LYMPHOSCINTIGRAPHY FOR SENTINEL NODE MAPPING USING A HYBRID SINGLE PHOTON EMISSION CT (SPECT)/CT SYSTEM IN ORAL CAVITY SQUAMOUS CELL CARCINOMA

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Abstract: Background. We assessed the added clinical value of fused single photon emission computed tomography (SPECT) and low-dose CT images compared with planar images for sentinel node (SN) mapping in patients with oral cavity squamous cell carcinoma (SCC).

Methods. Twenty consecutive patients with newly diagnosed biopsy-proven SCC of the oral cavity were enrolled. Scintigraphy was performed using a hybrid gamma-camera/low-dose CT system. Planar images and fused SPECT/CT images were interpreted separately. All patients underwent a sentinel node biopsy (SNB) followed by a neck dissection. All SNs underwent meticulous pathologic examination and immunohistochemistry staining (cytokeratin complex) in addition to routine pathologic examinations of the neck dissection specimen.

Results. The sensitivity for the detection of nodal metastases was 87.5%. SPECT/CT improved SN identification and/or localization compared with planar images in 6 patients (30%).

Conclusions. SPECT/CT SN mapping provides additional preoperative data of clinical relevance to SNB in patients with oral cavity SCC.

Keywords: hybrid SPECT/CT; lymphoscintigraphy; oral cavity SCC

A sentinel node (SN) is defined as the first lymph node in a lymph node bed to receive lymphatic drainage from a tumor. Lymphoscintigraphy and sentinel node biopsy (SNB) were first reported by Cabanas in 1977 for use in penile cancer. In 1992, Morton et al refined the technique and used it for the staging of disease in patients with intermediate-thickness malignant melanomas. Alex
and Krag were the first to report the use of SNB for head and neck squamous cell carcinoma (HNSCC). At surgery, the search for an SN may be performed either by use of blue dye injection and coloring of the nodes or by injection of labeled particles before surgery and localization of the nodes with the highest counts on a hand-held gamma detecting probe (GDP). Scintigraphic SN mapping before surgery is important in tumors located in body parts with ambiguous lymph node drainage, such as the head and neck. Drainage from these regions is unpredictable and is individual for each tumor. Mapping may therefore assist the surgeon in tailoring the field of surgery and provide guidance for the incision site.

Recent reports of SNB for HNSCC are rare and usually entail small numbers of patients. The accuracy of the technique is, however, reported as 90% to 100% in most of these small series. Data collected from 22 centers were reported at the first international conference on SNB in HNSCC. The conclusion was that SNB is an accurate technique in centers that performed more than 10 cases of SNB.

The preoperative localization of the SN is still unsatisfactory because of difficulty in determining the accurate anatomical localization of “hot” nodes on planar scintigraphy. Novel systems composed of a gamma camera and low-dose CT tube on the same gantry were recently introduced in the clinical practice of nuclear medicine. Single photon emission CT (SPECT) and CT data are acquired at the same clinical setting without changing the patient’s positioning, thus allowing for generation of accurate fused images combining the functional data of SPECT with the anatomical data of CT.

The purpose of the current study was to assess the potential role of SPECT/CT lymphoscintigraphy in the clinical setting of SNB for HNSCC.

**PATIENTS AND METHODS**

Twenty patients with SCC of the oral cavity were recruited to this prospective study during a 14-month period. The study included 6 women and 14 men with a mean age of 65 years. Disease in all patients was staged preoperatively as N0 based on clinical examination and diagnostic imaging (ultrasonography [US], CT, or MRI). Disease was also classified as T1 (n = 5, 25%), T2 (n = 8, 40%), T3 (n = 2, 10%), and T4 (n = 5, 25%). Primary tumors were located in the oral tongue or floor of mouth (n = 15), inferior alveolus (n = 4), and retromolar trigone (n = 1). All patients received a detailed explanation on the purpose, methods, and potential complications of sentinel node lymphoscintigraphy and biopsy and signed an informed consent approved by the institutional review board (IRB).

**Scintigraphic Technique.** In this study, 74 MBq (2 mCi) $^{99m}$Tc-rhenium colloid (TCK-17, CIS International, Gif-Sur-Yvette Cedex, France) divided into 4 equal aliquots of 0.4 mL each was injected at the borders of the primary tumor site using 25-gauge insulin syringes. The rhenium colloid preparation has a particle size of 50 to 100 nm, larger than the $^{99m}$Tc-antimony trisulfide colloid and the $^{99m}$Tc-sulfur colloid particles. The rhenium colloid product also contains gelatin; therefore, it was characterized by a slow migration from the injection site as well as by a prolonged accumulation in the sentinel nodes. The lymph node level shows binding of 3.06% ± 0.10% of the injected dose at the first hour and 3.83% ± 0.16% at the third hour (manufacturer’s information).

