CANCER
COMMUNICATIONS
Open Access

ORIGINAL ARTICLE

Individualized elective irradiation of the clinically node-negative neck in definitive radiotherapy for head and neck squamous cell carcinoma

Jia Kou[1,†] | **Li Lin**[1,†] | **Cheng-Yang Jiao**[2] | **Meng-Qiu Tian**[2] | **Guan-Qun Zhou**[1] |
Xue Jiang[2] | **Jun Ma**[1] | **Zhen-Yu Qi**[1] | **Yao Lu**[2,3] | **Ying Sun**[1] 🔘

[1] Department of Radiation Oncology, Sun Yat-sen University Cancer Center; State Key Laboratory of Oncology in South China; Collaborative Innovation Center for Cancer Medicine, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangzhou, Guangdong 510060, P. R. China

[2] Perception vision medical technology co. LTD, Guangzhou, Guangdong 510275, P. R. China

[3] School of Data and Computer Science, Sun Yat-sen University, Guangdong Province Key Laboratory of Computational Science, Guangzhou, Guangdong 510275, P. R. China

Correspondence
Ying Sun, Department of Radiation Oncology, Sun Yat-sen University Cancer Center; State Key Laboratory of Oncology in South China; Collaborative Innovation Center of Cancer Medicine; Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, 651 Dongfeng Road East, Guangzhou 510060, Guangdong, P. R. China.
Email: sunying@sysucc.org.cn

[†]Jia Kou and Li Lin contributed equally to this work.

Abstract

Background: Oral cavity (OC), oropharyngeal (OP), hypopharyngeal (HP), and laryngeal (LA) squamous cell carcinoma (SCC) have a high incidence of regional lymph node metastasis (LNM). Elective irradiation for clinically node-negative neck is routinely administered to treat lymph nodes harboring occult metastasis. However, the optimal elective irradiation schemes are still inconclusive. In this study, we aimed to establish individualized elective irradiation schemes for the ipsilateral and contralateral node-negative neck of these four types of cancer.

Methods: From July 2005 to December 2018, 793 patients with OC-SCC, 464 with OP-SCC, 413 with HP-SCC, and 645 with LA-SCC were recruited retrospectively. Based on the actual incidence of LNM and the tumor characteristics, risk factors for contralateral LNM, as well as node level coverage schemes for elective irradiation, were determined using logistic regression analysis. Additionally, we developed a publicly available online tool to facilitate the widespread clinical use of these schemes.

Results: For the ipsilateral node-negative neck, elective irradiation at levels I-III for OC-SCC and levels II-IVa for OP-, HP- and LA-SCC are generally recommended. In addition, level VIIa should be included in patients with OP-SCC. Multivariate analyses revealed that posterior hypopharyngeal wall and post-cricoid region involvement were independently associated with level VIIa metastasis in HP-SCC (all $P < 0.05$). For the contralateral node-negative neck, multivariate analyses revealed that ipsilateral N2b2-N3, tumors with body midline involvement, and degree of tumor invasion were the independent factors for contralateral LNM (all $P < 0.05$). In patients who require contralateral neck

irradiation, levels I-II are recommended for OC-SCC, and additional level III is recommended for patients with ipsilateral N3 disease. Levels II-III are recommended for OP-, HP-, and LA-SCC, and additional level IVa is recommended for patients with advanced T or ipsilateral N classifications. Furthermore, additional level VIIa is recommended only for OP-SCC with T4 and ipsilateral N3 disease.

Conclusion: Based on our findings, we suggest that individualized and computer-aided elective irradiation schemes could reduce irradiation volumes in OC-, OP- and HP-SCC patients, as compared to current guidelines, and could thus positively impact the patients' quality of life after radiotherapy.

KEYWORDS
clinically node-negative neck, elective irradiation, head and neck squamous cell carcinoma, individualization, neck node level

1 | INTRODUCTION

Oral cavity (OC)-squamous cell carcinoma (SCC), oropharyngeal (OP)-SCC, hypopharyngeal (HP)-SCC, and laryngeal (LA)-SCC have the highest incidences of all types of head and neck squamous cell carcinoma (HNSCC) [1]. Due to the vast submucosal lymphatic capillary network, these four cancers have a high propensity to metastasize to regional lymph nodes (LNs). Historical data have shown that 36%−70% of patients have clinically detectable regional lymph node metastasis (LNM). Even in the patients with negative LNs diagnosed by clinical examination, namely patients with clinically node-negative neck, there was still a 33% probability of pathologically confirmed regional LNM [2, 3]. These microscopically-identified occult metastatic LNs could develop into adenopathy during follow-up if untreated. Accordingly, the effectiveness of elective irradiation in the treatment of occult metastatic LNs was first demonstrated by Fletcher and supported later on by others [4–6]. Since then, elective irradiation of the clinically node-negative neck is routinely administered to treat LNs harboring occult metastasis.

In the process of elective irradiation, the selection of appropriate irradiation volume is one of the most important issue that needs to be addressed because insufficient radiation volume could impair tumor control and excessive radiation volume could cause unnecessary damage to normal tissue of the neck [7]. At present, for the selection of the elective irradiation volume for HNSCC, the most widely adopted guidelines were proposed by Grégoire et al. in 2000 [2], with reference to historically pathological data, and were recently updated in 2018 and 2019 [8, 9]. Nonetheless, these guidelines still have several limitations worth optimizing. First, tumor size, tumor grade, and tumor site are important risk factors for lymph node metastasis that

should be taken into consideration for treatment decisions [10–12], while the guidelines ignore the influence of these various tumor characteristics on LNM in the ipsilateral and contralateral neck. Second, the guidelines recommend unified irradiation schemes for the bilateral node-negative neck, although studies have constantly confirmed that the LNM rate of the contralateral neck is significantly lower than that of the ipsilateral neck [13, 14]. Taken together, to achieve more individualized precision radiotherapy of patients with HNSCC, the contralateral neck should be distinguished from the ipsilateral neck, and the elective irradiation guidelines should be refined based on corresponding tumor characteristics.

Therefore, the aim of the present study was to establish individualized elective irradiation schemes for the ipsilateral and contralateral node-negative neck, respectively, based on the actual LNM rate and corresponding tumor characteristics in a large patient cohort. Further, we developed an online tool to facilitate the widespread clinical use of the proposed elective irradiation schemes.

2 | MATERIALS AND METHODS

2.1 | Patients

The data of consecutive patients with non-metastatic, newly diagnosed pathologically-proven HNSCC in Sun Yat-Sen University Cancer Center (Guangzhou, China) between July 2005 and December 2018, were retrospectively retrieved for this study. We included patients who underwent baseline contrast-enhanced computed tomography or magnetic resonance imaging scans of the head and neck region, and all the images were acquired from our institutional Picture Archiving and

Communication System (PACS, General Electric Healthcare). We excluded patients who had a history of head and neck radiotherapy or surgery before they were diagnosed with OP-SCC/OC-SCC/HP-SCC/LA-SCC at our institution and those with an insufficient scanning scope for covering the primary site and neck. All patients were restaged according to the 7th edition of the American Joint Committee on Cancer and Union for International Cancer Control (UICC/AJCC) staging system [15]. For primary tumors, the pathological staging system was used for patients with surgery as the initial treatment after diagnosis; otherwise, the clinical staging system was used. For cervical LNs, the clinical staging system was used for all patients. The study was approved by the institutional review board (IRB reference No.: B2020-025-01) and the requirement to obtain informed consent was waived.

