Minimally invasive diagnostics for occult lymph node metastases in head and neck cancer

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2016

MINIMALLY INVASIVE DIAGNOSTICS FOR

OCCULT LYMPH NODE METASTASES IN HEAD AND NECK CANCER

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The research in this thesis was performed at the Tumor Biology Section of the Department of Otolaryngology-Head and Neck Surgery, VU University Medical Center, Amsterdam, The Netherlands. The research was financially supported by ZonMw, The Netherlands Organization for Health Research and Development, grant 80-82305-98-08106. The publication reflects only the author's view.

Printed by Ipskamp Drukkers B.V., Enschede
Cover: "La Speranza", "Hoop" (brons). Margot Homan. (www.margothoman.nl)
Layout: Mirjam Leppers, Persoonlijkproefschrift.nl

ISBN : 978-94-028-0263-4

VRIJE UNIVERSITEIT

MINIMALLY INVASIVE DIAGNOSTICS FOR OCCULT LYMPH NODE METASTASES IN HEAD AND NECK CANCER

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof. dr. V. Subramaniam,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de Faculteit der Geneeskunde
op dinsdag 11 oktober 2016 om 13.45 uur
in de aula van de universiteit,
De Boelelaan 1105

door Geertje Belia Flach

geboren te Westerschouwen

Promotoren: prof. dr. R. de Bree
prof. dr. C.R. Leemans

To my parents

CONTENTS

CHAPTER 1

General introduction

GENERAL INTRODUCTION

Head and neck squamous cell carcinoma
Head and neck squamous cell carcinoma (HNSCC) arises from the epithelium of the upper aerodigestive tract (Figure 1). HNSCC is the 9th most common cancer worldwide with annually 442,760 new cases of HNSCC (excluding nasopharynx cancer), which is 3.1% of the total cancer incidence.[1, 2] In the Netherlands, approximately 3,000 patients are newly diagnosed each year. The incidence of HNSCC is highest in the sixth decade of life.

Major risk factors for the development of HNSCC are use of tobacco and excessive alcohol consumption.[3] In a subset of HNSCC, especially those located in the oropharynx, human papilloma virus (HPV) is causally associated in the cancer development.[4-6] Furthermore, genetic predisposition is also contributive to HNSCC carcinogenesis as only a small proportion of individuals exposed to the similar environmental factors develop HNSCC.[7]

The most frequently affected subsites are the oral cavity, oropharynx, hypopharynx and larynx.
HNSCC is characterised by lymphogenic metastatic spread to the neck. Clinical and pathological classification of HNSCC is done according to the TNM-classification system of the Union for International Cancer Control (UICC) and American Joint Committee on Cancer (AJCC).[8,9] This classification system is based on the three components: the extent of the tumor (T), the presence of cervical lymph node metastases (N) and distant metastases (M).[10] The TNM-stage is derived from physical examination including investigation under general anesthesia, imaging, cytology of lymph nodes and histopathological investigation after surgical excision.

Staging according to this system is important, since it aids clinical decision making. When HNSCC is diagnosed, unfortunately only 1/3 of the patients have early stage cancer (stage I/II) with generally good prognosis, whereas 2/3 of the patients already have advanced stage disease (stage III/IV) with much worse prognosis. Curative treatment options for HNSCC include surgery and radiotherapy with or without chemotherapy, either alone or as combined therapy. A considerable part of the patients develop recurrent disease after primary therapy. The regional recurrence rate depends on tumor site, stage and therapy. A local recurrence occurs in 10-30% of patients and the annual risk for second primary tumor in the head and neck area is 3-4%.[11, 12] Therapies often affect anatomical structures and may change original metastatic disease patterns. Therefore, in case of recurrence or second primary tumor, re-assessment of disease staging including the presence of lymph node metastases is of critical relevance for optimal treatment planning. Despite increased insight in molecular biology of head and neck cancer, survival rates have not improved markedly during the last decades.[13]

This chapter describes the challenge of management of the clinically N0 (cN0) neck and the introduction of a novel minimally invasive diagnostic method in the diagnostic arena of HNSCC: sentinel node biopsy (SNB).

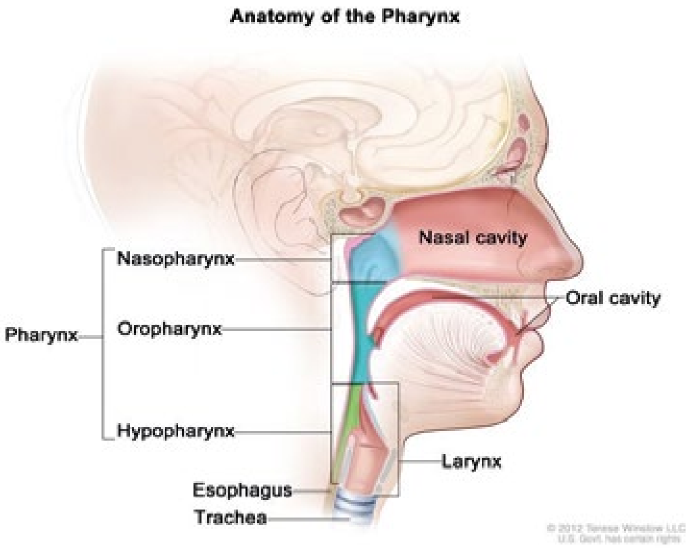


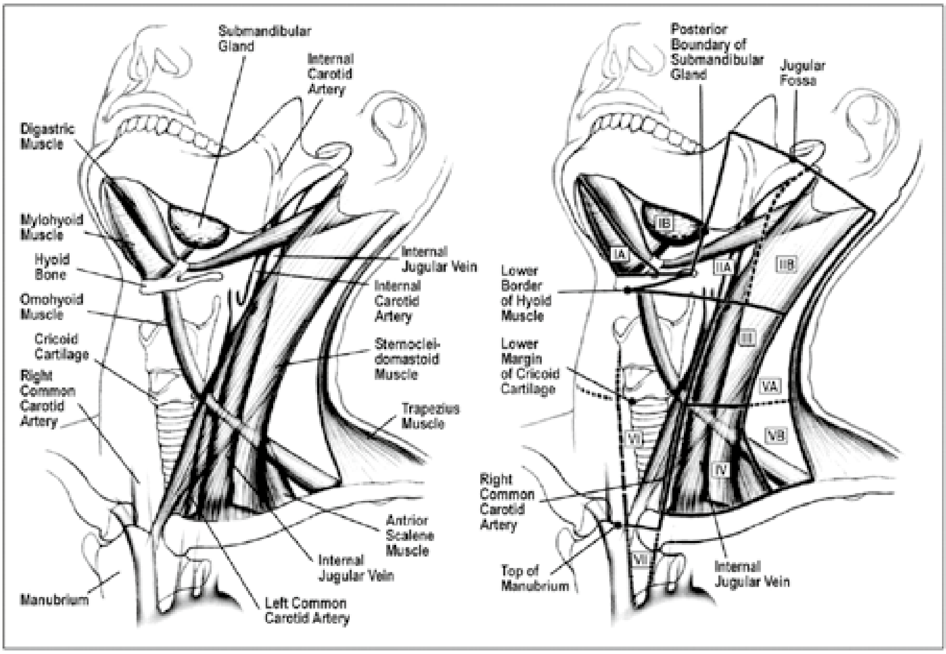
FIGURE 1. Head and neck, tumor subsites (source: 2012, Terese Winslow LLC)

Metastatic spread and management of the N+ neck

The most important route in the spread of HNSCC is through lymphatic pathways towards regional lymph nodes in the neck. The presence of lymph node metastases is an important prognostic factor for HNSCC, as it is strongly associated with the risk of developing further distant metastases. Of the patients without nodal metastases in the neck only 7% develop distant metastases, whereas of the patients with more than 3 lymph node metastases in the neck, distant metastases occur in almost 50%.[14] Table 1 depicts the current (7th edition) TNM staging system of the neck of the UICC and AJCC,[15] and Figure 2 the levels in the neck according to the American Academy of Otolaryngology - Head and Neck Surgery (AAO-HNS).[16]

Nx	Regional nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in a single ipsilateral lymph node, ≤ 3 cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node, > 3 cm but ≤ 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none > 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none > 6 cm in greatest dimension
N3	Metastasis in a lymph node, > 6 cm in greatest dimension

TABLE 1. Staging of the neck, classification system of the Union for International Cancer Control (UICC) and American Joint Committee on Cancer (AJCC)



Level I	Submental region (Ia), Submandibular region (Ib)
Level II	Subdigastric (high jugular) region: anterior (IIa) and posterior from accessory nerve (IIb)
Level III	Midjugular region
Level IV	Low jugular region
Level V	Posterior triangle
Level VI	Prelaryngeal and pre- and paratracheal region

FIGURE 2. Neck levels[106] (source: 2000, American Journal of Radiology)

The distribution of lymph node metastases depends strongly on the location of the primary tumor.[17] Oral cavity carcinomas mainly drain to neck levels I, II and III. More anterior located oral tumors drain to level Ia, or to level II and III, whereas more posteriorly located tumors drain to level Ib.[18] Solitary level IV metastases ('skip' metastases) are rare in oral cavity carcinomas, but they are described in lateral tongue carcinomas.[19]

In oropharyngeal HNSCC the majority of metastatic lymph nodes are present in levels II, III, IV; and in rare cases in the retropharyngeal area.

Lymphatic drainage of the larynx is separated into an upper and lower drainage system, based on embryological origins. The supraglottis drains into levels II and III and often bilaterally. From the glottic and subglottic region lymphatic vessels drain into levels III and IV, and occasionally to level VI (paratracheal nodes). The incidence of lymph node metastases is lowest from glottic cancer due to its avascularity and sparse lymphatic channels, and is higher in subglottic and supraglottic larynx cancer. Hypopharynx cancer drains into levels II, III, IV and VI. These tumors also frequently show bilateral spread, particularly when the primary tumor is close to or crosses over the midline.[17]

The choice of modality for therapy of the neck is generally dictated by the modality that is used for the primary tumor. The extend of treatment of the neck (neck levels) depends on neck stage and tumor factors.[20] In case of N2 or N3 disease, and in selected N1 disease, a (modified) radical neck dissection is performed. A classical radical neck dissection entails dissection of neck levels I-V, including resection of the sternocleidomastoid muscle, the internal jugular vein and the accessory nerve. In a modified radical neck dissection one, two or three non-lymphatic structures (muscle, vein or nerve) are preserved leading to lower postoperative morbidity. A selective neck dissection is applied in N0 disease, and also frequently in N1 disease, and implies dissection of only those levels with the highest risk of containing metastases depending on the location of the primary tumor site, with preservation of all aforementioned non-lymphatic structures.[20]

If histopathological examination of the neck dissection specimen reveals two or more lymph node metastases, the neck is postoperatively irradiated. When extranodal spread is present or surgical margins are positive, adjuvant chemoradiotherapy is generally indicated.[21]

Treatment options for regional recurrence after neck dissection and/or (chemo)radiotherapy are limited and outcome after salvage surgery is almost invariably fatal.

Detection of lymph node metastases

For prognosis and optimal treatment planning it is important to accurately determine the status of the lymph nodes in the neck. With palpation alone only clinical manifest lymph node metastases are detectable. If smaller nodal metastases are present, palpation alone is not accurate for staging the neck. Imaging is more reliable than palpation. For disease staging, conventional diagnostic imaging modalities include computerized tomography (CT) and magnetic resonance imaging (MRI), which are routinely used in the preoperative assessment of the primary tumor. In this setting, when contrast-enhanced, these can also be used to evaluate the neck and the status of the lymph nodes. Assessment of the lymph nodes is based on size, homogeneity and contrast-enhancement. Despite many studies, different criteria are still used for defining lymph nodes that contain metastases on imaging. Van den Brekel et al. proposed the following criteria: a minimal axial diameter of 10 mm (11mm for level II), groups of three or more borderline nodes and central radiolucency.[22] Criteria of Stoeckli et al. are: nodes of any size with clear evidence of non-fat low density on contrast-enhanced CT; more than 15 mm (greatest diameter) for nodes at level II, and more than 10 mm for nodes located in other levels, or a maximum longitudinal/short axis diameter less than 2.0; spherical shape (a supportive criterion in borderline sizes); and groups of 3 or more borderline nodes.[23] Other criteria such as different size measurement (maximal axial diameter), nodal shape or internal abnormalities have also been described.[24, 25]

Currently more advanced imaging modalities, such as positron emission topography (PET) have shown to be of complementary value for selected indications.[26] PET in combination with CT imaging (PET/CT) adds assessment by metabolic activity to size and homogeneity and anatomical localization, but its reliability for diagnosing lymph node metastases appears to be similar to the conventional methods.[27]

For detection of lymph node metastases in the neck, ultrasound (US) and especially in combination with guided fine needle aspiration cytology (USgFNAC) is of particular use. Besides the size of the lymph node, also the absence of an echogenic hilus, presence of cystic or coagulation necrosis, presence of abnormal vessels, presence of eccentric cortical hypertrophy and hypo-echoic sonomorphology play a role in the suspicion of nodal metastasis. USgFNAC combines assessment of imaging with cytopathological assessment. Lymph nodes that are at risk of harboring metastases are aspirated. Cytological slides are prepared from the aspirates for microscopic examination for presence of malignant cells by the pathologist. Selection of the most suspect lymph nodes for aspiration is crucial, and is based on the location of the primary tumor with its lymphatic drainage pattern and size criteria. Lymph nodes with a minimal axial diameter of 5 mm in level II and 4 mm in other neck levels are aspirated.[28, 29] In patients with a cN0 neck USgFNAC has a specificity of 100% and the sensitivity has been reported to vary between 48-77%.[30-33] It has been suggested that this variability in sensitivity is mainly due to the radiologists' experience in performing USgFNAC, as the creation of a representative aspirate with abundant cells from the nodes that are at highest risk is important for the results of USgFNAC.

Besides a preoperative diagnostic instrument for staging of the neck, USgFNAC can be used during follow-up to early detect regional recurrence or, in other words, to detect delayed lymph node metastases that were occult (clinically and radiological undetectable) and therefore missed at initial (preoperative) USgFNAC.

USgFNAC has the advantages of relatively low costs and lack of radiation exposure. However, the detection of occult lymph node metastases is limited, mainly due to sampling error of the aspirate. Moreover, accuracy strongly depends on the radiologists' experience. Furthermore, the retropharyngeal and paratracheal lymph nodes are not easy accessible for USgFNAC examination. Due to these factors further improvement of USgFNAC sensitivity is difficult.
Due to the lack of more accurate neck staging methods, management of the clinically N0 neck has been subject of debate for decades.

The clinically negative (cN0) neck
Management of the cN0 neck has become one of the most actively debated topics in the field of head and neck oncology. When the patient has a high likelihood of occult lymph node metastases, it is generally agreed that an elective -prophylactic- neck dissection is necessary. Similarly, when the patient is unable to visit for regular follow-up or when the neck needs to be entered to excise the primary tumor or to reconstruct the surgical defect after tumor excision, elective neck dissection is advised. When there is merely a high likelihood of occult lymph node metastases, the choice is between elective neck treatment (mainly elective neck dissection (END)) and observation. This dilemma particularly arises in the smaller (T1 and T2) carcinomas of the oral cavity and oropharynx, because these can usually be adequately excised via the transoral route without entering the neck.

The rationale *for elective neck treatment* is based on the following premises. Firstly, occult metastases will inevitably develop into clinically manifest disease. Secondly, despite regular follow-up, patients may develop extensive or even inoperable disease in the neck. Finally, untreated disease in the neck may give rise to distant metastases (rendering the patient incurable), during the interval that the occult lymph node metastasis is growing to a clinically detectable size.

The arguments *against elective treatment* of the neck are that many patients are subjected to unnecessary morbidity. Secondly, such treatment may remove or destroy a barrier to cancer spread in case of local recurrence or second primary tumor.

Observation can be improved by a so called 'wait and scan' strategy, which means strict surveillance of the neck using USgFNAC during follow-up. With a wait and scan strategy, in 18-21% of the patients with initial negative USgFNAC result, delayed lymph node metastases are detected and a salvage rate of 71-79% after therapeutic neck dissection has been reported.[34, 35]
In patients treated with elective neck dissection, the reported incidence of occult lymph node metastases is 10-36% with a regional recurrence rate of 3-12%.[36-39]

In most institutions a risk of occult metastases exceeding 20% is considered to be sufficient to justify elective treatment of the neck nodes in all HNSCC patients. This risk rate is based on a study in 1994 of Weiss et al. who performed a decision analysis to find a threshold value (20%) to choose the best management strategy for HNSCC patients with cN0 neck.[40] During the last decades Okura et al. re-used the decision analysis model with identical utilities but with input from their own survival analysis of a series of cT1-T4N0 oral cancer patients. This resulted in a threshold value of 44.4%, which means that a risk of occult metastases higher than 44.4% justifies elective neck treatment and with a risk below 44.4%, observation of the neck is acceptable. In other words, a higher risk can be taken with an observation strategy due to better salvage therapy, and the preventive arguments for elective neck dissection have become less important.[41] However, this is in contrast to the general opinion in healthcare issues nowadays: to reduce any risk and to not accept the possibility of recurrent disease if precautions can be taken.

There are two ways to approach the controversial issue of management of the cN0 neck: risk assessment based on characteristics of the primary tumor, or improvement of diagnostic accuracy in the detection of occult lymph node metastases.

The risk of occult metastases depends on tumor site, stage and other characteristics. Histopathological features of the primary tumor such as differentiation, thickness, depth of invasion, growth pattern, lymphangiogenic invasion, perineural invasion, degree of inflammatory reaction surrounding the tumor and numerous biomarkers have been evaluated with regard to their relevance in predicting nodal disease. Pedersen et al. reported that factors such as tumor thickness, perineural invasion, and differentiation grade were independent predictive factors for the presence of metastases in SNB patients.[42] A tumor depth of invasion of 4 mm or more is associated with an increased risk of lymph node metastases.[43, 44] Nevertheless, metastases frequently occur also in patients with tumor depth of invasion less than 4 mm. Measuring the tumor depth can be done preoperatively by intraoral ultrasound investigation or by excisional biopsy. However, as the definitive tumor depth is only known after tumor excision and histopathological investigation, this factor has not yet been implemented universally as decisive in management of the cN0 neck. The other features unfortunately have limited prognostic value.[45-47]
Currently, improvements in molecular biological diagnostic techniques are developing. In a Dutch multicenter trial, it has been shown that gene expression profiling by microarray hybridization of tumor biopsies can be used for neck staging, reaching a negative predictive value of 89%. However, due to a positive predictive value of 37%, decision making based on gene expression profiling alone would result in a substantial number of unnecessary neck dissections.[47]

The other approach is improving diagnostic accuracy in the detection of occult lymph node metastases. If (occult) lymph node metastases are reliably detected or excluded, elective neck treatment can be replaced by either therapeutic treatment or observation. To improve the detection of occult lymph node metastases, the lymph nodes that are at highest risk of harboring metastases should be selected. A known diagnostic method for this is the sentinel node biopsy (SNB) procedure.

Sentinel node biopsy

The sentinel node concept is based on the principle of an orderly and predictable pattern of lymphatic drainage and the existence of sequential metastatic spread of tumor cells through the lymphatic system. The first lymph node in a regional lymphatic basin that receives lymphatic flow from a tumor is considered to be the sentinel node (SN). The SN concept assumes that if lymph node metastases are present, they can always at least be found in the SN. And as a consequence, if the SN is tumor-negative, this would preclude the presence of lymphogenic metastases.

The sentinel node biopsy (SNB) procedure consists of three steps: identification, surgical removal and histopathological assessment of the sentinel node.[48] Identification of the SN starts with radioactive tracer injection in the primary tumor area. In Europe, mainly ^{99m}Technetium labelled nanocolloid (^{99m}Tc-nanocoll) is used as tracer, but other tracers also have been used.[49] The tracer consists of a gamma emitting radioisotope (^{99m}Tc) which is labelled to a small protein (nanocolloid) to remain in the lymph node. Using a gamma camera or single photon emission computed tomography-computed tomography (SPECT/CT) (both referred to as lymphoscintigraphy) the tracer is followed during migration, and radioactive uptake in the first draining lymph node (the SN) is visualized. Hot foci are denoted as SN and the localization of the identified SN is indelibly marked on the skin. Of note, lymphoscintigraphy is mainly performed the day before surgery.

Surgical removal of the SN via a small incision, is performed under gamma probe guidance to detect radioactivity, and optionally blue dye guidance for visual detection. Blue dye is injected intraoperatively around the tumor and also follows lymphatic vessels and accumulates in the draining lymph nodes, staining them blue.[50] The final step of the SN procedure is extensive histopathological examination of the SN. This consists of step-serial sectioning (SSS) with an interval of 150-250 µm of the entire lymph node. Of each level staining with hematoxyline-eosine (H&E) and pan-cytokeratin antibody (AE 1/3) is performed. Depending on size criteria, detected lymph node metastases are classified into isolated tumor cells (no larger than 0.2 mm in their greatest dimension; pN0i+), micrometastasis (> 0.2 mm but ≤ 2mm; pN1mi) or macrometastasis (> 2 mm; pN1) according to the criteria proposed by Hermanek et al.[51] If a lymph node metastasis is proven by SNB, lymph node dissection is performed.

In case of negative SNB, patients are kept under careful observation and are spared unnecessary and more extensive surgery. SNB is considered to be more precise in diagnosing occult lymph node metastases than imaging or cytology and is less invasive than elective lymph node dissection.

The history of the SNB concept started in 1959, when Gould presented a paper, entitled: "Observation on a sentinel node in cancer of the parotid." He suggested that an intraoperative frozen section of the SN could guide the surgeon in his decision concerning the necessity for a radical neck dissection.[52] Just two decades later, Cabanas demonstrated the existence of a sentinel node by performing lymphangiography via the dorsal lymphatics of the penis.[53] Guided by anatomical landmarks he determined which node was the SN. Also in testicular cancer, the lymphatic drainage was studied and revealed the existence of a sentinel node.[54] Later on, the retroperitoneum was surgically explored, based on observations of lymph node metastases to this area. Lymph nodes that were found in the retroperitoneum were called sentinels.[55]

Already since 1977, Morton et al. from the John Wayne Cancer Institute, performed cutaneous lymphoscintigraphy with colloidal gold to identify the lymphatic drainage pattern of melanomas. They also introduced intraoperative mapping to selectively remove the sentinel nodes during melanoma surgery.[56] Because this lymphatic mapping was based on anatomical patterns and therefore not interindividually reproducible, it took some more years to find acceptance of the sentinel node concept in the surgical world.

After the report of Morton et al. in 1992, about the use of intradermal isosulfan blue dye injection in cutaneous melanoma to intraoperatively visualize lymphatic channels and to localize the SN, the sentinel node concept became generally accepted.[56] In the same institute, almost simultaneously blue dye was introduced in breast cancer patients for sentinel node detection.[57] Shortly thereafter, radiolabelled colloids and gamma probe detection were introduced to identify the SN.[58]

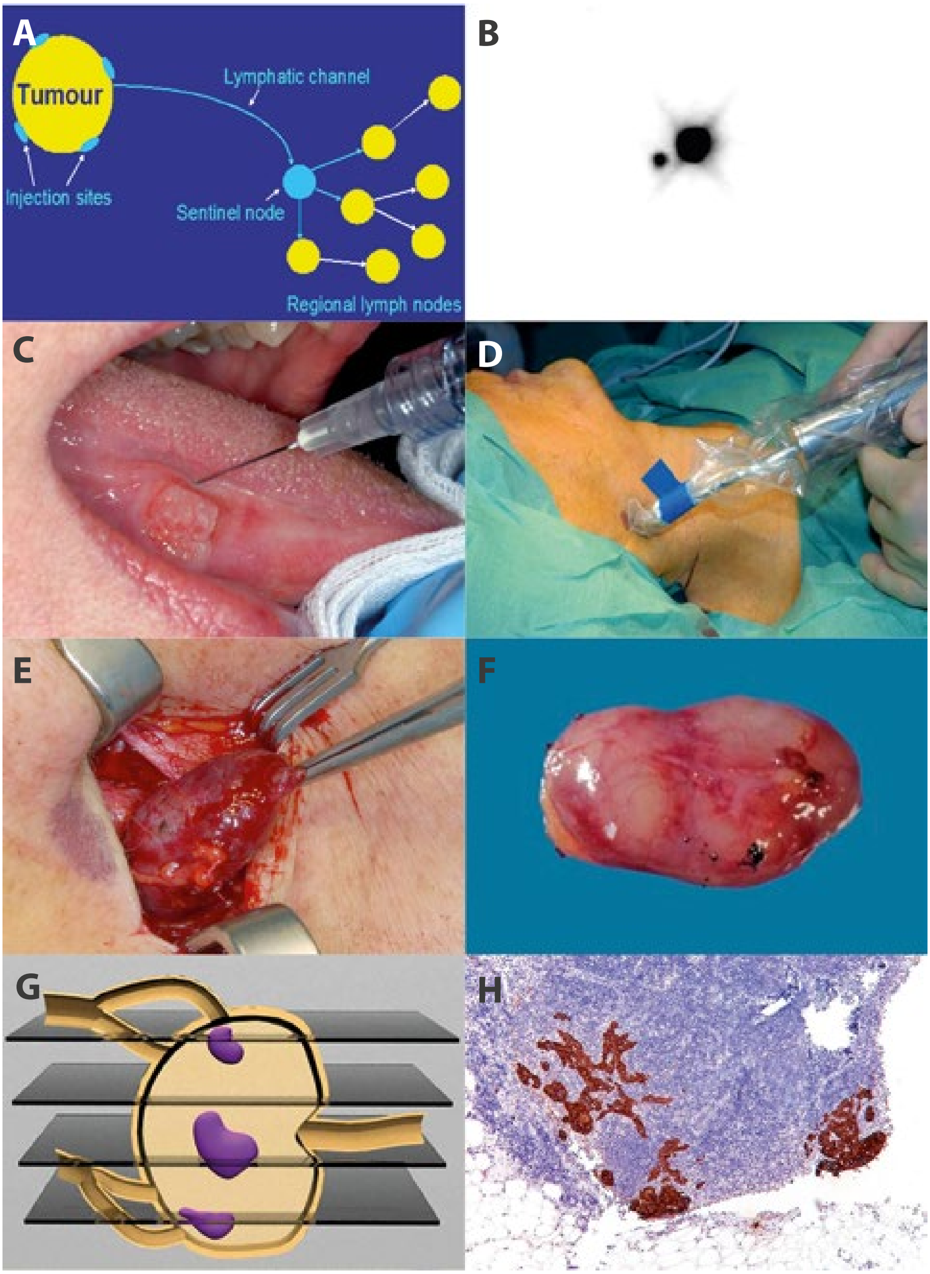


FIGURE 3. The sentinel node biopsy procedure
A: principle of SNB, peritumoral injection of ^{99m}Tc-nanocoll with distribution to regional lymph nodes,
B: lymphoscintigram with injection site and hot focus, C: peritumoral blue dye injection, D: intraoperative SN detection with handheld gamma probe,
E: surgical removal of the SN via a small incision in the neck, F: harvested SN,
G: histopathological investigation by step-serial sectioning,
H: immunohistochemical staining of a section of the SN using the pan-cytokeratin antibody AE1/AE3 demonstrating metastatic disease

Introduction of SNB in HNSCC started with a study on visualization of the cervical lymphatic vessels in the 1960s, and in the 1980s with mapping of lymphatic drainage from specific head and neck sites.[59]
SNB for staging of the clinically N0 neck to identify occult lymph node metastases is particularly relevant in patients in whom tumors can be transorally excised without entering the neck for tumor excision or surgical reconstruction. Therefore, SNB is mainly performed in early stage oral cancer. In Figure 3 the three steps of SNB with identification, surgical removal and histopathological assessment of the SN are depicted.
A recent meta-analysis of SNB in (mainly) oral and oropharyngeal squamous cell carcinoma patients showed a pooled sensitivity of 93% and negative predictive values ranging from 88 to 100%.[60]

The first studies of SNB were validation trials in which SNB was followed by END, which was considered as reference (gold) standard. Later on, SNB was used as diagnostic guide to decide on subsequent neck dissection during a second surgical procedure for positive SNB, or for observation during follow-up for negative SNB. In this situation, follow-up was the reference standard. The choice of reference standard influences accuracy rates: with routine histopathological examination, as is done in END, minimal disease can be missed, whereas step-serial sectioning and immunohistochemistry, as in SNB, can increase the yield of occult lymph node disease by as much as 15.2%.[61] This means, that by using END with routine histopathology as the reference standard, some false negative findings may be incorrectly scored true negative. Therefore, long-term observation of the untreated neck is the better reference standard to determine the value of diagnostic techniques for detection of occult lymph node metastases. It is important to appreciate that sensitivity of a diagnostic technique depends on the applied reference standard.[62]

Experience is needed before a surgeon starts performing SNB as diagnostic method, it carries a steep learning curve and sensitivity is strongly related to the surgeons' experience. At least ten SNB-assisted elective neck dissections is therefore recommended before SNB is performed alone.[63]

The largest SNB study in oral cancer is the Sentinel European Node Trial (SENT), in which 14 European hospitals included 420 patients with cT1-T2N0 oral cancer for SNB followed by observation in case of negative SNB result. At a median follow-up of 52 months, a sensitivity of 87%, a negative predictive value of 95% and disease-specific survival of 94% were found.[64]

The SNB procedure has since January 2016 been incorporated in the updated Dutch guideline for oral and oropharyngeal cancer as reliable first choice diagnostic instrument for staging the neck in cT1-T2N0 oral cancer.[65]

Sentinel node biopsy, novel indications and limitations

To reach high accuracy it is important to select appropriate patients for SNB. Patients should be clinically N0, preferably as assessed by CT or USgFNAC. This is necessary as with gross lymphatic tumor involvement in the lymph node, distortion of the normal nodal architecture may occur, resulting in aberrant lymphatic drainage patterns (the radioactive tracer by-passes the real SN) and the SNB result may be false negative. Therefore, SNB is indicated for staging of the cN0 neck, but not for staging of the clinically positive neck.[66]

The contralateral neck

According to the joint practice guidelines,[48] SNB is indicated to stage the cN0 neck in patients with an unilateral primary tumor, or to bilaterally assess the cN0 neck in primary tumors close to or crossing the midline. A third possible indication for SNB is to evaluate the status of the contralateral cN0 neck in primary tumors close to the midline with an ipsilateral positive neck. In this situation, SNB may select those patients who require bilateral neck dissection in case of positive SNB. This latter approach is under investigation.

Number of SNs

The classical theory of SNB is that there is one sentinel node, with direct lymphatic connection to the primary tumor. However, in clinical practice, patients can have more than one SNs, particularly in the head and neck area as the neck has a complex anatomy with a lymphatic system containing over a 100 lymph nodes on each neck side.

When multiple hot foci are identified on lymphoscintigraphy and marked as SN to be excised during surgery, in general the rule is that every excised hot node with a radioactivity count of 10% or more of the hottest node on that neck side is a SN.[48, 67] Previous theories that indicated harvesting only the three hottest lymph nodes or that stated a maximum amount of SNs have never led to a guideline principle. As the distribution of the radioactive tracer in the lymphatic basin is not predictable and lymphatic drainage is individually based, there is no expected amount of first echelon SNs.[48, 68, 69]

It is known that oral cancer can have multiple hot foci on lymphoscintigraphy and may have unpredictable lymphatic drainage patterns. As the lymphatic vessels, connecting the hot foci with the primary tumor area, are often invisible on lymphoscintigraphy it is not straightforward whether a focus should be considered as true SN or as second echelon lymph node. At the moment, explicit recommendations on how to interpret foci and drainage patterns on lymphoscintigraphy are lacking and definitions of the SN differ between centers.[48, 70]

In many centers SPECT/CT is used additionally for the purpose of anatomically localizing SNs, which is not possible using conventional static and dynamic planar imaging by a gamma camera. Nevertheless, SPECT/CT also results in more visible foci and therefore potentially more SNs.[71, 72] If these are more proximal to the primary tumor site, the additional SNs may have clinical relevance, but if they are more distally visualized, they may not be relevant. Both dynamic scanning directly after radioactive tracer injection and late static imaging remain important for distinguishing first echelon nodes from the delayed appearance of second echelon nodes. These lymphatic drainage patterns on imaging are the basis for SNB and guide the subsequent work with the gamma probe in the operating room, avoiding unnecessary resection of radioactive second echelon lymph nodes.

The floor of mouth

In carcinomas located in the floor of mouth (FOM), identification of a true SN can be exceptionally challenging. This is because of the 'shine through' phenomenon, a result of the short distance between SNs (level I and lingual lymph nodes) and the peritumoral injection site, in combination with the limited resolution of currently used techniques (Figure 4).[66, 73-75] Since most of the peritumoral injected tracer will remain at the injection site, a large focus is seen on lymphoscintigraphy. Uptake of the tracer in a SN close to the primary tumor may be hidden by this large radioactive focus of the injection site and such a SN may not be visualized and identified. Moreover, intraoperative detection of such a SN is often difficult because the gamma probe is not able to differentiate between radioactivity arising from the SN and the injection site. As a result, the reported sensitivity and negative predictive value are (significantly) lower in FOM carcinomas compared to other subsites in the oral cavity (80% vs. 96%, and 88% vs 98%, respectively).[76]

FIGURE 4. The 'shine through' phenomenon (source: 2014, Derrek Heuveling, Thesis) The shine through phenomenon: uptake of the tracer in a sentinel node (SN; red circle) close to the primary tumor (T) is hidden by the large focus of the injection site (yellow circle). This SN will not be visualized and thus not be identified as a SN.

Other tumor sites

The use of SNB in oral and oropharyngeal cancer has been evaluated in multiple studies. SNB application and reliability in other HNSCC sites is still under investigation. In various validation studies the feasibility of SNB in larynx cancer has also been evaluated.[77-88] As is to be expected from the localization, radioactive tracer injection is more difficult in laryngeal cancer than in oral and oropharyngeal cancer. Tomifuji et al. performed endolaryngeal tracer injection by flexible laryngoscopy the day before surgery, followed by lymphoscintigraphy. SNs were harvested during surgery including total laryngectomy with elective bilateral neck dissection. SNB was feasible and the neck status was reliably predicted.[85] In other studies the tracer was injected during surgery by direct laryngoscopy, directly followed by intraoperative detection of the SN by a handheld gamma probe, without lymphoscintigraphic imaging.[84, 87] If SNB is proposed as a staging method, it seems to be particularly useful when the laryngeal tumor is excised by transoral laser surgery. In these patients, the neck does not need to be entered to excise the primary tumor. In patients requiring total (or partial) laryngectomy the additional value of SNB is more limited, but may be still useful for avoiding unnecessary neck dissections.

Also in parotid gland carcinomas there may be room for SNB.[89]

Previous treatment

It is suggested that prior treatment in the head and neck area may change or block the lymphatic channels leading to lower identification rates or false negative results with SNB. By now, there is little evidence about the value of SNB after previous treatment. Pitman et al. performed SNB in 5 oral and oropharyngeal cancer patients with previous neck dissection. SNs could be detected and were located in neck levels outside the dissected levels.[90] In the study of Hart et al. 11 previously treated patients without previous neck dissection underwent SNB followed by END. SNB correctly staged the neck in 91%, according to END.[91] These results are promising and indicate the need for further evaluation of SNB alone as staging procedure in previously treated patients.

Patients' perspective and quality of life during SNB diagnostics and SNB based therapy

SNB is less invasive than END (elective neck dissection). SNB spares unnecessary neck dissection in 70% of cT1-T2N0 oral cancer patients. A neck dissection is associated with postoperative morbidity of the neck, resulting in impairment of the quality of life. Cheng et al. showed that in patients who underwent a (modified) radical neck dissection all had shoulder pain and 80% had drooping shoulder, whereas in patients with selective neck dissection functioning of the spinal accessory nerve was relatively normal, and decrease of shoulder strength lasted only 1 month with complete recovery at 6 months of follow-up.[92] In a study by Schiefke et al, health-related quality of life (QoL) of SNB and elective neck dissection patients was compared, revealing no difference in general QoL, but with fewer swallowing complaints and less fear of progression in SNB patients as compared to END patients.[93] SNB is associated with less postoperative morbidity, less impairment from cervical scars, less sensory dysfunction and better shoulder function than elective neck dissection.[93, 94]

It has been shown that more invasive procedures appear to result in lower health utility and that compared to watchful waiting, selective and modified radical neck dissection, SNB has a relatively high health utility which supports a role for this procedure in oral cancer patients.[95]

Nowadays, patients are more involved in decision making together with their physician. Treatment options in the management of the cN0 neck has been a physician's subject for years. With the implementation of SNB as a new diagnostic based neck strategy, the patients' perspective on SNB is highly important and should be taken into account.

Cost-effectiveness of SNB based treatment planning

With the increasing national healthcare the last few decades, there has been an increased focus on costs. The Government, health insurers and medical professionals emphasize the importance of cost-effectiveness in medical treatment and therefore promote development of guidelines.[96] Guidelines are viewed as useful tools for making care more consistent and efficient and for closing the gap between what clinicians do and what scientific evidence supports. Interest in clinical guidelines is widespread and has its origin in issues faced by most healthcare systems: rising costs; variation in service delivery with the presumption that at least some of this variation originates from inappropriate care; the intrinsic desire of healthcare professionals to offer, and of patients to receive the best care possible.[97] When looking at cost-effectiveness there is a difference in interest between society and the individual. The value of one's life is nearly infinite for the individual, while society places a far more conservative value on our lives; disease causes economic loss due to missed days of work or early death.[98] There are in effect 5 types of costs: direct and indirect costs within and outside healthcare, and intangible costs. The direct costs within healthcare include the actual amount of the health services resources directly involved in illness diagnosis and treatment. Direct costs outside healthcare include patient costs such as traveling costs. Indirect costs within healthcare are medical costs of diseases not related to the therapy under study, which arise as a consequence of life years gained. Indirect costs outside healthcare involve the economic loss of a worker's production secondary to the illness. The intangible costs of disease are described as the changes in the quality of life for the patient and family.[99-101]

There is no widely accepted way of incorporation economic considerations into guidelines. However it is clear that healthcare is expensive while resources are limited and therefore diagnostics and effects of treatment should be in balance with total costs. Economic evaluation can be looked at in three ways; first, a cost-identification analysis in which the financial consequences for providing care according to the guidelines is outlined. In this, all outcomes should be equivalent in terms of quality of life, survival and functional indices. The costs are the only metric examined. Second, a cost-effectiveness (or cost-utility) balance can be performed in which the costs of an intervention are measured against a particular intervention or effect. A separate balance can be made for each effect. The effects measured can be diagnosing a patient with a disease, longer survival or better quality of life. To calculate a cost-effectiveness balance is not easy. The effect is calculated against a reference script. This reference script should consist of the diagnostics or treatments used in best practice. Third, a cost-benefit analysis produces a ratio of the costs to an estimation of the monetized benefit of an intervention.[96, 97, 102] Cost analyses are complex and difficult to perform. It is unlikely that the majority of cost analyses can be calculated with the ideal standards of social perspective, outcome measurement, comprehensive costs accounting, appropriate comparison of interventions, discounting costs over time and sensitivity analyses for uncertainty. However, a deliberate cost analysis with acknowledged imperfections is preferable to none.[103]

In the debate of management of the cN0 neck, cost-effectiveness plays an important role. As with elective neck dissection a substantial number of patients undergo unnecessary surgery, whereas with observation patients are spared a neck dissection but some of them need more extensive neck treatment in second instance. With accurate preoperative neck staging (SNB) patients receive individualized therapy; neck dissection if necessary and observation if possible. However, SNB is a (minimal) invasive, expensive and time-consuming diagnostic procedure with its three steps of nuclear imaging, surgery and extensive histopathology. Therefore, the best management strategy of the neck is not only determined by the highest accuracy rate or the most individualized therapy, but also by the best quality of life and best cost-effectiveness that may be individual or society related.

