Photon, light ion, and heavy ion cancer radiotherapy: paths from physics and biology to clinical practice

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Abstract: External beam radiotherapy has proven highly effective against a wide range of cancers, and in recent decades there have been rapid advances with traditional photon-based (X-ray) radiotherapy and the development of two particle-based techniques, proton and carbon ion radiotherapy (CIRT). There are major cost differences and both physical and biological differences among these modalities that raise important questions about relative treatment efficacy and cost-effectiveness. Randomized clinical trials (RCTs) represent the gold standard for comparing treatments, but there are significant cost and ethical barriers to their wide-spread use. Meta-analysis of non-coordinated clinical trials data is another tool that can be used to compare treatments, and while this approach has recognized limitations, it is argued that meta-analysis represents an early stage of investigation that can help inform the design of future RCTs.

Keywords: Radiotherapy; cancer; clinical trials; meta-analysis; radiobiology; radiation physics

Submitted Dec 01, 2015. Accepted for publication Dec 03, 2015.
doi: 10.3978/j.issn.2305-5839.2015.12.18
View this article at: http://dx.doi.org/10.3978/j.issn.2305-5839.2015.12.18

Cancer is currently the No. 2 killer in the US and it is predicted to be leading cause of death by 2030 (1). Cancer has been combatted with ionizing radiation for more than 120 years, but only in the past 40 years has it gained widespread use with the combination of high-voltage linear accelerators capable of reaching deep seated tumors, and computed tomography to allow 3D treatment planning (2). Steady advances in the photon (X-ray) radiotherapy (XRT) field led to techniques such as 3D conformal radiotherapy and intensity-modulated radiation therapy (IMRT) which allow high doses to be shaped to tumors while minimizing doses to surrounding normal tissue (3). In the US there are more than 1.6 million new cancer patients per year (4). As recently as 2008, about 50% of patients received radiation as part of their cancer care, but in just the past 7 years this fraction as grown to more than 66%. Concomitant with advancements in XRT over the past 40 years has been the development of particle radiotherapy, including proton radiotherapy (PRT) and carbon ion radiotherapy (CIRT). In the US there are 14 operating PRT facilities, and another 15 are under construction. The vast majority of US radiotherapy patients are treated with XRT, with <1% treated with PRT since its introduction in 1990 (5). Beginning in 1994, at the National Institute of Radiological Sciences in Chiba, Japan, patients have been treated with CIRT, and there are now 5 CIRT centers operating in Japan and one each in Germany, Italy, and China (5).

The recent expansion of external beam radiotherapy modalities has fueled considerable debate as to the relative efficacy and cost-effectiveness of each modality. The simple part of the debate concerns costs. Currently XRT, PRT, and CIRT machines cost $3-5M, $25-50M, and $100M+, respectively, to which another $20-40M must be added to house the machine and ancillary equipment. The initial construction costs are the principal cost difference, as annual operating costs for each type of facility tend to be fairly similar (within a factor of two), thus treatment costs could be similar if initial construction costs did not need to be recovered (6), i.e., if construction costs were covered by governments or philanthropy. Far more complex questions concern the efficacy of each modality as applied to various tumor types and stages. The gold standard for

assessing relative treatment efficacy is through head-to-head randomized clinical trials (RCTs). Unfortunately there is a dearth of RCT data comparing XRT with either PRT or CIRT, so radiation oncologists, patient advocacy groups, and patients are forced to make decisions about treatment options using evidence from comparisons of non-RCTs, including rates of local (tumor) control, progression free survival (PFS), overall survival (OS), and side effects. Unlike RCT data, comparisons of uncoordinated studies are prone to a variety of biases, such as patient selection bias; differences in tumor staging and grading of side effects; differences in methodology used in patient follow up; and differences in the timing and periods of follow up. Such comparisons are further compromised by the fact that techniques continue to evolve (generally for the better), and this hinders retrospective comparisons because each time a new treatment strategy is introduced, it takes many years to establish long-term outcomes in cohorts that are large enough to reasonably compare with other treatment strategies. This issue is particularly problematic in the rapidly evolving fields of PRT and CIRT.

In the absence of RCT data, the best approach to judge treatment efficacy across modalities is to perform meta-analysis (7), as was recently done in a study by Qi *et al.* (8) in a comparison of XRT *vs.* PRT/CIRT for hepatocellular cancer (HCC). In this commentary the physical and biological features of XRT, PRT, and CIRT are presented, and the results of the Qi *et al.* meta-analysis are discussed in the context of the fundamental differences among XRT, PRT, and CIRT.

