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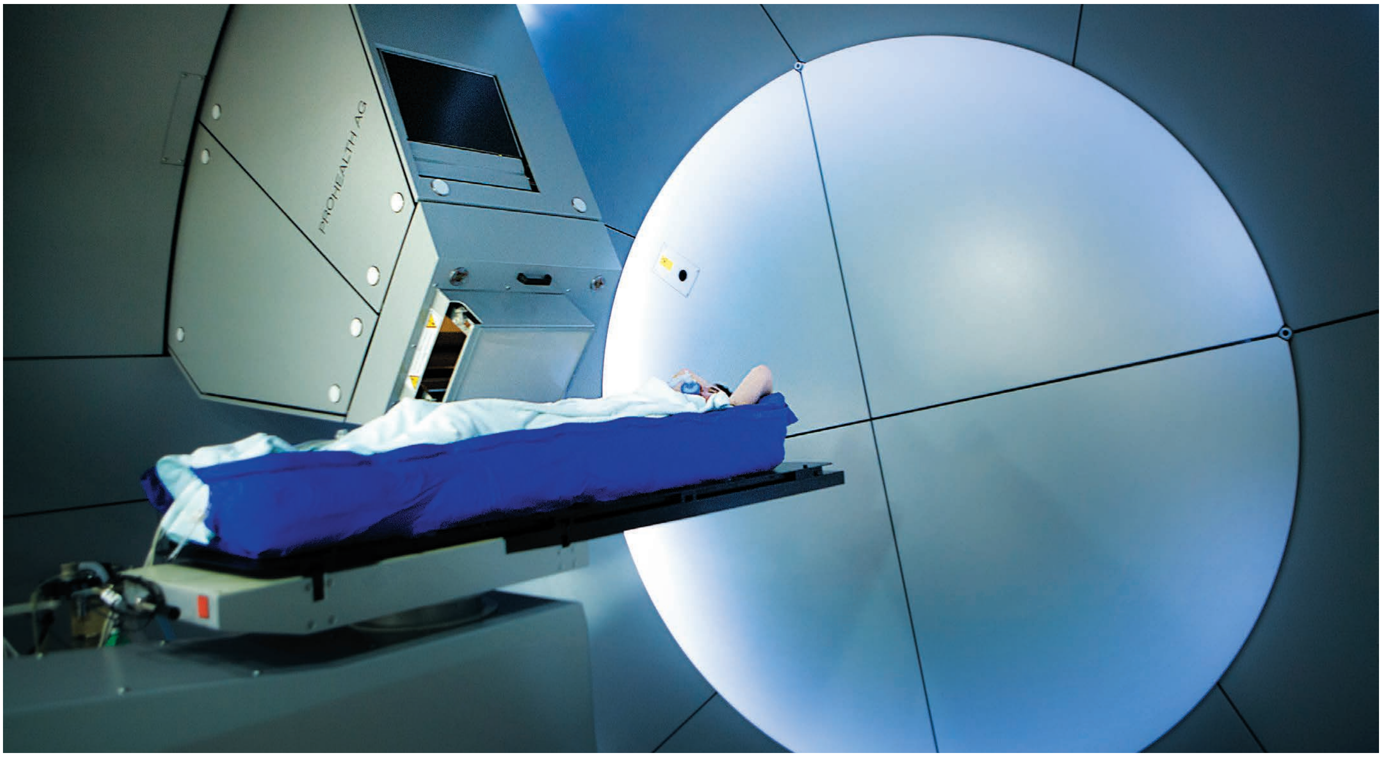


A proton-therapy machine at the Rinecker Proton Therapy Center in Munich, Germany.

Three ways to make proton therapy affordable

Shrink accelerators, sharpen beams and broaden health-care coverage so more people can get this type of radiation treatment, argue **Thomas R. Bortfeld** and **Jay S. Loeffler**.

If cost was not an issue, proton therapy would be the treatment of choice for most patients with localized tumours. Protons can be targeted more precisely than X-rays[1], so the tissues around the tumour receive two to three times less radiation. This lowers the chance of causing secondary tumours[2] or impairing white blood cells and the immune system[3]. High doses of protons can be delivered safely to hard-to-treat tumours: for instance, those at the base of the skull or in the liver. Such accuracy is crucial when treating cancers in children.

