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Predictors and Prevalence of Nodal Disease in Salvage Oropharyngectomy

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Abstract

OBJECTIVES—Patients with recurrent oropharyngeal cancer often require extensive salvage surgery. In patients with clinically N0 necks, the indication for concurrent neck dissection remains unclear. The aim of this study is to determine predictors, prevalence and distribution of nodal disease in patients treated with salvage oropharyngectomy.

STUDY DESIGN—Case series with data collection at a single tertiary academic NCI-designated comprehensive cancer center

METHODS—We analyzed patients treated with prior radiation or chemoradiation with persistent, recurrent or second primary squamous cell carcinoma of the oropharynx requiring oropharyngeal resection between 1998 and 2017 (n=95). Clinical and oncologic characteristics and treatment outcomes were collected and statistical analyses were performed.

RESULTS—The overall rate of nodal positivity was 21% (24/95) and the rate of occult nodal disease was 6% (4/65). Ipsilateral and contralateral level II were the most common areas to harbor positive nodes. Bivariate analysis revealed female sex (p=0.01), initial overall stage (p= 0.02) and N status (p=0.03), as well as recurrent overall and T stage (p=0.05) as predictors of nodal disease. On Multivariate analysis, recurrent T-stage continued to be significantly predictive of pathologic nodal disease. Both CT and PET-CT were moderately accurate in predicting nodal disease in the salvage setting (AUC 0.79 and 0.80 respectively).

CONCLUSION—Occult nodal disease is observed in few patients undergoing salvage oropharyngeal resection. This study identifies predictive factors for nodal disease in patient undergoing salvage oropharyngectomy and appropriate diagnostic tests in this setting.

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Introduction

The incidence of oropharyngeal squamous cell carcinoma (OPSCC) has risen in the past three decades, with large demographic shifts to nonsmoking, younger patients with HPV associated tumors.^{1,2} While both surgical and radiation based treatment paradigms are considered within the standard of care per the National Comprehensive Cancer Network (NCCN) guidelines, more than 80% receive radiation as part of their definitive treatment.³ There is an estimated 15–20% failure rate^{4,5} and salvage surgery is often required in this setting.⁶

While the prevalence and distribution of nodal disease is well described in primary oropharyngeal cancer,^{7–13} there are limited data in the salvage setting, and it thus remains unclear when to perform concurrent neck dissection with salvage oropharyngectomy for patients with clinically negative necks.^{14,15} The ability to detect occult nodal disease remains poor and it is critical to identify predictive factors to help to detect microscopic nodal disease in these patients. The primary goal of this study is to describe the prevalence and distribution of nodal disease in patients undergoing salvage surgery on the oropharynx after radiation, and to identify patient and disease factors that are predictive of clinically occult nodal disease.

Methods

Study Population

This is a single institution retrospective review of patients undergoing secondary pharyngeal resections performed between 1998 and 2017 (University of Michigan Institutional Review Board approval HUM00081554). All patients with a history of head and neck radiation were identified from institutional billing and pathology codes. There were a total of 984 patients identified with a history of head and neck radiation of which 129 patients underwent post radiation salvage oropharyngectomy. Thirty-four patients were excluded due to primary tumors located outside of the oropharynx (oral cavity = 26, other = 8) for a total of 95 patients (Figure 1).

Patient demographics, initial and recurrent tumor stage, nodal status, pathologic features, HPV status and treatment course were abstracted by two independent reviewers, and discordant variables were re-reviewed. Staging was collected from clinical documentation and radiographic findings and was performed in accordance with the seventh edition of the American Joint Committee on Cancer's staging system.¹⁶ Clinical nodal status was determined by exam findings on documentation alone (n=7) or with the addition of imaging reports (n=88). Pathologic nodal status was determined from synoptic pathology reports. Initial nodal status was determined from both clinical notes and pathology reports when available. Unilateral neck dissections in patients with midline tumors were considered ipsilateral with regard to neck dissection laterality. Patients who underwent observation without nodal dissection were counted as having positive nodal disease if they developed isolated regional recurrence. Time to recurrence was calculated from the date of completion of radiation/chemoradiation to date of salvage surgery using Kaplan-Meier calculations.

Statistical Analysis

Bivariate analyses were performed and associations between clinical variables were tested with nonparametric tests (i.e. Fisher's exact test, chi-square test with Monte Carlo estimates for error terms). p-values less than 0.05 were considered significant. A multivariate analysis was then performed using a backward selected binary logistic regression model. Variables with a p-value of less than 0.2 were included in the model. Sensitivity, specificity, positive predictive value and negative predictive value were calculated based off of pathologic nodal status (gold standard) and receiver operator characteristic curves were generated. Statistics were performed using SPSS version 25 software (IBM; Armonk, NY).

