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FULL PAPER

Predicting the dose absorbed by organs at risk during intensity modulated radiation therapy for nasopharyngeal carcinoma

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Objective: To develop a model for predicting the dose absorbed by organ at risk (OAR) during intensity modulated radiation therapy for nasopharyngeal carcinoma (NPC).

Methods: 55 patients underwent intensity modulated radiation therapy for NPC. The OARs were divided into several suborgans, and SPSS software was used to evaluate multiple linear method for fitting the normalized volume for each suborgan, normalized mean dose (D_{mean}) D_{nm} ($D_{\text{nm}} = D_{\text{mean}}/D_{\text{prescription}}$), and normalized $D_{10\%}-D_{100\%}$ values $D_{n10\%-n100\%}$ ($D_{n10\%-n100\%} = D_{10\%}-D_{100\%}/D_{\text{prescription}}$) for each OAR. Based on the Matlab software, the predicted $D_{n10\%-n100\%}$ value was fitted to obtain the predicted DVH curve.

Results: The multiple linear fitting formulas revealed significant results for the oral cavity $D_{n100\%}$ ($p = 0.017$),

the parotid gland $D_{n100\%}$ ($p = 0.001$), and the remaining OAR (all $p < 0.0001$). The correlation coefficients and p values indicated that the fitting formula was a good fit. The p values for the White test show that the prediction model is robust. This method was successfully used for verification cases.

Conclusion: The present study provided a simple and effective model for predicting the dose absorbed by OAR for NPC.

Advances in knowledge: This method is a relatively simple mathematical model, just use prescription dose and V_0-V_n to predict the D_{mean} and $D_{10\%-100\%}$, which predict does not require buying new modules of treatment planning software or extracting the distance of each sampling point of the OAR with the dose information.

INTRODUCTION

In recent decades, many reports have confirmed that intensity modulated radiation therapy (IMRT) improves the curative effects and the patient's subsequent quality of life.¹⁻⁷ In this context, the most fundamental principle of radiotherapy is to provide the highest possible dose to the tumor, while providing the lowest possible dose to the organ at risk (OAR). However, the delivered doses are influenced by various factors during the optimization process, such as physicians provide planners with optimization goals determined from population-based data, Radiation Therapy Oncology Group (RTOG) guidelines, or clinical knowledge and intuition. Although the dose absorbed by OAR is targeted within a tight range at most radiotherapy centers, there are few effective predictive and assessment tools, and the actual dose delivered to OAR typically depends on the operators' experience.

The relationships between the OAR and the target region are complex, which can lead to interpatient differences. Previous studies have demonstrated that the dose absorbed by OAR is related to their spatial position in relation to the target region.⁸⁻¹⁰ In this context, patients receiving IMRT for nasopharyngeal carcinoma (NPC) have several nearby OAR: the inner ears, oral cavity, parotid gland, larynx (glottic portion), postcricoid region of the hypopharynx, and esophagus. The present study selected these six OARS, and aimed to retrospectively develop a model for predicting the dose that would be absorbed by each OAR in these patients. The normalized mean dose of the OAR ($D_{\text{nm}} = D_{\text{mean}}/D_{\text{prescription}}$) was calculated by the predicting model, as well as the normalized $D_{10\%}-D_{100\%}$ values ($D_{n10\%-n100\%} = D_{10\%}-D_{100\%}/D_{\text{prescription}}$), and the findings were used to retrospectively optimize the existing IMRT plan for NPC. As serial organs have a higher priority weighting, compared to the target region, we did not consider serial organs in our analyses.

METHODS AND MATERIALS

Patient data

We retrospectively selected data from 55 patients who were undergoing IMRT for NPC at our department between 2013 and 2016 (T2: 23 cases, T3: 22 cases, T4: 10 cases, N0: 9 cases, N1: 14 cases, N2: 16 cases, N3: 10 cases, and N4: 6 cases).

Target region delineation

Enhanced CT imaging was performed using a CT scanner (LightSpeed Plus 4, General Electric Company, Wisconsin, Milwaukee, USA). The CT slice thickness of 2.5 mm. CT images were transferred to the Pinnacle³ 8.0 m (Philips, Fitchburg, WI) treatment planning software (TPS) to prepare IMRT plan. Target region delineation based on the International Commission on ICRU Reports 50 and 62.^{11,12} A radiation oncologist delineated the gross tumors volume (GTV) and clinical target volumes 1 and 2 (CTV1 and CTV2). The GTVs included visible tumors and/or enlarged or suspicious lymph nodes, CTV1 included the high-risk regions surrounding the primary tumors and the upper neck nodes at risk, and CTV2 included the mid-lower nodes at risk. The planning target values (PTVs) were defined as GTV + 3 mm (PGTV) and CTV + 3 mm. The target regions were identified and delineated by the same radiotherapist for all patients.

