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Original Article

Evaluation of machine learning models for predicting xerostomia in adults with head and neck cancer during proton and heavy ion radiotherapy

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ABSTRACT

Background and purpose: Few studies have examined the factors associated with xerostomia during proton and carbon ion radiotherapy for head and neck cancer (HNC), which are reported to have fewer toxic effects compared to traditional photon-based radiotherapy. This study aims to evaluate the performance of machine learning approaches in predicting grade 2 + xerostomia in adults with HNC receiving proton and carbon ion radiotherapy.

Materials and methods: A retrospective study involving 1,769 adults with HNC who completed proton or carbon ion radiotherapy was conducted. Xerostomia was graded using the Radiation Therapy Oncology Group criteria. Eight machine learning models with different combinations sampling methods and class weights were compared to identify the model with the highest balanced accuracy.

Results: The mean age of patients was 47.8 years (range 18–80), with 33.5 % female. The average total radiation dose was 71.0 GyE (SD = 5.7). Grade 1 xerostomia was recorded in 572 patients (32.3 %) and grade 2 in 103 patients (5.8 %). No cases of grade 3 or higher xerostomia were reported. A support vector machine with a linear kernel, a 1:2 positive-to-negative class weight, and SMOTE oversampling achieved the highest balanced accuracy (0.66) and AUC-ROC (0.69) for predicting grade 2 xerostomia, outperforming the logistic regression model (balanced accuracy:0.50, AUC-ROC.
0.67).

Conclusion: The prevalence of grade 2 radiation-induced xerostomia during proton and carbon ion radiotherapy was low in adults with HNC, posing challenges for accurate prediction. Further research is needed to develop improved methods for predicting xerostomia during proton and carbon ion radiotherapy.

Introduction

Head and neck cancer (HNC) is the seventh most common cancer worldwide, encompassing a diverse group of malignancies originating in the head and neck region [1,2]. This includes cancers of the oral cavity, hypopharynx, nasopharynx, oropharynx, lip, nasal cavity, paranasal sinuses, and salivary glands [1,3]. Due to the anatomical complexity and the tumors' proximity to normal tissues, radiotherapy is a commonly used treatment for HNC. However, radiotherapy inevitably damages normal cells in the surrounding tissues while targeting tumor cells, leading to a range of radiation-induced toxicities. Xerostomia, or dry mouth, is one of the most frequently reported side effects of radiotherapy for HNC and affects about 80 % of patients with HNC receiving radiotherapy [4–8]. It results from damage to the glandular tissues, reducing salivary production and causing persistent xerostomia [4,8,9]. Xerostomia often accompanies other issues such as altered taste, difficulties with mastication, swallowing, and speech, all of which can significantly reduce quality of life [4,10].

Particle therapy, an advanced form of radiation therapy using particle beams, offers superior dose distribution compared to photon-based radiotherapy [11,12]. Due to the Bragg peak effect, particle beams concentrate most of their energy within the tumor, minimizing exposure

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to surrounding tissues [13,14]. As a result, particle therapy is associated with lower radiation-induced toxicities compared to conventional photon-based radiotherapy [15–17]. For instance, the incidence of acute toxicity for grade 2 or higher xerostomia was only 7.6 % during proton therapy for patients with major salivary gland cancers [18].

Given the prevalence and negative consequences of xerostomia, it is crucial to identify predictors and design targeted interventions to prevent and minimize its risk. While most studies have focused on the toxicities associated with conventional photon-based radiotherapy [19–22], few have investigated xerostomia in patients with HNC undergoing particle therapy [18,23,24]. Additionally, traditional statistical methods have been primarily used to examine factors associated with xerostomia. It remains unclear whether advanced machine learning approaches can enhance predictive performance for xerostomia compared to these conventional methods. Therefore, this study aims to examine the prevalence of acute xerostomia during radiotherapy and evaluate the performance of machine learning approaches in predicting acute xerostomia in adults with HNC treated with proton and carbon ion radiotherapy.

Methods

This retrospective study included 1,769 consecutive patients with HNC who underwent radiotherapy at the Shanghai Proton and Heavy Ion Center between May 2015 and January 2023. The study was approved by the institutional review board of the Shanghai Proton and Heavy Ion Center (ethical code: 220601-EXP01). Inclusion criteria were: 1) adults aged 18–80 years, 2) pathologically confirmed primary HNC, 3) no pre-existing xerostomia before particle therapy, and 4) completion of particle treatment. Patients were excluded if they had a current second cancer or received radiotherapy for palliative purposes.

Treatment and acute xerostomia

Patients primarily received intensity-modulated proton or carbon-ion therapy delivered via pencil beam scanning. To account for differences in relative biological effectiveness (RBE) between particle and photon radiotherapy, doses were prescribed in gray equivalents (GyE) [17,25]. The planning and treatment techniques have been documented in previous studies [17,26–28]. Acute xerostomia during radiotherapy was graded according to the Radiation Therapy Oncology Group (RTOG) criteria (https://www.rtog.org). The grade was recorded at baseline and assessed weekly throughout the course of radiotherapy. During radiotherapy, patients were routinely evaluated twice per week (every Monday and Thursday) by the radiation clinical team and trained nurses through physical examination. Information on the grade of acute xerostomia was retrospectively extracted from medical records, along with the corresponding dose to the planning target volume (PTV) and radiotherapy fractions at the time of occurrence. PTV includes the gross tumor volume and margins accounting for setup errors and range uncertainty [17,26–28]. Acute xerostomia is defined as any instance of grade 1 or higher xerostomia occurring at any point during radiotherapy, while grade 2 + acute xerostomia refers to instances of grade 2 or higher xerostomia during the radiotherapy period.

