Original Article

Development of Prediction Model for Mean Parotid Dose of HNC Undergoing Radiotherapy - A Single Institutional Study

Soumen Bera, Dipika Choudhury, Sanjoy Roy, Partha Mukhopadhyay, Sandip Sarkar
Department of Radiation Oncology, Ruby General Hospital, Kolkata, West Bengal, India

Abstract

Aim: The aim of the study was to develop a simple prediction model based on previous treatment plans for head-and-neck cancer (HNC). **Materials and Methods:** This study was conducted on 95 patients who underwent volumetric-modulated arc therapy (VMAT) with curative intent for HNC at our institute between January 2016 and December 2022 with intact bilateral parotid glands. Two simple prediction models were used: one linear regression model and one exponential model. Both models use fractional overlapping parotid volume with planning target volume (PTV) as a predictor of mean parotid dose. The fractional overlapping volume was calculated as the difference between the volume of the parotid gland minus the volume of the parotid gland outside the PTV plus a 2 mm margin, divided by the volume of the parotid gland. Statistical calculations were done using data analysis tools and Solver in Microsoft Excel (Microsoft Office 2013, Redmond, WA, USA). To enhance the accuracy of the results, outliers were excluded with residuals >2 standard deviations below and above the residuals. R^2 and root-mean-square error were calculated for both models to evaluate the quality of the predictions. The normality of both models' residuals was validated using the Shapiro–Wilk test. **Results:** Both linear and exponential prediction models exhibited strong correlation statistics, with $r^2 = 0.85$ and 0.82, respectively. The authors found a fractional overlap of 16.4% and 18.9% in linear and exponential models that predict parotid mean dose 26 Gy. The implementation was carried out on a cohort of 12 prospective patients, demonstrating a remarkable improvement in minimizing the dose to the parotid glands. **Conclusion:** In this single-institutional study, the authors successfully developed a prediction model for mean parotid dose in HNC patients undergoing radiotherapy. The model showed promising accuracy and has the potential to assist planners in optimizing treatment plans and minimizing radiation-related toxicity. It is possible to avoid under sparing the organs at risks in some cases and wasting time or effort on physically impossible goals in others using this prediction model. As a result, planning resources can be used much more efficiently. Future studies should focus on validating the model's performance using external datasets and exploring its integration into clinical practice.

Keywords: Organs-at-risk dose prediction, parotid gland sparing, prediction model, volumetric-modulated arc therapy

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Introduction

Head-and-neck cancers (HNCs) are the most common cancers in developing countries, especially in Southeast Asia.[1] It is the most common cancer in males in India and the fifth-most common in females.[2] HNC accounts for 30% and over 200,000 cases of all cancers in the country.[3]

Radiotherapy is one of the standard modalities of treatment for patients with HNC. The treatment mechanism has changed rapidly in a few years from three-dimensional conformal radiotherapy to static field intensity-modulated radiotherapy (IMRT) to volumetric-modulated arc therapy (VMAT). Recent advancement like inverse planning facilitates us to improve dose conformity and reduces normal tissue toxicity significantly.

In the treatment of HNC, we have made efforts to use these techniques to spare the major salivary glands like parotid while improving target irradiation. Reduced xerostomia has been reported and attributed to improved dose distributions achievable with VMAT. Per Emami *et al.*,[4] TD5/5 and

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Address for correspondence: Mr. Soumen Bera, Department of Radiation Oncology, Ruby General Hospital, Kasba, Golpark, EM Bypass, Kolkata - 700 107, West Bengal, India.
E-mail: berasoumen725@gmail.com

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TD50/5 (the NTCP at 5% and 50%, respectively, within 5 years after radiotherapy) are 32 Gy and 46 Gy. In contrast, according to Eisbruch *et al*.,[5] the mean parotid gland dose must be at or below 26 Gy. Most of the time, the parotid overlaps with the planning target volume (PTV) in head and neck cases. The overlapping parotid plays a crucial role in determining the mean dose and, hence, the clinical outcome.

