Journal of Cranio-Maxillo-Facial Surgery 48 (2020) 711–718

Contents lists available at ScienceDirect

Journal of Cranio-Maxillo-Facial Surgery

journal homepage: www.jcmfs.com

Review

Management of the clinically N_0 neck in early-stage oral squamous cell carcinoma (OSCC). An EACMFS position paper

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ARTICLE INFO

Article history:
Paper received 23 May 2020
Accepted 20 June 2020
Available online 2 July 2020

Keywords:
Oral cavity
Oral squamous cell carcinoma
OSCC
Lymph node
Sentinel node
Depth of invasion

ABSTRACT

Metastasis of oral squamous cell carcinoma (OSCC) to the cervical lymph nodes has a significant impact on prognosis. Accurate staging of the neck is important in order to deliver appropriate treatment for locoregional control of the disease and for prognosis.

The management of the neck in early, low volume disease (clinically T_1/T_2 oral cavity tumours) has long been debated. The risk of occult nodal involvement in cT_1/T_2 OSCC is estimated around 20–30%.

We describe the natural evolutionary history of OSCC and its patterns of spread and metastasis to the local lymphatic basins. We discuss most published literature and studies on management of the clinically negative neck (cN_0). Particular focus is given to prospective randomized trials comparing the outcomes of upfront elective neck dissection against the observational stance, and we summarize the results of the sentinel node biopsy studies.

The paper discusses the significance of the primary tumour histological characteristics and specifically the tumour's depth of invasion (DOI) and its impact on predicting nodal metastasis. The DOI has been incorporated in the TNM staging highlighting its significance in aiding the treatment decision making and this is reflected in world-wide oncological guidelines.

The critical analysis of all available literature amalgamates the existing evidence in early OSCC and provides recommendations in the management of the clinically N_0 neck.

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1. Introduction and Purpose

Oral squamous cell carcinoma (OSCC) is one of the most common cancers globally with an estimated incidence of 275,000 new cases annually (Mooreet al, 2000; Jemal et al., 2011; Montero and Patel, 2015; Warnakulasuriya, 2009; Chow, 2020). The disease is staged based on the AJCC TNM system (Edgeet al, 2010; Aminet al, 2017).

Forty to fifty percent of patients with OSCC present with clinical stage I or II disease (De Zinis et al., 2006; Shimizu et al., 2006). The most common site of presentation is the oral tongue followed by the floor of mouth (FOM) (Funk et al., 2002; Li et al., 2013; Shah et al., 2019). In early oral cancer the rate of occult metastasis is estimated between 20 and 40%. Nodal metastasis comprises the most significant prognosticator with survival rates decreasing by as much as 50% in N_1 disease (Amit et al., 2013; Kowalski et al., 2000).

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https://doi.org/10.1016/j.jcms.2020.06.004
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Metastatic spread to two or more lymph nodes is an indication for adjuvant radiotherapy and if the tumour cells invade through the capsule of the lymph node (extracapsular/extranodal spread) additional chemotherapy should be administered to improve survival (Woolgar et al., 2003). A small T_1 OSCC of the anterior floor of mouth that has metastasised bilaterally (N2) meets the criteria for IV_A stage. This accounts for an expected 5-year overall survival (OS) of 34% and disease specific survival (DSS) of 52%, or less (Montero and Patel, 2015; Shah et al., 2019; Saggi et al., 2018). It is therefore prudent to establish the nodal status of the neck not only for prognosticating purposes, but most importantly for planning and delivering adjuvant treatment in a timely manner.

The management of the clinically N_0 neck has long been debated. The main policies that have been considered in managing the neck in early oral cancer are the following:

1. Upfront elective neck dissection (END)
2. Watch and wait policy, and more recently
3. Sentinel node biopsy (SNB)

The purpose of this paper is to critically analyse the existing literature and provide an evidence-based approach in the management of the neck in cT_1/T_2N_0 oral squamous cell carcinoma.

