



Lymphoscintigraphy for Sentinel Node Mapping in Head and Neck Cancer

Andrea Skanjeti, Anthony Dhomps, Cristina Paschetta, Jérémie Tordo, Roberto C. Delgado Bolton, Francesco Giammarile

► To cite this version:

Andrea Skanjeti, Anthony Dhomps, Cristina Paschetta, Jérémie Tordo, Roberto C. Delgado Bolton, et al.. Lymphoscintigraphy for Sentinel Node Mapping in Head and Neck Cancer. *Seminars in Nuclear Medicine*, 2021, 51, pp.39 - 49. <10.1053/j.semnuclmed.2020.07.004>. <hal-03492889>

HAL Id: hal-03492889

<https://hal.science/hal-03492889v1>

Submitted on 15 Dec 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons CC BY-NC 4.0 - Attribution - Non-commercial use - International License

Lymphoscintigraphy for Sentinel Node Mapping in Head and Neck Cancer

**Andrea Skanjeti¹, Anthony Dhomps², Cristina Paschetta³, Jérémie Tordo²,
Roberto C. Delgado Bolton⁴, Francesco Giammarile^{5,6,*}.**

- 1) Nuclear Medicine Department, Hospices Civils de Lyon and Université Claude Bernard Lyon 1, Lyon, France
- 2) Nuclear Medicine Department, Hospices Civils de Lyon, Lyon, France
- 3) IZOTOPCENTRUM, Nitra, Slovakia
- 4) Department of Diagnostic Imaging (Radiology) and Nuclear Medicine, University Hospital San Pedro and Centre for Biomedical Research of La Rioja (CIBIR), Logroño, La Rioja, Spain
- 5) Nuclear Medicine and Diagnostic Imaging Section, International Atomic Energy Agency (IAEA), Vienna, Austria
- 6) Centre Léon Bérard, Lyon, France

* Corresponding author: Francesco Giammarile / Email: F.Giammarile@iaea.org

ORCID IDs

FG: [ORCID ID: orcid.org/0000-0002-0550-7893]

RCDB: [ORCID ID: orcid.org/0000-0002-8071-6513]

Abstract

The aim of this comprehensive review is to describe and analyze the role of the sentinel node mapping in Head and Neck Cancers. For this purpose, head and neck neoplasms have been categorized in cutaneous malignancies and neoplasms of the upper aerodigestive tract. A concise description of lymphatic drainage will be the “prelude” for each section, as well as the description of the injection techniques, when specific. Concisely, the attention has been focused on detection rate of the sentinel node by lymphoscintigraphy for each cancer, and for those patients in which the sentinel lymph node has been identified, true positives rates, false negative rates and overall accuracy has been pointed out.

Overall, in cutaneous neoplasms of the head and neck, the detection rate is higher than 90%, however the false negative rate is still an issue, in particular in melanoma, inducing the need for newer developments. In fact, new tracers and techniques are already available, while prospective multicenter trials exploring the outcome impact are needed in the near future.

For the upper aerodigestive tract and in particular oral cavity and oropharynx, sentinel lymph node identification by lymphoscintigraphy allows avoiding unnecessary neck dissection and/or node irradiation. Even in this case, the main limit remains the risk of false negative rates. While, for patients affected by laryngeal and hypopharyngeal cancers the data seems very limited and, although the feasibility has been demonstrated, performances of this lymphoscintigraphy still need to be confirmed by multicenter studies.

Sentinel lymph node mapping in cutaneous cancers

Melanoma

Cutaneous melanoma is a malignant tumor of neural crest-derived cutaneous melanocytes [1]. The incidence of this neoplasm has increased rapidly over the past 30 years in most part of the world. Although melanoma only accounts for 1% of skin cancers, it is responsible for the majority of skin cancer deaths [2]. Up to 25% of these tumors are located in the Head and Neck (H&N) [3] and they have a worse prognosis compared with melanomas of other sites. The 10-year survival rate associated with H&N melanoma is approximately 60%, while the mortality rate increases to 70%, 80% and 90% in melanomas of the ear, face and eyelid, respectively [4].

In the last years, preventive care for skin cancers has been intensified, increasing proportion of shallow tumors among the newly diagnosed melanomas [5]. As reported in several studies at the time of diagnosis, approximately 85% of patients with H&N melanoma have localized disease, 10% have regional disease and 5% have systemic disease [6].

Since metastases occur in only 20% of all cases, complete lymph node dissection as a diagnostic procedure has become obsolete and unnecessary, representing an overtreatment in 80% of the patients [5]. Nevertheless, according to the Multicenter Selective Lymphadenectomy Trial I (MSLT-I), the sentinel node status is the strongest prognostic factor in patients with localized melanoma and has become the standard of care, in particular in those patients with intermediate-thickness melanomas. In fact, Morton first described sentinel node biopsy (SLNB) for staging cutaneous melanoma since 1992 [7]. According to the EANM Practice Guidelines for Lymphoscintigraphy and Sentinel Lymph Node Biopsy in Melanoma [8], sentinel lymph nodes (SLNs) are identified preoperatively by completely intradermal injection of ^{99m}Tc labelled sulphur colloid, nanocolloid or antimony trisulfide

around the melanoma site (4 to 6 deposits; total volume 0.4 ml). It has been shown that in case of injection into the subcutaneous tissue the colloid is not transported into the dermal lymphatic vessels and subsequently even to the SLN [9]. Anterior and lateral dynamic two-dimensional (2D) planar lymphoscintigraphy is performed during the first 10 minutes after injection by using a dual head gamma camera in the attempt to locate the sentinel node [10, 11]. If no immediate drainage is seen, images are acquired every 20 minutes for up to 2 hours after injection with the aim to capture any delayed drainage patterns [8, 9].

During surgery, in order to identify the SLN, 0.5-1 mL of isosulfan blue or methylene blue is injected intradermally surrounding the primary tumor or prior biopsy site. Intraoperatively, a sentinel lymph node is defined as a lymph node that accumulates blue-tracer or presents blue channels entering in it. Additionally, there are also considered as SLNs those radioactive lymph nodes that have count greater than 10% of the most radioactive or clinically suspicious lymph nodes [12].

The concept that the sentinel node is not simply the node closest to the primary lesion is especially true in the H&N regions, where the lymphatic drainage is very complex. Despite this, several commonly noted patterns of lymphatic drainage occur [13]. In particular, lesions of the forehead, upper face and lower face usually metastasize to the parotid nodes and cervical levels I to III, lesions of the coronal scalp and peri-auricular regions drain to the parotid and cervical levels II to V, while lesions of the posterior scalp more often drain to the suboccipital nodes and cervical levels II to V [14]. Anyway, on lymphoscintigraphy, aberrant drainage patterns, defined as drainage not predicted by classical lymphatic drainage patterns, are typically seen in 24-70% of H&N melanomas, while multiple draining nodal basins are seen in approximately 50% of melanomas of these regions [9]. Overall, Passmore-Webb et al. described a unilateral drainage in 93.1% of cases, a bilateral drainage in 3.9% and a contralateral one in only 2.9% [15].

The clinical impact of preoperative lymphoscintigraphy has been widely described in particular for the detection rate (DR) and false negative sentinel nodes. A systemic review shows that in H&N melanomas there is a high identification rate of the SLN (93.4% - range 64.8-100%) by scintigraphy [16]. Similar data are observed (94.7-99.4%) in more recent and larger studies, or in patients with greater mean Breslow depth, or with a greater proportion of ulcerated tumors or with ocular adnexal melanoma [10, 11, 16-18], Fig 1. In H&N melanomas, compared to melanomas of other regions, a higher false negative rate has been observed, estimated by de Rosa et al. to be 20.4% [16]. Patients with false-negative SLNs have shown a significantly worse overall survival, if compared to those with an initially positive SLN, suggesting that the removal of the correct SLN is crucial for melanoma patients [5]. This higher false negative rate may be attributed to the complex anatomy of these areas, the intricate and multiple lymph drainage pathways and the usually smaller size of lymph nodes, as well as the proximity of sentinel node to site injection [18, 19]. Some studies show that the false negative rate is also associated with male gender [20-22]. This relationship is curious and until now unexplained. Analysis of demographics reveals that approximately 75% of H&N melanomas occur in white male, showing that male gender is an adverse prognostic factor in melanoma [23], but currently it is not clear why this would be related to the accuracy of lymphatic mapping.