Although inverse planning has become more intelligent and automatic, the input of the planners is still the essential driving force for the quality of the plan. At the beginning of optimization, the best achievable dosimetry is unknown, which poses a major challenge to VMAT planning. The planner usually has to guide the optimization manually through a process of trial and error in order to achieve a more optimal plan. Therefore, the quality of the VMAT plan is greatly influenced by the experience of the planner, the amount of time available for the case, and the institutional/individual dose constraints set by physicians. A prediction model based on previously created treatment plans is a feasible solution in such a scenario to produce high-quality, consistent plans efficiently.

In this study, we attempt to develop a simple prediction model analyzing previous treatment plans to predict parotid gland doses of HNC. Numerous prior publications[6-14] have investigated similar research questions by employing regression analysis with either a single predictor or multiple predictors. Most of them used fractional overlapping volume of parotid with PTV as a predictor of mean parotid dose. Gensheimer *et al*.[12] reported that a cut point of 35% overlap best predicted a mean dose of <26 Gy. Whereas Hunt *et al*.[7] found that for static IMRT plans, achieving a Dmean <26.1 Gy for parotid gland sparing is feasible when the parotid-PTV overlap is less than approximately 20%. Therefore, there is observed variability in reporting the overlapping volume, which predicts a mean dose of 26 Gy. The objective of our study is to develop an institution-based prediction model that assists planners in estimating a predicted mean dose for the parotid gland before initiating the optimization process.

We anticipate that the proposed predictive model will serve as a guide to strike a balance between optimal coverage of the PTV and effective sparing of the parotid glands.

Materials and Methods

Selection criterion

This observational study was conducted on all patients who underwent VMAT with curative intent for HNC at our institute between January 2016 and December 2022. Ninety-five patients (190 parotids) were enrolled for a training dataset with intact bilateral parotid glands. There were 74 men and 21 women; age ranged from 25 to 84 years (mean 54.5 years and median 56 years).

Details of patient and primary treatment sites in head and neck are shown in Table 1.

Immobilization and imaging

The patients were simulated in the supine position on a best-fitted head support with a five-clamp thermoplastic immobilization mask around the head and neck. The computed tomography (CT) simulation of all HNC patients was undergone in SOMATOM Perspective 128 slices CT scanner (Siemens Medical Systems, Erlangen, Germany) with a 3-mm slice thickness. Contrast material was administered during scanning. The data were then transferred to contouring stations for target and organs-at-risk (OAR) delineation.

Target and organs-at-risk delineation

The definition of target volume follows the description of the International Commission on Radiation Units Report 50.[15] The neck nodal clinical target volumes (CTVs) were delineated referring to consensus guidelines by Grégoire *et al*.[16] For all patients, cervical neck nodal level I–V was delineated. The parotid glands were contoured separately as OARs as per the guidelines by Brouwer *et al*.[17] A 0.5 cm margin for the HNCs was added to CTV for obtaining the PTV according to our departmental protocol[18] to compensate for treatment setup and internal organ motion error. The other OARs considered were the spinal cord, brainstem, optic chiasma, optic nerve, eye, lens, lips, larynx, and cochlea.

Apart from OARs, some planning organ-at-risk volumes (for spinal cord and brainstem), control structures, and helping contours were also drawn by physicists to achieve dose constraints and local control of doses, for example, parotid – (PTV + 2 mm) which is used to calculate the fraction overlapping volume with PTV.

$$\text{Fractional overlapping volume} = (\text{Parotid Volume} - [\text{Parotid} - (\text{PTV} + 2\text{ mm})]\text{ volume})/\text{Parotid Volume} \quad (1)$$

A typical illustration of CTV to PTV margin and dose distribution around the target is given in Figure 1.

