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Original Investigation

The Quest for Evidence for Proton Therapy: Model-Based Approach and Precision Medicine

Joachim Widder, MD, PhD,[*] Arjen van der Schaaf, PhD,[*] Philippe Lambin, MD, PhD,[†] Corrie A.M. Marijnen, MD, PhD,[‡] Jean-Philippe Pignol, MD, PhD,[§] Coen R. Rasch, MD, PhD,[‖] Ben J. Slotman, MD, PhD,[¶] Marcel Verheij, MD, PhD,[#] and Johannes A. Langendijk, MD, PhD[*]

Department of Radiation Oncology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; [†]Department of Radiation Oncology, School for Oncology and Developmental Biology (GROW), Maastricht University Medical Center, Maastricht, The Netherlands; [‡]Department of Radiation Oncology, Leiden University Medical Center, Leiden, The Netherlands; [§]Department of Radiation Oncology, Erasmus Medical Center Cancer Institute, Rotterdam, The Netherlands; [‖]Department of Radiation Oncology, Academic Medical Center, Amsterdam, The Netherlands; [¶]Department of Radiation Oncology, VU Medical Center, Amsterdam, The Netherlands; and [#]Department of Radiation Oncology, Netherlands Cancer Institute, Amsterdam, The Netherlands

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Summary

Proton therapy can reduce normal tissue dose, but clinical benefit is still insufficiently demonstrated. Patients for whom there is no dosimetric difference in normal tissues of protons compared with photons will not benefit from proton therapy and should therefore neither undergo this therapy nor be included in clinical

Purpose: Reducing dose to normal tissues is the advantage of protons versus photons. We aimed to describe a method for translating this reduction into a clinically relevant benefit.

Methods and Materials: Dutch scientific and health care governance bodies have recently issued landmark reports regarding generation of relevant evidence for new technologies in health care including proton therapy. An approach based on normal tissue complication probability (NTCP) models has been adopted to select patients who are most likely to experience fewer (serious) adverse events achievable by state-of-the-art proton treatment.

Results: By analogy with biologically targeted therapies, the technology needs to be tested in enriched cohorts of patients exhibiting the decisive predictive marker: difference in normal tissue dosimetric signatures between proton and photon treatment plans. Expected clinical benefit is then estimated by virtue of multifactorial NTCP models. In this sense, high-tech radiation therapy falls under precision medicine. As

Reprint requests to: Joachim Widder, MD, PhD, Department of Radiation Oncology, University of Groningen, University Medical Center Groningen, PO Box 30.001, 9700RB Groningen, The Netherlands. Tel: +31-50-3610582; E-mail: j.widder@umcg.nl

Conflict of interest: J.W. and A.vdS. have research agreements through their departments with Philips, RaySearch, and Mirada Medical. P.L. has received research grants from ptTheragnostic and is co-inventor and patent holder of "mitochondrial DNA variations to predict side effecst of radiation" (pending). B.J.S. has received grants and personal fees from Varian Medical Systems and BrainLAB AG. J.A.L. has research agreements with Philips, RaySearch, and Mirada Medical. All other authors report no conflicts of interest.

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proton trials. Patient selection for prospective cohort studies as well as for randomized trials should be based on predictable benefit using multifactorial normal tissue complication probability models.

a consequence, randomizing nonenriched populations between photons and protons is predictably inefficient and likely to produce confusing results.
Conclusions: Validating NTCP models in appropriately composed cohorts treated with protons should be the primary research agenda leading to urgently needed evidence for proton therapy.

Introduction

There is widespread discussion regarding lack of evidence for proton treatment for a wide range of potential indications (1-5). Even for the most widely accepted conditions, pediatric tumors, issues remain as to whether superiority of protons over photons has sufficiently been shown (6). Reducing dose to normal tissues and organs outside of target areas evidently is the key feature of protons versus photons, but translation of these reductions into clinically relevant benefit has still not been demonstrated consistently, let alone issues regarding variable relative biological effectiveness (7-10). We will argue that the key issue is to identify patients who will most likely benefit from proton therapy, by translating physical evidence (a favorable dose delivery profile) into clinical outcome, thus establishing proton therapy in the precision medicine framework (11).

