Systematic Review: Charged-Particle Radiation Therapy for Cancer

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Background: Radiation therapy with charged particles can potentially deliver maximum doses while minimizing irradiation of surrounding tissues, and it may be more effective or less harmful than other forms of radiation therapy.

Purpose: To review evidence about the benefits and harms of charged-particle radiation therapy for patients with cancer.

Data Sources: MEDLINE (inception to 11 July 2009) was searched for publications in English, German, French, Italian, and Japanese. Web sites of manufacturers, treatment centers, and professional organizations were searched for relevant information.

Study Selection: Four reviewers identified studies of any design that described clinical outcomes or adverse events in 10 or more patients with cancer treated with charged-particle radiation therapy.

Data Extraction: The 4 reviewers extracted study, patient, and treatment characteristics; clinical outcomes; and adverse events for nonoverlapping sets of articles. A fifth reviewer verified data on comparative studies.

Data Synthesis: Currently, 7 centers in the United States have facilities for particle (proton)–beam irradiation, and at least 4 are under construction, each costing between $100 and $225 million. In 243 eligible articles, charged-particle radiation therapy was used alone or in combination with other interventions for common (for example, lung, prostate, or breast) or uncommon (for example, skull-base tumors or uveal melanomas) types of cancer. Of 243 articles, 185 were single-group retrospective studies. Eight randomized and 9 nonrandomized clinical trials compared treatments with or without charged particles. No comparative study reported statistically significant or important differences in overall or cancer-specific survival or in total serious adverse events.

Limitation: Few studies directly compared treatments with or without particle irradiation.

Conclusion: Evidence on the comparative effectiveness and safety of charged-particle radiation therapy in cancer is needed to assess the benefits, risks, and costs of treatment alternatives.

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Charged-particle radiation therapy is an alternative mode of radiation delivery for patients with cancer. This treatment is expensive but is becoming increasingly available.

**Context**

This review found that published evidence about the benefits and harms of charged-particle radiation therapy was derived mostly from small, single-group, retrospective studies. Of the 17 studies that compared treatments with or without charged particles, none reported statistically significant or important differences in overall or cancer-specific specific survival or in total serious adverse events.

**Implication**

We need better evidence to guide decision making about the indications for and the relative safety of charged-particle radiation therapy for cancer.

—The Editors

explicitly excludes radiation therapy with neutrons or other particles, such as π-mesons. We defined conventional radiation therapy as external photon-beam radiation guided by 2- or 3-dimensional imaging with or without the use of treatment planning computers or older technologies and without beam-intensity modulation. The Glossary defines commonly used terms.

**Overview of Contemporary Conformal Radiation Therapies**

On the basis of a fact sheet posted on the National Cancer Institute’s Web site (6), the following alternative conformal radiation therapy modalities were considered: photon intensity-modulated radiation therapy, stereotactic radiosurgery, stereotactic body radiation therapy, brachytherapy, and intraoperative radiation therapy.

Three of the authors summarized contemporary radiation therapy techniques on the basis of selected review articles and Internet sources. Two of the authors independently screened the first 100 reviews from PubMed and the first 100 results from Google (Google, Menlo Park, California) for relevance to the brief overview by using free text terms (such as “particle-beam therapy,” “proton beam therapy,” “intensity modulated radiotherapy,” “stereotactic radiosurgery,” “stereotactic body radiotherapy,” “brachytherapy,” and “intraoperative radiotherapy”).

**Systematic Review of Particle-Beam Radiation Therapy**

**Data Sources and Searches**

We searched MEDLINE from inception to 2 February 2008 by using such terms as “proton,” “charged particle,” and “helium ion” and text and Medical Subject Heading terms for cancer. The complete search strategy is published elsewhere (5). We limited searches to studies in humans. The search was updated to 11 July 2009 to include only randomized, controlled trials or nonrandomized comparative studies.

**Study Selection**

Four of the authors screened abstracts and further examined the full-text articles of all potentially eligible abstracts. We included studies of any design describing charged-particle radiation therapy in at least 10 patients with cancer and reporting any clinical outcome (survival, local tumor control, and change in symptoms) or any adverse event. We included studies regardless of whether charged-particle radiation therapy was used as standalone treatment or as part of multimodal therapy. We accepted studies published in English, German, French, Italian, and Japanese.

**Glossary**

Absorbed radiation dose: The amount of energy (measured in Gray [Gy]) deposited in a given volume of tissue.

Biologically effective dose: The biological effects of a given radiation dose depend on many factors, including type of radiation (photons or charged particles), energy of radiation, and composition of the tissue. The biologically effective dose incorporates relative biological effectiveness (RBE) (see “Relative biological effectiveness”) and correlates better with biological effects than does the radiation dose. It is usually related to the absorbed radiation dose by the following formula:

\[
\text{Biologically effective dose} = \text{RBE} \times \text{radiation dose}
\]

and is measured in (typically cobalt-60) Gray equivalents (GyE).

Brachytherapy (also called implant radiation therapy or internal radiation therapy): A type of radiation therapy that uses small encapsulated radioactive sources inserted in or adjacent to a tumor itself. The sources emit β radiation or α particles, which deposit their energy in the immediately neighboring tissue and deliver very little dose to distal tissues.

Cancer: The operational definition of cancer in this review is “histologically malignant tumors.” All other entities or diseases that have been treated with particle-beam radiotherapy are not considered “cancer” in this review; examples of these conditions are arteriovenous malformations, benign meningiomas, benign schwannomas, craniopharyngioma, or age-related macular degeneration.

Charged-particle radiation therapy: Includes external radiotherapy that uses protons, helium, carbon, neon, silicon ions, or other charged particles. Currently, only protons and carbon ions are in clinical use.

Intensity-modulated radiotherapy*: Conformal photon radiation is delivered to the target tumor by crossing multiple properly shaped radiation fields with modulated intensities through paths that spare radiosensitive and critical adjoining tissues.

Intraoperative radiotherapy: Typically, a single, focused high dose of photon radiation is delivered directly to a tumor while it is exposed during surgery.

Relative biological effectiveness: The ratio of the dose of (typically) cobalt-60 photon radiation that will produce a specified biological effect to the dose of charged-particle radiation required to produce the same effect. The exact values can differ across tissues or with particle energy or depth in the patient’s body.

Stereotactic body radiotherapy*: Multiple low-intensity radiation beams deliver a single high-dose fraction of external radiation to target lesions located outside the central nervous system.

Stereotactic radiosurgery*: Multiple low-intensity radiation beams deliver a single high-dose fraction of external radiation to target lesions in the central nervous system.

* One of the most advanced type of external (photon) radiotherapies.
We excluded studies that evaluated only treatment planning or dosimetry without providing any data on clinical outcomes or adverse event. We also excluded studies in which more than 20% of the patients did not have malignant conditions. Studies with fewer than 10 patients were screened for adverse events.

Data Extraction and Assessment of Evidence

Four authors independently recorded study characteristics (design, eligibility criteria, and follow-up period), patient characteristics (type of cancer, age, sex, and comorbidity), treatment characteristics (type of particle, total biologically effective dose, number of fractions, duration of radiation therapy, and prior and concurrent treatments), clinical outcomes (overall or cause-specific survival, outcomes related to local or distant tumor control, and others), and adverse events. One of the authors abstracted quantitative data on the rates of clinical outcomes only from comparative studies, which another author verified. Disagreements were resolved by consensus.

