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ORIGINAL RESEARCH

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Effect of relevant factors on radiation-induced nasopharyngeal ulcer in patients with primary nasopharyngeal carcinoma treated with intensity-modulated radiation therapy

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Abstract

Objective: To analyze the correlation between relevant factors and radiation-induced nasopharyngeal ulcer (RINU) in primary nasopharyngeal carcinoma (NPC) treated with intensity-modulated radiation therapy (IMRT).

Methods: Clinical data were collected for 599 patients with newly diagnosed NPC who had completed IMRT. The entire cohort was randomly divided into two subgroups. The relationship between RINU and IMRT dose-volume were statistically analyzed with ROC curves and the Chi-square test. Nutritional status during and after treatment was compared between patients with vs without RINU.

Results: The results obtained showed that dose-volume had no effect on the incidence of RINU ($P > .05$). Nutrition-related parameters differed significantly between patients with vs without RINU ($P < .05$).

Conclusion: The results obtained show that the incidence of RINU is not related to IMRT dose-volume in the treatment of primary NPC. The incidence of RINU was found to be related to nutritional status during and after radiation therapy.

Level of Evidence: 2a

KEYWORDS

dose-volume, intensity-modulated radiation therapy, nasopharyngeal carcinoma, nutrition-related parameters, radiation-induced nasopharyngeal ulcer

1 | INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a common malignant tumor of the head-and-neck region among populations in Southeast Asia and southern China.[1,2] Radiation therapy is currently the gold-standard treatment for NPC because of the ease with which NPC invades surrounding tissues, as well as the tumor's sensitivity to radiation.[3,4] In recent years, intensity-modulated radiation therapy (IMRT) has been used with increasing frequency. IMRT allows physicians to target the tumor region, which decreases the dose of radiation administered and thus spares adjacent organs.[4-7]

However, use of IMRT to treat NPC is associated with complications, including hematological and nonhematological toxicity. Nonhematological toxicity may result in radiation dermatitis, radiation mucositis, gastrointestinal issues, and/or nasopharyngeal ulcer. Of these complications, nasopharyngeal ulcer carries the most risk for mortality. Ulcers caused by exposure of tissue surrounding the nasopharynx (eg, mucosa, musculus longus capitis, parapharyngeal tissues,

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skull base) to radiation are known as radiation-induced nasopharyngeal ulcers (RINU). RINU are most dangerous when they involve the carotid sheath—particularly when the internal carotid artery is eroded.[8-10] Although previous studies have posited that RINU is related to the local administration of high doses of radiation during tumor treatment,[4] these studies focused on nasopharyngeal ulcers induced by second-course or multicourse radiation therapy for NPC recurrence. Few studies published to date have investigated RINU in patients with primary NPC.[11,12]

NPC is a dose-dependent tumor, and studies have shown that local failure commonly follows administration of the prescription dose-volume of radiation therapy.[13-15] The ability to define a subvolume of gross tumor volume prior to administering a boost dose of radiation therapy may improve local control and survival rates.

This study was designed to determine whether there exists any correlation between the incidence of RINU and the volume of high-dose radiation administered during IMRT for primary NPC. The role of nutritional indicators in patients with RINU is also investigated.

2 | MATERIALS AND METHODS

2.1 | Patient characteristics

During the period from January 2014 to March 2016, 599 consecutive patients who presented to our cancer center for treatment were included in the study. For all patients enrolled in the study, the diagnosis of NPC was confirmed by pathology. All patients had completed the entire course of IMRT (Table 1). Patients with metastasis were excluded from the study. Any other medical comorbidity was evaluated and controlled.

The pretreatment evaluation consisted of a detailed medical history, physical examination, dental evaluation, routine blood tests, biochemical tests, EB viral DNA analysis, nasopharyngoscopy, magnetic resonance imaging (MRI) of the head and neck, chest computed tomography (CT), ultrasonography of the abdomen, and bone emission computed tomography (ECT). In some cases, positron emission tomography-computed tomography (PET-CT) was performed to confirm the absence of distant metastasis.

