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Charged Issues: Particle Radiation Therapy

This issue of *Seminars in Radiation Oncology* revisits the issue of protons and charged particle radiation, one that was addressed in the April 2013 (volume 23, number 2) issue. We refer the reader to that issue, which included many excellent articles focused on proton and charged particle radiation therapy. Since the time of that publication, the number of charged particle facilities in operation has continued to increase, there has been a significant migration to delivery with scanned beams, and multiple, randomized clinical trials to compare outcomes with protons compared to photons have been activated. Hence, the editorial staff thought that another issue dedicated to proton and heavier charged particles would be of substantial interest to the community.

The unequivocal evidence that higher radiation doses to the tumor result in higher rates of local tumor control in animals[1] and patients[2] and that normal tissue radiation can result in toxicity[3] have spurred technical developments in radiation oncology to optimize therapeutic ratio by maximizing tumor dose and minimizing normal tissue radiation. The physical properties of charged particles, notably the absence of dose beyond the Bragg peak, made them a good choice for clinical trials designed to improve the therapeutic ratio. Initial studies established an estimate of the proton relative biological effectiveness (RBE) of 1.1 that appeared to be clinically appropriate and that has been adopted in most clinics.[4] In this issue, Unkelbach and Paganetti discuss important considerations relating to the RBE of proton beams, including the potential for linear energy transfer (LET) dose painting with scanned proton beams for better normal tissue sparing than is achievable with passive scattered delivery techniques. Notably, however, the use of scanned beams in the clinic must be accompanied by consideration of the robustness of the technique and methods to address physical range (and potentially biologic dose) uncertainty, another topic addressed by Unkelbach and Paganetti.

The pioneering clinical studies performed at the Massachusetts General Hospital (MGH)-Harvard Cyclotron Laboratory (HCL) demonstrated that protons could be used to deliver higher and more highly localized doses to tumors in patients than had been technically possible with 2D or 3D photons.[5] The tumors selected for initial study, choroidal melanoma, base of skull and cervical spine chordomas and chondrosarcomas, and prostate cancers, were chosen because local control at conventional photon doses were suboptimal and because these anatomical sites could be reached with the 160 MeV, fixed horizontal beam available at the HCL.[6]

The excellent results achieved in these tumors were duplicated in other facilities around the world.[7,8] Indeed, this sophisticated technology was not only transferable but its adoption in new facilities often yielded new technological and clinical advances.[9]

The Particle Therapy Cooperative Group (PTCOG) was formed in the 1980s[10] to share ideas and advance the field, with one of its goals to develop hospital-based particle facilities that could treat tumors anywhere in the body with rotational gantries analogous to those which were standard on clinical photon linear accelerators. This goal was achieved with the opening of the hospital-based proton facility with at Loma Linda University in 1990; multiple clinical facilities have since opened around the world. In 2002, 2 clinical proton centers with gantries capable of treating tumors throughout the body were in operation in the United States; in 2017, 25 proton centers were in operation in the United States and an additional 11 centers were under construction (facility statistics from National Association for Proton Therapy at www.proton-therapy.org). Worldwide, there are now 63 proton and heavier charged particle facilities, the majority proton centers (facility statistics from PTCOG, https://www.ptcog.ch). In 2002, there were 2 carbon ion facilities in operation (1 in Japan and 1 in Germany). In 2017, there are now 11 facilities in operation across the world, some of which have both proton and carbon ion capabilities (facility statistics from PTCOG, https://www.ptcog.ch).

The ongoing increase in new facilities is expected to accelerate the rate of technological advance in the field; the majority are proton centers but there are also dedicated carbon ion facilities, as well as several facilities with the capability to treat with either. Additional facilities are in various states of planning, construction, and commissioning. The current generation of clinical facilities, generally with rotational gantries, has greatly expanded the anatomical sites and clinical scenarios for which charged particle delivery is now technically possible. It was estimated that, by the end of 2015, over

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130,000 patients had been treated to date with protons and over 19,000 had been treated with carbon ions.

When protons were first employed clinically, the available 2D and 3D conformal photon techniques did not allow delivery of comparable target doses with photons. With the advent of intensity-modulated radiotherapy (IMRT), stereotactic radiation, and image guidance, advanced technology photon techniques could deliver high radiation doses to the target, albeit with higher integral dose to the patient, manifested as higher low-moderate radiation dose to adjacent normal tissues. The potential clinical benefit for charged particles would thus rest on whether charged particles would permit some combination of either higher radiation (or biologically effective) dose to the tumor or lower dose to normal tissues to improve the therapeutic ratio, ideally to a measurable and clinically significant degree.