Results

Prevalence and distribution of nodal disease

The overall rate of nodal positivity in this cohort was 21% (n=24/95). In clinically node negative (cN0) patients, the rate of pathologically positive nodal disease was found to be 6% (n=4/65), whereas in clinically node positive (cN+) patients, the rate of pathologically positive nodal disease was 67% (n=20/30) (Table 1). Ipsilateral level two followed by contralateral level two nodal basins were the most common location of nodal disease. Nine patients developed bilateral (n=5) or contralateral (n=4) disease. Seven of the nine patients were cN+ and two were cN0. Evaluation of specific subsites revealed six of the nine patients had tumors located in the base of tongue. An additional two patients had tumors of the tonsil with one of these extending into the base of tongue. There was also one patient with posterior pharyngeal wall recurrence who developed bilateral nodal disease. With regard to T stage, six of the nine patients had T4 disease with one T1, one T2 and one T3 tumor in the remaining three patients.

Predictors of nodal disease

Predictors of nodal disease on bivariate analysis are shown in Table 2. In the overall cohort, clinical predictors of pathologically positive nodal disease included female sex (44% vs. 19%, p=0.01), advanced overall stage of primary disease (27% vs. 0%, p=0.02), cN+ for primary disease (32% vs. 11%, p=0.03) and advanced recurrent T stage (33% vs. 15%, p=0.05). Positive nodal disease on CT and PET-CT imaging was also found to be a significant predictor of positive pathologic disease (CT – 68% vs. 12%, p<0.001, and PET-CT – 67% vs. 7%, p<0.001). These same variables were then evaluated stratifying by clinical nodal status (Supplemental Tables 1a,b). In cN0 patients, female sex (p=0.005) and recurrent T-stage (p=0.05) were found to be positive predictors of pathologically positive nodal disease. In the cN+ cohort, HPV status was significantly associated with pathologically positive nodal disease (p=0.02). Primary nodal status was also significant in the cN+ cohort. The remaining clinical factors did not predict pathologically positive nodal disease in either cohort.

When these variables are entered into the backward selected multivariate model, age at the time of recurrence, initial stage, time to recurrence, alcohol use, and T classification of the recurrent tumor were all important in the model (Table 3). T classification at the time of recurrence predicted nodal metastasis as patients with advanced T classification tumors were

more likely to have nodal metastasis compared to early T stage tumors (HR 7.0, 95% CI 1.3–38.3, $p=0.02$). Time to recurrence was also predictive of nodal metastasis as patients who recurred 2 years or more after treatment were less likely to have nodal metastasis when compared with patients who recurred less than 2 years after treatment (HR 0.1; 95% CI 0.02–0.7, $p=0.02$). The stage of the initial tumor did not predict nodal metastasis in the multivariate model ($p=0.99$). Older patients were less likely to have nodal metastasis compared to younger patients (HR 0.9; 95% CI 0.8–1.0, $p=0.08$), though this was not statistically significant. Alcohol use was protective as alcohol users were less likely to have nodal metastasis (HR 0.2; 95% CI 0.02–1.3, $p=0.09$), but again this was not statistically significant.

CT and PET performance in identifying nodal disease in the salvage setting

Given the strong predictive value of CT and PET-CT imaging on bivariate analysis, we further evaluated the test characteristics of these imaging modalities. Sensitivity, specificity, positive predictive value and negative predictive value were calculated for both CT and PET-CT and is shown in Table 4. PET-CT showed higher sensitivity compared to CT (86% vs. 68%), however CT was found to be more specific than PET-CT (88% vs. 81%). Positive (PPV) and negative predictive values (NPV) were similar for both tests with a PPV of 68% for CT and 67% for PET-CT and a NPV of 88% for CT and 93% for PET-CT. We next constructed receiver operator characteristic (ROC) curves for CT and PET-CT as shown in Figure 2. Both imaging modalities performed well with an area under the curve (AUC) of 0.78 for CT and an AUC of 0.80 for PET-CT.

Discussion

The rate of nodal positivity in our cohort was 21% which is a slightly lower compared to the 30–33% currently cited for primary oropharyngeal disease.^{7,11,12} The majority of patients in this cohort ($n=65/95$) presented with cN0 disease. It is in this population the decision for an elective neck dissection remains unclear. In our cohort, occult nodal disease was present in 6% of cN0 patients. This rate is notably lower than the rate of occult nodal disease in the primary setting which has been shown to be between 18–33%.^{7,9} As most literature suggests clinical benefit for elective neck dissection when the risk of occult nodal disease exceeds 15–20%,^{17–20} our data suggest these patients may not require neck dissections. This is similar to previous findings for second primaries in the head and neck in patients with history of prior head and neck radiation¹⁴ and dovetails with our prior work with salvage laryngectomy.¹⁵ However, as opposed to total laryngectomy, not all patients requiring salvage oropharyngectomy will require neck exploration. In the setting of large reconstruction with free tissue transfer though, neck exploration may be required for access to vessels, and in these patients, elective dissection may not add significant morbidity.

