Level IV neck dissection as an elective treatment for oral tongue carcinoma—a systematic review and meta-analysis

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Objective. The purpose of our systematic review was to investigate the prevalence of level IV involvement and skip metastases in patients with clinically negative neck (cN0) oral tongue squamous cell carcinoma (OTSCC). The occurrence of occult metastases to lower levels in the neck (levels IV and V) or the development of an erratic distribution of cervical metastases ("skip metastases") that bypass the upper neck levels (levels I to III) and go directly to level IV or V challenges the role of supraomohyoid neck dissection in the treatment of OTSCC; therefore, controversy exists over including level IV cervical nodes during an elective neck dissection of OTSCC.

Study Design. Our search included all studies published from 1989 until January 2018 in the Cochrane Library, PubMed, EMBASE, and Web of Science. Abstracts and full-text articles that were deemed potentially relevant were screened. Data from the studies were extracted by using standardized tables, and a meta-analysis was conducted.

Results. In total, 3000 abstracts and 269 full text articles were screened, and 11 studies were included in this analysis. Among the 498 patients included, 16 had level IV involvement, representing involvement of 2.8%. The incidence for skip metastasis to level IV was low as well.

Conclusions. We recommend elective neck dissection that includes levels I to III in selected patients with OTSCC and cN0 neck.
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Squamous cell carcinoma is the most common pathologic diagnosis among all oral cavity cancers. Oral tongue squamous cell carcinoma (OTSCC) has the most nodal metastases of among all oral cancers, and nodal involvement considerably lowers survival.[1] Some metastases are occult and are, therefore, undetectable on clinical examination and imaging. These are associated with several negative prognostic variables, such as depth of tumor invasion in the tongue.[2]

The most common practice in the treatment of oral cancers is selective neck dissection, which includes the lymph node groups at the highest risk for metastasis (levels I−III). The exception, which also includes level IV, is OTSCC, which has the highest rate of occult metastases in the neck and a greater risk for skip metastases. Even without clinical evidence of nodal involvement, there is at least a 20% risk of occult disease.[3]

There is ongoing controversy regarding the incidence of level IV metastases in OTSCC, with some reports of significant rates of skip metastases to either level III or IV. Some argue that level IV should be included in the elective neck dissection.[3,4] Conversely, there are also many reports with low incidence of level IV involvement and recurrences at this level, which, because of associated morbidities, should limit the neck dissection to levels I to III.[4]

The aim of our study was to examine whether level IV should be routinely included in elective neck dissections in OTSCC in clinical node-negative patients.

MATERIALS AND METHODS

Search strategy and databases

The electronic search of the literature for articles published between 1989 and January 2018 was conducted in PubMed, EMBASE, Web of Science, and Cochrane Library. For each search, we applied key words: for the PubMed and EMBASE search, the key words were "tongue" and ("cancer" or "carcinoma" or "neoplasm") and ("neck dissection" or "lymphadenectomy"); and for Cochrane Library, the key words were "oral cancer" and "neck level IV"; for Web of Science, we used the article by Robert M. Byers et al. [2] for citation reference because it is considered a groundbreaking article in the subject. The references of each article obtained were checked for additional relevant studies. Only articles published in the English language were included.

Statement of Clinical Relevance

In patients with oral tongue squamous cell carcinoma and no nodes in the neck, level IV involvement rate is less than 3%. Yet, because level IV involvement is found in some of these patients, it must be taken into consideration.

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Data extraction
Data from the studies were first extracted independently by using standardized data forms. Basic information regarding the study design, including the publication year, country where the study was performed, study duration, and number of cases in the study, was extracted. Furthermore, T stage, neck dissection type, the levels dissected, and levels that were pathologically positive were noted.

Inclusion criteria
Oral squamous cell carcinoma (OSCC) or OTSCC as the primary tumor; studies that investigated the frequency of cervical metastases to level IV from primary head and neck cancers; studies that involved mixed populations of either cN+ with cN0 or mixed types of primary oral cancers, were included only if they enabled a distinction of the targeted population (i.e., cN0 and OTSCC); all patients had level IV tumors dissected compared with other patient groups; the studies included had a separate histologic report of level IV for the presence of metastases.

