Effective Health Care
Technical Brief

Number XX (Provided by AHRQ)

Particle Beam Radiation Therapies for Cancer

Draft for public comment

DO NOT CITE OR CIRCULATE THIS DRAFT

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. #290-02-0022

Prepared by:
New England Medical Center Evidence-based Practice Center

Investigators
Thomas A. Trikalinos, MD, PhD
Teruhiko Terasawa, MD
Stanley Ip, MD
Gowri Raman, MD
Joseph Lau, MD

Disclaimer

This draft technical brief is distributed solely for the purpose of pre-release peer review. It has not been otherwise disseminated by AHRQ. It does not represent, and should not be construed to represent, an AHRQ determination or policy.

Table of contents

Disclaimer ……..
Table of contents v
Table of contents for figures vii
Table of contents for tables vii
Table of appendices vii
Executive summary ..... ES - 1
Background ..... ES - 1
Key questions of the Technical Brief ..... ES - 1
Answers to the key questions ..... ES - 3
Remaining issues & future research ..... ES - 7
Introduction 1
Statement of Work 3
Key questions 3
Methods 4
Terminology, definitions and conventions 4
(Charged) particle beam radiotherapy 4
Cancer 4
(Absorbed) radiation dose 4
Relative biological effectiveness 4
Biologically effective dose 4
End-of-page footnotes vs references 4
Gray literature searches 5
Published literature searches 5
Systematic literature scan 5
Study eligibility 5
Data abstraction 5
Synthesis of items of interest 7
Software 7
Results 8
Key question 1 8
1.a. What are the different particle beam radiation therapies that have been proposed to be used on cancer? 8
1.b. What are the theoretical advantages and disadvantages of these therapies compared to other radiation therapies that are currently used for cancer treatment? . 8
Description and pros and cons of radiotherapeutic alternatives to particle beam therapy 9
1.c. What are the potential safety issues and harms of the use of particle beam radiation therapy? 10
Key question 2 11
2.a What instrumentation is needed for particle beam radiation and what is the FDA status of this instrumentation? 11
Instrumentation 11
Treatment planning software/systems 12

FDA status of proton therapy equipment 13
Accreditation and training 13
2.b. What is an estimate of the number of hospitals that currently have the instrumentation or are planning to build instrumentation for these therapies? 13
2.c. What instrumentation technologies are in development? 15
Proton beam therapy using conventional accelerators (cyclotron) 15
Proton beam therapy using non-conventional accelerators (dielectric wall accelerator) 15
Key question 3 16
Literature selection 16
3.a. Types of cancer and patient eligibility criteria 17
Types of cancer studied 17
Specific patient inclusion and exclusion criteria 19
Mean or median ages 19
Periods of patient enrollment 19
3.b. Type of radiation, instrumentation and algorithms used 20
Type of charged particle radiation used 20
Details on instrumentation and treatment planning algorithms 21
3.c. Study design and size 21
3.d. Comparators 25
RCTs 25
Non randomized comparative studies 26
3.e. Length of followup 27
3.f. Concurrent or prior treatments 27
Prior interventions 27
Concurrent interventions 28
3.g. Outcomes measured 28
3.h. Adverse events, harms and safety issues reported 28
Discussion 31
References 35

Table of contents for figures

Figure 1. Depth-dose distributions for a spread-out Bragg peak of a particle beam for a single entry port 2
Figure 2. Schematic of a proton beam radiotherapy facility 11
Figure 3. Flow of the literature 16
Figure 4. All identified studies per center and cancer type 18
Figure 5. Enrollment periods for studies per cancer 20
Figure 6. Sample sizes of studies per cancer type 22
Figure 7. Non-comparative studies per center and cancer type. 23
Figure 8. Randomized and non-randomized comparative studies per center and cancer type. 24
Figure 9. Followup duration per cancer type 27

Table of contents for tables

Executive Summary Table 1. Answers to key question 1 ..... ES - 3
Executive Summary Table 2. Answers to the key question 2 ..... ES - 4
Executive Summary Table 3. Answers key question 3 ..... ES - 5
Table 1. List of treatment planning software/systems for particle beam therapy up to 2002 12
Table 2. Currently operating particle beam facilities in the USA 14
Table 3. Large particle beam facilities that are being built or planned in the USA 14
Table 4. Distribution of mean or median ages per cancer category excluding 7 studies on pediatric or adolescent populations 19
Table 5. Number of papers per cancer type and study design 22
Table 6. Comparators assessed in the randomized controlled trials 25
Table 7. Comparators assessed in the nonrandomized comparative studies 26

Table of appendices

Appendix A. Selected Internet links (radiotherapy organizations, companies, USA centers)
Appendix B. Ovid Medline search strategy
Appendix C. Table of eligible studies
Appendix D. Table of excluded studies
Appendix E. Table of screened case series and case reports
Appendix F. Centers that perform particle beam treatment (worldwide)
Appendix G. Summary Table

Executive summary

Background

Photon beam radiotherapy

Conventional cancer radiotherapy uses ionizing photon (X-ray) beams for the local or regional treatment of disease. Ionizing radiation damages the DNA of tumor and healthy cells alike, triggering complex biochemical reactions and eventually resulting in cellular death. Cellular damage increases with (absorbed) radiation dose – the amount of energy that ionizing radiation deposits to a volume of tissue.

Appropriate targeting of the beam is particularly important for tumors that are anatomically adjacent to critical body structures. To date, advances in imaging and radiation treatment planning technologies allow much more precise targeting of radiation therapy, compared to earlier years. The most advanced method for the delivery of high radiation doses with photon beams is intensity modulated radiation therapy (IMRT). IMRT delivers conformal radiation to the target tumor, by "crossing" multiple properly shaped beams of various intensities through paths that spare radiosensitive and critical adjacent tissues.

Charged particle beam radiotherapy

An alternative treatment modality is charged particle radiotherapy, which uses beams of protons or other charged particles such as helium, carbon or other ions instead of photons. Charged particles have different depth-dose distributions compared to photons. They deposit most of their energy in the last final millimeters of their trajectory (when their speed slows). This results in a sharp localized peak of dose, known as the Bragg peak. The initial energy (speed) of the charged particles determines *how deep* in the body the Bragg peak will form. The intensity of the beam determines *the dose* that will be deposited to the tissues. By adjusting the energy of the charged particles and by adjusting the intensity of the beam one can precisely deliver prespecified doses anywhere in the patient's body. To irradiate a whole tumor area, multiple Bragg peaks of different energies and intensities are combined to form a spread-out Bragg peak.

Key questions for the Technical Brief

Key question 1:

1.a. What are the different particle beam radiation therapies that have been proposed to be used on cancer?

1.b. What are the theoretical advantages and disadvantages of these therapies compared to other radiation therapies that are currently used for cancer treatment?

1.c. What are the potential safety issues and harms of the use of particle beam radiation therapy?

Key question 2:

2.a. What instrumentation is needed for particle beam radiation and what is the Food and Drug Administration (FDA) status of this instrumentation?

2.b. What is an estimate of the number of hospitals that currently have the instrumentation or are planning to build instrumentation for these therapies in the USA?
2.c. What instrumentation technologies are in development?

Key question 3:
Perform a systematic literature scan on studies on the use and safety of these therapies in cancer, with a synthesis of the following variables:

3.a. Type of cancer and patient eligibility criteria
3.b. Type of radiation, instrumentation and algorithms used
3.c. Study design and size
3.d. Comparator used in comparative studies.
3.e. Length of followup
3.f. Concurrent or prior treatments
3.g. Outcomes measured
3.h. Adverse events, harms and safety issues reported

Answers to the key questions

The following table summarizes answers to key question 1.

Executive Summary Table 1. Answers to key question 1

Key question	*Answer*
1.a. What are the different particle beam radiation therapies that have been proposed to be used on cancer?	Proton radiotherapy has been used in the vast majority (~87%) of patients who have received particle beam therapy to date. Other particles that have been used include carbon ions (~7%), helium ions (~3%) and other ions (~3%).
1.b. What are the theoretical advantages and disadvantages of these therapies compared to other radiation therapies that are currently used for cancer treatment?	The postulated advantages stem from the ability to precisely control the location and shape (in lateral dimensions and depth) of the spread-out Bragg peak, depositing little dose to adjacent critical areas. It is theorized that this results in fewer radiation-induced adverse events. Conversely, it is theorized that higher and more effective radiation doses can be deposited to the target area, while keeping the adverse events similar to those experienced with photon radiotherapy. The reported disadvantages are the high cost and the limited access to the technology.
1.c. What are the potential safety issues and harms of the use of particle beam radiation therapy?	None of the reported studies ascribed specific harms to the nature of the radiation (particles rather than photons). The following may be pertinent to light ions such as carbon ions and less so to protons: The early and late sensitivity of different tissues to light ion radiation may be different than what is already known for photons; therefore more data may need to be gathered to better appreciate the associations of dose and tissue-specific harms.

The following table summarizes answers to key question 2.

Executive Summary Table 2. Answers to the key question 2

Key question	***Answer***
2.a. What instrumentation is needed for particle beam radiation and what is the FDA status of this instrumentation?	Particle beam therapy requires large facilities that include the following components: Charged particle source; accelerator (cyclotron, synchrotron or cyclosynchrotron); system of vacuum tubes and shaping and focusing magnets to transfer the beam to the treatment room(s); specialized equipment (wedges) to adjust beam energies; beam delivery nozzles that shape the beam to match the dimensions of the target area; rotational gantries to deliver the beam to the patient with the desired direction; and patient positioning systems. The instrumentation that is used in US-based hospitals is FDA approved.
2.b. What is an estimate of the number of hospitals that currently have the instrumentation or are planning to build instrumentation for these therapies in the USA?	Six centers in the USA are currently active. Two additional centers are constructing large facilities for particle beam therapy (expected to be operational by 2009 or 2010), and one center has planned and will start constructing large facilities (expected to be operational in 2010). Several other hospitals consider developing smaller scale (single room) particle beam treatment facilities based on upcoming technologies (also see answer to question 2.b below).
2.c. What instrumentation technologies are in development?	A company has developed a proton beam treatment system that will treat one patient at a time and can fit in a single room, using a small cyclotron as an accelerator. The technology is not yet FDA approved. The first hospital to use it is expected to start treating patients in late 2008. Other companies have announced plans to develop similar single-room proton beam instrumentation that will be using a different kind of accelerator (dielectric wall accelerator). This technology is not yet FDA approved.

The following table summarizes answers to key question 3.

Executive Summary Table 3. Answers key question 3

Key question	*Answer*
3.a. Type of cancer and patient eligibility criteria	The following cancers have been treated with particle beam radiotherapy in the published literature: uveal melanomas, head and neck cancers (including intracranial tumors and tumors of the skull base and cervical spine), spinal tumors, gastrointestinal tumors (esophagus, pancreas, liver and bile ducts), lung, prostate, bladder, uterine and breast cancer, and bone and soft tissue malignancies. Patient populations within and across cancer categories were very heterogeneous. Identified studies included very different populations ranging from highly selected cases to all patients treated in a particle beam therapy center.
3.b. Type of radiation, instrumentation and algorithms used	Particle beam radiotherapy with protons was most commonly used in the examined literature. Information on instrumentation and treatment planning methodologies (algorithms) was typically not reported in detail.
3.c. Study design and size	The vast majority of studies were single arm, noncomparative, and with small sample sizes. A handful of reports on randomized (n=10) and nonrandomized comparative (n=13) studies were identified (see also answer to question 3.d below).
3.d. Comparator used in comparative studies	The identified comparative studies compared lower vs higher doses of particle beam therapy (4 and 1 reports on randomized trials and nonrandomized studies, respectively); particle beam therapy alone vs other treatment (3 and 8 reports on randomized and nonrandomized studies, respectively); or incorporation of particle beam therapy to a treatment strategy vs not (4 and 4 reports on randomized and nonrandomized studies, respectively). In the latter case, particle beam therapy was an add-on to surgery or was used as a localized radiotherapy boost on top of photon radiotherapy of a broader anatomical region.
3.d. Length of followup	Almost all studies had mean or median followup duration longer that 12 months, and several reported mean or median followup longer than 5 years. However, it is not always clear how many people were lost to followup and therefore excluded from the analyses.

Key question	***Answer***
3.e. Concurrent or prior treatments	Additional treatments varied with the type of malignancy from none to a combination of surgery and chemoradiotherapy. In most studies it was difficult to distinguish prior treatments that have failed from treatments that are part of a combined intervention approach.
3.f. Outcomes measured	Survival (overall and cause-specific) and outcomes related to local and distal disease control were reported by the majority of studies. However, definitions were quite variable. Depending on the type of cancer, various additional endpoints were assessed (e.g., vision loss or visual acuity for ocular cancers, bladder retention for bladder cancer).
3.g. Adverse events, harms and safety issues reported	Generally, the harms/complications observed were sustained in anatomic areas that were unavoidably exposed to the particle beam in the course of treatment. Serious harms that can appear in the treatment of cancer with particle beam therapy (alone or with other treatments) can be debilitating, irreversible, and life threatening. However, it is often impossible to ascribe specific harms to particle beam therapy rather than chemotherapy or other co-interventions. In screening through case reports and case series of less than 10 people, we did not identify mention of an adverse event or harm that was not already listed in the studies included in the literature scan.

Remaining issues & future research

This Technical Brief did not intend to assess outcomes or evaluate the validity of claims on the safety and effectiveness of particle beam radiotherapy. Such questions need be addressed in comparative studies.

It is likely that focused systematic reviews will not be able to provide a definitive answer on the effectiveness and safety of charged particle beam radiotherapies compared to alternative interventions. This is simply because of the relative lack of comparative studies in general, and randomized trials in particular.