Lymphoscintigraphy was performed 1 day before surgery, and the injected doses at the time of scintigraphy were larger than those with other radiopharmaceuticals to permit a probe reading 24 hours later. Planar images, including anterior, lateral, posterior, and, occasionally, oblique projections, were obtained within minutes after injection and continued until the sentinel nodes were identified, up to 24 hours after injection, if necessary. Most sentinel nodes were detected 1 to 3 hours after injection. The more delayed images also included areas remote from the primary lesion. This method was based on a previous publication that validated the accuracy of delayed images using this radiopharmaceutical. A $^{57}$Co flood source was placed between the patient and the camera, to define the body contour. A SPECT/CT emission/transmission study was performed using a hybrid system composed of a dual-head gamma camera with a low-dose X-ray tube installed in its gantry (Discovery VH consisting of a VGS gamma camera and a Hawkeye X-ray system; General Electric Medical Systems, GEMS, Haifa, Israel). This system allows both transmission and emission acquisitions to be performed without changing the patient’s position. Fused images overlaying the transmission (CT) and emission (SPECT) data were generated. SPECT acquisition parameters for SN detection include a matrix size of $128 \times 128$ pixels, 180° in the anterior L-mode rotation, and a 3° angle step with a 20- to
Before incision, an intraoperative hand-held GTP (Neoprobe 2000; Neoprobe, Dublin, OH) was used to identify the site with the highest counts along the lymphatic basin. Immediately after intubation (or after tracheotomy when airway obstruction was anticipated), a patent blue dye (2.5% in aqueous solution containing 0.6% sodium chloride, and 0.05% disodium hydrogen phosphate; Laboratoire Guerbet Cadex, France) was injected similar to the earlier colloid injection. Dye was injected immediately before surgery because it fades quickly after having been injected. At this point, a blue duct, or even a blue node, could direct the surgeon to the SN and assist in its dissection. After excision of the node, ex vivo counting was performed followed by probing of the lymphatic basin in search for additional nodes with high counts. Dissection was considered complete only after all “hot” nodes had been removed, after which a neck dissection (supraomohyoid neck dissection) was performed. The sentinel nodes were sent separately for pathologic examination. Orientation of the neck dissection specimen was provided to the pathologist by the surgeon, and the levels of the neck were marked immediately following the surgical procedure.

**Pathologic Examination.** Sentinel nodes were submitted to pathologic examination. If metastatic deposits of SCC were not found, the nodes were then serially sectioned and examined by immunohistochemistry for cytokeratin complex. The neck dissection specimen was examined for metastatic nodes by a designated head and neck pathologist (LRT).

**RESULTS**

The peritumoral colloid injections were uneventful, causing only minor discomfort during the act of injection. Sentinel nodes were identified by lymphoscintigraphy in 19 patients (95%) and intraoperatively in all 20 patients. Altogether, 61 sentinel nodes were identified in the 20-patient cohort, an average of 3.05 nodes per patient. After the pathologic examination of the neck dissection specimen, 5 patients were found to have a single-involved lymph node in their neck dissection specimen (stage N1), while 3 other patients had multiple metastatic nodes (stage N2b). Altogether, 40% of the patients had occult nodal metastases. The overall accuracy of SNB was 95% and the sensitivity for detecting occult cervical metastases was 87.5% (7/8 patients). The sensitivity was 100% for patients with oral tongue and floor of mouth (7/7) malignancy, and only 1 patient with a primary tumor located in the retromolar trigone had a nodal metastasis that was missed on SNB.

The preoperative SN mapping detected an average of 4.2 nodes per patient using planar images and an average of 3.6 using SPECT/CT images, which was higher than the number of radioactive or blue nodes found during surgery (an average of 2.6 nodes per patient). The SPECT/CT could localize the radioactive nodes better than the planar images because of its ability to correlate the radioactivity with known structures, such as the internal jugular vein and the carotid artery (Figure 1).

Comparison of the planar images and the fused SPECT/CT images demonstrated complete agreement in only 6 patients. In 4 patients, the primary site of injection was interpreted on planar images as an SN but was correctly interpreted as the site of injection by the fused images. In 2 patients, nodes at levels II or IV were missed on the planar images but identified on the fused images (Figure 2). At least the SN at level II may have been missed.
because it was obscured by the scattered radiation originating from the close injection site ("Shine-trough"). In 1 of these latter 2 patients, this missing node was positive for metastatic SCC. In 8 patients, differences existed between interpretation of the planar images and that of the fused SPECT/CT images, but no significant changes were found in the anatomical localization of the nodes.

During the surgical procedure, 61 sentinel nodes were identified using the GDP and 4 lymph nodes were stained by blue dye. Only 1 stained lymph node (negative for metastatic carcinoma) did not show high radioactive counts.

The surgical interventions were uneventful in all patients, and no perioperative mortality or significant morbidity occurred.

