both arms. Hence, the specific contribution of protons could not be assessed. Nor, at least for the present, can we draw any firm conclusions concerning the utility of C-ions in the treatment of prostate cancer." Finally, the Authors stated that the evidence base currently available for prostate tumours cannot support "the introduction, or significant extension, of hadron therapy as a major treatment modality" into standard clinical patient care.

Conclusions on prostate cancer

All analyses and reviews agree that currently available evidence is insufficient to demonstrate that charged particles therapies are better than alternative treatments for prostate cancer.

G. Skeleton and soft tissues tumours

There are only two reviews addressing the treatment of tumours of the skeleton and soft tissues. Both of them are included in HTA-reports (HTA-HAS: Blanchard 2010; KCE-Report: Huybrechts 2007). Huybrechts analysed the effectiveness of treatments with protons and carbon ions, while HTA-HAS focused on treatment with carbon ions.

The pathologies addressed within these studies are cervical spine chordomas; non-skull chondrosarcomas; unresectable sacral chordomas; sacrococcygeal chordomas and chondrosarcomas; osteosarcomas; unresectable skeleton chondrosarcomas; soft tissues sarcomas.

Results

Blanchard *2010 "Hadrontherapie par ions carbone - rapport préliminaire" (Haute Autorité de Santé - HAS)*

The HAS Report described the result of three studies on soft tissues sarcomas and skeleton sarcomas, in which a 5 years local control rate of 76% over 388 patients, and a 5 years overall survival rate of 54% were observed. Grade 3 toxicities were reported in 10% of patients.

The results according to pathological sub-types were as follows:

Osteosarcomas (65 patients): 5 years local control rate of 62%; 5 years overall survival of 28%.

Chondrosarcomas (63 patients): 5 years local control rate of 65%; 5 years overall survival of 59%.

Chordomas (126 patients): 5 years local control rate of 89%; 5 years overall survival of 85%.

The limitations of these studies are that they didn't specify the therapeutic modalities and are non-comparative.

In view of the lack of comparative data, the HAS Report stated that it is impossible to draw any conclusion.

Huybrechts *2007 "Hadrontherapie" (Federaal Kenniscentrum voor de Gezondheidszorg - KCE)*

Huybrechts remarked on the paucity of studies in chordomas and chondrosarcomas in anatomical areas other than skull base. Furthermore, the three primary studies considered in the report are case series reports. More than 50 patients with cervical spine chordomas/chondrosarcomas, unresectable sacral chordomas (30 patients), spinal (9) and sacrococcygeal (8) sarcomas were examined in these studies. The observed results were a 5-year overall survival rate of about 50% and a 5-year (or 3-year) local control rate of approximately 90%. Toxicities were observed in 2 patients with severe skin reactions.

Due to the heterogeneity of these case series, and lack of comparative studies, Huybrechts stated that there is no evidence in favour of proton or carbon ion therapy for non-skull base chordomas and chondrosarcomas.

Conclusions on skeleton and soft tissues tumours

Both the documents remarked that there is no evidence in favour of hadrontherapy for lack of comparative studies, and because the observed studies are heterogeneous with regard to the included population and results.

Economic aspects

Results

Although our search strategy did not include economic issues, seven of the 15 selected SRs and HTA reports dealt with economic aspects. Three of them are HTA Reports (HTA-VATAP: Flynn 2010; KCE-Report:

Huybrechts 2007; AHRQ: Trikalinos 2009), two are SRs (Lodge 2007; Ollendorf 2008) and the other two are Horizon Scanning reports (ANZHSN: Lee 2007a; ANZHSN: Lee 2007b).

Flynn *2010 "Brief overview: proton therapy for cancer" (VATAP - Veterans Health Administration Office of Patient Care Services Technology Assessment Program)*

Flynn et al in their HTA report involving several pathologies found many studies with cost analysis. These studies have therefore subsequently been called "misleading" when referred to as "economic evaluations". The report emphasizes that a cost-effectiveness analysis should be performed with cost and efficacy data relating to proton therapy and its alternatives. In the case of proton therapy, these kinds of studies are premature, until efficacy data from RCTs become available.

Huybrechts *2007 "Hadrontherapie" (Federaal Kenniscentrum voor de Gezondheidszorg - KCE)*

The authors performed a detailed cost analysis to compare two possible options for the treatment of Belgian patients: treatment abroad and treatment at a local centre to be constructed in Belgium. "Taking into account the indications with little, though poor, evidence and potential other indications, the total Belgian patient base is estimated at 51 (maximum 100) patients" (where 100 is the maximum expected number of patients in 2040). The overall cost of referring 51 Belgian patients abroad for HT was estimated at 1.7 million €, including travel and lodging cost. The investment cost of a new centre for Proton and Carbon-ion therapy with 3 treatment rooms was estimated at 159.6 million €. These figures take into account all costs, including building and finance cost. The operational costs, over an expected lifetime of 30 years, were estimated at 17.5 million €/year, assuming a two-shift 12.5 hours per workday operation. These figures take into account costs of personnel, fixed costs such as building maintenance and utilities, medical equipment and supplies, security and courier costs. The break-even point is calculated after twenty years of operation, on the hypothesis of 900 patient per year, and considering an annual reimbursement of 22.2 million € from national health insurance (RIZIV/INAMI), at an average reimbursement of 24,700 € per patient.

Ollendorf *2008 "Brachytherapy & proton beam therapy for treatment of clinically-localized, low-risk prostate cancer, final appraisal document" (Institute for Clinical and Economic Review - ICER)*

The authors assessed the effectiveness of three different therapies for patients with low-risk, localized prostate cancer: brachytherapy, IMRT, and Proton Beam Therapy (PBT). An economic model was constructed to compare the cost-effectiveness of the three technologies. The model also considered a strategy of deferred treatment. The model considered treatment costs, costs for management of toxicities, and patient time costs while in treatment, including lost workdays. For a cohort of 65 year-old patients, with T1 or T2 lesions, the economic model showed that brachytherapy is cost-saving and more effective than PBT and IMRT. The QALY of the three treatments are almost the same (13.90 for brachytherapy, 13.81 for IMRT and 13.70 for PBT). Large differences were observed in lifetime cost, varying from 29,575 US dollars brachytherapy, 41,591 US dollars for IMRT and 72,789 US dollars for PBT. The results for deferred treatment are almost the same as immediate treatment. Also for a cohort of 58 year-old men, the economic model shown that brachytherapy is cost-saving and more effective than IMRT, while PBT is more expensive and less effective than IMRT (Brachytherapy: QALY=17,78, lifetime cost=34,885 US dollars; IMRT: QALY=17.61, L. cost=47,194 US dollars; PBT QALY=17.48, L. cost=79,056 US dollars).

Lodge *2007 "A systematic literature review of the clinical and cost-effectiveness of hadron therapy in cancer"*

13 economic papers were selected by the systematic review by Lodge et al. The quality of these papers is defined as highly variable. In the discussion the authors remarked the need for high quality studies on cost-effectiveness of HT compared with all forms of conventional therapy and reported data from a study (Lundkvist, 2005) that estimated the average cost per QALY gained at € 10,130. Lodge et al reported the limitation of this study: only four type of cancer were considered (left-sided breast cancer, prostate cancer, head and neck cancer and childhood medulloblastoma); the validity of the model is questionable due to several assumptions made about the population.. Furthermore, with such high capital costs for HT, a budget impact analysis is necessary for decision makers.

Lee *2007a "Proton beam therapy for the treatment of neoplasms involving (or adjacent to) cranial structures" (Australian and New Zealand Horizon Scanning Network – ANZHSN)*

This Horizon Scanning described the result of two studies addressing potential cost impact. The first study (Goitein and Jermann, 2003) performed a cost analysis for proton and photon radiation therapy. They estimated the cost of the construction of a two-gantry proton facility at about € 62,500,000, whilst the construction of a two LINAC X-ray facility costs about € 16,800,000. They also estimated the operational costs per fraction at € 1,025 for proton therapy and at € 425 for photon therapy. They noticed that operational costs of a proton therapy facility are dominated (42%) by financial costs, due to the large initial investment. The largest operational cost of a photon facility is the personnel cost (51%). Noting that proton beam therapy is more expensive than photon therapy, the authors questioned whether the greater cost of proton beam therapy is clinically worthwhile. The second study discussed (Lundkvist 2005) is the same quoted above by Lodge, 2007.