Another issue of pre-surgical lymphoscintigraphy is the not observed drainage, in fact, in less than 10%, no lymphatic drainage is seen on preoperative lymphoscintigraphy [24]. According the analyses of Pavri et al. older age and tumor location in the H&N regions are the only tumor- or patient- specific factors showing to be predictive of non-visualization of SLN on preoperative lymphoscintigraphy; in any case, these factors are not related to a decrease in overall survival compared with melanoma-specific survival in a random cohort [9]. Among other risk factors of non-visualization of SLN in H&N melanomas, should also be taken in

account previous surgeries at adjacent sites and destruction of dermal lymphatics by a laser treatment [25].

In cases in which the primary lesion is in close proximity to the drainage, the visualization of SLN can be more difficult, due to background noise, low resolution and the planar nature of traditional planar lymphoscintigraphy. Therefore, for an accurate localization of the SLN in H&N melanoma, several studies have shown increased impact when using SPECT/CT after planar scintigraphy. In fact, SPECT/CT found additional nodal basins in 29.4%-38.1% of patients [18, 26]. The greatest utility of SPECT/CT is demonstrated in parotid/preauricular and level Vb/supraclavicular basin, where SPECT/CT shows an identification rate of SLN in 29.1 and 44%, respectively. In contrast, when drainage occurs in the other areas of the neck (level I-IV, Va and VI), where planar lymphoscintigraphy misses fewer than 5% of nodal basins, SPECT/CT adds very little in the detection of the SLN. Anyway, SPECT/CT changes the location and extent of incision in 81.1 and 45.2% of patients [26], therefore this method should be considered only as a complementary, not a substitute modality of planar lymphoscintigraphy [27].

Recently, newer labelling agents such as indocyanine green (ICG) with near infrared fluorescence imaging in association with ^{99m}Tc nanocolloid have been described, combining the benefits due to the attractive migrational properties of the radiolabeled colloid with the favorable optical imaging features of ICG. In H&N melanomas, this new hybrid tracer shows an increase of intraoperatively DR of SLNs from 88.7% of radiotracer alone to 96.5% after injection of ICG- ^{99m}Tc [15]. Another advantage of this hybrid compound is the long-lasting retention of ICG- ^{99m}Tc in the SLNs, which by only a single injection allows pre-operative SN mapping and intraoperative radiologically guided SLN identification in a similar fashion as its parenteral compound ^{99m}Tc -nanocolloid [2, 10, 28, 29].

Moreover, it has been demonstrated that the detection of SLN can be increased by the administration of ^{99m}Tc -tilmanocept [29]. In fact, this radiotracer is small (7 nm), and targets CD206 mannose-binding receptors of reticuloendothelial cells within lymph nodes [30] with subsequent fast radiotracer clearance from the injection site.

In conclusion, the management of melanoma continues to evolve rapidly and the development of novel radiopharmaceutical tracers, in association with the improvement of technologies and closer cooperation between the nuclear medicine physician and the surgeon represent a great potential for future developments, in particular in order to reduce the false negative rate of lymphoscintigraphy and to increase the detection rate.

Lymphoscintigraphy in patients affected by other cutaneous neoplasms

Merkel Cell Carcinoma

Merkel cell carcinoma (MCC) is a rare and distinct primary neuroendocrine aggressive cutaneous neoplasm, approximately 50% of the lesions appearing in the H&N region [31]. It was first described in 1972 by Toker, who called it a “trabecular carcinoma of the skin” [32]. Interestingly, this disease has been designated under several other names such as: cutaneous apudoma, cutaneous neuroendocrine carcinoma, endocrine carcinoma of the skin, and more [31]. Advanced age, immunosuppression, polyomavirus infection and rheumatoid arthritis seem to be few of the most recognized risk factors [33-35].

Epidemiologic data are variable across different continents. In Europe an incidence rate of 0.13 per 100,000 has been reported [36], while in the USA, the incidence rate was 0.79 per 100,000 [37] and the highest rate was found in Australia, 1.6 per 100,000 [38]. The overall survival is severely impacted by the initial disease dissemination, in fact, clinically apparent nodal disease reduce the overall survival from 40% to 27% compared to clinically occult

nodal disease [39]. Therefore, given the prognostic impact of nodal disease, the NCCN guidelines recommend Sentinel Lymph Node Biopsy in N0 patients clinically or N0 after imaging, because it is considered the most reliable tool to stage subclinical nodal disease [40].

Drainage patterns of H&N lymphatics, injection technique of lymphoscintigraphy in pre-surgery as well as imaging modalities: planar, SPECT/CT or Free Hand are described elsewhere in this paper.

Several studies have explored the role of lymphoscintigraphy in MCC with high or very high detection rate (DR) of the sentinel node [41-45]. Schwartz et al showed a DR of approximately 96%, while showing that lesion size, tumor thickness, mitotic rate, and infiltrative tumor growth were significantly and positively associated with a greater likelihood of a positive Sentinel Lymph Node [41]. The positivity rate (detection of the pathological sentinel node) was estimated to 45.2% in the detected lymph node population. Given the high a priori probability for each patient of their population, the authors recommended Sentinel Lymph Node Biopsy to each MCC patient if no clinical evidence of nodal dissemination was observed [41]. Another study [43], based on single-institution case series and literature-based case-level meta-analysis of 122 MCC patients, showed nodal involvement on 32% of the population. The recurrence rate was significantly higher in patients with positive sentinel node compared to those without nodal involvement and relapse free survival was significantly higher in patients treated by adjuvant nodal therapy compared to those without nodal therapy. Moreover, in patients with negative sentinel node the nodal adjuvant therapy was not related to higher survival, thus, showing the benefit of adjuvant nodal therapy, in positive SLNB [42]. Recently, a systemic review of twenty-nine papers exploring the role of sentinel lymph node biopsy in patients affected by MCC of H&N showed that SLNB was pathological in 30.9%, while nodal recurrence was observed in 10 patients with negative SLNB, implying a false negative rate of 19.2% particularly in MCC of the midline. Thus, the authors recommended

SLNB in eligible clinically nodal negative patients affected by H&N MCC [43]. In fact, it is not clear what eligible patients it implies. Some years ago a paper on more than 300 MCC has shown that patients with tumor size smaller than 10 mm nodal metastasis are quite rare (4%), while in the remaining population (tumor size greater than 10 mm) the rate was significantly higher (24%). Thus, suggesting that the regional nodal evaluation could be avoided in the first group, while was well supported for the second group [46]. Moreover, in negative sentinel node patients, monitoring of the nodal basin seems to be appropriate [47], while in patients with positive sentinel node, local and targeted treatments may control regional disease [48, 49]. However, further prospective and multicenter studies are needed to determine the impact of sentinel lymph node biopsy in disease free and overall survival of patients affected by MCC of the H&N [50].

In conclusion, the exploration of the sentinel node in MCC patients of the H&N seems a promising technique, Fig. 2. Nevertheless, given the rarity of the disease, prospective studies are missing in order to establish its impact in the outcome of these patients, while its feasibility, detection rate, sensitivity and false negative rate seem to be adequate, although from disparate trials.

