



Radiation-induced nasopharyngeal ulcers after re-irradiation with intensity-modulated radiotherapy in locoregional recurrent nasopharyngeal carcinoma patients: a dose–volume–outcome analysis

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Abstract

Objective To analyze the interrelation between radiation dose and radiation-induced nasopharyngeal ulcer (RINU) in locoregional recurrent nasopharyngeal carcinoma (NPC) treated with intensity-modulated radiation therapy (IMRT).

Methods Clinical data were collected from 363 patients with locoregional recurrent NPC who received re-irradiated with definitive IMRT from 2009 to 2017. Twenty-nine patients were diagnosed with RINU. Univariate and multivariate analyses were used to re-evaluate the first and second radiotherapy plans and to identify predictive dosimetric factors.

Results All dosimetric parameters were notably associated with the progression to RINU ($p < 0.01$) using paired samples Wilcoxon signed rank tests. Multivariate analysis showed that $EQD_{2-\sum_{D80}}$ (dose for 80 percent volume of the unilateral nasopharynx lesion) was an independent prognostic factor for RINU ($p = 0.001$). The area under the ROC curve for $EQD_{2-\sum_{D80}}$ was 0.846 ($p < 0.001$), and the cutoff point of 137.035 Gy could potentially be the dose tolerance of the nasopharyngeal mucosa.

Conclusions The sum of equivalent dose in 2 Gy fractions (EQD_2) in the overlapping volumes between initial and re-irradiated nasopharyngeal mucosal tissue can be effective in predicting the hazard of developing RINU in NPC patients undergoing radical re-irradiation with IMRT and we propose a $EQD_{2-\sum_{D80}}$ threshold of 137.035 Gy for the nasopharynx.

Keywords Nasopharyngeal carcinoma · Locoregional recurrence · Intensity modulated radiotherapy · Re-irradiation · Radiation-induced nasopharyngeal ulcers

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Abbreviations

RINU	Radiation-induced nasopharyngeal ulcer
NPC	Nasopharyngeal carcinoma
EQD_2	Equivalent dose in 2 Gy fractions
ROC	Receiver operating characteristics
IMRT	Intensity-modulated radiotherapy
AJCC	American joint committee on cancer
PTV	Planning target volume
CTV	Clinical target volume
GTV	Gross tumor volume
RTOG	Radiation therapy oncology group
DVH	Dose and volume histogram
UFI	Ulcer-free interval time
TTR	Time to relapse
LRRFS	Locoregional relapse-free survival
OS	Overall survival
CR	Complete response

QOL	Quality of life
CT	Computed tomography
MRI	Magnetic resonance imaging

Introduction

Nasopharyngeal carcinoma (NPC) is one of the high-occurrence cancer among head-and-neck malignancies in South-east Asia [1]. With the advancement of radiotherapy technology and the renewal of equipment, intensity-modulated radiotherapy (IMRT) has become the main treatment for NPC. Due to the high conformity of tumor coverage as well as the better sparing of normal structure in the IMRT era, the incidence rate of locoregional recurrence and radiotherapy-related toxicities has dropped significantly [2]. However, locoregional relapse rates of NPC patients treated with IMRT were reported, at around 4.8–13% [3–6]. Considering that patients with locoregional recurrent NPC could still obtain survival benefit by aggressive salvage therapy, high-dose re-irradiation has gained more acceptance and become the major treatment option over the last decade [7–9].

The major deficiency of re-irradiation for locoregional recurrent NPC in the IMRT era remains the concern for severe radiation-induced toxicity, including extensive fibrosis, soft tissue necrosis, osteoradionecrosis, etc. [7]. Radiation-induced nasopharyngeal ulcer (RINU) is defined as an ulceration of the surrounding and adjacent structures of the nasopharynx, such as the mucosa, musculus longus capitis, parapharyngeal tissues, and cranial base, which have been irradiated months or years previously [10]. Invasion of carotid sheath might be life-threatening, especially if internal carotid artery is affected. It is essential to obtain more accurate dose constraints for specific structures to avoid RINU in locoregional recurrent NPC patients re-irradiated with IMRT.

The aim of this study is to analyze the clinical characteristics and dose-volume effect of RINU after re-irradiated with IMRT for locoregional recurrent nasopharyngeal carcinoma. This will help to determine how the radiation dosages to the primary and relapse regions affect the occurrence of RINU and to provide a reference for optimizing the re-irradiation treatment plan.

Materials and methods

Patient selection and pretreatment evaluation

Between February 2009 and December 2017, the medical records of 363 consecutive locoregional recurrent NPC patients receiving IMRT according to our institutional treatment protocol at Fudan University Shanghai Cancer Center

were reviewed. Inclusion criteria were (1) aged ≥ 18 years, (2) both primary treatment and retreatment were performed in our cancer center using IMRT with a prescribed dose ≥ 60 Gy, (3) no less than 12 months since the previous treatment, (4) met the diagnosis criteria of RINU after re-irradiation. Exclusion criteria were (1) brachytherapy as part of first or second treatment, (2) developed RINU before re-irradiation. Among the 363 locoregional recurrent NPC patients, 29 patients developed RINU after re-irradiation. However, six patients were excluded due to missing data ($n=3$) or receiving intracavitary brachytherapy ($n=3$), leaving 23 evaluable patients.