TABLE 1 Patients' characteristics

Characteristic	No. of patients (%)
Age (years)	
Median	45
Range	11-72
Gender	
Male	445 (74.3%)
Female	154 (25.7%)
TNM stage	
T1/T2/T3/T4	41/149/221/188 (6.8/24.9/36.9/31.4%)
N0/N1/N2/N3	204/267/96/32 (34.1/44.5/16.1/5.3%)
I/II/III/IV	22/132/244/201 (3.7/22.0/40.7/33.6%)

2.2 | Target delineation

Target delineation was performed in accordance with the protocol in place at our institution.[5] Gross disease as determined by imaging, clinical, and endoscopic findings was evaluated as primary gross tumor volume (GTV-P) or gross tumor volume in involved lymph nodes (GTV-N). Tissues felt to harbor the risk of microscopic disease were evaluated as clinical target volume (CTV-1, CTV-2). CTV-1 was defined as the high-risk region that included GTV as well as a margin of 5-10 mm, including the nasopharyngeal mucosa (submucosal volume 5 mm). CTV-2 was defined as 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. Clinical target volume of the neck nodal regions (CTV-N) included disease at levels II-V, as recommended by the Radiation Therapy Oncology Group (RTOG) delineation consensus for head and neck malignancies. The planning target volume was determined by summing these volumes, each with an additional 3-mm margin. This measure is designed to compensate for variability in the clinical setup. The OAR included the brainstem, spinal cord, optic nerve, optic chiasm, temporal lobe, crystal, as well as the parotid, pituitary, and mandibular glands. A total dose of 6970-7000 cGy/31-35 fractions was administered, at 200-225 cGy/fraction, to the planning target volumes obtained for GTV-P and GTV-N. A total dose of 5950-6200 cGy/31-35 fractions at 170-200 cGy/fraction was administered to the planning target volume for CTV-1. A total dose of 5270-5600 cGy/31-35 fractions at 160-180 cGy/fraction was administered to the planning target volume for CTV-2 and CTV-N. The OAR dose was limited as proposed by RTOG.

2.3 | Treatment plan

Images of the targeted tumor area and OAR were transmitted to the pinnacle system for evaluation. The criteria for determining the prescribed dose were as follows: PTV volume receiving ≥110% prescription dose: < 20%; PTV volume receiving ≥120% prescription dose: < 5%; PTV volume receiving <93% prescription dose: < 1%. No more than 110% of the prescribed dose may be administered to areas beyond the PTV. OAR dose was evaluated according to RTOG criteria.

2.4 | Chemotherapy

Patients with T1-2N0 disease received radiation therapy only. Chemotherapy, (including neoadjuvant chemotherapy, concurrent chemotherapy) was included in the treatment plan for patients with stage T3-4 or N1-3 disease. Patients at stage T1-4N1-3M0 underwent two concurrent cycles of platinum-based chemotherapy. Patients with stage III-IV disease underwent 2-4 cycles of neoadjuvant chemotherapy prior to radiation therapy.

The neoadjuvant chemotherapy regimen consisted of TP (paclitaxol plus cisplatin) and GP (gemcitabine plus cisplatin). Ultimately, 72.5% (434/599) of patients underwent 1-3 cycles of neoadjuvant chemotherapy, and 59.9% (359/599) of patients underwent 1-2 cycles of concurrent chemotherapy.

2.5 | Evaluation during treatment

During the period when they were receiving radiation therapy, patients underwent blood and biochemical testing, weight measurement (at least once a week), and nasopharyngoscopy (at least once every 2 weeks). Upon completion of radiation therapy, patients also underwent MRI for visualization of the nasopharynx and adjacent structure.

2.6 | Follow-up after treatment

Within 3 months after radiation therapy, patients were followed with blood and biochemical testing, weight measurement (at least twice a week), and nasopharyngoscopy (at least every 6 weeks). MRI of the head and neck was performed within 3 months after radiation therapy. Regular follow-up was conducted every 3 months during the first 2 years after treatment. The end-points of observation included ulcer, death, recurrence and/or metastasis requiring re-treatment.

2.7 | Diagnostic criteria for nasopharyngeal ulcer

Ulceration of the nasopharynx and surrounding tissues (eg, mucous membrane, cephalus longus, parapharyngeal tissue, skull base) was visualized by nasopharyngoscopy and/or MRI. MRI and other imaging examinations were diagnosed by two independent radiographers.[4] Figure 1 depicts a typical case of RINU.

