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ORIGINAL RESEARCH

Prediction of Occult Contralateral Nodal Metastasis in Surgical Treated p16 Negative Oropharyngeal Squamous Cell Carcinoma

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Background: It is well known that p16 negative oropharyngeal squamous cell carcinoma (OPSCC) has a high probability of spreading to the ipsilateral neck. However, no consensus exists as to whether to perform elective treatment for clinical nodal negative in contralateral neck.

Methods: A total of 85 patients with p16 negative OPSCC who underwent primary tumor excision and bilateral neck dissections between 2005 and 2018 were analyzed retrospectively. Clinicopathologic variables were used to identify factors predicting occult contralateral nodal metastasis (OCNM). A nomogram was developed to assess the risk of OCNM and the model was validated internally by using bootstrap resampling.

Results: The overall prevalence of pathologically positive contralateral nodes was 30.6% (26/85) in our cohort, and the rate of OCNM was 18.3% (11/60). The presence of ipsilateral clinical extranodal extension (cENE) was significantly associated with contralateral neck metastasis (odds ratio, 5.662; 95% CI, 2.079–15.415) with increased risk of OCNM (odds ratio, 4.271; 95% CI, 1.045–17.458). Moreover, the concordance index of the proposed nomogram model without ipsilateral cENE was 0.623 and could increase to 0.717 with the inclusion of ipsilateral cENE in the calculation.

Conclusion: The risk of OCNM in p16 negative OPSCC with ipsilateral cENE is notable. Ipsilateral cENE-based nomogram might assist in individual decision-making regarding contralateral nodal negative neck management and help avoid the over- and under-treatment of p16 negative OPSCC.

Keywords: p16, oropharyngeal cancer, occult contralateral neck metastasis, extranodal extension, nomogram

Introduction

In recent decades, the prevalence of oropharyngeal squamous cell carcinoma (OPSCC) has been on the rise globally, and this trend is still increasing in Taiwan and the United States.[1–3] The presence of neck lymph node metastasis is one of the most significant prognostic factors in treating patients with OPSCC.[4,5] The chance of nodal metastasis is high in every tumor stage among patients with tonsil cancer.[6] In addition, the occult nodal metastasis rate of the ipsilateral side in OPSCC is approximately 30%, warranting the importance of neck treatment.[7,8] Further studies have investigated the risk of developing contralateral nodal metastases (CNM) in patients treated with surgical approaches and have demonstrated a risk of CNM ranging from 16% to 29%.[9,10] After the emergence of human papillomavirus (HPV) as the main etiologic agent in the development of OPSCC, Kato et al and Tritter et al have described the incidence of contralateral or bilateral nodal metastasis by clinical or imaging studies to be 14–26%.[11,12]

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More recently, Last et al studied the incidence of CNM in surgically treated HPV-related tongue base cancer, and they reported the rate of CNM to be up to 38.2%.[13] Currently, reports are still limited concerning the prevalence rate of pathological nodal positivity in contralateral neck cases among patients with HPV-negative OPSCC, and the incidence of occult contralateral nodal metastasis (OCNM) is not well known in this patient population. Clinically, the expression of p16 is recognized as a surrogate of HPV noted in the tumor cells of OPSCC;[14] therefore, this study aimed to identify the prevalence rate and risk factors of OCNM in p16-negative OPSCC. In addition, we aimed to develop a nomogram that could help individually predict the probability of OCNM and thus attempt to tailor treatment options.

Materials and Methods

Study Population

From the cancer database of the institute, we retrospectively enrolled patients diagnosed with p16-negative OPSCC who received radical surgery with bilateral neck dissection as primary treatment from January 2005 to December 2018 in Kaohsiung Chang Gung Memorial Hospital, Taiwan. The TNM stage was reclassified according to the eighth edition of the American Joint Committee on Cancer (AJCC) staging system.[15] The expression of p16 by immunohistochemistry was also determined according to the suggestion from the same staging system. Only p16-negative OPSCC patients who had upfront radical surgery with bilateral neck dissections were included for the analysis of CNM. The clinical status of neck nodal metastasis was determined by contrast-enhanced image studies preoperatively, including computed tomography scan or magnetic resonance imaging examination. Patients with contralateral cN0 disease who underwent radical surgery with bilateral neck dissections were selected to identify the OCNM, and all neck dissections were performed simultaneously with primary tumor resection. OCNM was defined as pathologically contralateral positive nodal metastases after the surgical intervention. Patients who (a) had any other cancer history, (b) had prior treatment for head and neck cancer, (c) had neoadjuvant therapy, (d) had a non-oropharyngeal primary site, (e) had simultaneous multiple origins of head and neck cancer, and (f) had non-squamous cell carcinoma were excluded from this study. Finally, detailed information on the clinical and pathological features of the 85 patients were retrospectively reviewed.

