


Postoperative Radiotherapy Omitting Level IV for Locally Advanced Supraglottic and Glottic Laryngeal Carcinoma

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Abstract

Background: Cervical lymph nodes metastases are one of the most significant prognostic factors in patients with laryngeal carcinoma, whether treatment by surgery or by radiotherapy. The current study retrospectively examined the postoperative radiotherapy of locally advanced supraglottic and glottic laryngeal carcinoma (at a greater risk of lymph node metastasis) to determine the effect of radiotherapy excluding cervical level IV lymph nodes. **Methods:** Patients of supraglottic type and glottic type were irradiated with level IV from January 2012 to June 2013, without level IV from July 2013 to December 2014, according to physicians' decision. Ninety-three patients were selective neck irradiation (SNI) of levels II-IV (Group A) and 87 patients were SNI of levels II and III (Group B). The comparison between Group A and Group B was made with observation of clinical risk of recurrence and radiation complications, as well as overall survival (OS), progress-free survival (PFS) and regional nodal recurrence-free survival. **Results:** No remarkable difference was observed in the distribution of recurrence, levels of relapse, OS, PFS and regional nodal recurrence-free survival between the 2 groups ($p > 0.05$). Mean radiation dose at level IV, thyroid and cervical esophagus showed significant difference between the 2 therapeutic groups ($p < 0.01$). As regard radiation complications, no significant difference was found in radiation dermatitis of any grade between the 2 groups ($p > 0.05$). However, there was remarkable difference in clinical hypothyroidism and radiation esophagitis between Group A and Group B ($p < 0.05$). **Conclusions:** Radiotherapy after surgery omitting level IV may improve the quality of life in patients with locally advanced supraglottic and glottic laryngeal carcinoma, won't worsen the prognosis as well.

Keywords

supraglottic laryngeal carcinoma, glottic laryngeal carcinoma, radiation therapy, radiation complication, selective neck irradiation

Abbreviations

CT, computerized tomography; CTV, clinical target volume; DVH, dose volume histogram; ECLI, electro-chemiluminescence immunoassay; FT4, free thyroxine; FT3, free triiodothyronine; GTVtb, gross tumor volume tumor bed; IMRT, intensity modulated radiotherapy; OS, overall survival; PET-CT, positron emission tomography-computerized tomography; PFS, progress-free survival; PTV, planning target volume; SNI, selective neck irradiation; TSH, thyroid stimulating hormone

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Introduction

Laryngeal carcinoma is one of the most common malignant carcinoma and comprises around 25% of all head and neck cancers,¹ of which glottic type and supraglottic type separately accounts for more than 50% and 30%~40%.^{2,3} Cervical lymph node metastasis is one of the most significant prognostic factors in patients with laryngeal carcinoma.⁴ The cervical lymph node metastasis rate of supraglottic carcinoma is about 55%, most of

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Table 1. Demographics and Treatment Characteristics.

Variables	Categories	Group A (n = 93)			Group B (n = 87)			p value
		Supraglottic	Glottic	Total	Supraglottic	Glottic	Total	
Gender	Female	7(7.5%)	4(4.3%)	11(11.8%)	6(6.9%)	6(6.9%)	12(13.8%)	0.694
	Male	32(34.4%)	50(53.8%)	82(88.2%)	30(34.5%)	45(51.7%)	75(86.2%)	
Age, years	—	63.1 ± 4.83	65.0 ± 3.78	64.2 ± 4.34	64.2 ± 5.74	65.4 ± 3.02	64.9 ± 4.37	0.286
Site of primary tumor	—	39(41.9%)	54(58.1%)	93	36(41.4%)	51(58.6%)	87	0.940
Postoperative pathologic T stage (AJCC 7th)	T2	2(2.2%)	0	2(2.2%)	4(4.6%)	0	4(4.6%)	0.381
	T3	25(26.9%)	36(38.7%)	61(65.6%)	23(26.4%)	36(41.4%)	59(67.8%)	
	T4	12(12.9%)	18(19.3%)	30(32.2%)	9(10.4%)	15(17.2%)	24(27.6%)	
Postoperative pathologic N stage (AJCC 7th)	N0	2(2.2%)	25(26.9%)	27(29.1%)	4(4.6%)	26(29.9%)	30(34.5%)	0.587
	N1	4(4.3%)	9(9.7%)	13(14.0%)	2(2.3%)	8(9.2%)	10(11.5%)	
	N2a	6(6.4%)	4(4.3%)	10(10.7%)	5(5.7%)	4(4.6%)	9(10.3%)	
	N2b	15(16.1%)	10(10.7%)	25(26.9%)	13(14.9%)	9(10.3%)	22(25.3%)	
	N2c	8(8.6%)	4(4.3%)	12(12.9%)	9(10.3%)	2(2.3%)	11(12.6%)	
	N3	4(4.3%)	2(2.2%)	6(6.5%)	3(3.4%)	2(2.3%)	5(5.7%)	
	IVa-b	33(35.5%)	25(26.9%)	58(62.4%)	30(34.5%)	23(26.4%)	53(60.9%)	
Overall stage*	III	6(6.4%)	29(31.2%)	35(37.6%)	6(6.9%)	28(32.2%)	34(39.1%)	0.842
	IVa-b	33(35.5%)	25(26.9%)	58(62.4%)	30(34.5%)	23(26.4%)	53(60.9%)	
Lead time [#] , days	—	25.8 ± 7.23	28.1 ± 5.54	27.1 ± 6.37	26.3 ± 6.76	26.1 ± 6.24	26.2 ± 6.42	0.329
Neck dissection	Modified radical	11(11.8%)	7(7.5%)	18(19.3%)	13(14.9%)	7(8.0%)	20(23.0%)	0.551
	Selective radical	28(30.1%)	47(50.5%)	75(80.6%)	23(26.4%)	44(50.6%)	67(77.0%)	

