

## Is there a Nordic solution for the ‘proton-problem’?

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According to data from the Particle Therapy Co-Operative Group (PTCOG) 20 proton treatment facilities have opened worldwide since 2015, an additional 30 are under construction and as of today there are two operational Scandinavian proton centres and two more are under construction [1]. In a few years there will be more than 100 facilities for proton therapy around the world and an additional couple of dozen centres for other hadron treatments.

These numbers show that particle therapy as a radiotherapy modality is rapidly evolving. Simultaneously evidence and indications for proton therapy are increasing, although at a slower pace. Hard evidence for clinical benefit is still scarce, despite promises for reduced long-term toxicity including reduced risk of treatment induced second primary malignancies.

As of today proton therapy is recommended for paediatric cancers, ocular melanomas, chordomas and chondrosarcomas. Although promising results are reported for other types of cancers, they are still based on small studies. Considering the high cost of establishing and operating proton therapy centres, questions have been raised about their cost effectiveness.

Furthermore, status for proton therapy is becoming an issue for the European Commission. A subgroup with experts on proton therapy from all over Europe has been created within the Directorate-General for health and food safety. The mission originates from the European Investment Bank to provide more clarity concerning key challenges and existing knowledge gaps, e.g. long-term health economic data together with clinical benefit.

A report from the subgroup is on the way and preliminary conclusions suggest that international collaboration is essential to increase the limited number of patients in clinical studies, and recommend that all new proton therapy centres should contribute to reinforce the international knowledge base (unpublished data).

Despite growing capacity, percentage of cancer patients receiving proton therapy remains low, close to one percent of all patients receiving radiotherapy in Sweden as well as in most countries with proton facilities [2]. According to the suggested potential of proton therapy the numbers should be at least tenfold [3]. So far, sparse evidence is used to explain the low utilisation. However, lack of hard evidence is

not the only reason suggested to explain why cancer patients treated with proton therapy remains at a low level. Other root causes need to be identified and handled if numbers are to increase. As of today, improvements in planning and delivery of conventional radiotherapy, high costs, and low availability are widely suggested as explanatory variables [2].

In a Nordic perspective, with two proton centres and two more up and running in a few years from now, the obstacle with low availability seems to be of less importance, although the distance the patient has to travel to Uppsala is still discussed as a limiting factor in Sweden. In addition, the issue on how referring centres better could identify candidates for proton therapy needs to be addressed. Among these and other issues that could increase the number of patients suitable for proton therapy, collaborative efforts were judged to be of immense importance when the Skandion Clinic in Uppsala invited to a Nordic workshop in November 2019. Physicians, physicists and RTT's from the Nordic countries were invited to broaden insights in these issues, increase collaboration, exchange experiences, and identify possible mutual research projects.

The workshop covered four areas, all resulted in papers published in this issue of the journal, addressing at least a few of the topics that constitutes the ‘proton problem’, i.e. the low number of patients being referred for proton therapy, and why huge investments and the opportunities this technique can bring haven't resulted in clear cut guidelines stating who and for what proton therapy shall be offered.

In the paper by Brandal et al., a Nordic-Baltic perspective on proton therapy indications and strategies for identification of patients for proton therapy are discussed [2]. As for indications, neoplastic entities, target volume localisation, size, internal motion, age, second cancer predisposition and dose escalation together with treatment plan comparison based on the ALARA-principle (as low as reasonably achievable doses) or normal tissue complication probability (NTCP) models were covered. An important conclusion was that the selection process for proton patients would benefit if decision making and referrals are integrated into the radiotherapy community and network, i.e. collaboration across medical specialties, involvement of key decision makers and

active knowledge dissemination throughout the health care system.

Dasu *et al* discusses another property of proton therapy which often is high-lighted from the 'proton sceptics', i.e. the uncertainty created by the difference in radiologic biologic effectiveness (RBE) for proton compared to photons [4]. As of today, this potentially increased RBE at the end of the particle range is considered at the stage of treatment planning, primarily by avoiding beams with distal edge facing a serial organised organs-at-risk (OARs) based on empirical observations and knowledge. More elaborated strategies to evaluate the plans and mitigate the problem are intensely investigated internationally as well as at the Nordic centres. The workshop also emphasised a need for close interaction with research groups that could help developing methods and tools for clinical implementation of the complex metrics that would make it possible to handle the variable RBE of proton beams.

Another subject covered at the workshop was patient's perspective in proton therapy, where focus was to describe and compare patient care in the Nordic countries.

The paper by Ohlsson-Nevo *et al.* describes the possibilities linked to systematic use of patient experiences on both individual and group level [5]. The participants concluded that inclusion of patients' perspectives in study protocols and systematic collection of patient-reported outcomes together with clinical outcomes is unique possibilities for future research on proton therapy. They also discussed barriers (e.g. geographic, logistic, or economic) for participation in national clinical trials as factors that contribute to the lack of evidence for proton therapy, primarily by limiting number of patients that are included in clinical trials. Despite these and other obstacles for proton therapy there is a firm confidence that the number of patients where proton therapy is the 'drug-of-choice' can increase. However, the advantage for protons you can see *in-silico*-studies comparing doses to OAR is obviously not enough to convince the sceptics in the radiotherapy community; they demand clinical trials with upfront comparisons between protons and photons. The workshop in Uppsala tried to cover that subject too. In the paper by Witt Nyström *et al.*, the authors made an inventory of clinical trials involving particle therapy in the Nordics, both active and coming trials, and concluded with disappointment that no common Nordic trial has yet been designed, although there is at least one in planning phase [6]. The workshop tried to identify reasons for this poor development, and stated that financial support was a limiting factor, at least in Sweden. The authors also raised question marks for the old-school focus on randomised control trials as the only way to find evidence, and pinpointed need for novelty in study design that better would serve the radiotherapy community. The standard procedure where it takes 10–15 years to reach end points as long term toxicity or survival in a clinical study create problems. Even results from

the most well-designed study might be obsolete when they are ready to publish, due to the rapid evolution in new technologies and machine learning together with new knowledge in other aspects of cancer care and treatment.

With proton centres in Denmark, Norway, and Sweden, together with a centre for boron neutron capture therapy in Finland scheduled to start this year, the tentative future for particle therapy in the Nordic countries is immense. Although the Uppsala workshop couldn't find answers to all questions raised in the field of particle therapy, it must be considered a good start. It was also a start for a new awareness that opportunities for mutual development in patient care, knowledge, training, and education will benefit if a platform for solid Nordic collaboration can be established, a development needed to acquire new knowledge from clinical studies, and a Nordic participation in solving the 'proton problem'.

Collaborative efforts in Europe are on the way, where an European proton therapy network (EPTN) has been established with a primary aim to overcome the lack of evidence for proton treatment for a large number of indications [7]. Denmark is already part of the EPTN and the other Nordic countries need to follow. Without scientific collaboration in Europe and the rest of the world there will never be enough power in clinical studies to build the knowledge needed to offer more patients the benefits that proton therapy can offer.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

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