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Original Research

Local control and failure patterns after intensity modulated radiotherapy with reduced target volume delineation after induction chemotherapy for patients with T4 nasopharyngeal carcinoma

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ABSTRACT

Background: The delineation of target volume after induction chemotherapy(IC) for nasopharyngeal carcinoma (NPC) is currently controversial. In this study, we aimed to analyze the long-term local control(LC) and failure patterns of T4 NPC treated with reduced target volume radiotherapy after IC.

Methods: From September 2007 to January 2013, 145 patients with T4 NPC were retrospectively reviewed. All patients received at least 1 cycle of IC followed by intensity modulated radiotherapy(IMRT). The gross tumor volume(GTV) was delineated according to the post-IC images for intracavity tumors and lymph nodes. The LC and overall survival (OS) rates were calculated using the Kaplan-Meier method. The location and extent of local failures were transferred to the pretreatment planning computed tomography (CT) for dosimetric analysis.

Results: With a median follow-up time of 95 months (range, 16–142 months), 23 local failures were found. The estimated 10-year LC and OS rates were 81.1%and 54.8% respectively. Among the 20 local failures with available diagnostic images, 18(90%) occurred within the 95% isodose lines and were considered in-field failures and 2(10%) were marginal. There was no outside-field failure.

Conclusions: In-field failure was the major pattern of local failure for T4 NPC. IMRT with reduced target volume after IC seems to be feasible. Further researches exploring optimal volume and radiation dose for local advanced NPC in the era of IC are warranted.

Introduction

Intensity modulated radiotherapy (IMRT) has become the standard technique for nasopharyngeal carcinoma(NPC), due to its capability of escalating tumor dose while sparing the adjacent organs [1–4]. Compared to conventional two-dimensional radiotherapy(2D-CRT), IMRT can significantly reduce the dose of parotid glands and other normal tissues and meanwhile increase the dose of tumor [5,6]. Local control and quality of life for patients with NPC has been significantly improved after IMRT [7–10]. However, radical dose is often difficult to achieve for T4 NPC since the tumor is very close or extend to critical organs at risk(OARs) such as the optic nerve, chiasm, brain stem, and temporal lobe [11]. Doctors and patients often have to make a choice between critical OARs protection and tumor coverage. It was reported that the incidence of temporal lobe injury was significantly lower when treated with IMRT compared with 2D-CRT for patients with T1, T2 and T3 disease($P = 0.005$, 0.016, and 0.001, respectively), but not for T4 patients ($P = 0.680$) [12].

Induction chemotherapy (IC) has been widely used for locoregionally advanced NPC (LA-NPC) in recent years. Since IC can achieve different degrees of tumor shrinkage and increase the distance between tumor and OARs, it is expected to further reduce the normal tissue dose and late toxicities [13,14]. Prospective studies have shown that IC combined with concurrent chemoradiotherapy (CCRT) significantly improved recurrence-free and OS rates with acceptable toxicities for LA-NPC [15–17]. However, the delineation of target volume after IC is currently controversial. Should the tumor shrinkage area be delineated in GTV(gross tumor volume) or CTV(clinical target volume)? And what's

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the optimal dose for this area? Several studies have showed that reducing the target volume after IC could achieve satisfactory LC and survival rates [18–20]. However, most of them were only short-term results, and both radiation dose and target volume delineation varied from study to study. In this study, we summarized our long-term results, including local control and failure patterns particularly for T4 NPC, in order to provide more evidence for the target volume delineation of T4 NPC in the era of IC.

Materials and methods

Patients

From September 2007 to January 2013, 145 patients with T4 classification NPC treated in Fudan University Shanghai Cancer Center were retrospectively reviewed. The inclusion criteria were: (1) pathologically confirmed NPC; (2) treated naive; (3) stage T4N0–3M0 according to the 8th edition of AJCC/UICC staging system; (4) treated with IC combined with radical IMRT; (5) complete pathologic and clinical data. The present study was approved by the Institutional Review Board of our Cancer Center (Approval number 2,009,224–1). Written informed consent was obtained from all participants.

