Freehand SPECT-guided sentinel lymph node biopsy in early oral squamous cell carcinoma

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INTRODUCTION

Lymph node metastases are adverse prognostic factors for survival in oral and oropharyngeal squamous cell carcinoma (SCC).[1] The presence of micrometastases in locoregional lymph nodes also negatively affects patient outcomes, as reported by Broglie et al.[2] Therefore, accurate staging and stage-adjusted excision of cervical nodes usually by means of elective neck dissection are crucial. However, lymph node involvement is only observed in 1 in 3 patients at histopathological workup, and the management of cN0 neck remains controversial in TNM stage I or II disease. Thus, sentinel lymph node biopsy (SLNB), now a standard of care in patients with melanoma and breast cancer, was recently assessed in validation and observation studies in patients with oral and oropharyngeal SCC with clinically absent lymph node metastases (cN0).[3–10] SLNB seems to be an alternative to elective neck dissection and has high sensitivity and negative predictive value. Furthermore, reduced morbidity and better quality of life compared to elective neck dissection were demonstrated.[11] In SCC of the floor of the mouth, reduced detection rates may result from a close proximity to the injection site and draining sentinel lymph nodes. Hence, the use of SLNB in patients with floor of the mouth cancer remains controversial and is therefore not recommended as a standard procedure in recent guidelines.

In this study, we present the case of a patient with a floor of the mouth tumor undergoing improved SLNB using freehand single-photon emission CT (fhSPECT), which is a 3-dimensional (3D) visualization system for intraoperative detection of radioactive hotspots.

CASE REPORT

A 44-year-old woman was referred to our department with a biopsy-proven cT1/cT2 SCC of the floor of the mouth (Figure 1). No lymph nodes suspicious for metastases were detected during the physical examination or after ultrasound and MRI scans. To rule out distant metastases or a secondary primary cancer, the patient underwent panendoscopy, bone scintigraphy, and chest radiography, resulting in no pathologic findings. SLNB, using fhSPECT (declipse SPECT, Surgiceye, Munich, Germany) was performed, followed by a bilateral elective neck dissection with excision of levels I–III and the cranial portion of level V. Application of fhSPECT was approved by the local ethics committee and patient provided written informed consent.

Before surgery, the patient underwent radionuclide lymphoscintigraphy. The most commonly used

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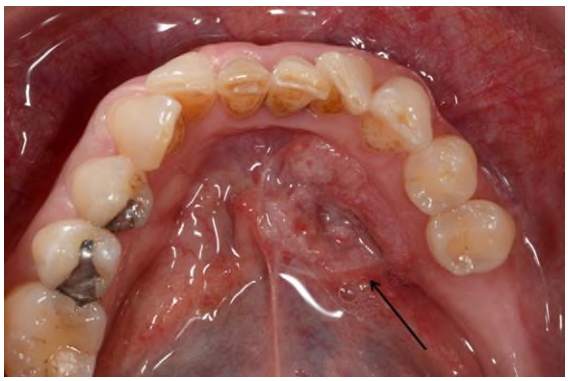

FIGURE 1. Early squamous cell cancer of the anterior floor of the mouth. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

radiopharmaceutical in Europe, 72MBq ^{99m}Tc-labeled nanocolloid (Nanotop; ROTOP, Dresden, Germany), which enables detection rates that are equal to the other radiocolloids (eg, ^{99m}Tc-sulfide colloids), was injected peritumorally.[12] Subsequently, image acquisition was initiated. Dynamic images of the head and neck were obtained in the anterior and anterior-oblique views. Ninety minutes after injection, static scanning of the head and neck was also performed on the anterior and anterior-oblique projections, followed by SPECT and low-dose CT (SPECT/CT) for improved anatomic localization of the sentinel lymph nodes. The tumor drained to a submandibular level I lymph node and a level III lymph node, both of which were located on the left side (Figure 2A–2C).

