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A Multi-institutional Investigation of the Prognostic Value of Lymph Nodal Yield in Advanced Stage Oral Cavity Squamous Cell Carcinoma (OCSCC)

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Abstract

Background—Although existing literature provides surgical recommendations for treating occult disease (cN0) in early stage oral cavity squamous cell carcinoma, a focus on late stage OCSCC is less pervasive.

Methods—The records of 162 late stage OCSCC pN0 individuals that underwent primary neck dissections were reviewed. Lymph node yield (LNY) as a prognosticator was examined.

Results—Despite being staged pN0, patients that had a higher LNY had an improved regional/distant control rates, DFS, DSS, and OS. LNY consistently outperformed all other standard variables as being the single best prognostic factor with a tight risk ratio range (RR = 0.95–0.98) even when correcting for the number of lymph nodes examined.

Conclusion—The results of this study showed that lower regional recurrence rates and improved survival outcomes were seen as lymph node yield increased for advanced T-stage OCSCC pN0. This suggests that increasing lymph node yield with an extended cervical lymphadenectomy may result in lower recurrence rates and improved survival outcomes for this advanced stage group.

Introduction

The extent of lymphadenectomy has been an independent prognostic factor in several cancers, with an association between higher nodal yields and improved survival.^{1–7} In the head and neck, the radical neck dissection, as described by Crile in 1906, was the first procedure used to address nodal metastases in patients with head and neck squamous cell carcinoma (HNSCC).^{8,9} The procedure is a comprehensive removal of the nodal basins in the lateral neck, but carries significant morbidity due to resection of the spinal accessory nerve, the jugular vein and the sternocleidomastoid muscle. For many years, this aggressive nodal resection was performed even when patients lacked clinical or radiographic evidence of positive cervical disease and was thought to have at least a 20% chance in upstaging patients due to the detection of occult metastases.¹⁰ Modifications in the technique, as described by Bocca and Pignatarto, led to the modified radical neck dissection, which removes the nodal basins, but preserves the aforementioned critical structures.¹¹ Further work by Byers and others helped delineate the patterns of lymphatic drainage based on the primary subsite within the aerodigestive tract, which led to the selective removal of at risk nodal basins specific for each subsite within the head and neck.^{12–15} The improvement in techniques and a better understanding of lymphatic pathways resulted in a paradigm shift in the latter part of the 20th century in which a selective neck dissection (SND) became routine surgical management for clinically node negative (cN0) neck as a way to address occult metastasis.^{16–18}

Surgical staging of a clinically and radiographically negative neck is important from both a prognostic and therapeutic standpoint.¹⁹ The rationale of a selective neck dissection is two-fold; (1) removing occult disease in the predicted high-risk nodal basin, and (2) histopathologic staging of the cervical lymph nodes. The accuracy of surgical staging in the neck is dependent on the true-positive rate for detecting occult disease by the pathologist and the lymph node yield at the time of surgery. Consequently, staging of the neck is dependent on the sensitivity of detecting occult disease + lymph node yield. Due to the current limits in detecting micrometastatic disease through conventional pathologic analysis, the true-positive rate or alternatively the false-negative rate (8–11%) will remain relatively constant until better detection methods are available.^{20–22} This is in stark contrast to pathologic examination of a sentinel node biopsy in melanoma of the head and neck in which the false-negative rate is < 1%.²³ The nodal yield, however, is not constant and is dependent on surgical technique and the extent of the cervical lymphadenectomy that is performed.

The impact of lymph node ratio (LNR) on HNSCC patients undergoing neck dissections has recently been investigated.^{24–26} This idea of LNR was highlighted in a study out of Memorial-Sloan Kettering in which they utilized lymph node density (LND) as a way to predict outcomes in patients with oral cavity squamous cell carcinoma (OCSCC).²⁷ LND was defined as the number of positive lymph nodes divided by the total number of excised lymph nodes. In this system, LND attempts to convey the extent of the neck dissection, surgical technique and the level of histopathologic scrutiny by underscoring two extremely significant parameters in the any lymphadenectomy: the extent of cancer spread (number of positive lymph nodes) and the extent of the surgical lymph node yield (total number of

lymph nodes removed during surgery). The authors demonstrated that LND was a significant predictor of outcomes in OCSCC patients with positive cervical disease, and lymph node yield (LNY) was not a significant contributor to outcomes. Presumably, the insignificance of LNY as a predictor of outcomes may be a result of a selection bias, as patients with and without cervical neck metastases were analyzed together, thus confounding the question of lymph node yield and its significance in outcomes.