All patients underwent a pretreatment evaluation, including medical history, physical examination, fiberoptic nasopharyngoscopy, complete blood counts, serum biochemistry profile, contrast-enhanced MRI of the head and neck, chest CT scan, abdominal ultrasound. ^{18}F -fluorodeoxyglucose positron emission tomography (^{18}F -FDG-PET) and whole-body bone scan using single-photon emission CT were performed when clinically indicated. For recurrent lesions, thirteen patients were diagnosed by pathological biopsy, and ten patients were diagnosed by at least two types of imaging techniques. Clinical stage was classified in accordance with the eighth edition of the American Joint Committee on Cancer (AJCC) staging system. This retrospective study was approved by the institutional review board of Fudan University Shanghai Cancer Center.

Intensity-modulated radiotherapy

All patients were immobilized in the supine position with thermoplastic masks from head to shoulder. For radiation treatment planning, contrast-enhanced CT was performed at 3–5 mm slice intervals. T1-weighted images from gadolinium-enhanced MRI were fused with the planning CT images for target delineation. All patients underwent radical IMRT with 6 MV photons and completed the prescribed radiation therapy as scheduled.

For the first radiation treatment, the total prescription dose was 66–72.6 Gy to the planning target volume (PTV) of the gross tumor volume of nasopharynx and enlarged retropharyngeal nodes (GTVnx), 66–72.6 Gy to the PTV of the gross tumor volume of the involved positive cervical lymph nodes (GTVnd), 60–63 Gy to the PTV of the clinical target volume 1 (CTV1), and 54–59 Gy to the PTV of the clinical target volume 2 (CTV2). The CTV1 was defined as the high-risk region of microscopic extension which encompassed the GTV plus a margin of 5–10 mm, the entire nasopharynx, retropharyngeal lymph nodal regions, skull base, parapharyngeal space, inferior sphenoid sinus, pterygoid fossae, clivus, the posterior third of the nasal cavity and maxillary sinuses, and any high-risk nodal regions. The CTV2 included the low-risk sites of microscopic extension.

The levels of cervical lymphatic drainage that were included were dependent on the tumor sites and nodal staging. The PTV was created by extending the CTV with a margin of 3–5 mm in all orientations. Nevertheless, when the CTV was close to critical structures, the margin of the PTV would be created as small as 1 mm. The dose per fraction was 2–2.2 Gy. Radiotherapy was given over 1 fraction a day, 5 days a week.

Re-irradiation was given to the locoregional recurrent sites, both target volumes and prescription doses were personalized, taking into account the initial radiation dose, interval time between the first and second radiotherapy, normal tissue constraints, and the clinical manifestation of radiation-related toxicities in the previous irradiated tissues. The prescription dosage was 60–70 Gy in 30–35 fractions at 2–2.1 Gy per fraction.

The organs at risk (OAR) included the temporal lobes, brainstem, spinal cord, optic chiasm, pituitary, optic nerves, eyeballs, lens, inner ears, parotid glands, temporomandibular joints, oral cavity, mandible, larynx, thyroid, trachea. The dose constraints for the OAR have been assessed in accordance with the protocols of the Radiation Therapy Oncology Group (RTOG) 0225 and RTOG 0615.

Chemotherapy

During the initial treatment, 95.7% (22/23) patients received chemotherapy: 5 received neoadjuvant chemotherapy, 4 received concurrent chemotherapy, 11 received induction + concurrent chemotherapy, and 2 received induction + adjuvant chemotherapy. 73.9% (17/23) patients were

treated with chemotherapy after their recurrence, eight patients underwent neoadjuvant chemotherapy, one patient received adjuvant chemotherapy, seven patients were performed with neoadjuvant + synchronized chemotherapy, and one patient received chemotherapy before and after radiotherapy. The regimens prescribed for induction and adjuvant chemotherapy consisted of PF (cisplatin 25 mg/m²/day, days 1–3, 5-fluorouracil 0.5 g/m²/day, days 1–3), TPF (docetaxel 60 mg/m²/day, day 1, cisplatin 25 mg/m²/day, days 1–3, and 5-fluorouracil 0.5 g/m²/day, days 1–3), TP (docetaxel 60 mg/m²/day, day 1, cisplatin 25 mg/m²/day, days 1–3), and GP (gemcitabine 1 g/m²/day, day 1, day 8, cisplatin 25 mg/m²/day, days 1–3). The induction and adjuvant chemotherapy regimens were given at 3-week intervals. The regimens for concurrent chemotherapy were as follows: cisplatin alone, nedaplatin alone, or Tegafur, Gimeracil and Oteracil Potassium Capsules. Epidermal growth factor receptor (EGFR: Nimotuzumab or Cetuximab) was given weekly to two patients during the first course of radiotherapy and to three patients during the second course of radiation therapy.

