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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.

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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

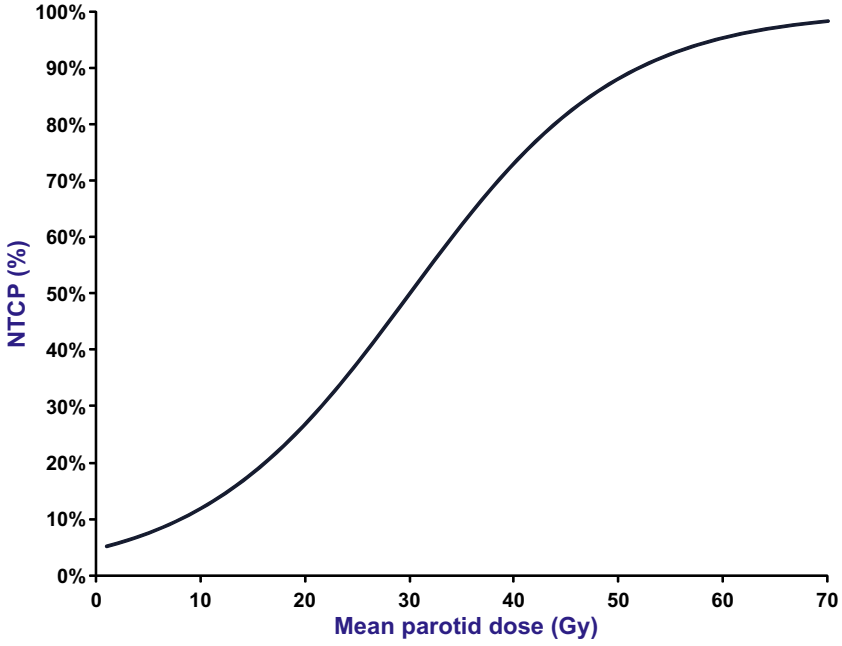

Fig. 1. Example of a Normal Tissue Complication Probability (NTCP) model describing the risk estimation on a given side effect (NTCP-value) as a function of the most relevant dose distribution parameter (in this case the mean parotid dose).

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 α 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

