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Sentinel Lymph Node Biopsy for Early Oral Cavity Squamous Cell Carcinoma

Rajith Mendis and Muzib Abdul-Razak

Abstract

Early stage oral cavity squamous cell carcinoma (OCSCC) has a significant risk of subclinical nodal metastases, which is the strongest independent prognostic factor for regional recurrence and survival. However current preoperative imaging modalities are unable to identify patients with micrometastases, and an observation strategy has been associated with inferior outcomes when compared to an elective neck dissection. Sentinel lymph node biopsy provides a safe and accurate staging procedure to select the patients who benefit from an elective neck dissection, while avoiding unnecessary surgery in the patients who are node negative. There is recent Level II evidence demonstrating equivalent oncological outcomes when compared with elective neck dissection. However, a multidisciplinary approach is required including reliable mapping of the sentinel lymph node, precise surgical technique and comprehensive histopathological analysis to ensure accurate results are obtained.

Keywords: Oral squamous cell carcinoma, oral cancer, head and neck cancer, sentinel lymph node, elective neck dissection, nodal metastases, lymphoscintigraphy

1. Introduction

Early stage oral cavity squamous cell carcinoma (T1N0 or T2N0) has a significant risk of between 20 and 44% [1–3] of harbouring subclinical nodal metastases. The presence of nodal metastases has been shown to be the strongest independent prognostic factor for predicting a poor outcome [4–6]. Current imaging techniques including computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and ultrasound (US) cannot accurately identify micrometastases preoperatively [7, 8]. Traditionally the only way to identify this was to perform an elective neck dissection (END), however this is unnecessary in the majority (60–80%) of patients who do not harbour occult nodal metastases, and has an associated morbidity [1]. This chapter will present the histopathological factors that have been used to risk stratify patients for an END, as well as the multifaceted technique and role of sentinel lymph node biopsy (SLNB) as a staging procedure for patients with OCSCC.

2. Histopathological factors

Various parameters have been investigated to further stratify the risk of subclinical nodal metastases, including tumour thickness and depth of invasion (DOI).

Tumour thickness measures the thickness of the tumour from the deepest point of invasion to the top of the granular cell layer, or if ulcerated, the ulcer base serves as the reference point. DOI is measured from the level of the basement membrane to the deepest point of invasion, and in the case of an ulcerated OCSCC, this level is estimated by creating an imaginary line from the adjacent basement membrane [1]. This avoids under-representing an ulcerated tumour or over-representing an exophytic tumour, and has been included in staging for OCSCC in the current 8th edition American Joint Committee on Cancer (AJCC) staging manual [9]. An increased risk of subclinical nodal metastases has been associated with varying tumour thicknesses, between 2 mm to 5 mm, with thicker tumours having a risk of nodal metastases between 44 and 50% [1, 8, 10]. The anatomical sub-site of the OCSCC may also play a role with a lesion thickness > 1.5 mm on the floor of mouth being associated with a risk of nodal metastases of 35% [11]; however, this has not been a consistent finding, with another study demonstrating a 4 mm cut-off associated with an increased risk of nodal metastases regardless of sub-site [5]. This study documented rates of local control, nodal disease, and survival rates of 91%, 8%, and 100%, respectively, for lesions <4 mm thick compared with 84%, 48%, and 74% for those ≥4 mm thick (p < .01). Despite this there are limitations with basing management decisions on the tumour thickness or DOI, as often this may not be assessable on a biopsy alone due to the sparse amount of biopsy material, and if assessable the biopsy may not be representative of the entire tumour [12], resulting in subsequent management decisions based more on clinical assessment.

Histopathological factors predicting for sub-clinical nodal metastases in the setting of sentinel lymph node biopsy (SLNB) have also been investigated with three variables identified including grade (G1 *vs* G2/G3), presence of lymphatic invasion and mode of invasion (cohesive *vs* dissolute) [13]. Interestingly, in this study DOI and tumour thickness were not reliable predictors of nodal metastasis demonstrating the inconsistency and uncertainty in basing management decisions on histopathological factors alone.

3. Benefit of elective neck dissection

Superior outcomes have been published in a prospective randomised controlled trial (RCT) involving patients with early OCSCC (T1/T2 tumours) without clinical evidence of nodal metastases, when they underwent an END compared to observation followed by neck dissection in the setting of nodal relapse [14]. In this study 3 year overall survival was 80% for patients undergoing END compared to 67.5% for patients undergoing delayed therapeutic dissection following relapse (p = 0.01). Subclinical nodal positivity in the END group was 29%, while nodal relapse rates in the observation group was 45% [14].

