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REVIEW ARTICLE

Head and neck cancer: towards a new paradigm with sentinel node localization

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Abstract In an attempt to improve the detection of occult lymph node metastasis and avoid the morbidity, burden and costs of unnecessary elective neck dissection, sentinel node biopsy has been introduced successfully in early oral cancer: a sensitivity of 93 % and negative predictive values of 80–100 % have been reported. In comparison with elective neck dissection (in all patients), sentinel node biopsy (with neck dissection only in if sentinel node is positive) is associated with less complications, less shoulder morbidity and lower costs. In case of a positive sentinel node, neck dissections can potentially be tailored to the individual patient. Results in other non-cutaneous head and neck sites are promising, but need further research before entering routine clinical practice. New developments in tracers and instruments may increase the sensitivity of sentinel node biopsy further and facilitate harvesting of sentinel nodes.

Keywords Head and neck cancer · Oral cancer · Sentinel lymph node · Occult lymph node metastasis · Neck dissection

Introduction

Head and neck cancer traditionally refers to malignant tumors that arise in the upper aerodigestive tract. The vast majority of these tumors are squamous cell carcinomas, which mainly arise from the mucosal epithelium of the oral cavity, pharynx and larynx. Malignant tumors arising from adjacent structures including the salivary gland, thyroid gland, soft tissues and bone are relatively infrequent. Head and neck squamous cell carcinoma (HNSCC) is the seventh most common cancer type worldwide, accounting for approximately 4 % of all malignant tumors [1]. HNSCC has a high propensity to metastasize through lymphatics to regional lymph nodes rather than to spread haematogeneously. Moreover, regional metastasis at time of diagnosis is one of the most important prognostic factors. The presence of cervical lymph node metastasis roughly reduces survival by half. Patients with multiple, contralateral or bilateral metastases in the neck have even a more markedly reduced survival. It is universally accepted that the neck has to be treated by either surgery with or without adjuvant (chemo)radiation or by primary (chemo)radiation in case of overt lymph node metastases. Unfortunately, there is no single noninvasive imaging technique, which could reliable detect occult lymph node metastasis reliable enough [2, 3].

Recently a meta-analysis comparing CT, MRI, PET and US for the detection of cervical lymph node metastasis in head and neck cancer patients with a clinically N0 neck was performed by Liao et al. [4]. The pooled estimates for sensitivity on a per-neck basis were 52 % (CI 39–65), 65 % (CI 34–87) 66 % (CI 47–80), and 66 % (CI 45–77) for CT, MRI, PET and US, respectively. The pooled estimates for specificity were 93 % (CI 87–97), 81 % (CI 64–91), 87 % (CI 77–93), and 78 % (CI 71–83) for CT, MRI, PET and US, respectively. In this study USgFNAC was not included, because of several methodological reasons [4]. The reported sensitivity of USgFNAC in clinically N0 neck was between 42 and 73 %. The aim of this review is to discuss the potential of sentinel node biopsy in

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the management of the clinically negative neck in head and neck cancer patients [3].

Dilemma in treatment of the neck

Consequently, the management of the clinically negative (cN0) neck is still a controversial issue. There is general agreement that elective treatment of the neck is indicated when there is a high likelihood of occult, i.e., clinically and radiologically undetectable, lymph node metastases, when the neck needs to be entered to resect the primary tumor or to reconstruct the surgical defect, or when the feasibility of regular follow-up is questionable [2, 3].

The rationale for elective (prophylactic) treatment is based on the following assumptions. First, occult metastases will inevitably develop into clinically manifest disease. Secondly, even with watchful waiting some patients will develop extensive or even inoperable disease in the neck with a wait and see policy. Finally, if left untreated, disease in the neck may be associated with a higher incidence of distant metastases, developing while the undetected lymph node metastasis is growing to a clinically detectable size. The arguments against elective treatment of the neck are as follows. Firstly, a large proportion of patients are subjected to the morbidity (e.g., shoulder dysfunction [5]) and costs of unnecessary treatment. Secondly, such treatment may remove or destroy a barrier to cancer spread and a route of cancer spread in case of local recurrence or second primary tumor.