Yet most hospitals do not offer proton therapy. The equipment is huge and expensive. Housed in multistorey buildings with halls the size of tennis courts, one proton centre with 2–3 treatment rooms typically costs more than US$100 million to build. To reach deep-seated tumours, the protons must be sped up to 60% of the speed of light (a kinetic energy of 235 megaelectronvolts; MeV) using a particle accelerator, such as a cyclotron or synchrotron. Rotatable gantries with wheels typically 10 metres across and weighing 100–200 tonnes direct the protons at the patient from a range of angles. Concrete shields, metres thick, are necessary to block stray neutrons.

"Nothing so big and so useless has ever been discovered in medicine," said Amitabh Chandra, director of health policy research at the John F. Kennedy School of Government at Harvard University in Cambridge, Massachusetts. He has compared a proton-therapy system to the Death Star from *Star Wars*.

Nonetheless, there are now more than 60 proton-therapy centres around the world, ▸

with 26 in the United States alone. Almost half of them (12) treated their first patient within the past three years. But construction delays and closures are also common. The companies that build the facilities and the investment groups that own them are increasingly struggling to make a profit. The Scripps Proton Therapy Center in San Diego, California, filed for bankruptcy in March, just three years after opening its doors.

What has gone wrong? Patient charges are high, often three to four times more than the priciest X-ray treatments. Fewer patients are being treated with protons than was anticipated: common diseases such as prostate cancer can be cured as effectively using other forms of radiation and surgery[4]. And in the United States, major insurance companies are denying proton therapy to up to 30% of eligible patients[5] on the basis that there are too few rigorously designed and completed clinical trials providing evidence of better outcomes. In our experience, however, this is a vicious cycle: such trials are difficult to conduct when patients are denied private health coverage[5].

> *"Sharpening the spot of the proton beam gives it the precision of a scalpel."*

The solution is to make proton-therapy facilities smaller and cheaper, with costs of around \$5 million to \$10 million, similar to high-end X-ray systems. A dozen 'miniaturized' facilities are in operation. We have installed one at Massachusetts General Hospital in Boston. Now academics, private researchers and investors need to make proton-therapy systems even smaller and more competitive so that more patients can benefit.

SHRINKING INFRASTRUCTURE

Proton-therapy technology is much more compact today than it was a few decades ago[6]. Superconducting magnets can confine protons in a tighter space. The weight of accelerators has gone down from hundreds of tonnes to less than 20, and their diameters have shrunk by a factor of 3 since the early 1990s. The smallest therapeutic accelerator so far is less than 2 metres in diameter — about the same footprint as a king-sized bed.

Yet, combined with the gantry and other equipment needed, even the most compact systems for sale today occupy a couple of hundred square metres. This is much larger than a conventional treatment room of 50 square metres. Most hospitals lack the money and space to construct a special building for proton therapy.

We have been testing how smaller systems can be squeezed into existing hospital buildings, working with the proton-technology vendor ProTom International in Wakefield, Massachusetts, and engineers at the Massachusetts Institute of Technology in Cambridge. Getting an accelerator and gantry into two basement X-ray rooms in our central Boston hospital cost about \$30 million, less than one-third of the cost of a dedicated centre but still about five times more than a top-end X-ray unit.

Both the equipment and the price tag need to shrink further if proton therapy is to replace X-rays. Fitting the facility into one room is the goal. This would allow hospitals to simply replace existing X-ray equipment with proton units without building work. Getting there will be technically challenging, even with rapid advances in magnets[6].

Gantries might need to have a smaller range of movement or be abandoned altogether[7]. Moving the patient relative to the beam is easier: fixed beams and a rotating chair were used in particle therapy before the 1990s. But it is difficult to position the patient accurately and repeatedly.

Three developments that have emerged in the past three years hold promise. Narrow 'pencil' beams that paint the radiation dose precisely onto a tumour reduce the need to treat patients from many angles (see 'Clinical benefits'). Rapid imaging methods can detect tiny changes in the patient's position, so that the beam can be shifted. And advanced 'soft robotics' built using malleable outer materials will soon allow patients to be positioned quickly and comfortably using robotic hands.

Pushing affordable proton technology forwards will require combined efforts from device companies, venture capitalists, academics and medical practitioners. But these groups currently work in silos. Most technology development is left to industry. Hospitals buy off-the-shelf and do not actively seek input from researchers. Only a few national labs in different countries work on technologies related to proton therapy. There are plans for a medical-research beamline at CERN, Europe's particle-physics lab near Geneva, Switzerland. But, overall, there has been little work in universities with the clear goal of improving the affordability and clinical utility of proton-therapy systems.

