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Development of a Normal Tissue Complication Probability Model for Dysphagia in PATHOS trial patients

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Topic

HPV or EBV related cancers

Keywords

NTCP, MDADI, PATHOS

Purpose/Objective

Normal Tissue Complication Probability (NTCP) models have the potential to enable head and neck (H&N) oncologists to adopt a personalised treatment strategy for their patients by quantifying individual risks to developing specific toxicities. [1] While NCTP models for dysphagia in patients receiving definitive radiotherapy for head and neck cancer are available [1-5], suitable models, that contain the most relevant OAR with reliable dose–response estimates, are lacking in the adjuvant (post-operative) setting. This study aimed to develop a NTCP model for dysphagia, following transoral surgery and adjuvant radiotherapy for patients in the PATHOS trial [NCT: A25317]. This trial examines whether reducing the intensity of adjuvant treatment following minimally invasive transoral surgery in HPV related Oropharyngeal Squamous Cell Cancer (OPSCC) patients, either by lowering radiotherapy (RT) dose or omitting chemotherapy, will result in improved swallowing function, whilst maintaining excellent clinical outcomes.[6]

Material/Methods

The dataset consisted of 116 patients allocated into arms B1 & C2 of PATHOS from Jul 2007 to Feb 2020, who received 60Gy in 30 fractions IMRT following transoral surgery. The model endpoint of dysphagia was defined as MDADI composite score <80 at 12months post treatment (MDADI_12m). Candidate predictors included mean dose in Gy to nine swallowing OARs (SWOARs). SWOARs were outlined as per PATHOS swallowing atlas by a single investigator and checked by 2 senior investigators.

To develop the prediction model, first a univariable analysis was conducted to show the raw uncorrected effects of each candidate variable on MDADI_12m. Next non-linear transformations were evaluated for continuous variables and multicollinearity was assessed. Finally a multivariate logistic regression analysis with stepwise backward elimination was used. Model performance was evaluated using discrimination specified by the area under the receiver operating curve (AUC) and calibration using calibration-in-the-large (CITL) and calibration slope (C-slope). [7] Internal validation was completed using bootstrapping and model performance was subsequently adjusted for optimism.

Statistical analysis was conducted using Stata© software (version 17.0 SE, statacorp).