Cutaneous Squamous Cell Carcinoma

Cutaneous Squamous Cell Carcinoma (cSCC) is the second most common malignancy in humans with variable incidence, from 25/100,000 inhabitants in France to 499/100,000 in Australian men [51-53]. Overall, it accounts for approximately 20% of non-melanoma skin cancers [54] and the most sun-exposed area are the commonest site of disease in particular in H&N regions [53, 54]. Moreover, other well-known risk factors are age and immunosuppression [55, 56]. Outcome after surgery is usually favorable for early stage

diseases, while in presence of high risk features (lesion thickness >4 mm, Clark level of 4 or greater, diameter greater than 2cm ear/lip site, perineal invasion or poorly differentiated histology [57]), regional metastatic dissemination can be observed [58], overall estimated 2-5%[50], with consequent higher mortality rate [59]. Moreover, regional lymph node metastases are related to a significant reduction of disease-free survival, estimated at 7.5% at 5 years, according a recent paper [60]. Consequently, the exploration of regional lymph nodes is of paramount importance to manage the treatment strategy and to increase overall survival in occult nodal disease [59].

Two systematic reviews [61, 62] showed the detection of pathological sentinel lymph nodes biopsies in similar rates, 10-13.5% of patients affected by high risk cSCC with false negative rates of 0-4.7%. Two other recent studies on cSCC showed 93.2-94% of detection rate, 11.6-15.1% of pathological sentinel nodes biopsies and 5.7-7.1% of false positive rate [53-63]. The authors highly recommended sentinel lymph node biopsy in suspected nodal disease in presence of risk factors such as angiolymphatic invasion, perineural invasion and clinical size. Other authors observed a relation between the tumor thickness and the presence of lymph node metastases, thus recommending performing sentinel lymph node biopsy in tumor thickness greater or equal to 5 mm and recommending to consider sentinel lymph node biopsy in tumor thickness greater or equal to 2 mm, in particular when other risk factors are detected [64]. Although these encouraging data, a recent cost-efficacy study concluded that the most cost-effective strategy in patients with H&N cutaneous squamous cell carcinoma is to not perform sentinel lymph node biopsy, regardless of patient's stage [65].

To conclude, in spite of these half-tone data, it seems intuitive to propose a more aggressive local treatment to patients with positive sentinel lymph node biopsy, aiming to improve regional control as well as survival. Thus, the sentinel lymph node biopsy in patients affected

by H&N cutaneous SCC remains a promising asset, paving the way to prospective multicenter studies in order to establish its role in the overall as well as in disease free survival.

Sentinel lymph node mapping in upper aerodigestive tract

Oral cavity and oropharynx cancers

Squamous cell carcinoma of the oral cavity (OCSCC) and the oropharynx (OPSCC) are among the most common cancers worldwide, accounting for more than 447,000 new cases and 228,000 deaths annually, mostly from the oral cavity, representing the eighth most prevalent form of cancer in developed countries [66]. Caused by multiple genetic alterations mostly from tobacco and alcohol exposure [67] OCSCC and OPSCC were historically used synonymously, but in last years it became more evident that they are in fact clinically and pathologically distinct diseases usually arising in separate demographic populations, particularly due to human papillomavirus-associated with OPSCC (p16-positive OPSCCs) [68]. It became essential to identify the site of origin of the tumor, its pattern of spread and behavior and therefore in distinguishing the anatomic subsites and borders of the oral cavity and oropharynx [69] for an adapted care of OCSCC and OPSCC. The oral cavity begins at the mucocutaneous junction of the lips and extends posteriorly, including the alveolar ridge and gums, the anterior two-thirds of the tongue, floor of the mouth, buccal mucosa, retromolar trigone, and hard palate. The oropharynx begins superiorly at the junction of the soft and hard palate and inferiorly at the circumvallate papilla of the tongue. It is bounded superiorly by the lower surface of the soft palate and inferiorly by the anterior surface of the epiglottis. Subsites of the oropharynx include the soft palate, tonsillar pillar, palatine tonsil, base (posterior 1/3) of tongue (BOT) containing the lingual tonsil, valleculae, and oropharyngeal walls. Works on the patterns of lymphatic metastasis demonstrated that oral cavity cancer metastasized mainly

to the cervical levels I to III [70,71] and oropharyngeal cancer mainly to levels II to IV and also in retropharyngeal space that, if involved, is associated with worse overall survival [72]. For patients with OPSCC, HPV/p16 positivity does not influence the distribution of cervical lymph node metastases [73].

Determining the states of cervical lymph nodes (LN) is of paramount importance for staging and so treatment planning because their involvement represents the most important prognostic factor for patients with oral or oropharyngeal SCC [74] as it reduces the 5-year survival rate by 50% [75]. Approximately 20-30% of the patients with early stage I or II have occult cervical metastases (micrometastases) [76] undetectable by current imaging techniques (CT, MRI, PET/CT, US). In 2020, current standard of care still remains to offer an elective neck dissection (END) [77] and/or definitive radiotherapy for patients with early stage cancer [78, 79]. Consequently, if the estimated chance of metastasis exceeds 20-30%, the corollary of this strategy is that up to 70-80% of stage I/II patients are overtreated with an unnecessary neck dissection or a bilateral elective node irradiation (ENI) that can induce important morbidities such as shoulder dysfunction (by spinal accessory nerve injury) or radiation-induced toxicity (mucositis, dysphagia, xerostomia) impairing the patient's quality of life [80-82]. Over the last 2 decades, much work has been undertaken to identify reliable predictors of occult metastases, of which tumor depth appears to be the best available [83]. However, the predictive value of tumor depth and other primary tumor characteristics is still insufficient to negate the need for surgical staging of the cervical node basin [84, 85].

In this context, sentinel lymph node biopsy (SNB) using historically preoperative lymphoscintigraphy and intraoperative gamma probe (with or without blue dye) appear to be a relevant technique for mapping the most likely lymphatic tumor dissemination pathways and thus aid the identification of lymphatic spread in a safety way for patients with early oral

cavity (OCSCC) and oropharynx cancers (OPSCC) staged cT1-T2N0. The current indications of SNB are [86, 87]:

- 1) To stage the ipsilateral/ contralateral cN0 neck patients with early lateralised oral cavity and oropharynx cancers;
- 2) To assess bilateral cN0 neck in primary tumors close to, or crossing, the midline;
- 3) To assess contralateral cN0 neck in primary tumors close to, or crossing, the midline presenting an ipsilateral cN+ neck [88];
- 4) To identify aberrant lymphatic drainage in previously treated neck [89];
- 5) To guide uni- or bilateral elective nodal irradiation [90].

European practice guidelines in medicine nuclear for SNB in early (cN0) oral and oropharyngeal SCC published in 2009 and 2019 [86, 87] recommend the realization of a pre-operative dynamic lymphoscintigraphy (immediately after radiotracer injection) followed by early planar images (shortly after dynamic acquisition) in order to visualize unilateral or bilateral lymphatic pathways and the order of drainage of SLNs. The good positioning requires an adequate anterior hyper-extension of the neck, especially to explore level I. Then, at 60-120 min post-injection, delayed planar images are used to distinguish SLNs from second-echelon lymph nodes (appearing mostly on delayed images) and SPECT-CT acquisition to provide accurate anatomical localization, depth evaluation of SLNs (surgical neck levels) and for identification of more (positive) SLNs [85]. The most common radiotracer used in Europe is ^{99m}Tc labeled nanocolloid. The total activity varies depending on the protocol (40-50 MBq for a one-day protocol and 70-120MBq for a two-day protocol) to ensure a sufficient remaining activity exceeding 10 MBq at the surgery for intra-operative gamma probe. Classically, four superficial peritumoral injections are recommended (in the subepithelium stroma containing high concentration of lymphatic capillaries) at cardinal

points with a distance of 0.1-0.5 cm around the tumor, each syringe containing a total volume of 0.1-0.2 mL diluted with saline solution.