Of note in the 'true' node negative patients in this study, which included pathological node negative patients in the END group and those who did not relapse in the observation group, *survival was equivalent.* This demonstrates that while patients with subclinical nodal metastases benefit from a neck dissection, the remaining 60–80% of patients without nodal metastases do not experience a survival benefit by undergoing a neck dissection (see **Figure 1**). It is also important to consider that even patients with a pathologically negative neck following END have a rate of regional failure up to 5–10% [3, 15].

This benefit of END has been reported in a previous observational study where patients with early (T1/T2) OCSCC had significantly improved outcomes undergoing END (median survival 12 years) compared to observation (median survival 4.1 years), with the majority (11/12) of recurrences in the observation group
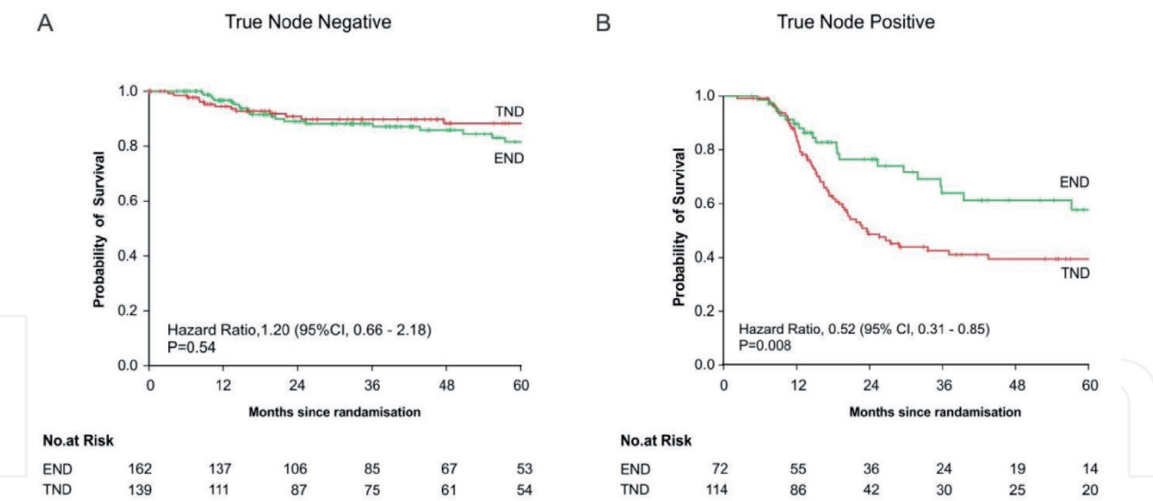
Figure 1.
Overall survival in 'true node negative' and 'true node positive' patients [14].

occurring as regional failures [2]. This benefit is selectively achieved in patients undergoing SLNB, as patients with a positive sentinel lymph node (SLN) undergo a completion neck dissection while the morbidity of the neck dissection is avoided when the SLNB is negative.

4. Technique of sentinel lymph node biopsy

There is marked heterogeneity in the published data assessing the role of SLNB in OCSCC including preoperative investigations, technique of identifying the SLN and the pathological assessment of the specimens [16]. The GETTEC (Groupe d'Etude des Tumeurs de la Tête et du Cou) guidelines [17] have attempted to standardise the technique in performing SLNB with recommendations for lympho-scintigraphy, surgery and pathological analysis. Of note, they recommend a median of three SLNs to be sampled, with a single SLN node considered insufficient to accurately determine the nodal pathological status.

SLNB for OCSCC presents unique challenges in relation to both the complex anatomy of the head and neck, in addition to the short distance between the primary lesion and the draining nodal basin, particularly for lesions located in the floor of mouth. This is due to the high activity at the adjacent injection site, which can be easily overlooked by planar lymphoscintigraphy and intraoperative gamma probes [18]. Intraoperatively, the close relationship between the primary lesion and the draining lymph nodes can result in so called 'shine through' of the radioac-tive tracer from the primary site with difficulties in identifying the SLN if it is in an adjacent nodal basin, particularly the submental (IA) and submandibular (IB) basins. Composite single photon emission computed tomography (SPECT) with concurrent CT combines functional and anatomical imaging to enhance topo-graphic orientation and diagnostic sensitivity, with more SLNs being detectable than by planar lymphoscintigraphy alone, as well as providing more detailed ana-tomical information to assist with intraoperative localisation [19]. **Figures 2** and **3** demonstrates the lymphoscintigraphy result and composite SPECT/CT for patients with unilateral and bilateral lymphatic drainage respectively. The SPECT/CT provides detailed anatomical information to assist with identification of the SLN.

