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Editorial

Achievements and challenges in normal tissue response modelling for proton therapy

Normal Tissue Complication Probability (NTCP) models are used to describe the relationship between the dose distribution to critical organs at risk and the development of a given radiation-induced side effect [1–3]. For head and neck cancer (HNC), NTCP models are typically based on multivariate logistic regression, which in addition to dose/volume based predictors may include variables related to baseline data as well as patient- and disease related factors. The model based approach (MBA) for selecting patients to proton therapy makes use of NTCP models to identify patients where proton therapy can be beneficial in terms of reduced side effects. The criterion for qualifying for proton therapy (or for inclusion into a clinical trial) is based on a reduction in NTCP (ΔNTCP) with protons compared to photons, and where the severity of the side effect of interest is reflected in a predefined threshold value. A detailed description of the methodology has previously been published [4,5], and the MBA has been accepted as a method to select patients to proton therapy by the Dutch health authorities. A wide range of NTCP models for common acute and late side effects after radiotherapy for HNC have been developed and are currently in use in the Netherlands [6,7]. The clinical experience with the MBA for selection of patients to proton therapy in HNC was recently reported by Tambas et al. [8]. By applying a ΔNTCP threshold of 5 % for grade III and 10 % for grade II side effects, 35 % of the patients were selected for protons. Predominantly, patients qualifying for proton therapy had locally advanced pharyngeal cancers, and were selected on the basis of the estimated reduction in NTCP for xerostomia and dysphagia. The authors reported the MBA to be time-consuming, especially during the learning curve period, but still clinically feasible.

The use of MBA in clinical practice requires the availability of NTCP models with high predictive power. During NTCP model development challenges such as missing data, multicollinearity, selection of relevant predictors and identification of non-linear relationships between the outcome and continuous variables are addressed in order to create well-fitted models [9]. The apparent performance of an NTCP model will usually be overly optimistic. To avoid overfitting of the data internal model validation is recommended, preferably by applying bootstrapping procedures where all steps in model development are repeated on several randomly sampled data sets. Discrimination and calibration are then assessed in both the original and bootstrap samples after which the model is corrected for optimism [9,10]. Despite this, the model's predictive power is typically reduced when used in new patients. However, validation of previously published NTCP models on own patient cohorts with model adjustments may improve prediction and is a prerequisite before clinical implementation of the model of interest.

Recently, a previously published NTCP model for dysphagia [11] was externally validated in a Danish patient cohort [12] and in the current volume of this journal, Kalendralis et al. [13] report the results from an external validation of an NTCP model for grade II dysphagia in 270 HNC patients. Both studies applied the closed testing procedure [14], which is an automated method that evaluate to what degree an NTCP model needs to be adjusted in order to improve performance when applied in the new patient cohort. The results from the external validation in the above mentioned studies differed, in the Danish patient cohort, updating the intercept resulted in a significant improvement in the model performance, whereas re-estimation of model coefficients significantly improved the performance in Kalendralis et al. [13].

The implementation of the MBA is challenging for several reasons. It requires prospective patient follow-up with continuous data collection for NTCP model development and validation, as well as patient registries for assessment of potential clinical benefits. Regular validation of the NTCP models is needed to ensure reliable models that are adjusted to changes in patient cohorts, treatment regimens and treatment techniques. Thus, the MBA is a resource-intensive methodology, and implementation in small centers with a limited number of patients may be challenging.

Furthermore, uncertainties in the NTCP models (i.e. predictor coefficients) as well as uncertainties in the actual delivered dose distributions could have a substantial impact on the accuracy of patient selection in the MBA. As shown in Bijman et al. [15], dose uncertainties could result in a selection accuracy as low as 60 %. In proton therapy, the clinically used constant relative biological effectiveness (RBE) factor of 1.1 is an additional pitfall [16]. It is becoming widely recognized that the RBE is not constant, but depends on parameters such as tissue α/β, dose and fraction sizes, as well as spatially varying depending on the linear energy transfer (LET), which represents radiation quality [17]. Preclinical evidence of the variable RBE effect is solid, but the proof of clinical impact remains statistically weak [18].

