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Occult Nodal Disease Prevalence and Distribution in Recurrent Laryngeal Cancer Requiring Salvage Laryngectomy

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Abstract

Objectives—The indications for neck dissection concurrent with salvage laryngectomy in the clinically N0 setting remain unclear. Our goals were to determine the prevalence of occult nodal disease, analyze nodal disease distribution patterns, and identify predictors of occult nodal disease in a salvage laryngectomy cohort.

Study Design—Case series with planned data collection.

Setting—Tertiary academic center.

Subjects—Patients with persistent or recurrent laryngeal squamous cell carcinoma after radiation/chemoradiation failure undergoing salvage laryngectomy with neck dissection.

Methods—We analyzed a single-institution retrospective case series of patients between 1997–2014 and identified those who had clinically N0 necks (n = 203). Clinical and pathologic data, including nodal prevalence and distribution were collected, and statistical analyses were performed.

Results—Overall, cN0 necks had histologically positive occult nodes in 17% (n=35) of cases. Univariate predictors of occult nodal positivity included recurrent T4 stage (34% T4 vs. 12% non-T4; p=0.0003), and supraglottic subsite (28% supraglottic vs. 10% non-supraglottic; p=0.0006). Histologically positive nodes associated with supraglottic primaries were most frequently positive in ipsilateral level II and III (17% and 16%). Positive nodes for glottic SCC were most frequently positive in the ipsilateral and contralateral paratracheal nodes (11% and 9%).

Conclusion—Histologically positive occult nodes are identified in 17% of cN0 patients undergoing salvage laryngectomy with neck dissection. Occult nodal disease varies in frequency and distribution based upon tumor subsite. Predictors of high (>20%) occult nodal positivity include T4 tumors and supraglottic subsite. In glottic SCCs, the most frequent sites of occult nodal disease are the paratracheal nodal basins.

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Conflicts of Interest: None

Keywords

Salvage; laryngectomy; neck dissection; node; prevalence; occult disease

Introduction

Informed by the Veterans Affairs (VA) Larynx Trial and subsequent multi-institutional studies^{1–4}, nonsurgical regimens designed to achieve organ preservation for advanced stage laryngeal squamous cell carcinoma (LSCC) have become an accepted standard of care as an alternative to primary laryngectomy⁵. For patients with recurrent LSCC after initial radiation therapy (RT) or chemoradiation (CRT), salvage laryngectomy is frequently necessary to achieve cure⁶.

The decision to perform concurrent neck dissection with salvage laryngectomy remains a subject of debate^{7–18}. The overall prevalence of nodal metastasis, while well described by Shah and colleagues in previously untreated patients¹⁹, is not well described in the salvage setting. For patients with clinically evident persistent or recurrent regional metastases, the need to salvage neck dissection is accepted and felt to justify the morbidity and associated risks. However, there are a proportion of patients who have occult positive nodal disease (cN0, pN+). In many patients, this is the case despite receiving radiation treatment to the neck and having normal preoperative imaging. Without neck dissection, these patients would have significant risk of treatment failure. Finally, our ability to risk stratify cN0 patients with recurrent primary disease based upon their probability of occult nodal positivity remains poor. Identification of discrete risk groups could help determine which patients may most benefit from elective neck dissection in the salvage setting.

At the University of Michigan, the majority of patients with LSCC who present with recurrent primary site disease and are cN0 routinely undergo concurrent selective neck dissection with salvage laryngectomy. Our primary goal was to examine the prevalence and distribution of nodal disease in salvage laryngectomy patients within our cohort. Additionally, we assessed occult nodal disease prevalence and clinical factors that may indicate increased risk of occult neck disease in our cohort. Finally, we sought to identify predictors of occult nodal disease within this cohort.

