Acta Oncologica, 2011; 50: 741–744

EDITORIAL

Particle Therapy – A next logical step in the improvement of radiotherapy

HÅKAN NYSTRÖM[1], ERIK BLOMQVIST[2], MORTEN HØYER[3], ANDERS MONTELIUS[2], LUDVIG PAUL MUREN[3], PER NILSSON[4], ZAHRA TAHERI-KADKHODA[5] & BENGT GLIMELIUS[2,6]

[1]*The Skandion Clinic, Uppsala, Sweden,* [2]*Uppsala University Hospital, Uppsala, Sweden,* [3]*Aarhus University Hospital, Aarhus, Denmark,* [4]*Skåne University Hospital, Lund, Sweden,* [5]*Sahlgrenska University Hospital, Gothenburg, Sweden and* [6]*Karolinska Institutet, Stockholm, Sweden*

Acta Oncologica has for more than two decades sponsored scientific symposia on emerging issues in all fields of oncology. The most recent symposia within radiation oncology have addressed stereotactic body radiotherapy in 2006 [1], image-guided radiotherapy in 2008 [2] and biology-guided adaptive radiotherapy in 2010 [3].

Following the experience from 2008 with an Acta Oncologica symposium co-localised with a symposium of the Nordic Association for Clinical Physics (NACP) [4], the present issue contains publications presented at the Acta Oncologica Symposium on Particle Therapy as well as at the back-to-back event of the NACP 2011 symposium [5], both held in Uppsala, Sweden, on April 13–15, 2011. The choice of topic this time came from the broad introduction of new particle therapy facilities around the globe, in particular proton therapy clinics. Although proton therapy was suggested as early as 1946 [6] and the first proton treatment worldwide of a cancer patient was performed in Uppsala already in 1957 [7], particle therapy has not become widely available and the capacity in the existing particle therapy facilities has been limited. This situation is however about to change and there is an almost exponential growth in the number of planned facilities.

Presently, the first hospital-based particle therapy facility in the Nordic countries is being established in Uppsala; the Skandion clinic. This facility is a national centre, designed to serve the whole population of Sweden. Still it is expected that at least for the first few years of operation, some capacity can also be offered to neighbouring countries, for example in the Nordic region. What makes this project unique, also in an international context, is the concept of cooperation between the seven academic oncology departments of the country [8]. Rather than referring patients to Uppsala for treatment, prescription, planning and all preparations will be made at the university clinics and patients will thereafter be treated at the Skandion clinic in Uppsala. Beside the opportunity to gather competence from a number of academic clinics into one single proton facility, this collaborative approach also offers a unique possibility for sharing experiences, not only between the cooperating clinics, but also with interested regional centres or even international partners, since a significant fraction of the collaboration will be conducted via teleconferencing [9]. In addition, the model is designed to promote scientific activities and to constitute a ground for extensive collaboration in clinical trials.

With the increased accessibility of particle therapy follows the challenge of distributing and sharing the proton-specific knowledge and expertise among all potential actors in radiation oncology, who are or will be considering treating patients that might benefit from proton therapy. To make a contribution in this direction, the organisers of this symposium invited some of the most distinguished and experienced actors on the particle therapy arena to share their most recent experiences. In addition, a large number of abstracts, mostly from the Nordic countries, were submitted for the proffered sessions and

Correspondence: Håkan Nyström, The Skandion Clinic, Box 6374, SE-751 36 Uppsala, Sweden. Tel: +49 70 6111597. E-mail: hakan.nystrom@skandion.se

(Received 18 May 2011; accepted 18 May 2011)

ISSN 0284-186X print/ISSN 1651-226X online © 2011 Informa Healthcare
DOI: 10.3109/0284186X.2011.590150

some of these contributions are published in the current issue of the journal.