Another consideration that may impact on the accuracy of lymphoscintigra-phy is the choice of radiotracer. These have different molecular characteristics as
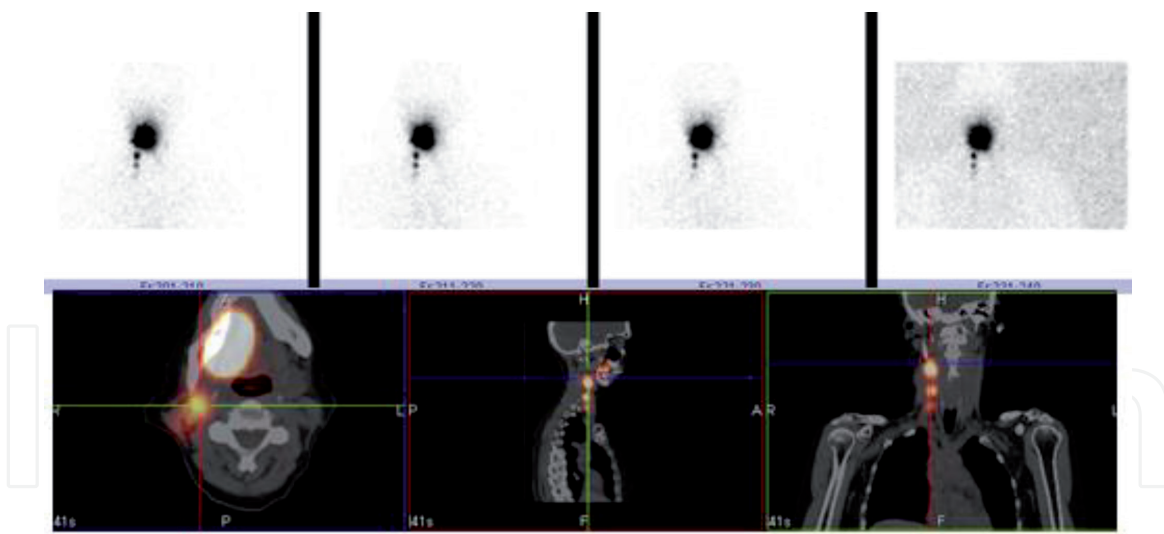
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Figure 2.
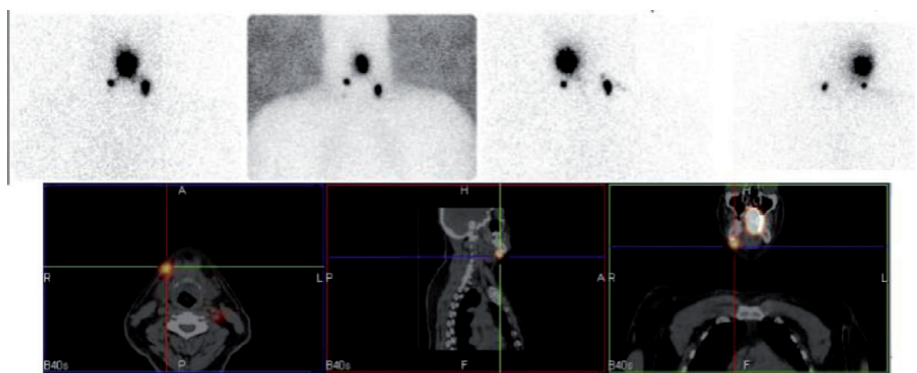*Lymphoscintigraphy and SPECT/CT demonstrating ipsilateral level 2 sentinel lymph node.*

Figure 3.
Lymphoscintigraphy and SPECT/CT demonstrating bilateral drainage from a lateralised tumour.

summarised in **Table 1,** which impacts the drainage characteristics, and this may be utilised to counteract the 'shine through' effect. The potential of [^{99m}Tc]Tilmanocept is of particular interest as it has a small molecular size of 7 nm facilitating rapid injection site clearance, and targets the CD206 receptor found on the reticuloendothelial cells in lymph nodes to promote accumulation within the SLN while reducing drainage to second tier nodes [21, 22]. A study assessing [^{99m}Tc]Tilmanocept in the setting of both OSCC and head and neck cutaneous SCC demonstrated a SLN detection rate of 97.6%, with a false negative rate of 2.56% [22]. This study included

Agent	Mean Particle size (nm)
Sulphur Colloid	100–220
Antimony trisulphide	3–30
Suphide nanocolloid	10–50
Nanocolloidal albumin	5–80
Rhenium sulphide nanocolloid	50–200
ICG-99mTc-Nanocolloid	5–80
Tilmanocept	~7

Table 1.
^{99m}TC labelled radiotracers [20].