2.2 | Diagnosis of clinically metastatic lymph nodes

In this study, clinically metastatic LNs were diagnosed from the results of pretreatment imaging examinations. The imaging diagnostic criteria for clinically metastatic LNs were: (1) the minimal axial diameter (MID) of the cervical LN was ≥ 10 mm, and the MID of the retropharyngeal LN was ≥ 5 mm; (2) nodal grouping: three or more contiguous LNs and any one of them had a MID ≥ 8 mm, and; (3) presence of signs of necrosis or extra-capsular invasion in any sized LN.

2.3 | Primary tumor and lymph node characteristics

For primary tumors, four characteristics were determined and recorded, according to physical examination, endoscopy, and imaging examinations. The first characteristic was the tumor subsite. The oral cavity includes seven subsites (buccal mucosa, retromolar gingiva, alveolar ridge, hard palate, oral tongue, floor of the mouth, and mucosal lip); the oropharynx was divided into four subsites (tonsil, soft palate, base of the tongue, and oropharyngeal wall); and the hypopharynx and larynx both include three subsites (hypopharynx: pyriform sinuses, post-cricoid region, and hypopharyngeal wall; and larynx: supraglottis, subglottis, and glottis). The second characteristic was the presence of a unilateral or bilateral tumor. Tumors that deviated to the left or right side were defined as unilateral tumors, otherwise, they were defined as bilateral tumors. The third characteristic was body midline involvement (presence/absence). The fourth characteristic was the

involvement of certain structures (oral cavity involvement in OP-SCC; oropharynx, post-cricoid, posterior hypopharyngeal wall, and esophagus involvement in HP-SCC; and post-cricoid, posterior hypopharyngeal wall, and subglottis involvement in LA-SCC). In regard to LNs, if the primary tumor was defined as a bilateral tumor, the LNs on both sides of the neck were also defined as ipsilateral LNs; otherwise, the LNs were separated into ipsilateral or contralateral LNs. It is noteworthy that the levels Ia, VIa, and VIb are located in the midline region of the body and bilateral sides of these levels are connected. Therefore, these levels were consistently classified as the ipsilateral levels and the LNs located in these levels were classified as the ipsilateral LNs in data analysis. In addition, to detailly explore the influence of ipsilateral LN metastasis on contralateral LN metastasis, we separately defined the ipsilateral N classification according to the features of metastatic LNs in the ipsilateral neck with reference to the 7th edition of the UICC/AJCC staging system. Specifically, we further divided N2b into N2b1 (distribution of multiple LNs in one level of the ipsilateral neck) and N2b2 (distribution of multiple LNs in more than one level of the ipsilateral neck).

2.4 | Elective irradiation of the ipsilateral node-negative neck

We aimed to propose elective irradiation schemes for the ipsilateral node-negative neck in OP-, OC-, HP-, and LA-SCC. The LNM rate of a certain level in the ipsilateral neck was defined as the ratio of the number of patients with clinically metastatic LNs on this level and the total number of patients with a certain type of cancer. First, we calculated the LNM rates for levels II-V of these four types of cancer. Given that level I is the first station of lymphatic drainage in OC-SCC and level VIIa (retropharyngeal LNs) is the first station in OP-SCC [16], the LNM rates in level I for OC-SCC and level VIIa for OP-SCC were also calculated. Although there is no consensus on what probability of LNs metastasis is considered relevant for therapy, the International Commission on Radiation Units and Measurements (ICRU) Report 83 [17] proposed that typically a probability of LNs metastasis higher than from 5% to 10% should be assumed to require treatment. In previous literature, Eisbruch et al. [18] also proposed guidelines of elective irradiation for HNSCC based on a 5% to 10% probability of LNs metastasis. Therefore, in this study, we supposed that levels with metastasis rates $\geq 5\%$ were considered necessary to undergo elective irradiation. The levels with metastasis rates <5% were further analyzed in patient subgroups with different T classifications.

Next, for certain levels (level Ib for OP-SCC, level VI and VIIa for HP-SCC, and level VI for LA-SCC), the LNM rates are generally very low. However, previous literature [19–22] reported that tumor size, tumor invasion structure, and other clinical factors were significantly associated with LNM in these levels; and the LNM in these levels were associated with poor survival of the patients. Therefore, the univariate and multivariate binary logistic regression analyses were performed to define high-risk factors for LNM in these levels. Covariates included histological grade, T classification, and structures with tumor involvement. We recommended elective irradiation of these levels in patients with any high-risk factors.

2.5 | Elective irradiation of the contralateral node-negative neck

In patients with unilateral tumors, high-risk factors for contralateral LNM were defined using univariate and multivariate binary logistic regression analyses. The covariates included histological grade, T classification, tumor subsite, body midline involvement (presence/absence), structures with tumor involvement, and ipsilateral N classification. Elective irradiation of the contralateral neck was recommended in patients with any high-risk factors, and the LNM rate of a certain level in the contralateral neck was defined as a ratio of the number of patients with clinically metastatic LNs on this level and the number of patients who were defined as requiring contralateral neck elective irradiation. Next, based on these patients, we also proposed elective irradiation schemes for the contralateral node-negative neck by applying the same methods used to analyze the ipsilateral neck. However, the levels with metastasis rates <5% were further calculated in patient subgroups with different T classifications and ipsilateral N classifications.

2.6 | Construction of an online tool for the widespread clinical use of our proposed elective irradiation schemes

To facilitate the widespread clinical use of our proposals, we constructed a publicly available online tool. The tool was developed based on the React front-end framework and KOA back-end framework. PostGreSQL was used as the server database to store data information. To improve the development efficiency and stability, several third-party plugins such as dicomParser, cornerstoneTools and WADOImageLoader, were imported.

The web server of this tool consists of application layer, analysis layer, and data layer. The application layer was used for user interaction, Dicom viewer, and exhibition of analysis results. The analysis layer uses Prolog, natural language analysis, to develop the deductive reasoning process and store reference data. The selection criteria entered by the users are analyzed and the results are finally returned. The data layer is mainly used to store image data and analysis results. The system architecture diagram of this on-line tool is shown in Figure S1.

2.7 | Statistical analysis

All variables used in our study were categorical variables. Univariate and multivariate binary logistic regression analyses were performed to define risk factors for LNs metastasis in certain nodal levels and contralateral neck. The odds ratio (OR) and its 95% confidence interval (CI) were calculated from the logistic regression analysis. Univariate and multivariate binary logistic regression analyses were performed by using Statistical Product and Service Solutions (IBM SPSS, version 22.0; Armonk, NY, USA). Statistical significance was set at a two-tailed $P < 0.05$.

3 | RESULTS

3.1 | Patients distributions

A total of 2315 patients with HNSCC were included in this study, comprising 793 patients with OC-SCC, 464 with OP-SCC, 413 with HP-SCC, and 645 with LA-SCC. The clinicopathological characteristics of the enrolled patients are shown in Table 1.