Diagnostic criterion for RINU

RINU was diagnosed in accordance with patients' clinical symptom, physical signs, and MRI imaging manifestations. MRI imaging features of RINU were reported by our colleagues in the previous study [10], which included inconsecutive nasopharyngeal mucosal line and/or a specific region of low signal intensity on contrast-enhanced T1-weighted images. Figure 1 shows defects in the nasopharyngeal wall on MRI scans of a typical by a patient in our cohort who

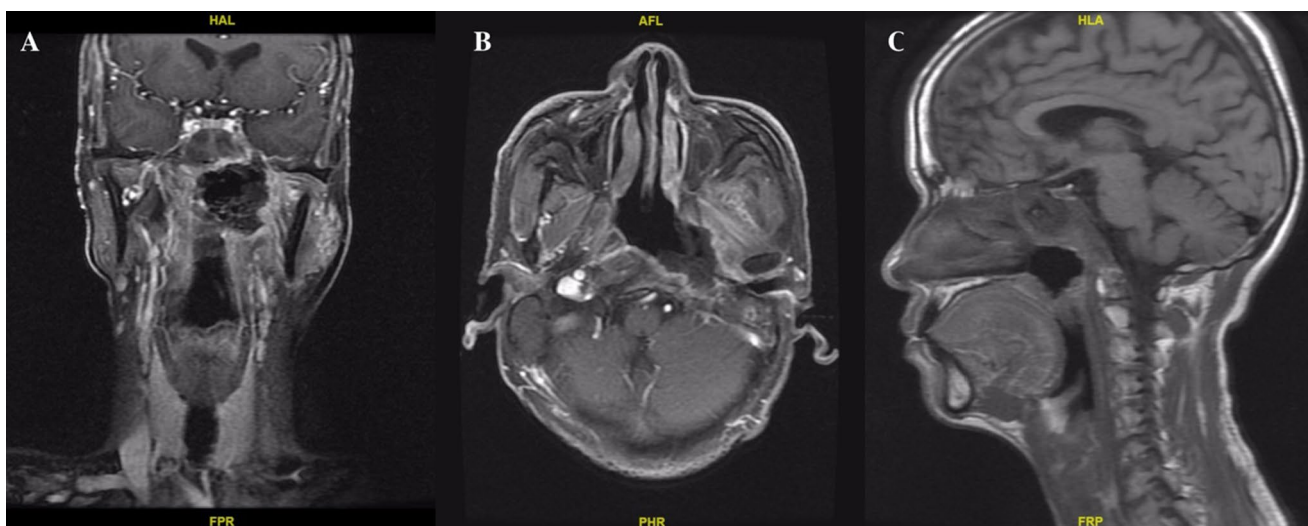


Fig. 1 MRI image of a 41-year-old man with rT3N1M0. **A** Coronal contrast-enhanced, T1-weighted MRI showed a large ulcer on the left posterior wall of the nasopharynx at 2 months after the completion of re-irradiation. **B** An abnormal nasopharyngeal cavity and soft tissue

defects were seen on transverse contrast-enhanced T1-weighted MRI. **C** Sagittal T1-weighted contrast-enhanced MRI manifested the mucosal ulcer eroding the roof of the nasopharynx

suffered from the RINU. Two radiologists with expertise in head-and-neck cancers reassessed each MRI scan individually in accordance with the criteria. Any distinction was settled by mutual agreement. 29 patients were diagnosed with nasopharyngeal ulcer and met the diagnostic criteria for RINU. At the time of diagnosis and follow-up MRI, all patients were clinically assessed.

Dose registration

The T1-weighted images of enhanced MRI which including the area and extent of RINU were fused with the planning CT images of the initial and the second course of radiotherapy. Original IMRT plans were reintegrated into the TPS. The volumes of ulcerous side and the corresponding unaffected contralateral nasopharynx were delineated respectively. The sum of the equivalent dose in 2 Gy fractions (EQD₂) in the overlapping volumes between initial and re-irradiated nasopharyngeal mucosal tissue of ulcer side and non-ulcer side was regarded as the variable in dosimetric analysis. EQD₂ was calculated at $\alpha/\beta = 3$ Gy, and the calculation formula of EQD₂ was $D[d + (\alpha/\beta)]/[2 + (\alpha/\beta)]$, where D = total dose and d = fractional dose. Dose-volume histogram (DVH) curves were exported from the original treatment plans on Pinnacle³ version 8.0 m (Philips Corp, Fitchburg, WI) TPS. Dose parameters encompassing the mean dose (EQD_{2-∑_{Dmean}}), maximum dose (EQD_{2-∑_{Dmax}}), minimum dose (EQD_{2-∑_{Dmin}}), absolute volume irradiated at n Gy (EQD_{2-∑_{Vn}}), dose over n volume (EQD_{2-∑_{Dncc}}), and dose over n percent volume (EQD_{2-∑_{Dn}}) were calculated from the DVH curves.