Treatment plan

A primary target dose of 60 Gy in 30 fractions was prescribed for each patient. Patients were treated on

Table 1: Details of patients and primary treatment sites

Patient Characteristics	Quantities
Gender	
Male	74
Female	21
Age (years)	
Range	25–84
Mean	54.5
Median	56
Primary site	
Base of tongue	65
Larynx	12
Oral cavity	10
Oropharynx	6
Hard palate	1
Nasopharynx	1

Clinac iX (Varian Medical Systems, Palo Alto, CA, USA). Volumetric-modulated arc therapy (VMAT) treatment plans were done with two 360° full arc using Eclipse treatment planning system (v13.6, Varian Medical Systems, Palo Alto, CA, USA). Table 2 shows the dose–volume constraints for PTV and OARs.

Prediction models

Two simple prediction models are used in this study: one linear regression model and one exponential model. Both models incorporate the fractional overlapping parotid volume with the PTV as a predictor of the mean parotid dose. The collected data include the volume of the entire parotid gland, the volume of the parotid gland outside the PTV with an additional 2 mm margin, and the mean parotid dose. Statistical calculations were done using data analysis tools and Solver Add-ins in Microsoft Excel (Microsoft Office 2013, Redmond, WA, USA).

Linear model

The formula for prediction of parotid gland dose based on a linear regression model is as follows:

$$\text{Predicted mean parotid dose} = A + B \times \text{Fractional Overlapping Volume} \quad (2)$$

where A and B are the coefficients of the linear fit. The method of least square fit is used to compute the coefficients A and B.

Exponential model

The exponential model follows the formula:

$$\text{Predicted mean parotid dose} = A + B \times (1\text{-exp}\ [\text{-Fractional Overlapping Volume}]) \quad (3)$$

where A and B are the coefficients of nonlinear fit. The method of least square fit is used to compute the parameters using transformed linear expression of the equation (3).

Results

It was found that plans with the same prescription doses and similar parotid overlaps differed in their mean parotid dose. In order to achieve the lowest possible mean parotid dose, the overlapped parotid area was underdosed. Average PTV coverage was ($V_{95\%}$) 98.3% range 96%–99.5%. For the overlapping PTV area (PTV ∩ Parotid), $V_{95\%}$ was 88.0%.

The total parotid volume ranges from 5.1cc to 60.3cc with an average of 26.03cc. The mean parotid dose ranges from 61.22 Gy (100% Overlap) to 9.37 Gy (0% Overlap) with an average of 34.24 Gy. Figure 2 illustrates the association between total parotid volume and mean parotid dose. Our investigation revealed an absence of a substantial correlation between these two variables, as indicated by a coefficient of determination ($r^2 = 0.05$).

Mean parotid dose versus fractional overlapping volume

Figure 3 presents a scatter plot depicting the relationship between the fractional overlapping volume and parotid mean dose.

The linear model analysis indicates a positive correlation between the fractional overlapping volume and the mean dose received by the parotid gland. On linear regression, there was a strong positive correlation between the two variables ($r^2 = 0.82$, $P < 0.0001$).

We used exponential regression to arrive at the equation that best fits the set of data for the exponential model.