The goal of radiotherapy is to deliver a lethal dose to the tumor while minimizing the dose to surrounding normal tissue. Minimizing normal tissue damage is particularly important when tumors are near critical structures, such as the brain, spinal cord and optic nerves, several structures in the head/neck region, heart, stomach and small bowel, the prostatic urethra, ovaries, rectum, bladder, and in pediatric patients. X-rays have no mass and interact weakly with matter, depositing energy along their entire path until they exit the body. In XRT the highest doses occur just below the skin, and deep seated tumors can only be treated safely by focusing beams on the tumor from many angles using a rotating gantry. The energy deposited by X-rays in tissue is diffuse, hence X-ray radiation is characterized as low linear energy transfer (LET) ionizing radiation, defined as a low rate of energy deposition per unit distance (9,10). Protons and carbon ions are charged particles with mass that have the important property of depositing low amounts of low LET energy when traveling at high speed (~70% of the speed of light) through tissue. Collisions of these particles with tissue cause the particles to slow down and eventually stop, and they deposit the bulk of their energy at the very end of their path, the so-called Bragg peak (10). The Bragg peaks for protons and carbon ions are so sharp, that to be clinically useful doses are delivered in sets of Bragg peaks to produce a spread out Bragg peak (SOBP) equal to the width of the tumor. Because no energy is delivered beyond the particle stopping point, normal tissue beyond the tumor receives almost no dose. The significant normal tissue sparing achieved with protons is the principal reason why PRT has been adopted to treat tumors near sensitive structures and in pediatric patients.

Carbon ions also slow and stop within the tumor but differ from X-rays and protons in that carbon ions deposit high LET radiation within the Bragg peak. This is the fundamental physical difference between CIRT and XRT or PRT. Like protons, carbon ions offer superior normal tissue sparing beyond the tumor compared to X-rays. However, a small fraction of carbon ions fragment into smaller, low LET ions that travel beyond the Bragg peak, such that there is a low dose "tail" that extends slightly beyond the tumor. Thus, PRT offers a slight advantage over CIRT in sparing normal tissue beyond the tumor. On the other hand, PRT delivers a substantially higher dose than CIRT to normal tissue in the entrance region before the SOBP (in front of the tumor), the so-called "plateau" region (10). Importantly, even though carbon ions deliver high LET doses in the SOBP, the dose in the plateau region is largely low LET, thus damage to normal tissue with CIRT in the entrance (plateau) region is manageable. Moreover, because the ratio of dose in the SOBP and plateau regions is higher with CIRT than PRT, CIRT offers superior normal tissue sparing overall. Thus, in terms of sparing normal tissue, the series is: XRT < PRT < CIRT.

With advanced XRT techniques, like IMRT, multiple beams deliver radiation shaped to the tumor through the use of rotating gantries and multi-leaf collimators (3), allowing high doses to tumors while large regions of normal tissue surrounding the tumor receive relatively low doses. With PRT and CIRT, far more normal tissue is spared any dose. Or one can spread even lower doses among larger regions of normal tissue by delivering multiple beams with rotating gantries. The radiosensitivity of organs at risk can inform these decisions. Because of the high energies required to accelerate, transport, and focus protons and carbon ions, PRT and CIRT gantries are larger, more costly, and more

complex that XRT gantries. Rotating gantries are rapidly becoming the standard in PRT: all 15 of the PRT facilities currently in construction in the US will have at least one gantry, and most will have 2-4 gantries. The Heidelberg Ion-Beam Therapy Center in Germany has operated since 2009 the only CIRT gantry currently in use; the world's second CIRT gantry has been installed at the NIRS in Chiba and is slated to begin patient treatments in March, 2016. Achieving higher doses to the tumor volume by safely spreading normal tissue dose could be particularly useful in treating large, difficult to manage tumors. This is an area ripe for research, particularly with larger animal models such as spontaneous canine tumors.

There is another physical difference between protons and carbon ions that relate to the accuracy of beam delivery. Because of their 12-fold larger mass, carbon ions tend to continue along straight tracks until they stop, more so than protons, thus protons produce a broader "halo" or penumbra around the target region (11). The smaller penumbra with carbon ions means that carbon ions can be delivered with higher precision, and CIRT may be particularly advantageous when treating tumors that abut highly sensitive tissues like the optic nerve or prostatic urethra. Thus, in terms of accurate tumor targeting, the series is XRT < PRT < CIRT.