Group A = selective neck irradiation of level II–IV; Group B = selective neck irradiation of level II and III.

*According to the 7th UICC/AJCC staging system.

[#] The time between surgery and the first fraction of IMRT.

which are located at level II followed by level III.^{5,6} The incidence of metastasis in patients with glottic carcinoma has been reported to happen approximately 80% at level II and nearly 20% at level III.⁷ Although it has very low incidence of lymph node positivity within level IV, some head and neck specialists still keep on surgical options for laryngeal carcinoma generally including levels II–IV.^{8,9} In fact, more than 90% of laryngeal carcinoma requiring selective cervical dissection only needs to be treated with levels II and III.^{10,11} For radiation therapist, level IV is considered in a radiation setting for routine treatment with locally advanced laryngeal carcinoma, thus it remains a dilemma to including level IV or not.

The complications of cervical radiotherapy at level IV of laryngeal carcinoma are mainly including thyroid dysfunction, radiation esophagitis and dermatitis. If selective neck irradiation (SNI) of levels II and III, without level IV, it may reduce the radiation complications associated with these lesions, so as to minimize the pain of the patients. The rate of cervical lymph node metastasis in patients with glottic carcinoma is about 5% in T1-T2 and about 20% in T3-T4.¹² Locally advanced head and neck disease carries a high risk of metastasis with a poor prognosis.¹³ Since all stages of supraglottic laryngeal carcinoma and locally advanced glottis carcinoma are prone to cervical lymph node metastasis, to reduce heterogenous in this study, we only retrospectively post-operative patients of supraglottic type and glottic type of locally advanced stages III-IV.

Patients and Methods

Patient Characteristics

This retrospective study was approved by the Ethics Committee of our hospital. Informed consent was obtained from all patients prior to treatment. The patients included: locally advanced

supraglottic type and glottic type (stage III and stage IV without distant metastasis), requiring radiotherapy after modified or selective radical neck dissection, without chemotherapy. All the patients, performed larynx enhanced CT, chest CT, color Doppler ultrasound of liver, bone scan or PET-CT before surgery. All the patients, undergone pretreatment physical, endoscopic and radiological examinations, had no abnormal thyroid function before radiotherapy, treated with IMRT, collected from January 2012 to December 2014 and follow-up ended in December 2019. Patients of supraglottic type and glottic type were irradiated with level IV from January 2012 to June 2013, without level IV from July 2013 to December 2014, according to physicians' decision over their clinical practice over time: selective neck irradiation (SNI) of level II, III and IV (Group A) and SNI of level II, III (Group B). Of the included patients, 75 were diagnosed with supraglottic carcinoma and 105 were diagnosed with glottic carcinoma, respectively. Demographics and treatment characteristics of SNI of level IV or not were summarized in Table 1. Twenty-three women and 157 men were included in this analysis. There was no significant difference between Group A and Group B in gender and age ($p > 0.05$). Other baseline disease characteristics and treatment of pre-radiotherapy were showed generally balanced between the 2 groups ($p > 0.05$). The distribution of involved positive lymph nodes after surgery confirmed by biopsy between Group A and Group B was shown in Table 2. No significant difference was found between the 2 groups ($p > 0.05$). There was no positive lymph nodes in level IV, but very few cases in level VI.