Following strict physics terminology, the very concept of "particle" therapy may be confusing, since almost anything of limited size, including electrons, photons and dust, can be related to as "particles". However, in the context of radiotherapy, a convention has developed where "particles" should be understood as positively charged ions, typically ranging from hydrogen up to carbon. Also within this restriction, not all particles are the same. Where the potential for improved radiotherapy with hydrogen ions, here after referred to as protons, is to be found in the superior dose distributions and the limited spill-over in dose to healthy tissues compared to conventional radiotherapy [10], the most interesting characteristics of carbon ions lies in the different biological effects of these particles compared to photons and protons. This potential advantage of carbon ions is due to their higher linear energy transfer (LET) causing an enhanced radiobiological effectiveness (RBE) [11]. Although the RBE of carbon ions is expected to be higher in slowly growing tissues with low α/β, their biological impact in high LET regions is supposedly less dependent on the cell cycle or oxygenation status of the cells. Thus, carbon ions should theoretically serve as a better treatment option for slowly growing radioresistant tumours and their inherent biological features could be used for targeted dose painting of hypoxic regions in the tumours [12]. As of February 2009, it was estimated that about 5300 cancer patients had been treated with carbon ions worldwide, compared to 61 000 treated with protons [13].

Currently, the most highlighted indications for carbon ion therapy are chondrosarcomas and chordomas of the skull base, malignant salivary gland and brain tumours, prostate cancer, early stage non-small cell lung cancer and hepatocellular carcinomas. Clinically, carbon ions are delivered in hypofractionated schedules as a sole treatment or in combination with photon therapy [14,15]. The published data suggest that compared to proton therapy, application of carbon ions yields superior local tumour control in skull base chordomas and early stage prostate cancer through delivery of higher biological effective doses in these tumours [13], although this has been debated [16]. Interestingly, the reported treatment-related morbidities after carbon ion treatments have been low despite the high biologically equivalent doses delivered [14]. However, the interpretation of the available data on carbon ion therapy is difficult since there has been no clinical trial comparing the efficacy or toxicities of carbon ions with protons or photons for any tumour type. Inter-institutional variations in fractionation, biological modelling of RBE estimation and target definition in carbon ion therapy may also complicate the assessment of the treatment results. Since it is expected that the availability of both proton and carbon ions in existing and upcoming heavy ion centres will increase significantly during the next decade, it will be even more important (or rather, urgent) to address the question of the potential benefit of carbon ions more thoroughly through multicentre randomised clinical trials.

In a recent analysis of published clinical studies [17] it was demonstrated that there is a clear dose–response relationship for non-small cell lung cancer (NSCLC) providing a base for dose-escalation to improve local control and subsequently disease-free survival for this disease. However, dose-escalation possibilities are limited with photon-based RT due the irradiation of nearby organs at risk. In particular, the dose to uninvolved lung tissue is a concern, where even the low dose bath (V_{5Gy} - V_{20Gy}) from intensity-modulated photon delivery techniques seems to have a significant negative impact on lung toxicity. The favourable physical properties of particle therapy is therefore a tempting way forward in order to increase the dose to the target volumes without exceeding normal tissue tolerance doses and to improve the therapeutic ratio. Particle therapy may be even more advantageous when combined with chemotherapy [18], which is frequently used for advanced tumours. An excellent review of the status of particle therapy, covering treatment planning comparisons as well as the outcome of clinical studies, for both early stage and locally advanced stage non-small cell lung cancer is given by Liao et al. [19] in this issue of Acta Oncologica. The main obstacle for proton therapy in this anatomical site is the large variations in tissue density within the treated region and that lung tumours move with the patients breathing, resulting in a risk of large deviations in delivered dose compared to the planned dose on static computed tomography (CT)-images. The situation becomes even more difficult if scanned particle beams are used and where the interplay-effect of target motion and dynamic beams will become harder to account for. Several proposals have been presented for alleviating these effects [20], for example by gating, rescanning and tracking [21]. If satisfying solutions can be found for the motion issue it is expected that particle therapy would play a significant role in the future treatment of lung cancer.

