Technical Brief

Number 1

Particle Beam Radiation Therapies for Cancer

Agency for Healthcare Research and Quality
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This report is based on research conducted by the Tufts Medical Center Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. HHSA 290-07-10055). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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Number 1

Particle Beam Radiation Therapies for Cancer

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the State Children's Health Insurance Program (SCHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments and Comparative Effectiveness Reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care. Technical Briefs are the most recent addition to this body of knowledge.

A Technical Brief provides an overview of key issues related to a clinical intervention or health care service—for example, current indications for the intervention, relevant patient population and subgroups of interest, outcomes measured, and contextual factors that may affect decisions regarding the intervention. Technical Briefs generally focus on interventions for which there are limited published data and too few completed protocol-driven studies to support definitive conclusions. The emphasis, therefore, is on providing an early objective description of the state of science, a potential framework for assessing the applications and implications of the new interventions, a summary of ongoing research, and information on future research needs.

Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly, while Technical Briefs will serve to inform new research development efforts.

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Executive Summary

Background

Radiotherapy with charged particles can potentially deliver maximal doses while minimizing irradiation of surrounding tissues. It may be more effective or less harmful than other forms of radiotherapy for some cancers. Currently, seven centers in the United States have facilities for particle (proton) irradiation, and at least four are under construction, each costing between $100 and $225 million. The aim of this Technical Brief was to survey the evidence on particle beam radiotherapy.

Methods

We searched MEDLINE from its inception to July 2009 for publications in English, German, French, Italian, and Japanese. We visited Web sites of manufacturers, treatment centers, and professional organizations for relevant information.

Four reviewers identified studies of any design describing clinical outcomes or adverse events with 10 or more cancer patients treated with charged particle radiotherapy. Each of four reviewers extracted study, patient, and treatment characteristics; clinical outcomes; and adverse events for nonoverlapping sets of papers. A different reviewer verified data on comparative studies.

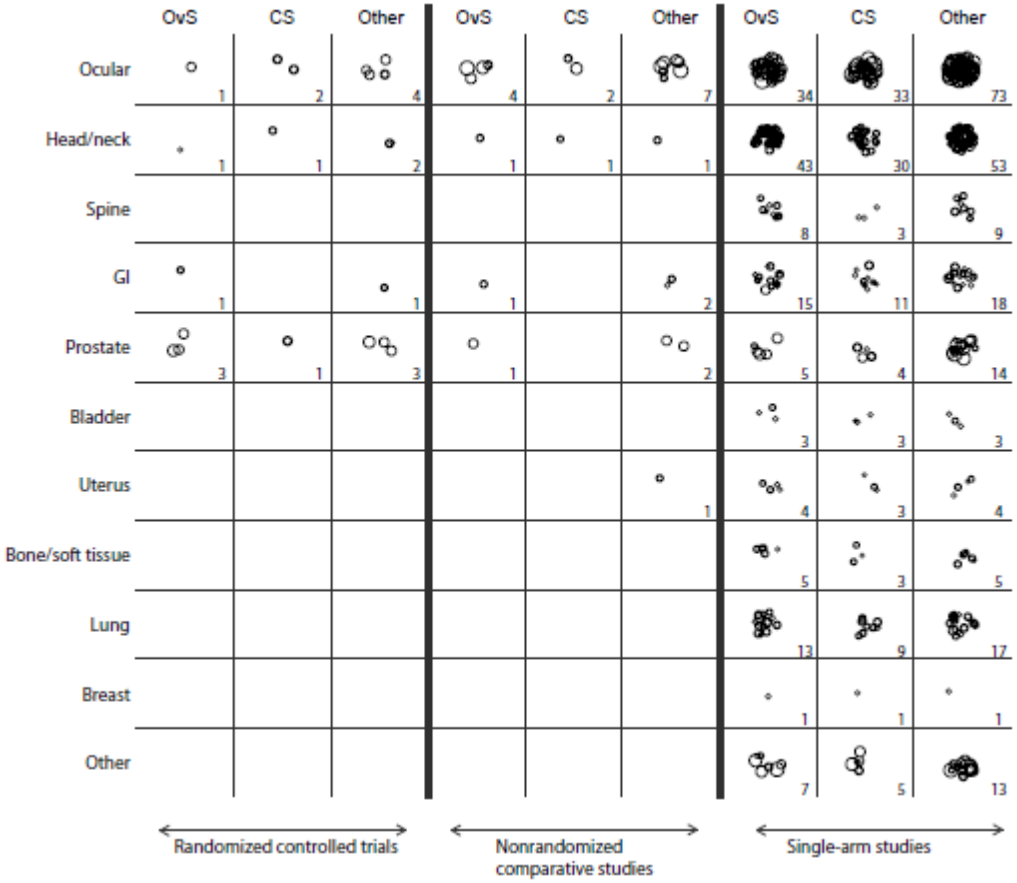
Results

Figure A summarizes study designs, diseases, and outcomes in the 243 eligible papers. Charged particle beam radiotherapy was used alone or in combination with other interventions for both common cancers (e.g., lung, prostate, breast) and uncommon cancers (e.g., skull base tumors, uveal melanomas). Out of 243 papers, 185 were single-arm retrospective studies, and another 35 studies were prospective single-arm trials. The number of included patients ranged from 10 to 2,645 (median 63). Seven studies (3 percent) focused on a pediatric population; most of the remaining studies reported mean or median age above 50 years. The reported followup periods ranged from 5 to 157 months (median, 36 months) for 188 studies that commented on the pertinent data. Thirty-one studies followed patients longer than 5 years. Two studies had mean followup longer than 10 years.

The spectrum of included patients varied depending on the cancer type. For uveal melanoma, for example, particle beam therapy was used for a wide range of melanoma locations (i.e., choroid plexus, ciliary body, or iris) and sizes. For non-small-cell lung cancer and hepatocellular carcinoma, patients who either refused surgery or were ineligible for other types of therapies received charged particle beam radiotherapy. Typically, studies did not provide detailed information on the cancer staging or explicit descriptions of the clinical context--i.e., primary stand-alone or adjuvant therapy to other therapies for newly diagnosed cancer, or salvage therapy after treatment failure to previous therapies.

Most studies reported patient relevant-clinical outcomes: 151 studies (62 percent) described overall survival; 112 studies (46 percent), cancer specific survival; and 210 studies (86 percent), other surrogate outcomes of overall survival. Some studies reported clinical outcomes that are relevant to the quality of life, such as eye retention rates or visual acuity in uveal melanoma or bladder conservation rates in bladder cancer.

Figure A. Current clinical evidence on charged particle radiotherapy



Notes: Each circle represents a study, with size proportional to the logarithm of the total number of participants included in a study. The number in each cell indicates the total number of studies. Each row shows studies addressing one specific cancer category, and the columns show study designs with reported clinical outcomes. The "Other" row includes studies reporting multiple different cancers. The "Other" columns include studies reporting any clinical outcomes other than overall survival or cancer-specific survival (e.g., disease-free survival, progression-free survival, tumor response rate, or quality of life).
Abbreviations: CS=cancer-specific survival; GI=gastrointestinal; OvS=overall survival.

Seventy-five percent of studies (188) reported the adverse events. Not all studies adopted established scales to evaluate adverse events. Generally, the harms or complications observed were sustained in structures (extraneous to the tumors) that were unavoidably exposed to the particle beam in the course of treatment. However, it was not clear whether the reported adverse events were exclusively attributable to charged particle radiotherapy or to other cointerventions in the case of multimodality treatment, or whether they also would have occurred with conventional radiation therapy.

Eight randomized and nine nonrandomized comparative studies compared treatments with or without charged particles. The eight randomized trials were reported in 10 publications and enrolled 1,278 patients in total (**Table A**). Primary outcomes were explicitly stated in only three trials, which also reported a priori sample size calculations. Three trials pertained to prostate cancer, whereas the remaining dealt with less common cancers (ocular melanoma, skull base and brain tumors, and pancreatic cancer). All trials enrolled a relatively small sample size, ranging from 15 to 393 patients and studied different comparisons (**Table A**). Most trials did not

compare charged particle radiotherapy with contemporary alternates. No trial reported significant differences in overall or cancer-specific survival or in total serious adverse events.

Table A. Comparators assessed in the randomized controlled trials

Cancer type and center	Comparison	N	Survival (overall/ specific)
Ocular (uveal melanoma)			
MGH (US)	Higher vs. lower dose proton RT	188	No/No
UCSF (US)	Helium RT vs. I-125 brachytherapy	136; 184	Yes/Yes
CPO (France)	Proton RT vs. proton RT + laser TTT	151	Yes/Yes
Head/neck (skull base chordoma/chondrosarcoma)			
MGH (US)	Higher vs. lower dose proton RT	96	Yes/No
Head/neck (brain glioblastoma)			
UCSF (US)	Higher vs. lower dose proton RT	15	Yes/Yes
GI (pancreatic cancer)			
UCSF (US)	Helium RT vs. photon RT	49	Yes/Yes
Prostate			
MGH and LLU (US)	Photon RT + standard-dose proton vs. photon RT + high-dose proton	393	Yes/Yes
MGH (US)	Photon RT + local photon boost vs. photon RT + local proton boost	202; 191	Yes/Yes

Abbreviations: CPO=Centre de protonthérapie d'Orsay; GI=gastrointestinal; LLU=Loma Linda University; MGH=Massachusetts General Hospital; N=number of enrolled patients; RT=radiotherapy; TTT=transpupillary thermotherapy; UCSF=University of California San Francisco.

Nine nonrandomized comparative studies were reported in 13 papers (estimated 4,086 unique patients). Comparators assessed in the nonrandomized comparative studies are shown in **Table B**. Charged particle radiotherapy was compared with: brachytherapy for uveal melanoma (four studies); conventional photon radiation for other cancers (six studies); surgery (three studies). None of the studies used advanced statistical analyses, such as propensity score matching or instrumental variable regressions, to better adjust for confounding. Overall, no study found that charged particle radiotherapy is significantly better than alternative treatments with respect to patient-relevant clinical outcomes.

Table B. Comparators assessed in the nonrandomized comparative studies

Cancer type and center	Comparison	N	Survival (overall/ specific)
Ocular (uveal melanoma)			
CPO (France)	Proton RT vs. I-125 brachytherapy	1272	Yes/No
UCSF (US)	Helium RT vs. I-125 brachytherapy	766	No/No
MGH (US)	Proton RT vs. enucleation	556	Yes/Yes
UCSF (US)	Helium RT vs. I-125 brachytherapy	426	No/No
CCO (UK)	Proton RT vs. I-125 brachytherapy vs. Ru-106 brachytherapy	267	Yes/No
MGH (US)	Proton RT vs. enucleation	120	Yes/Yes
UCSF (US)	Proton RT vs. proton RT + laser TTT	56	No/No
Head/neck (skull base adenocystic carcinoma)			
GSI (Germany)	SFRT/IMRT vs. SFRT/IMRT + carbon (ion) boost	63	Yes/Yes
Uterus			
NIRS (Japan)	Carbon RT vs. photon RT + brachytherapy	49	No/No
GI (Bile duct)			
UCSF (US)	Proton RT vs. photon RT	62	Yes/Yes
UCSF (US)	Surgery + photon RT vs. surgery + proton RT	22	No/No
Prostate			
LLU (US)	Watchful waiting vs. surgery vs. Stand-alone photon RT vs. photon RT + proton boost RT vs. Stand-alone proton RT	185	No/No
MGH (US)	photon RT + photon boost vs. photon RT + proton boost	180	Yes/Yes

Abbreviations: CCO=Clatterbridge Centre for Oncology; CPO=Centre de protonthérapie d'Orsay; GI=gastrointestinal; GSI=Gesellschaft fuer; IMRT=intensity-modulated radiotherapy; LLU=Loma Linda University; MGH=Massachusetts General Hospital; N=number of included patients; NIRS=National Institute of Radiological Sciences; RT=radiotherapy; SFRT=stereotactic fractionated radiotherapy; TTT=transpupillary thermotherapy; UCSF=University of California San Francisco.

Remaining Issues and Future Research

In summary, a large number of scientific papers on charged particle radiotherapy for the treatment of cancer currently exist. However, these studies do not document the circumstances in contemporary treatment strategies in which radiotherapy with charged particles is superior to other modalities. Comparative studies in general, and randomized trials in particular (when feasible), are needed to document the theoretical advantages of charged particle radiotherapy to specific clinical situations.

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 to be addressed in comparative studies.

The available slots for particle beam radiotherapy are very limited, and this may have impacted the design of studies conducted to date. Most eligible studies were noncomparative in nature and had small sample sizes.

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 with 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 relative safety and effectiveness of particle beam therapy vs. other treatment options in the context of current clinical practice. This is especially true for the treatment of common cancers.

Charged particle 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 (and as the associated costs decrease), it will also be increasingly used with much broader indications. This anticipated diffusion of the technology can have important implications (economic, regarding 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 vs. contemporary alternative interventions are proven in controlled clinical trials, along with concomitant economic evaluations.

Introduction

Photon Beam Radiotherapy

Most types of cancer radiotherapy use 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 prolonged abnormal cell function and 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] Apart from conventional external radiation therapy, several modalities have been developed that for radiotherapy delivery. 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.) IMRT and other radiotherapy delivery methods (i.e., conventional radiotherapy, stereotactic radiosurgery with photons and brachytherapy) are further discussed in the Results section of this Technical Brief.

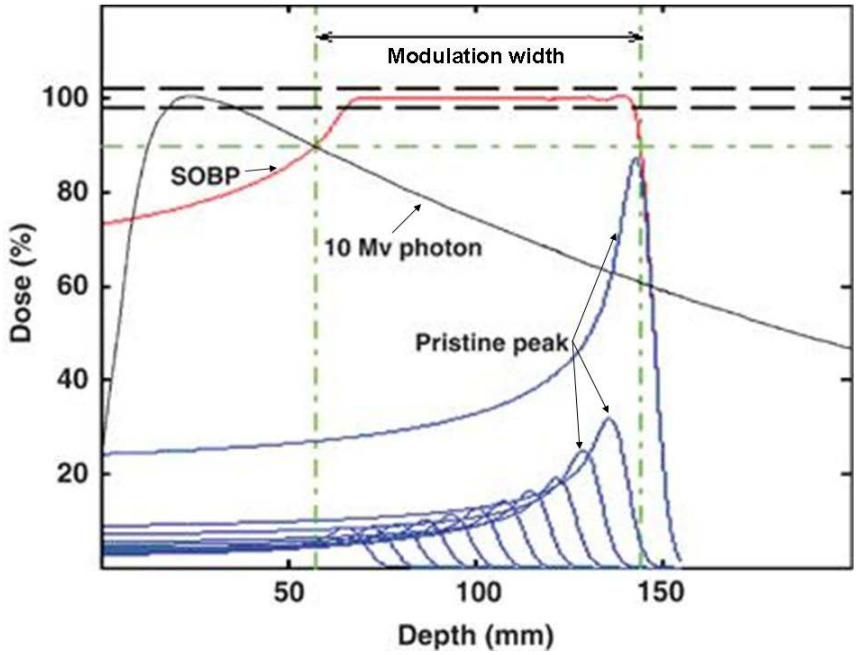
Charged Particle Beam Radiotherapy

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 deliver prespecified doses anywhere in the patient's body with high precision. 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 different RBE and 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 tumor area (in lateral dimensions and depth) using a *single* radiation field (something that is not possible with photon beams).[1] In general, a set of charged particle fields achieves dose reduction to uninvolved normal tissues, compared to photon radiotherapy. In practice, more than one entry port may be required with charged particles, especially when it is important to achieve adequate skin sparing. We discuss advantages and the disadvantages of charged particle therapy

and other radiotherapy options (e.g., external radiotherapy with photons and brachytherapy) in a specific section in this Technical Brief.

Ongoing research explores even more advanced methods to deliver charged particle beam radiotherapy. For example, intensity modulated proton therapy, or IMPT, is a methodology that uses a narrow proton beam (a "pencil" beam) that is "scanned" over the target volume by means of a magnetic field, while both the energy (speed) of the protons and the intensity of the beam are modulated. As of this writing, only the Paul Scherrer Institute (PSI) in Switzerland has facilities that deliver IMPT.

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 Medical Center 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 US?

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 ions 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 (in the patient's body).

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 10/29/2008.

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. We updated the aforementioned search to identify additional comparative studies on 07/11/2009. No additional comparative studies were found.

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 harms that were Grade 3 or higher as "severe"; and harms reported at least 3 months after irradiation as "late". 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 benefit of precise dose localization and have favorable dose-depth distributions, compared with conventional photon beam radiotherapy.[6] It is theorized that this translates to favorable clinical outcomes compared to conventional radiotherapy. Particle beams 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 adjacent 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 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

[i] Source http://ptcog.web.psi.ch – last accessed 10/29/2008, and Levin 2005.[1]

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]

We note that, even with charged particle beams, delivery of radiation therapy can be imprecise. Because of the way charged particles interact with matter, dose deposition with charged particle beams is dependent on tissue inhomogeneities (such as air cavities), posing obstacles to the calculation of the exact location of the distal Bragg peak. [9] Moreover, investigators have described a slight increase in the RBE of charged particles at the distal end of the beam,[3] which may affect treatment planning.