We considered clinically significant adverse events to be those that were grade 3 (severe and undesirable adverse events, which included any adverse event resulting in inpatient hospitalization or prolongation of hospitalization, any persistent or substantial disability or incapacity, or a congenital anomaly or birth defect), grade 4 (life-threatening adverse events), or grade 5 (adverse event–related death). We also defined “late” adverse events as those that were reported 3 or more months after irradiation (unless the primary study used a different definition) (7). We also recorded authors’ opinions on whether the reported toxicities and adverse events were specifically attributable to radiation therapy.

We assessed the hierarchy of evidence of cancer-related health outcomes by adapting an established classification system (8, 9). We considered randomized, controlled trials to provide the strongest evidence, nonrandomized comparative studies the next strongest, and single-group studies the weakest. We categorized efficacy outcomes as overall survival, cancer-specific survival, and all other efficacy outcomes (for example, quality of life; a surrogate outcome of overall survival, such as disease-free survival or progression-free survival; or local control rates).

Data Synthesis and Analysis

For all included studies, we provided descriptive statistics for study designs, clinical and treatment characteristics, and clinical outcomes and adverse events reported, using the publication as the unit of analysis. For comparative studies, we identified those with overlapping populations by comparing author lists, years, and centers of treatment.

Role of the Funding Source

The study was funded by the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services, which helped formulate the initial study questions but did not participate in the interpretation of the findings, or preparation, review, or approval of the manuscript for publication.

RESULTS

Charged-Particle Radiation Therapy and Alternative Contemporary Conformal Radiation Therapy Techniques

Contemporary conformal radiation therapy techniques have better dose distribution than conventional external photon radiation therapy; investigators claim that the former offer better tumor control because of safe dose escalation and fewer radiation-induced complications because of superior sparing of normal tissue. This makes conformal radiation therapy particularly appealing for surgically unapproachable tumors located adjacent to critical structures, such as the brainstem, cranial nerves, or the spinal cord.

Charged-Particle Radiation Therapy

Charged-particle radiation therapy uses beams of protons or other charged particles, such as helium, carbon, neon, or silicon, but only protons and carbon ions are
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Comparison of Various Radiation Therapy Modalities

| Type of Radiation | Modality          | Charge | Biological Effectiveness* | Location of Maximum Dose | Desirability |
|-------------------|-------------------|--------|--------------------------|--------------------------|--------------|
| Gamma ray or x-ray| Photon            | No     | 1.0 (reference)          | Near surface             | Reference    |
| Electron beam     | Electron          | –1     | 1.0×                     | Near surface             | Reference    |
| Proton beam       | Proton            | +1     | 1.1×                     | At depth                 | Better       |
| Heavy-ion beam    | Carbon or helium  | +2 or more | ≥3×                  | At depth                 | Best         |

* “Biological effectiveness” refers to the relative radiation dose (in Gy) required to produce the same biological effect as photon radiation. For example, carbon-ion therapy may only require 1 Gy to produce the same effect as 4 Gy of photon therapy, resulting in a relative biological effectiveness of 4× for carbon-ion therapy.

Currently in clinical use (10). Charged particles represent advancement over photons because the former have superior depth–dose distribution. Photons or electron beams deposit most of their energy near the surface (skin and normal tissues), with progressively smaller dose at larger depths, where the tumor may be located. In addition, photons continue to deposit the dose of radiation in normal tissues beyond the tumor. In contrast, charged particles deposit a low dose near the surface and almost all their energy in the final millimeters of their trajectory in the tumor; tissues beyond the tumor location receive very little of the dose. This pattern results in a sharp and localized peak dose, known as the Bragg peak (Figure 1). The initial energy of the charged particles determines how deep in the body the Bragg peak will form. The intensity of the beam—that is, how many particles traverse a particular area in unit time—determines the dose that will be deposited to the tissues. By adjusting the energy of the charged particles and the intensity of the beam, one can deliver prespecified doses anywhere in the body with high precision. If the tumor is larger than the Bragg peak width, multiple Bragg peaks of different energies and intensities are combined, forming a spread-out Bragg peak with a constant dose distribution in the tumor and a steep dose decline at the end (Figure 1) (11, 12).

Because charged particles damage cell DNA in qualitatively different ways than photons or electrons, the same amount of physical radiation can have much more pronounced biological effects, resulting in greater cellular damage (Table). The relative biological effectiveness (RBE) is the ratio of the dose required to produce a specific biological effect, with photons as reference radiation, to the charged particle dose that is required to achieve the same biological effect. The RBE of protons is approximately 1.1, which means that protons result in approximately 10% more biological damage per unit dose than photons (13). Heavier particles can have different RBE and dose distribution characteristics. For example, carbon ions have an RBE of approximately 4 (13). Charged particles have greater biological effectiveness than photon beams because they have a higher rate of energy deposition to tissues (higher linear energy transfer). Generally, the higher the linear energy transfer of the radiation, the greater the relative ability to damage cellular DNA (14, 15). An additional advantage of high linear energy transfer radiation is that it can affect hypoxic cells within a tumor, which are generally resistant to low linear energy transfer radiation, such as photons and electrons (12).

Charged-particle radiation therapy is expected to deliver biologically equivalent doses more precisely and with less radiation-induced morbidity than conventional photon radiation therapy. This could be beneficial in children, because they are considered more susceptible to radiation side effects and because development of secondary cancer is a concern (16). It is unclear whether the claimed high precision in dose delivery is beneficial, let alone mandatory, for all indications and particularly in adults. Several investigators have suggested that proton-beam radiation therapy may be indicated in approximately 15% of patients undergoing irradiation (17).

A common argument against the broader use of charged-particle radiation therapy is its high cost. Studies found proton-beam radiation therapy to be more expensive than conventional photon radiation (18–20), and evidence on cost-effectiveness is generally scarce (21). In addition, the number of facilities that can provide charged-particle radiation therapy is limited. Seven proton-beam facilities are in operation in the United States as of 8 July 2009, and at least 4 are currently under construction, at a cost of $100 to $225 million (4, 22). The facilities host the equipment for generation of the charged particles, their acceleration, transportation to typically 3 to 4 treatment rooms, and proper delivery to the patients according to the planned treatment scheme. Private companies have announced efforts to build less expensive, small-scale facilities that would fit all the necessary equipment into a single treatment room at a cost of about $20 million (23). Several U.S. hospitals have expressed interest in acquiring these small-scale facilities.

Intensity-Modulated Photon Radiation Therapy

Since its introduction more than a decade ago, intensity-modulated photon radiation therapy has spread worldwide and is currently available in most radiation therapy departments (9). In the United States, it became available to more than 70% of radiation oncologists within 5 years, despite sparse evidence of its benefit from prospective randomized studies and higher costs (9, 24); this phe-
nomenon has triggered concerns about similar adoption of charged-particle radiation therapy. One concern about intensity-modulated photon radiation therapy is that its higher integral dose and total increased volume of radiation exposure may increase the risk for secondary cancer and complications in normal tissue. Nevertheless, intensity-modulated photon radiation therapy is considered a standard of care for many cancer indications.

**Stereotactic Radiosurgery and Stereotactic Body Radiotherapy**

Stereotactic radiosurgery uses multiple low-intensity photon beams that converge to the same area and effectively deliver a single high dose of radiation to a target lesion in the central nervous system. With advances in imaging technologies and immobilization techniques that take better account of tumor motions caused by respiration, it is now possible to use stereotactic radiotherapy for cancer located outside the central nervous system. This radiotherapy technique is considered one of several approaches to delivering ablative radiation doses directly to the target lesion with acceptable toxicity in adjacent normal tissues (25).

