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NTCP Modelling for Dermatitis Among Photon- and Proton-Treated Nasopharyngeal Carcinoma Patients

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ABSTRACT

Purpose:
To develop normal tissue complication probability (NTCP) models for Grade 3 (G3) radiation dermatitis in nasopharyngeal carcinoma (NPC) patients treated with photon and proton therapy, and to evaluate their generalizability across the two treatment modalities.

Methods:
Our data included 106 photon patients and 110 proton patients, treated for NPC in our institution from 2024 to 2025. On top of clinical characteristics, the dose-volume histogram of skin contour for each patient was extracted from the treatment planning system. Dermatitis was graded weekly since the start of treatment, up to 6-7 weeks. Two NTCP models were constructed with G3 dermatitis as the endpoint: 1) logistic regression (LR) model, and 2) Lyman-Kutcher-Burman (LKB) model. Leave-one-out cross-validation (LOOCV) was done within the photon and proton cohort, and the model trained on photon cohort was also tested on the proton cohort. The calibration plot and Receiver Operating Characteristic (ROC) curve were plotted, and the area under the ROC curve (AUC) was calculated.

Results:
The LR model identified V45Gy to be highly predictive of ≥G3 toxicity. From the LKB model, the dose causing a 50% toxicity risk was found to be 50.0 Gy and 38.8 Gy for photon and proton cohort, respectively. LOOCV within photon and proton cohort individually achieved AUC of 0.48 to 0.85 for both LR and LKB models. LKB model trained on photon was found to be generalizable to the proton cohort (AUC = 0.86 [0.80-0.91]), but not so for LR model (AUC = 0.20 [0.12-0.28]).

Conclusion:
In this work, two NTCP models have been constructed for G3 dermatitis in NPC patients treated with photon and proton therapy. The dosimetric features identified from the modelling could serve as clinical goals to be considered during treatment plan optimization and evaluation, to minimize the occurrences of radiation dermatitis.

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INTRODUCTION

Radiation dermatitis is a common side effect associated with radiotherapy, for cancer sites including breast cancer and head and neck cancer (HNC). In the context of nasopharyngeal carcinoma (NPC), a type of HNC, toxicity modelling for radiation dermatitis has been done for tomotherapy[1] and proton therapy[2]. Nonetheless, comparison of toxicity modelling between photon and proton treatment modalities is still lacking in the literature.

On that account, our study aimed to develop normal tissue complication probability (NTCP) models for Grade 3 (G3) radiation dermatitis in NPC patients treated with photon and proton therapy, and to evaluate their generalizability across the two treatment modalities.

METHODS AND MATERIALS

Retrospective data was obtained from 106 photon patients and 110 proton patients treated for NPC in our institution from 1 Jan 2024 to 31 Dec 2025. All the patients were treated either with radiotherapy alone, induction chemotherapy or concurrent chemoradiotherapy (CCRT). On top of clinical characteristics, e.g., age, gender and cancer staging, the dose-volume histograms (DVHs) of two types of skin contours for each patient were extracted from the treatment planning system. These skin contours include 1) Skin_short: from the superior boundary of lymph nodes (LN) clinical target volume (CTV) till the inferior boundary of LN CTV + 5cm, and 2) Skin_hyoid: from the hyoid till the inferior boundary of LN CTV + 5cm. The occurrence and grade of dermatitis was recorded weekly since the start of the treatment, up to 6-7 weeks. The grading was done based on CTCAE v4 by an advanced practice radiation therapist as well as the physicians.

Two NTCP models were developed using G3 dermatitis as the endpoint. The first is a logistic regression (LR) model taking four clinical variables and 14 DVH parameters as its input. The second is the Lyman-Kutcher-Burman (LKB) model, which takes in purely DVH as its input. The performances of these models were evaluated through leave-one-out cross-validation (LOOCV) within the photon and proton cohort. The model trained on the photon cohort was also tested on the proton cohort, to check the generalizability of the model across treatment modalities. The calibration plot and Receiver Operating Characteristic (ROC) curve were plotted, and the area under the ROC curve (AUC) was calculated.