Description and Pros and Cons of Radiotherapeutic Alternatives to Particle Beam Therapy

The following descriptions do not constitute an exhaustive list.

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 is less of an issue with protons).[10]

IMRT

Modern radiotherapy delivery methods capitalize on advances in imaging and radiation treatment planning technologies and allow for 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.[2,11] IMRT is already used in many hospitals in the US.

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.[11]

Stereotactic radiosurgery with photons

Photon 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 e.g. by respiration, this technique 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.[12,13]

However, stereotactic radiosurgery with photons 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).[14]

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

Charged particle radiotherapy is less tolerant than photons of inadequacies in the planning, optimization and execution of radiation therapy. As the delivery of radiotherapy becomes more precise, several issues become more important. First, despite advances in medical imaging, the ability to distinguish tumor tissue from normal tissue is often limited, and this should be accounted for during treatment planning. Second, even when patient immobilization is excellent, one has to compensate for target tissue movements due to respiration, pulse, or peristalsis (e.g., using respiratory gating, widening the treatment volume margins or using other techniques). Third, with repeated treatments, it is important to accurately reproduce the alignment of the beam with the target area, and to account for the shrinkage of the irradiated target tissues as treatment sequence progresses.

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 (tissue

volumes that receive the same radiation dose) do not necessarily correspond to biologically iso-effective doses (in GyE) (tissue volumes that have received the same biologically effective dose).[10] In addition, the early and late radiosensitivity of various tissues could be different compared to what is known from photon radiotherapy.[10] Therefore treatment plans generated by different methods for light ions may not result in identical actual doses in a given patient. In contrast to other ions, to date experience with protons suggests that for the same biological dose, the sensitivity of different tissues to protons is the same as with photons.

Key Question 2

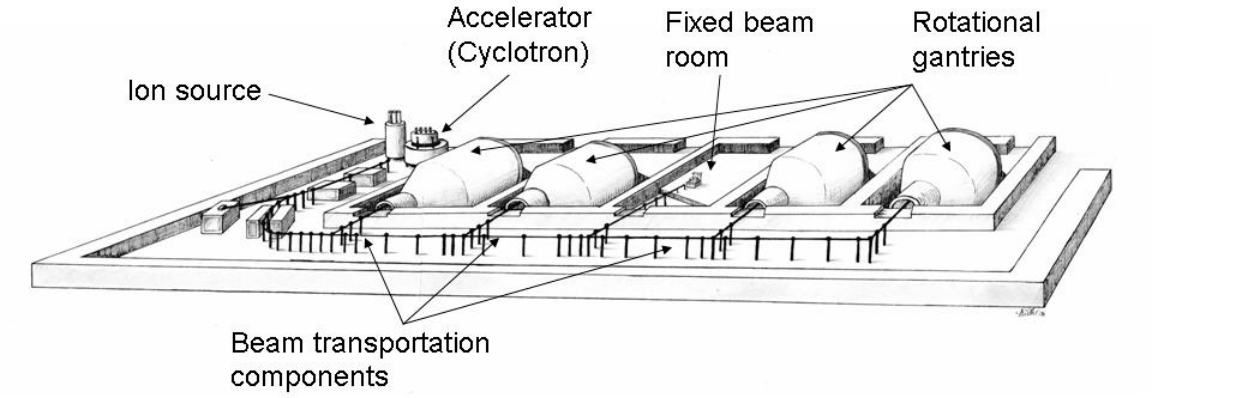
2.a. What instrumentation is needed for particle beam radiation and what is the FDA status of this instrumentation?
2.b. What is an estimate of the number of hospitals that currently have the instrumentation or are planning to build instrumentation for these therapies?
2.c. What instrumentation technologies 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 of several possible layouts 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 main accelerator is typically a cyclotron, 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).

3. The accelerated particle beam is then transported by a series of tubes that are under vacuum and shaping and focusing magnets towards the patient treatment rooms. Special devices (wedges) can decrease particle energy (speed) to desirable levels.
4. 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.
5. 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).
6. 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).
7. There is also a therapy control system that provide the interface to control and monitor equipment to deliver treatment to the patient.

The stages outlined above can differ for facilities that use other types of accelerators such as synchrotrons or synchrocyclotrons rather than cyclotrons. For example, synchrotrons offer the ability to control the energy, intensity and even the shape of the beam with electronic means, rather than physical means (wedges), but they deliver the beam in pulses rather than continuously. More detailed discussion of technical information is outside the scope of this Technical Brief.

Treatment Planning Software/Systems

Several pieces of software were developed for treatment planning since the early 80's. **Table 1** provides a list of treatment planning software/treatment planning systems released up to 2002.[15]

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,[15] http://ptcog.web.psi.ch/archive_particles.html (last accessed 10/29/2008).

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.[10] 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.[10]

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 cleared specific devices as substantially equivalent to a medical cyclotron using protons that was in commercial use during the 1960s and 70s. All US facilities that are currently active have FDA cleared instrumentation.[ii]

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.

[ii] Source: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm, Product Code "LHN" (last accessed 10/29/2008)

Training programs have been ongoing at the Massachusetts General Hospital and at the Loma Linda University for the past few decades. The training covers various aspects of proton therapy.

It is also advertised that, in the US, 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 is advertised to provide clinical, technical, interpersonal and administrative training for radiation oncologists, medical physicists, dosimetrists, radiation therapists and other staff.[iii]

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 US, 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 US.

Table 2. Currently operating particle beam facilities in the US

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
Procure Proton Therapy Center, OK	proton	[?]	1	?	1	2009	NA	NA

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 10/29/2008), Levin 2005,1 and http://procure.com/ok (last accessed 07/21/2009)

There are at least 3 large facilities that are in construction phase in the US (**Table 3**). 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**). As mentioned in the next section, several US hospitals have expressed interest in building smaller scale proton beam facilities.

[iii] Source: http://www.insideindianabusiness.com/newsitem.asp?id=28727 (last accessed 10/29/2008)

Table 3. Large particle beam facilities that are being built in the US

Institute	Now in construction	Parti-cle	Maximum Clinical Energy (MeV)	Treat-ment rooms	Gantries	Cost (million $)	Estima-ted start date
University of Pennsylvania, PA	Yes	proton	230	5	4	140	2009
Hampton University, VA	Yes	proton	[?]	5	4	225	2010
Northern Illinois Proton Treatment and Research Center, IL	Yes	proton	250	4	2	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 10/29/2008).

See also **Appendix F, Table F2** for a list of particle beam therapy centers that are being built 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). According to company websites, 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.[iv] 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, it is reported that 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 is advertised to include 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 2009.[v] 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,[vi] Orlando Regional at Orlando,

[iv] 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 10/29/2008).

[v] Source: http://news.barnesjewish.org/pr/bjh/siteman-proton-beam.aspx (last accessed 10/29/2008)

[vi] Source: http://www.browardhealth.org/body.cfm?ID=2066 (last accessed 10/29/2008)

Florida,[vii] 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.[viii]

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

Key Question 3

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

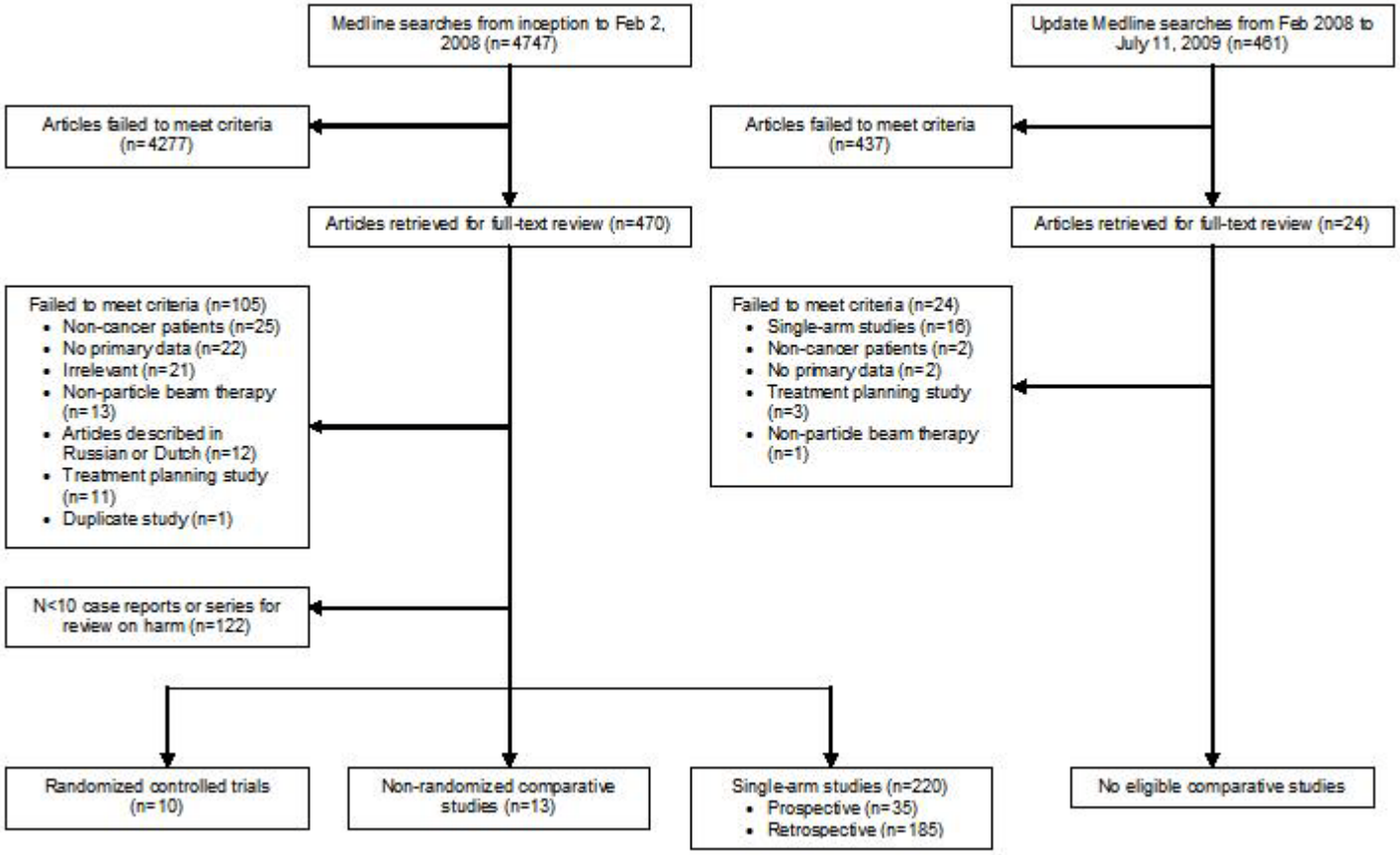
Literature Selection

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. The update search for comparative trials did not identify any additional eligible studies published after the initial search. **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.

[vii] Source: http://www.orlandohealth.com/media/media_news_details.aspx?NewsID=%20149 (last accessed 10/29/2008)

[viii] Source: http://www.tomotherapy.com/news/view/20080428_cpac_announcement/ (last accessed 10/29/2008)

Figure 3. Flow of the literature



The original search is shown on the left. The update search for comparative studies is shown on the right.
* Russian and Dutch
N: number of patients; RT: radiotherapy

3.a. Types of cancer and patient eligibility criteria

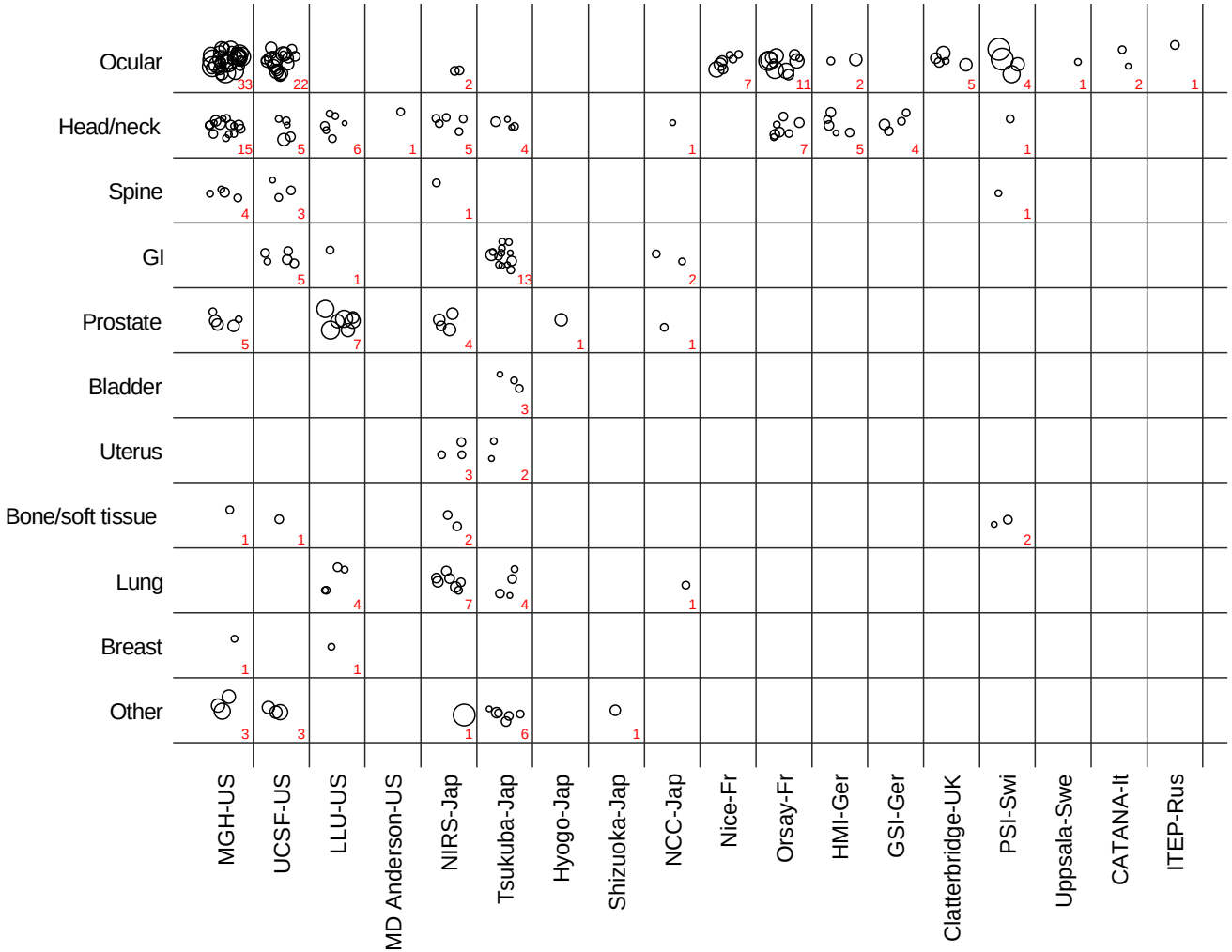
Types of Cancer Studied

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.[16-22]

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

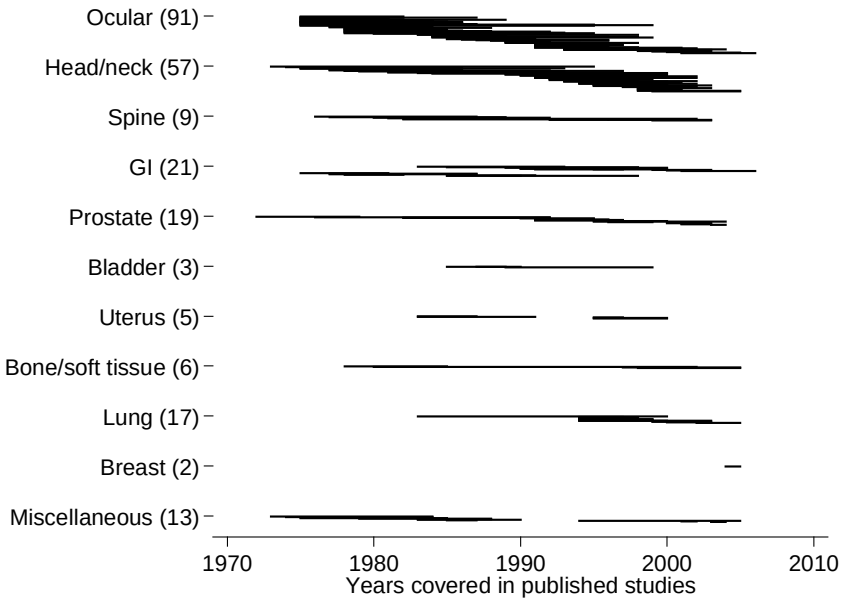
Cancer category	Number of identified papers	Mean or median age	
		Median value	Range
Ocular	91	58	35-66
Head/neck	50	49	33-66
Spine	9	51	41-66
GI (including liver & pancreas)	21	63.5	59-81
Prostate	19	69	66-73
Bladder	3	69	55-72
Uterus	5	60	56-64
Bone/soft tissue	5	41	29-50
Lung	17	72	71-75
Breast	2	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 booster irradiation of the main target lesion on top of conventional photon irradiation, or as the sole treatment.