Methods

Study Population

We performed an IRB-approved single-institution retrospective case series informed by a prospectively maintained database of patients with head and neck cancer (University of Michigan IRB HUM00081554). Inclusion criteria specified patients who underwent salvage laryngectomy with neck dissection between 1997–2014 for persistent or recurrent LSCC after RT/CRT failure (Figure 1). Surgical failures were excluded for this study, because they would typically have other options for treatment including further partial laryngeal surgery or radiation. Demographics, initial and recurrent clinical T classification and N classification, primary treatment modality, levels of neck dissections, and pathologic

recurrent T and N classification were tabulated. Recurrent clinical stage was determined by clinical exam notes, which included preoperative imaging (CT, PET, and/or MRI) in all of patients (78% CT, 12% PET, 9% CT + PET, 1% MRI). Patients were staged in accordance to the 7th edition American Joint Committee on Cancer (AJCC) Staging System²⁰. Overall, we identified 233 patients, with 30 patients presenting with clinical nodal disease and 203 patients who were cN0. Patient demographic information is shown in Table I.

Statistical Analysis

Bivariate 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). SPSS version 22 software (IBM; Armonk, NY) was used to perform statistical analyses. All statistical tests of significance were two-sided with α of 0.05.

Results

Overall Prevalence of Nodal Disease

The overall prevalence of pathologically positive (pN+) disease in our cohort (cN+ and cN0) was 24% (n=57). Figure 2 shows the distribution and prevalence of nodal disease in recurrent supraglottic (**2A**) and glottic (**2B**) LSCC. There were 29 patients with ipsilateral disease, 8 patients with contralateral disease, and 20 patients with bilateral disease. Overall the recurrent pathologic N classification in this cohort was 176 N0, 20 N1, 0 N2a, 8 N2b, 28 N2c, and 1 N3.

Patients who were presented with recurrent cN+ disease were significantly more likely to have cN+ at diagnosis prior to initial treatment (Table I; $p=0.0000001$) and to be current smokers ($p = 0.01$).

Of those with cN+ disease at the time of their recurrence, 73% had pN+ disease confirmed (22/30). Initial overall stage and initial treatment with CRT had values of $p = 0.06$ and $p = 0.07$, respectively in regards to recurrent cN+ disease. There were no other identifiable patient factors that correlated with recurrent cN+ disease (Table I; age, gender, ethnicity, T and overall stage, tumor subsite, and time from initial treatment to disease recurrence, initial treatment).

Next the rate of occult nodal positivity in recurrent cN0 LSCC patients was examined. (n=203). Overall, 35 patients who were initially cN0 had pathologic occult nodal disease (17%; Table II).

Distribution of Nodal Disease

Overall, supraglottic tumors had the highest prevalence of nodal positivity in ipsilateral levels II, III and paratracheal nodal basins (17%, 16%, and 15%, respectively; Figure 2A). Contralateral level II nodal disease was seen in 15% of patients with supraglottic LSCC. The remaining neck levels were demonstrated to have less than 10% nodal positivity rates.

Glottic tumors had a different pattern of nodal disease (Figure 2B). Nodal disease was most frequently identified in the ipsilateral and contralateral paratracheal nodes (11% and 9%,

respectively). Level II and III disease was less prevalent in glottic tumors than in supraglottic tumors (5% or less nodal positivity in ipsilateral and contralateral levels II and III).

Predictors of Occult Nodal Disease

We next evaluated for potential predictors of occult nodal positivity in patients with recurrent LSCC undergoing salvage surgery. We assessed initial tumor T, N and overall stage, initial treatment type, time to recurrence, and recurrent tumor subsite and T stage for correlation with occult nodal positivity (Table III). Clinical predictors of occult nodal disease on univariate analysis were recurrent supraglottic subsite (28% vs. 10%; $p=0.0006$) and recurrent T4 stage (34% vs. 12%; $p=0.0003$).

On bivariate analysis stratifying tumor subsite and T stage, recurrent supraglottic T4 status was a significant predictor of occult nodal disease (50% vs. 13%; $p=0.000006$). Other clinical factors (including initial stage, initial nodal status, initial treatment, and time to recurrence) did not predict occult nodal positivity.