Comparative studies (preferably randomized) are likely necessary to provide meaningful answers on the safety and effectiveness of particle beam therapy in the context of current clinical practice.

Particle beam radiotherapy can deliver radiation doses with high precision anywhere in the patient's body, while sparing healthy tissues that are not in its entry path. This can be a very important advantage for specific tumors that are anatomically adjacent to critical structures. However, it is very likely that, as this technology becomes increasingly available, it will also be increasingly used with much broader indications. This anticipated diffusion of the technology can have important implications (economic, prioritization of resources, and potentially on health outcomes). Especially for many common cancers, such as breast, prostate, lung, and pancreatic cancers, it is essential that the theorized advantages of particle beam therapy versus contemporary alternative interventions are proven in controlled clinical trials, along with concomitant economic evaluations.

Introduction

Photon beam radiotherapy

Conventional cancer radiotherapy uses ionizing photon (X-ray or gamma-ray) beams for the local or regional treatment of disease. Ionizing radiation damages the DNA of tumor and healthy cells alike, triggering complex biochemical reactions and eventually resulting in cellular death. Cellular damage increases with *(absorbed) radiation dose* (measured in Gray units, Gy) – the amount of energy that ionizing radiation deposits to a volume of tissue.

Ionizing radiation is harmful to all tissues, malignant or healthy. In clinical practice, lethal tumor doses are not always achievable because of radiation-induced morbidity to normal tissues.[1] Radiation therapists aim to maximize dose (and damage) to the target tumor and minimize radiation-induced morbidity to adjacent healthy tissues. This is generally achieved by *targeting the beam* to the tumor area through paths that spare nearby critical and radiosensitive anatomic structures; *selecting multiple fields* that cross in the tumor area through different paths, to avoid overexposing the same healthy tissues (as would be done by using a single field); and by *partitioning the total dose in fractions* (small amounts) over successive sessions. Because healthy tissues recover better and faster than malignant ones, with each radiotherapy session the accumulated cellular damage in the targeted tumor increases, while normal tissues are given the opportunity to repair.

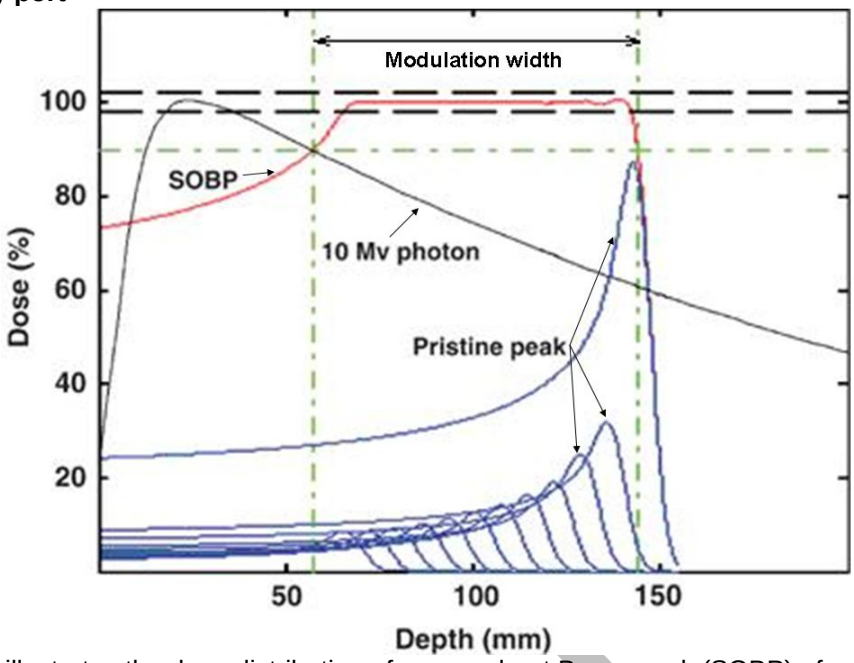
Appropriate targeting of the beam is particularly important for tumors that are anatomically adjacent to critical body structures. To date, advances in imaging and radiation treatment planning technologies allow much more precise targeting of radiation therapy, compared to earlier years.[1] The most advanced method for the delivery of high radiation doses with photon beams is intensity modulated radiation therapy (IMRT). IMRT delivers conformal radiation to the target tumor, by "crossing" multiple properly shaped beams of various intensities through paths that spare radiosensitive and critical adjacent tissues.[2] (The intensity of the beam expresses how many photons traverse a given area of tissue at a unit time.)

Charged particle beam radiotherapy

An alternative treatment modality is charged particle radiotherapy, which uses beams of protons or other charged particles such as helium, carbon or other ions instead of photons.[1] As illustrated in **Figure 1,** charged particles have different depth-dose distributions compared to photons. They deposit most of their energy in the last final millimeters of their trajectory (when their speed slows). This results in a sharp and localized peak of dose, known as the Bragg peak.

The initial energy (speed) of the charged particles determines *how deep* in the body the Bragg peak will form. The intensity of the beam determines *the dose* that will be deposited to the tissues. By adjusting the energy of the charged particles and by adjusting the intensity of the beam one can precisely deliver prespecified doses anywhere in the patient's body. To irradiate a whole tumor area, multiple Bragg peaks of different energies and intensities are combined (**Figure 1**).

Figure 1. Depth-dose distributions for a spread-out Bragg peak of a particle beam for a single entry port



The red line illustrates the dose distribution of a spread-out Bragg peak (SOBP) of a particle beam. The SOBP dose distribution is created by adding the contributions of the 12 "pristine" Bragg peaks (blues lines). The black curve is the depth-dose distribution of a 10 MV photon beam. The horizontal dashed black lines denote the clinically acceptable variation in the plateau dose of the SOBP (±2%). The horizontal green dashed-dot line corresponds to a dose of 90% of the plateau dose of the SOBP, and defines the modulation width. The modulation width can be changed by varying the number and intensity of the pristine Bragg peaks that are added. Note that there is no dose beyond the distal end of the SOBP at approximately 150 mm of depth, and that smaller dose is delivered to the entrance tissues compared to the SOBP. In contrast, the photon beam delivers maximum dose to the entry tissues, as well as substantial dose beyond 150 mm of depth.
Figure and parts of the legend adopted from Levin 2005.[1]
[Reproduced with permission from Levin et al. Br J Cancer 2005;93:849-54.]

As with photon therapy, the biological effects of charged particle beams increase with (absorbed) radiation dose. Because charged particles interact with tissues in different ways than photons, the same amount of radiation can have more pronounced biologic effects (result in greater cellular damage) when delivered as charged particles. The *relative biological effectiveness* (RBE) is the ratio of the dose required to produce a specific biological effect with Co-60 photons (reference radiation), to the charged particle dose that is required to achieve the same biological effect. The (general) RBE of protons is approximately 1.1.[3] Heavier particles can have higher RBE and better dose distribution characteristics. For example, carbon ions were reported to have an RBE around 3 in several tissues and experiments.[4]

Because of these physical characteristics of the charged particle beams it is possible to cover the exact tumor area (in lateral dimensions and depth) using a *single* radiation field (something that is not possible with photon beams).[1]

Statement of Work

The Agency for Healthcare Research and Quality (AHRQ) requested a Technical Brief on the role of particle beam radiotherapy for the treatment of cancer conditions. More specifically, the following key questions were defined by AHRQ after discussions with the Tufts EPC:

Key questions

Key question 1:

1.a. What are the different particle beam radiation therapies that have been proposed to be used on cancer?

1.b. What are the theoretical advantages and disadvantages of these therapies compared to other radiation therapies that are currently used for cancer treatment?

1.c. What are the potential safety issues and harms of the use of particle beam radiation therapy?

Key question 2:

2.a. What instrumentation is needed for particle beam radiation and what is the Food and Drug Administration (FDA) status of this instrumentation?

2.b. What is an estimate of the number of hospitals that currently have the instrumentation or are planning to build instrumentation for these therapies in the USA?

2.c. What instrumentation technologies are in development?

Key question 3:

Perform a systematic literature scan on studies on the use and safety of these therapies in cancer, with a synthesis of the following variables:

3.a. Type of cancer and patient eligibility criteria
3.b. Type of radiation, instrumentation and algorithms used
3.c. Study design and size
3.d. Comparator used in comparative studies.
3.e. Length of followup
3.f. Concurrent or prior treatments
3.g. Outcomes measured
3.h. Adverse events, harms and safety issues reported

Methods

This Technical Brief has three key questions, as described in the Statement of Work. Key questions 1 and 2 are addressed using information from gray literature searches and narrative review articles. Key question 3 is addressed with a systematic scan of the published medical literature.

Terminology, definitions and conventions

(Charged) particle beam radiotherapy

This includes external radiotherapy that uses protons, helium-, carbon, neon-, silicon- or other charged particles. External radiotherapy with electrons, neutrons or π-mesons is not discussed in this Technical Brief.

Cancer

The operational definition of cancer includes histologically malignant tumors. All other entities or diseases are not considered as "cancer" in this Technical Brief. Examples of other conditions are arteriovenous malformations, benign meningiomas, benign schwannomas, craniopharyngioma, or age-related macular degeneration.

(Absorbed) radiation dose

The amount of energy deposited in a given volume of tissue. It is measured in Gray (Gy).

Relative biological effectiveness

RBE is the ratio of the dose of (typically) Co-60 photon radiation that will produce a specified biological effect, to the dose of charged particle radiation required to produce the same effect. Exact RBE values can differ across tissues or with particle energy and/or depth.

Biologically effective dose

The biological effects of a given radiation dose depend on many factors, including type of radiation (photons vs charged particles), energy of radiation and the composition of the tissue. The biologically effective dose is a concept that incorporates the aforementioned factors, and correlates better with biological effects compared to radiation dose. Generally speaking, it is related to the (absorbed) radiation dose by the following formula:

$$\textit{Biologically effective dose} = \textit{RBE} \times \textit{radiation dose}$$

and is measured in (typically Co-60) Gray equivalents, or GyE.

End-of-page footnotes vs references

To distinguish Internet and gray literature sources from journal references we follow the convention of listing the former in the bottom of each page using lowercase latin numerals ([i, ii, iii, …]), and the latter in the References section in the end of the Technical Brief using arabic numerals ([1, 2, 3…]).

Gray literature searches

We searched the Internet using the following algorithm. We first searched Google for "particle beam therapy" and "proton beam therapy", and visited links we considered relevant among those in the first 10 pages of returned results. We visited links hosted in relevant websites or news items and identified the webpages of radiotherapy organizations, institutions that perform particle beam therapy around the world, and companies that develop particle beam therapy instrumentation and treatment planning software.

We also searched the FDA Center for Devices and Radiological Health (CDRH) database to identify particle beam therapy instrumentation that has received FDA clearance (we used the FDA product code "LHN" to identify relevant instrumentation). Finally, we queried the FDA Manufacturer and User Facility Device Experience (MAUDE) database for any reported harms with particle beam therapy instrumentation.

Selected websites and the corresponding links are provided in **Appendix A**. All listed links in this Technical Brief were active on 06/16/2008.

Published literature searches

We performed Ovid MEDLINE searches from 1950 onwards (last search 02/12/2008) using terms such as "proton", "charged particle", "helium ion" etc., along with text and MeSH terms for cancer. The complete search strategy is described in **Appendix B**. We limited searches to human subjects, but we did not set any language or geographical restrictions. We did not use methodological filters to select specific study designs.

Systematic literature scan

Study eligibility

Four reviewers screened citations at the abstract level to identify potentially relevant studies. All potentially eligible citations were retrieved in full text and were examined for eligibility. We included studies of any design describing particle beam radiotherapy in at least 10 patients with cancer, and reporting any clinical outcome (e.g., death, local tumor control, change in symptoms) or any harm (irrespective of whether it was attributed to particle beam radiotherapy or not). We included studies irrespective of the role of particle beam therapy in the patient management strategy (e.g., sole treatment or in combination with other treatments). We accepted studies published in English, German, French, Italian, and Japanese.

We excluded from the literature scan studies that compared different treatment plans/algorithms, as well as dosimetry-only studies (provided that they did not report any clinical outcomes or harms). We also excluded studies where more that 20% of patients had non-malignant conditions. Case series of less than 10 patients and case reports were not included in the literature scan, but were screened to identify potential harms.

Data abstraction

We used Epidata version 3.1 to abstract information on the items of interest in electronic forms.[5] The initial version of the data abstraction form was piloted with 15 papers on 5 different types of cancer, and was modified in an iterative process.

We abstracted data on the citation, study design (prospective single arm study, retrospective single arm study, randomized controlled trial [RCT] and nonrandomized comparative study), type of cancer, patient eligibility criteria, study followup and the period over which patients were treated, as reported in the primary studies. For comparative studies we noted the exact comparisons.

We also recorded the center/facility of particle beam treatment and the number of patients who were treated. We noted the type of particle, total biologically effective dose (in GyE), number of fractions, biologically effective dose per fraction (GyE), and the duration of radiation treatment in weeks. For studies reporting treatment with both particle and photon beams, the aforementioned quantities were extracted in total for both radiotherapy modalities. When the dose per radiation fraction was not reported, it was calculated assuming that all fractions were of equal size. Similarly, whenever total treatment duration was not reported, it was calculated assuming administration of 1 radiation fraction per day, 5 days a week.

We noted information on particle generation and acceleration, beam transportation and the name of treatment planning software or systems (algorithms).

From each study, we gathered information on prior and concurrent treatments (photon radiotherapy, brachytherapy, surgical intervention, chemotherapy, hormonal therapy). We considered "concurrent" all treatments that were administered simultaneously or successively, as long as it could be judged that they were administered as part of a single intervention strategy. "Prior treatments" were the initial failed interventions in patients who were treated for relapse. In practice however, the distinction of prior and concurrent treatments was difficult.

