COUNTERPOINTS

Current Controversies in Hematology and Oncology

Is Proton Beam Therapy Better Than Standard Radiation Therapy?

Proton beam therapy has many potential advantages over photon therapy for treatment of cancer therapy. The entrance dose is low, the exit dose is almost nonexistent, and most of the beam energy is deposited at a specified depth. But do these theoretical advantages translate into practical ones? Here, Drs Chuong, Mehta, Langen, and Regine make the case for proton beam therapy, whereas Drs Salama and Willett point to the advantages of photon therapy.

The Available Evidence Points to Benefits of Proton Beam Therapy

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Ionizing radiation was first used as a therapeutic anticancer modality more than a century ago. Since then, radiation oncologists have sought to improve their ability to deliver tumoricidal doses of ionizing radiation to intended targets while minimizing the dose to normal tissues, with the goal of administering a dose that is "as low as reasonably achievable" (the ALARA principle).

Major utilization shifts in photon radiotherapy over the past several decades—which notably were made in the absence of randomized clinical trials—have increased the therapeutic index of modern, highly conformal photon radiotherapy. Although we continue to strive to limit the dose to normal tissues, further improvements using photons are becoming increasingly difficult to achieve. A major reason for this is the inability to avoid the exit dose downstream from the target, which is a physical limitation of the megavoltage photon beam. Thus, increasing attention is being focused on proton beam therapy (PBT). Unlike photons, protons deposit nearly all of their energy

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A Paucity of Practicality Puts Photons Ahead of Protons

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Since Wilhelm Röntgen's discovery of the x-ray in 1895 and its application to the treatment of cancer, advances in technology have led to consistently improved cancer outcomes. Isocentric treatments, computer controlled radiotherapy, megavoltage energy therapy, intensity modulation, volumetric therapy, and image guidance all have significantly advanced the therapeutic index of treatments by improving the chance for appropriate delivery of radiotherapy, while minimizing the exposure of surrounding uninvolved organs.[1]

Recently, many have advocated proton beam therapy as the next technologic leap forward—one that will further enhance the therapeutic index. Not surprisingly, this enthusiasm has paralleled the establishment of a large number of proton beam therapy centers and a doubling of the number of Medicare beneficiaries receiving proton beam therapy.[2] Despite its many theoretical advantages, however, the data do not support a switch to proton therapy at this time.

Potential Advantages of Protons

Compared with photon therapy, the idealized physical properties of protons give it many *potential* advantages for

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The Available Evidence Points to Benefits of Proton Beam Therapy (cont)

at a defined and controllable depth from the skin surface, essentially avoiding the exit dose.

Advances in Proton Beam Therapy

Rapid technological advances have been made in photon delivery over the last 2 decades. These advances largely were spurred by the advent of intensity modulated radiation therapy (IMRT) and the integration of on-board volumetric imaging, although these innovations initially bypassed the world of PBT. Despite this, the clinical benefits of PBT were well documented in specific patient populations, such as children. Late adverse effects such as endocrinopathies, growth and developmental anomalies, cognitive dysfunction, and secondary malignancy are particularly evident in children because of their long-term survivorship.

Clear benefits of PBT over photon radiotherapy also have been shown for patients with radioresistant neoplasms such as chordomas, chondrosarcomas, and ocular melanomas, all of which require high radiation doses for local control that simply are not achievable with photons owing to exit dose limitations.

Despite the fairly significant initial costs, we posit that PBT can be cost-effective and that further prospective evaluation of PBT is warranted given the high probability of clinical benefit in select patient subsets, especially given the expanding utilization of pencil beam scanning (PBS) and image-guided proton therapy. These advances have made it possible to treat a number of conditions that could not be managed with passively scattered PBT.

Cost Considerations

PBT often is cited as being too expensive. Because abundant data from randomized trials of protons vs photons are not available at this time, some claim that PBT is wildly cost-inefficient. The true picture is, in fact, substantially different when we take into account crucial nuances.

First, although the up-front cost of a 4- or 5-room PBT treatment center can reach several hundred million dollars, a large percentage of that cost is attributable to the cyclotron or synchrotron, as well as massive rotational gantries that have a lifespan of 30 years or more. This is significantly longer than the 7-year average lifespan of a linear accelerator. In fact, the direct cost of a 4-gantry modern proton system is comparable to that of a high-end linear accelerator facility with 16-plus machines over its 30-year lifespan, after taking into account that the linear accelerator facility would require 3 or 4 replacements of all 4 units over this period.