Predictive Variables

The clinical and pathological characteristics such as gender, age, lifestyle habits, tumor location, laterality of primary tumor, clinical stage, histological grade, tumor thickness and clinical extranodal extension (cENE) in the ipsilateral neck were all statistically analyzed, with laterality of primary tumor being determined by physical examination and image studies. None of the tumors that crossed the midline were classified as lateralized. The cutoff values of tumor thickness were determined by the median values of two studied cohorts: 14 mm in the entire cohort and 12 mm in the contralateral cN0 cohort. The presence of cENE was determined by image studies of lymph nodes with indistinct margins or irregular capsular enhancement or infiltration into adjacent soft tissue. The adjuvant therapy for these patients after surgery was mostly based on the American National Comprehensive Cancer Network (NCCN) guideline.

Statistical Analysis

Statistical analyses were performed using the SPSS 22 software (SPSS/IBM Inc.). The outcomes of interest were the rate and potential risk factors of OCNM. Simple logistic regression analysis was performed to estimate the odds ratios (ORs) and 95% CIs of contralateral nodal disease for each covariate, while Fisher's exact test was applied to compare the distribution of categorical characteristics between the groups of patients with ipsilateral and contralateral lymph nodes, and the Log rank test was used to compare survival experiences between groups. A two-sided p value <0.05 was considered significant.

In addition, a predictive nomogram was created incorporating histological grade, tumor lateralization, tumor thickness, and ipsilateral cENE using the R software "rms" package (Version 5.1–0, Vanderbilt University, Nashville, TN, USA) with the endpoints of the pathologic status of lymph nodes in the contralateral cN0 neck. To ascertain the OCNM prediction accuracy of the nomogram, the concordance index (C-index) was derived for the proposed nomogram models with and without ipsilateral cENE; C-index values of 0.5 and 1.0 were considered as signifying random and perfect

predictability, respectively. In addition, the predictive model was internally validated using 1000 bootstrap techniques to address model overfit and obtain a relatively unbiased evaluation.

The calibration of this nomogram was assessed using 1000 bootstrap resamples to draw a plot of the predicted probabilities of OCNM against the actual probabilities of OCNM. This study was approved by the Medical Ethics and Human Clinical Trial Committees at Chang Gung Memorial Hospital (Ethical Application Reference number: 202201008B0). This study was conducted in accordance with the Declaration of Helsinki. Patients' consent to review their medical records was not required by this hospital's committees because the patient data remained anonymous in this study.

Results

Of the 85 patients, 81 patients (95.3%) were male, and 4 (4.7%) were female. The mean age during diagnosis for all was 53.6 years, ranging from 31 to 71 years; 79 patients (92.9%) had a smoking habit, 66 patients (77.6%) had the habit of alcohol drinking, and 64 patients (75.3%) had the habit of betel nut chewing. The most common tumor subsite was soft palate (n = 39, 45.9%), followed by base of the tongue (n = 36, 42.3%) and tonsil (n = 10, 11.8%). For histologic grade, 18 patients (21.2%) had well differentiated squamous cell carcinoma (WDSCC), 62 patients (72.9%) had moderately differentiated squamous cell carcinoma, and the remaining 5 patients (5.9%) had poorly differentiated squamous cell carcinoma. Sixty primary tumors (70.6%) were found across the midline. For clinical T classification, this cohort included T1 (n = 14, 16.5%), T2 (n = 27, 31.8%), T3 (n = 9, 10.6%), T4a (n = 28, 32.9%), and T4b (n = 7, 8.2%). The clinical status of neck nodal metastasis was present in 56 patients (82.5%), and 27 out of these 56 patients had clinical positive ENE noted by the image findings. The clinicopathological features of all 85 cases are listed in Table 1.