It is being increasingly realized that equating evidence-based medicine with randomized clinical trials (RCTs) is an undue simplification (12-16). Accordingly, official Dutch scientific and health care governance bodies have recently issued landmark reports dealing with the problem, which research methods would best lead to generating high-level evidence, for new health care technology in general and for proton therapy in particular (17, 18). In addition, the Dutch Health Council issued a report in 2009 directing that a model-based approach using a decision support system to select patients for proton therapy be adopted when reduction of toxicity forms the primary indication for using the technology (19, 20). The Royal Dutch Academy of Sciences issued a comprehensive foresight study of the methodology that should be applied to generate relevant evidence for new technology in health care in general (14). The arguments presented in this paper are in line with and build upon those reports.

Here we aimed at further elucidating several basic issues of the so-called model-based approach (1), a methodology designed to yielding evidence to inform rational selection of patients who would most likely derive clinically relevant benefit from proton therapy. In addition, it should become obvious that the question whether "protons" are better than "photons" for a certain tumor entity is not the most important question to be answered. Rather, proton treatment will only lead to improved clinical outcome due to less (serious) toxicity in patients, where 2 essential requirements are both met: (*1*) normal tissue sparing can actually be obtained with protons (Δdose); and (*2*) Δdose will actually result in clinically significant lower complication risk (or else lower normal tissue complication probability [ΔNTCP]). We must acknowledge that transforming dose into complication risk requires multifactorial (NTCP) models including nondosimetric features (eg, patients' age, concomitant chemotherapy) and that therefore a decrease of dose will not always lead to a relevant decrease of complication risk (20). The key research agenda for the near future should therefore be to validate this thesis by attempting to falsify the hypothesis that NTCP reduction actually leads to less clinical toxicity. RCTs enrolling patients where the above-mentioned requirements are not met are an inappropriate instrument to investigate proton therapy because the predictable difference will be too small to detect. This consideration strongly resembles biologically targeted agents that also should not be tested in patients who do not exhibit the corresponding biological marker. This paper addresses basic methodological issues related to providing scientific evidence for proton therapy.

Optimally delivered dose rather than technology matters

In numerous clinical situations, proton beams can achieve higher dose conformity than photon beams (5, 21-25). The issue of evidence for proton therapy thus comes down to demonstrating clinical superiority of higher conformity of a biologically equivalent therapeutic dose to the target, with less dose to organs and healthy tissues other than target volumes. This builds on the most basic principle of radiation therapy, proven in 1900 (26, 27): biological effects in tissues, intended or unintended, are proportional to the dose delivered to these tissues. The issue therefore is largely reduced to determining the magnitude and relevance of the clinical benefit associated with sparing healthy tissues. This also elucidates the fact that the methodology described here is not limited to proton radiation therapy but applies to other dose conformity improving technologies (eg, MR-linear accelerator) as well (28).

These arguments rest on state-of-the-art quality of technologies compared, rendering the term "proton therapy" especially ambiguous without further specification (passive scattering or pencil beam scanning; which image guidance; how is treatment adapted to changes; etc). There

is less ambiguity when (reliable) dose distributions are described irrespective of technology.

Nonenriched randomized clinical trials will not help

If an intervention is not potentially harmful, even in case it will not benefit a patient in question, and if it is not particularly costly, the issue of targeted delivery exclusively to patients likely to benefit from the intervention is not a big practical issue. However, for costly and potentially harmful procedures, untargeted administration of treatment becomes a serious problem: proton therapy is an excellent example of such an entity. Even a positive RCT, showing superiority of a costly and scarce intervention in an unselected population, will therefore automatically provoke the question how to rationally select a restricted subgroup of patients who should actually receive the intervention: thus, one is back to the need to define who will most likely benefit from the treatment. Research needs to be directed toward identification and quantification of the driving factors entailing a clinically relevant benefit rather than toward demonstrating a difference between proton and photon treatment in a population that has not specifically been enriched with individuals likely to experience a difference. In other words, large-scale RCTs in unselected populations will predictably not change clinical practice and, even more so, when suboptimal proton treatment delivery technology was used.