Second, the popular belief that PBT treatment costs more to administer than similar treatment delivered with photons is inaccurate. In fact, reimbursement rates vary drastically across the country based on the specific insurance carrier. As recent publications have demonstrated, reimbursement rates for PBT often are very similar to those for IMRT.[1] Crucially, a focus only on direct up-front costs at the time of treatment is hugely short-sighted because the indirect costs of managing and living with the late adverse effects of radiotherapy—many of which are related to exposure of normal tissues to low doses of radiation—are significantly reduced or even eliminated with PBT.

Multiple studies have reported that PBT may be more cost-effective than standard radiation therapy for specific patients, such as children, as measured in quality adjusted life years.[2-5] For instance, Hirano and colleagues modeled hearing loss as a function of cochlear dose in 6-year-old children who were treated for medulloblastoma with protons or photons, and concluded that the benefit in hearing provided by protons was at a societal willingness-to-pay value. Cost-effectiveness data in support of PBT have emerged for other disease sites, such as the head and neck.[6] Moreover, given recently published data showing that even low doses of radiation to the heart increase the likelihood of cardiac morbidity and mortality, it is highly probable that many patients with left-sided breast cancer would experience lower indirect cardiotoxicity costs with PBT.[7]

Third, being able to better limit radiation dose to normal tissues using PBT may allow for increased use of hypofractionation, which is a very cost-effective way to deliver radiotherapy. For example, a phase 3 trial (NCT01230866) is randomly assigning patients with low-risk prostate cancer to either 44 or 5 PBT fractions. Should a 5-fraction regimen be found to provide equivalent outcomes, this could significantly decrease the cost of PBT.

Fourth, more compact PBT facilities with 1 or 2 treatment rooms have recently become available and these cost considerably less to develop.

Lastly, as is seen with most technologies, costs are expected to continue to decline as proton technology continues to mature and delivery becomes more efficient.

Level 2 Data Support Clinical Benefit

PBT is often criticized for the lack of evidence supporting clinical benefit compared with photon-based radiotherapy.

Just as the widespread implementation of IMRT occurred without robust data from randomized clinical trials showing a benefit over older techniques, there is a lack of randomized level 1 evidence comparing photon- and proton-based radiotherapy. However, considerable data at level 2 and lower exist to support the value of this modality. It is simplistic to discredit PBT for a paucity of level 1 evidence, when we as a nation are just now gearing to conduct large-scale randomized phase 3 trials (with 14 proton centers, compared with >2200 photon centers[8]). In fact, most cancer therapies would need to be abandoned according to this logic because fewer than 10% of standard-of-care cancer treatment recommendations are based on level 1 evidence.[9]

An even more significant issue is one of informed consent and equipoise. Randomly assigning patients to 1 of 2 arms in a phase 3 trial requires confident belief that each arm is likely quite comparable in terms of outcome, with minimal possible inter-arm differences. In the context of protons vs photons, convincing patients that extra unnecessary radiation dose to their normal tissue will likely not be harmful when all principles of radiation exposure, protection, and therapy point in the opposite direction requires an enormous act of faith on the part of the patient.

As a case in point, a patient with an oropharyngeal cancer who achieves a 25-Gy reduction to the anterior oral cavity through the use of PBT instead of photon therapy is spared the radiation equivalent of 5 million unnecessary dental x-rays. The excessive use of diagnostic x-rays already has been implicated as a cause of secondary malignancies; therefore, when randomizing such a patient, where does equipoise rest? At an extra 100, 10,000, or 1,000,000 x-rays? More importantly, would insistent proponents of randomized data willingly expose themselves or their loved ones to this excess radiation dose if they could avoid it? If the answer is "not readily," then conducting large-scale randomized trials becomes ethically problematic. All of the individuals who call for this need to first and foremost ask themselves what they would choose for their own child if they were unconstrained by resources.

Despite these major constraints—as well as the existence of several dosimetric studies predicting a high probability of benefit for intensity modulated proton therapy (IMPT), clinical data from single-arm prospective studies, and several favorable retrospective reports—PBT is increasingly being studied in a randomized fashion. The data available to date, including the data being generated by the IMPT systems that have become more prevalent in the last few years, strongly suggest that PBS can lower treatment-related toxicity and permit dose escalation in patients who otherwise would not be optimal candidates using photons. The Particle Therapy Co-operative Group website lists more than 50 ongoing clinical trials using protons in a variety of disease sites.[10] Randomized trials comparing photons and protons, once thought to be almost impossible, currently are being developed or are underway for glioblastoma, low-grade glioma, head and neck cancer, prostate cancer, lung cancer, esophageal cancer, breast cancer, and many other types of cancer.