The fact that XRT and PRT employ low LET radiation, and CIRT employs high LET radiation, has several very important biological implications. Ionizing radiation creates DNA damage that is cytotoxic, principally DNA double-strand breaks (DSBs) (12). As noted above, low LET radiation produces diffuse ionizations along photon or proton tracks, and this produces diffuse DNA damage within tumor cells. In contrast, high LET carbon ions (in the SOBP/tumor region) cause dense ionizations that create clustered DNA damage that is less easily repaired by tumor cells than the diffuse, low LET damage, and this is reflected in the ~3-fold greater tumor cell killing per unit dose of carbon ion radiation compared to photons or protons (10,13,14). This difference is termed "relative biological effectiveness" (RBE); the RBE of carbon ions is 3 (relative to photon baseline RBE =1). Protons, being low LET radiation, have an RBE similar to photons (~1.1). Thus, in terms of tumor killing potential per unit dose, the series is: XRT ≈ PRT < CIRT.

The difference in RBE between photons/protons and carbon ions is now fairly well understood at a mechanistic level. First, dispersed DSBs produced by low LET photons and protons are primarily repaired by the dominant, fast DSB repair pathway, non-homologous end-joining (NHEJ), with the remainder repaired by the slow, homologous recombination (HR) pathway. NHEJ operates throughout the cell cycle, but HR is mostly limited to S and G2 phases (15,16). Importantly, the clustered damage created by carbon ions produces short DNA fragments that cannot be bound by the Ku70/Ku80 heterodimer (17), one of the earliest steps in NHEJ (18). Thus, DNA damage created by carbon ions is poorly repaired and has greater cytotoxicity because a fraction of the DSBs cannot be repaired by the dominant NHEJ repair pathway. Second, the damaging effects of low LET photon and proton radiation is strongly dependent on oxygen; approximately 3-fold higher doses of photons or protons are required to achieve a specific level of tumor cell killing under hypoxic *vs*. normoxic conditions (19). In contrast, carbon ions show much less dependence on oxygen and are therefore more effective against hypoxic tumors (10,19). Tumors resistant to low LET radiation are typically hypoxic, such as head and neck, and pancreatic cancers; recent evidence indicates most solid tumors have hypoxic regions (20). The reduced oxygen dependence of high LET carbon ions is probably due to their greater charge, which creates dense ionization tracks in the presence or absence of oxygen (13,14). Third, there is marked cell cycle phase dependence on cell killing with low LET radiation: S phase cells show greater radioresistance, due to upregulation of HR repair, but sensitivity to high LET radiation appears to vary little throughout the cell cycle (T. Kato, pers. comm.). Fourth, there is emerging evidence that high LET carbon ions are more effective than low LET radiation at suppressing metastasis in mouse and in vitro models (21-23), and that carbon ions are more effective in stimulating antitumor immunity (abscopal effect) in a mouse model (24). A potential explanation for the anti-metastatic effects of CIRT is based on the fact that bulk tumor cells grow rapidly and are generally sensitive to radio- and chemotherapy, whereas cancer stem-like cells grow slowly and may be naturally resistant to traditional therapies. Thus cancer stem cells may pose much greater risks of local recurrence, invasion, and metastasis. Thus, in terms of these many desirable biological effects, the series is: XRT ≈ PRT < CIRT.

Given the significant physical and biological advantages of CIRT over XRT and PRT outlined above, the considerable success of traditional XRT, the rapid growth of PRT worldwide, and the significant differences in upfront costs to install new facilities, it is vitally important to determine which modality is most effective against specific

cancers. RCTs could resolve these questions, but there are several significant barriers to this approach. First, RCTs are costly and while the NIH National Cancer Institute funds many RCTs, limited resources limit the number of trials that can be performed. Second, while insurance typically covers clinical trials funded or approved by the federal government, insurance carriers are not required to fund research costs (http://www.cancer.gov/about-cancer/treatment/clinical-trials/paying/insurance), which then fall to patients or institutions running the trials. With so many cancer types and stages, and three radiotherapy modalities to test, there are a vast number of potential RCTs that could be performed. This is further exacerbated by the fact that each modality is subject to continuous improvement. Add in tests of new combination chemo-radiotherapies, and strategies based on personalized medicine, and the number of RCT permutations is daunting. Finally, there is the question of clinical equipoise, first developed by Freedman in 1987 (25), which calls into question the ethical nature of randomizing patients to two treatment arms when there is "sufficient" evidence that one treatment is superior to the other; obviously in this case the "sufficient" evidence is not from RCTs, and is therefore not the gold standard. Hence, we sometimes find ourselves in a classic Catch-22: we may not adopt a new (potentially more effective) treatment without RCT data, yet an RCT may not be justified due to clinical equipoise. Not surprisingly, clinical equipoise is a topic of debate (26,27).