2.8 | Statistical analysis

All statistical analyses were performed with SPSS 13.0 statistical software (SPSS Inc, Chicago, IL, USA). Findings with $P < .05$ were considered statistically significant. An ROC curve was used to determine the best cut-off point for clinical application. Baseline characteristics were compared within groups using the Chi-square test or Fisher's exact test for categorical variables and the *t*-test for continuous variables.

Li et al. previously reported that a D3cc (dose to 3 mL of the nasopharynx) of 7367 cGy should be considered as the upper limit for dose tolerance of the nasopharynx. To avoid the development of RINU among NPC patients, this limit should be considered during optimization of the IMRT treatment plan.[4] In our study, the tumor volume exposed to 7400 cGy was selected for investigation of the relationship between radiation dose and risk for nasopharyngeal ulcer. A total of 299 patients (the first subgroup) were randomly selected to provide the derivation data. Validation data were obtained from

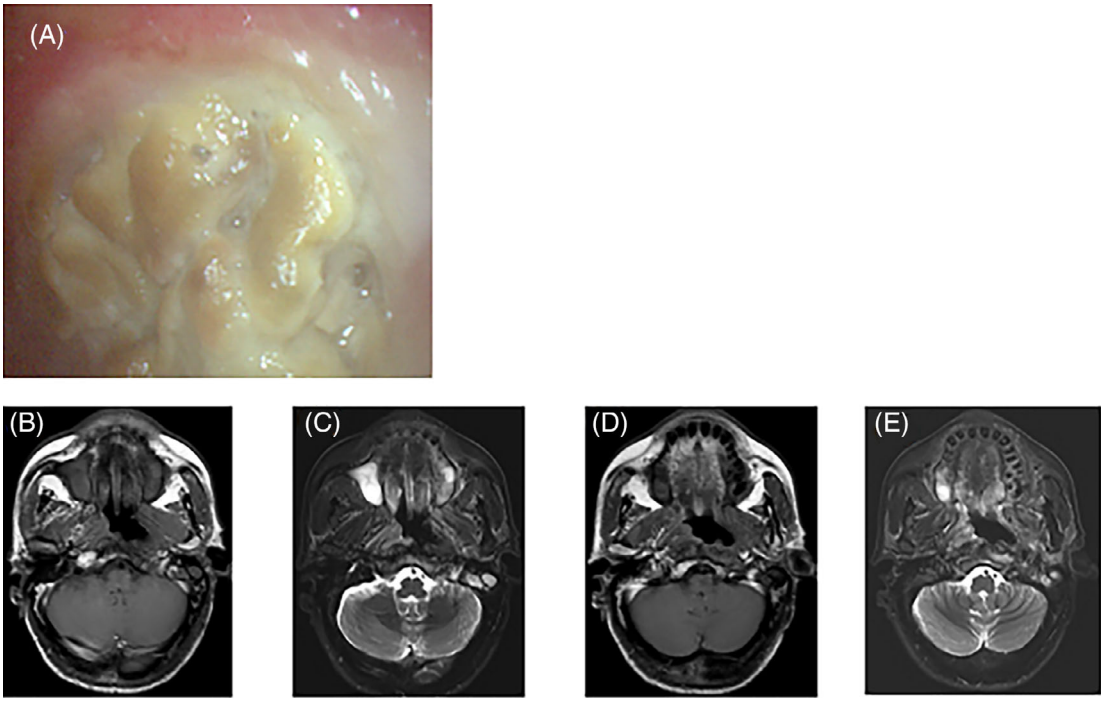

FIGURE 1 MRI for one patient with T4N1M0. The patient had undergone 2 cycles of neoadjuvant chemotherapy and 2 cycles of concurrent chemotherapy. A, RINU were observed by nasopharyngoscopy. B–E, Transverse contrast T1-weighted and T2-weighted MRI revealed an irregular nasopharyngeal cavity and destruction of the soft tissue, with the formation of large ulcer on the left posterior wall of the nasopharynx

evaluations of the remaining 300 patients (the second subgroup). The cut-off point was determined by analyzing ROC curves derived from the derivation data. These data provide criteria for choosing the "optimal" threshold value, defined as the value yielding the highest possible value for "sensitivity + specificity − 1".[16] The validation data were then divided into two groups, according to the ideal cut-off point for the tumor volume exposed to 7400 cGy. A Chi-square test was used to test the differences in the incidence of RINU among groups of patients exposed to various dose-volumes of radiation.