Administered doses and fractionations thereof were heterogeneous and varied by the type of cancer. Studies administered protons or photon plus protons with mean total dose ranging from 32 to 94 GyE depending on cancer category. When used as booster therapy, proton irradiation was added on top of conventional photon radiotherapy of 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 “hypofractionated” approach was used, with fraction doses in excess of 5.0 GyE, and

approximately 2 weeks' duration.[23-28] Most ocular melanoma studies adopted a four or five 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 ion 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 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 used "hypofractionated" approaches with the mean total dose of 70 to 76 GyE administered within a week.[29-32]

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 irradiation 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.

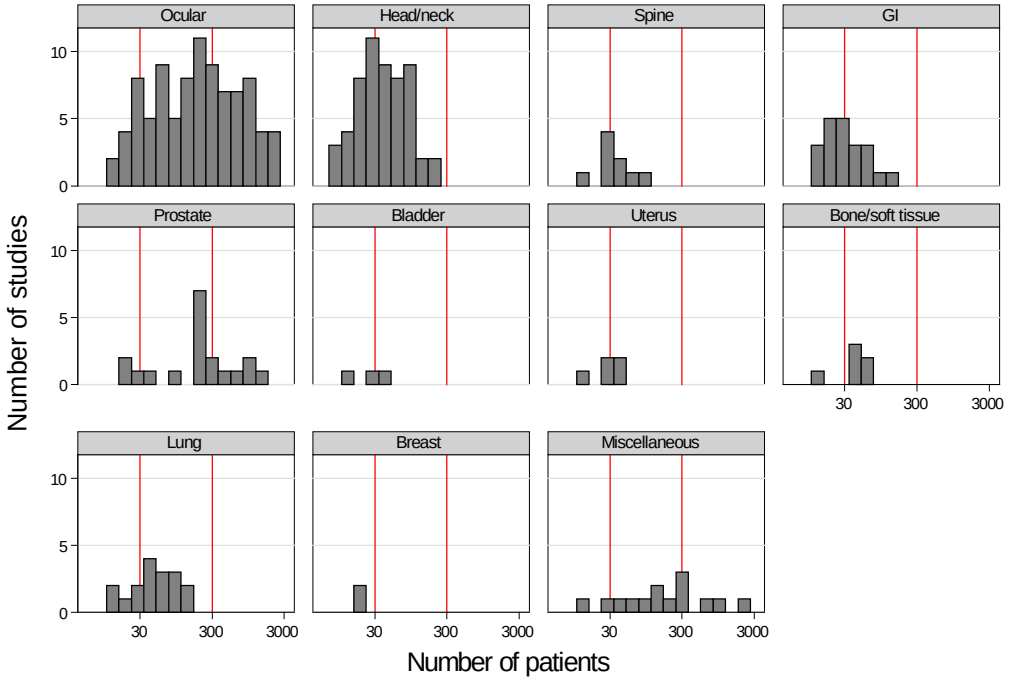
Table 5. Number of papers per cancer type and study design

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[33] and 4 comparative nonrandomized trials.[34-37]

Figure 6. Sample sizes of studies per cancer type

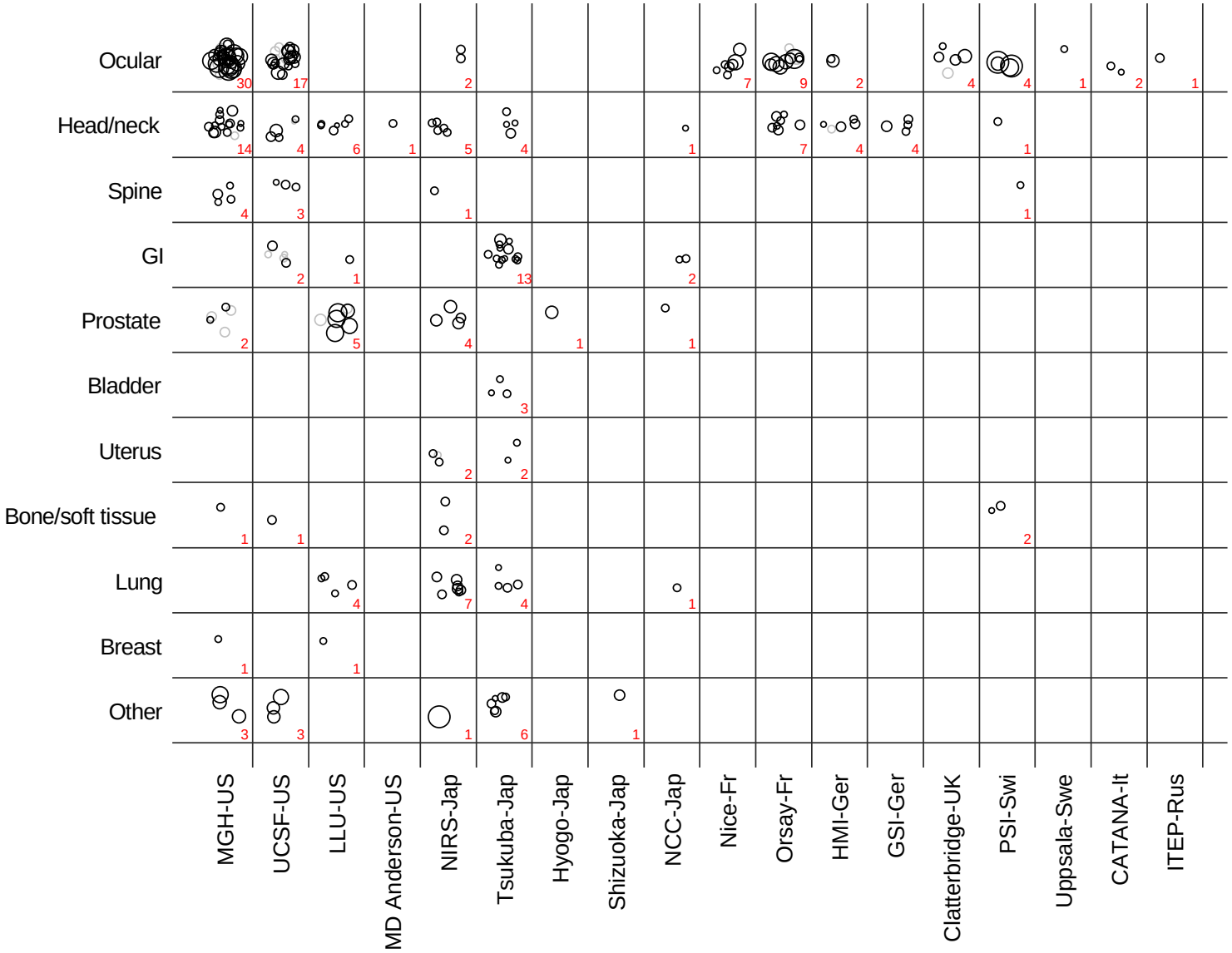


GI: Gastrointestinal

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. Noncomparative studies per center and cancer type

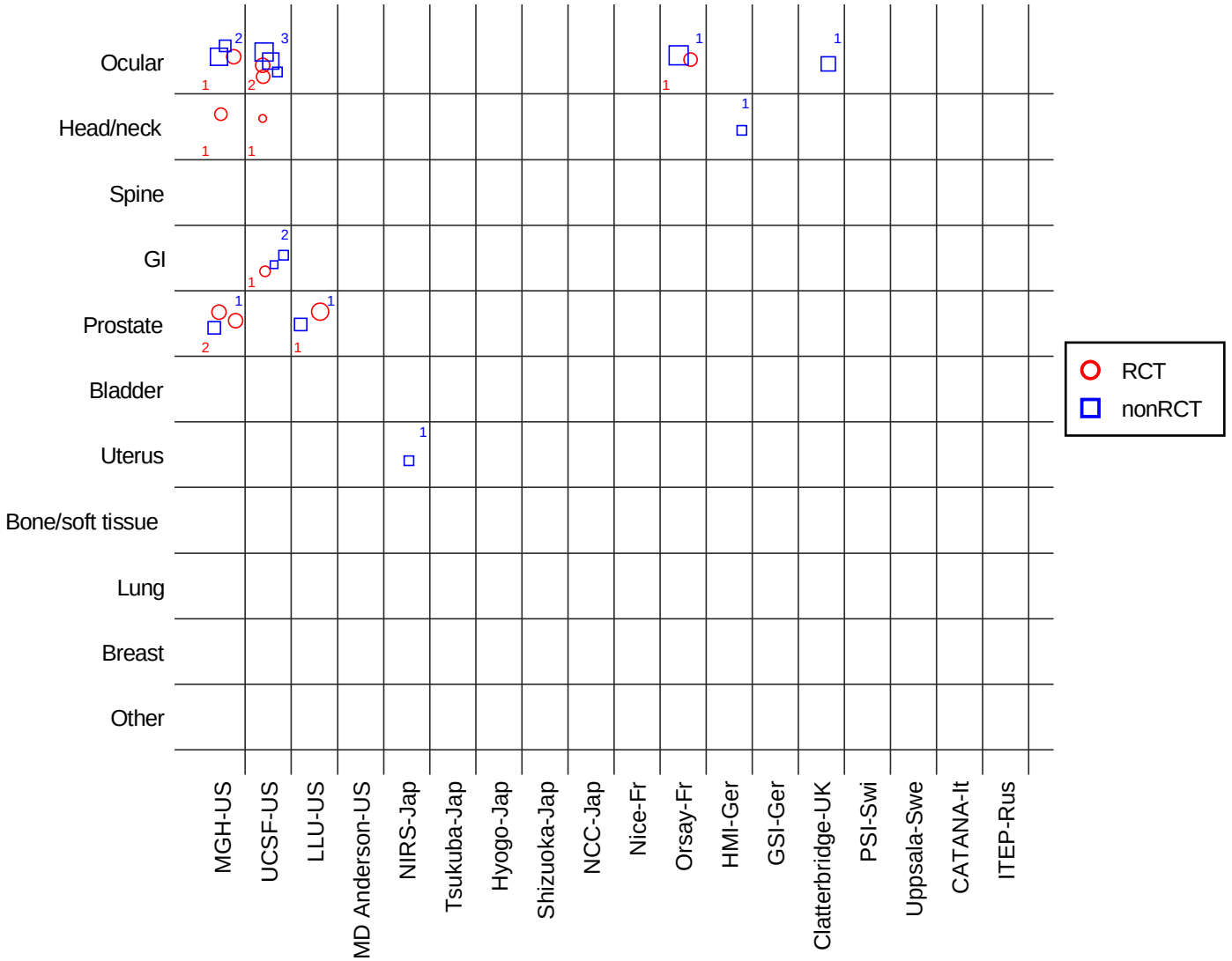


Each publication is represented by a circle, with size proportional to the logarithm of the total sample size. The red numbers in the right hand corner of each cell denote the total number of noncomparative studies.

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

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

Figure 8. Randomized and nonrandomized comparative studies per center and cancer type



Each publication is represented by a red circle (randomized trials, RCTs) or a blue square (nonrandomized 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 nonrandomized comparative studies.[34-46]

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 (US)[47]	Higher vs. lower dose proton RT	188	No/No
UCSF (US)[48,49]	Helium RT vs. I-125 brachytherapy	136; 184	Yes/Yes
Orsay (France)[50]	Proton RT vs. proton RT + laser TTT	151	Yes/Yes
Head/neck (skull base chordoma/chondrosarcoma)			
MGH (US)[51]	Higher vs. lower dose proton RT	96	Yes/No
Head/neck (brain glioblastoma)			
UCSF (US)[52]	Higher vs. lower dose proton RT	15	Yes/Yes
GI (pancreatic cancer)			
UCSF (US)[53]	Helium RT vs. photon RT	49	Yes/Yes
Prostate			
MGH & LLU (US)[33]	Photon RT + standard dose proton vs. Photon RT + high dose proton	393	Yes/Yes
MGH (US)[54,55]	Photon RT + local photon boost vs. Photon RT + local proton boost	202; 191	Yes/Yes

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

Nonrandomized 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) [35]	Proton RT vs. I-125 brachytherapy	1272	Yes/No
UCSF (US)[36]	Helium RT vs. I-125 brachytherapy	766	No/No
MGH (US)[37]	Proton RT vs. enucleation	556	Yes/Yes
UCSF (US)[34]	Helium RT vs. I-125 brachytherapy	426	No/No
[Wilson 1999 - Unclear center][46]	Proton RT vs. I-125 brachytherapy vs. Ru-106 brachytherapy	267	Yes/No
MGH (US)[45]	Proton RT vs. enucleation	120	Yes/Yes
UCSF (US)[38]	Proton RT vs. proton RT + laser TTT	56	No/No
Head/neck (skull base adenocystic carcinoma)			
GSI (Germany)[44]	SFRT/IMRT vs. SFRT/IMRT + carbon (ion) boost	63	Yes/Yes
Uterus			
NIRS (Japan)	Carbon RT vs. photon RT + brachytherapy	49	No/No
GI (Bile duct)			
UCSF (US)[56]	Proton RT vs. photon RT	62	Yes/Yes
UCSF (US)[43]	Surgery + photon RT vs. Surgery + proton RT	22	No/No
Prostate			
LLU (US)[40]	Watchful waiting vs. surgery vs. standalone photon RT vs. photon RT + proton boost RT vs. standalone proton RT	185	No/No
MGH (US)[39]	photon RT + photon boost vs. photon RT + proton boost	180	Yes/Yes

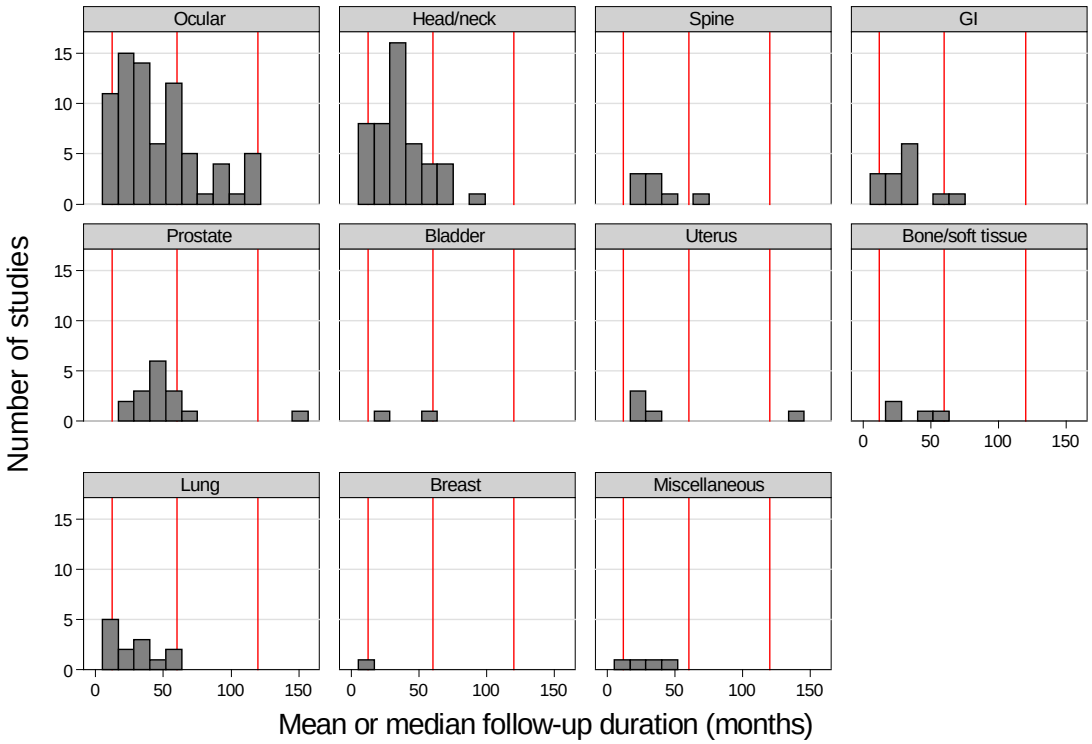
GI: Gastrointestinal; IMRT: intensity modulated radiotherapy; RT: radiotherapy; SFRT: stereotactic fractionated radiotherapy; TTT: transpupillary thermotherapy

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 booster 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"[18]); 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"[30]); and some used more detailed classification: e.g., one study defined local ("any recurrence at or adjacent to the initial primary site") vs. regional ("any recurrence in the regional lymph nodes") vs. metastatic ("any hematogenous recurrence") recurrence.[57]

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[58]) or the LENT-SOMA scales (e.g., Hug 2002[18]) 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) radiotherapy rather than chemotherapy or other cointerventions.

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

Most common radiotherapy modalities use 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 US 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 semistructured 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 Technical Brief focused only on studies with primary data in humans, and did not consider the large body of literature on dosimetric and simulation studies. The available slots for particle beam radiotherapy are very limited, and this may have impacted the design of studies conducted to date. The majority of studies included in the Technical Brief 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 the only comparisons that are being evaluated (at least in most types of cancers).