Table 1 Characteristics of Patients Who Had p16 Negative OPSCC Underwent Bilateral Neck Dissection (n = 85)

Characteristic		Patient Population	
		All (n=85)	With Contralateral cN0 Neck Finding (n=60)
Age, mean (SD), y		53.66 (10.461)	54.25 (10.043)
Sex	Male/Female	81 (95.3%)/4 (4.7%)	57 (95%)/3 (5%)
Smoking habit	Yes/No	79 (92.9%)/6 (7.1%)	55 (91.7%)/5 (8.3%)
Betel nut chewing habit	Yes/No	64 (75.3%)/21 (24.7%)	42 (70%)/18 (30%)
Alcohol consumption habit	Yes/No	66 (77.6%)/19 (22.4%)	43 (71.7%)/17 (28.3%)
Tumor location	Tonsil	10 (11.8%)	8 (13.3%)
	Soft palate	39 (45.9%)	32 (53.4%)
	Tongue base	36 (42.3%)	20 (33.3%)
Histological grade	WDSCC	18 (21.2%)	10 (16.7%)
	Non-WDSCC	67 (78.8%)	50 (83.3%)
Tumor Laterization	Lateralized	25 (29.4%)	20 (33.3%)
	Crossed midline	60 (70.6%)	40 (66.7%)
Clinical T classification	1+2	41 (48.3%)	34 (56.7%)
	3+4	44 (51.7%)	26 (43.3%)
Tumor size, mean (SD), mm		32.97 (17.178)	30.58 (15.843)
Tumor thickness, mean (SD), mm		15.90 (10.724)	14.62 (10.293)
Clinical N classification	0	29 (34.1%)	29 (48.3%)
	1	11 (12.9%)	11 (18.3%)
	2b	10 (11.8%)	10 (16.7%)
	2c	8 (9.4%)	0
	3b	27 (31.8%)	10 (16.7%)
Clinical ipsilateral nodal disease	N0	29 (34.1%)	29 (48.3%)
	N+	56 (65.9%)	31 (51.7%)
Ipsilateral cENE	Absent	56 (65.9%)	47 (78.3%)
	Present	29 (34.1%)	13 (21.7%)

Abbreviations: OPSCC, oropharyngeal squamous cell carcinoma; SD, standard deviation; WDSCC, well differentiated squamous cell carcinoma; cENE, clinical extranodal extension.

Overall, 26 patients (26/85 = 30.6%) had presence of contralateral positive neck nodes pathologically. Sixty patients (60/85 = 70.6%) had contralateral cN0 disease, and positive nodes were found in 11 necks after the neck dissections, so the rate of OCNM was 18.3% (11/60).

About 71% of the patients (n = 61) underwent adjuvant therapy after radical surgery with most of these (n = 47) undergoing adjuvant CCRT. During the follow-up period, recurrent tumors were noted in 26 patients (30.6%), including 10 patients (11.8%) who had local recurrence, 5 patients (5.9%) who had regional failure, 2 patients (2.4%) who had locoregional recurrence, and 10 patients (11.8%) who had distant metastasis disease. All the regional recurrences were located at the ipsilateral neck area, and no patient with contralateral nodal recurrence was noted in this cohort. At last contact, 37 patients had died, including 25 patients who had expired from the disease.

Contralateral Nodal Metastasis

The overall incidence of pathologically positive CNM was 26/85 (30.6%). Regarding these positive contralateral nodes, there were 3/10 (30%), 9/39 (23.1%), and 14/36 (38.9%) over-the-tumor locations in tonsil, soft palate and base of the tongue, respectively. The factors associated with CNM are described in Table 2. Compared with clinical ipsilateral negative nodal disease, clinical ipsilateral positive nodal status had a higher risk of contralateral nodal spread (OR, 4.044; 95% CI, 1.238–13.212). In addition, patients with ipsilateral cENE had an increased risk of contralateral nodal disease (OR, 5.662; 95% CI, 2.079–15.415). For the lateralization of the primary tumor, those with cross-midline tumors had a higher risk of CNM than those without them, but this did not reach statistical significance (OR, 3.039; 95% CI, 0.924–10.003, $p = 0.067$).

Occult Contralateral Nodal Metastasis

In this cohort, 25 patients had contralateral nodal disease clinically, but only 15 out of these 25 patients had metastatic lymph nodes with pathological proof. The other 60 patients had no contralateral nodal disease clinically, and OCNM was identified in 11 patients (18.3%) after surgical validation. The number of occult lymph nodes was identified—one in nine patients and two in two patients. Pathologic ENE was identified in two contralateral necks (2/11 = 18.2%) among these occult metastatic lymph nodes. The risk factors associated with OCNM are described in Table 3. Only the presence of ipsilateral cENE increased the risk of OCNM (odds ratio, 4.271; 95% CI, 1.045–17.458, $p = 0.043$).