2. OSCC high risk characteristics and patterns of spread

Oral squamous cell carcinoma comprises a malignant disease of epithelial origin in accordance with the principles of carcinogenesis (Hanahan and Weinberg, 2011). Its natural course and patterns of spread have been studied extensively (Brandwein-Gensler et al., 2005; Woolgar et al., 1995).

Tumours with clinically aggressive features such as rapid and endophytic growth are likely to histologically correlate with poor differentiation, non-cohesive pattern of spread, perineural and/or lymphovascular invasion and are more likely to metastasize early (Woolgar and Scott, 1995). Alveolar (gingival), floor of mouth, and retromolar OSCC penetrate into the bone directly through the attachment points of Sharpey's fibres to the cortex (Brown et al., 2002).

OSCC in previously untreated patients metastasises in the neck following predictable patterns that correspond with the respective lymphatic draining basins (Lindberg, 1972; Shah et al., 1990). The predominant pattern of lymphatic spread resembles the shape of an 'inverted cone' (Woolgar, 2007). Aggressive or rapidly spreading (fast-tracking) tumours may concomitantly affect several nodal levels through 'overflow' or 'flushing' and 'peppering' effects (Woolgar, 1999, 2007).

A *subsite* approach applies in the prediction of lymphatic nodal levels that may harbour occult metastases. Lateralised tumours, such as buccal, gingival, retromolar and maxillary OSCC metastasise first into ipsilateral levels I and IIa (Lindberg, 1972; Shah et al., 1990; Woolgar, 2007; Boeve et al., 2017) (Fig. 1).

The more anterior the tumour is located the higher the likelihood of Level I_A involvement and the more posterior the higher the chance of level IIa involvement. In buccal OSCC, the facial lymph node is at risk (Agarwal et al., 2016).

Tongue OSCC predominantly spreads to levels I and II with a small fraction (6–12%) of tumours metastasizing contralaterally or bilaterally depending on the tumour's proximity to the midline (Lindberg, 1972; Kowalski et al., 1999) and its histopathological aggressiveness (Fan et al., 2011) (Fig. 2).

The more posterior the tongue tumour, the higher the chance of level II_B and contralateral nodal metastasis, due to higher lymphatic interconnections posteriorly towards the base of tongue (Sharpe, 1981; Kowalski et al., 1999; Olzowy et al., 2011). Level II_B was involved in 5.4% of cN_0 OSCC cases only when other nodal levels were positive (32.4%) (Lim et al., 2004). In a study with 45.8% rate of occult neck metastases in cN_0 OSCC, 10.4% of level II_B were concomitantly involved (Elsheikh et al., 2005).

Tumours arising close to the midline such as the floor of mouth (FOM) or the palate spread to levels I and II_A with approximately 25% probability of bilateral or contralateral nodal involvement (Lindberg, 1972; Shah et al., 1990; Kowalski et al., 1999) (Fig. 3).

In the majority of OSCC patients, level IV is only involved when other neck levels are positive for metastasis. Byers et al. reported that clinically N_0 OSCC metastasised to level IV in 15.8% of the cases, where 5.5% accounted for true 'skip metastases' (Byers et al., 1997). Shah et al. reported 3% of level IV involvement in cN_0 OSCC (Shah et al., 1990). True skip metastases to level IV account for 2% or less of the cases, predominantly from tongue OSCC (Cariati et al., 2018; Crean et al., 2003; Warshavsky et al., 2019). Level V in cN_0 oral cancer is rarely involved (less than 1%) (Shah et al., 1990).

3. Approaches in the management of cN_0 OSCC

The management of the cN_0 neck in the oral cavity SCC has been a matter of controversy and scientific debate for the past 4 decades (Wei et al., 2006). Various imaging modalities including US, CT, MRI, PET have aimed to underpin an evidence-based approach, however large studies have demonstrated the limitation of any preoperative imaging in accurately staging the clinically negative neck (Van den Brekel et al., 1996; Ferlito et al., 2002).

Algorithmic models have also been introduced to aid with the dilemma of observing (watchful wait policy) or treating the neck prophylactically, with an acceptable threshold of 20% of probability of occult metastasis to favour elective neck dissection (END) (Weiss et al., 1994).