Predictors

The demographic and clinical characteristics of patients were collected from medical records. A total of 35 variables were extracted, including demographic factors, nutrition status at admission, disease and treatment history, tumor-related factors, treatment-related factors, laboratory test results, and procedures during radiotherapy (e.g., use of preventive medications for oral care, bite block cover, and tube feeding). A detailed list of all 35 variables is provided in Appendix A.

Feature selection was conducted using Recursive Feature Elimination across multiple models, including Logistic Regression, Lasso Regression, Decision Tree, Random Forest, XGBoost, Linear Discriminant Analysis (LDA), Support Vector Machine (SVM). A consensus score was calculated through consensus voting, and the top 15 features with the lowest total ranks were selected as the most important. This approach ensures robust selection by leveraging insights from diverse models. These 15 selected features were then used as predictors in the final prediction model, including gender, education level, religion, smoking history, drinking history, pre-radiotherapy white blood cell count, pre-radiotherapy lymphocyte count, pre-radiotherapy neutrophil count, BMI, T stage, radiation modality, concurrent chemotherapy (cisplatin), number of concurrent chemotherapy sessions, use of skin preventive medication, and use of compound gargle solution.

Analysis procedures

Descriptive analyses were performed to describe the characteristics of included patients and the incidence of grade 2 or higher acute xerostomia, using mean and standard deviation for numerical variables and count and percentage for categorical variables. The impact of different radiotherapy modalities on the incidence of grade 2 or higher acute xerostomia was assessed using logistic regression, adjusting for the other 14 selected predictor covariates. Missing data were imputed with the mean for continuous variables and the mode for categorical variables. Except for annual income (13.5 %) and M stage (7.0 %), the proportion of imputed data for each variable was less than 5 %, including education (2.7 %), religion (2.5 %), and six laboratory test results (0.7 %). After imputation, data were normalized with a StandardScaler to ensure a mean of 0 and a standard deviation of 1, enhancing model performance and convergence.

To identify the best prediction model, eight machine learning algorithms were employed: Logistic Regression, Lasso Regression, Decision Tree, Random Forest, XGBoost, LDA, SVM with Linear Kernel, and SVM with RBF Kernel. Due to the low positive rate for grade 2 xerostomia, the dataset was extremely imbalanced (positive vs negative, 1:16). To optimize model performance on the imbalanced dataset, each model was trained and tested using both the original and resampled training data with different negative/positive class weights. Four sampling methods were employed:(1) no sampling, where the original training data was used without modification; (2) Synthetic Minority Oversampling Technique (SMOTE), which generates synthetic samples for the minority class to balance the dataset [29,30]; (3) Adaptive Synthetic Sampling (ADASYN) [31,32], which creates synthetic samples for the minority class with a focus on harder-to-classify instances; and (4) random under-sampling, which reduces the number of samples in the majority class to match the size of the minority class. Different class weights for negative/positive class (1, 2, 4, 8, 10, 12, 14, 16, 20) were assigned to the models to optimize class balance. A series of model comparisons were conducted using various combinations of machine learning algorithms (N = 8), sampling methods (N = 4), and class weights (N = 9) to identify the best-performing model.

The low prevalence of Grade 2 xerostomia resulted in a highly imbalanced dataset, potentially impacting model performance. To assess this, a post-hoc sensitivity analysis was performed. To increase the prevalence of the target variable, we broadened it from Grade 2 + xerostomia to any xerostomia (Grade 1 +). The analysis procedures were then repeated to predict Grade 1 + xerostomia, ensuring consistency in methodology.

The dataset was randomly split into training and test sets with a ratio of 0.8:0.2. These models were trained on the training set and evaluated on the test set. The predictive performance was evaluated using balanced accuracy for imbalanced dataset (traditional accuracy for balanced dataset), area under the receiver operating characteristic curve (AUC-ROC), precision, recall, and F1 scores for both positive and negative classes [33,34]. Balanced accuracy is the average of recall for both the positive and negative classes. Unlike traditional accuracy, which only accounts for correctly classified cases, balanced accuracy

assesses performance across all classes [33,35]. It is particularly suitable for imbalanced datasets, such as the one used in this study. The best model was determined primarily based on balanced accuracy, with a focus on its performance in predicting the positive class. All analyses were conducted using Python (version 3.9.6).

Results

A total of 1,769 patients were included in this study, with a mean age of 47.8 years (SD = 12.9), and 33.5 % of the patients were female. About 60 % of the tumors were located in the nasopharynx (1,050 patients, 59.4 %), followed by the nasal sinuses (n = 271, 15.3 %). The radiotherapy modalities received were carbon ion (n = 683, 38.6 %), proton (103 patients, 5.8 %), combined carbon ion with proton (n = 463, 26.2 %), and combined carbon ion with proton and photon (n = 520, 29.4 %). The mean radiotherapy dose was 71.0 GyE (SD = 5.7). Detailed characteristics of the included patients are shown in Table 1.