While nowadays most primary HNSCC sites are treated primarily by (chemo)radiation, HNSCC in the oral cavity are generally treated surgically. Because early stage (T1–T2cN0) oral cancer can generally be resected transorally without entering the neck for resection of the primary tumor or reconstruction of the intraoral surgical defect, the aforementioned dilemma, elective treatment of the neck or follow-up (watchful waiting or wait and scan), is especially valid for these tumors.

Sentinel node procedure

In an attempt to improve the detection of occult lymph node metastasis in HNSCC, sentinel node biopsy (SNB) has been introduced in early stage oral cancer. SNB is a diagnostic staging procedure, which is widely applied in a variety of tumor types, including melanoma and breast cancer. The procedure aims to identify the first draining lymph node(s), the sentinel node(s) [SN(s)], which is most likely to harbor metastasis. Conceptually, the histopathologic status of the SN reflects the histopathological status of the rest of the nodal basin. Additional treatment of the nodal basin (e.g., surgery) should be performed in case of metastatic involvement of the SN. A negative SN, i.e., without metastasis, would justify refraining from treatment of the nodal basins.

In short, the routine SNB procedure consists of lymphoscintigraphy, biopsy and histopathological examination of the SN. In a two-day protocol 40–100 MBq and in a same day protocol 25–40 MBq of technetium-99m (^{99m}Tc)-labeled nanocolloidal injections of albumin, divided over four aliquots of 0.10–0.20 mL each, is generally peritumorally subcutaneously injected using surface (spray) local anesthesia only for intraoral and accessible oropharyngeal tumors and general anesthesia for deeper pharyngeal and laryngeal tumors, which can only be injected endoscopically. In general, directly after injections dynamic and static planar lymphoscintigraphy followed by single-photon emission tomography/computed tomography (SPECT/CT) imaging is performed [6]. Late imaging (2–4 h after injections) is generally only needed in patients with midline tumors and tumors in the oral cavity other than mobile tongue or lateral floor of mouth [7]. Based on the preoperative lymphoscintigraphy results the position of the SN is marked on the skin. SNB is performed under general anesthesia and intraoperative detection of the SN is possible by a combination of peritumorally injected blue dye (coloration) and a portable (free hand) gamma probe (radionuclide detection). Ideally, one or more blue and radioactive ('hot') SNs are identified and excised (Fig. 1). However, lymph nodes that are either blue or 'hot' alone are also considered to be SNs. After surgical removal, the SN is investigated by meticulous histopathological examination using stepped serial sectioning and immunohistochemistry. Current best practice guidelines for the provision of SNB in early oral squamous cell carcinoma (OSCC) patients have been outlined, which provide a framework for the currently evolving recommendations for its use [6].

The main radiopharmaceutical used in Europe is ^{99m}Tc-labeled nanocolloidal albumin with a mean particle size of 8–30 nm, whereas in the US of America this tracer is not approved and ^{99m}Tc-rhenium sulphide colloid (mean particle size 23–25 nm) and ^{99m}Tc-sulphide colloid (particle size <100–200 nm) are used. Also larger particles of ^{99m}Tc-labeled nanocolloidal albumin are used. Since these radiopharmaceuticals are registered for breast cancer and melanoma, all these tracers have to be used off-label. ^{99m}Tc-labeled-tilmanocept, a novel receptor-targeted radiopharmaceutical, recently received approval from the FDA for use in SNB for both melanoma, breast cancer and head and neck cancer [8, 9]. This tracer has only recently been tested in early oral cancer [9]. It is nonparticulate radiotracer that contains multiple mannose moieties with high affinity for the CD206 receptor found on macrophages

