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Risk and Rate of Occult Contralateral Nodal Disease in Surgically Treated Patients With Human Papillomavirus–Related Squamous Cell Carcinoma of the Base of the Tongue

Aisling S. Last, MD; Patrik Pipkorn, MD; Stephanie Chen, MD; Dorina Kallogjeri, MD, MPH; Joseph Zenga, MD; Jason T. Rich, MD; Randal Paniello, MD; Jose Zevallos, MD; Rebecca Chernock, MD; Douglas Adkins, MD; Peter Oppelt, MD; Hiram Gay, MD; Mackenzie Daly, MD; Wade Thorstad, MD; Ryan S. Jackson, MD

IMPORTANCE The optimal treatment strategy for patients with human papillomavirus (HPV)–related oropharyngeal squamous cell carcinoma (OPSCC) of the base of the tongue (BOT) has not been sufficiently studied.

OBJECTIVE To investigate the rate of and risk factors for occult contralateral nodal disease in patients with HPV-related BOT OPSCC undergoing transoral surgery and bilateral neck dissections.

DESIGN, SETTING, AND PARTICIPANTS This retrospective case series reviewed the medical records of patients with HPV-related BOT OPSCC who underwent transoral surgery and bilateral neck dissections from January 1, 2002, through December 31, 2018, at the tertiary care center of Washington University School of Medicine in St Louis. Patients had a median follow-up of 30.0 months (interquartile range, 11.0-60.4 months). Patients with recurrent disease or multiple synchronous OPSCC primary tumors were excluded for a total of 89 patients. Data were analyzed from January 1 through June 1, 2019.

MAIN OUTCOMES AND MEASURES The primary outcome was the rate of contralateral occult nodal disease. Secondary outcomes were potential risk factors for contralateral occult nodal disease and regional recurrence rates.

RESULTS Eighty-nine patients were included in the series, of whom 81 (91.0%) were men. The mean (SD) age was 60 (9) years. Overall, 34 patients (38.2%) had pathologic contralateral nodal metastases. Seventy patients had no clinical evidence of contralateral nodal disease. Of these 70, occult nodes were identified in 15 (21.4%). Risk of contralateral disease was higher when the primary tumor crossed midline (odds ratio, 6.23; 95% CI, 1.71-22.77). Of the 55 patients with no occult disease identified, only 2 (3.6%) received radiotherapy to the contralateral neck, and no regional recurrence of disease was noted.

CONCLUSIONS AND RELEVANCE Given the rate of occult contralateral nodal disease of 21.4%, it appears that contralateral elective neck dissection or radiotherapy should be recommended in patients with HPV-related BOT OPSCC. Patients with a pathologically negative result of contralateral neck dissection may not benefit from radiotherapy to that nodal basin. Future prospective investigations should evaluate functional and oncologic outcomes of contralateral elective neck dissection compared with elective radiotherapy in the contralateral neck for HPV-related BOT OPSCC.

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Ryan S. Jackson, MD, Department of Otolaryngology–Head and Neck Surgery, Washington University School of Medicine in St Louis, 660 S Euclid Ave, Campus Box 8115, St Louis, MO 63110 (jackson.ryan@wustl.edu).

Traditional risk factors for oropharyngeal squamous cell carcinoma (OPSCC) include tobacco and alcohol use. More recently, a rapid increase in OPSCC has been associated with human papillomavirus (HPV).[1,2] Human papillomavirus–associated disease is thought to represent a unique type of OPSCC biologically and clinically, with unique tumor characteristics, a better prognosis, and improved treatment responses compared with traditional tobacco- and alcohol-related OPSCC.[3,4]

Contralateral nodal disease remains an important prognostic characteristic of OPSCC because it is used for staging and treatment determination. Previous investigations have indicated that the HPV association may increase the risk of contralateral nodal disease,[5] although mixed results have been demonstrated.[6,7] Numerous risk factors have been associated with contralateral nodal metastases in OPSCC, including tumor extension across the midline and ipsilateral positive nodes.[8] Specifically, cervical lymph node metastases may be more common in HPV-related base of tongue (BOT) OPSCC compared with other oropharyngeal subsites.[7,9]

A recent National Cancer Data Base study[5] estimated contralateral nodal involvement to be 21.7% for patients with HPV-related BOT OPSCC. Given this high rate, many institutions perform elective radiotherapy to the contralateral nodal basin when no contralateral lymph nodes are clinically present to avoid contralateral neck dissection. This practice may lead to unnecessary bilateral neck radiotherapy in a large percentage of patients. In a recent prospective trial, Contreras et al[10] evaluated eliminating adjuvant radiotherapy among 72 patients with pathologic node-negative findings in the neck, but only 37 patients with oropharyngeal cancer were evaluated, and most cancers were not HPV related.

