

Intensity-modulated conformal radiation therapy and 3-dimensional treatment planning will significantly reduce the need for therapeutic approaches with particles such as protons

William R. Hendee, Moderator

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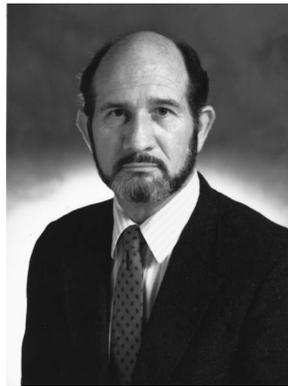
OVERVIEW

The advantage of radiation therapy with particles such as protons has been recognized for many years, and a few institutions have made substantial investments in accelerators for proton therapy. These advantages yield an improvement in the tumor to normal tissue dose relationship for protons compared with conventional therapeutic approaches employing high-energy x rays. However, improvements in the conventional approaches are significantly reducing the gap between dose distributions provided by proton therapy and those achievable with x-ray therapy. These improvements include intensity-modulated and conformal radiation therapy, sophisticated treatment planning systems, and eventually, image-guided intensity-modulated conformal radiation therapy. Whether these improvements reduce the need for further pursuit of particle (proton) therapy is the subject of this Point/Counterpoint issue.



Arguing for the proposition is T. Rockwell Mackie. Dr. Mackie^{b)} is a Professor in the University of Wisconsin Departments of Medical Physics and Human Oncology with membership in the University of Wisconsin Comprehensive Cancer Center and the Program in Biomedical Engineering. He is best known for his work on radiotherapy treatment planning including the convolution/

superposition and the Monte Carlo methods of dose computation. Recently he has concentrated his efforts on helical tomotherapy, which is the integration of radiotherapy optimization, intensity-modulated radiotherapy, and tomographic treatment verification. His career has involved co-founding two companies (Geometrics Corporation and TomoTherapy Corporation), serving on national committees, and being active in the AAPM.



Arguing against the proposition is Alfred R. Smith. Dr. Smith^{b)} is a Professor at Harvard Medical School, and a Biophysicist at Massachusetts General Hospital. He supervises clinical physics for proton therapy research conducted at the Harvard Cyclotron Laboratory and is Associate Director for the construction of the Northeast Proton Therapy Center at MGH. He has worked in neutron (M. D. Anderson Cancer Center), negative pi-meson (Los Alamos Scientific Laboratory), and multi-leaf conformal (Hospital of the University of Pennsylvania) therapy. At the NCI he initiated studies for the evaluation of treatment planning for heavy particles, x rays, electrons, brachytherapy, and radio-labeled antibodies. He is Past President of the AAPM and a Fellow of AAPM and ACMP.

^{a)}Suggestions for topics suitable for these Point/Counterpoint debates should be addressed to William R. Hendee, Medical College of Wisconsin, Milwaukee: whendee@post.its.mcw.edu.

^{b)}Persons participating in Point/Counterpoint discussions are selected for their knowledge and communicative skill. Their positions for or against a proposition may or may not reflect their personal opinions or the positions of their employers.

For the proposition

Thomas Rockwell Mackie

*University of Wisconsin, Departments of Medical Physics and Human Oncology, Madison, Wisconsin 53706
(Tel. 608-262-7358, e-mail: mackie@macc.wisc.edu)*

OPENING STATEMENT

Proton beam therapy, as practiced today, is much better than conventional photon beam radiotherapy but often inferior to photon intensity-modulated radiation therapy (IMRT). Because the cost of proton facilities is much greater than for photon IMRT, the cost effectiveness of photon IMRT is currently much superior.

Utilization of the Bragg peak of proton beams is most effective when there are highly sensitive tissues immediately distal to the target volume. Unfortunately, this aspect cannot always be used because of uncertainty in the proton range due to uncertainty in tissue density obtained from CT scans. Tissue density uncertainty has far less effect on photon beam 3D radiotherapy treatment planning.

Proponents of proton radiotherapy often do not point out that the lateral falloff in dose, the dose penumbra, at deeper depths from high-energy proton beams can be less steep than low-energy photon beams produced by linacs. This means that the beam area has to be made larger than a photon beam to ensure that a deep-seated target volume is not in the penumbra. The sharp penumbra of photons is what is being exploited in photon IMRT to conformally avoid neighboring sensitive tissue structures.

