

Carbon-ion cancer therapy shows promise

Radiation-resistant tumors are targets for heavy-ion particles. But high capital costs have prevented construction of treatment facilities in the US.

Particle beams offer benefits over conventional photon radiation for the treatment of many tumors. Currently, 49 facilities worldwide—including 14 in the US—are producing proton beams, and another 29 are under construction. But carbon-ion therapy, which can benefit patients with deep-seated or radiation-resistant tumors, remains in relative infancy, with eight centers operating and four under construction as of 1 April.

Through 2013, a total of 105 000 patients had been treated with proton beams, according to the Particle Therapy Co-Operative Group (<http://theijpt.org/doi/pdf/10.14338/IJPT.14-editorial-2.1>). During that time, around 13 000 had undergone carbon-ion therapy.

Proton and carbon-ion beams share certain advantages over conventional radiation therapies. (For more on proton therapy, see the article by Michael Goitein, Tony Lomax, and Eros Pedroni, *PHYSICS TODAY*, September 2002, page 45.) Charged particles lose most of their energy all at once at the end point of their transit. That phenomenon, known as the Bragg peak, allows a beam to be precisely tailored to the shape and depth of the tumor and leave the healthy tissue in front of the tumor largely unscathed, says Eric Colby, a physicist in the US Department of Energy's Office of Science. Because the particles are halted in the tumor, proton and carbon-ion therapies also minimize the exit dose that damages healthy tissues beyond the tumor. Photons, such as gamma rays and x rays, continue past the tumor and cause peripheral damage.

Compared with protons, however, the heavier carbon ions deposit more energy in the tumor tissue, so they are considerably more destructive to the tumor. Moreover, "the lesions . . . you produce are predominantly double-strand breaks [to DNA] that can hardly be repaired," says Thomas Haberer, scientific and technical director of Germany's Heidelberg Ion-Beam Therapy Center (HIT), which began using carbon ions to treat patients in 2009. Since cells have mechanisms to repair single-strand DNA breaks, damage to both strands is required to ensure lethality. By one measure, known as the

relative biological effect, carbon ions are up to three times as damaging to DNA as x rays, while protons are only modestly more lethal to the tumor than is radiation, notes James Deye, a physicist with the National Cancer Institute (NCI).

Heavier ions also require fewer treatment sessions. For liver cancer, for example, the full dose requires 30 treatment days of proton therapy. With carbon, just four days are needed, says Haberer. At HIT, both proton and carbon-ion treatments of certain brain tumors and tumors at the base of the skull have achieved an impressive five-year survival rate of 90%. But with carbon, "we typically spare the organs at risk, the brain stem and critical regions," he says. One recent trial at Japan's National Institute of Radiological Sciences (NIRS) showed a two-year survival rate of 48% for locally advanced pancreatic cancer treated with chemotherapy and carbon ions. That compares with 10–20% from a combination of radiation and chemotherapy.

In another trial, involving 185 patients with inoperable chordoma, NIRS achieved an 85% five-year survival rate when patients were treated with carbon ions, compared with 82% for patients who had their tumors surgically removed and were treated with protons. The results were presented by Tadashi Kamada, research director for charged particle therapy at NIRS, at a conference hosted by the University of Texas Southwestern Medical Center (UTSW) last November.

Beam delivery challenges

Carbon ions also have been effective in treating prostate, liver, recurrent rectal, and lung cancers, and for advanced bone and soft tissue sarcomas that are known to be radiation resistant, according to Kamada. Colby estimates that around 60 carbon-ion centers could accommodate the global demand for



HEIDELBERG ION-BEAM THERAPY CENTER

A 670-ton gantry at the Heidelberg Ion-Beam Therapy Center provides 360° rotation for carbon-ion beams to be aimed precisely at a patient's tumor. The treatment room (not visible) is located in the upper left-hand corner. The magnets (orange) used to direct the beams rotate on an axis perpendicular to the V-shaped stand.

the "most rigorously indicated" cancers. Perhaps one-third of radiotherapy patients might benefit from carbon ions, says Hak Choy, chair of radiation oncology at UTSW.

Although elements heavier than carbon could be used for therapy, they tend to cause more damage on the way to the tumor. "The sharpness of the 'scalpel' begins to dull very quickly as you move to larger nuclei," says Colby, because they tend to break up as they move through tissue. But for tumors that are very insensitive to radiotherapy, heavier oxygen ions may be desirable, says Haberer. HIT researchers are currently testing oxygen-ion beams and combinations of beams on glioblastoma cell cultures and comparing them with chemotherapy protocols.