Intensity-modulate radiotherapy

The detailed techniques of planning and delivery of IMRT were reported in our previous paper [21]. Briefly, a thermoplastic mask of head and shoulder was used for patient immobilization. Intravenous contrast-enhanced CT with a slice thickness of 5 mm of the head and neck region was performed for planning. Image fusion of the gadolinium-enhanced MRI both before and after IC was performed with the CT simulation images for target delineation. For MRI before IC, both T1 and T2 sequences were used. For MRI after IC, only T1 enhanced sequences were used. The target volumes were defined in accordance with the International Commission on Radiation Units and Measurements Reports 50 and 62. The primary gross tumor (GTV-P) and clinically positive lymph nodes (GTV-LN) was defined as all gross tumors determine by imaging, clinical and endoscopic findings. The CTV1 was defined as the high-risk region that included GTV-P plus 5 to 10 mm margin to encompass any microscopic extension, together with the high-risk nodal regions. The CTV2 was defined as lymph nodal regions at low risk. The PTV was defined as the GTV or CTV plus 3 to 5 mm margin in all directions to encompass any setup error. The GTV was based on the post-IC volume for intracavity tumors and lymph nodes. For infiltration tumors (bony structures of the skull base, pterygoid structures, or cervical vertebra invasion) and lymph node capsule invasion, the GTV was based on pre-IC volume. Examples of target delineation for GTV were showed in Fig. 1. The tumor shrinkage area after IC must be included in the high risk region(CTV1). Simultaneous integrated boost technique was used. The prescribed dose for primary gross tumor (PTV-G) and positive lymph nodes (PTV-LN) were 70–70.4 Gy and 66–70 Gy, respectively (in 32–35 fractions). A total dose of 60 Gy was prescribed to high risk region (PTV-C1) and 54 Gy to low risk region (PTV-C2).

Chemotherapy

Cisplatin based IC was given to all patients for 2–3 cycles depending on treatment response and tolerance. Concurrent chemotherapy was recommended for loco-regionally advanced patients. For patients could not tolerant or refused concurrent chemotherapy, adjuvant chemotherapy(AC) was adopted. Common regimen of IC and AC included TP (docetaxel 60–75 mg/m^2 on day 1, cisplatin 75 mg/m^2 on day 1 or 25 mg/m^2/day on days 1–3), GP (gemcitabine 1000 mg/m^2 on day 1 and day 8, cisplatin 75 mg/m^2 on day 1 or 25 mg/m^2/day on days 1–3), TPF (TP plus 5-fluorouracil 500 mg/m^2/day, continuous intravenous infusion for 120 h) or PF (cisplatin 75 mg/m2 on day 1 or 25 mg/m2/day on