20 patients with floor of mouth OSCCs, where [99mTc]Tilmanocept may be of particular use, and a SLN was successfully identified in all cases without any false negatives [22]. A recent comparison study between [99mTc]Tilmanocept and [99mTc] Nanocolloid found that [99mTc]Tilmanocept had higher rates of clearance from the primary injection site but also had reduced accumulation within the SLN, with a similar SLN to injection site ratio of radioactivity between the two radiotracers [23].
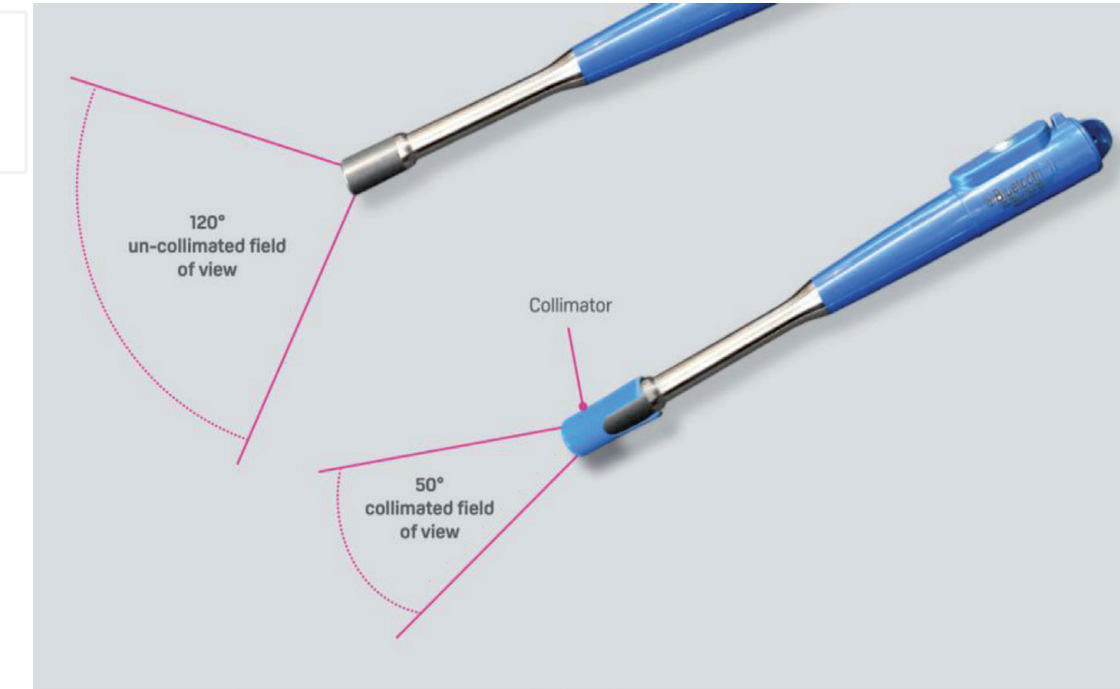

Figure 4.
Focused field of view with use of collimator. (This image is © 2021 Devicor Medical Products, Inc.; used with permission).

Figure 5.
Sentinel lymph node with blue dye on one surface facilitating visual identification.

This study demonstrated a high degree of agreement in the identification of SLNs between each radiotracer, however it is difficult to draw definitive conclusions with a small sample size, and further studies are required.

Specific surgical techniques can be employed to counteract the 'shine through' effect, including mobilisation of the fat pad between the submandibular gland and anterior belly of digastric to reflect the tissue, allowing for careful analysis with the handheld gamma probe while avoiding radiation from the primary tumour injection site [24]. A probe with an angled head (Neoprobe, Devicor Medical Products) with collimator attached is indispensable in such narrow spaces as in the neck to reliably locate the node. The collimator serves to decrease the field of view from 120 to 50 degrees while simultaneously increasing the spatial resolution of the probe (see **Figure 4**). Selective use of patent blue dye (Aspen Pharmacare) when the draining lymph nodes are in the submental and submandibular basins provides additional visual information to assist with identification of the SLN as demonstrated in **Figure 5**.

