Intraoperative 3-D imaging improves sentinel lymph node biopsy in oral cancer

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Abstract
Purpose The aim of this study was to prospectively evaluate the feasibility and potential advantages of freehand single-photon emission computed tomography (fhSPECT) compared with conventional intraoperative localization techniques for sentinel lymph node biopsy (SLNB) in oral cancer.
Methods Between November 2012 and February 2014, 23 consecutive patients with clinical T1/T2 oral squamous cell carcinoma and a cN0 neck were recruited. All patients underwent SLNB followed by elective neck dissection (END). All patients received preoperative lymphoscintigraphy. To detect the SLNs intraoperatively, fhSPECT with a combination of conventional acoustic SLN localization and 3-D visual navigation was used.
Results All but one of the SLNs detected by preoperative imaging were successfully mapped intraoperatively by fhSPECT (detection rate 98 %), including those in six patients with a tumour in the floor of the mouth. A histopathology analysis revealed positive SLNs in 22 % of patients. No further metastases were found in LNs resected during END. SLNB correctly predicted the final LN stage in all patients (accuracy 100 %). Additional radioactive LNs, which were not present on preoperative lymphoscintigraphy, were observed in three patients.
Conclusion FhSPECT is a feasible technology that allows the accurate identification of SLNs in oral cancer. FhSPECT overcomes the shine-through phenomenon, one of the most important limitations of SLNB, thereby confirming the importance of SLNB in patients with cN0 oral cancer.

Keywords Sentinel lymph node biopsy · Freehand SPECT · fhSPECT · Oral cancer · Elective neck dissection · 3D

Introduction

The presence of cervical lymph node (LN) metastases in patients with oral and oropharyngeal squamous cell carcinoma (SCC) predicts a poor prognosis and reduced survival [1, 2]. Despite improvements in preoperative staging, the incidence of occult metastases in patients with a cN0 neck is approximately 25 % [3]. Therefore, the combination of stage-adjusted elective neck dissection (END) and histopathological LN assessment remains the gold standard treatment in many countries, resulting in overtreatment in approximately 75 % of patients [4].

As an alternative to primary END, sentinel LN biopsy (SLNB) using either ^{99m}Tc-colloids or blue dye has been proposed with the aim of reducing the invasiveness and morbidity of surgery [5]. In breast cancer and melanoma patients, SLNB constitutes the standard of care [6, 7]. Additionally, in oral and oropharyngeal SCC, the feasibility of SLNB has been evaluated in multicentre studies [8–12]. In addition, a meta-analysis has shown an overall sensitivity and negative predictive value of 94 and 96 %, respectively [13]. One major advantage of SLNB compared with END is that it reveals unexpected individual lymphatic drainage, such as that to the contralateral LNs [14]. However, due to the complexity of

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cervical lymphatic drainage, SLNB has its limitations, is reserved for experienced centres and remains controversial. Moreover, the SLNs, especially in SCC with tumours of the floor of the mouth (FOM), can be masked due to the close proximity of the injected radiocolloid and the first draining LN (shine-through phenomenon), which leads to inferior detection rates [10–12, 14]. Preoperatively, this limitation may be overcome by the use of single-photon computed tomography/CT (SPECT/CT), which provides higher detection rates and better morphological information [15, 16]. However, the advantages of SPECT/CT cannot be transferred to the operating room.

Intraoperatively, SLNs are usually detected using a handheld acoustic gamma probe. Promising results have been described for a portable two-dimensional mini gamma camera, which provides images comparable to planar scintigraphy [17] but does not allow dedicated depth measurement or navigation to the SLN. More recently, freehand SPECT (fhSPECT) was introduced for navigational surgery, combining the acoustic information of a conventional gamma probe and intraoperative 3-D images with real-time visualization of radiotracer distribution within the surgical field. FhSPECT measures the depth of the hotspot within the region of interest to permit navigated surgery. Encouraging results using fhSPECT have been reported for SLNB in patients with melanoma and breast cancer [18, 19]. The first positive results with the use of fhSPECT-guided SLNB in the head and neck (HN) region have been presented in case reports and a case series of five patients (including two with oropharyngeal carcinoma) [20–23].

