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REVIEW ARTICLE

Promise and Pitfalls of Heavy-Particle Therapy

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ABSTRACT

Proton beam therapy, the most common form of heavy-particle radiation therapy, is not a new invention, but it has gained considerable public attention because of the high cost of installing and operating the rapidly increasing number of treatment centers. This article reviews the physical properties of proton beam therapy and focuses on the up-to-date clinical evidence comparing proton beam therapy with the more standard and widely available radiation therapy treatment alternatives. In a cost-conscious era of health care, the hypothetical benefits of proton beam therapy will have to be supported by demonstrable clinical gains. Proton beam therapy represents, through its scale and its cost, a battleground for the policy debate around managing expensive technology in modern medicine.

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INTRODUCTION

Particle therapy is a term used to distinguish this form of radiation therapy from conventional x-ray therapy, which uses mass-less photons. Particles may be neutral (such as neutrons) or charged (such as electrons, protons, pions, or helium, neon, silicon, argon, and carbon ions). Electrons are light particles routinely used in contemporary radiation oncology for treatment of skin and superficial lesions and are produced by the same linear accelerator equipment as photons. The generation of heavier particles, however, requires an expensive infrastructure, which is presently within the financial reach of only a few radiation therapy centers.

Most patients who have been treated with heavy-particle therapy were treated with protons. The experience with other heavy particles is limited to a few institutions, and no conclusion can yet be drawn about their effectiveness or toxicity. Photons, electrons, and protons of therapeutic energy all have a similar feature—low linear energy transfer, a descriptor of the density of ionization events. Protons can be considered to have radiobiologic properties similar to the familiar and well-understood photon and electron beams. Other heavy particles have high linear energy transfer, which leads to fundamental differences in radiobiologic interactions of these particles with the tumor and normal tissues. For these particles, one must consider new biology in addition to new physics. Thus, the knowledge of dose and fractionation generated in the field of conventional x-ray therapy is more easily translated into proton therapy than into other heavy-particle therapies.

Treatment with protons is not a new invention in the field of medicine. It was proposed in 1946,[1] and the first patients were treated at the Lawrence Berkeley National Laboratory in California in 1958.[2] As of March 2013, more than 107,000 patients globally had received part or all of their radiation therapy with heavy particles, and of those, more than 93,000 were treated with protons.[3] Currently, there are 11 treating proton centers in the United States and eight under construction. The use of proton therapy in clinical practice grew slowly for several decades but, over the last 5 years, it has gathered pace and has now moved into a public sphere with much media and patient attention. Its high start-up cost means that, in this age of economic restraint, it has come under considerable scrutiny. Payers and the public alike want evidence and quantification of benefit in terms of real clinical outcomes. This is the core of the controversy around the use of proton therapy.

PHYSICAL PROPERTIES: ADVANTAGES AND CONSIDERATIONS

Proton beams enter and travel through the tissue with minimal dose deposition along the path until the end of their paths, where a peak of energy deposition occurs (Fig 1). This phenomenon is known as the Bragg peak. The dose deposited before the Bragg peak is approximately 30% of the Bragg peak maximum dose, whereas beyond the Bragg peak, the dose falls practically to zero. By comparison, photons deposit their peak dose close to their entrance into the tissue, and thereafter, there is an exponential decrease of deposited dose with increasing depth. This

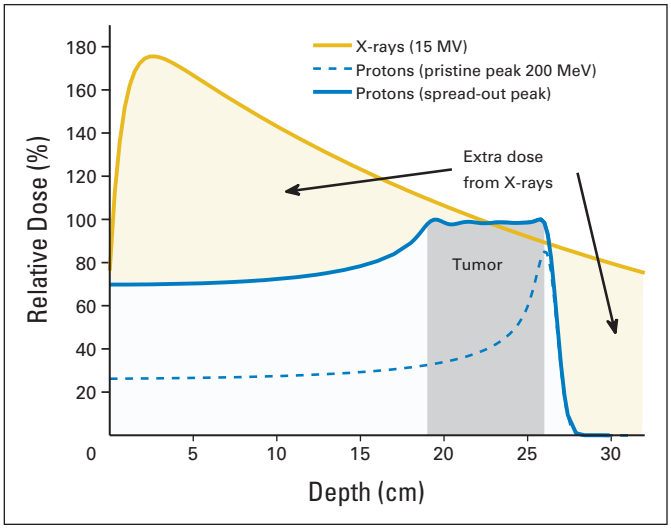

Fig 1. Comparison of relative depth dose distributions of photons versus protons.