Therefore, we aimed to determine the rate of contralateral occult nodal disease in patients with HPV-related BOT OPSCC undergoing transoral surgery and bilateral neck dissection. Second, we aimed to evaluate regional recurrence rates in these patients.

Key Points

Question What are the rate of and risk factors for occult contralateral nodal disease in human papillomavirus (HPV)–related squamous cell carcinoma (SCC) of the base of the tongue undergoing surgical treatment?

Findings In this case series of 89 patients with HPV-related SCC of the tongue base treated surgically, 15 of 70 with no clinical evidence of disease (21.4%) were found to have occult contralateral nodal disease. An increased risk of contralateral disease when the primary tumor crossed midline was found.

Meaning Based on these findings, contralateral elective neck dissection or radiotherapy is recommended in this patient population.

Methods

This study was approved by the institutional review board of Washington University School of Medicine in St Louis, St Louis, Missouri, which does not require informed consent for retrospective, deidentified medical record reviews. This study followed the reporting guideline for case series.

All consecutive patients with HPV-related BOT OPSCC who underwent primary treatment via transoral surgery and bilateral neck dissection were identified from January 1, 2002, through December 31, 2018, at the tertiary care center of Washington University School of Medicine in St Louis. The presence of clinical nodal disease was determined by results of physical examination and radiographically with contrast-enhanced imaging and positron emission tomography when available. Patients with bilateral neck dissections were exclusively identified to capture true occult nodal disease. Patients underwent a concurrent or staged contralateral neck dissection at the discretion of the surgeon, and neck levels IIa, IIb, III, and IV were dissected bilaterally in all patients. Patients were then evaluated for clinical nodal status of the contralateral neck, and patients with no clinical evidence of contralateral nodal disease who underwent bilateral neck dissection were included for analysis of occult nodal disease. Patients were excluded if they were being treated for recurrent disease or had multiple simultaneous OPSCC primary tumors.

Clinical and pathologic data were collected retrospectively from the electronic medical record. We determined HPV status using results of p16 immunohistochemistry. Primary tumor laterality was determined first from contrast-enhanced computed tomographic or magnetic resonance imaging if available, then positron emission tomography, physical examination, or operative note. The midline was measured by drawing a line from anterior to posterior between the genioglossus muscles. A measurement from the leading edge of the medial aspect of the tumor to this midline determined the distance from the midline for lateralized tumors. Tumors were classified as lateralized if none of the tumor crossed this midline or as crossing the midline if any of the tumor was across this line.

Statistical Analysis

Analysis was performed from January 1 through June 1, 2019, using SPSS, version 25 (IBM Corp). Logistic regression univariate analysis was performed to calculate odds ratios (ORs) and 95% CIs. Multivariate analysis was then performed using variables that were statistically significant in univariate logistic regression. We used χ^2 test of the Fisher exact test to compare distribution of categorical characteristics between the groups of patients with unilateral and contralateral lymph nodes, and Mann-Whitney test was used for comparison of continuous level characteristics. We used the log-rank test for comparison of survival experiences between the 2 groups. All statistical tests were 2 sided and evaluated to be significant at the α level of .05.

Results

We identified 202 patients with p16-positive BOT OPSCC. Of these, 113 patients (55.9%) had a unilateral neck dissection, and 89 (44.1%) underwent bilateral neck dissection (**Table 1**). Characteristics of the 89 patients who underwent transoral resection and bilateral neck dissection for HPV-related BOT OPSCC

Table 1. Patient Characteristics of All Patients Undergoing Transoral Surgery for p16-Positive BOT OPSCC

