Delineation of Neck Node Levels for Patients with Locally Advanced Supraglottic Cancer Receiving Radical IMRT: A Cross-Sectional Study in Mainland China

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Research Article

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Abstract

Background and purpose: In the era of IMRT for locally advanced supraglottic cancer (LA-SGC), the delineation of lymph node clinical target volumes (LN-CTV) remains controversial. We aim to survey the diversity of LN-CTV for LA-SGC patients undergoing radical radiotherapy in mainland China and to provide a basis for improving delineation consistency.

Methods: Radiation oncologists from one provincial cancer hospital, one randomly chosen provincial general hospital and one randomly chosen municipal general hospital from each of the 30 provinces of mainland China participated. The study included four representative cases (T2N1, T3N2b, T4N0, T4N2c) of LA-SGC chosen from the following four different groups: non-T4, low nodal burden (T2-3N0-1); non-T4, high nodal burden (T2-3N2-3); T4, low nodal burden (T4N0-1); and T4, high nodal burden (T4N2-3). Respondents were asked which lymph node levels should be included in high-risk (HR) or low-risk (LR) CTV for nodal prophylactic irradiation. The impact of risk factors was also assessed.

Results: Altogether, 164 chief or attending physicians completed valid questionnaires from all 82 hospitals in China. The criteria that HR-CTV included the node levels with positive lymph nodes and the next lower adjacent level (83.8%–90% agreement) were followed by most physicians (n=160, 97.6%). In the N0-1 stage (cases 1 and 3), ipsilateral levels II and III selected as HR-CTV and level IV as LR-CTV reached good agreement. Whether contralateral levels II and III should be included in HR- or LR-CTV remained controversial; more respondents were inclined to choose them as HR-CTV in case 3 (61.3%). Some respondents supported including contralateral level IVa in LR-CTV (61.9%-68.1%). In the N2 stage (cases 2 and 4), bilateral levels II–IVb other than HR-CTV regions were all included in LR-CTV was indicated in most respondents (75%–92.5%). Levels Ib and V were more likely included in CTV when there were multiple positive lymph nodes in the ipsilateral neck, and more respondents selected level V as HR-CTV in case 4. Nearly half of respondents selected ipsilateral level VIb as CTV when the subglottic region was involved (50.6%, 46.2% and 56.2% in cases 2 to 4, respectively). Tumours crossing the midline (141, 86%), extracapsular spread (132, 80.5%), T stage (142, 86.5%) and N stage (154, 93.9%) as risk factors influencing nodal level selection were shown to have good agreement (≥80%).

Conclusion: Most physicians selected involved nodal levels and lower adjacent levels as HR-CTVs in mainland China. Whether bilateral levels II–IV are included in CTV reached relative consensus but poor agreement for HR- or LR-CTV. The selection conditions of levels Ib, Va/b and VIb as CTVs require further research.

Introduction

Laryngeal cancer (LC) is a challenging clinical problem with a relatively high incidence rate among head and neck cancers. An estimated 26.4 per 100,000 new diagnoses and 14.5 per 100,000 deaths of LC occurred in 2015 in China[1]. In the United States, newly diagnosed LC affected an estimated 12,410 people in 2019[2]. More attention is paid to maintaining quality of life without compromising survival when

choosing the treatment modality because the larynx is a vital functional organ, used as speaking, breathing and swallowing. Definitive chemoradiation therapy as a larynx preservation strategy is recommended as the mainstay treatment for LC according to the NCCN guidelines. Patients who refuse surgery often prefer radiotherapy.

Precise delineation of the target volume is important for radical radiotherapy, especially in the era of highly conformal techniques, including intensity-modulated radiotherapy (IMRT). Compared to two-dimensional and three-dimensional conformal radiotherapy, IMRT reduces long-term toxicities such as xerostomia and dysphagia; nevertheless, radiation-induced dysphagia resulting in feeding tube intubation or weight loss remains a serious issue[3]. Meanwhile, the selection of lymph node clinical target volumes (LN-CTVs) has not yet reached consensus. For example, international guidelines support irradiating bilateral levels II-IV in LC patients with clinically negative lymph nodes[4]; however, the Danish Head and Neck Cancer Group excludes bilateral level IV from CTV[5]. The definitions of high-risk (HR) and low-risk (LR) CTV also vary. European criteria define isotropic expansion of 1 cm from the edge of positive lymph node (LN+) as HR-CTV[4], while North American criteria define node levels with LN + [6]. All anatomic subgroups of LC are always discussed together; however, supraglottic cancer has a much higher prevalence of LN metastases than does glottic cancer, especially in locally advanced stages[7]. In China, there is also no standard guideline for LN-CTV delineation for locally advanced supraglottic cancer (LA-SGC), and large differences exist among hospitals.