Target Volume Delineations for IMRT

All the patients received intensity-modulated radiotherapy (IMRT) in our institution. Gross Tumor Volume tumor bed

Table 2. Numbers of Lymph Nodes Involvement According to the 2 Therapeutic Groups Before Radiotherapy.

Lymph node	Side	Group A			Group B			p value
		Supraglottic	Glottic	Total	Supraglottic	Glottic	Total	
Level II	Ipsilateral	107(66.5%)	54(33.5%)	161	97(64.2%)	54(35.8%)	151	0.339
Level II	Contralateral	23(74.2%)	8(25.8%)	31	19(82.6%)	4(17.4%)	23	
Level III	Ipsilateral	45(72.6%)	17(27.4%)	62	35(71.4%)	14(28.6%)	49	
Level VI		1(25.0%)	3(75.0%)	4	1(33.3%)	2(66.7%)	3	
Total		176(68.2%)	82(31.8%)	258	152(67.3%)	74(32.7%)	226	

Group A = selective neck irradiation of level II–IV; Group B = selective neck irradiation of level II and III.

(GTVtb): sketched the gross tumor according to the localization of CT, laryngoscope and PET-CT (part of patients) before resection. Clinical Target Volume 1 (CTV1): the high-risk clinical target area, including 10 mm outside of GTVtb, avoided scaling out while encountering bone and cavity anatomical barrier, and the involving area of positive lymph nodes before resection in the neck. Clinical Target Volume 2 (CTV2): low risk clinical target area, including 5 mm outside of CTV1 and the whole larynx, avoided scaling out while encountering anatomical barrier, wherein the small target group also included cervical levels II and III. Meanwhile, the lower boundary of the target area was 20 mm more than it of the cervical positive lymph nodes (except that the only one case in this study reached 3 mm below the inferior boundary of the cricoid cartilage, the target area of the other patients did not reach the level IV). Besides, the large target group also included cervical levels II, III and IV. Planning Target Volume (PTV): margins of 3 mm was added to the GTVtb to generate PTV-GTVtb. Margins of 3 mm was added to the CTV1 to generate PTV1 and to the CTV2 to generate PTV2.

Radiotherapy Dose

Radiation was delivered via 6-MV photon field. The single dose of PTV-GTVtb was 2.0 Gy and the total dose was 60Gy-66 Gy (NCCN Clinical Practice Guidelines in OncologyTM Head and Neck Cancers. Version.1.2010). The single dose of PTV1 was 2 Gy and the total dose was 60 Gy. The single dose of PTV2 was 1.8 Gy and the total dose was 54 Gy. SNI was undergone to bilateral levels II-IV or levels II and III. Radiation dose in level IV, thyroid and cervical esophagus between the 2 groups was shown by the dose volume histogram (DVH) chart.

Observation of Radiation Complications

The fasting serum levels of Thyroid Stimulating Hormone (TSH), Free Triiodothyronine (FT3) and Free Thyroxine (FT4) were measured at the end of radiotherapy, 6 months and 12 months after radiotherapy by electro-chemiluminescence immunoassay (ECLI). TSH > 4.2 μ IU / ml was diagnosed subclinical hypothyroidism. FT4 < 12pmol/L or FT3 < 3.1pmol/L was diagnosed clinical hypothyroidism. Each patient was investigated weekly during and after radiotherapy

by a radiation oncologist who was blinded to the group of patients assigned to him. Acute esophageal toxicity (symptoms less than 3 months) was assessed by review of the time parameters concerning beginning or seizing of symptoms. The RTOG toxicity scale was used to grade the side effects. In grade 1, the patient has mild dysphagia or odynophagia; may require topical anesthetic, nonnarcotic agents, or soft diet. In grade 2, the patient has moderate dysphagia or odynophagia; may require narcotic agents or puree/liquid diet. In grade 3, the patient has severe dysphagia or odynophagia with dehydration or weight loss (>15% from pretreatment baseline) requiring nasogastric feeding tube or hyperalimentation. In grade 4, the patient has complete obstruction, ulceration, perforation, or fistula. As for radiation skin injury, it was recorded according to the RTOG radiodermatitis scoring (grade 1: follicular, faint or dull erythema, epilation, dry desquamation, decreased sweating; grade 2: tender or bright erythema, patchy moist desquamation, moderate edema; grade 3: confluent, moist desquamation other than skin folds, pitting edema; grade 4: ulceration, hemorrhage, necrosis).