The "high dose-volume ratio" is the ratio of tumor volume exposed to ≥7400 cGy as a fraction of gross tumor volume. The threshold for high dose-volume ratio was determined by ROC curves from the derivation data of 299 patients. A Chi-square test was used to test for the significance of differences in the incidence of RINU among patients with various dose-volume ratios, as determined from the derivation data for the remaining 300 patients. Figure 2 illustrates the above process in a simplified sequence flow diagram.

Depending on the residual tumor volume as visualized with radiography, some patients received boost doses. Boost started within 1 week after the first course radiation treatment. Partial cases were verified by pathology. A Chi-square test was used to determine the significance of differences in the incidence of RINU between patients who had received boost doses, compared with patients who had not.

Nutrition indicators including hemoglobin and body mass index (BMI) were analyzed. Deterioration in nutritional status during treatment and recovery after treatment were compared between patients with vs without RINU. Multivariate analysis was used to identify factors associated with RINU.

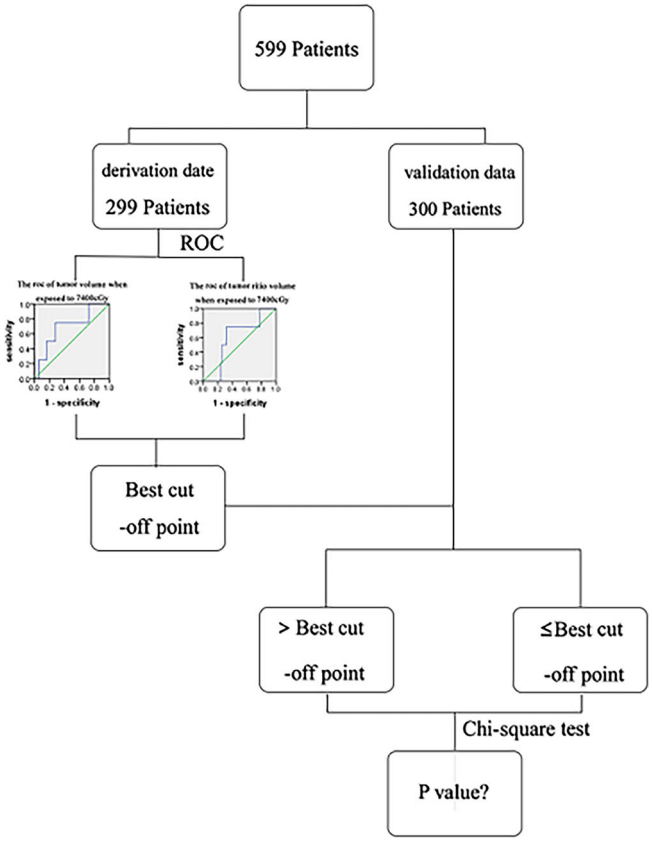

FIGURE 2 Flow diagram of algorithm

3 | RESULTS

The median follow-up time was 24 months (range, 9-32 months). At the end of the follow-up period, 56 patients had died, 43 patients had developed local and/or regional lymph node recurrence, and 62 patients had distant metastasis. During the follow-up period, nine patients developed nasopharyngeal ulcers. One of these cases occurred at the end of radiation therapy; the other eight cases occurred 4-7 months after radiation therapy. The characteristics of nine patients with RINU are shown in Table 2.

A derivation group comprising 299 patients was evaluated with ROC curves. "The tumor volume exposed to 7400 cGy" was used as the "test variable," and "whether the patients developed RINU" was used as the result variable. Use of this approach ultimately yielded a cut-off point of 23.55 cm^3. The validation data from 300 patients were then divided into two groups: D23.55 cc (dose to 23.55 mL of the nasopharynx) > 7400 cGy and D23.55 cc ≤7400 cGy. A Chi-square test was used to test for differences in the incidence of RINU between groups. There was no statistically significant difference between groups (2/223 vs 3/77, P = .209).

Using the derivation data for the group of 299 patients and the randomization categories described above, the ROC curves were used to determine the best cut-off point for the ratio of tumor volume exposed to 7400 cGy to GTV. The optimal cut-off point was 26.82%. The validation data from 300 patients were then divided into two groups (D26.82% > 7400 cGy and D26.82% ≤ 7400 cGy). A Chi-square test was performed to test for differences in the incidence of RINU between groups. No obvious statistical difference was identified (2/204 vs 3/96, P = .384).

