Received: 8 September 2021 | Revised: 26 September 2021 | Accepted: 18 October 2021

DOI: 10.1002/lio2.691

ORIGINAL RESEARCH

Laryngoscope Investigative Otolaryngology

Is it necessary for clinical tumor volume including neck muscles in target volume delineation of nasopharyngeal carcinoma?

Fei Chen MBBS[1] | Xiangquan Kong MD[2] | Haixia Wu MBBS[1] | Weining Fang MBBS[1] | Zhaodong Fei MD[1] | Zhupeng Wu MBBS[1] | Dan Zhao MBBS[1] | Liqin Ma MMed[1]

[1]Department of Radiation Oncology, Fujian Medical University Cancer Hospital, Fujian Cancer Hospital, Fuzhou, Fujian, China

[2]Department of Radiation Oncology, Xiamen Humanity Hospital, Fujian Medical University, Xiamen, Fujian, China

Correspondence
Liqin Ma, Department of Radiation Oncology, Fujian Cancer Hospital and Fujian Medical University Cancer Hospital, No. 420, Fuma Road, Fuzhou, Fujian 350014, People's Republic of China.
Email: maliqin3@126.com

Funding information
Fujian Province Natural Science Foundation, Grant/Award Number: 2020J011124

Abstract

Objectives: To calculate the shrinkage of the neck muscles and dosimetric changes and to clarify the necessity of covering part of the muscle in neck node region delineation for patients with nasopharyngeal carcinoma (NPC) treated with intensity-modulated radiotherapy.

Methods: In total, 44 patients with NPC were enrolled. Distances between the lateral border of the neck muscles and longitudinal midline were measured on every selected slice. This process was repeated three times, and the mean values of the three distances of planning computed tomography (CT) images and repeated CT images were adopted (labeled *d*1 and *d*2). The mean value of the differences between *d*1 and *d*2 was regarded as the medial shrinkage of the neck muscles. The initial clinical target volume of cervical lymph nodes (CTV-n) was shifted medially with the value of shrinkage, yielding a new CTV-n. Doses that covered 95% of the planning tumor volume (PTV) (D95), 99% of the PTV (D99), mean dose (Dmean), and maximum dose (Dmax) were used to calculate the dosimetric variation between the initial and new CTV-n. Comparisons were performed using the paired samples *t* test.

Results: The median *d*1 was 3.81 cm (range: 1.19-8.20 cm), and the median *d*2 was 3.68 cm (range: 0.94-9.59 cm), with a statistically significant difference ($P < .001$). The mean difference between *d*1 and *d*2 was 1.5 ± 3.1 mm (*SD*). The D95 and D99 of PTV of initial CTV-n decreased by 0.38% and 0.62% ($P < .001$ and $P < .001$, respectively).

Conclusion: Patients with NPC experienced medial shrinkage of the neck muscles by 1.5 mm, and the consequent dose variation was negligible. It is unnecessary to cover part of the muscles in the delineation of the CTV-n.

KEYWORDS
clinical target volume, intensity-modulated radiotherapy, nasopharyngeal carcinoma, neck muscles

Fei Chen, Xiangquan Kong, and Haixia Wu contributed equally.

1 | INTRODUCTION

Nasopharyngeal carcinoma (NPC) is one of the most common cancers with an unbalanced endemic distribution; more than 70% of new cases occur in East and Southeast Asia.[1] Intensity-modulated radiotherapy (IMRT) is the mainstay treatment modality for patients with NPC because it provides sharp dose gradients between the boundary of target volumes and vital normal tissues,[2-4] which maximizes both tumor coverage and sparing of organs at risk (OARs).[2,5] Vital structures are in close proximity to the tumor volumes in the head and neck region.[4] Small variables, including external daily setup variations and internal changes in the anatomy during the IMRT course, could greatly alter the actual dose delivery.[4] Previous studies have revealed that significant anatomic changes, such as weight loss, occurred in the course of IMRT,[6-10] which led to significant clinical consequences, including underdose of target volumes and overdose of normal tissues.