Follow-up and statistical analysis

After completion of initial radiotherapy, all patients were required to attend our outpatient clinic for follow-up every 3 months for the first 2 years, every 6 months between years 3 and 5, and annually thereafter. Each follow-up visit included a detailed medical history and examination, indirect nasopharyngoscope, blood routine examination, and blood biochemistry. Contrast-enhanced MRI of the nasopharynx, chest CT, ultrasound of the cervical lymphatic drainage area and abdomen were performed 3 months after the completion of IMRT and every 6–12 months thenceforward. If there was any evidence of locoregional recurrence or distant metastases, further investigations would be ordered.

Follow-up time was counted from the date of completion of the initial IMRT. SPSS software version 21.0 (IBM, Armonk, NY, USA) was used for data analysis. Ulcer-free interval time (UFI) was defined as the time elapsed between the completion of re-irradiation with IMRT and the date of diagnosis of RINU. Time to relapse (TTR) was the interval from the start of initial therapy to the point of locoregional

failure. Locoregional relapse-free survival (LRRFS) was defined as the time elapsed between diagnosis of the first locoregional recurrence and the next locoregional relapse. Locoregional recurrence was diagnosed based on contrast-enhanced MRI of the nasopharynx, with or without PET/CT, nasopharyngofiberscope, and biopsy. Overall survival (OS) was defined as the time from diagnosis of locoregional recurrence to death from any cause or date of last follow-up for surviving patients.

Actuarial rates for OS and LRRFS were generated via Kaplan–Meier method. Paired sample Wilcoxon signed rank tests were used to compare the dosimetric parameters in the paired contralateral nasopharyngeal mucosa (total dose in EQD₂), considering the differences between the paired samples by normality tests were failed to obey the normal distribution. Receiver operating characteristics (ROC) curve was performed to figure out the cut-off point for significant dosimetric parameters. Univariate and multivariate analysis (consisting of relevant dosimetric parameters in the paired-sample Wilcoxon signed rank tests) were performed using the Cox proportional hazards model. Two-tailed p values within 0.05 were regarded as statistically significant.

Results

Patient characteristics

Twenty-three patients who met the criteria for unilateral RINU after re-irradiation were enrolled in this study. There were 20 males and 3 females among the 23 patients. All patients had histologically confirmed nasopharyngeal carcinoma (WHO type II/III). The median age was 49 years old, with a range of 38–68 years old. Median TTR was 33 months (range 14–101 months). The recurrent lesion was ipsilateral to the primary lesion in 18 patients. The median ulcer-free interval was 10 months. In conformity with the eighth edition of AJCC staging system, nine patients were rT3, four were rT4. None of these 23 patients received nasopharyngeal boost. At the completion of initial treatment, all patients achieved a complete response (CR). Table 1 summarizes patients' characteristics.

Dosimetry analysis

Significant association between the dosimetric parameters and RINU manifested itself in the paired samples Wilcoxon signed rank tests (Table 2). Univariate COX regression analysis illustrated that the dosimetric parameters EQD_{2-∑_{Dmean}}, EQD_{2-∑_{Dmin}}, EQD_{2-∑_{Vn}} ($n = 20, 30, 40, 50, 60, 70, 75$), EQD_{2-∑_{Dncc}} ($n = 0.5, 1, 2, 3, 4, 5$), and EQD_{2-∑_{Dn}} ($n = 1, 5, 10, 20, 30, 40, 50, 60, 70, 80, 95$) were remarkably associated with

Table 1 Patient and tumor Characteristics

Variables	Number of patients (%)
Age(years)	
Median	49
Range	38–68
Sex	
Male	20(86.96%)
Female	3(13.04%)
Median follow-up, months (95% CI)	85(46.733–123.267)
Median time in months between RT and re-RT (range)	32(14–103)
Median dose first RT in Gy (range)	70.4(66–74)
Median dose re-RT in Gy (range)	66(60–70)
Primary TNM stage	
T0/T1/T2/T3/T4	0/1/9/9/4(0/4.35/39.13/39.13/17.39%)
N0/N1/N2/N3	0/10/7/6(0/43.48/30.43/26.09%)
I/II/III/IVA/IVB	0/4/9/10/0(0/17.39/39.13/43.48/0%)
Recurrent TNM stage	
rT0/rT1/rT2/rT3/rT4	2/8/3/6/4(8.70/34.78/13.04/26.09/17.39%)
rN0/rN1/rN2/rN3	14/8/1/0(60.87/34.78/4.35/0%)
I/II/III/IVA/IVB	5/6/6/4/2(21.73/26.09/26.09/17.39/8.70%)
Ulcer depth	
Carotid artery exposure	8(34.78%)
Bone destruction	11(47.83%)
Neither	7(30.43%)

