# Continuing Medical Education

Beginning with this issue, the Department of Radiation Oncology will offer free Continuing Medical Education credit to readers who read the designated CME article and successfully complete a follow-up test online. You can complete the steps necessary to receive your AMA PRA Category 1 Credit(s)™ by visiting **https://cme.utsouthwestern.edu/content/em1509a**.

# Radiation therapy with heavy ions: physical, biological, and clinical rationale

***After completing this activity, the participant should be better able to:***

- Differentiate the physical and biological characteristics of ion beam therapy from those of standard electron or photon therapy
- Identify tumor types well suited to ion beam therapy
- Discuss the current state of clinical experience with ion therapy

## Introduction

Tissue irradiation for cancer therapy historically has followed two main goals: 1) to increase conformity of deposited energy to the tumor target, with the aim of putting a more therapeutic dose to the target while maintaining the same healthy tissue absorption; and 2) to increase the biological effects of deposited energy in the target, with the aim of causing more biological damage with the same amount of deposited physical energy. (This increase in biological effect should happen in the target but not in the healthy tissue.) Keeping in mind these two goals, clinicians and scientists have evaluated various forms of ionizing radiation technology over the years.

At first, only superficial tumors were treated because only low-energy X-rays were available, prohibiting irradiation of deeply seated tumors. As technology advanced, it became possible to treat deeply seated tumors with high-energy X-rays (called photons). Further technological improvements in X-ray collimation and the introduction of accelerated protons[1, 2] allowed even higher dose conformity to the target, though the biological effects of the absorbed dose remained more or less unchanged. The introduction of accelerated heavy ions (ions heavier than protons) to cancer care[3, 4] has revolutionized the field of radiation oncology because their usage allows for meeting both of the goals stated above. In the following four sections we will describe the physical, biological, and clinical rationale for heavy ion cancer therapy as well as the technology needed for its clinical implementation.

## Physical advantages of heavy ion cancer therapy

The energy deposited to tissue via ionizing radiation either directly hits the DNA molecule of the cell and alters its bonds or splits surrounding water molecules and creates highly reactive free radicals that, if located in the vicinity of DNA, attack its bonds and alter it. Depending on the severity of the DNA damage, the cell is either capable of DNA repair or will die. The DNA damage caused by ionizing radiation is correlated with the amount of absorbed energy per unit mass of tissue, called the absorbed dose. The higher the absorbed dose, the more severe the DNA damage is.

A dose can be deposited via so-called conventional radiation (photons), relatively light, charged particles (protons), or charged particles heavier than a proton (for example, the nuclei of carbon atoms). Figure 1 shows how the absorbed dose behaves as a function of depth in a homogeneous water phantom (mimicking a patient's body) with low-energy X-rays, high-energy photons, and carbon ions. The low-energy X-rays exhibit an exponential decrease of their absorbed dose, making them unfit to be used for deeply seated tumors. The high-energy photons, like the 18MV photon beam in Figure 1, are more suitable for such deeply located tumors, but a substantial dose is still absorbed upstream and downstream of a thin tumor target (located at, say, 12.75cm depth).

In contrast, the depth profiles of charged particles exhibit a significant increase in dose at the end of their range, the so-called Bragg peak. Its position can be tuned to tumor depth by carefully selecting the incoming heavy ion's kinetic energy. The imparted energy per tissue density and unit track length (called the linear energy transfer, or LET) is proportional to the square of the projectile electric charge and inversely proportional to the square of its speed. For example, a therapeutic carbon nucleus (12C6+) with a range of 12.75cm in water initially carries a kinetic energy of about 3000 mega electron volts and loses about 0.01 mega electron volts per micrometer when it enters tissue. At the Bragg peak this loss is 10 times larger. Despite the Bragg peak giving an illusion of being very sharp, not all heavy ion particles stop at the same depth, leading to some range uncertainty as shown in the Figure 1 small panel. The heavier the ion is, the less pronounced this effect is, making the carbon ion peak sharper than, for example, a proton peak[5,6] and making carbon ion beam range prediction much more accurate than that of the proton beam. This range uncertainty is of clinical relevance but can be mitigated by not trying to stop the ion beam right in front of a sensitive organ.

