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REVIEW

A Nordic-Baltic perspective on indications for proton therapy with strategies for identification of proper patients

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ABSTRACT

The beneficial effects of protons are primarily based on reduction of low to intermediate radiation dose bath to normal tissue surrounding the radiotherapy target volume. Despite promise for reduced long-term toxicity, the percentage of cancer patients treated with proton therapy remains low. This is probably caused by technical improvements in planning and delivery of photon therapy, and by high cost, low availability and lack of high-level evidence on proton therapy. A number of proton treatment facilities are under construction or have recently opened; there are now two operational Scandinavian proton centres and two more are under construction, thereby eliminating the availability hurdle. Even with the advantageous physical properties of protons, there is still substantial ambiguity and no established criteria related to which patients should receive proton therapy. This topic was discussed in a session at the Nordic Collaborative Workshop on Particle Therapy, held in Uppsala 14–15 November 2019. This paper resumes the Nordic-Baltic perspective on proton therapy indications and discusses strategies to identify patients for proton therapy. As for indications, neoplastic entities, target volume localisation, size, internal motion, age, second cancer predisposition, dose escalation and treatment plan comparison based on the as low as reasonably achievable (ALARA) principle or normal tissue complication probability (NTCP) models were discussed. Importantly, the patient selection process should be integrated into the radiotherapy community and emphasis on collaboration across medical specialties, involvement of key decision makers and knowledge dissemination in general are important factors. An active Nordic-Baltic proton therapy organisation would also serve this purpose.

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Introduction

Amongst different heavier particle therapy modalities, proton therapy (PT) is hitherto the most clinically used [1]. The beneficial effects of protons are primarily based on reduction of low to intermediate radiation dose bath to normal tissue surrounding the radiotherapy target volume [2]. The advantageous dose distribution is supplemented by altered biological mechanisms of action leading to a higher radiobiological effect and increased tumour cell kill, clinically accounted for as 10% in protons and indeed much higher for heavier ions such as carbons [3,4]. Although some uncertainty remains, the relative biological effectiveness (RBE) of protons relative to photons or ^{60}C is estimated to 1.1. With the superior dose deposition compared to photon-based radiotherapy, protons offer two major advantages; reduced dose to organs at risk adjacent to the target and potentially dose escalation in treatment of radio-resistant tumours. There is therefore a worldwide belief that PT can improve outcomes for a proportion of cancer patients for whom radiotherapy is indicated, and so far more than 200.000 patients have been treated with this modality [1].

In the Nordic countries, proton therapy builds on a legacy from the Gustaf Werner Institute in Uppsala treating cancer patients from the 1950ies [5]. As part of the planning process for a new Swedish proton therapy centre, a prognosis stating that 14–15% of all cancer patients receiving radiotherapy would benefit from proton therapy was published [6]. The new Swedish centre "Skandionkliniken" has been operational from 2015, but so far less than 1% of all Swedish cancer patients receiving radiotherapy have been treated with protons at the clinic in Uppsala. This percentage is similar in other countries with proton therapy facilities, such as Germany, France and Switzerland [1]. The major reasons for the relatively low number of cancer patients treated with PT have not been scrutinised systematically, but several possible causes exist. First, it is a widespread opinion that technical

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development of photon-related hardware (more advanced conventional linacs, the introduction of MR-linac) and software (intensity modulated radiotherapy, IMRT) has reduced the gap in physical dose distribution between photons and protons. Availability, with cost as the obvious challenge, has been and still is another important issue. Third, and very important, the existing knowledge base for PT is not sufficient. Dosimetric comparisons showing PT superiority compared to photon radiotherapy need to be supported by clinical studies showing that patients do benefit from PT.

While it is usually of obvious importance to generate evidence on beneficial effects of novel treatments, it has been argued that randomised clinical trials are unethical in the case of proton therapy because of the protons' advantageous physical dose distribution. On the one hand, there are strong arguments for carrying out randomised trials to prove the superiority of proton therapy - not least because of its high cost [7–9]. On the other hand, Goitein and Cox argued that saving a large proportion of the brain or the abdomen for a dose of 25 Gy will always be beneficial, and that large randomised trials are not required [10]. In between, Braunstein and Warren proposed that experts should guide policy where they feel that there is not equipoise (e.g., in paediatric cancer), whereas well designed clinical trials should be carried out among equivocal sites where the benefit is less clear [11,12]. The challenge is to draw the line of *no equipoise* and *equivocal* based on the evidence of year 2020.