Variable	Patient Group, No. (%)[a]		*P* Value
	Unilateral (n = 113)	Bilateral (n = 89)	
Sex			
Male	96 (85.0)	81 (91.0)	.62
Female	12 (10.6)	8 (9.0)	
Smoking			
Never	59 (52.2)	37 (41.6)	.28
Past	39 (34.5)	37 (41.6)	
Current	14 (12.4)	15 (16.9)	
Comorbidity			
None	54 (47.8)	30 (33.7)	.01
Mild	47 (41.6)	38 (42.7)	
Moderate	6 (5.3)	17 (19.1)	
Severe	5 (4.4)	4 (4.5)	
Tumor location			
Lateralized	65 (57.5)	42 (47.2)	.17
Crossed midline	37 (32.7)	41 (46.1)	
Unknown	10 (8.8)	6 (6.7)	
Clinical T stage			
T0	21 (18.6)	18 (20.2)	.72
T1	39 (34.5)	24 (27.0)	
T2	34 (30.1)	27 (30.3)	
T3	13 (11.5)	12 (13.5)	
T4	6 (5.3)	8 (9.0)	
Clinical N stage			
N0	15 (13.3)	5 (5.6)	.02
N1	74 (65.5)	51 (57.3)	
N2	20 (17.7)	31 (34.8)	
N3	4 (3.5)	2 (2.2)	
Clinical contralateral nodal disease			
No	93 (82.3)	70 (78.7)	.60
Yes	20 (17.7)	19 (21.3)	
Pathologic T stage			
T1	50 (44.2)	32 (36.0)	.18
T2	41 (36.3)	34 (38.2)	
T3	15 (13.3)	11 (12.4)	
T4	5 (4.4)	12 (13.5)	
Unknown	2 (1.8)	0	
Pathologic N stage			
N0	9 (8.0)	4 (4.5)	.12
N1	86 (76.1)	63 (70.8)	
N2	14 (12.4)	22 (24.7)	
Unknown	4 (3.5)	0	
Adjuvant therapy			
None	21 (18.6)	17 (19.1)	.08
Radiotherapy	57 (50.4)	36 (40.4)	
Chemoradiotherapy	30 (26.5)	35 (39.3)	
Unknown	4 (3.5)	0	

Abbreviations: BOT, base of tongue; OPSCC, oropharyngeal squamous cell carcinoma.

[a] Percentages have been rounded and may not total 100. Data were missing for 1 patient in the unilateral group for all variables except for clinical and pathologic data and for 1 patient in the bilateral group for adjuvant therapy.

and met final inclusion criteria are shown in **Table 2.** Eighty-one patients were men (91.0%) and 8 were women (9.0%), with a mean (SD) age of 60 (9) years. Of these, 34 patients (38.2%) had pathologic evidence of positive contralateral neck nodes. Factors associated with contralateral nodal disease are described in **Table 3.** Compared with tumors that were lateralized, tumors that crossed the midline had an increased risk of contralateral nodal spread (OR, 7.37; 95% CI, 2.71-19.99), although the difference in tumor distance from midline was not significant. Advanced clinical and pathologic T stages

(T3-T4) compared with T1 to T2 disease were also risk factors for contralateral nodal disease (OR, 6.50; 95% CI, 1.54-27.49). Lymphovascular invasion within the primary tumor increased the risk of contralateral nodal spread (OR, 2.86; 95% CI, 1.18-6.94), whereas perineural invasion did not (OR, 2.16; 95% CI, 0.54-8.67). In addition, patients with a higher number of involved ipsilateral nodes (OR, 1.23; 95% CI, 1.02-1.48) as well as extracapsular spread (OR, 2.82; 95% CI, 1.04-7.67) had a higher risk of contralateral nodal disease. On multivariate analysis, laterization of the tumor (OR, 10.91; 95% CI, 3.47-34.34) was the only variable that remained significant.

Of the 89 patients undergoing transoral BOT resection and bilateral neck dissection, 19 had clinical evidence of contralateral nodal disease, and all had pathologically metastatic lymph nodes. Of the 70 patients who had no clinical evidence of contralateral nodal disease, occult nodal metastases were identified in 15 (21.4%) on final pathologic evaluation. The pathologic lymph node size measured a mean of 0.58 cm (range, 0.10-2.90 cm). The numbers of occult nodes identified per patient were 1 (n = 11), 2 (n = 2), 3 (n = 1), and 6 (n = 1). Extracapsular spread was identified in 7 contralateral necks (46.7%) with occult nodes. Risk factors associated with occult contralateral nodal disease are described in **Table 4**. Within this subset, only those tumors that crossed the midline were associated with increased risk of contralateral occult nodal disease (odds ratio, 6.23; 95% CI, 1.71-22.77).