Since first successful radioguided SNB procedures in H&N cancers in the 1993 [91, 92] several studies showed high performance in terms of detection sensitivity and negative predictive value (NPV) [93]. In 2005, Stoeckly et al. pooled data of 379 patients with oral cavity and oropharyngeal SCC from 20 centers and showed a SLN detection rate of 97% (IC 95 88-100%) and NPV of 96% (IC 95 88-100%) [94]. In 2013, another meta-analysis by Govers et al. analyzed 21 studies with 834 patients with oral cancers (508 OCSCC, 131 OPSCC and 195 with unclear localization) and reported a pooled sensitivity of 93% (IC 95 90-95%) and NPV ranging from 88% to 100% [95]. Civantos et al. proved that additional sectioning and immunohistochemistry improve NPV compared to standard histology using routine haematoxylin eosin staining only (96 vs 94%, respectively) [96]. Indeed, SNB has the benefit of reducing the number of LNs by superselecting and allowing more in-depth pathological evaluation only nodes reflecting the tumor lymphatic drainage, avoiding false negatives caused by micrometastasis. But it works if all SLNs are radiolocalized and removed for histologic examination. In 2010, Alkureishi et al. described in a 5-year follow-up European multicenter trial in 134 patients with oral cancer that patients with floor-of-the mouth tumors were associated with lower DR, sensitivity and NPV compared to other tumor sites (88 vs 93%; 80 vs 97% and 88 vs 98%, respectively) due to the radioactive scatter called “shine-through effect” caused by the close proximity between the tumor and the SLN generally localized at IA or IB levels [97]. To correct this, Melkane et al. suggested in 2012 to remove first the primary lesion, which is the highest “hot spot” [98]. Furthermore, another significant limitation of SNB procedure is the learning curve with statistically significant difference in the NPV between experienced surgeons and novice surgeons [99]. In 2017, Liu et al. in the largest meta-analysis with 3566 patients showed high diagnostic accuracy

estimating an hidden disease rate with a negative test result (risk of regional recurrence) of 2.6-3.9%, that is acceptable when considering the serious complications and 70%-80% overtreatment rate in traditional neck dissection procedure.

Although less data is available for oropharyngeal cancers, due to the complexity in the peritumoral injections requiring mostly a procedure under general anesthesia, Thomas et al. demonstrated in 2020 the feasibility and tolerability in a retrospective study with 10 patients of an awake injection technique for determining lymphatic drainage patterns [100]. In a meta-analysis published in 2013 (703 patients), Thompson et al. showed in a subset of 72 patients with oropharyngeal cancers that SNB provide an excellent NPV near to 100%, but other studies are still needed [101]. However, the probability of retropharyngeal lymphatic drainage for these tumors limits surgical options (difficult surgical accessibility) and radiotherapy alone is often privileged.

In addition to causing less comorbidities and as a consequence of the very satisfying diagnostic accuracy, Schilling et al. confirmed in a prospective European study (SENT) with 415 patients that sentinel node biopsy is a safe oncological procedure with a disease-free survival of 92% and a disease-specific survival of 94% [102]. Moreover, in a median follow up study of 5.6 years with 229 patients, Moya-Plana et al. showed in 2018 that there was no difference in terms of recurrence-free time (80.7% vs 77.7%) and overall survival (76.4% vs 78.7%) when comparing SNB and neck dissection, respectively, with fewer complications (8% vs 28%, $p < 0.0001$) like found in a previous study [103,104].

Some progresses have been made in the recent years to improve accuracy of SLNs detection and especially when the tumor is located in the floor of the mouth [105]. First, ^{99m}Tc -tilmanocept (Lymphoseek) is a novel radiotracer with an high affinity for receptor protein CD-206, which is found on the surface of macrophages and dendritic cells in the LN, and a small molecular size (7nm diameter versus 5 to 80 nm for ^{99m}Tc labeled nanocolloid)

permitting rapid injection site clearance and stable binding within target nodes [106]. In a phase III multi-institutional trial published in 2015, Agrawal et al. showed in 101 patients with OCSCC a NPV of 97.8% and an overall accuracy of 98.8% without significant differences between same-day and next-day procedures [107]. Among the 20 patients with floor-of-mouth tumors, the radiotracer identified at least one SLN in all patients (100%). Another example is the use of the hybrid tracer Indocyanine green (ICG)- ^{99m}Tc -nanocolloid [108] taking advantage of the beneficial hydrodynamic draining properties of ^{99m}Tc labeled nanocolloid (offering high tissue penetration and allowing surgical planning with pre-operative imaging) and the higher spatial resolution of the near-infrared fluorescence (NIRF) method which is not impaired by the shine-through phenomenon and does not interfere with primary tumor margins visibility contrary to blue dye [109]. Moreover, progresses are also made for intra-operative detection system with the emergence of freehand SPECT (FhSPECT) that generates 3D images during the SN biopsy. This new imaging system may aid the surgeon providing with information about the direction and depth of the SN in relation to the gamma probe [110]. As a consequence, FhSPECT makes in situ planning biopsy possible, which may contribute to make the incision at the correct place, reducing risk of morbidities [111]. However, high costs of these emerging techniques remain until now the main limit of their clinical use, in particular for FhSPECT and ICG which require the setup of an appropriate imaging system in the operative room.

To conclude, LN biopsy in patients with early squamous cell carcinoma of the oral cavity and the oropharynx is an efficient and safe oncological procedure that provides very good diagnostic accuracy while reducing comorbidities in a significant way avoiding unnecessary neck dissection and/or elective node irradiation. Even if the main limit still remains the risk of false negative due to “shine through effect” (mostly for floor-of-the mouth and anterior tongue tumors), several progresses have been made in the last decade especially with new

tracers like ^{99m}Tc -tilmanocept (Lymphoseek®) and the combination of ^{99m}Tc -nanocolloid with Indocyanine green (ICG), but other prospective studies are still needed to confirm their clinical superiority and to measure whether there is a real improvement of surgeon's comfort (improved detection, reduced operative time) and of his confidence in decision making.

Laryngeal and hypopharyngeal cancers

Laryngeal cancers are the second most common H&N cancers with approximately one-third of all cases, with a total of 177,422 new cases in the world in 2018. The median age at the diagnosis is 65 years and male-to-female ratio is roughly 7:1 [66], however with a constant reduction of the gap between the two genres, mostly due to the smoking increase among women. Incidence declined in recent years while 5-year survival rate has slightly decreased in the last 30 years, with marked fragility in lower socio-economics groups [112]. Hypopharyngeal cancers are more rare, counting for about 3% of all the H&N cancers, with the same age diagnosis and male prevalence [113]. Both share the main risk factors, which are cigarette smoking and alcohol consumption, the influence of HPV and in particular HPV-16 contamination is still debated [114]. Additional risk factors like Plummer-Vinson syndrome and gastro-esophageal reflux are also noted. Owing to the chronic aggression of the covering squamous epithelium, more than 95% of the histological tumor types of laryngeal and hypopharyngeal cancers is, as for oral cancers Squamous Cell Carcinoma (SCC) and its variants, followed by the neuroendocrine tumor for the larynx [66]. Although symptoms like hoarseness may be early warning signs, most clinical symptoms may go unnoticed with subsequent delayed diagnosis: 60% of larynx cancers being at an advanced stage III or IV disease at the time of diagnosis [115] and 60% of hypopharyngeal cancers are at an advanced stage with lymph node spread [116]. Initial diagnosis can be made by an exploration using flexible fiberoptic laryngoscopy, which can be challenging due to the depth of the lesions,