In contemplating the results of LND as a significant predictor of outcomes, and the failure of LNY as prognostic, we intuitively considered the highest risk OCSCC patients, T3/4, that are staged pathologically N0 in which the risk of occult disease can be as high as 56%. Consequently, we asked if the extent of the neck dissection, or alternatively lymph node yield, be a significant predictor of outcomes despite being staged pN0? Based on the results from other types of carcinomas, it is our hypothesis that an increased LNY should confer improved outcome, despite a pathologic false-negative rate of approximately 8–11%. Perhaps the only amenable factor that may improve outcomes is the extent of the neck dissection, a surgeon-dependent variable, which could be considered a surrogate marker for surgical quality. The primary aim of our study was to determine whether patients with advanced stage OCSCC (T3/4) with pathologically negative cervical metastases (pN0) have improved outcomes when an increased LNY was achieved. We did not, however, try to define a minimal threshold of lymph nodes that must be removed as most studies have, but rather attempted to ascertain the significance of each lymph node harvested, the combined additive affect, at the time of surgery.

Materials and Methods

Study Population

The University of Pittsburgh Medical Center, Case Western University Hospitals, and Loyola University Medical Center all maintain a prospective clinicopathologic database. After obtaining ethics approval by the institutional review board at each institution, we performed a multi-institutional, retrospective study of patients with T3/T4 pN0 oral cavity SCC undergoing surgical resection of the primary tumor with curative intent between 1979 and 2009, with or without adjuvant therapy for presumed adverse histologic features. The exclusion criteria included inadequate follow-up information, perioperative mortality, and patients that had bilateral neck dissections with > 4 lymph node difference removed from each side. If a patient underwent a bilateral neck dissection with 4 lymph node differences, the average number of lymph nodes was utilized in the analysis. The final study population consisted of 162 patients. Histopathological analysis of all samples were performed by pathologists in sectioned intervals, embedded in paraffin, and stained with heatoxylin-eosin.

Statistical Analysis

The primary outcomes measured were regional control rates without primary local recurrence, distant metastatic control, disease-free survival (DFS), disease-specific survival (DSS), and overall survival (OS). Local control rates at the primary sites were not analyzed, as this study's purpose was to examine the effects of LNY on regional and distant failures. Independent variables used in the analysis included age, gender, T-stage, type of neck

dissection, lymph node yield (LNY), positive margins, histopathologic grade, radiotherapy and chemotherapy. Each independent variable was assessed by univariate Cox Proportional Hazard analysis. Whether the variables demonstrated prognostic potential as suggested by the initial univariate analysis or not, all were included in a multivariable analysis utilizing a backward stepwise proportional hazard regression model. In each analysis, the least significant variable was eliminated until only variables with $p < 0.1$ were left. In order to ensure accuracy, if a variable was significant, we repeated this analysis while simultaneously correcting for the number of lymph nodes examined. A value of $P < 0.05$ and $P < 0.1$ was considered to indicate statistical significance for a univariate and multivariable stepwise regression, respectively. Analysis was performed using JMP (v10.0.2) software from the SAS Institute Inc.

Results

A total of 162 patients met the inclusion criteria. The distribution of patients' characteristics is shown in Table 1. The majority of patients were Caucasian male (75 % and 70%, respectively), diagnosed with T4pN0 (71%) squamous cell carcinoma (SCC) with the average age at diagnosis of 62 years (range, 18–90). The distribution of surgical and histological characteristics, as well as adjuvant treatment used is shown in Table 2. The majority of T3/4 pN0 patients identified in our database underwent a selective neck dissection (69%) followed by a modified radical (19%) and finally radical (12%). Histopathologic examination of the primary tumor demonstrated that the majority of tumors were moderately differentiated SCC (58%), and positive margins were only observed in a minority of patients (10%). Few patients in this cohort underwent post-surgical adjuvant chemotherapy (21%) and less than half had post-operative radiotherapy (42%). The mean and median LNY for the entire cohort were 29 ± 14 ($\pm$ SD) and 27.5, respectively with a range of 6–64 nodes. As expected the radical and modified radical neck dissection groups had the largest number of lymph node yield per side per procedure do to the more extensive resection.