Acute xerostomia occurred in 675 patients (38.1 %), with grade 1 xerostomia in 572 patients (32.3 %) and grade 2 in 103 patients (5.8 %). Grade 1 xerostomia occurred at an accumulated dose of 22.4 GyE to the PTV (SD = 14.7) over an average of 10.6 fractions (SD = 6.3). In contrast, grade 2 xerostomia occurred at an accumulated dose of 35.1 GyE to the PTV (SD = 14.2) over an average of 16.3 fractions (SD = 6.7).

Among the 103 patients with grade 2 acute xerostomia, 14 patients (2.0 %) were treated with carbon ion therapy, 2 patients (1.0 %) with proton therapy, 35 patients (7.6 %) with combined carbon ion with proton therapy, and 52 patients (10.0 %) with combined carbon ion with proton and photon therapy. Compared to carbon ion therapy alone, receiving combined carbon ion with proton therapy (aOR = 3.3, 95 % CI: 1.6–6.7) or combined carbon ion with proton and photon therapy (aOR = 4.3, 95 % CI: 2.1–8.7) significantly increased the odds of developing grade 2 acute xerostomia (Table 2).

Although logistic regression with original imbalanced dataset achieved a good performance in predicting negative classes of grade 2 acute xerostomia (patients without grade 2 xerostomia) with precision, recall, and F1 values of 0.94, 1.00, and 0.97, its performance in predicting the positive class (patients with grade 2 xerostomia) was poor, with precision, recall, and F1 values of 1, 0, 0. Therefore, the balanced accuracy for the logistic model was only 0.5, with a AUC-ROC value of 0.67.

To improve the model's performance in predicting positive classes of grade 2 acute xerostomia, additional models were used (detailed results can be found in Appendix B). Among them, an SVM with a linear kernel and a positive-to-negative class weight of 1:2 achieved the highest balanced accuracy (0.66) and an AUR-ROC value of 0.69 for predicting grade 2 acute xerostomia using the balanced dataset created with SMOTE oversampling approach. This model yielded relatively high precision, recall, and F1 scores for the positive class of 0.11, 0.74, and 0.19, respectively. It also maintained a good performance in predicting the negative class, with precision, recall, and F1 values of 0.95, 0.83, and 0.89. Since our goal was to prioritize correctly identifying the positive class over the negative class, the SVM model with a linear kernel, a positive-to-negative class weight of 1:2, and the SMOTE sampling approach was selected as the final model to predict grade 2 acute xerostomia. Table 3 shows the selected models with highest values for each evaluation metric.

Based on the best SVM model with linear Kernel, the importance of factors in predicting grade 2 acute xerostomia was ranked from highest to lowest, as shown in Fig. 1. The most important two factors were pre-radiotherapy neutrophil count and pre-radiotherapy white blood cell count, with smoking history, gender, and radiation modality following in importance.

The sensitivity analysis revealed improved model performance for predicting grade 1 + acute xerostomia compared to grade 2 + acute xerostomia. Among the models evaluated, the logistic regression model achieved the best performance in predicting grade 1 + acute xerostomia on the original dataset using a class weight of 1:1, with an accuracy of 0.73 and an AUC-ROC of 0.76 (Table 4).

Table 1
Characteristics of patients (N = 1769).

Characteristics		N (%)/Mean (SD)
Age		47.8 (12.9)
Sex	Male	1176 (66.5)
	Female	593 (33.5)
Marital status	Married	1607 (90.8)
	Single/divorced/window	162 (9.2)
Family annual income	<150 thousand	840 (47.5)
	150—300 thousand	337 (19.2)
	>30 thousand	361 (20.4)
	No answers	231 (13.1)
Tumor location	Nasopharynx	1050 (59.4)
	Nasal sinuses	271 (15.3)
	Oral cavity	138 (7.8)
	Oral pharynx (tonsils)	68 (3.8)
	Hypopharynx and larynx	60 (3.4)
	Parotid gland	108 (6.1)
	Other	74 (4.2)
Recurrence	No	1318 (74.5)
	Yes	451 (25.5)
Radiotherapy type	Carbon ion	683 (38.6)
	Proton	103 (5.8)
	Proton + carbon ion	463 (26.2)
	Carbon ion + photon + proton	520 (29.4)
Total radiotherapy dose		71.0 (5.7)
Targeted immunotherapy	No	1676 (94.7)
	Yes	93 (5.3)
Concurrent chemotherapy	No	1035 (58.5)
	Yes	734 (41.5)

Table 2
Impact of radiation modality on the prevalence of grade 2 + xerostomia.

