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Lymphatic Drainage Patterns in Oral Squamous Cell Carcinoma: Findings of the ACOSOG Z0360 (Alliance) Study

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Author Contributions

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Abstract

Objective—The purpose of our study was to correlate sentinel lymph nodes (SLN) found on planar lymphoscintigraphy (LS) to SLN found with gamma probe–directed sentinel lymph node biopsy (SLNB) for T1/T2 N0 oral cavity cancer.

Study Design—Prospective cooperative group trial.

Setting—Academic medical centers.

Subjects and Methods—One hundred forty adults with untreated T1/T2 N0 squamous cell carcinoma (SCC) of the oral cavity underwent planar LS, resection, SLNB, and neck dissection. Location of SLN by planar LS and SLNB and of metastases were compared to each other and historical data of regional metastases.

Results—SLNs located by planar LS and SLNB were predominantly in levels I through IV. There was heterogeneity in the number of SLNs found at planar LS and at SLNB, which was significantly different in levels II and III ($P < .0001$). In 14 of 33 cases with bilateral drainage on planar LS, SLNB detected only unilateral SLN. Sensitivity of planar LS in predicting the level of SLN was 41% to 63%, and specificity was 68% to 95%. Comparison of locations of the metastases to historical data showed fewer metastases to level I in our study ($P = .03$). Metastases occurred predominantly in levels I through III. In 1 case of a lateral tongue cancer, a contralateral SLN was the only positive node.

Conclusion—Lymphatic drainage patterns and metastases involved predominantly levels I through III. Planar LS is not sensitive for predicting the levels of SLN, and in levels II and III, the rate of detection of SLN between the 2 modalities is significantly different.

Keywords

oral squamous cell carcinoma; lymphoscintigraphy; sentinel lymph node

Introduction

Lymphatic drainage patterns from head and neck squamous cell carcinoma primary sites have been studied, and data on metastases to cervical lymph nodes have been published.[1–3] Knowledge of these data is used by head and neck surgeons and radiation oncologists in planning treatment of the neck in patients with head and neck cancer. Lymphoscintigraphy (LS) and sentinel lymph node biopsy (SLNB) are used to assess regional lymphatic drainage and pathological status in cancer patients. SLNB is common practice in breast cancer[4] and cutaneous melanoma.[5] In the head and neck, it is used primarily in melanoma[6] and occasionally in other skin cancers.[7] Its use also has been evaluated in thyroid cancer[8] and squamous cell carcinoma of the head and neck.[9–11] While there are published studies of LS and SLNB in patients with head and neck squamous cell carcinoma,[12,13] the relationship between LS, SLNB, and location of nodal metastases is not well documented. The American College of Surgeons Oncology Group (ACOSOG; now part of the Alliance for Clinical

Trials in Oncology) recently reported the results of its Z0360 study, which demonstrated that gamma probe–directed SLNB was feasible in patients with oral squamous cell carcinoma (OSCC) and has a negative predictive value for lymph node metastasis of 96%.[14] In the current report, we address a secondary endpoint of the study, namely, to compare the results for planar LS to those for gamma probe–directed SLNB in patients with early OSCC. In addition, we compare the location of metastatic lymph nodes in these patients to previously published data of Shah et al[2] of patients with T_1 to T_4 N_0 OSCC who were treated with primary surgical resection and elective neck dissection. Shah et al's group of patients included more with advanced-stage disease and had their nodes detected on routine pathology rather than on step sectioning and immunohistochemistry of SLN. Our goal was to determine if the drainage would be different in our patients in whom nodal metastases were being detected at an earlier stage.

Methods

Patients

The details of the ACOSOG Z0360 trial have been reported previously.[14] Adult patients with clinical T_1 or T_2 N_0 OSCC were recruited from 25 academic medical centers involved in the study. Patients signed informed consent approved by the institutional review board of each participating institution[i] for the original study, and this follow-up study was performed using de-identified data from the original study. Patients with minimally invasive cancers and cancers smaller than 6 mm were excluded, as were patients with previous neck surgery, neck radiation, neck trauma, lip involvement, or other recent cancer history. Evaluation of the patients included history, physical examination, biopsy of the primary, and either contrast-enhanced computed tomography or magnetic resonance imaging of the primary tumor and neck demonstrating no evidence of nodal metastasis.