In the cN+ cohort, 67% of patients had evidence of pathologically positive nodal disease, and while this is lower than previously cited rates,^{7,9,11} these data continue to support therapeutic neck dissections for cN+ patients in the salvage setting.

The most common nodal basins involved were ipsilateral and contralateral level two. Of the twenty-four patients with pathologically confirmed nodal disease, ten patients had ipsilateral

level two disease and five had contralateral level two disease. Level three was the next most commonly involved level with four and three patients having ipsilateral contralateral level three disease respectively. While most literature cites ipsilateral level two and three as the most common nodal drainage,^{7,9,11,21} our results revealed higher rates of contralateral level two disease compared to ipsilateral level three or four. These results are likely due to the fact that many patients underwent initial neck dissection and or radiation of the ipsilateral neck decreasing ipsilateral nodal burden in this cohort. Two patients with cN+ preoperative status had evidence of pathologic nodal disease in level one. In addition, there were three patients with level five disease, two on the ipsilateral side and one on contralateral level 5. While two of the patients had additional nodal burden in level two, one patient had isolated ipsilateral level five disease. However, all three patients were cN+. Overall the distribution of nodal disease in this salvage cohort supports a selective II-IV neck dissection unless there is clinical evidence of atypical distribution of disease.

With regard to contralateral and bilateral disease, the majority of patients in this cohort (6/9) had advanced tumors located in the base of tongue, mirroring prior studies.^{22,23} These results support consideration of bilateral selective neck dissection for such patients.

Overall, female sex initial stage, initial nodal disease and recurrent T stage were found to be significantly predictive of pathologic nodal disease on bivariate analysis. On multivariate analysis, recurrent T-stage and recurrence time less than 2 years from initial disease were the only two variables found to be significantly correlated with positive pathologic nodal disease suggesting possible use for these as predictive markers in the future. For patients with no evidence of pre-operative nodal disease, female sex and advanced T stage were found to be predictors of occult nodal disease. As these patients pose a more difficult choice of whether or not to pursue neck dissection, these factors may be helpful in aiding therapeutic planning.

Post-radiation imaging creates additional challenges due to tissue thickening and edema. In combination with previous surgery, there can often be distortion of normal tissue planes making it difficult to discern post-therapy changes from recurrent disease.^{24,25} PET-CT has been shown to have excellent accuracy in diagnosing recurrent tumors with sensitivities of 86–88%, specificity of 93–100%, PPV of 92% and NPV of 87%.^{24,25} Determination of nodal staging with CT-PET shows similar accuracy. In the primary setting PET-CT has shown to have good accuracy with sensitivity and specificity ranging from 79–96%, and specificity ranging from 80–99%.^{26–29} In the cN0 population, sensitivity and specificity are lower ranging from 57–79% and 82–85% respectively.^{30,31} These studies include previously untreated patients or a mixed population of primary and recurrent tumors. In contrast, this study revealed modest accuracy with PET-CT in detecting nodal disease in the salvage setting, similar to CT alone. Further, a study by Rosko et. al examined PET-CT prediction of pN positivity in cN0 recurrent larynx with a sensitivity of 17% and specificity of 97%.³² Overall these studies together with our results suggest that while in cohorts with both cN+ and cN0, PET-CT shows good accuracy, in cN0 populations, particularly in the salvage setting, CT-PET cannot solely determine the need for elective neck dissection.

Limitations

This study is limited by its retrospective nature. Additionally, due to the small number of cN0, pN+ patients, the sub-analysis of this cohort was limited. Not all radiation fields were able to be obtained and were therefore not included in analysis and may play a significant role in salvage nodal status. Further studies investigating the relationship between radiation fields and nodal burden may be warranted.

Conclusion

In summary, we identified a nodal positivity rate of 21% in conjunction with salvage oropharyngectomy for recurrent, persistent or second primaries of the oropharynx. However, occult nodal rate in the cN0 population was only 6%, calling into question the benefit of performing elective neck dissection. The distribution of nodal disease is consistent with primary oropharyngeal disease with the caveat that this cohort showed higher rates of contralateral level two disease. In patients undergoing salvage oropharyngectomy, predictors of nodal disease may help to guide treatment decisions. In addition, PET-CT may aid in predicting nodal burden. Further studies investigating the cN0 population in the salvage settings may be warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Synopsis

This study evaluates nodal prevalence and distribution in patients undergoing salvage oropharyngectomy and aims to identify factors predictive of positive nodal disease to help identify patients who may benefit from elective neck dissection in the salvage setting.