Table 2 Risk Factors for Contralateral Nodal Disease in All Patients (n = 85)

Risk Factor		Patient Population		Univariate Analysis OR (95% CI)	*p* value
		Contralateral pN0 Neck Finding (n=59)	Contralateral pN+ Neck Finding (n=26)		
Tumor location	Tonsil	7	3		
	Soft palate	30	9	0.7 (0.149, 3.279)	0.651
	Tongue base	22	14	1.485 (0.328, 6.717)	0.608
Tumor Laterization	Lateralized	21	4		0.067
	Crossed midline	38	22	3.039 (0.924, 10.003)	
Histologic Grade	WDSCC	14	4		0.389
	Non-WDSCC	45	22	1.711 (0.504, 5.811)	
Clinical	T1-2	31	10		0.234
T classification	T3-4	28	16	1.771 (0.691, 4.539)	
Tumor thickness	≤14mm	32	15		0.768
	>14mm	27	11	0.869 (0.342, 2.206)	
Clinical ipsilateral	N0	25	4		0.021*
nodal disease	N+	34	22	4.044 (1.238, 13.212)	
Ipsilateral cENE	Absent	46	10		0.001*
	Present	13	16	5.662 (2.079, 15.415)	

Note: *Statistically significant $p < 0.05$.
Abbreviations: WDSCC, well differentiated squamous cell carcinoma; cENE, clinical extranodal extension; OR, odds ratio; CI, confidence interval.

Table 3 Risk Factors for Contralateral Nodal Disease in Those with Clinically Negative Contralateral Neck Findings (n = 60)

Risk Factor		Patient Population		Univariate Analysis OR (95% CI)	*p* value
		Contralateral pN0 Neck Finding (n=49)	Contralateral pN+ Neck Finding (n=11)		
Tumor location	Tonsil	6	2		
	Soft palate	27	5	0.556 (0.086, 3.580)	0.536
	Tongue base	16	4	0.750 (0.108, 5.216)	0.771
Tumor Laterization	Lateralized	18	2		0.307
	Crossed midline	31	9	2.613 (0.508, 13.451)	
Histologic grade	WDSCC	9	1		0.466
	Non-WDSCC	40	10	2.25 (0.255, 19.886)	
Clinical	T1-2	28	6		0.875
T classification	T3-4	21	5	1.111 (0.298, 4.138)	
Tumor thickness	<12mm	23	4		0.526
	≥12mm	26	7	1.548 (0.401, 5.975)	
Clinical ipsilateral	N0	25	4		0.383
nodal disease	N+	24	7	1.823 (0.473, 7.033)	
Ipsilateral cENE	Absent	41	6		0.043*
	Present	8	5	4.271 (1.045, 17.458)	

Note: *statistically significant $p < 0.05$.
Abbreviations: WDSCC, well differentiated squamous cell carcinoma; cENE, clinical extranodal extension; OR, odds ratio; CI, confidence interval.

Nomogram for OCNM Prediction

A nomogram incorporating histological grade (WDSCC vs non-WDSCC), tumor lateralization (lateralized vs crossed midline), tumor thickness (<12 mm vs ≥12 mm), and ipsilateral cENE (present vs absent) was developed for the purpose of predicting individualized OCNM in the study population (Figure 1). The longer the line, the greater the impact of risk factors on the rate of OCNM. Each subtype in these variables was assigned a score. The cumulative sum of each "point" is the "total points." The corresponding "risk of occult contralateral nodal metastasis" of the "total points" is the predicted probability of OCNM suggested by our designed nomogram. Another nomogram incorporating histological grade, tumor lateralization, and tumor thickness was implemented for comparison. The C-index derived for the nomogram incorporating several clinicopathological features without ipsilateral cENE was 0.623, whereas that derived