In the European Sentinel Node Trial, the relative costs of a neck dissection versus SNB based strategy were estimated and compared. They concluded that SNB is more cost-effective than END.[104] In a recent cost-effectiveness study, 5 different strategies for diagnosing and treating cT1-T2N0 oral cancer patients were analyzed: END, watchful waiting (WW), gene expression profiling (GEP) followed by neck dissection (ND) or WW, SNB followed by ND or WW, and GEP with SNB for positive GEP, followed by ND or WW. For input of the cost analysis, clinical data and outcome results of these strategies were derived from different international studies. Assessment using a Markov decision analytic model predicted that SNB followed by ND (in positive SNB) or WW (negative SNB) is more cost-effective than the other strategies.[105] These cost-utility results seem promising for SNB, but with consideration of international financial differences, one should be aware that national analyses may show different results. Therefore, a financial cost-utility analysis should be done per country.

Outline of this thesis

As is explained above, a solution for the debate on management of the cN0 neck in HNSCC may be more accurate staging.

In **chapter 2,** we describe the results of a retrospective analysis on the outcome of a series of cT1-T2 oral cancer patients who were initially staged cN0 by USgFNAC and followed-up with a wait and scan policy with strict surveillance using USgFNAC. Survival rates were obtained from the patients remaining N0 and those who developed delayed lymph node metastases during follow-up. To place rates in perspective, a series of patients who underwent elective neck dissection for the cN0 neck were analyzed, while salvage rate and type of salvage therapy was also evaluated.

In **chapter 3**, the use of SNB in cT1-T2N0 oral and oropharyngeal patients was studied in a Dutch multicenter trial. The detection rate of occult lymph node metastases and accuracy rates with sensitivity and negative predictive value were obtained.

In HNSCC, a local recurrence or second primary tumor is not uncommon. Previous treatment of the neck (e.g. neck dissection and/or (chemo-)radiotherapy) may have influence on the lymphatics and may change or block original drainage patterns. The feasibility and accuracy of SNB in previously treated oral and oropharyngeal cancer patients is described in **chapter 4**.

Drainage of the radioactive tracer through the lymphatics is fast. Dynamic imaging is essential to discriminate the different lymph node echelons. Later imaging may reveal additional foci. In **chapter 5**, we retrospectively assessed the clinical value of additional foci visible on late static lymphoscintigraphy for accurate staging of the neck by SNB.

The first step in SNB, identification of true SN(s) by lymphoscintigraphy, is important for the following steps of SNB. Multiple foci with lack of visible lymphatic vessels on the lymphoscintigram may challenge true SN(s) identification. To keep SNB accurate but minimally invasive, it is important to critically interpret lymphoscintigraphy in a standard non-individual manner, and distinguish first echelon true SN(s) from second echelon lymph nodes. We performed an interobserver study on the interpretation of lymphoscintigraphy which is described in **chapter 6**.

SNB has shown to be accurate for staging of the cN0 neck in oral and oropharyngeal cancer, but other tumor sites are still under investigation. In **chapter 7**, the feasibility of SNB in patients with cN0 larynx carcinoma who needed total laryngectomy with elective neck dissection was studied. Patients with primary as well as recurrent laryngeal cancer were evaluated in this study.

The impact of a SNB based management strategy of the cN0 neck on health-related quality of life, psychological distress and shoulder function is evaluated in **chapter 8**. Also the patients' perspective on management of the neck, following an elective neck dissection strategy or a SNB based strategy was assessed.

If a novel management strategy is proposed as standard of care, it should preferably be cost-effective in comparison to previous management strategies. In **chapter 9** we describe the results of a model-based cost-utility analysis of 4 different management strategies for the cN0 neck.

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CHAPTER 2

Outcome of patients with early stage oral cancer managed by an observation strategy towards the N0 neck using ultrasound guided fine needle aspiration cytology: no survival difference as compared to elective neck dissection

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Oral Oncology 2013;49:157-164.

ABSTRACT

Objectives. Management of the clinically N0 neck in oral cancer patients remains controversial. We describe the outcome of patients with T1-T2 oral cancer and N0 neck based on ultrasound guided fine needle aspiration cytology (USgFNAC) who were treated by transoral excision and followed by a 'wait and scan' policy (W&S).

Methods. This retrospective analysis included 285 consecutive patients of whom 234 were followed by W&S and 51 underwent elective neck dissection (END). Survival rates were compared between groups and correction for confounding factors was performed.

Results. Of W&S patients, the 5-year disease-specific (DSS) and overall survival (OS) were 94.2% and 81.6% respectively. During follow-up 72.2% remained free of lymph node metastases and 27.8% developed delayed metastases. W&S patients with delayed metastases had a 5-year DSS and OS of 80.0% and 62.8%, respectively. In patients with positive END these rates were 81.3% and 64.2%, respectively. Between the groups, survival rates were not significantly different. Of the W&S patients with delayed metastases, 90.6% needed adjuvant radiotherapy versus 55.0% of patients with positive END.

Conclusions. With regard to survival, in patients with early stage oral cancer and cN0 neck a wait and scan policy using strict USgFNAC surveillance is justified as survival is not negatively influenced. Using a wait and scan follow-up strategy instead of elective neck treatment, unnecessary neck dissection and its accompanying morbidity can be avoided in 72.2% of patients. However, for the small proportion of patients with delayed metastases, more extensive treatment with adjuvant radiotherapy is needed.

INTRODUCTION

The single most important tumor-related prognostic factor in patients with head and neck squamous cell cancer is the status of the cervical lymph nodes.[1] Patients with lymph node metastases require treatment of the neck. When the neck needs to be entered for excision of the primary tumor or reconstruction of the surgical defect, a neck dissection needs to be performed. Currently, management of the clinically negative (cN0) neck in patients whose tumor can be resected transorally remains controversial. In general an elective neck dissection (END) is justified if the estimated risk of occult lymph node metastases exceeds 15-20%.[2] However, this policy inevitably results in overtreatment in some patients, since the incidence of occult lymph node metastases in patients treated with elective neck dissections is only 10-36%.[3-14]

Observation of the neck may be considered when a reliable diagnostic technique is available to reduce the risk of undetected lymph node metastases. Previous studies in patients with a cN0 neck have shown that ultrasound guided fine needle aspiration cytology (USgFNAC) is the most reliable diagnostic technique with a sensitivity of 48-73% and a specificity approaching 100%.[15-18] In 1992, we adapted our management of the cN0 neck in patients with T1-T2 oral carcinomas that can be excised transorally. USgFNAC is from then on routinely used as initial staging of the neck. In case of negative USgFNAC findings, these patients are treated by transoral excision with careful observation of the neck as an alternative to END if strict adherence to a surveillance protocol can be followed. After primary treatment the patients are subsequently regularly followed by clinical examination and USgFNAC of the neck, a so called 'wait and scan' policy (W&S).[19] While diminishing morbidity in the majority of patients, as a prerequisite this strategy should not negatively influence the patient in terms of disease control. This wait and scan policy has been evaluated in 2002 by Nieuwenhuis et al.[20] who analyzed 161 patients with T1-T2 oral and oropharyngeal cancer and cN0 neck by pre-treatment USgFNAC (1993-2000) focusing on regional control. These patients were treated by transoral excision and followed by USgFNAC of the neck at regular intervals during the first 2 years. This policy included strict follow-up of the neck with physical examination every 6 weeks and USgFNAC examinations every 3-4 months. During follow-up 21% of the patients developed lymph node metastases and 79% could be salvaged (88% regional control).[20]

As a follow-up on this study, we report on the outcome of the wait and scan policy in patients with T1-T2 oral cancer in terms of survival. Survival is an outcome parameter for treatment, and is a method to measure successful treatment. If the wait and scan policy is considered as an alternative for elective neck dissection, this policy should not harm the patient and survival should not be worse than elective neck management.

PATIENTS AND METHODS

Study population We studied a consecutive series of previously untreated patients who were treated by transoral excision for a T1-T2 carcinoma of the mobile tongue or floor of mouth during a 15 year period (1990-2004). All patients were classified clinically N0 by USgFNAC. Exclusion criteria were prior or simultaneous second primary tumor and adjuvant radiotherapy. A total of 285 patients were included. The patients were divided into 2 groups based on type of treatment of the neck: 234 patients were followed by the wait and scan policy (W&S) and 51 patients underwent direct elective neck dissection (END) (Figure 1). The patients who underwent END were treated prior to adaptation of the current wait and scan policy, or needed this because of technical reasons or were deemed unavailable for strict adherence to surveillance protocol.

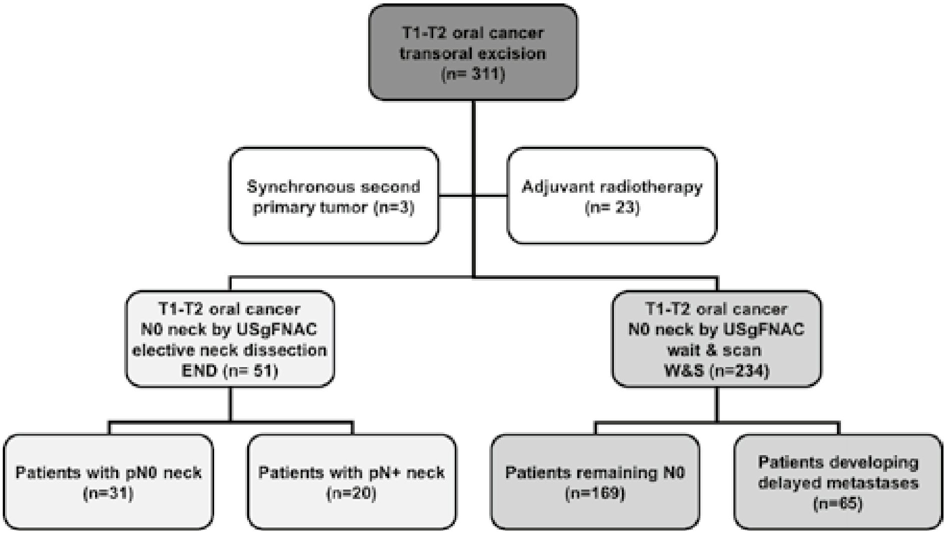


FIGURE 1. Study population
END: elective neck dissection,
W&S: wait and scan

USgFNAC All patients underwent preoperative USgFNAC for staging of the neck. During this diagnostic procedure, levels I to V of both sides of the neck were examined by ultrasonography using a 7.5-MHz linear array transducer 7 (Acuson Company, Mountain View, CA, and ATL HDI 3000, Bothell, WA). Lymph nodes measured with a minimal axial diameter of 4 mm in level II and 3 mm in other levels were selected for fine needle aspiration. Aspiration of these lymph nodes was performed using a syringe holder (Cameco, Taeby, Sweden) and a 0.6 x 25-mm needle. From each aspirate a cytological smear was prepared. Cytological results were considered tumor-positive if the cytopathologist noted atypical epithelial cells suspicious for or consistent with squamous cell carcinoma.

Follow-up Follow-up data were collected from the date of excision of the primary tumor until the date of last visit or death. In patients who developed a local recurrence or second primary tumor, the follow-up data were collected until the date of last visit or death, except in those who underwent treatment of the neck or who developed lymph node metastases during follow-up. Those patients were censored at the date of detection of the local recurrence or second primary tumor, because it is not possible to determine with certainty the cause of the metastases.

The 234 patients followed by the wait and scan policy underwent strict follow-up of the neck, including physical examination every 6 weeks and USgFNAC examinations every 3-4 months for at least the first post-treatment year. Those USgFNAC examinations during follow-up were performed following the same procedure as is described by performing the preoperative USgFNAC. A total of 749 ultrasonographic examinations were performed during follow-up (median 3, range 1-11 per patient).

Statistical analysis The outcome of the group of interest, the patients with a wait and scan policy, was compared with patients who underwent END. The W&S patients who developed delayed metastases during follow-up were then further analyzed and compared with patients having lymph node metastases in END. Chi-square test was used to compare various proportions between the groups, including sex, age, pT-classification, tumor site, tumor differentiation, perineural invasion, lymphangiogenic invasion, lymph node metastases, extracapsular spread, number of lymph node metastases, pN-classification, adjuvant radiotherapy for the neck, local recurrence and distant metastases. The Kaplan-Meier method was used to estimate 5-year disease-specific survival (DSS) and overall survival (OS). Kaplan-Meier curves were compared with the log-rank test. *P*-values < 0.05 were considered to be significant. Possible confounding factors were investigated by Cox-regression; we considered a variable a possible confounder when the Chi-square test showed a p-value < 0.1. Salvage after development of delayed lymph node metastases was defined as final disease control (no residual tumor or recurrence of disease) and was determined by the Kaplan-Meier method as a 5-year disease-specific survival from the time of treatment of delayed metastases.

RESULTS

Patient and tumor characteristics of W&S and END patients Patient and tumor characteristics are shown in Table 1. Patients in the W&S group were significantly older and had significantly more pT1 tumors as compared to patients treated by END. Tumor site and tumor differentiation were also statistically significantly different. Other variables did not show a significant difference between the groups (Table 1).

Of the 234 W&S patients, 169 (72.2%) remained free of lymph node metastases (N0) and 65 patients (27.8%) developed delayed lymph node metastases. Delayed lymph node metastases were detected 1 to 41 months after transoral excision of the primary tumor; 80.0% were detected during the first 12 months. Of the 51 patients treated by END, 39.2% had lymph node metastases. Chi-square test did not show a significant difference in metastases rate as compared to W&S patients ($p = 0.106$) (Table1). In the END group a total of 65 elective neck dissections were performed, 14 bilateral, of which 47 (72.3%) were modified radical, 14 (21.5%) selective level I - III and 4 (6.2%) selective level I - IV. In three patients metastases were also found in level IV and no metastases were found in level V. In 55.0% of positive END patients, adjuvant radiotherapy for the neck was needed.

	W&S		END		Chi-square test
	No. of patients	**%**	**No. of patients**	**%**	***p*-value**
Sex					
Male	139	59.4	31	60.8	0.855
Female	95	40.6	20	39.2	
Median age (range)	60.8 (29.7-87.6)		56.0 (29.0-82.3)		**0.019**[a]
pT-classification					
T1	160	68.4	2	3.9	**<0.001**[b]
T2	74	31.6	49	96.1	
Tumour site					
Lateral tongue	134	57.3	19	37.3	**0.009**
Floor of mouth	100	42.7	32	62.7	
Tumour differentiation					
Well differentiated	71	30.3	8	13.7	**0.037**
Moderately differentiated	139	59.4	37	72.5	
Poorly differentiated	10	4.3	5	11.8	
Unknown	14	6.0	1	2.0	
Perineural invasion					
Yes	24	10.3	8	15.7	0.877
No	119	50.9	37	72.5	
Unknown	91	38.9	6	11.8	
Lymphangiogenic invasion					
Yes	17	7.3	5	9.8	0.855
No	117	50.0	38	74.5	
Unknown	100	42.7	8	15.7	
Lymph node metastases	65	27.8	20	39.2	0.106
Local recurrence	20	8.5	5	9.8	0.774
Distant metastases	6	2.6	2	3.9	0.435[b]
Total	234		51		

TABLE 1. Univariate analysis for comparison of patient and tumour characteristics of patient followed by a wait and scan strategy (W&S) or patients undergoing elective neck dissection (END)
[a]Mann-Whitney U test, [b]Fisher's exact test

Patients with occult lymph node metastases The W&S patients with delayed lymph node metastases had significantly more pT1 tumors as compared to patients with positive END (Table 2). In patients with delayed metastases more nodal metastases were detected in the neck dissection specimen, although the number of metastases and pN-classification were not significantly higher as compared to patients with positive END (Table 2). Extracapsular spread however, was significantly more seen in patients with delayed lymph node metastases (Table 2).

Treatment for delayed metastases consisted in 64 patients of a neck dissection (55 unilateral and 9 bilateral). One patient with delayed metastases could not be treated with curative intent due to simultaneous local recurrence and distant metastases. Of the 73 neck dissections, 65 (89.0%) were modified radical, 7 (9.6%) selective level I - III and 1 (1.4%) selective level I - IV. In 12 patients metastases were also located in level IV and in 2 patients also level V was involved. Fifty-eight of the 64 (90.6%) patients received adjuvant radiotherapy because of multiplicity or extracapsular spread. One patient refused postoperative radiotherapy. Adjuvant radiotherapy for the neck was significantly more often indicated in patients with delayed metastases as compared to positive END patients ($p < 0.001$) (Table 2). Of the patients with delayed metastases, 6 of 65 patients (9.2%) developed a local recurrence and also 9.2% developed distant metastases during follow-up. These rates were comparable to the rates of positive END patients, who had a local recurrence rate of 10.0% ($p = 0.606$) and distant metastases rate of 5.0% ($p = 0.476$), respectively (Table 2).

After neck treatment for delayed metastases regional control was reached in 90.8% and final disease control in 80.7% of patients.

	W&S delayed metastases		**END nodal metastases**		**Chi-square test**
	No. of patients	**%**	**No. of patients**	**%**	***p*-value**
Sex					
Male	44	67.7	14	70.0	0.846
Female	21	32.3	6	30.0	
Median age (range)	59.1 (33.5-86.0)		56.8 (42.2-82.3)		0.562[a]
pT-classification					
T1	37	56.9	0	0	**<0.001**
T2	28	43.1	20	100	
Tumour site					
Tongue	40	61.5	8	40.0	0.089
Floor of mouth	25	38.5	12	60.0	
Tumour differentiation					
Well differentiated	9	13.8	2	10.0	0.733
Moderately differentiated	47	72.3	15	75.0	
Poorly differentiated	6	9.2	3	15.0	
Unknown	3	4.6	0	0	

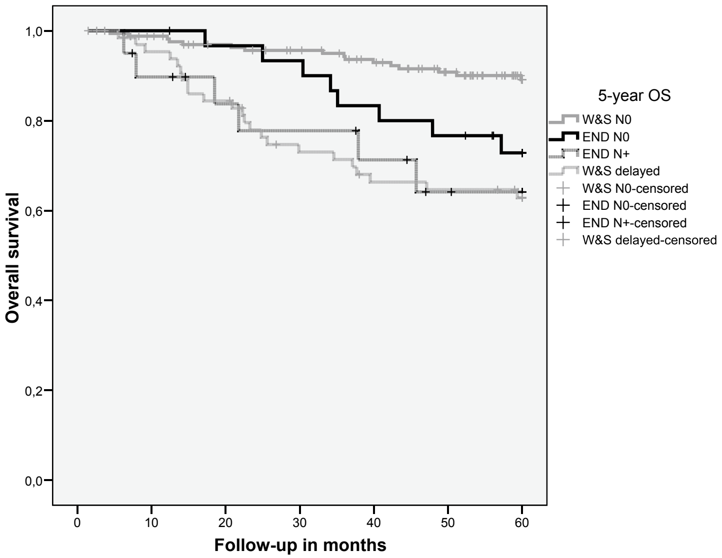
	W&S delayed metastases		END nodal metastases		Chi-square test
	No. of patients	**%**	**No. of patients**	**%**	***p*-value**
Perineural invasion					
Yes	8	12.3	4	20.0	0.483[b]
No	36	55.4	14	70.0	
Unknown	21	32.3	2	10.0	
Lymphangiogenic invasion					
Yes	7	10.7	1	5.0	0.226[b]
No	34	52.3	17	85.0	
Unknown	24	36.9	2	10.0	
Extracapsular spread					
Yes	54	84.4	8	40.0	**<0.001**
No	10	15.6	12	60.0	
No neck dissection	1		0	0	
Number of metastases					
1	24	37.5	12	60.0	0.089
2	14	21.9	6	30.0	
3	11	17.2	1	5.0	
≥4	15	23.4	1	5.0	
No neck dissection	1		0	0	
pN-classification					
N1	19	29.2	12	60.0	0.117
N2a	3	4.6	0	0	
N2b	36	55.4	7	35.0	
N2c	3	4.6	1	5.0	
N3	4	6.2	0	0	
Adjuvant RT for the neck					
Yes	58	90.6	11	55.0	**<0.001**
No	6	9.4	9	45.0	
No neck dissection	1		0		
Local recurrence	6	9.2	2	10.0	0.606[b]
Distant metastases	6	9.2	1	5.0	0.476[b]
Total	65		20		

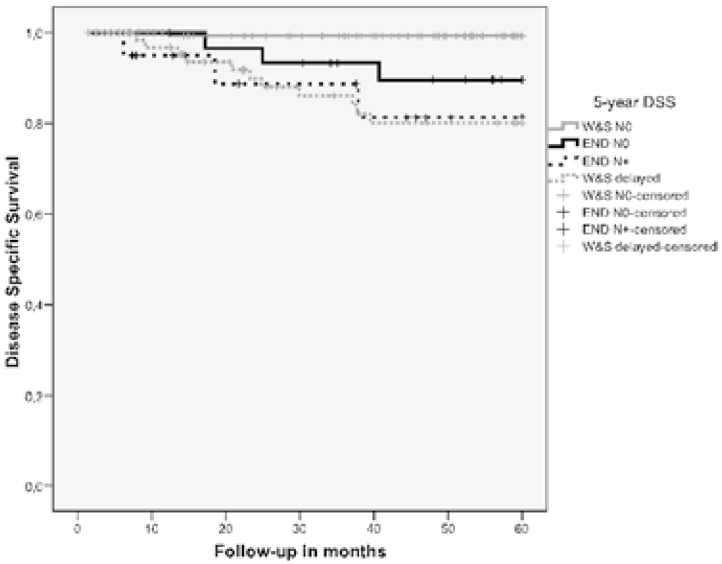
TABLE 2. Univariate analysis for comparison of patient and tumour characteristics of patients who developed delayed metastases with a wait and scan follow-up strategy (W&S) and patients with nodal metastases undergoing elective neck dissection (END)
RT: radiotherapy, [a]Mann-Whitney U test, [b]Fisher's exact test

Survival analysis Of the W&S patients, the 5-year DSS and OS were 94.2% and 81.6%, respectively. These survival rates were not significantly different in comparison with survival rates of END group, 86.5% ($p = 0.079$) and 69.5% ($p = 0.082$) respectively. When corrected for the confounders pT-classification, tumor differentiation, age and tumor site the difference in DSS between W&S and END remained insignificant ($p = 0.950$). For OS, correction for the confounders pT-classification, tumor differentiation and age was performed and the difference in survival remained insignificant as well ($p = 0.500$). Disease-specific survival of W&S patients was significantly different between T1 (96.6%) versus T2 (88.6%) ($p = 0.027$).
In Figure 2 disease-specific and overall survival is shown. For both study groups (W&S and END), survival curves of patients with or without lymph node metastases were separately presented. The W&S patients with delayed metastases had a 5-year DSS and OS of 80.0% and 62.8%, respectively (Figure 2). These survival rates were comparable to the patients with positive END, 81.3% ($p = 0.967$) and 64.2% ($p = 0.928$), respectively. After correction for the confounders number of metastases, tumor site, extracapsular spread and pT-classification, the difference in DSS remained insignificant ($p = 0.090$). The difference in OS remained insignificant as well ($p = 0.175$) when corrected for the confounders number of metastases, tumor site, adjuvant radiotherapy for the neck and extracapsular spread.

Of the patients who remained metastasis-free during W&S, the 5-year DSS and OS were 99.4% and 89.1%, respectively (Figure 2). Disease-specific survival was significantly higher as compared to END patients who were classified pN0, 89.6% ($p = 0.001$), but overall survival was comparable, 72.8% ($p = 0.19$). Correction for the confounders tumor differentiation and age in DSS analysis and for pT-classification and age in OS analysis, did not change this comparison (DSS $p = 0.044$ and OS $p = 0.129$, respectively).

FIGURE 2. The 5-year disease-specific survival and overall survival of W&S and END patients
W&S: wait and scan, END: elective neck dissection, DSS: disease-specific survival, OS: overall survival





	W&S N0	W&S delayed metastases	END N0	END N+
No. of patients	169	65	31	20
5-year DSS	99.4%	80.0%	89.6%	81.3%
5-year OS	89.1%	62.8%	72.8%	64.2%

DISCUSSION

This study presents a survival analysis of a large series of patients with T1-T2 cancer of the mobile tongue or floor of mouth with a wait and scan follow-up policy of the neck with regular USgFNAC. The 5-year DSS and OS of W&S patients were 94.2% and 81.6%, respectively, and these rates were comparable to those of END patients. The most important finding is that in W&S patients with delayed metastases the 5-year DSS and OS were similar to END patients with proven metastases in the neck dissection specimen: 80.0% and 62.8% to 81.3% and 64.2%, respectively.

Management of the clinically negative (cN0) neck in patients with T1-T2 oral cancer remains controversial. Although elective neck dissection can result in early treatment of occult lymph node metastases, the vast majority of these neck dissections turns out to be unnecessary. Moreover, these patients are subjected to morbidity such as shoulder morbidity, pain and sensibility disorders,[21,22] which may have major impact on health-related quality of life.[23,24] Furthermore, elective neck treatment may remove or destroy a barrier to cancer spread in case of local recurrence or second primary tumor which occur frequently in head and neck cancer patients.[25] Therefore, it is challenging to optimize management of the neck in T1-T2 oral cancer and tailor management in the individual patient.

Many studies[3-14, 26] have compared the outcome of elective neck dissection to observation of the neck, with two of them prospective.[3, 13] In the prospective study of O'Brien et al.[3] management of the cN0 neck in T1-T4 oral cancer patients was based on clinical criteria such as T-classification and tumor site, which makes comparison of survival between treatment options difficult. Yuen et al.[13] recently performed a prospective multicenter randomized trial in 71 T1-T2 oral cancer patients with cN0 necks evaluated by USgFNAC and the patients were stratified for T-classification. Observation of the neck consisted of ultrasonographic examination every 3 months during the first 3 years of follow-up, which strongly resembles our wait and scan follow-up policy. Although the sample size was limited, this study had the preferable study-design to compare the outcome of elective neck treatment with observation. The reported 5-year disease-specific survival rates were not significantly different (observation arm 87%, END arm 89%).[13]

Two studies showed statistical significant difference in disease-specific survival or overall survival between elective neck dissection and observation.[12,26] However, Huang et al.[12] did not describe surveillance of the neck in the observation arm and if absent or merely clinical, this may have influenced survival. Capote et al.[26] analyzed only END patients who were pN0, which obviously results in better overall survival in END patients. Three studies reported a significantly better disease-free survival in the END arm.[5,12,26] However, development of lymph node metastases after observation of the neck should be taken into account as an inevitable consequence of the adopted treatment policy.

In order to justify an observation policy, survival rates of patients with delayed metastases in a W&S policy should not be worse than rates of END patients with nodal metastases in the neck dissection specimen. In the current series the patients who developed delayed metastases (27.8%) did not have worse survival rates (DSS 80.0%, OS 62.8%) as compared to END patients with nodal metastases in the neck dissection specimen (DSS 81.3%, OS 64.2%), also when corrected for confounding factors.
Moreover, with regard to the total study groups after correction for confounding no significant difference in survival between W&S and END patients was found and survival rates were comparable to the reported rates in literature.[3-14,26] Of the W&S patients, 72.2% did not develop lymph node metastases during follow-up, meaning that they were saved from elective neck dissection with good survival rates (DSS 99.4%, OS 89.1%).

Although, DSS in the W&S group was significantly different between pT1 and pT2 tumors, pT2 tumors still had a 5-year DSS of 88.6%, which resembles the survival rates of END patients. Tsang et al. stated that a wait and scan policy would not be effective in pT2 tumors, but that conclusion was based on a 5-year DSS of 46% for pT2 tumors.[27]

A limitation of this study is that some tumor characteristics such as pT-classification and tumor site were not comparable between the study groups. This is a consequence of the retrospective study-design in which the groups were not matched. With survival analysis we therefore corrected for confounding factors.

We can assume that the delayed lymph node metastases were missed by preoperative USgFNAC. In a wait and scan policy, the diagnostic method should be highly sensitive. This is dependent on the cut-off level for aspiration and of the expertise of the radiologist.[28-30] A lower cut-off level will increase sensitivity. However, on the other hand aspiration of lymph nodes smaller than 3-4 mm is not useful as non-diagnostic smears will occur more often.[18,29,31]

Almost all patients with delayed metastases underwent a modified radical neck dissection and 90.6% needed adjuvant radiotherapy. In other series in patients treated by END, adjuvant radiotherapy for the neck was necessary in 79-93% of the patients with lymph node metastases in the END specimen.[5,9,11,13] With regard to pN-classification, the majority of patients with delayed metastases were classified ≥ pN2a (70.8%), while the END patients with lymph node metastases were mainly classified pN1 (60.0%). Possibly, patients with delayed metastases would have been classified pN1 if treated electively at the time of transoral excision and treatment of the neck would have been less extensive (type of neck dissection and need for adjuvant radiotherapy) as described in literature.[3-6,9-13]

After curative treatment (98.5%) for delayed metastases 90.8% of the patients were regionally controlled and 80.7% had ultimate disease control. Theoretically, patients with occult lymph node metastases in a wait and scan policy are more likely to develop distant metastases due to delayed detection and treatment. This was not reflected in our study. Of the patients with delayed metastases, 9.2% (6/65) had distant metastases, and 5.0% (1/20) in positive END patients. Since we also found metastases in level IV, we would recommend selective neck dissection of level I-IV in case of delayed lymph node metastases, although Wensing et al. suggested selective neck dissection of level I-III.[32] Yuen et al.[13] reported delayed lymph node metastases in 37% of the observed patients and nodal metastases in 22% of patients treated with elective selective neck dissection of level I-III. Salvage was successful in all (100%) patients with delayed metastases or nodal recurrence, and in both arms 15% died of distant metastases despite successful treatment of the neck.[13] Thus, in both studies, in which observation was accompanied by strict surveillance during follow-up, salvage rates after delayed metastases were high. Most delayed lymph node metastases were detected within the first year of follow-up (80.0%).

USgFNAC at initial staging seems useful in detecting lymph node metastases from a certain size, but is not reliable enough to detect occult lymph node metastases. If occult lymph node metastases could be detected initially, treatment could be further optimized: patients would be prevented from undergoing unnecessary elective neck dissection and from needing (more) extensive treatment of the neck if nodal metastases become manifest during follow-up in an observation strategy. Sentinel node biopsy (SNB) has been proven to be a reliable diagnostic method in the detection of occult lymph node metastases in T1-T2 oral cancer.[33-35] With a sensitivity and negative predictive value rate over 90%, SNB accurately predicts the regional status[36] and use of this technique in the primary setting of a cN0 neck allows adequate differentiation between those patients needing neck dissection for occult metastases and those in whom the neck can be observed. Compared to END, SNB offers a less invasive means of staging with lower morbidity.[37,38]

Conclusion Survival rates of patients with T1-T2 oral cancer who were classified cN0 by USgFNAC followed by a wait and scan policy are comparable to patients with elective neck dissection. In W&S patients with delayed lymph node metastases survival rates remained similar to patients with positive elective neck dissection. Patients with delayed metastases had more often extracapsular spread but the number of metastases in the neck dissection specimen did not significantly differ from positive elective neck dissection patients. After treatment for delayed metastases regional control of 90.8% was achieved and ultimate disease control was 80.7%. Using our wait and scan follow-up strategy instead of elective neck treatment, unnecessary neck dissection and its accompanying morbidity can be avoided in 72.2% of patients. However, for the patients with delayed metastases, who are a small proportion of the total W&S patient group, treatment more often includes adjuvant radiotherapy as compared to a policy of elective treatment of the neck.

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CHAPTER 3

Sentinel node biopsy in clinically N0 T1-T2 staged oral cancer: the Dutch multicenter trial

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Oral Oncology 2014;50:1020-1024.

ABSTRACT

Objectives. Results of the Dutch multi-institutional trial on sentinel node (SN) biopsy in oral cancer.

Methods. Patients were consecutively enrolled from 4 institutions, with T1-T2 oral cancer and cN0 neck based on palpation and ultrasound guided fine needle aspiration cytology. Lymphatic mapping consisted of preoperative lymphoscintigraphy. For intraoperative SN detection a gamma probe was used and in some patients additional blue dye. SN negative patients were carefully observed, SN positive patients were treated by neck dissection, radiotherapy or a combination of both. Endpoints of the study were risk of occult lymp node metastases, neck control, accuracy, 5-year disease-free survival (DFS), overal survival (OS) and disease-specific survival (DSS).

Results. Twenty of 62 patients (32%) had positive SNs. Macrometastases were found in 9 patients, micrometastases in 8, and isolated tumor cells in 3 patients. Median follow-up was 52.5 months. Of the 42 SN negative patients, 5 developed a regional recurrence of whom 4 patients could be successfully salvaged. DFS, OS and DSS of SN negative patients were 72.0, 92.7 and 97.4%, and for SN positive patients these numbers were 73.7, 79.7 and 85.0%, respectively (DFS: $p = 0.916$, OS: $p = 0.134$, DSS: $p = 0.059$, respectively). Neck control rate was 97% in SN negative and 95% in SN positive patients. Sensitivity was 80% and negative predictive value 88%.

Conclusions. SN biopsy is able to reduce the risk of occult lymph node metastases in T1-T2 oral cancer patients from 40% to 8%, and enables excellent control of the neck.

INTRODUCTION

Management of the clinically negative (cN0) neck in early stage oral squamous cell carcinoma (OSCC) has been an issue of debate for years. With roughly a 30% risk of occult lymph node metastases, elective neck dissection and watchful waiting lead to over- and undertreatment in a considerable proportion of patients.

Also in The Netherlands, management of the cN0 neck in early stage OSCC has been a controversial issue. A nationwide survey performed in 2009 among the 8 centers of the Dutch Head and Neck Society, revealed primary tumor related factors as site, size and thickness as indicators for management of the neck.[1] Few centers advocated a wait and scan policy in early stage OSCC, which included preoperative staging of the neck by ultrasound guided fine needle aspiration cytology (USgFNAC) and postoperative stringent follow-up using USgFNAC every 3 months. The majority of institutes however, performed neck management based on T-stage: wait and scan policy in T1 tumors and elective neck dissection in T2 oral cancers.[1]

A solution for this issue is more accurate staging of the neck to personalise treatment. Sentinel node biopsy (SNB) is rapidly gaining ground in the treatment of early stage OSCC. A recent meta-analysis on SNB for this indication reported a pooled sensitivity of 93% and negative predictive values varying from 88-100%.[2] Sensitivity seemed to be a function of the reference test: 94% in studies performing elective neck dissection versus 91% in studies applying clinical follow-up in case of negative SNB.[2] Currently, the long-term results of the Sentinel European Node Trial (SENT) are waiting for maturation. This is a prospective observational multicenter trial in which over 400 patients are enrolled who underwent SNB and were followed in case of SNB negative result. For years, decisions on elective treatment or watchful waiting have been made on risk assessments because a highly accurate method for staging of the neck was lacking. SNB is likely to play an important role in solving this issue.

The aim of the present prospective Dutch multi-institutional trial on SNB in T1-T2 oral cancer was to evaluate the risk of occult lymph node metastases after SNB in patients staged cN0 neck by USgFNAC. Neck control, accuracy and survival rates were assessed. Neck treatment was only performed after positive SNB and follow-up was used as reference standard.

PATIENTS AND METHODS

Between 2007 and 2010, 69 consecutive patients with cT1-T2N0 OSCC were prospectively enrolled for this study. The cN0 neck was defined as negative after USgFNAC diagnostics. Participating institutions were VU University Medical Center (VUmc), Netherlands Cancer Institute (NKI/AVL), University Medical Center Utrecht (UMCU) and University Medical Center Groningen (UMCG). The institutional ethics committee from the 4 institutions approved the study and written informed consent was obtained from each patient.

Of the initial 69 patients, seven were excluded for the analysis: four because of indadequate preoperative cN0 staging omitting USgFNAC, two who had a history of irradiation for a prior head and neck cancer and one due to infiltration of insufficient dose of radioactive ^{99m}Tc-nanocoll leading to inadequate SN detection in a two-day SNB protocol. The final study group consisted of 62 evaluable patients.

Sentinel node biopsy procedure All patients underwent planar lymphoscintigraphy the day before surgery. Between 19-27h prior to surgery 80-110 MBq of ^{99m}Tc-nanocoll was injected peritumorally in 3-6 (mostly 4) doses, immediately followed by dynamic lymphoscintigraphy (20 x 60s, 128 x 128 matrix, low energy high resolution collimator) in anterior or oblique views, with the patient in supine position with the tumor side facing the camera. Directly after dynamic imaging, static images (120s or 300s, 256 x 256 matrix) were made with a flood-field source in anterior and lateral projections. After 2-4h, static images (120s, 256 x 256 matrix) were made. The position of the SN was marked on the overlying skin with the use of a ^{57}Co point-source marker and a gamma probe. On lymphoscintigraphy, a focus was considered as SN if it was the first focus in any direction from the primary tumor and if it showed persistent activity during imaging. There was no limit on the number of SNs, and the neck level was considered not relevant. If a focus was clearly filled via a well-defined lymphatic track from a SN, this one was considered as second echelon node. However, if there was doubt, this focus was also considered as SN.

3

At surgery the use of peritumoral injected blue dye was optional depending on the surgeons preferences. The same accounted for resection of the primary tumor, which could be performed prior to, or after SNB. SNs were detected and excised intraoperatively with the aid of a handheld gamma probe. The location, neck level and number of harvested lymph nodes were recorded.

Reference test Patients only underwent subsequent neck dissection in case of positive SN result at histopathology. SN negative patients were followed, and regional recurrence during follow-up was defined as a false negative result.

Histopathological examination of SNs consisted of step-serial sectioning with an interval of 150-250 µm of the entire lymph node. Of each level stainings with hematoxyline-eosine (H&E) and pan-cytokeratin antibody (AE 1/3) were performed. Occult metastases were differentiated into isolated tumor cells (< 0.2 mm; i+), micrometastasis (≥ 0.2 mm and ≤ 2 mm; mi) or macrometastasis (> 2 mm; ma) according to the criteria proposed by Hermanek et al.[3] If any nodal tumor deposit was proven by SNB, a subsequent neck dissection of the involved neck side was performed during a second surgical procedure. According to national guidelines, patients received postoperative (chemo-)radiotherapy of the neck in case of multiple (i.e. ≥ 2) lymph node metastases and/or extranodal spread. Patients whose surgical margin of the primary tumor was close or positive were treated by re-excision if feasible or postoperative radiotherapy.

Patients were not further followed if the neck received radiation therapy in case of irradiation of the primary tumor and in case a patient developed a regional recurrence during follow-up in combination with a local recurrence or second primary tumor. In these situations, the cause of regional cancer spread is unclear.

Statistical analysis To compare patient and tumor characteristics between SNB negative and positive groups, Chi-square, Fisher's exact and Mann-Whitney U test were used.

Accuracy rates were calculated after follow-up. A p-value < 0.05 was considered statistically significant. Disease-free survival (DFS), overall survival (OS) and disease-specific survival (DSS) were calculated by Kaplan-Meier statistics, with the date of primary tumor resection and SNB as starting point. Log-rank test was used to compare survival rates between SN negative and positive status.

RESULTS

Table 1 shows patient and tumor characteristics. Between the SN positive and negative patients, only follow-up time was significantly different (Table 1). The overall median follow-up was 52.5 months (range 5.3-76.7). SN negative patients had a median follow-up of 59.3 (range 5.3-76.7). Seven patients (11%) experienced a local recurrence and three (5%) a second primary tumor, without regional disease.