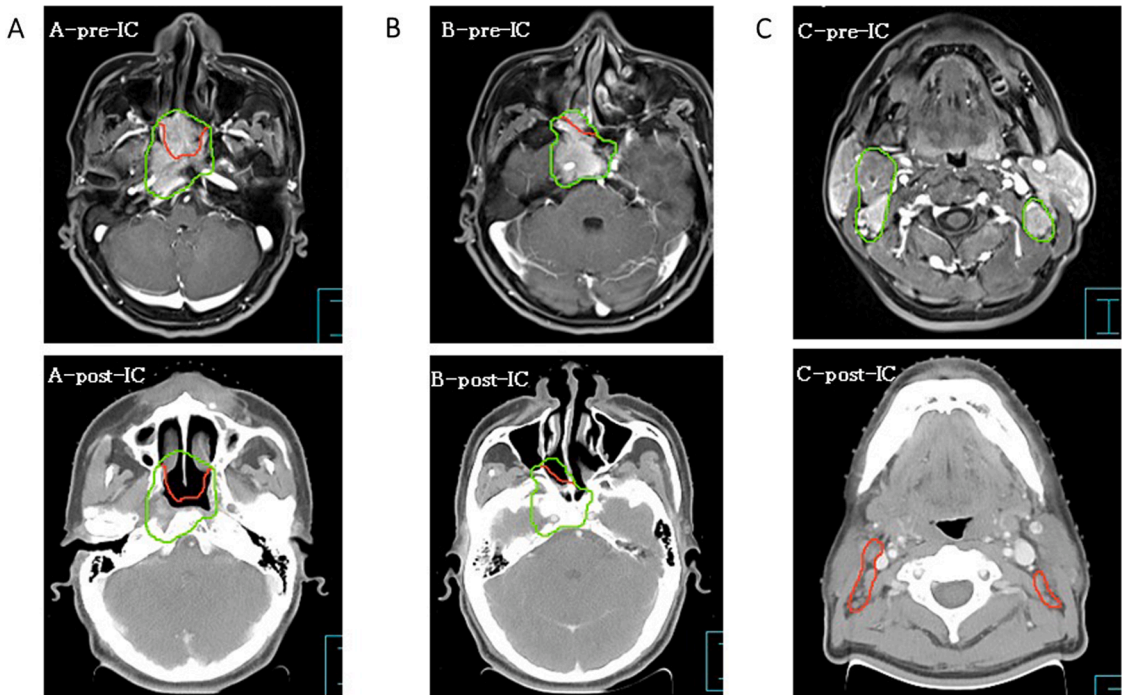

Fig. 1. Examples of target delineation for GTV after induction chemotherapy.
(A) A-pre-IC presents the tumor (green line) before induction chemotherapy (IC); A-post-IC shows that the regressing part of the intracavitary lesion after IC was not included in GTV (red line).
(B) B-pre-IC presents the extension of tumor (green line) before IC; B-post-IC shows that involved skull base (e.g., pterygopalatine fossa) were included in GTV (red line) regardless of the regression.
(C) C-pre-IC presents the positive lymph node (green line) before IC; C-post-IC shows that the GTV of lymph node (red line) was based on the post-IC volume.

days 1–3, 5-fluorouracil 500 mg/m^2/day, continuous intravenous infusion for 120 h). IC was repeated every 3 weeks. Concurrent chemotherapy consisted of cisplatin 25 mg/m^2 weekly or 75 mg/m^2 every 3 weeks during IMRT.

Patient evaluation

All patients were followed up every 3 months after IMRT in the first 2 years, every 6 months during the year 3–5, and once a year thereafter. Follow-up assessments included physical examination, MRI of nasopharynx, abdominal ultrasound scan, and chest CT or X-ray. If tumor recurrence was indicated by MRI, nasopharyngeal biopsy or PET-CT was performed. Additional tests were performed whenever they were clinically indicated.

Statistical methods

The follow-up period was calculated from the day of first treatment. The Statistical Package for Social Sciences (SPSS version 25.0) software was used for statistical analyses. The estimated local control (LC) and overall survival (OS) rates were calculated using the Kaplan-Meier method.

Definition of failure pattern

The images of MRI or CT scans obtained at the time of recurrence were transferred to the pretreatment planning CT. Image fusion of the recurrent images was performed with the planning CT. The recurrent tumor was delineated layer by layer as GTVrecur. The radiation dose received by GTVrecur was calculated with dose-volume histogram (DVH). The recurrent tumor was classified as inside or outside the high dose target volume, depending on the location of GTVrecur. If 95% of GTVrecur was within the 95% isodose, the recurrence was defined as "in field" failure; if 20 to 95% of GTVrecur was within the 95% isodose, the recurrence was categorized as "marginal" failure; if less than 20% of GTVrecur was inside the 95% isodose, it was defined as "outside" failure [5].

