

Carbon Ions-A New Horizon in Radiation Oncology

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Introduction

X-ray or photon therapy is by large the most widely used modality in radiation oncology. Particle therapy using light ions [ex- proton (^1H)] and heavier ions [ex- carbon (^{12}C)] is now gaining increasing attention and acceptance. In the United States of America (USA), the push has been towards proton therapy with several new centers opening in the last few years and many more planned in the near future. There are currently no operational ^{12}C centers in the USA. Clinical evidence with ^{12}C has been very limited emanating mostly from existing centers in Japan and Germany. To date about 100,000 patients have been treated with protons and about 12,000 with ^{12}C worldwide.

Robert Wilson in his seminal paper published in 1946 [1] was the first to propose that protons could be used in medicine. Soon its use started at Berkeley (USA), Uppsala (Sweden) in the 1950's and shortly thereafter at the Harvard Cyclotron (USA). The world's first hospital based proton center opened at Loma Linda in 1990. Early work with ^{12}C therapy was carried out at Lawrence Berkeley Laboratories during the 1970-80's [2]. Other particles evaluated for clinical use included helium, neon, silicon and argon. Unfortunately the clinical utilization of these particles was later discontinued in the USA. ^{12}C is felt to very favorable among the spectrum of ions with the maximum biological effect corresponding well with its physical dose deposition in the target.

Clinical trials with ^{12}C began at the National Institute of Radiological Sciences (NIRS), Chiba, Japan in 1994. Two other centers have since opened in Japan, Hyogo Ion Beam Medical Center (HIBMC), Hyogo (2001) and Gunma University, Gunma (2010). The other existing centers are the Heidelberg Ion-Beam Radiotherapy Center (HIT) in Heidelberg, Germany (2009), the Heavy Ion Research Facility in Lanzhou, China (2006) and the most recent addition being at Centro Nazionale di Adroterapia Oncologica (CNAO) in Pavia, Italy (2012). Several new centers are in the pipeline including at China, Austria, Germany and Japan. Exorbitant upfront costs and unclear clinical utility have limited their re-implementation thus far in the USA. However a renewed interest to introduce ion therapies (heavier than protons) has recently been expressed by few major institutions in the USA. Such an effort is also being encouraged by the US National Institute of Health (NIH) and the National Cancer Institute (NCI).

Physical Advantage

Dose distribution of a given form of radiation depends on its depth-dose characteristics in tissues. Response probability is dose and volume related. Treatment outcomes depend upon the probability of tumor cure compared to the probability of early or late complications. Achieving the best possible dose distribution is a key necessity to improving treatment outcomes. X-rays lack a charge and mass resulting in most of its energy being deposited in normal tissues near the body's surface, as well as energy deposition beyond the target site. It is to some degree thus in-efficient as radiation dose (integral dose) is wasted in non-target tissues.

Ions on the other hand exhibit the 'Bragg Peak' whereby the energy deposition increases with depth up to the sharp maximum at the end of their range. A pristine Bragg peak for a given energy is

too narrow to be useful and hence a Spread out Bragg Peak (SOBP) is achieved by varying the depth/energy characteristics based on target thickness resulting in homogeneous dose coverage. Minimal (^{12}C) to zero (^1H) dose is deposited distal to the end of the SOBP which can therefore be effectively used to carve out dose from surrounding critical structures. ^{12}C has a narrower penumbra than ^1H and this property would be clinically beneficial in further decreasing dose to the tissues in immediate vicinity of the target.

Radiobiological Advantage

Carbon ions transfer a higher energy per unit length of track, called linear energy transfer (LET), compared to photons, electrons or protons (0.2-5 vs. 75-300 Kev/ μm). This results in a much denser ionization along its track length causing more irreparable damage. Both direct and indirect (via free radicals from ionization of water) damage to the DNA strands are thus higher. This results in less oxygen dependence and higher potential to target hypoxic or anoxic otherwise radio-resistant tumors. ^{12}C also has cell-cycle independent kill as opposed to low LET radiation which exert most effect in radio-sensitive G2-M phase.

In summary, compared to protons and photons, ^{12}C exhibits biophysical advantages of a narrower penumbra, higher LET, higher relative biological effectiveness (1-1.1 vs. 2-3), lesser oxygen dependence, less cell cycle dependence and therapy requiring lesser number of fractions (hypo-fractionation).

Clinical Application

Carbon ions have been used with encouraging results in a variety of adult tumors and several phase I and II trials are ongoing and many completed [3]. Sites treated include skull base tumors like chordomas and chondrosarcomas, malignant nerve sheath tumors, atypical meningioma's, adenoid cystic carcinoma, paraspinal tumors, sarcomas, head and neck, lung, liver, prostate and recurrent tumors amongst others. ^{12}C unlike protons or photons, due to their increased biological effects, may not be ideal in the pediatric patients due to concerns of normal tissue toxicities. ^{12}C however is felt to be more effective in non-squamous histology cancers which can be relatively radio-resistant to damage by protons and photons.

Reduction in integral dose is leveraged to reduction in toxicity, allowing for dose escalation or intensification and better tolerance to chemotherapy, all resulting in a higher probability of tumor control

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and ultimately to reduce overall health care costs. It is not clear if carbon is clinically superior to proton [4]. Randomized controlled trials comparing ^1H with ^{12}C would be needed to answer this question and have been initiated in Germany for select tumors [4-7].

Conclusion

Carbon ions appear to be a promising modality in radiation oncology but whether it represents the ideal choice of ion for clinical use remains to be seen. An international effort is underway to establish its efficacy through well conducted experiments and trials. Earlier this year a P20 exploratory grant to support planning efforts of establishing a center for Particle Beam Radiation Therapy (PBRT) research has been launched in the USA by the NIH/NCI. With the phenomenal technological innovations in radiation oncology and accelerator technology, I remain optimistic that the full potential of ions and its clinical applicability will be better defined in the near future.

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