then complementary direct laryngoscopy under general anesthesia in the operating room became mandatory [117]. Additional exams used are ultrasound for laryngeal involvement, as well as CT scan, MRI and ^{18}F -FDG PET/CT for extension assessment. Signs of lymph node invasion are particularly sought after [118] but up to 30% of occult metastasis can be missed [119,120]. Cancer distribution rely on the anatomical regions, for the larynx which is subdivided in 3 parts, the supraglottic part extending from the epiglottis to the glottis level counts approximately 35% of laryngeal cancer. The glottis part which extends downwards to the true vocal cords counts roughly 65% and the subglottic stage which extends to the plane of the cricoid cartilage counts less than 5% [121]. The supraglottic part having the most abundant lymphatic network spreads most frequently to regional nodes, and supraglottic cancers can metastasize to levels II to IV of cervical nodes, and this bilaterally [122]. The network of the glottis being sparse, dissemination is rarer, especially visible in advanced stages, with unilateral pathway. Hypopharynx is composed of the lateral and posterior pharyngeal walls, the pyriform sinuses, the post cricoid area, and extending from the pharyngoepiglottic fold to the lower border of the cricoid cartilage. Eighty percent of the hypopharyngeal cancers derived from the pyriform sinuses [123] these tumors can easily metastasize to cervical nodes and distant sites due to numerous lymphatic and vascular networks, with mainly cervical jugular nodes within levels II to IV and retropharyngeal nodes involved [124]. Treatments recommended for these two cancers are based on surgery, radiotherapy and chemotherapy, with a distinction between endoscopic surgery like transoral laser microsurgery (TLM) or transoral robotic surgery (TORS) and an open approach like vertical hemilaryngectomy, in order to privilege the organ preservation [114,122]. As for tumors of the oral cavity, one of the most important prognostic factors is the presence of lymph node metastasis [125]. Even in the absence of clinical lymph nodes, occult lymph node involvement represents 20 to 30%, their spreading depending on the T stage, grade and

extension across the midline [126]. However, the management of nodal spreading tumors such as supraglottic and hypopharyngeal clinically N0 is not formally established, with teams performing systematic neck dissection, bilateral or unilateral, or even monitoring if the risk is estimated <20% [127]. Furthermore, neck dissection can be followed by side effects like nerve or vascular damage and delayed healing.

Although the SLN procedure is well established in oral cavity cancers, few studies have been published thereupon on laryngeal and hypopharyngeal cancers, with currently no recommendations of the use of SLN in these two cancers. The complicated access for injection making difficult the realization of a lymphoscintigraphy and the frequent discovery of diseases at advanced stages makes the use of SLNB investigational [128]. Two studies performed SNB intraoperatively using only handheld gamma probe for detection. Werner et al. found a global sensitivity of 89% in 50 patients, 17 of them actually having laryngeal and hypopharyngeal cancers, with a SNB biopsy within a 6 h delay after primary surgery [129]. A rigorous injection for the radiotracer and a well-trained surgeon were mandatory for the authors to ensure best results. Lawson et al. found a sensitivity of 100%, a specificity of 78% and a NPV of 100% for 29 patients with supraglottic cancers [130]. This study also showed that the absence of prior resection of the primary lesion could lead to the risk of a “shine-through effect”, having resulted in missing a SLN in the prelaryngeal space. Both papers used ^{99m}Tc Nanocolloid injections, with 4 to 5 injections sites with 37 to 44 MBq with direct endoscopy while under general anesthesia. Conversely, two studies performed SLN procedure before surgery with prior lymphoscintigraphy (LSG), Tomifuji et al. [131] found a sensitivity and a specificity of 83% and 100% respectively, with an accuracy of 95% and 7% of negative predictive value, in 20 patients with laryngeal and pharyngeal cancers. Hu et al. [132], found a DR of 91.1%, a sensitivity of 93.7%, a specificity of 100% (in patients with available SLN) or 82.7% (in overall population) with 6.3% FN (1/16) for 45 patients with laryngeal and

pharyngeal cancers. Tomifuji et al. used 74 MBq/mL of stannous phytate while Hu et al. 19 MBq of ^{99m}Tc sulfur colloid, both with 3 to 4 submucosal injections each adjacent to the tumor, with overlying skin marks and a planar LSG, one to six hours after injection [131, 132]. Both conclude that at least 3 lymph nodes must be identified and removed to be accurate. As discussed in the previous parts of this review, the quality of the pathology analysis protocol is also essential in the good performance of SLN procedure. The global consideration shared by all of these few studies shows the importance of the contribution of the SLN procedure in the decision of unilateral or bilateral dissection as well as the need for adjuvant therapy [131]. The use of the SNL procedure could also allow tailoring of territory to be irradiated to reduce the incidence and duration of radiation-related toxicities and could improve quality of life [133]. As for the oral cavity cancers, the current development of new tracers such as ^{99m}Tc -tilmanocept could make it possible to overcome the shine through effect and facilitate the implementation of SLN procedure [87]. Furthermore, new studies should improve our knowledge on this subject, such as Moya Plana et al. who will try to show if this technique is reliable and can make a therapeutic de-escalation for the treatment of small tumors of the larynx [134].

In conclusion, there is scarce evidence on the use of SLNB in laryngeal and hypopharyngeal cancers, with currently no recommendations. The difficulties for SLNB in these locations include the complicated access for injection making difficult the realization of a lymphoscintigraphy and the frequent discovery of diseases at advanced stages. As in other tumors, the quality of the pathology analysis protocol is essential. The common considerations shared by the few available studies shows the importance of SLNB procedure in the decision of unilateral or bilateral dissection and adjuvant therapy, as well as for tailoring the territory to be irradiated helping to reduce the incidence and duration of radiation-related toxicities and improve quality of life.

Conclusions

In summary, in cutaneous neoplasms of the head and neck, the detection rate is higher than 90%, however the false negative rate is still an issue, in particular in melanoma, inducing the need of newer developments. In fact, new tracers and techniques are already available, while prospective multicenter trials exploring the outcome impact are needed in the near future. For the upper aerodigestive tract and in particular oral cavity and oropharynx, sentinel lymph node identification by lymphoscintigraphy allows avoiding unnecessary neck dissection and/or node irradiation. Even in this case, the main limit remains the risk of false negative rates. While, for patients affected by laryngeal and hypopharyngeal cancers the data seems very limited and, although the feasibility has been demonstrated, the performance of lymphoscintigraphy in these locations still needs to be confirmed by multicenter studies.

References

- [1] O.A. Ahmed, C. Kelly. Head and neck melanoma (excluding ocular melanoma): United Kingdom National Multidisciplinary Guidelines. *The Journal of Laryngology & Otology* (2016), 130 (Suppl. S2), pp. 133-141.
- [2] A.J. Rosko, K.K. Vankoeverying, et al. Contemporary Management of Early-Stage Melanoma – A systematic Review. *JAMA Facial Plastic Surgery* (2017) | Review
- [3] O. Ruskin, A. Sanelli et coll. Excision margins and sentinel lymph node status as prognostic factors in thick melanoma of the head and neck: A retrospective analysis. *Wiley Periodicals, Inc.* 2016 Sep; 38(9): 1373-9.
- [4] C.M. Balch, J.E. Gershenwald et coll. Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol.* 2009; 27:6 pp. 199-206.
- [5] R.K. Rahimi-Nedjat, B. Al-Nawas et coll. Sentinel lymph node biopsy in malignant melanoma of the head and neck. *J. Craniomaxillofac Surg.* 2018 Jun; 46(6): pp. 1027-1031.

