Tidsskriftet Tidsskrift for Den norske legeforening

Proton therapy – a reality in Norway from 2023

PERSPECTIVES

EINAR DALE

Einar Dale, PhD and senior consultant at Oslo University Hospital. He has participated in various clinical groups as a member of the national proton therapy project group.
The author has completed the ICMJE form and reports no conflicts of interest.

EINAR WALDELAND

E-mail: einar.waldeland@ous-hf.no
Einar Waldeland, PhD, medical physicist and head of section at Oslo University Hospital. He has represented the South-Eastern Norway Regional Health Authority and Oslo University Hospital in the national proton therapy assessments.
The author has completed the ICMJE form and reports no conflicts of interest.

It has finally been decided to establish proton therapy as a national treatment option in Norway, and there will be centres in Oslo and Bergen from 2023. The majority of children and young adults who are to receive curative radiation therapy should be treated with proton therapy.

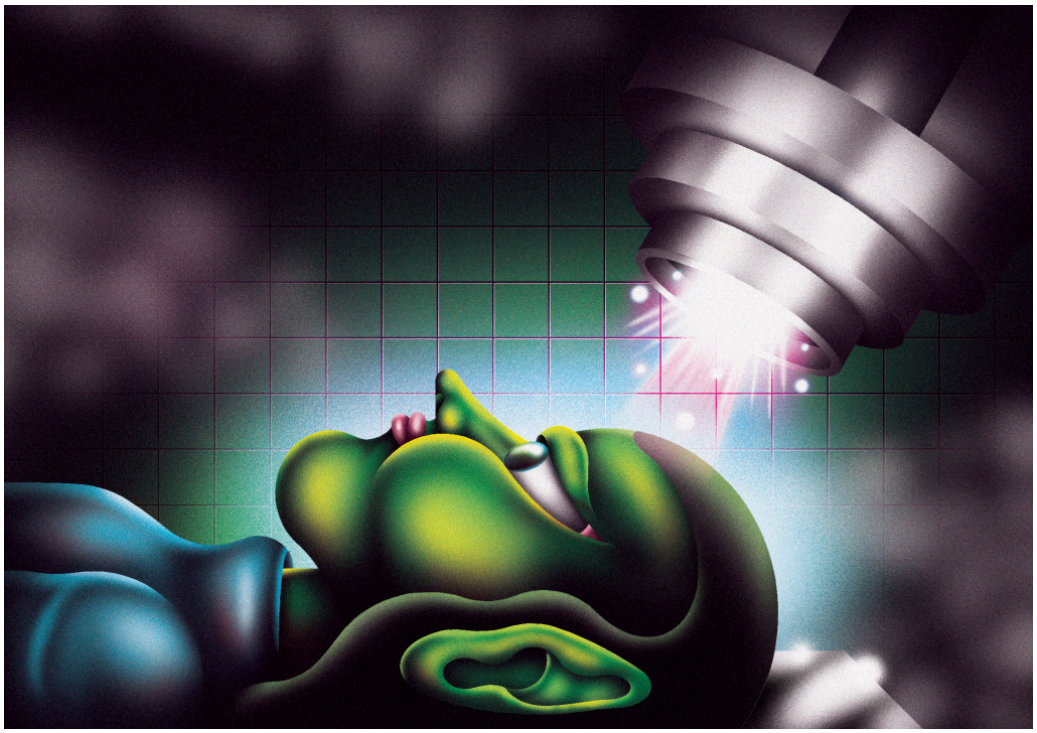

Illustration: Derek Ercolano

Particle therapy is used as a collective term for radiation therapy using heavy ions. In general, regular radiation therapy in Norway currently consists of photon therapy (high-voltage x-ray radiotherapy). The ion that is most commonly used in particle therapy is the proton, and of around 175 000 patients treated worldwide at the end of 2016, 150 000 were treated with proton therapy (1). The other ion in use today is the carbon ion, and globally a little more than 20 000 patients have received carbon ion therapy.

Although heavy ions have been used to a limited extent for therapeutic purposes since the 1950s, only in the last 20 years has this really become an intrinsic part of the cancer treatment programme. The number of patients treated has increased by a factor of almost ten in this period. The main advantage of proton and carbon ions in radiation therapy, compared with photons, is that the physical properties of the ions allow for a better radiation dose distribution for most tumours, so that they cause damage to the tumour rather than to normal tissue. This does not necessarily result in a higher cure rate, but in the adverse effects of radiation therapy (late effects) being less pronounced than is the case for current, regular photon therapy. This results in considerably improved quality of life for patients who live for many years after cancer treatment. A number of adverse effects may manifest themselves up to 15–20 years after radiation therapy, and therefore young patients, patients with a long life expectancy, and patient groups with major adverse radiation-related effects may derive most benefit from proton therapy.