Therefore, this cross-sectional study aimed to evaluate hospital variations in LN-CTV delineation for LA-SGC patients receiving radical IMRT in mainland China. The data regarding the selection and definition of LN target volume were addressed. We also analysed risk factors that may influence the determination. Finally, this work hopefully provides a basis for improving delineation consistency for LN-CTV.

Methods

Hospital selection

All provincial cancer hospitals, one randomly selected provincial general hospital and one randomly selected municipal general hospital were enrolled from each of 30 provinces (including 22 provinces, 4 province-level municipalities, and 4 autonomous regions) in mainland China. The Tibetan autonomous region was excluded for lack of radiotherapy equipment. Radiotherapy apparatus is scarce in Hainan, Qinghai and Ningxia provinces, and each had only tumour hospitals included. Two attending radiation oncologists in charge were considered for being recruited from the selected hospitals, with one medium-grade professional title and one high-grade professional title. All doctors specialised in head and neck cancer. The informed consent was obtained from the all participants or their respective legally authorized persons.

Case selection

According to a retrospective cohort study from patients with locally advanced laryngeal cancer collected between 2003 and 2011 from the National Cancer Data Base (NCDB), we defined the following 4 staging cohorts: non-T4, low nodal burden (T2-3N0-1); T4, low nodal burden (T4N0-1); non-T4, high nodal burden (T2-3N2-3); and T4, high nodal burden (T4N2-3). Four representative cases of LASGC patients were selected from these subgroups[8].

Case 1

The patient was a 64-year-old woman who had been smoking for more than 40 years. Diagnosis: Well-differentiated SGC with stage cT2N1; invading right ventricular band and aryepiglottic fold; an LN+ (the maximum short diameter was 2 cm, no invasion of capsule on MRI) in right level II.

Case 2

The patient was a 59-year-old man with hypertension for 5 years who had been smoking and drinking for 40 years. Diagnosis: SGC with stage cT4aN0 well differentiation; invading right ventricular band, vocal cords, paraglottic space, aryepiglottic fold, medial wall of pyriform sinus, belt-shaped muscle (limited to the right), and no positive LN on MRI.

Case 3

The patient was a 66-year-old man who had been smoking for 40 years and drinking for 20 years. Diagnosis: SGC with stage cT3N2b well differentiation; invading right ventricular band, paraglottic space, aryepiglottic fold, medial wall of pyriform sinus and fixed vocal cords; two LNs+ (the largest short diameter of the largest LN + was 3 cm, with extracapsular spread and necrosis on MRI) in right level II.

Case 4

The patient was a 54-year-old man with hypertension for 30 years who had been smoking and drinking for 40 years. Diagnosis: SGC with stage cT4aN2c well differentiation; invading right ventricular band, vocal cords, aryepiglottic fold, medial wall of pyriform sinus, paraglottic space, arytenoid cartilage, thyroid cartilage plate and belt-shaped muscle; five LNs+ (the largest short diameter of the largest LN + was 3 cm, without extracapsular spread and necrosis on MRI) in right levels II and III, two LNs+ (the largest short diameter was 2 cm, with extracapsular spread and necrosis on MRI) in left level II.

The neck node level definition followed the international consensus guideline updated in 2013[9]. We asked whether each lymph node level should be irradiated or not, then whether it should it be included in LR-CTV (dose 44–50 Gy) or HR-CTV (dose 54–63 Gy).

Numerous studies have identified that risk factors, including subregion involvement, pathological differentiation and midline involvement, affect the risk of LN metastasis, which may influence the choices of respondents[10–11]. Then, we attached these strings: subglottic region involvement to cases 2–4, poor differentiation and tumour crossing the midline to cases 1–4. Their influence on the selection of lymph

node levels was also estimated. Meanwhile, participants were asked "which factors will affect your determination of LN-CTV? For example, extracapsular spread, T stage and N stage, and so on."