The cost of charged particles is higher than photons, related primarily to the greater capital costs associated with accelerating protons (×1800 heavier than the electrons accelerated in linear accelerators) or carbon ions (×12 heavier than protons). It is therefore important for clinicians, patients, and health care systems to determine the clinical scenarios where charged particles provide clinical benefit compared to available photon, brachytherapy, or other treatment techniques. Clinical benefit could entail improvement in tumor control, reduction in radiation associated morbidity, or a combination thereof. The magnitude of benefit can be used to determine where charged particles would be ranked in terms of cost-effectiveness with respect to other oncologic and medical interventions. Because cost remains an important consideration for the decision to build and operate a proton center, the contribution from Schippers et al looks critically at the question of whether technological improvements can reduce the cost of proton radiation therapy, to what degree, and on what projected timeline.

With the increasing emphasis on evidence-based medical practice, the contribution from Langendijk et al offers a thoughtful overview of the clinical trial strategies to best compare protons with photons. There have been relatively few randomized clinical trials of proton radiotherapy completed to date. This was in part a reflection of the relative paucity of operating proton centers until recently, the fact that they were dispersed, were technologically limited to treatment of only selected clinical sites and usually a modest number of patients, the rarity of some of the tumors being studied such as base of skull chordomas and chondrosarcomas, and the inability until IMRT was available for photon-based techniques to deliver the kinds of doses that were achievable with protons, often making the photon arm too noncompetitive to meet the equipoise requirements of clinical trials. With image-guided photon IMRT often able to achieve tumor target doses comparable to those achievable with protons, albeit at the cost of the higher integral dose reflected in the low-moderate dose bath that accompanies photon IMRT, many clinical investigators are now supportive of randomized trials comparing protons with photons. The equipoise for these studies weighs the potential morbidity from the higher integral radiation dose to the patient from photons against the potentially greater disparity in the planned vs delivered radiation plan with protons than photons related to combined effects of proton range uncertainty,[11] the larger effect of radiologic heterogeneity on proton dose distributions,[12] greater degradation of proton treatment plans secondary to changes in the target or normal tissue over the course of treatment,[13] and differences in image guidance (in-room cone beam computed tomography is just being installed in many proton centers), as well as some ongoing uncertainty regarding the full clinical effect of the higher LET at the end of the proton range and the potential change in RBE on tumor control and normal tissue morbidity,[14] as discussed later. These randomized studies are discussed in several of the articles in this issue.

Within the broad clinical landscape, we have chosen selected anatomical sites for in-depth discussion of the emerging or potential role for protons. We have not included pediatric tumors since they were discussed by Merchant[15] in the 2013 *Seminars in Radiation Oncology* issue and because of the general consensus that the reduction in integral dose is likely to have the largest potential benefit in children. Nevertheless, important issues remain for further clarification in the pediatric population. Jones et al[16] questioned whether there might be an elevated risk of peripheral or subdural brain recurrences in children treated with protons for medulloblastoma owing to differences in the homogeneity of photon vs proton treatment plans. Whereas photon plans generally deliver a dose that is higher than the prescription dose in the peripheral and subdural areas, proton plans deliver a relatively homogenous physical dose. Jones et al[16] also speculated on the effect of the high LET component of proton radiation therapy compared to the low LET nature of photon RT, whereby variations in LET distribution might influence RBE-weighted dose, and thus the risk of tumor recurrence as well as normal tissue toxicity. There did not seem to be an increased propensity for peripheral lateral brain recurrences in a large cohort of medulloblastoma patients treated with proton therapy at MGH, nor was there a direct correlation of lower LET values and recurrence.[17] Nevertheless, cases of brainstem necrosis have been reported with proton radiation therapy in the pediatric population,[18] and further studies are in progress to determine if this is different than what would have been expected with photons or whether this is related to treatment technique[19,20] or LET-weighted dose distribution.[21]

Ahmed et al review the literature regarding the role of proton therapy in the treatment of adult brain and skull base tumors. They highlight the duality of use for protons for these tumors, including dose escalation for skull base tumors such as chordoma to optimize tumor control as well as minimizing normal brain radiation, which may have important quality of life benefits for patients with gliomas. NRG Oncology recently opened BN-005, which will evaluate cognitive function as the primary endpoint in a randomized phase II study of protons vs IMRT for isocitrate dehydrogenase (IDH) mutant low grade and grade III gliomas. The NRG Oncology BN001 is a currently open phase II trial comparing conventional photon radiation (60.0 Gy/30 fractions) to hypofractionated dose-escalated IMRT or proton therapy (75.0 Gy/30 fractions); there