For each study, we recorded whether the following outcomes where reported: overall or cause-specific survival, outcomes related to local tumor control (e.g., [no] local recurrence, complete remission, change in tumor size), outcomes related to distal disease control (metastasis, metastasis free survival), as well as any other clinical outcome, general (e.g., symptomatic relief) or disease-specific (e.g., rate of bladder conservation for bladder cancer).

We also recorded the different harms or adverse events, their timing (acute vs late) and severity, as reported in the primary studies. Unless otherwise classified in the primary studies, we considered as "severe" harms that were Grade 3 or higher; and as "late" harms reported at least 3 months after irradiation. It should be noted that harms may be incurred by radiation therapy or other treatment interventions, such as chemotherapy or surgery. We recorded the study authors' opinions on which harms were radiation-induced whenever they were reported; in all other cases we did not attempt to attribute specific harms to different interventions.

Note

It is not the intent of this Technical Brief to assess the outcomes of particle beam therapy for any specific condition.

The literature scan did not abstract numerical data on the rates of clinical outcomes or harms. Most studies were single-arm and comparisons across such studies are subject to confounding and can be misleading. Moreover, many studies refer to overlapping patient populations and are not independent.

Synthesis of items of interest

We generated a Summary Table summarizing the 8 items of Key Question 3 (see Statement of Work, items 3.a. to 3.h.) per type of cancer; this is provided in **Appendix G**. We described the 8 items across all identified papers using graphs and tables, and providing qualitative summaries.

We classified papers according to the different cancer types they described in the following categories:

- Ocular cancer, including mostly uveal melanoma (but also metastasis to the retina and conjunctival cancer)
- Head and neck cancers, including malignancies of the brain (e.g., glioblastoma); of the skull base and of the cervical spine (chordomas and chondrosarcomas), along with other malignancies (e.g., of the sinonasal tract)
- Spinal cancer, including sacral tumors, mainly chordomas and chondrosarcomas
- Gastrointestinal cancers, including liver, esophageal, pancreatic, and bile duct tumors
- Prostate cancer
- Bladder cancer
- Uterine cancer, including uterine cervix and body
- Bone and soft tissue cancers
- Lung cancer (non-small cell)
- Breast cancer
- Miscellaneous (including skin cancer and papers describing a center's experience with a variety of different cancers)

In addition, specific radiotherapy centers or institutes are no longer active, but were succeeded by another center in the same geographical area (and in the same academic environment). For example, the Harvard Cyclotron Laboratory has been succeeded by the Northeast Proton Therapy Center, and the Lawrence Berkeley Laboratory has been succeeded by the University of California San Francisco proton treatment center. In the presentation of literature scan results, we grouped papers originating from the currently inactive centers along with papers originating from the corresponding centers that succeeded them.

Software

Epidata version 3.1 was used to perform data extraction from eligible papers.[5] Stata/SE version 9 (Stata Corp, College Station, TX) was used for descriptive statistics and graphics.

Results

Key question 1

1.a. What are the different particle beam radiation therapies that have been proposed to be used on cancer?
1.b. What are the theoretical advantages and disadvantages of these therapies compared to other radiation therapies that are currently used for cancer treatment?
1.c. What are the potential safety issues and harms of the use of particle beam radiation therapy?

1.a. What are the different particle beam radiation therapies that have been proposed to be used on cancer?

As of December 2007 at least 61,800 patients have received particle beam radiotherapy around the world for various cancers and other diseases. The vast majority (approximately 54,000 or 87%) have received protons. Fewer patients have received radiotherapy with carbon ions (approximately 4,500 or 7%), helium ions (approximately 2,000 or 3%) or other ions.[i]

1.b. What are the theoretical advantages and disadvantages of these therapies compared to other radiation therapies that are currently used for cancer treatment?

Particle beams offer the theoretical benefit of precise dose localization and have favorable dose-depth distributions, compared with conventional photon beam radiotherapy.[6] They have a steep increase in energy deposition at the Bragg peak, and deposit very little dose in the normal tissues beyond the Bragg peak location (**Figure 1**). Therefore, the radiation dose in the normal tissues both at the radiation field entry site, and around the target area is less compared to photon radiotherapy.

For these reasons, it is expected that when one uses charged particles rather than photons to deliver a specific biologically effective dose to the tumor area, radiation-induced morbidity from normal tissue damage will be smaller. Conversely, one may have the opportunity to deliver higher (even lethal) doses to the tumor area with charged particles rather than photons, while inducing harms comparable to those seen with photon radiotherapy.[6]

The above is particularly appealing for inoperable tumors located close to critical structures.[7] In the case of uveal melanomas for instance, tumors may develop in close proximity to the optic disk, optic nerve and fovea. Proton beam radiotherapy can deliver therapeutic radiation doses with great precision so as to avoid surgical removal of the eye and preserve vision.[6] Other examples where precise radiation targeting is critical are

[i] Source http://ptcog.web.psi.ch – last accessed 06/16/2007, and Levin 2005.[1]

tumors of the skull base and spine (e.g., sarcomas, chordomas, and chondrosarcomas), that are adjacent to the brain, brain stem, cervical cord, optic chiasm, and spinal cord.[1]

It is theorized that the reduced cumulative dose to normal tissues with particle beam rather than photon radiotherapy is particularly beneficial to pediatric patients.[6,8] This is because children may be more susceptible to radiation side effects compared to adults.[8] In addition, a major concern is the potential for secondary radiation-induced malignancies that can appear long after treatment completion. There is evidence that such secondary malignancies increase with total radiation dose.[8]

Description and pros and cons of radiotherapeutic alternatives to particle beam therapy

Conventional photon radiotherapy

Conventional radiation therapy utilizes ionizing radiation in the form of X-rays generated by linear accelerators, or gamma rays emitted from isotopes such as Co-60. Photon beams deliver the maximum radiation dose just after entering the surface of human body, and gradually wane in energy deposition with penetration depth (**Figure 1**). Photon radiotherapy results in larger unnecessary radiation dose to normal structures compared to particle beam therapy. Contrary to particle beam therapy, the targeted tumor volume cannot be covered by a single radiation field in depth and lateral dimensions.

However, conventional radiotherapy is widely available and less costly than charged particle radiotherapy. For many patients in whom a whole region has to be irradiated (e.g., the whole pelvis in some patients with uterine cancer), the high precision of particle beam therapy may not be needed. Finally, substantial clinical experience has already accumulated on the biological effects of photons in various tissues and different doses. This is not true in the case of light ions such as carbon ions, (although it may be less of an issue with protons).[9]

IMRT

Advances in imaging and radiation treatment planning technologies allow much more precise targeting of photon radiotherapy, compared to conventional techniques. The most advanced method for the delivery of high radiation doses with photon beams is IMRT. IMRT delivers conformal radiation to the target tumor, by "crossing" multiple properly shaped radiation fields with various intensities through paths that spare radiosensitive and critical adjacent tissues.[2,10] IMRT is already used in many hospitals in the USA.

A possible concern is that IMRT has a higher integral radiation dose[1] and increases in the total volume of tissues exposed to radiation compared to conventional radiation therapy. It is theorized that this may translate to higher risk for secondary radiation-induced malignancies, especially in pediatric populations.[10]

Stereotactic radiosurgery

Stereotactic radiosurgery uses multiple photon beams of relatively low intensity that converge to the same area, effectively delivering a single, high-dose fraction of external radiation to a target lesion in the central nervous system. With advances in imaging technologies and immobilization techniques that take better account of tumor motions

caused by respiration, stereotactic radiosurgery is now possible for cancers located outside the central nervous system. It is now considered one of several approaches to deliver ablative radiation doses directly to the target lesion with acceptable toxicity in adjacent normal tissues.[11,12]

However, stereotactic radiosurgery is typically not used to irradiate large tumor areas.

Brachytherapy

Brachytherapy is another type of radiation therapy where one inserts small encapsulated radioactive sources in or adjacent to the treatment volume. Depending on the type of the source (and the intensity of the radiation) these may be inserted permanently or transiently. The sources emit beta radiation or alpha particles, which deposit all their energy in the immediately neighboring tissue, delivering very little dose to distal tissues. Depending on the type of cancer, the radiation source may be placed adjacent to the tumor (e.g., outside the sclera for some ocular cancers or in the uterus for some gynecologic malignancies), or may be directly implanted in the tumor (e.g., for prostate cancer).[13]

Brachytherapy has very specific indications. The insertion of the radioactive sources requires minor invasive procedures.

1.c. What are the potential safety issues and harms of the use of particle beam radiation therapy?

Generally speaking, the expected harms from a dose of radiation to a given tissue are considered to be determined by the biologically effective dose, rather than the type of the radiation (photon vs charged particles).

We found no claims that any harm was specific to the nature of the radiation (i.e., charged particles vs other types) in the literature we examined. Moreover, we found no mention of non-radiation related harms incurred by the instrumentation used to deliver radiotherapy with charged particles (e.g., injuring a patient during positioning in the treatment room).

In the previous sections we discussed expected benefits and harms stemming from the differential depth-dose distributions of different radiation delivery methods.

Cautionary note

Various charged particles (i.e., protons, helium or carbon ions) have different depth-dose distributions. Especially for light ions (such as carbon ions) and less so for protons, RBE values can vary with energy and/or depth. This means that isodoses (in Gy) in a given tissue (areas that receive the same radiation dose) do not necessarily correspond to biologically iso-effective doses (in GyE) (areas that have received the same biologically effective dose).[9] In addition, the early and late radiosensitivity of various tissues could be different compared to what is known from photon radiotherapy.[9] Therefore treatment plans generated by different methods for light ions may not result in identical actual doses in a given patient.

Key question 2

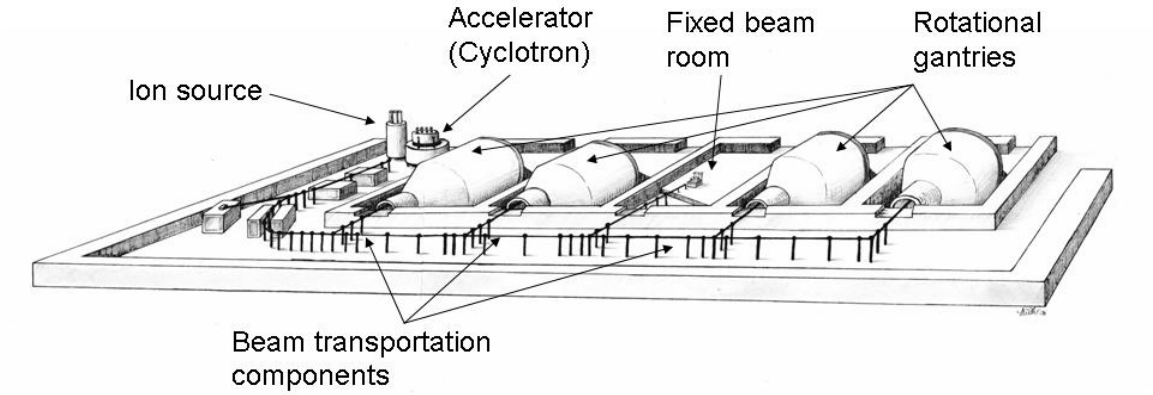
2.a. What instrumentation is needed for particle beam radiation and what is the FDA status of this instrumentation?
2.b. What is an estimate of the number of hospitals that currently have the instrumentation or are planning to build instrumentation for these therapies?
2.c. What instrumentation technologies are in development?

2.a What instrumentation is needed for particle beam radiation and what is the FDA status of this instrumentation?

Instrumentation

Figure 2 outlines a proton beam radiotherapy facility that has 5 treatment rooms, 1 with a fixed beam and 4 with rotational gantries. This is one possible layout of a particle beam treatment facility.

Figure 2. Schematic of a proton beam radiotherapy facility



Redrawn schematic of a proton therapy center.
Adapted from a schematic of the Rinecker Proton Therapy Center, RPTC, Munich, Germany, under construction by ACCEL Instruments (http://www.proton-therapy.com; last accessed 06/16/2008).

The following describes the course of a particle beam used for radiotherapy of cancer, from its generation, to the patient room.

1. The charged particles are generated by an ion source. The ion source is specific to the type of the charged particle (i.e., is different for protons, helium ions or carbon ions).
2. The charged particles are subsequently accelerated to low energies (of several MeV) by a linear accelerator, and are then injected in the main accelerator.
3. The main accelerator is typically a cyclotron, a synchrotron or a cyclosynchrotron, a large device that can accelerate the charged particles to higher energies (typically above 50 MeV). For clinical uses, the maximum energies that charged particle accelerators achieve are between 230 and 250 MeV (some centers have a maximum clinical energy of 430 MeV see **Appendix F, Table F1** for details).

4. The accelerated particle beam is then transported by a series of vacuum tubes and shaping and focusing magnets towards the patient treatment rooms. Special devices (wedges) can decrease particle energy (speed) to desirable levels.
5. The largest facilities in the world have 5 rooms (**Appendix F**) for treatment administration. In the treatment rooms, the particle beam has either fixed direction ("fixed beam" – horizontal, vertical, or at a specific angle), or can be delivered to any desirable direction by use of rotational gantries. Gantries are large devices that can rotate 360 degrees (full circle) to deliver the particle beam at the angle specified by the radiotherapy team.
6. Finally, the beam delivery nozzle has the ability to shape the beam so that it conforms to the stereometry of the tumor (both the cross-section shape of the tumors and the shape of the distal surface, by using collimators and compensators, respectively).
7. Patients are properly positioned to receive therapy. At least some centers use robotic instrumentation that is able to position patients accurately with 6 degrees of freedom (6 directions of movement or rotation).