Preoperative LS

Planar LS to identify the SLNs was performed within 18 hours before the scheduled operation. Unfiltered Tc-99m sulfur colloid was used, with a total administered activity of 0.4 to 0.5 mCi (14.8 to 18.5 MBq) if surgery was to be done the same day and approximately 1 mCi (37 MBq) if surgery was to be done the next day. Unfiltered Tc-99m sulfur colloid was selected based on a desire to use larger particles that would stay in first echelon draining lymph nodes and have less drainage to second- and third-tier nodes. The tracer was injected at 4 sites around the lesion and at a single site deep to the lesion. Topical anesthesia or a nerve block was permitted at the discretion of the physician performing tracer injection, but direct injection of local anesthetic into or around the tumor was proscribed.

Immediately after injection, dynamic images (30 to 60 sec frames for 30 min) were acquired in the ipsilateral anterior oblique projection using a gamma camera fitted with a low-energy general purpose collimator. Delayed planar emission and transmission images (in anterior and both anterior oblique projections) were obtained 1 to 2 hours after injection of the tracer. Each emission image was at least 10 minutes in duration and was followed by a 1- to 2-minute transmission image with a Co-57 or Tc-99m sheet source placed under the patient (or

on the opposing detector with a dual-head gamma camera). If surgery was planned for the next day, delayed images could optionally be repeated immediately before surgery. Single-photon emission computed tomography (SPECT) was not permitted in this trial. The images were interpreted by a nuclear medicine physician/radiologist at each participating site in usual clinical fashion, but results also were documented on a standardized case report form.

Surgery

At surgery, transoral resection of the primary was performed first. Then SLNB was performed using gamma probe guidance through small incisions within the planned incision for the neck dissection. All nodes identified were removed, including any with a count rate 10% or more of the node with the highest count rate. If more than 4 nodes met this criterion, at least 4 with the highest count rates were excised. Subsequently, the incisions were enlarged, and a level I through IV selective neck dissection was performed. A bilateral neck dissection and/or dissection of level V was performed if the lymphoscintigraphy or gamma probe–guided sentinel node biopsy indicated contralateral drainage or drainage to level V. Neck dissection specimens were then separated by lymph node levels. At each participating medical center the SLNs were analyzed for the presence of metastases, and the negative sentinel nodes were sent to a central laboratory at MD Anderson (Dr Adel El Naggar) for further pathological analysis. A careful search for non-sentinel lymph nodes within each neck dissection specimen was also performed, and these nodes were analyzed for the presence of metastases.

Data Analysis

The relationship between the locations of lymph nodes found with LS and SLNB was analyzed using the McNemar test. We also analyzed the locations of pathologically positive nodes and compared them to published data of Shah et al[2] using 2 × 2 tables and chi-square or Fisher's exact tests. Data collections and statistical analyses were conducted by the Alliance Statistics and Data Center using SAS (version 9.3). Data quality was ensured by review of data by the Alliance Statistics and Data Center and by the study chairperson following Alliance policies. The data lock date was July 30, 2013.

Results

One hundred forty eligible patients participated over a 3-year period. Patient demographics and tumor characteristics are shown in Table 1. The majority of the primary sites were oral tongue, followed by floor of mouth, retromolar trigone, buccal mucosa, and alveolar ridge. The majority of the tumors were clinically staged as T_2 but pathologically staged as T_1. In the records of 3 patients, the pathologic T stage was missing.