difference leads to an approximately 60% reduction in integral dose.[4] When two treatment plans with a same target volume and dose are compared side-by-side, in general, the normal tissues are exposed to less radiation with protons than with photons. In addition to the Bragg peak advantage, at shallow and moderate depths protons also have a sharper beam penumbra,[5] which is a measurement of the rapidity of dose falloff at the lateral edges of a beam. The sharper penumbra facilitates delivery of high radiation doses to targets that are close to critical structures, which are usually the dose-limiting factor, and this in turn can lead to target treatment dose escalation. Despite these advantages, there are other factors that need to be considered, which either negate the physical benefits or, at the very least, require detailed knowledge and experience with proton beam treatment to ensure that clinical outcomes are not jeopardized. The most fundamental issue is the challenge of knowing the stopping power for a charged particle in a water phantom, as used by dosimetrists at the time of planning, and even more so in an individual patient's tissues.[6] When external beams, either photons or protons, travel through the patient's body to reach the target, they traverse organs of different tissue densities. High-energy photon radiation treatment is less influenced by tissue heterogeneity than proton treatment.[7] Any change in the composition of the tissues (change in bone position during daily treatment, lung expansion, tumor volume change over the course of the treatment) will result in a marked effect on target coverage and dose to surrounding structures. Organ motion, both between fractions and during the delivery of radiation therapy, has been well described in multiple tumor sites,[8-10] and is not specific for proton beam therapy. However, because of greater influence of tissue heterogeneity, organ motion has a greater impact on the precise dose delivery with protons than with photons. The addition of a margin of uncertainty (Table 1) is commonly used to reduce potential tumor underdosing[11]; however, this leads to substantially higher volumes receiving prescription dose with protons in the immediate vicinity of the tumor, which can lead to higher complication rates. Newer planning and statistical assessment methods have begun to ameliorate these limitations.[12,13]

Table 1. Margin of Uncertainty by Proton Center

Proton Center	Uncertainty in Proton Beam Range
Massachusetts General Hospital	3.5% + 1 mm
MD Anderson Cancer Center	3.5% + 3 mm
Loma Linda University Medical Center	3.5% + 3 mm
University of Pennsylvania	3.5% + 3 mm
University of Florida	2.5% + 1.5 mm

NOTE. These margins were reported in 2012 and are often not fully generic, and adjustments may be made for certain sites based on the location of critical structures.[11]

CLINICAL APPLICATION

The lower integral dose and steeper dose gradient of proton therapy make it a desirable tool in many clinical situations. We refer readers to comprehensive summaries of potential applications and clinical experience with proton therapy,[14-19] and highlight the most common clinical scenarios. As we go through these scenarios, we look at the available evidence base on the use of proton therapy and highlight deficiencies where we see them.

PEDIATRIC TUMORS

Two important issues set children apart from adults in terms of the long-term effect of radiation therapy. First, their risk of secondary malignancies,[20] and second, their susceptibility to the deleterious effects of radiation on normal tissue and organ growth and function,[21] which can cause significant medical morbidity and devastating cosmetic outcomes. The lower integral dose achieved with proton beam should reduce the volume of irradiated tissue and improve both sequelae of the radiation therapy. A recent publication[22] compared patients treated with proton radiation between 1973 and 2001 with matched patients treated with photons in the Surveillance, Epidemiology, and End Results (SEER) Program cancer registry. With a median duration of follow-up of 6.7 years, second malignancies occurred in 5.2% of patients treated with protons versus 7.5% of patients treated with photons (adjusted hazard ratio, 0.52; $P < .01$). It has been noted that these additional malignancies occurred in the first 5 years after treatment, earlier than one would anticipate from a biological standpoint, triggering debate about the validity of the methods.[23] Another smaller retrospective study compared patients with retinoblastoma treated with protons at Massachusetts General Hospital and patients with retinoblastoma treated at Boston Children's Hospital between 1986 and 2011[24] and also found a reduction in 10-year in-field malignancies.