3.2 | Distribution and incidence of clinically metastatic lymph nodes

The distribution and incidence of clinically metastatic LNs in patients with OC-SCC, OP-SCC, HP-SCC, and LA-SCC are shown in Table 2 and Figure 1. Table S1 and S2 present these results by various tumor subsites. According to the results, 1114 (48.1%) out of 2315 patients presented with LNM. Patients with HP-SCC had the highest incidence of LNM (313/413, 75.8%), followed by patients with OP-SCC (325/464, 70.0%), OC-SCC (308/793, 38.8%), and LA-SCC (168/645, 26.0%). The incidences of contralateral LNM, as ranked from high to low, were as follows: HP-SCC (59/413, 14.3%), OP-SCC (60/464, 12.9%), LA-SCC (49/645, 7.6%), and OC-SCC (32/793, 4.0%).

TABLE 1 Clinicopathological characteristics of 2315 patients with head and neck squamous cell carcinoma

Characteristics	Number of patients (%)			
	OC-SCC $n = 793$	OP-SCC $n = 464$	HP-SCC $n = 413$	LA-SCC $n = 645$
Sex				
Male	569 (71.8)	409 (88.1)	393 (95.2)	624 (96.7)
Female	224 (28.2)	55 (11.9)	20 (4.8)	21 (3.3)
Age				
Median (range, yr.)	60 (12-97)	60 (22-89)	63 (28-93)	65 (32-92)
>60	390 (49.2)	218 (47)	254 (61.5)	446 (69.1)
≤60	403 (50.8)	246 (53)	159 (38.5)	199 (30.9)
Histologic grade*				
GX	33 (4.2)	33 (7.1)	39 (9.4)	51 (7.9)
G1-G2	724 (91.3)	331 (71.3)	285 (69.0)	501 (77.7)
G3-G4	36 (4.5)	100 (21.6)	89 (21.5)	93 (14.4)
T classification				
T1	216 (27.2)	78 (16.8)	17 (4.1)	193 (29.9)
T2	312 (39.3)	165 (35.6)	142 (34.4)	165 (25.6)
T3	160 (20.2)	80 (17.2)	117 (28.3)	195 (30.2)
T4	105 (13.2)	141 (30.4)	137 (33.2)	92 (14.3)
N classification				
N0	485 (61.2)	139 (30.0)	100 (24.2)	477 (74.0)
N1	116 (14.6)	75 (16.2)	93 (22.5)	57 (8.8)
N2a	3 (0.4)	19 (4.1)	5 (1.2)	2 (0.3)
N2b	143 (18.0)	137 (29.5)	114 (27.6)	44 (6.8)
N2c	28 (3.5)	54 (11.6)	44 (10.7)	46 (7.1)
N3	18 (2.3)	40 (8.6)	57 (13.8)	19 (2.9)
Stage				
I	191 (24.1)	37 (8.0)	6 (1.5)	187 (29.0)
II	199 (25.1)	52 (11.2)	38 (9.2)	134 (20.8)
III	161 (20.3)	75 (16.2)	100 (24.2)	157 (24.3)
IV	242 (30.5)	300 (64.7)	269 (65.1)	167 (25.9)
Ipsilateral N classification[†]				
N0	487 (61.4)	140 (30.2)	104 (25.2)	480 (74.4)
N1	120 (15.1)	86 (18.5)	98 (23.7)	62 (9.6)
N2a	4 (0.5)	20 (4.3)	7 (1.7)	4 (0.6)
N2b1	38 (4.8)	45 (9.7)	25 (6.1)	20 (3.1)
N2b2	126 (15.9)	133 (28.7)	122 (29.5)	59 (9.1)
N3	18 (2.3)	40 (8.6)	57 (13.8)	20 (3.1)
Primary tumor laterality				
Bilateral	22 (2.8)	32 (6.9)	57 (13.8)	129 (20.0)
Unilateral	771 (97.2)	432 (93.1)	356 (86.2)	516 (80.0)
Body midline involvement				
Present	160 (20.2)	151 (32.5)	224 (54.2)	346 (53.6)
Absent	633 (79.8)	313 (67.5)	189 (45.8)	299 (46.4)

Data are number of patients, with the percentage in parentheses;

*GX, grade could not be assessed, G1, well-differentiated, G2, moderately differentiated, G3, poorly differentiated, G4, undifferentiated;

[†]To better characterize LNs metastasis of the ipsilateral neck in patients with unilateral tumors, we separately defined the ipsilateral N classification according to the features of metastatic LNs in the ipsilateral neck with reference to the 7th edition of the UICC/AJCC staging system. Specifically, we continue to divide N2b into N2b1 (multiple LNs are distributed in one level of the ipsilateral neck) and N2b2 (multiple LNs are distributed in more than one level of the ipsilateral neck);

Abbreviations: HP, hypopharyngeal; LA, laryngeal; OC, oral cavity; OP, oropharyngeal; SCC, squamous cell carcinoma.

TABLE 2 Distribution and incidence of clinically metastatic lymph nodes in patients with OC-SCC, OP-SCC, HP-SCC, and LA-SCC

Levels	OC-SCC (n = 793) Ipsi (%)	Contra (%)	Total (%)	OP-SCC (n = 464) Ipsi (%)	Contra (%)	Total (%)	HP-SCC (n = 413) Ipsi (%)	Contra (%)	Total (%)	LA-SCC (n = 645) Ipsi (%)	Contra (%)	Total (%)
Ia*	29 (3.7)	NA	29 (3.7)	2 (0.4)	NA	2 (0.4)	2 (0.5)	NA	2 (0.5)	0 (0)	NA	0 (0)
Ib	153 (19.3)	14 (1.8)	160 (20.2)	14 (3.0)	0 (0)	14 (3.0)	3 (0.7)	3 (0.7)	5 (1.2)	3 (0.5)	1 (0.2)	3 (0.5)
II	208 (26.2)	13 (1.6)	209 (26.4)	305 (65.7)	48 (10.3)	308 (66.4)	256 (62.0)	37 (9.0)	259 (62.7)	128 (19.8)	40 (6.2)	134 (20.8)
III	82 (10.3)	4 (0.5)	85 (10.7)	132 (28.4)	14 (3.0)	137 (29.5)	170 (41.2)	19 (4.6)	175 (42.4)	86 (13.3)	16 (2.5)	93 (14.4)
IVa	15 (1.9)	1 (0.1)	16 (2.0)	28 (6.0)	4 (0.9)	31 (6.7)	64 (15.5)	10 (2.4)	69 (16.7)	34 (5.3)	7 (1.1)	39 (6.0)
IVb	0 (0)	0 (0)	0 (0)	4 (0.9)	0 (0)	4 (0.9)	4 (1.0)	3 (0.7)	3 (0.7)	1 (0.2)	0 (0)	1 (0.2)
Va	9 (1.1)	0 (0)	9 (1.1)	15 (3.2)	3 (0.6)	18 (3.9)	22 (5.3)	4 (1.0)	24 (5.8)	7 (1.1)	2 (0.3)	8 (1.2)
Vb	0 (0)	0 (0)	0 (0)	8 (1.7)	0 (0)	8 (1.7)	5 (1.2)	1 (0.2)	5 (1.2)	1 (0.2)	1 (0.2)	2 (0.3)
Vc	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.2)	1 (0.2)	1 (0.2)	0 (0)	0 (0)	0 (0)
VIa*	3 (0.4)	NA	3 (0.4)	0 (0)	NA	0 (0)	0 (0)	NA	0 (0)	7 (1.1)	NA	7 (1.1)
VIb*	0 (0)	NA	0 (0)	0 (0)	NA	0 (0)	27 (6.5)	NA	27 (6.5)	7 (1.1)	NA	7 (1.1)
VIIa	14 (1.8)	4 (0.5)	16 (2.0)	81 (17.5)	10 (2.2)	84 (18.1)	38 (9.2)	9 (2.2)	44 (10.7)	5 (0.8)	0 (0)	5 (0.8)
VIIb	2 (0.3)	0 (0)	2 (0.3)	2 (0.4)	1 (0.2)	3 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
VIII	1 (0.1)	0 (0)	1 (0.1)	3 (0.6)	1 (0.2)	4 (0.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
IXa	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Xa	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Xb	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Total	306 (38.6)	32 (4.0)	308 (38.8)	324 (69.8)	60 (12.9)	325 (70.0)	309 (74.8)	59 (14.3)	313 (75.8)	165 (25.6)	49 (7.6)	168 (26.0)

