Proton radiotherapy

Selection of patients for radiotherapy with protons aiming at reduction of side effects: The model-based approach

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A R T I C L E   I N F O

Article history:
Received 28 March 2013
Accepted 11 May 2013
Available online 5 June 2013

Keywords:
Proton therapy
Patient selection
Randomisation
NTCP-models

A B S T R A C T

Most new radiation techniques, have been introduced primarily to reduce the dose to normal tissues in order to prevent radiation-induced side effects. Radiotherapy with protons is such a radiation technique that due to its superior beam properties compared to photons enables better sparing of normal tissues. This paper describes a stepwise methodology to select patients for proton therapy when the primary aim is to reduce side effects. This method has been accepted by the Dutch health authorities to select patients for proton therapy. In addition, an alternative method is described in case randomised controlled trials are considered not appropriate.


Radiotherapy with protons is a promising technology in the field of modern radiation oncology. From a physical point of view, radiotherapy with protons has important advantages compared to the currently used photons due to its unique energy absorption profile. Proton beams are typically manipulated to generate a spread-out Bragg peak to yield a flat dose profile across the target volume followed by a rapid decrease to nearly zero dose distally from the target, which results in highly conformal dose depositions in the target.

Based on the physical principles of proton beams, there are two main applications where the superior properties of protons can be expected to produce a clinical benefit for cancer patients, i.e. improvement of local tumour control and prevention or reduction of radiation-induced side effects.

Certain categories of patients treated with photon therapy receive a radiation dose that is insufficient to fully eradicate the tumour, in particular when this tumour is located close to critical structures, hampering further dose escalation. By using protons, the energy dose deposited in the target can be optimised without simultaneously increasing the dose to critical organs. This strategy will be particularly useful when dose escalation can be expected to improve tumour control. For this purpose, conducting randomised controlled trials (RCT) in order to investigate if dose escalation with protons results in better local control without enhancing the dose to critical structures and thus increasing toxicity, would be the most suitable and valid approach.

A substantial percentage of cancer patients treated with radiotherapy may suffer from significant radiation-induced side effects negatively impacting quality of life [1–5]. In these cases, protons might be applied in an attempt to prevent or significantly reduce side effects by decreasing the dose to healthy tissues while maintaining the dose administered to the target. This approach is based on the observation that for many critical organs or normal tissues, the probability of radiation-induced side effects depends on the – relative and absolute – volumes of Organs at Risk (OARs) receiving certain doses of radiation [6–12]. Based on the results of numerous in-silico planning comparative studies, comparing dose distributions to OARs between photon and proton radiotherapy, it can be expected that proton radiotherapy will result in a reduction of radiation-induced side effects [13–21]. When translating these results from in-silico planning comparisons (ISPC) an optimal study design is required to clinically validate the benefit of protons when specifically applied to prevent side effects rather than improve tumour control [22].

Some late radiation-induced complications have very long latency times, e.g. the development of cardiovascular complications after irradiation for breast cancer generally takes at least 5 years, and the incidence in particular continues to increase over twenty years after initial treatment [23–25]. In such cases, an RCT would take at least 15–20 years to generate useful information regarding the primary endpoint. For such late endpoints, it would be unrealistic to conduct an RCT, given that radiotherapy is a rapidly
evolving technology where further improvement can be expected to occur much faster and the results based on outdated technology investigated in such RCT will never be applicable in future clinical practice.

Several authors have argued that in the case of proton radiotherapy, applying the standard RCT methodology in such toxicity-reducing trials would result in randomising patients between two radiation delivery technologies that yield the same tumour dose distribution and will thus yield the same tumour control probability, but where one technique would result in a predictably left-shifted (unfavourable) dose-toxicity curve. Such a situation is inconsistent with the general ethical prerequisite for RCT’s, the principle of ‘equipoise’ (balanced uncertainty) [26], where a certain outcome may be expected, but must not be predictable based on reasonably validated prediction models. This is particularly true in situations, where the predictable difference in toxicity is relatively large with an expected major impact on quality of life (e.g. severe visual impairment). As a consequence, RCT’s investigating the added value of protons compared to photons with regard to reduction of side effects, run the risk of being ethically compromised.

Considering that RCT’s are not always the most suitable methodology or practically feasible for validating proton radiotherapy, the following questions arise: (1) how to individually tailor the indication criteria in order to select patients who are expected to benefit from radiotherapy with protons in terms of reducing the risk of radiation-induced side effects, and (2) can we apply a methodologically sound approach other than RCT’s for the clinical validation of the predicted benefit when patients are actually treated with protons, when an RCT is considered not feasible.