In general, RCTs are needed to reliably assess the comparative efficacy (and sometimes safety) of interventions, as long as there is clinical equipoise (genuine uncertainty) over the preferred one.[59] For certain cancers (and specific outcomes) the choice between particle beam radiotherapy and other alternatives is easy to make. For example, in patients with uveal melanomas, particle beam radiotherapy will result in higher eye retention rates compared to

surgery (which typically involves enucleation of the eye). However, for many common cancers and for many clinical outcomes there is genuine clinical equipoise. Furthermore, pathophysiological rationale, however strong, is not sufficient to choose the optimal treatment. There are numerous examples of interventions that, despite very favorable and strong pathophysiological rationale, turned out to be harmful when evaluated in RCTs.

It has been argued that for the comparison between e.g., proton and conventional radiotherapy there is no real equipoise (protons are better):[60] First, the dose distributions that can be achieved with protons are in almost all cases superior to those possible with x-rays.[60,61] 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,"[60] and "[*verbatim*] practitioners of proton beam therapy have found it ethically unacceptable to conduct RCTs comparing protons with x-rays."[60]

The aforementioned line of reasoning is unsubstantiated, because it indiscriminately equates increased precision in delivering the planned radiation treatment with positive patient-relevant 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 precise radiation targeting can sometimes result in worse local disease control compared to conventional radiotherapy for some common cancers. Imaging limitations can underestimate the true extent of the disease and therefore mislead treatment planning; by its very nature, charged particle radiotherapy has less tolerance for inadequacies in treatment planning. (For example, there may be satellite lesions that are just distal to the fall-off of an incorrectly planned Bragg peak.) Finally, even the theorized reductions in the rate and severity of harms with particle beam therapy rather than conventional therapies have not yet been convincingly demonstrated in well-designed comparative studies.

It is not easy to decide for which cancers RCTs are necessary (and if so, for what comparisons e.g., proton radiotherapy vs. conventional radiotherapy, IMRT, or stereotactic radiosurgery). The theorized incremental clinical benefit with charged particle therapy vs. a specific type of photon based radiotherapy will vary across cancers, ranging from maximal to negligible (or even harm), and should be considered together with the corresponding incremental costs (and risks). Especially for common cancers, it is not clear where exactly along the continuum it becomes "unethical" to randomize patients.

Notwithstanding the need for RCTs, 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[62] or instrumental variable regression analyses[63]) can be used to explore the comparative effectiveness and especially 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.

We clarify that there is still need for research on clinical and technical issues pertinent to particle beam therapy. Treatment protocols for charged particle therapy are constantly being refined, and the underlying complexities and considerations can differ drastically with particle type, treatment planning methodologies, cancer type and patient comorbidities. In addition, ongoing rapid technological advances in medical imaging, treatment planning and radiotherapy

delivery methodologies mandate further studies to optimize charged particle radiotherapy protocols. However, to justify any widespread use of charged particle radiotherapy to common cancers and to better appreciate the expected benefits, risks and costs it is necessary to have more comparative studies in general, and randomized trials in particular.

With newer technological advances, particle beam therapies are expected to become increasingly available (and, perhaps, 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). 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 vs. 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[64] that included a systematic review[65] 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.

Conclusion

In brief, there are many 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 likely needed to document the theorized incremental advantages of particle beam therapy over other radiotherapies (e.g., IMRT, conventional radiotherapy or stereotactic photon radiosurgery) in many cancers. In addition, incremental benefits should be considered and interpreted with respect to corresponding incremental costs (and risks). This is especially important in the light of the anticipated diffusion of this technology to treating common cancers in which extreme precision in radiation delivery 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.

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

61. Glimelius B, Ask A, Bjelkengren G, et al. Number of patients potentially eligible for proton therapy. Acta Oncol 2005;44:836-49.

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

63. Stukel TA, Fisher ES, Wennberg DE, et al. 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.

64. Wilt TJ, Shamliyan T, Taylor B, et al. 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.

65. Wilt TJ, MacDonald R, Rutks I, et al. Systematic review: comparative effectiveness and harms of treatments for clinically localized prostate cancer. Ann Intern Med 2008;148:435-48.

Appendices

Appendix A. Selected Internet Links

Appendix Table A1. Internet links for radiotherapy organizations

Organization	URL address
Deutsche Gesellschaft fur Radiooncologie	http://www.degro.org/jsp_public/cms/index.jsp
European Society for Therapeutic Radiology and Oncology	http://www.estroweb.org/estro/index.cfm
American Society for Therapeutic Radiology and Oncology	http://www.astro.org/
National Association for Proton Therapy	http://www.proton-therapy.org/
Particle Therapy Cooperative Group	http://ptcog.web.psi.ch/

(Accessed June 16, 2008)

Appendix Table A2. Internet links for particle beam instrumentation companies

Company	URL address
Ion Beam Applications (IBA) Solutions	http://www.iba-worldwide.com/
Still River Systems Inc	http://www.stillriversystems.com/
Optivus Proton Therapy	http://www.optivus.com/
Siemens	http://www.medical.siemens.com/
Hitachi: Proton beam Therapy	http://www.pi.hitachi.co.jp/rd-eng/product/industrial-sys/accelerator-sys/proton-therapy-sys/proton-beam-therapy/index.html
ACCEL Instruments	http://www.proton-therapy.com/

(Accessed June 16, 2008)

Appendix Table A3. Internet links for particle beam treatment centers in the USA

Center/Institute	URL address
Francis H. Burr Proton Therapy Center (NPTC)	http://www.massgeneral.org/cancer/about/providers/radiation/proton/index.asp
Loma Linda University Proton Therapy Center	http://www.llu.edu/proton/index.html
University of California, Crocker Nuclear Lab	http://media.cnl.ucdavis.edu/crocker/website/default.php
Midwest Proton Radiotherapy Institute, Bloomington	http://www.mpri.org/
M.D. Anderson Proton Therapy Center, Houston	http://www.mdanderson.org/care_centers/radiationonco/ptc/
University of Florida Proton Therapy Institute, Jacksonville	http://www.floridaproton.org/

(Accessed June 16, 2008)

Appendix B. Ovid Medline Search Strategy

ID	Search term	Citations
1	particle beam.mp.	157
2	heavy ion*.mp. or exp Heavy Ions/	1411
3	light ion*.mp.	115
4	charged particle*.mp.	1114
5	boron neutron captrure.mp.	0
6	hadron$.mp.	168
7	proton$.mp. or exp Protons/	70128
8	Carbon ion.mp.	225
9	C-ion$.mp.	152
10	helium ion$.mp.	202
11	He-ion$.mp.	26
12	exp Alpha Particles/ or alpha irradiation.mp.	1872
13	(LET or linear energy transfer).mp.	12772
14	exp Particle Accelerators/	5736
15	or/1-14	90173
16	exp Radiotherapy/	98150
17	exp Radiotherapy, High-Energy/	14620
18	irradiation.mp. or exp Pituitary Irradiation/ or exp Lymphatic Irradiation/ or exp Cranial Irradiation/	107651
19	beam therap*.mp.	1047
20	pion* therap*.mp.	29
21	piontherap*.mp.	0
22	proton* therap*.mp.	380
23	protontherap*.mp.	55
24	neutron capture therap*.mp.	1288
25	neutron therap*.mp.	551
26	neutrontherap*.mp.	12
27	ion$ therap*.mp.	152
28	iontherap*.mp.	2
29	beam irradiation.mp.	1806
30	beam radiation.mp.	2485
31	radiation therap*.mp.	34480
32	particle therap*.mp.	111
33	hadron$therap*.mp.	39
34	hadrontherap*.mp.	39
35	particle beam therap*.mp.	10
36	charged particle therap*.mp.	47
37	or/16-36	195909
38	15 and 37	7458
39	limit 38 to humans	4776
40	remove duplicates from 39	4747

Appendix C. Table of Eligible Studies

Citation	PMID
Bladder	
Miyanaga N, Ami Y, Ohtani M, et al. Clinical study of proton radiotherapy in urological cancers [Japanese]. Nippon Hinyokika Gakkai Zasshi - Japanese Journal of Urology 1990;81(2):251-7.	2157915
Hata M, Miyanaga N, Tokuuye K, et al. Proton beam therapy for invasive bladder cancer: a prospective study of bladder-preserving therapy with combined radiotherapy and intra-arterial chemotherapy. International Journal of Radiation Oncology, Biology, Physics 2006;64(5):1371-9.	16580495
Tsujii H, Akaza H, Ohtani M, et al. Preliminary results of bladder-preserving therapy with definitive radiotherapy and intraarterial infusion of chemotherapy. Strahlentherapie und Onkologie 1994;170 (9):531-7.	7940124
Bone	
Delaney TF, Park L, Goldberg SI, et al. Radiotherapy for local control of osteosarcoma. International Journal of Radiation Oncology, Biology, Physics 2005;61(2):492-8.	15667972
Kamada T, Tsujii H, Tsuji H, et al. Efficacy and safety of carbon ion radiotherapy in bone and soft tissue sarcomas. Journal of Clinical Oncology 1920:4466-4471.	12431970
Reimers M, Castro JR, Linstadt D, et al. Heavy charged particle therapy of bone and soft tissue sarcoma. A phase I-II trial of the University of California Lawrence Berkeley Laboratory and the Northern California Oncology Group. American Journal of Clinical Oncology 1986;9(6):488-93.	2431614
Timmermann B, Schuck A, Niggli F, 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 2007;67(2):497-504.	17084557
Weber DC, Rutz HP, Bolsi A, 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 2007;69(3):865-71.	17606333
Zhang H, Yoshikawa K, Tamura K, et al. [(11)C]methionine positron emission tomography and survival in patients with bone and soft tissue sarcomas treated by carbon ion radiotherapy. Clinical Cancer Research 2004;10(5):1764-72.	15014030
Breast	
Bush DA, Slater JD, Garberoglio C, et al. A technique of partial breast irradiation utilizing proton beam radiotherapy: comparison with conformal x-ray therapy [see comment]. Cancer Journal 2007;13(2):114 -8.	17476139
Kozak KR, Smith BL, Adams J, et al. Accelerated partial-breast irradiation using proton beams: initial clinical experience. International Journal of Radiation Oncology, Biology, Physics2006;66(3):691-8.	17011445
Gastrointestinal	
Castro JR, Saunders WM, Quivey JM, et al. Clinical problems in radiotherapy of carcinoma of the pancreas. American Journal of Clinical Oncology 1982;5(6):579-87.	6762086
Castro JR, Chen GT, Pitluck S, et al. Helium charged-particle radiotherapy of locally advanced carcinoma of the esophagus, stomach, and biliary tract. American Journal of Clinical Oncology 1983;6(6):629-37.	6637875
Koyama S, Tsujii H, Yokota H, et al. Proton beam therapy for patients with esophageal carcinoma. Japanese Journal of Clinical Oncology 1994;24(3):144-53.	8007424
Linstadt D, Quivey JM, Castro JR, 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 1988;168(1):261-4.	3132732
Schoenthaler R, Phillips TL, Castro J, et al. Carcinoma of the extrahepatic bile ducts. The University of California at San Francisco experience. Annals of Surgery 1994;219(3):267-74.	8147607
Schoenthaler R, Castro JR, Halberg FE, et al. Definitive postoperative irradiation of bile duct carcinoma with charged particles and/or photons. International Journal of Radiation Oncology, Biology, Physics 1993;27(1):75-82.	8365945
Sugahara S, Tujii H, Tuji H, et al. [The value of frequent positioning of treatment field in radiotherapy of esophageal cancer] [Japanese]. Nippon Igaku Hoshasen Gakkai Zasshi - Nippon Acta Radiologica 1992;52(9):1308-14.	1437536

Citation	PMID
Sugahara S, Tokuuye K, Okumura T, et al. Clinical results of proton beam therapy for cancer of the esophagus. International Journal of Radiation Oncology, Biology, Physics 2005;61(1):76-84.	15629597
Head and Neck	
Al-Mefty O, Borba LA. Skull base chordomas: a management challenge. Journal of Neurosurgery 1997;86(2):182-9.	9010416
Austin-Seymour M, Munzenrider J, Goitein M, et al. Fractionated proton radiation therapy of chordoma and low-grade chondrosarcoma of the base of the skull. Journal of Neurosurgery 1989;70(1):13-7.	2535872
Austin-Seymour M, Munzenrider J, Linggood R, et al. Fractionated proton radiation therapy of cranial and intracranial tumors. American Journal of Clinical Oncology 1990;13(4):327-30.	2165739
Benk V, Liebsch NJ, Munzenrider JE, et al. Base of skull and cervical spine chordomas in children treated by high-dose irradiation. International Journal of Radiation Oncology, Biology, Physics 1995;31(3):577-81.	7852123
Berson AM, Castro JR, Petti P, et al. Charged particle irradiation of chordoma and chondrosarcoma of the base of skull and cervical spine: the Lawrence Berkeley Laboratory experience. International Journal of Radiation Oncology, Biology, Physics 1988;15(3):559-65.	3138208
Castro JR, Linstadt DE, Bahary JP, et al. Experience in charged particle irradiation of tumors of the skull base: 1977-1992 [see comment] [review] [35 refs]. International Journal of Radiation Oncology, Biology, Physics 1994;29(4):647-55.	8040010
Castro JR, Reimers MM. Charged particle radiotherapy of selected tumors in the head and neck. International Journal of Radiation Oncology, Biology, Physics 1988;14(4):711-20.	3350726
Castro JR, Phillips TL, Prados M, et al. Neon heavy charged particle radiotherapy of glioblastoma of the brain. International Journal of Radiation Oncology, Biology, Physics 1997;38(2):257-61.	9226311
Colli B, Al-Mefty O. Chordomas of the craniocervical junction: follow-up review and prognostic factors. Journal of Neurosurgery 2001;95(6):933-43.	11765837
Debus J, Haberer T, Schulz-Ertner D, et al. [Carbon ion irradiation of skull base tumors at GSI. First clinical results and future perspectives] [German]. Strahlentherapie und Onkologie 2000;176(5):211-6.	10847117
Fagundes MA, Hug EB, Liebsch NJ, et al. Radiation therapy for chordomas of the base of skull and cervical spine: patterns of failure and outcome after relapse. International Journal of Radiation Oncology, Biology, Physics 1995;33(3):579-84.	7558946
Fitzek MM, Thornton AF, Harsh G, et al. Dose-escalation with proton/photon irradiation for Daumas-Duport lower-grade glioma: results of an institutional phase I/II trial. International Journal of Radiation Oncology, Biology, Physics 2001;51(1):131-7.	11516862
Fitzek MM, Thornton AF, Varvares M, et al. Neuroendocrine tumors of the sinonasal tract. Results of a prospective study incorporating chemotherapy, surgery, and combined proton-photon radiotherapy. Cancer 2002;94(10):2623-34.	12173330
Fuss M, Hug EB, Schaefer RA, 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 1999;45(5):1117-26.	10613303
Gridley DS, Loredo LN, Slater JD, et al. Pilot evaluation of cytokine levels in patients undergoing radiotherapy for brain tumor. Cancer Detection & Prevention 1998;22(1):20-9.	9466045
Hasegawa A, Mizoe JE, Mizota A, et al. Outcomes of visual acuity in carbon ion radiotherapy: analysis of dose-volume histograms and prognostic factors. International Journal of Radiation Oncology, Biology, Physics 2006;64(2):396-401.	16182466
Hug EB, DeVries A, Thornton AF, et al. Management of atypical and malignant meningiomas: role of high-dose, 3D-conformal radiation therapy. Journal of Neuro-Oncology 2000;48(2):151-60.	11083080
Hug EB, Loredo LN, Slater JD, et al. Proton radiation therapy for chordomas and chondrosarcomas of the skull base [see comment]. Journal of Neurosurgery 1999;91(3):432-9.	10470818
Hug EB, Muenter MW, Archambeau JO, et al. Conformal proton radiation therapy for pediatric low-grade astrocytomas. Strahlentherapie und Onkologie 2002;78(1):10-17.	11977386
Hug EB, Sweeney RA, Nurre PM, et al. Proton radiotherapy in management of pediatric base of skull tumors. International Journal of Radiation Oncology, Biology, Physics 2002;52(4):1017-24.	11958897