**Brachytherapy and Intraoperative Radiation Therapy**

Brachytherapy and intraoperative radiation therapy have been used widely and have specific indications. Brachytherapy is used to treat cancer at many different sites (26) and may be more conformal than charged-particle radiation therapy because the radioactive sources are implanted directly into the tumor or postoperative cavity. It is one of the standard treatment options for prostate cancer and is a primary treatment option for some types of gynecologic cancer. However, brachytherapy requires at least a minor invasive procedure to insert radioactive sources, and thus similar limitations may apply in terms of its applicability to tumors in proximity to critical normal structures. Nevertheless, some studies indicate that brachytherapy may be more cost-effective than external radiation therapy (27, 28). In contrast to brachytherapy, where radioactive sources are implanted either temporarily or permanently, intraoperative radiation therapy is typically defined by delivery of a single fraction of external-beam radiation in the operating room suite. It requires dedicated radiation sources in the operating room, substantial shielding to protect operating room staff, and great logistical support; its overall utilization is therefore limited. Clinical outcome results have been reported in single-institution retrospective studies (29, 30).

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**Literature Selection and Overview of Current Information**

Our MEDLINE searches identified 4747 relevant abstracts. After initial screening, 470 articles were retrieved for full-text evaluation, 243 of which met our inclusion criteria (Appendix Figure, available at www.annals.org). The complete list of included and excluded citations is reported elsewhere (5). The update search for comparative studies yielded no eligible additional studies.

Appendix Table 1 (available at www.annals.org) summarizes study and clinical characteristics, safety, and efficacy outcomes in the eligible studies, by type of cancer. One hundred eighty-five of the 243 studies (76%) were retrospective cohort studies that described the experience of many centers in treating one or several types of cancer, and another 35 studies (14%) were prospective single-group trials (Figure 2). We found 8 randomized, controlled trials in 10 publications (4%) and 13 nonrandomized comparative studies (5%). The number of included patients ranged from 10 to 2645 (median, 63). Seven studies (3%) focused on pediatric populations; most of the remaining studies reported mean or median patient age older 50 years. One hundred eighty-eight studies (77%) reported follow-up ranging from 5 to 157 months (median, 36 months); 31 studies (16%) followed patients for more than 5 years, and 2 studies (0.2%) had a mean follow-up longer than 10 years.

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

Charged-particle radiation therapy was used as stand-alone treatment, as a localized boost therapy in addition to conventional photon radiation therapy, or in combination with other treatment modalities, such as surgery or chemotherapy. However, studies typically assessed these different treatment strategies involving charged-particle radiation therapy as a whole and did not always evaluate each specific strategy separately.

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

One hundred eighty-two studies (75%) reported on adverse events. Not all studies adopted established scales to evaluate adverse events (31–33). Generally, the harms or complications were sustained in structures extraneous to the tumors that were unavoidably exposed to the charged particle during treatment. However, it was not clear whether the reported adverse events were exclusively attributable to charged-particle radiation therapy or other co-interventions in the case of mul-
timodality treatment, and whether they would have also occurred with conventional radiation therapy.

**Comparative Studies**

*Randomized Trials.* Of the 8 trials reported in 10 publications that included 1276 patients in total (34–43), 3 studies (37, 38, 42) pertained to prostate cancer and the remaining studies (34–36, 39–41, 43) dealt with less common types of cancer (ocular melanoma, skull-base and brain tumors, and pancreatic cancer) ([Appendix Table 2](http://www.annals.org), available at www.annals.org). All trials had a relatively small sample size, ranging from 14 to 392 patients, and studied different comparisons: treatment with versus without charged-particle radiation therapy (3 trials) (34–38), treatment with a higher versus lower dose of charged-particle radiation therapy (4 trials) (39–42), and charged-particle radiation therapy with versus without thermotherapy (1 trial) (43).

Primary outcomes were explicitly stated in only 3 trials, which also reported a priori sample size calculations. No trials were designed to have a sufficiently large sample size or sufficient duration of follow-up and thus failed to
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...demonstrate statistically significant difference in overall or cancer-specific survival, whereas 4 trials reported statistically significant differences in various other outcomes. In 3 of 4 trials, the results favored the charged-particle radiation therapy group (better local control with helium ions than with brachytherapy for uveal melanoma [local control rates at last follow-up, 100% vs. 87%; \( P < 0.05 \)) (34, 35) or the group with the most intensive intervention (fewer eye enucleations for proton irradiation with laser thermotherapy versus proton irradiation alone for uveal melanoma [5-year enucleation rates, 3% vs. 20%; \( P = 0.02 \)) [43], and better local control [5-year local control rates, 67% vs. 48%; \( P < 0.001 \)] and freedom from biochemical failure of prostate cancer [freedom from biochemical failure, 80% vs. 61%; \( P < 0.001 \)] with higher versus lower dose of protons [42]). The fourth trial reported a significantly lower incidence of rectal bleeding with the conventional approach (lower cumulative dose) than with charged-particle radiation therapy (higher total dose) in patients with prostate cancer (8-year bleeding incidence rates, 12% vs. 32%; \( P = 0.002 \)) (37, 38).

Nonrandomized Comparative Studies. Thirteen articles reported on 9 nonrandomized comparative studies in an estimated 4086 unique patients (44–56) (Appendix Table 3, available at www.annals.org). Four studies compared charged-particle radiation therapy versus brachytherapy in uveal melanoma (44, 45, 48, 49), 6 studies versus conventional photon radiation therapy in other types of cancer (51–56), and 3 studies versus surgery (46, 47, 52, 53, 55). 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 radiation therapy is statistically significantly better than alternative treatments with respect to patient-relevant clinical outcomes.

DISCUSSION

Charged-particle radiation therapy is an alternative mode of radiation delivery that is becoming increasingly available. The infrastructure necessary for large charged-particle radiation therapy facilities is substantial and costly, but several companies are developing smaller-scale (and less costly) equipment. The theoretical advantages of this type of radiation therapy over alternate options have yet to be demonstrated in clinical studies, especially for common types of cancer. Specifically, comparative evidence is lacking on the safety and effectiveness of charged-particle radiation therapy versus alternatives therapies. In contrast, we found several noncomparative studies that reported case series or experience of treatment strategies incorporating charged-particle radiation therapy on overlapping patients between studies.

The few available randomized trials mainly assessed intermediate outcomes. Investigators frequently compared lower and higher doses of the same charged particles, and they rarely compared this type of radiation therapy with other treatment modalities. Studies comparing charged-particle radiation therapy strategies with contemporary alternatives that do not include charged-particle radiation therapy would be more informative. From that perspective and despite the very limited treatment slots, comparisons of different protocols for charged-particle radiation therapy should not be the only comparisons evaluated. Although randomized evidence is lacking, nonrandomized comparative studies in general failed to demonstrate a survival advantage of charged-particle radiation therapy over conventional radiation therapy.

Previous systematic reviews (57–60) have also uniformly pointed out the paucity of comparative evidence that demonstrates incremental value of charged-particle radiation therapy over conventional photon radiation therapy. Some of these reviews suggest that charged-particle radiation therapy may be a good alternative modality, especially for selected rare and specific types of cancer (such as head and neck cancer) for which conventional treatments would cause substantial risk to critical structures in close proximity to the tumor (57, 59, 60). Our findings concur with these suggestions.