Adaptive radiotherapy refers to acquiring a new set of imaging during treatment to correct daily tumor and normal issue variations.[11,12] Several studies of adaptive radiotherapy for head and neck cancer based on mid-treatment computed tomography (CT) found that replanning improved locoregional control and quality of life[13,14] and normal tissue sparing.[15] However, Zhao et al. observed no difference in disease control and toxicity, whereas replans improved target coverage and normal tissue dose.[16] In summary, adaptive radiotherapy has shown promising outcomes in patients treated with IMRT for head and neck cancer.

The international guideline for the delineation of the clinical target volumes (CTVs) for NPC defined the intermediate-risk (prophylactic dose) nodal regions as CTVn2 and low-dose CTV as CTVn3.[17] When an involved lymph node abuts a muscle and/or shows clear radiological indication of muscular infiltration, this muscle near the node should be included in the CTV.[17] However, for patients without indication of muscular infiltration due to the shrinkage of nodal masses during IMRT, whether a medial displacement of cervical lymph node CTV delineation covering part of the muscles is necessary to ensure sufficient exposure of cervical lymph nodes to recover the dosimetric changes is unknown. However, none of the current guidelines specifically mention the extent of coverage of the medial cervical lymph node CTV muscles, and there are marked variations in practice among clinicians. We conducted a study to calculate the shrinkage of neck muscles and dosimetric changes and to clarify the necessity to cover part of muscles in cervical lymph node CTV delineation for patients with NPC treated with IMRT.

2 | MATERIALS AND METHODS

2.1 | Patients

From May 2017 to August 2019, a total of 44 NPC patients (median age: 47 years; range: 26-69 years) treated with platinum-based chemotherapy concurrent with IMRT were enrolled at our institution. Each patient had a repeated plain CT scan at end of radiotherapy. The data included age; sex; tumor, node, metastasis stages; and magnetic resonance imaging (MRI) and CT images. The retrospective analysis was approved by the ethics committee of the Fujian Cancer Hospital (K2021-074-01) and was conducted in accordance with the principles of the Declaration of Helsinki.

2.2 | Radiotherapy

Before radiotherapy, all patients were immobilized in the supine position with head-and-neck thermoplastic masks, and CT simulation was performed with serial 3-mm slices from the vertex to 2 cm below the clavicles. Pretreatment contrast-enhanced planning CT and T1- and plain T2-weighted MRI were performed for staging and target volume delineation. Plain CT scans were repeated for each patient at the end of the radiotherapy.

Target volume delineation and radiotherapy dose were implemented using an institutional treatment protocol. The gross tumor volume (GTV) represented visible primary nasopharyngeal tumor (GTV-P) and enlarged or suspicious lymph nodes (GTV-N) identified for each patient clinically and radiographically based on MRI, CT, and clinical information. The CTVs included the area of high-risk tumor invasion around the nasopharynx and lymphatic levels of the neck (CTV1), and CTV2 was designed for other potentially involved regions, including the nasopharyngeal cavity, maxillary sinus, pterygopalatine fossa, posterior ethmoid sinus, parapharyngeal space, skull base, anterior third of the clivus and cervical vertebra, inferior sphenoid sinus, and cavernous sinus. In our cohort, the muscles in the vicinity of clinical target volume of cervical lymph nodes (CTV-n) were not included in the radiotherapy plans of all patients. Planning tumor volumes (PTVs) based on CTV, CTV1, and CTV2 with a 3-mm margin were created to account for daily setup variations. The OARs include the brain stem, spinal cord, optic nerve, optic chiasm, temporal lobe, and others. Each of the patients received IMRT with a total dose of 70 Gy in 35 fractions at 2.0 Gy/fraction to the PTV of the GTV-P and PTV of the GTV-N, 60 Gy at 2.0 Gy/fraction to the PTV of the CTV1, and 54 Gy at 1.8 Gy/fraction to the PTV of the CTV-2.

2.3 | Medial shrinkage of neck muscles

For both CT images of pre-radiotherapy and post-radiotherapy, longitudinal midlines were made at the same anatomical level every three slices from the superior second cervical vertebra to the 34th slice (12 slices were selected in total); each longitudinal midline had two intersection points with anterior and posterior borders of the vertebral column. Distances perpendicular to the longitudinal midlines between the lateral border of the neck muscles and two intersection points as well as their midpoint were measured on every selected slice (Figure 1). This process was repeated three times to minimize the measurement errors for each patient. The mean values of the three distances of planning CT images and repeated CT images were adopted (labeled $d1$ and $d2$). The mean value of the differences between $d1$ and $d2$ in all patients was regarded as the medial shrinkage of the neck muscles.