Overall treatment is shown in Table 2. All 19 patients undergoing a therapeutic contralateral neck dissection for clinical nodal disease had pathologically metastatic lymph nodes, and 17 received adjuvant radiotherapy to that nodal basin. Of the 15 patients with occult nodal disease in the contralateral neck, 9 (60.0%) received adjuvant radiotherapy to that nodal basin, whereas 6 (30.0%) received neck dissection alone. Only 2 (3.6%) of the 55 patients with a pathologic N0 finding in the contralateral neck received radiotherapy to the contralateral neck.

Median follow-up was 30.0 months (interquartile range, 11.0-60.4 months). Overall, recurrence was noted in 10 patients (11.2%), including 3 (3.4%) local, 1 (1.1%) locoregional, and 6 (6.7%) distant. Recurrence events based on clinical and pathologic nodal disease are shown in **Table 5**. No patients with pathologic negative contralateral neck status had a regional recurrence. Six patients (5.3%) with unilateral neck dissection had a contralateral nodal recurrence compared with 1 patient (1.1%) with bilateral neck dissection (P = .11).

Table 2. Characteristics of Patients Who Underwent Bilateral Neck Dissection

Characteristic	Patient Group[a] All (N = 89)	With Contralateral cN0 Neck Finding (n = 70)[b]
Sex		
Male	81 (91.0)	63 (90.0)
Female	8 (9.0)	7 (10.0)
Age, mean (SD), y	60 (9)	60 (9)
Smoking		
Never	37 (41.6)	33 (47.1)
Past	37 (41.6)	28 (40.0)
Current	15 (16.9)	9 (12.9)
Duration, mean (SD), pack-years	15 (22)	11 (20)
ACE-27 findings		
None/mild	68 (76.4)	54 (77.1)
Moderate/severe	21 (23.6)	16 (22.9)
Tumor location		
Lateralized	42 (47.2)	39 (54.3)
Crosses midline	41 (46.1)	26 (37.1)
Distance from midline, mean (SD), cm	0.41 (0.39)	0.45 (0.39)
Pathologic T stage		
T1-T2	66 (74.2)	57 (81.4)
T3-T4	23 (25.8)	13 (18.6)
Pathologic N stage		
N0	4 (4.5)	4 (5.7)
N1	63 (70.8)	55 (78.6)
N2	22 (24.7)	11 (15.7)
Margin		
Negative	87 (97.8)	68 (97.1)
Positive	2 (2.2)	2 (2.9)
LVI		
No	50 (56.2)	44 (62.9)
Yes	38 (42.7)	25 (35.7)
Unknown	1 (1.1)	1 (1.4)
PNI		
No	79 (88.8)	64 (91.4)
Yes	9 (10.1)	5 (7.1)
Unknown	1 (1.1)	1 (1.4)
Adjuvant therapy		
None	17 (19.1)	16 (22.9)
Radiotherapy	36 (40.4)	33 (47.1)
Chemoradiotherapy	35 (39.3)	21 (30.0)
Unknown	1 (1.1)	0
Recurrence		
None	79 (88.8)	65 (92.9)
Local	3 (3.4)	2 (2.9)
Locoregional	1 (1.1)	0
Distant	6 (6.7)	3 (4.3)

Abbreviations: ACE-27, Adult Comorbidity Evaluation–27; ECS, extracapsular lymph node spread; LVI, lymphovascular invasion; PNI, perineural invasion.

[a] Unless otherwise indicated, data are expressed as number (percentage) of patients. Percentages have been rounded and may not total 100.

[b] Refers to patients who on physical examination and imaging findings had no evidence of nodal disease in the contralateral neck.

Discussion

In patients with HPV-related BOT OPSCC undergoing transoral surgery with bilateral neck dissection, the overall rate of contralateral nodal disease was 38.2% and of occult contralateral nodal disease was 21.4%. The rate of contralateral nodal spread is consistent with other investigations of HPV-related OPSCC.[6,11,12] The risk of contralateral nodal spread appears to increase as the primary tumor crosses midline. This finding is consistent with those of other reports and may explain why tonsil cancers have a much lower risk of contralateral nodal spread compared with BOT cancers, given they are more lat-

