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A systematic review of normal-tissue complication models relevant to standard fractionation radiation therapy of the head and neck region published after the QUANTEC reports

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Abstract

There has recently been an increasing interest in model-based evaluation and comparison of different treatment options in radiation oncology studies. This is partly driven by the considerable technical advancements in radiation therapy of the last decade, leaving radiation oncologists with a multitude of options to consider. In lieu of randomized trials comparing all of these different treatment options for varying indications, which is unfeasible, treatment evaluations based on normal-tissue complication probability (NTCP) models offer a practical alternative.

The Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) effort culminating in a number of reports published in 2010 provided a basis for many of the since implemented dose-response models and dose-volume constraints, and was a key component for model-based treatment evaluations. Given that seven years have past since the QUANTEC publications and that patient-reported outcomes has emerged as an important consideration in recent years, an updated summary of the published radiation dose-response literature, that includes a focus on patient-reported quality of life outcomes, is warranted.

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Conflicts of interest

None

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Here, we provide a systematic review of quantitative dose-response models published after January 1st 2010 for endpoints relevant to radiation therapy for head and neck cancer, as these patients are typically at risk for a variety of treatment-induced normal tissue complications.

Keywords

Dose-response models; radiation therapy; head and neck; patient-reported outcomes

Introduction

Patients treated with radiation therapy (RT) for head and neck cancer are at risk for a variety of normal tissue complications and as technological advancements have made intensity-modulated radiation therapy (IMRT) and multi-modality imaging readily available, risk-adaptive treatment strategies are being increasingly utilized.[1–3] These improvements, and the increase in the number of HPV p16 positive tumors in recent years, have led to loco-regional control at the level of close to 80% for patients receiving definitive RT.[2,4,5] This means that organ at risk (OAR) determination as well as identifying important normal tissue complication probability (NTCP) dose-effect relationships and thresholds are key to facilitate further reduction of adverse effects and improvements of quality of life, since these are now considered critical factors in head and neck RT.[6,7]

The laudable effort by the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) group reported in 2010 provided a thorough review of the published clinical evidence for normal tissue dose-effect relationships.[8] Especially relevant to head and neck RT were the reports on salivary glands, esophagus, brainstem, hearing loss, larynx and pharynx.[9–13]

Given the rising interest in patient-reported outcomes as key components in normal tissue toxicity evaluation and treatment tailoring[14,15], as well as the emergence of new evidence since the QUANTEC reports, there is a need for an updated review of NTCP dose-response models for head and neck RT. This is especially relevant as model-based comparisons involving new RT treatment modalities such as proton therapy are becoming increasingly common and should always be based on the latest and most reliable evidence.[16–18]

To this end we performed a systematic review of studies presenting quantitative NTCP dose-response models for endpoints relevant to head and neck RT that were published after the reports from the QUANTEC group.

Methods and Materials

Search strategies and inclusion criteria

Potentially relevant records published after the QUANTEC reports, which became available in early 2010, were identified through a Pubmed search using various combinations of “Radiation therapy” or “Radiation-induced” and “Dose-volume” or “Dose-response” for each of the following endpoints; dysphagia, esophagitis, laryngeal edema, xerostomia, hypothyroidism, brainstem injury, optic neuropathy, oral mucositis, hearing loss, fatigue and

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secondary cancer. Records were filtered by publication date (between 01/01/2010 and 12/31/2016), language (English) and age (Adults ≥ 19 years), focusing on linear accelerator based fractionated RT for this review. Details of the selection process for records with quantitative dose-response models are provided in Figure 1. The specific search terms applied for each endpoint can be found as supplementary material.

All of the included records were reviewed with respect to dose-volume parameters and NTCP models for the corresponding OARs, including 95% confidence intervals, as well as for any clinical risk factors affecting the dose-response models, and whether the endpoints were scored by the physician or self-reported by the patients.

Mathematical expressions for relevant dose-response models

The following section provides the mathematical relationship and variable explanation for the different quantitative dose-response models encountered in this review.

Logistic regression

$$NTCP = \frac{1}{1 + e^{-S(\boldsymbol{X})}} \text{ where } S(\boldsymbol{X}) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_i x_i \quad (1)$$

β_0 is a constant and β_i represents the regression coefficient for the *i-th* covariate x_i.

Logit model

$$NTCP = \frac{1}{1 + \left(\frac{D_{50}}{D}\right)^k} \quad (2)$$

D_{50} is the dose leading to a 50% complication rate, D is the dose to the organ and k represents the slope of the dose-response curve.

Lyman equivalent model using generalized equivalent uniform dose (*gEUD*)

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-\frac{x^2}{2}} dx \quad (3)$$

$$t = \frac{gEUD - D_{50}}{m \cdot D_{50}}$$

$$gEUD = \left(\sum\nolimits_i v_i D_i^{1/n}\right)^n$$

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D_{50} is the dose leading to a 50% complication rate, m represents the slope of the dose-response curve, v_i is the i-th volume fraction of the organ, D_i is the dose to the i-th volume fraction and n describes the volume effect of the organ dose-response. For a mean dose model n =1. Note, that in this expression for $gEUD$ the usual parameter a is replaced by a =1 n, i.e. a is identified with the inverse of the volume effect parameter.

Logistic model

$$NTCP = \frac{1}{1 + e^{4\gamma_{50}\left(1 - \frac{D}{D_{50}}\right)}} \quad (4)$$

D_{50} is the dose leading to a 50% complication rate, D is the dose to the organ and γ_{50} is the relative change in complication rate per unit change in dose at the 50% level.

Log-logistic model using *gEUD*

$$NTCP = \frac{1}{1 + \left(\frac{D_{50}}{gEUD}\right)^{4\gamma_{50}}} \quad (5)$$

$$gEUD = \left(\sum_i v_i D_i^a\right)^{1/a}$$

Plateau excess absolute risk (EAR) model based on organ-equivalent dose (OED)

$$EAR\left(D, age_e, age_a\right) = \beta \cdot OED\left(D_i\right) \cdot \mu\left(age_e, age_a\right) \quad (6)$$

$$OED = \sum_i v_i \frac{1 - e^{-\alpha D_i}}{\alpha}$$

$$\mu\left(age_e, age_a\right) = e^{\left[\gamma_e\left(age_e - 30\right) + \gamma_a \ln\left(\frac{age_a}{70}\right)\right]}$$

Critically evaluating various dose-response models for a given endpoint

It is not straightforward to compare dose-response models from different studies due to varying choice of mathematical model, adjustment for multiple factors and variation in patient material and treatment. Therefore, we adopted the previously published concept of computing a relevance score for each report with a quantitative dose-response model, as a measure of how relevant the model is for estimating NTCP for the patient population in

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question.[17] The flow chart in Figure 2 depicts our adaptation of how to calculate the relevance score for head and neck cancer patients undergoing RT or chemo-RT in the modern IMRT era. The categories and scores were derived based on clinical and analytical judgment, as well as by adhering to the critical points brought to light in the QUANTEC reports related to head and neck patients.

Although the relevance score addresses the overall relevance of various models for the patient population in question, it does not provide much granularity in regards to the appropriateness of the applied statistical methodology. Therefore, we further included a checklist depicting whether key items from the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) consensus statement on model development and validation were addressed in the reviewed studies.[19]

To determine the consistency between various dose-response models we calculated the corresponding NTCP for each model based on the dose distribution from a randomly selected head and neck patient who received comprehensive nodal irradiation at our institution with static field IMRT. We further added a 10% variation in the relevant OAR dose metric to each calculation to illustrate whether models were consistent across some variation in dose.

Results

We identified a total of 59 eligible full-text records that after further review resulted in 21 records with quantitative dose-response models for either dysphagia, esophagitis, hypothyroidism, xerostomia, oral mucositis, hearing loss or secondary cancers, as depicted in Figure 1. We did not find any post-QUANTEC studies presenting data on brainstem injury after standard fraction RT, and hence refer to the QUANTEC report for the most recent data.[11]

The following sections provide a detailed overview based on the records reviewed for each of the endpoints included in this review. For endpoints covered in the QUANTEC reports, comparisons are made between the suggested QUANTEC dose-volume constraints and the results presented by the papers included in this review.

The identified quantitative dose-response models are presented in Table 1 for patient-reported quality of life (QoL) endpoints, in Table 2 for endpoints scored by physical examination or laboratory tests and in Table 3 for secondary cancer endpoints. It is worth mentioning that model parameters cannot be directly compared between studies since parameters in multivariable models depend on the other covariates.

Graphical illustrations of all listed dose-response models are provided as supplementary material along with a ".txt" file with Matlab code to generate a data file containing all model parameters presented in Tables 1 – 3. Furthermore, the calculated NTCP estimates comparing the various different models are provided as supplementary material.

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Dysphagia

Several reports identified the pharyngeal constrictor muscles (PCMs) as a critical OAR for treatment-induced dysphagia[20–22] along with the supraglottic larynx[20,23], whereas some separated the constrictor muscles into the superior, middle and inferior parts. Table 1 shows that age, tumor site and radiation technique can be important predictors for patient-reported dysphagia, whilst Otter et al. identified concurrent chemotherapy as an important predictor for grade ≥3 physician-scored dysphagia.[24] The timeline for dysphagia scoring ranged from within 8 weeks to 6 months following treatment, which should be taken into account when comparing various models since acute dysphagia may not necessarily have the same dose-response characteristics as late dysphagia.

Mean doses in the range of 50 to 60 Gy to the PCMs were found to be indicative of an increased risk of dysphagia in several studies[21,22], whereas a mean dose higher than 40 or 50 Gy to the larynx was associated with increased risk.[22,25] The QUANTEC report on larynx and pharynx recommends keeping the dose to the larynx and pharyngeal constrictors to below 60 Gy when possible, and to limit the volume receiving more than 50 Gy.[12] These recommendations are well in line with what was found in the updated reports included in this review, even with the considerable variability in endpoint definitions among the studies included in the QUANTEC review.

