VOLUME 26 · NUMBER 2 · JANUARY 10 2008

JOURNAL OF CLINICAL ONCOLOGY

COMMENTS AND CONTROVERSIES

Should Randomized Clinical Trials Be Required for Proton Radiotherapy?

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Recently, several articles have been published in the *Journal of Clinical Oncology*[1] and other[2-4] journals reviewing and commenting on the record of proton beam therapy, as well as an analysis including some critical commentary by Brada et al.[5] All of these articles make the uncontested point that there are almost no randomized clinical trials (RCTs) comparing proton beam therapy with conventional x-ray therapy. We wish to address the issues of why this is, whether RCTs would be appropriate, and whether they are necessary before proton beam therapy is widely promulgated and reimbursed.

In brief, the arguments for the use of protons in radiation therapy are as follows. (1) Owing primarily to their depth dose characteristics (for each proton beam, virtually no dose is administered distal to the target volume and substantially less dose is administered than x-rays proximal to the target volume), the dose distributions that can be achieved with protons are in almost all cases superior to those possible with x-rays (with or without intensity modulation, which can be achieved with both modalities). There is generally between two to three times less energy deposited by protons to the uninvolved normal tissues outside the target volume (variously described as integral dose or the dose bath) as compared with the energy that x-rays deposit. (2) There is virtually no difference in tissue response per unit dose between protons of therapeutic energies as compared with x-rays, so that the only relevant differences are physical. (3) Radiation delivered to normal tissues causes damage to them, just as it does to tumors, and the severity of that damage increases with increasing dose.

Item (1) has been documented exhaustively in treatment planning studies.[6] There is a large body of in vivo and in vitro evidence underpinning item (2).[7] Item (3) is corroborated in countless clinical reports over many decades. These points are not contested by any of the authors cited above, nor, to our knowledge, by any critics of proton beam therapy. They are not speculations—they are demonstrated facts.

It is therefore hard to imagine how any objective person could avoid the conclusion that there is, at the very least, a high probability that protons can provide superior therapy to that possible with x-rays in almost all circumstances. It is primarily for this reason that the practitioners of proton beam therapy have found it ethically unacceptable to conduct RCTs comparing protons with x-rays. Such a comparison would not meet a central requirement for performing RCTs, namely that there be equipoise between the arms of the trial.[8]

Brada et al[5] base their opinions on what they understand to be the requirements of evidence-based medicine. In our opinion, the issue has much more to do with the implications of evidence-based medicine than it does with the clinical effectiveness of protons. In short, does evidence-based medicine require that, under all circumstances, positive RCTs are a precondition for the promulgation and reimbursement of new technologies? If it does, and if one accepted evidence-based medicine, so defined, as the sole basis for making medical decisions, then one would have no choice but to agree with the position taken by Brada et al[5] and others. However, we find it impossible to believe that unethical clinical studies could be considered to be a prerequisite to the adoption of a medical therapy. It must surely be the case that there are circumstances under which even the most dedicated advocate of evidence-based medicine would agree that RCTs would be improper. In deciding whether the arms of a trial meet the equipoise standard, one can only rely on informed judgment. It is our argument that informed judgment leads to the conclusion that proton beam therapy is precisely such a circumstance.

Advocates of RCTs are prone to state that, although there may be good arguments for the superiority of one arm, one does "know" that there is an advantage. In addition, to justify the conduct of trials that seem not to be in equipoise, they cite trials in which the outcome was the reverse of what was expected. Taking this argument to its extreme, one would have to conclude that there is effectively no clinical knowledge except that learned from RCTs. But this is an untenable position. Knowledge is not a dichotomous quality. We know things with varying levels of confidence. Even when RCTs are available, rarely do they provide all the information that is needed to care most effectively for the patient. We make informed evaluations of the level of confidence one has in any given judgment (for example, virtually all informed persons judge that the validity of the above-listed points is established with extremely high confidence), and we must base our actions on information about which we have good confidence.

Brada et al[5] make the point more than once that the apparent advantage of protons at several tumor sites may be due to patient selection bias. Indeed, selection bias is a serious issue in comparing nonrandomized studies (as are the eligibility criteria in assessing the applicability of the conclusions of an RCT to the treatment of a

DOI: 10.1200/JCO.2007.14.4329

given patient), and it could bias the results in the way that Brada et al[5] imply. However, it is our experience that the bias tends to operate in the opposite direction. At least until recently, we perceived a strong tendency for physicians to refer their difficult cases for proton therapy, and to treat patients with more favorable prognoses themselves.