Medulloblastoma: Craniospinal Irradiation

Diseases that tend to disseminate throughout the entire neuroaxis, such as medulloblastoma, are treated with craniospinal irradiation (CSI). Dosimetric studies have long shown the substantial reduction in dose to normal tissues[25,26] with proton CSI when compared with photon CSI (Fig 2). Risk modeling studies indicate a 6- to 12-times lower risk of secondary malignancies in patients undergoing proton CSI in comparison with conventional or

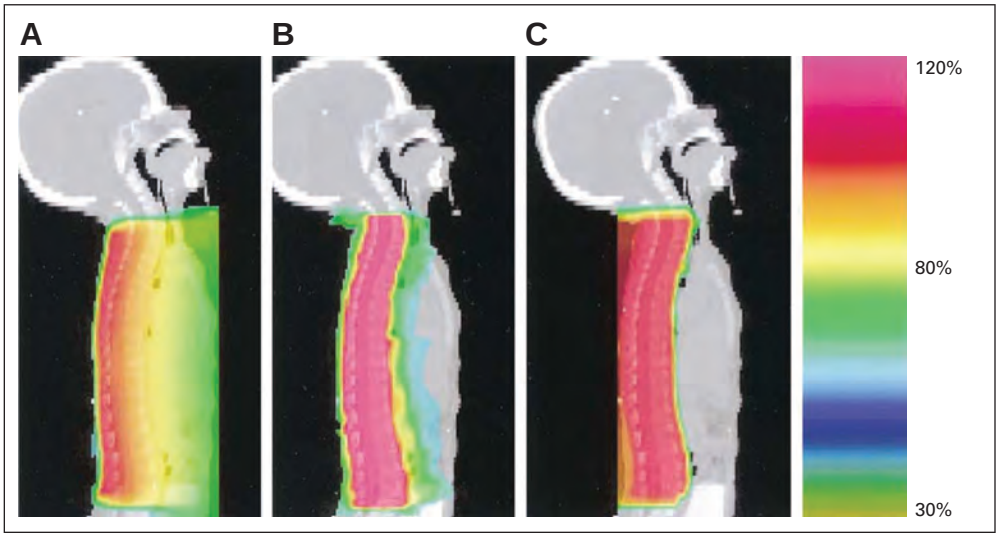

Fig 2. Isodose distribution in the sagittal projection along the spinal column for (A) x-rays, (B) intensity-modulated radiation therapy, and (C) protons.

intensity-modulated radiation therapy (IMRT) photon CSI.[27] A recent dosimetric study[28] focused on the CSI effect on breast tissue and found a nearly hundred-fold reduction when proton CSI was compared with photon CSI. Data from old Hodgkin lymphoma treatment studies suggested a decreased risk of secondary breast cancer.[29] By reducing or eliminating late toxicities of CSI, protons were estimated to save EUR 23,000 over the lifetime of a child.[30] A recent publication by Jimenez et al[31] reported on 15 patients younger than age 5 years treated with adjuvant proton therapy after surgical resection and high-dose chemotherapy with favorable local control and low rates of acute radiation-induced toxicities.

There is no other treatment in pediatric oncology that exposes so much of a child's tissue to so much radiation as craniospinal axis irradiation, and this is where the greatest long-term advantage for proton therapy might be anticipated. Some have argued that proton beam treatment is the only ethically appropriate treatment, and others argue that radiation-induced malignancies tend to occur in the high-dose regions (which are similar for both photons and protons) and that mandating that a child travel to a distant proton facility for lengthy treatment may impose both social and financial hardships on children and their families for what is still theoretical benefit.[32]

Rhabdomyosarcoma

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children, and it commonly arises in the head and neck region. In a dosimetric study of parameningeal RMS,[33] when compared with IMRT, protons substantially reduced the mean doses to the retina, optic nerve, parotid, and cochlea. Initial clinical experience with proton treatment reveals tumor control rate similar to historical outcomes but with reduced acute toxicity.[34] More mature experience treating orbital RMS with proton beam has now been reported revealing favorable local and distant control, comparable to historical series with photon radiotherapy, but a reduction in the loss of function of normal tissues.[35]

Ependymoma, Craniopharyngioma, Retinoblastoma, and Glioma

Dosimetric and clinical studies have been published for patients with ependymoma,[26,36,37] optic pathway glioma,[38] and craniopharyngioma,[38-40] suggesting an improved acute and long-term toxicity profile. The risk of secondary malignancy at 10 years was lower for patients with retinoblastoma treated with protons when compared with a similar group of patients treated with photons.[24]

ADULT MALIGNANCIES

Whereas almost every dosimetric plan using protons will look better when compared with an equivalent photon treatment plan, the potential clinical benefit in adults is not as large as it may be for children. Adult tissues are less prone to secondary malignancies and are not subject to the same growth and developmental issues. In the absence of the cost differential, physicians would in theory use the technique they felt most comfortable with in an attempt to minimize the dose to the normal tissues. However, because of the higher cost associated with proton treatment, superior dosimetry alone is insufficient to justify its choice. A measurable clinical advantage must be demonstrated before patients and insurance companies will embrace the higher premium associated with this treatment option. The radiation oncologist's desire to escalate radiation dose to improve tumor control is one of the opportunities for proton options to outperform the photon options. The desire to reduce dose to adjacent normal tissues is another. For every clinical scenario, however, a steep dose-response curve must first be proven, and the normal tissue toxicity that limits the ability to deliver this higher dose with photon-based treatments must exist. We discuss these issues for a range of adult malignancies, starting with those for which proton beam treatment is either most widely used (prostate cancer) or most commonly recommended (ocular melanoma and chordoma/chondrosarcoma of the axial skeleton). We then examine the other common malignancies in which proton beam must find a role if it is not to be regarded as a "boutique" therapy.