Although the reports included here were all studies of head and neck cancer patients treated with reasonably homogeneous radiation therapy regimens, some variability in the results obtained from the different studies is expected due to the use of different measurement tools and dysphagia definitions. It also appears that patient-reported outcomes are becoming an increasingly common tool for measuring dysphagia in a QoL-setting[20,22,23], and as such it would be pertinent to consider how subjectively scored dysphagia compares to for example Common Terminology Criteria for Adverse Events (CTCAE) grading.

Esophagitis

We identified four studies with quantitative dose-response models for esophagitis, defined as grade ≥2 acute esophageal toxicity, presented in Table 2. These models are based on data from cohorts of non-small cell lung cancer (NSCLC) patients treated with radiation and chemotherapy[26–28] as well as one study of central lung tumors treated with SBRT that was included for comparison with standard fractionation studies.[29] Two studies identified concurrent chemotherapy as an independent predictor of acute esophagitis with an OR of 4.5 (95% CI: 3.3, 6.1) in Huang et al.[26] and 14.1 (95% CI: 4.7, 42.2) in Wijsman et al.[28], whereas all patients in Kwint et al.[27] received concurrent chemotherapy so this was not assessable as an independent risk factor.

Esophageal toxicity was scored within a few weeks or months from the start of radiation therapy and esophageal mean dose or V_{50} were identified as the independent dosimetric predictors for the studies employing standard fractionation. In the study of SBRT the dose to the hottest 5 cm^3 of the esophagus (D_{5cc}) and the maximum dose, both converted to BED_{10}, were significant predictors. The recommendations from the reports utilizing standard fractionation are to limit the esophageal mean dose or the V_{50}, without specifying any

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specific cutoff points for dose constraints. The QUANTEC report on acute esophagitis summarized that the volume of esophagus receiving >40–50 Gy was indicative of increased esophagitis risk, but could also not determine any specific dose limits[13], essentially concluding that the mean esophageal dose should be limited to the extent that is reasonable in terms of still adequately treating the tumor target.

Since all dose-response models for esophagitis identified in this review are based on patients treated for lung cancer, the limitations of translating the models to treatment of head and neck cancer should be considered. For the models based on standard fractionation the dose per fraction would be similar to that in head and neck RT, although more likely including the inferior esophagus for lung cancer patients and the superior part for head and neck cancer patients. The potential difference in chemotherapy regimens should also be considered, with concurrent regimens consisting of cisplatin[27] or etoposide and cisplatin.[28] There is also a likely interplay between acute esophageal toxicity and later appearing dysphagia after head and neck cancer treatment that may not be portrayed in studies of lung cancer patients.

Xerostomia

For xerostomia the parotid glands are usually considered the critical OARs for stimulated salivary flow and the QUANTEC recommendations that are now widely implemented clinically for head and neck IMRT suggest limiting the mean dose to both parotid glands to <25 Gy, or at least one parotid gland to <20 Gy.[10] This was based on the endpoint definition of <25% of baseline salivary flow, while some of the updated reports included in this review used alternative definitions such as patient-reported QoL for dry mouth or sticky saliva[30], and scintigraphy of salivary excretion function.[31] While most of the dose-response models in the included reports were based on parotid gland dose, the model for patient-reported sticky saliva found dose to the contralateral submandibular gland, sublingual glands and soft palate to be significant predictors.[30] The protective effect of increasing mean dose to the sublingual glands in relation to the risk of sticky saliva could be biologically plausible as mentioned by the authors, since the sublingual glands are mainly responsible for mucous saliva secretion.

The study by Moiseenko and colleagues tested the validity of the QUANTEC xerostomia recommendations on an independent prospectively acquired dataset, and found that the suggested constraints performed well with a negative predictive value of 94%.[32] A subsequent study by Beetz and colleagues, aimed at testing the validity of the QUANTEC constraints in an independent dataset of patient-reported xerostomia, showed that whether or not the QUANTEC criteria were met was a significant risk factor at 6, 12, 18 and 24 months post treatment.[33] Some level of Xerostomia at baseline prior to RT was also found to be an important risk factor and should be considered when this information is available.[30,33]

Although the mean dose to the parotid glands, or at least the contralateral gland, has been shown to be strongly associated with xerostomia recent evidence suggests that there are stem cell regions within the parotid glands that are critical to the maintenance of the functionality of the gland, and hence may warrant targeted partial-gland sparing.[34]

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Oral mucositis

Several reports with quantitative dose-response models for acute oral mucositis were identified, all based on head and neck cancer patient cohorts, with some variation in the anatomical OAR definition. The volume encompassing the oral cavity and in some cases parts of the pharynx was most commonly used[24,35–37], although some studies used a mucosal surface OAR definition.[38–40] In a comparative analysis Dean et al. concluded that models based on an oral cavity definition and mucosal surface definition performed similarly for estimating acute mucositis and they recommend using the simpler oral cavity OAR contour.[39] The mucositis endpoint was homogeneously defined as CTCAE grade ≥3 acute oral mucositis, occurring during RT or up to 8 weeks post treatment.

The mean dose to the oral cavity was found to be an independent predictor of oral mucositis[24,35], as well as the volume of oral cavity receiving high doses per fraction[36] and the dose to the hottest 21 cm^3.[37] One report identified concurrent chemotherapy as an independent predictor along with oral cavity dose[37], whereas for the model presented by Bhide et al. all patients were treated with concurrent chemo-RT.[35]

Strigari et al. performed a meta-analysis of previously published studies to compare the ability of various NTCP models to identify tolerable vs. intolerable treatment schedules in relation to acute oral mucositis.[41] By comparing varying schedules of total dose in 2-Gy fractions (EQD_2) and overall treatment time they showed how well the different models could distinguish tolerable from intolerable treatments, with a general trend that treatment times longer than 38 days were considered tolerable. While most studies focused on the risk of developing oral mucositis, one study of 66 oropharyngeal cancer patients investigated whether the duration of grade 3 acute mucositis was related to the dose received by the oral mucosa, but failed to find a significant association.[42]

Although there was no QUANTEC report focused directly on oral mucositis, it has been recognized that dysphagia occurring at a later onset can be a consequence of preceding acute mucositis, and NTCP models for oral mucositis may be relevant to consider in relation to the risk of late dysphagia as well.[12]

Hypothyroidism

Hypothyroidism as determined through elevated TSH, or reduced T3 and T4 levels, typically appearing 1–2 years after treatment remains a fairly common normal tissue complication after head and neck RT. The mean thyroid dose[43–45] has been shown as important independent predictors of radiation-induced hypothyroidism (RIHT). Also, several studies have identified the thyroid volume receiving more than 30 to 35 Gy (V30-V35) as an important dose-volume constraint associated with the risk of RIHT.[46–48]

Importantly, the thyroid volume prior to treatment was found to be an important risk factor as well, with increasing pre-treatment thyroid volume showing a decreased risk of RIHT.[44,45,49] This further supports the consideration of the thyroid as a parallel structure organ, suggesting that limiting the irradiated volume would be key to reducing the complication risk.

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As RIHT is an endocrine complication it is not sufficient to consider only the thyroid gland as an OAR, since irradiation of the pituitary gland is also associated with an increased risk of RIHT. Thus, several of the studies included in this analysis excluded patients with nasopharyngeal cancer or limited the inclusion to patients with doses to the pituitary gland <40 Gy, as this is considered an important cutoff point.[43–45]

A meta-analysis of 33 published studies performed by Vogelius et al. in 2011 identified female gender, partial or hemi-thyroidectomy, Caucasian descent and lymphangiography as significant risk factors for hypothyroidism, whereas age and chemotherapy were not.[50] They also found a significant dose-response effect but highlighted the considerable uncertainty in the NTCP model parameters when comparing the results from different studies.

There was no QUANTEC report that covered RIHT.

Hearing loss

Several post-QUANTEC studies of radiation-induced hearing loss were identified but only one that reported quantitative dose-response models.[51] Some studies reported on hearing loss for patients treated with Gamma Knife radiosurgery and are not discussed further in this review, but referred to here for the interested reader.[52,53]

De Marzi et al. reported dose-response models separately based on considering the inner ear, cochlea or internal auditory canal as the critical OAR for 140 patients treated to the skull base with a mixture of photon and proton RT.[51] We only include the models based on inner ear and cochlea in Table 2 since these performed considerably better than the model based on the internal auditory canal, with areas under the receiver operating characteristics curve of 0.86 and 0.81 compared to 0.72, respectively. The mean cochlear dose for patients with grade 1–2 hearing loss was 54.6 ± 16 Gy_{RBE} (with a relative biological effectiveness (RBE) of 1.1 used for protons) and 36.8 ± 14 Gy_{RBE} for those without.

Another study of 17 patients treated with post-parotidectomy RT showed no evidence of ipsilateral or contralateral hearing loss during 2 years of follow-up, with all patients receiving a mean cochlear dose <45 Gy.[54] Furthermore, Champ et al. presented audiometric evaluation data from 154 patients treated for acoustic neuromas with RT in 1.8 Gy fractions. [55] These authors found that separating patients into groups receiving either ≤40 Gy or >40 Gy to be a significant predictor of hearing impairment.

Although there was no clear threshold dose determined in the QUANTEC report on radiation-induced hearing loss it recommends that the mean cochlear dose be kept ≤45 Gy, or ≤35 Gy if possible[9], which seems to agree well with the results from the studies included in this updated review.