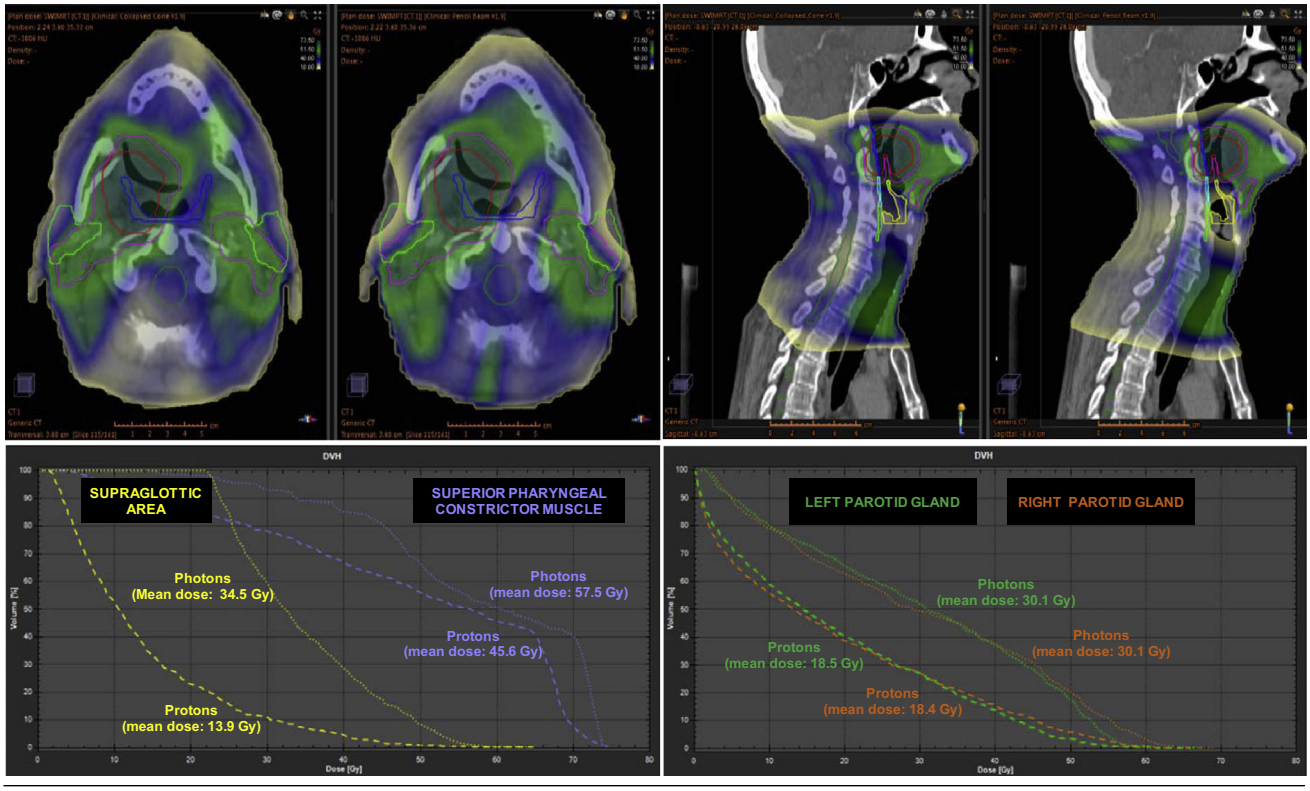

Fig. 2. Example of an individual In Silico Planning Comparative study in a patient with cT3N0M0 oropharyngeal cancer. In this case swallowing-sparing IMRT (SWIMRT), aiming at sparing to the parotid glands, the superior pharyngeal constrictor muscle (superior PCM) and supraglottic area, was compared to 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.

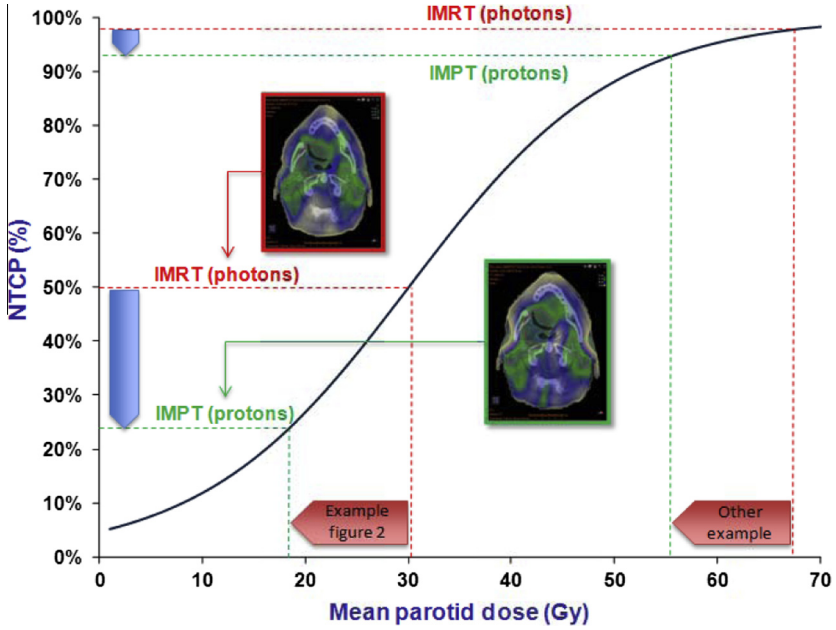

Fig. 3. Translation of the results of the individual ISPC-study depicted in Fig. 2 with regard to xerostomia. The reduction of the mean parotid dose from 30.1 Gy to 18.4 Gy (red arrow: example Fig. 2) corresponds with an estimated NTCP-value reduction for severe xerostomia from 50% to 24% according to 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.

