Study of the dose-volume parameters variation in tumor target volumes and organs at risk during nasopharyngeal carcinoma radiotherapy applying deformation registration

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Background: During intensity-modulated radiotherapy (IMRT) for nasopharyngeal carcinoma (NPC), the volume of the target volume and the organs at risk (OARs) will change constantly, which may lead to differences between the actual dose received and the initial planned dose. In this study, the cumulative dose of the two plans was obtained by deformable registration. This study provides an approach to evaluate the dose volume of IMRT for the NPC objective.

Methods: From July 2014 to May 2018, eighteen NPC patients who accepted simultaneous integrated boost IMRT were enrolled. All patients underwent simulation CT (CT_1) and replanning CT (CT_2) scans after 20–25 fractions of radiation therapy. The treatment plans were designed on CT_1 and CT_2 with the name of $Plan_1$ and $Plan_2$, respectively. The $Plan_{reg}$ and $Plan_{def}$ were obtained after registering from CT_2 to CT_1 using rigidity and deformation technology by Velocity. Then the dose-volume indices of the tumor target volumes and OARs at $Plan_1$, $Plan_2$, $Plan_{rig}$ and $Plan_{def}$ were compared.

Results: The gross tumor volume (GTV) and the left and right parotid gland volumes decreased by 20.8% (P<0.001), 36.8% (P<0.001) and 37.5% (P<0.001), respectively, from CT_1 to CT_2. There was no significant difference in the dose-volume index on the GTV and plan gross tumor volume (PGTV) between $Plan_1$ and $Plan_2$. The V_{30} of the left and right parotid gland and the D_{max} of the brainstem, left and right eyeballs, left and right lens, and left and right optic nerves were all lower in $Plan_2$ than in $Plan_1$ (the average decrease was 17.0% to 60.1%). The differences in some dose-volume parameters (including D_{mean}, D_{99} of the GTV and PGTV, D_{mean} of the parotid glands, D_{max} of the lens and optic nerves) between $Plan_{def}$ and $Plan_1$ were less than 5%. The differences in some dose-volume parameters (including D_{mean}, D_{95} of the GTV and PGTV, D_{mean}, D_{50} and V_{30} of the parotid glands, D_{max} of lens and optic nerves) between $Plan_{rig}$ and $Plan_1$ were less than 10%. The Dyce Similarity Coefficient of the target volume and OARs after deformation registration were higher than that after rigid registration.

Conclusions: The volume of the GTV and parotid glands were decreased during the IMRT for NPC. The dose-volume indices of the GTV and the OARs in $Plan_{def}$ were similar to those in $Plan_1$. Therefore, the dose-volume indices of $Plan_1$ can be used to evaluate the efficacy of radiotherapy and to predict radioactive damage.

Keywords: Nasopharyngeal carcinoma (NPC); image registration technique; dosimetry; radioactive damage

Introduction

Nasopharyngeal carcinoma (NPC) occurs mostly in Southeast Asia and southern China (1,2). Due to the particularity of its anatomical location, NPC is surrounded by many important tissues and organs. The vast majority of NPC are more sensitive to radioactivity, and consequently radiotherapy or radiotherapy-based comprehensive treatment has now become the main method for radical treatment of patients with NPC (3). For patients with early NPC after radical radiotherapy, the 5-year survival rate can reach 80%.

There are many important organs at risk (OARs) around the target volume of NPC, such as the parotid glands, brain stem, spinal cord, eyeballs, optic nerves and lens. The exposure doses by these OARs were closely related to the quality of life of patients after treatment. The key to improving the effect of radiotherapy is to ensure the dose of the target volume and to minimize the dose of normal tissues and OARs. Therefore, it is of great significance to accurately predict the dose of the target volume and OARs during the radiotherapy process for patients with NPC.