Optic neuropathy/vision impairment

We identified only a limited number of studies reporting on radiation-induced optic neuropathy (RION) or visual impairment after standard fractionation RT and neither presented a quantitative dose-response model. In a study by Farzin et al. in 2016 only two out of 213 patients treated for meningioma had visual problems attributed to RT, both with

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maximum doses to the optic nerve and chiasm close or just above 54 Gy.[56] Another study found that IMRT resulted in lower doses to the optic nerves and chiasm, although not significantly affecting the risk of RION in patients with meningioma and pituitary adenoma.[57]

In a small study of 10 meningioma patients higher mean eye dose appeared to be related to deteriorated vision, although with such limited patient numbers this should be considered anecdotal.[58]

The QUANTEC report on optic nerves and chiasm concluded that RION was rare if maximum doses to these structures were <55 Gy with standard fractionation, with a marked increase in risk >60 Gy.[59] The limited number of reports on RION post QUANTEC could reasonably be explained as a result of the widespread implementation of these recommendations and few patients receiving doses to the optic nerves and chiasm above the recommended 55 Gy constraint.

Fatigue

Fatigue has long been a known serious consequence of RT, especially in combination with concurrent chemotherapy. However, addressing this complication as dose-dependent phenomenon and attempting to identify the responsible OARs has only recently been undertaken and as such this was not addressed specifically in the QUANTEC reports. The definition typically involves the feeling of fatigue not relieved by rest, or how much fatigue impacts ones QoL on a daily basis, and can be scored using the CTCAE scale or using validated patient questionnaire instruments.[60,61]

In a retrospective analysis of the data from the PARSPORT trial, investigators found a significant association between mean dose to the brainstem, cerebellum and posterior fossa and risk of grade ≥2 fatigue, translating into an increased risk for patients receiving IMRT.[62] In a multivariate analysis of patients from the same trial, the mean dose to the cerebellum, basal ganglia and pituitary gland were significantly associated with increased risk of fatigue when adjusting for multiple clinical factors, albeit in a limited sample of only 40 patients.[63] Although this study found no association between chemotherapy and fatigue, a prospective study based on patient-reported questionnaires found significantly worse fatigue scores in patients receiving concurrent chemotherapy, compared to RT alone.[61]

Before quantitative dose-response models can be derived, the challenge remains to identify the pertinent OAR for radiation-induced fatigue and validation studies of the potential central nervous system OARs identified in the aforementioned studies should be undertaken, as well as further exploratory analyses and small-animal investigations.[64]

Secondary cancer

Studies of secondary cancer following RT require large cohorts with long follow-up, mainly due to the fact that they are rare events often associated with very long latency. We did, however, identify a few reports analyzing the risk of radiation-induced secondary cancers in the head and neck area, with dose-response models detailed in Table 3.

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The study by Morton et al. found an excess odds ratio per Gy of 0.09 (95% CI: 0.04, 0.16) for secondary esophageal cancer in a cohort of breast cancer survivors, along with a protective effect of hormonal therapy and a multiplicative effect of smoking and radiation.[65] Several studies have identified the importance of secondary thyroid cancer in childhood cancer patients treated with RT, but this does not appear to translate to adult patients.[66]

The study by Schneider et al. combined cohort data from atomic bomb survivors and long-term survivors of Hodgkin's lymphoma treated with RT to estimate dose-response parameters for several different anatomical sites, including mouth and pharynx and salivary glands.[67] Importantly, any models estimating the risk of secondary cancer induction are subject to considerable uncertainty not only because of sparse data but also due to the inherent assumption that the limited radiation exposure information from long-term follow-up studies can be translated to modern RT treatment settings.

Comparing various NTCP models for multiple endpoints

When rating different RT options for head and neck cancer patients a variety of endpoints need to be considered, as demonstrated by the multitude of normal tissue complications included in this review. While hard endpoints such as brainstem necrosis or spinal cord myelopathy should always be prioritized it is less clear whether dysphagia, xerostomia, mucositis or esophagitis should be considered more important for treatment comparisons. In addition several NTCP models may exist for the same endpoint and while previous efforts have attempted to compare models based on the quality of input data and appropriateness in relation to the patients being studied[17], this remains a pertinent issue. Here, we applied the computation of a relevance score to compare various NTCP models with regards to their relevance in estimating the risk of radiation-induced toxicities after head and neck RT. The checklist of items from the TRIPOD consensus statement highlights the variation in statistical methodology and reporting in the various modeling studies and can be found as supplementary table S1.

For comparing proton therapy to photon therapy options Blanchard et al. decided to test various NTCP models derived from photon treatments on a patient cohort treated with proton therapy.[16] They found that the photon-derived models performed well for estimating the risk of dysphagia, xerostomia and hypothyroidism, but less well for acute mucositis. When comparing NTCP estimates between photon and proton therapy another validation of the results would be concordance of results between different models evaluating the same endpoints, whereas discordant results would suggest that one treatment option might not be clearly preferable.

When it comes to simultaneously evaluating multiple different endpoints one approach could be to estimate the relative impact on quality of life from the various endpoints for example as quality-adjusted life years.[68] This would potentially allow for a single measure common scale assessment of all different endpoints, and would go along the lines of implementing patient-reported outcomes as key components in radiation oncology decision making.[69,70]

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Alternative strategies to overcome NTCP modeling limitations

As noted in the QUANTEC reports and many of the papers included in this review, classical NTCP modeling is subject to several limitations such as dealing with highly correlated dosimetric parameters, or the lack of spatial information in dose-volume histograms.

To overcome the limitation of correlated data, a functional data analysis approach was implemented by Dean et al. to model the risk of grade ≥3 dysphagia and oral mucositis.[71] This approach models dose-volume data as a continuous function, with components determined using unsupervised (principal components analysis), or supervised (partial least squares regression) analysis, as well as including clinical covariates in the model. Reducing the dimensionality of the dose data in this manner should provide more robust estimates of dose-response parameters and improve generalizability of the model, but does add more complexity to the interpretation of the model parameters.

Another intriguing alternative approach is presented by Buettner et al. in which they demonstrate a novel morphological model that includes regional dose variations throughout the parotid gland to predict patient-reported xerostomia.[72] Their results show that including the spatial information of the dose distribution revealed areas of the parotid gland with apparently increased radiation sensitivity, and performed significantly better than a model based on mean parotid dose. These results are in agreement with the recent evidence of stem cell regions within the parotid gland that may be chiefly responsible for the salivary function and post-RT recovery.[34] In contrast, the study by Dean et al. showed similar performance between models based on dose-volume data and those incorporating spatial dose information to predict grade ≥3 oral mucositis.[36]

Recent efforts have also been focused on moving away from OAR-based dose-response modeling, in favor of voxel-based analyses correlating risk of toxicity with three-dimensional dose maps. Monti et al. performed such an analysis for acute grade ≥3 dysphagia and found significantly higher doses in voxels corresponding to the anatomical location of the cricopharyngeus muscle and cervical esophagus.[73]

Conclusions

Given the variety of available dose-response models published since the QUANTEC reports and the increased awareness of the importance of model validation, dealing with correlated dosimetric data, spatial variation in radiation sensitivity and the importance of patient-reported outcomes, data-driven decision making is becoming a reality in modern day radiation oncology. The NTCP estimates provided in the supplementary material illustrate that models for hypothyroidism, oral mucositis, and xerostomia (depending on time point and definition) are generally consistent, whereas the estimates for dysphagia and esophagitis vary considerably between models. When models disagree the corresponding relevance score should provide an indication as to which models are more reliable in the setting of modern day head and neck RT.

Despite this, it remains vital to encourage data sharing to allow sufficiently powered validation studies, and to implement prospective model testing in trials comparing different

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treatment approaches, so that the models' ability to truly distinguish between optimal and sub-optimal treatment options can be evaluated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Reference list

1. Garg MK, Glanzman J, Kalnicki S. The evolving role of positron emission tomography-computed tomography in organ-preserving treatment of head and neck cancer. Seminars in nuclear medicine. 2012; 42(5):320–7. DOI: 10.1053/j.semnuclmed.2012.04.005 [PubMed: 22840597]
2. Gregoire V, Langendijk JA, Nuyts S. Advances in Radiotherapy for Head and Neck Cancer. J Clin Oncol. 2015; 33(29):3277–84. DOI: 10.1200/JCO.2015.61.2994 [PubMed: 26351354]
3. Kim Y, Tome WA. Risk-adaptive optimization: selective boosting of high-risk tumor subvolumes. Int J Radiat Oncol Biol Phys. 2006; 66(5):1528–42. DOI: 10.1016/j.ijrobp.2006.08.032 [PubMed: 17126211]
4. Rosenthal DI, Harari PM, Giralt J, Bell D, Raben D, Liu J, et al. Association of Human Papillomavirus and p16 Status With Outcomes in the IMCL-9815 Phase III Registration Trial for Patients With Locoregionally Advanced Oropharyngeal Squamous Cell Carcinoma of the Head and Neck Treated With Radiotherapy With or Without Cetuximab. J Clin Oncol. 2016; 34(12):1300–8. DOI: 10.1200/JCO.2015.62.5970 [PubMed: 26712222]
5. Soto DE, Kessler ML, Piert M, Eisbruch A. Correlation between pretreatment FDG-PET biological target volume and anatomical location of failure after radiation therapy for head and neck cancers. Radiother Oncol. 2008; 89(1):13–8. DOI: 10.1016/j.radonc.2008.05.021 [PubMed: 18555547]
6. Meyer F, Fortin A, Gelinas M, Nabid A, Brochet F, Tetu B, et al. Health-related quality of life as a survival predictor for patients with localized head and neck cancer treated with radiation therapy. J Clin Oncol. 2009; 27(18):2970–6. DOI: 10.1200/JCO.2008.20.0295 [PubMed: 19451440]
7. Wang X, Hu C, Eisbruch A. Organ-sparing radiation therapy for head and neck cancer. Nature reviews Clinical oncology. 2011; 8(11):639–48. DOI: 10.1038/nrclinonc.2011.106
8. Bentzen SM, Constine LS, Deasy JO, Eisbruch A, Jackson A, Marks LB, et al. Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC): an introduction to the scientific issues. Int J Radiat Oncol Biol Phys. 2010; 76(3 Suppl):S3–9. DOI: 10.1016/j.ijrobp.2009.09.040 [PubMed: 20171515]
9. Bhandare N, Jackson A, Eisbruch A, Pan CC, Flickinger JC, Antonelli P, et al. Radiation therapy and hearing loss. Int J Radiat Oncol Biol Phys. 2010; 76(3 Suppl):S50–7. DOI: 10.1016/j.ijrobp.2009.04.096 [PubMed: 20171518]
10. 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(3 Suppl):S58–63. DOI: 10.1016/j.ijrobp.2009.06.090 [PubMed: 20171519]
11. Mayo C, Yorke E, Merchant TE. Radiation associated brainstem injury. Int J Radiat Oncol Biol Phys. 2010; 76(3 Suppl):S36–41. DOI: 10.1016/j.ijrobp.2009.08.078 [PubMed: 20171516]
12. 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(3 Suppl):S64–9. DOI: 10.1016/j.ijrobp.2009.03.079 [PubMed: 20171520]
13. 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(3 Suppl):S86–93. DOI: 10.1016/j.ijrobp.2009.05.070 [PubMed: 20171523]

