

In the Crosshairs of Particles: Targeting Tumors With Even Greater Precision

In the fight against cancer, the only center in Europe that offers carbon therapy is the Heidelberg University Hospital, Germany. In cooperation with GSI (Gesellschaft für Schwerionenforschung – Center for Heavy Ion Research) in Darmstadt, physicians and patients are experiencing promising results.

By Martina Lenzen-Schulte, M.D.

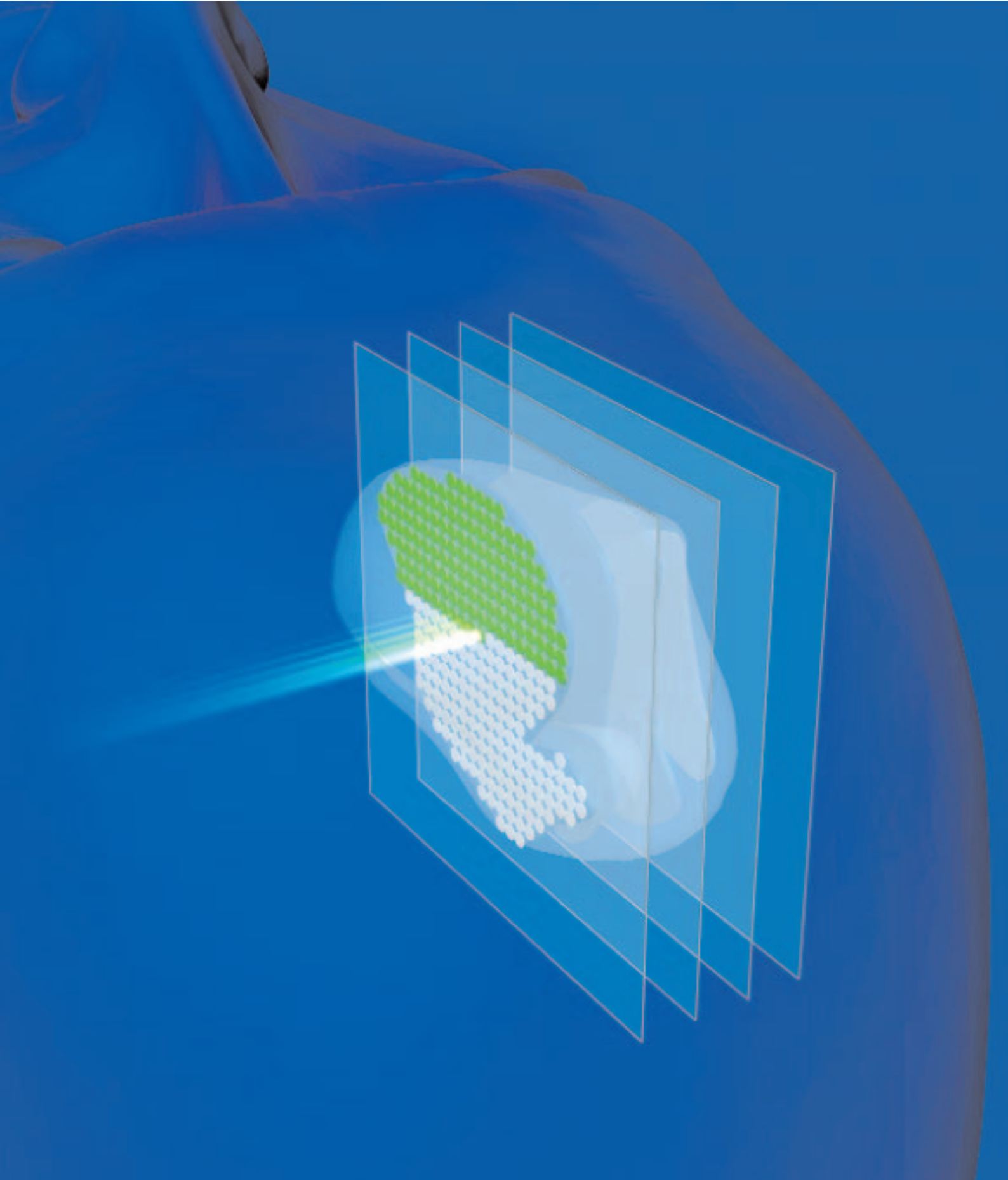
In 1987, Nobel Prize winner Allan M. Cormack was the only one of the laureates that did not talk about various successes at the yearly meeting of the laureates in Lindau, Germany. Instead, in his presentation he listed a number of shortcomings in radiation therapy. His core message was that “there is a frequent incapability of irradiating the many different forms of tumors without affecting healthy tissue as

well”. Professor Jürgen P. Debus, M.D., Head of the Department of Radiation Oncology at the University Hospital in Heidelberg, Germany, has no small part in delegating this kind of pessimism to the past.