The observational stance in cN_0 cases was based on the assumption that the neck can be therapeutically treated when and if patients develop an early recognised regional N_1 failure, however further studies showed that often the patients presented with N_2 or

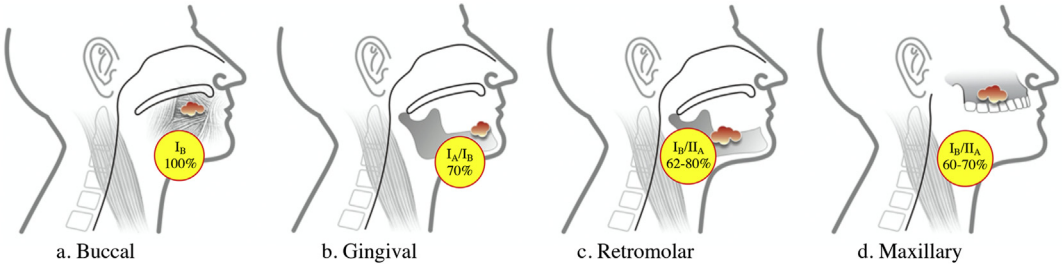

Fig. 1. Predominant lymph node levels for metastasis of lateralised OSCC tumours) (Lindberg, 1972; Shah et al., 1990; Woolgar, 2007; Boeve et al., 2017; Broglie et al., 2013; Sharpe, 1981; Essig et al., 2012). The estimated probability is demonstrated in the circles; a. Buccal b. Gingival (alveolar) c. Retromolar d. Maxillary OSCC.

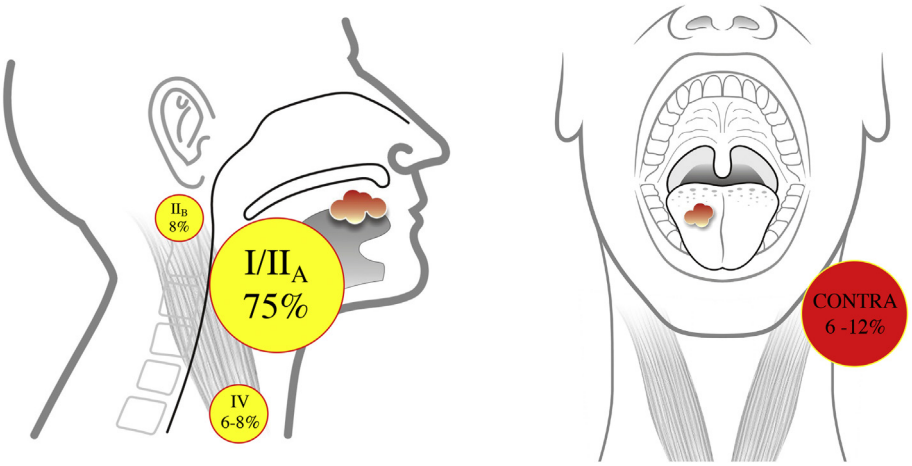

Fig. 2. Predominant lymph node levels for metastasis of tongue SCC (Lindberg, 1972; Shah et al., 1990; Woolgar, 2007; Broglie et al., 2013; Sharpe, 1981; Kowalski et al., 1999; Cariati et al., 2018; Crean et al., 2003; Elsheikh et al., 2005; Lim et al., 2004; Warshavsky et al., 2019). The estimated probability is demonstrated in the circles. Lateral view demonstrates ipsilateral commonly affected neck levels. Front view demonstrates the rate of possible contralateral neck nodal involvement.