(Fig. 4) [27]. 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

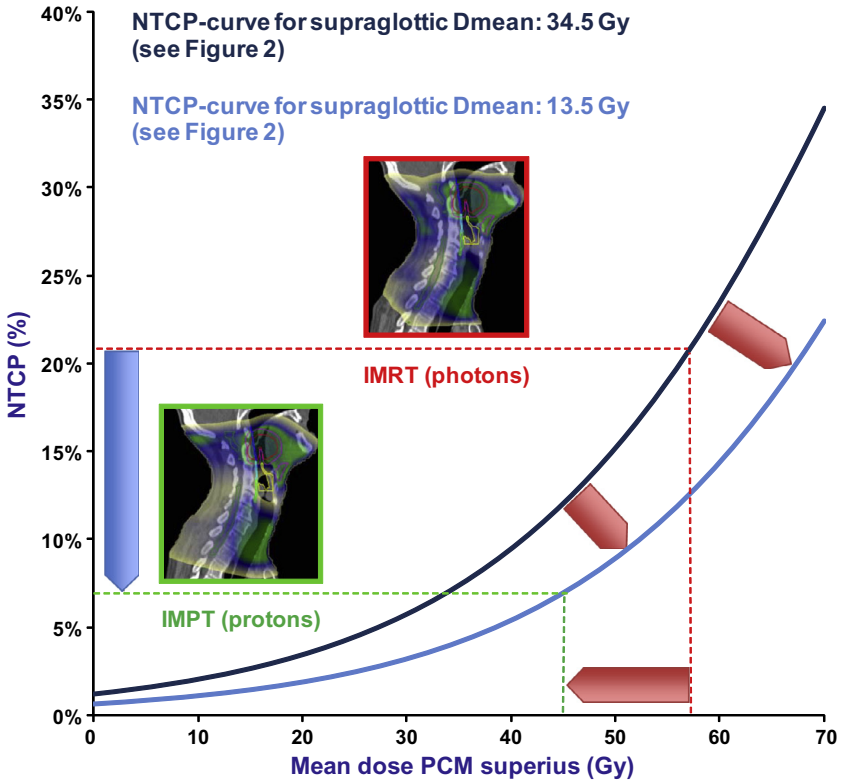

Fig. 4. Translation of the results of the individual ISPC-study depicted in Fig. 2 with regard to swallowing dysfunction RTOG grade 2–4. This toxicity endpoint depends on the mean dose to the superior PCM and to the supraglottic area. The upper (dark blue) and lower curves (light blue) describe the relationship 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%.

