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Proton radiotherapy

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

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ABSTRACT

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

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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

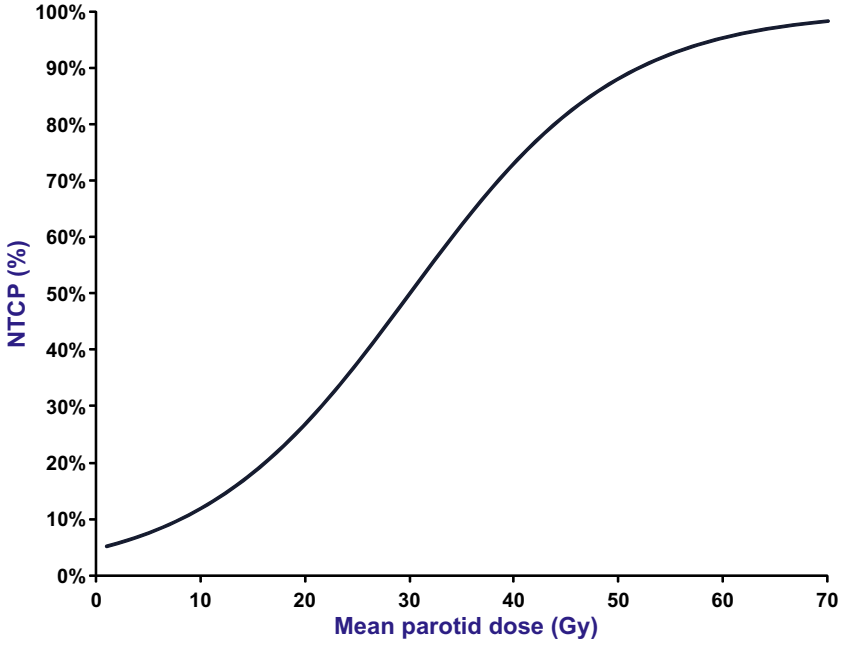

Fig. 1. Example of a Normal Tissue Complication Probability (NTCP) model describing the risk estimation on a given side effect (NTCP-value) as a function of the most relevant dose distribution parameter (in this case the mean parotid dose).