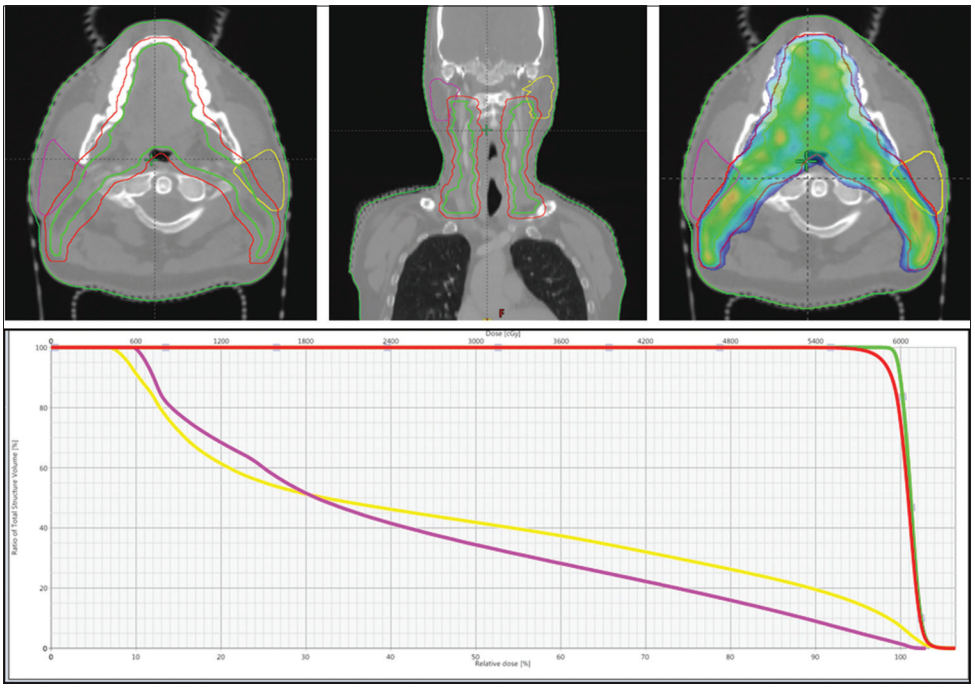

Figure 1: Delineation of planning target volume and organs-at-risks and dose distribution nearby parotid and dose-volume histogram

It also shows a strong positive correlation between two variables ($r^2 = 0.78$).

Excluding outliers

The presence of outliers, which are anomalous values that deviate from the expected normal distribution, can potentially introduce significant distortions in any regression model.

We discarded data points that had residuals (predicted dose–actual dose) >2 standard deviations below and above the residuals or errors. Both models have nine different data points as outliers which were discarded to get better prediction.

Regression statistics

There were 181 out of 190 data points that were fitted to both models after excluding outliers. Correlation coefficient shows a good improvement after the exclusion of the outliers. The r^2 in the linear model increased from 0.81 to 0.85, whereas in the exponential model, it increased from 0.78 to 0.82. Table 3 shows some regression statistics. The root-mean-square error (RMSE) for the linear fit model was 2.06 Gy, whereas it was 2.26 Gy for the exponential fit model.

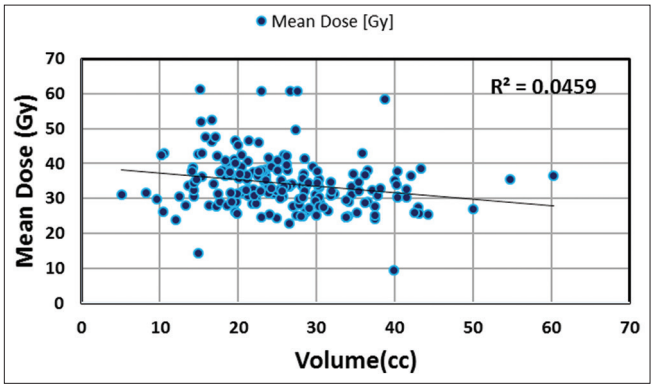

Figure 2: The relationship between total parotid volume and parotid mean dose. No significant correlation was found between two parameters ($r^2 = 0.05$)

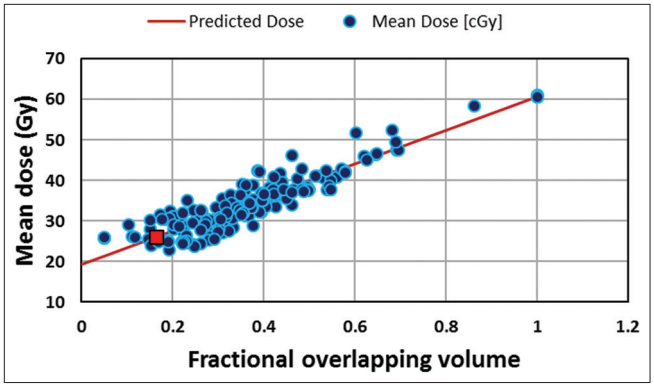

Figure 4: Predicted mean dose with fractional overlapping volume. The red marker denotes the mean dose of 26 Gy with fractional overlapping volume of 16.4% in linear model

Model outcome

Both prediction models showed good correlation statistics. We have found a fractional overlap of 16.4% and 18.9% in linear and exponential models that predict parotid mean dose 26 Gy, shown in Figures 4 and 5 as red marker. The observed cut-point values align closely with those reported by Hunt *et al*.[7] (20%) and Yaparpalvi *et al*.[10] (15%) but notably, deviate from the findings of Gensheimer *et al*.[12] (35%). When fractional overlap is 28.6% and 67.3%, the predicted dose is the same for both models and is 31.03 Gy and 47.04 Gy, respectively. The exponential model estimates a lower predicted mean dose below and above these two cut points.