Intensity-modulated radiotherapy (IMRT) is a routine clinical radiotherapy technique for NPC. It has a steep dose gradient distribution, which can reduce the exposure dose of OARs around the tumor while ensuring that the tumor target volume can be irradiated with a sufficient dose (4). However, some studies have shown that the volume and location of tumor target volume and OARs are different during the IMRT for NPC (5-7). In particular, the volume of the parotid glands was significantly reduced during IMRT for NPC (8). Differences in the volume of the parotid glands may lead to inadequate coverage of a radiation dose over the tumor target volume or excessive dosage of OARs, which deviates from the original plan. Deformed registration provides a feasible method for accurately accumulating radiation doses to target volume and OARs in NPC patients during radiotherapy. The purpose of deformed registration technology is to accumulate the dose through point-to-point registration, and then track the dose of the target volume and OARs during IMRT for NPC.

In the course of radiotherapy for NPC, the volume reduction in tumor target and OARs may not be synchronized with the changes in their dose volume indices. This study used registration technology to accumulate the dose of two plans of IMRT for NPC by rigid and deformed methods, and to thereby analyze the difference in the dose-volume index of the tumor target volume and OARs. This study provided an approach to evaluate the dose volume of IMRT for the NPC objective.

Methods

Patient characteristics

Eighteen NPC patients (13 males and 5 females) who received simultaneous integrated boost intensity-modulated radiotherapy (SIB-IMRT) from July 2010 to May 2018 were selected. The clinical stage was divided into 10 cases at the T_2 stage and 8 cases at the T_3 stage according to the AJCC 2010 staging standard T stage.

CT scanning and planning design

All patients underwent scanning and simulation on a Philips large-aperture CT, taking the supine position; fixing the head, neck, and shoulder with a thermoplastic mask; and scanning from the top of the head to the lower 3 cm of the clavicle with a layer thickness of 3 mm. The scanned CT image was transmitted to the Eclipse 13.5 planning system and the SIB-IMRT technique was used. The radiologist outlined the target volume, as well as OARs such as the parotid gland, brain stem, spinal cord, eyeballs, optic nerves, and lens. The dosage limitation conditions for OARs are a 50% parotid volume dose less than 30 Gy, brainstem dose less than 54 Gy, spinal cord dose less than 45 Gy, optic nerve dose less than 54 Gy, eyeball dose less than 50 Gy, lens dose less than 8 Gy, etc. $Plan_1$ was the IMRT plan on simulation CT before radiotherapy and $Plan_2$ was the IMRT plan on repeated simulation CT at the middle and late stages of radiotherapy. The prescribed dose was 66–70 Gy.

Image registration

The patient's two radiotherapy plans were imported into the velocity image registration software based on B-spline algorithm, and the repeated simulated CT_2 was registered into the first simulated CT_1 to obtain the transformed registration image CT_3. The dose distribution of $Plan_2$ and the dose distribution of $Plan_1$ were separately subjected to rigidity and deformation registration to obtain $Plan_{rig}$ and $Plan_{def}$.

Statistical indicators

The volume of the gross tumor volume (GTV) and bilateral

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parotid glands; average dose (D_{mean}), 95% volume dose (D_{95}) and 99% volume dose (D_{99}) of GTV; and plan gross tumor volume (PGTV) were measured and recorded. Indicators of various OARs include the bilateral parotid D_{mean}, 50% volume dose (D_{50}) and 30 Gy surrounded volume (V_{30}); maximum point dose (D_{max}) and 5% volume dose (D_5) of the brain stem; D_{max} of the bilateral eyeballs, optic nerves and lens; and Dice Similarity Coefficient (DSC) of the GTV, PGTV, parotid gland, brainstem, eyeballs, optic nerves and lens after deformation registration and rigid registration. (DSC=$2|A∩B|/(|A|+|B|)$). The volume of the target volume and OARs in CT_1 and CT_2 were A and B respectively.)

Statistical methods

The data are expressed in the form ($\overline{x}$±s). A paired *t*-test was performed using SPSS 19.0 statistical software. P<0.05 indicates that the difference is statistically significant.