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14. Dueck AC, Mendoza TR, Mitchell SA, Reeve BB, Castro KM, Rogak LJ, et al. Validity and Reliability of the US National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). JAMA oncology. 2015; 1(8): 1051–9. DOI: 10.1001/jamaoncol.2015.2639 [PubMed: 26270597]
15. Schmidt H, Merkel D, Koehler M, Flechtner HH, Sigle J, Klinge B, et al. PRO-ONKO-selection of patient-reported outcome assessments for the clinical use in cancer patients-a mixed-method multicenter cross-sectional exploratory study. Support Care Cancer. 2015; doi: 10.1007/s00520-015-3055-4
16. Blanchard P, Wong AJ, Gunn GB, Garden AS, Mohamed AS, Rosenthal DI, et al. Toward a model-based patient selection strategy for proton therapy: External validation of photon-derived normal tissue complication probability models in a head and neck proton therapy cohort. Radiother Oncol. 2016; 121(3):381–6. DOI: 10.1016/j.radonc.2016.08.022 [PubMed: 27641784]
17. Brodin NP, Maraldo MV, Aznar MC, Vogelius IR, Petersen PM, Bentzen SM, et al. Interactive decision-support tool for risk-based radiation therapy plan comparison for Hodgkin lymphoma. Int J Radiat Oncol Biol Phys. 2014; 88(2):433–45. DOI: 10.1016/j.ijrobp.2013.10.028 [PubMed: 24321783]
18. Langendijk JA, Lambin P, De Ruysscher D, Widder J, Bos M, Verheij M. Selection of patients for radiotherapy with protons aiming at reduction of side effects: the model-based approach. Radiother Oncol. 2013; 107(3):267–73. DOI: 10.1016/j.radonc.2013.05.007 [PubMed: 23759662]
19. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD). Annals of internal medicine. 2015; 162(10):735–6. DOI: 10.7326/L15-5093-2
20. Christianen ME, Schilstra C, Beetz I, Muijs CT, Chouvalova O, Burlage FR, et al. Predictive modelling for swallowing dysfunction after primary (chemo)radiation: results of a prospective observational study. Radiother Oncol. 2012; 105(1):107–14. DOI: 10.1016/j.radonc.2011.08.009 [PubMed: 21907437]
21. Mazzola R, Ricchetti F, Fiorentino A, Fersino S, Giaj Levra N, Naccarato S, et al. Dose-volume-related dysphagia after constrictor muscles definition in head and neck cancer intensity-modulated radiation treatment. Br J Radiol. 2014; 87(1044):20140543.doi: 10.1259/bjr.20140543 [PubMed: 25348370]
22. Mortensen HR, Jensen K, Aksglaede K, Behrens M, Grau C. Late dysphagia after IMRT for head and neck cancer and correlation with dose-volume parameters. Radiother Oncol. 2013; 107(3): 288–94. DOI: 10.1016/j.radonc.2013.06.001 [PubMed: 23791365]
23. Vainshtein JM, Moon DH, Feng FY, Chepeha DB, Eisbruch A, Stenmark MH. Long-term quality of life after swallowing and salivary-sparing chemo-intensity modulated radiation therapy in survivors of human papillomavirus-related oropharyngeal cancer. Int J Radiat Oncol Biol Phys. 2015; 91(5):925–33. DOI: 10.1016/j.ijrobp.2014.12.045 [PubMed: 25832685]
24. Otter S, Schick U, Gulliford S, Lal P, Franceschini D, Newbold K, et al. Evaluation of the Risk of Grade 3 Oral and Pharyngeal Dysphagia Using Atlas-Based Method and Multivariate Analyses of Individual Patient Dose Distributions. Int J Radiat Oncol Biol Phys. 2015; 93(3):507–15. DOI: 10.1016/j.ijrobp.2015.07.2263 [PubMed: 26460992]
25. Anderson NJ, Wada M, Schneider-Kolsky M, Rolfo M, Joon DL, Khoo V. Dose-volume response in acute dysphagia toxicity: Validating QUANTEC recommendations into clinical practice for head and neck radiotherapy. Acta Oncol. 2014; 53(10):1305–11. DOI: 10.3109/0284186X.2014.933874 [PubMed: 24980044]
26. Huang EX, Bradley JD, El Naqa I, Hope AJ, Lindsay PE, Bosch WR, et al. Modeling the risk of radiation-induced acute esophagitis for combined Washington University and RTOG trial 93–11 lung cancer patients. Int J Radiat Oncol Biol Phys. 2012; 82(5):1674–9. DOI: 10.1016/j.ijrobp.2011.02.052 [PubMed: 21658856]
27. Kwint M, Uyterlinde W, Nijkamp J, Chen C, de Bois J, Sonke JJ, et al. Acute esophagus toxicity in lung cancer patients after intensity modulated radiation therapy and concurrent chemotherapy. Int J Radiat Oncol Biol Phys. 2012; 84(2):e223–8. DOI: 10.1016/j.ijrobp.2012.03.027 [PubMed: 22560551]
28. Wijsman R, Dankers F, Troost EG, Hoffmann AL, van der Heijden EH, de Geus-Oei LF, et al. Multivariable normal-tissue complication modeling of acute esophageal toxicity in advanced stage

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non-small cell lung cancer patients treated with intensity-modulated (chemo-)radiotherapy. Radiother Oncol. 2015; 117(1):49–54. DOI: 10.1016/j.radonc.2015.08.010 [PubMed: 26341608]

29. Wu AJ, Williams E, Modh A, Foster A, Yorke E, Rimner A, et al. Dosimetric predictors of esophageal toxicity after stereotactic body radiotherapy for central lung tumors. Radiother Oncol. 2014; 112(2):267–71. DOI: 10.1016/j.radonc.2014.07.001 [PubMed: 25064471]
30. Beetz I, Schilstra C, van der Schaaf A, van den Heuvel ER, Doornaert P, van Luijk P, 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(1):101–6. DOI: 10.1016/j.radonc.2012.03.004 [PubMed: 22516776]
31. Chen WC, Lai CH, Lee TF, Hung CH, Liu KC, Tsai MF, et al. Scintigraphic assessment of salivary function after intensity-modulated radiotherapy for head and neck cancer: correlations with parotid dose and quality of life. Oral Oncol. 2013; 49(1):42–8. DOI: 10.1016/j.oraloncology.2012.07.004 [PubMed: 22854066]
32. Moiseenko V, Wu J, Hovan A, Saleh Z, Apte A, Deasy JO, et al. Treatment planning constraints to avoid xerostomia in head-and-neck radiotherapy: an independent test of QUANTEC criteria using a prospectively collected dataset. Int J Radiat Oncol Biol Phys. 2012; 82(3):1108–14. DOI: 10.1016/j.ijrobp.2011.04.020 [PubMed: 21640505]
33. Beetz I, Steenbakkers RJ, Chouvalova O, Leemans CR, Doornaert P, van der Laan BF, et al. The QUANTEC criteria for parotid gland dose and their efficacy to prevent moderate to severe patient-rated xerostomia. Acta Oncol. 2014; 53(5):597–604. DOI: 10.3109/0284186X.2013.831186 [PubMed: 23998646]
34. van Luijk P, Pringle S, Deasy JO, Moiseenko VV, Faber H, Hovan A, et al. Sparing the region of the salivary gland containing stem cells preserves saliva production after radiotherapy for head and neck cancer. Science translational medicine. 2015; 7(305):305ra147.doi: 10.1126/scitranslmed.aac4441
35. Bhide SA, Gulliford S, Schick U, Miah A, Zaidi S, Newbold K, et al. Dose-response analysis of acute oral mucositis and pharyngeal dysphagia in patients receiving induction chemotherapy followed by concomitant chemo-IMRT for head and neck cancer. Radiother Oncol. 2012; 103(1): 88–91. DOI: 10.1016/j.radonc.2011.12.027 [PubMed: 22280809]
36. Dean JA, Wong KH, Welsh LC, Jones AB, Schick U, Newbold KL, et al. Normal tissue complication probability (NTCP) modelling using spatial dose metrics and machine learning methods for severe acute oral mucositis resulting from head and neck radiotherapy. Radiother Oncol. 2016; 120(1):21–7. DOI: 10.1016/j.radonc.2016.05.015 [PubMed: 27240717]
37. Sanguineti G, Sormani MP, Marur S, Gunn GB, Rao N, Cianchetti M, et al. Effect of radiotherapy and chemotherapy on the risk of mucositis during intensity-modulated radiation therapy for oropharyngeal cancer. Int J Radiat Oncol Biol Phys. 2012; 83(1):235–42. DOI: 10.1016/j.ijrobp.2011.06.2000 [PubMed: 22104358]
38. Dean JA, Welsh LC, McQuaid D, Wong KH, Aleksic A, Dunne E, et al. Assessment of fully-automated atlas-based segmentation of novel oral mucosal surface organ-at-risk. Radiother Oncol. 2016; 119(1):166–71. DOI: 10.1016/j.radonc.2016.02.022 [PubMed: 26970676]
39. Dean JA, Welsh LC, Wong KH, Aleksic A, Dunne E, Islam MR, et al. Normal Tissue Complication Probability (NTCP) Modelling of Severe Acute Mucositis using a Novel Oral Mucosal Surface Organ at Risk. Clinical oncology. 2017; 29(4):263–73. DOI: 10.1016/j.clon.2016.12.001 [PubMed: 28057404]
40. Musha A, Shimada H, Shirai K, Saitoh J, Yokoo S, Chikamatsu K, et al. Prediction of Acute Radiation Mucositis using an Oral Mucosal Dose Surface Model in Carbon Ion Radiotherapy for Head and Neck Tumors. PLoS One. 2015; 10(10):e0141734.doi: 10.1371/journal.pone.0141734 [PubMed: 26512725]
41. Strigari L, Pedicini P, D'Andrea M, Pinnaro P, Marucci L, Giordano C, et al. A new model for predicting acute mucosal toxicity in head-and-neck cancer patients undergoing radiotherapy with altered schedules. Int J Radiat Oncol Biol Phys. 2012; 83(5):e697–702. DOI: 10.1016/j.ijrobp.2012.02.004 [PubMed: 22578541]
42. Yahya S, Benghiat H, Nightingale P, Tiffany M, Sanghera P, Hartley A. Does Dose to an Oral Mucosa Organ at Risk Predict the Duration of Grade 3 Mucositis after Intensity-modulated