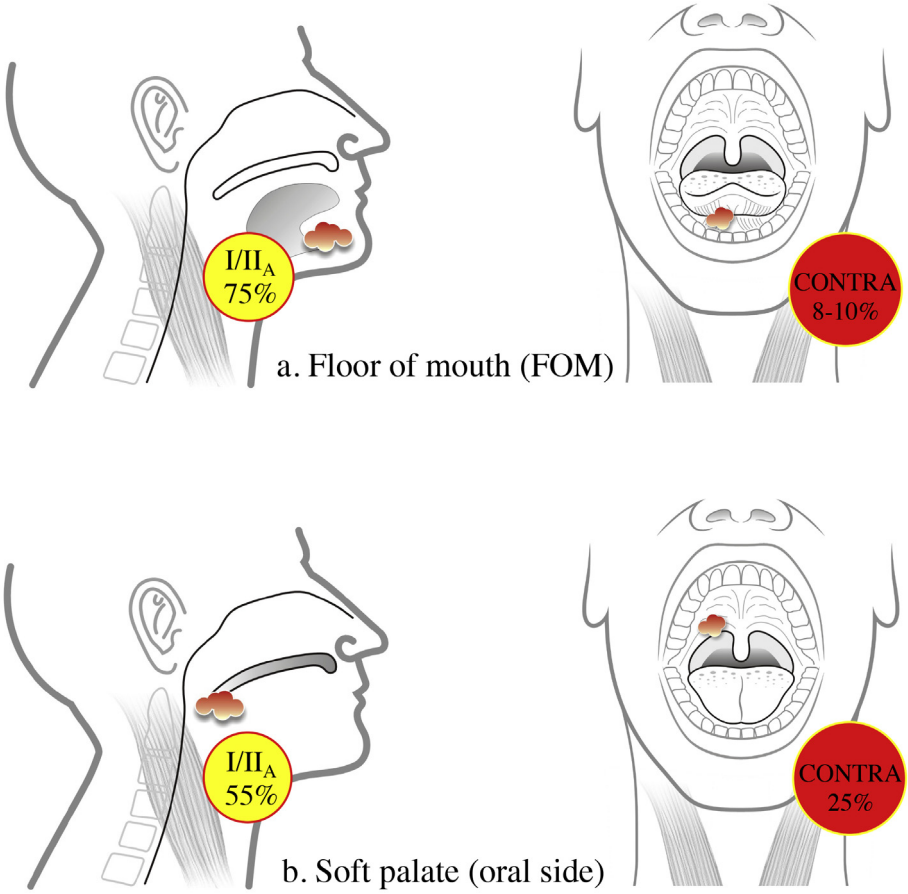

Fig. 3. Predominant lymph node levels for metastasis of OSCC arising in midline subsites (Lindberg, 1972; Shah et al., 1990; Woolgar, 2007; Broglie et al., 2013; Kowalski et al., 1999; Capote-Moreno et al., 2010). The estimated probability is demonstrated in the circles; a. Floor of mouth (FOM) b. Palatal OSCC (oral side).

N_3 disease ending with disappointing survival outcomes (Andersen et al., 1996; Lydiatt et al., 1993).

The superiority of END in achieving better survival outcomes has been demonstrated in numerous retrospective studies (Vandenbrouck et al., 1980; Fakih et al., 1989; Franceschi et al., 1993; Kligerman et al., 1994; Yuen et al., 1997; Beenken et al., 1999; Yii et al., 1999; Huang et al., 2008; Tai et al., 2012; Feng et al., 2014).

Substantial data with adequate power to seal the debate between the observational policy and upfront END in early stage OSCC have been obtained by prospective randomised clinical studies (Yuen et al., 2009; D'Cruz et al., 2015; Fasunla et al., 2011), with two large scale studies published by Tata Memorial Centre in India and

the UK (D'Cruz et al., 2015; Hutchison et al., 2019). In the former landmark randomised controlled trial (RCT), D'Cruz et al. demonstrated the significant DFS and OS benefit (DFS 69.5% and OS 80% in the END groups as opposed to DFS of 45.9% and OS of 67.5% in the observation and therapeutic ND group, respectively) in early-stage OSCC patients that underwent upfront elective neck dissection (D'Cruz et al., 2015). The UK nation-wide trial is published along with a meta-analysis and a concurrent real-world cohort and further emphasises the benefits of upfront END even with small cT1N0 disease. It also compares END with the SNB approach, which is perceived as a primarily diagnostic approach (Hutchison et al., 2019). The impact of the RCTs in the field has resonated in further large-scale meta-analyses (Abu-Ghanem et al., 2016; Ren et al., 2015; Oh et al., 2020; Cai et al., 2020) (Table 1).