Addressing these questions, a stepwise approach, referred to as the model-based approach, has been introduced in the Netherlands to properly select patients that will benefit from protons in terms of prevention of side effects and, subsequently, to validate the clinical benefit of protons compared to photons in case an RCT is considered inappropriate for reasons mentioned above. This model-based approach, which has been adopted by the Health Council of the Netherlands to select patients for proton radiotherapy will be described and discussed in the present paper.

**The model-based approach**

The model-based approach consists of two consecutive phases: phase α, aiming at the selection of patients who may benefit from protons, and phase β, aiming at the clinical validation of proton therapy by so-called sequential prospective observational cohort (SPOC) studies using appropriate historical comparisons as a reference or by RCT’s in selected situations.

**Phase α: model-based indications**

Phase α of the model-based approach consists of 3 steps, including: (1) the development and validation of Normal Tissue Complication Probability (NTCP) models in patients treated with state-of-the-art photon radiotherapy; (2) individual in silico planning comparative studies [21], and (3): estimation of the potential benefit of the new radiation technique in reducing side effects by integrating the results of ISPC into NTCP-models. The main purpose of these 3 steps is to select patients that will most likely benefit from protons compared to photons in terms of NTCP-value reductions.

**Step 1: NTCP models**

The basic principle in the development of most new radiation delivery techniques is to obtain the required dose to the target with the lowest possible dose to the normal tissues, assuming a relationship between dose distributions in OARs and the development of radiation-induced side effects. These relationships are generally described by NTCP-models. In general, the estimated risk for a given side effect, i.e. the NTCP-value, will increase with increasing dose to and increasing volume within an OAR that receives a certain dose (Fig. 1). The dose-volume parameter or parameters that are most important may vary widely between different side effects, e.g. the mean dose to the parotid glands is the most important prognostic factor for the development of hyposalivation and xerostomia [7], while for radiation pneumonitis, different dose-volume parameters are important, such as the mean dose to the lungs, the V5 (i.e. the percentage of the volume of the lungs that receives a dose of 5 Gy or more) and the V20 [11]. Moreover, the risk of some side effects may depend on more than one dose-volume

![Fig. 1. Example of a Normal Tissue Complication Probability (NTCP) model describing the risk estimation on a given side effect (NTCP-value) as a function of the most relevant dose distribution parameter (in this case the mean parotid dose).](image-url)
parameter (e.g. the risk of grade 2–4 swallowing dysfunction depends on the mean dose to the superior pharyngeal constrictor muscle and the mean dose to the supraglottic area) [27]. The most reliable dose-volume parameters are generally obtained from prospective cohort studies and should preferably be validated in independent cohorts. When the most important dose-volume parameters are established, radiotherapy treatment planning can be optimised by reducing these specific parameters as much as possible, without jeopardising the required dose to the targets and without enhancing the dose to other critical structures. Often the performance of the predictors can be further improved by adding patient related (e.g. general status, age) or environment related (e.g. concomitant chemotherapy) variables producing multivariable NTCP-models that can be expressed as nomograms [28,29].

**Step 2: in silico planning comparative (ISPC) studies**

The knowledge gained from NTCP-models can be used to identify patients who are expected to benefit from protons, using computer-based studies in which the dose distributions obtained with protons are simulated and compared with the best currently achievable photon treatment in each individual patient (individual tailoring of indications based on ISPC studies) (Fig. 2) [13–21]. ISPC studies eventually tell us the differences in the relevant dose distribution parameters to the targets and OARs between different radiation delivery techniques (e.g. between 3D-CRT and IMRT; IMRT and protons) either on a population level or on the level of individual patients. However, these differences in dose distribution parameters do not automatically entail a benefit in terms of a reduction in the risk of a given side effect. This is particularly the case if the development of a side effect depends on more than one dose-volume parameter, or if other confounding factors, such as the administration of concomitant chemotherapy, beside dose distributions influence the development of radiation-induced side effects, e.g. as has been found for rectal complications after radiotherapy for prostate cancer [30] and for radiation esophagitis after radiotherapy for lung cancer [31].

**Step 3: estimation of the clinical benefit**

The final step in phase \( \alpha \) will be to determine to what extent the advantage in physical dose distribution will translate into a clinically relevant beneficial effect by integrating the outcome of an individual ISPC-study into NTCP-models. In other words, will the reduction in dose translate into a lower NTCP-value? This step is required as similar absolute or relative reductions in the most relevant dose distribution parameters will not always translate into the same amount of reduction in NTCP values as illustrated in Fig. 3. The clinically relevant toxicity-reduction depends on the shape of the NTCP-curve and on the initial value of the dose distribution parameter (Fig. 3). Moreover, in case the risk of side effects depends on other factors as well, e.g. the administration of concurrent chemoradiation, the same reduction in dose could translate into markedly different NTCP-value reductions. For some side effects, the risk estimation may depend on two dose distribution factors, such as in the case of grade 2–4 swallowing dysfunction.