5. Histopathological analysis

The presence of nodal micrometastases (0.2 mm–2 mm) or isolated tumour cells (ITC) (<0.2 mm) [9] may be overlooked by standard histopathological analysis, with one study that reanalysed 76 neck dissection specimens with serial sectioning identifying previously undetected micrometastases in 7.9% of specimens [25]. These metastases occurred mainly in small (<1 cm) lymph nodes, without extranodal extension and therefore would not have been routinely identified on preoperative imaging. **Figure 6** demonstrates how micrometastases are detected more reliably by performing serial sectioning. Another smaller prospective study analysed 34 neck dissection specimens with serial sectioning and immunohisto-chemistry (IHC) in addition to standard haematoxylin–eosin staining (HES) and found that 3 patients (8.8%) were upstaged by the additional analysis, with two cases of micrometastases and one patient harbouring ITC [26]. Importantly the identification of these micrometastases did not warrant further treatment beyond the neck dissection which had already been performed [25]. However, the revised findings of node positivity has both a staging and prognostic impact on patients.

In another study in the setting of SLNB, serial sectioning and IHC upstaged 5 of 27 (19%) patients with nodal metastases [8], and a retrospective review of 272
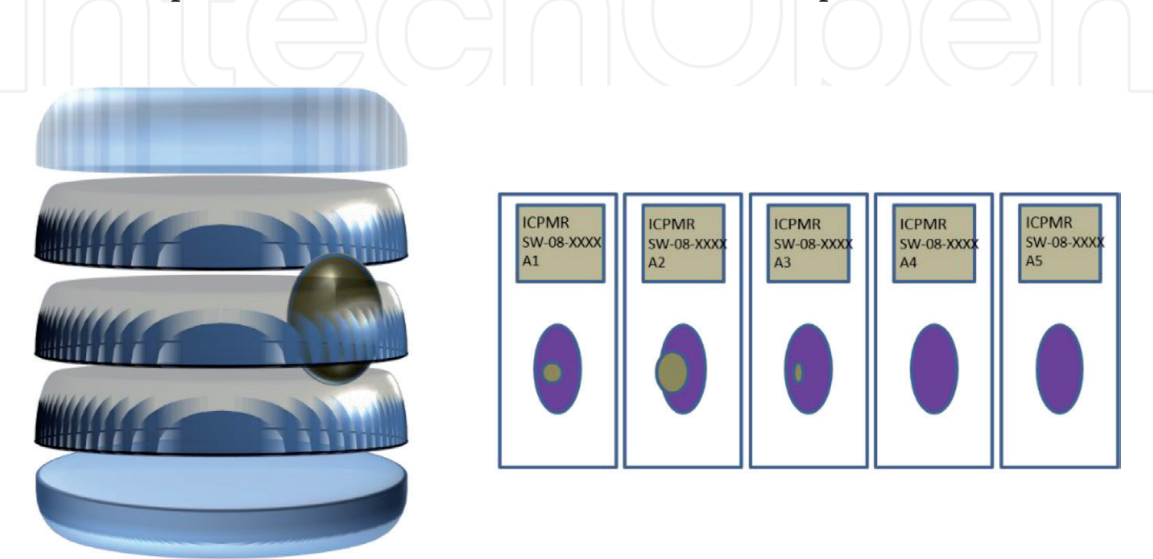

Figure 6.
Serial sectioning a lymph node.

patients undergoing SLNB found that 51.7% of their positive sentinel lymph nodes were only detected following serial sectioning and IHC [27]. The addition of IHC to standard HES increases both the sensitivity and negative predictive value of SLNB [16, 28, 29] and has now become part of the standard pathological assessment of SLNs in most institutions.

Performing serial sectioning and IHC (cytokeratin – AE1/AE3) is both labour and time intensive for the pathologist. By performing a SLNB, the detailed examination can be focused on the most likely lymph nodes which might harbour micrometastatic disease for each individual patient, providing the most precise staging and prognostic information.

6. Accuracy in predicting neck status

The Sentinel European Node Trial (SENT) was a large multicentre European study investigating SLNB in 415 patients with early OCSCC, of which subclinical nodal metastases were identified in 26% of the study population. The findings demonstrated the procedure to be safe, reliable and accurate with a SLN identified in 99% of cases, with 86% sensitivity, 95% negative predictive value and 14% false negative rate [30]. These results have been replicated in other similar studies, albeit with lower false negative rates of 2.56% [22] and 9.1% [31], and with higher rates of contralateral drainage (23–40%) [31, 32].