Here we describe a large cohort of patients with oral SCC who underwent 3-D image-guided SLNB using fhSPECT, and discuss the feasibility, advantages and limitations of this system for SLN detection and its potential impact on SLNB in the HN region.

Methods

Study design

Between November 2012 and February 2014, 23 consecutive patients with a diagnosis of clinical T1/2 oral cancer and a cN0 neck were enrolled in this prospective single-centre study. The study was approved by the local ethics committee, and all patients signed written informed consent. LN metastases were excluded by palpation, ultrasonography, and either contrast-enhanced CT (1 patient), magnetic resonance imaging (MRI, 3 patients) or both MRI and [^{18}F]FDG PET/CT including a contrast-enhanced CT scan of the HN region (19 patients). The inclusion of patients was mainly based on the results of CT and/or MRI. All patients underwent lymphoscintigraphy, including planar scintigraphy and SPECT (1 patient) or SPECT/CT (22 patients), the day before surgery. The detected number of SLNs served as a reference for intraoperative localization. During surgery, SLNs were detected and subsequently dissected with the guidance of fhSPECT. To avoid unnecessary artefacts all five surgeons involved were trained in fhSPECT before the start of the prospective trial as they had never worked with fhSPECT before. The degree of experience in SLNB varied among the participating surgeons: two senior surgeons had experience of more than ten SLNB procedures, one surgeon had experience of fewer than ten SLNB procedures, and two younger surgeons had not performed any SLNB procedures before the start of this study. All patients underwent a preexcision scan after preparation and before SLN resection. The resection of radioactive LNs was confirmed by an additional scan (interim scan or postexcision scan). Successful SLNB was documented by a final postexcision scan and ex vivo measurement of the resected tissue. Due to current guidelines, after SLNB, END was performed in all patients, followed by tumour resection and microvascular reconstruction [24].

Lymphoscintigraphy

The day before surgery, 60.3±20.6 MBq (range 25–102 MBq) ^{99m}Tc-nanocolloid was injected peritumorally in four deposits from 0.05 up to 0.1 ml. Subsequently, a dynamic planar series was obtained over 13 min followed by static images (5 min each) in the anteroposterior and lateral–oblique views of the HN. After 1.5 to 2 h, static images and additional SPECT/CT of the HN region were acquired.

The camera systems used consisted of a dual-head camera and SymbiaT hybrid camera (Siemens, Erlangen, Germany) for SPECT/CT equipped with a high-resolution low-energy collimator (140 keV, 15 % window). For SPECT and low-dose CT, the following acquisition parameters were used: 128×128 matrix, 40 frames, 20 s/frame and CARE Dose modulation (Siemens), 130 kV, and B30s kernel. The images were interpreted using a printed version and a dedicated workstation (esoft; Siemens). LNs were defined as SLNs if a lymphatic channel to the node was detectable in the dynamic/early static images or if they appeared first at a cervical level. Nodes that appeared in later images at the same levels were resected as additional SLNs if tracer uptake of >10 % was detectable compared with previously resected nodes.

Freehand SPECT

For the intraoperative localization of SLNs, declipseSPECT (SurgicEye, Munich, Germany) including a gamma probe (Crystal Probe; Crystal Photonics, Berlin, Germany) with an opening angle of 40° and a sensitivity rate of 22,016 cps/MBq was used. The region of interest was scanned with the handheld gamma probe in three different directions. To obtain sufficient data during scanning, the patient target and probe