Follow-Up

Follow-up was scored from the completion of operation to first documented clinical disease progression or first documented regional nodal recurrence or the last visit or death. All patients were reexamined every 2 to 3 months after radiotherapy and every 4 to 6 months in the third year. Physical examination and laryngoscope were performed every time. Larynx and chest CT and liver color Doppler ultrasound were done once or twice a year. PET-CT could be considered in the clinical suspected recurrence or metastasis. The relapsed number of cervical levels was counted at the first recurrence in each patient.

Statistical Analysis

Group A and group B were compared by means of the chi-square, Fisher's test, or nonparametric test. Comparison of radiation dose between the 2 groups was analyzed using the independent samples t-test. The rates of overall survival (OS), progress-free survival (PFS) and regional nodal recurrence-free survival were estimated using the Kaplan-Meier method. OS was calculated from the date of completion of operation to the date of death at the time of last contact. Meanwhile date for

Table 3. Recurrence According to the 2 Therapeutic Groups.

Variables	Categories	Group A (n = 93)			Group B (n = 87)			p value
		Supraglottic	Glottic	Total	Supraglottic	Glottic	Total	
Recurrence by distribution	NO	20(21.5%)	32(34.4%)	52(55.9%)	21(24.1%)	32(36.8%)	53(60.9%)	0.622
	Local	0	6(6.5%)	6(6.5%)	2(2.3%)	6(6.9%)	8(9.2%)	
	Ipsilateral neck	8(8.6%)	2(2.2%)	10(10.8%)	5(5.7%)	2(2.3%)	7(8.0%)	
	Bilateral neck	0	0	0	1(1.1%)	0	1(1.1%)	
	Distant metastasis	4(4.3%)	3(3.2%)	7(7.5%)	1(1.1%)	2(2.3%)	3(3.4%)	
	Local + Ipsilateral neck	5(5.4%)	4(4.3%)	9(9.7%)	4(4.6%)	2(2.3%)	6(6.9%)	
	Local + Bilateral neck	0	2(2.2%)	2(2.2%)	0	1(1.1%)	1(1.1%)	
	Local + Ipsilateral neck + Distant metastasis	1(1.1%)	2(2.2%)	3(3.2%)	2(2.3%)	4(4.6%)	6(6.9%)	
	Local + Bilateral neck + Distant metastasis	1(1.1%)	1(1.1%)	2(2.2%)	0	1(1.1%)	1(1.1%)	
Local + Distant metastasis	0	2(2.2%)	2(2.2%)	0	1(1.1%)	1(1.1%)		
Recurrence by neck level							0.567	
Ipsilateral	II	8(8.6%)	4(4.3%)	12(12.9%)	7(8.0%)	6(6.9%)	13(14.9%)	
	III	2(2.2%)	1(1.1%)	3(3.2%)	1(1.1%)	0	1(1.1%)	
	II + III	4(4.3%)	2(2.2%)	6(6.5%)	2(2.3%)	1(1.1%)	3(3.4%)	
	II + VI	0	1(1.1%)	1(1.1%)	1(1.1%)	1(1.1%)	2(2.3%)	
Contralateral	II	1(1.1%)	3(3.2%)	4(4.3%)	1(1.1%)	2(2.3%)	3(3.4%)	

Group A = selective neck irradiation of level II–IV; Group B = selective neck irradiation of level II and III.

patients who were alive or lost to follow-up was defined to be censored. PFS was calculated from the date of completion of operation to the date of progression at the time of last tumor imaging. Meanwhile date for patients without disease progression or who were lost to follow-up was defined to be censored. Regional nodal recurrence-free survival was calculated from the date of completion of operation to the date of neck lymph node relapse at the time of the last pathological diagnosis. Meanwhile date for patients without neck lymph node relapse or who were lost to follow-up was defined to be censored. Survival distributions of the 2 groups were compared by the log-rank test. Differences with p -values < 0.05 were considered statistically significant. Statistical calculations were performed using SPSS software, version 18.0.

