opposition to Cold War nuclear weapons testing. Moreover, misguided radiophobia tends to traumatize individuals who begin to fear natural radiation despite our ordinary daily exposure.

Inasmuch as the average dose of any substance does not determine average risk, particular care should be taken not to give credibility to the "ecological" or "collective-dose" fallacy. Simply put, a one-time dose of 400 aspirins can cause an individual's death, but that does not mean, in a group of 400 people taking one aspirin a day, one person will die. That logic fallacy is all too common among those who have excessive fear of radiation.

Investigative committees have acknowledged that nobody outside the reactor is likely to have died prematurely as a result of the accident. Under the umbrella of the Chernobyl Forum and World Health Organization, the conclusions are identical. There's no palpable evidence of statistically increased mortality—including thyroid cancer—from the spread of Chernobyl's radiation. Confusion about Chernobyl has arisen because many thousands of people in the affected areas of the former Soviet Union have since died of natural causes. Also, local residents were misled by media-induced expectations of ill health attributable to radiation exposure.

The most expensive and harmful action in response to Chernobyl was the displacement of more than 300 000 people from contaminated regions, where the radiation dose from fallout was about twice the natural dose. The evacuation led to mass psychosomatic disturbances, great economic loss, and serious social consequences to the populations of Belarus, Russia, and Ukraine. For rural areas of the former Soviet Union, preventive, diagnostic, and curative treatments were not as routine as in the West. Better medical attention, diagnosis, and treatment since then have resulted in significantly improved detection of latent thyroid cancers at early, often treatable stages. The low rate of actual correlative fatalities is partly because of post-accident remedial action and health care.

Of course, the relatively limited medical impact of the Chernobyl accident does not warrant any reduction in nuclear safety or public vigilance. Nor does it discount the very real and frightful psychological and economic trauma experienced by nearby inhabitants, as Toni Feder, author of the PHYSICS TODAY piece, compassionately described.

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On the value of carbon-ion therapy

In PHYSICS TODAY's October 2015 Readers' Forum (page 8), Robert Schulz and A. Robert Kagan take the stance that there is no justification, in terms of cost

or clinical benefit, for the development of carbon-ion therapy (CIT). Schulz and Kagan argue that the case for using proton-beam therapy (PBT) over intensity-modulated radiation therapy (IMRT) has not been made, and they then extrapolate that to CIT.

Comparing PBT to IMRT is inappropriate. Comparing intensity-modulated proton therapy to IMRT would provide more insight. Early adopters of proton therapy used passive scattering methods for dose delivery; they did not have the capability for intensity-modulated protons that they do now. Indeed, PBT clinical trials with scanning beams and better tumor localization via *in vivo* computed tomography imaging are ongoing. Yet centers with such systems are finding it difficult to overcome the mind-set, based on earlier, inappropriate comparisons, that questions the value of PBT.

Schulz and Kagan indicate that PBT is the result of physicists who were bored with cyclotron technology and that CIT is more of the same. They mention the start of CIT at the GSI Helmholtz Centre for Heavy Ion Research in Germany in 1997, yet they miss the initial clinical trials with heavy charged particles that included helium, carbon, and neon at the Lawrence Berkeley Laboratory between 1977 and 1992 and the earlier work at the National Institute of Radiological Sciences in Japan. The NIRS started CIT clinical trials in 1994 based upon the results of the Berkeley trials. The NIRS has now treated more patients by far than any other institution. Their success has led to an additional six CIT centers in Japan alone.

To suggest that clinical trials for CIT will probably never be carried out belies the truth; the NIRS and other CIT institutions in Japan have set up the Japan Carbon Ion Radiation Oncology Study Group to conduct clinical trials. The Heidelberg and Marburg Ion-Beam Therapy Centers in Germany and the National Center of Oncological Hadrontherapy in Italy run clinical trials. In the US, the National Cancer Institute (NCI) has taken steps to develop CIT research institutes through two exploratory grants. After the impressive early results seen at the NIRS, the NCI is funding a clinical trial of IMRT versus CIT for pancreatic cancer, to be conducted in Shanghai, China, in collaboration with Albert Einstein College of Medicine.

The authors also argue that the cost does not justify the benefit; they use the example of PBT and extrapolate it to CIT. Construction of a PBT facility no longer requires government support. Yes, the up-front cost is higher for PBT or CIT than for IMRT, but a PBT or CIT facility can be amortized over 25–30 years as opposed to the 7–10 years for IMRT.

The 60-fold cost difference that Schulz and Kagan claim is just not credible. A recently constructed Japanese CIT facility with four treatment rooms cost approximately $100 million compared with $10 million to equip four rooms for IMRT. Furthermore, in 2014 the anticancer drugs bevacizumab and cetuximab cost $9324 and $20 856, respectively, for a single eight-week cycle, and bevacizumab sales were more than $6.8 billion. If Medicare and insurance or other payers allow an expenditure of $250 000 for a cancer therapy that extends life by 12 months, how can one lament a therapy that will be in line with or less than some medical oncology charges (the NIRS charges $30 000 for CIT therapy)? There is no reimbursement rate in the US for CIT; however, CIT therapy is highly effective and can be

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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