Treatment planning software/systems

Several pieces of software were developed for treatment planning since the early 80's. Companies that provide instrumentation for charged particle radiotherapy also provide accompanying software for treatment planning. **Table 1** provides a list of treatment planning software/treatment planning systems released up to 2002.[14]

Table 1. List of treatment planning software/systems for particle beam therapy up to 2002

Year	*Created By*	*Software/system name*	*Comment*
1979–1993	LBL	LBL system	Not available
1980	MGH	Rx	
1980	MGH	EYEPLAN	Eyes only
1990–1996	MGH/Siemens	V-Treat (AXIOM)	Not available
198?–1991	PSI	PSI system/Pion	
1995	DKFZ/Royal Marsden	Voxelplan/Proxelplan	
1996	Radionics/MGH	P-Knife	Not available
1997	LLU/PerMedics	OptiRad 3D	FDA approved, commercial
1998	Tsukuba	Hitachi system	In-house system
1998	NCC/SHI	PTplan	In-house system
1998	DKFZ	OCTOPUS	Under development – eyes only
1994	Orsay/Curie	ISIS	
1998	CMS/MGH	FOCUS	Commercial release 1999
1998	DKFZ	KonRad Plus Protons	Research only
1989–2000	Clatterbridge, UK	EYEPLAN v1.6 (VMS)	Free; eyes only; research only
1999	GSI	TRiP98	Research
2000	Varian	Polaris	FDA approved for passive treatment modalities
2001	ITEP (Moscow)	ProGam	Adapted in PTF ITEP
2002	MDS Nordion	Helax-TMS	FDA approved for commercial use
2002	CMS/Mitsubishi	FOCUS/M	Commercial release 2001

DKFZ: Deutsches Krebsforshungszentrum; FDA: Food and Drug Administration; GSI: Gesellschaft für Schwerionenforschung; ITEP: Institute of Theoretical and Experimental Physics; LBL: Lawrence Berkeley Laboratory; LLU: Loma Limda University Medical Center; MGH: Massachusetts General Hospital; NCC: National Cancer Center (Japan); PSI: Paul Scherrer Institute.
Source: Sisterson 2005,[14] http://ptcog.web.psi.ch/archive_particles.html (last accessed 06/16/2008).

We repeat the note made in the answer to key question 2.c that –especially for light ions such as carbon ions and less so for protons– RBE values depend on energy and/or depth, complicating treatment planning.[9] Because this is an active area of research, treatment plans generated by different methods for light ions may not result in identical actual doses in a given patient.[9]

FDA status of proton therapy equipment

There are several companies that are undertaking construction of large scale particle treatment instrumentation and facilities. Currently, the FDA has approved specific devices and accompanying treatment planning software for medical use. All USA facilities that are currently active have FDA approved instrumentation.[i]

Accreditation and training

There is no specific mandatory accreditation for the operation of particle beam facilities. The specialized personnel would have to become proficient with the treatment planning software and in the operation of the patient positioning platforms and the rotational gantries.

At least in the USA, training programs are slated to be provided at the ProCure Training and Development Center (Bloomington, Indiana), a private center that will simulate a working proton therapy facility. The center will provide clinical, technical, interpersonal and administrative training for radiation oncologists, medical physicists, dosimetrists, radiation therapists and other staff.[ii]

2.b. What is an estimate of the number of hospitals that currently have the instrumentation or are planning to build instrumentation for these therapies?

As of this writing, at least 29 institutes around the world are currently operating facilities for particle beam radiation therapy (**Appendix F, Table F1)**: 7 in Japan, 6 in the USA, 3 in Russia, 2 in each of Switzerland, France, and Germany, and 1 in each of England, Canada, Italy, China, Sweden, South Africa and Korea. **Table 2** lists the ones that are currently operating in the USA.

[i] Source: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm , Product Code "LHN" (last accessed 06/16/2008)
[ii] Source: http://www.insideindianabusiness.com/newsitem.asp?id=28727 (last accessed 06/16/2008)

Table 2. Currently operating particle beam facilities in the USA

Institute	Parti-cle	Maximum Clinical Energy (MeV)	Beam direction			First patient	Patients treated	
			H	V	Gan		Number	Date of count
LLU, CA	proton	250	Y	–	Y	1990	11414	Nov-06
MPRI, IN	proton	200	Y	–	–	1993	379	Dec-07
UCSF, CA	proton	60	Y	–	–	1994	920	Mar-07
NPTC-MGH, MA	proton	235	Y	–	Y	2001	2710	Oct-07
MD Anderson Cancer Center, TX	proton	250	Y	–	Y	2006	527	Dec-07
FPTI, FL	proton	230	Y	–	Y	2006	360	Dec-07

FPTI: Florida Proton Therapy Institute; LLU: Loma Limda University Medical Center; NPTC-MGH: Northeast Proton Therapy Center-Massachusetts General Hospital; MRPI: Midwest Proton Radiotherapy Clinic; UCSF: University of California San Francisco.
N: number; NA: not applicable; H: horizontal; V: vertical; Y: yes; Gan: Gantry
Ordered by the time of treatment of the first patient. The table does not include two centers that are now inactive, namely the Lawrence Berkeley Laboratory in California (succeeded by UCSF) and the Harvard Cyclotron Laboratory in Massachusetts (succeeded by NPTC-MGH).
Source: Particle Therapy Cooperative Group, URL: http://ptcog.web.psi.ch/ (last accessed 06/16/2008), and Levin 2005.[1]

Table 3 lists the three facilities that are either in planning or construction phase in the USA. Around the world at least 9 additional particle beam centers have been planned, and 7 of them are in construction phase (4 in Germany, 1 in Switzerland, 1 in Italy and 1 in France; **Appendix F, Table F2**).

Table 3. Large particle beam facilities that are being built or planned in the USA

Institute	Now in construc-tion	Parti-cle	Maximum Clinical Energy (MeV) [Accelerator]	Treat-ment rooms	Gant-ries	Cost (mil-lion $)	Estima-ted start date
University of Pennsylvania, PA	Yes	proton	230 [Cyclotron]	5	4	140	2009
Hampton University, VA	Yes	proton	[?]	5	4	225	2010
Northern Illinois Proton Treatment and Research Center, IL	No	proton	250 [?]	4	2 or 3	159	2010

[?] This item could not be found.
Sources: Particle Therapy Cooperative Group, URL: http://ptcog.web.psi.ch/; Hampton University Proton Therapy Center http://www.hamptonu.edu/proton-therapy-institute/; Northern Illinois Proton Treatment and Research Center http://www.niu.edu/protontherapy/
(all last accessed 06/16/2008).
See also **Appendix F, Table F2** for a list of particle beam therapy centers that are being built or planned around the world.

2.c. What instrumentation technologies are in development?

Proton beam therapy using conventional accelerators (cyclotron)

The current particle beam treatment facilities are large and costly (**Table 3**). Private companies design smaller instrumentation that can fit in a single room and will be able to treat one patient at a time (with protons only – not with other charged particles). The same room will accommodate the cyclotron, the proton beam delivery system, a treatment couch with pendant control, a radiographic patient positioning system, proton beam treatment planning, and a link to a treatment record and verification system.[i] The cost of this newer instrumentation is reported to be 20 million US dollars.

Details on the proprietary technologies that allow the shrinkage of the whole facility to a single room have not been disclosed. However, the key technological advancement is the construction of a cyclotron that operates at a very large magnetic field (10 Tesla, using superconducting technology). The cyclotron weighs less than 20 tons, a 90% decrease in weight compared to other proton therapy cyclotrons.

As is the case for larger facilities, the new technology includes robotic patient positioning system, enabling clinicians to automatically reposition a patient from the control room.

The first such unit will be operated in the Barnes-Jewish Hospital, St Louis, Missouri, in late 2008.[ii] This center expects to treat approximately 250 patients each year. According to news items and press releases, several other hospitals have expressed interest in this new instrumentation, including Broward General at Ft. Lauderdale,[iii] Orlando Regional at Orlando, Florida,[iv] and Tufts Medical Center, Boston, Massachusetts. At least 17 hospitals have indicated interest in these smaller systems.

The FDA has not yet cleared this new instrumentation.

Proton beam therapy using non-conventional accelerators (dielectric wall accelerator)

Other companies have recently announced plans to built small (room size) proton beam therapy facilities using a dielectric wall accelerator instead of a cyclotron.[v]

The FDA has not yet cleared this new instrumentation (which is still in early development stage).

[i] The information pertains to the Clinatron250™ or Monarch250™ proton beam radiotherapy system, by Still River Systems; the information is accessible at http://www.stillriversystems.com/products.aspx?id=50 (last accessed 06/16/2008).

[ii] Source: http://www.barnesjewish.org/cancer/default.asp?NavID=3339 (last accessed 06/16/2008)

[iii] Source: http://www.browardhealth.org/body.cfm?ID=2066 (last accessed 06/16/2008)

[iv] Source: http://www.orlandohealth.com/media/media_news_details.aspx?NewsID=%20149 (last accessed 06/16/2008)

[v] Source: http://www.tomotherapy.com/news/view/20080428_cpac_announcement/ (last accessed 06/16/2008)

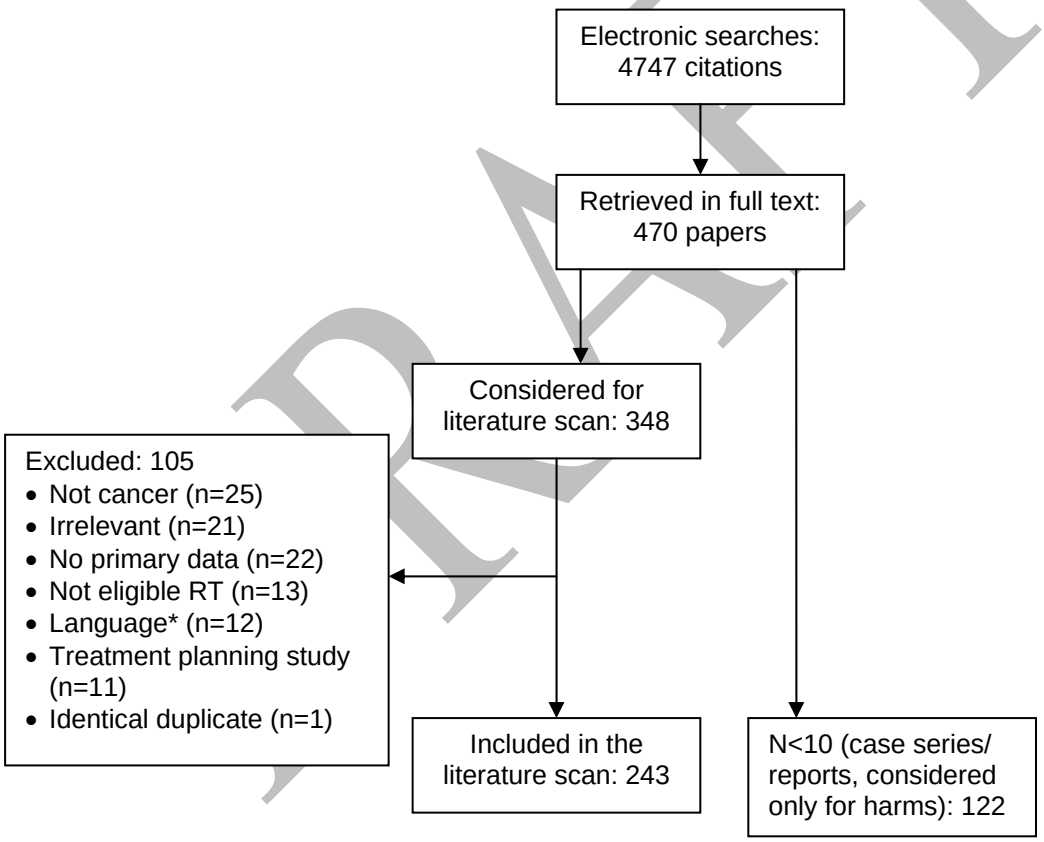
Key question 3

Section C describes the results of a systematic scan of the eligible published literature.

Literature selection

Our electronic searches yielded 4747 studies, 470 of which were retrieved in full text (**Figure 3**). Finally, 243 papers were included in the literature scan. **Appendices C** and **D** list the citations of the retrieved eligible papers and of the excluded papers (along with reasons for exclusion). **Appendix E** lists the citations of the case reports and case series papers that were examined for harms.