There is consensus that the extent of the END should be in the form of a selective I-IV neck dissection, as this is equally effective than more extensive, but morbid, types of ND (MRND, RD) (Huang et al., 2008), as long as there is a minimum yield of 18 lymph nodes (Ebrahimi et al., 2014; Zenga et al., 2019).

4. Sentinel node biopsy (SNB)

During the conflict between the observational management of the cN_0 neck and the upfront elective neck dissection the concept of sentinel node biopsy has emerged as a compromise between the two polarised stances.

This approach essentially involves preoperative injection of a radiotracer (nanocolloid labelled with Technetium 99 m, ^{99m}Tc) at the tumour site (submucosal tumour periphery), followed by planar lymphoscintigraphy in conjunction with SPECT/CT (single-photon emission computed tomography combined with low-dose CT) to localise the draining lymph nodes (Civantos et al., 2010; Den Toom et al., 2015; Schilling et al., 2015). Intraoperative adjuncts, such as visual blue dye, or fluorescence, alongside a gamma probe/Geiger meter-detection, aid further in tracing the echelon node that theoretically drains the site of the primary tumour (Civantos et al., 2010; Den Toom et al., 2015; Schilling et al., 2015). The latter should be the first lymph node to harbour occult metastasis. The protocol of SNB dictates that if the sentinel lymph node is found positive for metastasis then a formal neck dissection should be carried out (Civantos et al., 2010).

Table 1
Prospective Randomised Trials and Meta-Analyses on END vs Observation.

TYPE OF STUDY	Year	N	Subsite of Primary	Outcome
Prospective Randomised Trials				
Vandenbrouck et al.	1980	75	All	No Statistical difference END vs Observation
Fakih et al.	1989	70	Tongue	In favour of END
Kligerman et al.	1994	67	Tongue/FOM	In favour of END
Yuen et al.	2009	71	Tongue	No Statistical difference END vs Observation
D'Cruz et al.	2015	596	Tongue/FOM/ Buccal	In favour of END
Hutchison et al. (SEND)	2019	250	All	In favour of END
Meta-Analyses				
Fansula et al.	2011	283	All	In favour of END
Ren et al.	2015	779	All	In favour of END
Abu-Ghanem et al.	2016	3244	All	In favour of END
Hutchison et al. (SEND)	2019	958	All	In favour of END
Cai et al.	2020	5705	All	In favour of END
Oh et al.	2020	1317	Tongue/FOM/ Buccal	In favour of END

The inspiration for SNB originally stems from breast cancer, where axillary lymphadenectomy bears detrimental side-effects (lymphoedema and functional complications for the upper limb), hence the need for lesser invasive staging procedures (Pesek et al., 2012).

Conceptually fascinating, the SNB utilises and promotes modern imaging technologies and as expected has attracted marked research interest. Numerous units have published data on the diagnostic accuracy of this method in head and neck cancer (Broglie et al., 2013; Den Toom et al., 2015; Kovacs et al., 2009; Samant, 2014; Pedersen et al., 2016; Moya-Plana et al., 2018; Loree et al., 2019). The SNB topic has been studied in multi-centre trials (Civantos et al., 2010; Schilling et al., 2015; Miura et al., 2017; Ross et al., 2004) (Table 2). The false negative ratio (FNR) ratio varies from 5% to 27% (Pedersen et al., 2016; Milenovic et al., 2014) and is borderline acceptable (14%) in large scale studies (Schilling et al., 2015).

The ability to accurately identify the echelon node appears to be site-specific, with FOM tumours displaying higher false negative rates (usually due to “shine-through” artefact) in the range of 25% (Civantos et al., 2010; Milenovic et al., 2014; Alvarez et al., 2014). There is very little evidence to date about the usefulness of SNB in maxillary cancer (Boeve et al., 2017) and the current stance favours elective neck dissection as recurrences (all T-stage maxillary tumours) affect the contralateral neck in high ratio (45.5%) (Joosten et al., 2017).