Radiation modality	Total N	Total dose	Grade 2 + xerostomia N (%)	aOR (95 % CI) *	p-value
Carbon ion	683	64.1 ± 4.5	14 (2.0)	ref	
Proton	103	63.2 ± 4.5	2 (1.9)	0.9 (0.2–4.3)	0.947
Carbon ion + Proton	463	73.0 ± 2.1	35 (7.6)	3.3 (1.6–6.7)	<0.001
Carbon ion + Proton + Photon	520	73.4 ± 2.5	52 (10.0)	4.3 (2.1–8.7)	<0.001

* aORs, Adjusted odds ratios. aOR were estimated from logistic regression, controlling for covariates of gender, education level, religion, smoking history, drinking history, pre-radiotherapy white blood cell count, pre-radiotherapy lymphocyte count, pre-radiotherapy neutrophil count, BMI, T stage, radiation modality, concurrent chemotherapy (cisplatin), number of concurrent chemotherapy sessions, use of skin preventive medication, and use of compound gargle solution.

Discussion

Accurate prediction of the occurrence of grade 2 acute xerostomia could provide valuable information on the preventive management of xerostomia during routine patient care. Evidence on the associated factors of xerostomia during particle therapy is limited. This study examined the factors associated with acute xerostomia in a large sample of adults with HNC receiving proton and carbon ion therapy. Fifteen factors related to patients' demographic, tumor and treatment characteristics, and other clinical factors during radiotherapy were examined. Given the low prevalence of grade 2 xerostomia, eight machine learning models with different class weights and sampling methods were compared to achieve the best predictive performance in predicting grade 2 or higher acute xerostomia.

The rate of xerostomia in this study was relatively low. Although

Table 3
Selected models for predicting grade 2 xerostomia with highest values for each evaluation metric.

Model	Class Weight	Sampling Method	Balanced Accuracy	AUC-ROC	With grade 2 xerostomia			Without grade 2 xerostomia		
					Precision	Recall	F1 Score	Precision	Recall	F1 Score
SVM (Linear)	{0: 1, 1: 2}	SMOTE	**0.66**	**0.69**	0.11	0.74	0.19	0.97	0.57	0.72
Lasso Regression	{0: 1, 1: 14}	Random Under-sampling	0.55	0.48	0.07	**1.00**	0.13	**1.00**	0.11	0.19
Logistic Regression	{0: 1, 1: 8}	Random Under-sampling	0.54	0.61	0.07	**1.00**	0.13	**1.00**	0.08	0.15
SVM (Linear)	{0: 1, 1: 8}	No Sampling	0.63	0.65	**0.15**	0.43	0.22	0.95	0.83	**0.89**

Note: SVM, Support Vector Machine; SMOTE, Synthetic Minority Over-sampling Technique; AUC-ROC, Area Under the Receiver Operating Characteristic Curve.