Fifty-eight of 599 cases received boost doses because of residual lesions after radiography. Partial cases were verified by pathological analysis. Three cases were classified as T1, 12 as T2, 17 as T3, and 22 as T4. The boost dose was 400-450 cGy/2f for 22 cases, 600-675 cGy/3f for 33 cases, 900 cGy/4f for one case, and 1000 cGy/5f for two cases. Mean residual GTV was 26.58 ± 25.64 cm^3 (range, 2.84-105.4 cm^3); mean primary GTV was 98.51 ± 54.27 cm^3 (range, 17.09-246.32 cm^3). The mean ratio of residual GTV to target volume was 16.43 ± 2% (range, 2.99-97.57%). Two cases developed RINU (2/58). Both of these patients had stage-T4 disease, and both received the same boost dose of 600 cGy/3 f. Residual GTV was 12.22 (13.92% pre-GTV) in one case and 55.6 cm^3 (43.53% pre-GTV) in the other. The Chi-square test was used to compare the incidence of RINU in 58 patients who received boost doses (2/58) and in 541 patients who did not receive boost doses (7/541). The results showed that there was no significant difference between these groups (2/58 vs 7/541, P = .225). In addition, there were seven cases who developed ulcer in 188 patients with T4, therefore, we compared the incidence of RINU in patients with T4 (7/188) and with not T4 (2/411) by the Chi-square test and the results showed that there was significant difference between the two groups (7/188 vs 2/411, P = .005).

TABLE 2 The characteristics of nine patients with RINU

No	Sex	Stage	Prescription dose(cGy)	Boost Dose (cGy)	The time occurred the ulcer	Pre-BMI	Pre-Hgb	Min-BMI	Min-Hgb	BMI (3 months after RT)	Hgb (3 months after RT)
1	F	T4N1	6996/33f	0	at the end of RT	26.0	144	23.1	80	23.1	111
2	M	T4N2	6996/33f	0	6 months after RT	24.9	154	23.1	110	25.6	138
3	M	T4N1	6996/33f	0	5 months after RT	22.0	133	20.6	100	17.3	120
4	M	T4N2	6970/34f	0	4 months after RT	21.7	155	19.8	103	19.8	114
5	M	T4N2	7000/35f	600/3f	5 months after RT	24.3	147	23.8	94	19.8	110
6	M	T4N2	7000/35f	600/3f	4 months after RT	21.5	147	19.8	84	18.8	84
7	M	T3N0	6996/33f	0	6 months after RT	18.5	135	18.1	105	15.8	108
8	M	T2N2	6975/31f	0	4 months after RT	21.3	151	20.2	103	18.8	117
9	M	T4N2	6996/33f	0	7 months after RT	25.1	165	24.7	137	23.4	140

Abbreviations: Min-BMI/Hgb, the minimum of BMI/Hgb during treatment; BMI, body mass index; Hgb, hemoglobin.

Nutritional indicators including hemoglobin and BMI were analyzed. The mean serum concentration of hemoglobin was 148 ± 9.4 g/L (range, 133-165 g/L) and mean BMI was 22.81 ± 2.27 (range, 18.52-26.03) among nine patients with RINU before treatment. The mean serum concentration of hemoglobin and mean BMI was 145 ± 12.52 g/L (range 129-174 g/L) and 22.44 ± 2.84 (range, 15.01-29.02) for 590 patients without RINU before treatment, respectively. There was no significant difference between groups (P = .412; P = .667). During treatment, most patients presented with anemia and weight loss because of associated complications. An independent-samples t-test was performed to determine the significance of between-group differences in the nutritional indicators studied. Hemoglobin level and BMI decreased even more in patients with RINU than in patients without RINU (−46.1 ± 12.71 g/L vs −27.9 ± 13.49 g/L, P < .001; −1.68 ± 0.51 vs −0.95 ± 0.72, P = .002). Three months after treatment, hemoglobin and BMI were measured again. The extent of recovery in patients with RINU was far more limited than the extent of recovery in patients without RINU (−32.1 ± 14.00 g/L vs −6.1 ± 10.00 g/L, P < .001; −2.55 ± 1.52 vs −0.88 ± 0.97, P < .001).