Figure 1:
Identification and Selection of Salvage Oropharyngectomy Cohort

Figure 2:
ROC Analysis of CT vs. CT-PET - Receiver Operator Characteristic (ROC) curve for CT and PET-CT. The area under the curve (AUC) is 0.78 for CT and 0.08 for PET-CT.

Table 1:

Prevalence and Distribution of Nodal Disease Stratified by Subsite

Subsite		Level 1 (%)	Level 2 (%)	Level 3 (%)	Level 4 (%)	Level 5 (%)
Tonsil	Ipsilateral	1/15 (7)	6/20 (30)	2/20 (10)	0/18 (0)	0/7 (0)
	Contralateral	0/3 (0)	2/3 (67)	0/3 (0)	0/2 (0)	1/2 (50)
BOT	Ipsilateral	1/28 (4)	3/38 (8)	2/28 (5)	2/34 (6)	2/8 (25)
	Contralateral	0/17 (0)	3/22 (14)	3/22 (14)	1/20 (5)	0/1 (0)
Other Subsite (pharyngeal wall, soft palate)	Ipsilateral	0/8 (0)	1/10 (10)	0/9 (0)	1/9 (11)	0/2 (0)
	Contralateral	0/3 (0)	0/6 (0)	0/5 (0)	1/5 (20)	0/0 (0)
All subsites	Ipsilateral	2/51 (4)	10/68 (15)	4/67 (6)	3/61 (5)	2/17 (12)
	Contralateral	0/23 (0)	5/31 (16)	3/30 (10)	2/27 (7)	1/3 (33)

BOT -Base of tongue

Table 2:

Demographics and Predictors of pN+ Nodal Disease

		pN status			p value
		Count (n=95)	pN0 (n=71) Count (%)	pN+ (n=24) Count (%)	
Age	Mean (yr)	62.0	63.1	58.9	0.06
Sex	Male	70	57 (81)	13 (19)	0.01*
	Female	25	14 (56)	11 (44)	
Primary Tumor Site	Oral Cavity	4	3 (75)	1 (15)	0.8
	Oropharynx	62	45 (73)	17 (27)	
	Other	29	23 (79)	6 (21)	
Primary Overall Stage	Early (I/II)	17	17 (100)	0 (0)	0.02*
	Advanced (III/IV)	66	48 (73)	18 (27)	
Primary T Stage	Early (I/II)	40	32 (80)	8 (20)	0.8
	Advanced (III/IV)	40	31 (78)	9 (23)	
cN Primary	cN0	28	25 (89)	3 (11)	0.03*
	cN+	53	36 (68)	17 (32)	
Primary Neck Dissection	No	64	47 (73)	17 (27)	0.7
	Yes	31	24 (77)	7 (23)	
Initial Radiation	Definitive	76	57 (75)	19 (25)	0.9
	Adjunctive	19	14 (74)	5 (26)	
Initial Chemotherapy	No	34	27 (79)	7 (21)	0.4
	Yes	61	44 (72)	17 (28)	
Recurrent T -Stage	Early (I/II)	40	34 (85)	6 (15)	0.05*
	Advanced (III/IV)	55	37 (67)	18 (33)	
CT (nodal disease)	Negative	52	46 (88)	6 (12)	<0.001*
	Positive	19	6 (32)	13 (68)	
CT-PET (nodal disease)	Negative	28	26 (93)	2 (7)	<0.001*
	Positive	18	6 (33)	12 (67)	
Tobacco	No	18	13 (72)	5 (28)	0.8
	Yes	76	57 (75)	19 (25)	
EtOH	No	60	44 (73)	16 (27)	0.3
	Yes	24	20 (83)	4 (17)	
HPV	Negative	20	16 (80)	4 (20)	0.5
	Positive	20	13 (65)	7 (35)	
	Unavailable	55	42 (76)	13 (24)	

		<u>pN status</u>					
		Count (n=95)	pN0 (n=71)	Count (%)	pN+ (n=24)	Count (%)	p value
Time to recurrence	< 2 years	48	32	(67)	16	(33)	0.07
	> 2 years	47	39	(83)	8	(17)	

HPV – Human Papilloma Virus

Table 3:

Multivariate Analysis

Variable	Hazard Ratio (95% CI)	p-value
Older patients versus Younger [*] patients (per year)	0.9 (0.8–1.0)	0.08
Recurrent T3/T4 versus T1/T2 [*]	7.0 (1.3–38.3)	0.02
Alcohol users versus Non-users [*]	0.2 (0.02–1.3)	0.09
Recurrence >2 years versus <2years [*]	0.1 (0.02–0.7)	0.02

^{*} Reference variable

Table 4

Utility of CT and PET in determining pN status

	CT (%), 95% CI	PET (%), 95% CI
Sensitivity	68 (43–87)	86 (57–98)
Specificity	88 (76–96)	81 (64–93)
PPV	68 (49–83)	67 (49–81)
NPV	88 (80–94)	93 (78–98)