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Systematic review

Charged particles in radiotherapy: A 5-year update of a systematic review

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ABSTRACT

Although proton therapy has been used for many decades because of their superior dose distribution over photons and reduced integral dose, their clinical implementation is still controversial. We updated a systematic review of charged particle therapy. Although still no randomised trials were identified, the field is moving quickly and we therefore also formulated ways to move forward. In our view, the aim should be to build enough proton therapy facilities with interest in research to further improve the treatment and to run the needed clinical trials.

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Charged particle radiotherapy (CPT) has been under the spotlight for many years. Investigators are looking for an answer to the question: how does it influence the outcome of cancer patients [1–3]? Based on the dose distributions, it has been concluded that the use of protons may lead to improved coverage of the Planning Target Volume (PTV) and reduced doses to many organs at risk (OAR) [1–3].

Several systematic reviews performed during the last decade [2,4–11] investigating the clinical efficacy of CPT show that, for most indications, no firm conclusions can be drawn. In part this is due to a lack of high quality data, making adequate comparisons impossible. In addition, cost-effectiveness analysis of this technology also could not clearly demonstrate that CPT was more cost-effective than the most advanced photon[1] technology, such as stereotactic body radiotherapy (SBRT or stereotactic ablative radiotherapy, SABR) or intensity modulated radiotherapy (IMRT) [8,10,12–16]. The published results generated a world-wide debate between proponents and sceptics [13]. Because so many patients have been treated with protons and C-ions world-wide, we performed a new systematic review of the literature, 5 years after our previous publication [10]. The full report is available on line as a Supplementary file.

Our main goal was to explore to which extent previous recommendations were taken up by the radiation oncology community and to determine if it is possible to draw firm conclusions about the clinical and cost-effectiveness of CPT as compared to best current practice.

It was sobering to observe that no phase III trials have been performed and from the many retrospective and the few prospective series, we still cannot conclude that protons or C-ions are truly superior to X-rays. Moreover, many of the available clinical studies were performed at a time when the current proton techniques and the newest X-ray treatment, including imaging and adaptation, were not available. Our former conclusion thus still stands: except for rare indications such as childhood cancer, the gain from introducing proton therapies into clinical practice remains controversial. The contention that protons are more suitable when OAR dose constraints limit the delivery of the most appropriate tumour X-ray radiotherapy doses is compelling, but remains unproven. Nor do we know if CPT allows radiation dose escalation without increasing side effects – leading to improved local tumour control and survival. Where dose escalation is achievable by the most recent X-ray based techniques, the gain from proton therapy is confined to a reduction in dose to organs away from the target region. These arguments depend on the accuracy of the predicted dose distribution and sound estimates of the relative biological effectiveness (RBE) values for the cancer and for each normal tissue [17].

The debate between the advocates in favour of randomised studies for all circumstances, and those who consider this to be unethical when reduced radiation dose can be delivered to OAR, continues [18–23]. X-ray (photon) treatment and imaging techniques have significantly improved over recent decades with increased implementation of IMRT, arc and helical treatment and SABR in routine clinical practice [24–27]. Together with imaging developments such as CT-, MRI- and PET-based radiotherapy

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[1] Photons and X-rays are used in the text to describe the same beam quality as opposed to protons, which we consider to be light ions and ^{11}C that are heavy particles.

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planning, 4D-CT and improved dose calculation and optimisation algorithms, X-ray therapy allows the delivery of radiotherapy to high doses. Modern X-ray techniques in common malignancies such as non-small cell lung cancer are comparable to, or even superior to, that of protons therapy delivered with passive scattering techniques [28]. However X-ray techniques will always deliver a higher integral dose than protons and there is concern about low dose effects to a wider volume because of enhanced cancer induction and circulatory system risks [29–31]. At the same time proton therapy has also significantly improved, allowing the delivery of Intensity Modulated Proton Therapy (IMPT) with commercial systems [3].

At present, many planning studies show that for the high dose regions, the best available X-ray and proton treatments result in similar dose distributions within and around the tumour. However the medium and low dose volumes are smaller and receive less radiation dose with IMPT than with any X-ray technique [30–35]. Proponents of protons view the data as a proof that ultimately proton therapy will supersede X-rays because it is generally agreed that the ALARA (As Low As Reasonably Achievable) principle should be followed [1]. Arguments against this viewpoint are that a reduction of the medium and low dose volumes are not beneficial for the patient when only a shallow dose–response relationship between an intermediate dose and side-effects exists or when the side effects are of no clinical relevance or occur in only a small proportion of patients. Balanced arguments, considering many of the technical aspects have been published recently (e.g. [36,37]). When some OARs can be spared more effectively with protons than X-rays, even for the medium or low dose levels, more effective dose-escalation may be possible, either for radiotherapy or for combined radiation and systemic treatment.

Because the absorption and range of protons is more dependent on electron density inhomogeneity than X-rays, small shifts of the tumour or of the OARs in areas with high density gradients, e.g. in the lungs (where not only lung density but also tumour position varies with breathing), may directly result in large changes and errors in dose distribution. Adaptive radiotherapy techniques thus become even more important for protons than for X-rays, and these are in development for each modality [38,39]. Probability based treatment planning strategies taking into account volume changes and shifts of the tumour and the OARs have been described allowing more robust dose distributions for scanned proton beams, although there is a longer history of using respiratory gating techniques in proton therapy than in the case of X-ray therapy [40].

If proton therapy can fulfil its initial promise it may well turn out to be a cost-effective intervention [12]. It is necessary to break the current vicious circle where the lack of robust clinical data leads to a lack of evidence to support funding and further development of proton beam therapy in state-of-the-art treatment centres with responsibilities to produce robust clinical data [41,42]. The root cause of the problem facing proton therapy is the historic failure to leverage the collection and sharing of anonymised data in return for capital investment in what is, to all intents and purposes, still a developing and experimental technology. Unless the present culture is radically changed this collaborative failure will continue to be proton therapy's Achilles heel.

We believe that randomised phase III trials will be needed for some, but not necessarily all, situations to investigate the role of protons and their cost-effectiveness. Prospective phase II studies using the best available techniques and reporting agreed endpoints of clinical relevance are the minimum requirement. As recommended previously, all studies should be fully integrated in large international networks and databases to make reliable and rapid progress: this needs urgent implementation.

New particle beam centres should be funded with a provision for shared basic research, technical improvements and properly conducted trials. An enhanced level of global, or at least continental or national, governance of particle therapy is of paramount importance.

Only then, will we be in a position to clarify the real gain of CPT and to bring an otherwise endless debate to an unequivocal conclusion.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.radonc.2012.01.003.

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