Data are number of patients, with the percentage in parentheses; NA, figures are not available;

*Levels Ia, VIa, and VIb are located in the midline region of the body and were classified as the ipsilateral levels in data analysis, so there is no data of contralateral lymph node metastasis in these levels;

Abbreviations: HP, hypopharyngeal; LA, laryngeal; OC, oral cavity; OP, oropharyngeal; SCC, squamous cell carcinoma; Ipsi, ipsilateral neck; Contra, contralateral neck.

3.3 | Elective irradiation of the ipsilateral node-negative neck

Herein, OP-SCC was used as an example to demonstrate the results, while the results of the other three cancers are detailed in the Supplementary Materials.

The study flow diagram of OP-SCC is shown in Figure 2. Of the 464 patients with OP-SCC, the LNM rates of the ipsilateral neck were 17.5% (n = 81) for level VIIa, 65.7% (n = 305) for level II, 28.4% (n = 132) for level III, 6.0% (n = 28) for level IVa, 3.2% (n = 15) for level Va, 1.7% (n = 8) for level Vb, 0.9% (n = 4) for level IVb and 0% for level Vc (Table 2). According to the predefined 5% threshold, we recommend elective irradiation of levels VIIa and II-IVa for the ipsilateral node-negative necks. When analyzed in patient subgroups with different T classifications, the LNM rates of levels IVb, Va, Vb, and Vc were lower than 5%, even in patients with advanced primary disease (Table S3); therefore, elective irradiation of levels IVb and Va-Vc is not suggested for ipsilateral node-negative necks.

Among the 464 patients with OP-SCC, 3.0% (n = 14) had ipsilateral level Ib metastasis. Univariate and multi-variate logistic regression analyses demonstrated that T4 and oral cavity involvement were independently associated with ipsilateral level Ib metastasis (T4 vs. T1-3, 7.8% vs. 0.9%; OR 6.3; 95% CI 1.7–24.0; P = 0.007; oral cavity involvement, presence vs. absence, 8.0% vs. 1.4%; OR 3.7; 95% CI 1.2–11.7; P = 0.028; Table S4 and S5). Therefore, we suggest elective irradiation of the ipsilateral level Ib in OP-SCC patients with T4 disease or oral cavity involvement.

3.4 | Elective irradiation of the contralateral node-negative neck

Among OP-SCC patients with unilateral tumors, 13.9% (60/432) had contralateral LNM. Univariate and multi-variate analyses demonstrated that T3, T4, body midline involvement, tumors of midline subsites, and ipsilateral N2b2-N3 were independently associated with higher incidences of contralateral LNM (T3-4 vs. T1-2, 22.1% vs. 6.6%; OR, 2.5; 95% CI, 1.2–5.2; P = 0.012; body midline involvement, presence vs. absence, 29.8% vs. 7.7%; OR, 2.8; 95% CI, 1.4–5.3; P = 0.002; tumors of midline subsites,
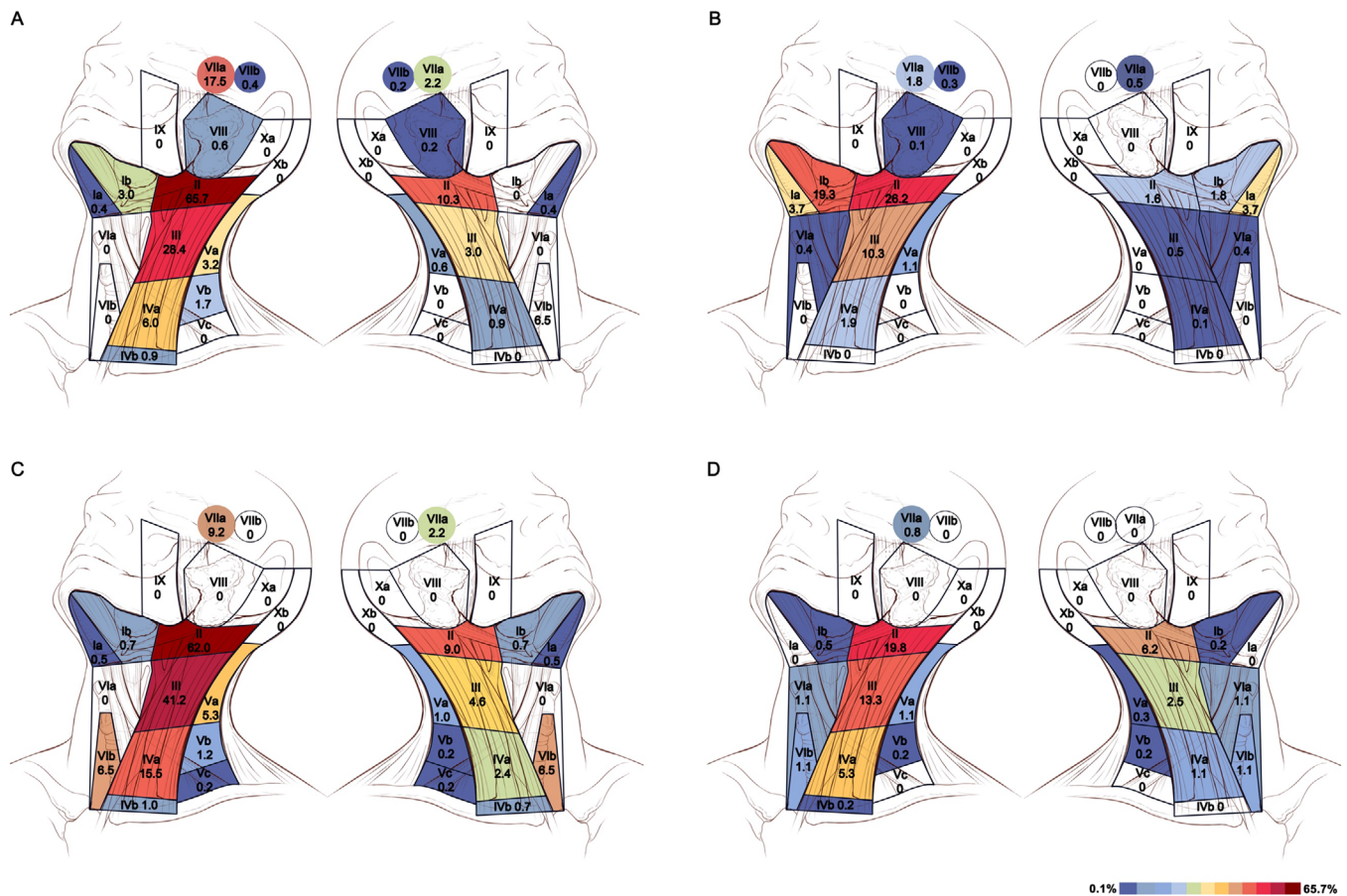
FIGURE 1 Distribution and incidence of clinically metastatic lymph nodes in patients with OP-SCC (A), OC-SCC (B), HP-SCC (C), and LA-SCC (D). The left and right neck were substituted for the ipsilateral and contralateral neck to illustrate the pattern of lymph node metastasis. The numbers represent the incidence of lymph node metastasis in each nodal level of the ipsilateral and contralateral neck. Color wash changing from blue through yellow to red indicates incidence increase. Levels Ia, VIa, and VIb are located in the midline region of the body. OP, oropharyngeal; OC, oral cavity; HP, hypopharyngeal; LA, laryngeal; SCC, squamous cell carcinoma