Statistical analysis

Different selections of neck node level were presented in figures (0 = unirradiated, 1 = as HR region, 2 = as LR region) for each case. The frequencies (n, %) as descriptive statistics of agreement were calculated. The chi-square test was used to determine whether there were significant differences between cases when strings were added, and a p-value < 0.05 was considered significant. The percentage of participants agreeing or strongly agreeing that risk factors had an impact on LN-CTV delineation was calculated using 95% confidence intervals.

Results

A sample of 164 valid questionnaires from 82 hospitals were finally received, and the recovery rate was 100%. The distribution of respondents by different qualifications and working years is shown in Table 1. Of the participants, nearly half were chief physicians with over 10 years of working experience.

Table 1
The qualification and working years of respondents.

Qualification	Working years, n(%)				Total, n
	0–5	5–10	10–15	Over 15	
Chief physician	3(3.6)	9(11.0)	36(43.9)	34(41.5)	82
Attending physician	15(18.3)	41(50.0)	21(25.6)	5(6.1)	82

Distribution of selection

Almost all respondents (160, 97.6%) followed the criteria that node levels with LNs + should be included in HR-CTV and most (83.8–90%) supported the next lower adjacent level also be in HR-CTV among four cases. Four physicians proposed an isotropic expansion of 1 cm from the edge of LNs + as HR-CTV and another neck level as LR-CTV. The selections of HR-CTV or LR-CTV in each case are shown in Fig. 1.

Case 1

(cT2N1M0): ipsilateral levels II–IV and contralateral levels II–IVa were included in CTV (61.9%), while ipsilateral levels II and III in HR-CTV (90%) reached good agreement, and ipsilateral level IV (66.9% for level IVa, 63.8% for level IVb) and contralateral level IVa (61.9%) in LR-CTV reached substantial agreement. Whether contralateral levels II and III should be included in HR- or LR-CTV (level II 46.9% vs 46.9%; level III 38.7% vs 51.3%) and contralateral IVb in LR-CTV or unirradiated region (52.5% vs 46.3%) were a matter of some dispute. Moreover, the choices of level IIa were consistent with level IIb, except contralateral level IIb, for nearly half of responders (51.4%) excluded it from CTV.

Case 2

(cT4aN0M0): more respondents agreed that bilateral levels II–IV were CTV (69.4%), in which ipsilateral levels II and III (87.5%) and contralateral level II (60%) were HR-CTV, and bilateral level IV was LR-CTV (60.6%). More physicians were inclined to take contralateral level III as HR-CTV (55%) and not LR-CTV. Some responders delineated ipsilateral levels Va (46.2%) and Vb (40%) as CTV. The selections of level IIb were nearly synchronized with level IIa.

Case 3

(cT3N2bM0): bilateral levels II-IV and ipsilateral levels Ib and Va/b were included in CTV (65% agreement), in which ipsilateral level Ib (55%), bilateral levels II and III (61.3%) as HR-CTV, and contralateral level IV (68.1% for level IVa, 63.8% for level IVb) as LR-CTV were supported by most physicians. The opinions regarding whether ipsilateral levels IV and Va/b were in HR- or LR-CTV (43.8% vs 42.5%; 42.5% vs 31.5%) and contralateral level Va/b were irradiated or not (40.6% vs 59.4%) were controversial.

Case 4

(cT4aN2cM0): The consensus was that bilateral levels Ib–Vb were included in CTV (66.9%), and ipsilateral levels Ib-Vb (57.5%) and contralateral levels Ib–III (49.4%) were included in HR-CTV. However, whether contralateral levels IV–Va should be defined as HR- or LR-CTV (30.6% vs 42.5%) remains controversial.

Risk factors

When the subglottic region was involved, 50.6%, 46.2% and 56.2% of respondents selected ipsilateral level VIb as HR/LR-CTV in cases 2 to 4, respectively, compared to 13.1%, 15%, 26.2%, respectively, when the subglottic region was not involved.