CLINICAL UTILITY

Although the utilization of proton therapy is growing, the gap between the number of patients receiving the treatment and those who could potentially benefit from it is still substantial (see 'Unmet need')[8]. The primary reason is cost; availability is another barrier, as are a lack of knowledge of the therapy's benefits and difficulties referring patients.

As technology improves, the number of patients who could benefit clinically from proton therapy will rise, too. The therapy is not like a pill: its success depends on how it is delivered. It has more room for improvement than other, more-established radiation treatments, such as X-rays. Developing proton therapy's physical advantages — in particular its ability to focus and thus lower the overspill of radiation — would make it the best treatment for most patients who need radiation therapy. In some cases, it might outperform surgery.

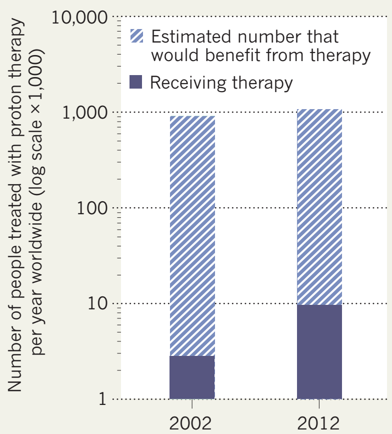
Sharpening the spot of the proton beam gives it the precision of a scalpel. Unlike X-ray photons, fast protons entering the patient are slowed because they interact with body tissues. Most of the beam's energy is deposited at a point (called the Bragg peak). The speed of the proton, or its kinetic energy, determines the depth at which the spot reaches below the skin. Protons with energies of around 50 MeV penetrate to a depth of a few centimetres; those at more than 200 MeV reach 30 cm. Uncertainties in this slowing process can affect whether the dose spot hits the tumour as intended, or overshoots into healthy organs.

Better imaging methods are needed to locate and guide the proton spot. Its position is currently known to within only 0.5 cm. This is similar to X-rays but blurs the radiation dose, making it impossible to stop the beam precisely in front of crucial structures such as the spinal cord. Improving the accuracy and precision from centimetres to millimetres is necessary. This is a particular challenge when targeting moving tumours, such as those in the lung and liver. Higher accuracy would mean that smaller margins would need to be irradiated around tumours — overshoot is the standard way to deal with uncertainties. This would transform treatments for lung cancer, for example, in which proton therapy does not yet show a substantial physical advantage over X-rays.

Several methods for measuring the range of the proton spot have been explored[9]. When protons interact with atomic nuclei, they give off γ-rays that can be tracked.

UNMET NEED

Many more patients might benefit from proton therapy than currently receive it, despite the growing number of facilities.



SOURCES: HTTP://PTCOG.CH (SOLID BARS); REF. 8 AND M.-L. YAP ET AL. J. GLOB. ONCOL. 2, 207–215; 2016 (HATCHED BARS).

Sound waves are also given off when tissues expand and contract as they are heated by pulses of protons. Such techniques have reached accuracies of a few millimetres in experimental settings, but do not yet have the millimetre accuracy needed for use in patients. The technical hurdles are surmountable but require more concerted efforts, both public and private.

HEALTH-CARE POLICY

The high cost of proton therapy means that most countries and insurers restrict its use. England and several European nations, including Denmark and the Netherlands, offer proton therapy only for cancer types for which the reduction of long-term side effects is thought to be greatest, such as tumours in the skull base (chordoma and chondrosarcoma), in the eyes (melanoma) and many tumours in children. In 2014, the American Society for Therapeutic Radiation Oncology (ASTRO) released a list of diagnoses that its experts recommended insurers should cover.

But individuals and tumours vary. Sarcomas, for instance, occur in many different forms and sites. The benefit of proton treatment depends on tumour size, shape and proximity to organs. People with breast cancer are not on the ASTRO list. But those with a tumour on their left breast might benefit because proton therapy could help to spare the heart from radiation damage[3].

The Netherlands has taken a step in the right direction, using individual treatment plans and a biological model of complications in normal tissues to select patients who stand to benefit most from proton therapy. But the probabilities of side effects predicted by biological dose–response models are uncertain. The models consider only severe complications, such as blindness, which are rare. They do not consider more common aspects such as a reduced IQ score in children, for instance.