Figure 3. Flow of the literature



* Russian and Dutch
N: number of patients; RT: radiotherapy

3.a. Types of cancer and patient eligibility criteria

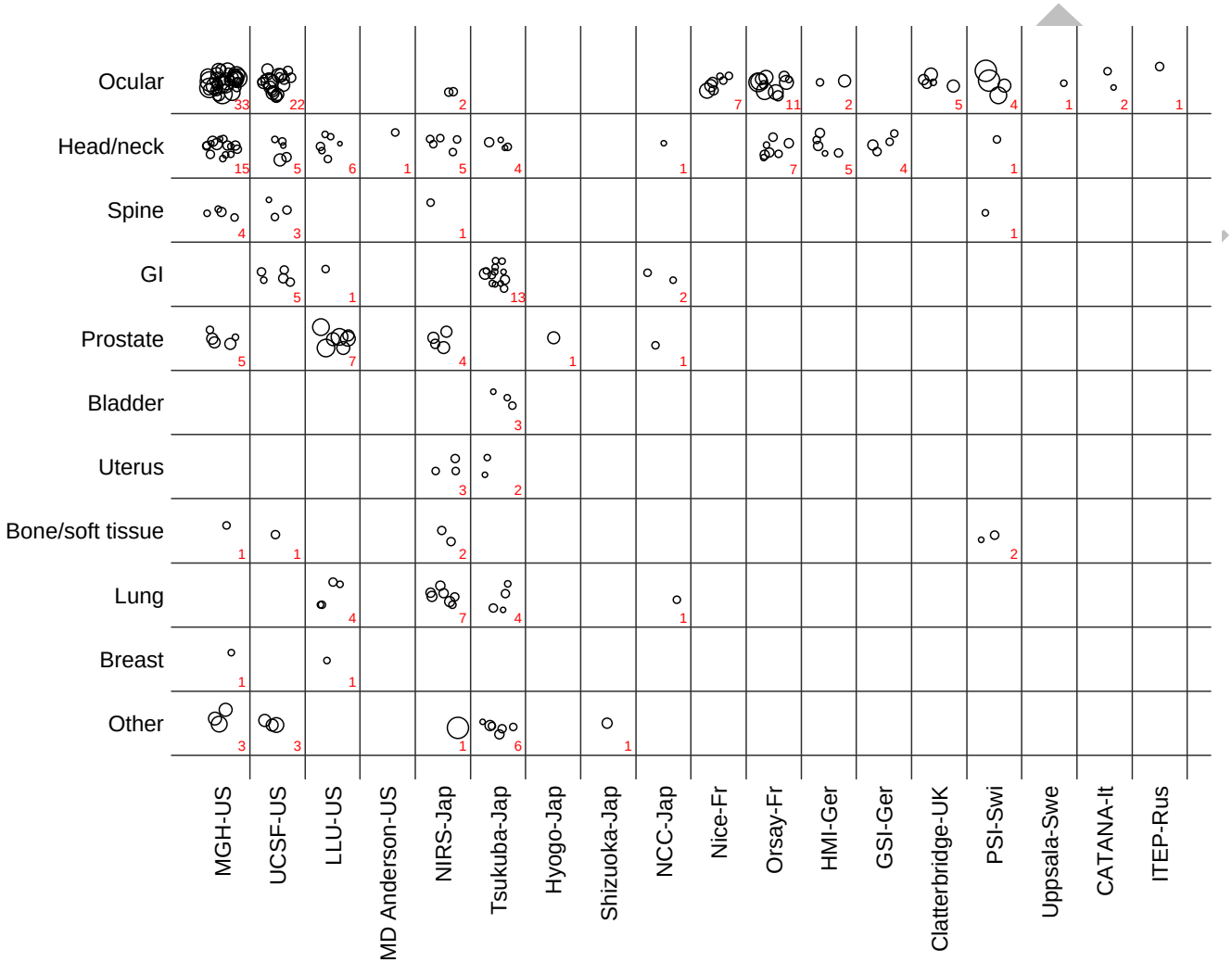
Types of cancer studied

Particle beam therapy has been used in a variety of cancers in the published literature. More than half of the identified papers described treatment of ocular cancers (uveal melanoma in particular), and cancers of the head and neck (brain tumors, and tumors arising from skull base, cervical spine and nearby structures).

In order of decreasing number of studies, the following types of malignancies were also described: gastrointestinal (esophageal cancer, hepatocellular carcinomas of the liver, pancreatic cancer), prostate, lung, spine and sacrum, bone and soft tissue, uterine (cervix and corpus), bladder, and miscellaneous (skin cancer or a compilation of a center's experience with a variety of cancers treated there) (**Appendix G, Summary Table**).

Figure 4 summarizes all identified papers per cancer type and center where the study was conducted. Studies shown in the same cell (i.e., studies from the same center describing a specific cancer) may include overlapping populations. Specific centers appear to have special interest on certain cancer types (**Figure 4**).

Figure 4. All identified studies per center and cancer type.



Each publication is represented by a circle, with size proportional to the logarithm of the total sample size. The red numbers in the right hand corner of each cell denote the total number of studies in each cell.

Shown are all studies that report the center in which the particle beam therapy was performed.

Specific patient inclusion and exclusion criteria

The vast majority of studies were retrospective cohorts describing the experience of a center in treating several types of cancer. The spectrum of included patients varied depending on the cancer type (**Appendix G, Summary Table**). For example, particle beam therapy was used in patients with non-small cell lung cancer (most stage I disease) who either refused surgery or had inoperable cancer. For uveal melanoma, particle beam therapy was used for a wide range of melanoma locations and sizes. For bone and soft tissue tumor, patients with either inoperable or metastatic disease were studied. Many studies did not provide information on the cancer staging of the included patients.

Mean or median ages

Only 7 papers focused on pediatric or adolescent populations, and they described the treatment of head and neck cancers or of soft tissue sarcomas.[15-21]

In the remaining papers, mean (or median) ages ranged from 29 to 81 years of age, and many of them described populations with mean age above 50 years (**Table 4**).

Table 4. Distribution of mean or median ages per cancer category excluding 7 studies on pediatric or adolescent populations

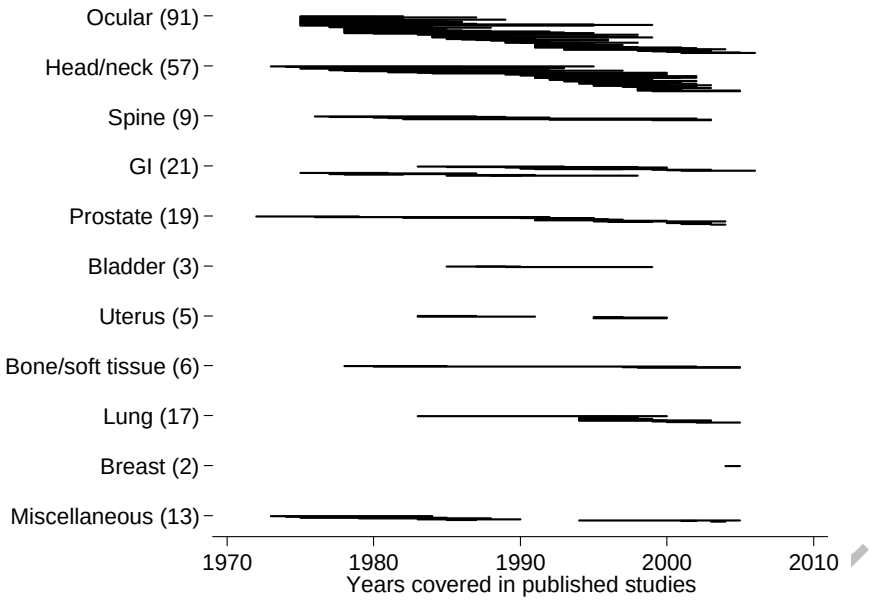
Cancer category	*Number of identified papers*	*Mean or median age*	
		Median value	*Range*
Ocular	91	58	35-66
Head/neck	50	49	33-66
Spine	9	51	41-66
GI (including liver & pancreas)	21	63.5	59-81
Prostate	19	69	66-73
Bladder	3	69	55-72
Uterus	5	60	56-64
Bone/soft tissue	5	41	29-50
Lung	17	72	71-75
Breast	2	62	NA
Miscellaneous	14	68.5	64-73

GI: Gastrointestinal [cancer]; NA: not applicable

Periods of patient enrollment

Identified studies reported on patients who were treated from the early 1970's onwards. Fifty-five percent of the papers reported the centers' experiences with particle beam therapy over a time span of 10 years or longer.

Figure 5. Enrollment periods for studies per cancer



GI: Gastrointestinal [cancer]
Shown are enrollment periods of identified studies per cancer classification. Each paper reporting information on coverage periods is represented by a thin horizontal line. Papers are grouped by cancer category and are ordered by calendar year of enrollment start, and total number of studied subjects. The total number of studies per cancer category is shown in the parentheses in the labels of the vertical axis; however, only 204 papers that reported the pertinent information are plotted.

3.b. Type of radiation, instrumentation and algorithms used

Type of charged particle radiation used

Proton beam therapy

One hundred twenty-seven papers reported proton beam radiation therapy for various types of cancer. Proton therapy was administered mainly as a single radiation modality, either stand-alone therapy or a part of combined modality therapy (e.g., surgery followed by adjuvant radiotherapy), for ocular melanoma, bone and soft-tissue sarcomas, non-small cell lung cancer, hepatocellular carcinoma, and breast cancer. For other cancers, such as malignant tumors in the head, neck, or spine (mainly consisting of chordoma or chondrosarcoma), prostate cancer, bladder cancer, uterine cancer, particle therapy was used either as a booster radiation to the main target lesion following conventional photon irradiation or as a stand-alone radiation treatment.

Administered doses and fractionations thereof were heterogeneous and varied by the type of cancer. Studies administered protons or photon plus protons with the mean total dose ranging from 32 to 94 GyE to main target lesions depending on the cancer categories. When used as a booster therapy, proton irradiation was added as booster therapy after performing conventional photon radiotherapy with 40 to 50 Gy. The reported fraction size varied across and within cancer categories, ranging from 2.0 to 5.0 GyE in most instances. Most commonly, the scheduled total activity was fractionated into approximately 20 to 40 doses (one per day) necessitating a one- to two-month treatment

period. In some studies where protons where the only radiotherapy (e.g., in non small cell lung cancer and breast cancer) a "hypo-fractionated" approach was used, with fraction doses in excess of 5.0 GyE, and approximately 2 weeks' duration.[22-27] Most ocular melanoma studies adopted a four or five radiation-fraction strategy, which was completed within a week.

Carbon-ion beam therapy

Thirty-nine publications mainly from two institutions (NIRS, Japan and GIS, Germany) reported use of carbon-ion beam therapy. In most cases, carbon therapy was used as the only radiation treatment. Treated cancers included malignant tumors in the head, neck and spine, non-small cell lung cancer, prostate cancer, uterine cancer, bone and soft-tissue sarcomas, ocular melanoma, and hepatocellular carcinoma.

Most studies administered carbon-ions with the mean total dose between 50 and 70 GyE with 15 to 25 treatment fractions during the overall treatment period of one to two months. Lung cancer and ocular melanoma studies adopted "hypo-fractionated" approach with the mean total dose of 70 to 76 GyE administered within a week.[28-31]

Helium/Neon/Silicon-ion beam therapy

A single currently inactive facility (University of California, Lawrence Berkeley Laboratory) reported 35 studies on the use of helium-, neon- or silicon-ions from 1982 to 1998. Treated cancer categories were mainly limited to malignant tumors in the head, neck and spine, ocular melanoma (helium-ions only), and some gastrointestinal cancers. These ions were used either as a local booster radiation following conventional photon irradiation or as the only radiation therapy. Most studies administered total doses between 60 to 76 GyE in 30 to 37 fractions during two to three months except for ocular melanoma studies in which four to five high-dose fractions were administered within 1-2 weeks.

Details on instrumentation and treatment planning algorithms

The identified studies did not provide details on the source of the particles, the accelerator, or the transportation of the beam to the patients (refer to Sections A and B for relevant information).

The description of the treatment planning algorithms (software/method) used by different centers is heterogeneous. Studies mentioned various specific pieces of software (e.g. EYEPLAN for ocular cancer), or alluded to the use of unspecified "treatment planning software" or "treatment planning system".

3.c. Study design and size

We identified 10 RCTs and 13 nonrandomized comparative studies (see **Comparators** in this section). The remaining 220 studies were single-arm studies (case series or cohort studies); 185/220 were retrospective in design.

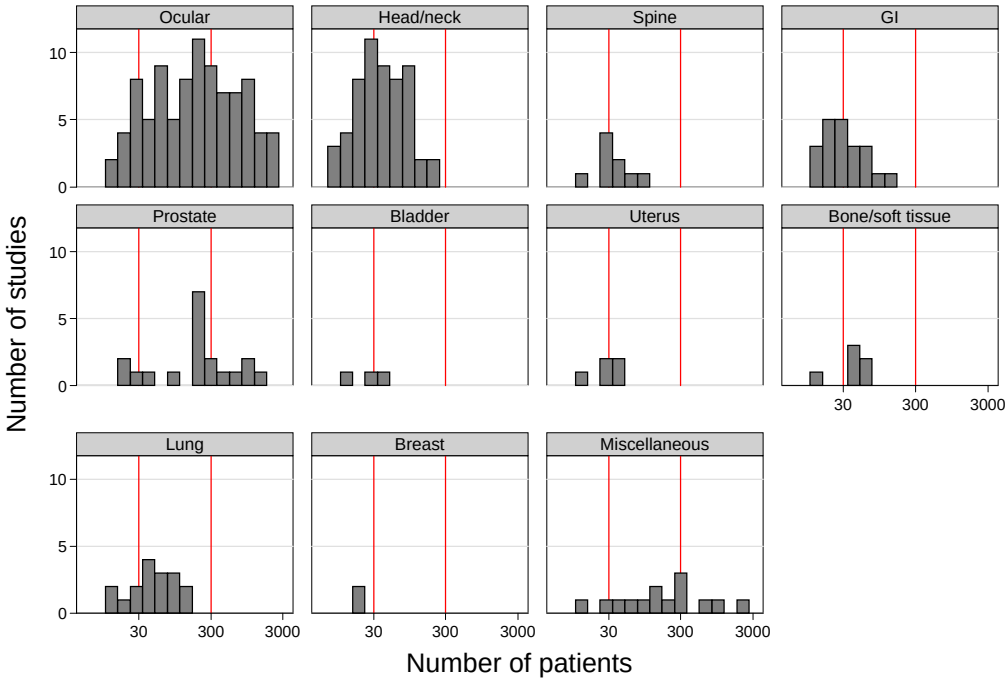
Table 5. Number of papers per cancer type and study design

Cancer type	*Single arm*	*RCTs*	*Nonrandomized comparative*	*Total*
Ocular	80	4	7	91
Head/neck	53	2	1	56
Spine	9	0	0	9
GI	18	1	2	21
Prostate	14	3	2	19
Bladder	3	0	0	3
Uterus	4	0	1	5
Bone/soft tissue	6	0	0	6
Lung	17	0	0	17
Breast	2	0	0	2
Miscellaneous	14	0	0	14