target for the tracking system were not allowed to be covered by anything, such as the arm of the scanning surgeon or surgical instruments. To achieve higher quality images with fewer artefacts and to improve the differentiation of the injection site and SLNs, optimal positioning of the patient had to be considered (e.g. raising the chin). Collected data were processed by fhSPECT, which enabled real-time visualization of the percentage distribution of the radiopharmaceutical at the tumour injection site and SLNs. Moreover, reconstructed images were fused with the real-time video of the surgical field, including anatomical structures, and presented on a touchscreen monitor. An additional depth measurement of the radioactive hotspots within the neck region enabled 3-D navigation to the tracer accumulations. Additional (technical) details describing the components of the system, the reconstruction algorithm and intraoperative setting in the HN region have been included in previous reports [21, 22, 25, 26]. Rigid fixation of the supplied patient target, including part of the optical tracking system, is crucial for proper fusion of the real-time video and reconstructed 3-D images to reveal the distribution of the radioactivity. In the present study, combining the fhSPECT system with components of another type of navigation hardware (Brainlab, Feldkirchen, Germany) provided rigid fixation on the patient's skull and thus smooth navigation.

Surgical procedure

Prior to incision, an optional scan was performed using fhSPECT (preincision scan). Then, the surgical procedure began with a MacFee skin incision to enable subsequent END after SLNB. All patients then underwent a 3-D scan to assess the number and location of SLNs (preexcision scan). The detected hotspots were compared with preoperative lymphoscintigraphy to determine the detection rate of fhSPECT. Using the information provided by fhSPECT, targeted navigation to the SLNs and subsequent dissection were performed. The combination of ex vivo measurement of the dissected tissue and a rescan (interim scan) of the affected region enabled successful removal of the SLN. If several SLNs were present, the procedure was repeated. The SLNB was finished with a final scan (postexcision) to demonstrate successful SLNB and to detect potentially remaining or additional radioactive nodes.

In all patients, END (level I–III) was subsequently performed. Of the 23 patients, 11 (48 %) underwent END on both sides of the neck, and in 5 (22 %), according to location of the primary tumour, the cranial portion of level V was resected. To determine the extent of the resection and determine appropriate microvascular reconstruction, the tumour was resected first, followed by SLNB, in three patients (13 %). In the remaining 20 patients (87 %), the primary tumour was resected after SLNB.

Histopathology

Resected SLNs or tissue samples obtained from neck dissection (ND) were fixed in 4 % neutral buffered formalin for 24 h. The number and size of nodes were assessed. Each LN was cut longitudinally through the hilum or longest pole-to-pole diameter into two or three parts (slices of thickness 2–3 mm), depending on the size of the LN, and processed en face. Initially, from each block, one section was routinely stained with H&E and evaluated for metastasis. If no metastasis was present in the SLNs, further serial sectioning as part of the sentinel protocol was performed. For this purpose, two consecutive slices were mounted every 150 μm throughout the entire block and numbered 1 and 2. All number 1 sections were stained with H&E and, if no metastasis was present, all number 2 sections underwent immunohistochemical staining with an anti-pan cytokeratin antibody (AE1/3). The largest dimension of metastatic infiltrate was reported (micrometastasis if ≤2 mm, or metastasis if >2 mm).

Results

The mean age of the patients was 58.7±13 years (range 30–86.2 years). Histopathological evaluation confirmed SCC in all patients: FOM in 6 patients (26 %), tongue in 11 (48 %), alveolar ridge in 2, cheek in 2, and palate in 2. Further more detailed information on the patients is presented in Table 1.

Histopathological evaluation

The mean number of SLNs was 3.1 (range 1–7). According to the histopathological work-up, metastases were present in 22 % of patients (5/23). The SLNs were located in levels I, II and IV. One patient showed an ipsilateral metastasis 4 mm in size (pN1), another patient showed two ipsilateral metastases up to 6 mm in size (pN2), and another patient showed two ipsilateral metastases 5 mm and 7 mm in size (pN2), which had been observed in the conventional histopathological work-up. Two patients showed micrometastases 1.5 mm in size (pN1 mi). One of these micrometastases was discovered only after an additional histopathological sentinel work-up including step serial sectioning with H&E staining and immunohistochemistry (Table 1). LNs resected by END showed no further metastases.