On the following day, intraoperative SLNB was conducted using fhSPECT guidance in addition to the acoustical information provided by a conventional gamma probe. FhSPECT is a technology that provides high resolution 3D images of the distribution of radioactivity in the body. In addition to a standard gamma probe, the system works with an infrared optical tracking system, including a "patient reference target" (reference geometry including infrared optical markers fixed on the patient skull) and a "probe reference target" (fixed on the gamma probe). This infrared system captures the relative position and orientation of the patient to the gamma probe. This information synchronized with the measured decay (activity) and 3D images are then reconstructed by the data processing unit using a dedicated mathematic algorithm and displayed on a monitor (Figure 3).[13,14]

In addition, the gamma probe serves as a navigated pointer and enables the surgeon to measure the distance between the tip of the probe and the sentinel lymph node in real time. As the result of a more recently technological innovation, the percentage uptake can be determined for every deposit in the 3D image. Combining all of this information, the differentiation between several activity deposits, including those in close proximity to one another, is feasible.

In the present case, hotspots that had previously been identified using lymphoscintigraphy were mapped in the fhSPECT scan (Figure 4A). Subsequently, 1 level III sentinel lymph node was easily detected and dissected using the acoustical and visual depth information. The absence of the first sentinel lymph node was verified by a second scan (Figure 4B). Remaining activity in the submandibular region was demonstrated (level I sentinel lymph node), which was scattered by the injection site during the measurement (shine-through phenomenon) using only the conventional acoustical gamma probe. In contrast, this sentinel lymph node was detected and dissected with the guidance of fhSPECT. In a subsequent measurement, no residual radioactivity was detected, with the exception of the injection site (Figure 4C). Because of the use of this innovative technique, an elective supraomohyoid neck dissection with an extension to the upper posterior triangle of the neck was performed preventively on both sides (I a/b, II a/b, III, and Va). Afterward, the patient received a resection of the primary tumor and microvascular reconstruction.

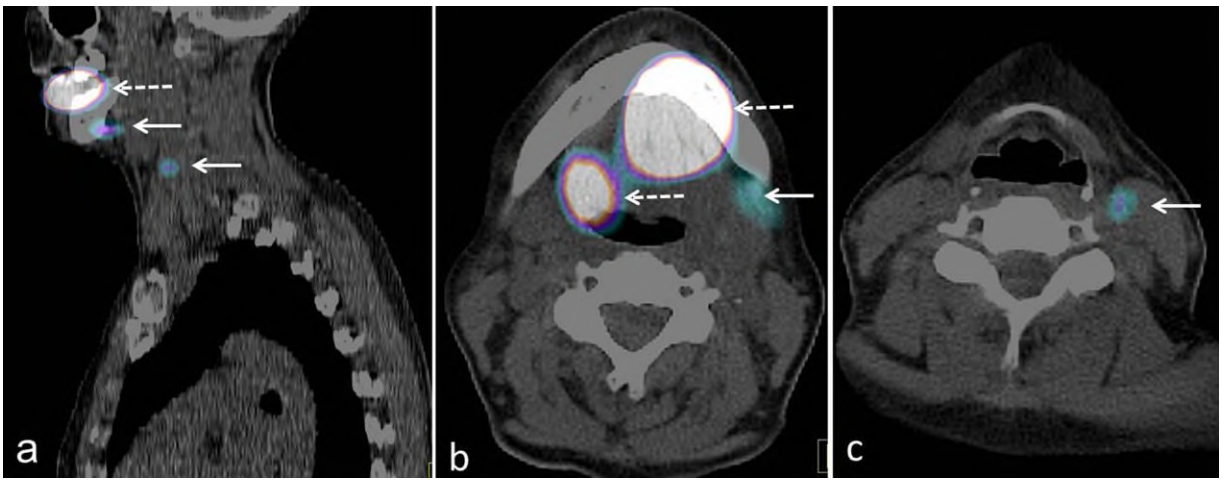

FIGURE 2. Preoperative combined single-photon emission CT and low-dose CT (SPECT/CT) images of lymphoscintigraphy showing the injection site (dotted arrow; A and B), a level I sentinel lymph node (arrow; A and B) and a level III sentinel lymph node (arrow; A and C). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