Results

Comparison of the Characteristics of Recurrence and Lymph Node Spread Between SNI Levels II-IV Group and SNI Levels II and III Group

Of the 93 patients in SNI levels II-IV group (Group A), 52(55.9%) had no recurrence, by contrast, 53(60.9%) had no recurrence out of 87 patients in SNI levels II and III group (Group B). Forty-one patients (44.1%) in Group A had tumor recurrences, of which 24(25.8%) patients were found to develop local recurrence, 14(15.1%) developed distant metastases, 22(23.7%) developed ipsilateral metastases, and 4(4.3%) developed bilateral neck metastases. A total of 34 patients (39.1%) in Group B had tumor recurrences, of which 23(26.4%) patients

were found to develop local recurrence, 11(12.6%) developed distant metastases, 19(21.8%) developed ipsilateral metastases, and 3(3.4%) developed bilateral neck metastases. No statistically significant difference was observed between the 2 groups ($p > 0.05$), as shown in Table 3. It also lists the distribution (sub) levels of nodal relapse. The number of patients with recurrence by neck level II was 19(20.4%) ipsilateral and 4(4.3%) contralateral metastases in Group A, as well as 18(20.7%) ipsilateral and 3(3.4%) contralateral metastases in Group B. Nine of the 93 patients with recurrence by neck level III in Group A, and 4(4.6%) in Group B. A total of 9(5.0%) patients had level III lymph nodes be involved, accompanied by positive nodes at level II. Three(1.7%) patients had positive nodes simultaneously at level VI and level II. No relapsed positive nodes was found in level IV. There was no significant difference between Group A and Group B in the distribution levels of relapse ($p > 0.05$).

Comparison of Survival Rates Between SNI Levels II-IV Group and SNI Levels II and III Group

The median follow-up time was 56.8 (5-68) months in Group A and 55.8 (6-67) months in Group B. The Kaplan-Meier 5-year estimate for overall survival (OS) were 50.2% in SNI levels II-IV group (Group A) and 52.2% SNI levels II and III group (Group B). Overall survival rates were not significantly different between Group A and Group B ($p > 0.05$, multiple intersections existed between the 2 groups) (Figure 1A). The 5-year progress-free survival (PFS) estimate rates in Group A and in Group B were 29.7% and 31.0%. The survival rates differences showed no significance ($p > 0.05$, multiple intersections existed

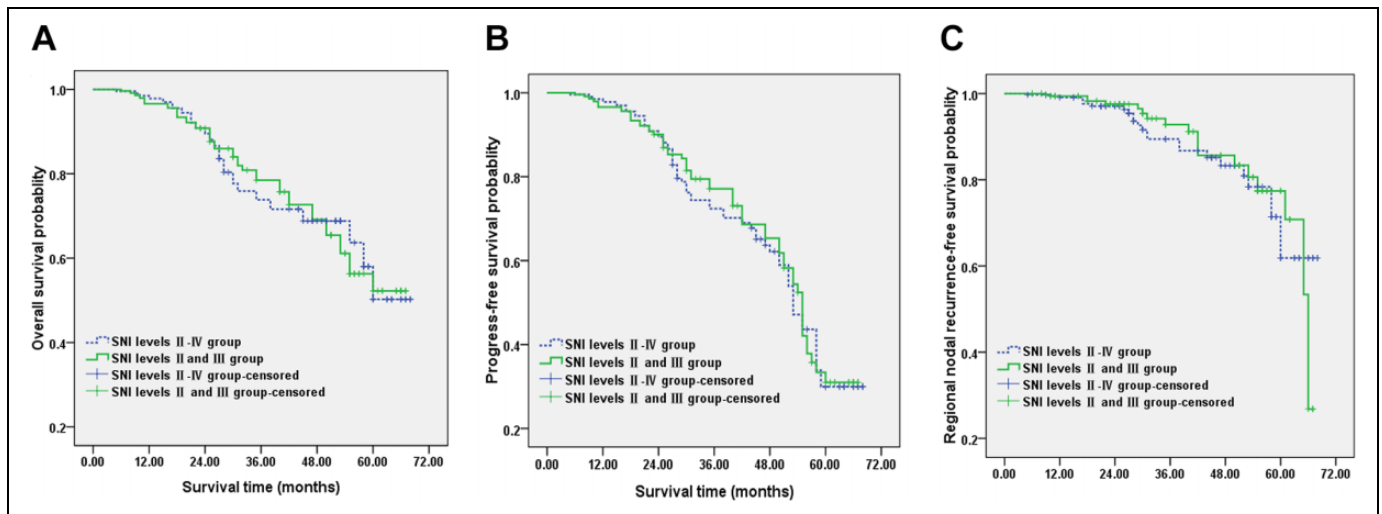


Figure 1. Comparison of the survival curve according to selective neck irradiation of level II-IV (Group A) and selective neck irradiation of level II, III (Group B). A, The overall survival curve. B, The progress-free survival curve. C, The regional nodal recurrence-free survival curve.

between the 2 groups) (Figure 1B). The Kaplan-Meier estimate for regional nodal recurrence-free survival was showed in Figure 1C. There was no significantly difference between Group A and Group B in 5 years ($p > 0.05$).