- [6] R.L. Siegel, K.D. Miller, A. Jemal. Cancer Statistics, 2015. *CA Cancer J Clin.* 2015 Jan-Feb; 65(1) pp. 5-29.
- [7] D.L. Morton, D.R. Wen et coll. Technical details of intraoperative lymphatic mapping for early stage melanoma *Arch Surg.* 1992 Apr; 127(4) pp. 392-399.
- [8] C. Bluemel, K. Herrmann, F. Giammarile et al. EANM practice Guidelines for Lymphoscintigraphy and Sentinel Lymph Node Biopsy in Melanoma. *Eur J Nucl Med Mol Imaging* 2015 Oct; 42(11) pp. 1750-1766.
- [9] S.N. Pavri, C. Gary et coll. Nonvisualization of Sentinel Lymph Nodes by Lymphoscintigraphy in Primary Cutaneous Melanoma: Incidence, Risk Factors, and a Review of Management Options. *Plast Reconstr Surg.* 2018 Oct; 142(4) pp. 527-534
- [10] M.M. May, C.M. Lohse et coll. Wide local excision prior sentinel lymph node biopsy for primary melanoma of the head and neck. *Int J Dermatol.* 2019 Oct; 58(10) pp. 1184-1190.
- [11] J.M. Roy, R.J. Whitfield, P.G. Gill. Review of the role of sentinel node biopsy in cutaneous head and neck melanoma. *ANZ J Surg.* 2016 May; 86(5) pp 348-55.
- [12] Azad AK, Rajaram MV, Metz WL, et al. gamma-tilmanocept, a new radiopharmaceutical tracer for cancer sentinel lymph nodes, binds to the mannose receptor (CD206). *J Immunol* 2015;195: 2019–29.
- [13] N. de Rosa, G.H. Lyman et al. Sentinel node biopsy for head and neck melanoma: a systemic review. *Otolaryngol Head Neck Surg* 2011; 145 pp. 375-382.
- [14] F.I. Ahmad, S.Y. Su et al. The Role of Sentinel Lymph Node Biopsy in the Management of Cutaneous Malignancies. *Facial Plast Surg Clin N Am* 27 (2019) pp. 119-129.
- [15] B. Passmore-Webb, B. Gurney et al. Sentinel lymph node biopsy for melanoma of the head and neck: a multicentre study to examine safety, efficacy, and prognostic value. *Br J Oral Maxillofac Surg.* 2019 Nov; 57(9), pp. 891-897.
- [16] M.L. Pfeiffer, O.K. Ozgur et al. Sentinel lymph node biopsy for ocular adnexal melanoma. *Acta Ophthalmol.* 2017 Jun; 95(4) pp. 323-328
- [17] F. Creighton, R. Bergmark, K. Emerick Drainage Patterns to Nontraditional Nodal Regions and Level IIB in Cutaneous Head and Neck Malignancy. *Otolaryngol Head Neck Surg.* 2016 Dec; 155(6) pp. 1005-1011
- [18] F.I. Ahmad, S.Y. Su et al. The Role of Sentinel Lymph Node Biopsy in the Management of Cutaneous Malignancies. *Facial Plast Surg Clin N Am* 27 (2019) pp. 119-129.
- [19] E. de Bree, R. de Bree Implication of the MSLT-1 for sentinel lymph node biopsy in cutaneous head and neck melanoma. *Oral Oncol.* 2015 Jul; 51(7) pp. 629-633.

- [20] D.Y. Lee, K.T. Huynh et al. Predictors and Survival Impact of False-Negative Sentinel Nodes in Melanoma. *Ann Surg Oncol*. 2016 May; 23(3) pp. 1012-1018.
- [21] A. Joosse, S. Collette et al. Gender differences in melanoma survival: female patients have a decreased risk of metastasis. *J Investig Dermatol*. 2011; 131(3) pp. 719-726.
- [22] E.L. Jones, T.S. Jones et al. Long-term follow-up and survival of patients following a recurrence of melanoma after a negative sentinel lymph node biopsy result. *JAMA Surg*. 2013; 148(5) pp.456-461.
- [23] Uren RF, Howman-Giles R, Thompson JF. Patterns of lymphatic drainage from the skin in patients with melanoma. *J Nucl Med* 2003;44 pp. 570-582
- [24] D. Schuitevoerder, L. Grinlington et al. Nonvisualized sentinel lymph nodes on lymphoscintigraphy in melanoma: predictive factors and surgical outcomes. *Nucl Med Commun*. 2017 May; 38(5) pp. 383-387.
- [25] E. Tardelli, S. Mazzarri et al. Sentinel Lymph Node Biopsy in Cutaneous Melanoma: Standard and New Technical Procedures and Clinical Advances. A systematic Review of the Literature. *Clin Nucl Med*. 2016 Dec; 41(12) pp.498-507
- [26] D.Y. Lee, K.T. Huynh et al. Predictors and Survival Impact of False-Negative Sentinel Nodes in Melanoma. *Ann Surg Oncol*. 2016 Mar; 23(3) pp. 1012-1018.
- [27] N.B. Sein, C.L. Wright, A. Agrawal Contemporary use of sentinel lymph node biopsy in the head and neck. *World J Otorhinolaryngol Head Neck Surg* . 2016 Jul 25;2(2):117-125.
- [28] N.S. van der Berg, O.R. Brouwer et coll. Multimodal Surgical Guidance during Sentinel Node Biopsy for Melanoma: Combined Gamma Tracing and Fluorescence Imaging of the Sentinel Node through Use of the Hybrid Tracer Indocyanine Green – ^{99m}Tc-Nanocolloid. *Radiology* 2015 May; 275(2) pp. 521-529.
- [29] N.B. Sein, C.L. Wright, A. Agrawal Contemporary use of sentinel lymph node biopsy in the head and neck. *World J Otorhinolaryngol Head Neck Surg*. 2016 Jul 25; 2(2) pp. 117-125.
- [30] Azad AK, Rajaram MV, Metz WL, et al. Gamma-tilmanocept, a new radiopharmaceutical tracer for cancer sentinel lymph nodes, binds to the mannose receptor (CD206). *J Immunol* 2015;195: 2019–29.
- [31] Suárez C, Rodrigo JP, Ferlito A, Devaney KO, Rinaldo A. Merkel cell carcinoma of the head and neck. *Oral Oncol*. 2004 Sep;40(8):773-9.
- [32] C Toker. Trabecular carcinoma of the skin. *Arch. Dermatol.*, 105 (1972), pp. 107-110
- [33] K Smith, H Skelton. Overview of Merkel cell carcinoma and recent advances in research. Editorial. *Int. J. Dermatol.*, 42 (2003), pp. 749-751

- [34] F Cirillo, M Buononato, G Lima, I Cafaro, P Alquati. Clinical experience on eight cases of Merkel cell carcinoma. *Tumori*, 89 (2003), pp. 146-151
- [35] Leroux-Kozal V, Lévêque N, Brodard V, et al. Merkel cell carcinoma: histopathologic and prognostic features according to the immunohistochemical expression of Merkel cell polyomavirus large T antigen correlated with viral load. *Hum Pathol*. 2015;46(3):443-453. doi:10.1016/j.humpath.2014.12.001
- [36] J.M. van der Zwan, A. Trama, R. Otter, N. Larranaga, A. Tavilla, R. Marcos-Gragera, et al. Rare neuroendocrine tumours: results of the surveillance of rare cancers in Europe project. *Eur J Cancer*, 49 (11) (2013 Jul), pp. 2565-2578
- [37] T.L. Fitzgerald, S. Dennis, S.D. Kachare, N.A. Vohra, J.H. Wong, E.E. Zervos. Dramatic increase in the incidence and mortality from Merkel cell carcinoma in the United States. *Am Surg*, 81 (8) (2015 Aug), pp. 802-806
- [38] D.R. Youlden, H.P. Soyer, P.H. Youl, L. Fritschi, P.D. Baade. Incidence and survival for Merkel cell carcinoma in Queensland, Australia, 1993–2010. *JAMA Dermatol*, 150 (8) (2014 Aug), pp. 864-872
- [39] Harms KL, Healy MA, Nghiem P, et al. Analysis of Prognostic Factors from 9387 Merkel Cell Carcinoma Cases Forms the Basis for the New 8th Edition AJCC Staging System. *Ann Surg Oncol*. 2016;23(11):3564-3571. doi:10.1245/s10434-016-5266-4
- [40] Bichakjian CK, Olencki T, Aasi SZ, et al. Merkel Cell Carcinoma, Version 1.2018, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2018;16(6):742-774. doi:10.6004/jnccn.2018.0055
- [41] Schwartz JL, Griffith KA, Lowe L, et al. Features predicting sentinel lymph node positivity in Merkel cell carcinoma. *J Clin Oncol*. 2011;29(8):1036-1041. doi:10.1200/JCO.2010.33.4136
- [42] Gupta SG, Wang LC, Peñas PF, Gellenthin M, Lee SJ, Nghiem P. Sentinel lymph node biopsy for evaluation and treatment of patients with Merkel cell carcinoma: The Dana-Farber experience and meta-analysis of the literature. *Arch Dermatol*. 2006;142(6):685-690. doi:10.1001/archderm.142.6.685
- [43] Karunaratne YG, Gunaratne DA, Veness MJ. Systematic review of sentinel lymph node biopsy in Merkel cell carcinoma of the head and neck. *Head Neck*. 2018;40(12):2704-2713. doi:10.1002/hed.25345
- [44] Penicaud M, Cammilleri S, Giorgi R, et al. Intérêt pronostique du ganglion sentinelle dans les carcinomes a cellules de Merkel de la tête et du cou [Prognostic value of sentinel