Debus is one of the pioneers who tried to target conventional X-ray or photon radiation right at the tumor. However, the decisive milestone in the precise irradiation of malignant structures belongs to particle therapy – in other words, radiation treatment with charged ions. Optimal adjustment of photon therapy to the shape of the tumor is limited. It can be adjusted only toward the top and the bottom and to the left or right of the malignant growth. Unfortunately, however, the beam discharges its energy also in the front and the back of the malignancy. As a result, treatment of deep-seated tumors has one decisive disadvantage: healthy tissue is

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Jürgen P. Debus, M.D., Ph.D., Heidelberg University Hospital, Germany



■ CARBON ION THERAPY allows a much more precise targeting of the tumor, sparing healthy tissue.



Professor Jürgen P. Debus, M.D., Ph.D.

Jürgen Debus is the head of the Department of Radiation Oncology at the Heidelberg University Hospital, Germany. From 1984 to 1991, Debus studied medicine and physics at the University of Heidelberg. In 1991, he received his Ph.D. in physics, followed by a medical degree a year later. Between 1992 and 1996, he worked as a resident in radiation therapy at the Department for Oncological Diagnostics and Therapy of the German Cancer Research Center (DKFZ) in Heidelberg as well as at the local university hospital. As early as 1995, he was introduced to proton therapy as a Clinical Fellow at the Massachusetts General Hospital in Boston, MA, USA. In 1996 he became the assistant medical director at the Heidelberg University Hospital and in 1997 he accepted the position as head of the clinical research department, Radiation Oncology at the DKFZ.

Since October 2003, he has been the director of physicians in the Department of Radiation Oncology at the Heidelberg University Hospital.

For more than ten years, Professor Debus has been a member of the “Radiation therapy with high-speed neutrons” group at the German Cancer Research Center. For approximately the same length of time, he has been coordinating the heavy ion therapy project at GSI in Darmstadt. As a member of various committees, he is involved in standardizing radiation therapy. He has received numerous prizes and awards for his scientific work and he is best known for his instrumental role in developing innovative as well as more precise and tissue-sparing radiation approaches for treating solid tumors.

irradiated as well. Organ structures located behind the tumor receive radiation too, even though irradiation shows weaker effects than in front of the malignant growth. To compensate for these side effects, the dose applied to the actual tumor was kept as low as possible; sometimes so low that the growth of the tumor could not be brought to a halt.

Carbon Ions Are Both Effective and Tissue Sparing

Targeting ions directly to the area where they begin to deploy their main effect is much easier than with conventional radiation therapy. Charged ions do not lose a significant amount of energy on their way to the target, nor to lateral tissue. Additionally, the structures located behind the malignancy are spared as well. For the oncologists at the Heidelberg University Hospital, the highly promising carbon ions are used for therapeutic purposes in cooperation with the Gesellschaft für Schwerionenforschung (GSI) in Darmstadt. The radiation oncologists in Heidelberg have been concentrating on treating rare tumors since 1997. Among these are chordomas and chondrosarcomas. "Our most recent results from studies show clearly that the best results are obtained with carbon ions, which also cause much less damage than conventional methods," recalls Debus. Destroying the tumor tissue in 83 percent of chordomas and 100 percent of chondrosarcomas are tumor control values that could not be achieved until now. The national health insurances, meanwhile, do accept refunding of this carbon ion therapy. "We are getting referrals from all over the nation and other European countries as well," says Daniela Schulz-Ertner, M.D., who coordinates the cooperation with Darmstadt. She knows all about the inconvenience that long traveling hours impose on cancer patients. "This is why we are trying to develop a patient's individual treatment plan as quickly as possible."

Three times a year for three weeks each, the Heidelberg radiation therapists are able to use the GSI particle accelerator in Darmstadt. Treatment is usually handled on an outpatient basis, since there are rarely any side effects

»Cost effective treatment of cancer can be achieved by particle therapy.«

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aside from general tiredness. During this time, an assistant medical director, a physician in residence, and two technical assistants take care of the patients. One of their numerous assignments is to check whether the beam is directly focused on the tumor. This is highly important, because irradiation is calculated accurately to the millimeter for a fixed reference point in a three-dimensional coordinate system. Only deviations below one millimeter are considered acceptable. For irradiating subcranial tumors, the patient receives a type of individually adapted gypsum mask prior to therapy. This solid mask prevents the head from moving. It is attached to the table prior to each session.

Driving to Darmstadt is a temporary solution, since the physicians are not working with a clinical facility. "To date, we did not have to send people away," says Dr. Daniela Schulz-Ertner, "but even for rare tumors, the current capacity barely accommodates our needs." In 2007, the University Hospital of Heidelberg will be moving into its own particle therapy center. Worldwide, only two other facilities of this kind exist. Both of them, the National Institute of Radiologic Science and the Hyogo Ion Beam Medical Center, are located in Japan.