Citation	PMID
Igaki H, Tokuuye K, Okumura T, et al. Clinical results of proton beam therapy for skull base chordoma [review] [38 refs]. International Journal of Radiation Oncology, Biology, Physics 2004;60(4):1120-6.	15519783
Kishimoto R, Mizoe JE, Komatsu S, et al. MR imaging of brain injury induced by carbon ion radiotherapy for head and neck tumors. Magnetic Resonance in Medical Sciences 2005;4(4):159-64.	16543700
McAllister B, Archambeau JO, Nguyen MC, et al. Proton therapy for pediatric cranial tumors: preliminary report on treatment and disease-related morbidities. International Journal of Radiation Oncology, Biology, Physics 1997;39(2):455-60.	9308950
Mizoe JE, Tsujii H, Hasegawa A, et al. Phase I/II clinical trial of carbon ion radiotherapy for malignant gliomas: combined X-ray radiotherapy, chemotherapy, and carbon ion radiotherapy. International Journal of Radiation Oncology, Biology, Physics 2007;69(2):390-6.	17459607
Mizoe JE, Tsujii H, Kamada T, et al. Dose escalation study of carbon ion radiotherapy for locally advanced head-and-neck cancer [see comment]. International Journal of Radiation Oncology, Biology, Physics 2004;60(2):358-64.	15380567
Nishimura H, Ogino T, Kawashima M, et al. Proton-beam therapy for olfactory neuroblastoma. International Journal of Radiation Oncology, Biology, Physics 2007;68(3):758-62.	17398027
Noel G, Feuvret L, Calugaru V, et al. Chordomas of the base of the skull and upper cervical spine. One hundred patients irradiated by a 3D conformal technique combining photon and proton beams. Acta Oncologica 2005;44(7):700-8.	16227160
Noel G, Feuvret L, Dhermain F, et al. [Chordomas of the base of the skull and upper cervical spine. 100 patients irradiated by a 3D conformal technique combining photon and proton beams] [French]. Cancer Radiotherapie 2005;9(3):61-74.	15979920
Noel G, Feuvret L, Ferrand R, et al. Radiotherapeutic factors in the management of cervical-basal chordomas and chondrosarcomas. Neurosurgery 2004;55(6):1252-60;discussion 1260-2.	15574207
Noel G, Habrand JL, Helfre S, 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 2003;40(5):309-15.	12652619
Noel G, Habrand JL, Jauffret E, et al. Radiation therapy for chordoma and chondrosarcoma of the skull base and the cervical spine. Prognostic factors and patterns of failure. Strahlentherapie und Onkologie 2003;179(4):241-8.	12707713
Noel G, Habrand JL, Mammar H, et al. Combination of photon and proton radiation therapy for chordomas and chondrosarcomas of the skull base: the Centre de Protontherapie D'Orsay experience. International Journal of Radiation Oncology, Biology, Physics 2001;51(2):392-8.	11567813
Noel G, Jauffret E, Crevoisier RD, et al. [Radiation therapy for chordomas and chondrosarcomas of the base of the skull and cervical spine] [French]. Bulletin du Cancer 2002;89(7-8):713-23.	12206985
O'Connell JX, Renard LG, Liebsch NJ, et al. Base of skull chordoma. A correlative study of histologic and clinical features of 62 cases. Cancer 1994;74(8):2261-7.	7922977
Pommier P, Liebsch NJ, Deschler DG, et al. Proton beam radiation therapy for skull base adenoid cystic carcinoma. Archives of Otolaryngology—Head & Neck Surgery 2006;132(11):1242-9.	17116822
Rosenberg AE, Nielsen GP, Keel SB, et al. Chondrosarcoma of the base of the skull: a clinicopathologic study of 200 cases with emphasis on its distinction from chordoma. American Journal of Surgical Pathology 1999;23(11):1370-8.	10555005
Santoni R, Liebsch N, Finkelstein DM, 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 1998;41(1):59-68.	9588918
Saunders WM, Chen GT, ustin-Seymour M, et al. Precision, high dose radiotherapy. II. Helium ion treatment of tumors adjacent to critical central nervous system structures. International Journal of Radiation Oncology, Biology, Physics 2002;11(7):1339-47.	4008290
Schulz-Ertner D, Haberer T, Jakel O, et al. Radiotherapy for chordomas and low-grade chondrosarcomas of the skull base with carbon ions. International Journal of Radiation Oncology, Biology, Physics 2002;53(1):36-42.	12007939
Schulz-Ertner D, Haberer T, Scholz M, et al. Acute radiation-induced toxicity of heavy ion radiotherapy delivered with intensity modulated pencil beam scanning in patients with base of skull tumors. Radiotherapy & Oncology 2002;64(2):189-95.	12242129

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Schulz-Ertner D, Karger CP, Feuerhake A, et al. Effectiveness of carbon ion radiotherapy in the treatment of skull-base chordomas. International Journal of Radiation Oncology, Biology, Physics2007;68(2):449-57.	17363188
Schulz-Ertner D, Nikoghosyan A, Didinger B, et al. Therapy strategies for locally advanced adenoid cystic carcinomas using modern radiation therapy techniques. Cancer 2005;104(2):338-44.	15937907
Schulz-Ertner D, Nikoghosyan A, Didinger B, et al. Carbon ion radiation therapy for chordomas and low grade chondrosarcomas—current status of the clinical trials at GSI. Radiotherapy & Oncology 2004;73 Suppl 2:S53-6.	15971310
Schulz-Ertner D, Nikoghosyan A, Jakel O, et al. Feasibility and toxicity of combined photon and carbon ion radiotherapy for locally advanced adenoid cystic carcinomas. International Journal of Radiation Oncology, Biology, Physics 2003;56(2):391-8.	12738314
Schulz-Ertner D, Nikoghosyan A, Thilmann C, et al. Carbon ion radiotherapy for chordomas and low-grade chondrosarcomas of the skull base. Results in 67 patients. Strahlentherapie und Onkologie 2003;179(9):598-605.	14628125
Schulz-Ertner D, Nikoghosyan A, Thilmann C, et al. Results of carbon ion radiotherapy in 152 patients. International Journal of Radiation Oncology, Biology, Physics 2004;58(2):631-40.	14751537
Slater JD, ustin-Seymour M, Munzenrider J, et al. Endocrine function following high dose proton therapy for tumors of the upper clivus. International Journal of Radiation Oncology, Biology, Physics 1988;15(3):607-11.	3138212
Slater JD, Yonemoto LT, Mantik DW, et al. Proton radiation for treatment of cancer of the oropharynx: early experience at Loma Linda University Medical Center using a concomitant boost technique. International Journal of Radiation Oncology, Biology, Physics 2005;62(2):494-500.	15890592
Suit HD, Goitein M, Munzenrider J, et al. Definitive radiation therapy for chordoma and chondrosarcoma of base of skull and cervical spine. Journal of Neurosurgery 1982;56(3):377-85.	7057235
Terahara A, Niemierko A, Goitein M, et al. Analysis of the relationship between tumor dose inhomogeneity and local control in patients with skull base chordoma. International Journal of Radiation Oncology, Biology, Physics 1999;45(2):351-8.	10487555
Tokuuye K, Akine Y, Kagei K, et al. Proton therapy for head and neck malignancies at Tsukuba. Strahlentherapie und Onkologie 2004;180(2):96-101.	14762662
Weber DC, Chan AW, Lessell S, et al. Visual outcome of accelerated fractionated radiation for advanced sinonasal malignancies employing photons/protons. Radiotherapy & Oncology 2006;81(3):243-9.	17050017
Weber DC, Rutz HP, Pedroni ES, et al. Results of spot-scanning proton radiation therapy for chordoma and chondrosarcoma of the skull base: the Paul Scherrer Institut experience. International Journal of Radiation Oncology, Biology, Physics 2005;63(2):401-9.	16168833
Yoshii Y, Maki Y, Narushima A, et al. [Use of radiotherapy by high-energy protons in the postoperative treatment of brain tumors] [Japanese]. Neurologia Medico-Chirurgica 1986;26(3):219-26.	2426616
Yoshii Y, Takano S, Tsurushima H, et al. Normal brain damage after radiotherapy of brain tumours. Clinical Oncology (Royal College of Radiologists) 1991;3(5):278-82.	1657115
Zhang H, Yoshikawa K, Tamura K, et al. Carbon-11-methionine positron emission tomography imaging of chordoma. Skeletal Radiology 2004;33(9):524-30.	15483754
Liver (Hepatocellular carcinoma)	
Ahmadi T, Itai Y, Onaya H, et al. CT evaluation of hepatic injury following proton beam irradiation: appearance, enhancement, and 3D size reduction pattern. Journal of Computer Assisted Tomography 1999;23(5):655-63.	10524841
Bush DA, Hillebrand DJ, Slater JM, Slater JD. High-dose proton beam radiotherapy of hepatocellular carcinoma: preliminary results of a phase II trial. Gastroenterology 2004;127(5 Suppl 1):S189-93.	15508084
Chiba T, Tokuuye K, Matsuzaki Y, et al. Proton beam therapy for hepatocellular carcinoma: a retrospective review of 162 patients. Clinical Cancer Research 2005;11(10):3799-805.	15897579
Hashimoto T, Tokuuye K, Fukumitsu N, et al. Repeated proton beam therapy for hepatocellular carcinoma. International Journal of Radiation Oncology, Biology, Physics 2006;65(1):196-202.	16563656
Hata M, Tokuuye K, Sugahara S et al. Proton beam therapy for hepatocellular carcinoma with limited treatment options. Cancer 107 (3):591 -8 , 2006	16804931

Citation	PMID
Hata M, Tokuuye K, Sugahara S et al. Proton beam therapy for aged patients with hepatocellular carcinoma. International Journal of Radiation Oncology, Biology, Physics 69 (3):805 -12, 2007	17524568
Hata M, Tokuuye K, Sugahara S, et al. Proton beam therapy for hepatocellular carcinoma patients with severe cirrhosis. Strahlentherapie und Onkologie 2006;182(12):713-20.	17149578
Hata M, Tokuuye K, Sugahara S, et al. Proton beam therapy for hepatocellular carcinoma with portal vein tumor thrombus. Cancer 2005;104(4):794-801.	15981284
Kato H, Tsujii H, Miyamoto T, et al. Results of the first prospective study of carbon ion radiotherapy for hepatocellular carcinoma with liver cirrhosis. International Journal of Radiation Oncology, Biology, Physics 2004;59(5):1468-76.	15275734
Kawashima M, Furuse J, Nishio T et al. Phase II study of radiotherapy employing proton beam for hepatocellular carcinoma. Journal of Clinical Oncology 2005;23(9):1839-46.	15774777
Matsuzaki Y, Osuga T, Saito Y, et al. A new, effective, and safe therapeutic option using proton irradiation for hepatocellular carcinoma. Gastroenterology 1994;106(4):1032-41.	7511552
Niizawa G, Ikegami T, Matsuzaki Y, et al. Monitoring of hepatocellular carcinoma, following proton radiotherapy, with contrast-enhanced color Doppler ultrasonography. Journal of Gastroenterology 2005;40(3):283-90.	15830288
Tsuji H, Okumura T, Maruhashi A ,et al. [Dose-volume histogram analysis of patients with hepatocellular carcinoma regarding changes in liver function after proton therapy] [Japanese]. Nippon Igaku Hoshasen Gakkai Zasshi - Nippon Acta Radiologica 1995;55(5):322-8.	7784153
Lung	
Bonnet RB, Bush D, Cheek GA, 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 2001;120(6):1803-10.	11742905
Bush DA, Dunbar RD, Bonnet R, et al. Pulmonary injury from proton and conventional radiotherapy as revealed by CT. AJR American Journal of Roentgenology 1999;172(3):735-9.	10063871
Bush DA, Slater JD, Bonnet R, et al. Proton-beam radiotherapy for early-stage lung cancer. Chest 1999;116(5):1313-9.	10559093
Bush DA, Slater JD, Shin BB, et al. Hypofractionated proton beam radiotherapy for stage I lung cancer. Chest 2004;126(4):1198-203.	15486383
Hata M, Tokuuye K, Kagei K, 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 2007;68(3):786-93.	17379439
Homma T, Ohtsu I, Tomioka S, et al. [Quantitative analysis of pulmonary functional damage due to heavy ion particle irradiation therapy for lung cancer] [Japanese]. Nihon Kokyuki Gakkai Zasshi 1999;37(2):97-101.	10214036
Kadono K, Homma T, Kamahara K, et al. Effect of heavy-ion radiotherapy on pulmonary function in stage I non-small cell lung cancer patients. Chest 2002;122(6):1925-32.	12475828
Koto M, Miyamoto T, Yamamoto N, et al. Local control and recurrence of stage I non-small cell lung cancer after carbon ion radiotherapy [see comment]. Radiotherapy & Oncology 2004;71(2):147-56.	15110447
Miyamoto 2007 (no record of UI number in file)	17903054
Miyamoto T, Baba M, Yamamoto N, 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 2007;67(3):750-8.	17293232
Miyamoto T, Yamamoto N, Koto M, et al. [Heavy-ion therapy for non-small cell lung cancer] [review] [5 refs] [Japanese]. Nippon Geka Gakkai Zasshi Journal of Japan Surgical Society 2002;103(2):250-5.	11904989
Miyamoto T, Yamamoto N, Nishimura H, et al. Carbon ion radiotherapy for stage I non-small cell lung cancer. Radiotherapy & Oncology 2003;66(2):127-40.	12648784
Miyamoto T. [Heavy ion therapy for non-small cell lung cancer--new, radical radiotherapy for advanced-age patients as an alternative to surgery] [Japanese]. Gan to Kagaku Ryoho [Japanese Journal of Cancer & Chemotherapy] 2003;30(2):209-14.	12610868
Nihei K, Ogino T, Ishikura S, et al. High-dose proton beam therapy for Stage I non-small-cell lung cancer. International Journal of Radiation Oncology, Biology, Physics 2006;65(1):107-11.	16458447
Nishimura H, Miyamoto T, Yamamoto N, et al. Radiographic pulmonary and pleural changes after carbon ion irradiation. International Journal of Radiation Oncology, Biology, Physics 2003;55(4):861-6.	12605963

Citation	PMID
Satoh H, Okumura T, Yamashita YT, et al. Proton irradiation for non-small cell lung cancer. Archives of Internal Medicine 1998;158(12):1379-80.	9645836
Shioyama Y, Tokuuye K, Okumura T, et al. Clinical evaluation of proton radiotherapy for non-small-cell lung cancer. International Journal of Radiation Oncology, Biology, Physics 2003;56(1):7-13.	12694818
Eye	
Bechrakis NE, Hocht S, Martus P, et al. [Endoresection following proton beam irradiation of large uveal melanomas] [German]. Ophthalmologe 2004;101(4):370 -6.	15067418
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Slater JD, Rossi Jr CJ, Yonemoto LT, et al. Conformal proton therapy for early-stage prostate cancer. Urology 1999;53(5):978-84.	10223493
Slater JD, Rossi Jr CJ, Yonemoto LT, et al. Proton therapy for prostate cancer: the initial Loma Linda University experience. International Journal of Radiation Oncology, Biology, Physics 2004;59(2):348-52.	15145147
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Rutz HP, Weber DC, Sugahara S, et al. Extracranial chordoma: Outcome in patients treated with function-preserving surgery followed by spot-scanning proton beam irradiation. International Journal of Radiation Oncology, Biology, Physics 2007;67(2):512-20.	17084540
Schoenthaler R, Castro JR, Petti PL, et al. Charged particle irradiation of sacral chordomas. International Journal of Radiation Oncology, Biology, Physics 1993;26(2):291-8.	8491686

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Kato S, Ohno T, Tsujii H, et al. Dose escalation study of carbon ion radiotherapy for locally advanced carcinoma of the uterine cervix. International Journal of Radiation Oncology, Biology, Physics 2006;65(2):388-97.	16626894
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Appendix D. Table of Excluded Studies

Appendix D Table. List of excluded studies and reasons for exclusion

Citation	PMID	Reason for exclusion
Abrahamsen JF, Fossa SD. Long-term morbidity after curative radiotherapy for carcinoma of the bladder. A retrospective study. Strahlentherapie und Onkologie 1990;166(9):580-3.	2120783	Not eligible RT
Allen BJ, Li Y, Rizvi SM, Russell PJ. Targeted alpha therapy of prostate cancer. Methods in Molecular Medicine 2003;81:333-57.	12725130	Not relevant
Anonymous. Special report: stereotactic radiosurgery for intracranial lesions by gamma beam, linear accelerator, and proton beam methods. Tecnologica MAP Supplement 1999:26-7.	10346748	No primary data
Archambeau JO, Bennett GW, Levine GS, et al. Proton radiation therapy. Radiology 1974;110(2):445-57.	4203944	No primary data
Archambeau JO, Slater JD, Slater JM, et al. Role for proton beam irradiation in treatment of pediatric CNS malignancies. International Journal of Radiation Oncology, Biology, Physics 1992;22(2):287-94.	1310964	No primary data
Ask A, Johansson B, Glimelius B. The potential of proton beam radiation therapy in gastrointestinal cancer. Acta Oncologica 2005;44(8):896-903.	16332599	No primary data
Austin JP, Urie MM, Cardenosa G, et al. Probable causes of recurrence in patients with chordoma and chondrosarcoma of the base of skull and cervical spine. International Journal of Radiation Oncology, Biology, Physics 1993;25(3):439-44.	8436522	No primary data
Austin-Seymour M, Munzenrider JE, Verhey L, et al. [Fractionated proton radiotherapy] [review] [23 refs] [Russian]. Meditsinskaia Radiologiia 1987;32(8):88-94.	3041170	Publication language
Austin-Seymour M, Urie M, Munzenrider J, et al. Considerations in fractionated proton radiation therapy: clinical potential and results. Radiotherapy & Oncology 1990;17(1):29-35.	2157240	No primary data
Barker FG, Butler WE, Lyons S, et al. Dose-volume prediction of radiation-related complications after proton beam radiosurgery for cerebral arteriovenous malformations [see comment]. Journal of Neurosurgery 2003;99(2):254-63.	12924697	No malignancy
Belletti S, Mensi A, Verzeletti L. Six years experience in the use of a 10 MeV microtron for radiation therapy. Acta Radiologica - Oncology 1984;23(5):375-8.	6095608	No primary data
Blomquist E, Carlsson J. Strategy for planned radiotherapy of malignant gliomas: postoperative treatment with combinations of high dose proton irradiation and tumor seeking radionuclides. International Journal of Radiation Oncology, Biology, Physics 1992;22(2):259-63.	1310961	No primary data
Bolsi A, Fogliata A, Cozzi L. Radiotherapy of small intracranial tumours with different advanced techniques using photon and proton beams: a treatment planning study. Radiotherapy & Oncology 200;68(1):1-14.	12885446	Tx planning study
Brandberg Y, Damato B, Kivela T, et al. The EORTC ophthalmic oncology quality of life questionnaire module (EORTC QLQ-OPT30). Development and pre-testing (Phase I-III). Eye 2004;18(3):283-9.	15004578	Not relevant
Bush DA, McAllister CJ, Loredo LN, et al. Fractionated proton beam radiotherapy for acoustic neuroma. Neurosurgery 2002;50(2):270-3;discussion 273-5.	11844261	No malignancy
Castro JR, Gademann G, Collier JM, et al. [Heavy particle radiotherapy at the University of California Lawrence Berkeley Laboratory. Clinical studies by the Northern California Oncology Group] [review] [26 refs] [German]. Strahlentherapie und Onkologie 1987;163(1):9-16.	3101214	No primary data
Carpentier A, Polivka M, Blanquet A, et al. Suboccipital and cervical chordomas: the value of aggressive treatment at first presentation of the disease. Journal of Neurosurgery 2002;97(5):1070-7.	12450028	No extractable data