**FIGURE 1.** Axial positron emission tomography (PET)/CT image shows a sentinel node at level IV. The exact location of the node relative to cervical structures is shown: the trachea and thyroid gland medially, the edge of the clavicles anteriorly, and the blood vessels (with no contrast) posterolaterally. The node was found easily intraoperatively, and radioactivity confirmed with the use of the intraoperative hand-held gamma detecting probe. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

**FIGURE 2.** Single photon emission CT (SPECT)/CT image of lymphoscintigraphy of a patient with oral tongue squamous cell carcinoma is shown on sagittal (right) and coronal views. Two sentinel nodes are detected at levels II and IV. The nodes were not palpated on physical examination preoperatively but were easily harvested and were positive for metastases on final pathologic analysis. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
DISCUSSION
Preoperative lymphoscintigraphy defines the drainage basins and the SN localization of an individual tumor site. This preoperative mapping is particularly important if the tumor is located in the head and neck since the lymphatic drainage in the head and neck region is especially complex. There are more than 350 lymph nodes and a rich lymphatic network, as well as a wide variability in the patterns of lymphatic drainage.\(^\text{10}\) Determination of the accurate number of draining basins is essential. A group of lymph nodes that belong to a single basin must be differentiated from multiple lymph nodes of several basins. In the latter case, each of the nodes may be an SN. Identifying more than a single draining basin indicates the need to identify, remove, and examine the SN of each of the basins separately.\(^\text{11}\)

The use of SNB in HNSCC is still being debated among head and neck surgeons. There are several reasons for it. Most head and neck mucosal sites (excluding the oral cavity) are not easily accessible for injection of the blue dye or radioactive labeled colloid. In patients with mucosal SCC of the oral cavity, the distance between the primary peritumoral injection site and the lymphatic basin is short. This proximity may result in the SN being obscured by the scatter radiation originating from the injection site.\(^\text{9,12}\) Finally, because sentinel nodes in patients with SCC of the oral cavity are located almost exclusively in levels I–III of the neck, close to major neural and vascular structures, such as the internal jugular vein, a supraomohyoid neck dissection may be an appropriate, safer procedure and not much longer than lymphoscintigraphy and SNB.

Regardless, because SNB may save unnecessary neck dissection in patients with HNSCC, it is extensively investigated. Werner et al\(^\text{13}\) reported the results of SNB in 90 patients with HNSCC and concluded that all “hot” nodes should be excised since if only nodes with the highest radioactive counts were to be excised, 39% of patients with regional metastases would have been missed. Previous reports have focused on the methodological details for optimizing lymphoscintigraphy, recommending acquisition of early images, the use of high-resolution collimation, multiple projections, and the use of markers and transmission images with a \(^{57}\)Co flood source to facilitate anatomical localization.\(^\text{14–20}\) Even then, there was a discrepancy between the lymphoscintigraphic and the actual number and location of SNs in up to 23% of the patients.

Lymphoscintigraphy has been found to predict the number of nodes accurately in only 81% of the basins, overlooking the nodes that were superimposed and could not be separated from other nodes or from the injection site or from the lymphatic channels. Nodes that were beyond the resolution of the planar images could not be identified either.\(^\text{21}\) The fused SPECT/CT images in this study were found to be accurate in the preoperative localization of sentinel nodes in this group of patients with SCC of the oral cavity. Thus, it achieved not only better separation of the primary site of injection from the SN region, but also a detailed anatomical localization of lymph nodes that were in proximity with each other or that were in sites not easily identified on planar images.

In a previous study by our group,\(^\text{22}\) we reported fused SPECT/CT lymphoscintigraphy to be of a clinical added value compared with planar images when assessed in 28 melanoma patients, 3 with disease located in the head region and in 6 patients with head and neck malignancy. Schillaci et al\(^\text{23}\) recently studied 81 patients with various clinical situations and compared planar images with fused SPECT/CT images. A more precise anatomical localization was achieved in 79 of these patients, and there was a significant impact on the result in 40% of the patients.

The results of the current study suggest that fused SPECT/CT added significant anatomical preoperative information in 6 of 20 of the study patients (30%). In the setup of sentinel node biopsy of patients with HNSCC, the impact of detailed anatomical location of the sentinel node, in particular with regard to its relation to vital structures such as the internal jugular vein and carotid artery, is of paramount importance. Another aspect is the proximity of the primary site of injection to the sentinel node, mainly in patients with floor of mouth carcinoma and sentinel nodes at level I of the neck. SPECT-CT identified all sentinel nodes in our patients with floor of mouth carcinoma. The use of blue dye had an additional value over the use of a gamma-probe technique in a single patient only. Jansen et al\(^\text{24}\) studied the accuracy of SNB for patients with melanoma of the head and neck. In agreement with our results, they found that only 53% of the sentinel nodes stained blue and that locating an SN was based on the blue staining only with no tracing of radioactivity in 4% of the patients. Likewise, the injection of a radioisotope was found to be superior to blue dye in women with early breast...
cancer. Our impression throughout the study was that the peritumoral injection of blue dye at the beginning of the surgical procedure might obscure the edges of the tumor and interfere with its surgical resection, necessitating wider margins of resection. Because it appears that blue dye adds minimal information to radio-tracing of sentinel nodes, its use during SNB should be critically questioned. In the setup of an SNB via a small incision, however, the stained blue nodes or lymphatic channels may still help the surgeon localize an SN.

In conclusion, fused SPECT/CT images improved preoperative identification and localization of sentinel nodes before SNB in patients with SCC of the oral cavity. The value of the additional use of blue dye injection to SNB of these patients is yet to be determined.

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REFERENCES