Our systematic review has limitations. The findings are based on a broad overview across all cancer categories, and they are not focused on specific indications for selected patient populations. However, given the general lack of comparative studies identified, it is unlikely that focused systematic reviews will provide a definitive answer on the effectiveness and safety of charged-particle radiation therapy compared with alternative interventions. In addition, we searched for studies in only 1 electronic database. It is questionable whether literature searches of multiple databases with no language restrictions would identify additional comparative studies or change our conclusions, judging from the included studies in existing systematic reviews that did so (57, 59, 60). Finally, we did not review the economic aspects of charged-particle radiation therapy. However, this would be most meaningful in the context of a cost-effectiveness analysis, which is beyond our scope.

Charged-particle radiation therapy may become much more accessible in the near future, as more institutions acquire the infrastructure and knowledge to administer it. As its availability increases, costs may decrease. We expect that such trends will inevitably increase the number of patients who will be treated with charged-particle irradiation. A central issue is whether the comparative effectiveness and safety of charged-particle radiation therapy versus other radiation therapy alternatives should be empirically documented before wider indications for charged-particle radiation therapy are endorsed. Several authorities have argued that this is not necessary (61, 62). Their rationale is that the dose distributions with charged particles are almost universally superior to those attained with photon beams; the biological effects of charged particles are very similar to those of photons, and therefore tissue responses to charged-particle irradiation are already known; and it is self-evident that sparing normal tissues from irradiation is beneficial.
However, this line of reasoning equates precision in radiation therapy delivery with clinical outcomes. In addition, despite a very favorable and strong pathophysiologic rationale for effectiveness benefit, interventions have turned out to be harmful when evaluated in randomized, controlled trials (for example, antiarrhythmics for premature ventricular contractions and erythropoietin for anemia in chronic kidney disease). In reality, it is very likely that there are many instances of clinical equipoise (63) between charged-particle radiation therapy and other modalities, for both common and rare types of cancer. For example, for many patients with prostate cancer, it is unclear whether conformal radiation therapy in general is more efficacious or safe than conventional radiation therapy (37, 38, 55, 56). For anatomically challenging tumors that are adjacent to critical structures, nonconformal radiation therapy may be contraindicated. However, it is unknown how charged-particle radiation therapy compares with more available and less expensive types of conformal radiation therapy, such as intensity-modulated radiation therapy, brachytherapy, or stereotactic radiation therapy. Again, a major issue is whether any differences are large enough to justify the differences in costs.

We believe that comparative studies, preferably randomized, controlled trials if feasible, coupled with concurrent economic analyses would be useful to inform the optional use of these technologies. Apart from randomized trials, proper analyses of nonrandomized comparisons in well-characterized patient cohorts may also be helpful (64, 65). Finally, the unadjusted treatment effects are very large in a nonrandomized study, it is unlikely that these effects are entirely attributable to biases; in such a scenario, a randomized comparison may not be necessary (66, 67).

In summary, several studies of charged-particle radiation therapy for cancer have been published. However, these studies do not document the circumstances in contemporary treatment strategies under which radiation therapy 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 radiation therapy in specific clinical situations.

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Note: The full report is available at http://effectivehealthcare.ahrq.gov.

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Tufts Medical Center has an agreement with American Shared Hospitals Services (ASHS) pursuant to which it will lease from ASHS a Clinatron 250 proton-beam radiation therapy system (Still River Systems, Littleton, Massachusetts). This system is in design and production by Still River Systems and will not be delivered to Tufts Medical Center for 2 to 3 years. Tufts Medical Center does not have a direct relationship with Still River Systems that in any way involves the Clinatron 250 proton-beam radiation therapy system.

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Appendix Figure. Study flow diagram.

MEDLINE searches from inception to 2 February 2008 (n = 4747) → Articles retrieved for full-text review (n = 470) → Failed to meet criteria (n = 4277) → <10 case reports or series for review on harm (n = 122) → Randomized, controlled trials (n = 10) → Nonrandomized comparative studies (n = 13) → Single-group studies (n = 220) → Prospective: 35 Retrospective: 185 → No eligible comparative studies

Updated MEDLINE searches from February 2008 to 11 July 2009 (n = 461) → Articles retrieved for full-text review (n = 24) → Failed to meet criteria (n = 437) → Failed to meet criteria (n = 24) → Single-group studies: 16 Not patients with cancer: 2 Not primary data: 2 Treatment planning study: 3 Not particle-beam therapy: 1

Articles retrieved for full-text review (n = 470) → Articles failed to meet criteria (n = 470) → Articles failed to meet criteria (n = 40) → Articles failed to meet criteria (n = 4277) → <10 case reports or series for review on harm (n = 122) → Randomized, controlled trials (n = 10) → Nonrandomized comparative studies (n = 13) → Single-group studies (n = 220) → Prospective: 35 Retrospective: 185 → No eligible comparative studies

Appendix Figure. Study flow diagram.
## Appendix Table 1. Clinical Characteristics of Study Patients and Safety and Efficacy Outcomes, by Type of Cancer

| Location and Type of Cancer* | Sample | Centers (Studies), n (n); Enrollment Period | Study Characteristics |
|------------------------------|--------|---------------------------------------------|-----------------------|
|                              | Age Range, y | Men, % | Disease Characteristics | Therapy | Noncomparative Studies | Comparative Studies |
| Ocular                       |         |        |                            |         | Type* Patients, n | Type* Patients, n |
| Uveal melanoma (melanoma of the choroid, ciliary body, or iris) | 35–66 | 20–64 | Various locations and sizes; metastases at baseline and bilateral location excluded in most | 11 (91); 1975–2006 | P (4) 50–2645 | RCT (3) 136–188 |
|                              |         |        |                            |         | R (81) 14–1922 | Non-RCS (7) 56–1272 |
|                              |         |        |                            |         | Higher (70 GyE) vs. lower (50 GyE) proton dose; protons + laser TTT vs. protons; helium ions vs. iodine-125 | Proton vs. enucleation; proton vs. iodine-125 or ruthenium-106; proton vs. proton + laser TTT; helium ion vs. iodine-125 |
| Head and neck                |         |        |                            |         |                              |                      |
| Chordoma, chondrosarcoma, or chordoid cancer | 13–66 | 34–73 | Various locations and stages; previously treated and untreated patients; most had chordoma or chondrosarcoma, but a few had meningioma, osteosarcoma, or other | 8 (33); 1974–2005 | P (2) 37, 67 | RCT (1) 96 |
|                              |         |        |                            |         | R (28) 10–223 | Different doses |
|                              |         |        |                            |         |                              |                      |
| Glial-cell tumor             | 6–55    | 41–71 | Various locations and sizes; previously treated and untreated patients; most had astrocytoma, glioblastoma multiforme, or glioma, but a few had meningioma | 4 (9); 1977–2002 | P (2) 20, 48 | RCT (1) 15 |
| (astrocytoma, glioblastoma multiforme) |         |        |                            |         | R (6) 7–93 | Different doses |
|                              |         |        |                            |         |                              |                      |
| Other head and neck          | 12–65   | 22–74 | Neuroblastoma, melanoma, liposarcoma, malignant meningioma, squamous, adenocytic, neuroendocrine, mesenchymal tumor | 6 (15); 1973–2005 | P (3) 19–36 | Non-RCS (1) 63 |
| (including oropharyngeal but not ocular) tumors |         |        |                            |         | R (11) 14–152 | SFRT or IMRT alone vs. with carbon particles |
|                              |         |        |                            |         |                              |                      |
| Spine                        |         |        |                            |         |                              |                      |
| Spine and sacral cancer      | 45–66   | 53–86 | Various locations; previously treated and untreated patients; chordoma, chondrosarcoma, osteosarcoma, giant cell | 4 (9); 1976–2003 | P (1) 23 | RCT (1) 49 |
| (choroidoma [4], glioblastoma [1], other [4]) |         |        |                            |         | R (8) 14–85 | Pancreas helium RT vs. photon RT |
|                              |         |        |                            |         |                              |                      |
| GI                           | 59–74   | 32–87 | Various locations and stages; squamous and adenocarcinoma, well and poorly differentiated | 2 (8); 1975–1998 | P (2) 46, 94 | RCT (1) 49 |
| Cancer (esophagus [3], pancreas [2], bile duct [2], unspecified [1]) |         |        |                            |         | R (3) 11–68 | Non-RCS (2) 22, 62 |
|                              |         |        |                            |         |                              |                      |

*Location and Type of Cancer: Ocular, Head and neck, Glial-cell tumor, Other head and neck (including oropharyngeal but not ocular) tumors; Spine, Spine and sacral cancer (choroidoma [4], glioblastoma [1], other [4]); GI, Cancer (esophagus [3], pancreas [2], bile duct [2], unspecified [1]).