Heavy ions have a huge advantage in comparison to photons and protons in terms of how rapidly the dose falls off at beam edges (called the penumbra, the lateral distance where the dose falls from 80% to 20% of its peak value). At tumor depths beyond 7cm this penumbra is larger than 10mm for photons and even larger for protons, while the carbon ion beam fall-off is below a couple of mm even for the largest therapeutic depths.[7] This allows placing the lateral edge of the heavy ion beam rather close to critical organs to utilize the very sharp dose fall-off.

Note that along its trajectory, the heavy ion projectile (due to nuclear interactions) fragments into lighter nuclei.[8,9] These fragments are often unstable and radioactive and continue to travel slightly beyond the Bragg peak, creating the small absorbed dose tail on the curve in Figure 1. But this also gives rise to another big advantage of heavy ions in that they can be imaged with positron emission (PET-CT) scanners, enabling in vivo dose monitoring.[10,11]

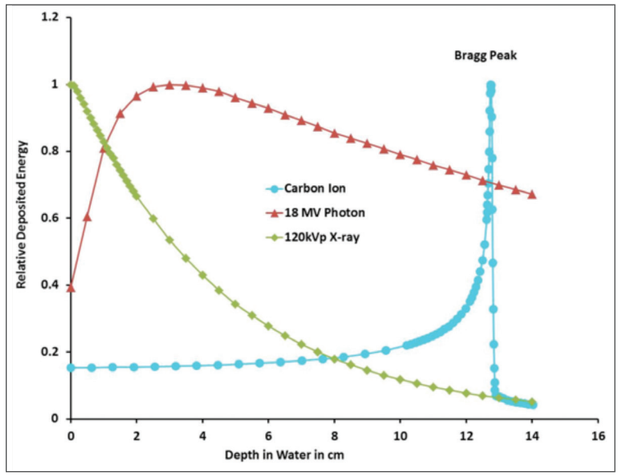


Figure 1

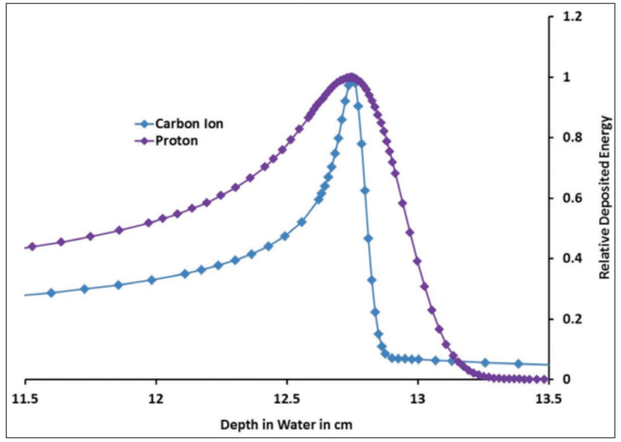


Figure 2

***Figure 1*** *shows the relative dose deposited in a water phantom as a function of depth for: X-rays generated by electrons accelerated in a 120 thousand-volt electric field; high-energy photons generated by electrons accelerated in an electric field of 18 million volts; and fully stripped nuclei of carbon atoms accelerated by 42 million volts. The curve peaks represent the maximum deposited dose. Note that for high-energy photons to deposit the same dose to the region where the Bragg peak occurs with carbon ions, healthy tissue at 3.5cm depth must receive 40% more dose.* ***Figure 2*** *compares the Bragg peak width of carbon ions and protons at a depth of 12.75cm. Carbon and proton data courtesy of Uli Weber.*

## Radiobiological advantages of heavy ion beams

The difference between how photons and heavy ions ionize tissue affects their biological effectiveness. The relative biological effectiveness (RBE) of a heavy ion is defined as the ratio of the dose needed to be delivered by photons to the dose delivered by heavy ions in order to achieve the same biological endpoint. The RBE depends on several parameters, such as: i) tissue type; ii) biological endpoint; iii) amount of absorbed dose; iv) heavy ion type; v) linear energy transfer (LET); and vi) oxygen content of the tissue. Consequently, RBE is different at every point of the irradiated tissue. This is taken into consideration during treatment planning.

