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Sentinel Node Localization in Head and Neck Tumors

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Sentinel lymph node biopsy (SLNB) is a minimally invasive method that was developed to stage the regional lymphatics of patients with cutaneous melanoma. Many studies performed worldwide have shown that SLNB is a feasible method to stage the cervical lymphatics in patients with head and neck squamous cell carcinoma (HNSCC). The accuracy of SLNB in patients with HNSCC is currently under investigation in a multicenter study sponsored by the American College of Surgeons Oncology Group that compares the results of SLNB with standard elective neck dissection. Research to date has also shown that multiple SLNs and individualized drainage patterns characterize head and neck mucosal sites. These findings suggest that lymphoscintigraphy alone may be useful to delineate the lymphatic basins that require treatment in patients with HNSCC and in patients whose head and neck lymphatics are disrupted because of prior surgery or irradiation.
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The sentinel or first draining lymph node (LN) is any node that receives lymph drainage directly from a tumor site. It is also the LN most likely to contain malignancy if the tumor has metastasized. Sentinel lymph node biopsy (SLNB) is based on the premise that malignancy proceeds from the primary tumor, to the SLN, and then onto the remaining regional lymphatics. It follows that the status of the SLN reflects the nodal status of the entire lymphatic basin. If the SLN is positive, regional lymphadectomy is recommended and, if it is negative, no further treatment is necessary.

Experience with SLNB in patients with cutaneous melanoma (CM) has shown that it is an accurate, minimally invasive technique for staging the regional lymphatics in clinically node negative (cN0) patients. Compared with a blanket policy of staging lymphadenectomy for all node-negative patients, SLNB is cost effective and minimizes the overall surgical morbidity. SLNB has revolutionized the treatment and has become the current standard of care for patients with intermediate-thickness CM.

Clinicians who treat patients with squamous cell carcinoma originating from mucosal sites of the head and neck (HNSCC) are faced with a nodal staging dilemma that is analogous to the experience with CM before the advent of SLNB. Specifically, the presence of occult regional metastases significantly downgrades the disease-related prognosis, and accurate identification of subclinical metastases is important for treatment planning. Contemporary imaging of the cervical lymphatics provides a modest improvement in accuracy compared with palpation because the average size of occult metastatic lymph nodes is 3 to 5 mm. Numerous studies suggest that neither radiographic nor positron emission tomography imaging is likely to differentiate normal and metastatic lymph nodes in this size range.[1-4] Hence, the most accurate method currently available to stage cN0 patients is elective lymphadectomy, also called elective neck dissection. Because the risk of occult metastases for most head and neck sites is approximately 30% to 40%, a blanket policy of elective neck dissection exposes the majority of patients who do not harbor occult metastases to the morbidity and cost of surgery that may not be directly beneficial. For these reasons, SLNB represents the near-perfect staging procedure and it is an attractive concept for cN0 patients with HNSCC. SLNB is currently used as a staging procedure in HNSCC at some European centers[5,6] and is under active investigation in the United States in an ongoing American College of Surgeons Oncology Group (ACOSOG) trial.

Challenges in the Identification of SLN

SLNB is a multidisciplinary technique. Nuclear medicine performs preoperative lymphoscintigraphy that directs the surgeon to the first echelon LNs. The surgeon uses a gamma

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probe and/or blue dye to identify and remove the LNs, and the pathologist determines whether metastases are present. The overall accuracy of the technique depends on the accuracy of all 3 phases. Clinicians with experience performing SLNB in head and neck tumors have shown that identification of the SLN presents a unique set of challenges compared with other anatomic sites. A discussion of these challenges and potential solutions is presented.

Occult Cervical Metastases

Occult cervical metastases, hence SLNs, are small. The difficulty with clinical detection is appreciated when measurements of metastatic LNs are examined. These studies demonstrate that approximately 33% to 58% of occult metastases are <3 mm, and in 25% of patients, LNs <3 mm were the only metastatic nodes detected in the neck. Furthermore, extracapsular spread (ECS), a pathologic finding known to increase the risk of recurrence, occurs in 33% to 36% of occult positive nodes.[7-9]

Intraoperative identification of these small nodes is challenging, especially when the SLN is located within a group of nodes or embedded in fat tissue. Many surgeons support the concurrent use of blue dye and the gamma probe to locate the SLN. The gamma probe directs surgeon to the specific area, and blue dye provides visual identification of LNs. Once the SLNs have been removed, the gamma probe can be used to confirm that the no radioactive foci persist in the neck