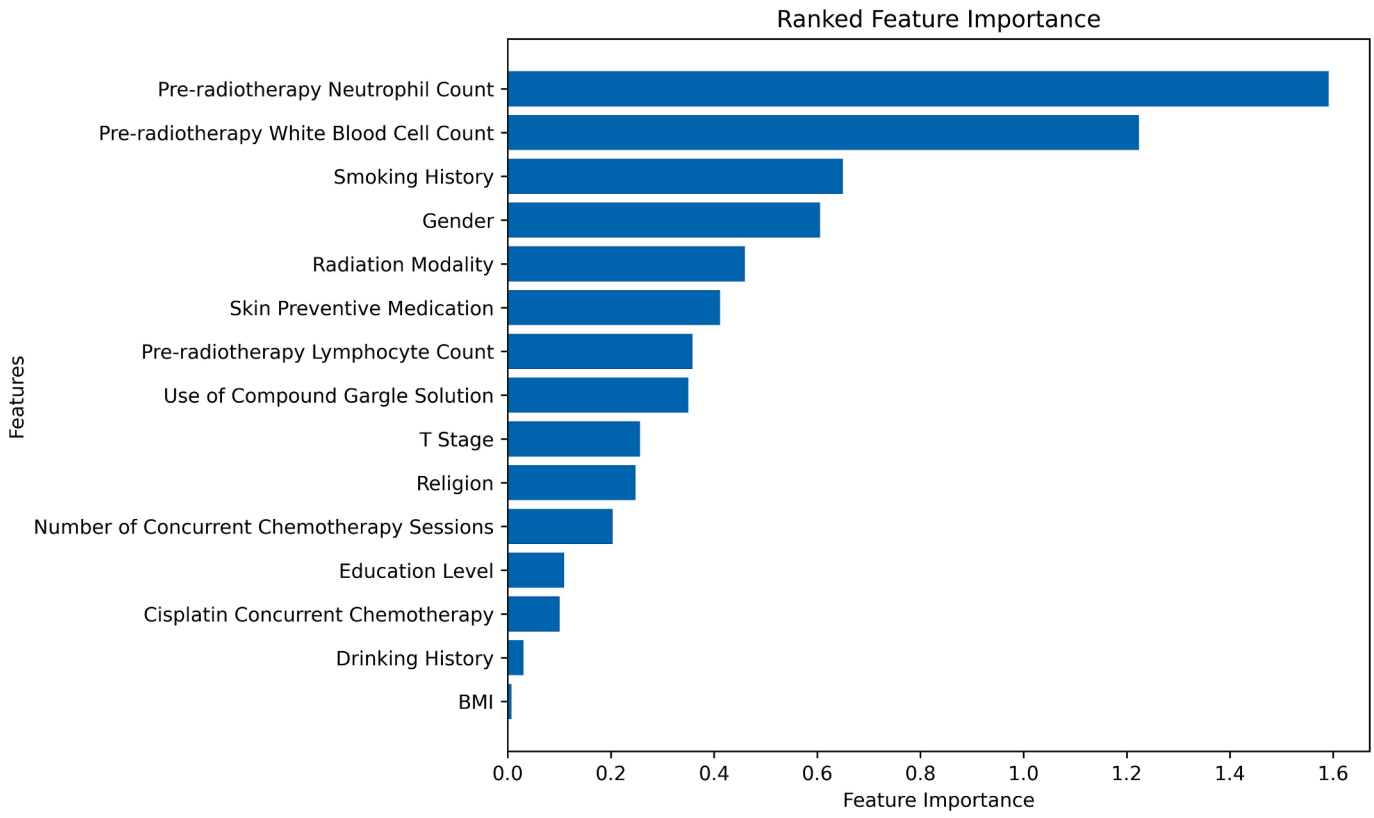

Fig. 1. Feature importance in predicting Grade 2 acute xerostomia.

Table 4
Selected models for predicting grade 1 + xerostomia with highest values for each evaluation metric.

Model	Class Weight	Sampling Method	Accuracy	AUC-ROC	With grade 1 + xerostomia			Without grade 1 + xerostomia		
					Precision	Recall	F1 Score	Precision	Recall	F1 Score
Logistic Regression	{0: 1, 1: 1}	No Sampling	**0.73**	**0.76**	**0.66**	0.57	0.61	0.76	0.82	**0.79**
Logistic Regression	{0: 1, 1: 2}	No Sampling	0.70	**0.76**	0.57	0.79	**0.66**	0.84	0.65	0.73
Logistic Regression	{0: 1, 1: 1}	SMOTE	0.69	**0.76**	0.58	0.69	0.63	0.79	0.70	0.74
Logistic Regression	{0: 1, 1: 12}	No Sampling	0.41	**0.76**	0.39	**1.00**	0.56	**1.00**	0.06	0.11
SVM (RBF)	{0: 1, 1: 1}	SMOTE	**0.73**	**0.76**	0.63	0.65	0.64	0.79	0.77	0.78
Logistic Regression	{0: 1, 1: 8}	ADASYN	0.40	**0.76**	0.38	**1.00**	0.55	**1.00**	0.05	0.09
Random Forest	{0: 1, 1: 12}	No Sampling	0.68	0.74	0.61	0.43	0.50	0.71	**0.83**	0.77

Note: SVM (RBF), Support Vector Machine with a kernel of Radial Basis Function; AUC-ROC, Area Under the Receiver Operating Characteristic Curve.

38.1 % of patients developed xerostomia, only 5.8 % experienced grade 2 xerostomia. This rate is significantly lower compared to about 50 %–80 % rates reported for patients undergoing photon-based radiotherapy [5,8,22,36–39]. This rate is also slightly lower than the 16 % pooled rate reported in a *meta*-analysis of 12 studies that included patients receiving particle therapy and mixed particle-photon therapy [40]. The lower incidence of xerostomia with particle therapy further supports the benefits of particle therapy over conventional photon-based radiotherapy.

The SVM model with a linear kernel, a positive-to-negative class weight of 1:2, and the SMOTE oversampling approach achieved the highest balanced accuracy in predicting grade 2 xerostomia. The dataset had only 5.8 % of patients with grade 2 xerostomia, creating a highly imbalanced class ratio that made accurate prediction challenging. While logistic regression performed well in predicting grade 1 + xerostomia (38.1 % prevalence), it failed to identify any actual positive cases of grade 2 + xerostomia, highlighting the need for more advanced approaches to address the imbalanced dataset in grade 2 xerostomia prediction. Therefore, additional machine learning models combined with multiple resampling approaches and positive-to-negative class weights

were added. One key strategy was SMOTE, an oversampling method that generates synthetic samples for the minority class by interpolating between existing samples and their nearest neighbors [29,30]. This balanced the class distribution and enhanced model performance. Additionally, setting the positive-to-negative class weight to 1:2 increased the penalty for misclassifying the minority class (grade 2 xerostomia), incentivizing the SVM to prioritize correct predictions for this class. The combination of SMOTE and class weight adjustment significantly improved the model's predictive performance for grade 2 xerostomia. Compared to logistic regression, this combined approach increased the AUC-ROC from 0.67 to 0.69 and the balanced accuracy from 0.50 to 0.66.

Xerostomia is a complex condition with various contributing factors during radiotherapy. Among these, pre-radiotherapy blood tests, particularly neutrophil count and white blood cell count, were key predictors in the linear SVM model for grade 2 xerostomia. Additionally, radiation modality emerged as an important predictor of grade 2 xerostomia. While most patients in our study underwent carbon ion and proton radiotherapy, their associated radiation doses varied significantly. Notably, patients who received a combination of carbon ion and proton therapy, with or without photon therapy, were exposed to average doses that were 10 GyE higher than those treated with carbon ion or proton therapy alone. This indicates that the difference in radiation modality is closely tied to differences in radiation dose, which plays a key role in the development of xerostomia.

