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Sentinel node biopsy in early oral squamous cell carcinoma - a safe diagnostic and therapeutic procedure

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Abstract

Sentinel node biopsy (SNB) is considered the standard surgical procedure for detecting occult neck node metastasis in oral squamous cell carcinoma (OSCC) in many centers around the world. Due to the fact that this method removes and evaluates the first lymph node(s) reached by the lymphatic flow from the tumor area, this has raised the question of whether SNB could also be considered a therapeutic procedure by targeted lymphadenectomy instead of elective neck dissection (END). Compared to END, its safety and low morbidity have been established. However, the surgical management of the clinical node-negative (cN0) neck in T1/T2 oral carcinoma has been under ongoing debate due to the lack of randomized studies comparing SNB to END in terms of overall survival (OS), disease-free survival (DFS) and neck recurrence rates (NRRs). In the last years, two prospective randomized studies have proven with high-level evidence the noninferiority of SNB compared to END in terms of oncologic outcome while reducing costs and morbidity. In our opinion, SNB should be offered as the new standard therapeutic procedure in early OSCC.

Keywords: Sentinel node biopsy, oral carcinoma, head and neck, micrometastasis

INTRODUCTION

SNB in clinically node-negative T1/T2 OSCC has been in use for over two decades and is accepted as a standard procedure for staging the cN0 neck. This is due to its high sensitivity for detecting occult metastases by tracing the complex lymphatic drainage of OSCC, even in the pretreated neck. The sensitivity of detecting micro-metastases seems to be superior to END, in which rates of missed micro-metastases and isolated tumor cells (ITC) by routine histological workup have been reported as being between 9 and 16%[1]. The safety of SNB as an oncological procedure and its superiority in terms of morbidity[2] and cost-efficacy[3,4] compared to END have been shown. However, there have been concerns about recommending SNB as the standard procedure for the cN0 neck. Firstly, up until two years ago, there was a lack of prospective and randomized controlled studies comparing SNB to END in terms of overall survival (OS), disease-free survival (DFS), and neck recurrence rates (NRRs). Secondly, the applicability of the SNB procedure for tumors of the floor of mouth (FOM) has been challenged due to the shine-through effect, when the radiation flare of the primary tumor overshines the hotspot of the sentinel node close to the injection side. Thirdly, it remained unclear if patients with a positive sentinel node needing subsequent completion neck dissection (CND) have a disadvantage compared to patients initially treated with END. In recent years, two prospective trials have independently demonstrated the noninferiority of SNB in terms of OS, DFS, and NRR compared to END, with the advantages of higher detection rates of occult metastases and reduced morbidity and cost[5,6]. There is even some evidence that a wait-and-scan strategy in isolated tumor cells (ITC) of positive sentinel nodes (SN) is non-inferior to CND in terms of OS and DFS[5]. The purpose of this narrative review is to give an update on the literature with the recommendation to reinforce the use of SNB as the standard diagnostic procedure for the staging of the cN0 neck in early-stage OSCC, and therapeutic procedure in case of tumor-negative sentinel nodes. In the case of positive sentinel nodes, CND is indicated as a therapeutic procedure in all cases according to current literature and guidelines.

STAGING AND RISK STRATIFICATION OF THE N0 NECK

Occult metastases in the cN0 neck of T1/T2 OSCC are reported to be present in 20%-30% of cases[7,8]. They remain undetectable even by current staging methods such as computed tomography (CT), magnetic resonance imaging (MRI), fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT), and ultrasonography (US) with US-guided fine-needle-aspiration cytology (USgFNAC)[9]. In particular, US in combination with USgFNAC seems to be the method with the highest accuracy in detecting nodal metastases in head and neck squamous cell carinomas[10]. It has a reported sensitivity of up to 73% and a specificity approaching 100%, but these rates were not reproduced in larger clinical settings[11]. This may be due to the fact that USgFNAC is dependent on the experience and skills of the ultrasonographer and cytopathologist. Assessing the diagnostic accuracy of FDG-PET/CT, a recent meta-analysis of 18 studies by Kim *et al*. showed a pooled sensitivity of 58% and a pooled specificity of 87% in detecting lymph node metastases in the cN0 neck[12]. The pooled positive predictive value was 62% and the pooled negative predictive value was 83%. Because of this reported low sensitivity and moderate specificity, FDG-PET/CT is not indicated to assess the nodal status in early oral carcinoma. In summary, none of the currently available imaging techniques are able to detect small or microscopic subclinical metastases.