Criticism of PBT for Prostate Cancer

PBT for prostate cancer has been the target of public criticism, with claims that profits and not science drive the recommendation for PBT. In the October 1, 2014 radio broadcast of *All Things Considered*, an economist stated that "we do know [that proton therapy] is substantially more expensive and substantially more lucrative for physicians and providers" than standard radiation.

In reality, physicians practicing in hospital-based proton facilities are reimbursed at the same Medicare rates whether they are using protons or photons. Further, and germane to this misleading line of thought, proton therapy facilities may in fact be less profitable than other radiation therapy centers because they are highly labor intensive, with higher operational costs.

The Cancer Letter reported on June 20, 2014 that approximately 85% of PBT patients have prostate cancer, reflecting a common misperception about PBT. Although a high percentage of patients may have prostate cancer when a proton center opens, this percentage decreases dramatically with time. Data from a multi-institutional prospective registry maintained by the Proton Collaborative Group (NCT01255748) show that although the cumulative percentage of prostate patients was initially more than 90%, it fell to 74% by 6 months, and has continued to decline to a current level of less than 50% (personal communication from Megan Dunn, PhD, of the Proton Collaborative Group). The Loma Linda Medical Center published the first large single-arm experience using PBT for prostate cancer, demonstrating high rates of tumor control with lower rates of serious late toxicity compared with the best photon series of the time.[11]

Two recent retrospective studies comparing proton-based vs photon-based therapy for prostate cancer have generated significant controversy.[12,13]

An analysis of the Surveillance, Epidemiology, and End Results (SEER) database concluded that PBT resulted in a higher rate of gastrointestinal morbidity. This finding was partly based on the surrogate outcome of colonoscopy claims, which was inappropriate—especially given that this population was willing to potentially travel long distances to receive PBT, and therefore might have been more vigilant about following up on health concerns. Study enrollment (applicable for many PBT patients) created a much lower, protocol-defined threshold for endoscopic evaluation to more accurately describe

changes after treatment.[12] Most importantly, many proton patients were treated to a higher total dose than their photon counterparts, and actual dosimetric information was not retrieved.

An analysis of the Medicare database was published more recently. This analysis concluded that no differences in 12-month toxicity existed. However, many of the toxicities that were evaluated were not relevant to prostate radiotherapy (eg, upper genitourinary tract dysfunction) whereas more relevant toxicities were not considered (eg, rectal bleeding).[13] In 2014, the National Association for Proton Therapy reported survey results on approximately 3800 prostate cancer patients treated with PBT from 12 centers, several with 10- to 20-year follow-up, representing the largest patient-reported survey of its kind for any radiation modality. The key findings were that 96% were satisfied with their outcomes, with 85% rating their quality of life as similar to or improved compared with baseline. For the subgroup treated only with PBT, 97% remained free of relapse, and urinary, bowel, and sexual function outcomes were reported at a level consistent with a cancer-free control group.[14]

Whereas the vast majority of published PBT studies have used passive scatter technology, the state-of-the art technique now uses PBS. This involves precisely "painting" the target spot by spot and layer by layer, using a narrow beam to deposit proton dose in spots of approximately 1 to 2 cm. PBS has expanded the indications for the use of protons. For example, complex head and neck targets now can be treated that were not treatable using conventional PBT. As more complicated cases can be treated using PBS, the proportion of prostate cases will continue to decrease further. This already has been seen at the MD Anderson Cancer Center, where between 2010 and 2014 the proportion of genitourinary cancer cases decreased from 44% to 27%, and the proportion of head and neck cases has increased from 0% to 11% (personal communication from Steven Frank, MD).

Conclusion

We do not dispute that modern photon therapy is a good tool for many cancer patients. It is also indisputable that IMRT has lowered several complications relative to 2- and 3-dimensional techniques by following the ALARA principle, although it never has been subjected to rigorous, extensive randomized testing. By further extending the ALARA principle, PBT likely provides a clinical benefit to certain patients that is not achievable with photons.

It is our responsibility as a radiation oncology community to more rigorously explore through high-quality clinical trials exactly which patients benefit most from PBT. In short, we already have substantial evidence that PBT is effective for many cancers, and the body of evidence is growing at an increasing rate as more proton centers are developed. To grow this database of knowledge further, we need to be open-minded to the same degree that allowed IMRT to revolutionize our field. Fair is fair, and physics is physics. It would be a shame if ALARA were to be ignored.