Lymphoscintigraphy could be useful in identifying the sentinel node in cases of bilateral or contralateral drainage (12–20%) depending on the proximity to the midline (approximately 2% of occult metastasis to the contralateral site) (Broglie et al., 2013; Schilling et al., 2015), or in cases of previously treated neck where the lymphatic drainage is expected to be altered (Flach et al., 2012).

Sentinel node positivity or ‘upgrade’ of the neck status rate varies from 8.7% (N = 103) (Kovacs et al., 2009) to 38% (N = 111) in SNB studies (Broglie et al., 2013), further necessitating formal neck dissection. The latter reveals additional positive lymph nodes (upstaging the disease to pN_2 or pN_3) in approximately 20% of the otherwise clinically staged as N_0 cases (Broglie et al., 2013; Den Toom et al., 2015; Pedersen et al., 2016; Moya-Plana et al., 2018; Loree et al., 2019; Milenovic et al., 2014; Rigual et al., 2013). All SNB studies demonstrate lower survival outcomes in the SNB positive patients (OS range 38%–71% in SNB positive patients).

Cost-effectiveness reports demonstrate that although SNB is cost-effective in SNB negative cases, the cost in SNB positive cases raises significantly (Hernando et al., 2016).

Therefore, despite the evidence that SNB benefits true pN_0 early-stage OSCC patients by sparing them from the potential morbidity of ND, the technique might prove disadvantageous for N (+) patients, as it is not therapeutic for this group and exposes those patients to two operative procedures, potentially delaying the delivery of adjuvant treatment.

It becomes prudent to attempt to predict the SNB result and therefore reserve this approach for patients who are not at high risk of occult nodal disease (Sawant et al., 2017). In two large SNB cohorts, Pedersen et al. (N = 253) (Pedersen et al., 2016) and Moya-

Table 2
Multi-centre SNB trials.

	Year	N	Subsite of Primary	% SNB(+)	FNR
Civantos et al.	2010	140	Tongue/FOM	28%	Tongue: 10% FOM: 25%
Schilling et al. (SENT)	2015	415	All	26%	14%
Miura et al.	2017	57	Tongue/FOM/Alveolus	17.8%	9.1%

Plana et al. (N = 229) (Moya-Plana et al., 2018) reported statistically significant association between sentinel node positivity and primary tumour characteristics such as T-stage, grade of differentiation, perineural invasion, lymphovascular involvement and tumour thickness or depth of invasion (DOI). Based on the aforementioned criteria, Pedersen et al. stratified the primary OSCC tumours in low- and high-risk for occult lymph node metastasis, reporting a rate of 12% and 70% respectively (Pedersen et al., 2016).

5. Primary (index) tumour depth of invasion and its significance to predict nodal metastasis

The propensity of OSCC to metastasize has been linked to its vertical growth in a manner comparable with the Breslow thickness in malignant melanoma (Breslow, 1979). The vertical dimension of a tumour's growth can be measured by its *thickness* or its *depth of invasion (DOI)*.

Although the terms *tumour's thickness* and *tumour's depth of invasion (DOI)* have often been interchangeably used in the literature, they are not synonymous (Moore et al., 1986; Lydiatt et al., 2017);

- *Tumour thickness* represents the vertical dimension of the tumour measured from the deepest point of invasion to its mucosal surface.
- Depth of invasion (DOI) is measured from the deepest point of invasion to the *basement membrane of the most normal adjacent mucosa* (Moore et al., 1986; Lydiatt et al., 2017).

This distinction is important and separates *'thick'*, exophytic tumours from ulcerated, 'endophytic' and highly invasive carcinomas. In this section however we make reference to the terms *'thickness'* and *'DOI'* with respect to their original use in the referenced articles.

Initial studies linked the metastatic potential of OSCC with the tumour *thickness* (Mohit-Tabatabai et al., 1986; Spiro et al., 1986). Subsequent studies substantiated these findings and further demonstrated site-specific differences in tumour *thickness* cut-offs (Woolgar and Scott, 1995; Kligerman et al., 1994; Sheahan et al., 2003; Urist et al., 1987; Po Wing Yuen et al., 2002).

