Technical Brief Number 1

Effective Health Care Program

Particle Beam Radiation Therapies for Cancer
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.

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Technical Briefs are designed to provide an overview of key issues related to clinical intervention or health care services, especially those for which there are limited published data or protocol-driven studies. They provide an early objective description of the state of science, a potential framework for assessing applications and implications, a summary of ongoing research, and information on future research needs.

The full report and this summary are available at www.effectivehealthcare.ahrq.gov/reports/final.cfm

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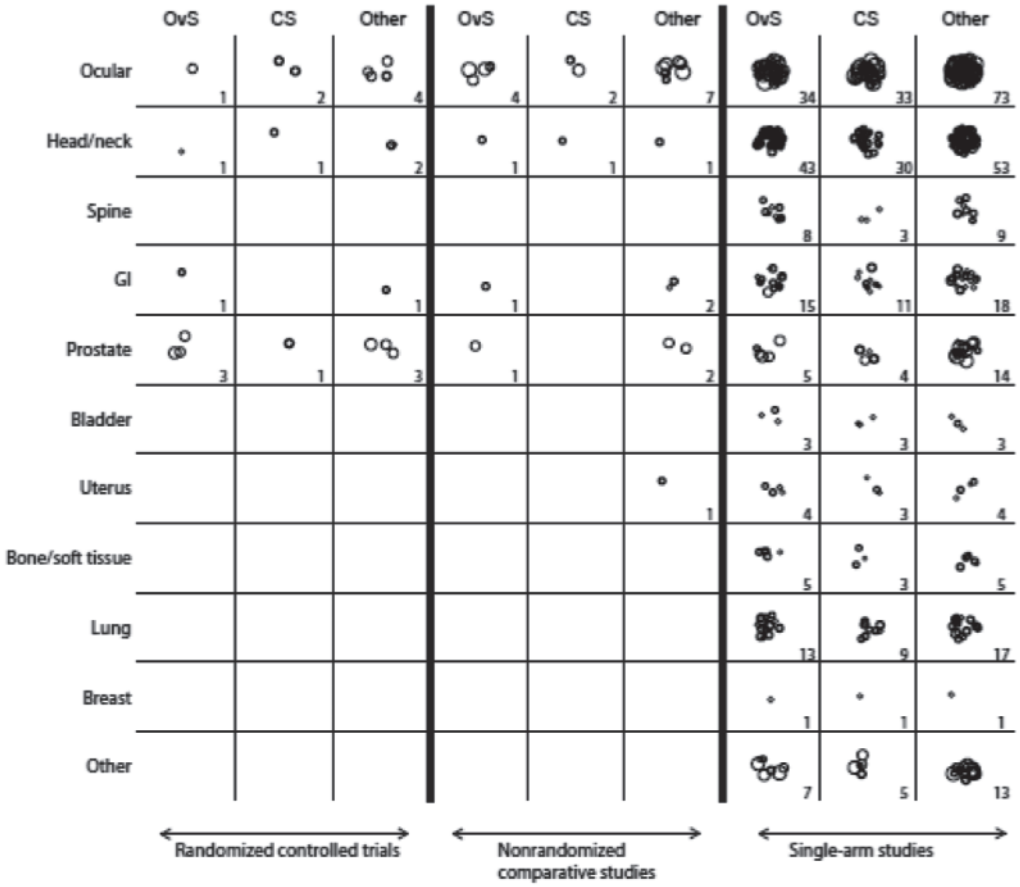
Results

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.

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.

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.

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	1,272	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 Schwerionenforschung; 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.

Full Report

This executive summary is part of the following document: Trikalinos TA, Terasawa T, Ip S, Raman G, Lau J. Particle Beam Radiation Therapies for Cancer. Technical Brief No. 1. (Prepared by Tufts Medical Center Evidence-based Practice Center under Contract No. HHSA-290-07-10055.) Rockville, MD: Agency for Healthcare Research and Quality. September 2009. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

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