Lymphoscintigraphy

A total of 55 SLNs were found preoperatively in levels I–V and targeted for dissection, with at least one SLN per patient (mean 2.3±0.9, range 1–6). Contralateral lymphatic drainage was present in three patients (13 %), and two patients (9 %)

Table 1 Patient characteristics

Patient	Age (years)	Tumour location	SLNs[a]			Metastasis		Pathological staging
			Number	Side	Level	Diameter (mm)	Level	
1	49.4	Cheek	2	Left	I			T1N0(0/21), G2
2	68.0	Tongue	2	Right	I-II			T1N0(0/38), G2
3	62.0	FOM	3	Right	I-III			T1N0(0/27), G2
4	45.8	FOM	2	Left	I-II	4	I	T1N1(1/49), G2
5	86.2	Tongue	1	Right	II			T3N0(0/21), G3
6	79.3	Alveolar ridge	3	Left	I-III	1.5	I	T1N1(1/16), G2
7	61.8	FOM	1	Right	II			T1N0(0/22), G2
8	45.5	Tongue	4	Right	I-III			T2N0(0/29), G2
9	61.3	Palate	2	Right	II			T1N0(0/30), G2
10	58.1	FOM	3	Right	II			T1N0(0/9), G2
11	53.8	FOM	1	Right	I			T1N0(0/16), G2
			1	Left	II			
12	74.0	Tongue	2	Left	II-III	Both up to 6	II	T2N2b(2/32), G3
13	54.7	FOM	4	Left	II-III			T1N0(0/42), G2
			2	Right	II			
14	45.5	Tongue	1	Right	II			T1N0(0/23), G2
15	58.7	Tongue	2	Right	I-II			T1N0(0/42), G3
16	63.5	Alveolar ridge	2	Left	I			T1N0(0/14), G2
17	41.0	Tongue	3	Right	I-II, IV	1.5	I	T1N1(1/34), G2
18	73.5	Cheek	3	Left	I-II			T1N0(0/12), G1
19	58.5	Tongue	3	Left	II-III, V			T1N0(0/52), G2
20	64.9	Tongue	3	Right	II-III			T1N0(0/28), G2
21	64.1	Tongue	1	Right	III			T1N0(0/13), G2
22	50.6	Tongue	2	Left	II-IV	5, 7	II, IV	T2N2b(2/60), G2
23	40.0	Palate	1	Right	II			T1N0(0/45), G1
			1	Left	II			

SLN sentinel lymph node, *FOM* floor of the mouth

[a] On lymphoscintigraphy

also showed retroclavicular radioactive nodes, which were excluded from surgery. In the subgroup of patients (18/23, 78 %) receiving an optional intraoperative preincision fhSPECT scan, a total of 43 LNs were detected by lymphoscintigraphy.

FhSPECT scanning procedure

An optional preincision scan was performed in 78 % of patients (18/23) with a mean duration of 98±31 s (range 59–168 s). The routinely performed preexcision scan had a mean duration of 88±22 s (range 43–132 s). During surgery, one to three interim scans per patient were necessary, depending on the number of SLNs. In two patients, an interim scan between the resection of two different SLNs was waived. The mean duration of the interim scans was 80±18 s (range 57–129 s). In all patients, a final postexcision scan was performed with a mean duration of 71±14 s (range 45–93 s). The duration of each scan was dependent on the scanning time itself and the reconstruction, which was related to the extent of the scanned area and the amount of data collected. Overall (metal) artefacts on images were observed in 65 % of patients (15/23). An interim scan in three patients and the final postexcision scan in one patient had to be repeated due to artefacts. In two patients, the preexcision scan had to be repeated due to a lengthy preparation time and considerable movement of the cervical anatomical structures. The overall mean duration of the scans (preincision, preexcision, interim, postexcision, and re-scans) was 83±23 s (range 43–168 s).