Multivariate analysis was performed to identify significant relationships among the following factors: age, sex, T-stage, N-stage, chemotherapy, tumor volume exposed to 7400 cGy, ratio of tumor volume exposed to 7400 cGy to GTV, decreases in levels of hemoglobin and BMI during treatment, and the extent of recovery of hemoglobin levels and BMI 3 months after treatment. The major independent prognostic factors were the recovery of hemoglobin [P = .001; OR = 61.696 (95%CI: 5.663-672.193)] and BMI [P = .006; OR = 17.680 (95%CI: 2.244-139.315)] 3 months after treatment for RINU.

4 | DISCUSSION

Nasopharyngeal ulcer is a serious complication of radiation therapy that affects some patients with NPC.[4,8-10] Some scholars believe that the formation of RINU may be caused by the rapid withdrawal of nasopharyngeal tumors that had previously invaded surrounding normal tissue after patients have undergone radiation therapy and the failure of normal tissue to repair the area affected by the tumor.[17] NPC is a dose-dependent tumor. Therefore, the survival of affected patients may be significantly enhanced by increasing the radiation dose administered to the target tumor volume. However, the presence of RINU limits the extent to which the dose of radiation may be increased. Willner et al.[18] evaluated the correlation between tumor volume and the total dose necessary to obtain local control. The results revealed a steep dose-response relationship. Hendrickson et al.[19] suggested that a higher dose to subvolumes significantly increased the probability of tumor control for head and neck cancer. We therefore sought to define a functional subregion of GTV for the administration of boost doses of radiation therapy. A retrospective analysis of the correlation between the volume of high-dose radiation therapy and the incidence of RINU after primary IMRT for NPC is therefore of practical significance.

According to previous reports, the risk of nasopharyngeal ulcer is 1-1.5% in patients who undergo an initial round of IMRT[15,20] and 15.7-31.5% in patients with local recurrences who are re-irradiated with IMRT.[11,12] The accumulative radiation dose was significantly associated with RINU in patients with recurrent NPC who had been treated with IMRT. Notably, RINU occurs at remarkably low rates in patients with primary diagnosed NPC. The question of whether the dose of radiation dose is the key factor affecting this finding remains to be determined. Our results showed that the incidence of RINU was 1.5% (9/599), which is in agreement with previous studies.

One previous study demonstrated that naive NPC patients treated with D3cc > 7367 cGy were more likely to develop nasopharyngeal ulcer after receiving IMRT.[4] We therefore sought to determine whether there was a relationship between radiation dose-tumor volume and risk of RINU. Firstly, we used the ROC curve to identify D23.55 cc = 7400 cGy as the cut-off point for assessing risk of RINU. The results showed no significant difference in risk for RINU between the D23.55 cc > 7400 cGy group and the D23.55 cc ≤7400 cGy group (P = .209). Using the same approach, we evaluated the relationship between risk for RINU and the ratio of tumor volume exposed to 7400 cGy to GTV. D26.82% = 7400 cGy was identified as the optimal cut-off point.

Radiation of this dose-volume did not increase risk for RINU among patients with a high exposure to a high dose of radiation (P = .384).

Yan et al.[21] studied the incidence of nasopharyngeal necrosis in 53 patients with NPC after radiation therapy. In most patients, necrosis was found in regions T3-4. The authors suggest that the intimate correlation between T-staging and risk for ulcer may reflect the difference in the dose prescribed for T3-4 (7040 cGy) vs T1-2 (6600 cGy). High-dose radiation may increase risk for ulcer. In our study, the Chi-square test between the incidence of RINU in patients with T4 and with not T4 showed that there was significant difference between the two groups (P = .005). The results supported the point that T-staging is associated with the risk for ulcer. However, in our study, the prescribed dose for T3-4 was 6970-7000 cGy; the prescribed dose for T1-2 was 6975 cGy; there was no difference between T-stages. Among 58 patients with residual lesions after radiography who were given boost doses of 400-1000 cGy after completion of the prescribed dose, only two developed ulcer. Statistical analysis revealed no rise in risk for ulcer with the administration of high-dose radiation (P = .225). When these findings are viewed in the context of results reported by others, dose does not appear to be a significant risk factor for ulcer in NPC patients who have undergone an initial round of IMRT. Therefore, we think that patients with T4 have higher risk for ulcer may because the local advanced tumor has a wider range of invasion and a wider range of receiving radiotherapy. Simultaneously, the relationship between the incidence of RINU and T-staging was not observed on multivariable analyses, we considered that this may be attributable to a certain collinearity between independent variables, during use of multiple independent variables for regression and that some independent variables with collinearity will be automatically eliminated. In another word, the results of our study implied that defining a subregion of GTV for the administration of a boost dose of radiation therapy may improve clinical outcomes without any associated increase in risk for RINU.

