Operative Techniques in Otolaryngology (2005) 16, 275-285

ELSEVIER

Operative Techniques in

Otolaryngology

Sentinel node biopsy in cancer of the oral cavity

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KEYWORDS
Sentinel lymph node biopsy;
Lymphatic metastases;
Carcinoma;
Squamous cell;
Head and neck cancer

Sentinel lymph node biopsy represents a less invasive technique for detecting subclinical lymphatic metastases in patients with a known primary malignancy. This procedure was developed to address the management of the lymphatics for cutaneous lesions, especially malignant melanoma. For melanoma, lymphatic drainage patterns are very unpredictable, and the therapeutic value of extensive formal lymphadenectomies remains controversial. The technique is increasingly being applied to other malignancies. Multiple small patient series have been published evaluating the application of lymphatic mapping and sentinel lymph node biopsy to cancer of the oral cavity. The technique requires the selection of patients without clinical or radiologic evidence of gross lymphatic cancer who are at risk for subclinical metastases. Subsequently, primary tumors are injected with a radioactive tracer, followed by radiologic imaging, and then gamma probe-guided lymph node excision through a small incision. Rigorous serial sectioning and immunohistochemistry is essential. Sentinel lymph node biopsy has not yet been validated as safe for oral cavity cancer, and a multi-institutional trial is currently completing accrual to correlate the histopathologic results of sentinel lymph node biopsy and subsequent selective neck dissection. The goal is to establish the predictive value of the less invasive procedure relative to formal lymphadenectomy. In this article, the authors describe the details of their surgical technique for sentinel lymphadenectomy as applied to oral squamous cell carcinomas.

Treatment of the N0 neck in patients with early invasive squamous cell carcinoma of the oral cavity is controversial. A "watchful waiting" policy has traditionally been used to avoid the morbidity of an elective neck dissection or radiation therapy in the majority of patients in whom neck metastases will truly never develop.[1-5] On the contrary, the weight of opinion in the recent literature argues against a generalized "watchful waiting" approach[6-9] and favors an elective neck dissection or radiation therapy in patients at risk for cervical metastases. Patients at risk have been identified by characteristics of the primary lesion, such as thickness >4 mm, size >2 cm, anatomic location, lymphovascular invasion, and perineural infiltration.[10-17]

The strongest argument for treating the cervical lymph nodes states that if clinically identifiable metastatic adenopathy is allowed to develop, factors may already be present that dramatically lower the probability of patient survival. In fact, nonpalpable metastatic lymph nodes can show extracapsular extension, vascular and perineural invasion, and other poor prognostic indicators before our ability to diagnose them on imaging studies.[18-22] Furthermore, multiple retrospective analyses have suggested that even for stage I and II disease, survival is enhanced in a statistically significant way by prophylactic treatment of the cervical lymphatics.[6-8]

Imaging studies, including computerized tomography (CT), magnetic resonance imaging (MRI), and ultrasonography, have been used to identify better grossly involved, nonpalpable nodes, and increase the safety of the "watchful waiting" approach. However, all of these predict lymph node involvement through size and shape, and, therefore, have a significant expected rate of false-positives and false-negatives. Central lymph node necrosis, although highly predictive, is a late finding.[23-25] The uptake of 2-deoxy-2-[^{18}F]-fluoro-D-glucose as measured by positron emission tomography (PET) has been reported as significantly more sensitive and only slightly less specific than MRI. However, foci of cancer smaller than 1 cm are below the resolution of PET,[23] as it is with CT and MRI.

Thus, when an early, invasive oral primary tumor is

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doi:10.1016/j.otot.2005.09.009

identified and no clinically or radiologically involved nodes are present, we must consider treatment of the lymph nodes. The 20% to 30% risk of occult metastases[26-30] must be weighed against the morbidity of dissecting necks that are not truly involved. To treat this group intelligently, it would be beneficial to have better diagnostic techniques to identify subclinical cervical metastases.

The controversy surrounding the treatment of the N0 neck in mucosal squamous carcinoma of the head and neck is analogous to that of elective regional lymphadenectomy in patients with invasive, intermediate-risk (1.0- to 4.0-mm thick) clinical node-negative melanoma of the extremities. For melanoma, sentinel lymph node biopsy has consigned this debate to medical history, as accrued experience from multiple centers has shown that the presence or absence of occult melanoma metastases to regional nodes can be determined with a high degree of accuracy with this less invasive technique. Patients with negative sentinel nodes can thereby be spared the expense and morbidity of surgery from which they could realize no benefit, whereas those with positive sentinel nodes proceed to lymphadenectomy for compelling therapeutic indications.