The residuals in linear model range from −7.9 Gy to 5.7 Gy with an average of 0.0 Gy and standard deviation of 2.9 Gy. Exponential model residuals range from −8.5 Gy to 6.2 Gy with an average of 0.0 Gy and standard deviation of 3.2 Gy. Figure 6 displays a plot illustrating the relationship between the number of patients and the residuals of two models over a specific time frame. Linear model overestimates (predicted dose > mean dose) the predicted dose in 95 cases out of 181 (52.5%), whereas the exponential model overestimates in 105 cases out of 181 (58%).

The normality of both model residuals was validated using Shapiro–Wilk test. Figures 7 and 8 show the histogram plots

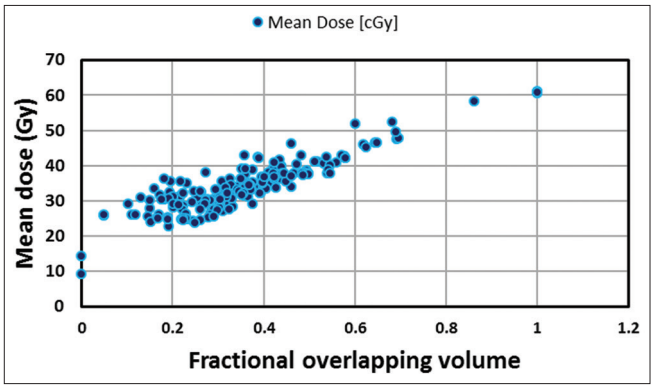

Figure 3: Scatter plot between the fractional overlapping volume and parotid mean dose

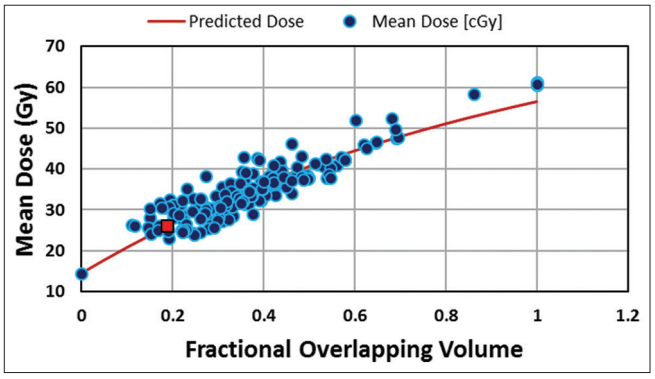

Figure 5: Predicted mean dose with fractional overlapping volume. The red marker denotes the mean dose of 26 Gy with fractional overlapping volume of 18.9% in exponential model