The predictive performance in our study was lower than that reported in other studies on adults with HNC treated with conventional photon therapy using normal tissue complication probability (NTCP), machine learning, or deep learning models. Two potential reasons may explain this difference. First, the low incidence of grade 2 xerostomia significantly impacted predictive performance. Model performance often declines when using imbalanced datasets with a low prevalence of positive cases because the underrepresentation of positive cases makes it challenging for the model to learn patterns effectively [41–43]. For example, studies with incidence rates of 52 %, 40 %, 34 %, 28 %, and 26 % reported AUC-ROC values of 0.82 [44], 0.79 [45], 0.70 [46], 0.68 [45], and 0.66 [47], respectively. Notably, our sensitivity analysis supports this observation: when the target was changed from grade 2 xerostomia (5.8 % prevalence) to grade 1 + xerostomia (38.1 % prevalence), the model's performance improved, with the AUC-ROC increasing from 0.69 to 0.76. Second, we did not have data on the radiation dose to salivary glands, a key predictor in NTCP models for xerostomia [44,48,49]. Despite the absence of salivary gland dose variables in our models, we achieved results comparable to a study that incorporated this data. That study, which had a 34 % incidence of grade 2 + xerostomia, evaluated three machine learning models using radiomorphologic dose patterns and clinical factors [46]. Their models achieved an average AUC-ROC of 0.70 [46], which is comparable to the AUC-ROC of 0.69 in our study without incorporating salivary gland dose data.

Strengths and limitations

The strengths of this study include its large sample size. Few studies have examined the factors associated with xerostomia among adults with HNC receiving particle therapy, especially with such a large sample. Additionally, this study improved predictive performance for the low prevalence of grade 2 xerostomia by comparing eight different models with various class weights and resampling approaches. The selected best-performing model outperformed the commonly used logistic regression model. However, the study also has limitations. First, as a retrospective study, our ability to select risk factors was constrained. For example, salivary gland dose—a key factor associated with xerostomia—was unavailable in our dataset, potentially affecting the predictive performance of our model. In the future, we plan to prospectively collect this variable to benchmark predictive performance against NTCP models for xerostomia. Secondly, no cases of grade 3 or higher xerostomia were observed, so this predictive model is only applicable to grade 2 xerostomia. Generalizing the model to grade 2 or higher xerostomia should be done with caution. Thirdly, although the sample primarily focused on patients receiving proton and carbon ion radiotherapy, 30 % of the patients underwent combined particle and photon-based radiotherapy. As suggested in Table 2, the actual rates of xerostomia would be even lower if only patients receiving particle therapy were included. Lastly, selection bias may be present, as the patients included in our study may not fully represent the broader population of head and neck cancer patients.

Conclusions

The prevalence of grade 2 xerostomia was low among adults with HNC receiving particle therapy. Xerostomia is a multifactorial side effect of radiotherapy, with various factors contributing to its development beyond just the type and dose of radiotherapy. In this study, T stage and concurrent chemotherapy were identified as the two most significant predictors of grade 2 xerostomia. Although our study improved predictive performance compared to commonly used logistic regression models, further exploration of advanced approaches is warranted to enhance predictive accuracy for xerostomia during proton and carbon ion radiotherapy.

CRediT authorship contribution statement

Lijuan Zhang: Writing – review & editing, Validation, Investigation, Data curation. **Zhihong Zhang:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis. **Yiqiao Wang:** Writing – review & editing, Investigation, Data curation. **Yu Zhu:** Writing – review & editing, Supervision, Project administration, Conceptualization. **Ziying Wang:** Writing – review & editing, Supervision. **Hongwei Wan:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

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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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2025.110712.

References

[1] Barsouk A, Aluru JS, Rawla P, Saginala K, Barsouk A. Epidemiology, risk factors, and prevention of head and neck squamous cell carcinoma. *Med Sci (Basel)* 2023;11.

[2] Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2024;74:229–63.

[3] Gormley M, Creaney G, Schache A, Ingarfield K, Conway DI. Reviewing the epidemiology of head and neck cancer: definitions, trends and risk factors. *Br Dent J* 2022;233:780–6.

[4] Pinna R, Campus G, Cumbo E, Mura I, Milia E: Xerostomia induced by radiotherapy: an overview of the physiopathology, clinical evidence, and management of the oral damage. *Therapeutics and Clinical Risk Management* 2015, 11(null):171-188.