Citation	PMID	Reason for exclusion
Char DH, Bove R, Phillips TL. Laser and proton radiation to reduce uveal melanoma-associated exudative retinal detachments. Transactions of the American Ophthalmological Society 2003;101:53--56;discussion 56-57.	14971563	Identical duplicate
Chauvel P, Iborra-Brassart N, Courdi A, et al. Proton therapy in ophthalmology: status report and problems encountered. Bulletin du Cancer Radiotherapie 1996;83 Suppl:215s-8s.	8949783	No primary data
Damato B, Lecuona K. Conservation of eyes with choroidal melanoma by a multimodality approach to treatment: an audit of 1632 patients. Ophthalmology 2004;111(5):977-83.	15121377	No extractable data
Dawson DM, Dingman JF. Hazards of proton-beam pituitary irradiation. New England Journal of Medicine 1970;282(25):1434.	5445533	No malignancy
Desjardins L, Levy-Gabriel C, Lumbroso-Lerouic L, et al. [Prognostic factors for malignant uveal melanoma. Retrospective study on 2,241 patients and recent contribution of monosomy-3 research] [French]. Journal Francais d Opthalmologie 2006;29(7):741-9.	16988624	Not relevant
Dubikaitis I, Fedotova TA. [Dynamics of the bioelectrical activity of the brain in patients with intrasellar pituitary adenomas irradiated with a proton beam] [Russian]. Zhurnal Nevropatologii i Psikhiatrii Imeni S - S - Korsakova 1985;85(3):372-5.	2986397	No malignancy
Feuvret L, Noel G, Weber DC et al. A treatment planning comparison of combined photon-proton beams versus proton beams-only for the treatment of skull base tumors. International Journal of Radiation Oncology, Biology, Physics 2007;69(3):944-54.	17889276	Tx planning study
Fitzek M. Letter by M. Fitzek on Hocht S, Bechrakis NE, Nausner M, et al. Proton therapy of uveal melanomas in Berlin: 5 years of experience at the Hahn-Meitner Institut: in: Strahlenther Onkol 2004;180(7):419-24 (DOI 10.1007/s00066-004-1222-5) [comment]. Strahlentherapie und Onkologie 2007;183(1):49;author reply 50.	17225946	No primary data
Fitzek MM, Linggood RM, Adams J, et al. Combined proton and photon irradiation for craniopharyngioma: long-term results of the early cohort of patients treated at Harvard Cyclotron Laboratory and Massachusetts General Hospital. International Journal of Radiation Oncology, Biology, Physics 2006;64(5):1348-54.	16580494	No malignancy
Frau E, Rumen F, Noel G, et al. Low-dose proton beam therapy for circumscribed choroidal hemangiomas. Archives of Ophthalmology 2004;122(10):1471-5.	15477458	No malignancy
Goodman GB, Skarsgard LD, Thompson GB, et al. Pion therapy at TRIUMF. Treatment results for astrocytoma grades 3 and 4: a pilot study. Radiotherapy & Oncology 1990;17(1):21-8.	2157239	Not eligible RT
Graffman S, Brahme A, Larsson B. Proton radiotherapy with the Uppsala cyclotron. Experience and plans. Strahlentherapie 1985;161(12):764-70.	3001977	No primary data
Gragoudas ES, Egan KM, Seddon JM, et al. Survival of patients with metastases from uveal melanoma. Ophthalmology 1991;98(3):383-9;discussion 390.	2023760	No primary data
Greiner R, Blattmann H, Thum P, et al. Anaplastic astrocytoma and glioblastoma: pion irradiation with the dynamic conformation technique at the Swiss Institute for Nuclear Research (SIN). Radiotherapy & Oncology 1990;17(1):37-46.	2108474	Not eligible RT
Gridley DS, Bonnet RB, Bush DA, et al. Time course of serum cytokines in patients receiving proton or combined photon/proton beam radiation for resectable but medically inoperable non-small-cell lung cancer. International Journal of Radiation Oncology, Biology, Physics 2004;60(3):759-66.	15465192	Not relevant
Griffin TW, Davis R, Laramore GE, et al. Mixed beam radiation therapy for unresectable squamous cell carcinomas of the head and neck: the results of a randomized RTOG study. International Journal of Radiation Oncology, Biology, Physics 1984;10(12):2211-5.	6439699	Not eligible RT

Citation	PMID	Reason for exclusion
Griffin TW, Weisberger EC, Laramore GE, et al. Complications of combined surgery and neutron radiation therapy in patients with advanced carcinoma of the head and neck. Radiology 1979;132(1):177-8.	451196	Not eligible RT
Gudjonsson O, Blomquist E, Lilja A, et al. Evaluation of the effect of high-energy proton irradiation treatment on meningiomas by means of 11C-L-methionine PET. European Journal of Nuclear Medicine 2000;27(12):1793-9.	11189942	No malignancy
Gudjonsson O, Blomquist E, Nyberg G, et al. Stereotactic irradiation of skull base meningiomas with high energy protons. Acta Neurochirurgica 1999;141(9):933-40.	10526074	No malignancy
Harsh GR, Thornton AF, Chapman PH, et al. Proton beam stereotactic radiosurgery of vestibular schwannomas. International Journal of Radiation Oncology, Biology, Physics 2002;54(1):35-44.	12182972	No malignancy
Heesters MA, Kamman RL, Mooyaart EL, et al. Localized proton spectroscopy of inoperable brain gliomas. Response to radiation therapy. Journal of Neuro-Oncology 1993;17(1):27-35.	8120569	Not eligible RT
Heimann H, Gochman R, Hellmich M, et al. [Dry eye symptoms following retinal surgery and ocular tumour therapy] [German]. Ophthalmologe 2004;101(11):1098-104.	15098135	Not relevant
Heufelder J, Cordini D, Fuchs H, et al. [Five years of proton therapy of eye neoplasms at the Hahn-Meitner Institute, Berlin] [German]. Zeitschrift fur Medizinische Physik 2004;14(1):64-71.	15104012	Not relevant
Hocht S, Wachtlin J, Bechrakis NE, et al. Proton or photon irradiation for hemangiomas of the choroid? A retrospective comparison. International Journal of Radiation Oncology, Biology, Physics 2006;66(2):345-51.	16887287	No malignancy
Holmberg K, Meijer AE, Harms-Ringdahl M, et al. Chromosomal instability in human lymphocytes after low dose rate gamma-irradiation and delayed mitogen stimulation. International Journal of Radiation Biology 1998;73(1):21-34.	9464474	Not relevant
Hug EB, Slater JD. Proton radiation therapy for pediatric malignancies: status report. Strahlentherapie und Onkologie 1999;175(Suppl 2):89-91.	10394409	Not relevant
Hug EB, Slater JD. Proton radiation therapy for chordomas and chondrosarcomas of the skull base [review] [35 refs]. Neurosurgery Clinics of North America 2000;11(4):627-38.	11082173	No primary data
Isacsson U, Lennernas B, Grusell E, et al. Comparative treatment planning between proton and x-ray therapy in esophageal cancer. International Journal of Radiation Oncology, Biology, Physics 1998;41(2):441-50.	9607363	Tx planning study
Jones DT, Schreuder AN, Symons JE, et al. Status report of the NAC particle therapy programme. Strahlentherapie und Onkologie 1999;175(Suppl 2):30-2.	10394392	Not relevant
Kang JH, Wilkens JJ, Oelfke U. Demonstration of scan path optimization in proton therapy. Medical Physics 2007;34(9):3457-64.	17926947	No primary data
Kang Y, Zhang X, Chang JY et al. 4D Proton treatment planning strategy for mobile lung tumors. International Journal of Radiation Oncology, Biology, Physics 67 (3):906 -14, 2007	17293240	Tx planning study
Kaplan ID, Castro JR, Phillips TL. Helium charged particle radiotherapy for meningioma: experience at UCLBL. University of California Lawrence Berkeley Laboratory. Int J Radiat Oncol Biol Phys. 1994 Jan 1;28(1):257-61.	8270449	No malignancy
Kaplan ID, Castro JR, Phillips TL. Helium charged particle radiotherapy for meningioma: experience at UCLBL. University of California Lawrence Berkeley Laboratory. International Journal of Radiation Oncology, Biology, Physics 1994;28(1):257-61.	8270449	No malignancy

Citation	PMID	Reason for exclusion
Keunen JE, Bleeker JC. [Eye-preserving treatment of uveal melanoma. Leidse Oogmelanoom Groep] [review] [26 refs] [Dutch]. Nederlands Tijdschrift voor Geneeskunde 1997;141(42):2005-9.	9550751	Publication language
Kiseleva VN, Grigorova TM, Poidenko VK, et al. [Results of combined gamma-proton irradiation of patients with cervical cancer] [Russian]. Akusherstvo i Ginekologiia 1986;(2):37-9.	3010758	Publication language
Kiseleva VN, Ruderman AI, Lebedev AI. [Prospects for using the Institute of Theoretical and Experimental Physics proton beam for treating gynecologic cancer patients] [Russian]. Voprosy Onkologii 1983;29(6):34-41.	6306925	Publication language
Kligerman MM, von Essen CF, Khan MK, et al. Experience with pion radiotherapy. Cancer 1979;43(3):1043-51.	371782	Not eligible RT
Kondrat'ev BV, Vinogradov VM, Shalek RA, et al. [Proton irradiation of the pituitary gland for alleviating pain in patients with disseminated prostate cancer] [Russian]. Voprosy Onkologii 2006;52(1):92-4.	16715713	Publication language
Konnov BA, Lebedeva NA, Potin VV, et al. [Results of the treatment of patients with prolactinoma using a high-energy proton beam] [Russian]. Akusherstvo i Ginekologiia 1988;(11):44-7.	2853579	No malignancy
Koyama-Ito H, Kanai T, Minohara S, et al. Carbon ion therapy for ocular melanoma: planning orthogonal two-port treatment. Physics in Medicine & Biology 2007;52(17):5341-52.	17762090	Tx planning study
Krejcarek SC, Grant PE, Henson JW, et al. Physiologic and radiographic evidence of the distal edge of the proton beam in craniospinal irradiation. International Journal of Radiation Oncology, Biology, Physics 2007;68(3):646-9.	17449195	Not relevant
Lee CH, Tait D, Nahum AE, et al. Comparison of proton therapy and conformal X-ray therapy in non-small cell lung cancer (NSCLC). British Journal of Radiology 1999;72(863):1078-84.	10700825	Tx planning study
Lee V, Hungerford JL. Proton beam therapy for posterior pole circumscribed choroidal haemangioma. Eye 1998;12(Pt 6):925-8.	10325987	No malignancy
Lo EH, Fabrikant JI. Delayed biologic reactions to stereotactic charged-particle radiosurgery in the human brain. Stereotactic & Functional Neurosurgery 1991;56(4):197-212.	1808645	No malignancy
Luu QT, Loredo LN, Archambeau JO, et al. Fractionated proton radiation treatment for pediatric craniopharyngioma: preliminary report. Cancer Journal 2006 Apr;12(2):155-9.	16630407	No malignancy
Makarova GV, Matveev BP, Leonova NS, et al. [Initial experience with the use of the proton beam at the Institute of Theoretical and Experimental Physics to treat prostatic cancer] [Russian]. Meditsinskaia Radiologiia 1987;32(8):66-70.	3041165	Publication language
Marks LB, Light KL, Hubbs JL, et al. The impact of advanced technologies on treatment deviations in radiation treatment delivery. International Journal of Radiation Oncology, Biology, Physics 2007;69(5):1579-86.	18035214	Not relevant
Minakova EI, Vasil'eva NN, Sviatukhina OV. [Single irradiation of the pituitary with a narrow beam of protons having 200 MeV of energy in generalized breast cancer] [Russian]. Meditsinskaia Radiologiia 1977;22(1):33-9.	865251	Publication language
Miyanaga N, Akaza H, Okumura T, et al. A bladder preservation regimen using intra-arterial chemotherapy and radiotherapy for invasive bladder cancer: a prospective study. International Journal of Urology 2000;7(2):41-8.	10710246	Not relevant
Mock U, Bogner J, Georg D, et al. Comparative treatment planning on localized prostate carcinoma conformal photon- versus proton-based radiotherapy. Strahlentherapie und Onkologie 2005;181(7):448-55.	15995838	Not relevant
Monzul' GD, Kondrat'eva AP, Ratner TG, et al. [Proton irradiation of bone metastases] [Russian]. Meditsinskaia Radiologiia 1984;29(6):17-20.	6330488	Publication language

Citation	PMID	Reason for exclusion
Monzul' GD, Letiagin VP, Ratner TG,et al. [Proton irradiation of the hypophysis and gamma therapy of multiple bone metastases in the complex treatment of breast cancer] [Russian]. Meditsinskaia Radiologiia 1987;32(8):49-55.	3041161	Publication language
Monzul' GD, Riabukhin I. [Treatment of disseminated breast cancer with combined irradiation of the hypophysis by protons and zone gamma irradiation of the skeleton] [Russian]. Voprosy Onkologii 1990;36(4):427-33.	2161162	Publication language
Mullins ME, Barest GD, Schaefer PW, et al. Radiation necrosis versus glioma recurrence: conventional MR imaging clues to diagnosis. American Journal of Neuroradiology 2005;26(8):1967-72.	16155144	Not relevant
Murray EM, Werner ID, Schmitt G, et al. Neutron versus photon radiotherapy for local control in inoperable breast cancer. Strahlentherapie und Onkologie 2005;181(2):77-81.	15702295	Not eligible RT
Noel G, Bollet MA, Calugaru V, et al. Functional outcome of patients with benign meningioma treated by 3D conformal irradiation with a combination of photons and protons. International Journal of Radiation Oncology, Biology, Physics 2005;62(5):1412-22.	16029801	No malignancy
Ohnishi T, Takahashi A, Yano T, et al. Hyperthermic enhancement of tumour growth inhibition by accelerated carbon-ions in transplantable human esophageal cancer. International Journal of Hyperthermia 1998 Apr;14(2):195-202.	9589324	Not relevant
Paquis P, Pignol JP, Breteau N. [Radiotherapy of high grade glioma: use of fast neutrons, therapy and enhancement by neutron capture] [French]. Neuro-Chirurgie 2000;46(1):23-33.	10790640	Not eligible RT
Pickles T, Goodman GB, Rheaume DE, et al. Pion radiation for high grade astrocytoma: results of a randomized study. International Journal of Radiation Oncology, Biology, Physics 1997;37(3):491-7.	9112443	Not eligible RT
Pommier P, Balosso J, Bolla M, et al. [The French project ETOILE: review of clinical data for light ion hadrontherapy] [French]. Cancer Radiotherapie 2002;6(6):369-78.	12504776	Not relevant
Porter RW, Detwiler PW, Han PP, et al. Stereotactic radiosurgery for cavernous malformations: Kjellberg's experience with proton beam therapy in 98 cases at the Harvard Cyclotron [comment]. Neurosurgery 1999;44(2):424-5.	9932903	No malignancy
Price J, Wei WC, Chong CY. Cranial nerve damage in patients after alpha (heavy)-particle radiation to the pituitary. Ophthalmology 1979;86(6):1161-72.	230438	No malignancy
Ronson BB, Schulte RW, Han KP, et al. Fractionated proton beam irradiation of pituitary adenomas. International Journal of Radiation Oncology, Biology, Physics 2006;64(2):425-34.	16257131	No malignancy
Ronson BB, Yonemoto LT, Rossi CJ, et al. Patient tolerance of rectal balloons in conformal radiation treatment of prostate cancer. International Journal of Radiation Oncology, Biology, Physics 2006;64(5):1367-70.	16488552	Not relevant
Ruderman AI, Novikova LA, Kiseleva VN. [Use of high energy protons in the combination treatment of cervix neoplasms] [Russian]. Meditsinskaia Radiologiia 1919:5-12.	4218881	Publication language
Schnabel K, Berberich W, Scharding B, et al. [Irradiation of grades III and IV astrocytomas with new types of radiation] [review] [32 refs] [German]. Strahlentherapie und Onkologie 1986;162(5):285-90.	3012809	No primary data
Schneider U, Lomax A, Besserer J, et al. The impact of dose escalation on secondary cancer risk after radiotherapy of prostate cancer. International Journal of Radiation Oncology, Biology, Physics 2007;68(3):892-7.	17459608	Not relevant
Schneider U, Lomax A, Lombriser N. Comparative risk assessment of secondary cancer incidence after treatment of Hodgkin's disease with photon and proton radiation. Radiation Research 2000;154(4):382-8.	11023601	Not relevant