Redefining Radiation Sensibility

In Japan, more than 2 000 patients have been treated with carbon ions. And the newest publications from Chiba are noteworthy indeed. Chiba has successfully treated patients suffering from prostate cancer that metastasized and was characterized by aggressive growth and poor blood values. Yet the results obtained in Chiba are better than those achieved with surgery. This contradicts one of the dogmas in radiation therapy, because



DANIELA SCHULZ-ERTNER, M.D., attending physician of the clinical radiology department at the Heidelberg University Hospital, heads the section of heavy ion therapy and coordinates the cooperation with GSI in Darmstadt.

up to now prostate cancer was considered to be of low radiation sensitivity. Schulz-Ertner explains the paradoxical findings: "It's not just that carbon ions can be focused more accurately, it's also that they are biologically more effective on different tissues compared to conventional therapy." At many locations, carbon ions tear the base pairing of DNA apart and lead to double-strand breaks. Compared to single-strand breaks caused by conventional radiology, clustered double-strand breaks cannot easily be repaired by the cell. Tumors which previously belonged to the domain of other specialties are suddenly

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falling within the range of radiation therapy. In addition to prostate cancers, this includes brain tumors such as glioblastoma, nonsmall-cell bronchial carcinoma of the lungs, soft tissue sarcoma and even melanoma. At times, melanomas grow within the paranasal sinus. To surgically remove them at a large enough safety distance, a large part of the bony cranium viscerale would have to be removed. First observations show that it might be possible to get the remaining, non-operable tumor under control with carbon ions, an approach considered unthinkable until now.

Tailor-Made Radiation Therapy

The center planned for Heidelberg will offer a wide spectrum of particle therapies. In addition to carbon ions, proton therapy will be available as well. This is a very popular method worldwide. More than 40 000 patients have been treated with proton therapy so far and new centers are being built everywhere. Proton therapy is considered a hybrid – just like other particles, the proton particle beam can be focused precisely on the tumor – however, the biological effect of protons doesn't differ from that of photons.

A system limited to proton-only therapy is technically less complex than a combined system offering both protons and other ions. In addition, therapy planning systems considering the biological effects of carbon ions have not been commercially available. This explains why, aside from the United States, proton therapy is a popular alternative in many countries.

Debus emphasizes the research objectives of the future center: "It is our task as a university clinic to define the type of radiation therapy most suitable for both the tumor and the patient." It is well known that focusing radiation on the tumor alone is not always the best approach. If the tumor does not grow slowly within defined limits, but rather shows signs of early metastases within its environment, it is not prudent to limit radiation just to the tumor. The types of methods that will be available in the future can be derived from current treatments for adenocystic carcinoma or for tumors of the salivary gland, tumors

that seed cancer cells early on along the nerves in their immediate vicinity. These require, on the one hand, a high radiation dose to bring them under control, if at all. On the other hand, the surrounding area has to be irradiated without exceeding a certain limit. Otherwise, damage occurs in normal tissue that is subject to radiation as well. Radiation oncologists in Heidelberg combined conventional radiation therapy with a boost of carbon therapy that directly attacked resistant tumors with a high dose. The results are better than any other radiation therapy protocols so far.

Advantages for All

Experts estimate that more than 1000 patients, based on a population of 10 million inhabitants, will profit from particle therapy. For Germany alone this would mean approximately 9000 patients per year. Debus, however, advises against relying on these estimated values. Experience has shown that a narrow range of application frequently falls short of its potential. The same applies to the very high costs for carbon therapy treatments, currently they run at approximately 25000 Euro per treatment course, which he considers a temporary estimate. It is assumed that treatment costs are lower in individual cases, since fewer sessions are needed in the future than in conventional radiation therapy treatments, which continue week after week. Recently, lung cancer was successfully treated in Japan involving not more than a single session using a carbon ion beam. Short-term thinking with respect to financial calculations is addressed by Debus as well: "Unfortunately we are not in a position today to calculate savings obtained from complex treatments. However, these savings will be possible in the future." Debus refers in this instance to patients subject to tissue-sparing and successful treatments that will considerably reduce follow-up costs. As early as today, it can be proven that modern, tumor-focused treatments of head/neck malignancies reduce dental problems far more than the previous method used. Children with brain tumors that were treated with protons in the United

ENLIGHT

Five future centers for carbon ion therapy are currently being planned or are already being built in Europe in the following cities:

- Heidelberg, Germany
- Pavia, Italy
- Wiener Neustadt, Austria
- Lyon, France
- Stockholm, Sweden

The work groups in the emerging units are already cooperating with the ESTRO (European Society for Radiotherapy), the EORTC (European Organization for Cancer Research), the CERN (Conseil Européen pour la Recherche Nucléaire), and the GSI (Gesellschaft für Schwerionenforschung) and are establishing the European network ENLIGHT (European Network for Light Ion Therapy). The European Union has been financially supporting ENLIGHT for a period of three years. The goal was to jointly work on topics concerning epidemiology of the shape and size of tumors and selection of patients, clinical studies, form and dose of radiation, biologic effectiveness of treatment, monitoring with positron emission tomography, and economic aspects of treatment. The purpose of the centers' cooperation is to make carbon ion therapy in Europe as effective as possible.

States suffer far less from bone growth abnormalities than children treated with the conventional method, where distortions of the cranial viscera are common. Come to think of it, this may have appeased Allan Cormack after all.

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