Lee *2007b "Proton beam therapy for the treatment of uveal melanoma" (Australian and New Zealand Horizon Scanning Network – ANZHSN)*

The Horizon Scanning, reporting on the treatment of uveal melanoma, noticed the lack of studies about the specific cost effectiveness of proton beam therapy for uveal melanomas.

Trikalinos *2009 "Particle Beam Radiation Therapies for Cancer. Technical Brief No. 1." (Agency for Healthcare Research and Quality - AHRQ)*

The authors pointed out the cost of the seven existing facilities for proton and heavy ion in the United States, and the cost of the four under construction. These costs range between 100 and 225 million US dollars.

Conclusions on economic aspects

Based on cost analysis, the capital and operational costs attributed to HT are significant. While economic modelling suggests that HT is potential cost-effective for a small number of cancers, assumptions made were almost uniformly based on low quality evidence of efficacy, which introduces uncertainty regarding the validity of these analyses.

While we did not undertake a systematic review of economic analyses, given the overwhelming lack of good quality evidence on efficacy, it is unlikely that any economic models on cost-effectiveness for HT will be able to overcome this problem until better quality evidence of efficacy from RCTs is available .

Discussion

Our literature search retrieved fifteen papers (HTA reports or systematic reviews) on the use of HT (mainly proton beam therapy and carbon-ion beam therapy) in different types of cancer, mostly those situated adjacent to critically important healthy tissues such as tumours of the head and neck, central nervous system, the eye, the lung, and the prostate.

Available literature on the use of HT for the treatment of head and neck tumours and skull base neoplasms suggests a better efficacy of HT if compared to traditional radiotherapy in patients with chordomas or adenoid cystic carcinoma. However all the retrieved HTA reports and systematic reviews highlight the methodological flaws affecting the presently available literature and the need for well-designed randomised controlled trials providing reliable conclusions on efficacy and safety of HT in comparison to other currently available treatments.

Regarding ocular neoplasms, the increased precision attributed to HT could potentially provide enhanced safety for large but rare ocular tumours adjacent to vital structures but available evidence is insufficient to draw conclusions on the impact of HT on important clinical outcomes.

Literature concerning the efficacy of HT for the treatment of lung tumours (NSCLC) is limited as well, due to the lack of RCTs. The quality of available evidence is too low to state clear conclusions, given uncertainty regarding reported estimates. For non-operable stage I NSCLC, a meta-analysis (Grutters 2010) suggests that both proton therapy and carbon ion therapy lead to statistically significant higher rates of overall survival and disease free survival than conventional radiotherapy, but all outcomes are similar to those achieved with stereotactic radiotherapy.

For gastrointestinal cancers, the examined secondary literature presented a reduced number of clinical trials, only one RCT on pancreatic cancer studying a very limited number of patients and no RCT on other tumours. We cannot draw conclusions from such scanty evidence.

The analysis of literature on pelvic cancer showed 3 non comparative studies on the bladder and 4 on the uterus (1 non-RCT), all enrolling few patients and thus insufficient to sustain any conclusions.

Prostate cancer has been studied in some comparative studies, including 3 RCTs investigating overall and cancer-specific survival as outcomes. However, the efficacy and safety of HT over other treatments is still not demonstrated.

For skeleton and soft tissues tumours there is no evidence favouring HT given the lack of comparative studies. Furthermore, the observational studies are heterogeneous with regard to study populations and results.

All the retrieved documents so far highlight the impossibility of drawing any firm conclusion on this technology as the available literature is scarce and of low quality. In particular, the body of literature is mainly made of case-series and observational studies with small populations with often a short follow-up;

in particular, even if hadrontherapy is not a new radiotherapy technique, randomised controlled trials comparing HT to other treatments are still lacking.

The increase in precision of proton/carbon ion beam in treating tumour sites close to healthy, sensitive tissues is the theoretical key advantage of HT. This seems to be crucial for those tumours located in proximity of healthy and sensitive tissues such as nerves, glands, and brain. Treatment with HT may theoretically allow their preservation minimising both acute and late and/or very late adverse events. Nonetheless, the body of evidence failed to demonstrate a reduction in the incidence of acute adverse events of HT compared with other RT techniques.
There were only few primary studies highlighting a possible effect in favour of HT on uveal melanoma, NSCLC, and skull base chordoma, but because of their limited methodological quality and design, they do not provide adequate evidence for the investment in such an economically and ethically sensitive venture as HT. When compared to more recent RT techniques (e.g. Intensity Modulated RadioTherapy-IMRT or Stereotactic RadioSurgery-SRS), HT failed to show any improvement in clinical outcomes.
For other tumours, the scarce body of evidence did not suggest any superiority of HT compared with traditional RT. As with HT use in other malignancies it is not possible to draw conclusions, due to the limits in design and methods of primary studies.
For radiological protection the higher theoretical precision of HT would allow for better dose conformation and, in turn, for a reduction in the risk of developing a secondary tumours subsequent to radiotherapy. The development of secondary tumours usually requires several years after the primary radiation exposure: thus, to assess the effectiveness of HT in reducing the risk of secondary tumours, long-term follow-up (> 10 years) studies should be considered. None of the studies included in the review showed to be suitable for such assessment.
Finally, capital and operational costs of HT are significant; for this reason, extreme caution should be exercised in planning these facilities according to the small number of indications for HT at this time.

Conclusions and recommendations

Due to the scarcity of good quality clinical studies (RCTs, prospective cohort studies, comparative studies, long-term follow-up studies) it is impossible to draw firm conclusions about either the efficacy or the effectiveness of any form of HT for cancer treatment.

In some cases, clinical studies suggested an increase of safety and efficacy by using HT instead of traditional RT for some type of rare tumours (uveal melanoma, skull and neck chordomas, and NSCLC). Nonetheless, there is uncertainty regarding these estimates, due to methodological and design biases of the available studies. Therefore presently available evidence is not sufficient to support routine clinical use of HT.

Italian facilities which introduced this technology should give priority to experimental use of HT and should aim at producing, in the next years, high quality evidence, setting up comparative studies adequate in design, methods and power with international collaboration. Besides, long term follow-up (15-20 years) within clinical studies should be encouraged for the assessment of very late effects of HT compared to other forms of radiotherapy. It is doubtful whether HT should be used outside well designed research protocols with ethical supervision.

Should uncertainty be resolved in the future, given the burden of disease, the size of the target population affected by pathologies for which HT is suggested to be more promising and the high costs associated with

HT, a dedicated need assessment analysis should be carried out to estimate the number of centres needed nationwide.

Appendix 1. Epidemiological impact of tumours for which HT treatment has been suggested

Tumors	Incidence	Estimated new cases per year
Chondroma / Chondrosarcoma skull base [(a)]	Around 1 case per million	near 60
Salivary glands [(b)]	Around 0.6 cases per 100.000	near 250
Uveal melanoma[(a)]	Around 6 cases per million	near 360
Lung (NSCLC) [(c)]	Male 111.1 cases per 100.000 Female 27.2 cases per 100.000	Male 30,384 Female 6,780
Liver [(c)]	Male 26,8 cases per 100.000 Female 12,1 cases per 100.000	Male 8,267 Female 3,699
Esophagus [(c)]	Male 7,2 cases per 100.000 Female 2,1 cases per 100.000	Male 2,025 Female 548
Pancreas [(c)]	Male 17,2 cases per 100.000 Female 16,9 cases per 100.000	Male 4,388 Female 4,214
Prostate [(c)]	113,1 cases per 100.000	23,518
Bladder [(c)]	Male 70,7 cases per 100.000 Female 16,3 cases per 100.000	Male 15,987 Female 3,326
Cervical [(c)]	9,8 cases per 100.000	3,418
Endometrial [(c)]	23.6 cases per 100.000	7,756
Soft tissue [(c)]	Male 3,3 cases per 100.000 Female 2,7 cases per 100.000	Not estimated

(a) Data collected from Chordoma foundation and Atlas of Genetics and Cytogenetics in Oncology and Haematology

(b) Data collected from The NORDCAN project.

(c) Data collected from Italian Association of Cancer Registries (AIRTUM).