**Noncomparative Studies:** P (1); R (13) 22, 62

**Comparative Studies:** RCT (3) 136–188, Non-RCS (7) 56–1272.

**Therapy:** Higher (70 GyE) vs. lower (50 GyE) proton dose; protons + laser TTT vs. protons; helium ions vs. iodine-125.

**Pancreas:** Helium RT vs. photon RT; bile-duct surgery + photon RT vs. surgery + photon RT; photon RT vs. proton RT.
### Appendix Table 1—Continued

| Instrumentation and Algorithms* | Characteristics of Particle Beam | Previous or Concurrent Interventions* | Follow-up, mo | Measure of Efficacy* | Serious Harms† |
|--------------------------------|---------------------------------|--------------------------------------|---------------|---------------------|----------------|
| No details; tantalum markers used to demarcate tumor on the sclera; specialized software (EYEPLAN§) | Protons (68); helium (21); carbon (2) | Dose: 45–80 GyE (majority 60–70) Fractions: 4–5 Unit dose: 13–16 Duration: 1–2 wk | Previous: surgical excision (1), proton or photon RT (1) Concurrent: TTT (1) | Survival: OS (40), CSS (37) Local control rate: local control rate: recurrence, response to therapy Other (24): metastasis, eye retention, visual loss, visual acuity, tumor size | Late: enucleation secondary to complications, neovascular glaucoma, ruberosis iridis, radiation maculopathy, radiation papillopathy, cataract, phthisis bulbi |
| Most studies reported using “treatment planning system” | Helium (1); proton (21); carbon (7); neon, carbon, helium, or silicon (2); ND (2) | Dose: 45–74 GyE Fractions: 8–57 Unit dose: 1.4 to 4 Duration: 3–12 wk | Previous: surgery (11); photon (2); ND (20) Concurrent: photon (9); surgery (5); ND (18) | Survival: OS (26), CSS (18), ND (6) Local control: local control rate (24), ND (9) | Acute: moderate hearing loss, grade 3 mucositis Late: brain edema, cranial nerve deficit, fat necrosis, hemiparesis, vision loss, osteitis, basilar artery injury, pituitary dysfunction, fatal complications, seizure, radiation necrosis of brainstem, radiation transaction of the cord, short-term memory loss, somnolence, depression, severe hearing loss, decreased psychomotor performance, temporal muscle fibrosis, brain ulceration,optic neuropathy, breast cancer |
| Most studies reported using “treatment planning system” | Protons (7), carbon (1) | Dose: 54–77 GyE Fractions: 33–77 Unit dose: 1.4 to 4 Duration: 7–10 wk | Previous: chemotherapy (2); photon (2) Concurrent: photon (6); surgery (3) | Survival: OS (6), CSS (5), ND (1) Local control: local control rate (5), ND (3) | Acute: grade 3 thrombocytopenia, grade 4 neurologic findings (minor), grade 3 acute otitis media Late: radiation necrosis requiring surgery, seizure, cataract, pituitary deficiency, moyamoya disease |
| Most studies reported using “treatment planning system” | Proton (8), carbon (6) | Dose: 20–76 GyE Fractions: 11–45 Unit dose: 1.4 to 4 Duration: 6–11 wk | Previous: chemotherapy (2); photon (2); ND (4) Concurrent: photon (4); surgery (1); chemotherapy (5) | Survival: OS (13), CSS (7), ND (2) Local control: local control rate (13), ND (2) | Acute: phrenic nerve paralysis, hemianopsia, cognitive deficits, seizure, focal necrosis with mass effect requiring surgery, grade 3 mucositis, tongue ulceration leading to fistula, recurrent bacterial infection and difficulties in wound healing (the patient had reconstruction of the orbit with a metal implant before radiation therapy) Late: vocal cord paralysis, epiglottitis, brain damage and necrosis, CSF leak with meningitis, visual loss, myelitis, osteonecrosis, esophageal stenosis, pariesis, memory loss, pituitary deficiency, seizure, ocular paralysis, hearing loss, cerebellar syndrome, paresis of the trigeminal nerve |
| No details on instrumentation or algorithms; specialized software (e.g., HIPLAN§) | Helium (1); neon (1); protons (4); carbon (1); neon and helium (1); ND (2) | Dose: 23–94 GyE Fractions: 16–37 Unit dose: 1.8–4.6 Duration: 4–14 wk | Previous: surgery (3); chemotherapy (1); photon (2); ND (4) Concurrent: photon (5); surgery (3); ND (2) | Survival: OS (9), CSS (4), ND (1) Local control: local control rate (8), ND (2) | Acute: worse than grade 3 skin reaction Late: radiation injury leading to colostomy; brachial, spinal cord, brachial plexus injury; visual complications; enucleation; osteonecrosis; secondary cancer |
| No details; iridium markers used to facilitate better localization of tumor; specialized software (e.g., LBL treatment planning system) | Helium (3); protons (2); neon and helium (2) | Dose: 32–81 GyE Fractions: 30–32 Unit dose: 1.8–3.5 Duration: 8–10 wk | Previous: surgery (2); chemotherapy (1); photon (2); brachytherapy (2); ND (2) | Survival: OS (7), CSS (4), ND (1) Local control: local control rate (6), ND (2) | Acute: GI bleeding, esophagitis worse than grade 3, cytopenia, fibrosis, radiation pneumonitis Late: radiation enteritis requiring surgery, esophageal ulceration requiring IV alimentation |
### Appendix Table 1—Continued