Comparison of Occult Nodal Disease Rates to Literature

We next compared our findings with other studies documenting occult nodal rates in salvage laryngectomy patients^{7–18}. Overall, 11 studies were identified, with a total of 537 patients. Occult nodal positivity rates ranged from 0–30% across these studies, with a combined average of 17% (Table IV).

Discussion

In our cohort, we identified an overall nodal burden rate of 24% (57/233 patients), suggesting that nodal disease is relatively common in the salvage larynx cohort. The clinically N+ cohort certainly warrants neck dissection in conjunction with salvage laryngectomy as the majority will have pathologic nodal disease confirmed. However, these patients make up only a small proportion of patients needing salvage laryngectomy (13% in our series; 30/233).

Whether to perform selective neck dissections in clinically N0 salvage laryngectomy cases remains contested. In our cohort, we found a prevalence of 17% occult nodal disease in clinically N0 necks, which is consistent with the average of rates found by other groups^{7–18}. Notably in most studies, preoperative imaging was not standardized, which could potentially confound occult nodal rates.

Historically, it has been suggested to offer neck dissection if risk of nodal disease is greater than 15–20%^{21–23}. In our cohort, overall occult nodal positivity rate was 17%, suggesting potential benefit for elective neck dissections in some salvage laryngectomy patients. For many of these patients, subsequent recurrences after salvage laryngectomy may not be resectable. The risk of nodal metastasis was significantly higher in clinically T4 patients and patients with recurrent disease of the supraglottis. Given their high rates of occult nodal disease, (34% and 28%, respectively), elective neck dissection is a strong consideration in these cases. Notably, however, risk of occult nodal disease should still be considered in

lower T stages, as rates are still 12% in T1–3 tumors. Interestingly, in our cohort, initial disease factors (including initial T, N, overall stage, subsite, and therapy rendered) did not predict occult nodal disease.

The main rationale to avoid neck dissection concurrent with salvage laryngectomy in the cN0 setting is the increased morbidity and potential complications, including fistula/wound healing^{24,25} and hypocalcemia²⁶. Pretreatment radiation fields significantly increase the risk of complications among this cohort. The addition of regional and free tissue augmentation has mitigated some of these risks in salvage laryngectomy, but they are not without consequence. As with all decisions, the proportionality of risks and benefits need to be weighed appropriately in light of the best clinical data along with surgeon and patient preference.

It is challenging to determine which levels to include in elective neck dissection among patients with recurrent LSCC. Currently, elective neck dissection for LSCC generally includes levels II–IV^{19,27}. In our cohort, recurrent supraglottic tumors had a sufficiently high percentage of ipsilateral and contralateral level II and III (17% and 16%, and 15% and 10%, respectively), and ipsilateral paratracheal (15%) nodal disease to warrant inclusion of these levels in any patients undergoing elective neck dissection. Inclusion of bilateral level II and III nodes for supraglottic tumors addresses the majority of nodal disease. For glottic tumors, we most frequently identified ipsilateral and contralateral paratracheal nodal disease (11% and 9%, respectively). Interestingly, most other salvage laryngectomy studies did not specifically investigate occult nodal disease in the paratracheal basins. In these patients, inclusion of the bilateral paratracheal nodes in elective neck dissection should be considered.

Our study has some limitations. Namely, we did not have access to complete outside records of radiation fields or initial imaging in many cases. Initial radiation fields to the lateral neck could potentially have an effect on subsequent occult nodal disease. Further follow-up analysis and prospective studies of the association of elective neck radiation fields and doses may inform radiation paradigms for primary treatment of LSCC. Although all patients in our cohort had preoperative imaging with CT, PET, or MRI, this was not standardized. Additionally, radiographic analysis of paratracheal nodes can be challenging. Future studies assessing the sensitivity, specificity and predictive values comparing these preoperative imaging modalities may provide valuable information as to ideal preoperative imaging in this cohort.