[5] Wang X, Eisbruch A. IMRT for head and neck cancer: reducing xerostomia and dysphagia. *J Radiat Res* 2016;57:i69–75.
[6] Kałużny J, Wierzbicka M, Nogala H, Milecki P, Kopeć T. Radiotherapy induced xerostomia: Mechanisms, diagnostics, prevention and treatment – Evidence based up to 2013. *Otolaryngol Pol* 2014;68:1–14.
[7] Marzi S, Farneti A, Marucci L, D'Urso P, Vidiri A, Gangemi E, et al. The role of patient- and treatment-related factors and early functional imaging in late radiation-induced xerostomia in oropharyngeal cancer patients. *Cancers* 2021;13:6296.
[8] Nathan C-A-O, Asarkar AA, Entezami P, Corry J, Strojan P, Poorten VV, et al. Current management of xerostomia in head and neck cancer patients. *Am J Otolaryngol* 2023;44:103867.
[9] Lin A, Helgeson ES, Treister NS, Schmidt BL, Patton LL, Elting LS, et al. The impact of head and neck radiotherapy on salivary flow and quality of life: results of the ORARAD study. *Oral Oncol* 2022;127:105783.
[10] Ribeiro LN, de Vasconcelos CM, de Oliveira Limirio JPJ. do Egito Vasconcelos BC, Moraes SLD, Pellizzer EP: Impact of low-level laser therapy on the quality of life of patients with xerostomia undergoing head and neck radiotherapy: a systematic review. *Support Care Cancer* 2024;32:118.
[11] Jensen AD. Particle therapy: Protons and heavy ions. *Anterior Skull Base Tumors* 2020;84:87–105.
[12] Durante M, Orecchia R, Loeffler JS. Charged-particle therapy in cancer: clinical uses and future perspectives. *Nat Rev Clin Oncol* 2017;14:483–95.
[13] Jäkel O. Physical advantages of particles: protons and light ions. *Br J Radiol* 2019;93.
[14] Byun HK, Han MC, Yang K, Kim JS, Yoo GS, Koom WS, et al. Physical and biological characteristics of particle therapy for oncologists. *Cancer Res Treat* 2021;53:611–20.
[15] Qiu X, Gao J, Hu J, Yang J, Hu W, Huang Q, et al. Particle beam radiotherapy in the treatment of WHO grade 2 and 3 meningiomas: an early experience from Shanghai Proton and Heavy Ion Center. *J Neurooncol* 2023;165:241–50.
[16] Kong L, Wu J, Gao J, Qiu X, Yang J, Hu J, et al. Particle radiation therapy in the management of malignant glioma: early experience at the Shanghai Proton and Heavy Ion Center. *Cancer* 2020;126:2802–10.
[17] Hu W, Hu J, Huang Q, Gao J, Yang J, Qiu X, et al. Particle beam radiation therapy for sinonasal malignancies: single institutional experience at the Shanghai Proton and Heavy Ion Center. *Cancer Med* 2020;9:7914–24.
[18] Chuong M, Bryant J, Hartsell W, Larson G, Badiyan S, Laramore GE, et al. Minimal acute toxicity from proton beam therapy for major salivary gland cancer. *Acta Oncol* 2020;59:196–200.
[19] Singla V, Nautiyal V, Gupta M, Kumar V, Mehra S, Ahmad M. Study of dosimetry and clinical factors for assessment of xerostomia in head and neck squamous cell carcinoma treated by intensity-modulated radiotherapy: a prospective study. *J Carcinog* 2021;20:14.
[20] Yang K, Xie W, Zhang X, Wang Y, Shou A, Wang Q, et al. A nomogram for predicting late radiation-induced xerostomia among locoregionally advanced nasopharyngeal carcinoma in intensity modulated radiation therapy era. *Aging (Albany NY)* 2021;13:18645–57.
[21] Onjukka E, Mercke C, Björgvinsson E, Embring A, Berglund A, Alexandersson von Döbeln G, Friesland S, Gagliardi G, Lenneby Helleday C, Sjödin H *et al*: Modeling of Xerostomia After Radiotherapy for Head and Neck Cancer: A Registry Study. *Front Oncol;* 2020, 10.
[22] Warwas B, Cremers F, Gerull K, Leichtle A, Bruchhage KL, Hakim SG, Schild SE, Rades D: Risk Factors for Xerostomia Following Radiotherapy of Head-and-Neck Cancers. *Anticancer Res* 2022, 42(5):2657-2663.
[23] Jakobi A, Stützer K, Bandurska-Luque A, Löck S, Haase R, Wack L-J, et al. NTCP reduction for advanced head and neck cancer patients using proton therapy for complete or sequential boost treatment versus photon therapy. *Acta Oncol* 2015;54:1658–64.
[24] Walser MA, Bachmann N, Kluckert J, Köthe A, Tully C, Leiser D, et al. Clinical outcome after pencil beam scanning proton therapy and dysphagia/xerostomia NTCP calculations of proton and photon radiotherapy delivered to patients with cancer of the major salivary glands. *Br J Radiol* 2023;96.
[25] Tsujii H, Kamada T, Baba M, Tsuji H, Kato H, Kato S, et al. Clinical advantages of carbon-ion radiotherapy. *New J Phys* 2008;10:075009.
[26] Yang J, Gao J, Qiu X, Hu J, Hu W, Wu X, et al. Intensity-modulated proton and carbon-ion radiation therapy in the management of head and neck sarcomas. *Cancer Med* 2019;8:4574–86.