Lymphatic Drainage Patterns

Lymphatic drainage patterns from head and neck sites are not as predictable as those observed in the extremities. Studies on CM of the head and neck have shown that 24% to 60% of the SLNs are found in unexpected or discordant sites.[10] Experience with preoperative lymphoscintigraphy in mucosal sites of the head and neck is characterized by ambiguous lymphatic drainage.[11,12] Figure 1 shows the results of lymphoscintigraphy in 2 patients with nearly identical early-stage tumors on the left lateral surface of the oral tongue. Surgery and radiation can cause alterations in lymphatic drainage patterns. Preoperative lymphoscintigraphy also identifies SLNs in nodal basins that are not typically removed with neck dissection such as the parotid, postauricular, retropharyngeal, and parapharyngeal space lymph nodes. For these reasons, it has been suggested that lymphoscintigraphy alone provides clinicians with information that can be used for planning neck dissection or cervical irradiation.

Multiple SLNs in Multiple LN Basins

Multiple SLNs in multiple LN basins are common in both squamous cell carcinoma (SCC) and CM of the head and neck. They occurs because lymphatic drainage away from the primary site occurs via multiple parallel lymphatic ducts. For example, in 2 recent series, the average number of SLNs in HNSCC was 2.9[11] and 2.8,[5] and these were located in 2 or more regional basins. Similarly, an average of 2.5 SLNs for CMs of the head and neck was reported recently. These series also demonstrated that unanticipated contralateral SLNs occur in 15% to 20% of patients.[13,14]

Figure 1 Results of lymphoscintigraphy in 2 patients who both had T2N0 squamous cell carcinoma of the left lateral oral tongue. These results changed the surgical plan in the patient shown in the bottom photograph, and she was consented for bilateral neck dissections. (Color version of figure is available online.)

The 2-hour gamma camera images often show multiple LNs, including second echelon nodes that do not require biopsy. The number of nodes imaged during lymphscintigraphy is a function of the particle size of the radiotracer, volume of injection, and the timing of camera images.[15] Distinguishing first and second echelon nodes will minimize the total the number of nodes that are biopsied which in turn reduces the operative time, the area dissected, the operative morbidity, and the total cost of pathologic examination. The distinction can be made by viewing the early dynamic images where parallel drainage to 2 nodes represents 2 SLNs, versus in sequence drainage to 2 nodes that would represent first and second echelon nodes.

Limitations of SLN Localization Using Standard Gamma Camera Imaging

The 3-dimensional anatomy of the head and neck lymphatic system is complex, and SLN localization using standard gamma camera imaging provides limited anatomic and spatial resolution concerning the location of the SLN. For example, a SLN located in level II on planar images can be deep or superficial to the great vessels, in the tail of the parotid gland, or in the submuscular recess of level II. Intraoperative localization of small, deep jugular chain nodes through a small cervical incision can be challenging because of the surrounding neurovascular structures. This situation is one in which the concurrent intraoperative use of blue dye and the gamma probe is most beneficial.

Distance Between the Primary Site and the SLN

The distance between the primary site and the SLN is small in many head and neck sites. For example, a floor of mouth tumor and the first echelon submandibular LNs can be within millimeters of each other, making the distinction between the focus of radiotracer uptake from the primary site and that of the SLN difficult to differentiate. Super high-resolution collimators, lead shielding of the primary site during gamma camera imaging and resection of the primary tumor before intraoperative SLN localization, have been suggested to minimize this problem. Despite these techniques, Ross and coworkers[5] recently showed that the identification rate for the SLN was 86% for floor of mouth tumors compared with 96% for other subsites in the oral cavity and oropharynx. This difference translated to a statistically significant ($P < 0.05$) decrease in sensitivity for SLNB in floor of mouth tumors (80%) compared with other oral cavity and oropharyngeal sites (100%).

Variation of Lymphatic System Characteristics

Experience suggests that the characteristics of the lymphatic system vary on the basis of the location of the primary site. Lymphatic flow rates are variable throughout the body, ranging from 1.5 cm/min in the head and neck lymphatics to 10.2 cm/min in the leg and foot.[16] Larson and coworkers[17] demonstrated both fine and large–caliber lymphatics in the tongue of dogs. Shoaib and coworkers[18] recommended that different radiotracers be used depending on the mucosal site to be studied. For tongue and floor of mouth sites, Albu-Res is preferred because its large particle size (200-1000 nm) functions better in studying high-density terminal lymphatics at these sites. Nanocolloid is used for all other upper aerodigestive tract sites because the smaller (<80 nm) particles are more readily attracted to lymphatics that are low density. The base of tongue lymphatics appear to be more delicate because they ruptured, resulting in extravasation of dye when the amount of dye injected in the cat tongue was greater than 0.1 mL. By comparison, 0.2-mL injections imaged the SLN without dye extravasation in the anterior tongue of the cats, whereas up to 5.0 mL of dye is used in breast and 1.0 mL in melanoma without sequela.[11]