Results

Patient characteristics

A total of 145 patients were enrolled in this study. Patient and treatment characteristics were detailed in Table 1. At the time of analysis, local recurrence was observed in 23 patients during follow-up. For patients with local recurrence, the median age was 47 years (33–73years). The ratio of men to women was 19: 4. There were 9 (39.1%) patients with N0–1 and 14 (60.8%) with N2–3. Eight (34.7%) patients received concurrent chemoradiotherapy. Eleven (47.8%) patients received adjuvant chemotherapy. For IC regimens, most of the patients (65.2%) received TPF regimen. Other regimens included GP for 13%, PF for 13% and TP for 8.7% of the patients. The median cycles of IC were 3 (range from 1 to 3 cycles).

Rates of overall survival and local recurrence

With a median follow-up time of 95 months (range, 16–142 months), the estimated 5- and 10-year overall survival rates for all patients were 72.2% and 54.8%, respectively (Fig. 2). The estimated 5- and 10-year local control rates were 85.2% and 81.1%, respectively(Fig. 2). The median time from first treatment to local recurrence was 31 months (range 12–97 months).

Dose-volume histogram data

The detailed DVH statistics of IMRT planning was shown in Table 2.

Table 1
Patient characteristics and treatment factors (n = 145).

Characteristic	Patients (%)
Gender	
Male	108 (74.5)
Female	37 (25.5)
Age (yr)	
Median (Range)	47 (9–75)
WHO histologic type	
II	37 (25.5)
III	104 (71.7)
Node classification	
N0–1	66 (45.5)
N2–3	79 (54.5)
IMRT duration (days)	45 (40–55)
Therapeutic schedule	
IC + RT	16 (11)
IC + CCRT	52 (35.9)
IC + RT + AC	70 (48.3)
IC + CCRT +AC	6 (4.1)
IC regimen	
TPF	82 (56.6)
GP	23 (15.9)
PF	17 (11.7)
TP	8 (5.5)
TTR(months)	
Median (range)	31 (12–97)

WHO, World Health Organization; IMRT, intensity-modulated radiotherapy; IC, induction chemotherapy; RT, radiotherapy; CCRT, concurrent chemoradiotherapy; AC, adjuvant chemotherapy; TTR, time to recurrence.

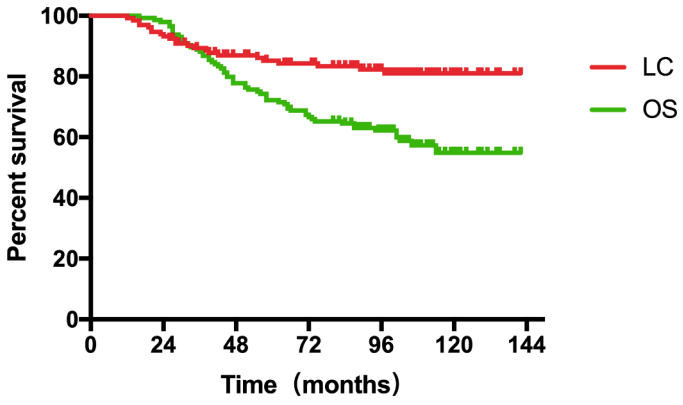

Fig. 2. Kaplan-Meier curves showing local control (LC) and overall survival (OS) rates for 145 patients with T4 nasopharyngeal carcinoma.

The dose coverage for positive lymph node was excellent and only 0.3% of the PTV-LN received less than 95% of the prescribed dose. However, the rate of dose coverage for primary tumor was relatively poor. There were 2.4% (0–7.5%) of the PTV-G receiving less than 95% of the prescribed dose. Only 87.8% of the PTV-G received more than 100% of the prescribed dose. The dose coverage for PTV-C1 and PTV-C2 was satisfactory. The average volume receiving more than 95% of the prescribed dose was 99.1% to PTV-C1 and 99.4% to PTV-C2.