Results

Change in the volume of the GTV and parotid gland

Compared with the initial simulated CT_1, the volumes of the GTV, left parotid gland and right parotid gland in the repeated simulated CT_2 decreased by 20.83% (P<0.001), 36.83% (P<0.001) and 37.47% (P<0.001), respectively. After deformation registration, the volume of the GTV decreased by 3.15% (P<0.001) compared with the initial positioning of the GTV, the left parotid volume decreased by 6.56% (P<0.001), and the right parotid volume decreased by 5.89% (P<0.001) (*Table 1*).

Dosimetric comparison in the target volume

There was no significant change in the dose indices of the GTV and PGTV between $Plan_2$ and $Plan_1$ (P>0.05). Compared with $Plan_1$, the D_{mean} of the GTV in $Plan_{def}$ and $Plan_{rig}$ decreased by 0.42% and 0.62%, respectively (*Table 2*), and the difference was statistically significant (P<0.05). The D_{mean} of the PGTV in $Plan_{def}$ and $Plan_{rig}$ decreased by 1.08% and 1.49%, respectively; the D_{95} of the PGTV in $Plan_{def}$ and $Plan_{rig}$ decreased by 2.77% and 5.49%, respectively; the D_{99} of the PGTV in $Plan_{def}$ and $Plan_{rig}$ decreased by 4.29% and 7.39% (*Table 2*); and these differences were statistically significant (P<0.05).

DSC comparison between rigid registration and deformation registration

The DSC of the target volume and the OARs after rigid registration and deformation registration, respectively, is shown in *Table 3*. The DSC of the target volume and the OARs after deformation registration was greater than the DSC of the rigid registration target volume and the OARs. The DSC difference between the left and right parotid deformation registration and rigid registration was significant (P<0.05).

Dosimetric comparison in the OARs

The dose distribution of each OAR in $Plan_1$, $Plan_2$, $Plan_{def}$ and $Plan_{rig}$ is shown in *Table 4*. Compared with $Plan_1$, the V_{30} of the left parotid gland in $Plan_2$ decreased by 33.5%, the D_{mean} of the right parotid gland decreased by 31.45%, the V_{30} decreased by 60.13%, and the D_{50} decreased by 28.35%. The difference was statistically significant (P<0.05). The D_{mean} of the left and right parotid glands in $Plan_{def}$ decreased by 1.98% and 2.3%, respectively, compared with $Plan_1$, and the difference was statistically significant (P<0.05). The changes in V_{30} and D_{50} of the left and right parotid glands between $Plan_{def}$ and $Plan_1$ were not significant (P>0.05). The D_{mean} of the left and right parotid in $Plan_{rig}$ decreased by 4.21% and 4.93% compared with $Plan_1$, V_{30} decreased by 7.68% and 10.35%, and D_{50} decreased by 3.37% and 3.46%, and this difference was statistically significant (P<0.05).

Compared with $Plan_1$, D_{max} and D_5 of the brainstem in $Plan_2$ were reduced by 17.04% and 27.3%, respectively. The D_{max} of the left eyeball, right eyeball, left lens, right lens, left optic nerve and right optic nerve were decreased by 36.43%, 28.48%, 24.95%, 24.29%, 44.69% and 41.1%, respectively. The difference was statistically significant (P<0.05). Compared with $Plan_1$, D_5 of the brainstem in $Plan_{def}$ was reduced by 3.3%. The D_{max} of the left eyeball, right eyeball, left optic nerve and right optic nerve were decreased by 6.13%, 3.44%, 5.67% and 5.19%, respectively. The difference was statistically significant (P<0.05).

Compared with $Plan_{rig}$, the D_{mean}, V_{30} and D_{50} of the left parotid gland in $Plan_{def}$ increased by 2.26%, 4.36% and 2.1%, respectively, and the difference was statistically significant (P<0.05). The difference in D_{mean}, V_{30} and D_{50} in the right parotid gland was not significant. The D_{max} of the OARs, such as the brainstem, eyeballs, lens and optic nerves, were all decreased.