Studies investigating potential treatment benefits of proton therapy need thus to be enriched with patients exhibiting a clinically relevant difference in toxicity risk, that is, a threshold ΔNTCP. Trials comparing photon treatment with proton treatment in nonenriched populations will test the hypothesis whether treatment with protons yields an outcome different from photons by a certain prespecified amount including patients who are highly unlikely to experience significantly lower toxicity, therewith increasing the noise and decreasing the power of the study. Such a comparative (randomized) trial is not the most suitable tool to answer the question who will benefit more, and who less, by a certain intervention but will rather yield an all-or-nothing result: the "winner takes all" (Fig. 1). The verdict of the study will apply to all patients who fulfill the eligibility criteria, even if truly the effect is only seen in a fraction of subjects, namely those who express a treatment-specific predictive marker (29). It is, thus, a logical consequence of this state of affairs that an intervention testing positive in a nonenriched RCT will become "indicated" for a too generously defined population, because it will also include individuals who will not benefit. Conversely, due to dilution of any effect by inclusion of patients who predictably will not benefit, a negative RCT might thus prohibit treating patients who actually are likely to benefit.

Predictive markers are always based on models

A predictive marker is a clinical or biological characteristic that provides information on the likely benefit from treatment (either in terms of efficacy or toxicity) in a defined cohort (30). Such predictive factors can be used to identify subpopulations of patients who are most likely to benefit from a given therapy (31). For example, certain mutations of the epithelial growth factor receptor (EGFR) are predictive for benefit in terms of progression-free survival

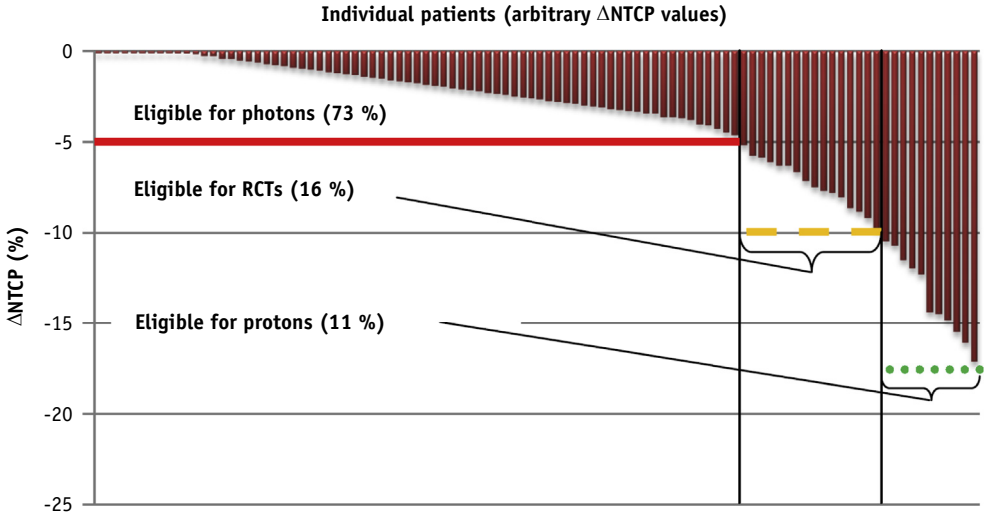

Fig. 1. Waterfall plot of ΔNTCP (protons minus photons). Patients with <5% absolute ΔNTCP (here 73% of the population) should receive photons; ΔNTCP ≥5% to 10% might best be treated in an RCT (here 16% of the population), and ΔNTCP >10% (11% of population) should receive protons (ethically problematic to include in RCTs). In a nonenriched RCT, a priori predictable toxicity differences would be ignored. *Abbreviations:* NTCP = normal tissue complication probability; RCT = randomized clinical trial.

from EGFR-tyrosine kinase inhibitor therapy in non-small cell lung cancer (NSCLC) (32), but not in squamous cell head and neck cancer (33).