The influence of poor differentiation and primary tumour crossing the midline is shown in Table 2. Over 80% of respondents took primary tumour crossing the midline (141, 86%), extracapsular spread (132, 80.5%), T stage (142, 86.5%) and N stage (154, 93.9%) into consideration when delineating CTV (shown in Fig. 2). Some physicians regarded the pathologic differentiation type of the primary tumour (115, 70.1%) and LN necrosis (95, 57.9%) as risk factors.

Table 2
Percentages of agreement on define contralateral neck levels II-IVb as HR- or LR-CTV when adding risk factors to cases.

Stages	Adding strings	Contralateral HR-CTV (%)		Contralateral LR-CTV (%)	
		Level II	Level III	Level IVa	Level IVb
T2N1	N	46.9	38.8	61.9	52.5
	C	93.8*	77.5*	75	68.1*
	P	72.5*	64.4*	74.4	71.3*
T4aN0	N	60	55	69.4	64.4
	C	88.1*	85.6*	71.9	66.9
	P	75*	75.6*	66.9	63.1
T3N2b	N	63.7	61.3	68.1	63.7
	C	86.9*	80.6*	66.3	62.5
	P	75.6*	76.3*	62.5	61.3
T4N2c	N	91.3	89.4	58.1	59.4
	C	91.9	90	49.4	52.5
	P	93.8	92.5	46.3	48.8

Abbreviation: HR = high risk; LR = low risk; CTV = clinical target volume; N = none; P = poor differentiation; C = crossing the midline. "*": p-value < 0.05 when compared with no adding strings.

Discussion

Most respondents preferred to follow the North American criteria to delineate HR-CTV, while few physicians followed the European criteria. The lower adjacent level next to the LN + level was also included in HR-CTV. In four cases, bilateral levels II–IV were mainly discussed, and physicians tended to enhance treatment for stage N2 compared with stage N0-1. The rate of selecting levels Ib and V as CTV increased in patients with stage N2. Subglottic region involvement indicates irradiation of level VIb. Tumours crossing the midline, extracapsular spread, T stage and N stage were considered risk factors for influencing nodal level determination.

cN0-1 stage

In the cN0-1 stage, ipsilateral levels II and III selected as HR-CTV and ipsilateral level IV as LR-CTV reached good agreement. The controversy turned on whether contralateral levels II and III should be included in HR- or LR-CTV and whether contralateral level IVb should be excluded from CTV. Ipsilateral levels II and III are considered HR-CTVs because they are the most frequently involved, even for patients

with cN0 stage. According to previous studies, the rate of occult metastases exceeded 20% in SGC[7 12 13]. Irradiating contralateral levels II and III also reached good agreement, regardless of whether the primary tumour was limited to one side or not, because SGC has a tendency to develop contralateral lymph node metastasis[14]. Because of the rare skip metastasis of nodal levels[13 15], ipsilateral level IV was included in LR-CTV if ipsilateral level II was involved, which would be in HR-CTV if level III was involved.

We found that the T stage may affect the delineation of level IIb by comparing cases 1 and 2. Some studies showed that level IIb rarely developed occult metastases (1–6%) in the cN0 stage when level IIa and IIb were analysed based on the pathological test results after surgery[16 17 18]. Omitting level IIb dissection was used clinically in some hospitals[16], and international consensus recommended level IIb could be omitted in cN0-1 stage if there was no LN + on the same side[4]. Our study showed that nearly half of responders omitted level IIb irradiation in the lateral cN0 neck in the T2N1 stage, but rarely (< 5%) excluded it from the bilateral cN0 neck in the T4aN0 stage. More participants tended to take level IIb as the irradiated region with increasing T stage.

Both late T stage and ipsilateral LN + contributed to contralateral metastasis. Gallo et al. reported that the rate of contralateral occult metastasis was up to 40% in SGC patients with clinically ipsilateral LN + [19]. Tomik et al. reported the outcomes of 1400 patients with LC who underwent neck dissection. The lymph node metastasis ratios were 0%, 23.8%, 34.3%, and 44.2% for stages T1–4, respectively[12]. In LA-SGC, it could reach 40.6% for the T3 stage and 58.3% for the T4 stage[20]. In our series, the rates of including contralateral level II in HR- or LR-CTV were approximately equal, while in T4 stage, more respondents included contralateral levels II and III in HR-CTV other than LR-CTV (60.6% vs 36.6%; 56% vs 39.4%). According to this result, T stage has more influence on contralateral neck metastases than ipsilateral single positive lymph nodes, which made more respondents choose contralateral levels II-III as HR-CTV in advanced T stage.