Establishment of proton therapy in Norway

The final decision to establish proton therapy as a treatment option for Norwegian cancer patients, with the construction of proton centres in Oslo and Bergen, was reached in the context of Norway's National Budget for 2018. Particle therapy has been the subject of assessment as a form of treatment in Norway since 2009 (Box 1) (2–5). During this period, the Skandion clinic in Uppsala opened for clinical use in 2015 as the only clinic in Sweden, while Denmark is building a national centre in Aarhus that will open in autumn 2018. The Oslo centre will be built at the Norwegian Radium Hospital, where it will complement the existing treatment programme and enable the hospital to become a complete cancer centre. Its treatment capacity will be almost identical to that of the

centre in Denmark, i.e. around 850 patients annually when all three treatment rooms are fully utilised, and in addition it will have a dedicated research room. The centre in Bergen is planned to comprise one treatment room and one research room.

Box 1 Assessment of particle therapy as a form of treatment in Norway

2010: A report from the Directorate of Health concluded that Norway should enter into a binding collaboration on proton therapy with the planned Skandion clinic in Uppsala, Sweden.

2013: A national working group, commissioned by the Norwegian Ministry of Health and Care Services, concluded that Norway should build a particle therapy centre providing both proton and carbon ion therapy.

2014: The idea phase for establishing regional proton centres located in Oslo, Bergen, Trondheim and Tromsø. Three options were considered: Current practice (no centres), gradual development of regional proton facilities, or establishment of proton facilities in all health regions by 2022.

2016: Concept phase planning with a view to deciding upon the final choice of concept and phasing in of proton facilities in Norway. The recommendation in the concept report was for the construction of two centres in Norway (Oslo and Bergen). The sizing of the facilities was to be based on relative population distribution and estimated need. In the longer term, centres were also to be developed in Trondheim and Tromsø to ensure optimal access to proton therapy in all regions.

2017: Pre-feasibility study phase based on the decision to establish proton therapy in Oslo and/or Bergen.

The benefits of proton therapy

Throughout the years of assessments in Norway, a great deal of discussion has taken place regarding the extent of the need for proton therapy, as well as the ethical aspects of the treatment (6–9).

The prevailing opinion based on our current knowledge is that the majority of children who are to receive radiation therapy with curative intent should be given proton therapy (6). It is known that reduced radiation to normal tissue reduces the risk of late effects and secondary cancer, and it is therefore highly probable that proton therapy is particularly advantageous for children (8). However, no randomised trials have been undertaken on children, as this is viewed as ethically problematic.

For adults the picture is more complex. Generally young adults with tumours in or near the central nervous system should be prioritised for the same reason as children. Chordomas, chondrosarcomas and ocular tumours that need external radiation therapy are considered to be relatively well-established indications for particle therapy (9, 10). In the case of sinonasal cancer, a number of studies have been undertaken that compared patient cohorts that have undergone particle and photon therapy. These studies have been included in a meta-analysis which concludes that particle therapy is beneficial for this diagnosis (11).

It has been estimated that the abovementioned established indications account for approximately 15 % of all particle therapy patients (12). For the remaining 85 % the indications are less certain. This group includes diagnoses such as lung cancer, breast cancer, prostate cancer, gastrointestinal cancer, gynaecological cancer, and cancer of the head and neck.

A paucity of randomised trials

Despite the fact that particle therapy has been in clinical use since the 1950s, few results from randomised trials are available (13). For many years attempts have been made to undertake such trials using proton therapy, but the results have not been forthcoming, presumably because it has proved difficult to recruit enough patients (14). There may be several reasons for this. The treatment plans for particle therapy most often entail lower radiation doses to normal tissue and a more individually tailored dose distribution to the tumour than is possible with photons. It may therefore be difficult to convince patients that there is genuine uncertainty related to the choice between particle and photon therapy. Another consideration is that the majority of proton therapy centres have been located in the United States, where the insurance companies do not cover treatment given as part of clinical trials.

An interesting question relates to whether there would have been any interest in measuring the clinical difference between particle and photon therapy in randomised trials if the two modalities had cost the same amount. Particle therapy is around three times more costly, however (13), and thus randomised trials are called for that demonstrate clinical gains. In future years, results from these types of studies will finally be available (13). It is worth mentioning that the issue is nothing new in the field of radiation therapy. Over a period of many years, new technology has been introduced (for example linear accelerators, radiation therapy based on CT imaging, intensity-modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT) and stereotactic radiation therapy), with almost no basis in randomised trials. Nevertheless, based on retrospective comparisons of therapeutic outcomes we know that these have provided improvements in treatment (15).

Model-based selection

In the absence of definitive results from randomised trials, so-called model-based selection constitutes an alternative strategy (16). When both proton and photon treatment plans are prepared for patients who do not fall within the standard indication group, it is shown that for some of these patients, the photon plan is almost as beneficial as the proton plan. Mathematical models have been developed that may assist in deciding which plan is most suitable. This applies particularly to prediction of the risk of adverse effects (Normal Tissue Complication Probability, NTCP). A study from the Netherlands on oropharyngeal cancer showed, for example, that half of the patients would be selected for proton therapy if the goal was to reduce the incidence of dysphagia (grade 2) as a side-effect of radiation therapy (17). The NTCP models can therefore be used as a tool for patient selection. Patients who receive proton and photon therapy should be followed up in order to measure the actual frequency of adverse effects. This can be transferred back to the NTCP models so that these are continuously improved and the accuracy of patient selection is enhanced.