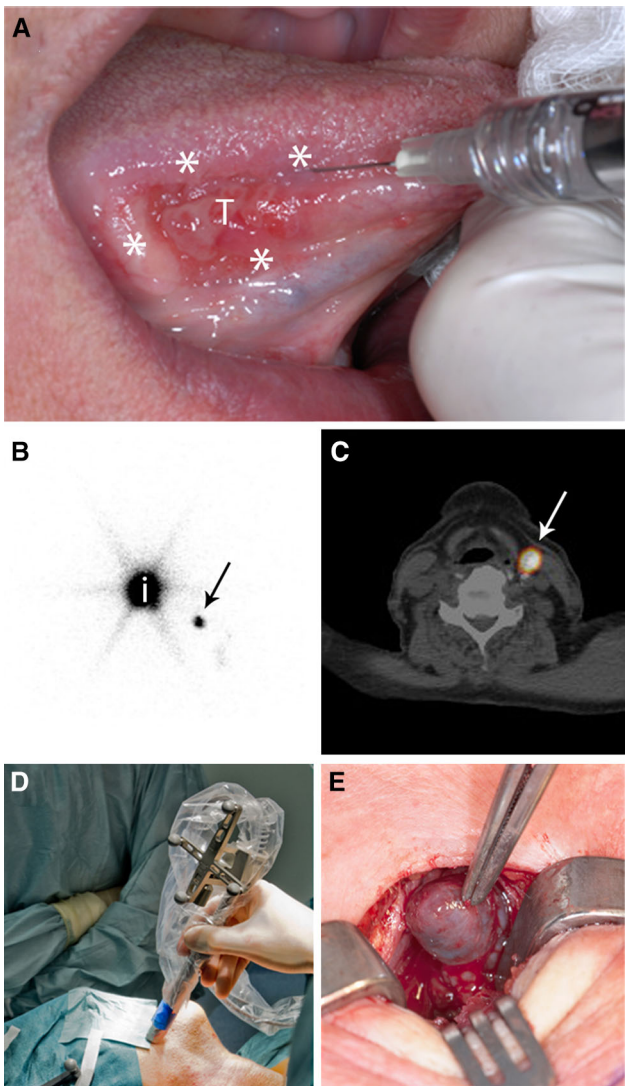

Fig. 1 Sentinel node procedure in a patient with a lateral tongue carcinoma. **a** Peritumoral injections (*asterisk*) of ^{99m}Tc-labeled Nanocoll (*T* primary tongue carcinoma); **b** planar lymphoscintigraphy (*i* injection site; *arrow* sentinel node); **c** SPECT–CT (*arrow* sentinel node); **d** intraoperative detection using gamma probe; **e** sentinel node biopsy (*blue* and hot) (color figure online)

and dendritic cells, enhancing targeting to these cells within the sentinel lymph node. In breast cancer and melanoma it may have improved clearance from the site of the primary tumor and enhanced retention within the sentinel node [8, 9]. There are currently no studies comparing these different radiopharmaceuticals head to head [6].

Accuracy

To safely assign patients to surgery or watchful waiting, high demands are put on feasibility and sensitivity of the SN procedure. Therefore, first SNB has to be validated for each tumor site and then its utility could be investigated. The sentinel node concept in OSCC had been validated in several studies in which all patients underwent an elective neck dissection after SNB [10]. The histopathological examination of the neck dissection specimen was used as reference (gold) standard. Although several studies had validated the SNB concept in OSCC, the American College of Surgeons Oncology Group (ACOSOG) Z0360 performed a validation study with 140 patients in 25 institutions and found a sensitivity of 90 % and a negative predictive value of 96 %, and these figures were even better for experienced surgeons [11]. A recent meta-analysis of these validation studies with 631 OSCC patients showed a pooled sensitivity and negative predictive value of 94 and 96 %, respectively [12]. Because routine histopathological examination (and not step-serial sectioning and immunohistochemistry) of the neck dissection specimen was used as the reference standard occult micrometastases might have been missed [13], potentially contributing to higher figures for sensitivity and negative predicting value. Therefore, to investigate the accuracy and utility of SNB only (without subsequent neck dissection in all patients) follow-up should be used as reference standard [14]. However, when new tracers or instruments are tested, the validation concept using elective neck dissection as reference standard should be considered.