Prostate Cancer

It has been reported that, at present, 70% of patients who receive proton beam treatment in the United States have prostate cancer. It is thus important to see whether any evidence supports this enthusiasm. Multiple randomized dose-escalation studies have shown that a higher radiation dose to the prostate gland leads to better cancer

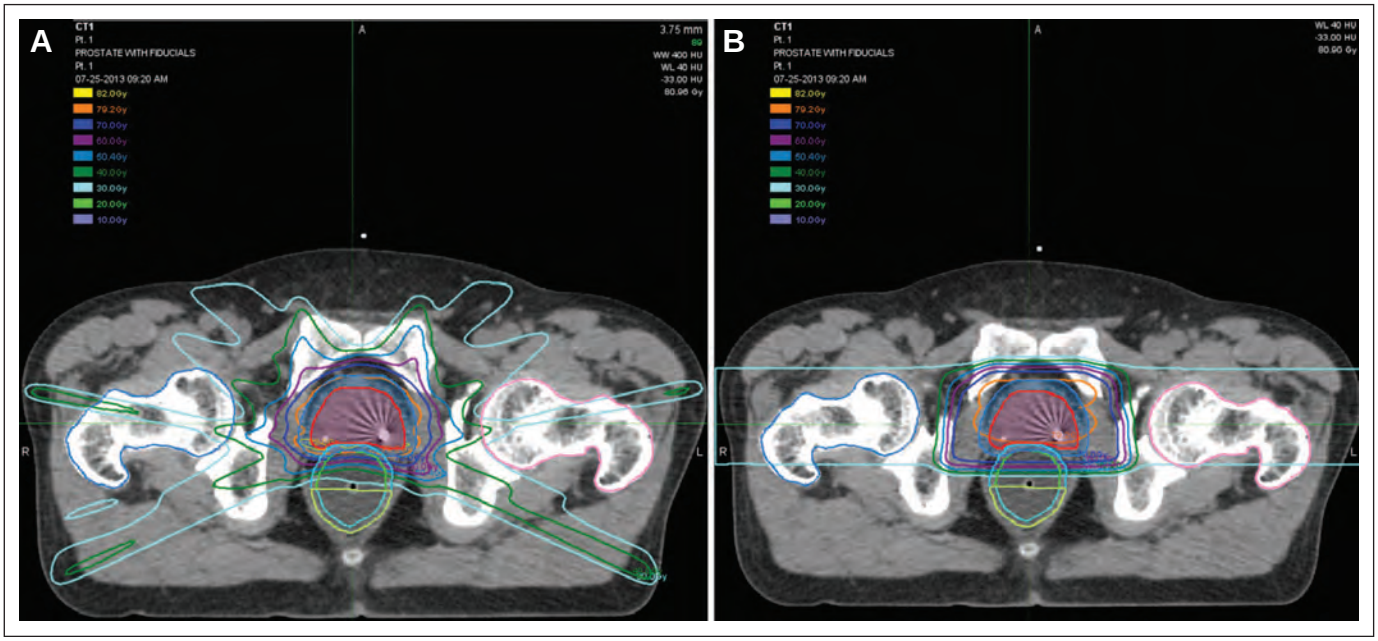

Fig 3. Radiotherapy treatment plans for one patient included in the study by Trofimov et al.[43] (A) Seven-field intensity-modulated radiation therapy and (B) three-dimensional conformal proton plan with two opposed lateral fields.