Tumours in the head and neck and cranial regions are often situated close to radiosensitive tissues like the optical structures, the pituitary gland, the brain stem, the spinal cord, the salivary glands and the muscles involved in swallowing. Thus, physical properties of proton beams make this modality particularly favourable for both orbital and sinonasal tumours as well as for tumours in the oropharynx and nasopharynx [22,23]. One of the largest patient groups treated with particles is eye melanomas [24] where around 20 000 patients have been treated worldwide since 1975 [25]. Other tumour entities for which particle therapy has been widely used are skull base chordomas, chondrosarcomas [26,27] and meningiomas [28–30].

In similarity to treatment of lung tumours, the challenge for particle therapy in the head and neck and skull base regions lies in the heterogeneity in the densities of the involved tissues, which put great demands on accurate dose calculation and delivery. Treatment planning comparisons between photon radiotherapy (mainly intensity-modulated treatments) and particle therapy have usually shown that protons are superior to photons [22]. However, the strict clinical evidence for this is sparse [16,31], but some studies indicate promising results for protons in a number of patient groups, particularly tumours in the oropharynx and nasopharynx [23] and skull base meningiomas.

Worldwide, prostate cancer is the most common tumour entity treated with protons, but the evidence for this is limited. The motivation for particle therapy for prostate cancer is the need for high radiation doses as well as the dose sparing effects on organs in the vicinity of the prostate. One randomised study from the Massachusetts General Hospital (MGH) was conducted on particle therapy of prostate cancer [32]. All patients in this study received conformal photon therapy (50.4 Gy) and the randomisation was between two proton boost doses (19.8 Gy (RBE) and 28.8 Gy (RBE), respectively). Together with other studies the MGH study forms a solid evidence for dose escalation in radiation therapy for prostate cancer in general, however, it does not prove that particle therapy is superior to photon therapy. Yet promising experience for carbon ions [14,33] as well as for protons [34] has been presented. However, in a recent case-control study from the MGH comparing outcomes in men treated for localised prostate cancer, combined photon/proton radiotherapy was not superior to permanent seed brachytherapy in terms of biochemical relapse free survival and quality-of-life [35].

Presently there are only few on-going studies for patients with prostate cancer (www.clinicaltrials.gov). One study is randomising between hypofractionated and conventional fractionated proton therapy, while all other studies are phase I or II trials focusing on low-, intermediate- or high-risk prostate cancer treated with protons alone or in drug combinations. There are no trials randomising between charged particles and photons. Unfortunately, the ongoing trials will not be able to prove the principle of charged particle therapy for prostate cancer and a trial comparing at least toxicity outcomes is urgently warranted.

For many paediatric malignancies, radiotherapy is an inherent part of the multimodal treatment. Paediatric patients are especially prone to acute and late side-effects of irradiation due to the radiosensitivity of the growing normal tissues, relatively large irradiated volumes and the additive side-effects of the combined chemotherapy agents. Model studies in tumour entities such as medulloblastoma [36] have clearly showed that compared to the best available photon therapies, modern proton therapy techniques could offer the best favourable outcomes in terms of risk reduction of second malignancies and non-cancer adverse events. In such settings, there is little controversy regarding the benefits of proton therapy in children. However, the implementation of proton therapy in treatment protocols of paediatric malignancies requires an efficient medical and practical decision flow which guarantees the timing of radiotherapy in conjunction with other treatment modalities. Moreover, the sensitivity of proton plans to anatomical changes [37] due to chemotherapy or surgery underscores the importance of incorporation of adaptive radiotherapy in proton treatment of children as well. Hence, the major challenge in application of proton therapy for children will not lie in defining indications but in building infrastructures which secure appropriate implementation of the technique in multi-modal treatment settings.

In summary, this issue of Acta Oncologica provides an excellent overview of the current status and new developments for some of the areas where particle therapy is believed to contribute significantly to improved radiotherapy for future cancer patients.

Declaration of interest: The authors report no conflict of interest. The authors alone are responsible of the content and writing of the paper.