These conclusions are drawn from statistical data analyses that resulted in adequately interpreted predictive models (30). Nothing but the application of these models renders the presence of an EGFR mutation a predictive marker (or predictive factor), and the models determine in which situation this is the case (eg, in NSCLC but not in head and neck cancer). It is critically important to realize that any biological or clinical feature becomes a predictive marker exclusively by virtue of a predictive model, even if the model employed is relatively simple. This applies for any molecular marker just as it applies for dose-volume parameters in radiation therapy.

Predictive markers of toxicity in radiation therapy

There are predictive markers of effectiveness as well as of toxicity, depending on the context (34). Numerous markers predict toxicities of cancer drugs, such as dihydropyrimidine dehydrogenase (DPYD)-deficiency and *DPYD* gene polymorphism for 5-fluorouracil toxicity (35-38), left ventricular ejection fraction for trastuzumab cardiotoxicity (39, 40), or elevated plasma homocysteine concentration for hematological toxicity of pemetrexed (41).

In notable contrast to drugs, toxicity of radiation therapy for a given tumor location depends on the dose-volume parameters (dosimetric signatures) in healthy tissues and organs at risk rather than on dose administered to the tumor. Moreover, tumor dose is to a much lesser degree proportional to normal tissue dose than in drug therapy, especially when considering photon versus proton therapy. Radiation toxicity can best be predicted using multifactorial NTCP models made up of dosimetric normal tissue signatures together with other clinical and patient-dependent factors. Nondosimetric factors aid in shaping the model to improve model fit in multiple situations, that is, to predict toxicity as accurately as possible in a variety of circumstances. Normal tissue dose-volume parameters (dose signatures) in turn are the factors that change when changing the radiation technique, 3-dimensional (3D)-conformal radiation therapy, intensity modulated radiation therapy (IMRT), passively scattered proton therapy, or intensity modulated proton therapy (IMPT), while clinical and patient factors typically remain unchanged in a treatment planning comparison situation. NTCP models translate normal tissue dose signatures into probabilities for toxicity.

From predictive toxicity markers to probability of toxicity

When it comes to whether proton treatment may be beneficial for a given patient, treatment plans must be compared, using state-of-the-art optimized plans for each modality. Typically, the tumor dose will be kept constant and all cofactors (eg, chemotherapy coadministration, age) will also be identical, if we disregard eventual differences of relative biological effectiveness between photons and protons for the moment (8-10). NTCPs are calculated for the respective treatment plans, yielding an individual photon-proton difference in NTCP. The actual ΔNTCP value will thus be driven by differences in normal tissue dose (because the other factors in the multifactorial NTCP model do not change), but again, the dose reduction in itself does not provide more than a clue. Actually, one and the same amount of dose reduction can mean quite different toxicity reductions, depending on the patient and significant cofactors (Fig. 2). For eventual treatment benefit from more conformal radiation therapy techniques such as IMPT (compared with IMRT), normal tissue dosimetric signatures function as predictive factors. In contrast to molecular predictive markers, which are typically categorical (absent or present), dosimetric signatures are continuous variables requiring much more sophisticated modeling to render them usable in the context of treatment selection (43).

Applying NTCP models, dosimetric signatures are translated into probabilities of toxicity reduction. When it is based on a logistic regression analysis, NTCP can be calculated as