After initial studies to validate the SN concept in early OSCC patients, several prospective observational studies have been reported. In these studies a neck dissection was performed only when the SN contained a metastasis, while a watchful waiting strategy was followed when the SN did not contain metastasis. In a European multicenter study [15] of 134 cT1/2N0 OSCC patients, 79 patients underwent SN biopsy as the sole staging tool, while 55 patients underwent SN biopsy followed by elective neck dissection (END). In 125 (93 %) patients the SN was successfully harvested. For the two groups together, using a reference standard of 5-year follow-up after SN biopsy staging, a sensitivity of 91 % and a negative predictive value of 95 % were found. The better performance of the SN biopsy-assisted END group (sensitivity 96 %, NPV 97 %) compared to the SN biopsy-alone group (sensitivity 87 %, NPV 94 %) can again be explained by the use of standard histopathological examination of the neck dissection specimen versus 5-year follow-up as a gold standard for metastasis. In a large single-center study no false-negative ipsilateral findings were found in a study of 103 oral and oropharyngeal patients. Lymphoscintigraphy revealed a hot spot in 98 %, the detection rate was 96 % and a mean of 2.65 SNs were harvested per patient [16]. In another single-center study of 79 cT1/2N0 patients lymphoscintigraphy showed a hot spot in 95 %, the peroperative detection rate was 99 %, and a mean of 2.7 SNs were harvested for a

Table 1 Results of meta-analyses, largest reported multicenter study and largest studies after latest meta-analysis

	Type	*n*	Sensitivity		Negative predictive value	
				95 % CI		95 % CI
Neck dissection						
Paleri et al. [10]	Meta-analysis	350	93 %	85–96		
Thompson et al. [12]	Meta-analysis	766	95 %	91–99	96 %	94–99 %
Govers et al. [19]	Meta-analysis	540	94 %	90–97 %	80–100 %	
Civantos et al. [11]	Multicenter study	140	90		96	
Follow up						
Govers et al.[19]	Meta-analysis	307	91	84–95	92–98	
Den Toom et al. [18]	Single center	90	93		97	
Flach et al. [20]	Multicenter study	307	80		88	
All						
Govers et al. [19]	Meta-analysis	847	93 %	90–95 %	80–100	

n number of patients included, *95 % CI* 95 % confidence interval

sensitivity of 91 % and a negative predictive value of 90 % [17]. A recent meta-analysis including 847 patients from 21 studies showed a pooled sensitivity of 93 % [95 % confidence interval (CI) 90–95 %] in oral cancer patients. When neck dissection was used as reference standard sensitivity was 94 % (CI 90–97 %), versus 91 % (CI 84–95 %) when follow-up was the reference standard. The vast majority of the studies included were performed in patients with early OSCC. The negative predictive values ranged from 80 to 100 % [18].

More recently a retrospective study of 90 previously untreated early OSCC patients with a clinically N0 neck who underwent SNB (only neck dissection after positive SNB) was reported: a lymphoscintigraphic identification rate of 98 %, surgical detection rate of 99 % and upstaging rate of 30 % were found. Using a median follow-up of 10 months the sensitivity was 93 % and the negative predictive value was 97 % [19]. A Dutch multicenter SNUS study of 62 OSCC patients showed a sensitivity of 80 % and a negative predictive value of 88 % with ultimate neck control rates of 97 % in SN-negative and 95 % in SN-positive patients. In this study the incidence of lymph node metastases was high (40 %), patients were selected after negative USgFNAC and also less experienced centers participated, which may account for the lower accuracy figures [20]. Civantos et al. [11] reported better results of experienced surgeons in the ACOSOG Z0360 study. In both meta-analyses and the ACOSOG Z0360 and SNUS studies, the number of patients per center is below 30. Ross et al. [21] reported on the first international conference on SNB in head and neck cancer that centers that had performed 10 or fewer cases had a lower sensitivity (57 %) in comparison with centers that had performed more than 10 cases (sensitivity 94 %). In small series the contribution of the first 10 patients on the results may be substantial. If only larger studies would have been included in the meta-analyses the pooled sensitivity and NPV may have even been higher. Table 1 shows the results of aforementioned studies in more detail.