With lymphoscintigraphy in each patient at least 1 focus was seen that could be identified as SN (100%). In total 241 foci were seen. Of these, 155 foci were marked as SN (mean 2.5 per patient, range 1-7). Additional foci that were not considered to be SN and consequently not marked were seen on early static imaging in 11 patients (22 foci, range 1-5), and on late static imaging in 27 patients (64 foci, range 1-5).

The surgical detection rate of SNB in 62 patients was 100%. A total of 206 lymph nodes were harvested of which 168 (82%) were considered a SN, as defined as hot (*n* = 122), hot and blue (*n* = 44) or blue (*n* = 2) (median 2, range 1-9 per patient). In 56 patients with a lateralized tumor, 125 SNs were found in the ipsilateral neck and 19 (13%) SNs contralaterally. In 12/56 (21%) patients, SNs were located bilaterally. Six patients had a midline tumor, with two having unilateral (*n* = 3 SNs) and four bilateral SNs (*n* = 21 SNs). A total of 96 incisions in 62 patients were made in the neck (median 1, range 1-4).

The median maximum diameter of SNs was 10 mm (range 3-35 mm). There were 38 harvested lymph nodes that were neither hot nor blue (in 20 patients, range 0-5 per patient), which did not harbor any tumor deposit.

SNB was positive for occult metastases in 20 patients (32%) with 22 positive SNs with a median maximum diameter of 14 mm (range 6-25 mm). All positive SNs were found in the ipsilateral neck (3 midline tumors). In the two patients with 2 positive SNs, metastases were found in 2 different neck levels (level Ib and III, level Ib and II, respectively). Distribution of SNs in the neck and histopathological status are shown in Table 2. Nine patients had a macrometastasis (one also having a macrometastasis in another SN, one having another micrometastasis) (7 pN1, 2 pN2b), eight patients had 1 micrometastasis (6 pN1mi, 2 pN2b due to node positive neck dissection) and three patients had isolated tumor cells in 1 SN (3 pN0i+).

The 20 SN positive patients were treated by subsequent neck dissection alone (*n* = 11), combined neck dissection and radiotherapy (*n* = 5), or radiotherapy (*n* = 4). The dissected neck levels were I-III (*n* = 4), I-IV (*n* = 2) and I-V (*n* = 10). Neck dissection revealed another metastasis in two patients, both in level I, whereas the positive SN had been found in level IV. Instead of a neck dissection, in four SN positive patients only primary radiotherapy of the neck was administered, because of severe co-morbidity in one patient, close surgical margin of the primary tumor for which radiotherapy was indicated in one patient, or for both reasons in two patients. One of these patients developed an ipsilateral regional recurrence (level Ia), initially diagnosed as a pT1N2b border of tongue carcinoma with 2 macrometastases in level Ib and III with extranodal spread. Chemotherapy was contraindicated due to age and co-morbidity. This patient died of disease.

TABLE 1. Patient and tumor characteristics
* *p*-value of Chi-square, Fisher's exact or Mann-Whitney U test

	Histopathology of SNB			
	Overall (%)	**Negative (%)**	**Positive (%)**	***p*-value***
Patients	62	42 (68)	20 (32)	
Sex				0.15
Male	33 (53)	25 (60)	8 (40)	
Female	29 (47)	17 (41)	12 (60)	
Median age (range)	61.2 (28.8-82.6)	60.7 (28.8-82.6)	62.7 (52.1-82.2)	0.11
Primary tumor site				0.71
Mobile tongue	33 (53)	23 (55)	10 (50)	
Floor of mouth	22 (36)	15 (36)	7 (35)	
Buccal mucosa	3 (5)	2 (5)	1 (5)	
Inferior alveolar process	2 (3)	1 (2)	1 (5)	
Lower lip	1 (2)	1 (2)	0 (0)	
Soft palate	1 (2)	0 (0)	1 (5)	
pT-classification				0.37
pT1	39 (63)	28 (67)	11 (55)	
pT2	23 (37)	14 (33)	9 (45)	
Order of surgery				0.79
First SNB	32	21 (66)	11 (34)	
First transoral excision	30	21 (70)	9 (30)	
Differentiation degree				0.77
Well	16 (26)	12 (29)	4 (20)	
Moderately	40 (65)	26 (62)	14 (70)	
Poor	6 (10)	4 (10)	2 (10)	
Surgical margins				0.56
Negative	30 (48)	22 (52)	8 (40)	
Close	28 (45)	17 (41)	11 (55)	
Positive	4 (7)	3 (7)	1 (5)	
pN-classification				
N0	42 (68)	42 (100)		
N0i+	3 (5)		3 (15)	
N1mi	6 (10)		6 (30)	
N1	7 (11)		7 (35)	
N2b	4 (7)		4 (20)	
Median follow-up (range)	52.5 (5.3-76.7)	59.3 (5.3-76.7)	49.5 (9.8-76.2)	**0.019**

Neck level	SNs	Histopathological status			
		no metastasis	i+	mi	ma
I	38	30	0	3	5
II	78	69	3	3	3
III	34	32	0	1	1
IV	16	13	0	2	1
V	1	1	0	0	0
VI	1	1	0	0	0
Total	168	146	3	9	10

TABLE 2. Localization and histopathological status of sentinel nodes
SNs: sentinel nodes, i+: isolated tumor cells, mi: micrometastasis, ma: macrometastasis

Of the 42 SN negative patients, five (12%) were diagnosed with a cervical lymph node metastasis during follow-up, detected after a median of 15.0 months (range 3.1-51.2, Table 3). In one patient distant metastases were detected shortly after regional recurrence. He received palliative radiotherapy and died of disease. The other four patients (80%) were successfully salvaged by neck dissection with or without postoperative radiotherapy. Those patients had a mean follow-up of 41.4 months (range 4.3-73.6) after salvage therapy. The neck control rate including salvage therapy after 5 years, estimated according to Kaplan-Meier, was 97.4% in SN negative patients, and 94.7% in SN positive patients (p = 0.546).

Using SNB, the risk of occult lymph node metastases in cN0 patients was reduced from 40% to 8%. The negative predictive value (NPV) of SNB was 88% (95%-CI 74-96%) and the sensitivity 80% (95%-CI 59-92%).

Pt	Tumor	SNs	Delayed lymph node metastases			Follow-up	
			Months	Level	Treatment	Status	Months
1	pT1 Buccal	1 IIa	3.1	2 I, III	MRND, CRT	and	76.7
2	pT2 Tongue	3 III	7.8	6 III, V, ens	RND, RT	and	49.4
3	pT1 FOM	4 I, IIa	15.0	1 I	MRND	and	61.0
4	pT1 FOM	1 III	22.9	3 III, V, ens	MRND, palliative RT, bone metastases	dod	29.3
5	pT2 FOM	3 IIa	51.3	2 I, ens	RND, segmental mandible, no RT*	lost	55.6

TABLE 3. Patients with false negative SNB
Pt: patient
SNs: sentinel nodes ipsilateral neck side,
ens: extranodal spread, MRND: modified radical neck dissection,
CRT: chemoradiotherapy,
RT: radiotherapy,
RND: radical neck dissection, and: alive no disease,
dod: died of disease, lost: lost to follow-up.
* Radiotherapy was indicated but patient refused

In 22 patients the primary tumor was located in the floor of mouth (FOM), of whom 7 (32%) patients had positive SNs. Follow-up revealed lymph node metastases in three of the 15 SN negative FOM patients, with a NPV of 80% (95%-CI 51-95%) and sensitivity of 70% (95%-CI 35-92%). In other tumor sites than FOM, we found a NPV of 93% (95%-CI 74-99%) and a sensitivity of 87% (95%-CI 58-98%) ($p = 0.329$ and $p = 0.358$, respectively).

The order of surgery differed among the patients (Table 1). In 32 patients SNB was performed prior to primary tumor resection (NPV 90%, sensitivity 85%), in the other 30 patients SNB was done after tumor surgery (NPV 86%, sensitivity 75%). Between those groups NPV and sensitivity of SNB were not significantly different ($p = 1.00$ and $p = 0.645$, respectively). The use of patent blue did not significantly influence accuracy: 45 patients with patent blue lead to NPV 89% and sensitivity 85%, 17 patients without use of patent blue revealed a NPV of 86% and sensitivity of 67% ($p = 1.00$, $p = 0.252$, respectively).

For the entire cohort DFS, OS and DSS were 72.0, 88.4 and 93.3%, respectively. For SN negative patients DFS, OS and DSS were 72.0, 92.7 and 97.4%, respectively and for SN positive patients 73.7, 79.7, 85.0%, respectively. There was a trend towards longer 5-year DSS in SN negative patients (DFS: $p = 0.916$, OS: $p = 0.134$, DSS: $p = 0.059$).

DISCUSSION

This study presents the results of the Dutch multi-institutional trial on SNB in cT1-T2N0 OSCC, using follow-up (median 52.5 months) as reference standard. SNB revealed regional disease in 32% of patients, with NPV 88% and sensitivity 80%. In these USgFNAC based cN0 neck patients the risk of occult lymph node metastases was reduced from 40 to 8% by SNB.

The first validation trials with SNB assisted elective neck dissection showed promising results for SNB, which lead to 'The first conference on sentinel node biopsy in mucosal head and neck cancer' and the first steps for a multicenter trial were taken.[4-9] In 'The second international conference on sentinel node biopsy in mucosal head and neck cancer' recommendations for uniform methodological requirements for accurate SNB were defined. From that moment single- and multicenter studies were conducted. In all meta-analyses, SNB shows highly accurate results.[2,10-12] To date, in the few long-term follow-up studies that are published, accuracy rates remain high.[13-15]

The choice of reference standard influences the accuracy of SNB.[16] When elective neck dissection is performed irrespective of the SNB result, histopathological examination is the reference. However, histopathology may miss minimal disease such as micrometastases and isolated tumor cells, especially if routine techniques and not step-serial sectioning with immunohistochemistry are used for examination of the neck dissection specimen.[16-18] Hence, use of histopathological examination as reference will overestimate sensitivity and negative predictive values.[16] Therefore, we considered histopathology of only SN positive patients by subsequent neck dissection in combination with long-term observation of SN negative patients to be a better reference standard to define the accuracy of the SNB procedure.

In the present study the prevalence of occult lymph node metastases by SNB was 32%. In a meta-analysis, the mean upstaging rate was 33% (range 14-60%).[2] The NPV of 88% (95%-CI 74-96%) is within the reported range of 88-100% of this meta-analysis, whereas our sensitivity of 80% (95%-CI 59-92%) is lower than the pooled sensitivity (93%, 95%-CI 90-95%).[2] The accuracy rates in large series reported by Broglie et al. (prevalence 37%, NPV 90%, sensitivity 91%) and Alkureishi et al. (prevalence 34%, NPV 95%, sensitivity 90%) seem to be higher than our rates, although within the 95% confidence intervals.[13,14] The slight differences may be caused by several reasons. First, in our study all patients underwent SNB alone, whereas in the study of Broglie et al. and Alkureishi et al. a proportion of the patients underwent SNB assisted elective neck dissection, which may lead to higher accuracy rates as discussed above.[13,14] Second, in our study 36% of patients had a FOM carcinoma, which may negatively influence accuracy, whereas in the other two studies this was 25% and 30%, respectively.[13,14]

Theoretically, the order of surgery (SNB followed by primary tumor resection or vice versa) may influence accuracy. It has been suggested that with prior tumor resection the radioactive overprojection in the neck is decreased, facilitating detection of SNs in the neck. The use of patent blue may also facilitate SN detection during surgery. However, in our study the order of surgery as well as use of patent blue did not significantly influence NPV and sensitivity rates.

In our study, accuracy rates of FOM tumors were lower than for other tumor sites, but not significantly different. Of the five false negative SN patients from the total cohort, three had a FOM tumor, and during neck dissection in two of those three patients a metastasis was found in level I (Table 3). Of the SN positive patients, three patients with a FOM tumor had a positive SN in level IV, while during neck dissection a second metastasis was found in level I. This can be due to re-routing when the metastatic lymph node in level I is not able to absorb radioactivity. However, in that case it would be expected that this node is found by USgFNAC. The problem of identification of the SN in level I in FOM tumors has been recognized as the 'shine-through' phenomenon. Due to the close spatial relation of the primary tumor with first draining nodes in the neck, SNB is less accurate. Because in FOM tumors the first echelon is often level I, occult lymph node metastases in SNs may be missed in patients with these tumors.[3,19,20] In the study of Alkureishi et al.[13] accuracy rates were significantly lower in FOM tumors as compared to other sites in the oral cavity. Technical improvements using preoperative PET/CT and intraoperative freehand SPECT and near-infrared fluorescence imaging may better visualize SNs close to the injection site.[21-24]

SNB is able to detect minimal disease and reveal aberrant drainage patterns. Preoperative USgFNAC for staging the cN0 neck is better than CT, MRI and PET,[25] but misses those micrometases and isolated tumor cells. Moreover, a pitfall of USgFNAC is the sampling error. In the present study, SNB detected 10 macrometastases which apparently were missed by USgFNAC. Concerning former wait and scan policy, SNB supplies early selection of the patients needing neck treatment. With regard to former elective neck dissection, SNB is able to detect lymphatic drainage to the contralateral neck (in our study, in 21% of patients with a lateralized tumor, although without positive SN), or to a lower neck level (in our study, in 3 patients with a positive SN in level IV). This information would not have been known in case of routine elective selective neck dissection, and metastases may have been missed.

Of the five false negative SN patients, four were successfully salvaged by (modified) radical neck dissection, and in three out of four postoperative radiotherapy was indicated. These few patients needed probably more extensive neck treatment than when elective neck dissection was performed in advance. However, the percentage of patients needing more extensive neck treatment due to misdiagnosing a metastasis is lower than with the previous wait and scan policy.[26] Moreover, including the false negative SN patients who underwent salvage neck dissection, SNB saved 60% (37/62) of patients from unnecessary elective neck treatment.

The clinical relevance of isolated tumor cells in a SN is yet unclear. With SNB the specific lymph node is already dissected and need for additional neck treatment is point of debate. A larger trial with long-term follow-up may be able to solve this question.

The present study showed a trend for better 5-year DSS for SN negative patients as compared to SN positive patients which is in line with the findings of Broglie et al.[27] They reported in 58 patients that occult lymph node metastasis detected by SNB shorten DSS significantly.

Conclusion The Dutch multi-institutional SNB trial for the detection of occult lymph node metastases in early stage oral cancer patients shows a high negative predictive value and a high sensitivity, using long-term follow-up as reference standard. SNB is able to reduce the risk of occult lymph node metastases in oral cancer patients from 40% to 8%, and enables an excellent neck control (97.4%). SNB therefore offers a valuable alternative to the current policy of elective neck dissection in early stage OSCC patients

ACKNOWLEDGEMENTS

The trial was financially supported by the Netherlands Organization for Health Research and Development (ZonMw), grant 80-82305-98-08106.

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CHAPTER 4

Sentinel node biopsy for oral and oropharyngeal squamous cell carcinoma in the previously treated neck

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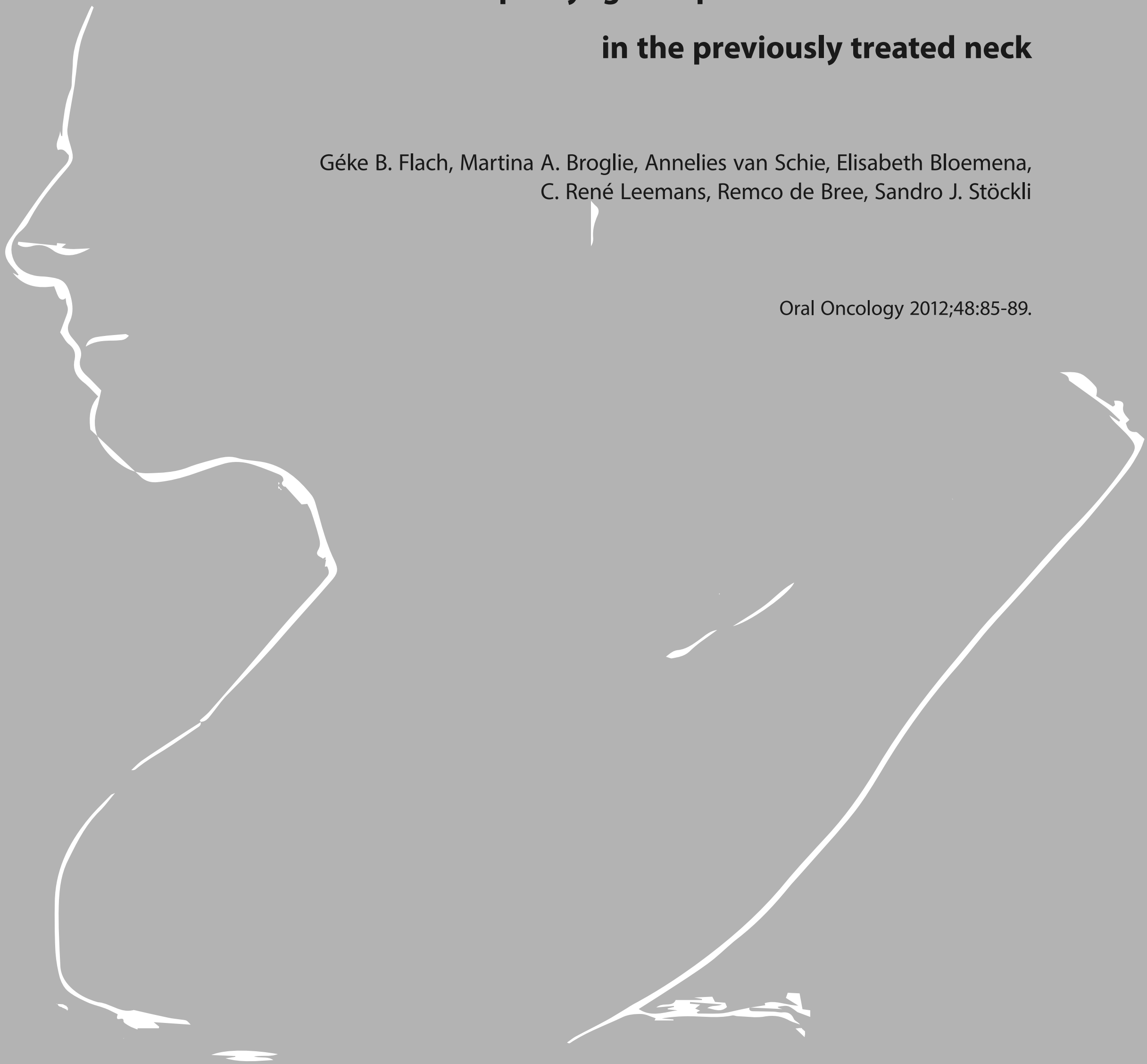
Oral Oncology 2012;48:85-89.



ABSTRACT

Objectives. In patients with early stage oral or oropharyngeal squamous cell carcinoma (OSCC) sentinel node biopsy (SNB) is a reliable method to detect occult disease in the neck. However, patients with a history of surgery or radiotherapy in the neck may have aberrant lymphatic drainage caused by disruption of lymphatic channels. Therefore, treatment of the same levels at risk as in the primary setting may not be appropriate. The aim of our prospective observational study was to evaluate the clinical application of SNB in previously treated OSCC.

Methods. Between 2003 and 2010 twenty-two patients were included. Lymph node mapping consisted of preoperative lymphoscintigraphy, SPECT/CT, intraoperative use of gamma probe and patent blue. Endpoints were the sentinel node (SN) detection rate, unexpected lymphatic drainage patterns, negative predictive value and regional tumor control.

Results. 4/22 (18%) patients were previously treated only on the contralateral site. The SN detection rate was 100% and unexpected drainage was found in 1/4 patients. The other 18 patients had ipsi- or bilateral previous neck treatment and a SN detection rate of 83%. The upstaging rate was 7% and 67% had unexpected lymphatic drainage patterns. The median follow-up was 22 months. Regional tumor control and negative predictive value were 100%.

Conclusions. SNB in previously treated OSCC patients is feasible. SN detection is reliable and regional tumor control after staging by SNB is excellent. Moreover, SNB renders an assessment of the individual lymphatic drainage pattern, compensating for a potential variability after previous treatment of the neck.

INTRODUCTION

In head and neck squamous cell carcinoma (HNSCC) the local recurrence rate is 10-30% and the annual risk for second primary tumors is 3 to 4%.[1-4] For optimal treatment planning in recurrent and second primary cancer accurate staging of the neck is essential. However, patients with a history of surgery or radiotherapy in the neck may demonstrate aberrant lymphatic drainage caused by disruption of lymphatic channels. Therefore, standard treatment of neck levels at risk as applied in the primary setting may not be possible or appropriate after previous neck treatment. As neither physical examination nor imaging are sufficiently reliable to exclude occult disease in the regional lymph nodes, histological examination of the lymph nodes at risk is required for exact neck staging and treatment.

The concept of sentinel node biopsy (SNB) is based on sequential metastatic spread. The sentinel node (SN) being the initial recipient of metastatic tumor cells, can therefore predict the involvement of the remaining lymphatic basin.[5-8] Compared to elective neck dissection (END) this technique offers a less invasive means of staging,[9,10] and permits detailed histological, immunohistochemical (IHC) and molecular examination of the small group of lymph nodes most likely to harbor occult disease. Of patients with clinically negative (cN0) necks 20-30% are subsequently found to harbor occult disease within the cervical lymph nodes.[11] Use of this technique in the primary setting of a cN0 neck allows to select those patients with occult metastases for neck dissection and to avoid overtreatment in the others. SNB is generally advocated in early stage (T1-T2) oral and oropharyngeal squamous cell carcinoma (OSCC) without previous treatment of the neck.[12-16] Treatment of the neck is thought to disturb the normal anatomy, leading to alterations in lymphatic drainage patterns and potentially higher false negative rates of SNB.

Aberrant lymphatic drainage has been observed in patients with breast cancer after prior axillary dissection but SNB in these cases was demonstrated to be still feasible.[17-22] However little is known about the application of SNB in previously treated OSCC. So far, only three pilot studies suggest its feasibility.[23-25] The aim of our study was to evaluate the clinical application of SNB in previously treated OSCC with regard to lymphatic drainage pattern, SN detection rate, negative predictive value (NPV) and regional tumor control.

PATIENTS AND METHODS

Between 2003 and 2010 twenty-two patients were prospectively enrolled in the study, 12 from the VU University Medical Center (VUmc) in Amsterdam, The Netherlands and 10 from the Swiss Centers at the Kantonsspital in St. Gallen and the University hospital in Zurich.

Patients with recurrent disease or second primary cancer in the oral cavity or oropharynx and a clinically N0 neck after previous treatment of the neck were included. Prior treatment of the neck was either selective or modified radical neck dissection, (chemo-)radiotherapy or a combination of these modalities.

In the VU University Medical Center patients underwent lymphoscintigraphy the day before surgery according to the procedure described by Nieuwenhuis et al.[26] In patients from Switzerland lymph node mapping was performed the same day 2h prior to surgery and consisted of a preoperative dynamic and static lymphoscintigraphy and additional SPECT/CT as described earlier.[27] The position of the SN was marked on the overlying skin with the use of a ^{57}Co point-source marker and a gamma probe.

Unexpected drainage patterns on lymphoscintigraphy were defined as: (1) contralateral drainage in unilaterally located tumors and (2) drainage to other neck levels than level I to III in oral tumors and level II to IV in oropharyngeal tumors.

In the patients from the VU University Medical Center blue dye was peritumorally injected. In both centers SNs were detected intraoperatively with the aid of a handheld gamma probe and excised selectively.

Histopathological examination of SNs consisted of step-serial sectioning (SSS) with an interval of 150-250 µm of the entire lymph node. Of each level stainings with hematoxyline-eosine (H&E) and pan-cytokeratin antibody (AE 1/3) were performed. Occult metastases were differentiated into isolated tumor cells (< 0.2 mm; itc), micrometastasis (≥ 0.2 mm and ≤ 2 mm; micro) or macrometastasis (> 2 mm; macro) according to the criteria proposed by Hermanek et al.[28] If a lymph node metastasis was proven by SNB, completion neck dissection was performed during a second surgical procedure.

Patient, tumor and treatment characteristics were recorded. Study endpoints were lymphatic drainage pattern, SN detection rate, NPV and regional tumor control.

RESULTS

Twenty-two patients, 15 male and 7 female with a mean age of 62 years (range 43-76) were included. In Table 1 all patients are shown with tumor characteristics, medical history and SNB results. The mean time between first treatment and recurrence or second primary tumor was 68 months (range 8-239 months).

The patient cohort consisted of 4/22 (18%) patients who were previously treated only on the contralateral site, one by surgery alone, two by surgery and radiotherapy and one by chemoradiotherapy. The detection rate of SNB in these 4 patients was 100%. The drainage pattern was unexpected in one patient with sentinel nodes located in the ipsilateral levels IV and V. Three of these 4 patients were nodal positive (1 itc, 2 macro).

The other 18 (82%) patients had ipsilateral (6/18) or bilateral (12/18) previous treatment of the neck. The neck treatment consisted of neck dissection (4/18), radiotherapy (6/18), neck dissection with adjuvant radiotherapy (3/18), chemoradiation (2/18) or neck dissection with adjuvant chemoradiation (3/18).

The tumor was located in the oral cavity in 15/18 (83%) and in the oropharynx in 3/18 (17%) patients. Tumors were staged as pT1 in 12/18 (67%) and pT2 in 6/18 (33%) patients according to UICC.[29] By means of lymphoscintigraphy hot spots could be detected in 15/18 cases. SPECT/CT detected 8 additional hotspots in 7 patients. Even with the guidance of the handheld gamma probe no SNs could be harvested in the three patients with negative lymphoscintigraphy, resulting in an ultimate SN detection rate of 83% (15/18). On average 2.7 SNs (range 1-6) per patient with an average size of 9.4 mm (range 2-19 mm) were removed. SNB was positive for occult metastasis in 1/15 (7%) patient revealing a micrometastasis.

Pt	Tumor site	Side	T-stage	Medical history tumor	Side	Previous treatment of the neck		SNB (+ve)	Neck levels SNB		N-stage
						Treatment	Ipsi/Contra		Ipsi	Contra	
1	Tongue	R	1	Tongue	L	Surg	C	5 (2 itc)	III, IV, V	-	N0 itc
2	Tongue	L	1	T3N2b tonsil	R	Surg + RT	C	3 (1 macro)	II	-	N1
3	Tongue	L	1	T1N2b vallecula	R	RT + CH	C	3 (1 macro)	II	-	N1
4	Pharyngeal arch	R	1	T2N3 tonsil	L	Surg + RT	C	3	I, III	-	N0
5	Tongue	R	2	T2N0 tongue	R	Surg	I	1 (1 micro)	-	II	N1
6	Tongue	R	2	T2N0 tongue	R	Surg	I	3	-	IV	N0
7	FOM	R	1	T1N0 FoM	R	Surg	I	2	II	-	N0
8	Inferior alveolar process	R	1	T1N1 inferior alveolar process	R	Surg	I	1	-	III	N0
9	Tongue	R	1	T4N0 glottic	R	RT	B	1	III	-	N0
10	FOM	L	1	T1N1 supraglottic	L	RT	B	6	I, V	IV	N0
11	FOM	L	1	T2N0 glottic	R	RT	B	1	II	-	N0
12	FOM	L	1	T2N0 supraglottic	L	RT	B	3	I	I	N0
13	Retromolar trigone	R	2	T2N2c tonsil	R	RT	B	1	retroph	-	N0
14	FOM	R	1	T2N0 tonsil	L	Surg + RT	B	2	IV	-	N0
15	Tongue	L	1	1) T1N0 tongue 2) N1 neck ipsi level IV	L	Surg + RT	I	3	II	I, IV	N0
16	FOM	R	1	T3N0 supraglottic	L	RT + CH	B	-	-	-	N0
17	Tongue	R	2	1) T3N0 tonsil 2) T2N1 supraglottic	L	RT + CH	B	-	-	-	N0
18	Tongue	L	2	T2N2b tonsil	R	Surg + RT + CH	B	2	II, V	-	N0
19	Tongue	R	1	T2N2b tongue	R	Surg + RT + CH	I	6	I	II, IV	N0
20	Uvula	M	1	T3N0 uvula	L	RT	B	6	III	III	N0
21	Soft palate	L	1	TxN2b CUP	R	Surg + RT	B	-	-	-	N2b
22	Soft palate	L	2	T2N2b piriform sinus	R	Surg + RT + CH	B	3	I, II, III	-	N0

TABLE 1. Tumor characteristics, previous treatment and results of SNB per patient. Pt: patient, FOM: floor of mouth, R: right side, L: left side, M: midline, CUP: cancer of unknown primary origin, Surg: neck dissection, RT: radiotherapy, CH: Chemotherapy, C: contralateral, I: ipsilateral, B: bilateral, macro: macrometastasis, micro: micrometastasis, itc: isolated tumor cell, retroph: retropharyngeal

4

Of the three SN-lacking patients, two were previously treated by bilateral chemoradiotherapy and one by contralateral neck dissection and bilateral postoperative radiotherapy. In the subsequently performed ipsilateral neck dissection, in one patient 3 lymph nodes were found to be positive resulting in a pN2b stage. The ultimate upstaging rate of all 18 patients was therefore 11%.

Localization of SNs is shown in Figure 1. In 7/15 patients only ipsilateral SNs were harvested. They were located in level II or III in 3/7, in level IV or V in 2/7, in the retropharyngeal space in 1/7 patient and in level I in 1/7 patient with oropharyngeal cancer. In 3/15 cases SNs were located only in the contralateral neck (one patient level II, one level III and one level IV) whereas 5/15 patients had bilateral SNs. Altogether 10/15 (67%) patients had unexpected lymphatic drainage patterns.

The median follow-up was 22 months (range 1-68 months). There was no regional recurrence. The regional tumor control rate as well as the NPV of negative SN was therefore 100%.

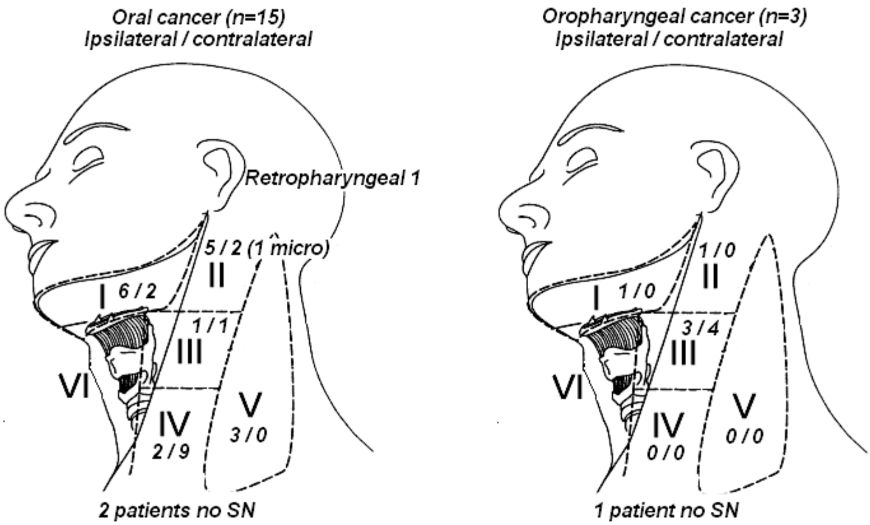


FIGURE 1. Localization of sentinel nodes in patients with ipsilateral or bilateral previous treatment of the neck (n = 18) micro: micrometastasis

DISCUSSION

The encouraging results of validation studies[12-16] about SNB in oral and oropharyngeal cancer led to the introduction of SNB in daily practice and a number of centers have subsequently abandoned END in the setting of a negative SNB.[11]

According to the recent guidelines,[30] SNB is indicated to stage the ipsilateral cN0 neck in patients with a unilateral primary tumor or to assess bilateral cN0 necks in primary tumors close to, or crossing the midline. The third possible indication is the assessment of the contralateral cN0 neck in primary tumors close to the midline with an ipsilateral positive neck to select patients for bilateral neck dissections in case of positive SNB. Patients who have received prior radiation or surgical treatment to the neck are routinely excluded from SNB protocols since prior treatment may influence the lymphatic channels leading to false negative results. Although lymphatic mapping and SNB may yield potentially useful information in these patients only two pilot studies have explored the applications of the SNB technique in this situation and suggested its feasibility.[23,24]

This study focused on SNB in a larger patient cohort with previous treatment to the neck, by surgery or radiotherapy with or without chemotherapy, or a combination of both. In patients with previous treatment of the contralateral side and unilateral primary tumor the SN-detection rate was expectably high.

In patients with a previously ipsi- or bilateral treated neck SNB was successful in 83%. Compared to the literature,[11,12,14] with SN-identification rates approaching 90-100% this is significantly lower. In a study about 11 previously treated patients the success rate of SNB was 100%.[23] Details about the side of previous neck treatment were not outlined. As we have seen in our cohort contralateral treatment does not seem to relevantly influence lymphatic mapping in unilateral tumors.

Furthermore only 7% of our patients with a previous ipsi- or bilateral neck treatment were found to be nodal positive. According to the literature the upstaging rate by SNB in OSCC is 30-40%.[12,14,31] The question arises whether we have missed occult disease by SNB due to disrupted lymphatic channels. None of our patients developed regional metastases. Therefore, the negative predictive value was 100%, although the follow-up was with a mean of 22 months quite low. Hart et al. reported a negative predictive value of 91%.[23] But in contrast to our study the NPV was defined as comparison of the SN pathology with that of the neck dissection specimen after performing both SNB and subsequent END in every patient. The problem behind this comparison is the different pathologic work up of the specimen. In contrast to routine histological evaluation of a neck dissection specimen SNB allows for considerably more accurate pathological staging using serial sections and IHC.[12,32] It is well known from various studies that the more precisely the lymph nodes of a neck dissection are examined, the more occult metastases are found.[16,27,33,34]

One further endpoint of this study was the incidence of unexpected drainage patterns after previous neck treatment. According to the reports of Shah et al. expected lymphatic drainage was defined as level I-III in oral carcinomas and level II-IV in oropharyngeal carcinomas.[24,25] SNs located in other neck levels were considered unexpected, as well as contralateral located SNs from unilateral tumors. With regard to this definition, in our study 67% of ipsi- or bilaterally and 25% of only contralateral treated patients had unexpected drainage patterns. The one patient in the only contralateral treated group with nodal disease in level IV had a primary of the oral tongue. It can be discussed however, whether drainage to level IV in oral cancer should be defined as unexpected, since primary tumors of the oral tongue may show a direct drainage to level IV.[35-37] In other studies, SNs were detected in level IV such as Ross et al.[38] who found 4% of occult disease in oral tongue cancer in level IV.

Moreover, contralateral drainage in unilaterally located carcinomas of the tongue or floor mouth has been described before.[39,40] The study of Ross et al.[38] showed 15%, and the study of Civantos et al.[41] 14% drainage outside the expected lymphatic basins which was supported by Shoaib et al.[40] These findings underline the strength of SNB in assessing the individual drainage pattern. Nevertheless, in our patients with ipsilateral previous treatment drainage to unexpected levels or neck side was significantly higher as compared to the contralateral treated patient group and in comparison to the literature. This supports the theory that a previous intervention can distort the normal lymphatic pathways and give rise to unexpected patterns of metastasis.

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Our results sustain the value of SNB in assessing the individual drainage pattern. In patients who received prior radiation or surgical treatment of the neck, SNs were often detected in unexpected neck levels but sometimes still found in the treated area, suggesting that not all lymph nodes and lymphatic channels were disrupted or that channels could possibly have regenerated. Wagner et al. performed a study in which patients underwent SPECT/CT before and after chemoradiotherapy followed by SNB.[42] He found that there was no constant effect of irradiation on lymphatic drainage, neither were tumor site or TNM stage predictive factors for the drainage patterns. As we know from previous studies there still exists a great inter-individual variability despite the knowledge on general cervical lymphatic drainage patterns.[31,35,38,40,41,43]

Conclusion SNB in previously treated patients is feasible. Moreover, SNB renders an assessment of the individual lymphatic drainage pattern, compensating for a potential variability after previous treatment of the neck. Even in this patient cohort SNB is a safe and accurate staging modality to select patients with occult lymph node disease for neck dissection. Further investigations with larger sample sizes and even longer observation time are necessary to support our preliminary results.

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CHAPTER 5

Visualization of the sentinel node in early stage oral cancer: Limited value of late static lymphoscintigraphy

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Nuclear Medicine Communications 2012;33:1065-1069.

ABSTRACT

Objectives. Various lymphoscintigraphic imaging protocols exist for sentinel node (SN) identification in early stage oral cancer. This study aimed to evaluate the clinical value of performing additional late lymphoscintigraphic imaging.

Methods. We retrospectively analyzed early (directly following injection of ^{99m}Tc-nanocoll) and late (2-4h after injection) imaging results of 60 early stage (T1-T2, cN0) oral cancer patients scheduled for SN procedure. Lymphoscintigraphic results of late imaging were categorized into: (a) no visualization of additional hot focus considered to be SNs, (b) additional hot focus visualized that are considered to be SNs and (c) hot focus visualized only during late imaging. Histopathological results of the harvested SNs were related to the corresponding hot focus.

Results. In all patients (n = 60) lymphoscintigraphy was able to visualize a hot focus that was identified as an SN. In 51/60 (85%) patients early imaging was able to visualize at least one hot focus, whereas in 9/60 (15%) patients, mostly with oral cavity tumors other than mobile tongue and floor of mouth tumors, only late imaging was able to visualize hot focus. In 14/51 (27%) patients late imaging resulted in additional visualized hot focus marked as SNs, resulting in a more extensive surgical procedure. These additionally removed SNs appeared to be of no clinical relevance, as all SNs identified during early imaging correctly predicted whether the neck was positive or negative for cancer.

Conclusions. Results of this study indicate that additional late lymphoscintigraphic imaging should only be performed in selected cases.

INTRODUCTION

The sentinel node (SN) procedure is a reliable alternative for staging of the neck instead of performing an elective neck dissection in early stage oral cancer.[1-3] Most important in this procedure is the correct identification of the SN, which is preoperatively based on lymphoscintigraphy. Once identified, gamma probe and blue dye guided surgical incision and exploration of the neck are performed to localize and remove the SN for histopathological examination.[4]

Lymphoscintigraphy can be performed at different time points after peritumoral injection of a radioactive labelled tracer. Tracer drainage and uptake in the SN depend mainly on the size of the particles that are used.[5] In Europe, mainly ^{99m}Tc-nanocoll is used as a tracer, and this tracer has a relatively small particle size resulting in rather fast lymphatic drainage. This may result in accumulation of tracer in additional lymph nodes, often the second echelon lymph nodes.

It is known that imaging at later time points after injection of the radiocolloid results in the appearance of a larger of hot focus.[6,7] However, it is often impossible to determine whether these hot focus are all true SNs or are second echelon lymph nodes (Figure 1). The usually complex and unexpected lymphatic drainage in the head and neck region – for example, drainage to multiple basins, drainage that bypasses basins, and contralateral drainage of well-lateralized tumors, makes this distinction even more difficult.[8] Once a hot focus visualized during late lymphoscintigraphic evaluation is considered to be an SN, the surgical procedure may be more extensive – for example, more exploration of the neck and/or more incisions. More extensive exploration to find the SN harbors the risk of more complications and morbidity, and may also negatively influence a possible neck dissection in case of a metastatic SN. At present, different lymphoscintigraphic imaging protocols exist.

This study aimed to evaluate the clinical relevance of lymphoscintigraphic imaging results directly after injection and at later time points. Therefore, we retrospectively analyzed the lymphoscintigraphic imaging results of 60 oral cancer patients and assessed the clinical relevance of routinely performed late static imaging by histopathological results.