SLNB and END

SLNB was performed within 21–23 h of preoperative lymphoscintigraphy. The node-based detection rate of the preincision scan was 77 % (33/43), whereas the preexcision scan correctly identified 98 % (42/43) of SLNs in this

subgroup of patients. The corresponding detection rate of the preexcision scan in the whole patient cohort was also 98 % (54/55). All except one of the preoperatively detected SLNs designated for dissection could be visualized with fhSPECT intraoperatively. In patient 17, one (level IV) out of three SLNs could not be detected. In this patient, only the SLN in level I demonstrated metastasis, and no further metastases were revealed during ND (levels I–III and IV–V). Therefore, the overall patient-based sensitivity of SLNB for the prediction of pN+ status was 100 %, and the negative predictive value was 100 %, using final ND-based node status as the gold standard. In one patient, an SLN in level V was not resected due to difficult surgical access and a high risk of comorbidity.

In seven patients (30 %), SLNs were located in a challenging area because of their close proximity to the injection site, although all of these SLNs could be detected using the combination of acoustic information, visualization and navigation with fhSPECT (Fig.1). In six of these seven patients (86 %) only the visualization and navigation provided by fhSPECT allowed the location of the SLNs to be determined. Additionally, SLNs in close proximity to each other could be reliably detected in five patients (22 %). In three patients, unexpected residual activity was detected after SLN dissection in a subsequent scan (Fig. 2). Despite a lower count rate compared with the first resected node, the hotspot was resected and identified as a further radioactive node (additional node) .

In subsequently performed END, 25.4±13.2 LNs (range 5–57) per patient were additionally resected. The overall average surgery time, including microvascular reconstruction, was 6.1±0.1 h (range 1.6–11.6 h). In two SLN-positive patients, caudal ND (level IV-V) was performed, including 19 and 22 LNs without further metastasis. In the other three SLN-positive patients, subsequent radiotherapy or radiochemotherapy was performed.

Discussion

Despite significant improvements in the imaging of oral and oropharyngeal SCC, histopathological assessment of locoregional LNs in cN0 necks is needed due to the presence of occult metastases in up to 25 % of patients [3]. Despite extensive preoperative diagnostic tests (e.g. [^{18}F]FDG PET/CT), we have also observed a rate of clinically occult metastases of 22 %.

Promising results of SLNB as an alternative to END have been reported [8, 10–13, 27]. However, SLNB is often reserved for experienced centres and is not universally established in everyday clinical use because of limitations due to the complexity of the cervical anatomical structures. In this prospective study, we demonstrated the feasibility and high sensitivity of fhSPECT-guided SLNB in 23 patients with oral SCC and a cN0 neck. Our findings suggest that using the additional intraoperative visualization and 3-D navigation provided by fhSPECT might overcome the shine-through phenomenon, which is one of the most important limitations in FOM tumours. FhSPECT-guided SLNB in oral and oropharyngeal SCC may also improve the selection of patients for ND, which is associated with higher morbidity rates than SLNB [5]. The node-based detection rate of fhSPECT was 98 % compared with preoperative lymphoscintigraphy. In agreement with the findings of previous studies [10, 17], 2.3 SLNs per patient were found, and contralateral lymphatic drainage was detected in three patients.

As many as seven scans per patient, including re-scans, were performed, depending on the number of SLNs present. The time per scan, with a mean duration of 83 s, was negligible, considering the average overall duration of surgery of 6.1 h. As previously reported in breast cancer and melanoma [18, 19], additional radioactive LNs with low activity, which therefore appeared scattered on preoperative lymphoscintigraphy, were detected (Fig. 2). All metastatic LNs were found among the SLNs, resulting in a sensitivity of 100 % and negative predictive value of 100 %. One reason why SLNB is not universally established as a routine application may be its reduced sensitivity rate (57 %) when used in less-experienced centres (fewer than cases) compared with fully experienced centres (94 %) [4, 14]. However, using fhSPECT, this issue may be overcome and the variability in experience compensated for. We found that 3-D navigation and visualization directed the surgeon more intuitively.