GI: gastrointestinal [cancers]; RCT: randomized controlled trial

Figure 6 shows histograms of study sample sizes per cancer category. Overall, 46 studies described more than 300 people. Among them were 1 RCT[32] and 4 comparative non-randomized trials.[33-36]

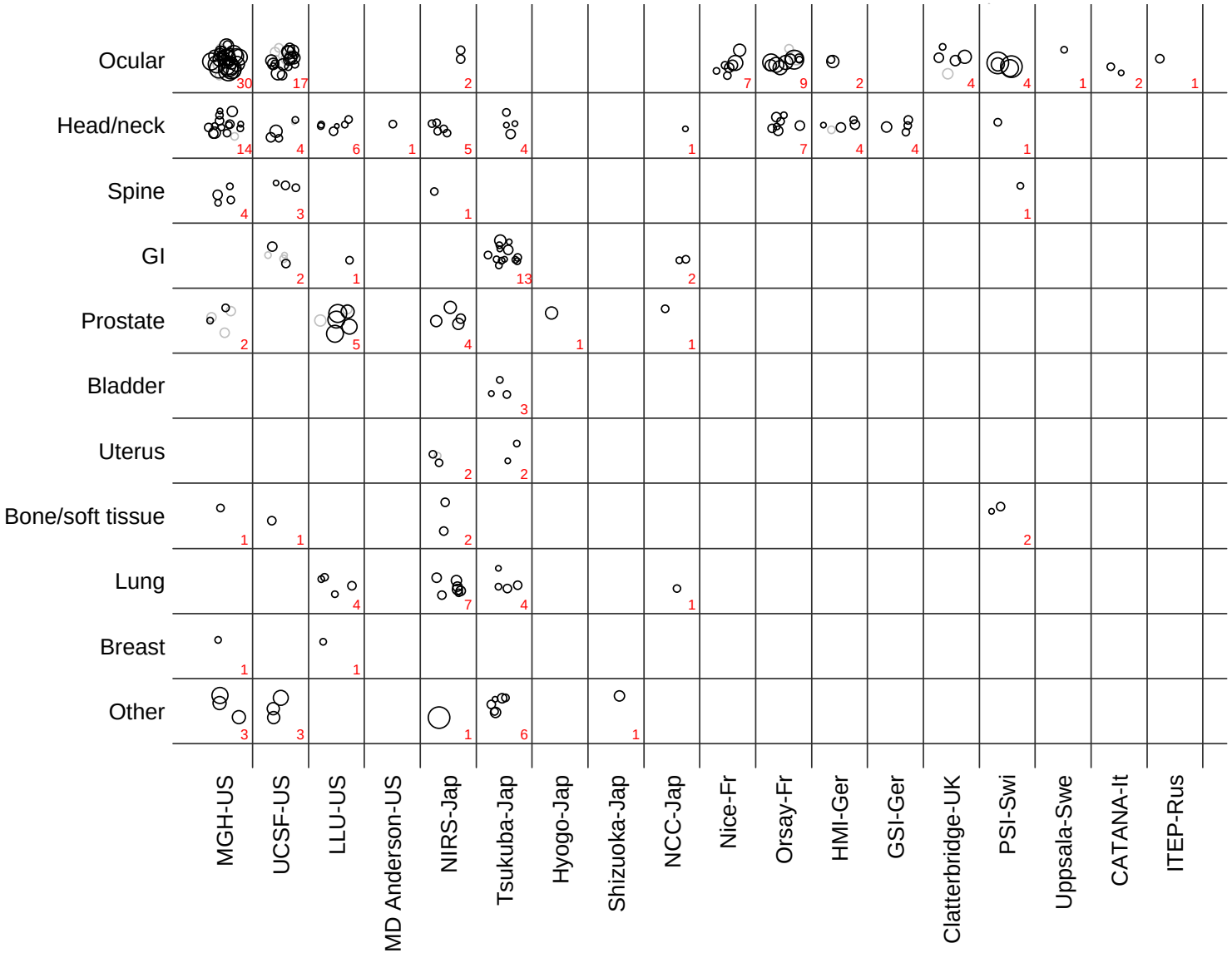
Figure 6. Sample sizes of studies per cancer type



GI: Gastrointestinal
The horizontal axis has been transformed to a logarithmic scale to accommodate the large range of total number of included patients per study. The reference lines at 30 and 300 are arbitrarily chosen to facilitate comparisons across the subgraphs per cancer type. The "miscellaneous" category includes studies that reported a center's cumulative experience on several cancer types, and a study on skin cancer treatment.

Figure 7 and **Figure 8** show how the identified studies break down into single arm studies, and comparative ones, respectively, per cancer type and center.

Figure 7. Non-comparative studies per center and cancer type.

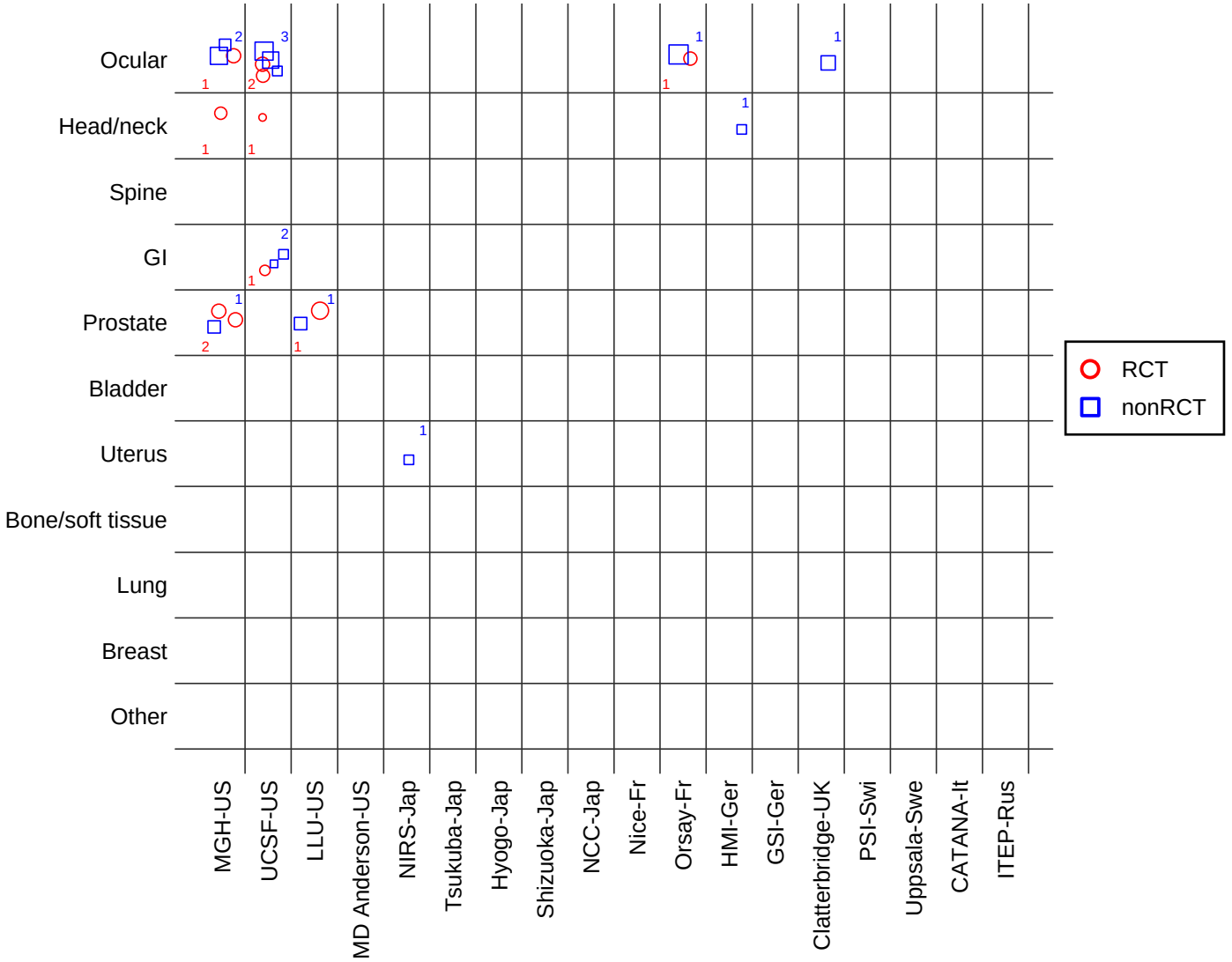


Each publication is represented by a circle, with size proportional to the logarithm of the total sample size. The red numbers in the right hand corner of each cell denote the total number of noncomparative studies.

The relative sizes of the markers are in the same scale with those in **Figure 4**.

Black circles: Shown are all non-comparative studies that report the center in which the particle beam therapy was performed.
For completeness, gray circles denote the comparative studies (their number is not included in the count.)

Figure 8. Randomized and non-randomized comparative studies per center and cancer type.



Each publication is represented by a red circle (randomized trials, RCTs) or a blue square (non randomized comparative studies, nonRCT) with size proportional to the logarithm of the total sample size.

The relative sizes of the markers are not in the same scale as in **Figure 4** or in **Figure 7**.

The red and blue numbers in each cell denote the total number of RCTs and non randomized comparative studies, respectively.

3.d. Comparators

In total we identified 10 papers describing 8 RCTs (**Table 6**) and 13 papers describing non-randomized comparative studies.[33-45]

RCTs

The identified RCTs compared lower vs higher doses of particle beam therapy; particle beam therapy vs other radiotherapy (e.g., brachytherapy or external photon therapy) or vs a combination with additional therapy (e.g. laser thermotherapy for uveal melanoma). **Table 6** lists the exact comparisons.

Table 6. Comparators assessed in the randomized controlled trials

Cancer type and center	***Comparison***	***N***	***Survival [Overall/ specific]***
Ocular (uveal melanoma)			
MGH (USA)[46]	Higher vs lower dose proton RT	188	No/No
UCSF (USA)[47,48]	Helium RT vs I-125 brachytherapy	136; 184	Yes/Yes
Orsay (France)[49]	Proton RT vs proton RT + laser TTT	151	Yes/Yes
Head/neck (skull base chordoma/chondrosarcoma)			
MGH (USA)[50]	Higher vs lower dose proton RT	96	Yes/No
Head/neck (brain glioblastoma)			
UCSF (USA)[51]	Higher vs lower dose proton RT	15	Yes/Yes
GI (pancreatic cancer)			
UCSF (USA)[52]	Helium RT vs photon RT	49	Yes/Yes
Prostate			
MGH & LLU (USA)[32]	Photon RT + standard dose proton vs Photon RT + high dose proton	393	Yes/Yes
MGH (USA)[53,54]	Photon RT + local photon boost vs Photon RT + local proton boost	202; 191	Yes/Yes

GI: Gastrointestinal; RT: radiotherapy; TTT: transpupillary thermotherapy

Non randomized comparative studies

Table 7 shows the identified 13 nonrandomized comparative studies. Comparators varied according to cancer type. For example, particle beam radiotherapy (as the only treatment) was compared to eye enucleation or brachytherapy in several studies on uveal melanoma. For treatment of other cancers particle beam radiotherapy was typically one of two or more components of the compared patient management strategies.

Table 7. Comparators assessed in the nonrandomized comparative studies

Cancer type and center	***Comparison***	***N***	***Survival [Overall/ specific]***
Ocular (uveal melanoma)			
Orsay (France) [34]	Proton RT vs I-125 brachytherapy	1272	Yes/No
UCSF (USA)[35]	Helium RT vs I-125 brachytherapy	766	No/No
MGH (USA)[36]	Proton RT vs enucleation	556	Yes/Yes
UCSF (USA)[33]	Helium RT vs I-125 brachytherapy	426	No/No
[Wilson 1999 - Unclear center][45]	Proton RT vs I-125 brachytherapy vs Ru-106 brachytherapy	267	Yes/No
MGH (USA)[44]	Proton RT vs enucleation	120	Yes/Yes
UCSF (USA)[37]	Proton RT vs proton RT + laser TTT	56	No/No
Head/neck (skull base adenocystic carcinoma)			
HMI (Germany)[43]	SFRT/IMRT vs SFRT/IMRT + proton boost	63	Yes/Yes
Uterus			
NIRS (Japan)	Carbon RT vs photon RT + brachytherapy	49	No/No
GI (Bile duct)			
UCSF (USA)[55]	Proton RT vs photon RT	62	Yes/Yes
UCSF (USA)[42]	Surgery + photon RT vs Surgery + proton RT	22	No/No
Prostate			
LLU (USA)[39]	Watchful waiting vs surgery vs standalone photon RT vs photon RT + proton boost RT vs standalone proton RT	185	No/No
MGH (USA)[38]	photon RT + photon boost vs photon RT + proton boost	180	Yes/Yes