Comparison of Radiation Complications Between SNI Levels II-IV Group and SNI Levels II and III Group

DVH charts of 2 patients, irradiation including level IV and excluding level IV were separately showed in Figure 2A and Figure 2B. As shown in Table 4, in SNI levels II-IV group (Group A), level IV lied in the radiation range, with mean radiation dose 52.6 Gy at level IV, 49.0 Gy at thyroid and 38.1 Gy at cervical esophagus. Accordingly, in SNI levels II and III group (Group B), level IV received 6.2 Gy of mean radiation dose, with 28.7 Gy at thyroid and 11.1 Gy at cervical esophagus. Independent samples t-test was estimated between Group A and Group B, with significant difference ($p < 0.01$, Table 4). There were a total of 75 patients in Group A developed thyroid dysfunction including subclinical and clinical hypothyroidism, as well as 30 in Group B. As shown in Table 5, there was significant difference in thyroid dysfunction between Group A and Group B ($p < 0.05$). Seventy-eight (83.9%) patients in Group A and 44 (50.6%) in Group B produced radiation esophagitis at all stages. Radiation esophagitis of Group B showed remarkable difference from Group A ($p < 0.05$). No significant difference was found in radiation dermatitis of any grade between Group A (93 patients) and Group B (85 patients) ($p > 0.05$). The above complications in each group are listed in Table 5.

Discussion

In the current study, data of locally advanced supraglottic type and glottic type patients (stages III and IV without distant metastasis) were retrospectively. No significant difference was

found for the results of OS, PFS and regional nodal recurrence-free survival, which suggest that the postoperative radiotherapy omitting level IV may not worsen the prognosis and there were no discrepancy in therapeutic efficacy between the 2 groups. It is reported that the presence of lymph node metastasis before treatment is an important prognostic factor for head and neck cancer, even though the presence of one positive lymph node is considered to reduce OS by 50%.¹⁴ In this study, there is no cervical lymph node metastasis found at level IV before and after treatment, which is common in our clinical practice. Our results may be supported by the following: the lymphatic fluid of supraglottic and glottic areas flows mainly into the lymph nodes of level II and III¹⁵; ipsilateral Levels II and III are reported to be the main regions of neck metastases^{16,17}; lymph nodes at level IV are found extremely infrequently^{6,18}; contralateral level IV shows no positive metastatic lymph nodes in any of the stages.^{11,19} Surgical reports showed that elective dissection of lymph nodes at levels II-IV is indicated for patients with T3 and T4 laryngeal cancers.²⁰ Besides, it is reported that metastasis at level IV may not play a role in a fatal prognosis.¹⁵

It is found in our daily work that recurrence and/or metastasis of laryngeal carcinoma after treatment may occur whether radiotherapy including level IV or not. Deleterious effect of neck recurrence on quality of life is worth of elective neck treatment, at least at the level of high-risk lymph nodes in different subgroups of patients.²¹ Therefore, we tend to choose patients at a greater risk of lymph node metastasis (patients of locally advanced stages III-IV supraglottic type and glottic type) for this study. Since advanced stage laryngeal cancer often requires a multimodal treatment of surgery and radiotherapy with or without chemotherapy, and its main influencing factors for treatment are related to the primary tumor.^{15,22} If treatment tailored to the site of the primary cancer, prophylactic neck radiotherapy will decrease the risk of recurrence and spread to ipsilateral or bilateral nodal sites.¹³ Thus, the