Patterns of local recurrence

Three patients were excluded in the dosimetric analysis because of the unavailability of diagnostic images. A total of 20 recurrences were analyzed, 18 (90%) occurred within the 95% isodose lines and were considered in-field failures, and 2 (10%) were marginal failures. There was no out-field failure. The average minimum (Dmin), maximum (Dmax) and mean(Dmean) dose delivered to GTVrecur for in-field failures were 58.1, 75.8 and 71.0 Gy, respectively. For marginal failures, the Dmin, Dmax and Dmean were 44.0, 77.4 and 68.9 Gy, respectively. The

Table 2
Dose–volume histograms (DVHs) statistics for patients with recurrent disease.

	Average (range) PTV-G	PTV-LN	PTV-C1	PTV-C2
Volume (cc)	115.3 (63.9–207.9)	65.9 (6.3–196.9)	608.2 (333.8–808.6)	117.4 (22.6–271.0)
Dmin (Gy)	58.9 (53.0–66.7)	58.7 (31.5–65.9)	40.3 (14.1–54.1)	67.2 (29.9–466.6)
Dmax (Gy)	76.8 (74.7–78.7)	73.2 (69.2–77.2)	76.3 (73.1–78.7)	61.3 (58.6–64.8)
Dmean (Gy)	72.3 (71.6–73.5)	68.9 (67.5–71.1)	65.8 (62.1–69.6)	56.5 (55.5–57.5)
V95%	97.6 (92.5–100)	99.7 (97.3–100)	99.1 (97.7–100)	99.4 (97.1–100)
V100%	87.8 (77.3–95.7)	91.1 (53.4–99.8)	95.5 (90.3–98.7)	95.5 (91.1–99.0)
V110%	0.1 (0–1.6)	1.4 (0–10.6)	41.9 (2.6–77.9)	3.3 (0–10.2)

PTV-G, planning tumor volume of primary tumor; PTV-LN, planning tumor volume of involved lymph nodes; PTV-C1, planning tumor volume of the high-risk region; PTV-C2, planning tumor volume of lymph nodal regions at low risk; Dmin, Minimum dose; Dmax, Maximum dose; Dmean, Mean dose; V95%, percentage of volume receiving≥ 95% of the prescribed dose; V100%, percentage of volume receiving ≥100% of the prescribed dose; V110%, percentage of volume receiving ≥110% of the prescribed dose.

sites and DVH statistics to recurrence tumors were detailed in Table 3.

Salvage treatment for local recurrence

Ten patients received re-irradiation with or without chemotherapy for local recurrent disease. Nine patients with synchronous distant metastasis received chemotherapy. One patient received surgery. And the remaining 3 patients received supportive and symptomatic therapy. All except one patients died at last follow-up. Six (27.3%) patients died of epistaxis, 10 (45.5%) patients died of disease progression, 1 (4.5%) patients died of other disease, and 5 (22.7%) patients died of unknown reason. All of the 6 patients who died of epistaxis received re-irradiation for recurrent disease. The median overall survival time after recurrence was 15.5 months (range 1–77 months).

Discussion

In the era of IMRT, local control and overall survival of patients with NPC have been greatly improved [10,22–24]. Reduction of treatment-related toxicities has translated into significant improvement of quality of life (QOL) [9,10,22,25]. However, for patients with T4 NPC, the wide range of tumor invasion makes the distance between target volume and important OARs too close. Radical dose to the tumor will inevitably cause damage to vital OARs including brain stem, temporal lobe, optic nerve and chiasm. For patients with locoreginally advanced NPC, how to reduce treatment-related toxicities and improve long-term QOL has always been the direction of efforts for radiologists.

With the publication of several randomized clinical trials [15–17], IC combined with CCRT has become one of the standard treatments for LA-NPC. IC has the advantage of reducing the tumor burden and shrinking the tumor volume. It has been reported that reducing the target volumes after IC is expected to further reduce late toxicities without compromising local and distant control for patients with LA-NPC [18,19,26]. However, the delineation of target volume and optimal dose for tumor shrinkage after IC is controversial.