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

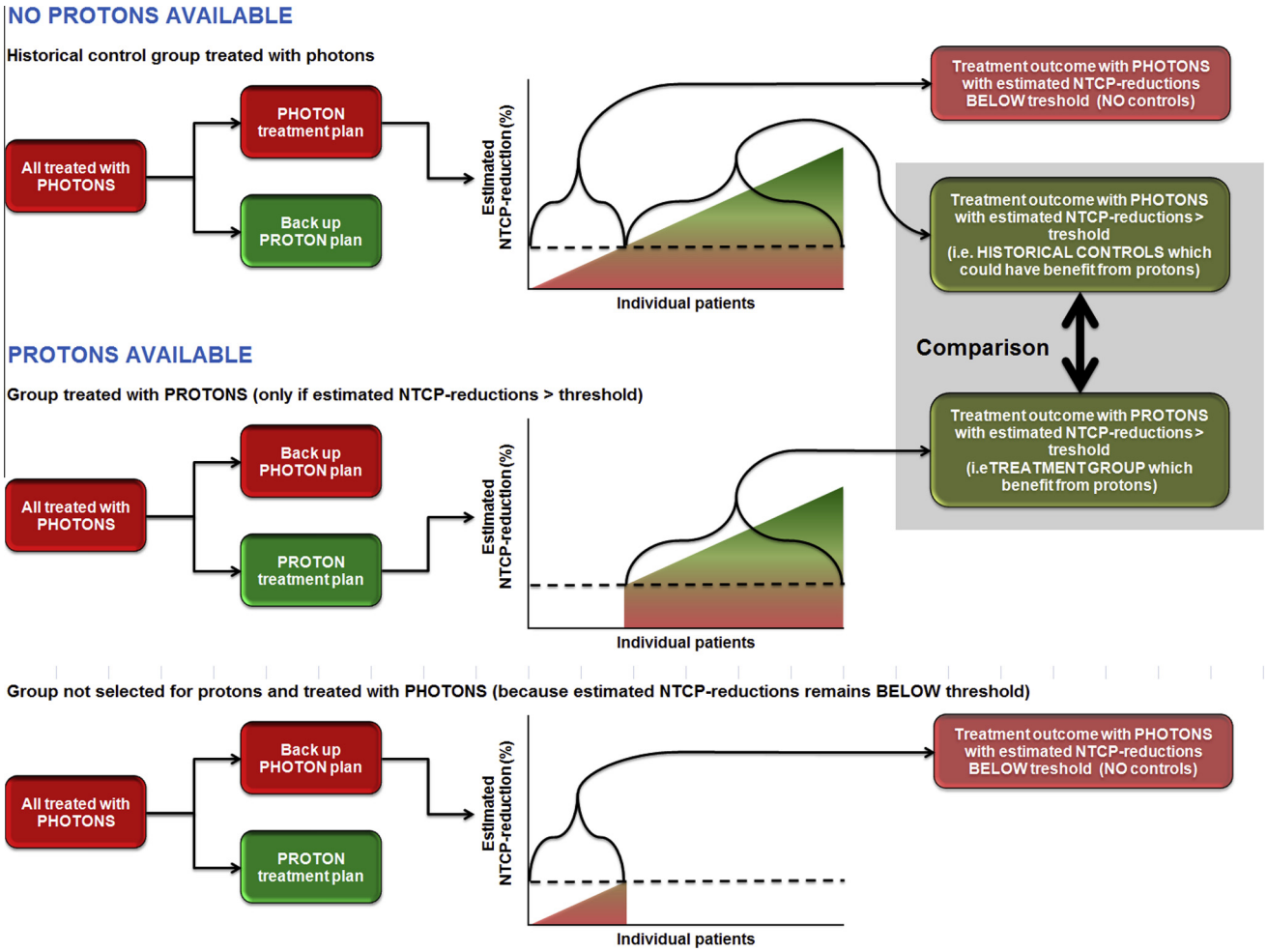

Fig. 5. Schematic overview of the clinical validation using sequential prospective cohort studies. The historical control group will be generated in the phase that protons are not available. For each patient included in such a study, a backup proton plan will be made to estimate the NTCP-value reduction in case this patient would have been treated with protons. Only patients with estimated NTCP-value reduction beyond the threshold will be used as nested case controls for patients that will be treated with protons in the near future. After the clinical introduction of protons, only patients with estimated NTCP-value reduction beyond the threshold will be selected for proton therapy. The results obtained in these patients will be compared to those obtained in the historical control group. Data on toxicity and patient-rated symptoms will be assessed according to similar standard follow up programes.

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 α.

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 number of RCT's [36].

It should be clearly emphasised that we do not intend to propagate this methodology as an alternative for RCT's in all circumstances, rather than to use this as the optimal approach when an RCT is considered not feasible or even inappropriate. In this regard, it is important to notice that there are some methodological problems that may hamper the interpretation of the results.