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A Paucity of Practicality Puts Photons Ahead of Protons (cont)

use in cancer therapy. These include a low entrance dose and almost nonexistent exit dose, with most of the beam energy deposited at a specified depth—known as the Bragg peak.[3] Computer simulations comparing proton beams—in idealized dose distributions and reference conditions—with standard photon beams often demonstrate far lower entry dose deposition, the same or better tumor coverage, almost nonexistent exit dose, and lower integral dose.[4,5]

Advocates of the use of proton therapy point to its inherent physical advantages, as well as these idealized proton dose distributions, as evidence to warrant widespread proton adoption.[6] As if the distinction were as clear as that between a sharp knife and a dull one, proponents of proton beam therapy claim that the advantages are so overwhelming that it is unethical to perform randomized trials to validate the utility of protons vs photons.[7] However, others have stated that the evidence supporting protons are lacking and that further study is needed.[8,9]

Surely, if idealized doses that take advantage of the inherent physical properties of proton therapy could in fact be delivered consistently, it would be difficult to argue against proton therapy. However, reality is far different. The current technology of proton therapy has yet to demonstrate improved outcomes vs photons. Furthermore, many uncertainties remain in proton treatment planning and delivery, including those related to radiobiologic effectiveness, planning calculations, and cost. Protons cannot be considered superior to photons at this point.

Planning and Delivery of Radiation

It is instructive to identify what is not different in the planning of proton and photon irradiation. For both proton and photon radiotherapy, patients undergo a similar computed tomography (CT) simulation that is often aided by the use of diagnostic metabolic CT and magnetic resonance images to outline the known extent of tumor as the gross tumor volume (GTV). Furthermore, the basic principles applying to creation of the clinical target volume, accounting for microscopic spread and subclinical tumor involvement, are the same with either modality. For photon treatments, the final step in creating targets for treatment is the planning target volume, which is a geometric expansion of the GTV to account for organ motion and set-up uncertainty. A similar standardized concept does not yet exist for proton therapy, however, as range uncertainties, lateral displacement, tissue heterogeneity, and dosimetric effects all influence proton planning and delivery.[10] The existence of these variations complicates efforts to plan and evaluate proton therapy dose distributions.

During the planning of proton beam radiotherapy, many necessary technical considerations result in a higher radiation dose being delivered to a given patient than would be possible under idealized conditions.[10] Often, clinical targets are larger than the width of a single Bragg peak, which necessitates the use of multiple Bragg peaks that are close in value but not identical. This spread-out Bragg peak (SOBP) creates a larger and more clinically useful volume of dose, which is of benefit for tumor coverage but also creates a higher amount of cumulative entrance dose compared with a single-energy Bragg peak.[3] Furthermore, given the inherent errors and uncertainties in the conversion of CT numbers from a planning CT to proton stopping power, proton range calculations are directly affected, with a margin of 3% to 4% added to account for this uncertainty on top of that needed for the SOBP.[11] Given these proton range uncertainties, the sharp distal proton penumbra is rarely used to spare organs at risk within 1 to 2 cm of the target volume.[12] Therefore, the idealized physical properties of protons are diminished, dulling the sharper knife.

> Uncertainties remain in our understanding of the interaction between protons and human tissues.

On a biological level, many uncertainties remain in our understanding of the interaction between protons and human tissues. It is often assumed that protons and photons are biologically similar, with protons having a 10% stronger biological effect throughout their entire path through the body, therefore requiring a conversion to photon doses via the Gray equivalent. However, this assumption is primarily based on animal modeling from the early days of proton therapy.[13] In reality, the relative biological effectiveness (RBE) may vary by as much as 10% from the mid part of the SOBP to the edge of the SOBP. Furthermore, RBE depends on the dose per treatment for protons, with a larger RBE seen with lower doses. This adds significant challenges when prescribing proton doses as extrapolations from photon doses, and additionally makes analysis of toxicity complicated.[14]

Significant Advances in Photon Therapy

The biological uncertainties of proton therapy are especially important to consider in light of the fact that significant advances have been made in photon therapy during the same period that proton therapy has been developed and expanded. The benchmark to which proton therapy is compared is much different today than it was just 10 years ago. Photon therapy now routinely includes the standard use of heterogeneity corrections (accounting for tissue differences between lung, soft tissue, bone, and air), daily volumetric image guidance, intensity modulation, respiratory motion assessment and management, and adaptive replanning based on tumor and normal tissue changes.