Table 3. Risk Factors for Contralateral Nodal Disease in All Patients

Risk Factor	Patient Population[a]		
	Contralateral pN0 Neck Finding (n = 55)[b]	Contralateral pN1+ Neck Finding (n = 34)[c]	Univariate Analysis, OR (95% CI)
Tumor location			
Lateralized	34 (61.8)	8 (23.5)	
Crosses midline	15 (27.3)	26 (76.5)	7.37 (2.71-19.99)
Unknown	6 (10.9)	0	
Distance from midline, mean (SD), cm	0.46 (0.40)	0.16 (0.24)	0.05 (0.00-4.69)
Clinical T stage			
T0	14 (25.5)	4 (11.8)	NA
T1-T2	34 (61.8)	17 (50.0)	1.75 (0.50-6.14)
T3-T4	7 (12.7)	13 (38.2)	6.50 (1.54-27.49)
Pathologic T stage			
T1-T2	45 (81.8)	21 (61.8)	2.79 (1.05-7.38)
T3-T4	10 (18.2)	13 (38.2)	
LVI			
No	36 (65.5)	14 (41.2)	
Yes	18 (32.7)	20 (58.8)	2.86 (1.18-6.94)
Unknown	1 (1.8)	0	
PNI			
No	50 (90.9)	29 (85.3)	
Yes	4 (7.3)	5 (14.7)	2.16 (0.54-8.67)
Unknown	1 (1.8)	0	
Clinical N stage in ipsilateral neck			
cN0	4 (7.3)	1 (2.9)	2.59 (0.28-24.18)
cN1+	51 (92.7)	33 (97.1)	
No. of positive nodes, mean (SD)	2 (2)	4 (5)	1.23 (1.02-1.48)
Largest node, mean (SD), cm	3.53 (1.52)	3.99 (1.38)	1.25 (0.92-1.70)
ECS			
Absent	22 (40.0)	7 (20.6)	
Present	29 (52.7)	26 (76.5)	2.82 (1.04-7.67)
Unknown	4 (7.3)	1 (2.9)	

Abbreviations: ECS, extracapsular lymph node spread; LVI, lymphovascular invasion; NA, not available; OR, odds ratio; PNI, perineural invasion.

[a] Unless otherwise indicated, data are expressed as number (percentage) of patients.

[b] Refers to patients who on analysis of pathologic findings had no evidence of disease in contralateral neck nodes.

[c] Refers to patients who on analysis of pathologic findings had at least 1 node with evidence of disease in the contralateral neck.

eralized. Kato et al[5] in a National Cancer Data Base study found patients with HPV-related BOT to have a 21.7% risk of contralateral nodal disease compared with 9.3% for tonsillar tumors. A main limitation of their investigation was the inclusion of only clinically apparent nodal disease, thus potentially underestimating the risk of contralateral nodal spread.

Overall, little work has evaluated occult nodal disease in HPV-related OPSCC. Few studies have evaluated ipsilateral occult nodal disease,[13-15] and evidence regarding the risk of occult contralateral nodal disease is even more limited. Lim et al[15] investigated 52 patients who had clinically negative contralateral neck findings and underwent an elective neck dissection. Only 23 of these involved the BOT, and HPV status was not evaluated in that population. They identified occult contralateral nodal disease in 11 patients (21%) but did not describe the primary tumor location. Lack of HPV status and location of the primary tumor of patients with occult nodal disease makes drawing conclusions on their data difficult.

Herein, we report the largest investigation, to our knowledge, of contralateral occult nodal metastases in patients with HPV-related BOT OPSCC who underwent elective contralateral neck dissection. Occult nodal disease was identified in the contralateral neck in 21.4% of patients. Tumors that crossed midline had a higher risk of occult contralateral nodal disease. We attempted to determine whether distance from midline affected the risk of contralateral occult disease but did not find the risk to be significant, possibly owing to a small number of cases that approached but did not cross the midline. Also, BOT tumors are not going to be far distances from the midline given the anatomical limitations of the lingual tonsils, thus making the distance gradient very narrow and further limiting analysis. The risk of contralateral spread may increase as the tumor approaches midline if examined in larger data sets. The T stage may also play a role because of the higher risk for advanced-stage primary site disease, but this was not statistically significant and may be owing to limited numbers of T3 and T4 tumors.