$$\mathrm{NTCP} = \left(1 + e^{-S}\right)^{-1}$$

where S denotes factors with respective coefficients including the intercept from the logistic regression equation, thus including the dosimetric and nondosimetric factors of the multifactorial NTCP model. Quite obviously, it is therefore impossible to "see" the amount of eventual clinical benefit from dose reduction in one or more critical organs by just looking at dose-volume histograms. In the near future, radiation treatment planning in general will increasingly rely on NTCP-based (and possibly TCP-based in addition) optimization and comparison of treatment plans (44). Information from translational research (eg, stem cell−sparing radiation therapy) may also be integrated into clinical practice via this route (45). For illustration (42), reduction of the mean dose to the superior pharyngeal constrictor muscle from 60 Gy (with IMRT) to 50 Gy (attainable by using IMPT) will lead to 14% risk reduction for feeding tube dependence 6 months after treatment in patients with severe weight loss at baseline but only to 5% risk reduction in otherwise similar patients not having lost weight (Fig. 2A). Illustrating the concept of dosimetric signature, if the dose in the inferior pharyngeal constrictor muscle is 60 Gy, the gain will be much more pronounced than if the inferior pharyngeal constrictor muscle receives 20 Gy (Fig. 2B). If the dose can be reduced by any means other than changing from photons to protons, equal effects are likely to result (eg, breath hold, spacers, and others) (46, 47); it is the biologically effective dose that matters, not technology. At this point, cost considerations will play a considerable role (48, 49).

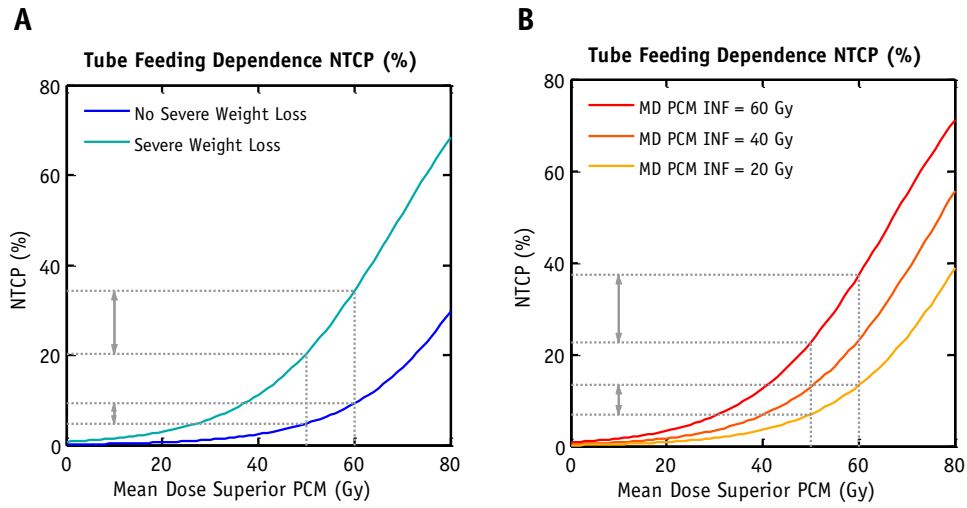

Fig. 2. NTCP model for feeding tube dependence 6 months post IMRT for head and neck cancer, using multifactorial logistic regression with LASSO-based selection of variables (42). NTCP is plotted against the mean dose in the superior pharyngeal constrictor muscle (PCM). (A) Curves are shown with or without severe weight loss at baseline (other variables set are fixed). (B) To convey the idea of "dosimetric signature," data show the effects of mean inferior PCM dose on NTCP plotted against mean superior PCM dose. *Abbreviations:* IMRT = intensity modulated radiation therapy; LASSO = least absolute shrinkage and selection operator; NTCP = normal tissue complication probability.

Absence of predicted NTCP advantage renders proton benefit unlikely

It is a consequence of the NTCP model–based approach that absence of the predictive marker of benefit, a difference in normal tissue dose signatures that will in turn result in a relevant ΔNTCP, renders any relevant benefit from proton therapy highly unlikely. Treating localized prostate cancer with protons without initially assessing the difference in normal tissue dose signatures resulting in a clinically relevant ΔNTCP (in other words, neglecting patient selection based on NTCP models) will predictably not benefit most patients. Recent data "not showing any benefit from proton treatment" are perfectly explained by the NTCP-based methodology (50). Accordingly, the interpretation of such data is critical: they do indeed show that diagnosis-and-stage–based selection (eg, localized prostate cancer) of patients for (outdated) proton therapy does not demonstrate benefit in these selected patients, but they do not show that proton therapy may not be beneficial for appropriately selected patients undergoing technically optimal proton treatment. Nobody would conclude that biologically targeted agents do not work, because they only work in patients exhibiting the respective predictive biomarker, or that a certain drug should be given to patients when they are known to carry a predictive marker for toxicity from that drug (51, 52). In that sense, proton therapy is another instance of precision medicine just like biologically targeted agents are (11). Only when the predictive marker is present is there a reasonable potential for proton therapy to confer a benefit in terms of toxicity for the patient in whom the marker had been demonstrated. The amount of benefit in turn, upon which the actual decision for proton treatment should reasonably be based, can only be estimated after calculating individual ΔNTCPs using NTCP models.