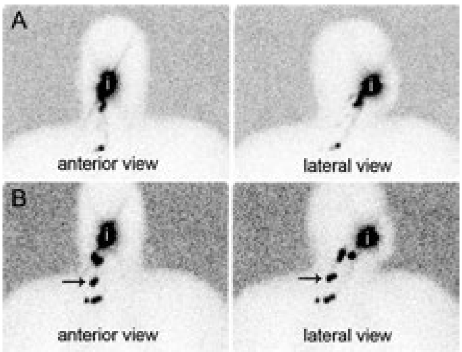

FIGURE 1. Early (A) and late (B) static lymphoscintigraphic imaging results of a patient with a cT2N0 lateral tongue carcinoma on the right side. During early image registration, hot foci were clearly visualized in level IIA and IV on the right side, with additional hot foci considered to be SNs detected during late imaging, of which two were located at a different level of the neck (level III, arrow). A positive SN was found in a lymph node harvested from level IV on the right side. Subsequent modified radical neck dissection showed no additional metastatically involved lymph nodes. I: injection site, SN: sentinel node

PATIENTS AND METHODS

Patients From February 2007 to July 2011, 60 previously untreated patients with histopathologically proven squamous cell carcinoma of the oral cavity were eligible for this study. All patients had a T1-T2 primary tumor, a clinically negative neck (cN0) and underwent ultrasound guided fine needle aspiration cytology (USgFNAC) showing no signs of metastasis. Patient and tumor characteristics are shown in Table 1.

Sentinel node procedure All patients underwent planar lymphoscintigraphy the day before surgery. Patients received four peritumoral injections of ^{99m}Tc-nanocoll (100 MBq total) (Nanocoll®; GE Healthcare, Eindhoven, The Netherlands) at a volume of 0.15-0.2 ml each. All injections were performed by the same persons (D.H., G.F., and R.B.). To avoid spillage of the radiocolloid, the patients were asked to perform a mouthwash immediately after injection. Subsequently, dynamic lymphoscintigraphic images were acquired (20 x 60s, 128 x 128 matrix, low-energy high-resolution collimator, e.cam dual-detector camera; Siemens Medical Solutions, Hoffman Estates, Illinois, USA). The patients were in supine position with the tumor side facing the camera. After this, a flood-field source image was obtained and a static image of 120s was acquired in the anterior projection to exclude superimposition of the injection site and SN and check for contralateral drainage. In the case of midline tumors, dynamic imaging was performed in the anterior position. Early imaging was always completed within 30 minutes of injection. Late anterior and lateral static imaging (2 x 120s) was routinely performed an average 2.5h (range 2-4h) after injection. It is noteworthy that single photon emission computed tomography/computed tomography (SPECT/CT) was not yet available at the time of lymphoscintigraphic evaluation of these patients. After visualization of the SNs, the position was marked on the overlying skin using a ^{57}Co point-source marker, and confirmed with a 14 mm diameter handheld gamma probe (Europrobe II; Eurorad, Strasbourg, France). The localization of the SN was classified into one of the six different lymph node levels in the neck according to the classification system of the American Academy of Otolaryngology - Head and Neck Surgery.[9] The criteria that we used to determine whether a hot focus is an SN or a second echelon lymph node are listed in Table 2.

At the start of surgery, 1 ml of patent blue V dye, diluted 1:3 (v/v) in water, was injected at four equally spaced points to completely surround the tumor. The position of the SN was verified by the handheld gamma probe and an incision was made to explore the area. All hot or blue nodes were excised; ex vivo confirmation of radioactivity-containing lymph nodes was determined using the handheld probe. Blue and/or lymph nodes containing more than 10% of the radioactivity counts of the hottest lymph node were considered to be SNs. Histopathological examination of SNs consisted of step-serial sectioning at intervals of 150-250 µm for the entire lymph node. At each level, staining procedures with hematoxyline-eosine (H&E) and pan-cytokeratin antibody (AE 1/3) were performed. Patients with a positive SN were treated by performing a neck dissection during a second surgical procedure, whereas patients with a negative SN were followed up by regular physical examination and ultrasound-guided fine needle aspiration cytology of the neck.

Number of patients	60
Male / female	32 / 28
Age	
Median	60
Range	29-81
T-stage of primary tumor	
T1	32
T2	28
Localization	
Mobile tongue	33 (55%)
Floor of mouth	20 (33%)
Inferior alveolar process	3 (5%)
Buccal mucosa	3 (5%)
Soft palate	1 (2%)

TABLE 1. Patient and tumor characteristics

	Sentinel node	Second echelon lymph node
Early imaging[a] (< 30min p.i.)	Hot focus with evident uptake	Caudal hot focus with clearly visible connecting lymphatic vessel from a cranial hot focus, not increasing in time
		Caudal hot focus with low uptake not increasing in time
Late static imaging (2-4h p.i.)	New hot focus visualized ipsilaterally or contralaterally	Newly visualized hot focus caudal from the sentinel node, not intense
	New hot focus visualized between a hot focus already identified during early imaging and the injection site	
	Caudal hot focus with previously low uptake, but now much more intense	
	In case of doubt, the newly visualized hot focus was considered to be a sentinel node	

TABLE 2. Criteria for differentiation between sentinel node and second echelon lymph node related to the time of imaging p.i.: postinjection, [a] dynamic and static imaging

RESULTS

In all patients lymphoscintigraphy was able to visualize at least one hot focus which was defined as an SN (Figure 2). In 51/60 (85%) patients 103 hot foci were visualized during early imaging whereas late static imaging demonstrated 26 additional hot foci considered to be SNs in 14/51 (27%) of these patients. All hot foci visualized during early imaging remained visible on late static imaging. In the remaining 9/60 (15%) patients, a total of 16 hot foci were visualized only on late static imaging. Of these nine patients two had mobile tongue tumors, two had floor of mouth (FOM) tumors, and five had other tumors, namely buccal mucosa, soft palate, and inferior alveolar process tumors. This resulted in a detection rate of hot foci of 94% (31/33) for mobile tongue tumors, 90% (18/20) for FOM tumors, and 29% (2/7) for other oral cavity tumors during early imaging (Figure 3).

There were 12 patients with paramedian or midline tumors, and 10 of them (83%; one mobile tongue tumor, eight FOM tumors, one soft palate tumor) showed bilateral lymphatic drainage, which was visible on early imaging in five (50%) of these patients. Overall, 145 hot foci (median 2, range 1-8) were detected after late static imaging.

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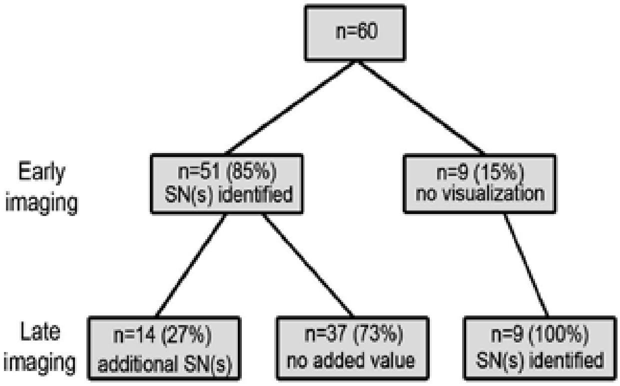

FIGURE 2. Schematic overview of lymphoscintigraphic early and late imaging results with respect to identification of SNs. SN: sentinel node

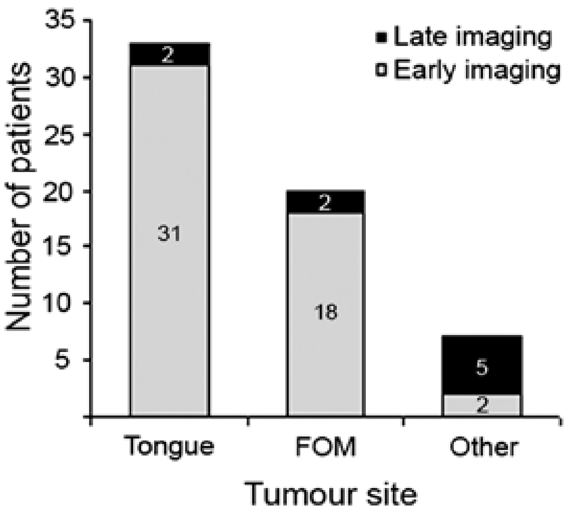

FIGURE 3. Visualization of hot foci in patients during early lymphoscintigraphic imaging or only on late imaging related to primary tumor site. Other tumors are buccal mucosa, inferior alveolar process and soft palate tumors. FOM: floor of mouth

Patient	Primary tumor site	Side	Level of hot focus	
			Early imaging	Late imaging
1	Buccal mucosa	R	1xIB R 1xIIA R 1xIV R	2xIB R
2	FOM	R	1xIIA R 1xIII R	1xIIA L 2xIV L
3	FOM	L	1xIIA L 1xIII L	1xIIA R
4	Mobile tongue	R	1xIIA R	1xIA R 1xIIA R
5	Mobile tongue	R	1xIIA R	1xIIA R 1xIV R 1xIV L
6	FOM	M	1xIV L	1xIB R 1xIIA R
7	Soft palate	M	1xIIA L	1xIIA R 1xIIB R
8	Mobile tongue	R	1xIV R	1xIIA R
9	FOM	R	1xV R	1xIIA R
10	Mobile tongue	R	1xIB R	1xIIA R
11	Mobile tongue	R	2xIIA R 2xIV R	1xIIA R 2xIII R 1xIV R
12	Mobile tongue	R	1xIB R 1xIIA R	1xIII R
13	FOM	L	1xV L	1xIB L 1xIIA L
14	FOM	L	1xIIA L	1xIB R

TABLE 3. Distribution of hot foci considered to be sentinel nodes related to the time of imaging of the patients with additional hot foci detected during late imaging
FOM: floor of mouth: R: right, L: left, M: midline

SN biopsy was performed for all patients and a total of 156 SNs (median 3, range 1-6) were excised during surgery. Blue dye was used in 57/60 patients in which 152 SNs were harvested. SNs were identified as hot and blue in 65/152 (43%), as hot only in 84/152 (55%), and as blue only in 3/152 (2%) excised SNs. Out of the additionally detected 26 hot focus during late imaging, six were located at the same level as a hot focus visualized during early imaging, whereas 20 hot foci were located at a different level (Table 3). In total, additional incisions were necessary in 11/14 (79%) of these patients (nine patients underwent one additional incision and two patients underwent two additional incisions) in order to excise the preoperatively identified SNs.

In 21/60 (35%) of patients, a histopathologically positive SN was found, which was located in a level of the neck that had been already visualized on early lymphoscintigraphic imaging in 17/21 patients. The remaining four patients with a positive SN showed drainage only during late imaging. Out of these 17 patients there were five patients in whom additional SNs were identified during late imaging. In one of these patients the additional hot focus, located between the primary tumor and a previously marked SN, corresponded with a positive SN. However, this finding had no clinical relevance as there was also a positive SN found at another level that was identified during early imaging. All 21 patients underwent a subsequent neck dissection (6 selective I-III, 6 selective I-IV, and 9 modified radical neck dissections). Three patients had additional metastatic lymph nodes in the neck dissection specimen (all modified radical neck dissections), whereas in 18/21 (86%) of patients no additional metastatic involvement was found. One (3%) out of the 39 patients with a negative SN developed ipsilateral lymph node metastases in neck levels. No hot foci were detected during lymphoscintigraphic evaluation in these levels in this patient. The remaining 38 out of 39 (97%) patients are all free of nodal disease with a median follow-up of 19 months (range 5-51 months).

DISCUSSION

In this study the additional value of late static imaging during preoperative lymphoscintigraphy was retrospectively assessed. Out of the 60 patients, late static imaging revealed additional hot foci considered to be SNs in 14/51 patients with hot foci on early imaging, whereas in nine patients hot foci were visualized only on late static imaging. In none (0/14) of the patients showing additional SNs during late imaging did these findings lead to a change in treatment, although the biopsy procedure in these patients was more extensive; that is, more incisions and more exploration of additional neck levels were necessary. Tumors in the oral cavity other than mobile tongue and FOM tumors seemed to have slower lymphatic drainage, as early lymphatic imaging was able to identify hot foci in only 29% of patients with these tumors. Because it is difficult to conclude from small numbers, we believe that late lymphoscintigraphic imaging should be considered for these tumors to minimize the risk of false negative results. The same is true for paramedian and midline tumors, for which bilateral drainage was observed in the majority (83%) of tumors, half of them visible only during late imaging.

The EANM and SENT joint practice guidelines advice that late static imaging is necessary only in case of no clear visualization of hot foci during early imaging.[4] However, there are only a few studies reporting on the different time points of imaging, with incongruent results.[6,7] As a consequence, there is no uniformly accepted lymphoscintigraphic imaging protocol with respect to SN identification in oral and oropharyngeal cancer. Nieuwenhuis et al.[7] evaluated lymphoscintigraphy results of 82 head and neck squamous cell carcinoma patients and concluded that early dynamic imaging is superior to late static imaging; however, they did not perform an SN biopsy to confirm the lymphoscintigraphic results. Some years later, the same group performed a histopathological validation study in 23 patients with T2-T4 oropharyngeal tumors planned for neck dissection.

In these patients, 23 SNs were identified preoperatively, and 30 additional radioactive lymph nodes were found in the neck dissection specimen. Lymph node metastases were always found in the SNs, whereas the 30 additionally detected radioactive lymph nodes were free of tumor. On the basis of these results, they suggested performing biopsy only of the first visualized SN.[10] However, De Cicco et al.[6] performed both early and late imaging and they suggested that it is not necessary to perform early image registration, as all metastatic lymph nodes were detected on late static images. In their study, however, it seems that results of early image registration would also have correctly identified the patients with a positive SN. Tartaglione et al.[11] recommend a 1-day protocol, with an interval of about 3h between dynamic lymphoscintigraphy and SN biopsy, to identify true SNs and avoid multiple and unnecessary node biopsies.

In recent years, SPECT/CT has been used more frequently as additional imaging tool for the detection and localization of SNs. In general, more hot foci are detected with this technique compared with planar lymphoscintigraphy.[12-15] However, these results should be interpret with caution. Although more hot foci are detected, this does not always mean that all these hot foci are true SNs: as the acquisition time of SPECT is much longer compared with that of planar lymphoscintigraphy, and SPECT imaging is often performed as the final imaging procedure – that is, at a later time point after injection of ^{99m}Tc-nanocoll – second echelon lymph nodes containing radiocolloid may become visible on SPECT images. Furthermore, additional hot foci detected next to the hot focus which was identified on planar LS should also be detected intraoperatively by the gamma probe. Therefore, we believe that SPECT/CT imaging is a helpful additional tool for detailed localization of a hot focus, but not for identification of true SNs. Recently, we developed a ^{89}Zr-nanocoll based tracer dedicated to PET/CT lymphoscintigraphy providing high-resolution images with visualization of connecting lymphatic vessels; this technique may be of additional value for identification of true SNs.[16]

Conclusion Our data indicate that routinely performed late static imaging is not necessary for the majority of oral cavity patients. Additional late lymphoscintigraphy should be performed if no hot foci are visualized during early image registration. Moreover, we believe that late lymphoscintigraphy should be considered in case of tumors other than mobile tongue and FOM tumors and if the tumor is located paramedian or in the midline. Performing additional late lymphoscintigraphy only in selected cases may reduce the extent of the SN biopsy procedure making it as minimally invasive as possible. Results of this study corroborate the current EANM and SENT guidelines.

ACKNOWLEDGEMENTS

This project was financially supported by the Cancer Center Amsterdam/VU Research Institute on Cancer and Immunology.

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CHAPTER 6

Practice variation in defining sentinel lymph nodes on lymphoscintigrams in oral cancer patients

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European Journal of Nuclear Medicine and Molecular Imaging 2014;41;2249-2256.

ABSTRACT

Objectives. Lymphoscintigraphic imaging and adequate interpretation of the lymphatic drainage pattern is an essential step in the sentinel node biopsy (SNB) procedure. In oral cancer, identification of the sentinel node (SN) can be challenging. In this study, interobserver variability in defining SNs on lymphoscintigrams was evaluated in patients with cT1-T2 stage N0 oral cancer.

Methods. Sixteen observers (head and neck surgeons, nuclear medicine physicians or teams of both) from various institutes were asked which criteria they use to consider a hot focus on the lymphoscintigram as SN. Lymphoscintigrams of 9 patients with 47 hot foci (3-9 per patient) were assessed, using a scale of 'yes / equivocal / no'. Bilateral drainage was seen in four of nine cases. In three cases additional late single photon emission computed tomography (SPECT)/CT scanning was performed. Interobserver variability was evaluated by kappa (κ) analysis, using linear weighted pairwise comparison of the observers. Conservative (equivocal analyzed as no) and sensitive (equivocal analyzed as yes) assessment strategies were investigated using pairwise kappa analysis.

Results. Various definitions of SNs on lymphoscintigrams were given. Interobserver variability of all cases using a 3-point scale showed fair agreement (71%, κ_w = 0.29). The conservative and sensitive analyses both showed moderate agreement: conservative approach κ = 0.44 (in 80% of the hot foci the observers agreed) and sensitive approach κ = 0.42 (81%) respectively. Multi-disciplinary involvement in image interpretation and higher levels of observer experience appeared to increase agreement.

Conclusions. Among 16 observers, there is practice variation in defining SNs on lymphoscintigrams in oral cancer patients. Interobserver variability of lymphoscintigraphic interpretation shows moderate agreement. In order to achieve better agreement in defining SNs on lymphoscintigrams specific guidelines are warranted.

INTRODUCTION

Sentinel node biopsy (SNB) has been introduced as the standard staging procedure of the clinically N0 neck in T1-T2 stage oral squamous cell carcinoma in many institutions. A meta-analysis of SNB studies reported a pooled sensitivity of 93% and negative predictive value rates varying from 88-100%.[1]

At the 'First international conference on SNB in head and neck cancer' Ross et al. reported that centers which had performed 10 or less cases had a lower sensitivity (57%) compared with more experienced ones (94%).[2] Centers that performed more than 20 cases did better than those who performed less than 20 but more than 10.[2] The American College of Surgeons Oncology Group (ACOSOG) Z0360 study of 140 patients in 25 institutions also showed that more experienced surgeons achieved better results.[3] This learning curve is probably due to the several steps involved in the SNB procedure (lymphoscintigraphy, surgical excision and histopathology). Lymphoscintigraphy is the first step and consists of peritumoral injection of a radiopharmaceutical, rapid positioning of the patient for planar imaging and interpretation of the scan. Other aspects such as the size of the colloid with its associated kinetics, the time frame between injection and scan, the scanning protocol and the availability of single photon emission computed tomography/computed tomography (SPECT/CT) imaging influence the visualization of lymphatics and lymph nodes in lymphoscintigrams. Lymphoscintigraphic interpretation is one of the most important steps in SNB procedure in order to pinpoint the correct hot focus as SN.

In an attempt to reduce variations, the joint practice guidelines[4] for SNB in early oral cancer were published in 2009 to provide evidence-based guidelines for the use of SNB, with a view to gain optimal accuracy rates and uniformity of the procedure in different institutes. On image interpretation, it states "On dynamic imaging, SNs are identified as one or more foci to which lymphatic drainage passes, and may be multiple, in one or several areas of the neck, ipsilateral and/or contralateral to the primary tumor. … Foci appearing only on later images are also labelled as SNs...".[4] Unfortunately, this description leaves room for variability in image interpretation.

In oral cancer, lymphoscintigraphic interpretation can be difficult due to the close spatial relation between the injection site and nodal basin. This is due to fast lymphatic drainage and to complex drainage patterns in the neck area. The mean number of harvested SNs in oral cancer is approximately 2.7 with a range of 1-8.[5] SNB is less invasive than neck dissection, resulting in better postoperative shoulder and sensory function.[6,7] However, the more SNs, the more echelons and bilateral drainage, the more invasive the SNB procedure will be, increasing morbidity. In addition, a higher number of SNs increases time needed for surgery and for histopathological examination. These factors contribute to the challenge involved in identifying the correct hot foci as SNs on lymphoscintigrams.

The aim of the present study was to evaluate variation in defining SNs on lymphoscintigrams and to assess the interobserver agreement of lymphoscintigraphic interpretation in oral cancer patients.

MATERIALS AND METHODS

Observers Nineteen head and neck oncology institutes who participate in the Sentinel European Node Trial (SENT) were invited to participate in this interobserver study and 16 institutions responded. Observers were nuclear medicine physicians and surgeons jointly (7 institutions), surgeons (6) and nuclear medicine physicians alone (3). Their experience varied from 6-200 cases of SNB in HNSCC patients (≤ 50 patients (6), > 50 patients (10)). SPECT/CT was routinely used in 9/16 institutes. A file with a general questionnaire and clinical information of nine cases for image interpretation was provided to each.

Defining SNs on lymphoscintigrams The observers were asked to describe in free text which criteria they used to identify a focus on lymphoscintigrams as SN that should be harvested.

Cases for image interpretation Nine patients (cases) with clinically T1-T2 stage oral cancer and N0 neck, based on ultrasound guided fine needle aspiration cytology, were selected from 2 institutions: VU University Medical Center, Amsterdam (VUmc) (6 cases) and Antoni van Leeuwenhoek Hospital/Dutch Cancer Institute, Amsterdam (AvL/NKI) (3 cases). These cases were selected to represent a mixture of simple to complex drainage patterns: three cases had more than 6 foci, in 3 cases SPECT/CT was used and 4 had bilateral drainage patterns. All patients had undergone SNB and transoral excision as a routine procedure in early stage oral cancer.

6

For interpretation of the lymphoscintigrams, images were included on a CD-rom with an instruction document for the viewer (K-pacs, Image Information Systems Ltd. V1.5.0).

Scanning protocol Between 19-27h prior to surgery 80-110 MBq of ^{99m}Tc-nanocoll was injected peritumorally in 3-6 (mostly 4) doses, immediately followed by dynamic lymphoscintigrams (20 x 60s, 128 x 128 matrix, low-energy high-resolution collimator) in anterior or oblique view, with the patient in the supine position with the tumor side facing the camera. Directly after initial dynamic imaging, static images (120 or 300s, 256 x 256 matrix) were made with a flood-field source in anterior and lateral projections. After 2-4h, static images (120s, 256 x 256 matrix) were made, followed by SPECT/CT in cases 7-9.

Image interpretation by case evaluation Table 1 shows tumor site, stage and lymphatic drainage of the nine cases. Figure 1 and Figure 2 show examples of a case. Each focus on the lymphoscintigram was given a number by the investigator. The observers were requested to interpret the lymphoscintigrams and to assess the nodal status of each focus using a 3-point scale: ‘yes, equivocal or no’ SN. A fourth option ‘I don’t know’ was provided, in case the observer felt unable to assess the foci on the lymphoscintigram. In the data-analysis the latter classification was processed as missing. After image interpretation the observers were asked to evaluate each case as ‘easy, moderate or difficult’. As the aim was to evaluate the current interobserver variability with regard to current knowledge from experience, literature, and guidelines,[4] we did not provide criteria with respect to the interpretation of the lymphoscintigrams.

Statistical analysis Image interpretation was firstly evaluated per case. Missing scores were deleted from further analysis. Agreement per case was defined as the percentage of most frequent scores of each focus within a case. Per case the number of potentially selected SNs was given. After the 3-point scale (‘yes, equivocal, no’) analysis, the data were reduced to a 2-point scale and obtained for a conservative and sensitive reading strategy dichotomizing the results by assigning the indecisive scores (equivocal) to either the ‘no’ (conservative) or to the ‘yes’ (sensitive) classification.

To determine the interobserver variability, we used agreement statistics (Agree 7, statistics program) and classified the kappa values according to Landis and Koch et al.: < 0 poor, 0.00-0.20 slight, 0.21-0.40 fair, 0.41-0.60 moderate, 0.61-0.80 substantial and 0.81-1.00 excellent agreement.[8] As there is no distinctive reference standard for the interpretation of lymphoscintigrams, kappa analysis was performed by pairwise comparison of the observers, to express consistency. Linear weighted pairwise kappa analysis was performed for a 3-point scale and pairwise kappa analysis for a conservative and sensitive strategy with a 2-point scale. Sub-analyses were conducted for professional background and experience level. Kappa scores are presented with 95% confidence interval (CI).

Case 2

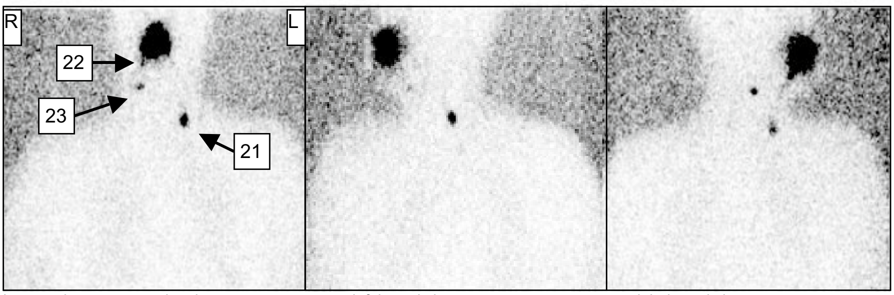
Clinical information:

- Male, 61 years
- T1N0 floor of mouth carcinoma on the left side
- Peritumoral injection of 103 MBq ^{99m}Tc-nanocoll, the day before surgery

Please view the images of **case 2** on the CD.

- The dynamic scan was made from the anterior side
- The early static scan contains 6 images:
  - Anterior side
  - Posterior view, not for use
  - Left lateral side
  - Posterior view, not for use
  - Right lateral side
  - Posterior view, not for use
- The late static scan contains 6 images:
  - Anterior side
  - Posterior view, not for use
  - Left lateral side
  - Posterior view, not for use
  - Right lateral side
  - Posterior view, not for use

After viewing the images, please fill in which hot foci you consider to be SN(s).



Late static scans: anterior view left lateral view right lateral view

This hot focus is:

- 21: O definitely SN O probably SN O no SN O I don't know
- 22: O definitely SN O probably SN O no SN O I don't know
- 23: O definitely SN O probably SN O no SN O I don't know

FIGURE 1. Example of a case

Case	Tumor stage and site	Lymphatic drainage	
		No. of foci	Lateralization
Case 1	T1N0 floor of mouth	4	Unilateral
Case 2	T1N0 floor of mouth	3	Bilateral
Case 3	T1N0 lateral tongue[a]	7	Contralateral
Case 4	T1N0 lateral tongue	5	Unilateral
Case 5	T2N0 floor of mouth	5	Bilateral
Case 6	T1N0 lateral tongue	8	Unilateral
Case 7[b]	T1N0 floor of mouth	3	Bilateral
Case 8[b]	T1N0 floor of mouth	3	Unilateral
Case 9[b]	T1N0 floor of mouth (m)	9	Bilateral

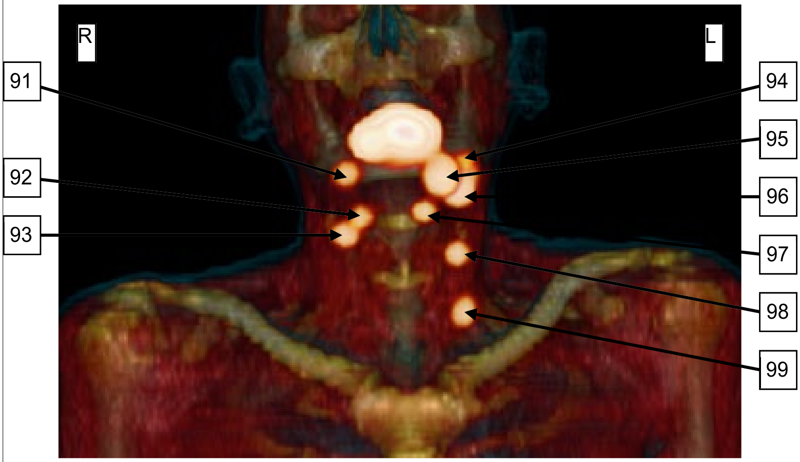
TABLE 1. Cases with tumor and lymphatic drainage characteristics
M: crossing midline
[a] medical history: 13 years ago radiotherapy for ipsilateral T2N0 soft palate carcinoma
[b] additional SPECT/CT

6

Case 9

Clinical information:

- Male, 67 years
- T1N0 anterior floor of mouth carcinoma on the right side crossing the midline
- Peritumoral injection of 80 MBq ^{99m}Tc-nanocoll, the day before surgery



SPECT/CT: MIP image (Maximum Intensity Projection), anterior view Thanks to NKI/AvL

FIGURE 2. Case 9 with SPECT/CT

RESULTS

Response A response rate of 84% (16/19) was achieved. In total 47 foci in 9 cases had to be classified. One observer had 23 of 47 foci with missing data and was subsequently deleted from further analysis.

Defining SNs on lymphoscintigrams Table 2 shows the criteria by which each observer considered a focus as SN. Nine observers considered the first visible focus to be SN, whereas for five observers each focus was a potential SN (2 did not describe this item). For eight observers there was no maximum of SNs. Four observers described 1-3 or 2-3 SNs as a maximum (4 observers undefined). Neck side was a relevant factor in 7 observers (irrelevant in 5, undefined in 4 observers), and neck level in 5 observers (irrelevant in 8, undefined in 3 observers). Definitions of second echelon nodes were given by 7 observers (9 observers undefined), as foci that are connected with an SN by a visible lymphatic vessel, whereas the others described them as later visible, less intense or more caudally than SNs.

Observer	Professional background	Which criteria do you use to 'label' a focus as SN that should be harvested? (e.g. what are your criteria to consider a focus to be SN; is level or neck side relevant for being a SN; when is a focus second echelon; do you have a maximum of SNs)
1	S	Normally a combination of the first hot focus to appear and hotness. I do not pay that much attention to every single hot focus, as if two are grouped together they will be harvested through a single incision. I do not like to make more than 3 incisions.
2	N	We use widely-accepted standard protocol for defining SN. This is the first node in each direction from the primary tumor which shows persistent activity during the imaging sequence. Level not taken to be important. Side is critical, so delayed imaging is always performed in lesions close to midline. No limit on number of SNs. A node which clearly fills via a well-defined track from a SN is a second echelon node- if there is doubt over order of filling, node is called a SN.
3	J	Every hot focus is a potential SN, which will be searched by the gamma probe.
4	S	No maximum of SNs, neck level is relevant as well as neck side.
5	S	Level and neck side are not relevant for being a SN. I do not have a maximum, but an average of 3-4. Any hot focus I consider of being SN. A second echelon is a late spill-over from SN.
6	J	Any lymph node that receives direct drainage is a SN. Second echelon is the hot focus regarded as a less visible node caudally of the SN. If surgically possible we suggest it to be removable. Both neck side and level is relevant. No maximum.
7	N	First echelon. Visible on early static scan (30min). Number of SNs: 1-3.
8	S	Our definition is: the first (or second) hot focus that appears is the SN. The level or neck side is not relevant for being a SN. In the literature: number of SNs: 2 or 3.
9	J	The sentinel lymph node is the first node which appears. If some nodes appear at the same time (+/-), all of them are considered as SN. Level or neck side are not relevant in order to consider SN. A hot focus is second echelon if this appears late and has less intensity. We do not have a maximum of SN.

Observer	Professional background	Which criteria do you use to 'label' a focus as SN that should be harvested? (e.g. what are your criteria to consider a focus to be SN; is level or neck side relevant for being a SN; when is a focus second echelon; do you have a maximum of SNs)
10	J	The first hot focus(i) which appear(s) on lymphoscintigram is considered SN(s). No matter if it is not in the first or second level: more relevant is the neck side related to the primary tumor. Second echelon: the second node which appears, or the second more evident node. No more than 2 or 3 SNs harvested in our hospital.
11	J	We consider SNs the nodes receiving lymphatic drainage directly from the tumor. We use the sequence or dynamic lymphoscintigraphy to distinguish SNs from second echelon nodes. Normally we biopt 2-3 SNs per patient. Located in neck levels near primary tumor.
12	S	Level + neck side.
13	J	First hot focus, closest to the tumor, same side.
14	J	Generally we consider all hot foci as SNs as we perform a static study. Neck side is relevant if the primary tumor not crosses the midline. Level is not so relevant. Although we have in many of the cases large numbers of hot focus(s), distant ones are usually not considered as SNs.
15	S	Localization on early scan images, level or neck side is not really relevant.
16	N	First lymph node in a certain 'basin' of drainage. Level or neck side is not relevant: it doesn't exclude a node for being a SN. No maximum of SNs. Second echelon à when there is a (reasonable) 'connection' visible between the SN and the next node in row.

TABLE 2. Sentinel node criteria
S: surgeon, N: nuclear medicine physician, J: joint team

Case evaluation The amount of equivocal scores varied per case from 11.7 to 20.0% (Table 3). Based on the opinion of the majority of observers, 1 case was considered easy, 6 moderate and 2 difficult (Table 3). This perception was independent of the drainage pattern (uni- or bilateral), the availability of SPECT/CT, experience with SPECT/CT, experience level with SNB and the professional background. The difficult cases had the most foci on imaging. The highest number of missing values was found in the case with the most foci (7.6%) (Table 3).

Agreement per case With a 3-point scale, agreement varied from 56% - 85% per case (Table 3). There was no evident difference in agreement between the conservative and sensitive reading strategy. The mean number of selected SNs per case was 3.0 with both reading strategies. The cases with the most foci (case 6 and 9) also had the most selected SNs (Table 3).

Case	Score		% Agreement per case ‡						Complexity
	Missing*	Equivocal	3-point scale		Conservative		Sensitive		
			Agreement	SNs	Agreement	SNs	Agreement	SNs	
Case 1	0.0%	11.7%	85%	1	97%	1	85%	1	Easy
Case 2	0.0%	20.0%	60%	2	67%	1	78%	3	Moderate
Case 3	1.0%	13.5%	70%	2	80%	2	74%	2 or 3	Moderate
Case 4	2.7%	15.1%	82%	2	94%	2	84%	2	Moderate
Case 5	0.0%	18.7%	75%	3	87%	3	81%	3	Moderate
Case 6	1.7%	16.1%	66%	3 or 4	75%	2 or 3	75%	4	Difficult
Case 7†	0.0%	20.0%	76%	3	76%	3	96%	3	Moderate
Case 8†	0.0%	13.3%	73%	3	73%	3	87%	3	Moderate
Case 9†	7.4%	16.0%	56%	5	70%	4	68%	5 or 6	Difficult

TABLE 3. Image interpretation, agreement analysis per case
* missing: foci that were not evaluated
† additional SPECT/CT
‡ agreement defined as the percentage of most frequent scores of each focus within a case: 3-point scale: 'yes, equivocal, no'; conservative and sensitive: equivocal foci considered as 'no' and 'yes', respectively.

Interobserver agreement of all cases Of the 47 foci in 9 cases, 10 foci had missing data and were not classified by 15 observers; hence, kappa statistics was performed with 15 observers and 37 foci. The interobserver variability as linear weighted pairwise comparison of the 15 observers with a 3-point scale, showed fair agreement (71%; κ_w = 0.29; 95%-CI 0.21-0.37). Pairwise analysis of the dichotomised scales resulted in moderate interobserver agreement: agreement between observers in 80% of the hot foci with κ = 0.44 (95%-CI 0.32-0.55) for conservative readings, and 81%, κ = 0.42 (95%-CI 0.31-0.52) for sensitive readings, respectively.

Sub-analysis for professional background showed slight agreement for surgeons, and fair agreement for nuclear medicine physicians and joint teams (Table 4). Conservative and sensitive readings resulted in fair agreement for surgeons and nuclear medicine physicians and moderate agreement for joint teams (Table 4). With a sub-analysis for experience level, it seems that more experience leads to improved agreement, although the differences are minimal (Table 5).

Observer (n)	Scale*	% Agreement	Kappa (95%-CI)
Surgeon (6)	3-point scale	70%	0.18 (0.11 - 0.26)
	Conservative	80%	0.33 (0.22 - 0.44)
	Sensitive	81%	0.27 (0.18 - 0.36)
Nuclear medicine physician (3)	3-point scale	80%	0.23 (0.08 - 0.38)
	Conservative	87%	0.35 (0.15 - 0.55)
	Sensitive	88%	0.40 (0.20 - 0.60)
Joint team (6)	3-point scale	74%	0.29 (0.20 - 0.38)
	Conservative	83%	0.45 (0.33 - 0.58)
	Sensitive	84%	0.42 (0.31 - 0.53)

TABLE 4. Interobserver variability according to professional background
95%-CI: 95% confidence interval
* scale: 3-point scale: 'yes, equivocal, no'; conservative and sensitive: equivocal foci considered as 'no' and 'yes', respectively.

Experience level (n)	Scale*	% Agreement	Kappa (95%-CI)
≤ 50 patients (6)	3-point scale	70%	0.23 (0.16 - 0.33)
	Conservative	78%	0.35 (0.21 - 0.48)
	Sensitive	82%	0.39 (0.25 - 0.54)
> 50 patients (9)	3-point scale	72%	0.30 (0.21 - 0.39)
	Conservative	80%	0.48 (0.35 - 0.60)
	Sensitive	83%	0.40 (0.30 - 0.51)

TABLE 5. Interobserver variability as a function of experience
95%-CI: 95% confidence interval
scale: 3-point scale: 'yes, equivocal, no'; conservative and sensitive: equivocal foci considered as 'no' and 'yes', respectively.

DISCUSSION

This is the first study that evaluates practice variation in definition of SN on lymphoscintigrams and observer agreement of image interpretation in oral cancer by multiple observers at different head and neck centers. There was substantial practice variation in defining SN on lymphoscintigrams. Nine cases were evaluated by 15 observers. Observer agreement was found to be moderate at best. Interobserver variability has been evaluated just once before, by Thomsen et al. in 2005, who reported excellent agreement.[9]

Sensitivity rates and negative predictive values of SNB procedures in oral cancer patients are generally above 90%.[1,10] It can be anticipated that with these excellent accuracy rates this technique is ready to be implemented worldwide. Ideally, physicians should provide consistent results. Interpretation of lymphoscintigrams is visual and is prone to observer variation. The extent to which high accuracy rates can be generalised, depends on consistency and reproducibility, also in image interpretation.

Thomsen et al. reported excellent interobserver agreement for evaluating foci in planar lymphoscintigrams (97.5%, $\kappa = 0.89$) and in SPECT/CT (95.5%, $\kappa = 0.82$) of 40 patients by 2 observers from the same institute.[9] In our study set-up we opted for multiple observers and a small number of cases. The observer panel in this study were European physicians from various countries and our results therefore give an impression of oral cancer SNB imaging interpretation in Europe.

In order to perform consistent lymphoscintigraphic evaluation, defining the SNB concept is essential. There are many definitions of the SN and many articles discuss the subject. The definition of Morton et al.[11] which says 'a sentinel node is the first draining lymph node on the direct lymphatic drainage pathway from the primary tumor site' best reflects the stepwise spread of cancer through the lymphatic system. This definition was also used in the SENT study protocol. However, this is a theoretical concept and does not always aid the clinician in interpreting a lymphoscintigraphic scan as an individual situation is not so clear-cut as this theory.

Describing how to interpret lymphoscintigrams with a view to identify hot foci as SN in a simple and straightforward way is not easy (Table 2). Many observers correctly considered SNs as the lymph nodes directly draining from the injection site, and/or single radioactive nodes in a basin, whereas other important criteria as uptake intensity, time of appearance, relevance of neck side and level were rated differently. We deliberately did not provide criteria for image interpretation in the interobserver study, as the aim was to evaluate the current observer variability in clinical practice using the current knowledge available from experience, literature and guidelines.[4]

Interobserver agreement can be influenced by a number of factors. If a single focus is visualized there will be no disagreement. However, in a complex nodal basin as the neck area, several foci are often visible. This harbors an increased risk of not identifying the correct SN and/or misinterpretation of second echelon nodes as SNs. This may lead to a higher interobserver disagreement. Foci on lymphoscintigrams are dependent variables within each case. However, in agreement statistics there is no correction for this, so that each focus was evaluated as a single independent case, although they are evidently not.