| Location and Type of Cancer* | Sample | Centers (Studies), n (\(n\); Enrollment Period) | Study Characteristics |
|-----------------------------|--------|-------------------------------------------------|----------------------|
|                             | Age Range, y | Men, % | Disease Characteristics | Noncomparative Studies | Comparative Studies |
|                             |        |        |                          | Type* Patients, n | Type* Patients, n |
|                             |        |        |                          | Therapy |
| Liver, hepatocellular carcinoma | 60–81 | 54–83 | Included patients were ineligible for other therapeutic strategies | 4 (13); 1985–2006 | P (3) 24–34 |
|                             |        |        |                          | R (10) 12–162 |
| Pelvis                      | 67–73 | 100 | Patients with T1–4 disease, with or without regional lymph node metastasis | 5 (19); 1972–2004 | P (3) 30–175 |
|                             |        |        |                          | RCT (3) 191–393 |
|                             |        |        |                          | Non-RCS (2) 180–185 |
| Bladder cancer, transitional and/or squamous-cell carcinoma | 55–72 | 80–87 | Various patients with T2 or worse disease | 1 (3); 1985–1999 | P (2) 25, 35 |
|                             |        |        |                          | R (1) 15 |
| Uterine cancer              | 56–64 | 0 | Various stages; previously treated and untreated patients | 2 (5); 1983–2005 | P (2) 31, 44 |
|                             |        |        |                          | R (2) 15, 25 |
|                             |        |        |                          | Non-RCS (1) 49 |
| Other                       |        |        |                          | Carbon RT vs. photon RT and brachytherapy |
| Skin cancer; Bowen, oral verrucous carcinoma, or squamous-cell carcinoma | 73     | 83  | Patients had declined surgery for primary disease | 1 (1); ND | P (1) 12 |
| Bone and soft-tissue sarcoma; chordoma, osteosarcoma, nerve sheath tumor, rhabdomyosarcoma; chondrosarcoma, liposarcoma, and other types | 4–50  | 51–66 | Inoperable patients or metastatic disease | 5 (6); 1978–2005 | R (6) 13–62 |
| Lung, NSCLC; adenocarcinoma, squamous-cell carcinoma, or large-cell carcinoma | 71–75 | 41–84 | Inoperable patients or declined surgery; mostly stage I | 4 (17); 1983–2005 | P (6) 21–79 |
|                             |        |        |                          | R (11) 13–146 |
| Breast cancer               | 46–75 | 0 | Lumpectomized cancer | 2 (2); 2004–2005 | P (2) 20 in each |

3-D = 3-dimensional; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CSF = cerebrospinal fluid; CSS = cancer-specific survival; DVT = deep venous thrombosis; GI = gastrointestinal; GyE = cobalt Gray equivalent; IMRT = intensity-modulated radiation therapy; IV = intravenous; LBL = Lawrence Berkeley National Laboratory (Berkeley, CA); MGH = Massachusetts General Hospital (Boston, MA); ND = no data; NSCLC = non–small-cell lung cancer; OS = overall survival; P = prospective cohort; PEI = percutaneous ethanol injection; R = retrospective cohort; RCS = randomized comparative study; RCT = randomized, controlled trial; RT = radiation therapy; SFRT = single-fraction radiation therapy; TACE = transarterial chemoembolization; TTT = transpupillary thermotherapy.

* Numbers in square brackets or parentheses are the numbers of studies.
† Excluding those that the authors attributed to co-interventions. Most studies did not explicitly distinguish acute from late harms.
‡ Range of means or medians.
§ Clatterbridge Centre for Oncology, Clatterbridge, United Kingdom.
¶ National Institute of Radiological Sciences, Chiba, Japan.
|| Sumitomo Heavy Industries, Tokyo, Japan (PT-PLAN/NDOSE System), and Deneba Systems, Miami, Florida (CANVAS 8).
| Instrumentation and Algorithms* | Characteristics of Particle Beam | Previous or Concurrent Interventions* | Follow-up, mo | Measure of Efficacy* | Serious Harms† |
|--------------------------------|----------------------------------|--------------------------------------|----------------|---------------------|-----------------|
| Type of Particle* | Dosing‡ | | | | |
| No details; iridium markers used to facilitate better localization of tumor; specialized software (e.g., PT-PLAN/NDOSE System, CANVAS 8¶) | Protons (12), carbon (1) | Dose: 50–80 GyE | Previous: surgery (4), TACE (6), PEI (4), proton RT (2), ablation (2), photon RT (1), none (2), ND (5) | 11–71 | Survival: OS (11), CSS (10) Local control (8) Other (5): response rate, metastasis |
| | | Fractions: 15–30 | Concurrent: TACE (2), none (7), ND (4) | | Acute: leukocytopenia, thrombocytopenia; increased total bilirubin, AST, and ALT levels; hepatic failure Late: infectious biloma, common bile-duct stenosis, GI bleeding, hepatic failure |
| | | Unit dose: 2.0–9.0 | Duration: 3–9 wk | | |
| No details; iridium markers used 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 GyE | Previous: none (12), ND (7) Concurrent: hormonal (7), photon RT (13) | 30–157 | Survival: OS (8), CSS (6), biochemical disease-free survival (7) Local control (9) Acute: proctitis, urinary tract complication (unclear) Late: GI bleeding, cystitis, hematuria, urethral stricture, dysuria |
| | | Fractions: 20–44 | | | |
| | | Unit dose: 1.8–3.6 | Duration: 5–9 wk | | |
| ND | Protons (add-on therapy) | Dose: 74–85 GyE | Previous: none (2), ND (1) Concurrent: resection + photon RT + chemotherapy | 21–57 | Survival: OS (3), CSS (3) Local control (3): recurrence-free survival, local control rate Other: bladder conservation (1) Late: macrohematuria requiring surgery |
| | | Fractions: 24–34 | | | |
| | | Unit dose: 1.8–3.0 | Duration: ND | | |
| ND | Protons (2), carbon (3) | Dose: 62–88 GyE | Previous: ND (5) Concurrent: photon (2), ND (3) | 26–139 | Survival: OS (4), CSS (3) Local control (5): recurrence-free survival, local control rate Late: hemorrhagic cystitis needing surgery, intestinal perforation, fistulas (vesicovaginal, rectovaginal, sigmoid-vesical) |
| | | Fractions: 24–30 | | | |
| | | Unit dose: 1.8–4.0 | Duration: 6–8 wk | | |
| ND | Protons | Dose: 55 GyE | Previous: none | 49 | OS Local control Other: response rate, metastasis Late: skin ulcer, fistula Acute: skin erythema |
| | | Fractions: 5 | Duration: 10 wk | | |
| HIPLAN software (2); spot-scanning technology (1); immobilization techniques (2); ND (3) | Protons (4), carbon (2) | Dose: 50–69 GyE | Previous: chemotherapy (3), surgery (2), none (1), ND (1) Concurrent: chemotherapy (2), none (2), ND (2) | 6–59 | Survival: OS (5), CSS (3) Local control rate (4) Late: osteomyelitis, pancytopenia and cataract focal frontal lobe necrosis, acute lymphoepithelial leukemia, failed allograft secondary to infection, DVT and ureteral stenosis, radiation recall reaction, symptomatic subcapsular cataract, symptomatic grade 3 brain necrosis |
| | | Fractions: 16–28 | | | |
| | | Unit dose: 1.5–3.0 | Duration: 4–10 wk | | |
| No details; iridium markers used to facilitate better localization of tumor; specialized software (e.g., HIPLAN) | Protons (8), carbon (9) | Dose: 51–98 GyE | Previous: lung resection (2), chemotherapy (1), ND (14) Concurrent: none (6), ND (11) | 6–59 | Survival: OS (13), CSS (9) Local control rate (11) Other (2): response rate, metastasis |
| | | Fractions: 10–24 | | | |
| | | Unit dose: 1.8–6.0 | Duration: 1–9 wk | | |
| ND | Protons | Dose: 32–40 GyE | Previous: none (2) Concurrent: surgery (2), chemotherapy or hormonal (1), ND (1) | 12 | Survival: OS (1), CSS (0) Local control rate (1) None |
| | | Fractions: 4–10 | | | |
| | | Unit dose: 4.0–8.0 | Duration: 1–2 wk | | |
## Appendix Table 2. Randomized, Controlled Trials of Charged-Particle RT, by Treatment Comparison