Appendix 2. Secondary literature search, included studies

Full bibliographic references

Amichetti M, Cianchetti M, Amelioi D, Enrici RM, Minniti G. Proton therapy in chordoma of the base of the skull: a systematic review. Neurosurgical review.2009;32:403-16 (1)

Bannuru RR, Dvorak T, Obadan N, Yu WW, Patel K, Chung M, Ip S. Comparative evaluation of radiation treatments for clinically localized prostate cancer: an updated systematic review. Ann Intern Med. 2011 Aug 2;155(3):171-8. Epub 2011 Jun 6. Review (2)

Bekkering GE, Rutjes AW, Vlassov VV, Aebersold DM, von Bremen K, Jüni P, Kleijnen J. The effectiveness and safety of proton radiation therapy for indications of the eye : a systematic review. Strahlenther Onkol. 2009 Apr;185(4):211-21. Epub 2009 Apr 16. Review (3)

Blanchard S, Dureuil B, Despeyroux S, Lefevre M, Muller F. Hadrontherapie par ions carbone - rapport préliminaire (Haute Autorité de Santé - HAS). February 2010 (4)

Flynn K, Brief Overview: Proton Therapy For Cancer. Veterans Health Administration Office Of Patient Care Services Technology Assessment Program (VATAP). April 2010 (5)

Grutters JP, Kessels AG, Pijls-Johannesma M, De Ruysscher D, Joore MA, Lambin P. Comparison of the effectiveness of radiotherapy with photons, protons and carbon-ions for non-small cell lung cancer: a meta-analysis. Radiother Oncol. 2010 Apr;95(1):32-40 (6)

Huybrechts M, Obyn X, Gailly J, Mambourg F, Vinck I, Ramaekers D. Health Technology Assessment (HTA). Brussel: Federaal Keniscentrum voor de Gezondheidszorg (KCE): 2007. KCE reports 67A (D/2007/10.273/50) (7)

Lee I. Proton beam therapy for the treatment of neoplasms involving (or adjacent to) cranial structures. (Australia and New Zealand Horizon Scanning Network - ANZHSN). May 2007 (8)

Lee I. Proton beam therapy for the treatment of uveal melanoma. (Australia and New Zealand Horizon Scanning Network - ANZHSN). May 2007 (9)

Lodge M, Pijls-Johannesma, M, Stirk L, Munro AJ, De Ruysscher D, Jefferson T. A systematic review of the clinical and cost-effectiveness of hadron therapy in cancer. Radiotherapy and Oncology.2007;l83(2):110-22 (10)

Ollendorf DA, Hayes J, McMahon P, et al. Brachytherapy & proton beam therapy for treatment of clinically-localized, low-risk prostate cancer. Boston, MA: Institute for Clinical and Economic Review, December 2008 (11)

Samson DJ, Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Proton Beam Therapy for Non-Small-Cell Lung Cancer. 2011 (12)

Samson DJ, Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Proton Beam Therapy for Prostate Cancer. 2011 (13)

Trikalinos TA, Terasawa T, Ip S, Raman G, Lau J. Particle Beam Radiation Therapies for Cancer. Technical Brief No. 1. (Prepared by Tufts Medical Center Evidence-based Practice Center under Contract No. HHSA-290-07-10055.) Rockville, MD: Agency for Healthcare Research and Quality. Revised November 2009 (14)

Wilt TJ, Shamliyan T, Taylor B, MacDonald R, Tacklind J, Rutks I, Koeneman K, Cho CS, Kane RL. Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008 Feb (15)

Appendix 3. Secondary literature search, excluded studies

1st Author/Agency	Year	Title	Language	Reasons for exclusion
NETTSC	2011	A Systematic Review of Positron Emission Tomography (PET) and Positron Emission Tomography/Computed Tomography (PET/CT) for the Diagnosis of Breast Cancer Recurrence (16)	English	Intervention
BlueCross BlueShield Association	2010	Proton beam therapy for prostate cancer (17)	English	Duplicates Samson DJ, 2011
Lance	2010	Proton therapy (18)	English	Not a SR
Mathis	2010	[Gamma Knife versus adapted linear accelerators: A comparison of two radiosurgical applications] (19)	German	Intervention
NETTSC	2010	A Systematic Review of Photodynamic Therapy in the Treatment of Pre-Cancerous Skin Conditions, Barrett's Oesophagus and Cancers of the Biliary Tract, Brain, Head and Neck, Lung, Oesophagus and Skin (20)	English	Intervention
Ross	2010	Interventions for treating brain arteriovenous malformations in adults (21)	English	Intervention
AETMIS	2009	Curative Treatment for Esophageal Cancer: Systematic Review of Neoadjuvant Therapy and Chemoradiotherapy Alone (22)	English	Intervention
Manchon	2009	Hadrontherapy in the treatment of cancer (23)	Spanish	Language
Viani	2009	Higher-than-conventional radiation doses in localized prostate cancer treatment: a meta-analysis of randomized, controlled trials (24)	English	Intervention
AHRQ	2008	Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer (25)	Spanish	Duplicates Wilt TJ, 2008
Konski	2007	Is proton beam therapy cost effective in the treatment of adenocarcinoma of the prostate? (26)	English	Not a SR
MaHTAS	2007	Imatinib Mesylate for Chronic Myeloid Leukemia & Gastrointestinal Stromal Tumourss (27)	English	Intervention
HAYES	2006	Proton beam therapy for prostate cancer (28)	English	Date of publication
HAYES	2004	Proton beam therapy for ocular tumours, hemangiomas, and macular degeneration (29)	English	Date of publication
Medical Technology Unit - Swiss Federal Office of Public Health	2003	Proton beam therapy for patients with ocular melanomas to deep seated tumours (30)	English	Date of publication
CEDIT	2002	Protontherapy (2 vols) (31)	English	Date of publication
Lundkvist	2002	Proton therapy of cancer: potential clinical advantages and cost-effectiveness (32)	English	Date of publication
SBU	2001	Stereotactic radiosurgery in treating arteriovenous malformations of the brain (33)	English	Date of publication

Appendix 4. Quality assessment (based on AMSTAR checklist criteria) of included HTA reports and SRs

Study	AMSTAR questions										
Item	1	2	3	4	5	6	7	8	9	10	11
Amichetti 2009	1	1	2	3	2	1	2	2	3	2	2
Bannuru 2011	1	1	1	2	2	2	1	2	2	2	1
Bekkering 2009	1	1	1	1	1	2	1	1	3	2	1
Blanchard 2010	1	2	1	1	2	1	2	1	1	2	2
Flynn 2010	1	2	2	1	1	1	2	3	4	2	1
Grutters 2010	1	1	1	1	1	1	2	2	1	2	1
Huybrechts 2007	1	2	1	1	2	1	3	1	2	2	1
Lee 2007a (cranial structures)	1	2	1	3	2	1	1	1	1	2	2
Lee 2007b (uveal)	1	2	1	1	1	1	1	1	3	2	1
Lodge 2007	1	1	1	1	2	1	1	1	3	2	2
Ollendorf 2008	1	3	1	2	2	2	1	2	1	1	2
Samson 2011a (NSCLC)	1	3	2	1	2	1	1	1	2	2	1
Samson 2011b (prostate)	1	2	2	2	2	1	1	1	2	2	2
Trikalinos 2009	1	1	1	1	1	1	1	1	2	1	1
Wilt 2008	1	3	1	2	2	1	1	1	2	2	1

Appendix 5. Primary literature search, excluded studies

1st Author, year	Title	Language	Excluded for
Nikoghosyan 2010	Randomised trial of proton vs. carbon ion radiation therapy in patients with chordoma of the skull base, clinical phase III study HIT-1-Study. (34)	English	Study protocol (proton vs. carcon ion therapy)
Nikoghosyan 2010	Randomised trial of proton vs. carbon ion radiation therapy in patients with low and intermediate grade chondrosarcoma of the skull base, clinical phase III study. (35)	English	Study protocol (proton vs. carcon ion therapy)
Wang 2009	Comparisons of dose-volume histograms for proton-beam versus 3-D conformal x-ray therapy in patients with stage I non-small cell lung cancer. (36)	English	Study design (not RCT)
Voelter 2009	Adjuvant intra-arterial hepatic fotemustine for high-risk uveal melanoma patients. (37)	English	Intervention
On-going trial (from clinicaltrial.gov)	Pilot Study of Lucentis Combined With Proton Beam Irradiation in Treating Wet Age-related Macular Degeneration (38)	No Results Available	
On-going trial (from clinicaltrial.gov)	Dose Escalation Study Using Respiratory Gated Proton Beam Radiotherapy for Hepatocellular Carcinoma (39)	No Results Available	
On-going trial (from clinicaltrial.gov)	Study of Respiratory Gated Proton Beam Radiotherapy for Inoperable Pancreas Carcinoma (40)	No Results Available	
On-going trial (from clinicaltrial.gov)	Proton Beam Therapy for Treatment of Hepatocellular Carcinoma (41)	No Results Available	
On-going trial (from clinicaltrial.gov)	Chemotherapy and Proton Radiation for the Treatment of Locally Advanced Lung Cancer (42)	No Results Available	