the progression of RINU. By contrast, the $EQD_{2-} \sum_{D_{max}}$ ($p = 0.053$) was not pronouncedly correlated with RINU. All the dosimetric parameters that showed significant statistical differences in the single-factor analysis were included in the multivariate analysis (Table 3). The development of RINU was conspicuously related to the $EQD_{2-} \sum_{D_{80}}$ ($\beta = 0.140$, $SE = 0.042$, $HR = 1.150$, $95\% \text{ CI} = [1.059-1.249]$, $p = 0.001$), demonstrating that $EQD_{2-} \sum_{D_{80}}$ is an independent prognostic factor for UFI in patients with locoregional recurrent NPC. The dose tolerance of the overlapping volume between the initial and retreatment target volumes of the nasopharynx was deduced using ROC curve analysis, to be specific, the optimum cut-off points for $EQD_{2-} \sum_{D_{80}}$. The area under the ROC curve for $EQD_{2-} \sum_{D_{80}}$ was 0.846 ($p < 0.001$). As shown in Fig. 2, the $EQD_{2-} \sum_{D_{80}}$ of 137.035 Gy might be reckoned as the upper limit of the cumulative dose for initial and re-irradiation of the nasopharynx (sensitivity = 0.739, specificity = 0.913). The mean $EQD_{2-} \sum_{D_{80}}$ for ulcer side was 141.46 Gy, and 126.67 Gy for non-ulcerated side.

Toxicities associated with re-irradiation

Acute adverse events: 7 patients (30.43%) complained of \geq Grade III mucositis, and grade I or II mucositis was observed in 16 patients (69.57%). Nineteen patients

(82.61%) suffered from grade I radiation dermatitis, and 4 patients (17.39%) developed grade II radiodermatitis.

Late adverse events: There was no subcutaneous fibrosis, visual loss or spinal cord or brainstem damage in our series. Two patients (8.7%) had grade II hearing deficit, 5 patients (21.74%) had grade II trismus, 3 patients (13.04%) had grade I or II cranial neuropathy, 3 patients had grade I or II temporal lobe necrosis, 23 patients (100%) had grade IV nasopharyngeal mucositis, and 7 patients (30.43%) had grade III cephalalgia.

Survival

The median follow-up time was 85 months (range 6–112 months). Twenty-three patients had died when follow-up ceased. Of these, 8 (34.78%) deaths were due to sudden massive nasal bleeding, 12 (52.17%) patients died of cachexia and multiple organ dysfunction, and 3 (13.05%) patients died of tumor progression. The median OS was 29 months, with 1-year, 2-year, 3-year, and 5-year OS rates of 87%, 58.7%, 40.7%, and 16.5%, respectively. The 3-year and 5-year LRRFS were 80.6% and 64.7%, respectively.

Table 2 Comparison of dosimetric parameters in ulcer side and the corresponding non-ulcer side