| Author, Year (Reference), by Comparison | Type of Cancer | Country and Year of Study | Study Purpose | Primary Outcome | Sample Size Estimation Performed? | Clinical Stage |
|----------------------------------------|----------------|---------------------------|---------------|----------------|-------------------------------|----------------|
| **Charged-particle RT vs. other RT**   |                |                           |               |                |                               |                |
| Char et al, 1989 (34) and 1993 (35)    | Uveal melanoma | United States, 1985–1991  | To compare 2 types of ocular RTs | Local control | Yes                            | Newly diagnosed small- to moderate-size tumor (<15 mm in diameter and <10 mm in height) |
| Lindstadt et al, 1998 (36)            | Pancreatic     | United States, 1978–1982  | To determine whether helium-ion RT improves local control and survival compared with conventional RT | Local control, survival | No                             | Locally advanced disease (T1–4, N0–2, M0) |
| Shipley et al, 1995 (37); Benk et al, 1993 (38) | Prostate       | United States, 1982–1992  | To compare higher-dose boosting by proton-beam RT with conventional-dose RT | Local control, survival | No                             | Locally advanced disease (T3–4, Nx, M0) |
| **Charged-particle RT alone vs. charged-particle RT plus other treatments** |                |                           |               |                |                               |                |
| Desjardins et al, 2006 (43)           | Uveal melanoma | France, 1999–2003         | To examine whether the addition of TTT reduces radiation-related complications | Radiation-induced glaucoma | Yes                            | Nonmetastatic large tumor (≥15 mm in diameter and ≥7 mm in height) |
| **Lower vs. higher doses of charged-particle RT** |                |                           |               |                |                               |                |
| Gragoudas et al, 2000 (39)            | Uveal melanoma | United States, 1989–1994  | To examine whether a smaller dose reduces radiation-induced complications without compromising local tumor control compared with the standard dose | Radiation-related complications | No                             | Newly diagnosed nonmetastatic small- to moderate-size tumors (<15 mm in diameter and <10 mm in height) near the fovea or optic disc |
| Santoni et al, 1998 (40)              | Skull-base chordoma and chondro-sarcoma | United States, 1984–1993  | To examine the correlation between temporal damage and dose (no explicit hypotheses) | Temporal lobe damage | No                             | Skull-base tumors |
| Castro et al, 1997 (41)               | Brain glioblastoma | United States, 1989–1992  | To examine whether an escalated dose could improve local control without excess brain injury | Local control | No                             | ND |
| Zietman et al, 2005 (42)              | Prostate cancer | United States, 1996–1999  | To examine whether an increased dose improves tumor control compared with a conventional dose | Local control | Yes                             | Localized disease (T1–2, Nx, M0) |

5-FU = 5-fluorouracil; GyE = cobalt Gray equivalent; ND = no data; NS = not significant; RT = radiation therapy; TTT = transpupillary thermotherapy.
* Survival rate or median survival time in the main analysis.
† Rate at last follow-up.
‡ Statistical analysis was not performed.
§ Based on reported 95% CIs of mean difference of increase in defect at various times. No trend analyses between the 2 doses for the follow-up period were performed.
## Appendix Table 2—Continued

| Treatment | Patients, \( n \) | Duration of Follow-up, mo | Overall Survival* \((P \text{ Value})\) | Cancer-Specific Survival, %* \((P \text{ Value})\) | Other Outcomes |
|-----------|-------------------|---------------------------|---------------------------------|---------------------------------|----------------|
| Helium RT, 70 GyE | 86 | Maximum, −93 | 84%† (NS) 81%† | 92† (NS) 92† | Helium better for local control \((P < 0.05)\), metastasis \((P < NS)\), and eye enucleation \((P = NS)\) |
| Iodine-125 brachytherapy, 70 GyE | 98 | Maximum, −93 | 81%† | 92† | |
| 5-FU + helium RT, 54–70 Gy | 30 | Maximum, −30 | 7.8 mo (0.29) | 3† (ND) | Helium better for local control \((P > 0.05)\); photon better for metastasis and combined outcome of local control and metastasis‡ |
| 5-FU + photon RT, 54–60 Gy | 19 | Maximum, −30 | 6.5 mo | 5† | |
| Photon RT, 50.4 Gy + local proton boost, 25.2 GyE | 103 | Median, 61 | 75% at 5 y (NS) | 86 at 5 y (NS) | Proton better for local control \((P < 0.09)\); photon better for total recurrence-free survival \((P < NS)\), rectal bleeding \((P < 0.002)\), and urethral stricture \((P = 0.07)\) |
| Photon RT, 50.4 Gy + local photon boost, 16.8 Gy | 99 | Median, 61 | 80% at 5 y | 83 at 5 y | |
| Photon RT, 60 GyE | 75 | Median, 38 | ND | ND | Proton + TTT better for radiation-related glaucoma \((P = NS)\), radiation-related retinal detachment \((P = 0.14)\), reduction in tumor thickness \((P = NS)\), and secondary enucleation \((P = 0.02)\) |
| Photon RT, 60 GyE + TTT | 76 | Median, 38 | ND | ND | |
| Photon RT, 50 GyE | 94 | Maximum, −102 | ND | 93† (0.79) | Lower dose better for visual acuity retention \((P = 0.81)\), visual field defects§, and local control \((P > 0.99)\); no difference in radiation-related complications \((P > 0.20)\) |
| Photon RT, 70 GyE | 94 | Maximum, −102 | ND | 92† | |
| Surgery + proton RT, 66.6 GyE | 44 | Median, 41 | ND | ND | Lower dose better for temporal lobe damage \((P = 0.30)\) |
| Surgery + proton RT, 72 GyE | 52 | Median, 41 | ND | ND | |
| Neon RT, 20 GyE | 7 | Median, 12.5 | 12.5 mo (NS) Median, 14 mo | ND | Lower dose better for time to treatment failure \((P = NS)\) |
| Neon RT, 25 GyE | 7 | Median, 12.5 | ND | ND | |
| Conventional photon RT, 50.4 Gy + proton RT, 19.8 GyE | 197 | Median, 5.5 | 97% at 5 y (0.80) | ND | Higher dose better for local control \((P < 0.001)\) and freedom from biochemical failure \((P < 0.001)\) |
| Conventional photon RT, 50.4 Gy + proton RT, 28.8 GyE | 195 | Median, 5.5 | 96% at 5 y | ND | |

*Denotes statistical significance; NS, not significant; †NS, not significant; ‡Combined outcome of local control and metastasis; §Visual field defects.
## Appendix Table 3. Nonrandomized Comparative Studies of Charged-Particle RT Versus Other Treatments, by Type of Cancer