Of course, it is really all about money. Can anyone seriously believe that, if protons were cheaper that x-rays, there would be similar objections raised as to their immediate and widespread use? This seemingly rigorous academic discussion, in reality, is driven by the uncontested fact that protons are more expensive than x-rays. Although we can understand (though not necessarily agree with) the desire to rely on RCTs to establish the advantage of a superior therapy, we find it totally unacceptable to insist on what we judge to be unethical RCTs purely to establish the financial cost-effectiveness of an admittedly better technology—nor would patients, if fully informed, consent to participate in such studies.

Regarding the issue of cost, the additional expense of protons is not so great as is often imagined, and there is good reason to think that it will come down. Goitein and Jermann[9] have analyzed the relative costs of proton beam therapy and high-technology x-ray therapy. They conclude that, with some foreseeable improvements, the ratio of costs is likely to be about 1.7. Although this represents an appreciable cost increment, it is substantially less than the costs of, for example, some expensive systemic therapies. At best, the benefit these expensive systemic therapies is probably no more than that of protons,[10] and such therapies often offer not improved local control or survival, but only a modest extension of the duration of palliation. Moreover, the recent surge of interest in acquiring proton beam facilities will almost certainly reduce the costs of proton therapy equipment through free-market competition, the design of smaller and less expensive facilities, and a normalization of reimbursement rates based on the real costs of proton treatments.

In our professional lives, we have lived to see almost identical arguments being made regarding new technologies, including the introduction of cobalt-60 teletherapy machines, the use of treatment simulators, the use of high-energy linear accelerators, the use of computed tomography, and so forth. We look back now on those arguments and wonder at the poor judgment that was evidenced then, and feel sure that history will judge the current controversy in the same manner.

We doubt that many of us, while healthy, would agree to receive, for example, 25 Gy to a large fraction of our brain or abdomen in exchange for some thousands of dollars, with no known or credibly hypothesized medical benefit. If we would not, how can we ask our sick patients to do so? Once proton beam therapy has become clinically available, is not the burden of proof on conventional x-ray therapy? Should not its advocates have to demonstrate that the cost savings achieved by using x-rays are not accompanied by undesirable additional morbidity? Do the users of x-ray therapy have the evidence to support such a claim?

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** James D. Cox, ProBeam (C) **Stock Ownership:** None **Honoraria:** None **Research Funding:** None **Expert Testimony:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Michael Goitein
Manuscript writing: Michael Goitein, James D. Cox
Final approval of manuscript: Michael Goitein, James D. Cox

REFERENCES

1. Schulz-Ertner D, Tsujii H: Particle radiation therapy using proton and heavier ion beams. J Clin Oncol 25:953-964, 2007
2. Olsen DR, Bruland ØS, Frykholm G, et al: Proton therapy: A systematic review of clinical effectiveness. Radiother Oncol 83:123-132, 2007
3. Lodge, Pils-Johannesma M, Stirk L, et al: A systematic literature review of the clinical and cost-effectiveness of hadron therapy in cancer. Radiother Oncol 83:110-122, 2007
4. Glimelius B, Montelius A: Do we need the randomized trials and can we do them? Radiother Oncol 83:105-109, 2007
5. Brada M, Pils-Johannesma M, De Ruysscher D: Proton therapy in clinical practice: Current clinical evidence. J Clin Oncol 25:965-970, 2007
6. Glimelius B, Anders A, Bjelkengren G, et al: Number of patients potentially eligible for proton therapy. Acta Oncol 44:836-849, 2005
7. Paganetti H, Niemierko A, Ancukiewicz M, et al: RBE values for proton beam therapy. Int J Radiat Oncol Biol Phys 53:407-421, 2002
8. Hellman S, Hellman DS: Of mice but not men: Problems of the randomized clinical trial. N Engl J Med 324:1585-1589, 1991
9. Goitein M, Jermann M: The relative costs of proton and x-ray radiation therapy. Clin Oncol 15:S37-S50, 2003
10. Schrag D: The price tag on progress: Chemotherapy for colorectal cancer. N Engl J Med 351:317-319, 2004

Acknowledgment

We thank H.D. Suit, MD, DPhil, for valuable discussions concerning the subject matter of this article.