References

[1] Grau C, Høyer M, Lindegaard J, Overgaard J. The emerging evidence for stereotactic body radiotherapy. Acta Oncol 2006;45:771–4.

[2] Grau C, Muren LP, Høyer M, Lindegaard JC, Overgaard J. Image-guided adaptive radiotherapy – integration of biology and technology to improve clinical outcome. Acta Oncol 2008;47:1182–5.

[3] Grau C, Olsen DR, Overgaard J, Høyer M, Lindegaard JC, Muren LP. Biology-guided adaptive radiation therapy – presence or future? Acta Oncol 2010;49:884–7.

[4] Muren LP, Petersen JB, Hansen J, Hafslund R. Medical physics in the Nordic Countries: The past, the present and the future. Acta Oncol 2009;48:165–8.

[5] Muren LP, Glimelius B. And they lived happily ever after… The marriage of Nordic Association for Clinical Physics and Acta Oncologica. Acta Oncol 2011 (this issue).
[6] Wilson RR. Radiological use of fast protons. Radiol 1946; 47:487–91.
[7] Falkmer S, Fors B, Larsson B, Lindell A, Näslund J, Stenson S. Pilot study on proton irradiation of human carcinoma. Acta Radiol 1962;58:33–51.
[8] Karlsson M, Björk-Eriksson T, Mattsson O, Mattsson S, Montelius A, et al. "Distributed proton radiation therapy" – A new concept for advanced competence support. Acta Oncol 2006;45:1094–101.
[9] Kristensen I, Lindh J, Nilsson P, Agrup M, Bergström P, Björk-Eriksson T, et al. Telemedicine as a tool for sharing competence in paediatric radiotherapy – Implementation and initial experiences from a Swedish project. Acta Oncol 2009;48:146–52.
[10] Nyström H. The role of protons in modern and biologically-guided radiotherapy. Acta Oncol 2010;49:1124–31.
[11] Singers-Sørensen B, Overgaard J, Bassler N. A review of the RBE-LET dependence for inactivation of V79, CHO and T1 Cells. Acta Oncol 2011 (this issue).
[12] Bassler N, Jäkel O, Søndergaard CS, Petersen JB. Dose- and LET-painting with particle therapy. Acta Oncol 2010;49: 1170–6.
[13] Suit H, DeLaney T, Goldberg S, Paganetti H, Clasie B, Gerweck L, et al. Proton vs. carbon ion beams in the definitive radiation treatment of cancer patients. Radiother Oncol 2010;95:3–22.
[14] Nikoghosyan AV, Schulz-Ertner D, Herfarth K, Didinger B, Münter MW, Jensen AD, et al. Acute toxicity of combined photon IMRT and carbon ion boost for locally advanced prostate cancer. Acta Oncol 2011 (this issue).
[15] Combs SE, Ellerbrock M, Haberer B, Habermehl D, Hoess A, Jäkel O, et al. Heidelberg Ion Therapy Center (HIT): Initial clinical experience in the first 80 patients. Acta Oncol 2010;49:1132–40.
[16] Brada M, Pils-Johannesma M, De Ruysscher D. Proton therapy in clinical practice: Current clinical evidence. J Clin Oncol 2007;25:965–70.
[17] Partridge M, Ramos M, Sardaro A, Brada M. Dose escalation for non-small cell lung cancer: Analysis and modelling of published literature. Radiother Oncol 2011;99:6–11.
[18] Vogelius IR, Westerly DC, Aznar M, Cannon GM, Korreman SS, Mackie TR, et al. Estimated risk of radiation pneumonitis after 3DCRT, IMRT and proton therapy after radiation therapy alone or combined with chemotherapy for lung cancer. Acta Oncol 2011 (this issue).
[19] Liao Z, Lin SH, Cox JD. Status of particle therapy for lung cancer. Acta Oncol 2011 (this issue).
[20] Rietzel E, Bert C. Respiratory motion management in particle therapy. Med Phys 2010;37:449–60.