presence *vs.* absence, 18.0% *vs.* 7.2%; OR, 2.8; 95% CI, 1.5–5.3; $P = 0.012$; N2b2-N3 *vs.* N0-N2b1, 26.3% *vs.* 6.0%; OR, 4.9; 95% CI, 2.6-9.4; $P < 0.001$; Table S6 and Table 3). Therefore, contralateral neck irradiation is recommended for patients with any of the high-risk factors. Accordingly, in our cohort, 86.3% (373/432) of OP-SCC patients with unilateral tumors were defined as requiring contralateral neck irradiation. The contralateral LNM rate was significantly higher in patients requiring contralateral neck irradiation than in those not requiring irradiation (58/373, 15.5% *vs.* 2/59, 3.4%, $P = 0.024$).

In 373 patients with OP-SCC requiring contralateral neck irradiation, the LNM rates of the contralateral neck were 2.7% ($n = 10$) for level VIIa, 12.3% ($n = 46$) for level II, 3.8% ($n = 14$) for level III, 1.1% ($n = 4$) for level IVa, 0.8% ($n = 3$) for level Va, and 0% for levels IVb, Vb, and Vc (Table S7). Therefore, we recommend elective irradiation of contralateral level II for all these patients. Subgroup analysis using patients with different T classifications and ipsilateral N classifications showed that the LNM rates of contralateral level VIIa in patients with T4 disease (9/128, 7%) and ipsilateral N3 (2/37, 5.4%) disease; of contralateral level III in patients with T4 (10/128, 7.8%), ipsilateral N2b1 (2/33, 6.1%), N2b2 (9/130, 6.9%) and N3 (3/37, 8.1%) disease; and of contralateral level IVa in patients with ipsilateral N3 disease (2/37, 5.4%) exceeded 5% (Table S7). Therefore, elective irradiation of contralateral level VIIa is recommended in patients with T4 disease and ipsilateral N3 disease; of contralateral level III in patients with T4 disease and ipsilateral N2b1-N3 disease; and of contralateral level IVa in patients with ipsilateral N3 disease. Given that no clinically metastatic LNs were identified in contralateral level Ib among all patients, elective irradiation of contralateral level Ib is not recommended for patients with a contralateral node-negative neck.
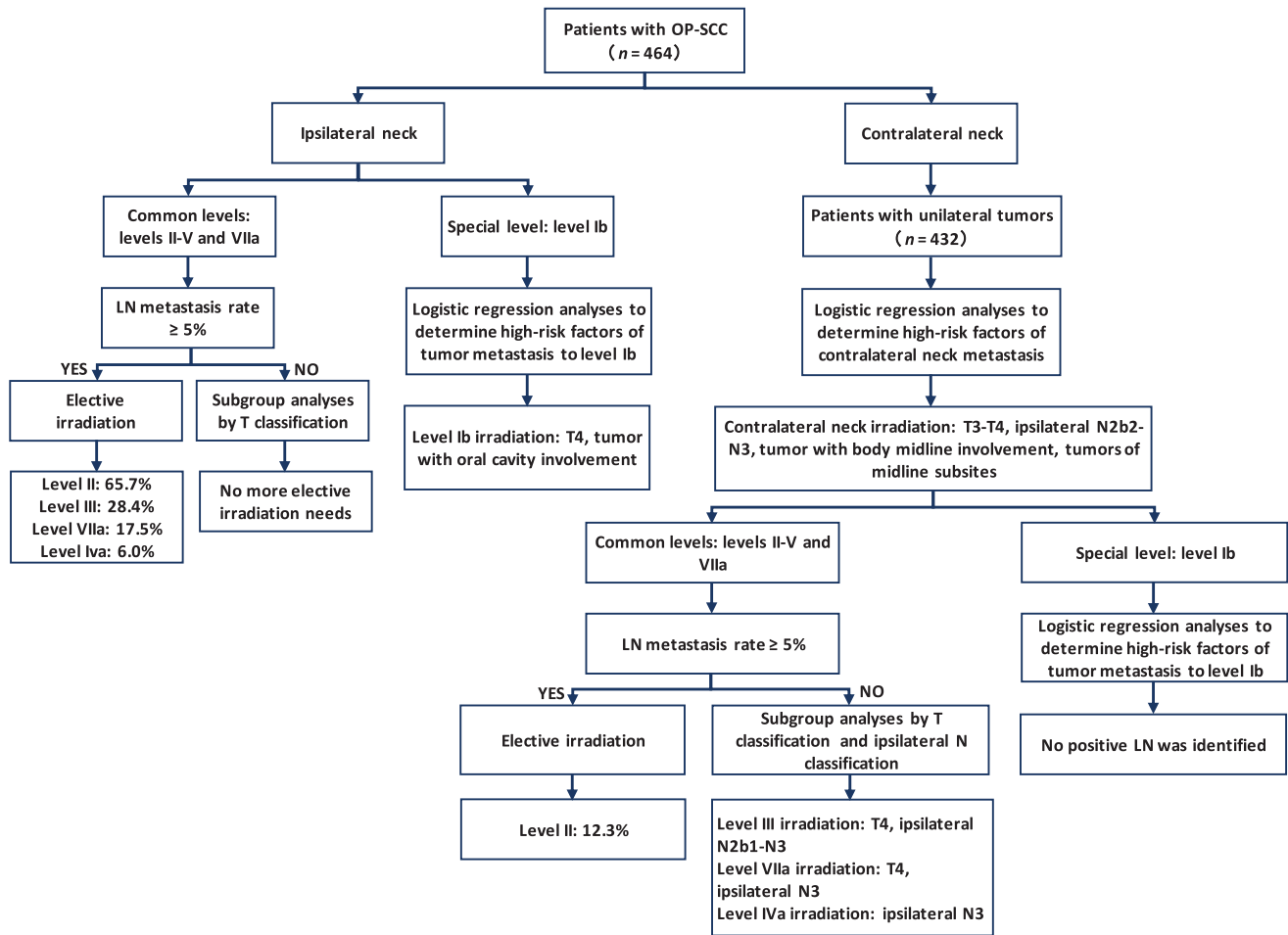
FIGURE 2 Study flow diagram of OP-SCC. OP, oropharyngeal; SCC, squamous cell carcinoma; LN, lymph node

TABLE 3 Multivariate logistic regression analysis of independent risk factors associated with contralateral lymph nodes metastasis in 432 patients with unilateral OP-SCC