Multiple proton scattering causes high-gradient hot and cold spots to develop if the beam travels through high-contrast heterogeneities or steep surface irregularities which are typical of head and neck radiotherapy. Multiple proton scattering also makes junctioning fields tricky. While possible in principle, it is highly unlikely that we will be making use of proton beam radiography for setup or dosimetric quality assurance in the near future. By contrast, photon IMRT can account for surface irregularities and tissue inhomogeneities, can reduce the need for elaborate field junctioning, and will be capable of geometric and dosimetric verification using an exit detector.

The cost-effectiveness of proton radiotherapy for the vast majority of patients must be questioned. Results of planning comparisons of conventional proton and IMRT photon radiotherapy indicate that photon IMRT is often the better plan when the dose distribution requires a complex conformal shape. Any radiotherapy department can now practice photon IMRT for a tiny fraction (2 to 5%) of the capital cost of a proton facility. And often, the photon IMRT patients will get a far better treatment! There are a few cases, such as eye tumors, whereby low-energy proton beams, will be superior. Unfortunately, there would not be enough cases, except possibly in the largest managed care networks, to keep a proton facility busy treating those patients that can really benefit from the expense.

Proton IMRT combined with x-ray verification capability may outperform photon IMRT but at an even greater expense. Before new proton facilities are built it would make sense to wait until proton radiotherapy is both capable of verifiable IMRT and its acceleration and beam transport technology is significantly reduced in price.

In summary, photon IMRT reduces the need for proton beam radiotherapy and other more exotic particle types. This is because photon IMRT is now more cost effective than proton radiotherapy in the vast majority of cases.

REBUTTAL

My esteemed colleague has confirmed my central point. The major difference between conventional proton beam radiotherapy and photon IMRT (IMXT) is cost. Professor Smith related a planning comparison for a nasopharynx case, where for equal NTCP, IMXT had a TCP of 86% and conventional proton radiotherapy had a TCP of 88%. Given uncertainty in biological models, these results are indistinguishable except that the proton treatment would have cost, by Professor Smith's estimates, 50% to 100% more.

The rest of my rebuttal will examine the issue of intensity-modulated proton radiotherapy (IMPT). IMPT is technically possible (I am a co-inventor, with Joseph Deasy and Paul Deluca, on an IMPT patent), however, IMPT will be even more expensive because both beam intensity and beam energy must be controlled simultaneously. Before IMPT is feasible, more accurate dose computation is required. Before IMPT is practical, the cost and size of proton accelerator systems must be reduced.

Perhaps the proponents of conventional proton radiotherapy and IMXT should join forces? The Bragg peak of a conventional proton beam could be exploited to deliver the bulk of the treatment dose but be augmented with the addition of IMXT. Junction difficulties could be reduced wherever possible by making the proton dose gradient in the match region low (and linear if possible). In this way, IMXT could deliver most of its dose to smaller volumes, near critical structures and at the boundaries of fields, where their placement could be radiographically verified. This combination could approach the theoretical advantages of IMPT at a fraction of the investment in time and money.

Until dosimetry issues are resolved and proton accelerators are reduced in price, IMPT is a questionable investment. What makes the most technical and financial sense is to concentrate research and development in IMXT and to adapt IMXT for use in conventional proton facilities as well.

Against the proposition

Alfred R. Smith

Northeast Proton Therapy Center, Department of Radiation Oncology, Massachusetts General Hospital, Boston, Massachusetts 02114 (Tel. 617-724-1197, e-mail: smith@hadron.mgh.harvard.edu)

OPENING STATEMENT

The proposition “intensity-modulated x-ray (IMXT) dose distributions (*rival those for protons, and therefore*) significantly reduce the need for protons,” is not supported by basic physics, treatment planning intercomparisons or clinical results. The proposition is unsupported for standard proton treatments and even less supported for intensity (fluence)-modulated proton treatments (IMPT).