PRT has been practiced in the US since 1990, and it is expanding rapidly, yet there is almost no RCT data comparing advanced XRT and PRT. This at least in part resulted from the need to recover the high initial costs of PRT facilities by maximizing patient throughput. This approach severely limits beam-time and other resources required for research. The NIRS has been treating patients with CIRT since 1994, conducting many non-RCTs. Several RCTs comparing PRT or IMRT *vs*. CIRT for chordoma, chondrosarcoma, and glioma are ongoing at the Heidelberg facility (28-32), and the NCI recently announced an RCT comparing XRT *vs*. CIRT for unresectable pancreatic cancer (https://www.fbo.gov/spg/HHS/NIH/RCB/BAA-N01CM51007-51/listing.html).

It is against this backdrop that Qi *et al*. (8) performed a large-scale meta-analysis of XRT *vs*. PRT/CIRT for HCC. The group analyzed results from 73 cohorts, including 53 XRT cohorts comprising 3,577 patients, and 20 cohorts that received PRT or CIRT comprising 1,627 patients. The XRT patients tended to be younger, and more tightly clustered about the mean, than PRT/CIRT patients, so if the results were skewed by age-bias, it would be expected to favor XRT. The investigators focused on key outcomes including OS, PFS, local control, and toxicity; functional status, and quality of life (QoL) were of interest but there was insufficient data to draw conclusions for these endpoints. XRT studies prior to 1990 were excluded to ensure comparisons included only "modern (XRT) techniques." Interestingly, OS was significantly higher for PRT/CIRT than XRT at 1, 3, and 5 years, and both PFS and local control rates were higher for PRT/CIRT, measured at the latest follow up periods in each study. Stereotactic body radiotherapy (SBRT) is a recent advance in the XRT field and when SBRT was compared to PRT/CIRT, local control and PFS were similar, but 5 year OS appeared to slightly favor PRT/CIRT; the authors note that more data is required to determine if this difference is significant. Importantly, toxicity was lower with PRT/CIRT compared to XRT. While the authors admit that their meta-analysis is not sufficient to drive clinical treatment of HCC from XRT to PRT and/or CIRT, the potential benefits of particle therapy for HCC revealed by this study justify RCTs to provide definitive answers. It is also clear, given the significant barriers to large-scale performance of RCTs noted above, that additional meta-analyses are warranted for other tumor types. Such studies will then inform choices about future RCTs.

It is unfortunate that Qi *et al*. could not evaluate QoL. If OS, PFS, local control and toxicity rates are similar for two treatments, QoL may be a key deciding factor (assuming costs are roughly similar). In this regard it is interesting that the NIRS has pursued an aggressive program of (non-randomized) dose-escalation/hypofractionation CIRT clinical trials that has reduced treatment courses to an average of only 12 fractions over 3 weeks, with several cancers currently being treated with 4 or 8 fractions over 1-2 weeks, and primary lung cancer now treated with a single fraction (33,34). XRT is similarly moving toward hypofractionation (SBRT), but to-date PRT continues to be practiced with standard courses of 30 or more fractions. While QoL tends to focus on toxicity and functional status following treatment, it is important to recognize that various QoL factors may be weighed differently by different patients. For example, a rural patient who must travel great distances for care will likely give greater consideration to treatment time than an urban patient who can make daily visits to clinic from their home. This is especially true if the rural patient's financial resources

are limited, such that it is difficult or impossible for family members to accompany them for 5–6 week courses of standard fractionated radiotherapy. Radiotherapy is highly successful and it will certainly continue to improve as new combinations of radiations, chemotherapeutics, and immunotherapy are brought to bear on challenging tumor types. The paths toward better treatments are many and rarely straightforward, but the twin goals of improving and extending patients' lives are a most worthy pursuit.

Acknowledgements

The author is supported by NIH grant R01 GM109645.

Footnote

Provenance: This is a Guest Perspective commissioned by Section Editor Wenjie Cai (Department of Radiotherapy Oncology, First Hospital of Quan-Zhou, Affiliated to Fujian Medical University, Fujian, China).
Conflicts of Interest: The author has no conflicts of interest to declare.

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Cite this article as: Nickoloff JA. Photon, light ion, and heavy ion cancer radiotherapy: paths from physics and biology to clinical practice. Ann Transl Med 2015;3(21):336. doi: 10.3978/j.issn.2305-5839.2015.12.18