The attraction of proton therapy is its potential reduction of morbidity in patients by better sparing of healthy tissue, however, at the same time there is concern of toxicity in critical organs at risk if the effective dose delivered is higher than expected at the distal edge of a beam. In addition, proton beams are less robust against anatomical changes occurring throughout the course of treatment. In particular, for HNC patients, tumor shrinkage or changes in the filling of air cavities/sinuses may result in deviations from the planned dose distribution. For HNC involving the skull base, these effects could lead to substantial increase in biological response in adjacent brain tissue. Kitpanit et al.

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found an overall risk of brain necrosis after proton therapy to be 7 % (at 2-year follow-up in 234 patients), of where the majority (5 %) presented in the temporal lobes [19]. The implementation of different dose constraints during proton planning was suggested to mitigate risk for these patients. Based on radiographic changes in 9/60 nasopharyngeal carcinoma patients treated with proton therapy, versus 20/506 patients treated with photon-based intensity modulated radiation therapy, Zhang et al. estimated the RBE for radiographic changes in the temporal lobe to be 1.18 [20]. Engeseth et al. found that 17 % of 127 patients had radiation-induced brain image changes (asymptomatic) following proton therapy of skull base HNC [21], with a statistical significant association to volumes receiving high doses in combination with increased LET [22]. Contrary, Niemierko et al. found no correlation between brain necrosis and LET in 50 HNC patients treated with protons [23].

As a consequence of existing uncertainties, strategic choices of beam configuration to avoid positioning of beams in organs at risk is implemented in proton therapy. This practice comes with somewhat unknown clinical impact, and at the very least represents a limitation during treatment planning. In addition, dose reporting for patient records and studies may be inappropriate and is a limiting factor for accumulating clinical evidence. In fact, phenomenological modeling based on in-vitro experiments have demonstrated that most dose/volume based indices used to evaluate tolerance doses are underestimated for a wide range of diagnoses when using an RBE of 1.1 [24], including for HNC [25]. Furthermore, a standardized reporting of LET is lacking, and can diverge by an order of magnitude depending on how the LET is defined (i.e. track-averaged, dose-averaged, LET spectrum or not mentioned) [26]. Clinical studies may further be obscured by the noise level of retrospective study designs, origin of e.g. necrosis, voxel-based analysis and assumptions of independence, creating a need for large multi-center and multi–country studies to reach the required effect size. Wagenaar et al. recently discussed how the number of HNC patients required to conclude on a toxicity relation of mean dose times dose-averaged LET would be unfeasibly high [27]. Choice of study design, selection of patients at risk of high dose and LET may be key, and new concepts such as e.g. dose-LET volume histogram [28] can be useful predictors. In addition, Yang et al. recently estimated empirical RBEs for mandible osteoradionecrosis in HNC patients treated with pencil beam scanning protons versus photon-based volumetric modulated arc therapy, using a case-matched cohort design. Depending on dose cut-off, the estimated RBEs were 1.24–1.58 at moderate dose levels [29]. Evidently, there is a need for conventions and development of appropriate methods for clinical studies of proton RBE, and to harmonize LET collection across centers [30].

The direct application of photon-based NTCP models in proton treated patients can lead to imprecise morbidity predictions, due to substantially different model parameters across the modalities [31,32]. From pre-clinical modeling data, the low α/β values typical of brain tissues have been shown to increase the RBE [33]. Toxicities and NTCP in proton therapy are also more affected by α/β variations compared to photon-based therapy, and thereby have increased sensitivity to inter-patient variability in α/β [34]. Not only the RBE but also NTCP depend on α/β, and the relative NTCP as function of α/β does not simply scale with the RBE. Dependency of RBE on α/β should therefore not be interpreted independently of NTCP.

In summary, the contribution of Kalendralis et al. [13] in the current volume is an important achievement within a research area that is essential for the further expansion of the scientifically founded indications of proton therapy.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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