Observers used a 3-point scale for SN selection to distinguish between foci that are definite SNs and foci that are doubtful, as for example second echelon nodes. Since in clinical practice there is no room for doubt, a 2-point scale analysis reflects reality best. Conservative and sensitive readings showed comparable agreement (80%; $\kappa = 0.44$ and 81%; $\kappa = 0.42$, respectively). A limitation of the present study is that surgeons are not asked which nodes (hot foci) they intend to remove. It can be anticipated that since the risk of missing a real SN outweighs the unnecessary harvesting of an additional lymph node, a sensitive strategy may be used in clinical practice. However, because it was shown that removing the three hottest nodes is generally sufficient,[12] not all equivocal nodes will probably be removed. A 2-point scale (remove yes or no) may also result in a different interobserver agreement compared to the 3-point scale (and its translation to a 2-point scale) used.

Based on the sub-analyses, a multi-disciplinary approach appears to result in improved agreement. This reemphasises the importance of multi-disciplinary involvement, with optimal combined use of lymphoscintigrams and surgicoanatomical information in SNB procedures.[4] Level of experience also seems to play a role in agreement.

Dynamic imaging is essential for the differentiation between SNs and second echelon nodes.[9,13] Additional static images, in anterior and lateral projections to gain 3D information, lead to a thorough map of the lymphatics. The addition of oblique projection enables visualization of SNs closer to the primary tumor.[9]

Nowadays static planar lymphoscintigraphy may be superseded by SPECT/CT, which combines lymphoscintigraphy with tomography, giving anatomic and spatial information facilitating SN biopsy. Nevertheless, in many centers SPECT/CT is performed in addition to static planar images with the principal purpose of anatomical localization of SN already identified by lymphoscintigraphy. However, SPECT/CT also results in more visible foci and therefore more SNs.[9,14] If these are more proximal to the primary tumor site, the additional SNs may have clinical relevance. However, not all additional foci are important to SNB procedures. In one study with planar lymphoscintigrams the value of late static imaging was questioned: no metastases were found in additional foci that were visualized in late imaging.[15] Nevertheless, both dynamic imaging directly after injection and late static imaging remain important to distinguish first echelon nodes from the delayed appearance of second echelon nodes. These image patterns are the basis and clarify the subsequent work with the gamma probe in the operating room, avoiding unnecessary resection of radioactive secondary lymph nodes.

A result of 'moderate agreement' demands improvement. It stands to reason that intensive multi-disciplinary cooperation would result in more uniformity. Interpretation of lymphoscintigrams should also be part of multicenter studies, as with clinicopathological conferences within the SENT trial. In order to improve agreement, more specific guidelines for image interpretation may be warranted. Factors as the visualization of afferent lymphatic ducts, the time of appearance of the lymph nodes, the intensity of uptake, and the neck node basin should be mentioned in these guidelines. Also interpretation of SPECT/CT which plays an increasing role in head and neck SNB, needs to be included in those guidelines. It may be necessary to initially evaluate preliminary guidelines with several experts. In the past, procedural guidelines have been drawn up for other malignancies.[16]

Conclusion Interpretation of lymphoscintigrams is an essential step in SNB procedure. In oral cancer lymphatic drainage may be complex due to the close spatial relation between the primary tumor site and nodal basin, the fast flow of radioactive colloid and the bilateral drainage. Among experienced SNB professionals there is variation in defining SNs on lymphoscintigrams. The interobserver agreement of lymphoscintigraphic image interpretation between 15 experienced observers from different centers, was moderate: for conservative reading agreement between observers in 80% of the hot spots with $\kappa = 0.44$ and for sensitive reading 81% and $\kappa = 0.42$, respectively. Multi-disciplinary involvement in image interpretation and experience of the observers in SNB seems to benefit agreement. To improve observer agreement and to gain uniformity in lymphoscintigraphic SN definition, guidelines on how to interpret lymphoscintigrams are warranted. Before implementing additional guidelines on image interpretation, evaluation of this proposal and its potential for equivocal use, is required.

ACKNOWLEDGEMENTS

Due to the participation of the following surgeons and nuclear medicine radiologists, it was possible to conduct a unique study on interobserver variability of lymphoscintigrams. We wish to thank the following observers: M. McGurk MD FRCS DLO FDS RCS (Guy's & St. Thomas' Hospital, London), P. Manoharan MBChB MRCP FRCR (The Christie NHS Foundation Trust, Manchester), B. Murby PP (The Christie NHS Foundation Trust, Manchester), S. Stoeckli MD PhD (Kantonsspital, St. Gallen), J.A. Werner MD PhD (Universitatsklinikum Standort, Marburg), S. Wiegand MD PhD (Universitatsklinikum Standort, Marburg), J.A. Sørensen MD PhD (Odense University Hospital, Odense), J. Mortensen MD DMSc (Rigshospitalet, Copenhagen), A. Bilde MD PhD (Rigshospitalet, Copenhagen), Jean Lumbroso MD (Institut Gustave Roussy, Villejuif), D. Dequanter MD (CHU Charleroi, Montigny Le Tilleul), P. Villarreal MD (Hospital Universitario Central de Asturias, Oviedo), M. E. Garcia Lucero (Hospital Universitario Central de Asturias, Oviedo), T. Poli MD (Parma University Hospital, Parma), C. Cidda MD (Parma University Hospital, Parma), G. Tartaglione MD (Cristo Re Hospital, Rome), M. Pagan MD (Cristo Re Hospital, Rome), MG Vigili MD (Cristo Re Hospital, Rome), G. Dolivet MD PhD (Center Alexis Vautrin, Vandoeuvre-Les-Nancy), R. Mastronicola MD (Center Alexis Vautrin, Vandoeuvre-Les-Nancy), L.B. Moreira MD PhD (Hospital Luterano Da Ulbra, Porto), J. Alvarez Amezaga MD (Hospital de Cruces, Bilbao), J Santamaria MD (Hospital de Cruces, Bilbao), L Barbier MD PhD (Hospital de Cruces, Bilbao), J. Genollá MD (Hospital de Cruces, Bilbao), K.P. Schepman MD PhD (UMCG, Groningen), M. Hobbelink MD (UMCU, Utrecht)

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CHAPTER 7

Sentinel node biopsy in laryngeal cancer: Feasible in primary cancer with previously untreated necks

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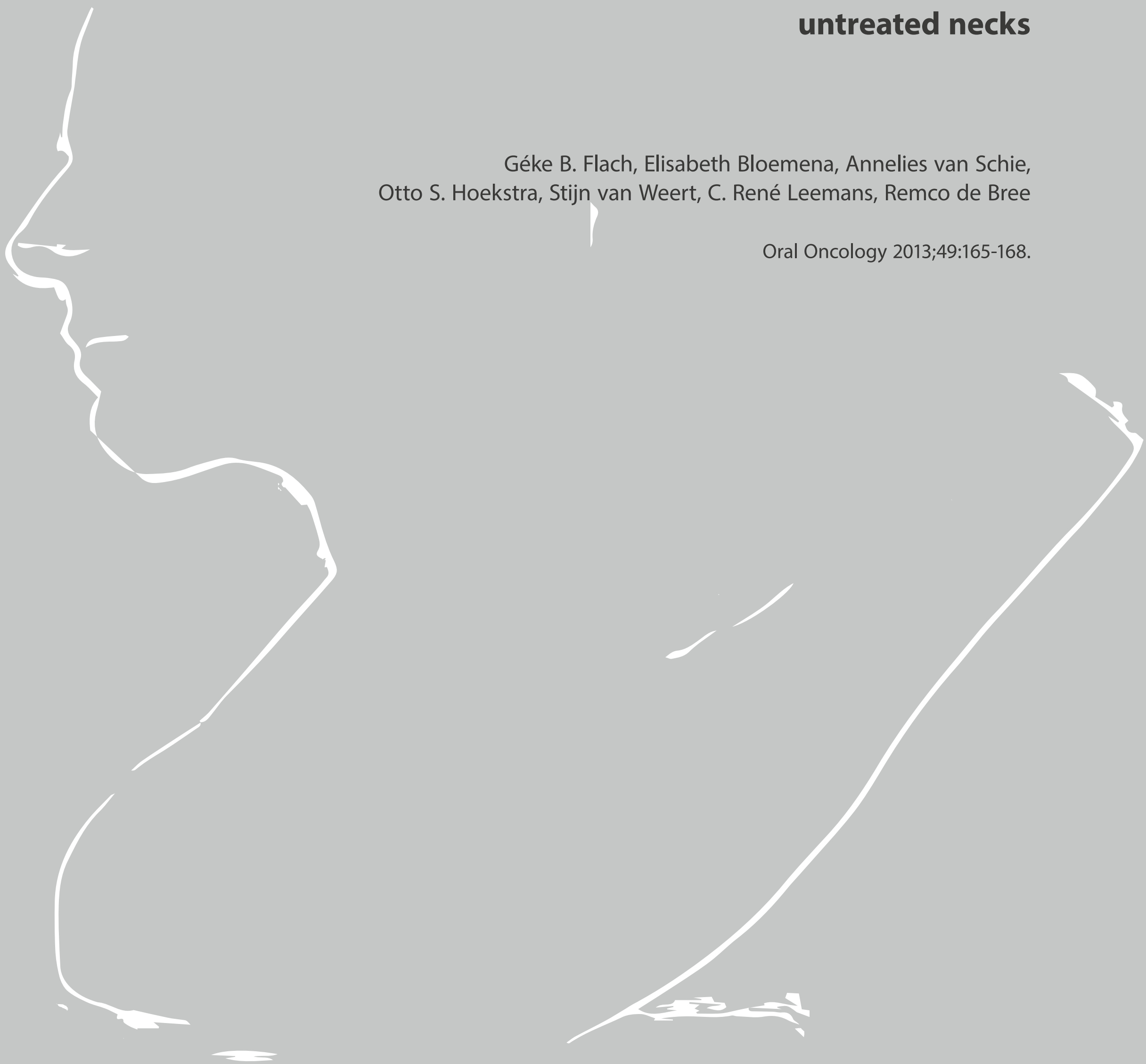
Oral Oncology 2013;49:165-168.



ABSTRACT

Objectives. With the current diagnostic techniques a considerable percentage of occult lymph node metastases are missed in the clinically negative (cN0) neck. Therefore, in patients with laryngeal cancer and cN0 neck a total laryngectomy is usually combined with elective neck dissection. Based on the risk of occult lymph node metastases the decision whether to perform a neck dissection or not is difficult. In recurrent laryngeal cancer or second primary tumors previous treatment possibly influences lymphatics and metastatic behavior. In this pilot study we investigated the feasibility of sentinel node (SN) identification and accuracy of sentinel node biopsy (SNB) in laryngeal cancer patients undergoing total laryngectomy with elective neck dissection.

Methods. Patients with cN0 laryngeal cancer were included. During surgery 40 MBq ^{99m}Tc-nanocoll was endoscopically injected around the tumor. Lymphoscintigraphy was not performed. We identified the SN ex vivo in the neck dissection specimen with a gamma probe. Histopathological examination of the neck dissection specimen served as reference test.

Results. We included 19 patients, 13 patients with untreated necks and 6 with prior neck treatment. SN identification was successful in 68.4% (13/19) of patients, and significantly higher in patients with untreated necks (92.3% versus 16.7%, $p < 0.01$). Four of 13 (30.7%) patients were upstaged by SNB. Sensitivity and negative predictive value would have been 80.0% and 87.5%, respectively.

Conclusions. With the current methodology, SN identification in laryngeal cancer patients undergoing total laryngectomy is feasible in patients with untreated necks. Further studies are needed to determine the exact accuracy of SNB in total laryngectomy patients.

INTRODUCTION

Sentinel node biopsy (SNB) is nowadays considered as a reliable neck staging procedure of the clinically negative (cN0) neck in T1-T2 oral and oropharyngeal squamous cell carcinoma.[1-3] Based on the encouraging results of several studies, many institutes have introduced SNB in daily practice and have abandoned elective neck dissection (END) as a staging and (in case of tumor positive lymph nodes) therapeutic procedure of the cN0 neck.[1-3] Moreover, SNB renders an assessment of the individual lymphatic drainage pattern, which may be directive in the extent of neck dissection. Besides oral cancer, SNB is still under investigation for head and neck squamous cell carcinomas (HNSCC) at other sites.

Laryngeal cancer is the most common form of HNSCC. The incidence of occult lymph node metastases in laryngeal cancer increases with T-stage and is correlated to the tumor subsite, showing a higher incidence in supraglottic (40%) than in subglottic (30%) and glottic carcinomas (10%). In T1-T2 stage glottic laryngeal cancer observation of the clinically N0 neck is allowed, whereas in more advanced (T3-T4) stage glottic cancer and in T2-T4 supra- or subglottic cancer, elective neck treatment of the cN0 is recommended.[4-6]

A total laryngectomy is indicated in patients with advanced stage tumors or as salvage surgery in case of recurrence after initial organ preservative treatment. In conjunction with a laryngectomy, management of the cN0 neck remains controversial; some clinicians prefer observation whereas others prefer to carry on a selective neck dissection (levels II-IV). Generally, in case of T3-T4 tumors elective neck dissection is recommended for the ipsilateral neck side, or bilaterally when the tumor crosses the midline.[7] Elective neck dissection comprises a selective lateral neck dissection of levels II-IV, because laryngeal tumors rarely metastasize to levels I and V and -if they do- only in patients with metastases in other levels.[8] About the paratracheal (level VI) lymph nodes, there are no well-defined criteria for performing a dissection and proper guidelines are lacking.[9] In case of salvage laryngectomy for recurrent cancer observation of the initial clinically N0 neck is acceptable,[10,11] whereas in case of a previous metastatic neck (although controversial) generally a comprehensive neck dissection (levels I-V) is recommended. If a more reliable staging technique of the neck is available unnecessary elective treatment of the neck can be avoided. Several studies have investigated SNB in laryngeal cancer.[12-23] Patients that were included had previously untreated T1-T4 laryngeal and hypopharyngeal tumors and treatment varied from transoral CO2 laser excision to partial or total laryngectomy and/or pharyngectomy.[12-15] In the present study, the aim was to evaluate the feasibility of SN identification and the potential accuracy of SNB during total laryngectomy and elective neck dissection for cN0 primary and recurrent laryngeal cancer patients.

PATIENTS AND METHODS

The institutional ethics committee approved this study and written informed consent was obtained from each patient.
Inclusion criteria were primary or recurrent laryngeal cancer, a clinically N0 neck based on computed tomography (CT), magnetic resonance imaging (MRI) and/or ultrasound guided fine needle aspiration cytology (USgFNAC). All patients were scheduled for total laryngectomy and uni- or bilateral elective neck dissection.

Prior to laryngectomy during the same surgical procedure, laryngoscopy was performed under general anesthesia to peritumorally inject in total 40MBq ^{99m}Tc-nanocoll (Nanocoll®, GE Healthcare, Eindhoven, The Netherlands) in a volume of 0.4 ml at four injection sites. The tracer substance was injected using a 1 ml syringe with luer lock and a butterfly needle (butterfly®-23 Hospiraveni systems, Donegal Town, Ireland). After injections, the pharynx and larynx were rinsed to prevent uptake of the tracer in the larynx in case of spill. Lymphoscintigraphy was not performed. Blue dye was not used. Subsequently, the planned laryngectomy and elective neck dissection were performed. After surgical resection (5-6h postinjection), detection of the sentinel node (SN) in the neck dissection specimen was done ex vivo by use of a 11 mm handheld gamma probe (Europrobe II, Eurorad, Strasbourg, France). Lymph nodes that were at least 15 counts per 10 seconds and > 10% of the highest node count in 10s, were considered SNs and were marked by a suture in the specimen.

On histopathology, all lymph nodes that were found in the neck dissection specimen were routinely bisected through the hilum or through the long axis of the node. If the thickness of the halves was more than 2.5 mm the slices were further sectioned to provide additional 2.5 mm thick blocks. Only SNs were then step-serially sectioned in 6 levels of 150 μm and stained by hematoxyline-eosine (HE) and pan-cytokeratin antibody (AE1/3). The other lymph nodes were not step-serially sectioned and were stained only with HE.

SN identification was defined as detection (and subsequent extirpation) of the sentinel node in the neck specimen. In evaluation the potential accuracy of SNB it is assumed that all identified SNs would have been biopsied successfully in vivo.

Primary endpoint was the feasibility of this SNB procedure during total laryngectomy for primary advanced stage and recurrent laryngeal cancer, assessed by the identification rate of SN. We distinguished patients with untreated necks from those with previous neck treatment. Secondary endpoint was the potential accuracy of SNB, using the histopathological examination of END as the reference standard. Chi-square test was used to compare the SNB identification rate between different patient groups. Significance levels were set at p-values < 0.05. The Kaplan-Meier method was used to estimate 3-year disease-specific survival (DSS) and overall survival (OS).

RESULTS

Between May 2008 and February 2010, 20 patients were included in the VUmc. One patient was excluded from further analysis because peroperatively the tumor appeared to be irresectable and the operation was interrupted.

All 19 patients were men with a mean age of 65.5 years (range 45.8-79.9). Patients were subdivided based on prior neck treatment: 13 without previous treatment and 6 with prior neck treatment. In Table 1 the patients are described by tumor characteristics, neck treatment and SN results.
SNs were successfully identified in 13 of 19 patients (68.4%), with a higher identification rate observed in patients with untreated necks as compared to patients with prior neck treatment (92.3% versus 16.7%, $p < 0.01$). With regard to primary and recurrent laryngeal cancer, no difference in SN identification was found (83.3% versus 42.9%, $p = 0.09$).

Patient	pT-stage	Laryngeal subsite	Tumor side	Previous treatment neck	Neck dissection	Number SN	pN-stage
1	T4a	Supraglottic	Bilat	xx	Bilat MRND	1	N2c
2	T3	Supraglottic	Bilat	xx	Bilat LII-IV	3	N1
3	T4a	Supraglottic	Bilat	xx	Bilat LII-IV	2	N0
4	T4a	Glottic	Bilat	xx	Bilat LII-IV, VI	2	N0
5	T4a	Glottic	Bilat	xx	Bilat LII-IV	2	N0
6	T4a	Glottic	R	xx	Bilat LII-IV	2	N1
7	T4a	Glottic	L	xx	Bilat LII-IV	2	N0
8	T4a	Transglottic	Bilat	xx	R MRND, L LII-IV, Bilat LVI	2	N2b
9	T4a	Transglottic	Bilat	xx	Bilat LII-IV, VI	1	N2c
10	T4a	Transglottic	Bilat	xx	Bilat LII-IV, VI	1	N0
11	T4a	Transglottic	Bilat	xx	Bilat LII-IV, VI	-	N0
12	Rec	Glottic	R	xx	Bilat LII-IV	5	N0
13	Rec	Subglottic	L	xx	Bilat LII-IV, VI	3	N0
14	T4a	Transglottic	L	Ipsi MRND, Bilat RT, Chemo	Contra LII-IV, Bilat LVI	-	N0
15	Rec	Supraglottic	R	Ipsi SND, Contra MRND, Bilat RT	Ipsi LIV	-	N2b
16	Rec	Supraglottic	R	Bilat RT	Bilat LII-IV	3	N0
17	Rec	Supraglottic	Bilat	Bilat RT	R MRND, L LII-IV, Bilat LVI	-	N0
18	Rec	Glottic	L	Ipsi MRND, Bilat RT, Chemo	Contra LII-IV	-	N0
19	Rec	Glottic	R	Bilat RT	Bilat LII-IV, VI	-	N0

TABLE 1. Patients described by tumor characteristics, medical history and treatment of the neck
Rec: recurrence, RT: radiotherapy, Chemo: chemotherapy,
Bilat: bilateral, Ipsi: ipsilateral, Contra: contralateral
MRND: modified radical neck dissection, SND: selective neck dissection
SN: sentinel node, xx: not performed, -: no SN found

Of the 13 patients with untreated necks, 11 had primary laryngeal cancer. Four of 13 patients (30.7%) were upstaged by SNB (Table 2). In 2 of these 4 patients, the SN was the only lymph node metastasis found by histopathological examination of which one showed only isolated tumor cells. In one patient SNB was false negative and staging of the neck after neck dissection revealed more metastases, resulting in a pN2c neck. Sensitivity and negative predictive value (NPV) of SNB in these patients would have been 80.0% and 87.5% respectively. In the 6 patients with previously treated necks, the only patient with identified SN did not have any metastases (Table 2). However, in one patient with unidentified SN lymph node metastases were found. Five of these 6 patients (83.3%) had recurrent laryngeal cancer.

SNB	Untreated neck			Previously treated neck			Total
	Neck dissection			Neck dissection			
	Positive	Negative	Total	Positive	Negative	Total	
Positive	4	0	4	0	0	0	4
Negative	1	7	8	0	1	1	9
No SN	0	1	1	1	4	5	6
Total	5	8	13	1	5	6	19

TABLE 2. Histopathological results of sentinel node biopsy and neck dissection
SNB: sentinel node biopsy, SN: sentinel node

Neck level	Laryngeal subsite				Total
	Supraglottic	Glottic	Transglottic	Subglottic	
II	3 (1 macro)	7 (1 itc)	2 (1 macro)	2	14
III	4	3	0	1	8
IV	0	3	0	0	3
VI	2	0	2 (1 macro)	0	4
Total	9	13	4	3	29

TABLE 3. Distribution of sentinel nodes
(): number of metastasis, macro: macrometastasis, itc: isolated tumor cells

7

DISCUSSION

Although sentinel node biopsy has found its place in staging of the clinically N0 neck in oral and oropharyngeal cancer, its use in laryngeal cancer is still under investigation.
In this study the SNB concept was evaluated in patients undergoing total laryngectomy and elective neck dissection for cN0 primary and recurrent laryngeal cancer. It is suggested that prior treatment may change or block the lymphatic channels leading to lower identification rates or false negative results with SNB. The few studies about SNB in previously treated necks in oral and oropharyngeal cancer revealed that SNB after prior treatment is still feasible and accurate.[24-26] In our study the identification rate of SNB in patients with untreated necks was statistically significantly higher as compared to patients with prior neck treatment. Moreover, comparison of the identification rate of patients with primary versus recurrent laryngeal cancer showed a tendency towards a higher rate in primary laryngeal cancer patients. Possibly anatomical difference of a lower density of lymphatic channels in the laryngeal mucosa as compared to the oral and oropharyngeal region leads to a higher impact of previous treatment to the lymphatic drainage pattern in the laryngeal area.

In 2 of the patients with untreated necks who were upstaged by SNB, the SN contained the only lymph node metastasis of the whole neck and one of these metastases was classified as isolated tumor cells. This metastasis would have been missed by routine histopathological examination. With a potential sensitivity of 80.0% and NPV of 87.5%, SNB seems accurate in laryngeal cancer patients with untreated necks. Other studies show comparable results in primary untreated laryngeal cancer.[13,14,16]

In patients with previous neck treatment the identification rate of SNB was low and the only metastatic patient (16.7%) was missed by SNB. These patients had mainly recurrent laryngeal cancer. This metastatic rate reflects the reported rates in literature, showing a prevalence of lymph node metastases during salvage laryngectomy and elective neck dissection of 12-31% in the cN0 neck.[27,28]

If proposed as a staging method, SNB should be feasible and reliable enough to replace elective neck dissection. SNB may prevent patients from unnecessary neck dissection and thereby from shoulder morbidity, pain and sensibility disorders which negatively influence health-related quality of life.[29] Moreover, if patients are prevented from neck dissection, a barrier to cancer spread is preserved in case of recurrence or second primary tumor. This study showed a sensitivity of 80.0% for SNB, meaning that if eventual treatment of the neck is based on SNB results, patients will have a 20.0% risk of lymph node metastases during follow-up after total laryngectomy. The question arises if the negative predictive value is high enough to refrain from elective neck dissection in case of a negative SNB. Because the neck is already entered for laryngectomy, intraoperative detection of metastases by SNB would be most advantageous. However, currently no fully reliable intraoperative technique to detect micrometastases is available, leading to a lower accuracy of SNB if peroperative decision for neck dissection would be made. On the other hand, if neck dissection after positive SNB would be performed in a second surgical setting, the neck has already been entered, leading to more difficult surgery. In our opinion the advantage of SNB instead of elective neck dissection during total laryngectomy does not overweigh the risk of delayed metastases and accompanying surgical difficulties. SNB may therefore be more useful in transoral laser surgery resected laryngeal cancer.[13]

If proposed as a lymphatic mapping method, SNB may assist elective neck dissection by determining the neck side and levels that should be dissected. In case of total laryngectomy for cN0 primary or recurrent cancer this may be of relevance. Especially a dissection of the contralateral neck is a controversial issue.[6,7] Cagli et al. states that the contralateral neck should only be treated electively if the ipsilateral neck side shows metastases or in case of midline tumors.[7] In our study, SNB showed bilateral drainage in 3 of five patients with lateralized tumors. For lymphatic mapping, imaging of radioactive tracer distribution in the neck is preferred over detection by the gamma probe. With radioactive tracer injection under general anesthesia imaging should be performed intraoperatively. In literature there are a few studies about intraoperative lymphatic mapping in head and neck cancer, using a mobile gamma camera or 3-D freehand SPECT.[30,31] Freehand SPECT is a 3-D tomographic imaging modality. Data acquisition is performed by a handheld detector, which can be moved freely. Heuveling et al. presented the first 3 head and neck cancer using 3-D freehand SPECT during SNB and the results are promising.[31]

As an assistant in lymphatic mapping, SN identification may also assist the histopathological examination of the neck dissection specimen. If SNs are marked in the specimen, these specific lymph nodes can be step-serially sectioned and stained by immunohistochemistry leading to more accurate staging of the neck by the possibility of detecting more reliable micrometastases or isolated tumor cells.

A limitation of our study is that SNs were detected ex vivo, excluding the neck levels which were not in the neck dissection specimen. Besides, in assessing the potential accuracy of SNB it was assumed in the present study that all identified SN ex vivo would have been harvested and examined successfully if SNB would have been performed in vivo. Therefore, the real accuracy of SNB in laryngeal cancer may be slightly lower if SN detection and biopsy are performed transcutaneously. Werner et al. showed that intraoperative lymphatic mapping in midline epiglottic tumors correctly identified the stage of metastatic disease.[23] Hu et al. and Tomifuji et al. performed lymphoscintigraphy one day before surgery and SNB was performed in vivo and followed by elective neck dissection.[12,14] They reported an overall accuracy of SNB of 98% and 95%, respectively. All three studies proposed further investigations on lymphatic mapping as a guide for uni- or bilateral elective neck dissection.[12,14,23]

7

Conclusion In this study we examined the feasibility of SN identification and the potential accuracy of SNB in patients with laryngeal cancer undergoing total laryngectomy and elective neck dissection. In patients with untreated neck SN identification is feasible and reliable. SNB may not yet be useful in peroperative decision making for the need for neck dissection until reliable intraoperative histopathological examination of the SN is available. However, lymphatic mapping might be useful in decision making for a contralateral neck dissection. To determine the clinical value of SNB in surgically treated cN0 laryngeal cancer undergoing total laryngectomy further studies are needed.

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CHAPTER 8

Patients' perspective on the impact of sentinel node biopsy in oral cancer treatment

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Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology 2016;122:279-286.

ABSTRACT

Objectives. Assessment of the impact of a sentinel node biopsy (SNB) based strategy in cT1-T2N0 oral cancer on the course of health-related quality of life, psychological distress and shoulder disability, and evaluation of the patients' perspective on neck management strategies.

Methods. Fifty-two patients (39 SNB negative, 13 SNB positive) completed the European Organization for Research and Treatment of Cancer (EORTC) questionnaires - QLQ-C30 and QLQ-H&N35, and the HADS, IES and SDQ questionnaires at baseline, after SNB diagnosis and at 6 months of follow-up. Objective shoulder measurements were performed after 2 years and interviews were conducted after 4.5 months of follow-up.

Results. All the scores of the questionnaires were not significantly different between SNB negative and SNB positive patients. Objective shoulder functioning was similar. Most patients preferred a SNB based strategy over an elective neck dissection strategy.

Conclusions. The impact of a SNB based strategy in patients with cT1-T2N0 oral cancer is comparable for SNB negative and SNB positive patients in terms of health-related quality of life, psychological distress and shoulder functioning. Most patients preferred the SNB based strategy over the elective neck dissection strategy.

INTRODUCTION

Management of the clinically negative (cN0) neck in patients with T1-T2 stage oral cancer has been a point of debate for years. In the past, elective neck dissection (END) was advocated when the risk of occult lymph node metastases exceeded 20%,[1] but later END was more often critically weighed against observation by using a 'wait and see' or 'wait and scan' strategy.[2-5]

Currently, the debate regarding management of the cN0 neck has changed. Sentinel node biopsy (SNB) has been found to be highly accurate in the detection of occult lymph node metastases. SNB reliably selects those patients who essentially need neck treatment.[6-8] With regard to the neck control rate, SNB based selection for neck dissection achieves results comparable with that of END.[7, 9-11]

If END and SNB are equally reliable, other factors become important in treatment decision making. It is known that patients undergoing therapy of the neck are subjected to adverse effects, such as shoulder pain, loss of shoulder function, sensibility disorders and psychological distress and often deteriorating health-related quality of life (HRQoL).[12-14] After selective neck dissection, patients report less of the abovementioned symptoms or deteriorated HRQoL, compared with patients after (modified) radical neck dissection.[14, 15] SNB may be less invasive than END and thus result in less shoulder problems and better HRQoL.

In the present study, a SNB based treatment strategy was investigated: In case of a SNB negative (SNB-) result, patients were kept under watchful waiting surveillance. In case of a SNB positive (SNB+) result, patients underwent a subsequent neck dissection. The primary aim of this study was to evaluate prospectively the impact of a SNB based strategy on the course of HRQoL, psychological distress and shoulder disability from diagnosis to 6 months of follow-up. The secondary aims were to obtain insight into long-term shoulder functioning and into the preference of patients in the management of the neck: an END strategy (neck dissection in all patients) or a SNB based strategy (neck dissection in case of positive SNB).

The results of this study may contribute to more insight into the patients' perspective and the impact of undergoing SNB in cT1-T2N0 oral cancer, and may aid in shared decision making on the management of the neck.

PATIENTS AND METHODS

Between 2008 and 2010, 58 consecutive patients with cT1-T2N0 oral cancer undergoing SNB and transoral resection were asked to participate in the study. All patients were staged cN0 by ultrasound guided fine needle aspiration cytology (USgFNAC) and underwent transoral excision and SNB. In case of a SNB- result, the patient was kept under surveillance during follow-up. In case of a SNB+ result, the patient underwent a subsequent neck dissection during a second surgical procedure, within 6 weeks (median 24 days, range 16-40). Depending on the neck level of the positive SNB and on the preference of the institute, patients underwent a selective neck dissection or modified radical neck dissection.

Patients were recruited from 4 institutions: VU University Medical Center (VUmc), Netherlands Cancer Institute / Antoni van Leeuwenhoek (NKI/AvL), University Medical Center Utrecht (UMCU) and University Medical Center Groningen (UMCG). The institutional ethics committee approved this study, and written informed consent was obtained from each patient. From the hospital files, patient and tumor data were

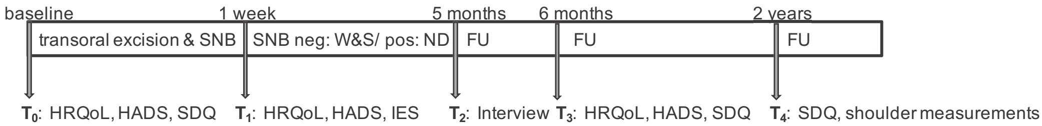

FIGURE 1. Timeline

retrieved. Patients completed questionnaires (pen and paper, at home) before surgical treatment with transoral excision and SNB (T_0); after SNB diagnosis, when they knew if a neck dissection was required or not (T_1); and at 6 months of follow-up (T_3). Semistructured interviews on the patients' perspective regarding neck management strategies were conducted at an intermediate time (T_2): after the patients' first USgFNAC surveillance visit in case of SNB- result, or when they were recovered from the subsequent neck dissection (SNB+). Objective shoulder measurements were carried out after approximately 24 months of follow-up (T_4). A timeline representing the consecutive measurements is shown in Figure 1.

Patient-reported outcome measures HRQoL was assessed with the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and the Head and Neck Cancer module (QLQ-H&N35). The QLQ-C30 comprises a global QoL scale, 5 functional scales, 3 symptom scales, and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, financial impact).[16] In the present study we used the global QoL, the functional scales and symptom scales, and 3 of the 6 single items: dyspnea, insomnia and appetite loss.
The QLQ-H&N35 module comprises 7 multiple-item scales (pain, swallowing, senses, speech, social eating, social contact and sexuality), and 11 single items (teeth, opening mouth, dry mouth, sticky saliva, coughing, feeling ill, using pain killers, nutritional supplements, feeding tube, loss of weight, gain of weight).[17] In the present study, we used the multiple-item scales, and 6 of the 11 single items: teeth, opening mouth, dry mouth, sticky saliva, coughing, feeling ill.
The scores of the QLQ-C30 and QLQ-H&N35 are linearly transformed to a scale from 0 to 100, with a higher score indicating a better level of functioning or global QoL, or a worse level of symptoms or problems.[18] The QLQ-C30 and QLQ-H&N35 were completed at T_0, T_1 and T_3 (Figure 1).

The Hospital Anxiety and Depression Scale (HADS) is a 14-item self-assessment scale for measuring distress (total HADS (HADS-T)) with two subscales, anxiety (HADS-A) and depression (HADS-D). The HADS was specifically designed for use in the medically ill.[19] The total HADS score ranges from 0 to 42 and the subscales from 0 to 21. A score ≥ 11 on the HADS-A or HADS-D is used to identify probable cases of anxiety or depression disorder, respectively. A total HADS score of > 14 is used as an indicator of a high level of psychological distress.[19, 20] The HADS was completed at T_0, T_1 and T_3 (Figure 1).

The Shoulder Disability Questionnaire (SDQ) was used to evaluate shoulder problems in daily life. The SDQ consists of 16 items related to functional shoulder limitation, in reference to the preceding 24 hours. Response options are: yes, no or not applicable. The total SDQ score is computed by dividing the number of positive (yes) responses by the total number of applicable items and multiplying this by 100. As a consequence, the SDQ score can range from 0 to 100, with a higher score indicating more severe disability.[21] The SDQ was completed at T_0, T_3 and T_4 (Figure 1).
Patients also completed study-specific questions about the presence of pain in the neck, skin numbness and sensitivity of the scar that could be answered with a yes or no at T_4.

The Impact of Event Scale (IES) was used to assess the impact of SNB diagnostics. The IES consists of 15 items with 2 domains: intrusive symptoms (7 items on intrusive thoughts, nightmares, intrusive feelings and imagery) and avoidance symptoms (8 items on numbing of responsiveness, avoidance of feelings, situations, ideas).[22] Patients were asked to rate the items on a 4-point scale according to how often each has occurred in the past 7 days after the event (SNB): not at all (0), rarely (1), sometimes (3) and often (5). A score per domain was obtained by summing the item scores (range 0-35 for intrusive and range 0-40 for avoidance). Per domain patients were categorized into subclinical, meaning no reaction (score 0-8), mild (score 9-25), moderately severe (score 26-43) and severe reaction (score > 43).[23, 24] The IES was completed at T_1, when the patient was just informed about the result of SNB (Figure 1).

Shoulder function To investigate the impact of undergoing SNB alone or with subsequent neck dissection, objective shoulder functioning was measured at long-term follow-up (T_4) (Figure 1). These measurements were carried out in a subgroup of 25 patients from the VUmc. Objective measurements on arm abduction and anteflexion (0-180°), arm endorotation and exorotation (0-90°), head rotation, flexion and extension (0-90°) were performed using an inclinometer according to a standardized protocol.[12]

Semistructured interview To obtain a better understanding of the patients' experience and preference for the type of therapy, semistructured interviews were conducted at T_2 (Figure 1) among the same subgroup of 25 patients from the VUmc.
Patients were asked to choose between 2 strategies for the neck: a strategy in which they undergo END, which combines staging and treatment of the neck but which may turn out to be unnecessary (the direct therapeutic strategy), or a strategy in which they undergo SNB to stage the neck and only in case of a positive SNB result undergo subsequent neck dissection (the diagnostic strategy). First, patients were asked to score their preference on a visual analogue scale (VAS) ranging from 0 (direct therapeutic strategy) to 100 (diagnostic strategy), and then they were asked to explain their preferences.
Furthermore, the emotional burden of undergoing SNB in the diagnostic work-up and the burden during follow-up visits was investigated by scoring on a VAS scale, ranging from 0 (no burden) to 100 (extreme). Emotional burden was described by intrusive thoughts and fear of tumor presence.

Statistical analysis Statistical analyses were performed using SPSS statistical software, version 20.0 (IBM Corp., Armonk, NY, USA). Differences in sociodemographic and clinical characteristics between SNB- and SNB+ patients were analyzed using the Chi-square test or the independent samples *t*-test as appropriate. Chi-square tests were also used to compare the number of probable cases of anxiety or depression (scores above cut-off on the HADS-A, HADS-D and HADS-T), the severity of symptoms on intrusion and avoidance by the IES at T_1 and the results of questions about sensibility and pain of the neck at T_4, between SNB- and SNB+ patients.
Mann-Whitney U tests were used to compare results of the IES at T_1, and to compare the results of the semistructured interviews at T_3.

Linear mixed models were used to analyze differences in the course of the subscales QLQ-C30, QLQ-H&N35, HADS and SDQ over time between and within SNB- and SNB+ patients. In these models, group (SNB- or SN+), assessment (T_0, T_1, T_3 and T_4) and their 2-way interaction were included as fixed effects and patients as random effects.
Shoulder measurements at T_4 were assessed per neck side and not by patients, making 3 groups: nonoperated neck, SNB neck and dissected neck. Comparison between the groups was done by using the linear mixed model, with fixed effect for group and random effect for patient (taking into account that 2 neck sides are paired for 1 patient).
Statistical significance was considered at $p < 0.05$.

Characteristics	SNB- patients n = 39	SNB+ patients n = 13	Chi-square test
	n	n	*p*-value
Age			0.50*
Mean (SD)	61 (10)	63 (13)	
Gender			0.52
Male	22	6	
Female	17	7	
Tumor site			0.98
Lateral tongue	20	7	
Floor of mouth	13	4	
Inferior alveolar process	3	1	
Buccal mucosa	2	1	
Lower lip	1	0	
Tumor stage			0.14
pT1	27	6	
pT2	12	7	
Surgical margin primary tumor			0.086
Negative	25	4	
Close	11	8	
Positive	3	1	
Adjuvant therapy primary tumor			0.56
Re-excision	4	2	
Radiotherapy	2	3	
No	8	4	
Unknown	25	4	
Adjuvant radiotherapy neck		2	
Follow-up			0.56
Local recurrence	3	2	
Regional recurrence	4	0	
Second primary tumor	2	1	
No	30	10	

TABLE 1. Patient and tumor characteristics of SNB- and SNB+ patients
SNB: sentinel node biopsy, SD: standard deviation, *: *t*-test

RESULTS

Study population Of the 58 recruited patients, 52 (90%) were included for analysis. Some patients dropped out because they received radiotherapy instead of a therapeutic neck dissection (4), and some because of local recurrence within 6 months for which they were received treatment, including neck therapy, which afected study group homogeneity (2).
Of the 52 patients, 39 (75%) had a SNB- result and 13 (25%) were SNB+. Between these groups, there were no significant differences with regard to sociodemographic or clinical characteristics (Table 1). SNB+ patients underwent a subsequent modified radical neck dissection (n=7) or a selective neck dissection (*n* = 6; 3 level I-IV and 3 level I-III) and 2 of these patients received adjuvant radiotherapy.