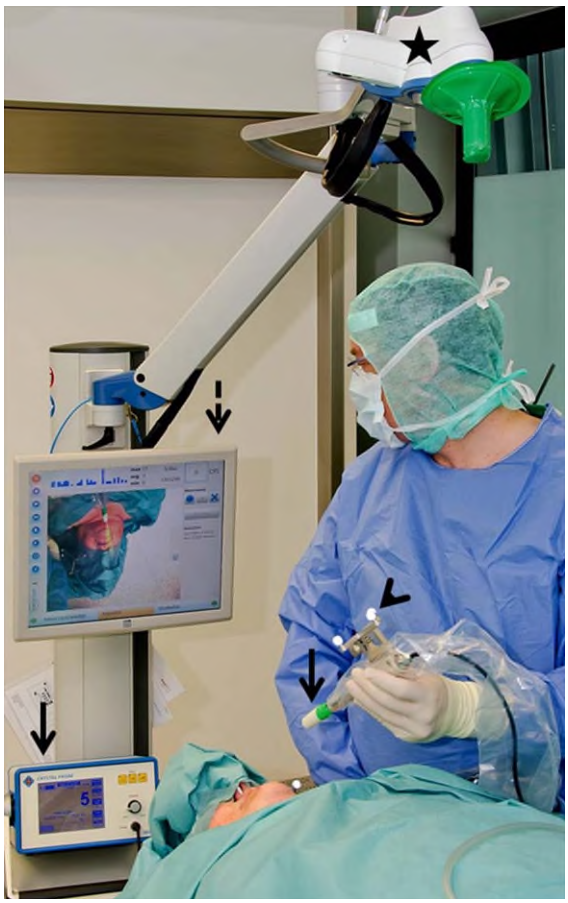

FIGURE 3. Intraoperative setting of freehand single-photon emission CT (fhSPECT) with the camera head (star), touch screen monitor (dotted arrow), and conventional gamma probe (arrows), including the optical tracking system (arrow head). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

The dissected sentinel lymph nodes and the tumor specimen were processed for further detailed histopathological analyses. The 2 sentinel lymph nodes were sectioned and stained using hematoxylin-eosin and immunocytochemistry (anti-pan cytokeratin antibody AE1/3, Figure 5). The presence and size of tumor deposits were documented. In our case, only the level I sentinel lymph node contained a metastasis of 4 mm in diameter. The primary carcinoma was rated as an oral SCC with a diameter of 12 mm, resulting in a TNM classification of pT1 N1 (1/30), R0, G2, and cM0. Because of the presence of the 4-mm metastasis in the submandibular sentinel lymph node, neck dissection of the caudal levels (IV and Vb) on the left side was added. However, the additionally dissected 19 lymph nodes were free of tumor metastases (pT1 N1; 1/49; R0 G2 cM0).

DISCUSSION

Oral and oropharyngeal SCCs account for approximately 5% of all solid malignancies.[12] In patients with early disease, the spread of carcinoma cells to cervical lymph nodes is the most important prognostic factor.[1] The involvement of lymph nodes is associated with a 5-year survival rate of 53%, compared to 82% in node-negative patients.[15] Even small tumor deposits in the lymph nodes significantly impact patient survival.[2] Consequently, accurate staging of the neck is crucial. In addition to palpation of the head and neck, morphologic imaging (eg, ultrasound, MRI, or CT) is routinely performed. Fine-needle aspiration cytology of cervical lymph