Table 1 Volume of the tumor target volume and parotid gland in positioning image CT_1, reset image CT_2 and registration image CT_3 (cm^3, $\bar{x}\pm s$)

Parts	CT_1	CT_2	CT_3	CT_1 & CT_2		CT_1 & CT_3	
				t	P	t	P
GTV	79.28±49.66	64.47±42.39	76.79±48.21	5.477	0.000	4.292	0.000
Parotid-L	16.76±4.74	10.77±4.07	15.61±4.43	9.972	0.000	5.735	0.000
Parotid-R	16.63±4.40	10.46±3.99	15.58±4.03	9.303	0.000	6.116	0.000

Table 2 Target volume the dose distribution (Gy, $\bar{x}\pm s$)

Target	Parameter	$Plan_1$	$Plan_2$	$Plan_{def}$	$Plan_{rig}$	t_1	P_1	t_2	P_2	t_3	P_3	t_4	P_4
GTV	D_{mean}	73.91±3.59	73.85±3.55	73.60±3.56	73.45±3.54	0.533	0.601	2.714	0.015	3.308	0.004	1.553	0.139
	D_{95}	71.93±3.49	71.79±3.91	71.35±3.78	70.51±4.13	0.853	0.405	1.792	0.091	2.361	0.030	1.432	0.170
	D_{99}	71.21±3.50	70.29±4.96	70.21±3.87	67.60±8.36	1.398	0.180	2.516	0.022	1.948	0.068	1.470	0.160
PGTV	D_{mean}	73.56±3.42	72.10±6.48	72.78±3.70	72.48±3.71	1.053	0.307	3.935	0.001	3.734	0.002	1.555	0.138
	D_{95}	70.99±3.43	69.14±6.46	69.09±5.12	67.12±7.47	1.313	0.207	3.319	0.004	2.553	0.021	1.441	0.168
	D_{99}	69.08±3.60	65.85±7.75	66.23±6.29	64.03±8.63	1.863	0.080	3.195	0.005	2.819	0.012	1.657	0.116

t_1-t_4, P_1-P_4 represent the values of $Plan_1$ and $Plan_2$, $Plan_1$ and $Plan_{def}$, $Plan_1$ and $Plan_{rig}$, and $Plan_{def}$ and $Plan_{rig}$ as paired *t*-tests, respectively.

Table 3 DSC for the deformation registration and rigid registration

Parts	Deformation DSC	Rigid DSC	t	P
GTV	0.76±0.10	0.73±0.10	1.744	0.099
PGTV	0.77±0.13	0.75±0.12	1.550	0.139
Parotid-L	0.70±0.09	0.56±0.16	5.158	0.000
Parotid-R	0.71±0.10	0.58±0.12	7.808	0.000
Brainstem	0.85±0.04	0.85±0.04	-0.368	0.718
Eye-L	0.87±0.05	0.84±0.07	1.971	0.065
Eye-R	0.87±0.06	0.82±0.09	1.985	0.064
Lens-L	0.50±0.24	0.44±0.24	1.044	0.311
Lens-R	0.51±0.25	0.43±0.26	1.464	0.162
Optic-L	0.61±0.17	0.49±0.22	2.664	0.016
Optic-R	0.57±0.14	0.50±0.19	2.001	0.062
Spinal cord	0.83±0.03	0.68±0.13	4.660	0.000