Variable	Median (P25, P75)		Wilcoxon signed rank test	
	Non-ulcer side	Ulcer side	Z	P
$EQD_{2-} \sum_{D_{max}}$	150.24 (146.04, 154.16)	152.88 (149.97, 157.26)	- 3.635	0.000
$EQD_{2-} \sum_{D_{min}}$	109.83 (94.89, 122.58)	128.76 (116.81, 132.42)	- 2.920	0.004
$EQD_{2-} \sum_{D_{mean}}$	133.72 (127.99, 141.61)	143.37 (141.13, 147.9)	- 4.045	0.000
$EQD_{2-} \sum_{V_{20}}$	9.89 (6.99, 13.26)	19.87 (9.52, 28.53)	- 4.015	0.000
$EQD_{2-} \sum_{V_{30}}$	9.89 (6.99, 13.26)	19.87 (9.52, 28.53)	- 4.015	0.000
$EQD_{2-} \sum_{V_{40}}$	9.89 (6.4, 13.26)	19.87 (9.52, 28.53)	- 4.106	0.000
$EQD_{2-} \sum_{V_{50}}$	9.32 (5.26, 12.7)	19.85 (9.52, 28.53)	- 4.136	0.000
$EQD_{2-} \sum_{V_{60}}$	7.91 (4.28, 12.13)	19.44 (9.52, 28.53)	- 4.197	0.000
$EQD_{2-} \sum_{V_{70}}$	2.99 (1.46, 6.68)	9.97 (3.99, 15.75)	- 4.076	0.000
$EQD_{2-} \sum_{V_{75}}$	0.09 (0, 1.04)	0.74 (0, 5.28)	- 3.464	0.001
$EQD_{2-} \sum_{D_1}$	148.87 (143.75, 153.49)	151.21 (149.01, 155.99)	- 3.924	0.000
$EQD_{2-} \sum_{D_5}$	145.4 (139.87, 151.48)	149.85 (147.49, 154.74)	- 4.106	0.000
$EQD_{2-} \sum_{D_{10}}$	144.29 (138.47, 150.65)	148.85 (146.35, 154.02)	- 3.945	0.000
$EQD_{2-} \sum_{D_{20}}$	143.48 (136.31, 149.42)	147.62 (144.71, 152.56)	- 3.893	0.000
$EQD_{2-} \sum_{D_{30}}$	142.72 (134.56, 148.08)	146.3 (143.32, 151.23)	- 3.893	0.000
$EQD_{2-} \sum_{D_{40}}$	141.17 (132.83, 145.58)	144.93 (142.28, 150.16)	- 3.893	0.000
$EQD_{2-} \sum_{D_{50}}$	136.29 (130.59, 143.18)	144.01 (141.55, 149.16)	- 3.945	0.000
$EQD_{2-} \sum_{D_{60}}$	134.8 (127.66, 142.05)	143.28 (140.69, 148.23)	- 4.045	0.000
$EQD_{2-} \sum_{D_{70}}$	130.89 (122.79, 140.71)	142.51 (139.75, 146.6)	- 4.106	0.000
$EQD_{2-} \sum_{D_{80}}$	123.68 (116.42, 139.91)	140.4 (137.96, 145.41)	- 4.167	0.000
$EQD_{2-} \sum_{D_{95}}$	122.51 (114.36, 138.22)	139.02 (136.15, 144.05)	- 4.136	0.000
$EQD_{2-} \sum_{D_{0.5cc}}$	143.94 (138.08, 149.92)	149.94 (146.97, 154.63)	- 4.197	0.000
$EQD_{2-} \sum_{D_{1cc}}$	142.33 (135.4, 148.55)	148.68 (145.09, 153.81)	- 4.197	0.000
$EQD_{2-} \sum_{D_{2cc}}$	137.06 (131.29, 144.78)	146.74 (142.93, 152.67)	- 4.197	0.000
$EQD_{2-} \sum_{D_{3cc}}$	133.03 (125.4, 139.33)	146.14 (141.95, 151.77)	- 4.197	0.000
$EQD_{2-} \sum_{D_{4cc}}$	129.11 (119.51, 136.02)	145.69 (137.62, 150.92)	- 4.197	0.000
$EQD_{2-} \sum_{D_{5cc}}$	126.8 (110.32, 132.28)	144.84 (133.71, 150.03)	- 4.197	0.000

EQD_{2-} , equivalent dose in 2 Gy fractions; D_{max} , maximum dose; D_{mean} , mean dose; D_{min} , minimum dose; V_n , absolute volume receiving n Gy; D_{ncc} , dose covering n volume; D_n , dose of n percentage volume

Discussion

RINU can occur as a serious complication during or after radiotherapy in NPC patients. In the era of IMRT, how to reduce the incidence of RINU and improve the quality of life of NPC patients remains an important question. The current study provides a unique insight into the direction in which future improvements can be made. In this study, we found that accumulated dose to the nasopharynx was an independent predictor of RINU in patients with locoregional recurrent NPC treated with two courses of IMRT. Therefore, we recommended dose limitation to the nasopharyngeal mucosa to prevent the development of RINU.

The IMRT technique can provide optimized dose delivery to the tumor targets and the surrounding critical organs compared to 3D conformal radiotherapy. Re-irradiation of NPC recurrence using IMRT is clinically profitable and has been

performed in several studies [11–14]. In the study by Hsiung et al. [15], lower doses to normal tissues and more homogeneous target doses can be achieved with IMRT schedules compared to 3D-CRT for the boost or salvage treatment of NPC. Qiu et al. [13] reported their treatment results of high-dose re-irradiation with IMRT for locally recurrent NPC in 70 patients. The 2-year LRRFS, disease-free survival (DFS), and OS rates were 65.8%, 65.8%, and 67.4%, respectively. In the study from Kong et al. [11], the 3-year local recurrence-free survival (LRRFS) and OS of recurrent NPC patients re-irradiated with IMRT were 85.1 and 46.0%, respectively. In the current study, the 3-year LRRFS and OS rates were 80.6% and 40.6%, respectively, which were similar to those in other studies.