The observational multicenter European Sentinel Node Trial (SENT) with more than 400 patients has completed accrual and is waiting for long-term follow-up.

Comparison of sentinel node biopsy and elective neck dissection

Staging

Occult metastases can be missed by routine histopathological techniques in up to 15.2 % [12]. In SNB the lymph node with the highest risk is examined step-serial sectioning and immunohistochemistry. Since the neck contains up to about 150 lymph nodes per side it is practically impossible in daily clinical practice to examine all lymph nodes from a neck dissection specimen so rigorously. Therefore, it can be expected that SNB or SNB assisted neck dissection stage the neck more reliable than neck dissection without SNB [22].

Extent of neck dissection

The levels dissected during elective neck dissection depend on the expected drainage pattern of the primary tumor site. However, Civantos et al. [11] found in 14 of the 103 (13.6 %) oral cavity carcinomas and head and neck cutaneous malignancies lymph node drainage patterns outside the expected lymph node basins. These unexpected sentinel node localizations include not only level IV and V and the contralateral neck, but also in 4 of the 43 oral cancer patients facial sentinel lymph nodes. Kovacs et al. [15] reported on the sentinel node distribution pattern in 103 patients with T1/2N0 oral and oropharyngeal cancer. Besides sentinel nodes in level IV (18/273) and level V (5/

273) also sentinel nodes in level VI (5/273) were found. Flach et al. [23] found in pretreated necks unexpected lymphatic drainage in 67 %. These findings underline the strength of SNB in assessing individual drainage patterns.

Recently, a report of a European multicenter study on 109 oral squamous cell carcinoma patients with positive SNB showed additional (non-SN) metastases in 34.4 % of the neck dissection specimens. The risk of non-SN metastases outside the adjacent basins of the positive sentinel lymph node was low (7.1 %), suggesting that in the vast majority of the patients with a positive SNB a (super)selective neck dissection may be sufficient [24]. It can be anticipated that using information obtained from the SNB procedure neck dissections can be tailored to the individual patient.

Morbidity

SNB is less invasive than elective neck dissection. Murer et al. [25] compared shoulder morbidity and postoperative complications between 33 SNB only and 29 elective neck dissection OSCC patients using questionnaires and objective measures of active shoulder function. SNB was associated with a shorter incision, significant less (no) complications and significant better (almost normal) shoulder function. Although all the complications were minor, they all occurred in patients after elective neck dissection [25]. Schiefke et al. [26] also found a significant minor disturbance of shoulder function in 24 HNSCC patients receiving SNB only compared to 25 HNSCC patients who underwent elective neck dissection assessed by patient symptom scores and objective measurements. SNB was also associated with significant less cervical skin numbness and less disturbance of protopathic (pain) sensitivity compared to elective neck dissection [26].

Costs

Apart from reducing neck dissection numbers, SNB may reduce treatment costs. Using a treatment model derived from the European Sentinel Node Trial (SENT) information, O'Conner et al. [27] produced estimates for relative treatment costs between patients managed through a traditional elective neck dissection or SNB pathway and found that the SNB approach is cheaper relative to the traditional surgical approach in the centers from Spain, United Kingdom and The Netherlands. Kosuda et al. [28] showed that SNB was also cost-effective (compared to elective neck dissection) using costs referred to billed costs based on the Japanese national insurance reimbursement system. A recent cost-effectiveness study in which five different strategies for management of the clinically N0 neck (defined as N0 after imaging and ultrasound-guided fine-needle aspiration cytology) in OSCC patients were compared, predicted that the SNB followed by neck dissection (if positive) or watchful waiting (if negative) is more cost-effective than elective neck dissection, watchful waiting, gene expression proofing (GEP) followed by neck dissection (if high risk) and GEP and SN (in case of high-risk GEP) followed by neck dissection (if SNB positive) or watchful waiting [29].