First, as the comparison between patients treated with photons and protons using sequential prospective cohort studies will be mainly historical, selection of patients for radiotherapy may change over time. It cannot be excluded that this may influence NTCP-models and thus the outcome in terms of side effects. Currently, most NTCP-models only include dose distribution parameters, while other independent prognostic or confounding factors are generally not taken into account. However, some authors showed that the relationship between dose distribution parameters and side effects may differ across different patient populations [30]. Moreover, changes in dose distributions due to different radiation delivery techniques may also affect the predictive power of NTCP models, as recently shown for patient-rated xerostomia and sticky saliva in head and neck cancer patients treated with either 3D conformal radiotherapy or IMRT [32–34]. Therefore, NTCP-models developed in patients treated with photons should always be validated among those treated with protons, prior to the direct comparison of toxicity rates.

For some radiation-induced side effects the precise association between the dose-volume parameters is less clear, and therefore the translation of observed differences in dose distributions between protons and photons into clinical benefits remains to be determined. In such cases, conducting an RCT is still the best methodology to test the clinical benefit of protons over photons. The same approach applies to relatively mild side effects, where other issues, such as cost-effectiveness, may become more important.

Second, conclusions from ISPC studies regarding the added value of protons can only be justified in case of straightforward comparisons with photons, meaning that the reference technique should at least include the most advanced and currently available photon techniques, such as IMRT or tomotherapy [21].

Another important prerequisite for a proper design of ISPC studies is the definition of appropriate endpoints, i.e. the most relevant dose-volume parameters following from NTCP-modelling studies, and to use these parameters with properly chosen dose constraints for treatment planning optimisation for all techniques included in the analysis. Only in this way can the results coming from ISPC studies be used to translate the dose distribution advantages of protons compared to photons into a clinical benefit.

Third, the model-based approach to select patients for protons assumes a similar dose distribution to the target and thus similar locoregional control rates as have been obtained with the currently used photons. 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 doses, 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

[1] Langendijk JA, Doornaert P, Verdonck-de Leeuw IM, Leemans CR, Aaronson NK, Slotman BJ. Impact of late treatment-related toxicity on quality of life among patients with head and neck cancer treated with radiotherapy. J Clin Oncol 2008;26:3770–6.

[2] Mrozek E, Shapiro CL. Survivorship and complications of treatment in breast cancer. Clin Adv Hematol Oncol 2005;3(211–22):238. Review.

[3] Egawa S, Shimura S, Irie A, et al. Toxicity and health-related quality of life during and after high dose rate brachytherapy followed by external beam radiotherapy for prostate cancer. Jpn J Clin Oncol 2001;31:541–7.

[4] Murata A, Brown CJ, Raval M, Phang PT. Impact of short-course radiotherapy and low anterior resection on quality of life and bowel function in primary rectal cancer. Am J Surg 2008;195:611–5.

[5] Jensen K, Bonde Jensen A, Grau C. The relationship between observer-based toxicity scoring and patient assessed symptom severity after treatment for head and neck cancer. A correlative cross sectional study of the DAHANCA toxicity scoring system and the EORTC quality of life questionnaires. Radiother Oncol 2006;78:298–305.

[6] Trott KR, Doerr W, Facoetti A, et al. Biological mechanisms of normal tissue damage: importance for the design of NTCP models. Radiother Oncol 2012;105:79–85.

[7] Deasy JO, Moiseenko V, Marks L, Chao KS, Nam J, Eisbruch A. Radiotherapy dose-volume effects on salivary gland function. Int J Radiat Oncol Biol Phys 2010;76(Suppl. 3):S58–63.

[8] Werner-Wasik M, Yorke E, Deasy J, Nam J, Marks LB. Radiation dose-volume effects in the esophagus. Int J Radiat Oncol Biol Phys 2010;76:S86–93.

[9] Gagliardi G, Constine LS, Moiseenko V, Correa C, Pierce LJ, Allen AM, et al. Radiation dose-volume effects in the heart. Int J Radiat Oncol Biol Phys 2010;76:S77–85.

[10] Rancati T, Schwarz M, Allen AM, Feng F, Popovtzer A, Mittal B, et al. Radiation dose-volume effects in the larynx and pharynx. Int J Radiat Oncol Biol Phys 2010;76:S64–9.