Appendix 6. Other references

Full bibliographic references

Akakura K. Heavy particle therapy for prostate cancer. Nippon Rinsho - Japanese Journal of Clinical Medicine. 2005;63(2):286-91. (43)

Benk VA, Adams JA, Shipley WU, . Late rectal bleeding following combined X-ray and proton high dose irradiation for patients with stages T3-T4 prostate carcinoma. International Journal of Radiation Oncology, Biology, Physics 1993;26(3):551-7. (44)

Brada M, Pijls-Johannesma M, de Ruysscher D. Current clinical evidence for proton therapy. Cancer Journal.2009;15(4):319-24. (45)

Brada M, Pijls-Johannesma M, De Ruysscher D. Proton therapy in clinical practice: current clinical evidence. J Clin Oncol. 2007;25(8):965-70. (46)

Bush DA, Hillebrand DJ, Slater JM, Slater JD. High-dose proton beam radiotherapy of hepatocellular carcinoma: preliminary results of a phase II trial. Gastroenterology 2004;127:S189–93 (47)

Castro JR, Phillips TL, Prados M, . Neon heavy charged particle radiotherapy of glioblastoma of the brain. International Journal of Radiation Oncology, Biology, Physics 1997;38(2):257-61. (48)

Char DH, Castro JR, Quivey JM, . Uveal melanoma radiation. 125I brachytherapy vs helium ion irradiation. Ophthalmology 1989;96(12):1708-15 (49)

Char DH, Quivey JM, Castro JR, . Helium ions vs iodine 125 brachytherapy in the management of uveal melanoma. A prospective, randomized, dynamically balanced trial. Ophthalmology 1993;100(10):1547-54 (50)

Char DH, Kroll S, Phillips TL, Quivey JM. Late radiation failures after iodine 125 brachytherapy for uveal melanoma compared with charged-particle (proton or helium ion) therapy. Ophthalmology. 2002;109(10):1850-4. (51)

Char DH, Kroll S, Quivey JM, Castro J. Long term visual outcome of radiated uveal melanomas in eyes eligible for randomisation to enucleation vs brachytherapy. British Journal of Ophthalmology 1996;80(2):117-24. (52)

Char DH, Bove R, Phillips TL. Laser and proton radiation to reduce uveal melanoma-associated exudative retinal detachments. American Journal of Ophthalmology 2003;136(1):180-2. (53)

Choi BO, Jang HS, Kang KM, . Fractionated stereotactic radiotherapy in patients with primary hepatocellular carcinoma. Jpn J Clin Oncol 2006;36:154–8. (54)

Ciulla TA, Danis RP, Klein SB, . Proton therapy for exudative age-related macular degeneration: a randomized, sham-controlled clinical trial. Am J Ophthalmol 2002;134:905–6. (55)

Desjardins L, Lumbroso-Le RL, Levy-Gabriel C, . Combined proton beam radiotherapy and transpupillary thermotherapy for large uveal melanomas: a randomized study of 151 patients [see comment]. Ophthalmic Research 2006;38(5):255-60 (56)

Desjardins L, Lumbroso L, Levy C, . [Treatment of uveal melanoma with iodine 125 plaques or proton beam therapy: indications and comparison of local recurrence rates] [French]. Journal Francais d Opthalmologie 2003;26(3):269-76. (57)

Fukumitsu N, Sugahara S, Nakayama H, Fukuda E, Tsboi K, Tokuuye K. A prospective study of hypofractionated proton beam therapy for patients with hepatocellular carcinoma. International Journal of Radiation Oncology, Biology & Physics.2009;74(3):831-6. (58)

Goitein M, Jermann M. The relative costs of proton and X-ray radiation therapy. Clinical Oncology 2003;15(1): S37-S50. (59)

Gragoudas ES, Lane AM, Regan S, . A randomized controlled trial of varying radiation doses in the treatment of choroidal melanoma. Archives of Ophthalmology 2000;118(6):773-8 (60)

Griffin TW, Pajak TF, Laramore GE, Duncan W, Richter MP, Hendrickson FR. Neutron vs photon irradiation of inoperable salivary gland tumors: results of an RTOG-MRC Cooperative Randomized Study. Int J Radiat Oncol Biol Phys. 1988; 15(5):1085-90 8 (61)

Harbour JW, Char DH, Kroll S, . Metastatic risk for distinct patterns of post-irradiation local recurrence of posterior uveal melanoma. Ophthalmology 1997; 104(11):1785-92; (62)

Harding SP, Sen J. Precision low-dose proton beam radiotherapy of subfoveal choroidal neovascularization in age-related macular degeneration (abstract). Orlando: American Academy of Ophthalmology, 2002: 281 (63)

Hata M, Tokuuye K, Sugahara S . Proton beam therapy for hepatocellular carcinoma with limited treatment options. Cancer 2006; 107:591–8. (64)

Hata M, Miyanaga N, Tokuuye K. Proton beam therapy for invasive bladder cancer: a prospective study of bladderpreserving therapy with combined radiotherapy and intraarterial chemotherapy. Int J Radiat Oncol Biol Phys 2006; 64:1371–9. (65)

Hirasawa N, Tsuji H, Ishikawa H, Koyama-Ito H, Kamada T, Mizoe JE . Risk factors for neovascular glaucoma after carbon ion radiotherapy of choroidal melanoma using dose-volume histogram analysis. Int J Radiat Oncol Biol Phys 2007; 67(2):538-43. (66)

Ishikawa H, Tsuji H, Kamada T, Yanagi T, Mizoe J-E, Kanai T, . Carbon ion radiation therapy for prostate cancer: Results of a prospective phase II study. Radiotherapy and Oncology. 2006; 81(1):57-64 (67)

Ishikawa H, Tsuji H, Kamada T. Risk factors of late rectal bleeding after carbon ion therapy for prostate cancer. Int J Radiat Oncol Biol Phys 2006; 66:1084–91. (68)

Kagei K, Tokuuye K, Okumura T. Long-term results of proton beam therapy for carcinoma of the uterine cervix. Int J Radiat Oncol Biol Phys 2003; 55:1265–71 (69)

Kato H, Tsujii H, Miyamoto T. Results of the first prospective study of carbon ion radiotherapy for hepatocellular carcinoma with liver cirrhosis. Int J Radiat Oncol Biol Phys 2004; 59:1468–76 (70)

Kato S, Ohno T, Tsujii H. Dose escalation study of carbon ion radiotherapy for locally advanced carcinoma of the uterine cervix. Int J Radiat Oncol Biol Phys 2006; 65:388–97 (71)

Kawashima M, Furuse J, Nishio T. Phase II study of radiotherapy employing proton beam for hepatocellular carcinoma. J Clin Oncol 2005; 23:1839–46. (72)

Koto M, Miyamoto T, Yamamoto N. Local control and recurrence of stage I non-small cell lung cancer after carbon ion radiotherapy. Radiother Oncol 2004; 71:147–56. (73)

Kuban DA, Tucker SL, Dong L, Starkschall G, Huang EH, Cheung MR. Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer. Int J Radiat Oncol Biol Phys. 2008; 70:67-74. (74)

Laramore GE, Krall JM, Griffin TW, Duncan W, Richter MP, Saroja KR. Neutron versus photon irradiation for unresectable salivary gland tumors: final report of an RTOG-MRC randomized clinical trial. Radiation Therapy Oncology Group. Medical Research Council. Int J Radiat Oncol Biol Phys. 1993;27(2):235-40 (75)

Linstadt D, Quivey JM, Castro JR. Comparison of helium-ion radiation therapy and split-course megavoltage irradiation for unresectable adenocarcinoma of the pancreas. Final report of a Northern California Oncology Group randomizedprospective clinical trial. Radiology 1988; 168:261–4 (76)

Lukka H, Hayter C, Julian JA, Warde P, Morris WJ, Gospodarowicz M. Randomized trial comparing two fractionation schedules for patients with localized prostate cancer. J Clin Oncol. 2005; 23:6132-8. (77)

Lundkvist J, Ekman M, Ericsson SR, Jonsson B, Glimelius B. Proton therapy of cancer: potential clinical advantages and cost-effectiveness. Acta Oncol 2005; 44:850–61 (78)

Miyamoto T, Yamamoto N, Nishimura H. Carbon ion radiotherapy for stage I non-small cell lung cancer. Radiother Oncol 2003; 66:127–40. (79)