Exclusion criteria
First, we excluded the studies on patients who had undergone previous surgical treatment, preoperative radiotherapy and/or chemotherapy, as well as studies that included recurrent tumors. Next, we excluded the studies that did not specify what type of neck dissection was done. We also excluded studies that described mixed and inseparable data on primary tumors involving sites other than the tongue.

Quality appraisal of methodology
The studies included in this review were assessed for possible bias according to the *Cochrane Handbook for Systematic Reviews of Interventions*.[5]

Statistical analysis
A 2-sided confidence interval (CI) for proportion was used to analyze the data. For the purposes of calculation, binomial distribution was used in small samples and normal distribution was used in large samples. Subsequently, a meta-analysis was conducted. We tested between-study heterogeneity by using I^2 value and demonstrated it in a forest plot. All tests were 2-sided, with a significance level of $P < .05$.

RESULTS
Study selection
The search strategy identified a total of 3000 articles (Figure 1): 1270 from PubMed, 1427 from EMBASE, 105 from the Cochrane library of randomized control trials, and 198 from Web of Science. The titles and abstracts of the articles were screened; 280 articles were deemed appropriate and were retrieved for detailed review. Of these, 269 studies were excluded because they either did not fulfill the inclusion criteria or met the exclusion criteria. Nineteen full-text articles were assessed for eligibility. Of these, 3 were excluded because the neck stage was not cN0; 3 other articles were excluded because the type of dissection was not specified; in 1 study the level IV involvement was a recurrence; and 1 study did not provide specific results regarding OTSCC. Finally, 11 articles were included in the final analysis of this review.[6-16] Tables I and II give details of each article included.

Data on 556 patients were pooled for statistical analysis. In the 11 included studies, 16 cases of level IV metastasis had been confirmed on pathologic examination.

Of the reviewed articles, 137 were excluded because they did not have sufficient data regarding level IV involvement; 31 because they reported data on a different type of primary tumor; 44 because they reported use of radiotherapy or chemotherapy before surgery; 15 because dissection of level IV tumors was performed not on a routine basis but, rather, on the basis of personal decision during surgery or other unspecified preoperative conditions; 13 because patients were not staged as cN0; and 29 because of other reasons listed in the inclusion and exclusion criteria.

Quality of the studies
The studies included in this review were assessed for possible bias according to the *Cochrane Handbook for Systematic Reviews of Interventions*.[6] No study was assessed as having a high risk of bias, all the 11 studies included in this review were assessed as having a low or unclear risk of bias. We demonstrated a moderate between-study heterogeneity (I^2 = 46.38%; P value = .0449; 95% CI 0.00−73.34).

Synthesis of results
The articles that were included were reports of studies performed in China, India, Italy, the United Kingdom, the United States, Turkey, Pakistan and Iran. Of the included articles, 4 were prospective and 7 were retrospective.[6-16]

Six of the 11 articles included in this analysis had their general population data referring to all patients included.[3,9,15-18] The median age of patients was 56.4 years, with the youngest being 44.89 years of age. The male population was the majority in all the studies. All patients had level IV tumors dissected, along with the other neck dissection levels (I−III).

In the 11 articles included, there were 16 incidents of level IV involvement. Of these, skip metastases were reported in 6 cases. The percentage of level IV