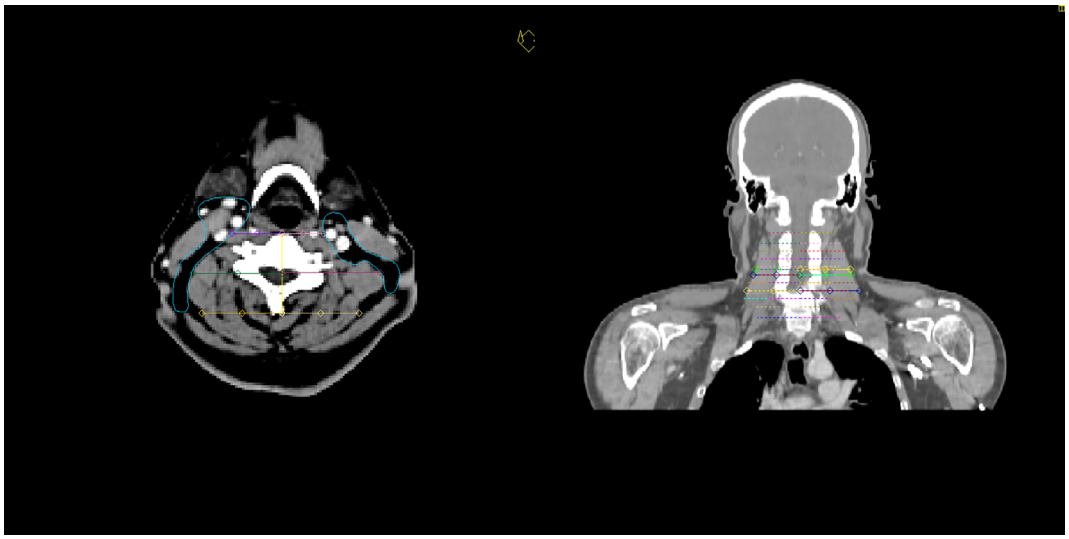

FIGURE 1 Example case of a 44-year-old man with T2N3M0 NPC. NPC, Nasopharyngeal carcinoma

2.4 | Dosimetric comparison in the CTV-n

In this study, the CTV-n was defined as the region covering the neck muscle space but not covering the neck muscles. Information about the initial CTV-n on pre-radiotherapy was collected from planning CT images. For each patient, the initial CTV-n was shifted medially with the mean value of the differences between *d*1 and *d*2, yielding a new CTV-n. The initial treatment plan was mapped to the new CTV-n with the same beam configuration. Dose-volume histograms (DVHs) of the initial and new CTV-n were calculated to evaluate the differences in the dose between them. The dosimetric parameters included the dose that covers 95% of the PTV (D95), dose that covers 99% of the PTV (D99), mean dose (Dmean), and maximum dose (Dmax).

2.5 | Statistical analyses

Comparisons between *d*1 and *d*2, as well as the dosimetric distribution of the initial and new CTV-n, were performed using the paired samples *t* test and then processed using SPSS version 26.0 software (SPSS Inc., Chicago, IL). Statistical significance was set at $P < .05$.

3 | RESULTS

3.1 | Patient characteristics

According to the eighth edition of the American Joint Committee on Cancer staging system, 1 patient had Stage I, 6 had Stage II, 25 had Stage III, and 12 had Stage IV NPC. From the entire cohort, 31 were men, and 13 were women. The specific characteristics of the patients were shown in Table 1.

3.2 | Medial shrinkage

The median *d*1 was 3.81 cm (range: 1.19-8.20 cm), and the median *d*2 was 3.68 cm (range: 0.94-9.59 cm), with a statistically significant

TABLE 1 Patient characteristics

Patient characteristic	n
Age (y)	Median 47 (range: 26-69)
Sex	
Male	31
Female	13
T category	
1	12
2	4
3	23
4	5
N category	
0	2
1	21
2	12
3	9
Stage group	
I	1
II	6
III	25
IVa	12
Cycles of CCT	
0	1
1	5
2	38

Abbreviation: CCT = Concurrent chemotherapy.