Limitations of current sentinel node procedure

From these data it can be concluded that the introduction of SNB in early oral cancer has been successful. This was recognized by the National Comprehensive Cancer Network (NCCN) and resulted in incorporation in the NCCN Clinical Practice Guidelines in Oncology of Head and Neck Cancers (version 2.2013): "Sentinel lymph node biopsy is an alternative to elective neck dissection for the identification of occult cervical metastasis in patients with early (T1 or T2) oral cavity carcinoma in centers where experience for this procedure is available. Its advantages include decreased morbidity and improved cosmetic outcome" [30]. However, in some subsites of the oral cavity, e.g., floor of mouth, these results are significantly worse. With respect to floor of mouth (FOM) tumors, detection of the SN appeared to be more difficult: SN successfully harvested in 88 vs. 96 % and a significantly lower sensitivity for FOM tumors compared to other sites (80 vs. 97 %) [15]. This is probably due to the close spatial relation between the primary tumor and the first draining lymph nodes (SNs). The injection site (around the primary tumor) produces a large hotspot on lymphoscintigraphy possibly hiding SN(s) in the close proximity of the primary tumor ("shine through"). It is therefore of utmost importance and challenging to improve SNB in patients with early OSCC at these subsites. Technical improvements are needed to bring SNB for carcinoma of all subsites in the oral cavity to the same high level. More precise information on the localization of the SN may reduce operating time and the risk of damaging vulnerable structures such as nerves and vessels in the neck improving the safety during surgery. Less extensive exploration will result in less fibrosis hampering an eventual subsequent neck dissection, resulting at the end in a reduction of complications and not-intended sacrificed structures in the neck.

Technical improvements

Although hybrid single-photon emission computed tomography with integrated computed tomography (SPECT–CT) has the potential to detect preoperatively

more SNs as compared to planar lymphoscintigraphy, it still has some difficulties in visualization of SNs in close spatial relation to the injection site [31]. However, SPECT–CT can improve visualization of the relation of SNs to several vital vascular and neural structures in order to be able to easier (reducing operating time) and more safely remove these nodes. Recently a PET-tracer, zirconium-89 (^{89}Zr)-nanocolloidal albumin, dedicated to lymphatic mapping and SN detection using high-resolution PET–CT was developed. Compared to gamma-based techniques, improved detection and more precise localisation of SNs could be achieved on PET–CT in a recently performed clinical feasibility studies. PET–CT was able to identify SNs close to the injection site and lymphatic vessels, which were not visualized on SPECT–CT [32]. Due to its particular nature and non-standardized variation in preparation, SNB agents, i.e., radiolabeled colloids (100–1,000 nm particle diameter) are retained for prolonged periods within the injection site, which in turn contributes to the phenomenon of the shine through effect. Recently, a receptor-targeted nonparticulate tracer, ^{99m}Tc-tilmanocept, was introduced, with smaller size and specific targeting the CD206 mannose receptors located on reticuloendothelial cells within lymph nodes permitting rapid clearance from the injection site and stable retention in SNs [8].

Also intraoperative detection of SNs close to the primary is often to be found difficult, due to the high amount of radioactivity present at the injection site (i.e., primary tumor). Gamma probe detection may fail in reliable differentiation between SN and injection site. Blue dye particles follow lymphatic vessels and accumulate in the draining lymph nodes giving them a blue staining. Real-time detection of this blue staining is only possible if there is no overlying tissue. Moreover, blue dye consists of small particles with a very poor retention in the SN and is therefore restrained to a short period of time. This is probably due to the fast lymphatic drainage in the head and neck area. As a consequence, the use of blue dye appeared to be of limited added value in the head and neck area [20].