In the United States, several hospitals have tried to recoup the costs of proton centres by focusing on common and easy-to-treat tumours such as prostate cancer. Insurers are reluctant to cover such treatment, but many wealthy men pay for themselves. So the most common cancer treated with protons is one in which it makes the least clinical difference.

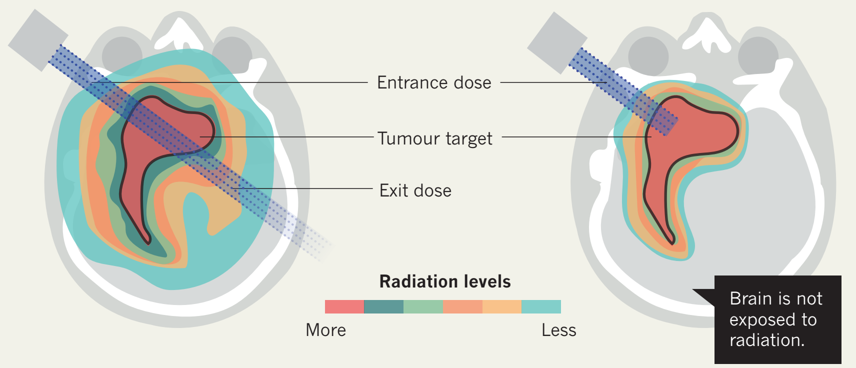
Because there are relatively few proton centres, patients must be referred to them from other hospitals. But many oncologists are unaware of what the therapy can do, and local, private physicians and hospitals fear losing revenue if their patients are treated elsewhere. Patients, too, are loath to travel long distances, sometimes between countries. As a consequence, too few patients are referred.

Sweden has improved these logistics. Since 2015, its proton centre in Uppsala has been run as a shared facility for all major hospitals in the country. Physicians and staff at the referring hospitals are involved in planning and in the treatment of their patients in Uppsala, and uptake has improved. This centralized approach might not work as well in a larger country. The United States will face its first test in 2019, when a proton centre will open in Manhattan that will be shared among a consortium of hospitals.

Greater use raises another problem. The specialized personnel needed are in short supply. One solution is to make the workflow of proton therapy similar to that of conventional X-ray therapy. Another is to rely more on automation, in particular for systems that guide treatment planners on the basis of knowledge pooled from experts.

CLINICAL BENEFITS

Beams of protons can be more tightly focused than beams of X-rays, killing cancer cells while sparing more of the surrounding tissue. This is beneficial for isolated tumours near sensitive parts of the body, such as the spinal cord and brain.



CONVENTIONAL RADIATION THERAPY
Beam passes through the patient, resulting in healthy cells being damaged by the beam.

PROTON THERAPY
Protons can be tuned to stop at the depth of the tumour and release their energy. Fewer healthy cells are exposed.

SOURCE: DOSE LEVELS FROM FIG. 1A, A. J. LOMAX *ET AL.* *RADIOTHER ONCOL.* **51**, 257–271 (1999)

NEXT STEPS

Partnerships are needed to make proton-therapy technology more practically useful. Hospitals must share knowledge about treating and interacting with patients as well as using therapy systems. Applied physicists and engineers in academia and at national and international labs should work with medical physicists on improving the beams, imaging and robotics. For example, a CERN spin-off company called ADAM (Application of Detectors and Accelerators to Medicine), based in Geneva, is working with its parent institution in the United Kingdom on a linear mini-accelerator for medicine. National physics and engineering societies and funding agencies should coordinate some of this research and publicize needs and progress.

As costs fall, the charges for proton therapy should be lowered to the level of sophisticated X-ray therapy within the next five to ten years. Insurance companies should move to the 'reference pricing' model, which establishes a common level of payment for different therapies that have similar anticipated outcomes[10]. This will help to build the evidence for the benefit of proton therapy (or lack of it) in new clinical applications. The Mayo Clinic in Rochester, Minnesota, has already entered into such arrangements with insurers. Collaborations between hospitals and health-care funders on a broader scale are needed[5].

To get the ball rolling, these ideas could be discussed at the upcoming Particle Therapy Co-Operative Group meeting in May 2018. The European and American societies for radiation oncology should be involved. Symposia or satellite workshops should be organized to discuss the technical questions at meetings of the American Physical Society and Physics for Health in Europe. ■

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