Nodal involvement significantly decreases survival[11,13]. Therefore, END has widely been used as an elective treatment with the intention of eradicating subclinical tumor deposits. In terms of staging the neck with END, the following disadvantages of END need to be highlighted: Taking into account that midline tumors drain bilaterally in around 60% of cases and > 10% of lateralized tumors drain to the contralateral neck[14], the morbidity doubles with bilateral END in the case of midline tumors. Contralateral neck metastases will be missed when performing an ipsilateral END in lateralized tumors. Even in the ipsilateral neck, occult metastases can be missed by selective dissection. In the oral cavity, carcinomas, END includes levels I-III, although Crean *et al.* have shown in a cohort of 55 patients that 10% of occult metastases occur in Level

IV[15]. END is not perfect for eliminating occult disease. Even with this extended procedure, the rate of missed micro-metastases in the routine histological workup of an END can be up to 16% and even higher in tongue carcinoma[1].

In the case of a pretreated neck, aberrant lymphatic drainage is even more prominent due to the disruption of lymphatic channels. In a multicenter prospective observational trial by Flach *et al.*, pretreated patients with a history of surgery or radiotherapy in the neck underwent SNB[16]. With a sentinel node detection rate of 100%, 67% of patients had unexpected lymphatic drainage patterns. Besides this high detection rate, regional tumor control was shown to be excellent (100%).

Many attempts have been made to predict the risk of nodal involvement in OSCC. Along with peri-neural invasion and grade of differentiation, depth of invasion (DOI) is the most evidence-based pathological predictive factor for nodal metastases[17] and is an independent predictor of OS and disease-specific survival (DSS)[18]. DOI has been incorporated in the AJCC 8th edition of the TNM classification because of the associated risk of metastasis. A common cut-off for elective treatment of the neck is a DOI of more than 4 mm, although in recent publications, this parameter has been questioned and no clinically useful cut-off values have been independently identified to accurately predict the patient's nodal status[17,19,20].

Another field of research to predict occult nodal involvement in cN0 neck are molecular markers associated with gene signatures. Due to the complexity of the metastatic process, analysis of multiple biomarkers in order to detect expression patterns are more promising than the search for one single marker. For example, a Dutch multicenter validation study of gene expression profiles[21] showed a negative predictive value of 89% in early OSCC, but its use in clinical practice has not yet been tested in a prospective study.

Multiple studies have proven that SNB is an effective surgical diagnostic procedure for detecting micro-metastasis and a safe oncological procedure with low morbidity. In the large Sentinel European Node Trial (SENT) by Schilling *et al.*, 94 patients out of a cohort of 415 patients showed a positive SN and 15 patients were recorded as a false-negative biopsy[14]. This makes a total of 109 out of 415 patients (26.3%) with occult metastasis. 369 primary tumors were positioned laterally, and of these, 10.8% (40/369) drained bilaterally and 2.4% (9/369) exclusively to the contralateral neck. Thus, 13.3% (49/369) of occult cervical metastasis would have been missed by conventional treatment of ipsilateral neck dissection. A meta-analysis by Liu *et al.* in 2017 with the inclusion of 66 studies and 3,566 patients, showed a pooled sentinel node identification rate of 96.3% with a pooled sensitivity of 87% and a pooled NPV of 94%[22]. Another meta-analysis by Yang *et al.* with the inclusion of 35 studies and 1,084 patients revealed a pooled overall sensitivity and NPV of SNB of 92% and 96%, respectively[23].

In conclusion, rather than trying to predict the patient's nodal status, SNB can determine the presence or absence of nodal metastasis in each individual and is the most sensitive and reliable diagnostic procedure for staging the cN0 neck in the complex lymphatic drainage in tumors of the oral cavity.