The tumour *thickness* threshold for FOM tumours beyond which the incidence of nodal metastasis rises over 20%, therefore indicating benefit from prophylactic/staging neck dissection is 1.5 mm (Mohit-Tabatabai et al., 1986; Balasubramanian et al., 2014). The threshold for tongue OSCC is set at 4–5 mm (Woolgar and Scott, 1995; Balasubramanian et al., 2014).

Further research on the field has clarified that it is the tumour's *depth of invasion (DOI)* that reflects more accurately its penetrative and infiltrative potential as opposed to its thickness (Moore et al., 1986).

Pentenero et al. and numerous reports showed positive correlation between DOI and nodal metastasis (Pentenero et al., 2005; Garzino-Demo et al., 2016; Melchers et al., 2012).

The strong correlation of either the tumour's *thickness* (cut-off 4 mm) or DOI with nodal metastasis has been demonstrated clearly in the randomised control trial of D'Cruz et al. (D'Cruz et al., 2015) and has been highlighted in a large-scale SNB study (N = 253) by Pedersen et al. (2016).

A summary of the critical tumour thickness and DOI beyond which tumour metastasis becomes more likely is demonstrated in Table 3.

All recent data suggest that the DOI is a better predictive parameter in comparison to thickness and the accepted DOI threshold beyond which the risk of nodal metastasis increases is 1.5 mm for FOM tumours and 4 mm for the rest of the oral cavity OSCC (Lydiatt et al., 2017).

The high prognostic significance of a tumour's DOI in staging the OSCC as well as predicting nodal metastasis and dictating the management of the neck has been reflected in the recent 8th AJCC classification update (Aminet al, 2017). The latter quoted the reports of Spiro et al. (1986) and Ebrahimi et al. (2019). Oral cavity tumours with DOI of 5 mm and above are staged as T2 and with 10 mm and above T3, irrespective of the tumour's surface diameter, acknowledging the significance of the vertical dimension of tumour growth in conjunction to the traditionally measured 'maximum diameter' (Edgeet al, 2010).

Current research is focusing on optimising and improving the ability to accurately measure the tumour's DOI with preoperative imaging (Brouwer de Koning et al., 2019; Tarabichi et al., 2019; Lam et al., 2004; Yesuratnam et al., 2014).

Apart from the DOI, other index tumour characteristics such as perineural invasion and pattern of infiltration (non-cohesive) have also been shown to correlate with positive nodal metastasis (prediction) potentially driving a future approach of individualised tumour risk-profiling (Sawant et al., 2017). Recent studies reveal that perineural invasion is a result of complex tumour molecular mechanisms and that is a reliable reflection of aggressive tumour biology (Galmiche et al., 2020; Saidak et al., 2020).

6. Existing worldwide guidelines

Although a significant proportion of OSCC patients present at an early stage of the disease, it is of interest to note that there is globally a lack of consensus amongst the published guidelines on the management of the cN_0 neck.

In Europe, the EHNS-ESMO-ESTRO guidelines do not provide explicit recommendation for the management of early (Stage I and II) OSCC and to the authors' best awareness have not been updated since the last AJCC classification upgrade (Gregoire et al., 2010). The German guidelines written by Wolff et al. strongly favour upfront elective neck dissection regardless of the T stage of the tumour (Wolff et al., 2012).

In the UK the 2016 NICE guidelines (National Collaborating Centre for Cancer, 2016) suggest that SNB should be offered for cT1-T2, N_0 OSCC tumours, referring to the 7th Edition of the staging, prior to the incorporation of the DOI in the T-staging system. The 2016 BAHNO guidelines (Kerawala et al., 2016) distinguish the T1 and T2 tumours based on thickness and set a cut-off of 4 mm above which elective neck dissection is recommended, whereas for thinner tumours SNB is preferred. The Scottish guidelines in the last update in 2006 favoured prophylactic END for all oral cavity cN_0 tumours (S.I.G.N. 2006).