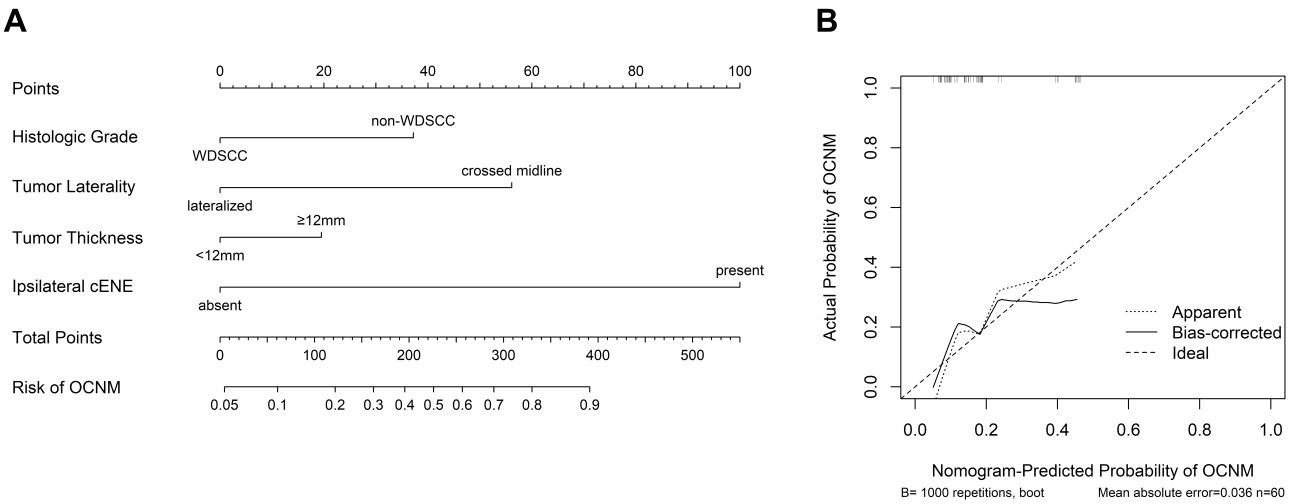

Figure 1 (**A**) Nomogram was constructed based on the data of clinical contralateral N0 group. The points of each feature were added to obtain the total points, and a vertical line was drawn on the total points to obtain the corresponding risk of OCNM. (**B**) Calibration curves of nomogram prediction of OCNM.
Abbreviations: OCNM, occult contralateral neck metastasis; WDSCC, well differentiated squamous cell carcinoma; cENE, clinical extranodal extension.

Table 4 Metastatic Risk Stratification and Individualized Treatment of Contralateral cN0 Disease in p16 Negative OPSCC Patients Based on Nomogram Scores

Total Points	Occult Metastasis Risk in Contralateral Neck	Treatment Option Regarding ND
0–121	Low risk	Ipsilateral ND
≥122	High risk	Bilateral ND

Abbreviations: OPSCC, oropharyngeal squamous cell carcinoma; ND, neck dissection.

for the nomogram model incorporating ipsilateral cENE and several clinicopathological features was 0.717. These results indicate that the nomogram incorporating clinicopathological factors including ipsilateral cENE had better performance in predicting the OCNM of patients with p16-negative OPSCC upfront radical surgery than the nomogram model with no ipsilateral cENE. The proposed predictive nomogram was internally validated using bootstrap techniques.

The example of nomogram usage in this cohort is shown as follows. A sample was randomly selected from the subjects. A patient who was diagnosed with p16-negative OPSCC with a pretreatment image study was revealed to be clinically negative in contralateral neck metastasis. Its tumor characteristics showed non-WDSCC in the histologic grade (score: 37.20), crossed midline of the primary tumor (score: 56.13), a tumor thickness ≥12 mm (score: 19.49), and the presence of ipsilateral cENE (score: 100). The total points added up to 212.82, and thus, the probability of OCNM was 46.19%.

According to our designed nomogram, if the scores of total points ≥122 corresponded to the probability of OCNM of more than 20% in the typical threshold, it would be necessary to perform elective neck dissection by surgeons for better clinical outcomes. A new risk stratification scheme based on nomogram scores was then proposed, which stratified p16-negative OPSCC patients into low- and high-risk groups of OCNM. Ipsilateral neck dissection was recommended for patients in the low-risk group, and bilateral neck dissection was recommended for patients in the high-risk group (Table 4).

Discussion

Nodal metastasis is the most important factor in the prognosis of HPV-negative OPSCC.[16] Givens et al[17] in a retrospective analysis showed that the five-year survival rate was 70% in N0, but this dramatically reduced to 27% in N1 or more advanced cases. Some authors have also shown that delayed neck metastasis from an untreated neck usually presents a higher incidence of extracapsular spread, multiple nodal metastasis, and the presence of skip metastases, reducing the salvage rates to less than 40% despite intensive treatment.[18,19] This finding highlights the importance of treating neck lymph nodes at the initial diagnosis of OPSCC.

With a higher proportion of patients of OPSCC presenting with neck nodal disease at the time of diagnosis, it is essential to perform neck dissection when ipsilateral nodal metastasis is present. Clinically, the primary radiation strategy is the mainstay in treating OPSCC, but the detailed histopathologic information is lacking; additionally, treatment guidelines for clinical contralateral N0 neck, especially among patients with HPV-negative OPSCC, are insufficient except for the primary tumor crossing the midline.