Morton et al[31] reintroduced this largely forgotten concept to surgical practice in a landmark publication describing the technical details and their early prospective clinical experience with sentinel lymph node biopsy in patients with clinical node-negative cutaneous malignant melanoma. Using injection of blue dye at the primary site, 259 sentinel nodes were identified in 194 of 237 lymphatic nodal basins, and the incidence of false-negative sentinel nodes (ie, the identified sentinel node is found disease-free when metastatic disease is present in the regional lymphatic vessels) was less than 1%.[32] Their model of initial sentinel node biopsy followed by completion lymphadenectomy, and detailed pathologic analysis and correlation of findings has been used to validate this technique at multiple anatomic sites in subsequent trials.

Based on the pioneering work of Alex et al,[33,34] sentinel node biopsy has more recently been performed using peritumoral intradermal injections of unfiltered ^{99m}Tc (technetium) sulfur colloid, or other radiotracer, and intraoperative gamma detection probes.[35-49] The use of ^{99m}Tc sulfur colloid and the gamma probe allows placement of the biopsy incision directly over the radiolabeled sentinel node(s), and the probe directs dissection straight to the node without disturbance of surrounding tissues. Sentinel node biopsy in melanoma using the gamma probe resulted in retrieval of sentinel nodes in 82% to 100% of cases, with a very low incidence of false-negatives confirmed by early follow-up.[37,38] In addition, a higher than expected incidence of bilateral drainage, "skip" drainage to a more distant node in a group than might be anticipated from the location of the primary melanoma, drainage to multiple lymph node groups in the neck, and unorthodox ipsilateral patterns of lymphatic drainage have been documented.[41,43,45-48]

As has occurred in clinically node-negative melanoma, sentinel node biopsy ultimately offers the exciting possibility of identifying those patients with clinically node-negative carcinoma of the oral cavity, and other head and neck sites that harbor occult metastases in the cervical lymphatics. Thus, after a significant experience with cutaneous lesions, we began, 7 years ago, to experiment with the use of this technology in the setting of selective neck dissection for oral cavity cancer.[50] Concurrent pilot studies at multiple institutions, including our own, have had promising results, although statistically significant data, such as are available in melanoma, remain to be acquired. It is important that a complete understanding of the technique, including an established false-negative rate, be available before incorporating it into routine clinical practice. For example, it is noteworthy that in breast carcinoma, the false-negative rate is higher than in melanoma, and the use of sentinel node biopsy as a replacement for axillary lymphadenectomy in this disease remains controversial.[51]

Because selective neck dissection is an excellent technique for staging the cervical lymphatics, with moderate, but generally acceptable morbidity, it is important that statistically significant, quality controlled data be generated before accepting the less invasive sentinel node biopsy approach. On the other hand, patients occasionally present with lesions that clinically appear relatively superficial (ie, less than 4-mm depth of invasion suspected), and these represent a group in which the "watchful waiting" approach remains the standard of care. In this group, the sentinel node biopsy approach might theoretically represent a more aggressive approach for patients who desire an evaluation of the lymph nodes above what is currently standard.

To validate this technique for invasive oral cavity cancer, a National Cancer Institute funded trial is currently in progress under the auspices of the American College of Surgeons Oncology Group (ACOSOG). This trial is modeled after the validation trials for melanoma, and involves narrow exposure sentinel node biopsy, followed by standard selective neck dissection of levels I through IV at the same sitting, with detailed pathologic analysis, immunohistochemistry, and pathologic correlation. It includes central pathologic review, auditing of sites, and, in short, multiple elements of quality control as required by a national cooperative group. There are more than 40 academic institutions in North America involved in this study, and, currently, 150 patients have been accrued into this study. The accrual of 161 patients will be necessary to show statistically the validity of the technique. It is anticipated that on completion of this study, if the results justify it, a randomized trial may follow, comparing initial sentinel node biopsy, with neck dissection for positive findings, to planned initial selective neck dissection. Details regarding our protocol are available at the ACOSOG Web site.[52]

Gamma probe-guided lymphadenectomy

The introduction of sentinel node biopsy for sites such as breast and oral cavity, where there is an established pattern of lymphatic drainage and a generally accepted procedure for selective lymphadenectomy with acceptable morbidity, has led to the concept of "gamma probe guided lymphadenectomy," in which patients who are advised to consider formal lymphadenectomy are offered concurrent sentinel node mapping and biopsy along with the formal dissection. This procedure allows the performance of validation studies