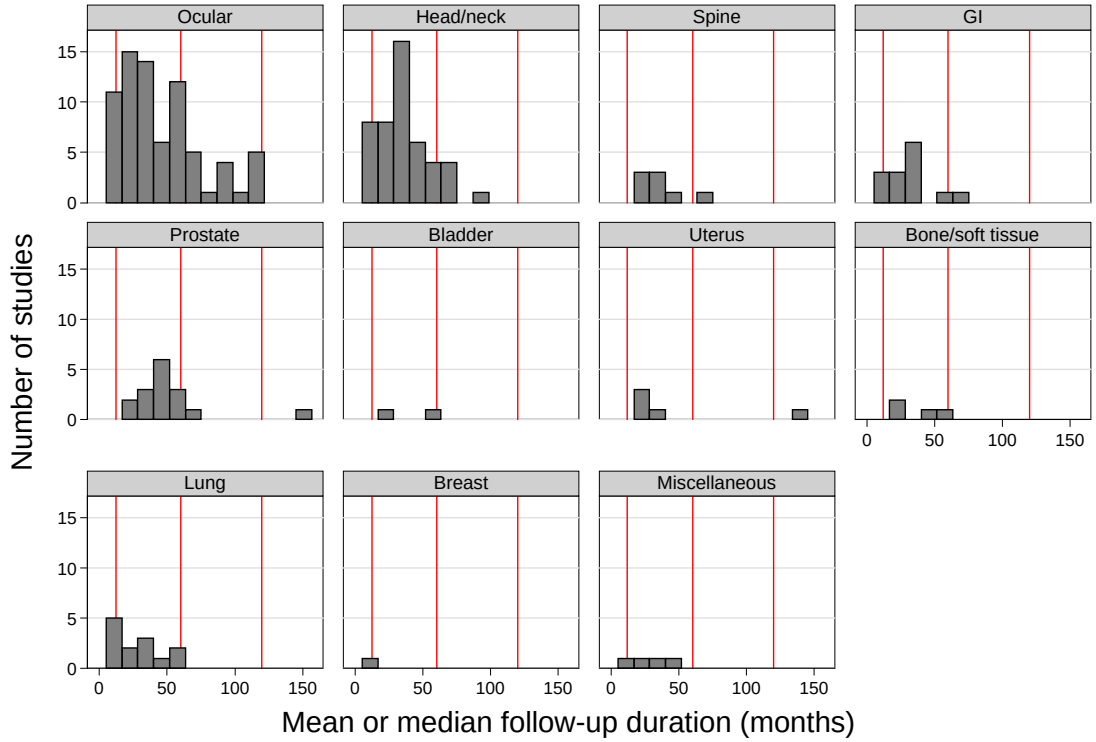
GI: Gastrointestinal; IMRT: intensity modulated radiotherapy; RT: radiotherapy; SFRT: stereotactic fractionated radiotherapy; TTT: transpupillary thermotherapy

3.e. Length of followup

Followup duration varied per type of cancer. For example, in patients with glial tumors it ranged from 5 to 39 months, whereas in patients with uveal melanoma it ranged from 6 to 120 months. This partly reflects expected survival in each cancer type, as well as the different time periods over which patients with different cancers were enrolled and studied (**Figure 5**).

Figure 9 summarizes the mean or median followup duration for the 188 studies that reported this information. Almost all (171/188) reported a mean followup longer than 12 months and 31 reported mean followup longer than 5 years. Many studies did not report how many people were lost to followup (or were excluded due to incomplete followup).

Figure 9. Followup duration per cancer type



GI: Gastrointestinal
The red reference lines correspond to mean followup duration of 12, 60 and 120 months.

3.f. Concurrent or prior treatments

Prior interventions

Particle beam therapy has been explored as to both primary therapy for *de novo* cases and salvage therapy for relapsed and/or refractory cases. Studies on ocular melanoma, prostate cancer, non-small lung cancer, bladder cancer, breast cancer, and skin cancers mainly included untreated *de novo* cases without prior therapy. On the other hand, most hepatocellular cancer cases enrolled in the literature had already received prior

therapeutic interventions such as transcatheter arterial chemoembolization (TACE), percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), surgery, or photon irradiation. Studies on malignant tumors in the head, neck, and spine, some gastrointestinal cancers, bone and soft-tissue sarcoma treated at least some recurrent/refractory cases (who had already failed surgery) in addition to *de novo* cases, chemotherapy, or conventional photon radiotherapy.

Concurrent interventions

Particle beam radiotherapy has been used alone, as a localized boost therapy on top of conventional radiotherapy, or in combination with other interventions. In most studies on ocular melanoma, hepatocellular carcinoma, non-small lung cancer, and uterine cancer, treatment consisted of irradiation (particle beam or photon plus particle beam) alone. Studies on other cancers described a combination of interventions including surgery or chemotherapy. For example, most treatment strategies employed for malignant tumors in the head, neck, and spine (mainly chordoma or chondrosarcoma) and breast cancer included surgery followed by adjuvant local irradiation. Radiotherapy for prostate cancer usually accompanied neoadjuvant, concurrent, or adjuvant hormonal therapy. Bladder cancer studies adopted multi-modality therapy comprising transurethral resection of the tumor lesion followed by chemoradiotherapy. Some head and neck cancer studies and bone and soft-tissue sarcoma studies also employed chemoradiotherapy depending on tumor histology.

3.g. Outcomes measured

Almost all studies reported overall survival, either as crude rates at specific followup durations (e.g., at 5 years or at the end of followup) or as time-to-event analyses (e.g., Kaplan Meier curves). A sizable fraction of these studies also reported cause-specific survival.

Many studies also reported rates of local control. However, the definitions of local control were heterogeneous within and across cancer types. Some defined local control anatomically (e.g., "no radiographic evidence of increase in size"[17]); some defined it by anatomic and clinical criteria (e.g., "absence of tumor growth on followup scans and absence of clinical signs of progression"); some used broad and non-specific criteria (e.g., "absence of evidence of tumor"[29]); and some used more detailed classification: e.g., one study defined local ("any recurrence at or adjacent to the initial primary site") versus regional ("any recurrence in the regional lymph nodes") versus metastatic ("any hematogenous recurrence") recurrence[56].

Most studies also reported crude rates of metastasis or distal disease. Cancer specific outcomes were also described. For example, studies on uveal melanoma reported rates of eye retention, vision retention, visual acuity and changes in tumor size, and studies on bladder cancer reported rates of bladder conservation.

3.h. Adverse events, harms and safety issues reported

Approximately 20 percent of the studies used either the RTOG/EORTC (e.g., Hata 2007[57]) or the LENT-SOMA scales (e.g., Hug 2002[17]) to grade severity when reporting the harms or complications. A number of the studies made the distinction of acute vs late

complications, but "acute" and "late" were not uniformly defined across studies. A typical definition for late events was at least 3 months after the radiation treatment. Studies often reported the number of specific harms and adverse events; however, these counts overlap, because the same patient may have experienced multiple harms. The number of patients who experienced at least one severe or serious adverse event was not routinely reported.

Most studies provided a textual description of the harms or complications. Generally, the harms/complications observed were sustained in structures (extraneous to the tumors) that were unavoidably exposed to the particle beam in the course of treatment (see **Summary Table** of **Appendix G,** where serious adverse events are summarized –less serious harms like alopecia, eye lash loss, mild dermatitis were reported in the various studies but not summarized in this table). As seen in the **Summary Table (Appendix G)**, serious harms that can appear in the treatment of cancer with particle beam therapy (alone or with other treatments) can be debilitating, irreversible, and life threatening. However, as mentioned in the Methods it is often impossible to ascribe specific harms to particle beam therapy rather than chemotherapy or other co-interventions.

In screening through case reports and case series of less than 10 people, we did not identify mention of an adverse event or harm that was not already listed in the studies included in the literature scan.

Discussion

Conventional radiotherapy uses photon irradiation in the locoregional treatment of cancer. Instead, particle beam radiotherapy uses beams of protons or other charged particles such as helium, carbon or other ions. Charged particles have different depth-dose distributions compared to photons. Their physical properties allow precise targeting of the Bragg peak (and therefore the radiation dose) anywhere inside the patient's body. The charged particle beam can be conformed to cover tumors of different shapes.

Few centers worldwide have the large and very expensive facilities to provide this treatment. Technological advances made possible the construction of smaller proton beam treatment instrumentation, and already several hospitals in the USA have expressed interest to obtain it.

We relied heavily on gray literature (Internet) searches to obtain information on the number of particle beam facilities around the world, their location, instrumentation and whether they are currently active or not. The same was true for information on emerging technologies. We explored the web in a semi-structured way to record information from institutional websites, and websites from organizations and companies constructing particle beam treatment facilities. However, we cannot be confident that we have obtained all existing important information, and we cannot verify the validity of the retrieved information from the various websites. Web searching was a necessary component of the methodology of the Technical Brief; relying on review articles (and published literature in general) would provide only limited or out of date information. Better methods for systematic Internet searches on new technologies have to be developed (and validated to the extent possible).

The majority of studies are noncomparative and relatively small in size. Most are retrospective and report a center's experience in treating patients with a given cancer, so that some publications from the same centers likely refer to overlapping populations. Studies report results over long followup periods (in excess of 12 months); however it is not clear whether few people are generally lost to followup or whether people without a minimum followup duration were routinely excluded. Reported outcomes included survival (overall and cause-specific) and outcomes pertaining to local and distal disease control.

Only a handful of RCTs and nonrandomized comparative studies were identified, and they compared lower vs higher doses of particle beam therapy, particle beam therapy alone vs other treatment, or incorporation of particle beam therapy to a treatment strategy vs not. Studies comparing strategies that include particle beam therapy against contemporary alternatives are most informative. From that point of view, comparisons between different types of charged particle therapies should not be a priority (at least in most types of cancers).

In general, randomized trials are needed to reliably estimate the efficacy and safety of interventions. It has been argued that for the comparison between e.g., proton and conventional radiotherapy there is no real equipoise (protons are better):[58] First, the dose

distributions that can be achieved with protons are in almost all cases superior to those possible with x-rays.[58,59] Second, the biological effects of protons are very similar to those of photons, so the only possible differences stem from their physical properties. Third, radiation harms normal tissues as it harms malignant ones, and sparing normal tissues from radiation is self-evidently beneficial. For these reasons, there is "[*verbatim*] a high probability that protons can provide superior therapy to that possible with x-rays in almost all circumstances",[58] and "[*verbatim*] practitioners of proton beam therapy have found it ethically unacceptable to conduct RCTs comparing protons with x-rays".[58]

The aforementioned line of reasoning is rather weak, because it equates increased precision in radiation targeting with positive patient outcomes. This is evidently not the case when broad radiotherapy fields are indicated (e.g., whole brain radiotherapy, whole pelvis radiotherapy) to treat disease that may be locally advanced: the high precision of charged particle therapy is neither necessary nor desirable. Using a similar rationale, it is simply unknown whether overly precise radiation targeting can actually result in better rates of local failure for the majority of patients with common cancers. (For example, there may be satellite lesions that are just distal to the fall-off of the Bragg peak.) Finally, the theorized reductions in the rate and severity of harms with particle beam therapy rather than conventional therapies have not yet been convincingly demonstrated.

Notwithstanding the need for randomized experiments, there are additional approaches that can provide potentially useful insights. Nonrandomized prospective comparative studies using proper statistical analyses that are superior to simple adjustments (such as propensity score-based analyses[60] or instrumental variable regression analyses[61]) can be used to explore the comparative effectiveness and safety of charged particle therapy vs conventional radiotherapy. Although nonrandomized designs cannot provide definitive evidence, their results may challenge conventional wisdom and formulate hypotheses for testing in randomized studies.

Furthermore, with newer technological advances, particle beam therapies are expected to become increasingly available and at reduced cost. They will likely be used to treat patients with broader indications. This anticipated diffusion of the technology can have important implications (on economic aspects, prioritization of resources, or even on health outcomes through yet unknown mechanisms). Especially for many patients with common cancers, such as breast, prostate, lung, and pancreatic cancers, where extreme precision in dose targeting is not a *sine-qua-non*, it is essential that the theorized advantages of particle beam therapy versus contemporary alternative interventions are first proven in controlled clinical trials. Concomitant economic evaluations would probably prove useful in informing cost-effectiveness or other economic analyses.

It is likely that focused systematic reviews will not be able to provide a definitive answer on the effectiveness and safety of charged particle beam radiotherapies compared to alternative interventions. This is largely because of the relative lack of comparative studies in general, and randomized trials in particular. For example, a recent Effective Health Care (EHC) report[62] that included a systematic review[63] on the comparative effectiveness and harms of treatments for clinically localized prostate cancer did not provide a definitive conclusion on the role of proton beam radiotherapy.

In brief, there are a substantial number of publications on particle (mainly proton) beam therapy for the treatment of cancer. However, they typically do not use a concurrent control, focus on heterogeneous populations, and employ different definitions for outcomes and harms. Comparative studies in general, and randomized trials in particular, are needed to document the theorized advantages of particle beam therapy. This is especially important in the light of the anticipated diffusion of this technology to treating common cancers in which extreme precision in radiation targeting is not a *sine-qua-non*. We anticipate that systematic reviews of the current literature will 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.

References

(1) Levin WP, Kooy H, Loeffler JS, Delaney TF. Proton beam therapy. *Br J Cancer* 2005; **93:** 849-54.

(2) Veldeman L, Madani I, Hulstaert F, De MG, Mareel M, De NW. Evidence behind use of intensity-modulated radiotherapy: a systematic review of comparative clinical studies. *Lancet Oncol* 2008; **9:** 367-75.

(3) Paganetti H, Niemierko A, Ancukiewicz M, Gerweck LE, Goitein M, Loeffler JS et al. Relative biological effectiveness (RBE) values for proton beam therapy. *Int J Radiat Oncol Biol Phys* 2002; **53:** 407-21.

(4) Matsufuji N, Kanai T, Kanematsu N, Miyamoto T, Baba M, Kamada T et al. Specification of Carbon Ion Dose at the National Institute of Radiological Sciences (NIRS). *J Radiat Res (Tokyo)* 2007; **48 Suppl A:** A81-A86.

(5) EpiData (version 3). A comprehensive tool for validated entry and documentation of data. The EpiData Association, Odense Denmark. [computer program]. Version 3.1 2004.