lymph node in Merkel cell carcinoma of the head and neck]. *Rev Laryngol Otol Rhinol (Bord)*. 2013;134(2):75-79.

- [45] Shnayder Y, Weed DT, Arnold DJ, et al. Management of the neck in Merkel cell carcinoma of the head and neck: University of Miami experience. *Head Neck*. 2008;30(12):1559-1565. doi:10.1002/hed.20899
- [46] Stokes JB, Graw KS, Dengel LT, et al. Patients with Merkel cell carcinoma tumors < or = 1.0 cm in diameter are unlikely to harbor regional lymph node metastasis. *J Clin Oncol*. 2009;27(23):3772-3777. doi:10.1200/JCO.2008.20.8272
- [47] Gunaratne DA, Howle JR, Veness MJ. Sentinel lymph node biopsy in Merkel cell carcinoma: a 15-year institutional experience and statistical analysis of 721 reported cases. *Br J Dermatol*. 2016;174(2):273-281. doi:10.1111/bjd.14240
- [48] Fang LC, Lemos B, Douglas J, Iyer J, Nghiem P. Radiation monotherapy as regional treatment for lymph node-positive Merkel cell carcinoma. *Cancer*. 2010;116(7):1783-1790. doi:10.1002/cncr.24919
- [49] Servy A, Maubec E, Sugier PE, et al. Merkel cell carcinoma: value of sentinel lymph-node status and adjuvant radiation therapy. *Ann Oncol*. 2016;27(5):914-919. doi:10.1093/annonc/mdw035
- [50] Ahmad FI, Su SY, Gross ND. The Role of Sentinel Lymph Node Biopsy in the Management of Cutaneous Malignancies. *Facial Plast Surg Clin North Am*. 2019;27(1):119-129. doi:10.1016/j.fsc.2018.08.004
- [51] Grange F. Épidémiologie du mélanome cutané : données descriptives en France et en Europe. *Ann Dermatol Venerol*; 2005 132: 975-982
- [52] Staples MP, Elwood M, Burton RC, Williams JL, Marks R, Giles GG. Non-melanoma skin cancer in Australia: the 2002 national survey and trends since 1985. *Med J Aust*. 2006;184(1):6-10.
- [53] Chabrillac E, Lusque A, Cavallier Z, et al. Cutaneous Squamous Cell Carcinoma Tumour Size is Associated with Sentinel Lymph Node Metastasis in a Cohort of 69 Patients. *Acta Derm Venereol*. 2019;99(13):1241-1245. doi:10.2340/00015555-3293
- [54] Alam M, Ratner D. Cutaneous squamous-cell carcinoma. *N Engl J Med*. 2001;344(13):975-983. doi:10.1056/NEJM200103293441306
- [55] Ramsay HM, Reece SM, Fryer AA, Smith AG, Harden PN. Seven-year prospective study of nonmelanoma skin cancer incidence in U.K. renal transplant recipients. *Transplantation*. 2007;84(3):437-439. doi:10.1097/01.tp.0000269707.06060.dc

- [56] Fortina AB, Piaserico S, Caforio AL, et al. Immunosuppressive level and other risk factors for basal cell carcinoma and squamous cell carcinoma in heart transplant recipients. *Arch Dermatol*. 2004;140(9):1079-1085. doi:10.1001/archderm.140.9.1079
- [57] Que SKT, Zwald FO, Schmults CD. Cutaneous squamous cell carcinoma: Incidence, risk factors, diagnosis, and staging. *J Am Acad Dermatol*. 2018;78(2):237-247. doi:10.1016/j.jaad.2017.08.059
- [58] Gore SM, Shaw D, Martin RC, et al. Prospective study of sentinel node biopsy for high-risk cutaneous squamous cell carcinoma of the head and neck. *Head Neck*. 2016;38 Suppl 1:E884-E889. doi:10.1002/hed.24120
- [59] Navarrete-Dechent C, Veness MJ, Droppelmann N, Uribe P. Cutaneous squamous cell carcinoma and the emerging role of sentinel lymph node biopsy. *G Ital Dermatol Venereol*. 2018;153(3):403-418. doi:10.23736/S0392-0488.18.05936-9
- [60] Feinstein S, Higgins S, Ahadiat O, Wysong A. A Retrospective Cohort Study of Cutaneous Squamous Cell Carcinoma With Lymph Node Metastasis: Risk Factors and Clinical Course. *Dermatol Surg*. 2019;45(6):772-781. doi:10.1097/DSS.0000000000001828
- [61] Kwon S, Dong ZM, Wu PC. Sentinel lymph node biopsy for high-risk cutaneous squamous cell carcinoma: clinical experience and review of literature. *World J Surg Oncol*. 2011;9:80. Published 2011 Jul 19. doi:10.1186/1477-7819-9-80
- [62] Ahmed MM, Moore BA, Schmalbach CE. Utility of head and neck cutaneous squamous cell carcinoma sentinel node biopsy: a systematic review. *Otolaryngol Head Neck Surg*. 2014;150(2):180-187. doi:10.1177/0194599813511949
- [63] Durham AB, Lowe L, Malloy KM, et al. Sentinel Lymph Node Biopsy for Cutaneous Squamous Cell Carcinoma on the Head and Neck. *JAMA Otolaryngol Head Neck Surg*. 2016;142(12):1171-1176. doi:10.1001/jamaoto.2016.1927
- [64] Takahashi A, Imafuku S, Nakayama J, Nakaura J, Ito K, Shibayama Y. Sentinel node biopsy for high-risk cutaneous squamous cell carcinoma. *Eur J Surg Oncol*. 2014;40(10):1256-1262. doi:10.1016/j.ejso.2014.05.009
- [65] Quinn PL, Oliver JB, Mahmoud OM, Chokshi RJ. Cost-Effectiveness of Sentinel Lymph Node Biopsy for Head and Neck Cutaneous Squamous Cell Carcinoma. *J Surg Res*. 2019;241:15-23. doi:10.1016/j.jss.2019.03.040
- [66] Bray F, Ferlay J, Soerjomataram I, et al: Global cancer statistics, 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 68:394-424, 2018