Nakano T, Suzuki Y, Ohno T. Carbon beam therapy overcomes the radiation resistance of uterine cervical cancer originating from hypoxia. Clin Cancer Res 2006; 12: 2185–90 (80)

Nihei K, Ogino T, Ishikura S. Phase II feasibility study of high-dose radiotherapy for prostate cancer using proton boost therapy: first clinical trial of proton beam therapy for prostate cancer in Japan. Jpn J Clin Oncol 2005; 35(12):745-52 (81)

Nishimura H, Miyamoto T, Yamamoto N . Radiographic pulmonary and pleural changes after carbon ion irradiation. Int J Radiat Oncol Biol Phys 2003; 55:861–6. (82)

Norkus D, Miller A, Plieskiene A, Janulionis E, Valuckas KP. A randomized trial comparing hypofractionated and conventionally fractionated threedimensional conformal external-beam radiotherapy for localized prostate adenocarcinoma: a report on the first-year biochemical response. Medicina (Kaunas) 2009; 45:469-75. (83)

Olsen DR, Bruland OS, Frykholm G, Norderhaug IN. Proton therapy - a systematic review of clinical effectiveness. Radiother Oncol 2007; 83(2):123- 32. (84)

Peeters ST, Heemsbergen WD, Koper PC, van Putten WL, Slot A, Dielwart MF. Dose-response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy ofradiotherapy with 78 Gy. J Clin Oncol 2006; 24:1990-6. (85)

Pijls-Johannesma M, Grutters JPC, Verhaegen F, Lambin P, de Ruysscher D. Do we have enough evidence to implement particle therapy as standard treatment in lung cancer? A systematic literature review. The Oncologist 2010 15:93-103. (86)

Pollack A, Zagars GK, Starkschall G, Antolak JA, Lee JJ, Huang E, . Prostate cancer radiation dose response: results of the M. D. Anderson phase III randomized trial. Int J Radiat Oncol Biol Phys. 2002; 53:1097-105. (87)

Pollack A, Hanlon AL, Horwitz EM, Feigenberg SJ, Konski AA, Movsas B. Dosimetry and preliminary acute toxicity in the first 100 men treated for prostate cancer on a randomized hypofractionation dose escalation trial. Int J Radiat Oncol Biol Phys. 2006; 64:518-26. (88)

Rossi CJ, Jr, Slater JD, Yonemoto LT. Influence of patient age on biochemical freedom from disease in patients undergoing conformal protonradiotherapy of organ-confined prostate cancer. Urology 2004; 64(4):729-32. (89)

Santoni R, Liebsch N, Finkelstein DM. Temporal lobe (TL) damage following surgery and high-dose photon and proton irradiation in 96 patients affected by chordomas and chondrosarcomas of the base of the skull. International Journal of Radiation Oncology, Biology, Physics 1998; 41(1):59-68. (90)

Sathya JR, Davis IR, Julian JA, Guo Q, Daya D, Dayes IS. Randomized trial comparing iridium implant plus external-beam radiation therapy with external-beam radiation therapy alone in node-negative locally advanced cancer of the prostate. J Clin Oncol. 2005; 23:1192-9. (91)

Seddon JM, Gragoudas ES, Egan KM, . Relative survival rates after alternative therapies for uveal melanoma. Ophthalmology 1990; 97(6):769-77. (92)

Seddon JM, Gragoudas ES, Albert DM, . Comparison of survival rates for patients with uveal melanoma after treatment with proton beam irradiation or enucleation. American Journal of Ophthalmology 1985; 99(3):282-90. (93)

Shea BJ, Hamel C, Wells GA, Bouter LM, Kristjansson E, Grimshaw J, Henry DA, Boers M. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. J Clin Epidemiol. 2009 Oct;62(10):1013-20 (94)

Shipley WU, Verhey LJ, Munzenrider JE, . Advanced prostate cancer: the results of a randomized comparative trial of high dose irradiation boosting with conformal protons compared with conventional dose irradiation using photons alone. Int J Radiat Oncol Biol Phys 1995; 32:3–12. (95)

Shipley WU, Zietman AL, Kaufman DS, Coen JJ, Sandler HM. Selective bladder preservation by trimodality therapy for patients with muscularis propria-invasive bladder cancer and who are cystectomy candidates – the Massachusetts General Hospital and Radiation Therapy Oncology Group experiences. Semin Radiat Oncol 2005; 15:36–41 (96)

Slater JD, Rossi CJ, Jr., Yonemoto LT. Conformal proton therapy for early-stage prostate cancer. Urology 1999; 53(5):978-84. (97)

Slater JD, Rossi CJ, Jr., Yonemoto LT. Proton therapy for prostate cancer: the initial Loma Linda University experience. Int J Radiat Oncol Biol Phys 2004; 59(2):348-52 (98)

Sugahara S, Tokuuye K, Okumura T. Clinical results of proton beam therapy for cancer of the esophagus. Int J Radiat Oncol Biol Phys 2005; 61:76–84. (99)

Sugane T, Baba M, Imai R, Nakajima M, Yamamoto N, Miyamoto T. Carbon ion radiotherapy for elderly patients 80 years and older with stage I non-small cell lung cancer. Lung Cancer 2009; 64(1):45-50. (100)

Talcott JA, Rossi C, Shipley WU. Patient reported long-term outcomes after conventional and high-dose combined proton and photon radiation for early prostate cancer. JAMA 2010; 303 (11):1046-53. (101)

Tsuji H, Ishikawa H, Yanagi T, Hirasawa N, Kamada T, Mizoe JE. Carbon-ion radiotherapy for locally advanced or unfavorably located choroidal melanoma: a phase I/II dose-escalation study. Int J Radiat Oncol Biol Phys 2007; 67(3):857-62. (102)

Tsuji H, Yanagi T, Ishikawa H, Kamada T, Mizoe J-E, Kanai T. Hypofractionated radiotherapy with carbon ion beams for prostate cancer. Int J Radiat Oncol Biol Phys 2005; 63(4):1153-60 (103)

Tsujii H, Akaza H, Ohtani M. Preliminary results of bladder-preserving therapy with definitive radiotherapy and intraarterial infusion of chemotherapy. Strahlenther Onkol 1994; 170:531–7 (104)

Wallner K, Merrick G, True L, Sherertz T, Sutlief S, Cavanagh W. 20 Gy versus 44 Gy supplemental beam radiation with Pd-103 prostate brachytherapy: preliminary biochemical outcomes from a prospective randomized multicenter trial. Radiother Oncol 2005; 75:307-10. (105)

Wilson MW, Hungerford JL. Comparison of episcleral plaque and proton beam radiation therapy for the treatment of choroidal melanoma. Ophthalmology 1999; 106(8):1579-87. (106)

Yeoh EE, Holloway RH, Fraser RJ, Botten RJ, Di Matteo AC, Butters J. Hypofractionated versus conventionally fractionated radiation therapy for prostate carcinoma: updated results of a phase III randomized trial. Int J Radiat Oncol Biol Phys. 2006; 66:1072-83. (107)

Yonemoto LT, Slater JD, Rossi CJ, Jr. Combined proton and photon conformal radiation therapy for locally advanced carcinoma of the prostate: preliminary results of a phase I/II study. Int J Radiat Oncol Biol Phys 1997; 37(1):21-9. (108)

Zambarakji HJ, Lane AM, Ezra E, Gauthier D, Goitein M, Adams JA. Proton beam irradiation for neovascular age-related macular degeneration. Ophthalmology 2006; 113(11):2012-9 (109)

Zietman AL, DeSilvio ML, Slater JD, Rossi CJ Jr, Miller DW, Adams JA. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. JAMA 2005; 294:1233-9. (110)

Zietman AL, Bae K, Slater JD, Shipley WU, Efstathiou JA, Coen JJ. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from proton radiation oncology group/american college of radiology 95-09. J Clin Oncol 2010;28:1106-11. (111)

References

1. Amichetti M, Cianchetti M, Amelioi D, Enrici RM, Minniti G. Proton therapy in chordoma of the base of the skull: a systematic review. Neurosurgical review.2009;32:403-16

2. Bannuru RR, Dvorak T, Obadan N, Yu WW, Patel K, Chung M, Ip S. Comparative evaluation of radiation treatments for clinically localized prostate cancer: an updated systematic review. Ann Intern Med. 2011 Aug 2;155(3):171-8. Epub 2011 Jun 6. Review