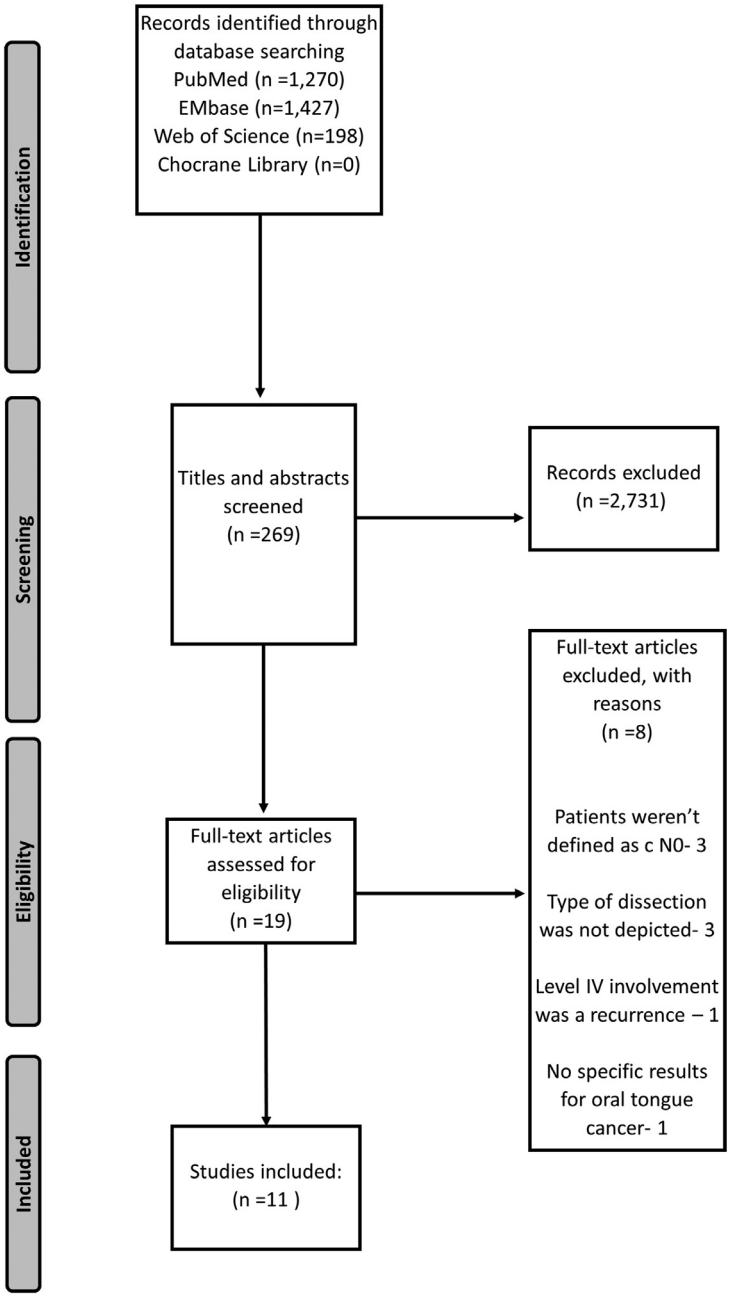

Fig. 1. Flow chart showing the process of study selection for the meta-analysis.

involvement was calculated to be 2.79%. Skip metastases incidence was 1.04%.

A forest plot was made to compare the data retrieved from the 11 articles (Figure 2).

The main results of the meta-analysis are described in Table III. The pooled estimated rate for cervical level IV metastasis in OTSCC was 2.8% (95% CI 1.594−4.497). Six of the 11 studies in this analysis (54.5%) had a clear indication of level IV involvement.

DISCUSSION

The extent of removal in selective neck dissections is determined by a predictable course of metastasis. According to previous studies, there are selected lymph node levels that are more likely to harbor metastases, depending on the primary tumor site. Lesions of the oral cavity usually metastasize to neck levels I, II, and III. Whenever positive nodes were found in other areas, disease was also found in the areas of highest risk[18,19]