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Radiotherapy for Oropharyngeal Cancer? Clinical oncology. 2016; 28(12):e216–e9. DOI: 10.1016/j.clon.2016.08.009 [PubMed: 27593973]

43. Bakhshandeh M, Hashemi B, Mahdavi SR, Nikoofar A, Vasheghani M, Kazemnejad A. Normal tissue complication probability modeling of radiation-induced hypothyroidism after head-and-neck radiation therapy. Int J Radiat Oncol Biol Phys. 2013; 85(2):514–21. DOI: 10.1016/j.ijrobp.2012.03.034 [PubMed: 22583606]
44. Boomsma MJ, Bijl HP, Christianen ME, Beetz I, Chouvalova O, Steenbakkers RJ, et al. A prospective cohort study on radiation-induced hypothyroidism: development of an NTCP model. Int J Radiat Oncol Biol Phys. 2012; 84(3):e351–6. DOI: 10.1016/j.ijrobp.2012.05.020 [PubMed: 22717243]
45. Ronjom MF, Brink C, Bentzen SM, Hegedus L, Overgaard J, Petersen JB, et al. External validation of a normal tissue complication probability model for radiation-induced hypothyroidism in an independent cohort. Acta Oncol. 2015; 54(9):1301–9. DOI: 10.3109/0284186X.2015.1064160 [PubMed: 26248025]
46. Akgun Z, Atasoy BM, Ozen Z, Yavuz D, Gulluoglu B, Sengoz M, et al. V30 as a predictor for radiation-induced hypothyroidism: a dosimetric analysis in patients who received radiotherapy to the neck. Radiat Oncol. 2014; 9:104.doi: 10.1186/1748-717X-9-104 [PubMed: 24885512]
47. Fujiwara M, Kamikonya N, Odawara S, Suzuki H, Niwa Y, Takada Y, et al. The threshold of hypothyroidism after radiation therapy for head and neck cancer: a retrospective analysis of 116 cases. J Radiat Res. 2015; 56(3):577–82. DOI: 10.1093/jrr/rrv006 [PubMed: 25818629]
48. Kim MY, Yu T, Wu HG. Dose-volumetric parameters for predicting hypothyroidism after radiotherapy for head and neck cancer. Japanese journal of clinical oncology. 2014; 44(4):331–7. DOI: 10.1093/jjco/hyt235 [PubMed: 24482412]
49. Cella L, Liuzzi R, Conson M, D'Avino V, Salvatore M, Pacelli R. Development of multivariate NTCP models for radiation-induced hypothyroidism: a comparative analysis. Radiat Oncol. 2012; 7:224.doi: 10.1186/1748-717X-7-224 [PubMed: 23270411]
50. Vogelius IR, Bentzen SM, Maraldo MV, Petersen PM, Specht L. Risk factors for radiation-induced hypothyroidism: a literature-based meta-analysis. Cancer. 2011; 117(23):5250–60. DOI: 10.1002/cncr.26186 [PubMed: 21567385]
51. De Marzi L, Feuvret L, Boule T, Habrand JL, Martin F, Calugaru V, et al. Use of gEUD for predicting ear and pituitary gland damage following proton and photon radiation therapy. Br J Radiol. 2015; 88(1048):20140413.doi: 10.1259/bjr.20140413 [PubMed: 25671247]
52. Brown M, Ruckenstein M, Bigelow D, Judy K, Wilson V, Alonso-Basanta M, et al. Predictors of hearing loss after gamma knife radiosurgery for vestibular schwannomas: age, cochlear dose, and tumor coverage. Neurosurgery. 2011; 69(3):605–13. discussion 13–4. DOI: 10.1227/NEU.0b013e31821a42f3 [PubMed: 21471832]
53. Hayden Gephart MG, Hansasuta A, Balise RR, Choi C, Sakamoto GT, Venteicher AS, et al. Cochlea radiation dose correlates with hearing loss after stereotactic radiosurgery of vestibular schwannoma. World Neurosurg. 2013; 80(3–4):359–63. DOI: 10.1016/j.wneu.2012.04.001 [PubMed: 22484770]
54. Jereczek-Fossa BA, Rondi E, Zarowski A, D'Onofrio A, Alterio D, Ciocca M, et al. Prospective study on the dose distribution to the acoustic structures during postoperative 3D conformal radiotherapy for parotid tumors: dosimetric and audiometric aspects. Strahlenther Onkol. 2011; 187(6):350–6. DOI: 10.1007/s00066-011-2170-5 [PubMed: 21603994]
55. Champ CE, Shen X, Shi W, Mayekar SU, Chapman K, Werner-Wasik M, et al. Reduced-dose fractionated stereotactic radiotherapy for acoustic neuromas: maintenance of tumor control with improved hearing preservation. Neurosurgery. 2013; 73(3):489–96. DOI: 10.1227/NEU.0000000000000019 [PubMed: 23756743]
56. Farzin M, Molls M, Kampfer S, Astner S, Schneider R, Roth K, et al. Optic toxicity in radiation treatment of meningioma: a retrospective study in 213 patients. J Neurooncol. 2016; 127(3):597–606. DOI: 10.1007/s11060-016-2071-7 [PubMed: 26852221]
57. Astradsson A, Wiencke AK, Munck af Rosenschold P, Engelholm SA, Ohlhues L, Roed H, et al. Visual outcome after fractionated stereotactic radiation therapy of benign anterior skull base tumors. J Neurooncol. 2014; 118(1):101–8. DOI: 10.1007/s11060-014-1399-0 [PubMed: 24532196]