[21] Munck af Rosenschöld P, Aznar M, Nygaard DE, Persson GF, Korreman SS, Engelholm SA, et al. A treatment planning study of the potential of geometrical tracking for intensity modulated proton therapy of lung cancer. Acta Oncol 2010; 49:1141–8.
[22] Ask A, Björk-Eriksson T, Zackrisson B, Blomquist E, Glimelius B. The potential of proton beam radiation therapy in head and neck cancer. Acta Oncol 2005;44:876–80.
[23] Mendenhall NP, Malyapa RS, Su Z, Yeung D, Mendenhall WM, Li Z. Proton therapy for head and neck cancer. Acta Oncol 2011 (this issue).
[24] Gragoudas ES. Proton beam irradiation of uveal melanomas: The first 30 years. Invest Ophthalmol Vis Sci 2006;47: 4666–73.
[25] Particle Therapy Co-Operative Group (PTCOG) home page [Internet]. Available from: http://ptcog.web.psi.ch/
[26] Munzenrider JE, Liebsch NJ. Proton therapy for tumors of the skull base. Strahlenther Onkol 1999;175(Suppl II): 57–63.
[27] Amichetti M, Cianchetti M, Amelio D, Maurizi Enrici R, Minniti G. Proton therapy in chordoma of the base of the skull: A systematic review. Neurosurg Rev 2009;32: 403–16.
[28] Gudjonsson O, Blomquist E, Nyberg G, Pellettieri L, Montelius A, Grusell E, et al. Stereotactic irradiation of skull base meningiomas with high energy protons. Acta Neurochir 1999;141:933–40.
[29] Hug E, DeVries A, Thornton AF, Munzenride JE, Pardo FS, Hedley-Whyte ET, et al. Management of atypical and malignant meningiomas: Role of high-dose, 3d-conformal radiation therapy. J Neurooncol 2000;48:151–60.
[30] Noël G, Bollet MA, Calugaru V, Feuvret L, Haie-Meder C, Dhermain F, et al. Functional outcome of patients with benign meningioma treated by 3D conformal irradiation with a combination of photons and protons. Int J Radiat Oncol Biol Phys 2005;62:1412–22.
[31] Olsen DR, Bruland ØS, Frykholm G, Norderhaug IN. Proton therapy – A systematic review of clinical effectiveness. Radiother Oncol 2007;83:123–32.
[32] Zietman AL, DeSilvio ML, Slater JD, Rossi CJ Jr, Miller DW, Adams JA, et al. Comparison of conventional-dose vs. high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: A randomized controlled trial. JAMA 2005;294:1233–9.
[33] Tsuji H, Yanagi T, Ishikawa H, Kamada T, Mizoe JE, Kanai T, et al, Hypofractionated radiotherapy with carbon ion beams for prostate cancer. Int J Radiat Oncol Biol Phys 2005;63: 1153–60.
[34] Coen JJ, Bae K, Zietman AL, Patel B, Shipley WU, Slater JD, et al. Acute and late toxicity after dose escalation to 82 GyE using conformal proton radiation for localized prostate cancer: Initial report of American College of Radiology phase II study 03-12. Int J Radiat Oncol Biol Phys Epub 2010 Oct 5.
[35] Coen JJ, Zietman AL, Rossi CJ, Grocela JA, Efstathiou JA, Yan Y, et al. Comparison of high-dose proton radiotherapy and brachytherapy in localized prostate cancer: A case-matched analysis. Int J Radiat Oncol Biol Phys Epub 2011 Apr 4.
[36] Brodin P, Aznar M, Kiil-Berthelsen A, Munck af Rosenschöld P, Nilsson P, Vogelius I, et al. Quantifying patient benefit of proton therapy compared to modern photon treatment for children receiving craniospinal irradiation. Acta Oncol 2011 (this issue).
[37] Lassen-Ramshad Y, Vestergaard A, Muren LP, Høyer M, Petersen JB. Does the need for plan adaptation in radiotherapy increase when using protons? – A case study of a child with a brain tumour. Acta Oncol 2011 (this issue).