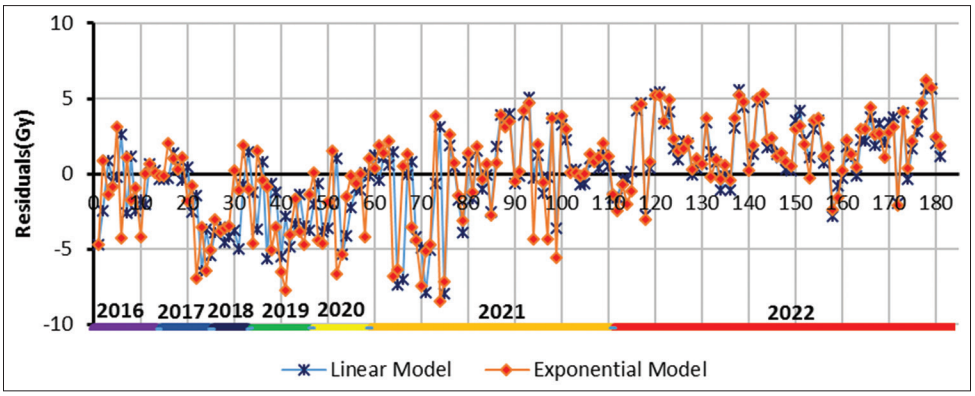

Figure 6: Plot of both models' residuals with time frame

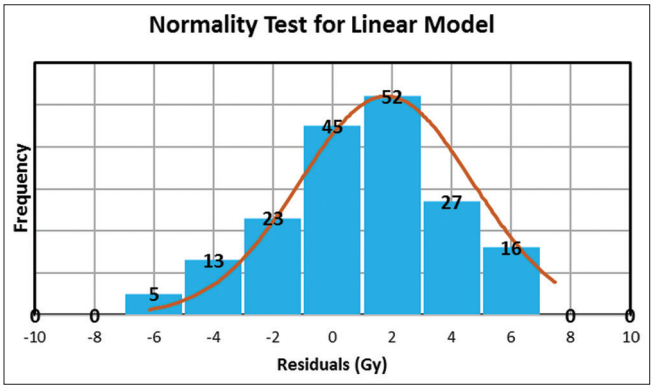

Figure 7: Histogram of the linear model's residual and normality test

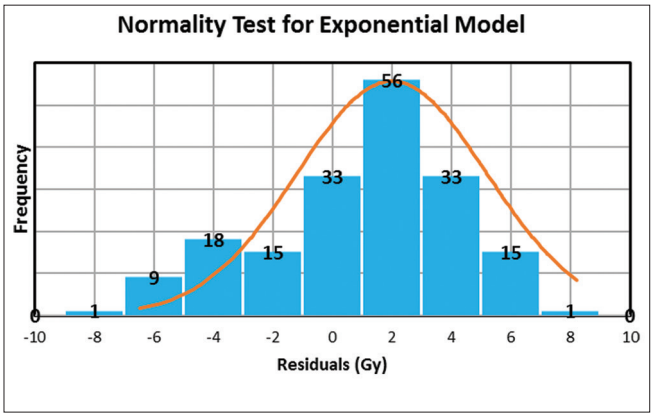

Figure 8: Histogram of the exponential model's residual and normality test

of residuals and normal distribution curves for linear and exponential models, respectively.

Implementation

We have implemented the prediction models in 12 upcoming patients (24 parotid glands). The plot of Model predictions and plan mean dose is given in Figure 9. The residual statistics are as follows: 3.6 Gy ± 2.4 Gy for linear model and 3.6 Gy ± 2.6 Gy for exponential model. Prediction overestimation (predicted dose > mean dose) has drastically changed and is 91.7% for both models. This illustrates the fruitful outcome of those types of prediction models and also indicates the model prediction could be improved if those data points were included in the training dataset.

Table 2: Details of planning target volume and organ-at-risk constraints

Structure	Constraint	Priority
PTV	$V_{95\%}$ >95% D_{max} <107%	Maximum
Spinal cord	D_{max} <45Gy	High
Brainstem	D_{max} <54Gy	High
Optic chiasma	D_{max} <54Gy	High
Optic nerve	D_{max} <54Gy	High
Eye	D_{max} <45Gy	High
Lens	D_{max} <7Gy	High
Lips	D_{mean} <45Gy	Intermediate
Larynx	D_{mean} <45Gy	Intermediate
Parotid	D_{mean} <26Gy	Intermediate
Cochlea	D_{mean} <45Gy	Intermediate

PTV: Planning target volume

Discussion

In this single-institutional study, we successfully developed a prediction model using a cohort of HNC patients and evaluated its accuracy and potential clinical application. This model shows the power of using previous experience in VMAT planning to predict and maintain the quality of future cases. The findings indicate that if the fractional overlapping volume exceeds 16.4% and 18.9% in linear and exponential models; it is unlikely to achieve a mean dose of 26 Gy. The obtained r^2 = 0.85 and 0.82, along with the corresponding RMSE values of 2.06 Gy and 2.26 Gy in the linear and exponential models, respectively, provide evidence of higher accuracy achieved in this study.