When elective neck dissection is not performed, patients often receive radiotherapy to bilateral nodal basins for BOT tumors to treat occult disease. Bilateral neck radiotherapy may increase the severity of xerostomia and dysphagia compared with unilateral radiotherapy. Chronic radiotherapy-associated dysphagia has been correlated with a higher radiotherapy dosage to the pharyngeal constrictors and extrinsic tongue musculature.[16] However, 53 of 55 patients with patho-

Table 4. Risk Factors for Contralateral Nodal Disease in Those With Clinically Negative Contralateral Neck Findings

Risk Factor	Patient Population[a]		Univariate Analysis, OR (95% CI)
	Contralateral pN0 Neck Findings (n = 55)[b]	Contralateral pN1+ Neck Findings (n = 15)[c]	
Primary tumor location			
Lateralized	34 (61.8)	4 (26.7)	6.23 (1.71-22.77)
Crosses midline	15 (27.3)	11 (73.3)	
Unknown	6 (10.9)	0	
Distance from midline, mean (SD), cm	0.46 (0.40)	0.31 (0.27)	0.32 (0.004-25.05)
Clinical T stage			
T0	14 (25.5)	2 (13.3)	NA
T1-T2	34 (61.8)	10 (66.7)	2.06 (0.40-10.62)
T3-T4	7 (12.7)	3 (20.0)	3.00 (0.40-22.30)
Pathologic T stage			
T1-T2	45 (81.8)	12 (80.0)	0.87 (0.27-4.74)
T3-T4	10 (18.2)	3 (20.0)	
LVI			
No	36 (65.5)	8 (53.3)	1.75 (0.55-5.59)
Yes	18 (32.7)	7 (46.7)	
Unknown	1 (1.8)	0	
PNI			
No	50 (90.9)	14 (93.3)	0.89 (0.09-8.64)
Yes	4 (7.3)	1 (6.7)	
Unknown	1 (1.8)	0	
N stage in ipsilateral neck			
N0	4 (7.3)	1 (6.7)	1.10 (0.11-10.63)
N1+	51 (92.7)	14 (93.3)	
No. of positive nodes, mean (SD)	2 (2)	3 (4)	1.12 (0.90-1.39)
Largest node, mean (SD), cm	3.53 (1.52)	3.87 (1.29)	1.18 (0.78-1.78)
ECS			
Absent	22 (40.0)	5 (33.3)	1.37 (0.40-4.65)
Present	29 (52.7)	9 (60.0)	
Unknown	4 (7.3)	1 (6.7)	

Abbreviations: BOT, base of tongue; ECS, extracapsular lymph node spread; LVI, lymphovascular invasion; NA, not available; OR, odds ratio; PNI, perineural invasion.

[a] Unless otherwise indicated, data are expressed as number (percentage) of patients.

[b] Refers to patients who on analysis of pathologic findings had no evidence of disease in contralateral neck nodes.

[c] Refers to patients who on analysis of pathologic findings had at least 1 node with evidence of disease in the contralateral neck.

logically negative contralateral neck findings (96.4%) were spared radiotherapy to that nodal basin. None of these patients had regional recurrence events. Therefore, elective neck dissection alone is likely sufficient in managing the pathologically negative contralateral neck in these patients and may improve long-term quality-of-life outcomes by sparing them the morbidity associated with bilateral neck irradiation.

Our institution has investigated eliminating elective contralateral neck radiotherapy to lateralized tonsillar cancer and found reduced toxic effects in these patients compared with those with bilateral neck radiotherapy.[17] More recently, in a phase 2 trial, Contreras et al[10] evaluated eliminating adjuvant therapy to the pathologically N0 neck in 72 patients with no isolated treatment failures and no residual long-term deficits in swallowing or xerostomia quality-of-life outcomes. Although contralateral neck dissection is not without risk, complications related to modern selective neck dissection in the patient with clinically node-negative disease are approximately 2%.[18] Prospective studies are needed to evaluate the oncologic and functional outcomes of elective contralateral neck dissection compared with radiotherapy for HPV-related BOT OPSCC.