THE DILEMMA OF TREATING THE N0 NECK

SNB is the most accurate diagnostic procedure for staging the cN0 neck and is now incorporated in many national guidelines including those from The Netherlands, United Kingdom (NICE), and USA (NCCN). For many years, two main strategies have been carried out all over the world, depending on the presumed risk of subclinical nodal involvement: END and a wait-and-scan strategy. Weiss *et al.* stated in 1994 that END should be performed if the risk of nodal metastasis exceeds 20%[24]. This recommendation was based on a computer model executing sensitivity analysis on the variable of the probability of occult metastasis, extracted from the current literature and ratings for outcome by physicians. Since this time, imaging technologies have improved diagnostic accuracy, histopathological risk factors (e.g., DOI) for nodal spread have been identified and molecular markers have been investigated to predict nodal metastasis. Furthermore, radical neck dissection has widely been replaced by selective ND[25] with significantly lower morbidity, especially for shoulder function[26]. Many investigations have been undertaken to establish reliable models for choosing optimal management strategies taking into account probability of subclinical nodal metastasis, probability of complete removal of subclinical metastases by END, negative impact on quality of life by END, recurrence after END, successful salvage rate, survival and quality of life. The conclusion drawn from these observations is to recommend that early OSCC should undergo END. The complex constellations of these factors and different applications of preoperative staging methods and follow-up strategies account for the variations of clinical practice in different centers around the world. This makes comparison between management strategies difficult, as elaborated in detail in the review by De Bree *et al*.[11]

In a large single-center randomized landmark trial from 2015, D'Cruz *et al*. evaluated OS and DFS in a cohort of 500 prospectively randomized patients with stage T1 or T2 OSCC undergoing either END or watchful waiting followed by neck dissection for nodal relapse[17]. In a 3-year follow-up period, the elective node group showed a significantly improved rate of OS (80%) and DFS (69.5%) in comparison to the therapeutic-surgery group (67.5% and 45.9%, respectively). This trial showed convincingly that END should be favored over watchful waiting in patients with early OSCC. A newer meta-analysis of prospective studies by Ding *et al*. from 2018 confirmed these findings, especially for tumors of the tongue and the FOM[27]. Given that occult metastases in the cN0 neck of T1/T2 OSCC are around 30%, this means that about 70% of patients undergo an unnecessary neck dissection with associated morbidity and cost. In midline tumors, the morbidity doubles, and taking the results from the SENT-Trial that 12% of the lymphatic drainage was contralateral, 6% of patients with a positive contralateral SN would have been missed by conventional treatment of ipsilateral neck dissection. Considering recurrence rates after END, in the series of Gainly *et al*., the recurrence rate was 18%, whereas 39% of recurrences occurred in the contralateral neck[28]. This is a further disadvantage of ipsilateral END in cN0 necks. The dilemma of managing the cN0 neck has driven the search for equivalent alternative management strategies such as SNB.

EVIDENCE FOR SNB IN THE CN0 NECK

As already shown, SNB showed a higher sensitivity and NPV than END with the advantage of reduced morbidity and cost. In terms of long-term neck control rate including salvage surgery with a follow-up period of 5 years, Swiss data from Broglie *et al*. showed a neck control rate of 96% in SN-negative and 80% in SN-positive patients[29]. All SN-positive patients underwent CND. Until a few years ago, there was a lack of high-level evidence demonstrating the equivalence or noninferiority of SNB in neck node management for T1-T2N0 OSCC compared to END. A meta-analysis by Crocetta *et al*. from 2020 assessing exactly this question was not able to include any randomized studies and evaluated 9 observational studies[30]. Pooled risk ratios showed no difference in DSS, OS and NRR; however, the limited number of included studies with limited sample size and comparability issues due to low methodological quality led the authors to conclude that the evidence level was too low to make it useful for clinical decision making.

In 2020, the Senti-MERORL trial was published by Garrel *et al*. from France, data from 307 patients randomly assigned to an SNB and an END group were assessed for neck-node recurrence-free survival (RFS), DSS, and OS[5]. In both groups, patients showed the same rate of neck failure (approximately 10% in the two arms). Neck node RFS was equivalent in both groups at 2 years (89.6% in the SNB arm and 90.7% in the END arm, respectively) and the 5-year RFS and the 2- and 5-year DSS and OS were not significantly different between the two arms. The functional outcomes were significantly worse in the END group at 6 months after surgery. Only 29.3% of patients in the SNB group had to undergo CND and the authors declared this as the main advantage of the SNB technique. It has to be noted that intraoperative histopathologic analysis of SN was performed by imprint cytology or frozen section examination. In case of a positive SN, CND was performed. If SN positivity was detected only after the initial surgery by serial sectioning and immune-histochemical analysis[31], CND was performed during a second surgical procedure. An interesting aspect of this trial is that neck node recurrence and loco-regional recurrence rates were not different in the 11 patients with ITCs compared with the SN-negative group. This finding suggests that the ITC status does not seem to require CND. Garrel *et al*. concluded that all these advantages establish the SNB strategy as the reference technique[5].