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58. Abouaf L, Girard N, Lefort T, D'Hombres A, Tilikete C, Vighetto A, et al. Standard-fractionated radiotherapy for optic nerve sheath meningioma: visual outcome is predicted by mean eye dose. Int J Radiat Oncol Biol Phys. 2012; 82(3):1268–77. DOI: 10.1016/j.ijrobp.2011.04.010 [PubMed: 21640493]
59. Mayo C, Martel MK, Marks LB, Flickinger J, Nam J, Kirkpatrick J. Radiation dose-volume effects of optic nerves and chiasm. Int J Radiat Oncol Biol Phys. 2010; 76(3 Suppl):S28–35. DOI: 10.1016/j.ijrobp.2009.07.1753 [PubMed: 20171514]
60. Aynehchi BB, Obourn C, Sundaram K, Bentsianov BL, Rosenfeld RM. Validation of the Modified Brief Fatigue Inventory in head and neck cancer patients. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2013; 148(1): 69–74. DOI: 10.1177/0194599812460985 [PubMed: 22972874]
61. Rosenthal DI, Mendoza TR, Fuller CD, Hutcheson KA, Wang XS, Hanna EY, et al. Patterns of symptom burden during radiotherapy or concurrent chemoradiotherapy for head and neck cancer: a prospective analysis using the University of Texas MD Anderson Cancer Center Symptom Inventory-Head and Neck Module. Cancer. 2014; 120(13):1975–84. DOI: 10.1002/cncr.28672 [PubMed: 24711162]
62. Gulliford SL, Miah AB, Brennan S, McQuaid D, Clark CH, Partridge M, et al. Dosimetric explanations of fatigue in head and neck radiotherapy: an analysis from the PARSPORT Phase III trial. Radiother Oncol. 2012; 104(2):205–12. DOI: 10.1016/j.radonc.2012.07.005 [PubMed: 22883107]
63. Powell C, Schick U, Morden JP, Gulliford SL, Miah AB, Bhide S, et al. Fatigue during chemoradiotherapy for nasopharyngeal cancer and its relationship to radiation dose distribution in the brain. Radiother Oncol. 2014; 110(3):416–21. DOI: 10.1016/j.radonc.2013.06.042 [PubMed: 23953411]
64. Renner M, Feng R, Springer D, Chen MK, Ntamack A, Espina A, et al. A murine model of peripheral irradiation-induced fatigue. Behavioural brain research. 2016; 307:218–26. DOI: 10.1016/j.bbr.2016.03.035 [PubMed: 27012391]
65. Morton LM, Gilbert ES, Hall P, Andersson M, Joensuu H, Vaalavirta L, et al. Risk of treatment-related esophageal cancer among breast cancer survivors. Ann Oncol. 2012; 23(12):3081–91. DOI: 10.1093/annonc/mds144 [PubMed: 22745217]
66. Ron E, Lubin JH, Shore RE, Mabuchi K, Modan B, Pottern LM, et al. Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. 1995. Radiat Res. 2012; 178(2):AV43–60. [PubMed: 22870979]
67. Schneider U, Sumila M, Robotka J. Site-specific dose-response relationships for cancer induction from the combined Japanese A-bomb and Hodgkin cohorts for doses relevant to radiotherapy. Theor Biol Med Model. 2011; 8:27.doi: 10.1186/1742-4682-8-27 [PubMed: 21791103]
68. Sassi F. Calculating QALYs, comparing QALY and DALY calculations. Health policy and planning. 2006; 21(5):402–8. DOI: 10.1093/heapol/czl018 [PubMed: 16877455]
69. Niska JR, Halyard MY, Tan AD, Atherton PJ, Patel SH, Sloan JA. Electronic patient-reported outcomes and toxicities during radiotherapy for head-and-neck cancer. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2017; doi: 10.1007/s11136-017-1528-2
70. Shuman AG, Larkin K, Thomas D, Palmer FL, Fins JJ, Baxi SS, et al. Patient Reflections on Decision Making for Laryngeal Cancer Treatment. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2017; 156(2): 299–304. DOI: 10.1177/0194599816683377 [PubMed: 28116989]
71. Dean JA, Wong KH, Gay H, Welsh LC, Jones AB, Schick U, et al. Functional Data Analysis Applied to Modeling of Severe Acute Mucositis and Dysphagia Resulting From Head and Neck Radiation Therapy. Int J Radiat Oncol Biol Phys. 2016; 96(4):820–31. DOI: 10.1016/j.ijrobp.2016.08.013 [PubMed: 27788955]
72. Buettner F, Miah AB, Gulliford SL, Hall E, Harrington KJ, Webb S, et al. Novel approaches to improve the therapeutic index of head and neck radiotherapy: an analysis of data from the PARSPORT randomised phase III trial. Radiother Oncol. 2012; 103(1):82–7. DOI: 10.1016/j.radonc.2012.02.006 [PubMed: 22444242]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

73. Monti S, Palma G, D'Avino V, Gerardi M, Marvaso G, Ciardo D, et al. Voxel-based analysis unveils regional dose differences associated with radiation-induced morbidity in head and neck cancer patients. Scientific reports. 2017; 7(1):7220.doi: 10.1038/s41598-017-07586-x [PubMed: 28775281]

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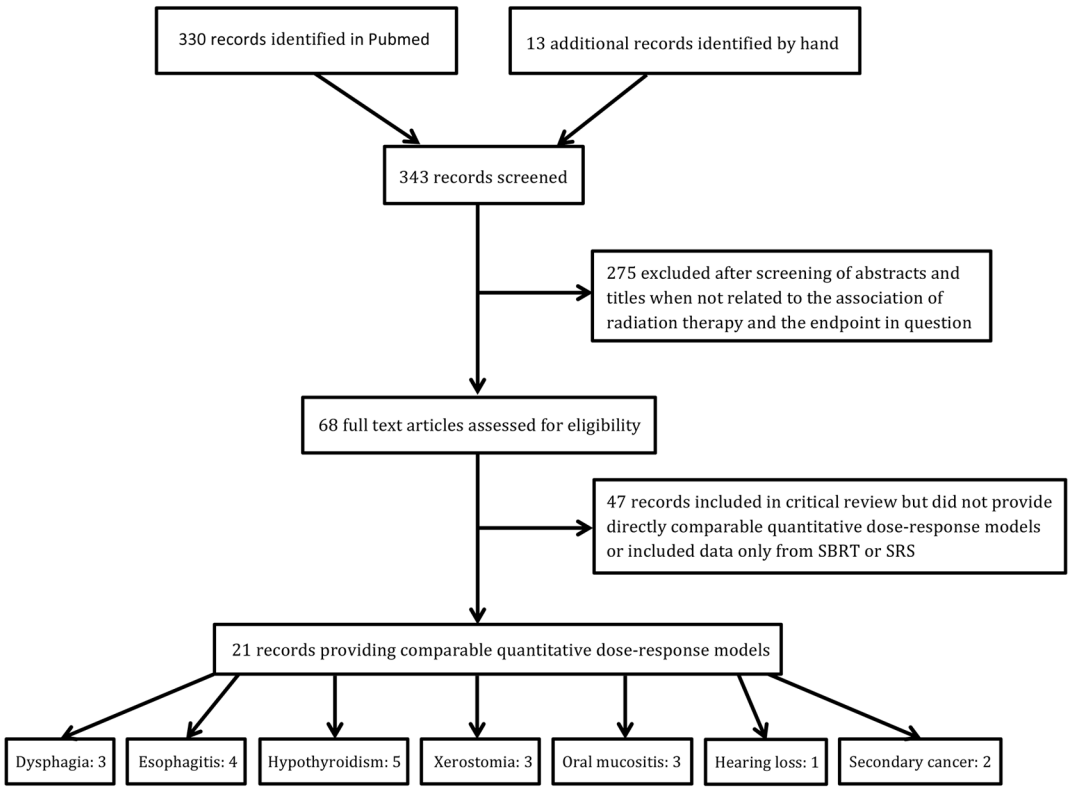

Figure 1.

Flow chart illustrating the selection process for identifying studies with quantitative dose-response models included for detailed review.

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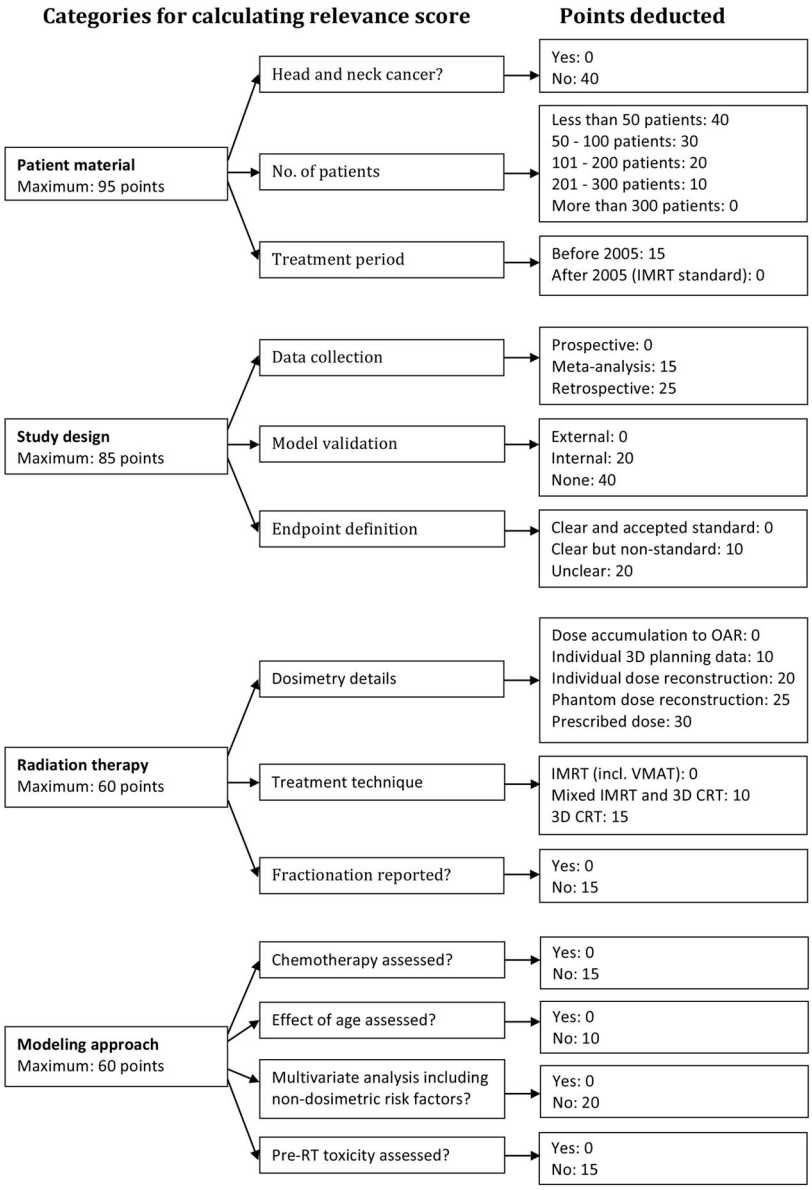

Figure 2.

Schema illustrating the relevance score computation and the weights assigned to the various categories. The highest relevance score a report can be assigned is 300 and the lowest score is zero. The number of points deducted in each category represents the weight assigned to deviation from the ideal scenario.

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Table 1

Dose-response models for head and neck normal tissue toxicity endpoints scored by patient self-reporting using quality of life questionnaires. Relevance scores presented as total and (patient material, study design, radiation therapy, modeling approach).