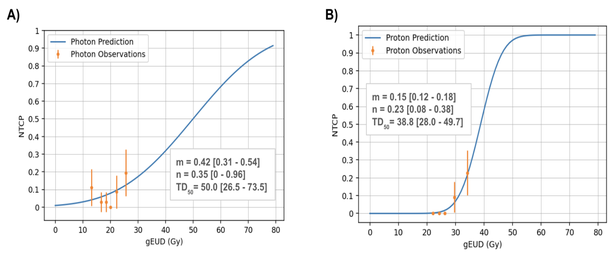

Figure 2. NTCP vs gEUD curves for (A) photon and (B) proton cohorts, generated from LKB modelling.

RESULTS

The baseline characteristics of our dataset along with the univariable analysis results for ≥G3 dermatitis are shown in **Table 1**. Results from the LR model **(Figure 1)** revealed the importance of V45Gy as a ≥G3 dermatitis predictor, for both photon and proton cohorts. **Figure 2** shows the NTCP curves from LKB modelling for both cohorts. For the photon cohort, m = 0.42 (95% CI: 0.31 - 0.54), n = 0.35 (95% CI: 0 - 0.96), and TD_{50} = 50.0 (95% CI: 26.5 - 73.5) Gy. For the proton cohort, m = 0.15 (95% CI: 0.12 - 0.18), n = 0.23 (95% CI: 0.08 - 0.38), and TD_{50} = 38.8 (95% CI: 28.0 - 49.7) Gy.

The ROC curves and calibration plots are shown in **Figure 3**. LOOCV within the photon cohort yielded AUCs of 0.48 (95% CI: 0.30 – 0.66) and 0.69 (95% CI: 0.50 – 0.85), while LOOCV within the proton cohort yielded AUCs of 0.84 (95% CI: 0.77 – 0.90) and 0.85 (95% CI: 0.79 – 0.90), for LKB and LR, respectively. As for the predictions done on proton data using photon-trained model, the LKB model achieved a high AUC of 0.86 (95% CI: 0.80 – 0.91), outperforming the LR model with an AUC of 0.20 (95% CI: 0.13 – 0.28).

Table 1. Baseline characteristics of patients and univariable analysis results for ≥G3 dermatitis. *P < 0.1. †P < 0.05.

	G3 or higher dermatitis			
Characteristics	<G3 (n=201)	≥G3 (n=15)	OR [95% CI]	*P* value
Age	53.1 (13.1)	51.2 (10.9)	0.99 [0.95–1.03]	0.586
Weight	68.3 (13.8)	63.6 (12.6)	0.97 [0.93–1.01]	0.207
Gender				
Female	37 (18.4%)	7 (46.7%)	Ref.	Ref.
Male	164 (81.6%)	8 (53.3%)	0.26 [0.09–0.80]	0.020†
T stage				
1	90 (44.8%)	4 (26.7%)	Ref.	Ref.
2	33 (16.4%)	5 (33.3%)	3.35 [0.81–14.9]	0.094*
3	52 (25.9%)	5 (33.3%)	2.14 [0.52–9.37]	0.285
4	26 (12.9%)	1 (6.67%)	0.95 [0.03–7.24]	0.966
N stage				
1	41 (20.4%)	1 (6.67%)	Ref.	Ref.
2	77 (38.3%)	6 (40.0%)	2.85 [0.45–75.7]	0.303
3	58 (28.9%)	6 (40.0%)	3.78 [0.59–100]	0.180
4	25 (12.4%)	2 (13.3%)	3.04 [0.23–98.9]	0.393
Chemotherapy				
RT alone (RT)	69 (34.3%)	2 (13.3%)	Ref.	Ref.
Induction chemotherapy (IC)	100 (49.8%)	7 (46.7%)	2.29 [0.52–17.3]	0.294
Concurrent chemoRT (CCRT)	32 (15.9%)	6 (40.0%)	6.07 [1.27–47.9]	0.023†
RT Techniques				
SIB	96 (47.8%)	13 (86.7%)	Ref.	Ref.
Sequential	105 (52.2%)	2 (13.3%)	0.15 [0.02–0.57]	0.003†
RT modality				
Photon	98 (48.8%)	8 (53.3%)	Ref.	Ref.
Proton	103 (51.2%)	7 (46.7%)	0.84 [0.28–2.45]	0.741
Prescription dose (GyE)	71.7 (2.31)	70.7 (1.91)	0.81 [0.63–1.03]	0.085*