In 2021, Hasegawa *et al*. assessed in a multicenter, randomized trial with the same question as Garrel *et al*. with slightly different endpoints[5,6]. They investigated whether there was a difference in survival between patients treated with END or SNB in T1-T2 N0 OSCC with a follow-up period of 3 years. Intraoperative multi-slice frozen section analysis was performed and ITCs were treated as metastasis-positive. The SN Group (137 patients) showed noninferiority with a 12% margin compared to the END group (134 patients) in terms of 3-year OS (87.9% *vs*. 86.6%) and DFS (78.7% *vs*. 81.3%). The shoulder morbidity was significantly higher in the END than in the SNB group. Interestingly, to enhance the clinical utility of SNB, a DOI ≥ 4 mm has been chosen as an exclusion criterion for T1 carcinomas. Furthermore, the authors mention that step-serial sections may be more accurate but are not feasible during surgery. Concerning ITC, the authors highlight that further study is needed to confirm whether CND is required or SNB may be sufficient. In summary, the study proved that SNB was non-inferior and less invasive than END and SNB was suggested as the standard procedure. The clinical results of the studies by Garrel *et al*. and Hasegawa *et al*. are summarized in Table 1[5,6].

A recent meta-analysis from Gupta *et al.* integrated the two trials from Garrel and Hasegawa and an Indian trial from Sundaram *et al*., comparing SNB with END in the management of N0 neck in early-stage oral and/or oropharyngeal squamous cell carcinoma (OOSCC)[32,33]. The study included 608 patients from three prospective randomized trials and found that SLNB was oncologically non-inferior to END, with similar rates of OS, isolated neck nodal recurrence, and loco-regional recurrence. However, SNB was associated with lower functional morbidity, as indicated by a pooled analysis of neck-shoulder function.

In a recent position paper from the European Association for Cranio-Maxillofacial Surgery (EACMS), Vassiliou *et al.* highlight the importance of the accurate staging of the neck in early OSCC to deliver appropriate treatment for loco-regional control of the disease and for prognosis[34]. The paper raises concerns about the safety of SNB in those patients who prove to be harboring occult metastatic disease, potentially delaying the delivery of adjuvant treatment. In response to this concern, McMahon *et al*. tested the hypothesis that patients undergoing SNB for early OSCC who harbor occult metastases may be at greater risk of mortality due to prolonged overall treatment times compared to those identified as pN-positive on END[35]. The trial found no difference in DSS or OS between the groups, indicating that patients undergoing SNB as the initial neck staging modality in early OSCC and are identified as pN-positive do not appear to be at a survival disadvantage compared with those staged with END. Table 2 summarizes clinical results from different trials supporting SNB as standard procedure in cN0 neck over END.

REQUIREMENTS FOR SUCCESSFUL SNB

The advantages of SNB can only be realized if the method is carried out correctly and certainfactors are considered. In 2019, Schilling *et al.* published a consensus guideline[36] with 16 up-to-date pragmatic

Table 1. Clinical results of the main two randomized prospective trials using ipsilateral ND compared with SNB in cN0 T1 or T2 OSCC

Refs.	Patients	Mean follow-up period	2-years follow-up	Statistical significance	Neck functionality
Garrel *et al*.[5]					
ND group	139	3.1 years	RFS: 89.6% (95%CI: 0.83%-0.94%)	Equivalence with $P < 0.01$	Significantly worse until 6 months
SNB group	140		RFS: 90.7% (95%CI: 0.84%-0.95%)		Better
			3-years follow-up		
Hasegawa *et al*.[6]					
ND group	137	4.95 years	OS: 87.9% (lower limit of one-sided 95%CI, 82.4), DFS: 78.7% (lower limit 95%CI, 72.1)	*P* for noninferiority < 0.001	Worse
SNB group	134	4.74 years	OS: 86.6% (lower limit 95%CI, 80.9), DFS: 81.3% (lower limit 95%CI, 75.0)		Significantly better