The Nordic Collaborative Workshop on Particle Therapy held in Uppsala in November 2019 focused on several issues related to PT. Establishing a consensus on PT indications as of today and strategies for identifying patients assumed to benefit from PT was the theme of one of the meeting workshops. This paper aims to summarise the workshop discussions and conclusions and discusses lines of development needed to ensure the optimal use of proton therapy in the Nordic-Baltic region.

Indications for proton therapy

A principle goal for PT is to reduce treatment related morbidity and long-term survival is therefore a prerequisite. Patients with incurable cancer and expected short survival should therefore in general not receive protons. Comorbidity is also a feature influencing the indication. For example, in patients suffering from coronary artery disease and ischaemic heart failure qualifying for NYHA class IV, the 1-year survival is 60–70%. Such a patient, although suffering from a curable neoplasm, will probably not benefit from protons. Also, in patients with radio-resistant neoplasms, protons may allow escalation of radiation dose and thereby increase the chance of cure without or with only modest increase in morbidity.

As alluded to, there are only very few randomised studies evaluating the effect of treatment with protons and so far very few randomised controlled trials comparing protons and photons have been published [13,14]. One compared passive scattered protons to IMRT for locally advanced non-small cell lung cancer and failed to show reduced morbidity with protons [13]. However, there are several shortcomings of this study, emphasising the importance of obtaining a robust trial design. A phase 2 study in locally advanced oesophageal cancer randomising between preoperative protons and IMRT did show that proton patients had less total toxicity burden (composite adverse effects) compared to photon patients [14]. Numerous cohort studies suggest equivalence in tumour control and favourable toxicity profiles of protons compared to photons [15,16]. Even more papers on treatment planning exercises demonstrate obvious advantageous dose distributions with protons in a number of clinical indications [17–19].

Neoplastic entity

Most review papers and guidelines have, on the basis of modest level evidence, pointed at few and relatively narrow indications for proton therapy based on neoplastic entity [20–23]. Examples are childhood cancers and adult medulloblastoma, meningioma and ependymoma where PT is often considered beneficial. Tumour entities such as chordoma and chondrosarcoma, in which the possibility of dose escalation is an important co-factor, are frequently listed as proton therapy indications based on favourable published outcomes. This applies not least to chordomas and chondrosarcomas in the base of the skull and the sacrum where gross total resection is most often hard to accomplish, whereas chondrosarcomas in other locations are often treated surgically. The possibility of dose escalation is favourable also in the case of carbon ion therapy for adenoid cystic carcinoma.

Anatomy, localisation and size of radiotherapy target volume

The high importance of radiotherapy target volume localisation is mirrored by its key position in proton therapy literature and guidelines [20–23]. This is related to the sparing of non-target tissue and a promise for lower toxicity, particularly in the long term, which probably is the main advantage of PT. For targets in the vicinity of an organ at risk (OAR) such as the brain stem, spinal cord, optic apparatus, heart and rectum, protons can be prioritised, and the sparing effect of protons increases with increasing size of the radiotherapy target volume. Lowering the dose to an OAR is of particular interest where radiotherapy dose objectives to the target cannot be met due to constraints related to the OAR. An example of disease sites listed as suitable for proton therapy is given in Table 1, which is a part of ASTRO proton beam therapy guidelines [23]. However, it should be kept in mind that a scanned proton beam has a less sharp lateral penumbra [24]. That is one reason why a proton beam will not always provide a dose distribution superior to photons. Besides the lateral penumbra, there are still a number of physical and biological issues related to motion, air-filled cavities, adaptation to anatomical changes, range uncertainties and radiobiological effectiveness of protons and heavier ions that are not fully solved, and to some extent limit the full utilisation of particle therapy [25].

Table 1. List of indications for proton therapy as defined by ASTRO*.