control.[41] It is also clear that IMRT can now deliver doses as high as or even higher than can be safely delivered with protons. One study, for example, delivered 81 Gy with remarkably low levels of bowel and bladder toxicity.[42] Thus a principal argument for the use of protons—that a higher dose of radiation can be given more safely—appears incorrect. Why might this be so? Because the prostate gland sits deep within the pelvis, the beam path distance to the target is great. At this depth, the lateral penumbra of the proton beam is not so sharp. Dosimetric comparisons do reveal a reduction in the rectal volume receiving 30 Gy or more (V30), but the V70 was the same (Fig 3). Bladder V60 and V70 were substantially higher with proton plans, yet the mean dose to the bladder was lower (Fig 4).[43] Most rectal toxicity appears to be associated with the high-dose region.[44] Talcott et al[45] performed a cross-sectional study using quality-of-life questionnaires comparing men with prostate cancer who had been treated with similar doses of radiation with either photons or protons. They found no difference in the late effects as perceived by the patients. Two SEER database analyses found no difference in the likelihood of treatment for cancer recurrence or treatment for complications when comparing photons with protons with one unanticipated exception. The likelihood of treatment for rectal bleeding appeared to be higher among the proton-treated patients.[46,47] There are limitations to the SEER data that may confound these conclusions; nevertheless, there is little evidence to suggest that there is any clinical benefit for patients with prostate cancer from proton beam.

In 2013 the American Society for Therapeutic Radiology and Oncology (ASTRO) participated in the Choosing Wisely campaign led by the American Board of Internal Medicine. Among other suggestions for cost-conscious care, ASTRO recommended that physicians discuss these limitations in knowledge with patients before electing proton treatment and that, ideally, proton treatment for prostate cancer would be within the context of a clinical trial or registry.[48] A multi-institutional randomized phase III National Cancer Institute trial (9368 PARTIQoL [A Phase III Randomized Clinical Trial of Proton Therapy Versus IMRT for Low or Intermediate Risk Prostate Cancer; ClinicalTrials.gov ID NCT01617161]), comparing proton beam to IMRT, is now in its second year and is expected to shed light on this controversial topic. It is also important to remember that prostate brachytherapy is a competitive, highly conformal, and cost-effective treatment modality for patients with prostate cancer.[49]

Uveal Melanoma

Uveal melanoma is the most common primary intraocular malignancy in adults, with treatment options that include surgical enucleation, plaque brachytherapy, and external beam therapy with protons or photons. A detailed review on this topic has recently been published.[16,50] A recent literature-based meta-analysis[51] appeared to show a reduced rate of local recurrence when charged-particle therapy was compared with brachytherapy, but there were no significant differences in mortality or enucleation rates. Most experts still believe that the majority of uveal melanomas can be equally well treated with either proton beam therapy or brachytherapy. Tumors that overlay the optic disc may make it more difficult to access the brachytherapy plaque, whereas large posterior lesions favor brachytherapy because proton beam therapy is more likely to result in cataract formation (H. Shih, personal communication, December 2013).

Chordoma and Chondrosarcoma

Chordomas and chondrosarcomas are locally aggressive primary bone tumors. Chordomas arise in the skull base and spine, whereas chondrosarcomas most frequently appear in the pelvis, proximal femur, and scapula. It is often difficult to achieve complete surgical resection in axial locations such as skull base, mobile spine, and sacrum; hence, radiation therapy is commonly used as an alternative or as an adjuvant. The same anatomic relationships that limit surgical