The shape of the logarithm of cell survivor fractions (SF) resembles an inverted parabola for photon irradiation but is very linear for heavy ions. As a consequence, the RBE is the largest for small doses and decreases as the dose increases.

Conventional radiotherapy of oxygen-deficient (hypoxic) tumors is a big challenge because they tend to be radioresistant, often needing three times more dose to achieve the same tumor kill as in norm-oxic tumors. Heavy ion irradiation shows promising results,

namely that this ratio is substantially decreased and approaches the value of one. Furthermore, the RBE for hypoxic cells is greater than those of norm-oxic ones, showing the big potential role for heavy ion irradiation.[12-14]

In vitro radiobiological experiments have shown that the RBE exhibits maxima at different LET values depending on the heavy ion type (even if the depth, tissue type, biological endpoint, and tissue oxygenation are the same). For example, the RBE max occurs at around 25keV/micron for protons but at 10 times higher LET for neon ions and at around 200keV/micron for carbon ions.[14-17] This is a consequence of differences between lighter and heavier ions in their track structure (or spatial distribution of dose across a trajectory). This fact explains the huge biological advantage carbon ions exhibit with respect to photons and protons, namely that their RBE is relatively low and close to that of photons or protons in the entrance region of the body (where healthy tissue is located) but their RBE is high at the Bragg peak placed at the tumor. Even though the value of LET at which the maximum RBE occurs for a given heavy ion type is almost independent of what biological endpoint is considered (cell inactivation, DNA damage, etc.), the magnitude of this maximum RBE strongly depends on the tissue's biological properties. Cells with poor repair capacities show little or no RBE increase for heavy ions with respect to protons, but cells with strong repair capabilities (e.g., radioresistant tumors) exhibit large RBE maxima and therefore are clinically well suited for heavy ion irradiation.[18,19]

## Heavy ion therapeutic beam technology

The production of therapeutic photon radiation is relatively cheap and simple and is done by accelerating light electrons in an electric field of 18 million volts and colliding them with a tungsten target. The produced radiation is laterally collimated to conform to the tumor shape, but multiple entry directions are needed in order to spread out the unwanted upstream dose (Figure 1) to a large tissue volume. Such irradiators are relatively small, about twice the size of a human body.

Protons and heavier ions need much greater acceleration (e.g., 860 million volts) to reach therapeutic depth. This is done via circular accelerators of about 20 meters in diameter.

Charged particles have a third unique advantage over photons. Their electric charge can be utilized to control their lateral direction of motion by a magnetic field, which can be used to precisely position the heavy ions within the tumor lesion. This delivery technique is called pencil beam scanning.[20]

## Clinical experience with heavy ion radiotherapy

The potential physical and biological advantages of heavy ion therapy relative to conventional X-ray irradiation have long been of interest to radiation oncologists. Charged particle therapy for cancer treatment began in the mid-1950s in Berkeley, California, at a facility initially designed for basic particle physics research, subsequently known as the Lawrence Berkeley National Laboratory (LBNL).[21] Clinical studies of various types of charged particle irradiation, including proton, helium ion, neon ion, and carbon ion therapy, continued at the LBNL through 1992.[21] This pioneering research laid the framework for subsequent clinical investigations into the utility of heavy ion radiotherapy.

In 1994, investigators at the HIMAC facility located at the National Institute for Radiological Sciences (NIRS) in Chiba, Japan, began treating patients with carbon ion radiotherapy, and in 1997 the Gesellschaft fur Schwerionenforschung (GSI) facility in Darmstadt, Germany, also began a carbon ion cancer treatment program. The latter program was subsequently discontinued, and the Heidelberg Ion-Beam Therapy (HIT) Center began operations in 2009.[21] Multiple other carbon ion treatment programs have initiated patient treatments at various facilities in Japan and Europe over the past 15 years (see Table 1). Although there are numerous proton treatment centers in the United States, since the closing of the heavy ion cancer treatment program at the LBNL there have been no active treatment facilities delivering this therapy in the U.S.