Tumor variables	Incidence of contralateral LNs metastasis (%)	OR	95% CI	P
T classification		2.5	1.2-5.2	0.012
T1-2	15/228 (6.6)			
T3-4	45/204 (22.1)			
Ipsilateral N classification*		4.9	2.6-9.4	< 0.001
N0-N2b1	16/265 (6.0)			
N2b2-N3	44/167 (26.3)			
Body midline involvement		2.8	1.4-5.3	0.002
Absent	24/311 (7.7)			
Present	36/121 (29.8)			
Primary tumor subsites†		2.8	1.5-5.3	0.012
Non-midline structure	12/166 (7.2)			
Midline structure	48/266 (18.0)			

Data are number of patients, with the percentage in parentheses;

*To better characterize LNs metastasis of the ipsilateral neck in patients with unilateral tumors, we separately defined the ipsilateral N classification according to the features of metastatic LNs in the ipsilateral neck with reference to the 7th edition of the UICC/AJCC staging system. Specifically, N2b1 denotes that multiple LNs are distributed in one level of the ipsilateral neck; N2b2 denotes that multiple LNs are distributed in more than one levels of the ipsilateral neck;

†Primary tumor subsites: non-midline structure (tonsil), midline structure (soft palate, base of the tongue and pharyngeal wall);

Abbreviations: LNs, lymph nodes; OP, oropharyngeal; SCC, squamous cell carcinoma.

TABLE 4 Recommendations for elective irradiation of the node-negative neck in OP-, OC-, HP- and LA-SCC

	Levels to be electively irradiated	
Tumor types	Ipsilateral node-negative neck	Contralateral node-negative neck*
OP-SCC	II, III, IVa, VIIa, (Ib)[†]	II, (III)[‡], (IVa)[§], (VIIa)[‖]
OC-SCC	Ib, II, III, (Ia)[¶], (IVa)	Ib, II, (III)[§]
HP-SCC	II, III, IVa, Va, (VIb)[**], (VIIa)[††]	II, III, (IVa)[‡‡], (VIb)[**]
LA-SCC		
Supra/subglottis	II, III, IVa, (VIa, VIb)[‡‡]	II, III, (IVa)[‡‡], (VIa, VIb)[§§]
Glottis	II, III, (IVa)[¶], (VIa, VIb)[§§]	II, III, (IVa)[‡‡], (VIa, VIb)[§§]

*Elective contralateral neck irradiation: OP-SCC patients with T3-T4 disease, ipsilateral N2b2-N3 disease, tumors with the body midline involvement, or tumors of midline subsites. OC-SCC patients with ipsilateral N2b2-N3 disease or tumors with the body midline involvement. HP-SCC patients with ipsilateral N2b2-N3 disease, tumors with the body midline, posterior hypopharyngeal wall, or post-cricoid region involvement. LA-SCC patients with ipsilateral N2b1-N3 disease or tumors with the body midline involvement;

[†]T4 classification or tumor with oral cavity involvement;

[‡]T4 classification or ipsilateral N2b1-N3 classification;

[§]Ipsilateral N3 classification;

[‖]T4 classification and ipsilateral N3 classification;

[¶]T3-T4 classification;

[#]T4 classification;

[**]Tumor with esophagus involvement;

[††]Tumor with posterior pharyngeal wall or post-cricoid region involvement;

[‡‡]T4 classification and ipsilateral N2b2-N3 classification;

[§§]Tumor with subglottis involvement;

Abbreviations: OC, oral cavity; OP, oropharyngeal; HP, hypopharyngeal; LA, laryngeal; SCC, squamous cell carcinoma.

3.5 | Summary of elective irradiation schemes for OP-SCC

For the ipsilateral node-negative neck, elective irradiation of levels VIIa and II-IVa is recommended for all patients. Additionally, ipsilateral level Ib is suggested in patients with T4 disease or oral cavity involvement. For the contralateral node-negative neck, elective irradiation is proposed for patients with T3-T4 disease, ipsilateral N2b2-N3 disease, tumors with body midline involvement, and tumors of midline subsites (including the base of the tongue, soft palate, and oropharyngeal wall). In all these patients, elective irradiation of contralateral level II is recommended. Additionally, contralateral level III irradiation is recommended for patients with T4 and ipsilateral N2b1-N3 disease; contralateral level VIIa irradiation is recommended for patients with T4 and ipsilateral N3 disease, and; contralateral level IVa irradiation is recommended for patients with ipsilateral N3 disease. Our proposals for the elective irradiation schemes for OP-SCC, as well as OC-SCC, HP-SCC, and LA-SCC are summarized in Table 4.

3.6 | An online tool to facilitate the clinical application of our proposals

A publicly available online tool (http://lymph.pvmedtech.com) was constructed to facilitate the clinical use of our

elective irradiation recommendations for node-negative necks. For node-positive necks, we referred to the elective irradiation schemes proposed by Gregoire et al. [8]. By inputting the characteristics of the primary tumor and metastatic LNs, elective irradiation schemes for the right and left sides of the neck were recommended and delineated based on a set of computed tomography scans.

4 | DISCUSSION

In this study, we established individualized elective irradiation schemes for ipsilateral and contralateral clinically node-negative neck by analyzing the incidence of LNM in patients with OC-SCC, OP-SCC, HP-SCC, and LA-SCC. Our work represents the first study to address the distinct elective irradiation proposals for ipsilateral and contralateral node-negative necks. Our results suggest reduced irradiation volumes for the contralateral neck as opposed to the volumes suggested by guidelines [8, 9], which recommended the same irradiation volumes for bilateral side of the neck. A reduced irradiation volume might help to alleviate radiation-induced toxicities, thus improving the quality of life in cancer survivors [23–25]. Notably, we explored a computer-aided implementation process and constructed a publicly available online tool which might facilitate the widespread clinical use of our proposals.

At present, there are two main guidelines that have reached some consensus for the elective neck irradiation of OC-, OP-, HP- and LA-SCC [8, 9]. Namely, elective irradiation of ipsilateral levels I-III is recommended for the ipsilateral node-negative neck in OC-SCC, and that of ipsilateral levels II-IVa is recommended in patients with OP-, HP- and LA-SCC (T1N0 glottic tumors excluded). For the contralateral neck, the guidelines recommend that the elective irradiation schemes follow the same rules as those for the ipsilateral neck. However, these elective irradiation strategies ignore the impact of T classification on bilateral LNM and the ipsilateral N classification on contralateral LNM, as well as the lower LNM rates in the contralateral neck than those in the ipsilateral neck. Therefore, to draw better proposals, we included these factors in our analysis.

Previous studies have confirmed that the depth of invasion, dimension, and thickness of the primary lesion as well as the T classification were related to regional LNM in HNSCC [26–28]. Lim et al. [29] reported that the occult LNM rate in patients with T3-T4 disease was significantly higher than that in patients with T1-T2 disease (25%–36% *vs*. 0%–5%). In addition to T classification, the ipsilateral N classification has also been confirmed to be associated with contralateral LNM [30, 31]. Moreover, although the pattern of LNM in the contralateral neck was found similar to that in the ipsilateral neck, the incidence of LNM at certain levels of the contralateral neck was significantly lower than that at the corresponding levels of the ipsilateral neck [13, 14]. Taken together, these suggest that it might be more reasonable to propose distinct elective irradiation schemes for the ipsilateral and contralateral node-negative neck based on the invasion extent of the primary lesion and ipsilateral LNs.