Some investigators suggested not irradiating bilateral level IV in the cN0 stage because occult metastasis rarely occurs[21]. Danish national guidelines for head and neck cancer radiotherapy also excluded them from CTV[24]. However, these previous studies were not much concerned about risk factors. Lim et al. observed that 33.3% of patients with LC (57.5% were SGC) in the T4N0 stage had ipsilateral level IV metastases, while 0%, 3.3%, and 5.9% had ipsilateral level IV metastases in the T1–3 stages, respectively. Our data also showed that more responses agreed to irradiate contralateral level IV in the T4N0 stage (69.4%) than in the T2N1 stage (53.7%). Perhaps bilateral level IV should not be omitted in the T4N0 stage, and further research is needed.

cN2 stage

In the cN2 stage, the bilateral levels II–V other than HR-CTV regions were all included in LR-CTV, which was indicated in most respondents (75–92.5%). Compared to the cN0-1 stage, more respondents preferred to include ipsilateral level IV and contralateral levels II-III in HR-CTV. Levels Ib and Va/b were

more likely included in CTV when there were multiple LNs + in the ipsilateral neck. Level VIb was selected as the CTV when the subglottic region was involved.

The main debates focused on the delineation of ipsilateral levels Ib and Va/b. Level Ib dissection was not generally performed in SGC unless patients had LNs + through clinical exam suggested, so the data of the level Ib metastasis rate were limited. Roberto et al. reported that only 2% of patients with LA-LC (cT3-4N1-2) had level Ib metastases[22]. Usually, the number of ipsilateral LN + regions ≥ 4, anterior involvement of level II, maximum dimension of LN + in level IIa ≥ 3 cm or with extracapsular spread may contribute to level Ib metastases, leading HR-CTV to include level Ib in nasopharyngeal carcinoma[23, 24]. The criteria of level Ib irradiation in head and neck cancers follow. In the present study, when multiple LNs + with adverse histological features were found in level II, level Ib was selected as CTV by 64.4–70% of respondents. As previous trials showed, involvement of ipsilateral level V occurred in less than 10% of LC but occurred in 16% when level IV had LNs+. Additionally, more than one level of infiltration contributed to level V metastases[25]. In these conditions, CTV should include level Va/b. Our study showed that the more LNs + exited in the ipsilateral neck, the more physicians included level Va/b in HR-CTV (49.4% when five LNs + existed vs 17.5% when two LNs + existed).

Risk factors

Many retrospective studies reported that infiltration in Level VIb was associated with subglottic region involvement. Garas et al. reported that 26.6% of patients with subglottic squamous cell carcinoma had spread to paratracheal nodes[15]. Additionally, Gorphe et al. showed that level VIb involvement was associated with pathologic subglottic extension, lysis of the cricoid cartilage, and tracheal extension[26]. In cases 2–4, we found that nearly half of respondents selected ipsilateral level VIb as CTV when the lesion extended to the subglottic region. When adding poor differentiation or primary tumour crossing the midline, more people considered contralateral levels II and III as HR-CTV and level IVb as LR-CTV. However, they had little influence on the determination of case 4, owing to the advanced T and N stages. These two factors enhance the treatment of the contralateral neck in the N0-2b stage.

For the question regarding which risk factors may influence physicians in delineating CTV, most respondents took tumours crossing the midline, extracapsular spread, T stage and N stage into consideration. However, how these factors change radiation oncologists' decisions in specific situations needs deeper investigation.

There are several limitations to our study. First, the disputes regarding which method of HR-CTV delineation would be better were not addressed. European criteria are complicated in clinical application compared to North American criteria. It is reasonable to apply the 1-cm expansion around LN + for HR-CTV because it would cover more than 99% of likely tumour extension[27]. The geometric margins resulted in more uniform and left less room for misinterpretation[28], but it adds burden to physicians when formulating treatment plans, which may lead most hospitals in mainland China to use the North American criteria. Second, we only chose some risk factors associated with LN metastasis from

published reports in which certain missing information is inevitable. We could also not analyse how the other risk factors mentioned in the questionnaire influent physicians in specific situations. In addition, HPV status, conditions of retropharyngeal lymph nodes and combination treatments (chemotherapy, targeted therapy or immunotherapy) are not present in designed cases, which may affect the final results.