Discussion

In the process of IMRT, although IMRT is more effective than conventional radiotherapy in increasing the target dose, the radiation exposure of normal tissues and OARs is relatively low (9,10). However, for NPC, factors such as changes in the patient weight, volume of tumors and OARs may have a certain impact on dose assessment. Anatomical changes may result in an insufficient target dose and excessive exposure of OARs. The difference between the actual dose received by the patient and the radiotherapy plan designed by simulation CT was 15% (11). Lu *et al.* (12) compared the repeated simulated CT with the initial simulated CT in 12 patients with NPC and found that the volume of the PGTV was reduced by an average of 16.4%±27.3%. In this study, the tumor target volume of repeated simulated CT was reduced by 20.83% on average compared with that of the initial simulated CT, and the difference between the Plan deformation, $Plan_2$ and $Plan_1$ dose evaluation showed that the D_{mean}, D_{95} and D_{99} of the GTV were not significant. Cheng *et al.* (13) and Wang *et al.* (14) showed that in the course of radiotherapy for NPC, the volume of the tumor target was smaller than that before radiotherapy, but the target dose index did not decrease. In this study, it was found that the volume of the target gradually decreased during IMRT for NPC, and this conclusion is consistent with most studies (12-14). The dose index of the target volume was basically the same in the four plans. Therefore, the dose index of target volume in the initial plan can accurately evaluate the efficacy of radiotherapy.

Table 4 Dose distribution of OARs ($\bar{x}\pm s$)

OARs	Parameter	Plan$_1$	Plan$_2$	Plan$_{def}$	Plan$_{rig}$	t$_1$	P$_1$	t$_2$	P$_2$	t$_3$	P$_3$	t$_4$	P$_4$
Parotid-L	D$_{mean}$ (Gy)	29.73±6.94	24.06±11.57	29.02±6.55	28.31±6.21	2.089	0.052	2.152	0.046	4.138	0.001	3.814	0.001
	V$_{30}$ (%)	36.15±17.39	25.52±23.64	34.88±17.00	33.20±15.98	2.247	0.038	2.055	0.056	5.345	0.000	3.204	0.005
	D$_{50}$ (Gy)	24.75±5.97	20.92±10.22	24.36±5.78	23.83±5.63	1.488	0.155	1.531	0.144	3.709	0.002	4.029	0.001
Parotid-R	D$_{mean}$ (Gy)	30.07±4.37	20.23±7.65	29.39±4.51	28.65±4.99	4.813	0.000	2.643	0.017	3.587	0.002	1.792	0.091
	V$_{30}$ (%)	36.2±14.54	14.84±16.37	34.29±14.20	32.90±14.70	5.117	0.000	2.049	0.056	3.489	0.003	1.752	0.098
	D$_{50}$ (Gy)	25.00±4.69	17.21±6.98	24.62±4.57	24.18±4.97	3.726	0.002	1.466	0.161	2.412	0.027	1.823	0.086
Brainstem	D$_{max}$ (Gy)	50.41±11.06	40.80±13.80	49.90±10.84	50.03±10.99	2.578	0.020	0.371	0.715	0.283	0.780	-1.119	0.279
	D$_5$ (Gy)	45.52±10.45	31.82±14.75	44.00±10.00	44.10±10.05	3.374	0.004	3.965	0.001	3.687	0.002	-1.910	0.073
Eye-L	D$_{max}$ (Gy)	31.53±16.44	20.35±16.22	30.12±16.00	30.19±15.97	3.738	0.002	5.478	0.000	5.472	0.000	-0.811	0.429
Eye-R	D$_{max}$ (Gy)	32.24±18.68	22.45±22.56	31.17±18.46	31.36±18.32	2.908	0.010	3.340	0.004	2.421	0.027	-1.134	0.272
Lens-L	D$_{max}$ (Gy)	5.17±1.42	3.83±2.14	5.20±1.68	5.22±1.67	3.180	0.005	-0.201	0.843	-0.392	0.700	-0.868	0.398
Lens-R	D$_{max}$ (Gy)	5.24±1.52	3.93±2.25	5.16±1.57	5.16±1.54	2.791	0.013	1.122	0.277	1.258	0.226	-0.218	0.830
Optic-L	D$_{max}$ (Gy)	40.77±26.36	20.99±21.59	38.49±24.82	38.66±24.96	3.728	0.002	3.503	0.003	3.638	0.002	-1.422	0.173
Optic-R	D$_{max}$ (Gy)	41.28±26.08	22.75±23.82	39.19±24.74	39.41±24.87	3.536	0.003	2.788	0.013	3.071	0.007	-1.110	0.282

t$_1$-t$_4$, P$_1$-P$_4$ represent the values of Plan$_1$ and Plan$_2$, Plan$_1$ and Plan$_{def}$, Plan$_1$ and Plan$_{rig}$, and Plan$_{def}$ and Plan$_{rig}$ as paired t-tests, respectively.