Yan et al.[21] noted that most patients with nasopharyngeal ulcer have anemia and suggested that malnutrition may play an important role in the incidence of nasopharyngeal ulcer. Our study evaluated the role of nutritional indicators, including hemoglobin and BMI, in the incidence of RINU. Hemoglobin levels and BMI have decreased more among patients with RINU than among patients without RINU (-46.1 ± 12.71 vs -27.9 ± 13.49, $P < .001$; -1.68 ± 0.51 vs -0.95 ± 0.72, $P = .002$). After 3 months of therapy, these parameters remained further from baseline levels in patients with RINU, compared with patients without RINU (-32.1 ± 14.00 vs -6.1 ± 10.00, $P < .001$; -2.55 ± 1.52 vs -0.88 ± 0.97, $P < .001$). We therefore speculated that nutritional supports are vital to prevent RINU. Malnutrition may result in hypoxia, necrosis, and delayed tissue healing, which can facilitate the development of RINU. The pain caused by RINU and other common treatment-related problems (eg, mucositis, nausea, vomiting, xerostomia) may also result in compromised food intake, leading to unintentional weight loss or even malnutrition during treatment.[22-25] This can cause a vicious circle from ulcer accompanied by pain and infection, to inadequate nutrient intake, to delayed ulcer healing. Malnutrition and insufficient oxygen may lead to tissue breakdown and development of a chronic, nonhealing wound.[26] Enhancing nutritional support for patients with a primary diagnosis of IMRT may therefore help to decrease the incidence of RINU.

5 | CONCLUSION

The study demonstrated that the incidence of RINU is not related primarily to regular doses of radiation but is associated with nutritional status during radiation therapy and recovery after radiation therapy. Enhancing nutritional support for newly diagnosed patients treated with IMRT may therefore help to decrease the incidence of RINU. Therefore, it is suggested that patients should pay more attention to nasopharyngeal care and nutritional support during and after radiation therapy.

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CONFLICT OF INTEREST

The authors have no relevant conflicts of interest to disclose.

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BIBLIOGRAPHY

1. Wei KR, Zheng RS, Zhang SW, Liang ZH, Ou ZX, Chen WQ. Nasopharyngeal carcinoma incidence and mortality in China in 2010. *Chin J Cancer*. 2014;33(8):381-387.
2. Cao SM, Xu YJ, Lin GZ, et al. Estimation of cancer burden in Guangdong Province. *Chin J Cancer*. 2015;34(12):594-601.
3. Wei WI, Sham JS, Ep H, et al. Nasopharyngeal carcinoma. *Lancet*. 2016;387(10022):1012-1024.
4. Li Y, Xu T, Qian W, Lu X, Hu C. Radiation-induced nasopharyngeal ulcers after intensity modulated radiotherapy in primary nasopharyngeal carcinoma patients: a dose-volume-outcome analysis. *Oral Oncol*. 2018;84:1-6.
5. Chen C, Fei Z, Pan J, Bai P, Chen L. Significance of primary tumor volume and T-stage on prognosis in nasopharyngeal carcinoma treated with intensity-modulated radiation therapy. *Jpn J Clin Oncol*. 2011;41(4):537-542.
6. Lee AW, Ng WT, Chan LL, et al. Evolution of treatment for nasopharyngeal cancer-success and setback in the intensity-modulated radiotherapy era. *Radiother Oncol*. 2014;110(3):377-384.
7. Huang TL, Chien CY, Tsai WL, et al. Long-term late toxicities and quality of life for survivors of nasopharyngeal carcinoma treated with intensity-modulated radiotherapy versus non-intensity-modulated radiotherapy. *Head Neck*. 2016;38(Suppl 1):E1026-E1032.
8. Chen MY, Mai HQ, Sun R, et al. Clinical findings and imaging features of 67 nasopharyngeal carcinoma patients with postradiation nasopharyngeal necrosis. *Chin J Cancer*. 2013;32(10):533-538.
9. Auyeung KM, Lui WM, Chow LC, Chan FL. Massive epistaxis related to petrous carotid artery pseudoaneurysm after radiation therapy: emergency treatment with covered stent in two cases. *AJNR Am J Neuroradiol*. 2003;24(7):1449-1452.