![Fig. 2](image-url). Example of an individual In Silico Planning Comparative study in a patient with cT3N0M0 oropharyngeal cancer. In this case swallowing-sparing IMRT (SWIMRT), aiming at sparing to the parotid glands, the superior pharyngeal constrictor muscle (superior PCM) and supraglottic area, was compared to swallowing-sparing intensity modulated proton therapy (SWIMPT). Efforts were made to reduce the dose to the parotid glands as much as possible and subsequently to reduce the dose to the superior PCM and supraglottic areas based on the NTCP-model published by Christianen et al. [27]. Details on the SWIMRT and SWIMPT techniques have been previously described. In this case, a marked reduction of the dose to the supraglottic area and both parotid glands could be obtained with protons. The superior PCM could be spared to a lesser extent because this OAR partly overlapped with the PTV. Upper left panel: Transversal CT-slides comparing photons with protons. There is a clear sparing of both parotid glands with protons and moderate sparing of the superior PCM. Upper right panel: sagittal CT-slides comparing photons with protons particularly illustrating sparing of supraglottic area (yellow area). Lower left panel: dose volume histograms of the superior PCM and supraglottic area comparing photons with protons. Lower right panel: dose volume histograms of the parotid glands comparing photons with protons.
In this way, the NTCP-value reduction for each individual patient can be estimated. Indeed, recent ISPC studies have shown that the estimated NTCP-reductions of protons compared with photons may vary widely among individual patients with apparently similar tumours (primary site and stage), e.g. in clinically node-negative oropharyngeal cancer patients, the NTCP-value

Fig. 3. Translation of the results of the individual ISPC-study depicted in Fig. 2 with regard to swallowing dysfunction RTOG grade 2–4. This toxicity endpoint depends on the mean dose to the superior PCM and to the supraglottic area. The upper (dark blue) and lower curves (light blue) describe the relationship between the mean dose to the PCM and the risk on grade 2–4 RTOG swallowing dysfunction when the mean supraglottic dose is 34.5 Gy (SWIMRT) and 13.5 Gy (SWIMPT), respectively, according to the NTCP-model described by Christianen et al. [27] the dose reductions to these two structures obtained with SWIMPT results in an estimated NTCP-value reduction from 21% to 7%.

Fig. 4. Translation of the results of the individual ISPC-study depicted in Fig. 2 with regard to xerostomia. The reduction of the mean parotid dose from 30.1 Gy to 18.4 Gy (red arrow: example Fig. 2) corresponds with an estimated NTCP-value reduction for severe xerostomia from 50% to 24% according to the NTCP-model published by Semenenko. However, exactly similar absolute dose reductions (red arrow: other example) result in a minimal estimated NTCP-value reduction when the initial dose is much higher, due to the shape of the NTCP-curve.
reductions that could be obtained with Intensity Modulated Proton Therapy (IMPT) as compared to IMRT varied between 8% and 28% for hyposalivation and between 4% and 18% among patients for patient-rated xerostomia [32–34]. The percentage of individuals who will be ultimately selected for proton radiotherapy will then depend on the threshold chosen for the NTCP-value reductions of the side effects in question. If, in this example, a threshold of 10% NTCP-value reduction would be applied for hyposalivation, 70% of the patients would be selected for proton radiotherapy.

Whenever the integration of the results of an individual ISPC study indicates that proton therapy is not expected to provide a clinically relevant NTCP-value reduction, there is consequently no reason to select this patient for proton therapy. Alternatively, in that case, the available best photon technique should be offered. In this respect, it should be emphasised that it does not make sense to include such patients in an RCT either, as there is no benefit to be expected from the new technique. In this regard, it would make sense to introduce this procedure also for selecting patients for RCT’s. In particular when the results of ISPC studies indicate that only a relatively small percentage of patients is likely to benefit from protons, the model-based approach is required to prevent false negative results.