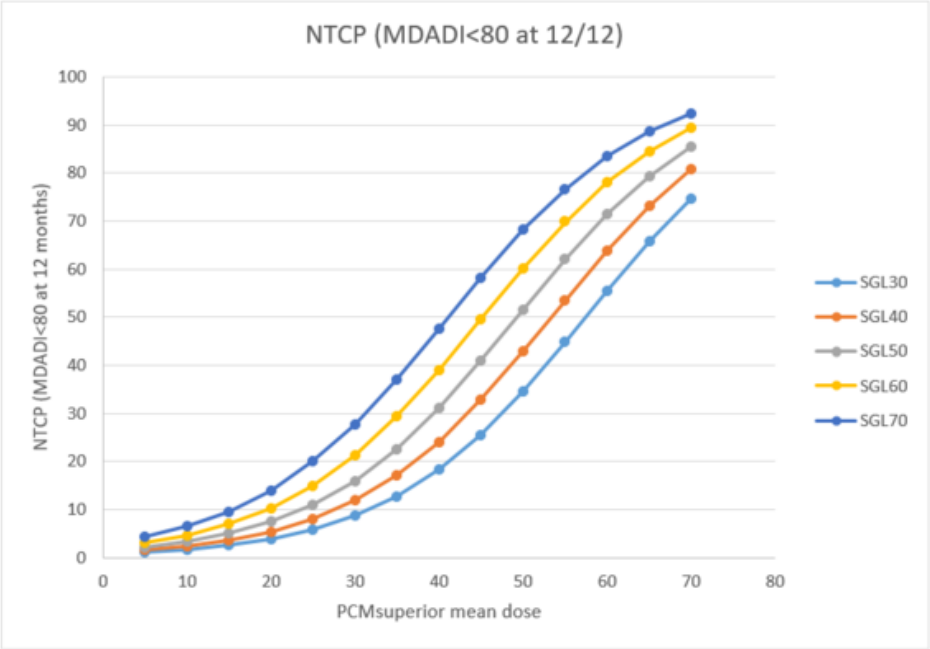
Results

The prevalence of MDADI_12m of <80 was 54%. Following pre-selection based on clinical expertise and prior knowledge, the candidate predictor variables included in the model were as follows; superior, middle and inferior pharyngeal constrictors, crico-oesophgeal inlet, supraglottic and glottic larynx and oral cavity. The multivariable model with the best performance consisted of the superior pharyngeal constrictor muscle (PCM_Superior) and the supraglottic larynx (Larynx_SG). In individual cases the risk of MDADI_12m <80 can be estimated using the following equation: NTCP MDADI_12m = $1/(1+ e^{-S})$, where S= -5.99 + (mean dose PCM Superior x 0.086) + (mean dose Larynx_SG x 0.035). (Figure 1)

Apparent model performance is presented in the calibration plot (Figure2). The AUC was 0.70 (p=0.001) showing good discrimination indicating good potential performance in populations with similar case-mix. The measures of CITL, ratio of expected to observed endpoints and C-slope were 0, 1 and 1 respectively indicating apparent perfect calibration performance as we would expect when we fit the developed model in the development cohort.

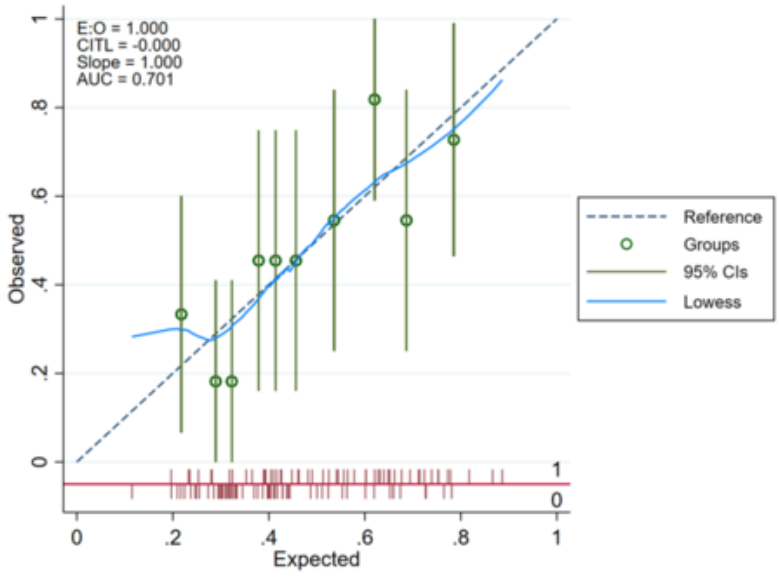
Optimism adjusted AUC, CITL and C-slope were 0.66, -0.003 and 0.73 respectively indicating good internal performance in terms of discrimination and minimal mis-calibration in CITL. However the C-slope of 0.66 suggests a moderate amount of shrinkage is required to adjust the predictor effects in the model for overfitting.

Figure 1: NCTP MDADI_12m



Normal tissue complication probability curves for MDADI_12m with each curve representing a 10 Gy increase in dose to the supraglottic larynx plotted against dose to PCM Superior mean dose. Abbreviations: NTCP = normal tissue complication probability, PCM = pharyngeal constrictor muscle, SGL = mean dose supraglottic larynx

Figure 2: Calibration Plot of Apparent Model Performance.



Calibration plot showing visual calibration across 10 risk groups of individuals. The lowess smoother shows that there is some miscalibration at the individual level in the lower and higher risk patients, though there is less data at these risk probabilities as indicated by the spike plot at the bottom of the graph. Abbreviations: AUC= Area under the curve; E:O= ratio of expected versus observed endpoints; CITL=Calibration in the large.

Conclusion

A novel NTCP model for MDADI_12m was developed to identify patients at risk for dysphagia after transoral surgery and adjuvant radiotherapy in PATHOS. Mean doses to the PCM_Superior and Larynx_SG were most predictive. An NTCP model including these parameters could be used to direct limited resources such as speech and language therapy to patients who are at highest risk of dysphagia, as well as in treatment planning to prioritise SWOAR optimisation. In future this model will need to be further updated in a larger dataset and externally validated before use in clinical practice.

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Distinctions in Tumor Microenvironment Between PD-L1 Positive versus Negative Head and Neck Squamous Cell Carcinoma (HNSCC)

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