Table I. Characteristics of the studies included in the systematic review

Author	*Year published*	*Location*	*Recruitment years*	*Type*	*Total number of cases*	*Number of relevant cases*	*Male population (%)*	*Median age*	*T Classification*
Yuen[6]	1999	University of Hong Kong, Queen Mary Hospital, Hong Kong, China	1991–1997	Prospective analysis	50	50	54	61	T1: 19; T2: 31
Akhtar[7]	2007	Khan University Hospital, Karachi, Pakistan	1995–2006	Retrospective cohort study	94	94	61.7	55	T1: 32; T2: 62
Vishak [9]	2014	Columbia Asia Hospital, Yeshwantpur, Bangalore, India	2006–2007	Retrospective analysis	57	57	75.4	44.89	T1 only
Agarwal[10]	2016	Medanta Hospital, Medanta Cancer Institute, Gurgaon, India	2011–2015	Prospective study	231	84	82.3	62.4	NA
Byers[11]	1988	Anderson Hospital, M. D. Anderson Hospital and Tumor Institute, Houston, Texas	1970–1979	Retrospective, nonrandomized study	428	48	NA	NA	NA
Shah[12]	1990	Memorial Sloan-Kettering Cancer Center, New York, NY	1965–1986	Retrospective review	501	58	71.3	60	NA
Woolgar[13]	1999	Mersey Regional Centre, Walton Hospital, Liverpool, UK	1999–1997	Retrospective study	189	70	65.6	60.5	T1-15; T2-86; T3-24; T4-64
Motiee-Langeroudi[14]	2016	Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Iran	2012–2014	Prospective study	32	32	62.5	54.41	T1-19; T2-12; T3-1
Dogan[15]	2014	Dokuz Eylul University School of Medicine, Izmir, Turkey	1990–2011	Retrospective study	67	40	50.7	58	T1-17; T2-20; T3-3; T4-0
De Cicco[16]	2006	European Institute of Oncology and University of Milan, Milan, Italy	2002–2004	Prospective study	14	14	85.7	51.8	T2-8; T3-3; T4-3
Pitman[8]	2002	The University of Pittsburgh School of Medicine, Pittsburgh, PA	NA	Retrospective review	20	9	NA	53.7	T1-3; T2-3; T3-3

NA, not available.

Table II. Results of the studies included in the systematic review

Author	*Median follow-up*	*Examination of the neck (clinically)*	*Technique*	*Levels dissected*	*Number of LNs examined*	*Number of metastatic LNs or the number of patients with LN metastasis*	*Number of cases with level IV involvement*	*Calculated % of level IV involvement*	*Skip metastases to level IV alone*
Yuen[6]	25 months	18 patients had no preoperative radiologic examination, the others had ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI)	45 selective I, II, III neck dissections (43 ipsilateral, 2 bilateral), and 5 full neck dissections (4 radical and 1 modified radical)	NA	2,826	31 LN	0	0	**NA**
Akhtar[7]	4 years	NA	All patients had partial glossectomy and modified radical neck dissection (sparing accessory nerve)	I–V	NA	30 patients	4	3.76%	**0**
Vishak[12]	NA	NA	All 57 patients underwent modified neck dissection (MND): 22 patients underwent MND1 and 35 patients underwent MND2	I-V	NA	NA	2	1.14%	**1**
Agarwal[10]	NA	Physical examination, pan endoscopic examination, and radiologic examination by contrast-enhanced CT, MRI, or positron emission tomography	Extended supraomohyoid neck dissection (from level I–IV)	I-IV	NA	16 in level IB 9 in level IIA 1 in level III	0	0	**0**
Byers[11]	2 years	NA	Suprahyoid, supraomohyoid, anterior, and functional neck dissection, or combinations of each in cases in which bilateral lymphadenectomies were performed	NA	NA	NA	0	0	**NA**
Shah [12]	NA	NA	Radical neck dissections	NA	Average of 39 LN	30	2	3%	**NA**
Woolgar[13]	NA	Palpation under general anesthesia during clinical staging/endoscopic evaluation (EUA) and MRI; 56 patients had, in addition, CT.	16 radical dissections 65 modified neck dissections of levels I–V 159 modified neck dissection of levels I–IV	I-V I-IV	115	NA	4	5.7%	**4**
Motiee-Langroudi[14]	NA	Neck ultrasonography and CT or MRI were used		I-IV	NA	NA	2	6.25%	**1**