Table 5. Recurrence Events Based on Contralateral Neck Clinical and Pathologic Positive Findings

Recurrence	Patient Group, No. (%) of Recurrences			
	cN-Positive/ pN-Positive (n = 19)	cN0/ pN-Positive (n = 15)	cN0/pN0 (n = 55)	Total (n = 89)
Local	1 (5.3)	1 (6.7)	1 (1.8)	3 (3.4)
Local plus regional	1 (5.3)	0	0	1 (1.1)
Distant	3 (15.8)	2 (13.3)	1 (1.8)	6 (6.7)
All	5 (26.3)	3 (20.0)	2 (3.6)	10 (11.2)

Limitations

Several limitations to this study are primarily related to sample size and retrospective design. Risk of selection bias occurs because this cohort represents a select patient population managed at a single tertiary care center. Management

decisions are complex and made on an individual basis in a multidisciplinary fashion. Only patients with available p16 immunohistochemistry were included, limiting the sample size, especially early in the study. Sample size was further limited, especially early on, because practice patterns changed from an institutional preference of elective contralateral neck radiotherapy to neck dissection. In addition, the incidence of contralateral nodal disease may be underestimated, because this study included only patients undergoing upfront surgery to the contralateral neck. The pathologic nodal status of patients treated with contralateral neck elective radiotherapy is unknown to date. Despite these limitations, this study includes a relatively large number of patients with HPV-related BOT OPSCC managed with elective dissection of the contralateral neck who were able to successfully avoid bilateral neck radiotherapy.

Conclusions

In this study, among patients with HPV-related BOT OPSCC, the rate of contralateral nodal disease was 38.2% overall, with a 21.4% rate of occult nodal disease. Tumors that crossed midline had a significantly increased risk of contralateral disease. Given the rate of occult contralateral disease, elective contralateral neck dissection or radiotherapy is recommended. Patients undergoing elective contralateral neck dissection with no occult nodes identified can likely be spared radiotherapy to that neck. Future prospective investigations should evaluate oncologic and functional outcomes of elective neck dissection compared with elective radiotherapy in the contralateral neck for HPV-related BOT OPSCC.

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Author Affiliations: Department of Otolaryngology–Head and Neck Surgery, Washington University School of Medicine in St Louis, St Louis, Missouri (Last, Pipkorn, Chen, Kallogjeri, Rich, Paniello, Zevallos, Jackson); Department of Otolaryngology and Communication Sciences, Medical College of Wisconsin, Milwaukee (Zenga); Department of Pathology and Immunology, Washington University School of Medicine in St Louis, St Louis, Missouri (Chernock); Division of Oncology, Department of Medicine, Washington University School of Medicine in St Louis, St Louis, Missouri (Adkins, Oppelt); Department of Radiation Oncology, Washington University School of Medicine in St Louis, St Louis, Missouri (Gay, Daly, Thorstad).

Author Contributions: Drs Kallogjeri and Jackson had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Pipkorn, Zenga, Paniello, Zevallos, Jackson.
Acquisition, analysis, or interpretation of data: Last, Pipkorn, Chen, Kallogjeri, Rich, Zevallos, Chernock, Adkins, Oppelt, Gay, Daly, Thorstad, Jackson.
Drafting of the manuscript: Last, Pipkorn, Jackson.
Critical revision of the manuscript for important intellectual content: Pipkorn, Chen, Kallogjeri, Zenga, Rich, Paniello, Zevallos, Chernock, Adkins, Oppelt, Gay, Daly, Thorstad, Jackson.
Statistical analysis: Last, Chen, Kallogjeri, Jackson.
Administrative, technical, or material support: Zenga, Paniello, Adkins, Oppelt.
Supervision: Pipkorn, Zevallos, Gay, Jackson.

Conflict of Interest Disclosures: Dr Kallogjeri reported ownership of stock and serving as consultant for PotentiaMetrics, unrelated to the present study. Dr Oppelt reported receiving personal fees from Bristol-Myers Squibb, Merck & Co, and Eisai Co, Ltd, outside the submitted work. Dr Thorstad reported having a spouse who works for Elekta, which makes medical hardware and software. No other disclosures were reported.

REFERENCES

1. Osazuwa-Peters N, Simpson MC, Massa ST, Adjei Boakye E, Antisdel JL, Varvares MA. 40-year incidence trends for oropharyngeal squamous cell carcinoma in the United States. *Oral Oncol*. 2017; 74:90-97. doi:10.1016/j.oraloncology.2017.09.015

2. Mourad M, Jetmore T, Jategaonkar AA, Moubayed S, Moshier E, Urken ML. Epidemiological trends of head and neck cancer in the United States: a SEER population study. *J Oral Maxillofac Surg*. 2017; 75(12):2562-2572. doi:10.1016/j.joms.2017.05.008

3. Klozar J, Koslabova E, Kratochvil V, Salakova M, Tachezy R. Nodal status is not a prognostic factor in patients with HPV-positive oral/oropharyngeal tumors. *J Surg Oncol*. 2013;107(6):625-633. doi:10.1002/jso.23292