As one of the most important limitations of SLNB, a significant and clinically relevant reduced detection rate (88 %) and sensitivity (80 %) have been observed in FOM tumours compared with other locations of primary cancer (96 % and 97 %), an outcome that is caused by the close proximity of the injection site and radioactive nodes [12]. However, such limitations may be mainly attributed to the use of conventional, acoustic gamma probes. With fhSPECT, the localization of SLNs in all six FOM tumours was possible. In 30 % of patients (7/23), SLNs in close proximity to the injection site could be reliably detected. Importantly, in six of these seven patients (86 %) localization was only possible due to the additional visualization and navigation provided by fhSPECT. Moreover, fhSPECT enabled scanning of dedicated regions of interest, and as a result, scattering artefacts due to the injection site could be excluded. We also suggest not scanning the entire cervical region but rather scanning the cranial, caudal, and contralateral levels separately. In particular, our results suggest that the shine-through phenomenon, which is one of the most important limitations of SLNB in the HN region, might be overcome using fhSPECT. In this challenging setting, a combination of fhSPECT tools was used, specifically acoustic information and real-time visualization, including fused 3-D images and depth measurements.

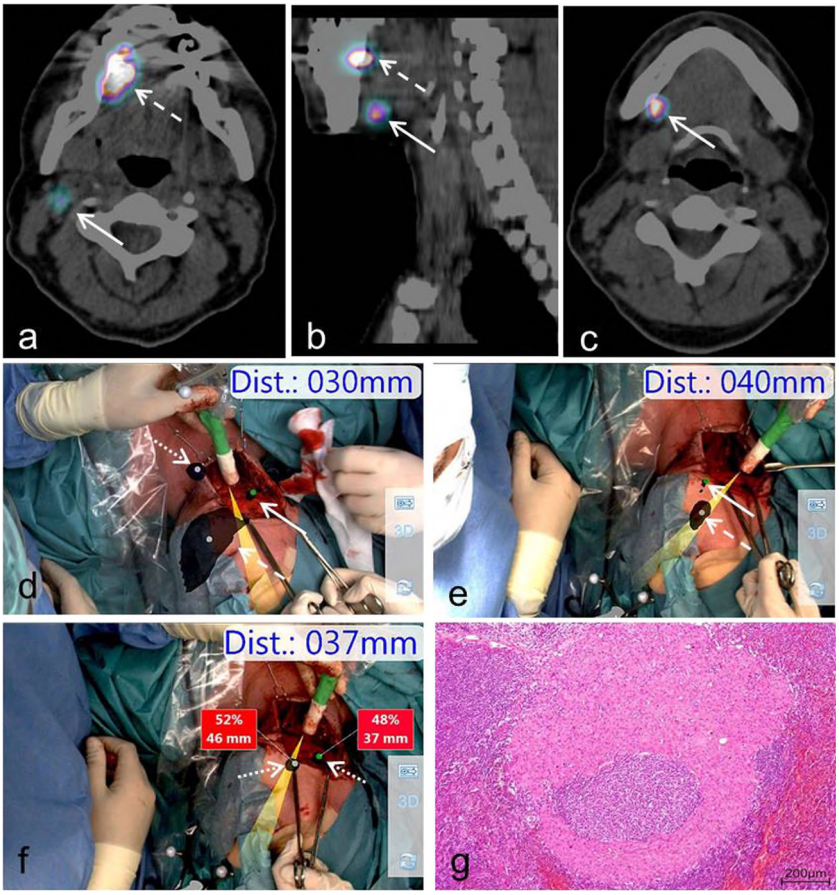

Fig. 1 Preoperative scintigraphy and corresponding intraoperative fhSPECT images. **a**–**c** Preoperative scintigraphy (SPECT/CT) images show two SLNs (*arrows*) and the injection site (*dashed arrows*). **d** Preoperative fhSPECT scan including the injection site (*dashed arrow*) and a SLN in level II (*arrow*) and a metal artefact (*dotted arrow*). **e** Interim fhSPECT scan after dissection of the SLN in level II, showing the injection site (*dashed arrow*) and submandibular SLN (*arrow*). **f** Postexcision fhSPECT scan without any residual activity. Only uncommon high uptake due to metal artefacts (*dotted arrows*) is present; navigating to these "hotspots" no activity (counts) could be measured and therefore the artefacts were confirmed. **g** Metastasis in the submandibular SLN