Lymph nodes were visualized by LS in 84% of patients; the scans of the remaining 16% did not demonstrate visible nodes. All but 1 patient had SLN found during SLNB. Table 2 shows the rate and distribution in the neck of the lymph nodes found by LS and SLNB, respectively. Four patients had insufficient documentation of the location of the SLN found at surgery and thus were excluded from the calculations. The majority of the lymph nodes were found in levels I through IV. Forty patients had drainage to lymph nodes in levels IV

and/or V detected by LS and/or SLNB, but only 5 of these patients had no evidence of drainage to levels I, II, or III. The McNemar test was used to assess the difference between the distribution of the lymph nodes found during LS and SLNB; the differences were statistically significant in levels II and III where fewer nodes were detected by LS than by SLNB ($P < .0001$). The sensitivity and specificity of planar LS predicting the site of SLN for each neck level are shown in Table 3 and ranged from 41% to 63% and 68% to 95%, respectively.

Thirty-three patients had evidence of bilateral lymphatic drainage on LS and/or SLNB. Fourteen out of 33 had bilateral drainage on imaging only, with no contralateral SLN found at surgery. Six out of 33 had bilateral SLN found at surgery with no evidence of bilateral drainage seen on LS. Thirteen out of 33 had bilateral drainage patterns on LS and bilateral SLN found at surgery. One out of the 33 had a left lateral tongue/floor of mouth primary with the only node detected by LS seen on the right (contralateral) and the only SLN found at surgery also on the right, which was negative for cancer. One other patient had a lateral tongue lesion with bilateral SLN, but the positive SLN was contralateral. No patient had contralateral N positive disease not predicted by LS or SLN biopsy.

Regional metastases to cervical lymph nodes occurred in 26% of our study patients and 34% of the patients in the study by Shah et al.[2] The majority of pathologically involved lymph nodes in our patients and those of Shah et al were found in levels I, II, and III of the neck (Table 4). Two patients in our study had insufficient documentation of the location of the involved node and were excluded from the calculations. There were very few metastases to level IV in both groups and only 1 to level V in Shah et al's study. The only level in which there was a significant difference between our patients and those of Shah et al was level I, with a lower rate of level I metastases found in our study ($P = .03$).

Discussion

In this study, as in the published data on regional lymphatic metastases in patients with OSCC, the majority of nodes harboring metastatic disease were located in levels I, II, and III of the neck. However, there was more frequent localization of tracer to levels IV and V nodes by LS and SLNB than would be expected based on the metastatic patterns. A plausible explanation for this may be that the lymphatic drainage of unfiltered Tc-99m sulfur colloid does not exactly duplicate the behavior of draining cancer cells. Perhaps the difference in size (0.1–1μm for unfiltered Tc-99m sulfur colloid particles[15] and 10–30 μm for eukaryote cells) may be an issue, or other factors could be playing a role. Presumably more downstream drainage will be detected with radiocolloid. Also, at the time of the LS, the local lymphatic system is "flooded" with radiocolloid all at once, as opposed to a limited number of cancer cells flowing into the lymphatic channels at any one time. This may lead to the radiocolloid overwhelming the first echelon nodes and flowing to downstream nodes. Furthermore, flooding the system with radiocolloid may elucidate or open alternative lymphatic channels flowing directly to lower level nodes.[16] Cancer cells may be more likely to be trapped by the lymph nodes, increasing the likelihood of metastases in the upper, first echelon nodes.

There appears to be a statistically significant difference between the planar LS results and the locations of SLNs found by gamma probe–directed SLNB in levels II and III of the neck. In both of these levels, more patients had lymph nodes found by SNLB than by LS. Additionally, only 84% of patients in our study had lymph nodes detected by planar LS. The most likely explanation for this is that the retention of much of the radiocolloid dose at the primary injection site leads to “blooming” on the image that prevents detection of SLNs that are close to the primary site. The sensitivity of LS in predicting the sites of the SLN ranged from 41% to 63%. This likely reflects the difficulty of localizing nodes on the planar LS images used in this study. Results may have been different if current imaging methods employing hybrid SPECT/CT[17] had been used, but SPECT/CT was not widely available at the time of this study, and we recognize this as a limitation of our study. More surprising is that some patients with bilateral drainage on LS had unilateral nodes identified by gamma probe–directed SLNB. Since gamma photon detection is involved in both techniques, one must presume that there was low-level transient activity that had washed out by the time the intraoperative gamma probe measurement was performed. For reasons we do not understand, this drainage was not retained in lymph nodes. Whether this drainage is clinically significant is impossible to determine on this study. Alternatively, a “false-positive” site on imaging could have reflected swallowed tracer or inadvertent contamination of the skin during the injection that would have been eliminated by cleansing the skin before surgery. A third explanation is that contralateral activity was missed by the surgeon at the time of SLNB. These findings suggest that planar LS may be of limited utility and that it may not be necessary to perform planar LS prior to SLNB.