Citation	PMID	Reason for exclusion
Shibuya H, Tsujii H. The structural characteristics of radiation oncology in Japan in 2003. International Journal of Radiation Oncology, Biology, Physics 2005;62(5):1472-6.	16029809	No primary data
Studer UE, Gerber E, Zimmermann A, et al. Late results in patients treated with pi-mesons for bladder cancer [see comment]. Cancer 1993;71(2):439-47.	8422636	Not eligible RT
Suit HD, Goitein M, Munzenrider J, et al. Increased efficacy of radiation therapy by use of proton beam. Strahlentherapie und Onkologie 1990;166(1):40-4.	2154047	No primary data
Taghian AG, Kozak KR, Katz A, et al. Accelerated partial breast irradiation using proton beams: Initial dosimetric experience. International Journal of Radiation Oncology, Biology, Physics 2006;65(5):1404-10.	16730137	Tx planning study
Takahashi T, Mitsuhashi N, Furuta M, et al. Apoptosis induced by heavy ion (carbon) irradiation of two human tumours with different radiosensitivities in vivo: relative biological effectiveness (RBE) of carbon beam. Anticancer Research 1998 Feb;18(1A):253-6.	9568086	Tx planning study
Trofimov A, Nguyen PL, Coen JJ, et al. Radiotherapy treatment of early-stage prostate cancer with IMRT and protons: a treatment planning comparison. International Journal of Radiation Oncology, Biology, Physics 2007;69(2):444-53.	17513063	Tx planning study
Tsunemoto H, Ishikawa T, Morita S, et al. Indications of particle radiation therapy in the treatment of carcinoma of the esophagus. International Journal of Radiation Oncology, Biology, Physics 1992;22(2):321-4.	1310967	No primary data
Tsunemoto H, Morita S, Ishikawa T, et al. Proton therapy in Japan. Radiation Research 1985;Supplement 8:S235-43.	3003785	No primary data
Vernimmen FJ, Harris JK, Wilson JA, et al. Stereotactic proton beam therapy of skull base meningiomas. International Journal of Radiation Oncology, Biology, Physics 2001;49(1):99-105.	11163502	No malignancy
Watkins L, Khudados ES, Kaleoglu M, et al. Skull base chordomas: a review of 38 patients, 1958-88. British Journal of Neurosurgery 1993;7(3):241-8.	8338644	Not eligible RT
Weber DC, Bogner J, Verwey J, et al. Proton beam radiotherapy versus fractionated stereotactic radiotherapy for uveal melanomas: A comparative study. International Journal of Radiation Oncology, Biology, Physics 2005;63(2):373-84.	16168832	Tx planning study
Weber DC, Lomax AJ, Rutz HP, et al. Spot-scanning proton radiation therapy for recurrent, residual or untreated intracranial meningiomas [see comment]. Radiotherapy & Oncology 2004;71(3):251-8.	15172139	No malignancy
Weber DC, Chan AW, Bussiere MR, et al. Proton beam radiosurgery for vestibular schwannoma: tumor control and cranial nerve toxicity. Neurosurgery 2003;53(3):577-86;discussion 586-8.	12943574	No malignancy
Wittig A, Moss RL, Stecher-Rasmussen F, et al. Neutron activation of patients following boron neutron capture therapy of brain tumors at the high flux reactor (HFR) Petten (EORTC Trials 11961 and 11011). Strahlentherapie und Onkologie 2005;181(12):774-82.	16362787	Not eligible RT
Woodruff KH, Castro JR, Quivey JM, et al. Postmortem examination of 22 pancreatic carcinoma patients treated with helium ion irradiation. Cancer 1984;53(3):420-5.	6318947	Not relevant
Zherbin EA, Konnov BA, Mel'nikov LA, et al. [Proton therapy: clinico-methodological aspects, treatment results] [Russian]. Meditsinskaia Radiologiia 1987;32(8):17-22.	3041155	Publication language
Zografos L, Chamot L, Bercher L, et al. [Contribution of ultrasound biomicroscopy to conservative treatment of anterior uveal melanoma] [French]. Klinische Monatsblatter fur Augenheilkunde 208:414-417.	8766068	Tx planning study

Citation	PMID	Reason for exclusion
Zografos L, Egger E, Bercher L, et al. Proton beam irradiation of choroidal hemangiomas. American Journal of Ophthalmology 1998;126(2):261-8.	9727520	No malignancy
Zografos L, Gailloud C, Bercher L. [Irradiation treatment of choroidal hemangiomas] [review] [20 refs] [French]. Journal Francais d Opthalmologie 1989;12(11):797-807.	2700992	No malignancy
Zytkovicz A, Daftari I, Phillips TL, et al. Peripheral dose in ocular treatments with CyberKnife and Gamma Knife radiosurgery compared to proton radiotherapy. Physics in Medicine & Biology 2007;52(19):5957-71.	17881812	Not relevant

RT: radiotherapy; Tx: treatment

Appendix E. Table of Screened Case Series and Case Reports

Citation	PMID
Bacchetti S, Bressan P, Della MG. Melanoma of the choroid above the optic disc: considerations concerning a clinical case. Ophthalmologica 1998;212(Suppl 1):53-6.	9730752
Bhattacharyya N, Thornton AF, Joseph MP, et al. Successful treatment of esthesioneuroblastoma and neuroendocrine carcinoma with combined chemotherapy and proton radiation. Results in 9 cases. Archives of Otolaryngology—Head & Neck Surgery 1997;123(1):34-40.	9006501
Char DH, Castro JR, Quivey JM, et al. Helium ion charged particle therapy for choroidal melanoma. Ophthalmology 1980;87(6):565-70.	7413146
Char DH, Crawford JB, Castro JR, et al. Failure of choroidal melanoma to respond to helium ion therapy. Archives of Ophthalmology 1983;101(2):236-41.	6824468
Chazalon-Pauleau E, Roux L, Patte JH, et al. [Conjunctival melanoma at corneoscleral limbus on primary acquired melanosis. A case report] [French]. Journal Francais d Opthalmologie 2007;30(8):e22.	17978670
Colli BO, Al-Mefty O. Chordomas of the skull base: follow-up review and prognostic factors. Neurosurgical Focus 2001;10(3):E1.	16734401
Coppeto JR, Roberts M. Fibrosarcoma after proton-beam pituitary ablation. Archives of Neurology 1979;36(6):380-1.	454238
Croughs P, Deman C, Richard F, et al. Treatment of retinoblastoma using accelerated protons] [French]. Bulletin de la Societe Belge d Ophtalmologie 1992;243:81-5.	1338776
Currier BL, Papagelopoulos PJ, Krauss WE, et al. Total en bloc spondylectomy of C5 vertebra for chordoma. Spine 2007;32(9):E294-9.	17450062
D'Hermies F, Meyer A, Morel X, et al. [Neovascular glaucoma following proton-beam therapy. Case report] [French]. Journal Francais d Opthalmologie 2001;24(1):95-101.	11240479
DeVries A, Munzenrider JE, Hedley-Whyte T, et al. [The role of radiotherapy in the treatment of malignant meningiomas] [German]. Strahlentherapie und Onkologie 1999;175(2):62-7.	10065140
Dithmar S, Diaz CE, Grossniklaus HE. Intraocular melanoma spread to regional lymph nodes: report of two cases. Retina 1920:76-79.	10696752
Dziuk E, Merta A, Bocian E. Accidental irradiation of skin on hands with a proton beam of 4 MeV energy. Strahlentherapie 1973;146(6):685-92.	4792265
Fries PD, Char DH, Crawford JB, et al. Sympathetic ophthalmia complicating helium ion irradiation of a choroidal melanoma. Archives of Ophthalmology 1987;105(11):1561-4.	3675290
Fukumitsu N, Tokuuye K, Sugahara S, et al. A patient surviving for eight years after proton and x-ray irradiation for advanced esophageal cancer. Acta Oncologica 2006;45(8):1132-4.	17118851
Gear HC, Kemp EG, Kacperek A, et al. Treatment of recurrent orbital haemangiopericytoma with surgery and proton beam therapy. British Journal of Ophthalmology 2005;89(1):123-4.	15615763
Gerber DS, Campo RV. Acute and chronic keratitis with ulceration after corneal exposure to helium ion irradiation. American Journal of Ophthalmology 1987;104(2):189-90.	3618720
Gohongi T, Tokuuye K, Iida H, et al. Concurrent proton beam radiotherapy and systemic chemotherapy for the metastatic liver tumor of gastric carcinoma: a case report. Japanese Journal of Clinical Oncology 2005;35(1):40-4.	15681604
Goodman DF, Char DH, Crawford JB, et al. Uveal melanoma necrosis after helium ion therapy. American Journal of Ophthalmology 1986;101(6):643-5.	3717245
Gradoudas ES, Goitein M, Koehler A, et al. Proton irradiation of choroidal melanomas. Preliminary results. Archives of Ophthalmology 1978;96(9):1583-91.	99132
Graffman S, Haymaker W, Hugosson R, et al. High-energy protons in the postoperative treatment of malignant glioma. Acta Radiologica: Therapy, Physics, Biology 1975;14(5):443-61.	173141
Gragoudas ES, Goitein M, Koehler AM, et al. Proton irradiation of small choroidal malignant melanomas. American Journal of Ophthalmology 1977;83(5):665-73.	405869
Gragoudas ES, Carroll JM. Multiple choroidal metastasis from bronchial carcinoid treated with photocoagulation and proton beam irradiation. American Journal of Ophthalmology 1979;87(3):299-304.	219697

Citation	PMID
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Appendix F. Centers That Perform Particle Beam Treatment (Worldwide)

Appendix Table F1. Operating particle beam facilities around the world

Institute	Country	Parti-cle	Maximum Clinical Energy (MeV)	Beam direction			First patient	N treated	Date of N treated
				H	V	Gan			
ITEP, Moscow	Russia	proton	250	Y	–	–	1969	4024	Dec-07
St.Petersburg	Russia	proton	1000	Y	–	–	1975	1327	Dec-07
PSI, Villigen	Switzer-land	proton	72	Y	–	–	1984	4875	Dec-07
Dubna	Russia	proton	200***	Y	–	–	1999	402	Dec-07
Uppsala	Sweden	proton	200	Y	–	–	1989	840	Dec-07
Clatterbridge	England	proton	62	Y	–	–	1989	1701	Dec-07
Loma Linda	USA	proton	250	Y	–	Y	1990	11414	Nov-06
MPRI(2)	USA	proton	200	Y	–	–	1993	379	Dec-07
UCSF	USA	proton	60	Y	–	–	1994	920	Mar-07
Nice	France	proton	65	Y	–	–	1991	3129	Sep-06
Orsay	France	proton	200	Y	–	–	1991	4143	Dec-07
iThemba Labs	South Africa	proton	200	Y	–	–	1993	500	Dec-07
HIMAC, Chiba	Japan	ion	800/u	Y	Y	–	1994	3795	Jan-08
TRIUMF, Vancouver	Canada	proton	72	Y	–	–	1995	130	Dec-07
PSI, Villigen	Switzer-land	proton **	250*	–	–	Y	1996	320	Dec-07
G.S.I. Darmstadt	Germany	ion**	430/u	Y	–	–	1997	384	Dec-07
HMI, Berlin	Germany	proton	72	Y	–	–	1998	1014	Dec-07
NCC, Kashiwa	Japan	proton	235	–	–	Y	1998	552	Dec-07
HIBMC,Hyogo	Japan	proton	230	–	–	Y	2001	1658	Dec-07
HIBMC,Hyogo	Japan	ion	320	Y	Y	–	2002	271	Dec-07
PMRC(2), Tsukuba	Japan	proton	250	–	–	Y	2001	1188	Dec-07
NPTC, MGH Boston	USA	proton	235	Y	–	Y	2001	2710	Oct-07
INFN-LNS, Catania	Italy	proton	60	Y	–	–	2002	151	Dec-07
Shizuoka	Japan	proton	235	Y	–	Y	2003	570	Dec-07
Wakasa WERC,Tsuruga	Japan	proton	200	Y	Y	–	2002	49	Dec-07
WPTC, Zibo	China	proton	230	Y	–	Y	2004	537	Dec-07
MD Anderson Cancer Center, Houston, TX	USA	proton	250	Y	–	Y	2006	527	Dec-07

Institute	Country	Parti-cle	Maximum Clinical Energy (MeV)	Beam direction			First patient	N treated	Date of N treated
				H	V	Gan			
FPTI, Jacksonville, FL	USA	proton	230	Y	–	Y	2006	360	Dec-07
NCC, Ilsan	South Korea	proton	230	Y	–	Y	2007	155	Dec-07

N: number; H: horizontal; V: vertical; Gan: Gantry
* degraded beam for 1996 to 2006; dedicated 250 MeV proton beam from 2007 onwards
** with beam scanning (all others with spread beam)
*** degraded beam
Ordered by the time of treatment of the first patient.

Source: Particle Therapy Cooperative Group, available at http://ptcog.web.psi.ch/. Accessed June 16, 2008.

Appendix Table F2. Particle beam facilities that are being planned around the world

Institute	Country	In construc-tion	Particle	Maximum Clinical Energy (MeV) [Accelerator]	Treat-ment rooms	Gantries	Start date
RPTC, Munich	Germany	Y	proton	250 [SCC]	5	4	2008
WPE, Essen	Germany	Y	proton	230 [Cyc]	4	3	2009
Heidelberg/GSI Darmstadt	Germany	Y	proton, ion	430 [SCC]	3	1	2008
PTC, Marburg	Germany	Y	proton, ion	430 [Syn]	4	0	2010
Kiel	Germany	N	proton, ion	430 [Syn]	3	0	2012
RPTC, Koeln	Germany	N	proton	250 [SCC]	5	4	?
PSI, Villigen	Switzer-land	Y	proton	250 [SCC]	3	+1	2007/08
UPenn	USA	Y	proton	230 [Cyc]	5	4	2009
Northern Illinois PT Res.Institute, W. Chicago, IL	USA	N	proton	250	4	2	2010
Med-AUSTRON	Austria	N	proton, ion	? [Syn]	3 to 4 (?)	2	?
Trento	Italy	N	proton	230 [Cyc]	2	1	2010?
CNAO, Pavia	Italy	Y	proton, ion	430 [SCC]	3 to 4	1	2009?
iThemba Labs	South Africa	N	proton	230 [SCC]	3	1	?
CPO, Orsay	France	Y	proton	230 [Cyc]	3	1	2010

Cyc: Cyclotron; N: no; SCC: Synchrocyclotron; Syn: synchrotron; Y: yes
Source: Particle Therapy Cooperative Group, available at http://ptcog.web.psi.ch/. Accessed June 16, 2008.

Also, Tufts Medical Center (Boston, MA, USA) announced plans to start building a particle beam facility.