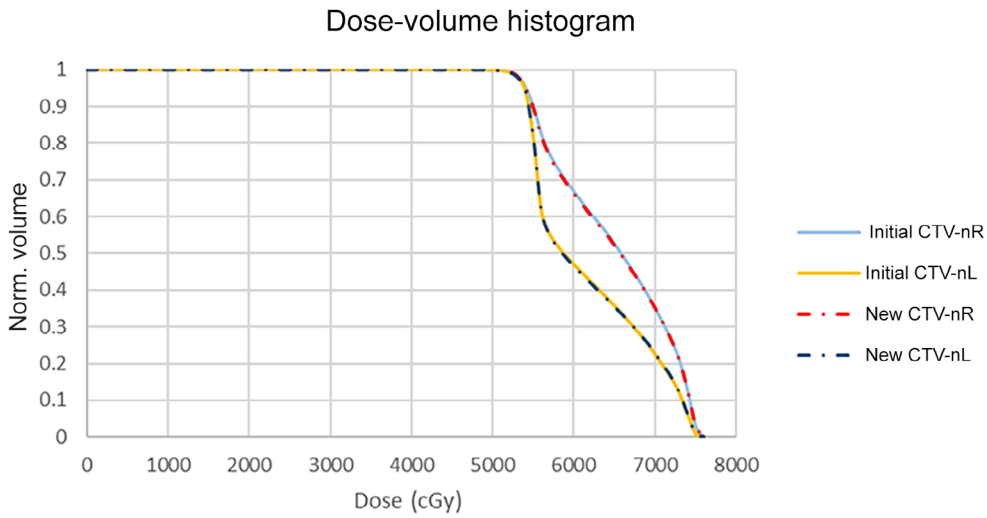

FIGURE 2 Dose-volume histogram of a 44-year-old man with T2N3M0 NPC. CTV-nL = Clinical target volume of left cervical lymph nodes; CTV-nR = clinical target volume of right cervical lymph nodes; NPC, nasopharyngeal carcinoma

	Initial CTV-n (mean ± *SD*)	New CTV-n (mean ± *SD*)	*P* value
D95 (Gy)	55.19 ± 1.42	54.98 ± 1.32	<.001
D99 (Gy)	52.88 ± 1.22	52.55 ± 1.16	<.001
Dmax (Gy)	75.38 ± 1.34	75.36 ± 1.38	.432
Dmean (Gy)	63.82 ± 2.38	63.72 ± 2.36	<.001

TABLE 2 The dosimetric comparisons in CTV-n

Abbreviations: CTV-n = Clinical target volume of cervical lymph nodes; D95 = dose to 95% of the volume; D99 = dose to 99% of the volume; Dmax = maximum dose; Dmean = mean dose.

difference ($P < .001$). The mean value of the difference between *d*1 and *d*2 was 1.5 mm, which demonstrates that a mean medial shrinkage of 1.5 mm occurred in the neck muscles during the IMRT course.

3.3 | Changes of dose distribution

For the PTV of the new CTV-n, both D95 and D99 decreased significantly compared with the initial value. D95 in the DVHs of the initial and new CTV-n are shown in Figure 2. The D95 and D99 of the PTV of the initial CTV-n were decreased by 0.38% and 0.62% ($P < .001$ and $P < .001$), respectively. The Dmean of the PTV of the initial CTV-n decreased by 0.15% ($P < .001$). Additionally, the Dmax of the PTV of the initial CTV-n decreased by 0.02%, without a statistically significant difference ($P = .432$). The absolute values of the dose variations are shown in Table 2.