SLNB allows for identification of unexpected lymphatic drainage patterns, and the SENT trial found that bilateral drainage was identified in 10% of lateralised tumours, and 2.4% had exclusive contralateral drainage. The patients with contralateral drainage, 7 of 49 had positive SLNs, with 5 of the patients draining exclusively contralaterally [30]. The rate of contralateral drainage for lateralised tumours has been documented in other studies to be as high as 23–40% [31, 32].

The detection of contralateral drainage is a major benefit of performing a SLNB as it allows accurate mapping of the lymphatic drainage for each individual patient, and for patients with lateralised tumours with contralateral drainage, these nodes will not be addressed if they undergo a unilateral END. If there were undetected subclinical nodal metastases in these nodes, these patients would then be at risk of a contralateral nodal failure.

The accuracy of SLNB has been further investigated by a systematic review/ meta-analysis assessing the performance of SLNB as a staging procedure for OCSCC and documented it to be reliable with a sensitivity of 88% and specificity of 99%. However, when assessing covariates, performing IHC on the SLN significantly improved the sensitivity to 93% [29]. In addition to the differences in processing of specimens, there was a degree of heterogeneity in the articles in relation to measurement of failure with a combination of END and clinical follow up to detect potential false negatives. Despite this the review demonstrated that SLNB is highly accurate across several different institutions, with an improvement in quality of life including pain, shoulder mobility and scarring when compared to END [29].

7. Outcomes following sentinel lymph node biopsy

A systematic review assessing outcomes in patients with early OCSCC managed with either a SLNB or END found no significant difference in overall survival or disease free survival between the two approaches [33]. This study analysed 5 separate studies with a total of 560 patients and reported 10 more neck recurrences per 1000 patients undergoing the SLNB strategy compared with END, although this

was not statistically significant. Conversely SLNB avoided the need for a neck dissection in 64% of patients. While this did demonstrate robust outcomes for patients treated with SLNB, none of the included studies were randomised and as such the overall quality of the evidence was considered low.

Two RCTs have been subsequently published comparing SLNB and END for early OCSCC with both demonstrating equivalent oncological outcomes, and their findings are summarised in **Table 2** and **Figure 7**. The Senti-MERORL trial was a multi-centre RCT with 307 patients that documented a 25% rate of SLN positivity, with these patients proceeding to a neck dissection [15]. There was a mean follow up of 4.95 years, and rates of nodal recurrence were 10.1% in the neck dissection group and 9.3% in the SLNB group, which was not a statistically significant difference. Equivalent locoregional disease control, disease specific survival and overall survival were demonstrated at 2 and 5 years [15]. When looking at the nodal recurrences in patients initially classified as pathologically node negative (pN0), there were 11 patients (10% of the 109 pN0 patients) in the END group and 8 patients (8% of the 99 pN0 patients) in the SLNB group, demonstrating similar rates of nodal staging failure between the two strategies.

A Japanese RCT compared 137 patients in the neck dissection arm and 134 patients in the SLN arm. They found a 34% rate of SLN positivity, and regional recurrence rates were 9.5% and 11.2% in the END and SLNB groups respectively.

	Garrel et al. [15]		Hasegawa et al. [34]	
	SLNB (n = 140)	END (n = 139)	SLNB (n = 134)	END (n = 137)
Age	60.8 (mean)	59.1 (mean)	63 (median)	63 (median)
Sex				
Male	88 (63%)	101 (73%)	89 (66%)	90 (66%)
Female	52 (37%)	38 (27%)	45 (34%)	47 (34%)
Site of primary				
Oral Tongue	124 (89.2%)	119 (85.6%)	109 (81.3%)	114 (83.2%)
Floor of mouth			13 (9.7%)	14 (10.2%)
Lower gingiva			7 (5.2%)	6 (4.4%)
Buccal mucosa			5 (3.7%)	3 (2.2%)
Oropharynx	15 (10.8%)	20 (14.4%)		
T1	88 (63%)	91 (66%)	26 (19%)	25 (18%)
T2	52 (37%)	48 (35%)	108 (81%)	112 (82%)
Positive lymph nodes	35 (25%)[a]	30 (22%)	46 (34%)	34 (25%)
Frozen section/ Imprint cytology	21 (15%)		32 (24%)	
H&E/IHC	12 (9%)		14 (10%)	
Adjuvant treatment				
Radiotherapy	23 (16%)	28 (20%)	4 (3%)	3 (2%)
Chemoradiotherapy	10 (7%)	6 (4%)	0	3 (2%)
Nodal recurrence	13 (9%)	14 (10%)	15 (11%)	13 (10%)
Follow up (months)	56.9 (mean)	59.4 (mean)	37 (median)	37 (median)
Overall Survival	82.2% at 5 y	81.8% at 5 y	87.9% at 3 y	86.6% at 3 ys