Difficulty Accessing Sites of the Upper Aerodigestive Tract

Some sites of the upper aerodigestive tract are difficult to access. Most of the research on SLNB in HNSCC has been performed on tumors of the oral cavity and oropharynx because these sites are amenable to transoral injection of radiotracer. Surgical access to the larynx and pharynx for precise radiotracer injection requires endoscopic evaluation under general anesthesia, which presents logistic problems for gamma camera imaging. By the time the patient has been transported from the operating room to the nuclear medicine suite the critical period for dynamic imaging will have passed. Transport between the operating room and nuclear medicine suite under general anesthesia presents unique challenges, as does a second anesthetic for SLNB and tumor removal after gamma camera imaging. Accordingly, investigators have modified the technique for SLNB in patients with laryngopharyngeal tumors. The radiotracer is injected in the operating room with the patient under general anesthesia, and the gamma probe alone is used to identify the SLNs. Because of the proximity of the tumor to the SLNs, transoral excision of the primary tumor takes place before SLNB. Werner and coworkers[19] reported endoscopic radiotracer injection, followed by transoral laser excision of the tumor and SLNB with the gamma probe alone in 50 patients with SCC of the laryngopharynx. The overall sensitivity of this method was 89%. If this technique can be corroborated by others and is efficacious in long-term follow-up, it will represent a minimally invasive approach to some laryngeal tumors that may otherwise require total laryngectomy and neck dissection.

Variations in Techniques

There is no standardized technique for identification of the SLN in head and neck tumors, making comparisons among studies difficult. Techniques vary from the particle size of the radiotracer, timing of gamma camera images, and criteria for identification of the SLN among others. Multi-institutional studies examining CM have used a standard technique that facilitates accurate comparison of large patient numbers.[20] The result of these standardized studies is robust statistical power that has identified highly refined groups of node positive and node negative patients. Today SLNB findings are incorporated into the nodal staging system for CM.[21] A standardized technique will facilitate similar study of SLNB in HNSCC.

Recent Technological Advances

In summary, many technical details specific to the head and neck contribute to the challenge of identifying the SLNB in these sites. Recent technologic advances in imaging show future promise for improving the accuracy of SLNB in head and neck tumors. A discussion of these follows.

Three-dimensional resolution of the head and neck on planar gamma camera images does not differentiate between the deep and superficial cervical lymph nodes. New-generation lymphoscintigraphy techniques have begun to address this issue. For example, a hybrid single-photon emission computed tomography (SPECT) and low-dose CT scanner provides spatial localization of SLNs. In a study of 34 patients with head and neck SCC or CM, combined SPECT-CT was compared with dynamic gamma camera images. Lymph nodes that were not found on planar images because of the proximity to the primary site or because they were in transit or in unpredicted lymph node basins were identified on the fused images. SPECT-CT proved beneficial in 44% of the head and neck tumors and 50% of the truncal melanomas. This technology also identified lymph nodes that were <10 mm, which were not considered suspicious on CT scan because of their small size, as a result of the uptake of radiotracer in the SLNs.[22] Other studies have corroborated these findings.[23,24] The advantage of better anatomic detail is minimizing the overall time and morbidity of surgery as well as the more accurate identification of SLNs.

Another technique recently studied in a porcine model is dynamic magnetic resonance lymphoscintigraphy. Carbon dye or ultra-small supermagnetic of iron oxide (ie, USPIO, particle size 20 nm) was used to image regional lymphatics after the interstitial injection of both the tongue and hind leg.[25,26] Axial and sagittal images in a fluoroscopic mode were recorded for 2 minutes followed by static images at various intervals to 48 hours. The SLN was identified on early images and second echelon nodes were visualized on the 48-hour images. The first draining nodes were localized with a needle, and the lymphatic basins were explored in the operating suite. In all cases, the needle was located in carbon stained nodes that were easily visualized. Second echelon nodes were not visualized in the operating room, presumably because of the low concentration of carbon dye. This technique addresses spatial and anatomic resolution as well delineating the filling sequence in the cervical lymph nodes. Further study is required because it was suggested that lymph nodes not seen on regular MR images due to their small size might not be visualized with iron or carbon radiotracers.

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