| Author, Year (Reference), by Type of Cancer | Country and Year of Study | Clinical Stage | Treatment | Patients, n | Duration of Follow-up, mo | Overall Survival* (P Value) | Cancer-Specific Survival, %* (P Value) | Other Outcomes |
|--------------------------------------------|---------------------------|----------------|-----------|-------------|--------------------------|-----------------------------|--------------------------------|----------------|
| *Uveal melanoma*                           |                           |                |           |             |                          |                             |                                 |                |
| Desjardins et al, 2003 (44)                | France, 1989–1998         | Other than small anterior tumors (1991–1998) | Proton RT, 60 GyE | 926         | Median, 60              | 77%† (0.05)                 | ND                           | Brachytherapy better for local control (P = 0.74) and metastasis-free survival (P = 0.002) |
|                                            |                           | All cases (1989–1991); small anterior tumors (1991–1998) | Iodine-125 brachytherapy, 90 GyE | 346         |                           | 80%† ND                     | ND                           |                |
| Harbour et al, 1997 (45)                   | United States, 1978–1995  | Nonmetastatic unilateral tumor | Helium RT, 50–80 GyE | 341         | Median, 52              | ND                          | ND                           | Helium therapy better for local control (P < 0.001)† |
|                                            |                           |                | Iodine-125 brachytherapy, 50–80 GyE | 427         |                           | ND                          | ND                           |                |
| Char et al, 1996 (48)                      | United States, 1978–1993  | Newly diagnosed small- to medium-size tumor (<15 mm in diameter and <70 mm in height) nontangential to the optic disc | Helium RT, 70 GyE | 196         | Median, 67              | ND                          | ND                           | Brachytherapy better for freedom from visual loss§ (P > 0.05); helium therapy better for retention of 50% of the baseline visual acuity§ (P > 0.05)† and retention of good eyes§ (P > 0.05)‡ |
|                                            |                           |                | Iodine-125 brachytherapy, 70 GyE | 230         |                           | ND                          | ND                           |                |
| Char et al, 2003 (50)                      | United States, dates not given | Untreated tumors with ≥15% exudative retinal detachments | Proton RT, 56 GyE | 45          | Median, 25              | ND                          | ND                           | Proton + TTT better for visual acuity loss at 1 y (P = NS) |
|                                            |                           |                | Proton RT, 56 GyE + TTT | 11          | Median, 13              | ND                          | ND                           |                |
| Seddon et al, 1990 (46) and 1985 (47)      | United States, 1975–1984  | Untreated nonmetastatic unilateral tumor | Proton RT Enucleation | 556         | Median, 60              | 71% at 7 y (NS)∥ | 84%† (NS)∥| |
|                                            |                           |                |                                                         | 257∥        | Median, 92              | 63% at 7 y (NS)∥ | 75†                      |                |
| Wilson and Hungerford, 1999 (49)           | United Kingdom, 1988–1996 | Unilateral tumor | Proton RT, 60 GyE | 267         | Mean, 45                | 94% at 5 y (0.06) | 96% at 5 y (ND) | Iodine-125 brachytherapy and proton RT better than ruthenium-106 brachytherapy for local recurrence (P = 0.01 for both†) and visual outcome (P < 0.001 for both†); no statistical analyses performed for metastasis and eye enucleation |
|                                            |                           |                | Iodine-125 brachytherapy, 100 GyE | 190         |                           | ND                          | ND                           |                |
|                                            |                           |                | Ruthenium-106 brachytherapy, 100 GyE | 140         |                           | 87% at 5 y (ND) | ND                       |                |
| *Skull-base adenocystic carcinoma*         |                           |                |               |             |                          |                             |                                 |                |
| Schulz-Ertner et al, 2005 (51)            | Germany, 1995–2003        | Locally advanced disease | Photon RT, **54 Gy + local proton boost, 18 GyE | 29          | Median, 16              | 76% at 4 y (0.64) | ND                      | Proton boost better for disease-free survival (P = 0.19) and locoregional control (P = 0.08) |
|                                            |                           |                | Photon RT, **66 Gy | 34          | Median, 24              | 78% at 4 y (ND) | ND                       |                |
| *Bile-duct carcinoma*                      |                           |                |               |             |                          |                             |                                 |                |
| Schoenthaler et al, 1993 (52) and 1994 (53)| United States, 1977–1987  | Locally advanced disease (T2–4, Nx, M0) | Surgery†† + charged-particle RT (helium or neon), 60 GyE | 22          | Minimum, 60              | 14 mo (0.009) | ND                      | Surgery + charged-particle RT better for disease-free survival (no statistical analysis done) |
|                                            |                           |                | Surgery†† + photon RT, 46 GyE | 45          |                           | 11 mo                         | ND                       |                |
|                                            |                           |                | Surgery†† alone | 62          |                           | 6.5 mo                         | ND                       |                |
| *Cervical cancer*                          |                           |                |               |             |                          |                             |                                 |                |
| Nakano et al, 2006 (54)                    | Japan, 1995–2000          | Advanced disease (stage II–IV) | Carbon RT, 52.8–72.8 GyE | 49          | Median, 27              | ND                          | ND                           | No statistical analysis done for disease-free survival or local control |
|                                            |                           |                | Photon RT, 50.6 Gy + brachytherapy, ‡‡ 22–24 GyE | 30          |                           | ND                          | ND                           |                |

*Continued on following page*
### Appendix Table 3—Continued

| Author, Year (Reference), by Type of Cancer | Country and Year of Study | Clinical Stage | Treatment | Patients, n | Duration of Follow-up, mo | Overall Survival* (P Value) | Cancer-Specific Survival, %* (P Value) | Other Outcomes |
|------------------------------------------|---------------------------|----------------|-----------|-------------|-------------------------|----------------------------|------------------------------------------|----------------|
| **Prostate cancer**                      |                           |                |           |             |                         |                            |                                          |                |
| Galbraith et al, 2001 (55)               | United States, dates not given | Localized disease | Photon RT + proton-beam RT, 74–75 GyE | 47 | Maximum, 18 | ND | ND | No overall difference observed for health-related quality of life§§, health status§§, or treatment-specific symptoms§§ |
|                                           |                           |                | Photon RT, 74–75 GyE | 24 | ND | ND | ND |                |
|                                           |                           |                | Photon RT, 65–70 Gy | 25 | ND | ND | ND |                |
|                                           |                           |                | Surgery alone | 59 | ND | ND | ND |                |
|                                           |                           |                | Observation alone | 30 | ND | ND | ND |                |
| Duttenhaver et al, 1983 (56)             | United States, 1973–1979 | Localized disease (T1–4, Nx, M0) | Photon RT, 50 Gy + local proton boost, 24 Gy¶¶ | 116 | ND | 64% at 5 y (NS) | ND | No significant difference for disease-free survival or clinical local recurrence–free survival |
|                                           |                           |                | Photon RT, 50 Gy + local photon boost, 18 Gy¶¶ | 64 | ND | 64% at 5 y | ND |                |

**5-FU = 5-fluorouracil; GyE = cobalt Gray equivalent; ND = no data; NS = not significant; RT = radiation therapy; TTT = transpupillary thermotherapy.**  
* Survival rate or median survival time in the main analysis.  
† Rate at last follow-up.  
‡ Adjusted value by multivariate regression analysis.  
§ Visual loss was defined as visual acuity of 6/120 or worse, and good eye was defined as 6/12 or better. Only patients with pretherapy visual acuity of 6/12 or better were assessed for visual loss (n = 400) and retention of 50% of the baseline visual acuity (n = 409), and only those with pretherapy visual acuity of 6/12 or better (n = 302) were assessed for retention of good eye.  
|| Proton-beam RT was statistically significantly better if follow-up was limited to the first 2 years after treatment (hazard ratio, 2.1 [95% CI, 1.1 to 3.9]; P < 0.05).  
¶ Only patients who underwent enucleation in the same 10-year period as proton-beam RT (between July 1975 and 1984) were considered.  
** Fractionated stereotactic RT or intensity-modulated RT.  
†† 26% of patients also received chemotherapy.  
‡‡ Either cobalt-60 or iridium-192.  
§§ Measured by using the Medical Outcomes Study instrument.  
|| Measured by using the Southwest Oncology Group Prostate Treatment-Specific Symptoms Measure.  
¶¶ 45% of patients in the photon RT group and 48% of patients in the photon plus proton RT group underwent transurethral resection of prostate cancer.