Conclusion

In mainland China, most physicians follow North America criteria of CTV delineation. For patients with LA-SGC, bilateral levels II–IV are generally irradiated. However, which nodal level should be included in HR- or LR-CTV showed poor agreement, especially for contralateral levels II–IV. Levels Ib, Va/b and VIb are selected as CTVs under some circumstances, such as multiple lymph node metastasis in the ipsilateral neck and subglottic region involvement. Other risk factors, such as tumour crossing the midline, extracapsular spread, T stage and N stage, also influenced decisions regarding delineating LN-CTV, which needs further research to indicate

List Of Abbreviations

CTV clinical target volumes

HR high-risk

IMRT intensity-modulated radiotherapy

LA locally advanced

LC laryngeal cancer

LN lymph node

LN+ positive lymph node

LR low-risk

MRI magnetic resonance imaging

NCDB National Cancer Data Base

SGC supraglottic cancer

Declarations

- **Ethics approval and consent to participate:** The authors have no conflict of interest. This study involving human participants was reviewed and approved by Ethics Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences. Confirming that all methods were

performed in accordance with the relevant guidelines and regulations in the methods section and the informed consent was obtained from the all participants or their respective legally authorized persons.

• **Consent for publication:** Not applicable.

• **Availability of data and materials:** The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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Figures