(*continued on next page*)

Table II. Continued

Author	*Median follow-up*	*Examination of the neck (clinically)*	*Technique*	*Levels dissected*	*Number of LNs examined*	*Number of metastatic LNs or the number of patients with LN metastasis*	*Number of cases with level IV involvement*	*Calculated % of level IV involvement*	*Skip metastases to level IV alone*
			Extended supraomohyoid (level I–IV) neck dissection						
Dogan[15]	NA	Neck nodal staging was based on physical examination and contrast-enhanced CT findings	The patients underwent extended supraomohyoid neck dissection that included levels I–IV, or radical or modified radical neck dissection that included levels I–V	I–IV	NA	27 patients	0	0	**0**
De Cicco[16]	31.6 months	Absence of clinical and/or imaging evidence of cervical metastases after CT and/or MRI; no evidence of distant metastases as assessed by clinical examination, chest radiography, abdominal ultrasonography and bone scanning	Bilateral selective level I–IV neck dissection extended to the lymph nodes of level V, with preservation of the cervical branches of the cervical plexus.	I-IV	774	9	2	14.286%	**NA**
Pitman[8]	NA	NA	Selective neck dissection (SND)	I–IV	256	5	0	0	**NA**

LN, lymph nodes; *NA,* not available.

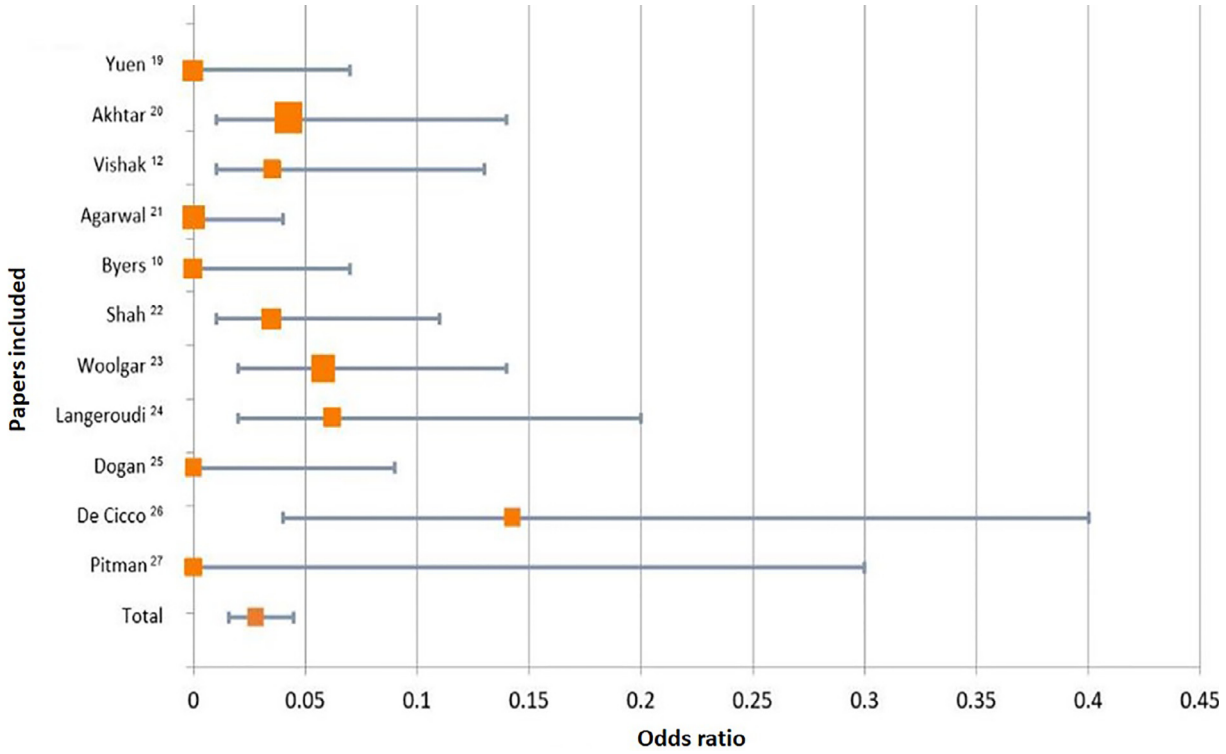

Fig. 2. Forest plot showing oral tongue squamous cell carcinoma (OTSCC) involvement of level IV. The pooled estimated rate for cervical level IV metastasis in OTSCC was 2.8% (95% confidence interval [CI] 1.594−4.497), far less than the 20% rule set by Weiss.[21] The *Y-axis* lists the articles included. The horizontal distance of a box from the *Y*-axis shows the difference between the test and control in relation to no observable effect.

In our review, 498 patients with oral squamous cell carcinoma of the oral tongue had clinical N0, and of these, 16 had level IV neck involvement, yielding a calculated percentage of 2.8%. This finding is much lower than the 15.8% that was reported by the sentinel work by Byers et al.[3] but agrees with the findings reported by others.[13,20]

Occult metastases are too small to be detected clinically or by using imaging modalities, and skip metastases do not follow predictable patterns of metastasis, making them easy to miss on routine examinations or to omit them in the plan for a neck dissection.

Table III. Summary of the data used in the Forest plot (as shown in Figure 2)