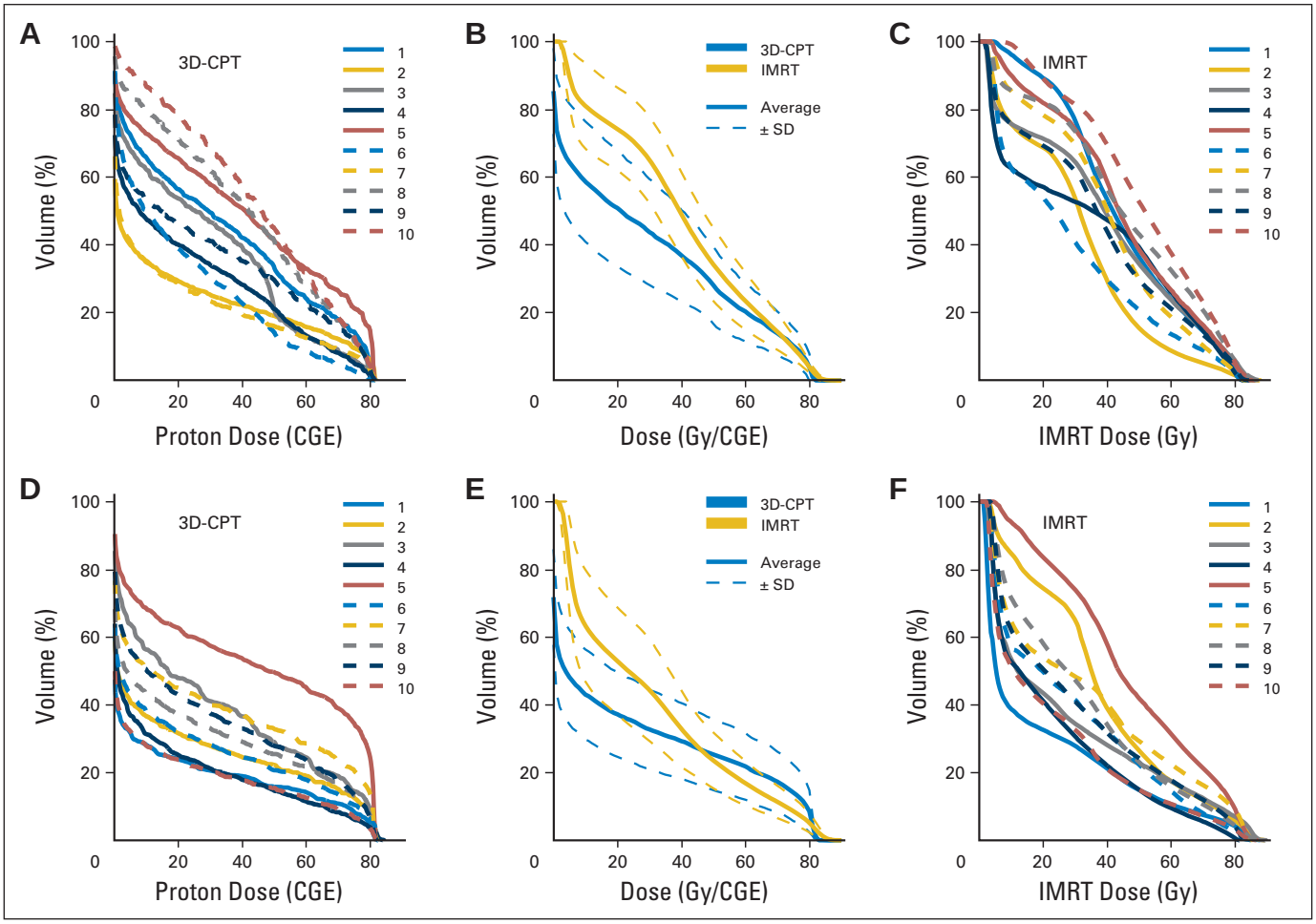

Fig 4. Dose-volume histograms (DVHs) in the study by Trofimov et al[43] for (A-C) the rectum and (D-F) the bladder. Individual DVH from 10 three-dimensional conformal proton therapy (3D-CPT) and intensity-modulated radiation therapy (IMRT) plans are shown in (A, D) and (C, F), respectively. Plots (B) and (E) show curves obtained by averaging, over the irradiated volume, of the DVH from 10 plans, as well as one-standard-deviation (SD) variability bounds (dashed lines). CGE, cobalt Gray equivalent.

extirpation affect the delivery of adequate radiation dose. Schulz-Ertner and Tsujii[16] have reviewed the historical results with particle therapy. Although excellent local control was achieved, it must be remembered that the evidence consists largely of single-institution series and may reflect some case selection bias. As IMRT and fractionated stereotactic radiation with photons have improved, dose escalation has been attempted with these modalities; however, initial reports do not seem to replicate the rates of local control achieved with particle therapy.[52,53] Particle therapy, on a relatively thin evidence base, has established itself as the standard of care for these rare malignancies.

Breast Cancer

Adjuvant radiation therapy improves both tumor control and overall survival in women with breast cancer,[54] yet both secondary malignancy and cardiac toxicity may adversely affect the outcomes. Several dosimetric studies revealed substantial reduction in lung, heart, and contralateral breast doses when whole breast proton plans were compared with photon plans.[55-57] A pilot study treated 12 patients with proton therapy after mastectomy to 50.4 Gy; the patients appeared to tolerate the treatment well, with the maximum skin toxicity during treatment being only grade 2.[58] This is important because it had been suggested that protons would actually increase the skin dose and worsen the cosmetic outcomes.

Another clinical scenario that often presents a challenge to photon therapy is the patient with bilateral implants after mastectomy, and protons may play a role here.[59]

As accelerated partial breast irradiation with large daily fractions is gaining acceptance among physicians and patients, protons are being evaluated as a delivery method.[60-62] Kozak et al[63] reported significant acute skin toxicity when a single-field proton beam per fraction was used. However, this issue was resolved in more recent phase II trials that used multiple fields per day.[64,65]

It seems unlikely that proton beam will be widely used in breast cancer and more likely that it will find selective use in certain clinical scenarios in which the patient's anatomy poses cardiac or pulmonary risks with photon therapy.