Clinical proton beams are characterized by depth-dose distributions having a relatively uniform low-dose entrance region, followed by a region of uniform high dose (the spread-out-Bragg peak) at the tumor/target, then a steep fall-off to zero dose. In contrast, single x-ray beams exhibit an exponentially decreasing depth dose after a maximum near the surface, a nonuniform dose across the target, and appreciable dose beyond the target. Therefore, compared to protons, single x-ray beams deliver higher doses to normal tissues/organs proximal to the tumor, nonuniform dose across the tumor, and significant dose to tissues beyond the tumor where the proton dose is zero. The physical advantage of protons for single beams extends to multibeam treatments, including intensity modulation. Compared to x rays in comparable beam configurations, protons will always have superior dose distributions. Moreover, proton beams can be aimed directly at critical structures lying beyond the target in situations where x-ray beams might be disallowed in IMXT. As a consequence, for equal normal tissue complication probability (NTCP), protons deliver higher tumor dose, thus increased tumor control probability (TCP). Conversely, for equal TCP, protons deliver less dose to normal tissues/organs and hence produce lower NTCPs than do x rays.

Treatment planning intercomparisons have been conducted between IMPT and IMXT for nasopharynx and paranasal sinus carcinomas, Ewing’s sarcoma, and non-small-cell lung cancer.¹ For nasopharynx, when total NTCPs are normalized to 5%, the total TCP was 97% for IMPT compared to 86% for IMXT assuming $D_{50}(\text{tumor}) = 67.5$ Gy. Our standard, non-IMPT, proton plan gave a TCP of 88%. The results for the other clinical sites were similar. Generally, IMPT plans reduce integral dose by about a factor of two compared to IMXT. It is axiomatic that normal tissues/organs should not be unnecessarily irradiated.

Using standard, non-IMPT, proton boost treatments, clinical studies have demonstrated: superior TCP (80% at 3 years), without visual damage, for paranasal tumors; TCP = 97 and 92% at 5 and 10 years, respectively, for skull-base chondrosarcomas; and superior results in a subgroup of poorly differentiated prostate tumors. For uveal melanomas, using protons alone, the 5-year actuarial TCP is 96% within

the globe (99% in the high dose volume), with 90% of patients retaining their eye.

If protons and x-rays cost the same, there would be no justification for using x rays for external-beam cancer treatments. The additional cost factor for proton therapy over that for high-technology x-ray therapy is now 1.5–2.0. This will decrease with time. Patients/providers are paying these additional costs to receive the superior clinical benefits offered by protons. Many more proton therapy facilities are needed.

REBUTTAL

Dr. Mackie states that proton therapy, as practiced today, is often inferior to photon intensity-modulated therapy (IMXT). We have seen no data supporting this claim. IMXT gives a bath of irradiation to normal tissues/organs that is not present in standard proton plans, therefore, for the same NTCP, TCP will be higher for standard protons (target coverage is comparable). More importantly, IMPT plans will *always* be superior to IMXT plans. This is dictated by the laws of physics and is unchangeable. In the new proton facility at MGH, IMPT will be delivered with scanned pencil beams.

Dr. Mackie’s descriptions of proton beam delivery are misleading. When beams are pointed directly at critical tissues/organs immediately distal to the target, protons will irradiate only a small fraction of the down-stream nontarget volume because they stop, whereas photons will irradiate all structures in their path distal to the target (and also deliver more dose upstream of the target). Up to medium depths, lateral penumbra is comparable for photons and protons and, except for small, spherical volumes, the photon penumbra cannot overcome the advantage of the stopping and sharp distal fall-off of protons. Proton treatment fields are fully compensated for surface irregularities, tissue inhomogeneities, and shape of distal target volume. We use an x-ray tube in the treatment nozzle to set-up and verify treatments. Field junctions and patched fields are routinely used.

Proton treatment capacity is the problem, not patient accrual. We have a 3–4 month waiting list for treatments; in our new facility we will treat two shifts/day. Dr. Mackie misstated the relative expense of photons and protons by a factor of 10 if one compares 30-year costs of facilities having 3–4 treatment rooms. Patients and referring physicians will make treatment decisions based on superior clinical results rather than relatively small differences in expense.

¹For nasopharynx, IMPT performed by T. Lomax, PSI, Switzerland and IMXT performed by T. Bortfeld, DKFZ, Germany. For other sites IMPT and IMXT performed by T. Lomax.