3. Bekkering GE, Rutjes AW, Vlassov VV, Aebersold DM, von Bremen K, Jüni P, Kleijnen J. The effectiveness and safety of proton radiation therapy for indications of the eye : a systematic review. Strahlenther Onkol. 2009 Apr;185(4):211-21. Epub 2009 Apr 16. Review

4. Blanchard S, Dureuil B, Despeyroux S, Lefevre M, Muller F. Hadrontherapie par ions carbone - rapport préliminaire (Haute Autorité de Santé - HAS). February 2010

5. Flynn K, Brief Overview: Proton Therapy For Cancer. Veterans Health Administration Office Of Patient Care Services Technology Assessment Program (VATAP). April 2010

6. Grutters JP, Kessels AG, Pijls-Johannesma M, De Ruysscher D, Joore MA, Lambin P. Comparison of the effectiveness of radiotherapy with photons, protons and carbon-ions for non-small cell lung cancer: a meta-analysis. Radiother Oncol. 2010 Apr;95(1):32-40

7. Huybrechts M, Obyn X, Gailly J, Mambourg F, Vinck I, Ramaekers D. Health Technology Assessment (HTA). Brussel: Federaal Keniscentrum voor de Gezondheidszorg (KCE): 2007. KCE reports 67A (D/2007/10.273/50)

8. Lee I. Proton beam therapy for the treatment of neoplasms involving (or adjacent to) cranial structures. (Australia and New Zealand Horizon Scanning Network - ANZHSN). May 2007

9. Lee I. Proton beam therapy for the treatment of uveal melanoma. (Australia and New Zealand Horizon Scanning Network - ANZHSN). May 2007

10. Lodge M, Pijls-Johannesma, M, Stirk L, Munro AJ, De Ruysscher D, Jefferson T. A systematic review of the clinical and cost-effectiveness of hadron therapy in cancer. Radiotherapy and Oncology.2007;l83(2):110-22

11. Ollendorf DA, Hayes J, McMahon P, et al. Brachytherapy & proton beam therapy for treatment of clinically-localized, low-risk prostate cancer. Boston, MA: Institute for Clinical and Economic Review, December 2008

12. Samson DJ, Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Proton Beam Therapy for Non-Small-Cell Lung Cancer. 2011

13. Samson DJ, Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Proton Beam Therapy for Prostate Cancer. 2011

14. Trikalinos TA, Terasawa T, Ip S, Raman G, Lau J. Particle Beam Radiation Therapies for Cancer. Technical Brief No. 1. (Prepared by Tufts Medical Center Evidence-based Practice Center under Contract No. HHSA-290-07-10055.) Rockville, MD: Agency for Healthcare Research and Quality. Revised November 2009

15. Wilt TJ, Shamliyan T, Taylor B, MacDonald R, Tacklind J, Rutks I, Koeneman K, Cho CS, Kane RL. Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008 Feb

16. Pennant M, Takwoingi Y, Pennant L, Davenport C, Fry-Smith A, Eisinga A, Andronis L, Arvanitis T, Deeks J, Hyde C A systematic review of positron emission tomography (PET) and positron emission tomography/computed tomography (PET/CT) for the diagnosis of breast cancer recurrence. Health Technol Assess. 2010 Oct; 14(50):1-103

17. BlueCross BlueShield Association Proton beam therapy for prostate cancer Volume 25, No. 10 June 2011

18. Lance JM. La protontherapie. [Proton therapy] Montreal: Agence d'evaluation des technologies et des modes d'intervention en sante (AETMIS). Informative Note. 2010

19. Mathis S, Eisner, W Gamma Knife versus adapted linear accelerators: A comparison of two radiosurgical applications HTA-Bericht 2010, Nr. 046

20. Fayter D, Corbett M, Heirs M, Fox D, Eastwood A. A systematic review of photodynamic therapy in the treatment of pre-cancerous skin conditions, Barrett's oesophagus and cancers of the biliary tract, brain, head and neck, lung, oesophagus and skin Health Technology Assessment 2010; 14(37): 1-129

21. Ross J, Al-Shahi Salman R. Interventions for treating brain arteriovenous malformations in adults. Cochrane Database of Systematic Reviews 2010, Issue 7.

22. Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS). Traitement curatif du cancer de l'œsophage : revue systématique sur la thérapie néoadjuvante et la chimioradiothérapie seule. Rapport préparé par Faïza Boughrassa. ETMIS 2009;5(9): 1-125.

23. Manchón P, Espinàs JA, Borràs JM. La hadronterapia en el tratamiento del cáncer. Madrid: Plan de Calidad para el Sistema Nacional de Salud. Ministerio de Ciencia e Innovación. Agència d'Avaluació de Tecnologia i Recerca Mèdiques de Cataluña; 2009. Informes de Evaluación de Tecnologías Sanitarias, AATRM núm. 2007/20.

24. Viani GA, Stefano EJ, Afonso SL. Higher-than-conventional radiation doses in localized prostate cancer treatment: a meta-analysis of randomized, controlled trials. International Journal of Radiation Oncology, Biology, Physics 2009; 74(5): 1405-1418

25. Wilt T J, Shamliyan T, Taylor B, MacDonald R, Tacklind J, Rutks I, Koeneman K, Cho C S, Kane R L. Comparative effectiveness of therapies for clinically localized prostate cancer. Rockville, MD, USA: Agency for Healthcare Research and Quality. Comparative Effectiveness Review; 13. 2008

26. Konski A, Speier W, Hanlon A, Beck J R, Pollack A. Is proton beam therapy cost effective in the treatment of adenocarcinoma of the prostate? Journal of Clinical Oncology 2007; 25(24): 3603-3608

27. MaHTAS, Health Technology Assessment Section, Ministry of Health Malaysia Imatinib Mesylate for Chronic Myeloid Leukemia & Gastrointestinal Stromal Tumours Technology Review Report 001/07, 2007

28. HAYES, Inc.. Proton beam therapy for prostate cancer. Lansdale: HAYES, Inc.. Directory Publication. 2006

29. HAYES, Inc.. Proton beam therapy for ocular tumors, hemangiomas, and macular degeneration. Lansdale, PA: HAYES, Inc 2004: 26

30. Medical Technology Unit - Swiss Federal Office of Public Health. Proton beam therapy for patients with ocular melanomas to deep seated tumours. Medical Technology Unit - Swiss Federal Office of Public Health (MTU-SFOPH). 2003

31. Comite d'Evaluation et de Diffusion des Innovations Technologiques. Protontherapy (2 vols) Paris: Comite d´Evaluation et de Diffusion des Innovations Technologiques (CEDIT). 01.10. 2002

32. Lundkvist J, Ekman M, Ericsson S R, Jonsson B, Glimelius B. Proton therapy of cancer: potential clinical advantages and cost-effectiveness. Acta Oncologica 2005; 44(8): 850-861

33. Swedish Council on Technology Assessment in Health Care. Stereotactic radiosurgery in treating arteriovenous malformations of the brain - early assessment briefs (Alert) The Swedish Council on Health Technology Assessment (SBU). 2002

34. Nikoghosyan AV, Karapanagiotou-Schenkel I, Münter MW, Jensen AD, Combs SE, Debus J. Randomised trial of proton vs. carbon ion radiation therapy in patients with chordoma of the skull base, clinical phase III study HIT-1-Study. BMC Cancer. 2010 Nov 5;10:607

35. Nikoghosyan AV, Rauch G, Münter MW, Jensen AD, Combs SE, Kieser M, Debus J. Randomised trial of proton vs. carbon ion radiation therapy in patients with low and intermediate grade chondrosarcoma of the skull base, clinical phase III study. BMC Cancer. 2010 Nov 5;10:606.

36. Wang C, Nakayama H, Sugahara S, Sakae T, Tokuuye K. Comparisons of dose-volume histograms for proton-beam versus 3-D conformal x-ray therapy in patients with stage I non-small cell lung cancer. Strahlenther Onkol. 2009 Apr;185(4):231-4.

37. Voelter V, Schalenbourg A, Pampallona S, Peters S, Halkic N, Denys A, Goitein G, Zografos L, Leyvraz S. Adjuvant intra-arterial hepatic fotemustine for high-risk uveal melanoma patients. Melanoma Res. 2008 Jun;18(3):220-4

38. Susanna S Park Phase 1 Pilot Open Label Prospective Observational Study of Safety and Tolerability of Lucentis Combined With Proton Beam Irradiation in Treating Exudative Age-related Macular Degeneration NCT00517010

39. Tae Hyun Kim, National Cancer Center Korea Dose Escalation Study Using Respiratory Gated Proton Beam Radiotherapy for Hepatocellular Carcinoma NCT00662246

40. Tae Hyun Kim, National Cancer Center Korea Study of Respiratory Gated Proton Beam Radiotherapy for Inoperable Pancreas Carcinoma NCCCTS-07-226

41. David A. Bush, Loma Linda University Department of Radiation Medicine Phase I/II Study of Proton Beam Therapy for Treatment of Hepatocellular Carcinoma NCT00614913

42. David A. Bush, Loma Linda University Chemotherapy and Proton Radiation for the Treatment of Locally Advanced Lung Cancer NCT00614484

43. Akakura K. Heavy particle therapy for prostate cancer. Nippon Rinsho - Japanese Journal of Clinical Medicine. 2005;63(2):286-91.