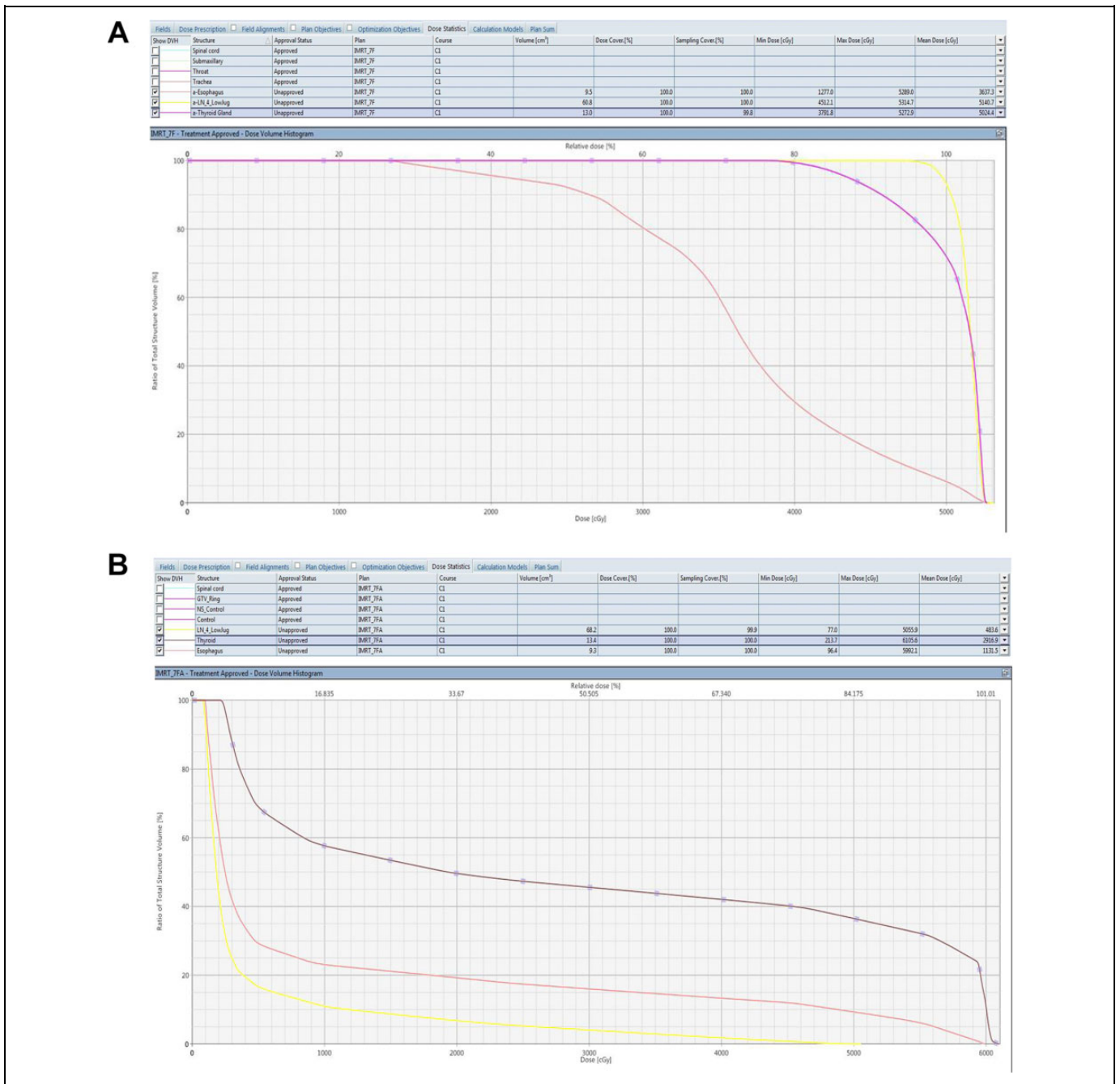


Figure 2. The dose volume histogram (DVH) chart of level IV lymph nodes (LN-4), thyroid and esophagus treated with intensity-modulated radiotherapy (IMRT). A, Selective neck irradiation of level II-IV. B, Selective neck irradiation of level II, III.

Table 4. Comparison of Mean Radiation Dose Between the 2 Therapeutic Groups.

Area	Mean radiation dose (Gy)		p value
	Group A (n = 93)	Group B (n = 87)	
Level IV	52.6 ± 1.45	6.2 ± 1.16	0.001
Thyroid	49.0 ± 1.49	28.7 ± 2.17	0.001
Esophagus	38.1 ± 1.29	11.1 ± 1.15	0.001

Group A = selective neck irradiation of level II–IV; Group B = selective neck irradiation of level II and III.

incidence of late metastatic development seems to depend on the location and the extension of the primary tumor. From our data, whether the distribution of recurrence or the level of lymph node involved, the effect of radiotherapy omitting level IV or not seems unchanged.

To minimize the postoperative morbidity, some experts proposed a highly selective neck dissection by the omission of levels IIb and IV.^{19,23} Indeed, for radiotherapy, there are no important organs at level IIb that need to be avoided. The advantage of omitting Level IV is that it prevents complications

Table 5. Radiation Complications According to the 2 Therapeutic Groups.