The course of quality of life, psychological distress and shoulder complaints Between SNB- and SNB+ patients, no significant differences were found in the course of scores over time on the QLQ-C30, QLQ-H&N35, HADS, or SDQ questionnaires (Table 2, see next 2 pages).

Within the SNB- and SNB+ group, the course of various scales of the QLQ-C30, QLQ-H&N35, HADS and SDQ changed significantly, and 3 distinct patterns were distinguished. For several of these scales, a clear worsening was reported after transoral excision and SNB diagnosis (T_1) compared with baseline (T_0) and the values at 6 months of follow-up (T_3): role functioning, fatigue, pain, swallowing, senses, speech, social eating, opening mouth, feeling ill among SNB- patients, and fatigue, speech and social contact among SNB+ patients. A second pattern comprised a worsening after SNB diagnosis which lasted up to 6 months of follow-up compared to baseline: dry mouth and shoulder functioning (by SDQ, until 2 years of follow-up) for SNB+ patients. A third pattern comprised an improvement after SNB diagnosis and at 6 months of follow-up compared with baseline: emotional functioning, insomnia, HADS-A and HADS-T for SNB- patients (Table 2, see next 2 pages).

Psychological distress A high level of psychological distress (HADS-T > 14) was present in 35% at baseline (T_0), 27% at T_1 and 20% at follow-up (T_3) in SNB- patients; in SNB+ patients this was 8% at all time points. These differences were not statistically significant (T_0 $p = 0.075$, T_1 $p = 0.19$ and T_3 $p = 0.31$). A probable case of anxiety (HADS-A ≥ 11) was present in 24% at baseline, 15% at T_1, and 6% at T_3 in SNB- patients, versus 0%, 0% and 8% in SNB+ patients, respectively. Differences were not statistically significant (T_0 $p = 0.064$, T_1 $p = 0.16$ and T_3 $p = 0.78$). A probable case of depression (HADS-D ≥ 11) was present in 11% at baseline, 12% at T_1 and 14% at T_3 in SNB- patients versus 0% at all time points in SNB+ patients, again not statistically significant (T_0 $p = 0.22$, T_1 $p = 0.21$ and T_3 $p = 0.31$).
With regard to the IES, of the SNB- patients, 61% had no symptoms, 29% had mild symptoms and 10% moderately severe intrusive symptoms, versus 58% no symptoms and 42% moderately severe intrusive symptoms in SNB+ patients ($p = 0.45$). For avoidance symptoms, a normal reaction was found in 53% of SNB- patients, a mild reaction in 38% and a moderately severe reaction in 9%. In SNB+ patients no reaction on avoidance was found in 58% of patients, 25% had mild reaction and 17% moderately severe reaction ($p = 0.65$).

Shoulder function Objective shoulder measurements were performed at a median of 28 months after diagnosis (range 12-43 months; T_4). The response rate was 84% (21 out of 25 invited patients); dropouts resulted from refusal, lost to follow-up and recurrent disease. There were 13 SNB- and 8 SNB+ patients. Analysis was done per neck side, distinguishing 3 neck categories: a 'normal' nonoperated neck (20), SNB neck (13) and a dissected neck (9). Comparison of the results by linear mixed model analysis did not show any statistical significant difference between the different neck categories (Table 3, see next 2 pages).

For study-specific questions, SNB+ patients reported significantly more often numbness of the skin of the neck (75% SNB+ versus 23% SNB-, p = 0.029), whereas the presence of pain (38% SNB+ versus 46% SNB-, p = 0.53) and sensitive scar (13% SNB+ versus 23% SNB-, p = 0.50), were similarly reported.

Semistructured interviews Interviews were taken at a median of 4.5 months follow-up (range 2-8 months; T_2). The response rate was 88% (22/25 patients); dropouts resulted from refusal, lost to follow-up and recurrent disease. Of these patients, 14 were SNB- and 8 SNB+.

Of all patients, 19 of 22 (86%) preferred the SNB based strategy (VAS 100) over the END strategy (VAS 0), and the mean VAS score was 79.7% (SD 31.3). Three (14%) patients preferred the END strategy; all 3 were SNB+ (37.5% of all SNB + patients). Median VAS scores of SNB- and SNB+ patients showed a significant difference: SNB- patients had a significantly higher preference for the SNB based strategy (Table 4).
Investigation of the emotional burden by intrusive thoughts and fear of tumor presence did not reveal a significant difference between SNB- and SNB+ patients (Table 4).

		SNB- patients n= 14	**SNB+ patients n= 8**	**Mann-Whitney U test**
VAS scales		**median (range)**	**median (range)**	***p*-value**
Preference treatment strategy: surgical (VAS 0) – diagnostic (VAS 100)		98 (52-100)	82(0-97)	**0.009**
USgFNAC	**Intrusive thoughts**	23 (0-74)	24 (5-75)	0.41
	Fear of tumor presence	40 (0-86)	36 (8-74)	0.73
SNB	**Intrusive thoughts**	48 (0-95)	34 (8-54)	0.52
	Fear of tumor presence	40 (0-90)	27 (3-53)	0.47
Follow-up	**Intrusive thoughts**	9 (0-80)	21 (5-42)	0.13
	Fear of tumor presence	25 (0-81)	16 (3-32)	0.32

TABLE 4. Results of quantitative questions during semi-structured interview: comparison of the burden of SNB- with SNB+ patients
SNB: sentinel node biopsy, USgFNAC: ultrasound guided fine needle aspiration cytology

	SNB- patients n= 40				SNB+ patients n= 14				Mixed Model analysis
	mean (SD)			*p*-value	mean (SD)			*p*-value	*p*-value
	T_0	T_1	T_3		T_0	T_1	T_3		
EORTC QLQ-C30									
Functioning scales									
Global quality of life	71 (24)	69 (19)	72 (22)	0.47	73 (19)	68 (15)	66 (23)	0.57	0.60
Physical functioning	82 (23)	79 (24)	84 (17)	0.19	87 (20)	81 (22)	84 (14)	0.15	0.92
Role functioning	82 (24)	70 (29)	82 (22)	**0.006**	83 (24)	72 (23)	72 (24)	0.062	0.32
Emotional functioning	67 (29)	76 (30)	85 (20)	**0.001**	76 (15)	79 (23)	83 (21)	0.26	0.47
Cognitive functioning	85 (24)	85 (25)	91 (19)	0.22	92 (13)	82 (18)	86 (20)	0.24	0.38
Social functioning	86 (27)	86 (18)	88 (24)	0.74	90 (13)	85 (17)	95 (11)	0.19	0.74
Symptom scales									
Fatigue	28 (26)	36 (29)	24 (25)	**0.006**	20 (19)	33 (17)	21 (21)	**0.001**	0.70
Nausea/vomiting	6 (15)	1 (4)	4 (14)	0.089	3 (6)	0 (0)	1 (5)	0.57	0.85
Pain	25 (28)	28 (26)	20 (25)	0.13	31 (23)	15 (15)	21 (26)	0.059	0.11
Dyspnoea	14 (24)	10 (18)	13 (22)	0.71	6 (19)	8 (15)	10 (16)	0.21	0.55
Insomnia	27 (36)	16 (31)	13 (23)	**0.033**	8 (15)	14 (22)	21 (29)	0.52	0.053
Appetite loss	16 (29)	13 (29)	7 (18)	0.22	14 (30)	6 (13)	13 (29)	0.74	0.43
EORTC QLQ-H&N35									
Pain	29 (24)	37 (27)	18 (17)	**<0.001**	39 (23)	38 (18)	21 (22)	0.065	0.70
Swallowing	7 (14)	23 (22)	6 (12)	**<0.001**	17 (21)	17 (17)	14 (19)	0.83	0.068
Senses	8 (20)	16 (22)	14 (20)	**0.025**	4 (10)	11 (18)	8 (13)	0.57	0.94
Speech	12 (21)	23 (24)	16 (20)	**0.023**	5 (7)	19 (17)	3 (7)	**0.001**	0.34
Social eating	16 (24)	27 (25)	15 (21)	**0.004**	27 (29)	21 (18)	13 (15)	0.33	0.11
Social contact	11 (21)	13 (20)	10 (19)	0.77	1 (3)	7 (11)	5 (6)	**0.024**	0.65
Sexuality	19 (29)	24 (36)	17 (31)	0.40	14 (16)	25 (26)	11 (15)	0.19	0.72
Teeth	19 (31)	20 (31)	18 (23)	0.92	17 (27)	39 (40)	33 (35)	0.20	0.084
Opening mouth	16 (30)	32 (42)	10 (21)	**0.002**	17 (22)	19 (26)	23 (34)	0.32	0.14
Dry mouth	27 (33)	35 (31)	32 (33)	0.15	11 (16)	22 (26)	38 (23)	**0.040**	0.064
Sticky saliva	17 (29)	22 (31)	24 (32)	0.29	6 (13)	27 (33)	31 (26)	0.11	0.15
Coughing	21 (25)	19 (23)	18 (27)	0.76	19 (17)	6 (13)	10 (16)	0.057	0.48
Feeling ill	14 (26)	23 (31)	11 (18)	**0.032**	8 (21)	11 (22)	5 (13)	0.64	0.81

	SNB- patients n= 40				SNB+ patients n= 14				Mixed Model analysis
	mean (SD)			*p*-value	mean (SD)			*p*-value	*p*-value
	T_0	T_1	T_3		T_0	T_1	T_3		
HADS									
Anxiety	6 (5)	4 (4)	4 (4)	**0.002**	4 (3)	4 (3)	4 (3)	0.42	0.25
score ≥ 11	24%	15%	6%		0%	0%	8%		
Depression	4 (4)	4 (4)	3 (4)	0.27	2 (2)	2 (2)	3 (3)	0.092	0.20
score ≥ 11	11%	12%	14%		0%	0%	0%		
Total	11 (9)	8 (8)	7 (7)	**0.018**	5 (5)	6 (5)	6 (6)	0.96	0.19
score >14	35%	27%	20%		8%	8%	8%		
SDQ	T_0	T_3	T_4		T_0	T_3	T_4		
SDQ	9 (21)	15 (31)	18 (30)	0.45	10 (20)	36 (35)	23 (35)	**0.001**	0.072

TABLE 2. Results of linear mixed model analyses regarding the course of QLQ-C30, QLQ-H&N35 and HADS from baseline to 6 months follow-up, and of SDQ, from baseline to 2 years follow-up of patients with SNB- and SNB+ results
SNB: sentinel node biopsy, SD: standard deviation

8

Movement	Nonoperated neck n=20	SNB neck n=13	Dissected neck n=9	Comparison Mixed Model
	mean (SD)	mean (SD)	mean (SD)	*p*-value
Abduction 0-180°	164 (13)	155 (32)	160 (13)	0.39
Anteflexion 0-180°	159 (16)	158 (26)	162 (14)	0.58
Endorotation 0-90°	70 (17)	71 (14)	72 (13)	0.84
Exorotation 0-90°	76 (13)	75 (20)	77 (14)	0.71
Head rotation 0-90°	68 (14)	67 (11)	71 (11)	0.63
Head flexion 0-90°	53 (12)	52 (7)	53 (16)	1.00
Head extension 0-90°	52 (11)	54 (9)	49 (13)	1.00

TABLE 3. Objective shoulder measurements at late follow-up (T_4): comparison of shoulder function in different neck types using mixed model analysis, taking the paired neck side per patient into account
SNB: sentinel node biopsy, SD standard deviation

DISCUSSION

The primary aim of this study was to evaluate the impact of SNB on the course of HRQoL, psychological distress and shoulder disability from diagnosis to the 6-month of follow-up among patients with early stage oral cancer. There were no significant differences between SNB- and SNB+ patients. In both groups, the course of HRQoL, distress and shoulder disability changed significantly over time. For several HRQoL scales and subjective shoulder functioning, a clear worsening was reported from the time of diagnosis to 6 months of follow-up (and to 2 years of follow-up for shoulder functioning). In contrast, a clear improvement was reported for emotional functioning, insomnia, and psychological distress, which may be indicative for the patients' trust in SNB negative findings. These results are important contributions to the findings of the few studies that have been carried out before.[25, 26]

The temporarily worsening of HRQoL scales, such as swallowing, speech, social eating and opening mouth are more likely to be (at least partially) attributed to the primary tumor and its treatment which was performed at the same time as SNB. Other scales, such as fatigue, pain, role functioning, social contact and senses may have temporarily deteriorated as a result of oncologic treatment in general.
In patients who underwent a neck dissection, the submandibular gland was routinely removed, and this may have caused increased dry mouth during follow-up in SNB+ patients,[27] as it cannot be explained by the fact that postoperative radiotherapy was given to only 3 of 13 (23%) SNB+ patients (versus 2 of 39 (0.05%) SNB- patients).

The two earlier studies on HRQoL in patients with oral cancer undergoing SNB were cross-sectional: Govers et al. investigated health utility by the EQ-5D among 174 patients at 1 to 13 years after treatment. Compared with watchful waiting or SNB, neck dissection resulted in lower health utility.[26]
Schiefke et al., investigated HRQoL 2 years after treatment among 24 SNB and 25 END patients. No differences were found between both groups with respect to generic HRQoL (QLQ-C30), but END patients reported significantly more severe swallowing complaints (QLQ-HN35), which may be caused by impairment of muscular structures as a result of END.[25] A longitudinal study is of course different from a cross-sectional survey which may explain the differences in result between our prospective study and these other studies.

With respect to psychological functioning, scores of HADS and IES questionnaires and interview scores on emotional burden were only elevated in a minority of patients. Moreover, the scores revealed no significant difference between SNB- and SNB+ patients. Schiefke et al. showed that fear of tumor progression was significantly lower in SNB patients as compared to END patients.[25] It may be that the stepwise therapy of SNB and subsequent neck dissection in case of a SNB+ result, does not have the same psychological impact that direct END does. SNB is a precise diagnostic investigation, and in case of a SNB+ result subsequent neck dissection is a reliable therapy. It often happens that in the neck dissection specimen after a SNB+ result, no additional metastases are found. Patients are then informed that the neck dissection therapy has been successful. This may be a relief, in comparison with direct END after which patients who have metastases are informed that they had metastases that were removed.

A secondary aim was to obtain insight into long-term shoulder functioning. Although objective shoulder functioning after 2 years of follow-up was similar between groups, SNB+ patients experienced impaired sensibility more often. In the literature, the prevalence of shoulder dysfunction after END is estimated to be 22-39%.[14, 28] Schiefke et al. reported that shoulder function (Constant score), discomfort of cervical scars and sensory dysfunction were all significantly better after SNB than after selective neck dissection (level I-III).[25] Murer et al. showed significantly less postoperative morbidity and better shoulder functioning

(Neck Dissection Impairment Index (NDII) and Constant Score) in SNB patients compared with END patients, whereas in a subset analysis comparing subsequent neck dissection after SNB+ and direct END, no significant difference was found.[29] In general, it is expected that a neck dissection after SNB is more difficult because of scar tissue and may therefore lead to more shoulder complaints, but this has not yet been shown by shoulder disability studies.

Although no differences were observed by objective shoulder measurements in our study, impaired sensibility of the neck was more often reported by SNB + patients undergoing subsequent neck dissection than by patients undergoing SNB alone (SNB -). If there is hardly any difference in HRQoL, psychological distress and shoulder function between patients who undergo SNB alone and SNB with subsequent neck dissection, the question arises, how do patients perceive a SNB based neck strategy. Do they prefer a stepwise strategy in which they receive individualized treatment with the risk of undergoing two operations, or do they prefer a direct therapeutic strategy with elective neck dissection in advance, which may be unnecessary but which avoids the stepwise management? In this study, the majority of the patients preferred the diagnostic strategy above the direct therapeutic strategy. However, this finding may be biased by the fact that all patients had undergone SNB and there was no control group in whom patients had undergone END. Interesting is that the 3 patients who preferred END were all SNB + and had undergone subsequent neck dissection. This asks for further analysis of the patients' perspective through interviews with differently treated patients to compare their preferences: patients who underwent SNB alone, patients who underwent SNB with subsequent neck dissection and patients who underwent END. In this situation, a time trade-off analysis can be used and a health economics study may be performed.

A limitation of this study is the relatively small number of participating patients. Furthermore, in this study, all patients underwent the SNB based strategy with subsequent neck dissection when necessary. Nowadays, an END is usually a selective neck dissection, whereas in the present study SNB+ patients not only received a selective neck dissection but also MRND, which is associated with increased morbidity. This influences comparison of and END strategy with a SNB strategy. The lack of direct comparison of SNB with END patients or with a control (healthy group) can also be considered as a limitation.

A strength of this study is that we prospectively investigated HRQoL, psychological distress, and shoulder functioning, among cT1-T2N0 oral cancer patients undergoing SNB and that we assessed their perspective on the management of the neck.

Conclusion The impact of a SNB based diagnostic strategy for staging and management of the cN0 neck in patients with cT1-T2 oral cancer was comparable for SNB- patients and SNB+ patients (who required a subsequent neck dissection) in terms of the course of HRQoL and psychological distress. Both groups experienced problems after treatment, which improved at 6 months of follow-up. Although objective shoulder functioning was similar, patients who underwent neck dissection (SNB+ patients) experienced subjectively more shoulder disability after 2 years of follow-up. Most patients preferred a SNB based strategy over an END strategy.
These results may contribute to general preference and implementation of this SNB based selection strategy.

ACKNOWLEDGEMENTS

The authors like to thank dr. T.T.A. Peters for objective shoulder function measurements.

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CHAPTER 9

Cost-utility of sentinel lymph node biopsy in cT1-T2N0 oral cancer

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Oral Oncology 2016;53:20-26.

ABSTRACT

Objectives. To calculate the cost-utility of different strategies for the detection of occult lymph node metastases in cT1-T2N0 oral cancer.

Methods. A decision tree followed by a Markov model was designed to compare the cost-utility of the following strategies: (a) USgFNAC (ultrasound guided fine needle aspiration cytology), (b) SNB (sentinel node biopsy), (c) USgFNAC and, if negative SNB and (d) END (elective neck dissection). Data were collected from 62 patients in four Dutch head and neck centers. Utilities were measured with the EQ-5D questionnaire and resource use was recorded from patient charts. Costs were calculated from a hospital perspective. Uncertainty was explored with scenario analyses and probabilistic sensitivity analyses.

Results. With a 5- or 10-year time horizon, SNB results in the highest number of additional quality-adjusted life years (QALYs, 0.12 and 0.26, respectively) for the smallest additional costs (€ 56 and € 74, respectively) compared to USgFNAC. With a lifetime horizon END results in the highest number of additional QALYs (0.55) for an additional € 1,626 per QALY gained compared to USgFNAC. When we make different assumptions regarding the duration of disutility's (≥ 5 years) or the improvement (≥ 3%) of sensitivity of SNB, SNB is the most favorable strategy from all time horizons.

Conclusions. SNB is a good diagnostic strategy to evaluate cT1-T2N0 oral cancer. SNB is the preferred strategy in a 5- or 10-year time horizon. From a lifetime horizon, END may be preferred. SNB may become the optimal strategy from all time horizons if its sensitivity can be slightly improved.

INTRODUCTION

The management of the clinically N0 (cN0) neck in T1-T2 oral cancer patients is controversial. Either elective neck dissection (END) or watchful waiting (WW) is performed, depending on the perceived chance of occult lymph node metastases. Nowadays, more and more evidence supports the use of diagnostic tools to stage the clinically negative neck more reliable, in addition to palpation and/or imaging techniques (ultrasound, CT, MRI and/or PET). When uncertainty about the existence of occult lymph node metastases decreases, undertreatment and overtreatment (unnecessary surgery) can be reduced. Diagnostic tools to do so include ultrasound guided fine needle aspiration cytology (USgFNAC), sentinel node biopsy (SNB) and molecular markers. Currently, the diagnostic performance of SNB seems most promising.[1,2]

Introducing SNB in the routine management of cT1-T2N0 oral cancer impacts costs as well as clinical outcomes. Three previous studies were published about the cost-effectiveness of SNB compared to other approaches. In 2003, Kosuda et al. showed SNB to save $ 1,218 per stage cN0 patient and avoid 7 surgical deaths per 1,000 patients, as compared to neck dissection.[3] In 2013, O'Connor et al. used multicenter trial data on 481 cT1-T2N0 oral cancer patients to calculate the relative cost ratio for treatment with traditional surgery (including END) as compared to SNB, followed by either surgery (following positive SNB) or WW.[4] Costs of the SNB approach were only 48% of the costs of the traditional surgical approach. In 2013, Govers et al. published a Markov decision analytic model to evaluate the cost-effectiveness of five strategies: END, WW, gene expression profiling (GEP) followed by neck dissection or WW, SNB followed by neck dissection or WW, and GEP and SNB (for positive GEP) followed by neck dissection or WW.[5] Over a 5-year time horizon, SNB was the most cost-effective strategy, costing € 3,356 per QALY (quality-adjusted life year) gained as compared to END. Outcomes were sensitive for utility values, which were taken from expert opinion. Analysis on the expected value of perfect information showed further information on quality of life to be valuable.

The current study expands on the evidence from Govers et al.[5] Information from a different, prospective, multicenter clinical trial ('SNUS trial') is used to compare four strategies for the detection of occult lymph node metastases and treatment choice: (A) USgFNAC followed by neck dissection or radiotherapy when positive and WW when negative, (B) SNB followed by neck dissection or radiotherapy when positive and WW when negative, (C) USgFNAC and, if negative, SNB followed by neck dissection or radiotherapy when positive and WW when negative, and (D) END. As opposed to the study from Govers et al., clinical outcomes, economic outcomes and quality of life estimates were obtained from the trial. In this article, the cost-utility of the various diagnostic and treatment strategies will be presented, with the aim to inform routine clinical practice.

DFS = disease-free survival, DSS = disease-specific survival, END = elective neck dissection,
GEP = gene expression profiling, HNSCC = head and neck squamous cell carcinoma,
ICUR = incremental cost-utility ratio, OS = overall survival, QALY = quality-adjusted life year, SNB = sentinel node biopsy, USgFNAC = ultrasound guided fine needle aspiration cytology, WW = watchful

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METHODS

In order to calculate cost-utility of the various strategies, a decision model was designed and informed with data from the SNUS trial.

The SNUS trial Sixty-two patients with T1-T2 oral cancer and cN0 neck based on palpation and USgFNAC were enrolled from four centers of the Dutch Head and Neck Society.[6] SNB negative patients were carefully observed. Positive patients were treated by neck dissection, radiotherapy or a combination of both (see Figure 1). Endpoints of the study were risk of occult lymph node metastases, neck control, accuracy, 5-year disease-free survival (DFS), overall survival (OS) and disease-specific survival (DSS).
Twenty of 62 patients (32%) had positive SNB. Macrometastases were found in 9 patients, micrometastases in 8, and isolated tumor cells in 3 patients. Median follow-up was 52.5 months. Of the 42 SNB negative patients, 5 developed a regional recurrence of whom 4 patients could be successfully salvaged. DFS, OS and DSS of SNB negative patients were 72.0%, 92.7% and 97.4%, and for SNB positive patients these numbers were 73.7%, 79.7% and 85.0%, respectively (DFS: $p = 0.916$, OS: $p = 0.134$, DSS: $p = 0.059$). Neck control rate was 97% in SNB negative and 95% in SNB positive patients. Sensitivity was 80% and negative predictive value 88%.[6]

Model structure and transition probabilities Using patient level data from the SNUS trial and additional literature, four different diagnostic and treatment strategies were compared. In Microsoft Excel 2010, a decision tree was designed to model the diagnostic pathways (see Figure 2). A Markov model represented the subsequent follow-up (see Figure 3), with a cycle length of one year. Transition probabilities for the four strategies were obtained from Dutch studies. The probabilities as well as the data sources are presented in Figure 2. The probability of neck recurrence after treatment of the neck was assumed to be 0.05,[6] for all strategies, independent of the diagnostic method.

Overall survival rates in the first five years were obtained from Flach et al. (2013)[7] and were 95%, 78%, 71%, 66% and 63% for years 1 to 5, respectively. Overall survival after five years was based on Dutch life tables from Statistics Netherlands (2015), combined with 20% excess mortality since the conditional long-term survival of Dutch head and neck squamous cell carcinoma (HNSCC) patients remains poorer compared to the general population.[8]

The time horizons of the model were 5 years, 10 years and lifetime.

Figure 1. Study design of the trial

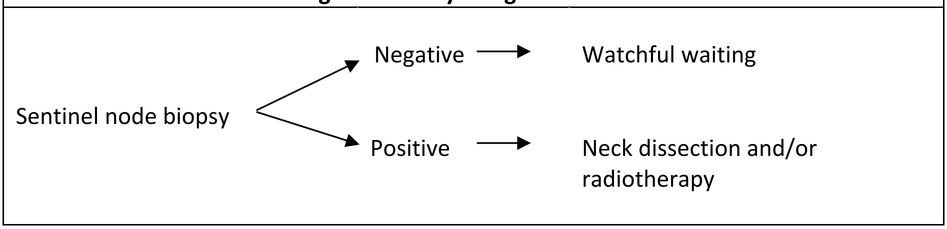

FIGURE 1. Study design of the trial

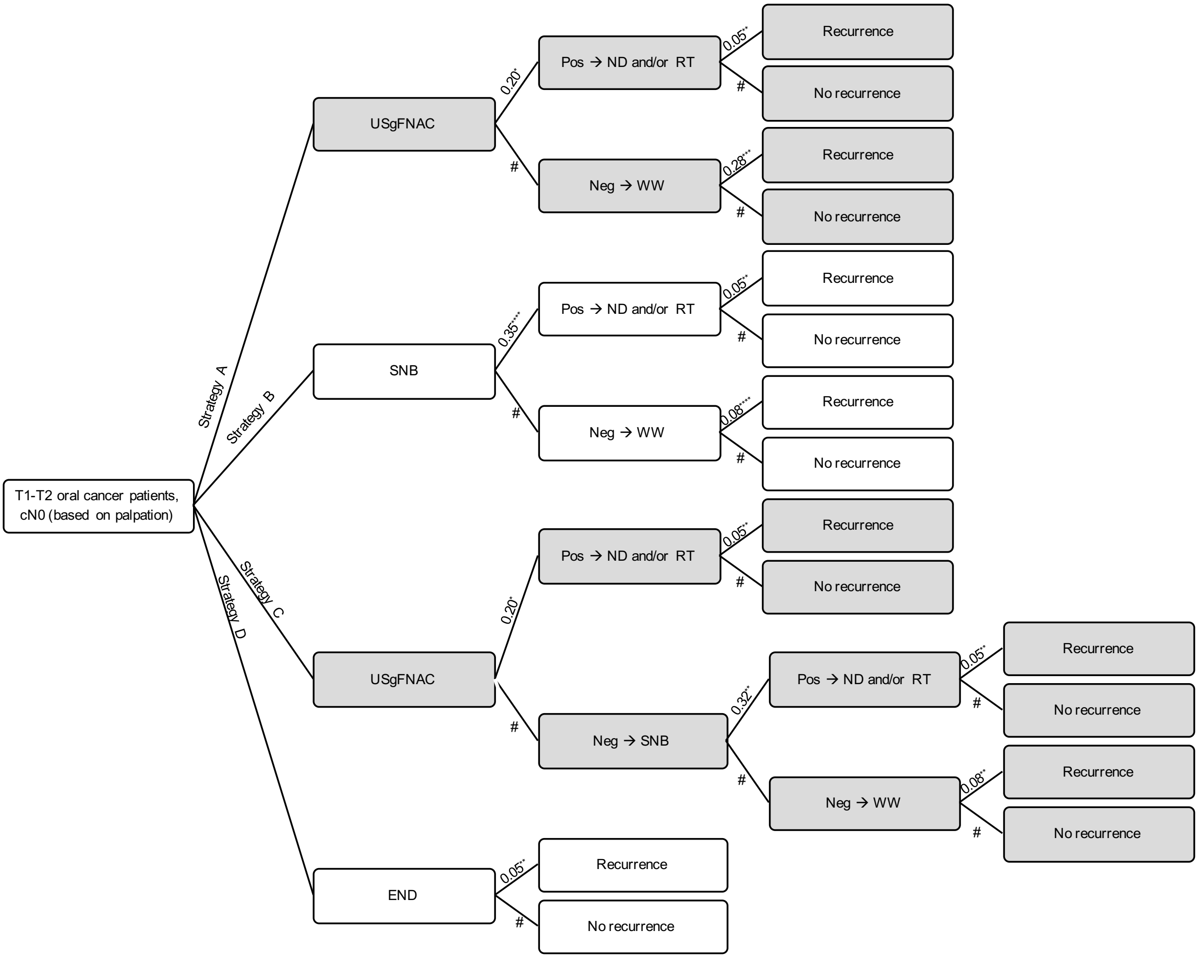

FIGURE 2. Decision tree to model the diagnostic pathways
USgFNAC: ultrasound guided fine needle aspiration cytology
SNB: sentinel node biopsy

END: elective neck dissection WW: watchful waiting Pos: positive result Neg: negative result

Sources:
* = Takes RP et al. The value of ultrasound with ultrasound-guided fine-needle aspiration biopsy compared to computed tomography in the detection of regional metastases in the clinically negative neck. Int J Radiat Oncol Biol Phys 1998;40:1027-32.
** = Flach GB et al. Sentinel lymph node biopsy in clinically N0 T1-T2 staged oral cancer: the Dutch multicenter trial. Oral Oncol 2014;50:1020-4.
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**** = Unpublished data (2010) reported to The Netherlands Organisation for Health Research and Development (ZonMw), Project 170881005.

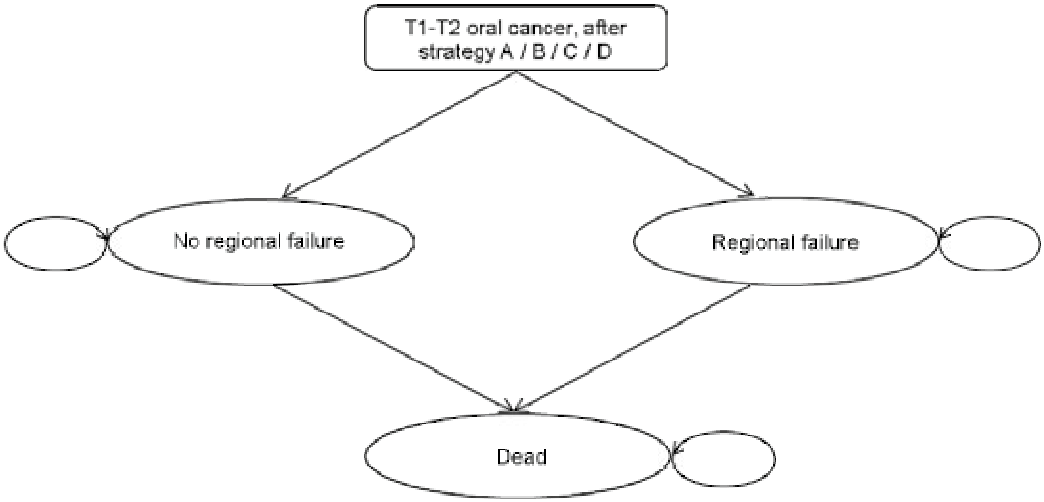


FIGURE 3. Markov model to represent follow-up

Model input - health state utilities Patient health-related quality of life was measured in SNUS trial patients,[9] using various instruments including the EQ-5D. Since the utility associated with undergoing USgFNAC and SNB was similar, equal utility was assumed for all patients in strategy A, B, and C who did not need treatment. This utility was 0.84, which was calculated by averaging the utility for all SNUS trial patients without regional failure (*n* = 49).

The average outcome for SNUS trial patients with regional failure was 0.79 (*n* = 2). The disutility of regional failure therefore is (0.84-0.79 =) 0.05. Since only two patients experienced regional failure in the SNUS trial, the uncertainty associated with this estimate is high. However, the estimate seems reasonable in the light of available literature. For example, Weiss et al. report a disutility of regional failure of 0.06.[10] For patients who received treatment of the neck (without regional failure), average utility was 0.77 (*n* = 18). This utility is applied to all patients in strategy D, and those patients in strategy A, B and C who were tested positive (and were therefore treated with ND or RT). The disutility after ND or RT is therefore (0.84-0.77 =) 0.07. This is relatively high compared to the disutility of ND reported by Weiss et al. (0.03).[10] Also, it is 0.01 higher than the disutility of regional failure. However, the differences are small and non-significant.

Since quality of life losses usually resolve over time,[11] in the base-case we assume the utility to return to 0.84 after one year, for all patients. In the base-case, the discount rate for effects was 1.5%, consistent with Dutch pharmacoeconomic guidelines.

Model input - costs Resource use was recorded from hospital databases and patient charts and included inpatient hospital stays and consultations, day-care treatments, outpatient visits, surgery, radiotherapy, diagnostic imaging and laboratory testing including pathological and microbiological diagnostics. Costs were calculated from a hospital perspective and included direct medical costs only, in 2015 Euros. Unit costs were preferably obtained from the Dutch cost manual 2015, alternatively from the VU University Medical Center or, in case both were unavailable, from Dutch tariffs. Follow-up costs were calculated per year and are presented in Table 1. In the base-case, the discount rate for costs was 4%, consistent with Dutch pharmacoeconomic guidelines.

TABLE 1. Follow-up costs per year in 2015 Euro
*Including intensive care admissions

Year		Daycare	Hospital admissions*	Medical imaging services & procedures	Out-patient visits	Pathology	Total costs, excluding strategy-specific costs	Total costs, strategy A	Total costs, strategy B	Total costs, strategy C	Total costs, strategy D
1	Regional failure	344	10,484	859	3,519	145	15,351	16,202	18,064	18,295	19,098
	No regional failure	68	7,352	496	2,967	134	11,012	11,863	13,725	13,956	14,759
2	Regional failure	60	2,544	525	2,191	43	5.363				
	No regional failure	0	850	117	893	12	1.872				
3	Regional failure	107	2,712	338	718	38	3.914				
	No regional failure	0	79	107	494	10	690				
4	Regional failure	98	2,432	114	0	28	2.672				
	No regional failure	0	0	14	82	28	125				

TABLE 2. Base case results, discounted (4% costs, 1.5% effects)

	5-year horizon			10-year horizon			Lifetime horizon		
	Life years	QALYs	Costs (€)	Life years	QALYs	Costs (€)	Life years	QALYs	Costs (€)
Strategy A	4,47	3,58	17.159	8,30	6,44	17.510	16,35	11,64	18.021
Strategy B	4,63	3,70	17.216	8,65	6,70	17.584	17,10	12,16	18.120
Strategy C	4,62	3,68	17.625	8,62	6,67	17.992	17,02	12,10	18.525
Strategy D	4,65	3,67	18.007	8,70	6,69	18.378	17,20	12,19	18.917

Data analyses Costs, effects and cost-effectiveness were calculated per diagnostic strategy. Incremental cost-utility ratios (ICURs) were presented for all strategies as compared to strategy A, since this strategy had the lowest cost. Various scenario analyses as well as probabilistic sensitivity analyses were performed. In the probabilistic analyses, 1.000 runs were performed. Beta distributions were used to reflect the uncertainty in transition probabilities and utilities. Triangular distributions (± 30%) were used to reflect the uncertainty in cost parameters. Results of the probabilistic analyses are presented in cost-effectiveness planes, showing the uncertainty around the ICUR estimates. Cost-effectiveness acceptability curves illustrate the probability that a strategy is cost-effective given a range of willingness to pay thresholds.

RESULTS

Cost-utility analysis of base-case Table 2 shows the total life years, QALYs and costs per patient per strategy. Strategy D is the most expensive strategy, costing € 18,007 to € 18,917, depending on time horizon. With a 5-year or 10-year time horizon, strategy B results in the highest number of QALYs. However, with a lifetime horizon, strategy D has the highest QALY gain.

Table 3 presents the ICURs for all strategies as compared to strategy A, which has the lowest costs. With a 5- or 10-year time horizon, strategy B results in the highest number of additional QALYs (0.12 and 0.26, respectively) for the smallest additional costs (€ 56 and € 74, respectively). With a lifetime horizon strategy D results in a higher number of additional QALYs (0.55 more than strategy A) for an additional € 1,626 per QALY gained compared to strategy A.

Scenario analyses Table 4 presents scenario analyses to examine the impact of alternative parametric assumptions on the estimated ICURs. Alternative assumptions with respect to discounting rates (0.0% and 3.5% for both costs and effects) did not result in different conclusions with respect to the optimal strategies. When the disutility's related to treatments and recurrences are assumed to last for 5 years or even lifetime, this makes strategy B a better strategy over all time horizons, followed by strategy C. Decreasing the disutility for treatment of the neck makes strategy D more favorable. Improving sensitivity of SNB with 3% makes strategy B the best strategy over all time horizons, even becoming dominant when sensitivity improves further. When additional costs are involved to improve sensitivity, strategy B remains relatively favorable.

