exquisitely targeted, so the number of treatments required per patient has dropped. Indeed, a CIT single-dose clinical trial for lung cancer is ongoing at the NIRS. Reducing treatment number and overall duration will dramatically contain costs.

Delaying construction of CIT facilities in the US until clinical results from existing facilities justify costs is not supported by the arguments in Schulz and Kagan's letter. Facility costs have dropped substantially, and highly promising clinical results warrant further investigation and independent validation. The potential for CIT to overcome the challenge of tumor radioresistance—which limits the efficacy of photon and proton therapies—whether by overcoming hypoxia or by overcoming the genetic mechanisms of tumor radioresistance via a truly increased relative biological effectiveness is not just marginal enhancements as described by Schulz and Kagan. Furthermore, the potential for CIT plus immunotherapy, reduced adverse normal tissue responses, and improved quality of life after therapy are just some of the potential advantages we can expect from CIT. Academic CIT facilities with robust basic, preclinical, and clinical research capabilities are required. Such centers should be capable of implementing new engineering and physics enhancements and should be considered national resources.

We cannot emphasize this point more strongly: For those of us proposing to implement CIT, the history of justifying PBT is one of caution and a path to be avoided, not followed. And finally, CIT originated in the US. Now is the time for its return.

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Kudos to Robert Schulz and A. Robert Kagan for raising the issue of the costs and benefits of proton therapy and other forms of charged-particle radiotherapy. The topic continues to be an important one, particularly in view of the recent national political attention given to affordable health care.

As they indicate, the best way to prove efficacy of a treatment modality is to conduct a randomized controlled trial. But such trials are costly, in part because cancer can take years to develop. In lieu of those data, retrospective studies can give an indication of the promise of a clinical intervention. A recent review in *Lancet Oncology* points to a potential benefit of proton radiotherapy over conventional radiotherapy for the relatively rare cases of paranasal sinus and nasal cavity malignancies.[1]

Toward the end of their letter, Schulz and Kagan state that "about 90%" of cancer mortality is caused by metastases and that in such instances radiation is used primarily to render palliative care to the patient; it is not curative. Although cancer mortality is due primarily to metastatic disease,[2] cases ending in mortality constitute a minority of all cancer diagnoses. To focus only on those cases is misleading and pessimistic. The five-year survival rate for all cancer diagnoses[3] is 64%. In the majority of cancer diagnoses, the patient goes on to live a cancer-free, or cancer-controlled,[4] life for at least five years, and radiation, including proton-beam therapy, often plays a crucial role in the outcome.

The discussion of what society is willing to pay to treat its cancer patients is a needed one. However, to focus only on the terminal, metastatic cases misses the big picture of how the disease is currently diagnosed and treated.

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▶ **Schulz replies:** Let's face reality. Radiation therapy is now entering its second century, and despite phenomenal gains in its technology, in many cases it still plays second fiddle to the surgeon's scalpel. Its role is often crucial, but, like surgery, its impact on clinical outcomes is fast approaching a plateau beyond which future improvements in relative survival will be measured in single digits.

The most important technical advances in radiation therapy have dealt with the generation of dose distributions. The goal is to concentrate dose to the tumor while minimizing it to surrounding normal tissues, thus enhancing the therapeutic ratio and reducing treatment-induced morbidities. No doubt, beams of charged particles come closer to achieving that goal than do high-energy x rays; however, the differences are usually small and the results from x rays clinically acceptable.

The only way to prove that carbon-ion therapy (CIT) is superior to intensity-modulated radiation therapy (IMRT) is by rigorously controlled, randomized clinical trials that would take between 5 and 10 years to yield statistically significant results. Let's suppose that for four or five of the most common cancers, CIT yields relative five-year survival rates that are 15% higher than those for IMRT. What do we do? There are perhaps a half million patients per year in the US. Let's be optimistic and accept that each CIT facility can treat 5000 patients per year. One hundred CIT facilities would cost on the order of $20 billion and, even with the most favorable politics, take 10 years to assemble. That is a highly unrealistic scenario.

I am as intrigued as the next physicist by the gadgetry of particle-beam therapy, but cancer is a biological problem, and its ultimate cure will be provided by biologists and physicians with specific expertise in genetics, molecular biology, immunotherapy, and related fields. The pace of present-day research suggests that soon there will be other drug therapies; indeed, those currently in clinical trials are yielding promising results for pancreatic cancer and metastatic melanoma, two of the most deadly cancers. On the practical side, new drugs, as they are developed, can be readily provided to patients in all parts of our country. Whereas with CIT the patient has to travel to a center, with drug therapy the treatment can travel to the patient, without the pouring of a single ton of concrete or the precision machining of waveguides and superconducting magnets.

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