Kaplan-Meier estimates of the entire cohort for 2.5- and 5-year regional control rates were 80% and 67%, and distant control estimates were 79% and 71%, respectively. Kaplan-Meier estimates for 2.5- and 5-year DFS, DSS, and OS were as follows: DFS, 79% and 70%; DSS, 76% and 67%; and OS, 64% and 42% (Figures 1A–E).

Patients were further analyzed on the basis of a number of standard parameters that included age, gender, race, dissection type, T-stage, histological grade, adjuvant therapy (irradiation and chemotherapy), and positive margins as well as the non-standard parameter, LNY. A univariate analysis showed lymph node yield to be the only significant prognostic predictor for regional recurrence, DFS, and OS. The regional recurrence: Risk Ratio per node examined was 0.95; 95% CI, 0.93–0.98, $P = 0.0004$; DFS: RR= 0.97; 95% CI, 0.94–0.99, $P = 0.003$, and OS: RR= 0.98; 95% CI, 0.97–0.99, $P = 0.01$. A univariate analysis for DSS and distant metastatic control similarly demonstrated LNY to be a significant prognostic predictor: DSS - RR per node examined = 0.97; 95% CI, 0.95–1.0, $P = 0.02$; distant control - RR per node examined = 0.97; 95% CI, 0.94–0.99, $P = 0.01$). For the type of neck

dissection performed (SND vs. MRND), DSS: RR, 3.05; 95% CI, 1.21–10.25, $P = 0.02$; distant control; RR, 3.77; 95% CI, 1.33–15.77, $P = 0.009$, Table 3.

We next investigated whether a multivariable analysis would validate our univariate significant predictors. With this in mind, we first created a multivariable model that included all of the variables. We then conducted a backward stepwise proportional hazard (Cox) regression analysis. In addition, if a variable was significant, we repeated this analysis while simultaneously correcting for the number of lymph nodes examined to ensure accuracy. Utilizing this model, LNY, positive margins, and T-stage (T3 versus T4) were statistically significant for regional control rates: LNY - RR, 0.95; 95% CI, 0.93–0.98, $P = 0.0003$; positive margins - RR = 2.3, 95% CI, 0.31–01.1, $P = 0.09$; T-stage - RR, 2.08; 95% CI 0.84–4.40, $P = 0.048$. For DFS, LNY was the only significant prognostic factor: LNY - RR, 0.97; 95% CI, 0.94–0.99, $P = 0.003$. Positive margins demonstrated a trend towards significance (RR, 2.1, 95% CI, 0.8–4.4, $P = 0.10$). LNY was the only significant predictor for DSS: RR, 0.97; 95% CI, 0.95–1.0, $P = 0.02$, with the type of neck dissection no longer being significant. However with respect to distant control rates, LNY and type of neck dissection remained prognostic: LNY - RR, 0.97; 95% CI, 0.94–1.0, $P = 0.03$; SND vs. MRND - RR, 2.63; 95% CI, 0.88–11.3, $P = 0.09$. Finally for OS, LNY and age per decade demonstrated significance: LNY - RR, 0.98; 95% CI, 0.97–01.0, $P = 0.01$; age - RR, 1.17; 95% CI, 0.98–01.4, $P = 0.075$.

Discussion

Most recently the head and neck literature has investigated lymph node ratio (LNR) ratio as a predictor of survival. An editorial by Spillane et al in regards to the concept of LNR in melanoma quite poignantly states that LN ratio is not a new concept, and an international Nodal Ratio Working Group has existed for several years.³⁶ An association between lower LN ratio and improved survival has been shown for cancers of the colon, lung, stomach, bladder, pancreas, and now OCSCC. As in most of the published papers on LNR, authors report a targeted threshold that confers an improvement in outcomes. Spillane further questions the validity of this concept stating,

“What does this mean? Does use of LN ratio make sense when explained in terms of surgical procedure undertaken and anatomical constraints? Is it plausible that, say, Person A with 10 nodes dissected from the groin and 2 nodes positive (LN ratio = 0.2) will have a DSS similar to that of Person B who has 40 nodes dissected from the groin with 8 nodes positive (LN ratio = 0.2)? Is the amount of surgery required proportional to the extent of lymph node involvement (or high risk levels, inserted)? For minimally involved nodal basins, is less than a thorough CLND adequate? Clearly this is not a practical solution. The surgeon does not know exactly how many lymph nodes are involved at the start of a CLND. Therefore doing less than an accepted minimum extent CLND is illogical. CLNDs are standard operations and their extent should be dictated by anatomical boundaries. They should be performed using standard techniques that are well described in the literature and hopefully taught to all surgeons who undertake them.”³⁶