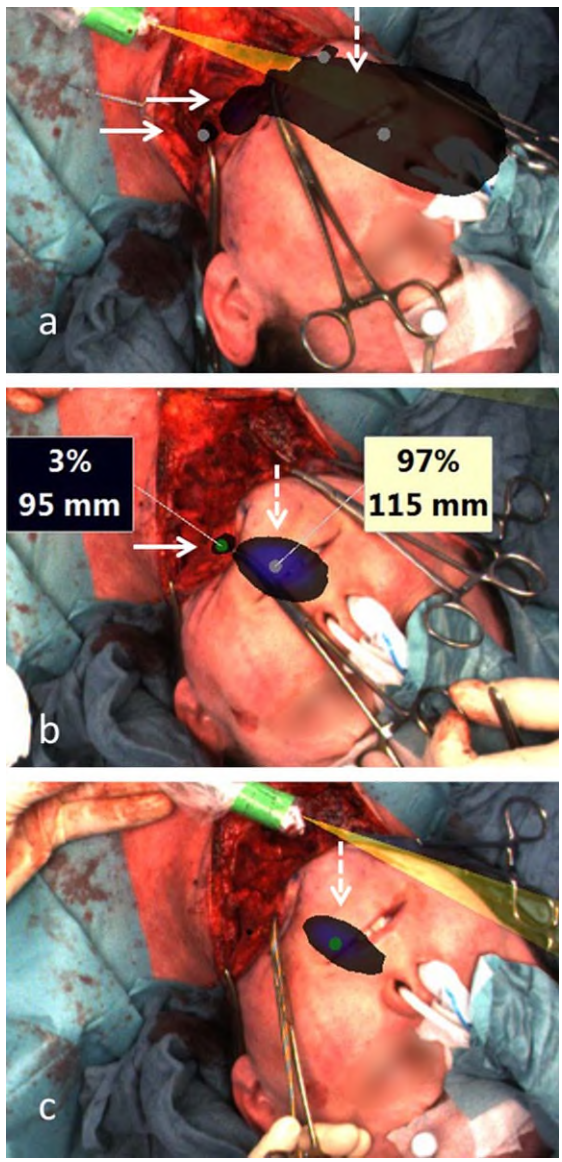

FIGURE 4. Three-dimensional images shown on the touch screen monitor during sentinel lymph node biopsy. (A) First scan demonstrating the injection site around the primary tumor (dotted arrow) and the level I and level III sentinel lymph nodes (arrows); (B) second scan after resection of the level III sentinel lymph node showing the remaining submandibular activity (arrow), the relative uptake of the sentinel lymph node (3%), and the distance of the hotspot from the gamma probe tip (95 mm) compared to the injection site (97%; 115 mm); and (C) postoperative scan demonstrating no remaining activity with the exception of the injection site (dotted arrow). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

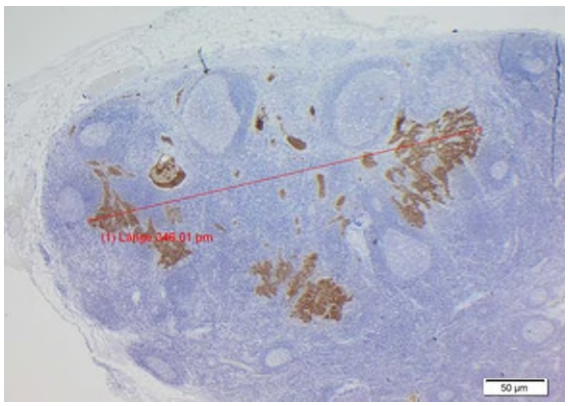

FIGURE 5. Immunocytochemistry demonstrating the lymph node metastasis with the diameter of 4 mm in the submandibular sentinel lymph node after being stained with anti-pan cytokeratin antibody AE1/3. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

nodes represents a more invasive method with a maximum sensitivity of 85%, depending on the clinicians' experience and is controversially discussed.[16] Hence, all of the available modalities lack sensitivity regarding the detection of lymph nodes metastases, especially small tumor deposits.

Because of the presence of occult lymph node metastases in cN0 patients, elective neck dissection of the cranial lymph node levels and histopathological processing of the resected nodes is the procedure of choice. However, no occult metastases are found during pathological analyses in up to 70% of patients, resulting in overtreatment in a considerable number of patients.[1] SLNB was evaluated in many feasibility trials over the past decades and showed similar sensitivity to elective neck dissection.[3,4,10] Similar recurrence rates compared to elective neck dissection were also described in observation trials.[17]

In addition to a detection rate>95%, an overall sensitivity of 90% to 95%, a negative predictive value of nearly 95%,[4,6,10] reduced morbidity, decreased costs, and a better quality of life compared to elective neck dissection have also been reported.[11] Furthermore, individual lymphatic drainage can be detected using this technique, which is observed in tumors in the anterior part of the mouth floor and the tongue.[18] However, severe pitfalls exist, including poor performance identifying true sentinel lymph nodes in floor of the mouth carcinomas. In such tumors, the sentinel lymph nodes may be masked because of radioactive scattering from the primary injection site, resulting in a reduction of the detection rate from 96% to 88% and a decrease of sensitivity from 97% to 80% and of negative predictive value from 98% to 88%, respectively.[3] These data were further confirmed in the multicenter ACOSOG-Z0360 validation trial.[4,6] Therefore, further research is advised.[3] A learning curve also affects the success of sentinel lymph node detection. Centers with less experience (<10 cases) had significantly lower sensitivity (57%) than well-trained centers (94%).[1,12]

