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Clinical Trial Strategies to Compare Protons With Photons

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The favorable beam properties of protons can be translated into clinical benefits by target dose escalation to improve local control without enhancing unacceptable radiation toxicity or to spare normal tissues to prevent radiation-induced side effects without jeopardizing local tumor control. For the clinical validation of the added value of protons to improve local control, randomized controlled trials are required. For the clinical validation of the added value of protons to prevent side effects, both model-based validation or randomized controlled trials can be used. Model-based patient selection for proton therapy is crucial, independent of the validation approach. Combining these approaches in rapid learning health care systems is expected to yield the most efficient and scientifically sound way to continuously improve patient selection and the therapeutic window, eventually leading to more cancer survivors with better quality of life.

Introduction

There is a widespread and ongoing discussion on the presumed lack of evidence of protons over photons, which is the most frequently used radiation technique and currently still considered the reference standard for most indications.[1-5] The term "lack of evidence" is often used when results from randomized controlled trials (RCTs) comparing a new treatment modality (eg, protons) with the current standard (eg, photons) is lacking. In this respect, it is important to note that new radiation techniques have rarely been introduced in clinical practice based on the results of RCTs.[6]

Most new radiation techniques are clinically introduced because they allow for better dose conformity (eg, intensity modulated radiotherapy [IMRT], volumetric modulated arc therapy or RapidArc, and protons) and thus better sparing of normal tissues without jeopardizing target dose coverage. To justify the introduction of such techniques in clinical practice, radiation oncologists generally refer to the "ALARA principle," ie, the principle of radioprotection stating that whenever ionizing radiation is applied in humans, animals, or materials, exposure should be "as low as reasonably achievable."[7] As compared to diagnostic imaging, the ALARA principle is considered even more relevant in radiotherapy as the levels of dose exposure administered are markedly higher and more likely to result in clinically apparent acute and late side effects and secondary tumor induction. However, the question arises to what extent the much higher capital and operational costs of proton therapy compared to photon therapy translate into clinically relevant reductions of radiation-induced side effects.

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In view of the rising costs of health care, there is a growing societal demand that before the introduction of a new technology in health care such as proton therapy, it must have been shown to be cost-effective, instead of simply referring to the ALARA principle.

On the other side of the spectrum, there are those who propose a direct comparison of protons and photons using the classical approach of an RCT as the one and only acceptable standard of evidence-based medicine, like that used for drug approval. However, there is a growing awareness among different stakeholders that evaluating new technologies with the assessment paradigm used for drug approval may not be the most optimal approach either.[8] RCTs for comparing radiation technologies are much more challenging than for pharmaceutical drugs, owing to the interplay between technological complexity, user skills, local workflows (eg, range and dose verification procedures), additional equipment (eg, treatment planning systems), and learning curve issues, which may all influence the benefits and risks for protons and confuse standardization of the treatment arms. In addition, owing to rapid technological developments in proton therapy, there is a continuous threat that at the time the results of RCTs become available, the outcome will be based on outdated technology and thus not be considered valuable and practice changing. This is not uncommon and has been seen for example for IMRT in head and neck cancer, where results from RCTs that compared IMRT vs 3-dimensional conformal radiotherapy became available when IMRT was already widely used in routine clinical practice.[6] Recently, The Royal Netherlands Academy of Arts and Sciences (KNAW) produced a Foresight Report on the Evaluation of New Technology in Health Care, providing guidelines for research suitable for assessing and inferring the benefits and performance of new technology in health care.[8] They concluded that an RCT is not always the most optimal study design for evaluating the benefit of technology, that a one-size-fits-all approach for the evaluation of medical devices is impossible and that for different types of new applications, different research approaches are required.

In this paper, alternative approaches for an evidence-based sustainable clinical introduction of proton therapy are discussed in addition to methodological problems of RCTs for comparing protons with photons, especially in relation to the eventual introduction of protons into routine clinical practice.

Clinical Applications of Proton Therapy

The favorable beam properties of protons over photons can be translated into clinical benefits in roughly 2 ways.

First, protons can be applied to escalate the dose to the target to improve local tumor control and subsequent overall survival without enhancing additional or unacceptable side effects. According to the Dutch Health Council, dose escalation is the expected future indication for proton therapy in approximately 15% of the cases. This strategy, primarily aiming at improving outcome in terms of efficacy requires the classical approach of an RCT as neither the benefit in terms of improvement of local control and overall survival are known, nor the risks of increasing the dose beyond levels that are normally given to normal tissues in or nearby the target.

Second, protons can be applied to decrease the dose to normal tissues with an equivalent target dose, primarily aiming to prevent acute and late radiation-induced side effects or secondary tumor induction while maintaining similar local tumor control. In the Netherlands, this is the expected application in 85% of the future patients. For this application, clinical validation can be obtained through RCTs under certain specific conditions, but for this strategy alternative methodologies, like the so-called model-based approach, can be considered as well.[1,2]

The Model-Based Approach

The model-based approach is based on the principle that the risk of radiation-induced side effects can be reliably predicted by multivariable normal tissue complication probability (NTCP) models, which are prediction models describing the relationship between dose-volume parameters and the risk on a given side effects.[1] Multivariable NTCP-models consist of at least 1 or more dose-volume parameters either or not in combination with other independent predictors (eg, the addition of concurrent chemotherapy or age).[9-11] The model-based approach can be used to select patients for protons (*model-based selection*); in addition, for the model-based approach it is also essential to continuously and prospectively validate the clinical models for protons (*model-based validation*).

Model-Based Selection

In model-based selection we distinguish 3 steps.

The first step in the model-based approach is to select an NTCP-model or a set of NTCP-models from literature, for acute and late radiation-induced side effects that are considered most relevant (Fig. 1).

In the second step, the dose-volume parameters of the selected NTCP-models are used for optimization of radiotherapy treatment plans, either based on photons or protons (model-based optimization). As prevention of radiation-induced side effects can only be expected when the relevant dose metrics with protons are lower than with photons, the differences between the best proton plan and the best photon plan (Δdose) with respect to the dose-volume parameters in the NTCP-models is assessed by performing a planning comparison study in every single patient.

Step 3 determines to what extent Δdose translates into a difference in complication probability (ΔNTCP) by integrating the results of the planning comparative study into NTCP-models. This final step is necessary as not every Δdose will translate into a clinically relevant ΔNTCP, for example, because the dose with photons already remains under a predefined threshold for a given complication or because of a relatively flat dose-response relationship in the respective Δdose area.