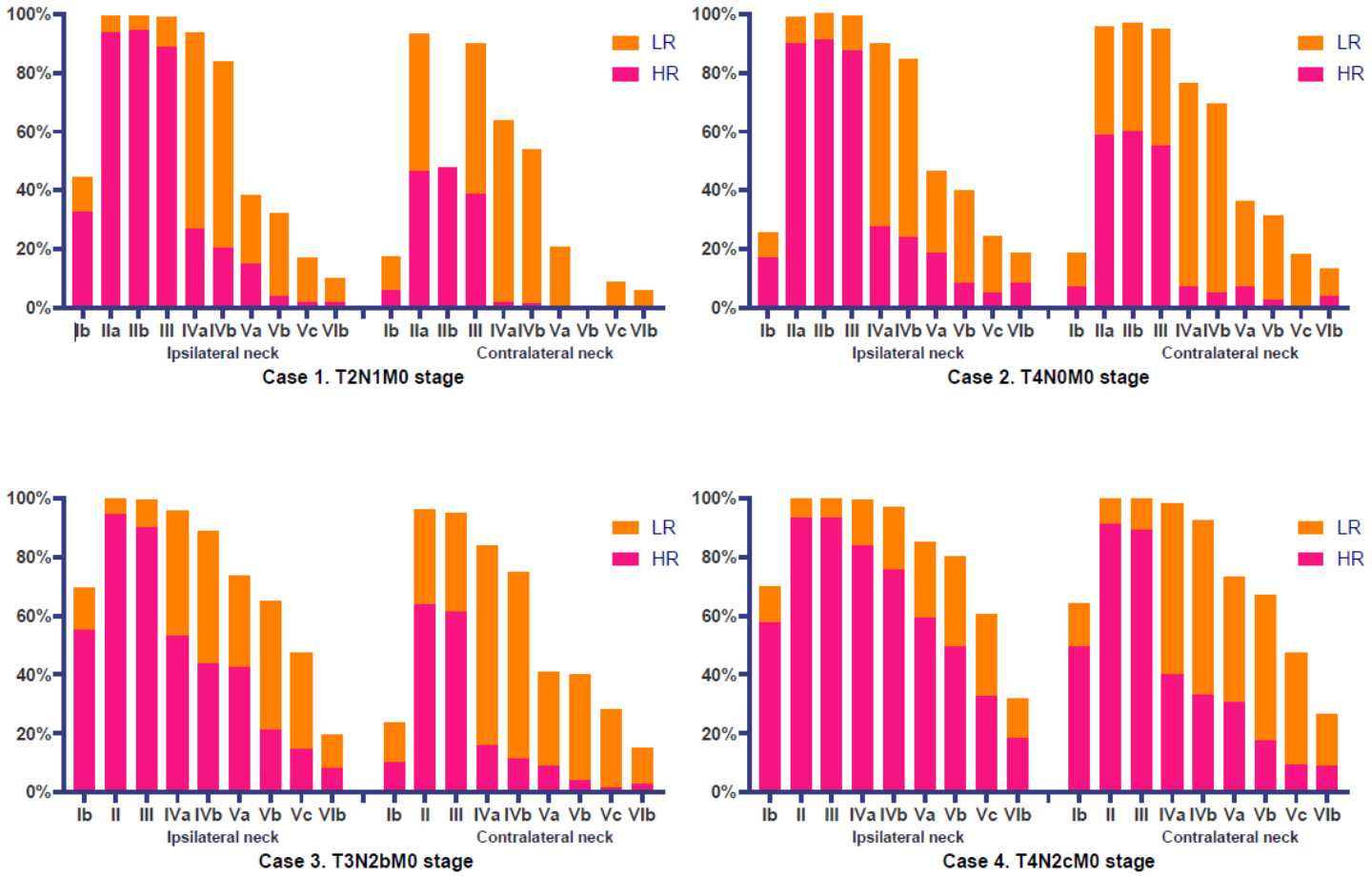

Figure 1

Frequency of different nodal levels selection for high-risk (HR) and low-risk (LR) clinical target volumes in case 1-4.

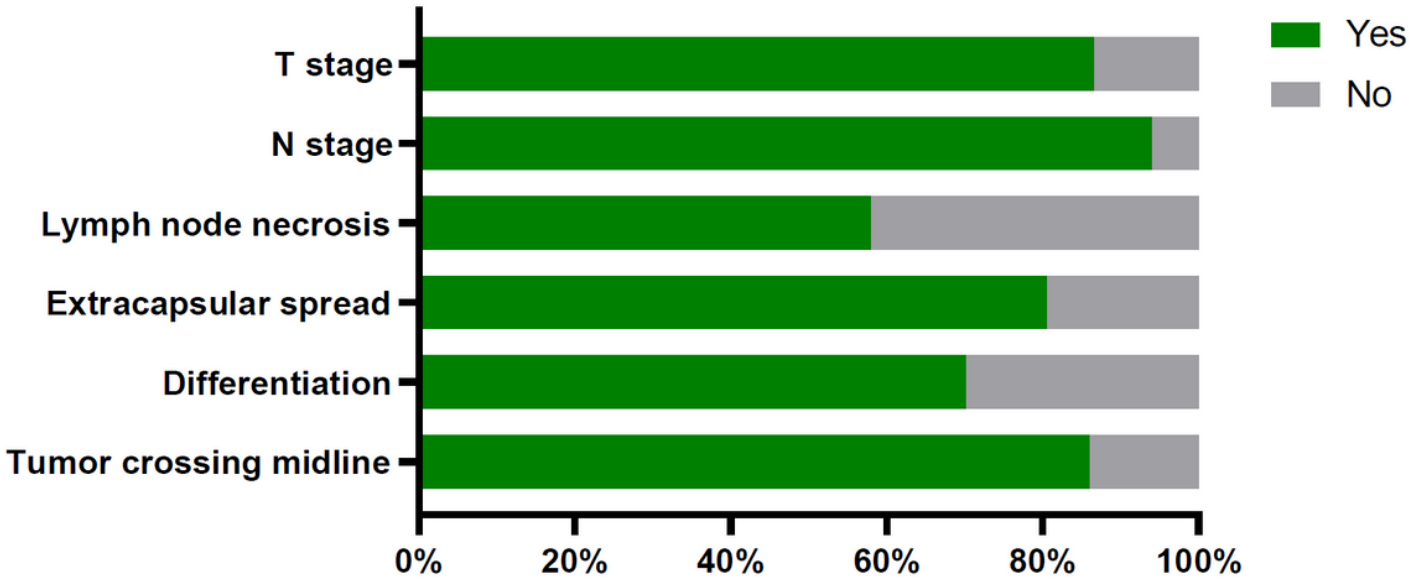

Figure 2

Percentage of respondents to whether these risk factors influenced nodal clinical target volumes in locally advanced supraglottic cancers.