Specifically, for the ipsilateral node-negative neck, our recommended elective irradiation schemes are almost consistent with the guidelines in these four types of cancers, except for some slight differences. First, we suggest that level Ia could be spared in OC-SCC patients with early T classification. Although the guidelines do not distinguish level Ia from level Ib, the low incidence of tumor metastasis in level Ia in our study in patients with T1-T2 disease (0.9%–3.2%) might support the exemption of level Ia in those patients. Second, level IVa could be spared in glottic LA-SCC patients with early T classification because of the paucity of lymphatics in the true vocal cords [15] and the extremely low incidence of LNM to level IVa in patients with T1-T2 disease (0.5%–0.9%). Third, for level Va, since our results and historical data demonstrated that LNM rates were higher than 5% [13, 32], we suggest that level Va might be included in patients with HP-SCC.

For elective irradiation schemes of the contralateral node-negative neck, the guidelines recommend covering levels II-IVa for all patients with OP-SCC, HP-SCC, and LA-SCC (T1N0 glottic tumors excluded). However, our study only suggested level IVa irradiation in patients with advanced ipsilateral N or T classifications, and we regard it as reasonable to spare the lower neck in other patients for the following reasons: *(a)* our study and historical data [13, 30] consistently demonstrated an extremely low incidence of tumor metastasis to the contralateral level IVa (our study, 0.1%–2.5%; historical data, 0%–5%); *(b)* in a study published by Kjems et al [33], among 471 patients with OP-SCC who received elective irradiation of the bilateral or ipsilateral levels I-III, only eight patients experienced LN relapse outside the neck irradiation field, and only one case occurred in the contralateral level IV; and *(c)* sparing the lower neck would reduce radiation doses to the thyroid and might reduce the incidence of long-term hypothyroidism [34, 35]. In addition, we suggest sparing the contralateral level III in most patients with OC- and OP-SCC, except for those with advanced ipsilateral N and T classifications. This is another clinically relevant difference between our proposals and the guidelines for reducing irradiation volumes.

However, because the treatment strategies that patients receive in a real clinical scenario are not consistent with our recommended strategies, it is unknown whether patients would actually benefit from the strategies proposed in this retrospective study. To address this issue, we intend to conduct prospective clinical trials to verify whether our recommended elective irradiation schemes, by which the irradiation volumes were reduced when compared to the guidelines, could improve patients' quality of life without compromising their treatment outcome. Considering that some of the patients in this study did not have pathological results of LNM, we only referred to the imaging results to diagnose the clinically metastatic LNs. We acknowledge this limitation; however, studies have shown good sensitivity and specificity for modern imaging diagnoses of LNM, and imaging is crucial for the diagnosis of LNM at the levels outside the typical neck dissection areas [36–39]. Another limitation is that the majority of patients in this study did not receive pretreatment HPV detection. Therefore, all patients were restaged according to the 7th edition of the UICC/ AJCC staging system.

5 | CONCLUSIONS

We proposed individualized and computer-aided elective irradiation schemes for the ipsilateral and contralateral clinically node-negative neck. Our proposals could reduce irradiation volumes compared with those recommended in the current guidelines, and thus, might have a positive impact on patients' quality of life after radiotherapy.

AUTHOR CONTRIBUTIONS
Study concept and design: JK, LL, YS.
Data acquisition: JK, LL, GQZ, YS.
Data analysis and interpretation: JK, LL, CYJ, MQT, XJ.
Manuscript preparation: JK, LL.
Critical revision: All authors.

ORCID
Ying Sun https://orcid.org/0000-0002-5888-2929

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424. https://doi.org/10.3322/caac.21492.
2. Grégoire V, Coche E, Cosnard G, Hamoir M, Reychler H. Selection and delineation of lymph node target volumes in head and neck conformal radiotherapy. Proposal for standardizing terminology and procedure based on the surgical experience. Radiother Oncol. 2000;56(2):135–50. https://doi.org/10.1016/s0167-8140(00)00202-4.
3. Shah JP. Patterns of cervical lymph node metastasis from squamous carcinomas of the upper aerodigestive tract. Am J Surg. 1990;160(4):405–9. https://doi.org/10.1016/s0002-9610(05)80554-9.
4. Fletcher GH. Elective irradiation of subclinical disease in cancers of the head and neck. Cancer. 1972;29(6):1450–4.
5. Goffinet DR, Gilbert EH, Weller SA, Bagshaw MA. Irradiation of clinically uninvolved cervical lymph nodes. Can J Otolaryngol. 1975;4(5):927–33.
6. Mendenhall WM, Million RR, Cassisi NJ. Elective neck irradiation in squamous-cell carcinoma of the head and neck. Head Neck Surg. 1980;3(1):15–20. https://doi.org/10.1002/hed.2890030105.
7. Langendijk JA, Doornaert P, Verdonck-de Leeuw IM, Leemans CR, Aaronson NK, Slotman BJ. Impact of late treatment-related toxicity on quality of life among patients with head and neck cancer treated with radiotherapy. J Clin Oncol. 2008;26(22):3770–6. https://doi.org/10.1200/jco.2007.14.6647.
8. Grégoire V, Grau C, Lapeyre M, Maingon P. Target volume selection and delineation (T and N) for primary radiation treatment of oral cavity, oropharyngeal, hypopharyngeal and laryngeal squamous cell carcinoma. Oral Oncol. 2018;87:131–7. https://doi.org/10.1016/j.oraloncology.2018.10.034.
9. Biau J, Lapeyre M, Troussier I, Budach W, Giralt J, Grau C et al. Selection of lymph node target volumes for definitive head and neck radiation therapy: a 2019 Update. Radiother Oncol. 2019;134:1–9. https://doi.org/10.1016/j.radonc.2019.01.018.
10. Chronowski GM, Garden AS, Morrison WH, Frank SJ, Schwartz DL, Shah SJ et al. Unilateral radiotherapy for the treatment of tonsil cancer. Int J Radiat Oncol Biol Phys. 2012;83(1):204–9. https://doi.org/10.1016/j.ijrobp.2011.06.1975.
11. Shah JP. Cervical lymph node metastases–diagnostic, therapeutic, and prognostic implications. Oncology (Williston Park, NY). 1990;4(10):61–9; discussion 72, 6.
12. Dünne AA, Budach VG, Wagner W, Werner JA. Management of N0 neck in head and neck cancer: current controversies. Onkologie. 2004;27(4):363–7. https://doi.org/10.1159/000079089.
13. Mukherji SK, Armao D, Joshi VM. Cervical nodal metastases in squamous cell carcinoma of the head and neck: what to expect. Head Neck. 2001;23(11):995–1005. https://doi.org/10.1002/hed.1144.
14. Kowalski LP, Magrin J, Waksman G, Santo GF, Lopes ME, de Paula RP et al. Supraomohyoid neck dissection in the treatment of head and neck tumors. Survival results in 212 cases. Arch Otolaryngol Head Neck Surg. 1993;119(9):958–63. https://doi.org/10.1001/archotol.1993.01880210046007.

15. Edge S, Byrd D, Compton C, Fritz A, Greene F, Trotti A. AJCC Cancer Staging Manual, 7th ed. New York, NY: Springer; 2010.