[a]Includes 2 positive cases out of 8 undergoing END due to localization failure.
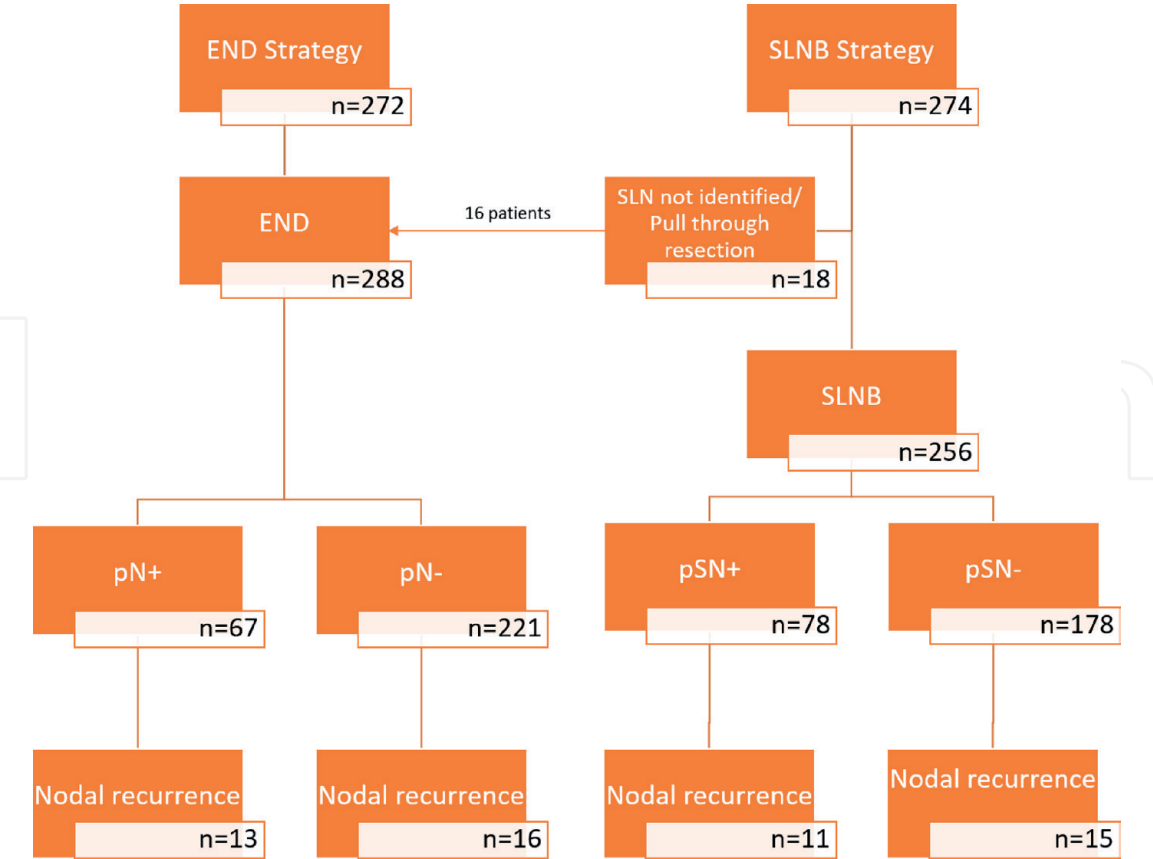
Table 2.
Comparison of two RCTs.

Figure 7.
Combined RCT outcomes of nodal recurrence. (Adapted from Garrel et al. [15], Hasegawa et al. [34]).

This study demonstrated equivalent 3 year overall survival and disease free survival between the END group (87.9% and 81.3%) and the SLN group (86.6% and 78.7%) [34]. Both studies demonstrate high-level evidence to support the use of SLNB as a staging procedure for patients with early T1 or T2 OCSCC.