Compared with protons, heavy ions

are much more difficult to direct to the target. Currently, HIT is the world's only carbon-ion facility with a beam that can be rotated 360°. Accommodating the large magnets needed to bend the ion beams—carbon beams are almost three times as difficult to bend as protons—required HIT to build an enormous gantry weighing 670 tons (see photo on page 24). Lighter-weight gantries are common at proton-beam centers; the rotational flexibility provides a full range of angles optimized to reach the targeted tumor.

"If you strap the patient to the table and move the gantry, you can get sub-millimeter accuracy to the target," says Choy. "If you move the patient around, and the patient isn't in a fixed position, the organs can move around. So the position isn't as accurate." The other seven carbon-ion centers, in Asia and Europe, have fixed horizontal or vertical beams.

A superconducting gantry system weighing less than half of HIT's is nearing completion at Japan's NIRS, where carbon-beam treatments have been performed since 1994. The number of patients treated with carbon at that facility will surpass the 10 000 mark this year, says NIRS scientist Toshiyuki Shirai. Toshiba Corp will complete installation of the four-magnet gantry in September, and another six months to a year of tests will be required before treatments begin, says Shirai.

US looks to catch up

Patients have been receiving treatment with carbon-ion beams in Japan, Germany, Italy, and China for years. But the US, despite having pioneered heavy-ion treatment at Lawrence Berkeley National Laboratory (LBNL) in clinical trials that ran from 1975 through 1992, notably lacks any treatment capability. With the recent award of four grants, two federal agencies are hoping to stimulate the establishment of at least one US heavy-ion therapy center.

In February DOE awarded a three-year, \$2 million grant to LBNL to design a superconducting beam-bending magnet. Although the first prototype will be for directing proton beams—to mitigate technical risk, says Colby—a scaled-up prototype to steer carbon ions will follow. The work should lead to carbon-ion treatment centers that are more versatile and less expensive to build than the Heidelberg facility.

The LBNL project has support from industry—Varian Particle Therapy, which builds proton therapy systems, is contributing an \$850 000 cryostat for testing the magnets. And Switzerland's

Paul Scherrer Institute, which has designed and built two generations of gantries for proton beams, is detailing one of its experts to the lab's project, says Colby.

The goal of the LBNL grant is to produce a magnet that will permit a smaller, simpler, and more capable gantry than the NIRS system, one that could be commercialized by a US company, says Colby. Only one superconducting magnet will be required, for the final bend, and it will be one-fifth the weight of the Toshiba magnets. Unlike the NIRS system, the LBNL design will permit beam adjustment during patient scanning without having to adjust the final bend; that capability will shorten treatment time.

A second DOE grant, valued at \$820 000, was awarded to MIT and ProNova Solutions, a Tennessee proton-beam supplier, for the design of an iron-free superconducting cyclotron. Nearly 60% of the world's particle-beam cancer therapy centers use cyclotrons to accelerate the ions to the required energy. An iron-free version would weigh one-sixth as much as current cyclotrons, according to DOE's announcement. ProNova Solutions is contributing employee time valued at \$405 000 to the effort.

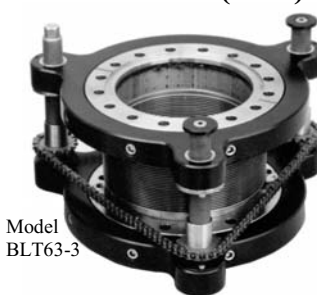
Coinciding with the DOE grants, the NCI awarded planning grants to UTSW and to the University of California, San Francisco, to help them develop plans for heavy-ion-beam research centers. The awards are each for \$1 million over two years. A consortium headed by UTSW is proposing to build a heavy-ion-beam treatment center beginning in 2017, says Choy, UTSW's principal investigator for the NCI grant project. The facility could cost as much as \$250 million, but funding sources haven't yet been identified. Choy says he's hoping to assemble financing from university, state, federal, and foundation sources.

"The grants were meant to plant a flag in the ground to show NCI's interest in this arena," says Deye. The primary focus of the NCI is on cancer research. "If a clinical facility were to be built in the US, we would like to have a research agenda." It's not entirely clear how a research program would be structured in a therapy center, he says. One possibility would be to have a beamline devoted to research in addition to others devoted to patient therapy.

Last fall, the University of Colorado, Colorado State University, and NIRS launched a \$200 000 feasibility study for a carbon-ion treatment facility to be located at the University of Colorado with an estimated cost of \$300 million.

David Kramer

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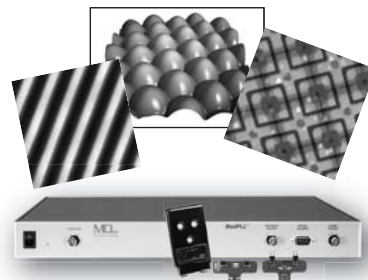
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