OSCC: Oral squamous cell carcinoma; ND: neck dissection; SNB: sentinel lymph node biopsy; RFS: neck node recurrence-free survival; OS: overall survival; DFS: disease-free survival; CI: confidence interval.

recommendations based on current evidence and expert opinion brought together at the eighth international symposium for SNB in head and neck cancer that was held in London in 2018. Based upon these recommendations, a number of points are summarized in the current study, which in the view of the authors, are particularly pertinent to making SNB a successful treatment option [Table 3].

(1) Preoperative staging should always include imaging of the neck with the use of MRI, CT or US or a combination of these modalities. US can be combined with FNAC in case of enlarged or abnormal cervical nodes and reaches high sensitivity and specificity as stated previously[37,38].

(2) It is recommended that the primary tumor can be reliably excised with clear margins and the defect repaired locally without requiring access to the neck. This may be difficult in some cT2 tumors of the floor of mouth (FOM), gingiva, buccal mucosa, retro-molar region, and palate without requiring free flap reconstruction of the defect.

(3) SNB should always be undertaken with a radiotracer and not with an optical tracer alone. The radiotracer of choice is technetium-99m (99mTc); however, an optical tracer can be added in order to increase intraoperative detection rates. The standard routine SNB procedure consists of preoperative peri-lesional injections of 99mTc-labeled radiotracers followed by dynamic lymphoscintigraphy using planar and single photon emission tomographic/computed tomographic (SPECT/CT) imaging. Intraoperatively, the SNs are identified by radionuclide detection with a handheld gamma probe. Additional optical tracers can be injected at the tumor site in order to have visual confirmation of SN detection. Blue dye is an optical tracer in widespread use for many years, but there are a few disadvantages such as the short wash-out time, staining the injection side (with the risk of impeding identification of the tumor margins), and a reported 1% risk of allergic reactions[39]. Moreover, it is questionable if blue dye adds any significant value to the SNB procedure[40]. Alternative optical tracers such as Indocyanine green (ICG) in combination with a near-infrared (NIR) camera to visualize the fluorescent dye during surgery have been developed and tested in recent years. ICG can be administered shortly before surgery or even combined with 99mTc-Nanocoll forming a multimodal tracer (ICG-99mTc-Nanocoll)[41]. Christensen *et al.* showed in 30 OSCC patients using the hybrid tracer that 12% of SN could only be identified by NIR, while the majority of those were located in level I close to the primary tumor[42]. The novel radiolabeled tracer ^{99m}Tc-Tilmanocept was

Table 2. Clinical results supporting SNB as standard procedure in cN0 neck over END

Study	Design	Patients	Follow-up	Endpoints	Results
Hasegawa *et al.*[6]	Multicenter, randomized controlled trial	SNB arm: *N* = 134; END arm: *N* = 137	3 years	OS, DFS	Noninferiority shown with SNB compared to END in terms of 3-years OS (87.9% *vs.* 86.6%) and DFS (78.7% *vs.* 81.3%); shoulder morbidity significantly higher in END group; ITCs treated as metastasis-positive
Garrel *et al.*[5]	Randomized controlled trial	SNB arm: *N* = 140; END arm: *N* = 139	5 years	Neck-node RFS, DSS, OS	Neck-node RFS equivalent in both arms at 2 years (89.6% in END arm and 90.7% in SNB arm); functional outcomes significantly worse in END group until 6 months after surgery; 29.3% of patients in SNB group underwent CND; no difference in neck node recurrence rate and locoregional recurrence rate found in patients with ITCs compared to SN-negative group
Sundaram *et al.*[33]	Randomized controlled trial	*N* = 58	1 year	effectiveness nodal metastases identification SNB *vs.* END	similar rate of neck nodal relapse in both arms
Schilling *et al.*[14]	Prospective cohort study	*N* = 415	3 years	Sentinel node identification rate, sensitivity, NPV, DSS	Positive SN: 26%; false-negative biopsy: 14%; occult metastasis in 13% of tumors positioned laterally; pooled sentinel node identification rate: 96.3%; pooled sensitivity: 86%; pooled NPV: 95%. OS: 88%, DFS: 92%, DSS: 94%
Broglie *et al.*[29]	Prospective cohort study	*N* = 111	5 years	Neck control rate including salvage surgery	SN-negative: 96%, SN-positive: 80% (all underwent CND)
Crocetta *et al.*[30]	Meta-analysis	5 observational studies	22 months-5.6 years	DSS, OS and NRR	No difference found
Gupta *et al.*[32]	Meta-analysis	*N* = 608	1-4.95 years	OS, NRR, LRR, neck-shoulder function	Pooled HR of death for SNB versus END not statistically significant; rates of isolated NNR and LRR were similar. Pooled analysis of the neck-shoulder function significantly favored SNB
McMahon *et al.*[35]	Retrospective comparative survival analysis	*N* = 38 (Group 1); *N* = 146 (Group 2)	≥ 22 months	DSS, OS	No difference in DSS or OS was found between the groups. Patients undergoing SNB as the initial neck staging modality in early OSCC and are identified as pN-positive do not appear to be at a survival disadvantage compared with those staged with END.