(6) Schulz-Ertner D, Tsujii H. Particle radiation therapy using proton and heavier ion beams. *J Clin Oncol* 2007; **25:** 953-64.

(7) Brada M, Pijls-Johannesma M, De RD. Proton therapy in clinical practice: current clinical evidence. *J Clin Oncol* 2007; **25:** 965-70.

(8) Geenen MM, Cardous-Ubbink MC, Kremer LC, van den BC, van der Pal HJ, Heinen RC et al. Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. *JAMA* 2007; **297:** 2705-15.

(9) Gueulette J, Wambersie A. Comparison of the Methods of Specifying Carbon Ion Doses at NIRS and GSI. *J Radiat Res (Tokyo)* 2007; **48 Suppl A:** A97-A102.

(10) Mendenhall WM, Amdur RJ, Palta JR. Intensity-modulated radiotherapy in the standard management of head and neck cancer: promises and pitfalls. *J Clin Oncol* 2006; **24:** 2618-23.

(11) Chang BK, Timmerman RD. Stereotactic body radiation therapy: a comprehensive review. *Am J Clin Oncol* 2007; **30:** 637-44.

(12) Timmerman RD, Kavanagh BD, Cho LC, Papiez L, Xing L. Stereotactic body radiation therapy in multiple organ sites. *J Clin Oncol* 2007; **25:** 947-52.

(13) Patel RR, Arthur DW. The emergence of advanced brachytherapy techniques for common malignancies. *Hematol Oncol Clin North Am* 2006; **20:** 97-118.

(14) Sisterson J. Treatment planning systems for proton and ion beam therapy. *Particles* 2005; 10.

(15) Benk V, Liebsch NJ, Munzenrider JE, Efird J, McManus P, Suit H. Base of skull and cervical spine chordomas in children treated by high-dose irradiation. *International Journal of Radiation Oncology, Biology, Physics 31 (3):577 -81* , 1995.

(16) Fuss M, Hug EB, Schaefer RA, Nevinny-Stickel M, Miller DW, Slater JM et al. Proton radiation therapy (PRT) for pediatric optic pathway gliomas: comparison with 3D planned conventional photons and a standard photon technique. *International Journal of Radiation Oncology, Biology, Physics 45 (5):1117 -26* , 1999.

(17) Hug EB, Muenter MW, Archambeau JO, DeVries A, Liwnicz B, Loredo LN et al. Conformal proton radiation therapy for pediatric low-grade astrocytomas. *Strahlentherapie und Onkologie 178 (1):10-7 ,* 2002.

(18) Hug EB, Sweeney RA, Nurre PM, Holloway KC, Slater JD, Munzenrider JE. Proton radiotherapy in management of pediatric base of skull tumors. *International Journal of Radiation Oncology, Biology, Physics 52(4):1017 -24 ,* 2002.

(19) McAllister B, Archambeau JO, Nguyen MC, Slater JD, Loredo L, Schulte R et al. Proton therapy for pediatric cranial tumors: preliminary report on treatment and disease-related morbidities. *International Journal of Radiation Oncology, Biology, Physics 39 (2):455 -60 ,* 1997.

(20) Noel G, Habrand JL, Helfre S, Mammar H, Kalifa C, Ferrand R et al. Proton beam therapy in the management of central nervous system tumors in childhood: the preliminary experience of the Centre de Protontherapie d'Orsay. *Medical & Pediatric Oncology 40 (5):309 -15,* 2003.

(21) Timmermann B, Schuck A, Niggli F, Weiss M, Lomax AJ, Pedroni E et al. Spot-scanning proton therapy for malignant soft tissue tumors in childhood: First experiences at the Paul Scherrer Institute. *International Journal of Radiation Oncology, Biology, Physics 67 (2):497 -504 ,* 2007.

(22) Bush DA, Dunbar RD, Bonnet R, Slater JD, Cheek GA, Slater JM. Pulmonary injury from proton and conventional radiotherapy as revealed by CT. *AJR American Journal of Roentgenology 172 (3):735 -9,* 1999.

(23) Bush DA, Slater JD, Bonnet R, Cheek GA, Dunbar RD, Moyers M et al. Proton-beam radiotherapy for early-stage lung cancer. *Chest 116 (5):1313 -9,* 1999.

(24) Bush DA, Slater JD, Shin BB, Cheek G, Miller DW, Slater JM. Hypofractionated proton beam radiotherapy for stage I lung cancer. *Chest 126 (4):1198 -203 ,* 2004.

(25) Bonnet RB, Bush D, Cheek GA, Slater JD, Panossian D, Franke C et al. Effects of proton and combined proton/photon beam radiation on pulmonary function in patients with resectable but medically inoperable non-small cell lung cancer. *Chest 120 (6):1803 -10,* 2001.

(26) Hata M, Tokuuye K, Kagei K, Sugahara S, Nakayama H, Fukumitsu N et al. Hypofractionated high-dose proton beam therapy for stage I non-small-cell lung cancer: preliminary results of a phase I/II clinical study. *International Journal of Radiation Oncology, Biology, Physics 68(3):786 -93 ,* 2007.

(27) Kozak KR, Smith BL, Adams J, Kornmehl E, Katz A, Gadd M et al. Accelerated partial-breast irradiation using proton beams: initial clinical experience. *International Journal of Radiation Oncology, Biology, Physics 66 (3):691 -8 ,* 2006.

(28) Miyamoto T, Baba M, Sugane T, Nakajima M, Yashiro T, Kagei K et al. Carbon ion radiotherapy for stage I non-small cell lung cancer using a regimen of four fractions during 1 week.[see comment]. *Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer 2(10):916 -26 ,* 2007.

(29) Miyamoto T, Baba M, Yamamoto N, Koto M, Sugawara T, Yashiro T et al. Curative treatment of Stage I non-small-cell lung cancer with carbon ion beams using a hypofractionated regimen. *International Journal of Radiation Oncology, Biology, Physics 67 (3):750 -8 ,* 2007.

(30) Hirasawa N, Tsuji H, Ishikawa H, Koyama-Ito H, Kamada T, Mizoe JE et al. Risk factors for neovascular glaucoma after carbon ion radiotherapy of choroidal melanoma using dose-volume histogram analysis. *International Journal of Radiation Oncology, Biology, Physics 67 (2):538 -43 ,* 2007.

(31) Tsuji H, Ishikawa H, Yanagi T, Hirasawa N, Kamada T, Mizoe JE et al. Carbon-ion radiotherapy for locally advanced or unfavorably located choroidal melanoma: a Phase I/II dose-escalation study. *International Journal of Radiation Oncology, Biology, Physics 67 (3):857 -62* , 2007.

(32) Zietman AL, DeSilvio ML, Slater JD, Rossi CJ, Jr., Miller DW, Adams JA et al. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial.[see comment]. *JAMA 294 (10):1233 -9,* 2005.

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

(34) Desjardins L, Lumbroso L, Levy C, Mazal A, Delacroix S, Rosenwald JC et al. [Treatment of uveal melanoma with iodine 125 plaques or proton beam therapy: indications and comparison of local recurrence rates]. [French]. *Journal Francais d Opthalmologie 26 (3):269 -76* , 2003.

(35) Harbour JW, Char DH, Kroll S, Quivey JM, Castro J. Metastatic risk for distinct patterns of postirradiation local recurrence of posterior uveal melanoma. *Ophthalmology 104 (11):1785 -92 ; discussion 1792 -3,* 1997.

(36) Seddon JM, Gragoudas ES, Egan KM, Glynn RJ, Howard S, Fante RG et al. Relative survival rates after alternative therapies for uveal melanoma. *Ophthalmology 97 (6):769 -77* , 1990.

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

(38) Duttenhaver JR, Shipley WU, Perrone T, Verhey LJ, Goitein M, Munzenrider JE et al. Protons or megavoltage X-rays as boost therapy for patients irradiated for localized prostatic carcinoma. An early phase I/II comparison. *Cancer 51 (9):1599 -604* , 1983.

(39) Galbraith ME, Ramirez JM, Pedro LW. Quality of life, health outcomes, and identity for patients with prostate cancer in five different treatment groups. *Oncology Nursing Forum 28 (3):551 -60,* 2001.

(40) Nakano T, Suzuki Y, Ohno T, Kato S, Suzuki M, Morita S et al. Carbon beam therapy overcomes the radiation resistance of uterine cervical cancer originating from hypoxia. *Clinical Cancer Research 12(7 Pt 1):2185 -90* , 2006.

(41) Schoenthaler R, Castro JR, Petti PL, Baken-Brown K, Phillips TL. Charged particle irradiation of sacral chordomas. *International Journal of Radiation Oncology, Biology, Physics 26 (2):291 -8* , 1993.

(42) Schoenthaler R, Phillips TL, Castro J, Efird JT, Better A, Way LW. Carcinoma of the extrahepatic bile ducts. The University of California at San Francisco experience. *Annals of Surgery 219 (3):267 -74* , 1994.

(43) Schulz-Ertner D, Nikoghosyan A, Didinger B, Munter M, Jakel O, Karger CP et al. Therapy strategies for locally advanced adenoid cystic carcinomas using modern radiation therapy techniques. *Cancer 104 (2):338 -44* , 2005.

(44) Seddon JM, Gragoudas ES, Albert DM, Hsieh CC, Polivogianis L, Friedenberg GR. Comparison of survival rates for patients with uveal melanoma after treatment with proton beam irradiation or enucleation. *American Journal of Ophthalmology 99 (3):282 -90* , 1985.

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

(46) Gragoudas ES, Lane AM, Regan S, Li W, Judge HE, Munzenrider JE et al. A randomized controlled trial of varying radiation doses in the treatment of choroidal melanoma. *Archives of Ophthalmology 118 (6):773 -8* , 2000.

(47) Char DH, Castro JR, Quivey JM, Phillips TL, Irvine AR, Stone RD et al. Uveal melanoma radiation. 125I brachytherapy versus helium ion irradiation. *Ophthalmology 96 (12):1708 -15* , 1989.

(48) Char DH, Quivey JM, Castro JR, Kroll S, Phillips T. Helium ions versus iodine 125 brachytherapy in the management of uveal melanoma. A prospective, randomized, dynamically balanced trial. *Ophthalmology 100 (10):1547 -54* , 1993.

(49) Desjardins L, Lumbroso-Le RL, Levy-Gabriel C, Dendale R, Delacroix S, Nauraye C et al. Combined proton beam radiotherapy and transpupillary thermotherapy for large uveal melanomas: a randomized study of 151 patients.[see comment]. *Ophthalmic Research 38 (5):255 -60,* 2006.

(50) Santoni R, Liebsch N, Finkelstein DM, Hug E, Hanssens P, Goitein M et al. 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 41 (1):59 -68,* 1998.

(51) Castro JR, Phillips TL, Prados M, Gutin P, Larson DA, Petti PL et al. Neon heavy charged particle radiotherapy of glioblastoma of the brain. *International Journal of Radiation Oncology, Biology, Physics 38 (2):257 -61* , 1997.

(52) Linstadt D, Quivey JM, Castro JR, Andejeski Y, Phillips TL, Hannigan J et al. 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 randomized prospective clinical trial. *Radiology 168 (1):261 -4,* 1988.

(53) Shipley WU, Verhey LJ, Munzenrider JE, Suit HD, Urie MM, McManus PL et al. 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.[see comment]. *International Journal of Radiation Oncology, Biology, Physics 32 (1):3-12* , 1995.

(54) Benk VA, Adams JA, Shipley WU, Urie MM, McManus PL, Efird JT et al. 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 26 (3):551 -7* , 1993.

(55) Schoenthaler R, Castro JR, Halberg FE, Phillips TL. Definitive postoperative irradiation of bile duct carcinoma with charged particles and/or photons. *International Journal of Radiation Oncology, Biology, Physics 27 (1):75 -82* , 1993.

(56) Weber DC, Rutz HP, Bolsi A, Pedroni E, Coray A, Jermann M et al. Spot scanning proton therapy in the curative treatment of adult patients with sarcoma: the Paul Scherrer institute experience. *International Journal of Radiation Oncology, Biology, Physics 69 (3):865 -71,* 2007.

(57) Hata M, Tokuuye K, Sugahara S, Tohno E, Nakayama H, Fukumitsu N et al. Proton beam therapy for aged patients with hepatocellular carcinoma. *International Journal of Radiation Oncology, Biology, Physics 69 (3):805 -12,* 2007.

(58) Goitein M, Cox JD. Should randomized clinical trials be required for proton radiotherapy? *J Clin Oncol* 2008; **26:** 175-6.

(59) Glimelius B, Ask A, Bjelkengren G, Bjork-Eriksson T, Blomquist E, Johansson B et al. Number of patients potentially eligible for proton therapy. *Acta Oncol* 2005; **44:** 836-49.

(60) D'Agostino RB, Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med* 1998; **17:** 2265-81.

(61) Stukel TA, Fisher ES, Wennberg DE, Alter DA, Gottlieb DJ, Vermeulen MJ. Analysis of observational studies in the presence of treatment selection bias: effects of invasive cardiac management on AMI survival using propensity score and instrumental variable methods. *JAMA* 2007; **297:** 278-85.

(62) Wilt, T. J., Shamliyan, T, Taylor, B, MacDonald, R, Tacklind, J, Rutks, I, Koeneman, K, Cho, C-S, and Kane, RL. Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer. Comparative Effectiveness Review No. 13. (Prepared by Minnesota Evidence-based Practice Center under Contract No. 290-02-00009.) Rockville, MD: Agency for Healthcare Research and Quality.; 2008.

(63) Wilt TJ, MacDonald R, Rutks I, Shamliyan TA, Taylor BC, Kane RL. Systematic review: comparative effectiveness and harms of treatments for clinically localized prostate cancer. *Ann Intern Med* 2008; **148:** 435-48.