The parotid gland is sensitive to radiation, and the volume of the parotid gland changes significantly during radiotherapy for NPC. Fung *et al.* (15) transmitted the original plan dose distribution of NPC radiotherapy to the new CT to form a synthetic plan compared with the original plan dosimetry, the dose of the OARs increased, and the D$_{mean}$ of the left and right parotid glands significantly increased. In this study, we found that the volume of the parotid gland changed significantly compared with the initial location CT, and the left and right parotid glands were reduced by 36.83% and 37.47%, respectively. Compared with Plan$_1$, the V$_{30}$ of the left parotid gland in Plan$_2$ decreased by 36.15%; the D$_{mean}$, V$_{30}$ and D$_{50}$ of the right parotid gland decreased by 30.07%, 36.2% and 25%, respectively. The dose-volume evaluation of Plan$_{def}$ and Plan$_1$ showed that the D$_{mean}$ of the left and right parotid glands decreased by 1.98% and 2.3%, respectively, and the V$_{30}$ and D$_{50}$ of the left and right parotid glands were not statistically significant. These studies have shown that the parotid gland volume shrinks as the dose is absorbed during radiotherapy, and the proportion of shrinkage is not synchronized with the shrinkage of the tumor target volume. In this study, it was found that the dose-volume index of parotid glands in Plan$_1$ and Plan$_2$ was significantly different. The dose-volume index of Plan$_1$ and Plan$_2$ may

not accurately predict the radiation damage of parotid glands during radiotherapy. However, deformation accumulation is an objective method to eliminate the effect of volume shape change, and the difference in the dose-volume index between the Plan$_1$ and Plan$_{def}$ were less than 5%. Therefore, it can be considered that the use of the initial planned dose-volume index can accurately predict the radiation damage of the parotid gland during IMRT for NPC.

Compared with the initial simulated CT, repeated simulated CT was deformed to different degrees, and therefore, the dose distribution of the two plans cannot be accumulated directly. Image registration method is needed to deform and accumulate the dose. Janssens *et al.* (16) used the Demons algorithm based on the image grayscale and the Morphons algorithm based on the edge and line to achieve the deformation registration. In this study, deformation registration and rigid registration based on the B-spline algorithm were adopted. The DSC of the target volume and OARs in the deformation registration were larger than that in the rigid registration, especially with respect to the parotid glands (P<0.05), which shows that deformation registration was superior to rigid registration.

The volume changes in the brain stem, eyeballs, optic nerves, and lens during IMRT for NPC were very small.

Compared with Plan$_1$, Plan$_2$ showed a significant difference (P<0.05) in the dose index of these OARs, which was attributed to the shrinking of the GTV volume, and the variation in the dose-volume index in Plan$_{def}$ compared with Plan$_1$ were very small.

Conclusions

In summary, during IMRT for NPC, the volume of the tumor target volume and parotid gland were significantly reduced. However, there was no significant difference between the dose-volume index of the tumor target and OARs in the first planning and the dose-volume index accumulated by deformation registration. Therefore, the dose-volume index of the initial plan can be used to evaluate the curative effect of NPC patients in the whole radiotherapy process and to predict the radiation damage.

Acknowledgments

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2019.11.06). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective study was approved by the Institutional Review Board (IRB) and the Ethics Committee of the Shandong Cancer Hospital, and the number/ID of the approval 201806033. Individual informed consent was waived due to the retrospective nature of the study.

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