In 2017, Yang et al. [19] firstly reported a prospective randomized trial comparing survivals and QOL of patients treated with target volumes based on pre-(Arm A) or post- (Arm B) IC imaging. The results showed that there was no significant difference in 3-year locoregional control, overall survival, distant failure-free survival and progression-free survival. However, the doses given to vital OAR were significantly decreased and the QOL were significantly improved in Arm B. The dose delivered to disappeared GTV after IC was 64 Gy. Then in 2019, Zhao et al. [18] published their excellent 10-year results of a phase 2 study including 112 patients with target volumes based on post-IC imaging. The prescribed dose to primary tumor shrinkage after IC was 60 Gy, which was lower than that in the study of Yang et al. [19] The 10-year LC, OS and distant failure-free survival (DFFS) were 89.0%, 75.9% and 83.3% respectively. All of the local recurrences were in-field failures and only 2 regional recurrences were marginal or out-field failures. According to the basic principles of radiobiology [27], high tumor burden requires increased radiation dose to achieve tumor control. However, once the gross tumor has shrunk to subclinical lesions

Table 3
Details of recurrent patients.

No.	Site of relapse	Location of the recurrence volume	Dose–volume histograms statistics to recurrence volume GTVrecur (cc)	Dmin (Gy)	Dmax (Gy)	Dmean (Gy)	V_{95} (cc)	$V_{95\%}$ (%)	Type of relapse[a]
1	Skull base, cavernous sinus	GTV	9.3	61.8	74.0	72.0	9.2	99.2	In-field
2	Pharyngeal recess	CTV1	8.0	66.0	73.8	72.1	8.0	100	In-field
3	Skull base	GTV	4.7	68.1	74.6	71.6	4.7	100	In-field
4	Skull base, cavernous sinus, nasopharynx	CTV1	13.9	48.5	75.2	69.9	13.6	97.9	In-field
5	Nasal septum	CTV1	7.1	70.4	75.5	72.7	7.1	100	In-field
6	Nasopharynx, hard palate, skull base, orbit, ethmoid sinus	CTV1	32.9	37.6	75.4	70.9	32.2	97.7	In-field
7	RPN	CTV1	13.0	61.5	74.3	68.7	13.0	100	In-field
8	Cavernous sinus, skull base	CTV1	10.5	51.5	77.0	70.0	9.9	94.3	Marginal
9	Nasopharynx, RPN	GTV	8.8	69.1	75.7	72.3	8.8	100	In-field
10	Skull base, sphenoid sinus	CTV	15.2	63.3	77.3	71.9	15.2	100	In-field
11	Skull base, musculus longus capitis	CTV1	8.1	61.0	75.8	72.0	8.1	100	In-field
12	Skull base, musculus longus capitis	CTV1	6.2	59.0	74.6	71.0	6.2	100	In-field
13	Skull base, cavernous sinus	Marginal to CTV1	71.0	36.6	77.8	67.8	60.9	85.8	Marginal
14	Skull base	CTV1	13.3	61.7	76.5	72.9	13.3	100	In-field
15	Nasopharynx	CTV1	52.1	57.0	75.3	71.1	52.1	100	In-field
16	Nasopharynx	GTV	3.1	67.9	76.3	72.7	3.1	100	In-field
17	Nasopharynx	GTV	9.8	66.7	77.3	72.3	9.8	99.8	In-field
18	Skull base	CTV1	30.3	53.8	76.5	69.1	29.3	96.6	In-field
19	Nasopharynx	CTV1	44.0	50.1	76.8	71.6	43.8	99.4	In-field
20	Musculus longus capitis, skull base	CTV1	16.3	50.6	76.2	67.6	15.7	96.2	In-field

Vrecur, volume of recurrent tumor; Dmin, Minimum dose; Dmax, Maximum dose; Dmean, Mean dose; V95, tumor volume receiving at least 95% of the prescribed dose; V95%, percentage of volume receiving at least 95% of the prescribed dose; GTV, gross tumor volume; CTV, clinical target volume; RPN, retropharyngeal lymph nodes.
[a] In-field refers to at least 95% of the recurrence volume receiving more than 95% of the prescribed dose; Marginal refers to 20–95% of the recurrence volume receiving 95% of the prescribed dose; Outside refers to less than 20% of the recurrence volume receiving 95% of the prescribed dose.