As local control and survival rates have improved, quality of life (QOL) has increasingly been a priority. Radiation-related late complications are detrimental factors that

Table 3 Univariate and multivariate analyses of relationship between dosimetric parameters and UFI

Prognostic factor	Univariate analysis		Multivariate analysis	
	P	HR (95%CI)	P	HR (95%CI)
$EQD_{2-} \sum_{Dmax}$	0.053	1.078(0.999–1.163)	–	–
$EQD_{2-} \sum_{Dmin}$	0.007	1.050(1.014–1.088)	–	–
$EQD_{2-} \sum_{Dmean}$	0.001	1.176(1.073–1.289)	–	–
$EQD_{2-} \sum_{V20}$	0.001	1.046(1.018–1.076)	–	–
$EQD_{2-} \sum_{V30}$	0.001	1.046(1.018–1.076)	–	–
$EQD_{2-} \sum_{V40}$	0.001	1.047(1.018–1.076)	–	–
$EQD_{2-} \sum_{V50}$	0.001	1.047(1.019–1.076)	–	–
$EQD_{2-} \sum_{V60}$	0.001	1.048(1.021–1.076)	–	–
$EQD_{2-} \sum_{V70}$	0.000	1.058(1.026–1.091)	–	–
$EQD_{2-} \sum_{V75}$	0.034	1.071(1.005–1.140)	–	–
$EQD_{2-} \sum_{D1}$	0.042	1.081(1.003–1.166)	–	–
$EQD_{2-} \sum_{D5}$	0.020	1.093(1.014–1.177)	–	–
$EQD_{2-} \sum_{D10}$	0.015	1.096(1.018–1.181)	–	–
$EQD_{2-} \sum_{D20}$	0.011	1.105(1.023–1.192)	–	–
$EQD_{2-} \sum_{D30}$	0.005	1.126(1.036–1.224)	–	–
$EQD_{2-} \sum_{D40}$	0.002	1.148(1.052–1.253)	–	–
$EQD_{2-} \sum_{D50}$	0.001	1.159(1.063–1.264)	–	–
$EQD_{2-} \sum_{D60}$	0.001	1.158(1.065–1.260)	–	–
$EQD_{2-} \sum_{D70}$	0.001	1.166 (1.069–1.273)	–	–
$EQD_{2-} \sum_{D80}$	0.001	1.150(1.059–1.249)	0.001	1.15(1.059–1.249)
$EQD_{2-} \sum_{D95}$	0.001	1.137(1.052–1.228)	–	–
$EQD_{2-} \sum_{D0.5 cc}$	0.008	1.098(1.024–1.177)	–	–
$EQD_{2-} \sum_{D1cc}$	0.004	1.107(1.032–1.188)	–	–
$EQD_{2-} \sum_{D2cc}$	0.001	1.124(1.050–1.204)	–	–
$EQD_{2-} \sum_{D3cc}$	0.000	1.118(1.052–1.187)	–	–
$EQD_{2-} \sum_{D4cc}$	0.001	1.088(1.037–1.142)	–	–

Table 3 (continued)

Prognostic factor	Univariate analysis		Multivariate analysis	
	P	HR (95%CI)	P	HR (95%CI)
$EQD_{2-} \sum_{D5cc}$	0.000	1.083(1.036–1.132)	–	–

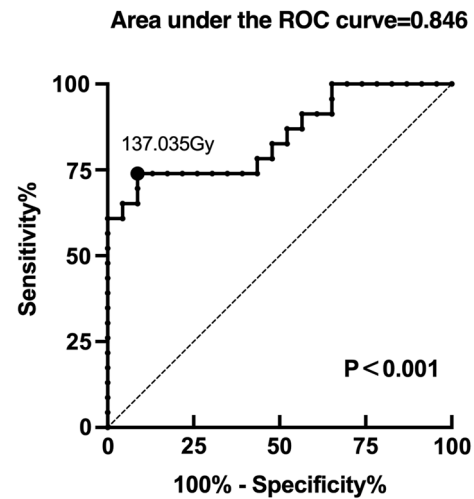


Fig. 2 ROC curve for the $EQD_{2-} \sum_{D80}$ (dose of 80 percentage volume). The cut-off point for $EQD_{2-} \sum_{D80}$ (as the tolerated dose in the nasopharyngeal mucosa) was determined to be 137.035 Gy for recurrent NPC patients treated with IMRT. At an $EQD_{2-} \sum_{D80}$ of 137.035 Gy, the sensitivity and specificity for predicting RINU were 0.739 and 0.913, respectively

negatively affect QOL. As reported by Chan et al. [7], even though the use of IMRT, the risk of any grade ≥ 3 complications was exceeding 70% among patients re-irradiated for locally recurrent NPC. These late toxic reactions were inevitable since the tumor was encapsulated, embedded or surrounded by the normal structures. Radiation-induced nasopharyngeal ulcer is one of the serious complications after radical radiotherapy. Based on previous studies, the crude incidence rate of radiation-induced nasopharyngeal necrosis in NPC patients first irradiated with IMRT was 1.9–3.3% [16, 17], while 11–40.5% of patients developed grade 3–5 late adverse events after re-irradiation of recurrent NPC with IMRT, which led to RINU [11, 18, 19]. Nearly half of all patients who suffered from RINU may develop life-threatening massive nasopharyngeal hemorrhage. In the data of Kong et al. [11], a total of 184 recurrent NPC patients who underwent re-irradiation with IMRT died at the time of analysis, and 44 of them died of profuse epistaxis. In the study of Hua and colleagues [20], approximately 30% of patients who received IMRT for recurrent NPC died from severe nasal hemorrhage owing to mucosal necrosis. In our study, 34.78% of

the patients died due to massive bleeding. All the above results enlighten us that there is a predominant need to study the mucosal tolerance, and to devise a way to prevent such adverse effects.