Group 1 indications for proton therapy
Malignant and benign primary central nervous system tumours
Advanced (e.g., T4) and/or unresectable head and neck cancers
Cancers of the paranasal sinuses and other accessory sinuses
Non-metastatic retroperitoneal sarcomas
Re-irradiation cases where cumulative critical structure dose would exceed tolerance dose
Hepatocellular cancer
Ocular tumours, including intraocular melanomas
Tumours that approach or are located at the base of skull, including but not limited to chordomas and chondrosarcomas
Primary or metastatic tumours of the spine where the spinal cord tolerance may be exceeded with conventional treatment or where the spinal cord has previously been irradiated
Primary or benign solid tumours in children treated with curative intent and occasional palliative treatment of childhood tumours
Patients with genetic syndromes making total volume of radiation minimisation crucial, such as but not limited to NF-1 patients and retinoblastoma patients
Group 2 indications for proton therapy
Non-T4 and resectable head and neck cancers
Non-metastatic prostate cancers
Breast cancers
Thoracic malignancies, including non-metastatic primary lung and oesophageal cancers
Abdominal malignancies, including non-metastatic primary pancreatic, biliary and adrenal cancers
Pelvic malignancies, including non-metastatic rectal, anal, bladder and cervical cancers

Group 1 indications are defined based on medical necessity and published clinical data. Group 2 indications are a list of specified but not complete indications for proton therapy in the context of evidence development [23].
*American Medical Association. Proton beam therapy model policy. 2017. Available from www.astro.org. [cited 2020].

Age

Proton therapy is generally accepted as a standard of care in radiotherapy of most cancers in children and young adolescents based on the expectancy of reduced risk of severe late effects and secondary cancer [26,27]. There is a general belief that the risk of secondary cancer is a function of integral dose to the body, but the steepness of the function and the possibility of a threshold dose for development of secondary cancer have not been clarified [28]. For most organs a higher radiation dose will lead to a higher risk of secondary cancer, with an exception for the thyroid [29–31]. Use of pencil beam scanned (PBS) protons increases the conformity and reduces the integral body dose and the neutron dose [32]. This will primarily have impact for young patients receiving radiation therapy for brain, head and neck cancer, lymphoma, truncal sarcoma, breast and pelvic neoplasms. Although secondary cancer probably is one of the serious late effects seen, one should also remember that a reduction of the rate and severity of other detrimental late effects such as cognitive decline, cerebro- and cardiovascular disease and endocrine dysfunction will be clinically meaningful for young individuals receiving radiotherapy [33–35].

Second cancer predisposition

The impact of hereditary factors on the risk of developing a secondary cancer after radiation therapy is not clearly understood. However, in case of cancer syndromes such as Li Fraumeni and neurofibromatosis, which entail a weakened DNA repair ability, radiation is related to excess risk of secondary cancer [36,37]. It is also known that patients treated for retinoblastoma and Ewing sarcoma have an increased risk of secondary cancer compared to other cancer patients [38,39]. Whether this is related to a hitherto unknown cancer predisposition or not is unknown. In patients with these diagnoses or cancer predisposing hereditary syndromes, the body radiation dose should be minimised whenever radiotherapy is indicated – making PT an attractive modality.

Combined therapy approach and dose escalation

Some of the largest gains in radiation therapy are in patient groups where radiation is part of a multidisciplinary approach, often combined with a systemic antineoplastic therapy [40–44]. A large amount of evidence has shown that radiation related morbidities increase with addition of chemotherapy and biological therapies, thereby motivating to minimise radiation exposure to organs at risk. Similarly, organ sparing approaches may be important in cases where very high doses are desired to obtain optimal local tumour control, as in the case of chordoma [45].

Re-irradiation

Re-irradiation has been put forward as an important indication for proton therapy and the main reason for this is the ability of protons to spare non-target tissue for irradiation dose. This capacity enables re-irradiation to adequate doses in problematic anatomical localizations, e.g., in the vicinity – although not immediate - of critical OAR. It should be kept in mind, however, that range uncertainties and penumbra issues might be potential problems when the radiotherapy target volume is touching the OAR.

Selection by comparative treatment planning

Comparative planning is an appealing strategy for decisions on photons or protons for individual patients. In addition, it may be used as a biomarker to identify patients for randomised clinical trials comparing photons and protons. The first part of comparative planning is principally an easy task: for a given radiotherapy target volume a photon plan and a proton plan are made. The modality that gives the best results in terms of OAR dose distribution can be selected.

However, making optimal proton therapy plans presupposes experience and skills which may be basic and suboptimal compared to experience in photon planning. This raises questions if the comparison is skewed and it is important that comparative planning is performed by skilled professionals in a proton centre or network. This is not least true whenever there is scarcity of time, such as in medulloblastoma were radiotherapy should start preferably by day 28 and at the latest by day 40 from surgery. Furthermore, the basis for models in use when comparative evaluation criteria shall be defined is seldom built on strong evidence.