Conclusion

The incidence of and risk factors for occult nodal disease among patients undergoing salvage laryngectomy are critical considerations when determining indications for concurrent neck dissection in this setting. Overall, clinically negative necks were pathologically positive in 17% of patients, which should help surgeons in operative planning and is consistent with prior published findings. Patients with advanced recurrent T classification and with tumors involving the supraglottic larynx appear to have higher rates of occult nodal disease. Based on our findings, we would recommend selective neck dissection for T4 tumors and supraglottic tumors. The distribution of nodal disease by neck

level varies based upon laryngeal subsite, and should be taken into account when planning elective neck dissection in the salvage setting. Inclusion of bilateral levels II and III in supraglottic tumors and bilateral paratracheal nodes in glottic tumors may be warranted in these cases.

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Figure 1. Identification and Selection of Salvage Laryngectomy Cohort
Flow diagram for identification and stratification of patients.

Figure 2. Positive Node Prevalence and Distribution

Supraglottic (**2A**) and glottic (**2B**) nodal positivity rates. In the diagrams, tumor is considered on the right to account for ipsilateral and contralateral disease patterns.

Table I
Salvage Laryngectomy Patient Characteristics

Demographic and initial tumor and treatment variables for recurrent cN0 and cN+ patients. Initial N+ status correlated with recurrent cN+ status.

	cN0	cN+	p-value
Age at Salvage	61.6 +/- 9.7	58.6 +/- 10.1	0.12
Gender			
Male (n = 198)	173 (87%)	25 (13%)	0.79
Female (n = 35)	30 (86%)	5 (14%)	
Ethnicity			
Caucasian (n = 210)	181 (86%)	29 (14%)	0.38
Black (n = 13)	12 (92%)	1 (8%)	
Other/Unknown (n = 10)	10 (100%)	0 (0%)	
Initial Overall Stage			
I (n = 58)	49 (84%)	9 (16%)	0.06
II (n = 66)	62 (94%)	4 (6%)	
III (n = 55)	48 (87%)	7 (13%)	
IV (n = 35)	26 (74%)	9 (26%)	
Unknown (n = 19)	18 (95%)	1 (5%)	
Initial T Stage			
T1 (n = 59)	49 (83%)	10 (17%)	0.21
T2 (n = 73)	68 (93%)	5 (7%)	
T3 (n = 55)	48 (87%)	7 (13%)	
T4 (n = 26)	20 (77%)	6 (23%)	
Tx (n = 20)	18 (90%)	2 (10%)	
Initial Nodal Status			
N0 (n = 178)	164 (92%)	14 (8%)	0.0000001
N+ (n = 37)	22 (59%)	15 (41%)	
Nx (n = 18)	17 (94%)	1 (6%)	
Initial Subsite			
Supraglottis (n = 94)	78 (83%)	16 (17%)	0.44
Glottis (n = 136)	122 (90%)	14 (10%)	
Subglottis (n = 1)	1 (100%)	0 (0%)	
Unknown (n = 2)	2 (100%)	0 (0%)	
Initial Therapy			
RT (n = 137)	124 (91%)	13 (9%)	0.07
CRT (n = 96)	79 (82%)	17 (18%)	
Time to Recurrence (mo)	24.0 +/- 34.6	16.8 +/- 28.3	0.28

	cN0	cN+	p-value
Smoking Status at Salvage			
Current (n = 92)	73 (79%)	19 (21%)	0.01
Former (135)	125 (93%)	10 (7%)	
Never (n = 6)	5 (83%)	1 (17%)	

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Table II
Nodal Disease Positivity in Salvage Laryngectomy Patients

Nodal positivity in the salvage laryngectomy cohort for recurrent cN0 (17%), cN+ (73%), and all patients (24%).

	pN0	pN+
Salvage cN0 (n = 203)	168 (83%)	35 (17%)
Salvage cN+ (n = 30)	8 (27%)	22 (73%)
Salvage total (n = 233)	176 (76%)	57 (24%)

Table III
Clinical Predictors of Occult Nodal Positivity (univariate)

Univariate predictors of occult nodal disease include advanced T stage and supraglottic subsite.