4 | DISCUSSION

Previous studies have revealed that significant anatomic changes occur during IMRT in patients with head and neck cancer, including weight loss and shrinkage of the primary tumor and nodal mass.[5,6,8,10] Barker et al. found that the gross target volumes and parotid glands decreased in volume at a median rate of 1.7% to 1.8% and 0.6%, respectively, per day in the course of radiotherapy.[6] Furthermore, many studies have shown that anatomical changes may influence the dose distribution of target volumes and OARs. Ahn et al. and Hansen et al. studied the dosimetric effect of anatomic changes between planning CT and repeated CT scans and observed inadequate doses to target volumes.[8,18] In addition, an innovative study demonstrated that a medial shift of the parotid correlated highly with weight loss during radiotherapy.[6] This implies that medial displacements of target volumes and normal tissues occur as a result of weight loss and underdosage of target volumes could occur.

International guidelines for the delineation of the CTV for NPC have not yet provided a practical reference for appropriate contouring of CTV-n regarding whether it covers part of muscles in the vicinity of CTV-n or not. Consequently, there are marked variations in practice regarding the CTV-n delineation among different centers. In this study, a statistically significant difference was observed in the distances from the lateral border of the neck muscles to the longitudinal midlines between planning and repeated CT images, which indicated that patients in our cohort experienced significant anatomic shrinkage in the neck region. To further investigate the influence of medial shrinkage, a new CTV-n was generated with the initial CTV-n shifting medially (1.5 mm) and its DVHs were calculated. The study found that the dose-volume parameters (including D95, D99, and Dmean of the PTV of the initial CTV-n) were all significantly higher than those of the new CTV-n (all $P < .001$). However, the absolute values of the dose variation between the initial CTV-n and new CTV-n were negligible. Furthermore, individualized asymmetric planning target volumes of 2-5 mm are used to account for daily setup errors,[8] and 2-3 mm expansion from the CTV-n is generally applied in target volume delineation in clinical practice to cover daily positioning errors. By reason of the foregoing,

the medial shrinkage of the neck muscles by 1.5 mm will be included in the expansion from the CTV-n, which is reasonably considered insignificant during IMRT. In other words, it is unnecessary to cover part of the neck muscles in CTV-n delineation during IMRT.

There are some limitations to this study. The mean value of the difference between *d*1 and *d*2 was regarded as the medial shrinkage of the neck muscles, which was unrepresentative, especially for patients who experienced distinct weight loss. Second, this study was conducted in a single center with only 44 patients; thus, results regarding medial shrinkage need to be validated by more centers for generalizability. In addition, manual errors existed even though the measurements were repeated thrice. As a retrospective cohort study, the potential selection bias cannot be ignored. In summary, the results of medial shrinkage (1.5 mm) and consequent dosimetric variations during IMRT require a larger cohort and further research to confirm.

5 | CONCLUSIONS

In our cohort, patients with NPC experienced medial shrinkage by 1.5 mm of the neck muscles. Medial shrinkage was included in the expansion from CTV-n, and the consequent dosimetric variations were considered negligible. It is unnecessary to cover part of the neck muscles in CTV-n delineation during IMRT, which requires a larger cohort and further research to confirm.

CONFLICT OF INTEREST

The authors declare no conflicts of interest in this work.

AUTHOR CONTRIBUTIONS

Liqin Ma: Study design; clinical data analysis; writing – original draft; writing – editing. **Fei Chen:** Study design; clinical data analysis; writing – original draft; writing – review and editing; data collection. **Zhaodong Fei:** Study design; clinical data analysis; writing – original draft; writing – review and editing. **Haixia Wu:** Data collection; writing – editing. **Xiangquan Kong:** Clinical data analysis; writing – review; writing – editing. **Weining Fang:** Writing – editing. **Zhupeng Wu:** Writing – editing. **Dan Zhao:** Writing – editing.

ETHICS STATEMENT

This study was approved by the ethics committee of Fujian Medical University Cancer Hospital, Fuzhou, China (K2021-074-01).