ALARA and dose volume metrics

As low as reasonably achievable (ALARA) radiation dose to non-target organs or OAR is a general principle in all radiotherapy planning. This concept has also been proposed in the selection of patients for proton therapy; if a treatment plan comparison between protons and photons reveals that protons results in less dose to critical organs at risk, protons should be preferred. However, a reduction in morbidity will only be observed under certain conditions. As a starting point, it is a prerequisite that there is a relevant and significant morbidity caused by photon irradiation, and secondly the proton dependent radiation dose reduction should be of such magnitude that it results in clinically significant reduced toxicity. With this in mind, selection criteria based on dose-volume metrics have started to emerge for proton therapy [46]. For example, a model has been constructed for selection of patients with brain tumours both in Sweden and Denmark. Danish selection criteria advise patient selection based on dose-volume metrics to whole brain (minus CTV and brainstem), hippocampus, pituitary gland, brain stem and optic system, some of them being age-dependent [47]. However, these selection criteria are pragmatic and based on weak evidence.

NTCP models

The normal tissue complication probability (NTCP) model has been proposed as a tool for selection of patients for proton therapy for some neoplastic entities [48]. Difference in terms of NTCP (ΔNTCP) can be assessed by comparing doses to OAR from photon and proton plans of individual patients. Regulatory bodies need to decide how large this ΔNTCP should be to justify referral for proton therapy. It is assumed that dose-response relationships known from treatment with photons can be used to predict improvement in morbidity profiles when photons are exchanged for protons, and that a reduction in dose to an important OAR by use of protons translates directly to a reduction in morbidity risk.

To illustrate the heterogeneity of already existing NTCP models with relevance for selection of patients for particle therapy, we did a review of published models. A large number of models for 3 D-CRT and IMRT were found for head and neck, breast, lung and prostate cancer (Supplementary Tables 1–4 and summarised in Table 2). They focus on various objective measures or morbidities scored by different systems related to dose-volume metrics in various OARs and using a range of statistical models. In 19 papers on NTCP models predicting morbidity risks of radiotherapy of the head and neck region, nine organs were studied. Morbidity was assessed by several endpoints and analyses were based on Lyman-Kutcher-Burman (LKB) model or logistic regression analysis. Similar heterogeneity was observed for NTCP-models related to radiotherapy of breast, lung and prostate cancer. There was a lack of published NTCP models for the brain and abdominal targets other than prostate and bladder.

Discussion

Selection of patients for particle therapy varies considerably across the world and is dependent on national guidelines, tradition, healthcare organisation, costs and community factors. Reimbursement practice determined by insurance companies or national bodies will often define patient groups relevant for referral to particle therapy. Cost differences between photons and protons may vary between tumour types and are dependent on fractionation schedule, but are generally 2–3 times higher for protons [49,50]. Nonetheless, protons may be cost-effective although cost-effectiveness analyses of protons are based on assumptions and entail great uncertainty. Analyses assuming sparing of cognitive and neuroendocrine functions indicate that protons are cost saving in treatment of childhood medulloblastoma [51,52]. Other tumour types have been assessed, but with even less clear conclusions [53]. Prospective clinical data are required for more comprehensive investigations on this issue.

Availability of particles, which varies considerably across the world, is also a very important factor for patient selection. With a growing number of particle therapy installations, availability will not be as limiting in the Nordic-Baltic region in the near future. Referral practice should be seamless and smooth and referral criteria should be based on guidelines related to neoplastic entities, age, tumour localizations and clinical trial inclusion. This will facilitate generation of clinical evidence to support the theoretical advantages of proton therapy, leading to improved evidence-based guidelines for proton therapy and further development of referral practice. The support of clinical studies is of utmost importance.

In the Netherlands, the model-based indication methodology was approved by the health Council and the Health Care Insurance Board and is now an accepted strategy for proton therapy patient selection. It should be considered as a biomarker that predicts a patient's likelihood of benefiting from one or the other therapy and should be used for enrichment of randomised clinical trials. The model-based approach is appealing since it relates directly to the main focus of proton therapy, which is to reduce radiation related morbidity. However, the model also has shortcomings. First of all, it assumes equality or at least a known relationship between biological effect of photons and protons, which is still a controversial matter [54]. The finding of a variation in linear energy transfer (LET, amount of energy deposited) and RBE around the Bragg peak, the point where the proton beam stops and deposits most of its energy, complicates this

Table 2. Summary of normal tissue complication probability (NTCP) models relevant for particle therapy*.