10. Tian YM, Guan Y, Xiao WW, et al. Long-term survival and late complications in intensity-modulated radiotherapy of locally recurrent T1 to T2 nasopharyngeal carcinoma. *Head Neck*. 2016;38(2):225-231.
11. Qiu S, Lin S, Tham IW, et al. Intensity-modulated radiation therapy in the salvage of locally recurrent nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys*. 2012;83(2):676-683.
12. Chen HY, Ma XM, Ye M, Hou YL, Xie HY, Bai YR. Effectiveness and toxicities of intensity-modulated radiotherapy for patients with locally recurrent nasopharyngeal carcinoma. *PLoS One*. 2013;8(9):e73918.
13. Li JX, Huang SM, Jiang XH, et al. Local failure patterns for patients with nasopharyngeal carcinoma after intensity-modulated radiotherapy. *Radiat Oncol*. 2014;9:87.
14. Kong F, Ying H, Du C, et al. Patterns of local-regional failure after primary intensity modulated radiotherapy for nasopharyngeal carcinoma. *Radiat Oncol*. 2014;9:60.
15. Yin Z, Gao L, Luo J, et al. An analysis of clinical and dosimetric factors for postradiation nasopharyngeal necrosis in intensity-modulated radiotherapy for nasopharyngeal carcinoma. *Chin J Radiat Oncol*. 2016;25(5):438-442.
16. Greiner M, Pfeiffer D, Smith RD, et al. Principles and practical application of the receiver-operating characteristic analysis for diagnostic tests. *Prev Vet Med*. 2000;45(1–2):23-41.
17. Wang F, Fu Z, Wang L, et al. Diagnosis and treatment of nasopharyngeal huge and deep ulcer after first radiotherapy for nasopharyngeal carcinoma. *J Prac Oncol*. 2011;26(3):275-277.
18. Willner J, Baier K, Pfreundner L, et al. Tumor volume and local control in primary radiotherapy of nasopharyngeal carcinoma. *Acta Oncol*. 1999;38(8):1025-1030.
19. Hendrickson K, Phillips M, Smith W, Peterson L, Krohn K, Rajendran J. Hypoxia imaging with [F-18] FMISO-PET in head and neck cancer: potential for guiding intensity modulated radiation therapy in overcoming hypoxia-induced treatment resistance. *Radiother Oncol*. 2011;101(3):369-375.
20. Lee AW, Ng WT, Hung WM, et al. Major late toxicities after conformal radiotherapy for nasopharyngeal carcinoma-patient- and treatment-related risk factors. *Int J Radiat Oncol Biol Phys*. 2009;73(4):1121-1128.
21. Yan F, Ye Z, Wang F, Wang L, Li W, Fu Z. Clinical and imaging characteristics of 53 ulcers of post-radiation nasopharyngeal necrosis in patients with nasopharyngeal carcinoma. *Mol Clin Oncol*. 2016;5(4):351-356.
22. Langius JA, Doornaert P, Spreeuwenberg MD, et al. Radiotherapy on the neck nodes predicts severe weight loss in patients with early stage laryngeal cancer. *Radiother Oncol*. 2010t;97(1):80-85.
23. Elting LS, Cooksley CD, Chambers MS, Garden AS. Risk, outcomes, and costs of radiation-induced oral mucositis among patients with head-and-neck malignancies. *Int J Radiat Oncol Biol Phys*. 2007;68(4):1110-1120.
24. Jager-Wittenaar H, Dijkstra PU, Vissink A, et al. Changes in nutritional status and dietary intake during and after head and neck cancer treatment. *Head Neck*. 2011;33(6):863-870.
25. Jin T, Li KX, Li PJ, et al. An evaluation of nutrition intervention during radiation therapy in patients with locoregionally advanced nasopharyngeal carcinoma. *Oncotarget*. 2017;8(48):83723-83733.
26. Marx RE. Osteoradionecrosis: a new concept of its pathophysiology. *J Oral Maxillofac Surg*. 1983;41(5):283-288.

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