In our cohort, the prevalence of positive CNM in patients with p16-negative OPSCC was 30.6% after validation of curative surgery for primary site and bilateral neck dissections. Our results showed that the rate of pathologically positive CNM is higher than other investigations of OPSCC. The reason for these results might be due to more extensive tumor involvement in this cohort.

Before the era of HPV as the main etiology in the development of OPSCC, some authors had found that the chance of developing CNM was between 16% and 29% in patients having OPSCC treated by surgical approaches.[9,10] Kato et al[11] in a National Cancer Database study found patients with HPV-negative OPSCC had a 14.5% risk of contralateral nodal disease. In our cohort, the prevalence of positive CNM in patients with p16-negative OPSCC was 30.6% after validation of curative surgery for primary site and bilateral neck dissections. Larger and more extensive tumor involvement in this series could be the reason. In addition, our results revealed that the contralateral metastasis rate would be significantly higher than those without if ipsilateral positive nodal disease, the presence of ENE and a higher number of involved

ipsilateral nodes were noted pathologically. This correlation has been previously observed among patients with hypopharyngeal cancer. Basically, elective bilateral neck dissections are recommended for surgical management from these reports.[20,21] Nowadays, the TNM stage of HPV-negative OPSCC is classified together with hypopharyngeal cancer as a group according to the eighth edition of the AJCC system.

Some previous studies have described that a crossed-midline tumor and the tumor location over the tongue base in OPSCC possess increasing risk of CNM.[11,13] In our study, a crossed-midline tumor also showed a higher risk of CNM but did not reach statistical significance ($p = 0.06$), possibly due to the limited case number in this cohort. The primary tumor location might also play a role because a tumor over the tongue base has relatively less distance from the midline than primary tonsil cancer, but this did not reach significance and might also be due to limited study numbers in our series.

To this day, few reports have focused on OCNM in HPV-negative OPSCC. Lim et al[22] have demonstrated a 16% rate of OCNM in 43 patients with clinical contralateral N0 tonsillar cancer. This study might include both HPV-positive or HPV-negative tumors because the HPV status is unknown. McMullen et al[23] studied patients with pT1-2 N0-3 (AJCC, eighth edition) OPSCC disease treated with transoral robotic surgery and bilateral neck dissection, including 24 patients with p16-positive tumors and 8 patients with p16-negative tumors, where the OCNM rate was 12.5% (1/8) in p16-negative OPSCC. To the best of our knowledge, this is a large series of investigations about tissue proof by neck dissection in contralateral occult nodal metastases among patients with p16-negative OPSCC. The proportion of OCNM was up to 18.3% (11/60) in this cohort, also revealing that the presence of ipsilateral cENE produced significantly higher risk of OCNM. Our study also established a multivariate nomogram that integrated clinicopathological variables, including histologic grade, tumor lateralization, tumor thickness and ipsilateral cENE, which could yield a feasible result (C-index: 0.717). The nomogram could provide more accurate and individualized predictions of OCNM of patients with p16-negative OPSCC than the nomogram model without ipsilateral cENE being incorporated. It could aid surgeons in the identification of patients who could achieve favorable results from more neck management.

Several limitations should be addressed in this study. Firstly, this is a retrospective, single-institute study. Head and neck surgeons might have different treatment opinions in different historical backgrounds, and selection bias in patients and data collection could occur. Secondly, the incidence of contralateral nodal disease could be confined to those patients undergoing surgery in this cohort. The contralateral neck as treated by elective radiotherapy was not available in this cohort, thereby not precisely reflecting the prevalence rate of CNM. Thirdly, the sample size is limited, and finally, the study results and proposed nomogram were not validated using an independent data set. External validation of the results using an independent patient cohort could strengthen the derived evidence revealing that ipsilateral cENE is a good predictor of OCNM in p16-negative OPSCC.

Conclusion

In this study, the incidence of contralateral nodal disease among patients with p16-negative OPSCC was 30.6%, and the chance of OCNM was 18.3%. The presence of ipsilateral cENE denoted significantly higher risk of CNM and OCNM. The ipsilateral cENE–based nomogram developed in this study could be useful in the application of ipsilateral cENE and provide individualized prediction of OCNM for patients with p16-negative OPSCC. Furthermore, larger cohort studies are necessary to validate this issue.

Disclosure

The authors report no conflicts of interest in this work.

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