DSS: Disease-specific survival; OS: overall survival; NRR: neck recurrence rate; RFS: recurrence-free survival; DFS: disease-free survival; NPV: negative predictive value; LRR: loco-regional recurrence; HR: hazard ratio; SNB: sentinel node biopsy; END: elective neck dissection; CND: consecutive neck dissection; ITC: isolated tumor cells.

specifically developed for SNB and had properties that may be of benefit particularly for tumors of the FOM, such as rapid clearance from the injection site, rapid uptake, and high retention within the SN. A validation study in head and neck squamous cell carcinoma of the skin and mainly the oral cavity showed promising results with an SN identification rate of 97.6%, a false negative rate of 2.56%, and an NPV of 97.8%. Larger trials are needed to determine if ^{99m}Tc-tilmanocept surpasses the accuracy of routinely used ^{99m}Tc-nanocolloidal tracers in detecting SN, especially in the oral cavity. A full outline of radiotracers is given as a complementary guideline to the consensus guidelines[43]. These improvements in intraoperative detection methods increase assurance that the SN is found. Furthermore, they facilitate detection, especially in tumors of the FOM, which may otherwise be missed due to the shine-through effect[42].

Table 3. Main requirements for successful SNB

#	Requirement
1	Preoperative staging with MRI, CT, or US imaging of the neck with or without FNAC.
2	Reliable excision of the primary tumor with clear margins and local defect repair without requiring access to the neck.
3	Use of a radiotracer (99mTc), and optical tracers can be added to increase the intraoperative detection rate.
4	Special attention to tumors of the anterior floor of the mouth due to "shine-through effect" masking nodal hotspots close to the injection site.
5	Adequate histopathologic assessment of SNs through step-serial sectioning (SSS) and routine staining with H&E in combination with immunohistochemistry for cytokeratin.
6	A skilled team with experience in SNB, including a surgeon, a nuclear medicine physician, and a pathologist.
7	Appropriate patient selection with early-stage OSCC without clinical evidence of nodal involvement.

(4) Tumors of the anterior FOM have to be handled with particular care. The gamma signal from the primary tumor site can mask nodal hotspots close to the injection site (so-called “shine-through effect”), leading to missed SN in level I and a false negative SNB procedure. In a recent series from Den Toom *et al.* with 488 patients, SNB had a significantly lower sensitivity in FOM tumors than in non-FOM locations (63% and 86%, respectively)[44]. To deal with this problem, Stoeckli *et al*. proposed a surgical technique addressing the problem of the shine-through effect in FOM tumors by routinely investigating level I nodes of the pre-glandular triangle with a gamma probe after submental and pre-glandular fat pad mobilization[45]. In this study, with 40 prospectively enrolled FOM OSCC patients, 50% of SN were only detected intraoperatively and not by preoperative lymphoscintigraphy and the ultimate neck control rate including salvage treatment achieved 100%. The false negative rate and NPV were 8.3% and 96.4%, respectively.