With this understanding our goal was to answer the question, is the extent of a neck lymphadenectomy more important (denominator in LNR), as undetectable micrometastatic disease may be removed in high-risk T3/4 pN0 OCSCC? Based on our results the answer to this question is clearly yes. Univariate analysis consistently demonstrated that LNY was prognostic for all outcomes measured. When a multivariate backward stepwise proportional hazard (Cox) regression analysis was performed, LNY consistently outperformed all other standard variables as being the single best prognostic factor with a tight risk ratio range ($RR = 0.95-0.98$) even when correcting for the number of lymph nodes examined. The math assumes that the hazard (rate of recurrence) is directly related to the number of nodes. Under this assumption, the effect on the odds is multiplicative. Initially, it may appear that this risk ratio is clinically insignificant, however this is for **EACH** node removed. Theoretically if the odds of recurrence for patient A with 10 nodes removed is 1 to 3 (25% probability), then for each additional node the odds will become $(1/3) * 0.97^n$ where n is the number of nodes. Consequently, if patient B had 20 lymph nodes removed, the odds for ten additional nodes would become $(1/3) * (0.97)^{10}$; that's 0.97 to the tenth power which is equal to 0.737. As a result this reduces the odds of recurrence to 0.737 to 3, a 19.7% probability. The key point is that a range or threshold does not exist because our data demonstrates that the hazard is proportional to the number of lymph nodes removed. Of course the surgeon is limited by the anatomy, which supports Spillane's claim that doing less than the required surgery is "illogical."

Others have used methods such as median number of LNs, LN quartiles, and ranges of LNs harvested as their method for stratifying patients into low, medium and high risk (see references herein). We have chosen not to use this method in our analysis as this arbitrarily stratifies patients into cohorts and would be difficult to set a minimum level that is acceptable. In our analysis, utilizing the backward stepping regression model, we have shown that each lymph node harvested has a significant contribution to the overall improvement in all outcomes measured, including distant metastasis, even when correcting for the number of lymph nodes examined.

Indirect evidence supporting the claim that LNY confers an improvement in survival can be derived from our neck dissection type analysis. The majority of neck dissections were SND and MRND. When a SND was the procedure of choice, this carried a $RR = 2.63$ when compared to a MRND for distant control. In addition, the number of pN0 necks observed in a radical, modified radical, and selective neck dissection decreased as the detection of positive nodes can be assumed to be directly proportional to the decreasing LNY achieved in each dissection type. However, we are not suggesting that a radical neck dissection be the procedure of choice for this cohort of patients, but rather a more comprehensive extended neck dissection may be warranted in advanced T-stage OCSCC (T3/4) and perhaps even early cN+ disease.

In our data, a subset of patients demonstrated regional control with distant failure ($n = 11$). In the 1906 a series of 132 patients by Crile, 36 received a radical *en bloc* neck dissections, and 96 were more selective; comparable to the procedure called "supra-omohyoid neck dissection" in current terminology. At 3-year follow-up, the patients who underwent radical *en bloc* dissections had better overall survival. Thus, the radical block dissection had shown

itself to be four times more effective than the less radical surgical procedures.⁹ Our investigation circumstantially supports this claim.

With respect to adjuvant therapy, conventional wisdom leads one to believe that post-operative adjuvant radiation therapy would confer improvement in outcomes. To our surprise, adjuvant radiation did not demonstrate an improvement in any outcome. Thus it is conceivable to believe that in late T-stage OCSCC cN0 that the initial surgical removal of the maximum number of lymph nodes confers the best survival advantage by removing occult disease that may have been missed on histopathologic analysis. Iype et al in their study, also observed that in oral cavity TxpN0, patients that received radiation therapy did not have improved outcomes compared to those that did not.³⁷

There are several limitations of this retrospective study. The subsites of the primary lesion in the oral cavity were not analyzed, which is known to have an impact on regional recurrence.³⁸ The reason for this is two-fold: (1) this would have reduced the power of the study, and (2) due to the advanced nature of the primary lesions, we could not be confident that the origin within the oral cavity was accurate as these lesions are presumably large and invade adjacent subsites. Another limitation that this study suffered is the levels of regional recurrences could not be identified in all patients. This makes it difficult to clearly define what the extent of the neck dissection should be (anatomically). Even though we were unable to elucidate the level of the failure in these cases, the site of regional recurrence always occurred on a surgically treated side. With this understanding we feel the assumption has to be the one that gives the patient the better chance of regional control, which would be to perform a more comprehensive neck dissection to maximize lymph node yield in advanced T-stage disease.