				Weight (%)	
Study	*Sample size*	*Proportion (%)*	*95% confidence interval [CI]*	*Fixed*	*Random*
Yuen[6]	50	0.000	0.000−7.112	8.99	9.70
Akhtar[7]	94	4.255	1.171−10.538	16.75	12.87
Vishak[12]	57	3.509	0.428−12.107	10.23	10.36
Agarwal[10]	84	0.000	0.000−4.296	14.99	12.32
Byers[11]	48	0.000	0.000−7.397	8.64	9.49
Shah	58	3.448	0.420−11.908	10.41	10.45
Woolgar[13]	70	5.714	1.579−13.989	12.52	11.41
Motiee-Langeroudi[14]	32	6.250	0.766−20.807	5.82	7.51
Dogan[15]	40	0.000	0.000−8.810	7.23	8.58
De Cicco[16]	14	14.286	1.779−42.813	2.65	4.26
Pitman[8]	9	0.000	0.000−33.627	1.76	3.04
Total (fixed effects)	**556**	**2.785**	**1.594−4.497**	**100**	**100**
Total (random effects)	**556**	**2.893**	**1.258−5.174**	**100**	**100**

Between-study heterogeneity was found to be moderate (I^2 = 46.38%; *P* value = .0449; 95% CI 0.00−73.34; Cochran's Q = 18.6501; degrees of freedom = 10).

The calculated weight (%) to each paper favors the control group (i.e., not to include level IV in an END) or the treatment (i.e., the dissection should be extended to include level IV, based on Weiss's 20% rule).

Table IV. Summary of the measures done to determine clinical neck involvement

	Measures to determine clinical neck involvement				
Paper	*Clinical examination*	*Ultrasonography*	*Computed tomography*	*Magnetic resonance imaging*	*Other*
Yuen[6]		V	V	V	
Akhtar[7]	V				No specification regarding which radiologic examination was done
Vishak[12]					No specification
Agarwal[10]	V	Only when one of the above investigations was contraindicated	V	V	Panendoscopic examination, positron emission tomography
Byers[11]					1980 American Joint Committee on Cancer Staging System; not reported
Shah [12]					Retrospective review; not reported
Woolgar[13]	V		In selected patients.	V	Endoscopic evaluation (EUA)
Motiee-Langeroudi[14]	V	V	V	V	
Dogan[15]	V		V		
De Cicco[16]			V	V	When no evidence of distant metastases was assessed, chest radiography, abdominal ultrasonography and bone scanning were done
Pitman[8]	V				

Some of the articles included in our study had been published more than 30 years ago. At that time, medical diagnostic tools were used less often. In addition, the quality of the imaging techniques has improved since then. Thus, fewer metastasized lymph nodes were reported earlier in the literature compared with recent studies. Table IV compares the different articles included in our review.