Prescription doses and plan evaluation

Based on the RTOG 0615 and 0225 guidelines,^{13,14} the per-fraction doses for PGTVs were defined as 2.10–2.25 Gy and the total dose was defined as 66–70 Gy. The per-fraction dose for PTV1 was defined as 1.80–2.05 Gy and the total dose was defined as 60–66 Gy. The per-fraction dose for PTV2 was defined as 1.80 Gy and the total doses were defined as 54–56 Gy. To evaluate the dose distribution of the target, the following parameters were calculated for the PTV: minimal dose delivered to 95% of the target volume.

Limiting requirements for OAR

Based on the RTOG 0615 and 0225 guidelines, the maximum mean doses were ≤ 45 Gy for the unilateral inner ear, ≤ 40 Gy for the oral cavity, and ≤ 26 Gy for the parotid gland. In cases with an oversized intersection of the parotid gland and PTV2, with a unilateral $D_{50\%}$ of <30 Gy or the minimum dose, the maximum mean doses were defined as ≤ 45 Gy for the larynx (glottic portion), the postcricoid region of the hypopharynx, and the esophagus.

Treatment planning design

The 55 cases of NPC were treated using IMRT. We selected the 6 MV X-ray co-planar 9-beam average divisions (gantry angle at 160°, 120°, 80°, 40°, 0°, 320°, 280°, and 240°) via the Direct Machine Parameter Optimization algorithm and dose engine (the grid resolution of a 4 mm dose grid with a 2 mm fluence grid was used, including the heterogeneity correction) on the Pinnacle³ 8.0 m TPS.

Before the plan optimization, the PTV2 was extended externally to several rings (0.3 cm in width). The intersection regions for ring₁–ring_n and the OAR (ring₁–ring_n $\cap$ OAR) were considered for each suborgan to perform the parameter optimization.

Figure 1. Red line indicated GTVnx, green line indicated PGT-Vnx, yellow line indicated CTV1, bright blue line indicated PCTV1, orange line indicated CTV2, mountain blue line indicated PTV2, red shadow indicated the intersection of PTV2 and right parotid, green shadow indicated the intersection of ring₁ and right parotid, blue shadow indicated the intersection of ring₂ and right parotid, yellow shadow indicated the intersection of ring₃ and right parotid, pink shadow indicated the intersection of ring₄ and right parotid, lavender shadow indicated the intersection of ring₅ and right parotid, steel blue shadow indicated ring₆ and right parotid, slate blue shadow indicated the intersection of ring₇ and right parotid, and olive shadow the intersection of ring₈ and right parotid. CTV, clinical target volume; GTV, gross tumors volume; PTV, planning target value.

The uniform dose for each suborgan was regarded as the optimization restrictive condition to make constant adjustments for values and weight. The dose of the intersection area of OAR and the target area was recognized as the prescription dose, and the dose of the target area was guaranteed to keep the absorbed dose of each OAR as low as possible so that the requirements of the evaluation were met. When numerous suborgans were present, suborgans weight parameters were adjusted to smaller values (with respect to the target region). The intersecting regions for Patient 54's ring₁–ring_n and right parotid gland are shown in Figure 1.

Absorbed dose prediction model

Based on the patients' data, we calculated the normalized volume for each subOAR ($V_{\text{ring1-ringn} \cap \text{OAR}}/V_{\text{OAR}}$), the normalized mean doses for each OAR ($D_{\text{nm}} = D_{\text{mean}}/D_{\text{prescription}}$), and the normalized $D_{10\%}$ – $D_{100\%}$ values ($D_{n10\%-n100\%} = D_{10\%}-D_{100\%}/D_{\text{prescription}}$). Using SPSS 13 software, the Pearson correlation test was used to analyze the correlation between the normalized volumes