Phase β: clinical validation

Prospective observational study

The abovementioned model-based approach results in the selection of a specific cohort of patients that will be eligible for treatment with protons, i.e. patients with an expected NTCP-value reduction beyond the defined threshold (e.g. 10%) (Fig. 5). From this point of view, it would be methodologically unsound to compare the toxicity results of these patients with the results of those not selected for protons after the same selection procedure. It is obvious that patients with no or minor overlap, or those with major overlap between target volumes and OARs are less likely to benefit from a more conformal radiation dose delivery. As a consequence, these patients will by definition bear different risk profiles for radiation-induced side effects and would negatively or positively bias the results when compared with patients actually selected for proton radiotherapy. Therefore, it is preferable to follow exactly the same model-based procedure in patients who have been or currently are treated with photons irrespective of the outcome of phase α. In this way, the results obtained in a population treated with the current standard (e.g. photon IMRT) can be considered a valid historical reference for those who will be treated...
actually treated with protons. Moreover, this reference population can be used for the statistical power analysis in order to estimate the required number of patients needed to be treated with protons to show a significant benefit of the new technique.

An important prerequisite of such an approach is that patients be subjected to exactly similar follow up procedures in which relevant baseline and treatment characteristics, acute and late radiation-induced morbidity and patient-rated quality of life are determined in a well structured standardised prospective programme. Preferably, similar prospective observational studies should already be conducted and performed among patients treated with photons before proton therapy is available to avoid selection bias based on phase \( \alpha \).

The validity of protons can then be determined in two ways. First, the difference in the incidences of side effects between the two techniques can be evaluated by direct comparison. Second, the NTCP-model obtained in patients treated with photons should be validated in those treated with protons.

**Discussion**

The model-based indication methodology as described in the current paper was developed following lively discussions on how to clinically introduce proton therapy in the Netherlands. The current practice in the Netherlands is that new treatment modalities will only be approved for reimbursement by health care insurance companies if there is level I-II scientific evidence. This kind of evidence is not available for proton therapy and it was expected that it would not be available for the next decade, assuming that RCT’s for radiation technologies aiming at reduction of side effects will be difficult to perform for previously discussed reasons and may be ethically unjustified due to lack of equipoise. Moreover, RCT’s or other clinical study designs evidently can only be performed when sufficient capacity for proton therapy is available. Eventually, the model-based approach was approved by the Health Council and by the Health Care Insurance Board that advises the Minister of Health and guides implementation of procedures into the Dutch statutory health insurance. This approach will enable future Dutch proton centres to treat patients with proton therapy, who will likely profit from this new technology, and whose treatment will therefore be reimbursed, if predefined nationally agreed-upon indication criteria based on expected NTCP-value reductions are met. It will be mandatory that patients treated with protons will be subjected to standard follow up programmes that are similar to ongoing follow up programmes for patients currently treated with photons.

Recently, Vergeer et al. applied the same model-based approach to estimate the benefit of IMRT over 3D-CRT in patients with head and neck cancer [35]. In that study, the authors showed that the reduction of the mean dose to the salivary glands as obtained by IMRT indeed resulted in lower estimates of patient-rated and physician-rated xerostomia. Later on, similar effects were found in a reduction of the mean dose to the salivary glands as obtained by IMRT compared to 3D-CRT. However, in some patient groups, e.g. in head and neck cancer, several studies have reported that patient’s anatomy may significantly change during a course of fractionated radiation regarding both the tumour volume and target volumes as well as the surrounding normal healthy tissues [37–38]. Such changes are important when highly conformal treatment planning techniques like protons are considered and may result in marked differences between the planned and the actually delivered dose distribution [39]. As protons are more sensitive to variations in density heterogeneities along their beam path and therefore to patient setup errors, these changes may in some cases severely jeopardise adequate dose coverage to the target and thus hamper locoregional control. In addition, daily set up errors may also cause deviations between the actually given dose and the prescribed dose. These problems, however, account for both RCT’s and sequential prospective cohort studies. Therefore, clinical validation studies require extensive measures to ensure adequate target dose distribution, including smart beam set up configurations, robust planning techniques (e.g. Distal Edge tracking, Probabilistic Planning [39–43]), routine image-guided radiotherapy and plan adaptation and extensive quality assurance programmes.

**Conclusion**

Radiotherapy with protons is a promising radiation technique, which can be used to reduce the dose to OARs, resulting in less radiation-induced side effects with similar dose to the target and subsequent locoregional tumour control. For the introduction of proton radiotherapy a two-phase model-based approach has been
adopted by the Dutch Health Council and the Dutch Health Care Insurance Board that permits concomitant validation of the technique. Patients will be eligible for proton treatment in the Netherlands, if individually applied validated NTCP models predict clinically relevant less toxicity. Method and results will be validated using sequential prospective cohort studies.

**References**