Appendix G. Summary Table

Summary Table. Summary of the 8 items of section C per type of cancer

Cancer Type, Histology	Patient populations	Available study types	Instrumentation and algorithms	Characteristics of particle beam (range of means or medians) [doses in GyE]	Prior or concurrent interventions	Efficacy (number of studies reporting outcome)	Serious harms (excluding those attributed to co-interventions by authors)
Ocular							
Uveal melanoma (melanoma of the choroid, ciliary body, iris)	Ages: 35-66 Males: 20-64 Enrolled: 1975-2006 Variety of locations and sizes – metastasis a baseline and bilateral location excluded in most	11 centers 91 studies Non-comparative: 4 P: n=50-2645 81 R: n=14-1922 Comparative, RCT (3): Sizes: 136-188 Higher (70 GyE) vs lower (50 GyE) proton dose Protons + laser TTT vs protons He ions vs I-125 Comparative, nonRCT (7): Sizes: 56-1272 Proton vs enucleation Proton vs I-125 or Ru-106 Proton vs Proton + laser TTT He ion vs I-125	No details on instrumentation No details on algorithms *Other:* Use of tantalum markers to demarcate tumor on the sclera Specialized software (EYEPLAN)	Protons (68), He (21), Carbon (2): Dose: 45-80 (majority 60-70) Fractions: 4-5 Unit dose: 13-16 Duration: 1-2 wk	*Prior Tx:* Surgical excision (1) Proton or photon RT (1) Concurrent Tx: TTT (1)	Follow-up: Survival: OS (40); CSS (37) Local control (37): Local control, recurrence, response to Tx *Other (24):* Metastasis Eye retention Visual loss Visual acuity Tumor size	[Most studies do not explicitly distinguish acute from late] Late: Enucleation (secondary to complications) Neovascular glaucoma Rubeosis iridis Radiation maculopathy Radiation papillopathy Cataract Phthisis bulbi

Cancer Type, Histology	Patient populations	Available study types	Instrumentation and algorithms	Characteristics of particle beam (range of means or medians) [doses in GyE]	Prior or concurrent interventions	Efficacy (number of studies reporting outcome)	Serious harms (excluding those attributed to co-interventions by authors)
Head and neck							
chordoma, chondrosarcoma, or chondroid cancer	Ages: 13-66 Males: 34-73% Enrolled: 1974-2005 Various: previously treated & untreated; chordoma, chondrosarcoma, also a few meningioma, osteosarcoma, & others	8 centers 33 studies Non-comparative: 2 P: n=37, 67 28 R: n=10-223 Comparative: 1 RCT(different doses): n=96	*Most studies report using "treatment planning system"*	He (1); proton (21); C (7); Ne or C or He or Si (2); ND (2) Dose: 45-74 Fractions: 8-57 Unit dose: 1.4 to 4 Duration: 3-12 wk	*Prior Tx:* surgery (11); Photon (2); ND (20) *Concurrent Tx:* photon (9); surgery (5); ND (18)	Follow-up: 9-72 mo *Survival:* OS (26); CSS (18); ND (6) *Local control:* (24); ND (9)	Acute: moderate hearing loss; gr 3 mucositis Late: brain edema, cranial nerve deficit, fat necrosis, hemiparesis, visual loss, osteitis, basilar artery injury, pituitary dysfunction, fatal complications, seizure, radiation necrosis of brain stem, radiation transaction of the cord, short-term memory loss, somnolence, depression, severe hearing loss, ↓psychomotor performance, temporal muscle fibrosis, brain ulceration, optic neuropathy, breast cancer

Cancer Type, Histology	Patient populations	Available study types	Instrumentation and algorithms	Characteristics of particle beam (range of means or medians) [doses in GyE]	Prior or concurrent interventions	Efficacy (number of studies reporting outcome)	Serious harms (excluding those attributed to co-interventions by authors)
glial cell tumor (astrocytoma, glioblastoma multiforme)	Ages: 6-55 Males: 41-71% Enrolled: 1977-2002 Various: previously treated & untreated; astrocytoma, glioblastoma multiforme, glioma, also a few meningioma	4 centers 9 studies Non-comparative: 2 P: n=20, 48 6 R: n=7-93 Comparative: 1 RCT(different doses): n=15	*Most studies report using "treatment planning system"*	Proton (7); C (1) Dose: 54-77 Fractions: 33-77 Unit dose: 1.4 to 4 Duration: 7-10 wk	*Prior Tx:* chemo (2); Photon (2) *Concurrent Tx:* photon (6); surgery (3)	Follow-up: 5-39 mo *Survival:* OS (6); CSS (5); ND (1) *Local control:* (5); ND (3)	Acute: gr 3 thrombocytopenia, gr 4 neurologic findings (minor?), gr 3 acute otitis media Late: radiation necrosis requiring surgery, seizure, cataract, pituitary deficiency, Moyamoya disease

Cancer Type, Histology	Patient populations	Available study types	Instrumentation and algorithms	Characteristics of particle beam (range of means or medians) [doses in GyE]	Prior or concurrent interventions	Efficacy (number of studies reporting outcome)	Serious harms (excluding those attributed to co-interventions by authors)
Other head & neck (including oropharyngeal but not ocular) tumors	Ages: 12-65 Males: 22-74% Enrolled: 1973-2005 neuroblastoma, melanoma, liposarcoma, malignant meningioma, squamous, adenocystic, neuroendocrine, mesenchymal tumor	6 centers 15 studies Non-comparative: 3 P: n=19-36 11 R: n=14-152 Comparative: Non-randomized (SFRT or IMRT alone vs with carbon particles): n=63	*Most studies report using "treatment planning system"*	Proton (8); C (6) Dose: 20-76 Fractions: 11-45 Unit dose: 1.4 to 4 Duration: 6-11 wk	*Prior Tx:* chemo (2); Surgery (7) *Concurrent Tx:* photon (4); surgery (1); chemo (5)	Follow-up: 12-90 mo *Survival:* OS (13); CSS (7); ND (2) *Local control:* (13); ND (2)	Acute: phrenic nerve paralysis, hemianopsia, cognitive deficits, seizure, focal necrosis with mass effect requiring surgery, gr 3 mucositis, tongue ulceration leading to fistula, recurrent bacterial infection & difficulties in wound healing (had reconstruction of orbit with a metal implant prior to radiation Rx) Late: vocal cord paralysis, epiglottitis, brain damage & necrosis, CSF leak with meningitis, visual loss, myelitis, osteonecrosis, esophageal stenosis, paresis, memory loss, pituitary deficiency, seizure, ocular paralysis, hearing loss, cerebellar syndrome, paresis of the trigeminal nerve

Cancer Type, Histology	Patient populations	Available study types	Instrumentation and algorithms	Characteristics of particle beam (range of means or medians) [doses in GyE]	Prior or concurrent interventions	Efficacy (number of studies reporting outcome)	Serious harms (excluding those attributed to co-interventions by authors)
Spine							
Spine & sacral cancer (chordoma (4), glioblastoma (1), others (4))	Ages: 45-66 Males: 53-86% Enrolled: 1976-2003 Various: previously treated & untreated; chordoma, chondrosarcoma, osteosarcoma, giant cell	4 centers 9 studies Non-comparative: 1 P: n=23 8 R: n=14-85 Comparative: None	No details on instrumentation No details on algorithms *Other:* Specialized software (e.g., HIPLAN)	He (1); Ne (1); proton (4); C (1); Ne & He (1); ND (2) Dose: 23-94 Fractions: 16-37 Unit dose: 1.8-4.6 Duration: 4-14 wk	*Prior Tx:* surgery (3); chemo (1); Photon (2); ND (4) *Concurrent Tx:* photon (5); surgery (3); ND (2)	Follow-up: 20-65 mo *Survival:* OS (9); CSS (4); ND (1) *Local control:* (8); ND (2)	Acute: ≥Gr 3 skin reaction Late: radiation injury leading to colostomy; brain stem, spinal cord, brachial plexus injury; visual complications; enucleation; osteonecrosis; secondary malignancy
Gastrointestinal							
Gastrointestinal cancer (esophagus (3), pancreas (2), bile duct (2), unspecified (1))	Ages: 59-74 Males: 32-87% Enrolled: 1975-1998 Various: squamous, adenocarcinoma, well & poorly differentiated	2 centers 8 studies Non-comparative: 2 P: n=46, 94 3 R: n=11-68 Comparative: RCT (1): [Pancreas] He RT vs photon RT: 49 non-RCT (2): [Bile duct] Surgery + Photon RT vs Surgery + Proton RT: 22 [Bile duct] Photon RT vs Proton RT: 62	No details on instrumentation No details on algorithms *Other:* Use of iridium markers to facilitate better localization of tumor Specialized software (e.g., LBL's treatment planning system)	He (3); proton (2); Ne & He (2) Dose: 32-81 Fractions: 30-32 Unit dose: 1.8-3.5 Duration: 8-10 wk	*Prior Tx:* surgery (2); chemo (1); ND (2) *Concurrent Tx:* chemo (2); photon (2); brachy (2); ND (2)	Follow-up: 7-73 mo *Survival:* OS (7); CSS (4); ND (1) *Local control:* (6); ND (2)	Acute: GI bleed; ≥Gr 3 esophagitis; cytopenia, fibrosis; radiation pneumonitis Late: radiation enteritis requiring surgery; esophageal ulceration requiring IV alimentation

Cancer Type, Histology	Patient populations	Available study types	Instrumentation and algorithms	Characteristics of particle beam (range of means or medians) [doses in GyE]	Prior or concurrent interventions	Efficacy (number of studies reporting outcome)	Serious harms (excluding those attributed to co-interventions by authors)
Liver, HCC	Ages: 60-81 Males: 54-83% Enrolled: 1985-2006 Patients ineligible for other Tx strategies	4 centers 13 studies Non-comparative 3 P: n=24, 30, 34 10 R: n=12-162 Comparative None	No details on instrumentation No details on algorithms *Other:* Use of iridium markers to facilitate better localization of tumor Specialized software (e.g., PT-PLAN/NDOSE, CANVAS 8)	Protons (12) & Carbon (1) Dose: 50-80 Fractions: 15-30 Unit dose: 2.0-9.0 Duration: 3-9 wk	*Prior Tx:* Surgery (4) TACE (6) PEI (4) Proton RT (2) Ablation (2) Photon RT (1) None (2) ND (5) *Concurrent Tx:* TACE (2) None (7) ND (4)	Follow-up: 11-71 mo *Survival:* OS (11); CSS (10) *Local control (8)*: local control rate *Other (5)* response rate metastasis	Acute: ↓WBC, ↓PLT ↑Total Bilirubin ↑AST/ALT Hepatic failure Late: Infectious biloma Common bile duct stenosis GI bleeding Hepatic failure

Cancer Type, Histology	Patient populations	Available study types	Instrumentation and algorithms	Characteristics of particle beam (range of means or medians) [doses in GyE]	Prior or concurrent interventions	Efficacy (number of studies reporting outcome)	Serious harms (excluding those attributed to co-interventions by authors)
Pelvis							
Prostate cancer Adenocarcinoma	Ages: 67-73 Males: 100% Enrolled: 1972-2004 Patients with T1-4 +/- regional lymphnode metastasis	5 centers 19 studies Non-comparative 3 P: n=30-175 10 R: n=16-1255 Comparative, RCT: 3 (n=191-393) Photon RT plus standard dose vs. high-dose proton boost RT Photon RT plus photon boost RT vs. proton boost RT Photon RT plus photon boost RT vs. proton boost RT Comparative, non-RCT: 2 (n=180-185) Photon RT plus photon boost RT vs. proton boost RT Watchful waiting vs. surgery vs. standalone photon RT vs. photon RT plus proton boost RT vs. standalone proton RT	No details on instrumentation No details on algorithms *Other:* Use of iridium markers to facilitate better localization of tumor Specialized software (e.g., HIPLAN, modified MGH 3-D planning system, FOCUS-M)	Protons (15) & Carbon (4) Dose: 54-80 Fractions: 20-44 Unit dose: 1.8-3.6 Duration: 5-9 wk	*Prior Tx:* None (12) ND (7) *Concurrent Tx:* Hormonal (7) Photon RT (13)	Follow-up: 30-157 mo *Survival:* OS (8); CSS (6) biochemical disease-free survival (7) *Local control (9)*: local control rate *Other (0)*	Acute: Proctitis Urinary tract complication (unclear) Late: GI bleeding Cystitis, hematuria, urethral strincture, dysuria)

Cancer Type, Histology	Patient populations	Available study types	Instrumentation and algorithms	Characteristics of particle beam (range of means or medians) [doses in GyE]	Prior or concurrent interventions	Efficacy (number of studies reporting outcome)	Serious harms (excluding those attributed to co-interventions by authors)
Bladder cancer Transitional and/or squamous cell carcinomas	Ages: 55-72 Males: 80-87% Enrolled: 1985-1999 Various patients with size T2 or greater	1 center 3 studies Non-comparative: 2 P: n=25, 35 1 R: n=15 Comparative None	ND	Protons (add-on therapy) Dose: 74-85 Fractions: 24-34 Unit dose: 1.8-3.0 Duration: ND	*Prior Tx:* None (2), ND (1) *Concurrent Tx:* Resection + photon RT + chemotherapy	Follow-up: 21-57 mo *Survival:* OS (3); CSS (3) *Local control:* (3): Recurrence-free survival, local control rate *Other (1):* Bladder conservation	Acute: None Late: Macrohematuria requiring surgery
Uterine cancer	Ages: 56-64 Males: 0% Enrolled: 1983-2005 Various: both previously treated & untreated patients	2 centers 5 studies Non-comparative: 2 P: n=31, 44 2 R: n=15, 25 Comparative, non-RCT: 1 Carbon RT vs Photon RT & brachytherapy: 49	ND	Protons (2) & Carbon (3) Dose: 62-88 Fractions: 24-30 Unit dose: 1.8-4.0 Duration: 6-8 wk	*Prior Tx:* ND (5) *Concurrent Tx:* photon (2), ND (3)	Follow-up: 26-139 mo *Survival:* OS (4); CSS (3) *Local control:* (5): Recurrence-free survival, local control rate *Other (x):*	Acute: None Late: hemorrhagic cystitis needing surgery; intestinal perforation; fistulas (vesico-vaginal, recto-vaginal, sigmoid-vesico)
Others							
Skin cancers Bowen, oral verrucous carcinoma, squamous cell carcinoma	Ages: 73 Males: 83% Enrolled: ND Refused surgery for primary disease	1 center 1 study Non-comparative 1 P: n=12 Comparative None	ND	Protons Dose: 55 Fractions: 5 Unit dose: 10 Duration: 1 wk	*Prior Tx:* None *Concurrent Tx:* None	Follow-up: 49 mo *Survival:* OS *Local control*: Local control rate *Other* Response rate Metastasis	Acute: Skin erythema Late: Skin ulcer fistula

Cancer Type, Histology	Patient populations	Available study types	Instrumentation and algorithms	Characteristics of particle beam (range of means or medians) [doses in GyE]	Prior or concurrent interventions	Efficacy (number of studies reporting outcome)	Serious harms (excluding those attributed to co-interventions by authors)
Bone and soft tissue, sarcoma Chordoma, osteosarcoma, nerve sheath tumor, rhabdomyosarcoma, Chondrosarcoma, liposarcoma, and other types	Ages: 4-50 Males: 55-83% Enrolled: 1973-2005 Inoperable patients or metastatic disease	5 centers 6 studies Non-comparative 14 R: n=12-2371 Comparative None	HIPLAN software (2) Spot-scanning technology (1) ND (3) Immobilization techniques (2) ND (3)	Protons (4) & Carbon (2) Dose: 50-69 Fractions: 16-28 Unit dose: 1.5-3.0 Duration: 4-10 wk	*Prior Tx:* Chemotherapy (3) Surgery (2) None (1) ND (1) *Concurrent Tx:* Chemotherapy (2) None (2) ND (2)	Follow-up: 6-59 mo *Survival:* OS (5); CSS (3) *Local control (4)*: local control rate *Other (nd)*	Acute: Grade 1 or 2 Grade 3 or 4 Organ toxicities Late: osteomyelitis panyhypopituitarism & cataract focal frontal lobe necrosis Acute lymphocytic leukemia Failed allograft secondary to infection DVT and ureteral stenosis Radiation recall reaction Symptomatic subcapsular cataract Symptomatic grade 3 brain necrosis
Lung, NSCLC Adenocarcinoma, squamous cell carcinoma, or large cell carcinoma	Ages: 71-75 Males: 41-84% Enrolled: 1983-2005 Inoperable patients or refusal of surgery Mostly stage I	4 centers 17 studies Non-comparative 6 P: n=21-79 11 R: n=13-146 Comparative None	No details on instrumentation No details on algorithms *Other:* Use of iridium markers to facilitate better localization of tumor Specialized software (e.g., HIPLAN)	Protons (8) & Carbon(9) Dose: 51-98 Fractions: 10-24 Unit dose: 1.8-6.0 Duration: 1-9 wk	*Prior Tx:* Lung resection (2) Chemotherapy (1) ND (14) *Concurrent Tx:* None (6) ND (11)	Follow-up: 6-59 mo *Survival:* OS (13); CSS (9) *Local control (11)*: local control rate *Other (2)* response rate metastasis	Acute: Pneumonitis Late: Skin reaction Pulmonary fibrosis Pleural effusion

Cancer Type, Histology	Patient populations	Available study types	Instrumentation and algorithms	Characteristics of particle beam (range of means or medians) [doses in GyE]	Prior or concurrent interventions	Efficacy (number of studies reporting outcome)	Serious harms (excluding those attributed to co-interventions by authors)
Breast cancer	Ages: 46-75 Males: 0% Enrolled: 2004-2005 Lumpectomized cancers	2 centers 2 studies Non-comparative: 2 P: both n=20 Comparative None	No details on instrumentation No details on algorithms	Protons Dose: 32-40 Fractions: 4-10 Unit dose: 4.0-8.0 Duration: 1-2 wk	*Prior Tx:* None (2) *Concurrent Tx:* Surgery (2) Chemo/hormonal Tx (1) ND (1)	Follow-up: 12 mo *Survival:* OS (1); CSS (0) *Local control (1)*: local control rate *Other (0)*	Acute: None Late: None