Table 1. The correlation coefficients of different OAR in the Equation 1 fitting

Dn r	Dnm	Dn10	Dn20	Dn30	Dn40	Dn50	Dn60	Dn70	Dn80	Dn90	Dn100
r (inner ear)	0.984	0.975	0.985	0.988	0.988	0.986	0.984	0.981	0.972	0.948	0.900
r (oral cavity)	0.957	0.968	0.969	0.959	0.945	0.941	0.937	0.924	0.903	0.875	0.702
r (parotid)	0.977	0.907	0.948	0.964	0.964	0.963	0.953	0.937	0.899	0.820	0.507
r (larynx)	0.919	0.894	0.884	0.886	0.891	0.893	0.899	0.889	0.845	0.892	0.825
r (hypopharynx)	0.955	0.927	0.950	0.961	0.965	0.960	0.938	0.912	0.886	0.836	0.730
r (esophagus)	0.978	0.951	0.851	0.975	0.969	0.954	0.927	0.933	0.909	0.880	0.843

OAR, organ at risk.

of the sub OAR and D_{nm} or $D_{n10\%-n100\%}$ of each OAR, and a multiple linear regression analysis was used to fit the data for the normalized volumes of the sub OAR and D_{nm} or $D_{n10\%-n100\%}$ of each OAR. This technique allowed us to develop a model for predicting D_{nm} and $D_{n10\%-n100\%}$ based on the known normalized volume(s) for the organ(s) at risk.

Dose-volume histogram (DVH) curve fitting

Based on the Matlab software, the predicted $D_{n10\%-n100\%}$ value was fitted to obtain the predicted DVH curve.

RESULTS

Multivariate linear fitting

The volume of the suborgan had a significant correlation with D_{nm} and $D_{n10\%-n100\%}$ of each OAR (all $p < 0.05$). Multivariate linear fitting of normalized suborgan volumes, with their D_{nm} and $D_{n10\%-n100\%}$ values, provided the following formula:

$$Y = B_c + B_0 \times V_0 + B_1 \times V_1 + \dots + B_n \times V_n \quad (1)$$

Y predicts the D_{nm} or $D_{n10\%-n100\%}$ of the each OAR, $D_{prescription}$ is prescription dose of PTV2, V_0 is the normalized intersection volume of PTV2 and the OAR, V_1 is the normalized intersection volume of ring₁ and the OAR, and V_n is the normalized intersection volume of ring_n and the OAR. The values of B_c and B_0 – B_n for the various Y can be obtained by SPSS 13 software.

Figure 2. The predicted values and actual values for D_{nm} (oral cavity).

The correlation coefficients for the different OAR after fitting using Equation 1 are shown in Table 1. These findings revealed significant results for the oral cavity $D_{n100\%}$ ($p = 0.017$), the parotid gland $D_{n100\%}$ ($p = 0.001$), and for the remaining OAR (all $p < 0.0001$).

Robustness of prediction model

We have compared all predicted and actual values of the prediction model. The mean absolute error is less than 0.05, which shows that the model has good prediction method. When the model shows heteroskedasticity, the model prediction function will fail. Therefore, we use the White test to test the heteroskedasticity of the prediction model. All p -values are greater than 0.05 for the White test, indicating that the heteroskedasticity problem is not significant. The prediction model is robust and can be used for interval estimation and prediction. The predicted values and actual values for D_{nm} (oral cavity) are shown in Figure 2. For D_{nm} (oral cavity), the mean absolute error is equal to 0.019, and $p = 1$ for the White test.

Verification cases

This method was adopted to optimize the IMRT for 20 verification cases of NPC: the planner had to repeatedly adjust the optimized parameters of the OARs ensure that the prescription dose curve surrounds the tumor target, and that the OARs received as low dose as possible.

The treatment planning comparison was facilitated by defining the relative model excess as equal to the difference between D_{plan} and D_{pred} , divided by D_{pred} ($\delta = [D_{plan} - D_{pred}] / D_{pred}$). In this calculation, D_{plan} is the D_{mean} and $D_{10\%-100\%}$ of each OAR based on the verification cases optimization methods, and D_{pred} is the predicted value of D_{mean} and $D_{10\%-100\%}$ of each OAR using the

Table 2. The δ average values of the each OAR

OAR	δ
Inner ear	0.038 ± 0.057
Oral cavity	0.044 ± 0.054
Parotid	0.012 ± 0.058
Larynx	0.020 ± 0.034
Hypopharynx	0.014 ± 0.038
Esophagus	0.043 ± 0.091

OAR, organ at risk.