Evidence for proton therapy will thus need to be generated primarily by validating model-based estimates relative to observed (toxicity) outcomes. Such validation may include recalibration or other statistical operations (53). Crucial experiments for proton therapy yielding high-level evidence would have to attempt to falsify the hypothesis that reduced normal tissue dose actually entails reduced toxicity (43). Prospective data registration programs are a suitable method for this quest, generating the data necessary to validate (ie, attempt to falsify) the NTCP models with actual patient outcomes. IMRT-derived NTCP-models retrieved from prospectively followed patients currently form the backbone of the methodology (54). These photon-based NTCP models may need updating to be applicable for IMPT, leading to increasingly more accurate patient selection as more evidence is collected. This cycle of refinement will therefore very likely result in corroborating evidence for clinical benefit of proton therapy in precisely defined populations.

In a second step, treatment intensification (for tumors where it seems appropriate) by randomizing lower versus higher radiation dose should be investigated. The question at this point is no longer whether proton therapy is more efficacious than photon therapy but whether intensifying radiation to the target volume confers an overall clinical benefit. In oncology, serious treatment-related toxicity and mortality always compete with tumor-related symptoms and mortality, as was recently suggested by the Radiation Therapy Oncology Group (RTOG) lung dose escalation trial, among other possible explanations contributing to the unintended results (55). Additionally, (nonstereotactic) radiation dose escalation

inadvertently implies dose escalation to normal tissues inside the clinical target volume (CTV) regardless of radiation source, so that higher dose to neoplastic tissue automatically confers higher dose to normal tissue and organs located within the CTV (eg, large airways, blood vessels, or esophagus in lung cancer treatment). This in turn implies an increased risk for side effects or complications due to within-CTV normal tissue irradiation, a risk competing with tumor control, which is the reason why dose escalation requires RCTs to investigate its eventual overall benefit.

Conclusions

Improving dose distribution, not any specific technology, has been the central issue determining progress in radiation therapy, and this still applies for proton therapy. We have shown how applying NTCP models forms the decisive link in generating evidence regarding the value of proton therapy, because this approach helps to create enriched cohorts of patients who are likely to benefit from protons. In these enriched cohorts, actual benefit must be demonstrated using appropriate study designs (prospective cohort studies, RCTs in selected situations). In this respect, high-tech radiation therapy is a kind of precision medicine. RCTs may be legitimate instruments with which to gain evidence about the superiority of proton treatment in appropriately enriched populations, if expected differences in toxicity are small (Fig. 1). In case serious radiation-induced toxicity will be predictably lower when certain dose distributions are available for a given patient that can be achieved only with protons, it is hard to argue why patients should be subjected to the risk of a less favorable dose distribution in an RCT. Using information from this patient to validate the NTCP model upon which the treatment was selected seems to be a better option. Rapid learning approaches would then be more appropriate (15, 16). Radiation being around for some 120 years with more than ample proof of its toxic effects does not qualify as an unknown or unexpected risk factor for tissue damage. The existence of a validated predictive model of toxicity for a specific situation is incommensurable with the Helsinki obligation that "measures to minimize risks must be implemented" (56). Non-enriched RCTs (eg, Proton Therapy vs IMRT for Low or Intermediate Risk Prostate Cancer; NCT01617161; ClinicalTrials.gov) carry a high risk of producing confusing results for reasons discussed in this paper.

An NTCP model-based approach to proton treatment redefines how we conceptualize indications for certain radiation techniques including, but not limited to, the proton-photon debate.

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