ORCID

Haixia Wu https://orcid.org/0000-0003-2298-3039

BIBLIOGRAPHY

1. Chen Y-P, Chan ATC, Le Q-T, Blanchard P, Sun Y, Ma J. Nasopharyngeal carcinoma. *The Lancet*. 2019;394(10192):64-80.
2. Yao X, Gong G, Zuo G, Ren J, Su M, Yin Y. Study of the dose-volume parameters variation in tumor target volumes and organs at risk during nasopharyngeal carcinoma radiotherapy applying deformation registration. *Transl Cancer Res*. 2019;8(8):2886-2892.
3. Chen C, Fei Z, Chen L, Bai P, Lin X, Pan J. Will weight loss cause significant dosimetric changes of target volumes and organs at risk in nasopharyngeal carcinoma treated with intensity-modulated radiation therapy? *Med Dosim*. 2014;39(1):34-37.
4. Bhide SA, Davies M, Burke K, et al. Weekly volume and dosimetric changes during chemoradiotherapy with intensity-modulated radiation therapy for head and neck cancer: a prospective observational study. *Int J Radiat Oncol Biol Phys*. 2010;76(5):1360-1368.
5. Wang W, Yang H, Hu W, et al. Clinical study of the necessity of replanning before the 25th fraction during the course of intensity-modulated radiotherapy for patients with nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys*. 2010;77(2):617-621.
6. Barker JL Jr, Garden AS, Ang KK, et al. Quantification of volumetric and geometric changes occurring during fractionated radiotherapy for head-and-neck cancer using an integrated CT/linear accelerator system. *Int J Radiat Oncol Biol Phys*. 2004;59(4):960-970.
7. Sobel S, Rubin P, Keller B, Poulter C. Tumor persistence as a predictor outcome after radiation therapy head and neck cancers. *Inl J Rodiation Uncology Biol Phys*. 1976;1:873-880.
8. Hansen EK, Bucci MK, Quivey JM, Weinberg V, Xia P. Repeat CT imaging and replanning during the course of IMRT for head-and-neck cancer. *Int J Radiat Oncol Biol Phys*. 2006;64(2):355-362.
9. Han C, Chen YJ, Liu A, Schultheiss TE, Wong JY. Actual dose variation of parotid glands and spinal cord for nasopharyngeal cancer patients during radiotherapy. *Int J Radiat Oncol Biol Phys*. 2008;70(4):1256-1262.
10. Thomas Barkley H Jr, Fletcher GH. The significance of residual disease after external irradiation of squamous-cell carcinoma of the oropharynx. *Radiology*. 1977;124:493-495.
11. Gensheimer MF, Le QT. Adaptive radiotherapy for head and neck cancer: are we ready to put it into routine clinical practice? *Oral Oncol*. 2018;86:19-24.
12. Schwartz DL, Garden AS, Shah SJ, et al. Adaptive radiotherapy for head and neck cancer—Dosimetric results from a prospective clinical trial. *Radiother Oncol*. 2013;106(1):80-84.
13. Yang H, Hu W, Wang W, Chen P, Ding W, Luo W. Replanning during intensity modulated radiation therapy improved quality of life in patients with nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys*. 2013;85(1):e47-e54.
14. Chen AM, Daly ME, Cui J, Mathai M, Benedict S, Purdy JA. Clinical outcomes among patients with head and neck cancer treated by intensity-modulated radiotherapy with and without adaptive replanning. *Head Neck*. 2014;36(11):1541-1546.
15. Schwartz DL, Garden AS, Thomas J, et al. Adaptive radiotherapy for head-and-neck cancer: initial clinical outcomes from a prospective trial. *Int J Radiat Oncol Biol Phys*. 2012;83(3):986-993.
16. Zhao L, Wan Q, Zhou Y, Deng X, Xie C, Wu S. The role of replanning in fractionated intensity modulated radiotherapy for nasopharyngeal carcinoma. *Radiother Oncol*. 2011;98(1):23-27.
17. Lee AW, Ng WT, Pan JJ, et al. International guideline for the delineation of the clinical target volumes (CTV) for nasopharyngeal carcinoma. *Radiother Oncol*. 2018;126(1):25-36.
18. Ahn PH, Chen CC, Ahn AI, et al. Adaptive planning in intensity-modulated radiation therapy for head and neck cancers: single-institution experience and clinical implications. *Int J Radiat Oncol Biol Phys*. 2011;80(3):677-685.

How to cite this article: Chen F, Kong X, Wu H, et al. Is it necessary for clinical tumor volume including neck muscles in target volume delineation of nasopharyngeal carcinoma? *Laryngoscope Investigative Otolaryngology*. 2021;6(6):1353-1357. doi:10.1002/lio2.691