Currently, 3 indications for SLNB are accepted for patients with clinical T1 or T2 oral and oropharyngeal SCC.[12] The first indication is the assessment of the ipsilateral cN0 neck in patients with unilateral cancer. Second, SLNB is recommended in patients with bilateral cN0 and a primary tumor in close proximity to or crossing the midline. In the latter case, the third indication is the staging of the contralateral cN0 neck with the ipsilateral cN+ neck, to decide if bilateral neck dissection is necessary. In our report, SLNB was used to assess the neck on both sides because of a tumor crossing the midline.

SLNB enables a more precise histopathological evaluation, including step-serial sectioning and immunohistochemistry because only a few lymph nodes need to be investigated. As a consequence, this technique also permits the detection of minimal tumor involvement, which would potentially be missed in the routine assessment of the lymph nodes dissected with elective neck dissection.[1] An upstaging in 34% of cases because of hematoxylin-eosin staining and additional pathological workup immunohistochemistry was observed.[3]

SLNB is a well-established concept in breast cancer and melanoma patients and was successfully adopted in patients with oral and oropharyngeal SCC. In 1996, the feasibility of SLNB in oral and oropharyngeal SCC was initially described.[12] Two common techniques are used to detect the first draining lymph node of the primary tumor by injecting dye or radioactive colloids, which is the preferred technique in oral and oropharyngeal SCC. Compared to breast cancer and melanoma, the technique is compromised by the high density of lymph nodes in head and neck carcinoma. Further obstacles originate from individual pathways and the close proximity of sentinel lymph nodes to the primary injection site.[19] Several studies have demonstrated the potential advantages of using additional SPECT/CT data. First, more sentinel lymph nodes were identified using combined anatomic (CT) and functional (SPECT) imaging. Second, even sentinel lymph nodes adjacent to the injection site can be detected precisely. Finally, artifacts, such as skin contamination, can be easily revealed on tomographic images.[19,20]

In the operating room, the identification rate in patients with sentinel lymph node*s* in close proximity to the primary tumor can be reduced. With the 1-dimensional acoustical information derived from a gamma probe, the surgeon is frequently unable to discriminate the sentinel lymph node from the injection site because of the shine-through phenomenon.[3] Several technical innovations have been brought to the operating room to improve localization by providing intraoperative imaging (eg, fluorescence imaging and mini gamma cameras).[21,22]

To date, fhSPECT represents the only technique that provides 3D images of the radioactivity distribution and real-time depth measurements even intraoperatively. This device was successfully evaluated in breast cancer and melanoma.[14,23,24] The authors demonstrated that this device achieved higher resolution than a 1-dimensional acoustical gamma probe because of scanning from different directions, and this device also enabled the visualization of low activity accumulations. Regarding oral SCC, only a proof of concept has been previously reported. In this short letter, Heuveling et al[25] only reported the feasibility of the use of fhSPECT in the complex head and neck area. They presumed a possible reduction of the

false-negative rate, but this hypothesis was not confirmed in the report because no metastases were observed and no additional elective neck dissection was performed.

In our case presentation, we not only confirmed the feasibility of fhSPECT for SLNB in oral SCC, but also demonstrated that this technique allowed for the detection of sentinel lymph nodes in the most challenging setting with close proximity to the injection site. Accordingly, the technique overcomes the limitation of the shine-through phenomenon in floor of the mouth tumors, resulting in the reduction of the false-negative rate.

This is important, especially in the present case, because only the submandibular sentinel lymph node contained a metastasis (pN1; 1/49) and determined final disease stage, patient management strategy, and prognosis. This encouraging patient example reinforces the need for prospective clinical trials establishing SLNB overtreatment by elective neck dissection in patients with oral SCC.

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