Technical innovations to improve intraoperative SN localization include intraoperative real-time imaging, freehand SPECT and fluorescence imaging. Intraoperative real-time imaging with the portable gamma camera provides an overview of all radioactive spots and can show SNs near the injection site by adjusting its position. Another advantage may be the certainty it can provide about the completeness and accuracy of SN excision by showing the remaining activity. This portable gamma camera was able to visualize SNs at difficult sites more efficiently and identifies 9 additional SNs in 6 of the 25 head and neck melanoma or OSCC patients [33]. Freehand SPECT is designed to determine the position of the detector relative to the patient through which 3D images are generated. This provides the surgeon information about the direction and depth of the SN in relation to the probe. The possibility of generating images in the operating room could be used again after the procedure, but before closing the wounds, in order to confirm harvesting of all hot spots. In this way remaining hot spots can be excluded. Promising results in OSCC patients have been reported [34, 35].

NIR fluorescence imaging is also a very attractive option to facilitate intraoperative detection. NIR dyes have the advantage in exhibiting reasonable tissue penetration of excited and emitted light with negligible autofluorescence, resulting in higher target-to-background contrast. NIR fluorescence imaging provides high-resolution images which can be obtained in real time during the surgical procedure, even if the structure of interest is covered by some tissue (in contrast to blue dye). Another advantage of NIR fluorescence imaging is that it is much better suited for detection of SNs close to the primary, because there is negligible influence of fluorescence signal coming from the injection site. The feasibility of near NIR fluorescence-guided SN detection has been demonstrated in HNSCC where fluorescence imaging of indocyanin green (ICG) was used as fluorescent tracer [36]. Other tracers with improved optical properties have been tested in HNSCC in preclinical settings [37]. Radiolabeled tracers other than colloid with other characteristics, e.g., ^{99m}Tc-tilmanocept, may improve intraoperative differentiation between SN and injection site [8].

Sentinel node biopsy in other head and neck sites

The experience with other non-cutaneous head and neck sites is limited. Only small series have been reported. Since SNB may be particularly valuable in surgically treated HNSCC patients if the neck should not be entered for resection of the primary tumor or reconstruction of the surgical defect, SNB may be useful in transorally resectable laryngeal and hypopharyngeal tumors, e.g., using (micro)endoscopic laser and/or robotic surgery. Thompson et al. [11] found in their meta-analysis for SNB (using histopathological examination of the neck dissection specimen as reference standard), a negative predictive value of 100 % for all 72 oropharyngeal, 5 hypopharyngeal and 58 laryngeal with upstaging from N0 to N+ in 46, 60 and 28 %, respectively. More recently, Flach et al. [38] found for SNB a sensitivity of 92.3 % (incidence 31 %) to detect occult lymph node metastasis in 13 laryngeal cancer patients with previously untreated necks. SNB in parotid tumors have also been reported [39]. Before SNB incorporation into routine clinical practice, as in early oral cancer at an increasing number of centers, larger series are needed for these other head and neck sites.

Conclusion

SNB is a reliable diagnostic staging technique of the clinically negative neck in early oral carcinoma. Using SNB early stage OSCC patients can avoid unnecessary elective neck dissection, which may reduce morbidity and costs and improve the quality of life. However, there is room for improvement for tumor sites with close spatial relation of the potential SNs as in FOM tumors. New tracers for gamma imaging, PET and fluorescence imaging, ^{89}Zr-, ICG- and IRDye800CW- nanocolloidal albumin and ^{99m}Tc-tilmanocept, have been developed and are currently tested in early oral cancer patients as single or hybrid tracers. These improvements may increase the sensitivity of SNB further and limit the exploration needed to harvest SNs, reducing the risk of complications and operating time.

Conflict of interest Remco de Bree declares no conflict of interest.

Human and animal studies This article does not contain any studies with human or animal subjects performed by the author, besides studies which are reviewed, described and referred to in the reference list.

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