As mentioned, in the study by Byers et al.,[3] the rate of skip metastases to neck level IV lymph nodes was 15.8%. On the basis of this finding, those authors recommended extending neck dissections to include level IV in patients with early-stage OTSCC. However, this study included patients with different T stages and different N stages (i.e., not only cN0). Although it was concluded that the rate of skip metastasis is as high as 15.8%, when excluding all patients with clinically positive neck lymph nodes, only 5 cases with skip metastases in neck level IV were found among the initial neck dissection specimens. In 8 patients, there were subsequent recurrences in previously undissected level IV. Thus, when analyzing Byers' data, of the 270 patients in their study, only 13 had level IV involvement, although they had clinically negative neck lymph nodes, resulting in 4.8% calculated level IV involvement.[3] Because there was not enough data regarding occurrence rates of metastases to level IV in previously untreated necks, the rate of occult metastasis could not be determined from the findings of that study. The inclusion of positive neck nodes in Byers et al.'s article excluded it from the current systematic review and final meta-analysis.

In a study by Shah et al.,[12] of the 182 patients with OTSCC, 3% had level IV involvement (2 of 58 patients). Those authors concluded that if they had performed a supraomohyoid neck dissection, instead of the radical neck dissection that they did perform, 3.5% of the patients would have had nodal metastases left behind, mostly at level IV.

Two studies investigated the optimal treatment for the neck by using a decision tree model.[21,22] Weiss et al.'s[21] frequently cited study concluded that patients with head and neck primary SCC and stage N0 neck status should undergo treatment of the neck if the probability of occult cervical metastasis is greater than 20%. However, Okura et al.[22] present a much higher threshold of 44.4%. The difference in these studies demonstrates that contributing factors other than

disease stage must be taken into consideration when deciding on a treatment regimen or when making a decision analysis. These considerations may include the follow-up regimen and salvage capabilities in case regional failure is encountered.

The indication for elective neck dissection is a very important and complex matter. Decisions on the extent of a neck dissection cannot be made on the basis of only 1 parameter because of the percentage of positive lymph nodes in region IV, as reported in the articles mentioned above. Decision analysis is affected by local factors unique to each cancer center as well as by disease characteristics, such as the T stage, primary tumor's location, depth of invasion, or histopathologic type of tumor. Therefore, each cancer center should take into consideration specific data depending on the resources of the medical center, patients' health care accessibility, follow-up schedules and protocols, and surgical capabilities. In this way, each cancer center can make its own specific decision analysis and can decide on a more aggressive or moderate standard of care.

It is standard practice at our institution to perform a selective I–III elective neck dissection in all but very small and superficial T1 OTSCCs and in patients with severe comorbidities that pose a real hazard with regard to prolonged anesthesia. In cases of a tumor that approaches the base of the tongue and/or has infiltrative borders and in cases of clinically positive lymph nodes at level III identified during surgery, we extend the neck dissection to include ipsilateral level IV. This approach, however, has some limitations because it is almost impossible to find micrometastases of occult lymph nodes on frozen section or on clinical examination.

Limitations

The retrospective nature of most of the studies included is one of the limitations of this review, and we had to contend with it while collecting data; furthermore, focusing on OTSCC, specifically level IV neck dissection, limited the number of studies included. Another limitation was the classification of level IV in the earlier studies that were identified in the literature search.

CONCLUSIONS

Our review indicated that in patients with OTSCC and cN0, the rate of level IV involvement is less than 3%; thus, extending neck dissection to include level IV may not be warranted in all patients. However, because level IV involvement is found in some of these patients, it must be considered. More studies should be performed for a more extensive and proper evaluation of level IV metastasis in OTSCC when planning the treatment strategy because regional recurrences of OTSCC may be hard to control and carry a grave prognosis.

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PRESENTATION

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