Lung Cancer

The use of proton therapy in patients with non–small-cell lung cancer (NSCLC) has theoretical advantages in terms of sparing chest organs at risk and at the same time maintaining adequate target coverage. A recent meta-analysis of dosimetric studies revealed both

statistically and clinically significant decrease in lung and heart dose with proton beam plans in comparison with photon plans.[66] The utility of protons in the treatment of locally advanced as well as early-stage NSCLC has been studied in both prospective and retrospective series, as previously reviewed.[67-69] The standard dose for locally advanced NSCLC has been approximately 60 to 63 Gy; however, local failure rates associated with this dose level are 50% or higher. Radiation biology predicts an increase in local control on dose escalation,[70] although the Radiation Therapy Oncology Group 0617 (RTOG 0617; High-Dose or Standard-Dose Radiation Therapy and Chemotherapy With or Without Cetuximab in Treating Patients With Newly Diagnosed Stage III Non-Small Cell Lung Cancer That Cannot Be Removed by Surgery) randomized phase III trial in locally advanced NSCLC treated with three-dimensional chemoradiation therapy or IMRT failed to demonstrate improved survival in the 74-Gy arm compared with the 60-Gy arm.[71] This unanticipated outcome could relate to increased toxicity when delivering 74 Gy with photon techniques.[72] If this were true, protons may offer an opportunity for safe dose escalation. A phase II trial of 44 patients treated with 74 Gy (radiobiologic equivalent) proton radiation therapy with concurrent paclitaxel-carboplatin reported encouraging results, with a median survival time of 29 months with no grade 4 to 5 events and no local failures in nine patients.[73] A subsequent randomized phase II trial comparing protons versus IMRT for 66 Gy and 74 Gy dose levels with concurrent chemotherapy is nearing completion (NCT00915005; Image-Guided Adaptive Conformal Photon Versus Proton Therapy). Proton therapy may also be useful in the setting of trimodality therapy for stage IIIA NSCLC in which it is important to spare the contralateral lung, especially in patients who are pneumonectomy candidates (NCT01565772; Proton Radiation Therapy With Cisplatin and Etoposide Followed by Surgery in Stage III Non-Small Cell Lung Cancer).

For medically inoperable early-stage NSCLC, photon-based stereotactic body radiation therapy (SBRT) has become the standard of care. A recent literature-based meta-analysis compared particle beam therapy with SBRT and found no significant differences in survival between SBRT and particle beam treatments[74] in patients with inoperable stage I NSCLC. Photon-based SBRT is particularly challenging for centrally located tumors because of excessive toxicity.[75] The sharper lateral penumbra and the use of active scanning might allow for a better sparing of the critical structures with proton-based SBRT or hypofractionated regimens (NCT01511081: Stereotactic Body Radiotherapy [SBRT] Versus Stereotactic Body Proton Therapy [SBPT]). In addition, the ability of proton beam radiation to achieve adequate target coverage with only two to three beams may be advantageous in settings of poor lung function, prior chest irradiation, or for multifocal lung cancers that require more than one treatment course.[76]

Realizing the potential benefits of proton therapy in patients with lung cancer is a technical challenge, mainly because of problems with delivering protons to moving targets that are surrounded by tissues with large inhomogeneities. Proton radiation therapy for lung cancer is still in its early stages of clinical testing, particularly with regard to the development of appropriate dose algorithms, intensity-modulated proton therapy (IMPT) optimization, motion management, volumetric image guidance, and adaptive planning techniques.[67]

Brain Tumors

Glioblastoma is a primary brain tumor, which is now treated with a maximal safe resection, followed by adjuvant radiation therapy to 60 Gy with concurrent and adjuvant temozolomide. Before the era of concomitant chemotherapy, proton beam therapy was explored as a means of dose escalation. Two small phase I/II trials[77,78] have suggested small gains in tumor control and survival rates but, unfortunately, with a marked increase in necrosis requiring surgical intervention. Ultimately, failure of therapy outside the high-dose regions indicated that dose escalation alone was not the optimal approach to this disease. Current investigations are using proton therapy in the management of low-grade and favorable high-grade gliomas in hopes of reducing radiation-associated adverse effects in patients achieving at least several years of survival.

Meningiomas are at the other end of the spectrum of brain tumors, with the majority of patients achieving long-term tumor control and often normal life expectancies. Here the main goal of therapy is also not to dose escalate but to minimize the unwanted cerebral adverse effects of radiation and to minimize decrement to the patient's quality of life. Several series have suggested that proton beam may be a step forward in this regard[79-81] and the University of Pennsylvania is now enrolling patients onto a feasibility and phase II study of protons in the management of meningiomas and hemangiopericytomas.