Examples from other countries and continents are similar with the Japanese head and neck cancer guidelines highlighting the controversy in managing the neck in early OSCC (Nibu et al., 2017), whereas Canadian guidance published in 2015 accepts a 4 mm DOI threshold, above which they favour elective ND (S.C.A.O.C.C. 2015).

The most concise and comprehensive guidelines globally are the NCCN and ASCO guidelines (NCCN, 2019; Koyfman et al., 2019). The former incorporates the DOI in an explicit evidence-based treatment decision algorithm. The NCCN strongly suggests END for tumour DOI 4 mm or above and reserves SNB only for thin OSCC of a DOI up to 2 mm. For intermediate depth tumours the guideline suggests correlation with other tumour and patient characteristics pointing towards a more individualised approach (NCCN, 2019). The ASCO guidelines favour upfront elective neck dissection and also recommend a lowthreshold for elective surgical treatment of the contralateral neck in tumours proximal to the midline (Koyfman et al., 2019).

Table 3
Vertical tumour growth cut-offs associated with higher risk of nodal metastasis. Nomenclature referring to tumour *thickness* and/or *DOI* preserved in relation to the original articles referenced.

	Tongue	FOM	Buccal	Cumulative
Thickness	3 mm (Po Wing Yuen et al., 2002)-4 mm (Balasubramanian et al., 2014)	1.5 mm (Mohit-Tabatabai et al., 1986) 2 mm (Balasubramanian et al., 2014)	6 mm (Urist et al., 1987)	3 mm (Spiro et al., 1986) 4 mm (Pedersen et al., 2016) 5 mm (Sheahan et al., 2003)
DOI	4 mm (Fakih et al., 1989)	-	4 mm (Cariati et al., 2019)	3 mm (D'Cruz et al., 2015)

7. Recommended policy

Based on the current best available evidence we propose that elective neck dissection should comprise the default mainstay treatment of the cN_0 neck. Elective surgical management of the neck has the following advantages:

1. Accurate staging; Selective neck dissection allows analysis of all the nodal basins in the draining region of the primary tumour and provides the most reliable means of staging.
2. Locoregional Control; END pre-empts the best opportunity for locoregional control of the disease (prophylactic and therapeutic management).
3. Adjuvant treatment planning; Pathological assessment of the regional lymph nodes allowing timely planning and delivery of appropriate adjuvant therapy (RT or CRT).

The primary tumour depth of invasion (DOI) constitutes indisputably a key parameter in the evaluation of the risk for nodal occult metastasis and the overall prognosis of the disease and it should be taken under consideration in the treatment planning (primary and adjuvant).

SNB risks de-escalating the therapeutic approach in high risk cancers and should be reserved for carefully selected cases, when nodal metastasis in unlikely to occur. SNB has a role in clinically thin (less than 2 mm DOI) tongue, buccal and alveolar SCC while it can also be considered in histologically “favourable” SCCs of 2–4 mm DOI. SNB should not be employed in FOM tumours due to the inherent site-specific inaccuracies of the technique and its high false negative ratio in this anatomical subsite.

FOM tumours should be considered high-risk for regional failure and should be approached differently, due to the early preponderance of tumours to spread (DOI 1.5 mm). In FOM OSCC strong consideration for bilateral selective neck dissection must be given.

Estimation of DOI preoperatively cannot always be guaranteed with accuracy. Correlation with other clinical (site, endophytic growth profile), radiological and histopathological (evidence of poor differentiation, perineural invasion, lymphovascular spread, non-cohesive pattern of infiltration from the initial biopsy specimen) evidence is recommended, with a low threshold to embark on END.

Future research should be targeted on more accurate profiling of the primary tumours and assist in tailoring the extent of the surgical management to decisively intercept the biological aggressiveness of the disease. Lymphoscintigraphy and sentinel node biopsy may be of value as a diagnostic mapping procedure, and further research should be undertaken in its applicability in tracing the nodal involvement in tumours proximal to the midline and previously treated patients (recurrent or metachronous disease) where altered or aberrant lymphatic drainage is expected.

Competing interests

None declared.

Acknowledgements

The authors wish to thank Mr Francis Vassiliou for the graphic design of the illustrations.

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