Figure 3. The solid red line indicated plan DVH of inner ear, the dotted black line indicated predicted DVH of inner ear. DVH, dose-volume histogram.

Equation 1. δ values near 0 indicate similarity between the planning and prediction values.

For example, in the case of D_{mean} , $\delta = (D_{\text{mean}} - D_{\text{pred}})/D_{\text{pred}}$. The δ average values for each OAR are shown in Table 2. Using SPSS 13 software, statistical differences were determined using a two-sided paired *t*-test. Differences with a *p* value of < 0.05 were considered significant. The D_{plan} and D_{pred} were not significantly different ($p > 0.05$) of each OAR.

The predicted and plan DVH curve for Patient 7's of verification cases are shown in Figures 3–8.

DISCUSSION

In this study, we considered each of the six OARS in cases of NPC. We used SPSS software to perform correlation analysis of the suborgans' normalized volumes, D_{nm} , and $D_{\text{n10\%-n100\%}}$, which revealed a significant correlation between the two indexes. Thus, we performed the data fitting using multivariate linear fitting, the correlation coefficients and *p*-values indicated that

Figure 4. The solid red line indicated plan DVH of oral cavity, the dotted black line indicated predicted DVH of oral cavity. DVH, dose-volume histogram.

Figure 5. The solid red line indicated plan DVH of parotid, the dotted black line indicated predicted DVH of parotid. DVH, dose-volume histogram.

the fitting formula was a good fit. The *p*-values for the White test show that the prediction model is robust. After the fitting, we were able to create a model to predict the D_{mean} and $D_{10\%-100\%}$ for individual OAR based on a known prescription dose and V_0-V_n , which may be helpful for optimizing the IMRT plan. Predicting the dose absorbed by OAR during radiotherapy is critically important,^{15–22} our method is a relatively simple mathematical model, just use prescription dose and V_0-V_n to predict the D_{mean} and $D_{10\%-100\%}$, which predict does not require buying new modules of TPS or extracting the distance of each sampling point of the OAR with the dose information.

The D_{plan} and D_{pred} were not significantly different ($p > 0.05$) of each OAR. This shows that for the verification cases, the predicted values accurately predicted the planned values. We also use the Matlab software to perform curve fitting on the predicted $D_{10\%-100\%}$ to obtain the predicted DVH curve. In this way, the planner can obtain the predicted DVH curve before making the

Figure 6. The solid red line indicated plan DVH of larynx, the dotted black line indicated predicted DVH of larynx. DVH, dose-volume histogram.

Figure 7. The solid red line indicated plan DVH of hypopharynx, the dotted black line indicated predicted DVH of hypopharynx. DVH, dose-volume histogram.

IMRT plan, which can more intuitively understand the difference between the planned and predicted DVH curves.

In IMRT planning, the process model for the acquisition of sub-OAR volumes can be edited into scripts to improve efficiency. Simultaneously, more IMRT plan data can be added to the original data to yield an updated and more accurate fitting formula. The methods used in the present study can also be applied before planning in other disease states to obtain the prediction value of D_{nm} and $D_{n10\%-n100\%}$.

Consider Score ($100 \times [1 - \delta]$); Scores closer to 100 indicated a closer relationship between the planned and predicted values of D_{nm} and $D_{n10\%-n100\%}$. The Score threshold can be set for standardizing the D_{nm} and $D_{n10\%-n100\%}$ of each OAR, and the Score above the threshold need to be further optimized until a satisfactory score is obtained under the condition of the target prescription evaluation. It can be an IMRT planning quality control means and reduces the influence of subjective factors. Its clinical significance in terms of the potential improvements to patient toxicity

Figure 8. The solid red line indicated plan DVH of esophagus, the dotted black line indicated predicted DVH of esophagus. DVH, dose-volume histogram.

There are several factors that can affect the results of IMRT plan optimization. For example, to better protect the parotid gland, physicists and doctors must reach a consensus for each patient to determine whether to use a lower dose for the intersection volume of the parotid gland and the target volume.

Therefore, further studies are needed to evaluate a larger sample of patients from multiple centers, in order to more accurately fit the predictive model, eliminate subjective factors, and establish the absorbed dose prediction models for different diseases, machines, and planning systems.

CONCLUSION

The present study developed a simple and practical method for predicting the D_{nm} and $D_{10\%-100\%}$ for specific OAR in patients with NPC. This method may also be useful for predicting these parameters for patients with other stages or diseases that are being treated using IMRT.

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