	5-year horizon			**10-year horizon**			**Lifetime horizon**		
	B	C	D	B	C	D	B	C	D
Incremental costs (€)	56	465	847	74	481	868	99	504	897
Incremental utility	0,12	0,10	0,09	0,26	0,23	0,26	0,52	0,46	0,55
ICUR (€/QALY)	468	4.603	8.966	279	2.081	3.357	190	1.087	1.626

TABLE 3. ICUR results comparing strategy B, C and D to strategy A, discounted (4% costs, 1.5% effects)
ICUR: Incremental cost-utility ratio

	Parameters	ICUR, 5-year horizon			ICUR, 10-year horizon			ICUR, lifetime horizon		
		B	C	D	B	C	D	B	C	D
1	**Base-case**									
	Costs (€)	56	465	847	74	481	868	99	504	897
	QALYs	0,12	0,10	0,09	0,26	0,23	0,26	0,52	0,46	0,55
	ICUR (€/QALY)	468	4.603	8.966	279	2.081	3.357	190	1.087	1.626
2	**No discounting** (instead of 4% for costs and 1.5% for effects)									
	Costs (€)	-23	394	757	1	416	785	51	461	841
	QALYs	0,13	0,11	0,10	0,29	0,25	0,29	0,62	0,55	0,67
	ICUR (€/QALY)	-182	3.682	7.467	4	1.640	2.746	81	830	1.265
3	**Discounting 3.5%** (for costs as well as effects)									
	Costs (€)	47	457	837	65	474	858	93	499	889
	QALYs	0,11	0,09	0,09	0,24	0,21	0,23	0,42	0,37	0,44
	ICUR (€/QALY)	418	4.866	9.720	277	2.304	3.785	220	1.337	2.035
4	**Disutility's remain for 5 years** (instead of resolving after 1 year)									
	Costs (€)	56	465	847	74	481	868	99	504	897
	QALYs	0.10	0.05	-0.08	0.24	0.19	0.08	0.50	0.42	0.38
	ICUR (€/QALY)	572	8,470	-10,457	305	2,600	10,472	199	1,207	2,386
5	**Disutility's remain for life** (instead of resolving after 1 year)									
	Costs (€)	56	465	847	74	481	868	99	504	897
	QALYs	0.10	0.05	-0.08	0.22	0.14	-0.10	0.43	0.28	-0.14
	ICUR (€/QALY)	572	8,470	-10,457	338	3,534	-8,651	229	1,800	-6,403
6	**Disutility for patients who received treatment of the neck = 0.03*** (instead of 0.07)									
	Costs (€)	56	465	847	74	481	868	99	504	897
	QALYs	0.13	0.11	0.13	0.27	0.24	0.29	0.53	0.47	0.58
	ICUR (€/QALY)	443	4,176	6,643	272	1,992	2,977	188	1,063	1,534
7	**Sensitivity of SNB improves with 3%** (87%→90% in strategy B, 80%→83% in strategy C after negative USgFNAC)									
	Costs (€)	-33	395	847	-14	412	868	14	437	897
	QALYs	0.13	0.11	0.09	0.28	0.25	0.26	0.56	0.49	0.55
	ICUR (€/QALY)	-252	3,669	8,966	-48	1,675	3,357	24	885	1,626
8	**Sensitivity of SNB improves with 3% against an additional cost of €500**									
	Costs (€)	467	797	847	486	814	868	514	839	897
	QALYs	0.13	0.11	0.09	0.28	0.25	0.26	0.56	0.49	0.55
	ICUR (€/QALY)	3,601	7,394	8,966	1,707	3,306	3,357	914	1,699	1,626

TABLE 4. Cost-utility modelling results for the base-case as well as 6 scenario analyses. ICURs per strategy, as compared to strategy A
In the scenario analyses, separate model inputs were changed to evaluate the effect on the incremental cost-utility ratios (ICURs), per strategy as compared with strategy A.
*This is the disutility of neck dissection reported by Weiss et al.[10]
SNB: sentinel lymph node biopsy

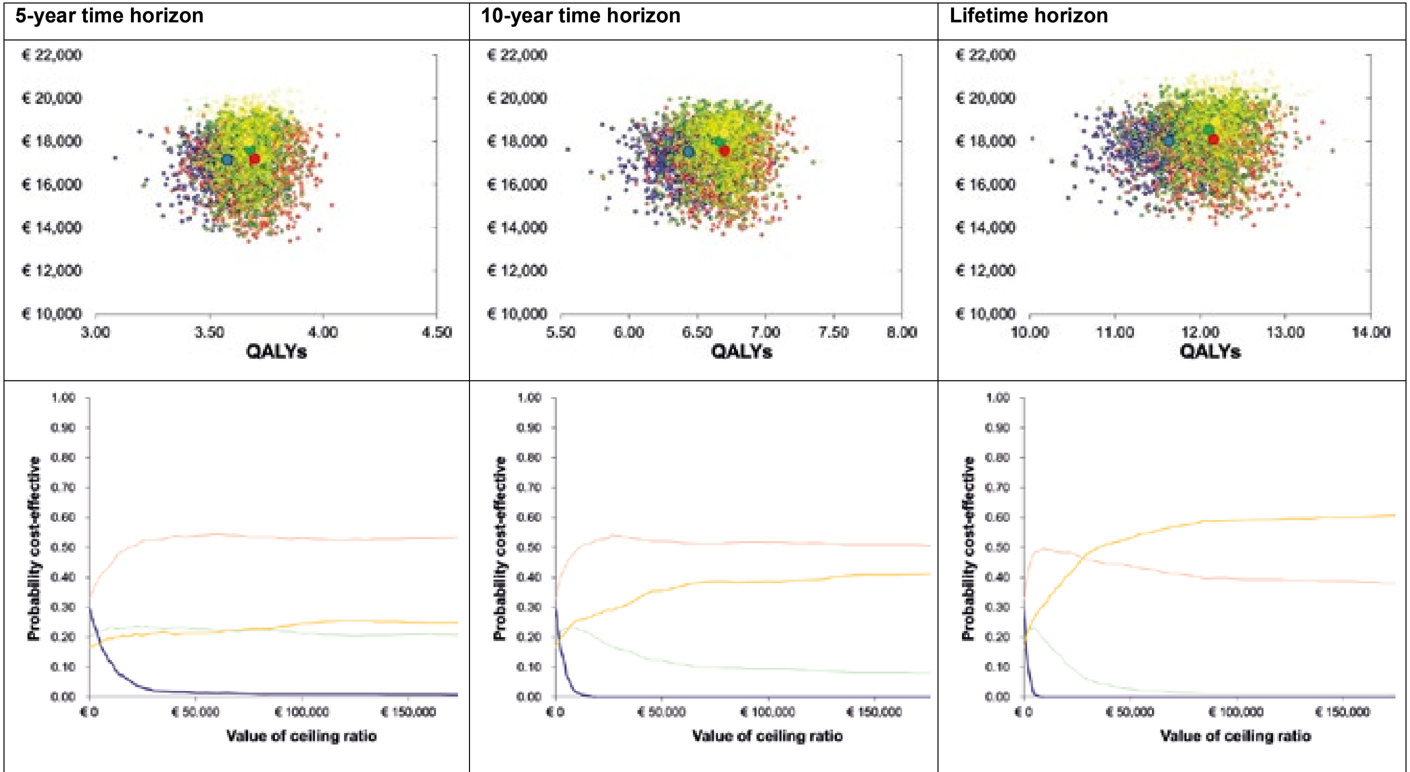
Probabilistic sensitivity analyses In Figure 4, the scatter plots reveal that the differences between the strategies are small compared to the uncertainty around the ICUR point estimates. Furthermore, the cost-utility acceptability curves in Figure 4 show that strategy B has the highest probability of being the most cost-effective diagnostic strategy, with a 5-year and 10-year time horizon. With a 5-year horizon, strategy B is the most cost-effective strategy in 53% of the cases. With a 10-year horizon, strategy B is the most cost-effective strategy in 50% of the cases. However, with a lifetime horizon, strategy D has the highest chance of being the most cost-effective option when the willingness to pay is ≥ € 28.000 per QALY gained. With a lifetime horizon, strategy B is the most cost-effective strategy in 38% of the cases, while strategy D is the most cost-effective strategy in 61% of the cases.

DISCUSSION

With a 5- or 10-year time horizon, SNB is the most favorable diagnostic strategy since it results in the highest number of QALYs gained with only small increases in costs compared to USgFNAC. However, with a lifetime horizon, END results in the highest quality of life gain for only an additional € 1,626 per QALY gained compared to USgFNAC. The reason for this is that END is associated with the smallest number of recurrences, which are costly and reduce life expectancy. However, scenario analyses show that -even with a lifetime horizon- strategy B (SNB) is more favorable than D (END) when we make different assumptions regarding the duration of disutility's or the sensitivity of SNB. Surgeons more experienced in SNB obtain significantly better results.[12] Sensitivity of SNB in the SNUS-trial was relatively low (80%), probably due to limited experience in most of the four Dutch head and neck centers at that moment. It is likely that with an increase in experience the sensitivity of SNB will improve, since a meta-analysis showed a sensitivity of 93% (95%-confidence interval (CI): 90-95%)[1] and two large single center studies showed sensitivities of 93%[13] and 91%[14] and negative predictive values of 97%[13] and 90%.[14] Therefore, it can be anticipated that SNB will also become the most favorable diagnostic strategy with a lifetime horizon in the near future.

It should be noted that base-case disutility's were based on EQ-5D results from the SNUS trial. The quality of life of oral cancer patients can be measured in a variety of ways, using either specific or generic measures.[15] The EQ-5D is a generic scale which allowed us to calculate utilities to be used in the economic evaluation. Generic scales cover all major aspects of a person's health and are applicable independent of the person's condition. Specific scales focus on one disease, site, symptom, domain or treatment[16] and may be more sensitive and therefore better able to show differences between strategies.
Although the EQ-5D did not pick up significant utility differences within the SNUS trial, differences between strategies may exist with respect to specific symptoms or preferences. For example, patients

Figure 4. Cost-utility planes and cost-utility acceptability curves for the four strategies, per time horizon.



The scatter plots show the incremental cost-utility point estimates (large dots) as well as the bootstrapped incremental costs and utility pairs (smaller circles). The acceptability curves show the probability that a strategy is the most cost-effective strategy, for a range of monetary values that a decision-maker might consider the maximum acceptable cost-utility ratio.

Blue = strategy A.
Red = strategy B.
Green = strategy C.
Yellow = strategy D.

FIGURE 4. Cost-utility planes

reported to prefer a SNB based diagnostic strategy over END.[9] Such preferences have not been incorporated in the current model and would have further favored the strategies with SNB.
Even though they used the EQ-5D as well, Govers et al.[17] did show differences in mean health utilities between strategies: 0.804 for watchful waiting, 0.863 for SNB, 0.834 for supraomohyoid neck dissection and 0.794 for modified radical neck dissection, adjusted for age, gender and time after diagnosis. This high utility value after SNB supports a strategy with SNB. Furthermore shoulder disability scores after SNB were relatively low.[17]

To our knowledge, the current study and a study by Govers et al.[5] are the only publications presenting the cost-utility of different diagnostic strategies for clinically N0 T1-T2 oral cancer. Kosuda et al. (2003) did calculate costs and deaths, but only from the procedures themselves. They did not provide any information about the clinical benefits involved with the various strategies or the costs involved with follow-up or recurrences.[3] The same is true for O'Connor et al. (2013). They calculated the relative costs of SNB compared to a traditional surgical approach, without evaluating clinical benefits or any costs other than those of the standard treatment protocol.[4]

Govers et al. (2013) created a decision tree and a Markov model, with a 5-year time horizon, showing SNB to be the most cost-effective strategy. The ICUR was € 3.356 per QALY gained compared to END.[5] In our study as well, SNB was the most cost-effective strategy at a 5-year time horizon. Compared to END, in our study SNB was both cheaper and more effective than END, resulting in a negative ICUR. Effects associated with both strategies were fairly similar in our study and the study from Govers et al. The SNB strategy resulted in 3.70 QALYs in our study and 3.63 QALYs in the study from Govers et al.[5] The END strategy resulted in 3.67 QALYs in our study and 3.61 QALYs in Govers et al. Costs for all strategies were substantially higher in our study, probably because more types of costs were included (e.g. all hospitalisations, outpatient visits and diagnostics) and measured in daily practice.

The most important limitations of the current study lie in the assumptions we had to make to inform the model. Since utility and cost differences between the strategies are small, alternative assumptions have a large effect on the ICURs. Most transition probabilities, utilities and costs were based on the SNUS trial, with a total of sixty-two patients from four of the eight centers of the Dutch Head and Neck Society. In other hospitals or countries, the patient population, tumor characteristics, test characteristics and costs may be different. However, this is the first study evaluating the cost-effectiveness of these diagnostic strategies based on actual resource use and quality of life, both measured in the same patient population.

Conclusion The current study shows SNB to be a good diagnostic option to evaluate cT1-T2N0 oral cancer. SNB is the preferred strategy in a 5- or 10-year time horizon, but from a lifetime horizon, END may be preferred. SNB may become the optimal strategy from all time horizons if patient's preferences are taken into account, or if its sensitivity is slightly improved, which is easily reached when centers are more experienced.

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CHAPTER 10

General discussion and future perspectives

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

SNB has proven its accuracy in preoperative staging of the cN0 neck in T1-T2 oral cancer patients, with a pooled sensitivity of 93% (95%-confidence interval (CI): 90-95%) in oral cancer patients and a negative predictive value ranging from 80 to 100%.[1, 2] With respect to floor of mouth (FOM) carcinomas, detection of the SN appeared to be more difficult: SN was successfully harvested in 88% versus 96% at other subsites ($p = 0.14$), sensitivity and negative predictive value for FOM tumors were significantly lower 80% vs. 97% and 88% vs. 98% ($p = 0.034$).[3] Ross et al. also reported that the SN identification rate in FOM carcinomas is significantly lower and the false negative rate is higher.[4] Although in other studies no significant difference was found probably due to low number of patients, pooling of 3 large studies[3, 5, 6] revealed a significant lower mean sensitivity for FOM tumors compared to other sites (82.5% (95%-CI: 72.6-92.3%) vs. 95.2% (95%-CI: 91.0-99.3%); $p = 0.008$) and a significant lower mean negative predictive value for FOM tumors compared to other sites (92.5% (95%-CI: 88.0-97.0%) versus 97.3% (95%-CI: 95.0-99.6%) $p = 0.043$). The most likely reason for these findings is the frequently close spatial relation between FOM carcinomas and the SNs. In this situation SNs may be masked during lymphoscintigraphy as a result of projection of the radioactive injection site over hot foci in the neck, the so called 'shine through' phenomenon leading to a false negative result. This problem can be approached and may be solved by different ways: elective (super)selective neck dissection or technical improvements of the SNB procedure.

A first solution could be to perform standardly a superselective neck dissection of level I in all patients with FOM carcinomas regardless of the SNB result. By taking out level I, the hidden SN that may be invisible on lymphoscintigram due to overprojection of the radioactivity from the primary tumor site, is automatically harvested. The gain is a lower false negative rate in FOM carcinomas. A drawback is that unnecessary lymph nodes in level I may bed excised too. Hamad et al. suggests further research to establish the benefits and sensitivity of combining level I node clearance with SNB procedures in FOM cancer.[7]

Lymphoscintigraphy has a limited resolution and this may hamper precise localization of SNs, particularly with the complex anatomy of the neck and the abundance of neck nodes. If SNs are difficult to identify during surgery, extensive exploration in the neck is needed, which increases the risk of surgical complications and formation of fibrosis and scar tissue postoperatively. These postoperative effects negatively influence a following surgical procedure, which is the case when a subsequent neck dissection is needed in SNB positive patients. In a fibrotic neck, sparing of structures like the internal jugular vein is more difficult during neck dissection and the risk of damaging other important structures (e.g. lingual nerve, hypoglossal nerve, spinal accessory nerve and branches of the facial nerve) is increased.

To overcome the problem of limited resolution and lack of anatomical information on planar lymphoscintigraphy, technical improvements on preoperative imaging for the identification of (true) SNs have been developed. With the addition of CT in SPECT/CT, anatomical information is obtained in combination with the radioactive distribution, and hot foci can be better localized in the neck facilitating surgical excision of a SN.[8] Moreover, foci that are closely related to the injection site have been detected more frequently.[8] In PET/CT scintigraphic and anatomical information are also combined, with a higher resolution than SPECT/CT. Moreover, contrary to SPECT/CT, PET/CT can provide dynamic imaging, which is important in differentiating SNs from second echelon nodes. Recently a PET-tracer, ^{89}Zr-nanocolloidal albumin, has been developed for the purpose of lymphatic mapping and SN detection using high resolution PET/CT.[9] In preclinical and clinical feasibility studies PET/CT showed improved detection and more precise localization of SNs.[9, 10] However, for intraoperative localization of the SN, the usefullness of a PET tracer and a PET probe seems to be limited compared with the excellent performance of a gamma probe.

For intraoperative localization of SNs portable gamma cameras and freehand SPECT (fhSPECT) were developed. First experiences with these instruments were positive and showed additional value for SN detection at the operation theatre, and this was confirmed in a larger series of patients.[11-14] However, in another study fhSPECT was only of additional value in 24% of the patients.[15] Moreover, as solution for the 'shine-through' phenomenon in case of FOM carcinoma and level I SN detection the use of fhSPECT is not clear yet.[14, 15]

The fhSPECT can be integrated with a video or other imaging modalities.[16] Recently, the 3D nuclear images of fhSPECT have been fused with ultrasound (US), combining functional and anatomical information and making SN visualization on US possible.[17, 18] In a recent study, the feasibility of fhSPECT/US was evaluated in a series of 6 patients with oral cancer and head and neck skin cancer.[19] fhSPECT/US was able to correctly identify SNs: lymph nodes that were not selected for fine needle aspiration cytology (FNAC) based on US only. In USgFNAC it may be of additional value to aspirate the lymph nodes that are at highest risk; not only size and consistency but also lymphatic drainage as risk factor can be used. However, the well-known limitations of FNAC for detection of occult lymph node metastases as sampling-error and insufficient aspirated material for cytology, remain.[19] Nevertheless, it has potential to reduce the need for invasive SN biopsy due to improvement of USgFNAC.

Another approach to support accurate SNB in tumors that are closely related to the neck, is to reconsider the radiopharmaceutical. ^{99m}Tc-nanocolloid (Nanocoll®) is widely known for its favorable particle size distribution and radio-labelling properties. Recently, a CD206 receptor-targeted non-particulate tracer, ^{99m}Tc-tilmanocept (Lymphoseek®) was introduced. It allows to exhibit two features that may favor its utility in the management of oral cancer: more rapid clearance from the injection site due to its smaller size, and sustained SN uptake without distal lymph node accumulation due to binding specificity to lymphatic tissues.[20]

In a multicenter SNB study using ^{99m}Tc-tilmanocept in early oral and skin cancer patients the SN detection rate and false negative rate of FOM cancer was similar to cancers at other oral subsites.[21] In a comparative meta-analysis on SNB in breast cancer ^{99m}Tc-nanocolloid was compared to ^{99m}Tc-tilmanocept. It seems that ^{99m}Tc-tilmanocept offers improved ability to detect the SN, and its receptor-specific binding properties offer improved SN localization.[22] However, comparative results for oral cancer are not performed yet. Head to head comparison of tilmanocept with nanocolloid is needed and for accurate comparison ideally a randomized controlled trial should be performed.

Use of a dye may facilitate SN detection during surgery when radioactivity of the SN is overshined by the primary tumor. However, the use of blue dye is of limited added value in the head and neck area. It has a relatively low molecular weight-compound and therefore, the retention of the blue stain in the SN is poor and the visibility is short. Moreover, real-time detection of the blue dye is only possible if there is no overlying tissue.[4]

An alternative to blue dye to visualize the SN is fluorescent imaging. The use of near-infrared (NIR) fluorescence imaging is relatively new, but has the potential to guide surgeons during surgery in real-time.[23] Bredell et al. performed a study in which indocyanine green (ICG) was injected peritumorally in oropharyngeal carcinoma. After visualization of cervical lymph nodes by NIR they concluded that ICG is potentially valuable in SNB of the head and neck.[24] In the study of Murase et al. ICG was used as well, separately injected from ^{99m}Tc-tin colloid, and visualized SNs. However, the authors mentioned the need for removal of overlaying fatty and muscle tissue to visualize ICG, and an increased number of visualized potential SNs using ICG.[25] To improve retention in the (true) SN(s), ICG has been adsorbed to human serum antibody (HSA) by Van der Vorst et al.[26] ICG:HSA proved to be feasible to show SNs in the neck, and lymph node metastases could be detected. However, ICG:HSA migrated fast to second echelon lymph nodes in the neck.[26] ICG was then labelled to ^{99m}Tc-nanocoll and in comparison to the conventional ^{99m}Tc-nanocoll it showed the same lymphatic distribution.[27] ICG-^{99m}Tc-nanocoll is clinically off label used as a NIR fluorescent tracer used for SN detection.[27] Van den Berg et al. showed that using ICG-^{99m}Tc-nanocoll for SNB in oral cancer is feasible and that the addition of fluorescence imaging is of particular additional value when SNs are located in close proximity to the primary tumor.[28]

More recently a novel nanocolloid-based fluorescent tracer has been developed: nanocoll-IRDye800CW. This tracer makes use of the novel NIR fluorescent dye IRdye800CW. In a preclinical validation study this tracer seems to be better suitable for intraoperative NIR-fluorescence guided SN detection compared to ICG, because of better retention time of the tracer in the SN.[29] A NIR camera for fluorescence detection can be added to a portable gamma camera, leading to intraoperative concomitant radio- and fluorescence-guided SNB. Additional to the NIR camera an opto-nuclear probe has been developed that is able to intraoperatively detect SNs by gamma and fluorescence tracing.[30]

Another solution could be a magnetic nanoparticle tracer. Superparamagnetic iron oxide (SPIO) has been approved for intravenous use in contrast-enhancing MRI scanning of the liver. In humans, this agent is incorporated into the reticuloendothelial system. Interstitial administration of SPIO is taken up as iron oxide in lymph nodes.[31, 32] This has led to the development of a new SNB technique using a SPIO tracer-guide and a handheld magnetometer instead of radioisotopes.[33]

Preoperative three-dimensional high-resolution imaging by SPIO-MR sentinel lymphography accurately identifies the lymphatic pathways and primary SNs, and provides detailed anatomical information. Recently the use of such a tracer for intraoperative detection with a handheld magnetometer was successfully evaluated in multiple clinical trials in breast cancer patients.[31, 33] Rubio et al. showed that SPIO is equivalent to the ^{99m}Technetium radiotracer for SN detection.[34] This interstitially administered magnetic tracer can be used both for pre-operative imaging and intraoperative SN localization, with equal performance to imaging and localization with a radioisotope.[35]

However, the used magnetometer suffers from some fundamental drawbacks which hampers its implementation. Firstly, the magnetometer used in these trials is not only sensitive for the magnetic particles, but also to the diamagnetic body. This fundamentally lowers the detection limit of the system. Secondly this magnetometer cannot operate in the vicinity of standard surgical instruments, complicating the procedure.

A new handheld magnetic probe which could provide a solution for FOM carcinomas was developed, which is only sensitive to the magnetic nanoparticles, and not to the human diamagnetic body (NIM-Magnetic Detection-group, University of Twente). This may result in an increased sensitivity in the clinical situation, allowing for a lower dosage, and thus a less prominent injection spot, limiting the 'shine-through' effect. Furthermore, this probe can be used in vicinity of standard surgical instruments, simplifying the use. The first prototype has a high spatial resolution allowing for detection near the injection spot, and achieves sufficient tissue penetration for intraoperative detection of SNs. Combined with high resolution preoperative MR imaging, it potentially meets all the demands to successfully perform SNB in oral carcinoma.

As SNB in oral cancer has proven its high accuracy, improving will be challenging. However, besides use and accuracy, improving efficiency and decreasing morbidity and time consumption can be improvement goals as well. An efficient SNB procedure means selection of the true SNs with correct distinction from second echelon lymph nodes. When only the true SNs are selected, the operation time may become shorter, and less (false) SNs are harvested leading to lower morbidity. Efficient SNB also means, less extensive histopathology and performing step-serial sectioning only as far as necessary.[36]

The results described in this thesis confirm the usefulness and success of SNB in cT1-T2N0 oral cancer. Neck staging by SNB is accurate, observation of the neck after negative SNB is safe and SNB allows for individualized therapy. In all 14 European head and neck centers that were involved in the Sentinel European Node Trial (SENT), SNB has become standard of care in early stage oral cancer. Main findings of this SENT trial were a sensitivity of 87%, negative predictive value of 95% and disease-specific survival of 94% in 420 cT1-T2N0 oral cancer patients with a median follow-up of more than 4 years. Institutes from several smaller multicenter trails, such as the SNUS trial in The Netherlands have also implemented SNB. After the SNUS trial was completed, all 4 participating centers and 1 new Dutch center currently perform SNB in the routine diagnostic work-up of oral cancer. However, there is room for more widespread implementation, nationally and internationally. A randomized clinical trial comparing a SNB based strategy with END is needed to shed light on the issue of SNB safety. This may be of help to introduce SNB to institutes that were not involved in the research phase of SNB.

Recently, the National Comprehensive Cancer Network (NCCN) has recognized the success of neck staging by SNB in early stage oral cancer. SNB is since then incorporated in the NCCN Clinical Practice Guidelines in Oncology of Head and Neck Cancers (version 2.2014): "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. …"[37]

The guideline underlines the experience needed for accurate SNB, and it provides an alternative to SNB with neck dissection: "Sentinel node biopsy is a technically demanding procedure. Procedural success rates for sentinel node identification as well as accuracy of detecting occult lymphatic metastasis depend on technical expertise and experience. Hence, sufficient caution must be exercised when offering it as an alternative to elective neck dissection."[37]

Since January 2016, the Dutch guideline on head and neck cancer endorses the reliability of SNB for staging the cN0 neck.[38] SNB is incorporated in the management of cT1-T2N0 oral cancer: "Perform, if possible, a SNB procedure. In patients with a positive SN a neck dissection during second surgery will be performed. A neck dissection is a valuable alternative to SNB."[38] Incorporation in the guidelines may convince the centers that are not familiar with SNB yet to consider it as a new strategy. This addition to the guideline is due to be implemented in 2018.

The current 'Joint practice guidelines for radionuclide lymphoscintigraphy for sentinel node localization in oral/oropharyngeal squamous cell carcinoma'[39] are helpful in the theory behind the SNB procedure, and the crucial elements of each step in the procedure are clearly explained. However, to make the SNB procedure more accessible for inexperienced institutes, guidelines may need to include more practical information. For example, according to the results of our interobserver study, explanation on how to interpret lymphoscintigrams could be given in more detail in the guideline.[40] Moreover, to perform accurate SNB it is known that a learning curve in practical skills is essential. For centers considering to implement SNB, it is recommended to have performed at least ten SNB-assisted ENDs before performing

SNB alone with observation of the neck. For surgeons who are not familiar yet with SNB, theoretical training by the guidelines alone is not enough, they should be trained during hands-on courses and 'how we do it' sessions.

Studies on SNB in melanoma and breast cancer have preceded oral cancers studies. Procedures and theories have been adopted, critically weighed and adapted. We can learn from these data and verify the theories and outcome results in our oral cancer series. The long-term results of several large oral cancer studies, as the SENT trial and for example the studies from Glasgow, Switzerland and our Dutch multicenter study will provide us more insight into the clinical behavior of the lymphatics in oral cancer. After time, more oral cancer patients will have undergone SNB, and more data will be available. Sub-analyses may provide new information or will raise new questions. One of the current research questions of clinical outcome is the clinical relevance of isolated tumor cells (ITC). What we know from breast cancer studies, is that the presence of isolated tumor cells negatively influence survival, but that the need for subsequent axillary lymph node dissection is debated.[41, 42] In oral cancer, with a small series of patients, ITC has shown to have significant impact on survival, but its clinical relevance on therapy strategy is not yet known.[43] In the meantime, all clinical studies should uniformly report their data on the amount of metastatic deposits, i.e. ITC, micrometastases and macrometastases in SNs and in the presence of additional non-SN metastases, as well as uniformly perform survival analyses of these subgroups. Until more is known about the clinical relevance of tumor deposits in the SNs, patients with ITC still will undergo a subsequent neck dissection.

To conclude with, SNB is clinically useful in the management of cT1-T2N0 oral squamous cell carcinoma patients, and allows for individualized therapy. New techniques may improve SNB, particularly of more challenging subsites as the floor of mouth. More and larger studies are awaited for.

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CHAPTER 11

English summary

SUMMARY

Head and neck squamous cell carcinoma (HNSCC) is the 9th most common cancer worldwide. Subsites in HNSCC are the oral cavity, oropharynx, hypopharynx and larynx. The stage of disease is categorized in the TNM-classification system: the extent of the tumor (T), the presence of cervical lymph node metastases (N) and distant metastases (M). The TNM-stage is important since it determines the patients' treatment options. The status of the neck, whether lymph node metastases are present or not, is one of the most important prognostic factors. Staging the neck with conventional diagnostic methods is not accurate enough, particularly in patients with a clinically negative (cN0) neck. It is known that in patients with cT1-T2N0 oral squamous cell carcinoma the risk of occult (clinically undetectable) lymph node metastases is about 30%. Management of the neck in these patients, has therefore been subject of debate for years. The dilemma is to choose for elective neck dissection which means that occult lymph node metastases are removed, but that the majority (60-70%) of patients undergo unnecessary treatment. Or to choose for observation of the neck with the drawback that 30-40% of the patients develop delayed lymph node metastases. In an attempt to avoid unnecessary elective neck dissection, observation may be an acceptable option, unless early detection of delayed lymph node metastases is guaranteed. Ultrasound guided fine needle aspiration cytology (USgFNAC) has been the most reliable conventional technique in the detection of lymph node metastases and is easily repeated during follow-up to detect delayed metastases. Another solution for this debate may be more accurate staging at pretreatment.

Sentinel node biopsy (SNB) is a diagnostic method in which lymph nodes that are at highest risk to harbor metastases, are detected and meticulously histopathologically examined. If a metastasis is diagnosed in the sentinel node, the neck is in principle treated by a neck dissection. If the sentinel node is free of tumor, the neck will be observed during follow-up. More accurate staging of the cN0 neck, leads to individualized management of the neck.

The aim of this thesis was to assess the management of the cN0 neck in T1-T2 oral cancer patients by a minimal invasive diagnostic strategy. This was done by retrospective evaluation of the 'wait and scan' strategy by USgFNAC in terms of survival, evaluation of the use of sentinel node biopsy (SNB) to detect occult lymph node metastases in cN0 oral cancer patients, analysis of the effect of previous treatment on the use of SNB, evaluation of the additional value of late lymphoscintigraphic imaging, interobserver analysis of lymphoscintigraphic interpretation, assessment of the health-related quality of life and cost-effectiveness of a SNB based diagnostic strategy in oral cancer, and assessment of the feasibility of SNB in the larynx.

During the 1990s and early 2000s, before the introduction of SNB, careful observation of the USgFNAC negative neck has been the strategy in cT1-T2N0 oral cancer patients at VU University Medical Center (VUmc). This observational strategy was called 'wait and scan' (W&S), meaning strict surveillance by using USgFNAC of the neck during follow-up to detect delayed lymph node metastases early. Previous studies from VUmc have shown high salvage rates using this W&S strategy. We set out to report on survival data of this policy. The study described in **chapter 2** is a retrospective survival analysis of patients with cT1-T2N0 oral cancer who were treated by transoral excision and followed by the W&S strategy. The aim was to investigate the outcome of the observational W&S strategy. Of the 285 included patients, 234 had been followed by W&S and, as a reference, 51 patients had undergone elective neck dissection (END). Survival rates were compared between groups and correction for confounding factors was performed.

Of the W&S patients, 27.8% had delayed metastases and the 5-year disease-specific (DSS) and overall survival (OS) were 94.2% and 81.6%, respectively. W&S patients with delayed metastases had a 5-year DSS and OS of 80.0% and 62.8%, respectively. Of the patients who underwent END with a diagnosed metastasis, these figures were 81.3% and 64.2%, respectively. Between W&S and END patients, survival rates were not significantly different. Of the W&S patients with delayed metastases, 90.6% needed postoperative radiotherapy versus 55.0% of patients with positive END.

We concluded that a W&S strategy using strict USgFNAC surveillance is justified as survival is not negatively influenced. With this strategy unnecessary neck dissection and accompanying morbidity could be avoided in 72.2% of patients. For the small proportion of patients with delayed metastases more extensive treatment with adjuvant radiotherapy was needed. To minimize the proportion of patients needing more extensive treatment a more accurate preoperative diagnostic method to stage the cN0 neck is warranted.

In **chapter 3** the accuracy of SNB for staging of the cN0 neck in oral and oropharyngeal patients was evaluated. In a Dutch multicenter trial with 4 participating institutes, sixty-two patients with cT1-T2 oral and oropharyngeal cancer and N0 neck based on USgFNAC were included. All patients underwent preoperative lymphoscintigraphy and intraoperative gamma probe guidance to identify and detect the SN(s). SNB negative patients were carefully observed during follow-up and SNB positive patients were treated by subsequent neck dissection, radiotherapy or a combination of both. SNB detected lymph node metastases in 32% (20/62) of patients. Of the 42 patients with a SNB negative result, 5 developed delayed lymph node metastases, of whom 4 patients could be successfully salvaged. Disease-free (DFS), overall (OS) and disease-specific (DSS) survival of SNB negative patients were 72.0%, 92.7% and 97.4%, respectively. For SNB positive patients these numbers were 73.7%, 79.7% and 85.0%, respectively (DFS: $p = 0.916$, OS: $p = 0.134$, DSS: $p = 0.059$, respectively). With SNB the risk of occult lymph node metastases was reduced from 40 to 8%. A sensitivity of 80% and negative predictive value of 88% of SNB were found. Neck control rate was 97% in SNB negative and 95% in SNB positive patients.

This study revealed that SNB substantially reduces the risk of occult lymph node metastases in cT1-T2N0 oral cancer patients and enables excellent control of the neck.

It is known that previous treatment of the neck (e.g. neck dissection and/or (chemo)radiotherapy) may have influence on the lymphatics and may change or block original drainage patterns. Therefore, in case of a local recurrence or second primary tumor, therapy of the neck focusing on the neck levels at risk as it would be in the primary setting may not be appropriate. In **chapter 4** a prospective observational study was conducted to evaluate the clinical application of SNB in 22 oral cancer patients who were previously treated on the neck. Of the patients, 4/22 (18%) were previously treated only on the contralateral neck side. The SN detection rate was 100%, unexpected drainage was found in 25% of patients and 75% had a lymph node metastasis in the SN. The other 18 patients had ipsi- or bilateral previous neck treatment and a SN detection rate of 83%. In 7% of the patients the cN0 neck was upstaged by SNB, and 67% of the patients had unexpected lymphatic drainage patterns. The median follow-up was 22 months. Regional tumor control and negative predictive value were 100%.

Conclusions of this study were that SNB in previously treated oral cancer patients is feasible and reliable, and that regional tumor control after staging by SNB is excellent. SNB renders an assessment of the individual lymphatic drainage pattern, compensating for potential alterations after previous treatment of the neck.

In clinical practice, diagnostic imaging procedures should be useful and efficient. In **chapter 5** the clinical value of performing late lymphoscintigraphic imaging was questioned. For this study, lymphoscintigrams of 60 cT1-T2N0 oral cancer patients were retrospectively assessed. Both scans: early (directly following injection of ^{99m}Tc-nanocoll and late (2-4h after injection) lymphoscintigrams were evaluated. Foci visible on late lymphoscintigrams were categorized: (a) no visualization of additional foci considered to be SNs; (b) additional foci visualized that are considered to be SNs and (c) foci visualized only during late imaging. Histopathological results of the harvested SNs were related to the corresponding foci.

In all 60 patients a focus visible on lymphoscintigram was identified as SN. Early imaging was able to visualize at least one focus in 51/60 (85%) patients, whereas in 9/60 (15%) patients only late imaging was able to visualize foci. In this latter group of patients most oral tumor sites were other than mobile tongue and floor of mouth (FOM). In paramedian and midline tumors, bilateral drainage was observed in the majority (83%) of tumors, with half of them only being visible during late imaging. In 14/51 (27%) patients, late imaging resulted in additionally visualized foci which were marked as SNs, resulting in a more extensive surgical procedure. With histopathological examination, no metastases were found in those SNs from additionally visualized foci. Therefore, it can be concluded that these additional foci visible on lymphoscintigraphy were clinically not relevant. Moreover, all SNs identified during early imaging correctly predicted whether the neck was positive or negative for cancer.

The results of this study indicated that additional late lymphoscintigraphic scans are only useful in patients with oral tumors located other than the mobile tongue and FOM, and in patients with paramedian or midline tumors. Based on these findings we suggested to perform late lymphoscintigraphy only in patients with oral cancer other than oral tongue and midline or paramedian tumors.

Adequate interpretation of the lymphatic drainage pattern is an essential step in the SNB procedure. In oral cancer, identification of the SN can be challenging if multiple foci are visible on lymphoscintigraphy. In **chapter 6** interpretation of lymphoscintigraphic imaging was assessed. To keep SNB accurate but minimal invasive, it is important to critically interpret the lymphoscintigram and distinguish the first echelon with true SNs from second echelon nodes. We performed an interobserver study to assess the interobserver variability in defining SNs on lymphoscintigrams of cT1-T2N0 oral cancer patients. Sixteen observers (head and neck surgeons, nuclear medicine physicians or teams of both) from various European institutes were asked to interpret lymphoscintigrams to select SNs of 9 patients with 47 foci (3-9 per patient) using a scale of 'yes/equivocal/no'. Interobserver variability was evaluated by kappa (κ) analysis, using linear weighted pairwise comparison of the observers. Conservative (equivocal scored as no) and sensitive (equivocal considered as yes) assessment strategies were investigated using pairwise kappa analysis.

Interobserver variability of all cases using a 3-point scale showed fair agreement (71%, κ_w = 0.29). The conservative and sensitive analyses both showed moderate agreement: conservative approach κ = 0.44 (in 80% of the foci the observers agreed) and sensitive approach κ = 0.42 (81% agreement). More foci and bilateral drainage resulted in lower agreement, whereas a multidisciplinary assessment (team of both) in image interpretation and a higher level of observer experience appeared to increase agreement.

The results of this study showed that among observers there is practice variation in defining SNs on lymphoscintigraphy with moderate interobserver agreement. To achieve higher agreement specific guidelines are warranted.

SNB has shown its value in accurate detection of occult lymph node metastases in oral and oropharyngeal cancer, whereas in other HNSCC sites SNB is still under investigation. In patients with laryngeal cancer and cN0 neck a total laryngectomy is usually combined with elective neck dissection(s). Based on the risk of occult lymph node metastases the decision whether to perform an elective neck dissection or not is difficult. In **chapter 7** the feasibility of SN identification and potential accuracy of SNB in laryngeal cancer patients undergoing total laryngectomy with elective neck dissection was investigated. During surgery 40MBq ^{99m}Tc-nanocoll was endoscopically injected around the tumor. Lymphoscintigraphy was not performed. We identified the SN ex vivo in the neck dissection specimen with a gamma probe. Histopathological examination of the neck dissection specimen served as reference test.

We included 19 patients, of whom 13 laryngeal cancer patients with untreated necks and 6 with prior neck treatment. SN identification was successful in 68.4% (13/19) and was significantly higher in patients with untreated necks (92.3% versus 16.7%, $p < 0.01$). In 4 of 13 (30.7%) patients with successful SN identification metastases were found and patients were upstaged by SNB. Sensitivity and negative predictive value were 80.0% and 87.5%, respectively.

This study revealed that SN identification in laryngeal cancer patients undergoing total laryngectomy is feasible in patients with untreated necks. Further studies are needed to determine the usefulness and accuracy of SNB in laryngectomy patients.

Health-related quality of life and psychological aspects of a therapy gain more interest. Of the study in **chapter 8** the primary aim was to evaluate prospectively the impact of a SNB based strategy (surveillance in SNB negative (SNB-) and subsequent neck dissection in SNB positive (SNB+) patients) in cT1-T2N0 oral cancer patients on the course of health-related quality of life, psychological distress and shoulder disability from diagnosis to 6 months follow-up. The secondary aims were to obtain insight into long-term shoulder functioning and into the preference of patients for an END strategy or a SNB based strategy.

A series of 52 patients (39 SNB-, 13 SNB+) completed the EORTC QLQ-C30 (quality of life-cancer module), QLQ-H&N35 (quality of life-head and neck cancer module), HADS (hospital anxiety and depression scale), IES (impact of event scale) and SDQ (shoulder disability questionnaire) questionnaires at baseline (before transoral excision and SNB), after SNB diagnosis, and at 6 months follow-up. Objective shoulder measurements were investigated after 2 years follow-up. Interviews on neck management strategies were conducted after 4.5 months follow-up.

The course of the mean scores on the QLQ-C30, QLQ-H&N35, HADS, IES and SDQ questionnaires over time was not significantly different between SNB- and SNB+ patients. Median IES subscale scores showed subclinical reactions. Results of SDQ increased significantly in SNB+ patients at 6 months follow-up, which partly recovered at late follow-up. At 2 years follow-up no significant differences in objective shoulder measurements were found, but SNB+ patients reported more often skin numbness of the neck. Most patients preferred a SNB based strategy over an END strategy.

With this study it can be concluded that the impact of a SNB based strategy in cT1-T2N0 oral cancer patients is comparable for SNB- and SNB+ patients (with subsequent neck dissection) in terms of HRQoL, psychological distress and shoulder functioning. Most patients preferred a SNB based strategy over an END strategy.

In **chapter 9** a cost-effectiveness study was performed. If a novel management strategy is proposed to become standard of care, it should preferably be cost-effective compared with previous management strategies. A model to calculate the cost-utility of different strategies for the detection of occult lymph node metastases in cT1-T2N0 oral cancer was created. A decision tree followed by a Markov model was designed to compare the cost-utility of the following strategies: (a) USgFNAC, (b) SNB, (c) USgFNAC and if negative, SNB and (d) END. Data were collected from 62 patients in four Dutch head and neck centers. Utilities were measured with the EQ-5D questionnaire and resource use was recorded from patient charts. Costs were calculated from a hospital perspective (2015 Euros). The cycle length was one year, with 5-year, 10-year and lifetime horizons. Uncertainty was explored with scenario analyses and probabilistic sensitivity analyses.