Endpoint definition	Patient material	Time point	Significant non-dosimetric risk factors	Model and parameters (95% CIs)	Reference
Dysphagia					
Moderate to severe liquid swallowing based on EORTC QLQ-H&N35 *	354 head and neck cancer patients treated with chemo-RT 1.5 – 2 Gy/fx	6 months post RT	Radiation technique: (IMRT vs. 3DCRT)	Logistic regression: $\beta_{\text{SG larynx mean dose}}$ = 0.074 (0.030, 0.11) $\beta_{\text{Radiation technique}}$ = −1.21 (−2.12, −0.27) Constant = −5.98 *AUC = 0.75 (0.68–0.83)*	Christianen et al. 2012[20] *Relevance score: 215 (80, 35, 40, 60)*
Moderate to severe soft food swallowing based on EORTC QLQ-H&N35			Age: (>65 vs. 18–65 y) Tumor site: (Oro/nasopharynx vs. Other) Radiation technique: (IMRT vs. 3DCRT)	Logistic regression: $\beta_{\text{Middle PCM mean dose}}$ = 0.061 (0.030, 0.095) β_{Age} = 1.20 (0.41, 2.00) $\beta_{\text{Tumor site}}$ = 1.12 (0.31, 1.93) $\beta_{\text{Radiation technique}}$ = −0.91 (−1.77, −0.073) Constant = −5.83 *AUC = 0.79 (0.72–0.86)*	
Moderate to severe soft food swallowing based on EORTC QLQ-H&N35			Age: (>65 vs. 18–65 y)	Logistic regression: $\beta_{\text{Superior PCM mean dose}}$ = 0.049 (0.030, 0.068) $\beta_{\text{SG larynx}}$ = 0.048 (0.010, 0.086) β_{Age} = 0.80 (0.020, 1.57) Constant = −6.89 *AUC = 0.77 (0.70–0.84)*	
Moderate to severe choking when swallowing based on EORTC QLQH& N35			-	Logistic regression: $\beta_{\text{Esophagus inlet muscle V60}}$ = 0.020 (0.010, 0.030) $\beta_{\text{SG larynx mean dose}}$ = 0.066 (0, 0.31) Constant = −7.07 *AUC = 0.77 (0.67–0.86)*	
Xerostomia					
Xerostomia based on EORTC QLQH& N35 criteria	178 head and neck cancer patients treated with IMRT or chemo-IMRT 2 Gy/fx	6 months post RT	Baseline xerostomia: (Yes vs. No)	Logistic regression: $\beta_{\text{Contralat. parotid mean dose}}$ = 0.047 (0.020, 0.077) $\beta_{\text{Baseline xerostomia}}$ = 0.72 (0.0, 1.44) Constant = −1.44 *AUC = 0.68, R_2 = 0.13*	Beetz et al. 2012[30] *Relevance score: 240 (75, 55, 50, 60)*
Sticky saliva based on EORTC QLQH& N35 criteria			-	Logistic regression: $\beta_{\text{Contralat. submand. mean dose}}$ = 0.075 (0.030, 0.12) $\beta_{\text{Sublingual glands mean dose}}$ = −0.06 (−0.10, −0.02) $\beta_{\text{Soft palate mean dose}}$ = 0.026 (0.0, 0.049)	

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Endpoint definition	Patient material	Time point	Significant non-dosimetric risk factors	Model and parameters (95% CIs)	Reference
				Constant = −3.24 *AUC = 0.70, R_2 = 0.17*	

AUC – Area under the receiver operating characteristics curve

R_2 – Pseudo R_2 values measuring goodness-of-fit

*European Organisation for Research and Treatment of Cancer head and neck cancer module quality of life questionnaire 35

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Table 2

Dose-response models for head and neck normal tissue toxicity endpoints scored by the treating physician based on clinical examination or laboratory tests. Relevance scores presented as total and (patient material, study design, radiation therapy, modeling approach).

Endpoint definition	Patient material	Time point	Significant non-dosimetric risk factors	Model and parameters (95% CIs)	Reference
Dysphagia					
Grade 2–4 swallowing dysfunction based on RTOG/EORTC SWALM6 *	354 head and neck cancer patients treated with chemo-RT 1.5 – 2 Gy/fx	6 months post RT	-	Logistic regression: $\beta_{\text{Superior PCM mean dose}}$ = 0.057 (0.039, 0.077) $\beta_{\text{SG larynx mean dose}}$ = 0.037 (0.010, 0.058) Constant = −6.09 *AUC = 0.80 (0.75–0.85)*	Christianen et al. 2012[20] *Relevance score: 215 (80, 35, 40, 60)*
Physician-scored Grade ≥3 pharyngeal dysphagia based on CTCAE † v3.0	253 head and neck cancer patients treated with RT or chemo-RT 1.8 – 2.4 Gy/fx	Within 8 weeks post RT	Concurrent chemo: (Yes vs. No) Gender‡	Logistic regression: $\beta_{\text{Inferior PCM mean dose}}$ = 0.03 (0.01, 0.53) $\beta_{\text{Concurrent chemo}}$ = 0.81 (0.09, 1.73) β_{Gender} = 0.27 Constant = −2.39 *AUC = 0.62 (0.55–0.69)*	Otter et al. 2015[24] *Relevance score: 215 (85, 45, 40, 45)*
Physician-scored Grade ≥3 dysphagia based on CTCAE v3.0	148 head and neck cancer patients treated with induction chemotherapy followed by concurrent chemo-IMRT 2.2 – 2.4 Gy/fx	Within 8 weeks post RT	-	Logit model: $D_{50,\text{ total PCM}}$ = 44.5 (36, 53) $k_{\text{total PCM}}$ = 2.6 (0.8, 4.5) R_2 = *0.65*	Bhide et al. 2012[35] *Relevance score: 170 (75, 45, 50, 0)*
Esophagitis					
RTOG grade ≥2 acute esophagitis	374 NSCLC patients treated with pretreatment or concurrent chemotherapy and 3DCRT 1.8 – 2.5 Gy/fx	Within 3–4 weeks from start of RT	Concurrent chemo: (Yes vs. No)	Logistic regression: $\beta_{\text{Esophagus mean dose}}$ = 0.069 (0.058, 0.080) $\beta_{\text{Concurrent chemo}}$ = 1.50 (1.19, 1.81) Constant = −3.13 *AUC = 0.83*	Huang et al. 2012[26] *Relevance score: 160 (40, 40, 35, 45)*
Acute esophageal toxicity grade ≥2 based on CTC v3.0	139 NSCLC patients treated with concurrent chemotherapy and IMRT 2.75 Gy/fx	Within 3 months from start of RT	-	Logistic regression: $\beta_{\text{Esophagus V50}}$ = 0.027 (0.005, 0.049) Constant = −0.52 *Performance measures N/A*	Kwint et al. 2012[27] *Relevance score: 145 (35, 45, 50, 15)*
Acute esophageal toxicity grade ≥2 based on RTOG grading	149 NSCLC patients treated with chemo- IMRT 2 Gy/fx	During RT and within a few weeks post RT	Concurrent chemo: (Yes vs. No) Gender: (Female vs. Male) T stage: (cT3/4 vs. cT1/2)	Logistic regression: $\beta_{\text{Esophagus mean dose}}$ = 0.12 (0.06, 0.17) $\beta_{\text{Concurrent chemo}}$ = 2.65 (1.55, 3.74) β_{Gender} = 1.20 (0.31, 2.10) $\beta_{\text{T stage}}$ = 0.99 (0.11, 1.87) Constant = −6.42 *AUC = 0.82,* R_2 = *0.41*	Wijsman et al. 2015[28] *Relevance score: 170 (35, 40, 50, 45)*