(5) Adequate histopathological assessment of the SNs is crucial. Detection of micro-metastases by step-serial sectioning (SSS) of the entire SN and routine staining with H&E in combination with immunohistochemistry for cytokeratin is much more accurate than routine histopathological evaluation of a neck dissection specimen[46]. This is of great importance considering that the presence of ITCs, micro- and macro-metastasis has a significant impact on tumor control and survival in early OSCC, and may otherwise be missed in a routine histopathological workup[47]. In reverse, the method takes several days and does not allow a single-step procedure with CND in case of positive SN. Intraoperative frozen section analysis is the most commonly used technique along with imprint cytology, whereas, in OSCC, the NPVs of the frozen section range from 83% to 99%[46,48,49]. In order to improve the intraoperative evaluation of sentinel nodes, alternative techniques such as quantitative real-time reverse transcriptase-polymerase chain reaction (qRT-PCR) have been developed. Ferris *et al*. proposed a qRT-PCR assay which demonstrated a concordance of qRT-PCR with final pathology ranging from 93% to 98% with excellent reproducibility and linearity[50]. pRT-PCR is validated for breast cancer, but it has not yet been validated for OSCC.

(6) SNB requires multidisciplinary collaboration between nuclear medicine/radiologists, surgeons, and pathologists, to ensure the accuracy of the results. Schilling *et al*. proposed a rigorous training program for SNB surgeons to reduce the false negative rate below 10% and a minimal workload of 10 cases per year and per surgeon to ensure proper quality and outcome of the procedure[51]. A prospective multi-institutional trial by Civantos *et al*. has shown that NPV was higher in SNB performed by more experienced surgeons than for less experienced surgeons[52].

(7) In case of a negative SN, a close follow-up regime is mandatory in order to detect recurrences early and improve the chances for salvage surgery. Especially the first two years are decisive because most recurrences occur within this time[2]. Patients should undergo at least a US review every 3 months during this period[36].

UNRESOLVED QUESTIONS ABOUT SNB

High-level evidence is now present to promote SNB as the standard diagnostic procedure for early OSCC. In the case of negative sentinel nodes, the procedure is also therapeutic; in the case of positive sentinel nodes, CND has to be added. Nevertheless, some questions remain unresolved. One question regards the management of ITC. It is well-accepted that all patients with a positive SNB require further neck treatment. The consensus guidelines by Schilling *et al.* recommend considering ITCs as a positive SNB and consequently advise patients to undergo CND[36]. In the SENT trial, the group with ITC showed a better OS than patients with micro- and macro-metastasis. Other studies did not show significant differences between ITC and micro- and macro-metastasis on OS[47,53]. However, the management of ITC remains controversial. In the trial by Garrel *et al.*, patients with ITC showed no difference in neck node recurrence and loco-regional recurrence rates compared to the SN negative group, whereby this observation could be caused by the small sample size[5]. Further studies are needed to assess this question. In the meantime, considering ITCs as positive may be the safer option for patients.

Another field of investigation is the search for improvement in the intraoperative detection of SN by imaging technologies in combination with optical tracers and intraoperative pathological assessment. To address the problem of lower accuracy in tumors of the FOM, new methods such as the optical tracer ICG show promising results. Other techniques such as CT lymphography, MRI lymphography using contrast agents or superparamagnetic iron oxide, contrast-enhanced ultrasound mapping using microbubbles, and freehand SPECT are under investigation for use in head and neck cancer. Further studies are awaited to demonstrate the superiority of these novel developments. To address the problem of intraoperative pathological assessment, qRT-PCR seems the most promising technique. It is worth investigating in larger clinical trials in order to perform the sentinel procedure in one step and thus spare the patient a second operation in cases of positive SN.

CONCLUSION

SNB is an accurate and individualized method for the detection of occult metastasis in early OSCC, even in the pretreated neck. It is widely recognized as a standard procedure for staging the neck and incorporated into multiple national consensus guidelines. Two recent prospective randomized trials have now independently proven the noninferiority of SNB compared to END with reduced cost and lower morbidity. In conclusion, SNB should be offered to patients with T1/T2 cN0 OSCC, provided that the technical prerequisites are given for successful SNB.

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Authors' contributions

Made substantial contributions to the conception, design, literature review and writing of the article: Savaria FN, Stoeckli SJ

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