[11] Marks LB, Bentzen SM, Deasy JO, et al. Radiation dose-volume effects in the lung. Int J Radiat Oncol Biol Phys 2010;76:S70–6.

[12] Michalski JM, Gay H, Jackson A, Tucker SL, Deasy JO. Radiation dose-volume effects in radiation-induced rectal injury. Int J Radiat Oncol Biol Phys 2010;76:S123–9.

[13] Stuschke M, Kaiser A, Pöttgen C, Lübcke W, Farr J. Potentials of robust intensity modulated scanning proton plans for locally advanced lung cancer in comparison to intensity modulated photon plans. Radiother Oncol 2012;104:45–51.

[14] Efstathiou JA, Paly JJ, Lu HM, et al. Adjuvant radiation therapy for early stage seminoma: proton versus photon planning comparison and modeling of second cancer risk. Radiother Oncol 2012;103:12–7.

[15] Wolff HA, Wagner DM, Conradi LC, et al. Irradiation with protons for the individualized treatment of patients with locally advanced rectal cancer: a planning study with clinical implications. Radiother Oncol 2012;102:30–7.

[16] Schwarz M, Pierelli A, Fiorino C, et al. Helical tomotherapy and intensity modulated proton therapy in the treatment of early stage prostate cancer: a treatment planning comparison. Radiother Oncol 2011;98:74–80.

[17] Moon SH, Shin KH, Kim TH, et al. Dosimetric comparison of four different external beam partial breast irradiation techniques: three-dimensional conformal radiotherapy, intensity-modulated radiotherapy, helical tomotherapy, and proton beam therapy. Radiother Oncol 2009;90:66–73.

[18] van der Laan HP, van de Water TA, et al. Rococo cooperative group. The potential of intensity-modulated proton radiotherapy to reduce swallowing dysfunction in the treatment of head and neck cancer: a planning comparative study. Acta Oncol 2013;52:561–9.

[19] Van de Water TA, Bijl HP, Schilstra C, Pijls-Johannesma M, Langendijk JA. The potential benefit of radiotherapy with protons in head and neck cancer with respect to normal tissue sparing: a systematic review of literature. Oncologist 2011;16:366–77.

[20] Van de Water TA, Lomax AJ, Bijl HP, et al. Potential benefits of scanned intensity-modulated proton therapy versus advanced photon therapy with regard to sparing of the salivary glands in oropharyngeal cancer. Int J Radiat Oncol Biol Phys 2011;79:1216–24.

[21] Roelofs E, Engelsman M, Rasch C, et al. ROCOCO Consortium. Results of a multicentric in silico clinical trial (ROCOCO): comparing radiotherapy with photons and protons for non-small cell lung cancer. J Thorac Oncol 2012;7:165–76.

[22] Roelofs E, Persoon L, Qamhiyeh S, et al. Design of and technical challenges involved in a framework for multicentric radiotherapy treatment planning studies. Radiother Oncol 2010;97:567–71.

[23] Aleman BM, van den Belt-Dusebout AW, Klokman WJ, Van't Veer MB, Bartelink H, van Leeuwen FE. Long-term cause-specific mortality of patients treated for Hodgkin's disease. J Clin Oncol 2003;21:3431–9.

[24] Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med 2013;368:987–98.

[25] Henson KE, McGale P, Taylor C, Darby SC. Radiation-related mortality from heart disease and lung cancer more than 20 years after radiotherapy for breast cancer. Br J Cancer 2013;108:179–82.

[26] Bentzen SM. Randomized controlled trials in health technology assessment: overkill or overdue? Radiother Oncol 2008;86:142–7.

[27] Christianen ME, Schilstra C, Beetz I, et al. Predictive modelling for swallowing dysfunction after primary (chemo) radiation: results of a prospective observational study. Radiother Oncol 2012;105:107–14.