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Endpoint definition	Patient material	Time point	Significant non-dosimetric risk factors	Model and parameters (95% CIs)	Reference
Acute esophageal toxicity grade ≥2 based on CTCAE v4.0	125 patients with central lung tumors treated with SBRT 6 – 20 Gy/fx	During RT or within 4 months post RT	-	Logistic regression (BED10 doses): $\beta_{\text{Esophagus D5cc}}$ = 0.106 (0.047, 0.165) $\beta_{\text{Esophagus Dmax}}$ = 0.044 (0.019, 0.070) Constant = −3.90[††] *Performance measures N/A*	Wu et al. 2014[29] *Relevance score: 105 (35, 20, 50, 0)*
Hypothyroidism					
Clinical or sub-clinical hypothyroidism based on CTCAE v4.02	65 head and neck cancer patients treated with RT or chemo-RT, excluding nasopharynx if pituitary gland dose >40 Gy 1.8 – 2 Gy/fx	Within 12 months post RT	-	Lyman EUD mean dose model: $D_{50,\text{ Thyroid mean dose}}$ = 60 (56, 73) $m_{\text{Thyroid mean dose}}$ = 0.27 (0.20, 0.39) *Performance measures N/A*	Bakhshandeh et al. 2013[43] *Relevance score: 130 (50, 45, 35, 0)*
Clinical or sub-clinical hypothyroidism as elevated TSH[§] with or without reduced T4 levels	105 head and neck cancer patients treated with chemo-RT, excluding nasopharynx 1.5 – 2 Gy/fx	2 years post RT	Thyroid volume (cm^3)	Logistic regression: $\beta_{\text{Thyroid mean dose}}$ = 0.062 (0.029, 0.096) $\beta_{\text{Thyroid volume}}$ = −0.19 (−0.30, −0.08) Constant = 0.011 *AUC = 0.85 (0.78–0.92)*	Boomsma et al. 2012[44] *Relevance score: 215 (75, 55, 40, 45)*
Clinical or sub-clinical hypothyroidism as elevated TSH and/or reduced free T3 or T4 levels	53 patients with Hodgkin's Lymphoma treated with sequential chemo-RT 1.5 – 1.8 Gy/fx	Median follow-up 32 months post RT	Thyroid volume (cm^3) Gender: (Male vs. female)	Logistic regression: $\beta_{\text{Thyroid V30 (cm}^3\text{)}}$ = 0.26 (0.08, 0.44) $\beta_{\text{Thyroid volume}}$ = −0.27 (−0.49, −0.05) β_{Gender} = −2.21 (−3.88, −0.54) Constant = 1.94 *AUC = 0.87 (0.75–0.95)* $AUC_{External}$ *= 0.91 (0.76–0.98)*	Cella et al. 2012[49] *Relevance score: 155 (10, 50, 35, 60)* **Externally validated**
Biochemical hypothyroidism as elevated TSH levels	198 head and neck cancer patients, excluding nasopharynx, treated with RT or chemo-RT 2 – 2.1 Gy/fx	Within 25 months post RT	Thyroid volume (cm^3)	Logistic regression: $\beta_{\text{Thyroid mean dose}}$ = 0.18 (0.10, 0.37) $\beta_{\text{Thyroid volume}}$ = −0.30 (−0.62, −0.15) Constant = −4.92 *Calibration plot Pearson's r = 0.97*	Ronjom et al. 2015[45] *Relevance score: 260 (75, 75, 50, 60)* **Externally validated**
Clinical or sub-clinical hypothyroidism based mainly on elevated TSH	Meta-analysis of 4 studies for dose-response data for RT	Between 1 and 11 years post RT	-	Logistic model: $D_{50,\text{ Thyroid mean dose}}$ = 45 (28, 62) $\gamma_{50,\text{ Thyroid mean dose}}$ = 1.40 (0.50, 2.20) *Performance measures N/A*	Vogelius et al. 2011[50] *Relevance score: 110 (40, 30, 15, 25)*
Xerostomia					
Xerostomia based on post-treatment salivary excretion function ratio <45% on scintigraphy (per parotid gland)	31 head and neck cancer patients treated with IMRT or chemo-IMRT 1.8 – 2 Gy/fx	1 or 2 years post RT	#	Lyman EUD mean dose model (1 year): $D_{50,\text{ Parotid mean dose}}$ = 43.6 (CI N/A) $m_{\text{Parotid mean dose}}$ = 0.18 (CI N/A) *Performance measures N/A* Lyman EUD mean dose model (2 years):	Chen et al. 2013[31] *Relevance score: 185 (55, 35, 50, 45)*

Endpoint definition	Patient material	Time point	Significant non-dosimetric risk factors	Model and parameters (95% CIs)	Reference
				$D_{50,\ \text{Parotid mean dose}}$ = 44.5 (CI N/A) $m_{\text{Parotid mean dose}}$ = 0.30 (CI N/A) *Performance measures N/A*	
Grade 4 xerostomia based on LENTSOMA [¶] criteria for salivary flow measurements	66 head and neck cancer patients treated with RT or chemo-RT 1.7 – 2.7 Gy/fx	3 months post RT	-	Logistic model: $D_{50,\ \text{Spared parotid mean dose}}$ = 22.2 (16.4, 28.4) $\gamma_{50,\ \text{Spared parotid mean dose}}$ = 0.83 (0.44, 1.36)	Moiseenko et al. 2012[32] *Relevance score: 150 (65, 45, 40, 0)* **Validated QUANTEC criteria**
		12 months post RT	-	Logistic model: $D_{50,\ \text{Spared parotid mean dose}}$ = 32.4 (26.3, 39.9) $\gamma_{50,\ \text{Spared parotid mean dose}}$ = 0.97 (0.58, 1.53) *NPV for QUANTEC criteria = 94%*	
Oral mucositis					
Grade ≥3 oral mucositis based on CTCAE v2	351 head and neck cancer patients from 6 different trials treated with RT or chemo-RT 2 – 2.4 Gy/fx	Within 8 weeks post RT	Unknown primary: (Yes vs. No) Parotid primary: (Yes vs. No)	Penalized logistic regression (*per fx*): β_{V180cGy} = 0.212 *(V180cGy-53.6)/27.5 β_{V220cGy} = 0.194 *(V220cGy-10.5)/11.1 $\beta_{\text{Unknown primary}}$ = −0.025 *((Yes=*1, No=0*) −0.044)/0.205 $\beta_{\text{Parotid primary}}$ = −0.303 *((Yes=*1, No=0*) −0.209)/0.406 *AUC = 0.72 ± 0.09, Brier score = 0.23 ± 0.02*	Dean et al. 2016[36] *Relevance score: 245 (95, 65, 40, 45)*
Grade ≥3 oral mucositis based on CTCAE v3.0	253 head and neck cancer patients treated with RT or chemo-RT 1.8 – 2.4 Gy/fx	Within 8 weeks post RT	-	Logistic regression: $\beta_{\text{Oral cavity mean dose}}$ = 0.030 (0.0, 0.058) *AUC = 0.62 (0.55–0.69)*	Otter et al. 2015[24] *Relevance score: 215 (85, 45, 40, 45)*
Grade ≥3 oral mucositis based on CTCAE v3.0	164 oropharyngeal cancer patients treated with IMRT or chemo-IMRT 1.3 – 2.2 Gy/fx	During RT	Concurrent chemo: (Yes vs. No)	Logistic regression: $\beta_{\text{Oral cavity D21cc/week}}$ = 0.016 (0.009, 0.023) $\beta_{\text{Concurrent chemo}}$ = 1.42 (0.51, 2.32) Constant = −5.4 $AUC_{D21cc/week\ cutoff}$ *= 0.77 (0.69–0.85)*	Sanguineti et al. 2012[37] *Relevance score: 200 (60, 45, 50, 45)*
Grade ≥3 oral mucositis based on CTCAE v3.0	144 head and neck cancer patients treated with induction chemotherapy followed by concurrent chemo-IMRT 2.2 – 2.4 Gy/fx	Within 8 weeks post RT	-	Logit model: $D_{50,\ \text{oral cavity}}$ = 51 (40, 61) $k_{\text{oral cavity}}$ = 1.0 (0.6, 1.5) R_2 *= 0.80*	Bhide et al. 2012[35] *Relevance score: 170 (75, 45, 50, 0)*
Hearing loss					
Grade 1–2 hearing loss based on CTCAE v4.03	140 patients treated with skull base RT with combined proton and photon RT 1.8 – 2 Gy/fx	Within 2 years post RT	-	Log-logistic gEUD model (Cochlea): $D_{50,\ \text{Cochlea}}$ = 56.0 (53.6, 58.5) $\gamma_{50,\ \text{Cochlea}}$ = 2.8 (1.9, 4.2) $a_{,\ \text{Cochlea}}$ = 1.2 (0.1, 3.6)	De Marzi et al. 2015[51] *Relevance score: 75 (20, 20, 35, 0)*

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Endpoint definition	Patient material	Time point	Significant non-dosimetric risk factors	Model and parameters (95% CIs)	Reference
				AUC = 0.81 ± 0.04 Log-logistic gEUD model (Inner ear): $D_{50,\ \text{Inner ear}}$ = 53.6 (51.8, 55.4) $\gamma_{50,\ \text{Inner ear}}$ = 2.8 (2.1, 3.7) $a_{,\ \text{Inner ear}}$ = 0.1 (0.1, 0.6) *AUC = 0.86 ± 0.03*	

AUC – Area under the receiver operating characteristics curve

R_2 – Pseudo R_2 values measuring goodness-of-fit

*Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer Late Radiation Morbidity Scoring Criteria assessed at 6 months

†Common Terminology Criteria for Adverse Events

‡No ref info for gender in logistic regression model

††Constant value estimated from Fig. 2 in Wu et al. (29)

§Thyroid-stimulating hormone

#Certain non-dosimetric risk factors affecting quality of life but not part of dose-response model

¶Late Effects Normal Tissue Task Force-Subjective, Objective, Management, Analytic criteria

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Table 3

Dose-response models for secondary cancers in the head and neck region based on cohort studies of long-term cancer survivors. Relevance scores presented as total and (patient material, study design, radiation therapy, modeling approach).

Secondary cancer

Endpoint definition	Patient material	Time point	Significant non-dosimetric risk factors	Model and parameters (95% CIs)	Reference
Treatment-related esophageal cancer in a cohort of breast cancer survivors	Nested case-control study of 289,748 breast cancer survivors with 252 cases and 488 matched controls	Between 5 and 37 years post breast cancer treatment	Smoking: (Current vs. Nonsmoker) Hormonal therapy in last 5 years: (Yes vs. No)	Linear model: $EOR/Gy_{\text{Esophagus mean dose}} = 0.09$ (0.04, 0.16) $OR_{\text{Smoking}} = 2.4$ (1.1, 5.7) $OR_{\text{Hormonal therapy}} = 0.4$ (0.2, 0.8) *Performance measures N/A*	Morton et al. 2012[65] *Relevance score: 110 (40, 20, 5, 45)*
Radiation-induced secondary cancer of the mouth and pharynx	Cohort study based on atomic bomb survivors receiving high doses and Hodgkin's lymphoma patients treated with RT	Time factors included in model	Age at exposure: (Continuous) Attained age: (Continuous)	EAR plateau OED model: $\alpha_{\text{Mouth and pharynx}} = 0.045$ $\beta_{\text{EAR}} = 0.73$ (0.30, 1.60) $\gamma_{\text{age at exposure}} = -0.024$ $\gamma_{\text{attained age}} = 2.38$ *Performance measures N/A*	Schneider et al. 2011[67] *Relevance score: 85 (40, 10, 5, 30)*