END has an associated morbidity including shoulder dysfunction, pain and contour changes [16]. Comparison of morbidity associated with SLNB or a neck dissection demonstrates low rates of morbidity overall, however, in one study all the morbidity occurred following neck dissection, with no cases of shoulder dysfunction in the SLNB group [6]. Quality of life assessments demonstrate improved tactile sensitivity and reduced pain sensitivity in the SLNB group, with no significant difference in the presence of lymphoedema although there was trend towards improved symptoms in the sentinel lymph node biopsy group [35]. Functional outcomes were also assessed in the two RCTs, with the Senti-MERORL study finding an initial functional difference between the two groups favouring SLNB at 6 months, however this resolved by 12 months [15]. Hasegawa reported that the END group had persisting inferior scores at 12 months post operatively, when assessing neck stiffness and shoulder dysfunction compared to the SLN group [34].

8. Future directions

It is widely accepted that macrometastases and micrometastases should undergo a completion neck dissection, however management of ITC remains uncertain without a clear consensus. This is a significant issue as the incidence of ITC ranges between 14 and 27% of positive SLNs [27, 30, 36] and the two RCTs managed this subgroup with differing strategies. The Senti-MERORL trial treated ITC with observation, and in those 11 patients there were no nodal recurrences [15]. Conversely

the Japanese RCT treated ITC with a completion neck dissection [34], however subgroup outcome data was not published. A retrospective Dutch study analysing outcomes for patients undergoing SLNB for OCSCC found a SLN positivity rate of 22% (107/488 patients) and of these patients, 15 (14%) had ITC, 31 (29%) had micrometastases and 61 (57%) had micrometastases. 13 of the patients with ITC underwent a neck dissection with 1 patient having additional positive lymph nodes, and the other 2 patients had adjuvant radiotherapy, and did not develop regional recurrence during follow up [36]. While ITC is considered to represent node negative disease in the setting of breast cancer [9], management of these patients remain uncertain in the setting of OCSCC and further data is required to clarify both the natural history and management outcomes for this subset of patients.

Intraoperative lymphoscintigraphy is a developing technique which has particular utility in the management of oropharyngeal or laryngeal SCC with a SLNB. These tumours are unable to be injected with a radiotracer in an awake patient for a preoperative assessment [37]. Indocyanine green (ICG) is readily taken up by lymphatics and can be identified intraoperatively using a near-infrared fluorescence camera to locate the sentinel lymph node [38]. The use of ICG does not cause any staining of the primary site as seen with use of patent blue dye, and also provides an immediate result, which offers obvious benefits in the setting of intraoperative sentinel lymph node identification. However, it does not provide the detailed drainage information with anatomical referencing that is provided by performing radiotracer based lymphoscintigraphy with a SPECT/CT. While techniques such as skin compression have been described to identify lymphatic drainage and the SLN before making a skin incision [37], often the skin flaps need to be raised to comprehensively assess the nodal basins [39]. In addition, the ICG signal spreads rapidly with time and thus second tier lymph nodes can be hard to distinguish from the true sentinel lymph node [40]. The use of hybrid tracers which assemble ICG with a radiocolloid to increase the retention time in the sentinel lymph node has been described [38], and may have an increasing future role, along with the use of intraoperative SPECT scanners, to counteract the disadvantages of using ICG alone. However, this is an exciting new tool which can be utilised to expand the utility of the SLN technique.

9. Conclusion

Early OCSCCs have a risk of subclinical nodal metastases to the draining cervical lymph nodes, which has a negative impact on the patient's prognosis and survival. The subclinical nature limits the ability to identify these with current imaging techniques including a PET scan. Despite this, there is recent high quality evidence demonstrating that treating this disease surgically has superior survival outcomes compared with an observation strategy. However, the patients *without* subclinical nodal metastases (up to 80%) do not gain any benefit by undergoing a neck dissection.

SLNB technique represents a minimally invasive technique allowing treatment de-intensification without compromising the oncological efficacy. SLNB has been demonstrated to provide an accurate and safe staging procedure to assess for subclinical nodal metastases with added benefits over an END including identification of out-of-field drainage, as well as a more detailed pathological assessment of the SLN However, a high quality multidisciplinary approach is required including accurate preoperative lymphoscintigraphy, precise surgical technique and detailed pathological assessment to ensure reliable results and good patient outcomes.

Acknowledgements

Conflict of interest

The authors declare no conflict of interest.

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