Variables	Categories	Group A (n = 93)			Group B (n = 87)			p value
		Supraglottic	Glottic	Total	Supraglottic	Glottic	Total	
Thyroid dysfunction	Subclinical hypothyroidism	17(18.3%)	19(20.4%)	36(38.7%)	10(11.5%)	14(16.1%)	24(27.6%)	0.003
	Clinical hypothyroidism	18(19.4%)	21(22.6%)	39(41.9%)	2(2.3%)	4(4.6%)	6(6.9%)	
Radiation esophagitis	I	14(15.1%)	19(20.4%)	33(35.5%)	13(14.9%)	15(17.2%)	28(32.2%)	0.006
	II	17(18.3%)	12(12.9%)	29(31.2%)	3(3.4%)	6(6.9%)	9(10.3%)	
	III	8(8.6%)	8(8.6%)	16(17.2%)	3(3.4%)	4(4.6%)	7(8.0%)	
Radiation dermatitis	I	17(18.3%)	23(24.7%)	40(43.0%)	20(23.0%)	23(26.4%)	43(49.4%)	0.456
	II	12(12.9%)	20(21.5%)	32(34.4%)	10(11.5%)	18(20.7%)	28(32.2%)	
	III	10(10.7%)	7(7.5%)	17(18.3%)	6(6.9%)	8(9.2%)	14(16.1%)	

Group A = selective neck irradiation of level II–IV; Group B = selective neck irradiation of level II and III.

associated with radiotherapy lesions. Neck irradiation omitting level IV can avoid irradiation of thyroid, esophagus, tracheostomy and lung tip, thereby reducing radiation damage to corresponding organs and reducing irradiation dose, as well as reducing bone marrow suppression. Thyroid gland is more sensitive to radiation, and more than half volume of thyroid gland is located in the irradiation range of level IV, so thyroid gland is extremely vulnerable to damage, resulting in disorder of metabolism of the body. The major complications of radiotherapy associated with level IV are thyroid dysfunction, radiation esophagitis and dermatitis. The results of this study showed that there was remarkable decrease in thyroid dysfunction and radiation esophagitis after radiation excluding level IV. In China, in order to simply keep the respiratory tract unobstructed and sputum aspiration of the laryngocarcinoma patients, it is advocated the use of metal tracheal cannula after tracheotomy. Metal tracheal cannula has such characteristics as cheap price, cleanable and not easy to block, so it permits a long wearing time. In the irradiation including level IV, medical staff will replace the metal tracheal cannula with a plastic tracheal cannula to facilitate radiotherapy. Neck irradiation without level IV can also avoid damage caused by tracheal cannula replacement.

It is questioned to remove level IV, probably because risk for associated morbidity may increase accordingly. However, level IV nodes are rarely the solely involved nodes in head and neck primary tumors.²⁰ It is well-known fact that metastasis preferentially proceeds along lymph node levels and rarely bypasses or skips the succeeding level.¹⁷ In this study, 9 patients had level III lymph nodes be involved after radiotherapy, accompanied by positive nodes at level II, without level IV be involved. Three patients had positive nodes simultaneously at level VI and level II (the recurrence sites of these patients all in the radiation field). Even if patients with laryngeal carcinoma had lymph node metastasis at level IV in clinical practice, large lymph nodes would appear at level III simultaneously, and were located within 20 mm below the lower bound of level III.

The present study has several limitations. Firstly, to lessen heterogeneous population, the retrospective design limited the collection of the stage; secondly, for the strictly matching conditions, the sample is still small; thirdly, there was discrepancy

sample size between Group A and Group B, as well as between supraglottic and glottic laryngeal carcinoma. It may be feasible to omit level IV in the patients with locally advanced supraglottic and glottic laryngeal carcinoma. However, a larger prospective clinical trial might be warranted to endorse the benefit.

Conclusions

Our findings suggest that the postoperative radiotherapy omitting level IV will not worsen the prognosis in supraglottic and glottic laryngeal carcinoma. Moreover, radiotherapy without level IV may reduce radiation damage and relieve suffering of patients.

Authors' Note

Our study was approved by The Ethics Committee of Xuzhou Medical University Affiliated Hospital (approval no. XYFY2016-YL031-02). All patients or the patients' carer provided written informed consent prior to enrollment in the study.

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Declaration of Conflicting Interests

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