Additionally, reliable identification of SLNs located in close proximity on preoperative lymphoscintigraphy was achieved in 22 % of patients.

Using fhSPECT, SLNB may also be performed more rapidly and thus become a more attractive alternative to END. Indeed, Govers et al. performed a cost-effectiveness study in 2013 and found that SLNB followed by ND or watchful waiting appears to be the most cost-effective strategy [28]. In particular, a preexcision scan before starting SLNB and a postexcision scan at the end of SLNB should be performed to compare the results and confirm the successful resection of all SLNs or detect remaining additional radioactive LNs. Time can also be saved by waiving interim scans and resecting more than one SLN between two scans, an approach that was implemented in two patients in this study. The preincision scan (prior to skin incision) facilitates orientation in relation to the location of SLNs, making it possible to plan the approach. The information obtained from this preincision scan is

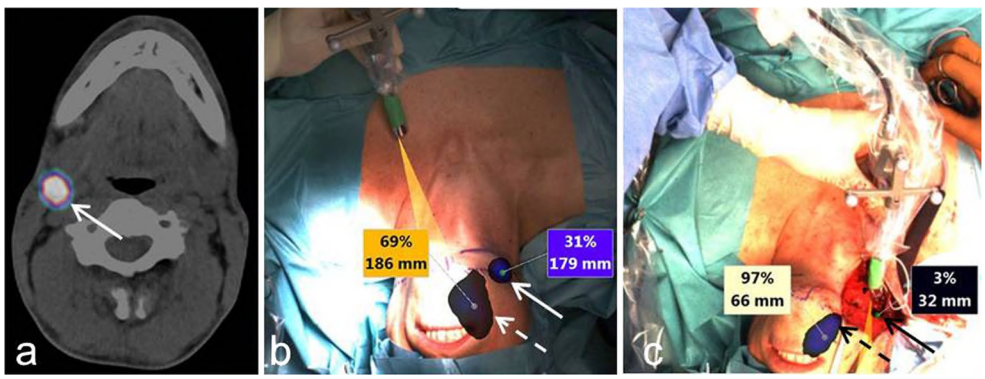

Fig. 2 Additional radioactive node. **a** Preoperative scintigraphy (SPECT/CT) image shows a SLN dorsal to the glandula submandibularis on the right side. **b** Preincision scan with the injection site (*dashed arrow*) and a SLN in level II (*arrow*). The boxes show the percentage distribution of radioactivity in the scanned region. **c** Scan after SLN dissection showing the remaining activity. The radioactive tissue was also resected. The histological work-up revealed a LN without metastasis

particularly important for planning the surgical approach if the radiopharmaceutical is injected intraoperatively and thus no preoperative SPECT/CT images are available. However, further prospective multicentre trials are necessary to address this approach especially because of the low percutaneous detection rate seen in the present study. In the present study, a standard surgical approach was necessary because of subsequent END; therefore, the preincision scan was negligible in 22 % of patients. In summary, we conclude that at least a preexcision scan and a postexcision scan are mandatory, with an optional interim scan.