The rates and locations of metastatic nodes in this study and the published data of Shah et al[2] are similar. Only in level I was there a significant difference between the 2 groups, with a lower rate of level I metastases seen in our data. Our data confirm that regional metastasis in early OSCC occurs predominantly in levels I, II, and III. There was less than a 2% chance of finding a metastatic node in level IV, and none were found in level V.

Conclusion

Lymphatic drainage from early OSCC is predominantly to levels I, II, and III of the neck. Planar LS and SLNB show drainage to levels IV and V at higher rates than involvement of these levels with actual lymph node metastases. The concordance of lymph nodes found at planar LS and SLNB is relatively poor in levels II and III. In addition, 16% of patients with OSCC who undergo lymph node mapping with planar LS did not show detectable tracer uptake in the regional nodes, and the sensitivity of planar LS in predicting the site of gamma probe–detected SLN is low, thereby limiting its usefulness to the surgeon during gamma probe– directed SLNB.

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Table 1

Patient and Tumor Characteristics.

Characteristics	No.	%
Demographics		
Male	85/140	60.7
Female	55/140	39.3
Median age (y)	58 (range, 24 to 90)	
Clinical T stage		
T1	52/140	37.1
T2	88/140	62.9
Pathologic T stage[a]		
T1	77/137	56.2
T2	58/137	42.3
T3	1/137	0.7
T4	1/137	0.7
Tumor location		
Oral tongue	95/140	67.9
Floor of mouth	26/140	18.6
Alveolar ridge	4/140	2.9
Retromolar trigone	8/140	5.7
Buccal mucosa	7/140	5.0

[a] For 3 patients, pathologic T stage was missing.

Table 2

Sentinel Lymph Nodes Found on Lymphoscintigraphy (LS) and Sentinel Lymph Node Biopsy (SLNB) in Each Neck Level.[a]

	Level I	Level II	Level III	Level IV	Level V
LS, n (%)	42/136 (30.9)	75/135 (55.6)	44/136 (32.4)	22/135 (16.3)	6/136 (4.4)
SLNB, n (%)	50/136 (36.8)	101/135 (74.8)	78/136 (57.4)	24/135 (17.8)	3/136 (1.5)
P value	.28	<.0001	<.0001	.85	.51

[a] A P value of <.05 indicates a significant difference between the 2 methods at that neck level.

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Table 3

Sensitivity and Specificity of Planar Lymphoscintigraphy (LS) Predicting the Location of Sentinel Lymph Node at Time of Surgery.

	Level I	Level II	Level III	Level IV	Level V
Sensitivity, %	50.0	63.3	41.0	41.7	0[a]
Specificity, %	80.2	67.6	79.3	89.2	95.5

[a]Due to no cases where LS detected a level V node *and* a level V node was found at sentinel lymph node biopsy.

Table 4

Positive Nodes at Each Neck Level in the Current Study[a] and Published Data by Shah et al.[2]

	Level I	Level II	Level III	Level IV	Level V
Current study, n (%)	15/138 (10.9)	22/138 (15.9)	10/138 (7.2)	2/138 (1.4)	0/138 (0.0)
Shah et al,[2] n (%)	38/192 (19.8)	21/192 (10.9)	17/192 (8.9)	6/192 (3.1)	1/192 (0.5)
P value	.03	.18	.60	.48	.99

[a]Two patients had insufficient documentation of the location of the involved node and were excluded from these calculations.