With a 5- or 10-year time horizon, SNB resulted in the highest number of additional quality-adjusted life years (QALYs, 0.12 and 0.26, respectively) for the smallest additional costs (€ 56 and € 74, respectively) compared with strategy (a) (USgFNAC). With a lifetime horizon END resulted in the highest number of additional QALYs (0.55) for an additional € 1,626 per QALY gained compared to USgFNAC. When making different assumptions regarding duration of disutility's (≥ 5 years) or improvement of sensitivity of SNB (≥ 3%), SNB appeared to be the most favorable strategy from all time horizons.

The results of this study revealed that SNB is cost-effective in patients with cT1-T2N0 oral cancer. SNB may become the optimal strategy from all time horizons if its sensitivity could be slightly improved.

11

CHAPTER 12

Nederlandse samenvatting

SAMENVATTING

Hoofd-halskanker is wereldwijd het 9e meest voorkomende tumortype. Sublokalisaties van hoofd-halskanker betreffen de mondholte, orofarynx, hypofarynx en larynx. Ziektestadiering wordt gedaan middels het TNM-classificatiesysteem: tumoruitbreiding (T), aanwezigheid van lymfkliermetastasen (N) en aanwezigheid van afstandsmetastasen (M). Het TNM-stadium is belangrijk aangezien het de therapeutische opties bepaalt. De status van de hals, of er lymfkliermetastasen zijn of niet, is één van de meest belangrijke prognostische factoren. Met de huidige conventionele diagnostische onderzoeken is het stadiëren van de hals onvoldoende accuraat, met name bij patiënten met een klinisch negatieve (cN0) hals.

Het is bekend dat bij patiënten met een cT1-T2N0 plaveiselcelcarcinoom van de mondholte het risico op occulte (klinisch niet-detecteerbare) lymfkliermetastasen ongeveer 30% is. Bij deze patiënten is het beleid ten aanzien van de hals al jaren onderwerp van discussie. Het dilemma bestaat uit te kiezen voor een electieve behandeling van de hals middels een halsklierdissectie, wat betekent dat occulte lymfkliermetastasen worden verwijderd, maar waarbij de meerderheid (60-70%) van de patiënten deze behandeling onnodig zal ondergaan. Of te kiezen voor observatie van de hals met het nadeel dat 30-40% van de patiënten lymfkliermetastasen ontwikkelen die in een later stadium worden ontdekt en dan alsnog behandeld moeten worden. Om onnodige halsklierdissecties te voorkomen, is observatie van de hals een acceptabele optie mits lymfkliermetastasen alsnog tijdig worden ontdekt. Echogeleide dunne naald aspiratie cytologie (USgFNAC) is de meest betrouwbare conventionele techniek om lymfkliermetastasen te detecteren, en kan eenvoudig regelmatig worden uitgevoerd gedurende follow-up. Een andere oplossing voor dit dilemma is de preoperatieve diagnostiek naar lymfkliermetastasen in de hals te verbeteren en nauwkeuriger maken.

De schildwachtklierprocedure (sentinel node biopsy, SNB) is een diagnostische methode die de lymfklieren met het hoogste risico op lymfkliermetastasen, de zogeheten schildwachtklieren, opspoort om zorgvuldig te onderzoeken middels gedetailleerd histopathologisch onderzoek. Wanneer een schildwachtklier een lymfkliermetastase bevat, wordt de hals in principe behandeld middels een halsklierdissectie. Wanneer er geen lymfkliermetastase gevonden wordt in de schildwachtklier, zal geen behandeling van de hals plaatsvinden en zal de patiënt poliklinisch worden vervolgd. Met accuratere diagnostiek van de cN0 hals, krijgt de patiënt behandeling op maat.

Het doel van dit promotieonderzoek was hoe met behulp van minimaal invasieve diagnostische strategieën sturing gegeven kan worden aan management van de cN0 hals bij patiënten met T1-T2 mondholtecarcinoom. Hiervoor werd een retrospectieve survival analyse uitgevoerd van een 'wait and scan' beleid met regelmatige USgFNAC gedurende follow-up bij patiënten met een cT1-T2N0 mondholte carcinoom; er vond een prospectieve observatiestudie plaats waarin de schildwachtklierprocedure (SNB) als diagnostische work-up bij cT1-T2N0 mondholtecarcinoom patiënten ter detectie van occulte lymfkliermetastasen werd geëvalueerd; het toepassen van SNB bij patiënten met eerdere behandeling van mondholte of hals werd onderzocht; de toegevoegde waarde van late lymfoscintigrafie ten behoeve van de accuratesse van SNB werd geëvalueerd; er vond een analyse van de interobserver variabiliteit bij de interpretatie van lymfoscintigrafische scans plaats; de kwaliteit van leven en kosten-effectiviteit van SNB werd onderzocht, en tenslotte vond evaluatie van de toepassing van SNB in een andere tumorlokalisatie, het larynxcarcinoom, plaats.

Voor de introductie van SNB in de jaren 1990 en 2000, was in het VU medisch centrum (VUmc) observatie van de cN0 hals op basis van USgFNAC de behandelstrategie bij patiënten met cT1-T2N0 mondholtecarcinoom. Deze observationele strategie bestond uit een zogeheten 'wait and scan' (W&S) beleid met stricte follow-up met USgFNAC van de hals om lymfkliermetastasen die pas later detecteerbaar zijn alsnog tijdig op te sporen. Eerdere studies vanuit VUmc hebben aangetoond dat met een W&S beleid een hoge 'salvage rate' (succesvolle curatieve behandeling na alsnog ontstaan van lymfkliermetastasen) kan worden bereikt.

We hebben een studie uitgevoerd naar survival (overleving) met dit beleid. De studie die is beschreven in **hoofdstuk 2** betreft een retrospectieve survival analyse van patiënten met een cT1-T2N0 mondholtecarcinoom die behandeld waren met transorale excisie voor de primaire tumor en een W&S beleid voor de hals. Het doel was om de overleving met het W&S beleid te onderzoeken.

Van de 285 geïncludeerde patiënten, volgden 234 patiënten het W&S follow-up beleid en 51 patiënten hadden een electieve halsklierdissectie (END) ondergaan. De overlevingscijfers van beide groepen werd vergeleken en er werd gecorrigeerd voor variabelen die de uitkomst konden beïnvloeden (confounders).

Van de patiënten met W&S ontwikkelden 27,8% alsnog een lymfkliermetastase waarvoor zij behandeld werden met een halsklierdissectie. De 5-jaars ziekte specifieke (DSS) overleving en 5-jaars algehele overleving (OS) waren respectievelijk 94,2% en 81,6%. W&S patiënten met lymfkliermetastasen in de follow-up hadden een 5-jaars DSS en OS van respectievelijk 80,0% en 61,8%. Van de END patiënten bij wie een lymfkliermetastase in het dissectiepreparaat was gediagnosticeerd, waren de 5-jaars DSS en OS respectievelijk 81,3% en 64,2%. De overlevingsdata van W&S en END patiënten waren niet significant verschillend. Van de W&S patiënten met alsnog gediagnosticeerde lymfkliermetastasen had 90,6% naast een halsklierdissectie ook postoperatieve radiotherapie van de hals nodig, tegenover 55,0% van de END patiënten met lymfkliermetastase.

Wij concludeerden dat een W&S strategie met stricte USgFNAC gedurende follow-up is gerechtvaardigd aangezien het de overleving niet negatief beïnvloedt. Met deze strategie kan een onnodige halsklierdissectie met bijkomende morbiditeit worden voorkomen in 72,2% van de patiënten. Voor het kleine aantal patiënten dat gedurende follow-up alsnog een lymfkliermetastase blijkt te hebben, was intensievere behandeling nodig met adjuvante radiotherapie. Om het aantal patiënten dat deze intensievere behandeling nodig heeft te reduceren, is een accuratere preoperatieve diagnostische methode nodig om de cN0 hals te stadiëren.

In **hoofdstuk 3** is de accuratesse van SNB onderzocht bij patiënten met een klein mondholte- en orofarynxcarcinoom met cN0 hals. Het betrof een Nederlandse multicenterstudie met 4 deelnemende centra en gezamenlijk werden 62 patiënten met cT1-T2 mondholte- en orofarynxcarcinoom en cN0 hals op basis van USgFNAC geïncludeerd. Alle patiënten ondergingen preoperatief een lymfoscintigram en peroperatief werden schildwachtklieren (SN) met behulp van een gamma probe opgespoord. Patiënten met SNB negatieve uitslag (geen lymfkliermetastase) werden geobserveerd gedurende follow-up, en patiënten met SNB positieve uitslag (lymfkliermetastase) ondergingen een halsklierdissectie, radiotherapie of een combinatie van beide. Met SNB werden lymfkliermetastasen ontdekt in 32% (20/62) van de patiënten. Van de 42 patiënten met SNB negatieve uitslag ontwikkelden er 5 alsnog een lymfkliermetastase, en 4 van hen konden alsnog succesvol worden behandeld. De ziektevrije (DFS), algehele (OS) en ziekte specifieke (DSS) overleving van de SNB negatieve patiënten waren respectievelijk 72,0%, 92,7% en 97,4%. Voor SNB positieve patiënten waren deze respectievelijk 73,7%, 79,7% en 85,0% (DFS: p = 0,916, OS: p = 0,134, DSS: p = 0,059, respectievelijk). Met SNB kon het risico op occulte lymfkliermetastasen worden gereduceerd van 40 naar 8%. De sensitiviteit en negatief voorspellende waarde van SNB waren respectievelijk 80% en 88%. De regionale controle was 97% bij SNB negatieve patiënten en 95% bij SNB positieve patiënten.

Deze studie toonde aan dat met SNB het risico op occulte lymfkliermetastasen bij patiënten met cT1-T2N0 mondholte- en orofarynxcarcinoom substantieel wordt gereduceerd en excellente regionale controle wordt bereikt.

Het is bekend dat eerdere behandeling van de hals (bijv. halsklierdissectie en/of (chemo)radiotherapie) invloed heeft op de lymfedrainage en dat het originele lymfedrainage patroon kan worden veranderd of geblokkeerd. Het kan daarom zijn dat in geval van een locaal recidief of tweede primaire tumor, behandeling van de hals uit andere halslevels zal moeten bestaan dan in de oorspronkelijke situatie verwacht mag worden. In **hoofdstuk 4** is een prospectieve observationele studie uitgevoerd om de klinische toepassing van SNB bij 22 patiënten met mondholte- of orofarynxcarcinoom en een eerder behandelde hals te onderzoeken.

Bij 4/22 (18%) van de patiënten was uitsluitend de contralaterale hals eerder behandeld. Bij alle 4 de patiënten konden SNs worden geïdentificeerd, onverwachte lymfedrainage werd gezien in 25% van de patiënten en 75% had een lymfkliermetastase in de SN. Bij 18/22 (82%) van de patiënten was de ipsilaterale hals of de hals beiderzijds eerder behandeld. Van deze patiënten was de SN detectie waarde 83%. Bij 7% werd een lymfkliermetastase gevonden en 67% had onverwachte lymfedrainage patronen. De mediane follow-up was 22 maanden. Regionale tumor controle en negatief voorspellende waarde waren beide 100%.

Conclusies uit deze studie waren dat SNB uitvoerbaar en nauwkeurig is bij patiënten met mondholte- en orofarynxcarcinoom en eerder behandelde hals, en tot excellente regionale tumor controle leidt. Met SNB worden individuele lymfedrainage patronen in kaart gebracht die afwijkend van normaal kunnen zijn vanwege eerdere behandeling van de hals.

Beeldvormende diagnostiek moet nuttig en efficiënt zijn. In **hoofdstuk 5** werd de klinisch toegevoegde waarde van een late fase lymfoscintigram geëvalueerd. Van 60 patiënten met cT1-T2N0 mondholtecarcinoom werden in retrospectieve opzet de lymfoscintigrafische scans van zowel de vroege (direct na injectie van ^{99m}Tc-nanocoll) als late fase (2-4 uur na injectie) beoordeeld. Foci zichtbaar op de late fase scans werden als volgt gecategoriseerd: (a) geen additionele foci zichtbaar die als SNs kunnen worden beschouwd; (b) additionele foci zichtbaar die als SNs kunnen worden beschouwd; (c) foci alleen zichtbaar op late fase scan. De histopathologische resultaten van de chirurgisch verwijderde SNs werden gekoppeld aan de corresponderende foci.

Bij alle 60 patiënten kon een zichtbaar focus op het lymfoscintigram worden geïdentificeerd als SN. Met de vroege fase scan kon in 51/60 (85%) van de patiënten tenminste één focus worden gevisualiseerd, terwijl bij 9/60 (15%) uitsluitend op de late fase scan een focus zichtbaar was. Van deze laatste 9 patiënten bleek het mondholte carcinoom niet in de mobiele tong of mondbodem gelokaliseerd te zijn. Bij patiënten met paramediane en op de middellijn gelegen tumoren werd in de meerderheid (83%) bilaterale lymfedrainage gezien, waarbij dit in de helft van de gevallen uitsluitend op de late fase scan zichtbaar was. Bij 14/51 (27%) patiënten toonde het late fase lymfoscintigram additionele foci die als SN werden beschouwd, waardoor de chirurgische procedure uitgebreider werd met verwijdering van meer SNs. In deze additionele zichtbare foci werden met histopathologisch onderzoek geen lymfkliermetastasen gevonden. Deze additioneel verwijderde SNs bleken dus klinisch niet relevant, aangezien in die patiënten alle SNs die reeds met de vroege fase scan zichtbaar waren, de hals correct hadden gestadieerd.

De resultaten van deze studie impliceren dat een additionele late fase lymfoscintigram uitsluitend nuttig is bij patiënten met een mondholtecarcinoom met andere lokalisatie dan de mobiele tong of mondbodem en bij patiënten met paramediane en over de middellijn gelegen tumoren.

Adequate interpretatie van het zichtbare lymfedrainage patroon is een essentiële stap in de SNB procedure. Bij het mondholtecarcinoom kan identificatie van de SN een uitdaging zijn wanneer meerdere foci zichtbaar zijn op het lymfoscintigram. In **hoofdstuk 6** werd de interpretatie van lymfoscintigrafische beeldvorming geanalyseerd. Om de SNB procedure accuraat maar minimaal invasief te houden, is kritische interpretatie van het lymfoscintigram van groot belang met het onderscheiden van eerste echelon lymfeklieren met ware SNs en tweede echelon lymfeklieren. We voerden een interobserver studie uit om de interobserver variabiliteit te onderzoeken van lymfoscintigrafische scans beoordelen met identificatie van SNs.

Zestien observers (hoofd-halschirurgen, nucleair geneeskundigen of teams van beide) uit verschillende Europese instituten werden gevraagd om de lymfoscintigrammen van 9 patiënten met in totaal 47 zichtbare foci (3-9 per patiënt) te beoordelen en SNs te identificeren volgens een schaal met drie opties 'ja/twijfel/nee'. De interobserver variabiliteit werd berekend met kappa (κ) analyse en lineair gewogen paarsgewijze vergelijking van de observers. Zowel een conservatieve (twijfel geïnterpreteerd als nee) als een sensitieve (twijfel geïnterpreteerd als ja) strategie werden geanalyseerd met paarsgewijze kappa analyse.

De interobserver variabiliteit van alle casus met gebruikmaking van een 3-puntsschaal leverde een matige overeenkomst (71%, κ_w = 0,29). Zowel de conservatieve als de sensitieve analyse leverden een gemiddelde overeenkomst: conservatief κ = 0,44 (in 80% van de foci oordeelden de observers overeenkomstig)en sensitief 81%, κ = 0,42 (81% overeenkomstig). De aanwezigheid van meerdere zichtbare foci en bilaterale lymfedrainage op het lymfoscintigram resulteerde in een lagere overeenkomst, terwijl interpretatie door multidisciplaire observers (team) en meer ervaren observers tot een grotere overeenkomst leidde.

Met de resultaten van deze studie kan worden geconcludeerd dat er tussen observers variatie bestaat bij de interpretatie van lymfoscintigrafische beelden met een gemiddelde overeenkomst (agreement). Om de interobserver agreement te kunnen verbeteren zijn specifieke richtlijnen voor interpretatie nodig.

SNB is van klinische waarde bij de detectie van occulte lymfkliermetastasen in mondholte- en orofarynxcarcinomen, maar bij andere tumoren in het hoofd-halsgebied is de toepassing van SNB nog in een onderzoeksfase. Bij patiënten met een larynxcarcinoom en cN0 hals die een totale laryngectomie zullen ondergaan, wordt meestal beiderzijds een electieve halsklierdissectie uitgevoerd. Gebaseerd op het risico op occulte lymfkliermetastasen is de beslissing om een electieve halsklierdissectie uit te voeren niet gemakkelijk. In **hoofdstuk 7** is de uitvoerbaarheid van SN detectie en de potentiele accuratesse van SNB onderzocht bij patiënten met cN0 larynxcarcinoom gepland voor totale laryngectomie en beiderzijds electieve halsklierdissectie. Bij aanvang van de operatie werd endoscopisch 40 MBq ^{99m}Tc-nanocoll peritumoraal geïnjecteerd. Er werd geen lymfoscintigram gemaakt. De operatie werd uitgevoerd, en ex vivo werden met een gamma probe in het resectiepreparaat de SNs geïdentificeerd en vervolgens gemarkeerd. Deze SNs werden uitvoering histopathologisch onderzocht. De uitslag van histopathologisch onderzoek van de gehele halsklierdissectie diende als referentiestandaard.

Er werden 19 patiënten geïncludeerd, bij 13 patiënten was de hals niet eerder behandeld geweest, bij de andere 6 patiënten wel. SNs konden succesvol worden geïdentificeerd in

68,4% (13/19) van de patiënten en het identificatiepercentage was significant beter bij patiënten zonder eerder behandelde hals (92,3% versus 16,7%, $p < 0{,}01$). Bij 4/13 (30,7%) patiënten met geïdentificeerde SNs werd een lymfkliermetastase in de SN gevonden. De sensitiviteit en negatief voorspellende waarde van SNB waren respectievelijk 80,0% en 87,5%.

Deze studie toonde aan dat identificatie van de SN uitvoerbaar is tijdens laryngectomie bij patiënten met een larynxcarcinoom zonder eerdere behandeling van de hals. Er zijn meer studies nodig om het nut en de accuratesse van SNB bij een totale laryngectomie te onderzoeken.

Gezondheid gerelateerde kwaliteit van leven en psychologische aspecten van een behandeling krijgen steeds meer aandacht in het zorgproces. Van de studie in **hoofdstuk 8** was het primaire doel om prospectief de impact van een SNB gebaseerde behandelstrategie (observatie indien SNB negatief (SNB-) en aanvullende halsklierdissectie indien SNB positief (SNB+)) bij patiënten met cT1-T2N0 mondholtecarcinoom te evalueren in termen van kwaliteit van leven, psychische belasting en schouder functie gedurende de periode vanaf diagnose tot 6 maanden follow-up. Secundaire doelen waren evaluatie van de schouderfunctie na 2 jaar follow-up en evaluatie van het patiënten perspectief ten aanzien van behandeling van de cN0 hals: voorkeur voor een electieve halsklierdissectie (END) of een op SNB gebaseerde strategie.

Alle 52 patiënten (39 SNB-, 13 SNB+) vulden de volgende vragenlijsten in op vaste meetpunten (baseline, na diagnose SNB, en na 6 maanden follow-up): EORTC QLQ-C30 (quality of life-cancer module), QLQ-H&N35 (quality of life-head and neck cancer module), HADS (hospital anxiety and depression scale), IES (impact of event scale) en SDQ (shoulder disability questionnaire). Objectieve schouderfunctie testen werden na 2 jaar follow-up uitgevoerd. Interviews betreffende het patiënten perspectief werden uitgevoerd na 4,5 maand follow-up.

De uitkomsten van de vragenlijsten QLQ-C30, QLQ-H&N35, HADS, IES en SDQ gedurende de verschillende metingen in de tijd waren niet significant verschillend tussen SNB- en SNB+ patiënten. Met de IES werd in beide groepen geen verhoogd risico op piekeren of vermijding gevonden. Schouderklachten waren na 6 maanden follow-up significant hoger, maar herstelden weer na 2 jaar follow-up. Objectieve schoudermetingen gedurende late follow-up toonden geen verschil tussen SNB- en SNB+ patiënten, maar SNB+ patiënten ervaarden wel vaker een verdoofd gevoel in de hals. De meeste patiënten prefereerden een SNB gebaseerde behandelstrategie boven END.

Met deze studie werd geconcludeerd dat de impact van het ondergaan van een SNB gebaseerde behandelstrategie bij het cT1-T2 mondholtecarcinoom vergelijkbaar is voor SNB- en SNB+ patiënten in termen van kwaliteit van leven, psychische belasting en schouderfunctie. De meeste patiënten verkiezen een SNB gebaseerde behandelstrategie boven END.

In **hoofdstuk 9** is een studie naar kosteneffectiviteit uitgevoerd. Wanneer een nieuwe behandelstrategie is ontwikkeld en is voorgesteld als standaard methode, dan is deze bij voorkeur kosteneffectief ten opzichte van voorgaande behandelstrategieën. Een model was vervaardigd om de kosteneffectiviteit te berekenen van verschillende behandelstrategieën ter detectie van occulte lymfekliermetastasen bij het cT1-T2 mondholtecarcinoom. Een beslisboom gevolgd door Markov model werd ontwikkeld om de kosteneffectiviteit van de volgende strategieën te vergelijken: (a) USgFNAC, (b) SNB, (c) USgFNAC en indien negatief, SNB, en (d) END. Data van 62 patiënten werden verzameld vanuit vier Nederlandse ziekenhuizen. Utiliteiten werden bepaald middels de EQ-5D vragenlijst en data werden verkregen uit de medische dossiers. Kosten werden berekend vanuit ziekenhuisperspectief (tarieven 2015 Euro's). De cyclusduur was 1 jaar, met extrapolatie naar tijdshorizonnen van 5 jaar, 10 jaar en levenslang. Onzekerheid werd onderzocht met scenarioanalyses en probabilistische gevoeligheidsanalyses.

Met een 5- en 10-jaar tijdshorizon, heeft SNB het hoogste aantal additionele 'quality-adjusted life years' (QALYs, 0,12 en 0,26, respectievelijk) tegenover de laagste additionele kosten (€ 56 en € 74, respectievelijk) vergeleken met strategie (a) (USgFNAC). Met een levenslang tijdshorizon heeft END het hoogste aantal additionele QALYs (0,55) tegenover additionele kosten van € 1.626 per gewonnen QALY vergeleken met USgFNAC. Met veranderen van aannames, in de duur van de (dis)utiliteiten (≥ 5 jaar) of verbetering van de sensitiviteit van SNB (≥ 3%), blijkt SNB de gunstigste strategie voor elke tijdshorizon te zijn.

De resultaten van deze studie laten zien dat SNB kosteneffectief is bij patiënten met cT1-T2N0 mondholtecarcinoom. SNB kan de optimale strategie voor alle tijdshorizonnen zijn wanneer de sensitiviteit enkele percentages hoger ligt dan in deze studie.

CHAPTER 13

List of publications

LIST OF PUBLICATIONS

Patients' perspective on the impact of sentinel node biopsy in oral cancer treatment.
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CHAPTER 14

Dankwoord

&

Curriculum vitae auctoris

DANKWOORD

Dit proefschrift is tot stand gekomen in samenwerking met vele anderen, waarvoor mijn grote dank. In het bijzonder wil ik noemen:

Prof. dr. R. de Bree, beste Remco, aan jou dank ik het meest. Dankjewel voor je begeleiding van begin tot het einde. Je bent een doorzetter pur sang met een extreem uithoudingsvermogen, eentje die zich vastbijt en niet loslaat. Ik heb veel van je geleerd, je hebt me steeds gemotiveerd de voortgang erin te houden, me soms gevraagd tot uitersten te gaan. Dat ging niet altijd zonder slag of stoot, maar zoals jij weet, en ik ook, een duursporter stopt niet tot de finish is gehaald. Ik deel je liefde voor het sporten. Mijn promotietraject noemde ik wel eens de ultieme duursport. Dank voor je onuitputtelijke motivatie.

Prof. dr. C.R. Leemans, beste René, bedankt voor de mogelijkheid die je mij geboden hebt zowel mijn promotieonderzoek als de opleiding tot KNO-arts te volbrengen aan je kliniek. Bedankt voor je begeleiding bij het lezen van vele manuscripten.

Prof. dr. E. Bloemena, beste Elisabeth, met jou en Remco vormden wij de Nederlandse drie-eenheid binnen de Europese SENT trial. Wij troffen elkaar daarom geregeld op buitenlandse meetings en dat was met genoegen. Zowel voor de Nederlandse SNUS studie als de Europese SENT heb jij ongelofelijk veel werk verzet en ben je bijzonder betrokken geweest. Zonder jouw inzet had mijn onderzoek niet kunnen gloriëren. Bedankt!

Geachte leden van de leescommissie, prof. dr. E. Bloemena, beste Elisabeth, prof. dr. M.W.M. van den Brekel, beste Michiel, prof. dr. O.S. Hoekstra, beste Otto, dr. M.J.H. Witjes, beste Max, dr. R. Valdés Olmos, beste Renato, dank jullie wel dat jullie zitting wilden nemen in de lees- en promotiecommissie.

Heren dr. W.M.C. Klop, dr. R.J.J. van Es en dr. K.P. Schepman, beste Martin, Robert en Kees-Pieter, jullie gingen met ons in zee door te participeren in de Nederlandse SNUS studie. De samenwerking verliep soepel. Bedankt voor de inclusie van patiënten en dank voor jullie begeleiding op afstand. We hebben een mooi resultaat bereikt!

Prof. dr. O. Hoekstra, beste Otto, research is je op het lijf geschreven. Ging een manuscript jouw kant op, dan vreesde je voor de feedback. Die was niet gering en supernuttig, wat maakte dat je de tijdrovende verbeteringen niet kon overslaan. Sterker nog, manuscripten werden er beter van! Bedankt voor je betrokkenheid en je toegankelijkheid voor overleg en uitleg.

Drs. A. van Schie, beste Annelies, dankjewel voor je tijd en opgewekte betrokkenheid. Je kwam met praktische en nuttige suggesties, overleg met jou was positief en plezierig.

Prof. dr. J.A. Castelijns, beste Jonas, bedankt voor je medewerking aan de totstandkoming van dit proefschrift. Je was immer geïnteresseerd in de voortgang en voor een extra patiënt voor echo onderzoek was altijd nog plek. Dankjewel.

Prof. dr. I. van der Waal, beste Isaäc, u was vooral betrokken bij de eerste periode van mijn promotieonderzoek. Ik heb uw blijvende interesse in het onderzoek en de voortgang zeer gewaardeerd. Bedankt voor uw support!

Prof. dr. I.M. Verdonck-de Leeuw, beste Irma, jij begeleidde het psychosociale deel van mijn onderzoeksproject. Je bijdrage aan het artikel over kwaliteit van leven en het patiëntenperspectief middels interviews die jij uitvoerde, was absoluut onmisbaar. Dankjewel voor je hulp.

Prof. dr. C.A. Uyl-de Groot, beste Carin, jouw aandeel betrof de kosteneffectiviteitsanalyse. We hebben door de jaren heen geregeld contact gehad en dit heeft geleid tot een mooie publicatie. Dankjewel voor je hulp.

Naomi van der Linden, dankjewel voor jouw bijdrage aan de studie naar kosteneffectiviteit. Ik voorzag de data, jij de analyse. We hebben elkaar nooit ontmoet, maar des te meer emailcontact. De publicatie is een prachtig resultaat geworden. Het ga je goed Down-under!

Prof. dr. S.J. Stöckli, dear Sandro, thank you for our pleasant cooperation. We published a very interesting article by putting our patients series together. My visit to your Hals-Nasen-Ohrenklinik was a great experience during my residency and remains a good memory. I enjoyed our versatile conversations at the many meetings.

M.A. Broglie, dear Martina, we had a lot of contact during the setup of our joint article. Seeing you at the SENT meetings and in Sankt Gallen was a pleasure.

C. Schilling, dear Clare, thank you for all your efforts in the SENT trial. The many interim analyses and updated results that you created during all those years is amazing. Thanks for enjoyable meetings.

Prof. dr. M. McGurk, dear Mark, as the pioneer of the European SENT trial I thank you for your efforts. The results so far are excellent and there is more to come.

All members of the SENT trial, thank you for the very pleasant cooperation. Sharing our experiences in patient care and SN research is inspiring. Thank you for your participation in the interobserver study and for enabling all interesting international meetings.

Heren van de sectie KNO-tumorbiologie, als beginnende arts-onderzoeker spring je enigszins in het wetenschaps-diepe. Het helpt om deel uit te maken van een researchgroep te midden van biologen, chemici en analisten.

Prof. dr. R.H. Brakenhoff, beste Ruud, hoewel mijn klinische studies weinig van doen hadden met het laboratorium, voelde je je betrokken bij mijn onderzoek en was je een motivator. Dank voor je hulp bij de totstandkoming van het eerste artikel en voor je morele steun. Het door mij intensief verzamelde paraffine materiaal en de bewerkte samples in de vriezer kunnen denk ik inmiddels wel weg.

Dr. B.M.J. Braakhuis, beste Boudewijn, jouw hulp was veelzijdig. Liep jij binnen voor koffie, dan kwam er een nuttige suggestie voort uit het gesprek: aanpak van een studieopzet, opbouw van een database, keuze voor statistische methode of aanvraag bij de medisch ethische commissie. Jij gaf op het juiste moment de juiste adviezen. Dankjewel voor het delen van je kennis en kunde. Het ga je goed in Frankrijk!

Prof. dr. G.A.M.S. van Dongen, beste Guus, qua wetenschap hebben wij nauwelijks samengewerkt maar als motivator heb je wel een rol gespeeld. Ik bewonder je carrièrepad, en nog meer je oprechte interesse in de persoon achter diens functie. Dankjewel voor de inspirerende contactmomenten. Ik waardeer je aanwezigheid tijdens mijn verdediging.

Hoofd-halschirurgen Simone Eerenstein, Stijn van Weert en Hakki Karagozoglu, dank voor de prettige samenwerking, voor jullie betrokkenheid en voor het includeren en opereren van patiënten in verschillende klinische studies.

Joop Kuik, dank voor je statistische begeleiding in het eerste uur. Het was een plezier om statistiek of SPSS les van je te krijgen. Je afscheidsborrel in de Volkstuin van Oud-Sloten hebben Lisa en ik met genoegen bezocht.

Birgit Witte, dank voor al je hulp bij de statistiek. Ik kon laagdrempelig bij je terecht, waarna ik met nieuwe motivatie verder kon, dank daarvoor. Dat we elkaar tegenkwamen op de Weissensee afgelopen jaar waar jij notabene Nederlands Kampioen geworden bent, is een geweldige herinnering!

Ton Houffelaar en Jacqueline Geskus, bedankt voor jullie technische, kunstmatig intelligente en mentale ondersteuning!

Hans Borgstein, dankjewel voor het nalezen en corrigeren van verschillende Engelse teksten.

Mijn promotieonderzoek betrof voor het grootste deel klinische patiëntgebonden studies waarbij vele disciplines betrokken waren: afdelingen KNO-heelkunde/hoofdhalschirurgie, Mond- Kaak en Aangezichtschirurgie, Nucleaire Geneeskunde en Radiologie, Pathologie en het Operatiecomplex. Veel dank voor de prettige samenwerking en medewerking aan verpleegkundig personeel afdeling 1C, verplegend en administratief personeel polikliniek KNO, Trudi Limpens, secretariaat Vanessa, Gerrie, Marjon en Boukje. MNW-ers, hotlab en balie medewerkers afdeling Nucleaire Geneeskunde, in het bijzonder Arthur van Lingen, Saskia Cornielje, Ton de Vries en Henri Greuter. Medewerkers afdeling Radiologie. Medewerkers afdeling Pathologie en Cytologie. Operatie assistenten, Arris Schuurkamp in het bijzonder.

Lieve collegae AIOS, bedankt voor jullie collegiale gezelligheid. Een opleiding kun je niet alleen, al is het maar dat je niet in je eentje een anonieme Direct of SetQ kunt invullen. De opleidingstijd komt nooit meer terug, jammer, ik zou me graag nog even omringen met jullie vertrouwde warmte.
Lieve Anne Marijn, Thadé, Willem en Eveline, collegae van het eerste uur KNO-opleiding. Goede herinneringen heb ik aan onze etentjes met de Pink Ladies, de 'beste mensen' kerstkaart op het ijs, slapen in een bizarre B&B in Leiden en een onvergetelijke KNO-skitrip!

Mijn collegae onderzoekers bij de KNO-tumorbiologie, kamergenoten op kamer 125, d'overkant van de patio, in het CCA-gebouw of in het RNC: Bernard Tijink, Lisa van der Putten, Peggy Graveland, Lars Perk, Tieneke Schaaij-Visser, Hester van Zeeburg, Frederieke Dijk, Sanne Martens-de Kemp, Marlon Lindenbergh-van der Plas, Maria Vosjan, Derrek Heuveling, Anne-Marie Krebber, Annette van Nieuwenhuizen, Ruth Cohen, Danielle Vugts, Charlotte Schouten, Sara Hakim, Michelle Rietbergen, Remco Nagel, Laura Korsten, Steven Mes, Jeroen Kraak. Artsen-onderzoeksstage: Mark Tenhagen, Inne den Toom, Thomas Peters. Analisten: Arjen Brink, Marijke Buijze, Marijke Stigter van Walsem, Michiel de Maaker, Tijs Wu. Dank voor jullie gezelligheid, de koffiemomenten en het delen van kennis en promotiewetenswaardigheden.

Mark Tenhagen, jouw onderwerp voor wetenschappelijke stage overlapte met mijn retrospectieve studie. Samen hebben we heel, heel veel dossiers doorgenomen en uren gespendeerd in het medisch archief. Je inzet was groot, net als je enthousiasme. Dankjewel voor je hulp. Veel succes in je carrière als chirurg.

Inne den Toom, jij bent min of meer Derreks en mijn sentinel node telg. Een mooi artikel heb je gepubliceerd uit de data die op de plank lag. Een aantal andere artikelen ligt in het verschiet. Ik wens je veel succes in je carrière!

Lisa van der Putten, lieve Lisa, jij bent een speciale onderzoekscollega, en ook een paranimf. Tijdens de KNO-opleiding hebben wij vele avonden doorgehaald om voortgang in het onderzoek te houden onder het motto gedeelde smart is halve en de aanhouder wint. Dankjewel voor de-moed-erin-houden, de introductie van Joling&Jandino, en voor alle gezelligheid. Jouw verdediging nadert met rasse schreden, succes!

Peggy Graveland, paranimf, lieve Pek, we konden goed met elkaar overweg, en onze studies gingen heel goed samen: jij had tumorsamples, beenmerg en bloed nodig, ik de lymfklieren. Bij afwezigheid van de een kon de ander de studie voortzetten. Was het daarom dat mensen ons door elkaar haalden, jij Jut, ik Jul? Dank voor je gezelligheid, de introductie van en verslaving aan het Nederlandse lied en je rustgevende vissen. Ik heb een toptijd met je gehad!

Derrek Heuveling, paranimf, lieve Derrek, sentinel node is onze middle name, en zo delen wij een niet-bloedverwante familienaam. Wij zagen markt voor de sentinel node op allerlei gebieden. Jij had een hoger tempo met je onderzoek en jouw verdediging is dan ook een voorbeeld voor hoe ik de mijne zal gaan doen. Dank voor het delen van ups en downs, van kennis inclusief de niet-nuttige, en voor het plezier!

Als tegenhanger van de mentale inspanning, zocht ik fysieke uitdaging. Alpe d'HuZes 2013 voor KWF kankerbestrijding en de Amsterdam Marathon 2012 namens VUmc Cancer Center Amsterdam staan met een glimlach in mijn geheugen. Dank voor alle donaties en sportieve support!

Rasechte Skuldantes, Senaat, oud-hockeyteamgenootjes en liefhebbende vrienden, dank dat jullie er zijn.
Mijn lieve Zeeuwse vriendinnen Marit, Loes en Marika, lieve Maartje, lieve Carolien dank jullie voor het delen wat onze band tot vriendschap maakt, samen lachen, relativeren en vriendinnenliefde.

Lieve Leonie, Peter, en Philip Jan! Dank voor jullie steun en Lee, voor je meelevende adviezen. Natuurlijk mag PJ komen logeren.

Lieve Philipp Jan, Kim en Beaudine! Jullie vormen een klankbord. Dank voor jullie vertrouwen. Tot gauw, hoog tijd voor speelpartijtjes met Beau.

Mijn lieve ouders, jullie deelden mijn blijdschap bij elke publicatie die was gelukt en leefden mee bij tegenvallende momenten. Lieve papa en mama, dank voor jullie onuitputtelijke bemoediging.

Het is volbracht, het is af, opluchting, blijdschap en trots!
De voldoening is oneindig.

CURRICULUM VITAE AUCTORIS

Géke Flach werd op 5 oktober 1980 geboren in Renesse op Schouwen-Duiveland. In 1998 behaalde zij haar Atheneum diploma aan het Buys Ballot College te Goes.

In het studiejaar 1998-1999 studeerde zij medische biologie aan de Vrije Universiteit Amsterdam en behaalde zij haar propedeuse. Van 1999 tot 2007 studeerde zij geneeskunde aan de medische faculteit van het VU medisch centrum. In 2002-2003 was zij lid van de senaat van het studentencorps aan de Vrije Universiteit/LANX. Tijdens haar laatste studiejaar volgde zij een keuze co-schap KNO-heelkunde in het Grote Schuur Hospitaal te Kaapstad bij prof. dr. J. Fagan, waarna zij het artsexamen behaalde in mei 2007.

Per juni 2007 ving haar promotieonderzoek aan onder begeleiding van prof. dr. R. de Bree, waarvan de resultaten in dit proefschrift beschreven staan. Ze was ruim 3 jaar werkzaam als arts-onderzoeker bij de sectie Tumorbiologie van de afdeling KNO-heelkunde/Hoofd-halschirurgie in het VU medisch centrum. In dezelfde periode begeleidde zij als mentor een groep geneeskundestudenten bij hun bacheloropleiding.

In oktober 2010 startte zij met de opleiding Keel-Neus-Oorheelkunde in het VU medisch centrum onder prof. dr. C.R. Leemans. Tijdens het laatste jaar van haar opleiding volgde zij een stage rhinologie, rhinoplastiek en aangezichtschirurgie bij PD. dr. A.J. Tasman, in de Hals-Nasen-Ohrenklinik van prof. dr. S.J. Stöckli in het Kantonsspital te Sankt Gallen, Zwitserland. In augustus 2015 werd zij als Keel-, Neus en Oorarts ingeschreven in het register van het College Geneeskundige Specialismen (CGS).

Momenteel is zij werkzaam als KNO-arts, chef de clinique, bij het zelfstandig behandelcentrum De Vijf Meren Kliniek in samenwerking met het Spaarne Gasthuis, op lokaties te Hoofddorp en Haarlem.

Géke Flach is een enthousiaste sportliefhebber. Ze heeft veel gehockeyd en enkele jaren het VUmc bedrijfshockey damesteam aangevoerd. Buiten haar werk heeft ze een grote liefde voor duursporten als hardlopen, wielrennen, triathlon en schaatsen, en ligt haar hart in de Alpen bij het toerskiën.