16. Grégoire V, Ang K, Budach W, Grau C, Hamoir M, Langendijk JA et al. Delineation of the neck node levels for head and neck tumors: a 2013 update. DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines. Radiother Oncol. 2014;110(1):172–81. https://doi.org/10.1016/j.radonc.2013.10.010.

17. International Commission on Radiation Units and Measurements (ICRU) report 83: 4. Definition of volumes. J ICRU. 2010;10(1):41–53.

18. Eisbruch A, Foote RL, O'Sullivan B, Beitler JJ, Vikram B. Intensity-modulated radiation therapy for head and neck cancer: emphasis on the selection and delineation of the targets. Semin Radiat Oncol. 2002;12(3):238–49. https://doi.org/10.1053/srao.2002.32435.

19. Xiao R, Ward MC, Yang K, Adelstein DJ, Koyfman SA, Prendes BL et al. The prognostic impact of level I lymph node involvement in oropharyngeal squamous cell carcinoma. Head Neck. 2019;41(11):3895–905. https://doi.org/10.1002/hed.25927.

20. Wang H, Wu R, Huang X, Qu Y, Wang K, Liu Q et al. The pattern of cervical lymph node metastasis and risk factors of retropharyngeal lymph node metastasis based on magnetic resonance imaging in different sites of hypopharyngeal carcinoma. Cancer Manag Res. 2020;12:8581–7. https://doi.org/10.2147/cmar.S245988.

21. Wang D, Yu S, Zhai L, Xu J, Li B. Patterns of regional lymph node failure of locally advanced hypopharyngeal squamous cell carcinoma after first-line treatment with surgery and/or intensity-modulated radiotherapy. BMC Cancer. 2020;20(1):283. https://doi.org/10.1186/s12885-020-06793-6.

22. Buckley JG, MacLennan K. Cervical node metastases in laryngeal and hypopharyngeal cancer: a prospective analysis of prevalence and distribution. Head Neck. 2000;22(4):380–5.

23. Navran A, Heemsbergen W, Janssen T, Hamming-Vrieze O, Jonker M, Zuur C et al. The impact of margin reduction on outcome and toxicity in head and neck cancer patients treated with image-guided volumetric modulated arc therapy (VMAT). Radiother Oncol. 2019;130:25–31. https://doi.org/10.1016/j.radonc.2018.06.032.

24. Jellema AP, Slotman BJ, Doornaert P, Leemans CR, Langendijk JA. Unilateral versus bilateral irradiation in squamous cell head and neck cancer in relation to patient-rated xerostomia and sticky saliva. Radiother Oncol. 2007;85(1):83–9. https://doi.org/10.1016/j.radonc.2007.03.002.

25. Al-Mamgani A, van Rooij P, Tans L, Verduijn GM, Sewnaik A, Baatenburg de Jong RJ. A prospective evaluation of patient-reported quality-of-life after (chemo)radiation for oropharyngeal cancer: which patients are at risk of significant quality-of-life deterioration? Radiother Oncol. 2013;106(3):359–63. https://doi.org/10.1016/j.radonc.2012.12.014.

26. Jang JY, Kim MJ, Ryu G, Choi N, Ko YH, Jeong HS. Prediction of lymph node metastasis by tumor dimension versus tumor biological properties in head and neck squamous cell carcinomas. Cancer Res Treat. 2016;48(1):54–62. https://doi.org/10.4143/crt.2014.332.

27. Ganly I, Goldstein D, Carlson DL, Patel SG, O'Sullivan B, Lee N et al. Long-term regional control and survival in patients with "low-risk," early stage oral tongue cancer managed by partial glossectomy and neck dissection without postoperative radiation: the importance of tumor thickness. Cancer. 2013;119(6):1168–76. https://doi.org/10.1002/cncr.27872.

28. Tomifuji M, Imanishi Y, Araki K, Yamashita T, Yamamoto S, Kameyama K, et al. Tumor depth as a predictor of lymph node metastasis of supraglottic and hypopharyngeal cancers. Ann Surg Oncol. 2011;18(2):490–6. https://doi.org/10.1245/s10434-010-1219-5.

29. Lim YC, Lee SY, Lim JY, Shin HA, Lee JS, Koo BS, et al. Management of contralateral N0 neck in tonsillar squamous cell carcinoma. Laryngoscope. 2005;115(9):1672–5. https://doi.org/10.1097/01.mlg.0000184791.68804.0b.

30. Chung EJ, Oh JI, Choi KY, Lee DJ, Park IS, Kim JH, et al. Pattern of cervical lymph node metastasis in tonsil cancer: predictive factor analysis of contralateral and retropharyngeal lymph node metastasis. Oral Oncol. 2011;47(8):758–62. https://doi.org/10.1016/j.oraloncology.2011.05.013.

31. Vergeer MR, Doornaert PA, Jonkman A, Kaanders JH, van den Ende PL, de Jong MA, et al. Ipsilateral irradiation for oral and oropharyngeal carcinoma treated with primary surgery and postoperative radiotherapy. Int J Radiat Oncol Biol Phys. 2010;78(3):682–8. https://doi.org/10.1016/j.ijrobp.2009.08.042.

32. Lindberg R. Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. Cancer. 1972;29(6):1446–9.

33. Kjems J, Gothelf AB, Håkansson K, Specht L, Kristensen CA, Friborg J. Elective nodal irradiation and patterns of failure in head and neck cancer after primary radiation therapy. Int J Radiat Oncol Biol Phys. 2016;94(4):775–82. https://doi.org/10.1016/j.ijrobp.2015.12.380.

34. Rønjom MF, Brink C, Bentzen SM, Hegedüs L, Overgaard J, Johansen J. Hypothyroidism after primary radiotherapy for head and neck squamous cell carcinoma: normal tissue complication probability modeling with latent time correction. Radiother Oncol. 2013;109(2):317–22. https://doi.org/10.1016/j.radonc.2013.06.029.

35. Bakhshandeh M, Hashemi B, Mahdavi SR, Nikoofar A, Vasheghani M, Kazemnejad A. Normal tissue complication probability modeling of radiation-induced hypothyroidism after head-and-neck radiation therapy. Int J Radiat Oncol Biol Phys. 2013;85(2):514–21. https://doi.org/10.1016/j.ijrobp.2012.03.034.

36. Kelly HR, Curtin HD. Chapter 2 squamous cell carcinoma of the head and neck-imaging evaluation of regional lymph nodes and implications for management. Semin Ultrasound CT MR. 2017;38(5):466–78. https://doi.org/10.1053/j.sult.2017.05.003.

37. Liao LJ, Lo WC, Hsu WL, Wang CT, Lai MS. Detection of cervical lymph node metastasis in head and neck cancer patients with clinically N0 neck-a meta-analysis comparing different imaging modalities. BMC Cancer. 2012;12:236. https://doi.org/10.1186/1471-2407-12-236.

38. Sun J, Li B, Li CJ, Li Y, Su F, Gao QH et al. Computed tomography versus magnetic resonance imaging for diagnosing cervical lymph node metastasis of head and neck cancer: a systematic review and meta-analysis. Onco Targets Ther. 2015;8:1291–313. https://doi.org/10.2147/ott.S73924.

39. van den Brekel MW, Stel HV, Castelijns JA, Nauta JJ, van der Waal I, Valk J et al. Cervical lymph node metastasis: assessment of radiologic criteria. Radiology. 1990;177(2):379–84. https://doi.org/10.1148/radiology.177.2.2217772.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.