

Protons and Parachutes

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Thirty-three years ago the first patient was treated with fractionated proton radiation therapy at the Harvard University Cyclotron by a group from the Massachusetts General Hospital (Boston, MA).¹ The argument for protons was at that time fairly compelling, given that the technical delivery of radiation therapy was crude by today's standards. However since that time, the delivery of x-ray treatments has become much more sophisticated and we are able to produce far improved dose distributions that theoretically should produce a clinical benefit. Over the course of the three decades since protons were first used, what clinical information do we have to suggest that protons add a clinical advantage over high quality x-ray therapy for any of the common adult solid tumors?

The argument has been made recently in the *Journal of Clinical Oncology* (Goitein et al²) that randomized clinical trials are not necessary because of the clear advantage in dose distribution, which therefore "must" produce a better clinical result. The question of the need for randomized trials is one that arises in the use of much new technology, and has been discussed in other sources related to protons.^{3,4} At times, a straw man argument has been constructed to suggest that randomized trials are not needed, and then nicely torn down—but what has been destroyed is only the straw man, not reality.

Radiation dose distributions are a model for clinical reality; they are not clinical reality. Models usually predict outcomes effectively when they are used to predict situations within the realm from which the models were derived (ie, interpolated from the data). The use of those models to predict outcomes extrapolated beyond the range of the initial data, produces answers that are much more suspect.

Some individuals have made fun of the possible use of randomized clinical trials for technology assessment. An article written a few years ago asked why we do not perform randomized trials of the value of parachutes compared with free falling from airplanes.⁵ It is clearly ludicrous to perform randomized trials of parachutes. I am not an expert on parachutes (to say the least), but I can make a pretty good guess as to what parachute makers do. I imagine that they do mathematical calculations based on their physics and engineering knowledge, develop a design that they retest against the mathematical model, and that they then build test parachutes. These they probably test in a model that is even closer to the daily situation by using simulators, and then perhaps they throw a 70-kg dummy out of an airplane to determine how the parachute functions. They likely measure many parameters such as drag, and so on, against existing parachute designs. I am pretty confident that they do not just take their engineering models, build a parachute, and sell it to the public. They do not do randomized trials, but they come close.

With protons we are at the level of the initial parachute construction. There are virtually no clinical studies (only mathematical models) that even suggest an advantage to the use of protons for most adult solid tumors. When intensity-modulated radiation therapy, also a somewhat controversial new technology, was initiated about 15 years ago, a substantial number of studies were done that strongly suggested a decrease in clinical toxicity in diseases such as prostate cancer, and head and neck cancer. Randomized clinical trials were generally not performed, but at least there was solid phase II data that gave a strong indication of decreased adverse effects. Those data simply do not exist for protons after more than 30 years of use.

It is difficult to perform randomized phase III trials of an expensive new technology, given that the expensive equipment must be purchased up front; if the technology does not produce a benefit, then the purchaser is stuck with a huge financial burden. The health care system in the United States does not produce an easy way around that problem. In addition, it is not feasible or reasonable in a phase III study to evaluate formally every minor technical alteration of a therapeutic approach. However, that does not mean that phase III trials should not be done when possible, and in most situations at least some randomized trials can be performed. The idea that it is unethical to perform randomized trials is absurd. There are few situations where we have compelling enough data from phase II studies to state that we should not perform a randomized study, and the proton situation is certainly not one such situation. Clearly, there are unexpected effects with the use of protons that could result in a randomized trial with an outcome that not only is not positive, but that in fact could show a disadvantage to protons. If we cannot perform phase III studies, as an absolute minimum there needs to be compelling data arising from well-designed and extensive phase II studies; however, for protons, those compelling phase II data do not exist for common adult tumors. I am not a believer that everything can, or should, be tested in phase III trials. But I am a firm believer that strong and convincing clinical data are needed for the use of clinical interventions.

Can we believe the mathematical models? It is what we do not know that is likely to get us into trouble, but even from what we do know, would we predict that protons would be superior for some common diseases? What about prostate cancer? Sophisticated x-ray therapy at present produces few acute adverse effects, and the adverse effects that do occur generally are related to the immediate proximity of the rectal wall (which cannot be avoided with protons), and the presence of the urethra in the radiation field. Given that the urethra goes directly through the prostate, the urethra also will not be avoided with protons. What about head and neck cancer? Low-energy x-rays

are almost ideally suited for treatment of the neck in that they have skin-sparing effects while treating to full dose the nodes just below the skin. Proton dose distributions cannot accomplish this, and would likely produce either more skin toxicity or poorer nodal tumor control. The presence of tissue heterogeneities, air cavities, and bone produce only a small effect with x-rays, but can have a large effect with protons and result in decreased tumor dose or increased normal tissue dose.

It is worth noting that in the discussion of randomized trials of protons, the argument was not made that in a few specific situations the models and the logic for the use of protons was so compelling that randomized trials should not be performed. Rather, the argument was made that *no* randomized trials need to be performed at all. If this is not what was meant, then one needs to specify what parameters define the situation in which no randomized trials are needed, and that obviously suggests that in other situations randomized trials would be appropriate.

Of course, as others have correctly stated, much of this discussion is about money. Proton facilities are much more expensive than x-ray facilities, and even very optimistic projections of the cost of protons suggest that they would be twice as expensive to use as x-rays. Institutions are installing proton machines because they are extremely well reimbursed. However, to justify this increased expense there needs to be *some* evidence for a benefit, and an expensive technology should

have higher standards of benefit than a technology with minimal costs. Phase III trials are always much preferred, but in some situations they are not needed and in other situations they are not feasible. However, at a minimum, high-quality phase II studies are needed to show a strong likelihood of a benefit to an expensive intervention. It is hard for me to imagine that after more than 30 years of clinical use, it would not be more apparent at present if there truly were a major advantage to using protons to treat common solid tumors. Perhaps those individuals who think otherwise would be happy to jump out of an airplane with a parachute that is based on a mathematical model, but was never tested.

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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