Introduction of proton therapy in Norway

After many years of planning, the medical community now faces the tangible introduction and establishment of proton therapy in Norway in 2023. It is a prerequisite that the introduction of this treatment modality should form part of the international effort to increase knowledge regarding proton therapy. There should be equal access to

proton therapy throughout the country, and equal access to the related research facilities must be ensured. This represents a pleasing extension to the treatment programme for Norwegian cancer patients.

LITERATURE

1. Particle Therapy Co-Operative Group.. 2018. Particle Therapy Co-Operative Group.https://www.ptcog.ch (1.3.2018).

2. Protonterapi som behandlingstilbud til norske pasienter. Rapport fra arbeidsgruppe. Oslo: Helsedirektoratet, 2010.

3. Planlegging av norsk senter for partikkelterapi. Rapport utarbeidet av Helse Vest i samarbeid med Helse Sør-Øst, Helse MidtNorge, Helse Nord og Helsedirektoratet. Oslo: Helse og omsorgsdepartementet, 2013. http://www.medfys.no/nfmf-documents/Opplastet/downloads/2013/06/Planlegging_av_norsk_senter_for_partikkelterapi-_13_juni_2013.pdf (14.5.2018).

4. Idéfaserapport – Regionale sentre for protonterapi, Rapport utarbeidet av Helse Vest i samarbeid med Helse Sør-Øst, Helse Midt-Norge og Helse Nord. Oslo: Helse og omsorgsdepartementet, 2014. https://helse-nord.no/Documents/Styret/Styrem%C3%B8ter/Styrem%C3%B8ter%202014/20141217/Styresak%20146-2014-1%20Regionale%20protonsentre%20-%20id%C3%A9faserapport,%20vedlegg.pdf (14.5.2018).

5. Konseptfase – etablering av protonbehandling. Sluttrapport. Trondheim: Sykehusbygg HF, 2016.

6. Gondi V, Yock TI, Mehta MP. Proton therapy for paediatric CNS tumours - improving treatment-related outcomes. Nat Rev Neurol 2016; 12: 334 - 45. [PubMed] [CrossRef]

7. Waldeland E. Protonterapi i Norge? Tidsskr Nor Legeforen 2010; 130: 850 - 2. [PubMed][CrossRef]

8. Wang C, King CR, Kamrava M et al. Pattern of solid and hematopoietic second malignancy after local therapy for prostate cancer. Radiother Oncol 2017; 123: 133 - 8. [PubMed][CrossRef]

9. Combs SE. Does proton therapy have a future in CNS tumors? Curr Treat Options Neurol 2017; 19: 12. [PubMed][CrossRef]

10. Allen AM, Pawlicki T, Dong L et al. An evidence based review of proton beam therapy: the report of ASTRO's emerging technology committee. Radiother Oncol 2012; 103: 8 - 11. [PubMed][CrossRef]

11. Patel SH, Wang Z, Wong WW et al. Charged particle therapy versus photon therapy for paranasal sinus and nasal cavity malignant diseases: a systematic review and meta-analysis. Lancet Oncol 2014; 15: 1027 - 38. [PubMed][CrossRef]

12. Kjellberg J, Kürstein Kjellberg P. Partikelterapi i Danmark. Analyse av de økonomiske, organisatoriske og patient-relaterede konsekvenser og forudsætninger ved indførelse af partikelterapi i Danmark. København: Dansk Sundhedsinstitut, 2008. www.kora.dk/media/529774/dsi-2520.pdf (1.3.2018).

13. Durante M, Orecchia R, Loeffler JS. Charged-particle therapy in cancer: clinical uses and future perspectives. Nat Rev Clin Oncol 2017; 14: 483 - 95. [PubMed] [CrossRef]

14. Mitin T, Zietman AL. Promise and pitfalls of heavy-particle therapy. J Clin Oncol 2014; 32: 2855 - 63. [PubMed][CrossRef]

15. Bentzen SM. Randomized controlled trials in health technology assessment: overkill or overdue? Radiother Oncol 2008; 86: 142 - 7. [PubMed][CrossRef]

16. Langendijk JA, Lambin P, De Ruysscher D et al. Selection of patients for radiotherapy with protons aiming at reduction of side effects: the model-based approach. Radiother Oncol 2013; 107: 267 - 73. [PubMed][CrossRef]

17. Arts T, Breedveld S, de Jong MA et al. The impact of treatment accuracy on proton therapy patient selection for oropharyngeal cancer patients. Radiother Oncol 2017; 125: 520 - 5. [PubMed][CrossRef]

Publisert: 3. September 2018. Tidsskr Nor Legeforen. DOI: 10.4045/tidsskr.18.0250
Received 15.3.2018, first revision submitted 1.5.2018, accepted 14.5.2018.