Most carbon ion radiotherapy treatments to date have been delivered through a limited number of fixed-beam portals. Rotating gantries, well established in isocentric X-ray irradiation, are a recent addition to carbon ion radiotherapy treatment facilities, as is the use of pencil beam scanning (as opposed to passive scattering) beam treatments. These advances are expected to facilitate and improve on delivery of carbon ion therapy in its current form.

A systematic approach to dose-escalation studies with carbon ion radiotherapy was instituted at NIRS at the program's inception, and, to date, well more than 7,000 patients have been treated with carbon ion irradiation at this center. Phase I and II protocols at NIRS primarily evaluated hypofractionated treatment regimens. Multiple tumor types have been studied, including (given the unique physical and biological aspects of carbon ion irradiation) salivary gland and skull base tumors previously deemed appropriate for clinical study with neutron and proton radiotherapy.[22] More common malignancies such as lung, breast, and prostate cancer have also been studied.

Early-phase studies established tolerable and effective dose-fractionation regimens (with or without concurrent chemotherapy) for various tumor sites. In general, these studies have shown carbon ion radiotherapy to be a safe and efficacious treatment for a broad spectrum of tumors, including those commonly considered to be radioresistant. How these results compare to the best results seen with contemporary X-ray-based irradiation or chemo-irradiation is a subject of much debate.

So far there are no phase III randomized clinical trials comparing carbon ion radiotherapy with X-ray or proton radiotherapy. Such lack of randomized comparisons between unconventional and conventional radiation methods has been a major source of contention over the expansion of proton facilities in the United States (where the controversy stems from lack of proton versus X-ray studies).[23] However, there is growing interest in conducting such studies. Promising results from such trials may help facilitate the growth of carbon ion radiotherapy facilities in the U.S.

A review of treatment results from the NIRS for patients with locally advanced pancreatic cancer (LAPC) illustrates the potential clinical benefits of carbon ion radiotherapy. LAPC is associated with a very poor prognosis, with inadequate local control outcomes with conventional treatments (chemotherapy and/or radiotherapy with X-ray irradiation), and frequent development of metastatic cancer. Median survival for patients treated with current standard therapies is around one year, and two-year survival is only about 10-20%. Investigators at NIRS conducted a phase I/II trial for selected patients with LAPC.[24] The number of radiation fractions was set at 12, and patients were also treated with concurrent gemcitabine. The dose-per-fraction was escalated and a total dose of 55.2 GyE was safely reached, as was a concurrent gemcitabine dose of 1000 mg/m2. For patients treated in the dose range of 45.6 to 55.2 GyE, the 2-year overall survival was 54%.

These and other promising results with carbon ion radiotherapy may represent the clinical realization of the putative benefits of heavy ion treatment. Further clinical research is necessary to determine the true role of carbon ion treatments in modern clinical oncology. Results from randomized comparisons with X-ray therapy, at least in some tumor sites, are expected to help further define this role.

*Arnold Pompos, Ph.D., is a medical physicist and Assistant Professor of Radiation Oncology; Jeffrey Meyer, M.D., is a radiation oncologist and Assistant Professor of Radiation Oncology.*

**References viewable in the online version of the article at https://cme.utsouthwestern.edu/content/em1509a.*

| Center and Location | Year Operations Began | Type of Ion Used |
|---|---|---|
| Heavy Ion Medical Accelerator in Chiba (HIMAC) *Chiba, Japan* | 1994 | Carbon |
| Hyogo Ion Beam Medical Center *Hyogo, Japan* | 2002 | Carbon, Proton |
| IMP-CAS *Lanzhou, China* | 2006 | Carbon |
| Heidelberg Ion Beam Therapy Center *Heidelberg, Germany* | 2009 | Carbon, Proton |
| Gunma University Heavy Ion Medical Center *Gunma, Japan* | 2010 | Carbon |
| Centro Nazionale di Adroterapia Oncologica (CNAO) *Pavia, Italy* | 2011 | Carbon, Proton |
| Saga Heavy Ion Medical Accelerator *Saga, Japan* | 2013 | Carbon |
| SPHIC *Shanghai, China* | 2014 | Carbon, Proton |

*Table 1. Current heavy ion treatment facilities*