Head and Neck Cancers

Proton therapy has been used on a clinical trial basis at several institutions for the treatment of nasopharyngeal carcinoma (P. Busse, personal communication, December 2013), oropharynx,[82] sinonasal, and paranasal sinus malignancies.[83,84] The value of protons for the most important head and neck sites (nasopharynx and paranasal sinuses) resides in the ability to limit the dose to optic structures and brainstem and secondarily the mandible and salivary glands. Dosimetric analysis shows that a significant reduction in dose to radiosensitive structures such as the mandible and the parotid gland[50] may be achieved, potentially leading to decreased risk of mandibular osteoradionecrosis and xerostomia. However, the head and neck area is like the lung because of air cavities that may be variably filled with tumor or fluid and there is also the problem of the complexity and inhomogeneity of the bones; thus, this area is a considerable challenge for proton physicists.

GI Malignancies

The role of heavy-particle therapy in the treatment of hepatocellular carcinoma has been reviewed by Skinner et al.[85] Clinical evidence reveals a promising local control and toxicity profile of the proton beam in the treatment of hepatocellular carcinoma, and the ability to spare more liver with integral dose reduction might make it a preferable treatment modality for patients with Child-Pugh class B and class C cirrhosis. Nevertheless, the experience is limited to only a few institutional series, and additional research is greatly needed in this field. The potential advantage of protons is simultaneously being narrowed by the advances in SBRT in this disease. SBRT is now in routine use, and it has also developed a considerable body of evidence against which protons will have to be measured. The treatment of locally advanced esophageal cancer requires either chemotherapy alone or chemotherapy in combination with surgery. Noncancer deaths are

common in the first year of treatment and are largely related to cardiopulmonary toxicity.[86] The ability of protons to spare the heart might decrease cardiac toxicity and death, but this requires further clinical investigation.[50]

FUTURE DEVELOPMENT

Technical Advances

Most of the clinical experience with proton therapy to date comes from the use of passively scattered beam technology. Just as IMRT was an important technological advance in our ability to deliver photon therapy—reducing toxicity and allowing for dose escalation in select clinical situations—so the corresponding advance in proton therapy will be the introduction and clinical assessment of pencil-beam scanning technology, which will allow for IMPT. This technology had been demonstrated to improve the dose distribution and is now being introduced into some of the established proton centers. If IMRT decreased the gap between photons and protons to a nearly undetectable level, so the introduction of IMPT might be expected to increase it again. This remains to be seen.

Another benefit of proton therapy is the ability to see the beam track in tissue for a short period of time after treatment within a positron emission tomography scanner and even quantitate the dose delivered. This in vivo dosimetry offers truly unique opportunities for assessing treatment delivered and for real-time quality assurance.

A third important step forward will be the development of smaller and more affordable proton beam units. These might allow a substantial decrease in the cost difference between particle and x-ray therapy. As this difference is dialed down, the heat in the debate over the cost-effectiveness of the particle therapy will be, too, and clinicians will no longer feel driven to use a proton hammer for all nails in order to amortize the debts on large facilities. One can anticipate a time when they mix and match the beams of various properties to individualize the best treatment beam for each patient.

Evidence Development

As we move toward a value-based system of medical practice and payment, the current evidence base supporting the use of proton therapy will be judged thin and wanting. It will not be enough to say that this is simply a "sharper knife" and therefore does not require formal testing. Proton beam is more than just a technical advance and actually introduces some biologic unknowns. The radiobiologic effectiveness of proton beam therapy relative to photon therapy is just an estimate and may differ according to tissue or fraction size. When uncertainties of this nature are at work, the clinical outcome becomes more unpredictable. Although randomized controlled trials are the gold standard for the development of medical evidence, they may be inappropriate for most uses of proton beam. In some situations the benefits are intuitively clear (such as pediatrics), and trials are unethical. In others, the benefits are likely to be small or nonexistent such as with skin cancer, and proton beam therapy should not be considered. However, there is a gray zone, as in prostate or lung cancer, in which the advantages or disadvantages cannot be known. When one considers the enormous economic and policy implications of using proton beam therapy for these common diseases, randomized trials would serve to quantitate the benefit to the patient and inform the policy debate. For the majority of other clinical situations, the prospective collection of clinical data, including patient-reported quality-of-life outcomes, in data registries will be sufficient for comparative studies.[87]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Timur Mitin
Collection and assembly of data: Timur Mitin
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

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