Many of these processes remain very challenging in the clinical delivery of protons,[10] although proton beam therapy continues to advance as well.[15] Smaller, less expensive, more efficient treatment units using pencil beam scanning are being designed, often to fit into a conventional photon vault.[16] Until these technical challenges can be overcome with certainty, however, proton therapy will not be used to its full potential.

Proton Therapy for Children?

Many believe that despite these caveats, there are specific clinical scenarios in which proton therapy as currently delivered is superior to photon therapy. In particular, the treatment of pediatric cancers,[17] chordomas,[18] and uveal melanomas[19] often are touted as clinical indications for proton therapy. However, the evidence to support the use of protons for these indications is sparse. Based on the limited data available, it can be stated that proton therapy does not appear to lead to worse outcomes than photon therapy in these patients. Although the lower integral dose—with the hope of fewer second malignancies—certainly is a strong consideration in the case of pediatric malignancies, the advantages have not been proven.[20]

Dosimetric Benefit vs Clinical Benefit

For common cancers occurring predominantly in adults, the published clinical data do not support the idea that the dosimetric benefits of protons translate into any clinical benefit. A systematic review of the available literature did not support the clinical superiority of protons over photons.[21] A recent update of this review could not find a single randomized study evaluating the effectiveness of protons.[22]

Two population-based analyses have assessed the clinical impact of proton therapy compared with intensity-modulated radiation therapy for a commonly treated malignancy, prostate cancer. One of these analyses demonstrated a higher rate of gastrointestinal toxicity and hip fracture in those treated with protons (although erectile dysfunction was decreased), whereas the other found lower acute urinary toxicity but no differences in long-term toxicity.[23,24] Apart from these analyses, data supporting the use of proton therapy for non–small cell lung cancer have been from single-arm, uncontrolled phase 2 studies.[25] Ongoing phase 3 studies that are comparing the use of proton vs photon therapy for dose-escalated treatment of locoregionally advanced non–small cell lung cancer and prostate cancer will address the clinical utility, if any, for protons.

The Issue of Cost

Additionally, the cost of operating a proton center is quite high, as is the reimbursed cost of treatment. For example, one report stated that the median Medicare reimbursement for prostate cancer treatment with protons was $32,428, which is much higher than the cost of intensity-modulated photons at $18,575.[26] Given the lack of any proven clinical benefit to protons as of now, the value to society of paying the increased costs for proton therapy should be questioned. This is of particular importance in light of the advent of population-based health care through the Affordable Care Act.

Conclusion

Given the continued uncertainties regarding proton beam therapy planning and delivery, the lack of evidence supporting the use of protons over photons, the higher cost of proton therapy, and limited access and expertise with proton techniques, protons continue to lag behind contemporary photons. Photon therapy should continue to be considered the standard of care for all radiotherapy indications.

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Table 1 Incidence of Adverse Events Occurring in ≥5% of Patients Randomized to PROVENGE

	PROVENGE (N = 601)		Control* (N = 303)	
	All Grades n (%)	Grade 3-5 n (%)	All Grades n (%)	Grade 3-5 n (%)
Hypertension	45 (7.5)	3 (0.5)	14 (4.6)	0 (0.0)
Anorexia	39 (6.5)	1 (0.2)	33 (10.9)	3 (1.0)
Bone pain	38 (6.3)	4 (0.7)	22 (7.3)	3 (1.0)
Upper respiratory tract infection	38 (6.3)	0 (0.0)	18 (5.9)	0 (0.0)
Insomnia	37 (6.2)	0 (0.0)	22 (7.3)	1 (0.3)
Musculoskeletal chest pain	36 (6.0)	2 (0.3)	23 (7.6)	2 (0.7)
Cough	35 (5.8)	0 (0.0)	17 (5.6)	0 (0.0)
Neck pain	34 (5.7)	3 (0.5)	14 (4.6)	2 (0.7)
Weight decreased	34 (5.7)	2 (0.3)	24 (7.9)	1 (0.3)
Urinary tract infection	33 (5.5)	1 (0.2)	18 (5.9)	2 (0.7)
Rash	31 (5.2)	0 (0.0)	10 (3.3)	0 (0.0)
Sweating	30 (5.0)	1 (0.2)	3 (1.0)	0 (0.0)
Tremor	30 (5.0)	0 (0.0)	9 (3.0)	0 (0.0)

*Control was non-activated autologous peripheral blood mononuclear cells.

Cerebrovascular Events. In controlled clinical trials, cerebrovascular events, including hemorrhagic and ischemic strokes, were reported in 3.5% of patients in the PROVENGE group compared with 2.6% of patients in the control group.

(See Adverse Reactions [6] of full Prescribing Information.)

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