Even though the exact mechanism of RINU is unascertained, a conjecture accepted broadly is that high radiation dosage may elicit hypovascular–hypoxic–hypocellular condition which may result in the breakdown of tissues and a chronically non-healing lesion [21]. Moreover, nutritional deficiency and infection have been reported to play an important role in the development of nasopharyngeal ulcer [16, 22]. MRI, nasopharyngoscopy, and pathohistological examination are advantageous for the diagnosis of RINU. Compared with the recurrence of NPC, the MRI images of RINU reveal the defect of soft tissues around the nasopharynx, low signal on T1-weighted images, high or slightly high signal on T2-weighted images, and mild or no enhancement when performing the contrast-enhanced MRI [23]. Nasopharyngoscopy shows that the nasopharynx is covered with a large amount of scab and sticky secretions, mostly yellowish-brown in color. The necrotic mucosa is flocculent with varying degrees of tissue loss, some of the ulcers are deep, and in severe cases, the pulsation of the internal carotid artery may be visible. The ulcer may also destroy the clivus and the basal wall of the sphenoid sinus posteriorly and superiorly, exposing the bone. The biopsy pathology is necrotic tissue without tumor cells, excluding nasopharyngeal ulcers due to tumor recurrence [24].

In the current study, all dosimetric variables were statistically significantly associated with the emergence of RINU, and there was a remarkably high degree of association between these factors. According to the Cox proportional hazards model, the $EQD_{2-\sum D_{80}}$ emerged as the most valuable predictor, suggesting that the accumulated dose to the nasopharynx plays an important role in the RINU occurrence. Some studies also identified dose as an essential hazard factor for the incidence of RINU in re-irradiated patients. Yu et al. [19] observed that the cumulative total prescribed dose to the GTV over 141.5 Gy in two courses of radiation was correlated with lethal nasopharyngeal necrosis. Analogously, Hua et al. [25] found that the accumulated prescription dose over 120 Gy was significantly correlated with post-radiation nasopharyngeal necrosis. The utilization of $EQD_{2-\sum D_{80}}$ cut-off value to avert the emergence of RINU in patients undergoing two courses of IMRT may be clinically necessary, and we recommend an $EQD_{2-\sum D_{80}}$ threshold of 137.035 Gy for the nasopharyngeal mucosa. If such a dose limit is inaccessible, our results still furnish a theoretical basis that can be utilized to predict the occurrence of RINU in patients with recurrent nasopharyngeal carcinoma who have received two courses of IMRT, and thus to identify potential preventive strategies to decrease the possibility

of severe bleeding. For patients at high risk of RINU, prophylactic arterial embolization is recommended prior to re-irradiation to decrease the incidence of fatal bleeding during or after radiotherapy.

Currently, immunochemotherapy has become the preferred treatment option for recurrent and/or metastatic NPC. Although most of patients enrolled in the clinical trials were metastatic patients, immunotherapy combined with chemotherapy also demonstrated good efficacy in locoregional recurrent lesions [26–29]. For patients with non-operable locoregional recurrent disease, the timing of intervention and optimal RT dose of immune-combination chemotherapy followed by recourse radiotherapy deserves further investigation.

Our study has several important limitations. Firstly, all analyses are susceptible to selection bias owing to the limited sample size. Secondly, toxicities were retrospectively identified according to chart reviews, and it is conceivable that not all complications were obtained. Thirdly, due to the lack of a clear formula for the reparation of radiation-induced mucosal damage, this component was ignored in the calculation of EQD_2 . Finally, our data were merely gathered from a single center, therefore, these results need to be verified in other datasets and further disquisition is expected to reach a statistically convincing conclusion.

Conclusion

Based on this study, we suggest that the $EQD_{2-\sum D_{80}}$ limit for the nasopharyngeal mucosa should be 137.035 Gy, for patients with recurrent NPC who have undergone radical re-irradiation with IMRT. This research presents valuable insight into the prevention of RINU from the standpoint of radiation dose, and physicians should be circumspect about the high nasopharyngeal doses when reviewing and approving second-course IMRT treatment plans. Further explorations are necessitated to identify independent predictors of RINU in recurrent NPC patients, which may suggest strategies to forestall the occurrence of RINU in the IMRT era.

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Author contributions MSN and FFK conducted data analysis and drafted the manuscript. GSP, RPZ and CRD participated in data collection. CSH and HMY participated in the design of the study. All authors read and approved the final manuscript.

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Availability of data and materials The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors have declared that no competing interest exists.

Ethics approval The present study was approved by the Institutional Review Board of Fudan University Shanghai Cancer Center (Approval number 2009224–1).

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