Costs and benefits of particle-beam therapies

Just over 13 years ago, an article entitled "Treating cancer with protons" by Michael Goitein, Tony Lomax, and Eros Pedroni appeared in PHYSICS TODAY (September 2002, page 45). At that time there were three or four hospital-based proton-beam facilities in the US. Today there are about a dozen, with perhaps a half dozen more in the planning stage. Because more than 100 000 patients have undergone proton-beam therapy (PBT), one might assume that a case has been made for that expensive and complex treatment modality, in the form of longer survival times and lower levels of radiation-induced toxicities compared with those routinely obtained with modern x-ray-based systems.

Unfortunately, that case has not been made. Currently, for the vast majority of cancers, the clinical outcomes of PBT are indistinguishable from those of its main competitor—intensity-modulated radiation therapy (IMRT), which is computer controlled and x-ray based. Therefore, the question persists: With costs of $40 million for installing a PBT treatment room and $32 000 for a typical treatment versus $5 million to install an IMRT room and $19 000 for a typical treatment, why are hospitals so eager to join the PBT club? One suggestion is that for the same patients treated, a PBT facility can generate far greater financial returns than an x-ray therapy facility.

The Issues and Events piece by David Kramer (PHYSICS TODAY, June 2015, page 24) about carbon-ion therapy (CIT) brings to mind our experience with PBT. Indeed, the arguments for CIT parallel the early ones presented for PBT. Another round of particle accelerators no longer in great demand for nuclear-physics research became available to radiation biologists, medical physicists, and oncologists. Mainly because the dose distributions for carbon ions are a tad more tightly defined than those for protons, Bleddyn Jones[1] and others have argued that curative tumor doses could be delivered while generating even lower levels of radiation-induced toxicities. The first cancer patients to undergo CIT at the GSI Helmholtz Centre for Heavy Ion Research in Darmstadt, Germany, started receiving treatment in 1997; patients continue to receive CIT at the upgraded facility in Heidelberg.

Although from the beginning the pragmatists among the radiation oncology community thought it unlikely that CIT would produce survival and toxicity levels even 5% better than IMRT, it also seemed reasonable that research at the existing facilities be pursued until it was supported or overwhelmed by cost–benefit analyses. As the capital costs for a CIT facility are at least 60 times those for an IMRT facility, to say nothing of far higher operating costs, the benefits of CIT would have to be incredibly large to approach those for IMRT.

The most reliable way to determine the efficacy of one treatment modality compared with another is the prospective randomized controlled trial (RCT) in which patients with the same and similarly staged disease and the same performance status are randomly assigned to receive either the experimental or reference treatment. RCTs are expensive to carry out, and depending on the end points and rates of patient accrual, they can take years to complete. No RCTs have compared CIT with any other commonly used radiation modality, and judging from the history of PBT, it seems unlikely that any ever will be carried out. Current clinical reports for disease sites considered amenable to CIT suffer from small numbers of patients, show survival times comparable to those obtained by other treatment modalities, and may suffer from patient-selection bias. Presently, no statistically significant clinical data support CIT's role in the treatment of cancer. Nevertheless, plans are being developed for an up-to-date CIT facility, using superconducting magnets, to be built in the US. The logic behind that endeavor is elusive.

While the debate about the merits of PBT and CIT continues, we should bear in mind that regardless of whether a primary tumor is surgically resected or sterilized by ionizing radiations, about 90% of cancer deaths are caused by metastatic disease. Currently, metastases are most effectively treated with systemic agents—that is, chemotherapy. Although radiation may be used to palliate the symptoms of specific metastases, that application hardly calls for CIT or PBT. New surgical techniques may decrease operative mortality and morbidity but are unlikely to increase disease-specific survival. Likewise, more precisely defined dose distributions may lower the doses to normal tissues and thereby encourage the delivery of more aggressive tumor doses. However, years of experience make it clear that the delivery of tumor doses greater than those generally accepted as clinically efficacious is fraught with the dangers of local organ toxicity and long-term morbidities.

We don't mean to suggest that the role of ionizing radiation in cancer therapy has reached a plateau. Far more promising clinical trials are under way than those that use beams of charged particles. For example, irradiated tumors release tumor antigens, which in sufficient numbers could attack metastases. Interestingly, the addition of various growth factors at the time of irradiation enhances antigen production. The longtime goal of priming the immune system to attack the patient's own cancer may be at hand.

Curing cancer is a complex biological problem to be solved by biologists. The design and construction of a carbon-ion accelerator that mimics the geometric aspects of an IMRT system is indeed a technical achievement, but one that doesn't warrant repetition until the clinical results of the current CIT facilities can justify their costs.

Reference

1. B. Jones, *Br. J. Radiol.* **79**, 24 (2006).

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