	Number of papers/patients	Models	Organs at risk	Principal end-point
Head and neck cancer	19/3.956	LKB (7) Logistic regression (12)	Parotid glands (8) Other salivary glands (1) Constrictor muscles (5) Supraglottic larynx (1) Pharynx (1) Oral cavity (2) Thyroid gland (2) Cochlea (1)	Salivary flow (5) Xerostomia (1) Organ specific quality of life (5) Dysphagia Video fluoroscopy (1) Tube feeding (1) Mucositis (4) Hypothyroidism (2) Tinnitus (1)
Breast cancer	11/13.586	LKB (9) Logistic regression (4)	Heart (2) Lung (2) Skin (2) Breast (5)	Cardiac mortality (1) Cardiac events (1) Pneumonitis (1) Lung injury (1) Skin toxicity (2) Breast fibrosis (4) Aesthetic outcomes (1)
Lung cancer	11/2.847+**	LKB (10) Logistic regression (2)	Lung (7) Oesophagus (4)	Pneumonitis (7) Oesophagitis (4)
Prostate cancer	23/11.372	LKB (16) Logistic regression (9) Artificial neural network (1)	Rectum (20) Bladder (3)	Proctitis/necrosis/fistula/stenosis (1) Rectal bleeding (12) Stool frequency (1) Faecal incontinence (8) Gastrointestinal toxicity (3) Genitourinary toxicity (2) Urinary incontinence (1) Haematuria (1)

*For study details, see Supplementary Tables 1–4. **One study did not report patient numbers; one study was a review of published studies.

matter even further. Clinical treatment planning systems are only able to calculate a distribution of physical dose and a validated algorithm for LET/RBE dose calculation has yet to be developed.

A large number of NTCP models have been established, primarily for head and neck, lung, breast and rectum cancers. These models are simplistic and based on a few well-defined morbidities and do not include low dose bath to other structures. NTCP models may therefore considerably underestimate normal tissue saving effects of protons. Model selection implies a ΔNTCP larger than 5 or 10 percent for late effects to justify referral of a patient to protons. However, the outlier values 5 and 10 percent represent large differences when it comes to severe side effects with major impact on a patient's quality of life, such as swallowing dysfunction. Also, existing models were created aiming at characterising dose dependent radiation morbidity in photon radiotherapy - not model-based selection. Because of significant variability in patient selection, concomitant systemic therapies, statistical methods, organs and morbidity endpoints used for modelling, there is great variability in conclusions. Furthermore, most models are based on physicians' scores, imaging or functional measures and not on patient reported outcomes, which are probably the most relevant endpoints, and the majority of models have not been validated.

Finally, assuming equal conditions and quality in treatment planning for photons and protons is illusionary. The first years of comparative treatment planning in the Netherlands, Denmark and Sweden have shown that extensive education, training and dedicated time for proton treatment planning are necessities to achieve fair conditions in treatment plan comparisons. There is an obvious need for more experience in model-based selection and to have the models' clinical value tested in randomised trials.

In the Nordic region, Boron neutron capture therapy (BNCT) is in its most advanced stages in Helsinki, Finland, where glioblastoma and head and neck cancer patients were treated between 1999 and 2011. Clinical operation on a new hospital based facility is planned from 2021. So far, there is consensus that BNCT should still be regarded an experimental treatment modality.

Conclusion

With two existing Scandinavian PT facilities (Uppsala, Sweden and Aarhus, Denmark) and two more under construction (Oslo and Bergen, Norway), PT capacity in the Nordic-Baltic region will become among the highest in the world. To ensure that all patients suitable for PT are offered this as standard of care or as part of a clinical study, several measures are necessary. On a political level, appropriate reimbursement strategies for PT are necessary, as well as establishment of clinical trial units and funding opportunities for clinical PT-related research. This is a prerequisite for generation of hard evidence related to PT. Furthermore, knowledge dissemination is vital. In Sweden, patient selection and preparation for treatment including treatment planning take place in referring oncology centres. The Danish approach builds on selection by comparative treatment planning taking place in the referring oncology centres in 80% of the patients. There is a need for referral guidelines and teaching courses, as well as involvement of key decision makers such as multidisciplinary national tumour group leaders. Also, the referral process from outside institutions must be seamless and referring oncologists must view PT as an integral part of patient care. An active Nordic-Baltic proton therapy organisation would be an ideal organisation for heightening

professional and public PT awareness and enable collaborative studies, clinical as well as translational.

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