[27] Kong L, Hu J, Guan X, Gao J, Lu R, Lu JJ. Phase I/II trial evaluating carbon ion radiotherapy for salvaging treatment of locally recurrent nasopharyngeal carcinoma. *J Cancer* 2016;7:774–83.
[28] Yang J, Gao J, Wu X, Hu J, Hu W, Kong L, et al. Salvage carbon ion radiation therapy for locally recurrent or radiation-induced second primary sarcoma of the head and neck. *J Cancer* 2018;9:2215–23.
[29] Chawla NV, Bowyer KW, Hall LO, Kegelmeyer WP. SMOTE: synthetic minority over-sampling technique. *J Artif Intell Res* 2002;16:321–57.
[30] Elreedy D, Atiya AF. A comprehensive analysis of synthetic minority oversampling technique (SMOTE) for handling class imbalance. *Inf Sci* 2019;505:32–64.
[31] Gosain A, Sardana S: Handling class imbalance problem using oversampling techniques: A review. In: *2017 international conference on advances in computing, Commun Informat (ICACCI): 2017*: IEEE; 2017: 79-85.
[32] He H, Bai Y, Garcia EA, Li S. ADASYN: Adaptive synthetic sampling approach for imbalanced learning. In: *2008 IEEE international joint conference on neural networks (IEEE world congress on computational intelligence): 2008*: Ieee; 2008: 1322-1328.
[33] Brodersen KH, Ong CS, Stephan KE, Buhmann JM: The balanced accuracy and its posterior distribution. In: *2010 20th international conference on pattern recognition: 2010*: IEEE; 2010: 3121-3124.
[34] Goutte C, Gaussier E: A probabilistic interpretation of precision, recall and F-score, with implication for evaluation. In: *European conference on information retrieval: 2005*: Springer; 2005: 345-359.
[35] Zhu J, Pu S, He J, Su D, Cai W, Xu X, et al. Processing imbalanced medical data at the data level with assisted-reproduction data as an example. *Biodata Min* 2024;17:29.
[36] Lee MG, Freeman AR, Roos DE, Milner AD, Borg MF. Randomized double-blind trial of amifostine versus placebo for radiation-induced xerostomia in patients with head and neck cancer. *J Med Imaging Radiat Oncol* 2019;63:142–50.
[37] Arbab M, Chen Y-H, Tishler RB, Gunasti L, Glass J, Fugazzotto JA, et al. Association between radiation dose to organs at risk and acute patient reported outcome during radiation treatment for head and neck cancers. *Head Neck* 2022;44:1442–52.
[38] Berger T, Noble DJ, Shelley LEA, McMullan T, Bates A, Thomas S, et al. Predicting radiotherapy-induced xerostomia in head and neck cancer patients using day-to-day kinetics of radiomics features. *Phys Imaging Radiat Oncol* 2022;24:95–101.
[39] Schulz RE, Bonzanini LIL, Ortigara GB, Soldera EB, Danesi CC, Antoniazzi RP, et al. Prevalence of hyposalivation and associated factors in survivors of head and neck cancer treated with radiotherapy. *J Appl Oral Sci* 2021;29:e20200854.
[40] Yahya N, Mohamad Salleh SA, Mohd Nasir NF, Abdul Manan H. Toxicity profile of patients treated with proton and carbon-ion therapy for primary nasopharyngeal carcinoma: a systematic review and meta-analysis. *Asia Pac J Clin Oncol* 2024;20:240–50.
[41] Japkowicz N, Stephen S. The class imbalance problem: a systematic study. *Intell Data Anal* 2002;6:429–49.
[42] He H, Garcia EA. Learning from imbalanced data. *IEEE Trans Knowl Data Eng* 2009;21:1263–84.
[43] Krawczyk B. Learning from imbalanced data: open challenges and future directions. *Prog Artif Intell* 2016;5:221–32.
[44] Beetz I, Schilstra C, Burlage FR, Koken PW, Doornaert P, Bijl HP, et al. Development of NTCP models for head and neck cancer patients treated with three-dimensional conformal radiotherapy for xerostomia and sticky saliva: the role of dosimetric and clinical factors. *Radiother Oncol* 2012;105:86–93.
[45] Sheikh K, Lee SH, Cheng Z, Lakshminarayanan P, Peng L, Han P, et al. Predicting acute radiation induced xerostomia in head and neck Cancer using MR and CT Radiomics of parotid and submandibular glands. *Radiat Oncol* 2019;14:131.
[46] Jiang W, Lakshminarayanan P, Hui X, Han P, Cheng Z, Bowers M, et al. Machine learning methods uncover radiomorphologic dose patterns in salivary glands that predict xerostomia in patients with head and neck cancer. *Adv Radiat Oncol* 2019;4:401–12.
[47] Chu H, de Vette SPM, Neh H, Sijtsema NM, Steenbakkers RJHM, Moreno A, et al. Three-dimensional deep learning normal tissue complication probability model to predict late xerostomia in patients with head and neck cancer. *Int J Radiat Oncol*Biology*Physics* 2024.
[48] Van den Bosch L, van der Schaaf A, van der Laan HP, Hoebers FJP, Wijers OB, van den Hoek JGM, et al. Comprehensive toxicity risk profiling in radiation therapy for head and neck cancer: a new concept for individually optimised treatment. *Radiother Oncol* 2021;157:147–54.
[49] 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;105:101–6.