4. Wang MB, Liu IY, Gornbein JA, Nguyen CT. HPV-positive oropharyngeal carcinoma: a systematic review of treatment and prognosis. *Otolaryngol Head Neck Surg*. 2015;153(5):758-769. doi:10.1177/0194599815592157

5. Kato MG, Ellis MA, Nguyen SA, Day TA. Predictors of contralateral-bilateral nodal disease in oropharyngeal cancer: a National Cancer Data Base study. *Head Neck*. 2018;40(2):338-348. doi:10.1002/hed.24964

6. Tritter AG, Mehta V, Samuelson M, et al. Incidence of contralateral-bilateral nodes in the human papillomavirus era. *Laryngoscope*. 2017;127 (6):1328-1333. doi:10.1002/lary.26439

7. Amsbaugh MJ, Yusuf M, Cash E, et al. Distribution of cervical lymph node metastases from squamous cell carcinoma of the oropharynx in the era of risk stratification using human papillomavirus and smoking status. *Int J Radiat Oncol Biol Phys*. 2016;96(2): 349-353. doi:10.1016/j.ijrobp.2016.06.2450

8. Capote-Moreno A, Naval L, Muñoz-Guerra MF, Sastre J, Rodríguez-Campo FJ. Prognostic factors influencing contralateral neck lymph node metastases in oral and oropharyngeal carcinoma. *J Oral Maxillofac Surg*. 2010;68(2):268-275. doi:10.1016/j.joms.2009.09.071

9. Sood AJ, McIlwain W, O'Connell B, Nguyen S, Houlton JJ, Day T. The association between T-stage and clinical nodal metastasis in HPV-positive oropharyngeal cancer. *Am J Otolaryngol*. 2014;35 (4):463-468. doi:10.1016/j.amjoto.2013.12.008

10. Contreras JA, Spencer C, DeWees T, et al. Eliminating post-operative radiation to the pathologically node negative neck: long-term results of a prospective phase II study [published online June 27, 2019]. *J Clin Oncol*.

11. Dziegielewski PT, O'Connell DA, Szudek J, et al. Neck metastases in oropharyngeal cancer: necessity and extent of bilateral treatment. *Head Neck*. 2013;35(10):1461-1467.

12. Chung E-J, Oh J-I, Choi K-Y, 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):758-762. doi:10.1016/j.oraloncology.2011.05.013

13. Loganadane G, Kelly JR, Lee NC, et al. Incidence of radiographically occult nodal metastases in HPV+ oropharyngeal carcinoma: implications for reducing elective nodal coverage. *Pract Radiat Oncol*. 2018;8 (6):397-403. doi:10.1016/j.prro.2018.03.009

14. Plonowska KA, Strohl MP, Wang SJ, et al. Human papillomavirus–associated oropharyngeal cancer: patterns of nodal disease. *Otolaryngol Head Neck Surg*. 2019;160(3):502-509. doi:10.1177/0194599818801907

15. Lim YC, Koo BS, Lee JS, Lim JY, Choi EC. Distributions of cervical lymph node metastases in oropharyngeal carcinoma: therapeutic implications for the N0 neck. *Laryngoscope*. 2006;116(7):1148-1152. doi:10.1097/01.mlg.0000217543.40027.1d

16. Head MDA, Neck Cancer Symptom Working G; MD Anderson Head and Neck Cancer Symptom Working Group. Beyond mean pharyngeal constrictor dose for beam path toxicity in non-target swallowing muscles: dose-volume correlates of chronic radiation-associated dysphagia (RAD) after oropharyngeal intensity modulated radiotherapy. *Radiother Oncol*. 2016;118 (2):304-314. doi:10.1016/j.radonc.2016.01.019

17. Chin RI, Rao YJ, Hwang MY, et al. Comparison of unilateral versus bilateral intensity-modulated radiotherapy for surgically treated squamous cell carcinoma of the palatine tonsil. *Cancer*. 2017;123 (23):4594-4607. doi:10.1002/cncr.30931

18. D'Cruz AK, Vaish R, Kapre N, et al; Head and Neck Disease Management Group. Elective versus therapeutic neck dissection in node-negative oral cancer. *N Engl J Med*. 2015;373(6):521-529. doi:10.1056/NEJMoa1506007