One limitation of fhSPECT is that the patient cannot be moved during or after the scanning process if scanning artefacts and projecting the distribution of radioactivity on incorrect anatomical structures in the real-time video are to be avoided. If the patient is moved, navigation is impossible, and the scanning process must be repeated (interim scan). Despite our awareness of this limitation, a re-scan was necessary in two patients in this study. An additional limitation is caused by artefacts, a nonconforming hotspot on the reconstructed images, due to metal surgical instruments within the scanned area. However, the 3-D navigation tool enables differentiation between real accumulation of the radiopharmaceutical and these artefacts. In comparison to the injection site and true SLN, these artificial hotspots showed uncommonly high values of percentage uptake, which further simplifies differentiation (Fig. 1f). After navigating to the artificial hotspot, no activity was measured, and it was therefore possible to identify this site as an artefact. Nevertheless, in four patients, a re-scan had to be performed because many artefacts were observed and differentiation using the navigation tool would have been far too time-consuming.

Compared with END, one advantage of SLNB is the possibility for a more detailed work-up, including step serial sectioning and immunohistochemistry, because only a few LNs need to be investigated [10]. In our cohort, the tissue resected during SLNB contained an average of 3.1 SLNs (range 1–7). Upstaging due to sentinel node protocols has been reported previously [8]. In the present study, a micrometastasis was revealed in one of five patients as a result of the dedicated sentinel protocol. In 2013, Broglie et al. also found reduced overall survival rates and disease-specific survival in these patients [1].

One limitation of this study was that only 23 patients with oral SCC were included. Thus, the negative predictive value and sensitivity of 3-D image-guided SLNB using fhSPECT in the HN region should be assessed in a prospective, multicentre trial including other primary tumour locations in the HN region. However, this study cohort is the largest patient group receiving fhSPECT-guided SLNB to date. Furthermore, the most frequently discussed limitation of SLNB, i.e. the reduced detection rate and shine-through phenomenon in oral cancer, especially FOM tumours, was addressed in the present study. A limitation of the study design was that ideally an additional scan with only the conventional acoustic gamma probe should have been performed separate from fhSPECT by a second independent surgeon. However, due to time constraints and clinical demands this was impossible. Moreover, no dedicated depth measurements of the SLNs were performed. Both aspects should be addressed in further prospective (multicentre) trials. A further limitation of this prospective trial may have been that END served as the gold standard. LNs resected via END could not be worked up with a dedicated sentinel protocol because step serial sectioning and immunohistochemical staining of 25.4 LNs per patient would have been too time-consuming and costly; as a result, isolated tumour cells or micrometastases could have been missed.

In summary, considering that up to 75 % of patients are overtreated with END and may suffer from the associated risks and reduced quality of life, SLNB is an alternative approach that allows a more extensive histopathological work-up of fewer LNs. The fhSPECT scanning procedure is simple to perform, is fast, and enables less experienced surgeons to navigate more intuitively during SLNB. Indeed, the present study suggests that fhSPECT overcomes important limitations of SLNB in the HN region. FhSPECT-guided SLNB confirms the importance of SLNB and may be practice-changing in cN0 patients. Moreover, the combination of fhSPECT-navigated surgery with new radiopharmaceuticals (^{99m}Tc-tilmanocept) or fluorescence tracers [29, 30] may further strengthen the relevance of SLNB in HN tumours, and SLNB may become the overall standard of care in cN0 patients.

However, further multicentre studies including larger patient cohorts and other tumour locations in the HN region are necessary to confirm our promising results.

Conclusion

To the best of our knowledge, this is the largest patient cohort with oral SCC in which SLNB was performed using fhSPECT, and the results demonstrated an impressive detection rate of 98 % and a sensitivity and negative predictive value of 100 %. In the present study, fhSPECT also achieved reliable detection rates in FOM tumours and SLNs located in close proximity, which overcomes the main limitation of conventional SLNB. If these promising results can be confirmed in larger patient cohorts that include other tumour locations in the HN region, SLNB may become the overall standard of care in cN0 patients.

Disclosure A.K.B. and K.H. are cofounders and shareholders of SurgicEye GmbH, Munich, Germany.

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