44. Benk VA, Adams JA, Shipley WU, . Late rectal bleeding following combined X-ray and proton high dose irradiation for patients with stages T3-T4 prostate carcinoma. International Journal of Radiation Oncology, Biology, Physics 1993;26(3):551-7.

45. Brada M, Pijls-Johannesma M, de Ruysscher D. Current clinical evidence for proton therapy. Cancer Journal.2009;15(4):319-24.

46. Brada M, Pijls-Johannesma M, De Ruysscher D. Proton therapy in clinical practice: current clinical evidence. J Clin Oncol. 2007;25(8):965-70.

47. Bush DA, Hillebrand DJ, Slater JM, Slater JD. High-dose proton beam radiotherapy of hepatocellular carcinoma: preliminary results of a phase II trial. Gastroenterology 2004;127:S189–93

48. Castro JR, Phillips TL, Prados M, . Neon heavy charged particle radiotherapy of glioblastoma of the brain. International Journal of Radiation Oncology, Biology, Physics 1997;38(2):257-61.

49. Char DH, Castro JR, Quivey JM, . Uveal melanoma radiation. 125I brachytherapy vs helium ion irradiation. Ophthalmology 1989;96(12):1708-15

50. Char DH, Quivey JM, Castro JR, . Helium ions vs iodine 125 brachytherapy in the management of uveal melanoma. A prospective, randomized, dynamically balanced trial. Ophthalmology 1993;100(10):1547-54

51. Char DH, Kroll S, Phillips TL, Quivey JM. Late radiation failures after iodine 125 brachytherapy for uveal melanoma compared with charged-particle (proton or helium ion) therapy. Ophthalmology. 2002;109(10):1850-4.

52. Char DH, Kroll S, Quivey JM, Castro J. Long term visual outcome of radiated uveal melanomas in eyes eligible for randomisation to enucleation vs brachytherapy. British Journal of Ophthalmology 1996;80(2):117-24.

53. Char DH, Bove R, Phillips TL. Laser and proton radiation to reduce uveal melanoma-associated exudative retinal detachments. American Journal of Ophthalmology 2003;136(1):180-2.

54. Choi BO, Jang HS, Kang KM, . Fractionated stereotactic radiotherapy in patients with primary hepatocellular carcinoma. Jpn J Clin Oncol 2006;36:154–8.

55. Ciulla TA, Danis RP, Klein SB, . Proton therapy for exudative age-related macular degeneration: a randomized, sham-controlled clinical trial. Am J Ophthalmol 2002;134:905–6.

56. Desjardins L, Lumbroso-Le RL, Levy-Gabriel C, . Combined proton beam radiotherapy and transpupillary thermotherapy for large uveal melanomas: a randomized study of 151 patients [see comment]. Ophthalmic Research 2006;38(5):255-60

57. Desjardins L, Lumbroso L, Levy C, . [Treatment of uveal melanoma with iodine 125 plaques or proton beam therapy: indications and comparison of local recurrence rates] [French]. Journal Francais d Opthalmologie 2003;26(3):269-76.

58. Fukumitsu N, Sugahara S, Nakayama H, Fukuda E, Tsboi K, Tokuuye K. A prospective study of hypofractionated proton beam therapy for patients with hepatocellular carcinoma. International Journal of Radiation Oncology, Biology & Physics.2009;74(3):831-6.

59. Goitein M, Jermann M. The relative costs of proton and X-ray radiation therapy. Clinical Oncology 2003;15(1): S37-S50.

60. Gragoudas ES, Lane AM, Regan S, . A randomized controlled trial of varying radiation doses in the treatment of choroidal melanoma. Archives of Ophthalmology 2000;118(6):773-8

61. Griffin TW, Pajak TF, Laramore GE, Duncan W, Richter MP, Hendrickson FR. Neutron vs photon irradiation of inoperable salivary gland tumors: results of an RTOG-MRC Cooperative Randomized Study. Int J Radiat Oncol Biol Phys. 1988; 15(5):1085-90

62. Harbour JW, Char DH, Kroll S, . Metastatic risk for distinct patterns of post-irradiation local recurrence of posterior uveal melanoma. Ophthalmology 1997; 104(11):1785-92;

63. Harding SP, Sen J. Precision low-dose proton beam radiotherapy of subfoveal choroidal neovascularization in age-related macular degeneration (abstract). Orlando: American Academy of Ophthalmology, 2002: 281abstract

64. Hata M, Tokuuye K, Sugahara S . Proton beam therapy for hepatocellular carcinoma with limited treatment options. Cancer 2006; 107:591–8.

65. Hata M, Miyanaga N, Tokuuye K. Proton beam therapy for invasive bladder cancer: a prospective study of bladderpreserving therapy with combined radiotherapy and intraarterial chemotherapy. Int J Radiat Oncol Biol Phys 2006; 64:1371–9.

66. Hirasawa N, Tsuji H, Ishikawa H, Koyama-Ito H, Kamada T, Mizoe JE . Risk factors for neovascular glaucoma after carbon ion radiotherapy of choroidal melanoma using dose-volume histogram analysis. Int J Radiat Oncol Biol Phys 2007; 67(2):538-43.

67. Ishikawa H, Tsuji H, Kamada T, Yanagi T, Mizoe J-E, Kanai T, . Carbon ion radiation therapy for prostate cancer: Results of a prospective phase II study. Radiotherapy and Oncology. 2006; 81(1):57-64

68. Ishikawa H, Tsuji H, Kamada T. Risk factors of late rectal bleeding after carbon ion therapy for prostate cancer. Int J Radiat Oncol Biol Phys 2006; 66:1084–91.

69. Kagei K, Tokuuye K, Okumura T. Long-term results of proton beam therapy for carcinoma of the uterine cervix. Int J Radiat Oncol Biol Phys 2003; 55:1265–71

70. Kato H, Tsujii H, Miyamoto T. Results of the first prospective study of carbon ion radiotherapy for hepatocellular carcinoma with liver cirrhosis. Int J Radiat Oncol Biol Phys 2004; 59:1468–76

71. Kato S, Ohno T, Tsujii H. Dose escalation study of carbon ion radiotherapy for locally advanced carcinoma of the uterine cervix. Int J Radiat Oncol Biol Phys 2006; 65:388–97

72. Kawashima M, Furuse J, Nishio T. Phase II study of radiotherapy employing proton beam for hepatocellular carcinoma. J Clin Oncol 2005; 23:1839–46.

73. Koto M, Miyamoto T, Yamamoto N. Local control and recurrence of stage I non-small cell lung cancer after carbon ion radiotherapy. Radiother Oncol 2004; 71:147–56.

74. Kuban DA, Tucker SL, Dong L, Starkschall G, Huang EH, Cheung MR. Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer. Int J Radiat Oncol Biol Phys. 2008; 70:67-74. [PMID:17765406]

75. Laramore GE, Krall JM, Griffin TW, Duncan W, Richter MP, Saroja KR. Neutron versus photon irradiation for unresectable salivary gland tumors: final report of an RTOG-MRC randomized clinical trial. Radiation Therapy Oncology Group. Medical Research Council. Int J Radiat Oncol Biol Phys. 1993;27(2):235-40

76. Linstadt D, Quivey JM, Castro JR. Comparison of helium-ion radiation therapy and split-course megavoltage irradiation for unresectable adenocarcinoma of the pancreas. Final report of a Northern California Oncology Group randomizedprospective clinical trial. Radiology 1988; 168:261–4

77. Lukka H, Hayter C, Julian JA, Warde P, Morris WJ, Gospodarowicz M. Randomized trial comparing two fractionation schedules for patients with localized prostate cancer. J Clin Oncol. 2005; 23:6132-8. [PMID: 16135479]

78. Lundkvist J, Ekman M, Ericsson SR, Jonsson B, Glimelius B. Proton therapy of cancer: potential clinical advantages and cost-effectiveness. Acta Oncol 2005; 44:850–61

79. Miyamoto T, Yamamoto N, Nishimura H. Carbon ion radiotherapy for stage I non-small cell lung cancer. Radiother Oncol 2003; 66:127–40.