In a study conducted by Ranjith *et al*.,[13] a multiple linear regression model was constructed using nine predictors, resulting in reported r^2 = 0.7695 and an RMSE value of 2.89 Gy. Interestingly, these outcomes are comparable to the results of our study, despite utilizing a single predictor.

Furthermore, the prediction model's potential clinical application extends beyond treatment planning. It can

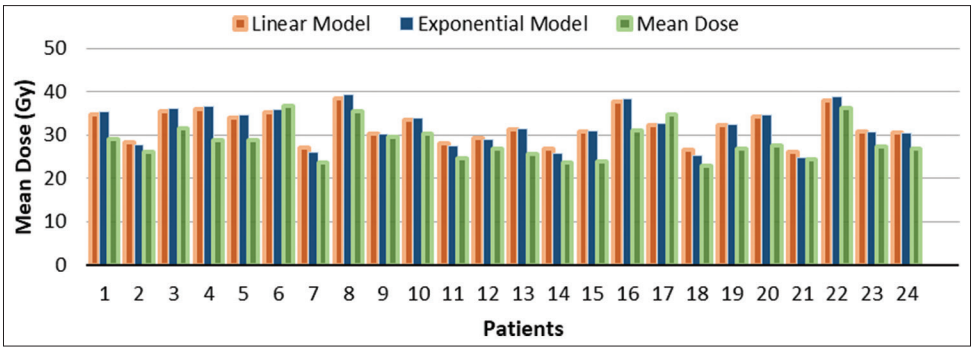

Figure 9: Plot of both models' prediction and actual plan mean dose

Table 3: Regression statistics

	Linear model	Exponential model
A	19.2	14.5
B	41.3	66.3
r^2	0.85	0.82
RMSE (Gy)	2.06	2.26

RMSE: Root-mean-square error

assist clinicians in making informed decisions regarding dose constraints, fractionation schemes, and treatment techniques. This individualized approach to radiotherapy can lead to better treatment outcomes and reduced morbidity in HNC patients. While the prediction model for mean parotid dose in HNC patients undergoing radiotherapy shows promise, it is important to acknowledge its potential drawbacks and limitations. These drawbacks include:

i. The prediction model was developed using data from a single institution, which may introduce biases related to patient selection, treatment protocols, and technological variations. This limits the generalizability of the model to other treatment centers or patient populations. Further validation using diverse datasets from multiple institutions is necessary to assess the model's robustness and generalizability
ii. The prediction model relies on a single variable available within the dataset used for model development. There are many more additional factors, for example, patients' body type: lean, obese, tumor stage, variability in contouring organs, uncertainty and error margin, evolving treatment techniques, etc., that influence mean parotid dose that was not considered in this study. Incorporating these characteristics could enhance the model's accuracy and predictive power
iii. Our study focuses on a primary target dose of 60 Gy delivered in 30 fractions. It is important to note that there are various other dose prescriptions currently being used in clinical practice, which have not been encompassed within the scope of this study.

Conclusion

Volumetric arc therapy (VMAT) in HNC is associated with reduced early and late toxicity, improving the quality of life for patients.[19,20]

Using this type of prediction model, it is possible to avoid under sparing the OARs in some cases and wasting time or effort on physically impossible goals in others. The cutoff values derived for both models of parotid glands' fractional overlapping volume with the 2 mm expansion of the PTV can be extremely useful tools for planners. Planners should inform physicians when the PTVs provided by physicians yield overlap equal to or greater than cutoff and discuss whether the physician should modify the PTVs in order to achieve parotid sparing or keep the PTVs as is, accepting the possibility that they may not spare the intended parotid gland(s). This allows for a much more efficient use of resources in the planning process.

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Conflicts of interest

There are no conflicts of interest.

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