	pN0	pN+	p-value
Initial Overall Stage			
I (n = 49)	44 (90%)	5 (10%)	0.39
II (n = 62)	50 (81%)	12 (19%)	
III (n = 48)	41 (85%)	7 (15%)	
IV (n = 26)	19 (73%)	7 (27%)	
Unknown (n = 18)	14 (83%)	4 (17%)	
Initial T Stage			
T1 (n = 49)	44 (90%)	5 (10%)	0.46
T2 (n = 68)	54 (79%)	14 (21%)	
T3 (n = 48)	41 (85%)	7 (15%)	
T4 (n = 20)	15 (75%)	5 (25%)	
Tx (n = 18)	14 (83%)	4 (17%)	
Initial Nodal Status			
N0 (n = 164)	135 (82%)	29 (18%)	0.89
N+ (n = 22)	19 (86%)	3 (14%)	
Nx (n = 17)	14 (82%)	3 (18%)	
Initial Subsite			
Supraglottis (n = 78)	60 (79%)	18 (21%)	0.33
Glottis (n = 122)	105 (86%)	17 (14%)	
Subglottis (n = 1)	1 (100%)	0 (0%)	
Unknown (n = 2)	2 (100%)	0 (0%)	
Initial Therapy			
RT (n = 124)	103 (83%)	21 (17%)	0.89
CRT (n = 79)	65 (82%)	14 (18%)	
Time to Recurrence (mo)	25.2 +/- 36.5	18.2 +/- 23.5	0.28
Recurrent T Stage			
T1 (n = 11)	10 (91%)	1 (9%)	0.0003
T2 (n = 91)	82 (90%)	9 (10%)	
T3 (n = 51)	43 (84%)	8 (16%)	
T4 (n = 50)	33 (66%)	17 (34%)	
Recurrent Subsite			
Supraglottis (n = 81)	58 (72%)	23 (28%)	0.0006
Glottis (n = 120)	108 (90%)	12 (10%)	
Subglottis (n = 2)	2 (100%)	0 (0%)	

	pN0	pN+	p-value
Recurrent Subsite and T Stage			
Supraglottis T1 (n = 4)	3 (75%)	1 (25%)	0.000006
Supraglottis T2 (n = 29)	23 (79%)	6 (21%)	
Supraglottis T3 (n = 24)	20 (83%)	4 (17%)	
Supraglottis T4 (n = 24)	12 (50%)	12 (50%)	
Glottis T1 (n = 6)	6 (100%)	0 (0%)	
Glottis T2 (n = 61)	58 (95%)	3 (5%)	
Glottis T3 (n = 27)	23 (85%)	4 (15%)	
Glottis T4 (n = 26)	21 (81%)	5 (19%)	
Subglottis (n = 2)	2 (100%)	0 (0%)	

Table IV
Other Studies on Occult Nodal Positivity in Salvage Laryngectomy Patients

Overall occult nodal positivity rate (cN0, pN+) is 17% on average across other studies.

	pN0	pN+	Preoperative imaging
Deganello et al, 2014 (n = 7)	7 (100%)	0 (0%)	CT
Koss et al, 2014 (n = 53)	38 (72%)	15 (28%)	Variable
Pezier et al, 2014 (n = 28)	26 (93%)	2 (7%)	CT
Basheeth et al, 2013 (n = 38)	35 (92%)	3 (8%)	CT
Amit et al, 2013 (n = 42)	34 (81%)	8 (19%)	Variable
Bohannon et al, 2010 (n = 38)	35 (92%)	3 (8%)	Variable
Farrag et al, 2006 (n = 29)	28 (97%)	1 (3%)	CT
Yao et al, 2005 (n = 31)	28 (90%)	3 (10%)	Variable
Wax et al, 1999 (n = 34)	28 (82%)	6 (18%)	Variable
Petrovic et al, 1997 (n = 161)	132 (82%)	29 (18%)	Variable
Kligeman et al, 1995 (n = 76)	53 (70%)	23 (30%)	Variable
Total (n = 537)	444 (83%)	93 (17%)	--