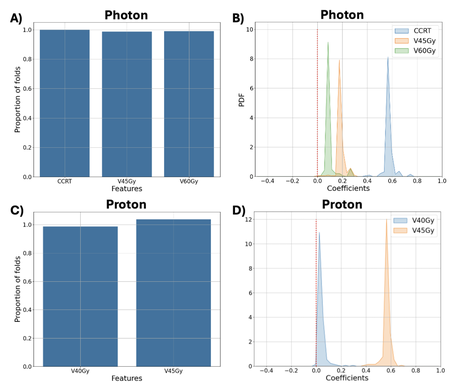

Figure 1. Feature selection frequency and regression coefficient distributions from logistic regression models for ≥G3 acute dermatitis in photon (A, B) and proton (C, D) therapy, aggregated across nested cross-validation. Bars indicate the proportion of LOOCV iterations in which each feature was selected, while shaded curves show the distribution of corresponding regression coefficients; the dashed red line denotes zero.

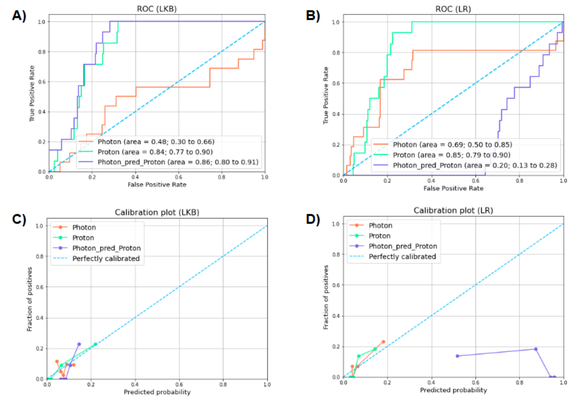

Figure 3. (A,B) Receiver Operating Characteristic curves with the area under the curve shown, and (C,D) calibration plots, for LOOCV results within photon and proton cohorts as well as photon-trained predictions on proton using LKB and LR models.

DISCUSSION

From the LKB models, the values of TD_{50} for photon and proton cohorts were found to be 50.0 Gy and 38.8 Gy, respectively. This shows that a lower dose is required by proton compared to photon to cause a 50% toxicity risk, suggesting a higher biological effect induced by proton.

Comparing the AUCs from both models, LKB demonstrated a higher generalizability of photon-trained model on proton cohort, but LR's performance was more stable within each individual cohort. This could be explained by the presence of a significant clinical predictor, CCRT, in the photon cohort, but not in the proton cohort **(Figure 1)**. Therefore, the LKB model, which was solely dosimetric-based, could not predict the toxicity risk for the photon cohort as well as it did for the proton cohort. On the other hand, the LR model, incorporating feature selection, was able to provide modality-specific modelling, hence resulting in non-generalizable models.

CONCLUSIONS

Two NTCP models have been developed for ≥G3 dermatitis in photon- and proton-treated NPC patients. The findings from both the LR and LKB models indicate that developing modality-specific models may provide better predictive performance. Following external validation, these models could potentially be integrated into treatment planning systems to support toxicity prediction during the treatment planning process.

REFERENCES

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2. Fang, K. *et al.* Acute radiation dermatitis among patients with nasopharyngeal carcinoma treated with proton beam therapy: Prognostic factors and treatment outcomes. *Int. Wound J.* **20**, 499–507 (2022).