[28] Egelmeer AG, Velazquez ER, de Jong JM, et al. Development and validation of a nomogram for prediction of survival and local control in laryngeal carcinoma patients treated with radiotherapy alone: a cohort study based on 994 patients. Radiother Oncol 2011;100:108–15.

[29] Dehing-Oberije C, De Ruysscher D, Petit S, et al. Development, external validation and clinical usefulness of a practical prediction model for radiation-induced dysphagia in lung cancer patients. Radiother Oncol 2010;97:455–61.

[30] Peeters ST, Hoogeman MS, Heemsbergen WD, Hart AA, Koper PC, Lebesque JV. Rectal bleeding, fecal incontinence, and high stool frequency after conformal radiotherapy for prostate cancer: normal tissue complication probability modeling. Int J Radiat Oncol Biol Phys 2006;66:11–9.

[31] De Ruysscher D, Van Meerbeeck J, Vandecasteele K, et al. Radiation-induced oesophagitis in lung cancer patients. Is susceptibility for neutropenia a risk factor? Strahlenther Onkol 2012;188:564–7.

[32] Beetz I, Schilstra C, van der Schaaf A, et al. NTCP models for patient-rated xerostomia and sticky saliva after treatment with intensity modulated radiotherapy for head and neck cancer: the role of dosimetric and clinical factors. Radiother Oncol 2012;105:101–6.

[33] Beetz I, Schilstra C, van Luijk P, et al. External validation of three dimensional conformal radiotherapy based NTCP models for patient-rated xerostomia and sticky saliva among patients treated with intensity modulated radiotherapy. Radiother Oncol 2012;105:94–100.

[34] Beetz I, Schilstra C, Burlage FR, et al. Development of NTCP models for head and neck cancer patients treated with three-dimensional conformal radiotherapy for xerostomia and sticky saliva: the role of dosimetric and clinical factors. Radiother Oncol 2012;105:86–93.

[35] Vergeer MR, Doornaert PA, Rietveld DH, Leemans CR, Slotman BJ, Langendijk JA. Intensity-modulated radiotherapy reduces radiation-induced morbidity and improves health-related quality of life: results of a nonrandomized prospective study using a standardized follow-up program. Int J Radiat Oncol Biol Phys 2009;74:1–8.

[36] Nutting CM, Morden JP, Harrington KJ, et al. PARSPORT trial management group. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. Lancet Oncol 2011;12:127–36.

[37] van Elmpt W, Öllers M, Lambin P, De Ruysscher D. Should patient setup in lung cancer be based on the primary tumor? An analysis of tumor coverage and normal tissue dose using repeated positron emission tomography/computed tomography imaging. Int J Radiat Oncol Biol Phys 2012;82:379–85.

[38] Schwartz DL, Garden AS, Shah SJ, et al. Adaptive radiotherapy for head and neck cancer-dosimetric results from a prospective clinical trial. Radiother Oncol 2013;106:80–4.

[39] McGowan SE, Burnet NG, Lomax AJ. Treatment planning optimisation in proton therapy. Br J Radiol 2013;86:255545.

[40] Lomax AJ. Intensity modulated proton therapy and its sensitivity to treatment uncertainties 2: the potential effects of inter-fraction and inter-field motions. Phys Med Biol 2008;53:1043–56.

[41] Lomax AJ. Intensity modulated proton therapy and its sensitivity to treatment uncertainties 1: the potential effects of calculational uncertainties. Phys Med Biol 2008;53:1027–42.

[42] Unkelbach J, Bortfeld T, Martin BC, Soukup M. Reducing the sensitivity of IMPT treatment plans to setup errors and range uncertainties via probabilistic treatment planning. Med Phys 2009;36:149–63.

[43] Pommier P, Lievens Y, Feschet F, Borras JM, Baron MH, Shtiliyanova A, et al. Simulating demand for innovative radiotherapies: an illustrative model based on carbon ion and proton radiotherapy. Radiother Oncol 2010;96:243–9.