after IC, we suppose it is reasonable to decrease the radiation dose to prophylactic dose. So in our study, the prescription dose for area of tumor shrinkage was 60 Gy, which was the same as Zhao et al.'s study [18]. The long-term results showed satisfactory local control and overall survival with fewer marginal recurrences, which further confirmed the feasibility of prophylactic dose to the post-IC primary tumor shrinkage. It was worth noting that the estimated 10-year LC (81.1%) and OS (54.8%) rates in our study were relatively lower than that in the study of Zhao et al.(89% for LC and 75.9% for OS)[18]. We attributed this to the high proportion of stage T4 patients in our study (100% vs. 25.9%).

It should be noted that in the above studies including our present study, for the bony structures of skull base invasion, the target volume was delineated based on pre-IC images regardless of the tumor regression after IC. Can the skull base invasion also be delineated based on post-IC images? Wang et al. [26] reported their 5-year results of 57 patients for whom all tumor regression field was outlined in CTV1 including skull base invasion. The relevant dose prescribed to CTV1 was 60 Gy. The 5-year locoregional relapse-free survival, OS, and DFFS rates were 87.7%, 82.2% and 85.8%, respectively. All locoregional recurrences were in the GTV-residual region and were in-field failures. The results support the feasibility of reducing the volume and radiation dose for tumor regression area after IC, especially for patients whose tumor is close to or directly invades the orbit, optic nerve, chiasm or brain stem. However, since tumor shrinkage of the skull base invasion after IC cannot be clearly shown on the MRI, it is necessary to be cautious in clinical application. It is recommended to perform it in an experienced cancer center.

In the present study, 90% of the recurrence were in-field failures, only 10% were marginal failures. There was no out-field failure. No recurrence happened in the tumor shrinkage, which means that reduction of RT dose for tumor shrinkage does not cause additional local recurrence. Our results showed that IMRT with reduced GTV after IC is safe and feasible. Recurrence in high-dose region suggests radioresistance of tumor cells [28]. For these patients, improving the radiosensitivity is of primary importance. With the rise of immunotherapy, combined chemotherapy and immunotherapy has achieved excellent effects in recurrent and metastatic NPC, with an ORR rate of 91% [29]. Researches focusing immunotherapy on LA-NPC are also on the way. Whether immunotherapy combined with chemotherapy or radiotherapy can bring innovation in the delineation of target volume for LA-NPC, by reducing the tumor volume or dose, or reducing the dose of OAR and increasing the patients' QOL are worthy of further study.

As the optimal target volume and dose of IMRT after IC is still controversial, clinicians need to fully communicate with the patients and their families so as to formulate individualized target volume delineation scheme according to different conditions of each patient. For patients with tumor adjacent to brain stem, optic nerve and chiasm, it seems to be more reasonable and feasible to delineate the target volume according to post-IC images. Further researches exploring optimal target volume and RT dose for LA-NPC in the era of IC are warranted.

Conclusion

Our long-term results showed that in-field failure was the major pattern of local failure for T4 NPC. IMRT with reduced target volume after IC seems feasible. Further researches exploring optimal volume and radiation dose for local advanced NPC in the era of IC are warranted.

CRediT authorship contribution statement

Fang-Fang Kong: Conceptualization, Visualization, Data curation, Writing – review & editing, Formal analysis. **Meng-Shan Ni:** Conceptualization, Visualization, Data curation, Writing – review & editing, Formal analysis. **Rui-Ping Zhai:** Data curation, Formal analysis, Writing – review & editing. **Hong-Mei Ying:** Conceptualization, Visualization, Writing – review & editing. **Chao-Su Hu:** Conceptualization, Visualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare that there is no conflict of interests.

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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