80. Nakano T, Suzuki Y, Ohno T. Carbon beam therapy overcomes the radiation resistance of uterine cervical cancer originating from hypoxia. Clin Cancer Res 2006; 12: 2185–90

81. Nihei K, Ogino T, Ishikura S. Phase II feasibility study of high-dose radiotherapy for prostate cancer using proton boost therapy: first clinical trial of proton beam therapy for prostate cancer in Japan. Jpn J Clin Oncol 2005; 35(12):745-52

82. Nishimura H, Miyamoto T, Yamamoto N . Radiographic pulmonary and pleural changes after carbon ion irradiation. Int J Radiat Oncol Biol Phys 2003; 55:861–6.

83. Norkus D, Miller A, Plieskiene A, Janulionis E, Valuckas KP. A randomized trial comparing hypofractionated and conventionally fractionated threedimensional conformal external-beam radiotherapy for localized prostate adenocarcinoma: a report on the first-year biochemical response. Medicina (Kaunas) 2009; 45:469-75. [PMID: 19605967]

84. Olsen DR, Bruland OS, Frykholm G, Norderhaug IN. Proton therapy - a systematic review of clinical effectiveness. Radiother Oncol 2007; 83(2):123- 32.

85. Peeters ST, Heemsbergen WD, Koper PC, van Putten WL, Slot A, Dielwart MF. Dose-response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy ofradiotherapy with 78 Gy. J Clin Oncol 2006; 24:1990-6. [PMID: 16648499]

86. Pijls-Johannesma M, Grutters JPC, Verhaegen F, Lambin P, de Ruysscher D. Do we have enough evidence to implement particle therapy as standard treatment in lung cancer? A systematic literature review. The Oncologist 2010 15:93-103.

87. Pollack A, Zagars GK, Starkschall G, Antolak JA, Lee JJ, Huang E, . Prostate cancer radiation dose response: results of the M. D. Anderson phase III randomized trial. Int J Radiat Oncol Biol Phys. 2002; 53:1097-105. [PMID:12128107]

88. Pollack A, Hanlon AL, Horwitz EM, Feigenberg SJ, Konski AA, Movsas B. Dosimetry and preliminary acute toxicity in the first 100 men treated for prostate cancer on a randomized hypofractionation dose escalation trial. Int J Radiat Oncol Biol Phys. 2006; 64:518-26. [PMID: 16242256]

89. Rossi CJ, Jr, Slater JD, Yonemoto LT. Influence of patient age on biochemical freedom from disease in patients undergoing conformal protonradiotherapy of organ-confined prostate cancer. Urology 2004; 64(4):729-32.

90. Santoni R, Liebsch N, Finkelstein DM. Temporal lobe (TL) damage following surgery and high-dose photon and proton irradiation in 96 patients affected by chordomas and chondrosarcomas of the base of the skull. International Journal of Radiation Oncology, Biology, Physics 1998; 41(1):59-68.

91. Sathya JR, Davis IR, Julian JA, Guo Q, Daya D, Dayes IS. Randomized trial comparing iridium implant plus external-beam radiation therapy with external-beam radiation therapy alone in node-negative locally advanced cancer of the prostate. J Clin Oncol. 2005; 23:1192-9. [PMID: 15718316]

92. Seddon JM, Gragoudas ES, Egan KM, . Relative survival rates after alternative therapies for uveal melanoma. Ophthalmology 1990; 97(6):769-77.

93. Seddon JM, Gragoudas ES, Albert DM, . Comparison of survival rates for patients with uveal melanoma after treatment with proton beam irradiation or enucleation. American Journal of Ophthalmology 1985; 99(3):282-90.

94. Shea BJ, Hamel C, Wells GA, Bouter LM, Kristjansson E, Grimshaw J, Henry DA, Boers M. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. J Clin Epidemiol. 2009 Oct;62(10):1013-20

95. Shipley WU, Verhey LJ, Munzenrider JE, . Advanced prostate cancer: the results of a randomized comparative trial of high dose irradiation boosting with conformal protons compared with conventional dose irradiation using photons alone. Int J Radiat Oncol Biol Phys 1995; 32:3–12.

96. Shipley WU, Zietman AL, Kaufman DS, Coen JJ, Sandler HM. Selective bladder preservation by trimodality therapy for patients with muscularis propria-invasive bladder cancer and who are cystectomy candidates – the Massachusetts General Hospital and Radiation Therapy Oncology Group experiences. Semin Radiat Oncol 2005; 15:36–41

97. Slater JD, Rossi CJ, Jr., Yonemoto LT. Conformal proton therapy for early-stage prostate cancer. Urology 1999; 53(5):978-84.

98. Slater JD, Rossi CJ, Jr., Yonemoto LT. Proton therapy for prostate cancer: the initial Loma Linda University experience. Int J Radiat Oncol Biol Phys 2004; 59(2):348-52

99. Sugahara S, Tokuuye K, Okumura T. Clinical results of proton beam therapy for cancer of the esophagus. Int J Radiat Oncol Biol Phys 2005; 61:76–84.

100. Sugane T, Baba M, Imai R, Nakajima M, Yamamoto N, Miyamoto T. Carbon ion radiotherapy for elderly patients 80 years and older with stage I non-small cell lung cancer. Lung Cancer 2009; 64(1):45-50.

101. Talcott JA, Rossi C, Shipley WU. Patient reported long-term outcomes after conventional and high-dose combined proton and photon radiation for early prostate cancer. JAMA 2010; 303 (11):1046-53.

102. Tsuji H, Ishikawa H, Yanagi T, Hirasawa N, Kamada T, Mizoe JE. Carbon-ion radiotherapy for locally advanced or unfavorably located choroidal melanoma: a phase I/II dose-escalation study. Int J Radiat Oncol Biol Phys 2007 ;67(3):857-62.

103. Tsuji H, Yanagi T, Ishikawa H, Kamada T, Mizoe J-E, Kanai T. Hypofractionated radiotherapy with carbon ion beams for prostate cancer. Int J Radiat Oncol Biol Phys 2005; 63(4):1153-60

104. Tsujii H, Akaza H, Ohtani M. Preliminary results of bladder-preserving therapy with definitive radiotherapy and intraarterial infusion of chemotherapy. Strahlenther Onkol 1994; 170:531–7

105. Wallner K, Merrick G, True L, Sherertz T, Sutlief S, Cavanagh W. 20 Gy versus 44 Gy supplemental beam radiation with Pd-103 prostate brachytherapy: preliminary biochemical outcomes from a prospective randomized multicenter trial. Radiother Oncol 2005; 75:307-10. [PMID: 16086912]

106. Wilson MW, Hungerford JL. Comparison of episcleral plaque and proton beam radiation therapy for the treatment of choroidal melanoma. Ophthalmology 1999; 106(8):1579-87.

107. Yeoh EE, Holloway RH, Fraser RJ, Botten RJ, Di Matteo AC, Butters J. Hypofractionated versus conventionally fractionated radiation therapy for prostate carcinoma: updated results of a phase III randomized trial. Int J Radiat Oncol Biol Phys. 2006; 66:1072-83. [PMID: 16965866]

108. Yonemoto LT, Slater JD, Rossi CJ, Jr. Combined proton and photon conformal radiation therapy for locally advanced carcinoma of the prostate: preliminary results of a phase I/II study. Int J Radiat Oncol Biol Phys 1997; 37(1):21-9.

109. Zambarakji HJ, Lane AM, Ezra E, Gauthier D, Goitein M, Adams JA. Proton beam irradiation for neovascular age-related macular degeneration. Ophthalmology 2006; 113(11):2012-9

110. Zietman AL, DeSilvio ML, Slater JD, Rossi CJ Jr, Miller DW, Adams JA. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. JAMA 2005; 294:1233-9. [PMID: 16160131]

111. Zietman AL, Bae K, Slater JD, Shipley WU, Efstathiou JA, Coen JJ. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from proton radiation oncology group/american college of radiology 95-09. J Clin Oncol 2010;28:1106-11. [PMID: 20124169]

Agenas - Agenzia nazionale per i servizi sanitari regionali

Sezione A.G.P. - Centro Stampa

Via Puglie 23, 00187 – Roma .
Tel. 06.427491 – fax. 06.42749488
www.agenas.it e-mail info@agenas.it