Conclusion

Variations in lymph node count for neck dissections are related to the thoroughness of pathological assessment, biological variations between patients, and the extent of surgery. The results of this study showed that lower regional recurrence rates and improved survival outcomes were seen as lymph node yield increased for advanced T-stage OCSCC pN0. This suggests that increasing lymph node yield with an extended cervical lymphadenectomy may result in lower recurrence rates and improved survival outcomes for this advanced stage group. It also suggests that external beam radiation may not be as effective as a thorough lymphadenectomy in controlling occult metastatic disease. Since the time Crile introduced the “radical” neck dissection a slow paradigm shift has occurred in the head and neck community in which “less is better” to limit patient morbidity. This may be adequate for early T-stage OCSCC, but this investigation supports the claim that for advanced T-stage OCSCC pN0 a more thorough neck dissection with a higher lymph node yield may impart better outcomes and perhaps “more surgery is de rigueur.

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Figure 1.

Kaplan-Meier plots are shown (A) regional control, (B) disease-free survival, (C) disease-specific survival, (D) distant control, and (E) overall survival.

Table 1

Patient variables

Variable	All patients (n = 162)
Gender [n (%)]	
Male	114 (70)
Female	48 (30)
Age (yr, range)	62 (18 –90)
Race [n (%)]	
White	121 (75)
African-American	7 (4)
Other	34 (19)
Mean f/u [months (range)]	30 (1–188)
T stage [n (%)]	
T3	47 (29)
T4	115 (71)

Table 2

Surgical, histological and adjuvant treatment variables

Variable	Total cohort, n = 162 [n (%)]
Type of neck dissection	
Selective	111 (69)
Modified Radical	31 (19)
Radical	20 (12)
Lymph node yield	
Range	6 – 64
Mean ($\pm$ SD)	29 ($\pm$ 13.7)
Median	27.5
Histological grade	
Poor	32 (20)
Moderate	94 (58)
Well	34 (21)
	2 (1)
Positive margins	
Yes	16 (10)
No	142 (88)
Unknown	4 (2)
XRT	
Yes	68 (42)
No	90 (56)
Unknown	4 (2)
Chemotherapy	
Yes	34 (21)
No	126 (78)
Unknown	2 (1)

Table 3

Univariate analysis for regional control, distant control, DFS, DSS and OS

Variable	Regional Control	Distant Control	DFS	DSS	OS
Lymph Node Yield					
	$P = 0.0004$	$P = 0.012$	$P = 0.003$	$P = 0.003$	$P = 0.01$
Per node examined	RR = 0.95	RR = 0.97	RR = 0.97	RR = 0.97	RR = 0.98
	CI, 0.94–0.99	CI, 0.94–0.99	CI, 0.94–0.99	CI, 0.94–0.99	CI, 0.97–1.0
Neck Dissection					
		$P = 0.009$	$P = 0.07$	$P = 0.02$	
SND vs. MRND		RR = 3.8	RR = 2.1	RR = 3.05	
		CI, 1.3–15.7	CI, 0.94–5.56	CI, 1.21–10.25	

SND = Selective neck dissection; MRND = Modified radical neck dissection

Table 4

Multivariate Analysis of Regional control, distant control, DFS, DSS and OS

Variable	Regional Control	Distant Control	DFS	DSS	OS
Lymph Node Yield					
Per node examined	$P = 0.0003$	$P = 0.028$	$P = 0.003$	$P = 0.003$	$P = 0.014$
	RR = 0.95	RR = 0.97	RR = 0.97	RR = 0.97	RR = 0.98
	CI, 0.93–0.98	CI, 0.94–1.0	CI, 0.94–0.99	CI, 0.94–0.99	CI, 0.97–1.0
Neck Dissection					
		$P = 0.09$			
SND vs. MRND		RR = 2.63			
		CI, 0.88–11.3			
T-stage					
	$P = 0.048$				
	RR = 2.1				
T4 vs. T3	CI, 0.84–4.40				
Positive margins					
	$P = 0.09$		$P = 0.1$		
	RR = 2.3		RR = 2.1		
	CI, 0.85–5.2		CI, 0.8–4.4		
Age					
					$P = 0.075$
					RR = 1.14
					CI, 0.75–1.4
Per decade of age					

SND = Selective neck dissection; MRND = Modified radical neck dissection