- [67] Warnakulasuriya S, Maeda H, Greenspan JS: (2020) Pathology of oral and oropharyngeal cancers. Textbook of Oral Cancer. Textbooks in Contemporary Dentistry. Springer, Cham, pp. 69-80
- [68] Kato MG, Baek CH, Chaturvedi P, et al. Update on oral and oropharyngeal cancer staging - International perspectives. World J Otorhinolaryngol Head Neck Surg 6(1):66-75, 2020
- [69] Vogel DWT, Zbaeren, P, Thoeny HC: Cancer of the oral cavity and oropharynx. Cancer Imaging 10:62-72, 2010
- [70] Farmer RW, McCall L, Civantos FJ, et al: Lymphatic drainage patterns in oral squamous cell carcinoma: Findings of the ACOSOG Z0360 (Alliance) Study. Otolaryngol Head Neck Surg 152:673-677, 2015
- [71] Mølstrøm, J, Grønne M, Green, A, et al: Topographical distribution of sentinel nodes and metastases from T1–T2 oral squamous cell carcinomas. European Journal of Cancer 107:86-92, 2019
- [72] Doumas S, Fort-Schaale A, Skoulakis C, et al: Current thinking on the management of abnormal retropharyngeal nodes in patients with oral, oropharyngeal, and nasopharyngeal squamous cell carcinoma: a structured review. Br J Oral Maxillofac Surg 57:515-528, 2019
- [73] Amsbaugh MJ, Mehran Y, Cash E, et al: Distribution of cervical lymph node metastases from squamous cell carcinoma of the oropharynx in the era of risk stratification using human papillomavirus and smoking status. International Journal of Radiation Oncology*Biography*Physics 96:349-353, 2016
- [74] Mamelle G, Pampurik J, Luboinski B, et al: Lymph node prognostic factors in head and neck squamous cell carcinomas. The American Journal of Surgery 168:494-498, 1994
- [75] Broglie MA, Haerle SK, Huber GF, et al: Occult metastases detected by sentinel node biopsy in patients with early oral and oropharyngeal squamous cell carcinomas: Impact on Survival. Head & neck 35(5):660-6, 2013
- [76] Gourin CG, Conger BT, Porubsky ES, et al: The Effect of Occult Nodal Metastases on Survival and Regional Control in Patients With Head and Neck Squamous Cell Carcinoma. Laryngoscope 118: 1191-1194, 2008
- [77] D'Cruz, AK, Vaish R, Neeti K, et al: Elective versus Therapeutic Neck Dissection in Node-Negative Oral Cancer. N Engl J Med 373:521-529, 2015
- [78] Gill A, Vasan N, Givi B, et al: AHNS Series: Do you know your guidelines? Evidence-based management of oral cavity cancers. Head & Neck 40:406-416, 2018

- [79] Adelstein D, Gillison ML, Pfister DG, et al: NCCN Guidelines Insights: Head and Neck Cancers, Version 2.2017. *J Natl Compr Canc Netw* 15:761-770, 2017
- [80] Inoue H, Nibu K, Saito M, et al: Quality of Life After Neck Dissection. *Arch Otolaryngol Head Neck Surg* 132:662-666, 2006
- [81] Bradley PJ, Ferlito A, Silver CE, et al. Neck treatment and shoulder morbidity: still a challenge. *Head Neck* 33:1060-1067, 2011
- [82] Jellema AP, Slotman BJ, Doornaert P, et al: Unilateral versus bilateral irradiation in squamous cell head and neck cancer in relation to patient-rated xerostomia and sticky saliva. *Radiother Oncol* 85:83-89, 2007
- [83] Kane SV, Gupta M, Kakade AC, et al: Depth of invasion is the most significant histological predictor of subclinical cervical lymph node metastasis in early squamous carcinomas of the oral cavity. *Eur J Surg Oncol* 32:795-803, 2006
- [84] Goerkem M, Braun J et Stoeckli SJ: Evaluation of Clinical and Histomorphological Parameters as Potential Predictors of Occult Metastases in Sentinel Lymph Nodes of Early Squamous Cell Carcinoma of the Oral Cavity. *Ann Surg Oncol* 17:527-535, 2010
- [85] den Toom IJ, van Schie A, van Weert S, et al: The added value of SPECT-CT for the identification of sentinel lymph nodes in early stage oral cancer. *Eur J Nucl Med Mol Imaging* 44:998-1004, 2017
- [86] Alkureishi LWT, Burak Z, Alvarez JA et al: Joint Practice Guidelines for Radionuclide Lymphoscintigraphy for Sentinel Node Localization in Oral/Oropharyngeal Squamous Cell Carcinoma. *Eur J Nucl Med Mol Imaging* 36:1915-1936, 2009
- [87] Giammarile F, Schilling C, Gnanasegaran G, et al: The EANM practical guidelines for sentinel lymph node localisation in oral cavity squamous cell carcinoma. *Eur J Nucl Med Mol Imaging* 46:623-637, 2019
- [88] Capote-Moreno A, Naval L, Muñoz-Guerra MF, et al: Prognostic Factors Influencing Contralateral Neck Lymph Node Metastases in Oral and Oropharyngeal Carcinoma. *Journal of Oral and Maxillofacial Surgery* 68:268-275, 2010
- [89] Flach GB, Broglie MA, van Schie A, et al: Sentinel node biopsy for oral and oropharyngeal squamous cell carcinoma in the previously treated neck. *Oral Oncology* 48:85-89, 2012
- [90] de Veij Mestdagh PD, Schreuder WH, Vogel WV, et al: Mapping of sentinel lymph node drainage using SPECT/CT to tailor elective nodal irradiation in head and neck cancer patients (SUSPECT-2): a single-center prospective trial. *BMC Cancer* 19:1110, 2019

- [91] Alex JC, Krag DN: Gamma-probe guided localization of lymph nodes. *Surg Oncol* 2:137-143, 1993
- [92] de Bree R, Nieweg OE: The history of sentinel node biopsy in head and neck cancer: From visualization of lymphatic vessels to sentinel nodes. *Oral Oncology* 51:819-823, 2015
- [93] Paleri V, Rees G, Arullendran P, et al: Sentinel node biopsy in squamous cell cancer of the oral cavity and oral pharynx: A diagnostic meta-analysis. *Head Neck* 27:739-747, 2005
- [94] Stoeckli SJ, Pfaltz M, Ross GL, et al: The Second International Conference on Sentinel Node Biopsy in Mucosal Head and Neck Cancer. *Annals of surgical oncology* 12(11):919-924, 2005
- [95] Govers TM, Hannink G, Merks MAW, et al: Sentinel node biopsy for squamous cell carcinoma of the oral cavity and oropharynx: A diagnostic meta-analysis. *Oral Oncology* 49:726-732, 2013
- [96] Civantos FJ, Zitsch RP, Schuller DE, et al: Sentinel Lymph Node Biopsy Accurately Stages the Regional Lymph Nodes for T1-T2 Oral Squamous Cell Carcinomas: Results of a Prospective Multi-Institutional Trial. *J Clin Oncol* 28:1395-1400, 2010
- [97] Alkureishi LWT, Ross GL, Shoaib T, et al: Sentinel Node Biopsy in Head and Neck Squamous Cell Cancer: 5-Year Follow-Up of a European Multicenter Trial. *Ann Surg Oncol* 17:2459-2464, 2010
- [98] Melkane AE, Mamelle G, Wycisk G, et al: Sentinel node biopsy in early oral squamous cell carcinomas: A 10-year experience. *The Laryngoscope* 122:1782-1788, 2012
- [99] Manca G, Volterrani D, Mazzarri S, et al: Sentinel Lymph Node Biopsy of Oral/Oropharyngeal Squamous Cell Carcinoma: Techniques, Indications, Advantages, and Accuracy. *Clin Nucl Med* 40(5):401-4, 2015
- [100] Thomas CM, Khan MN, Mohan R, et al: Lymphatic mapping with SPECT-CT for evaluation of contralateral drainage in lateralized oropharyngeal cancers using an awake injection technique. *Head & Neck* 42:385-393, 2020
- [101] Thompson CF, St. John MA, Lawson G, et al: Diagnostic value of sentinel lymph node biopsy in head and neck cancer: a meta-analysis. *Eur Arch Otorhinolaryngol* 270:2115-2122, 2013
- [102] Schilling C, Stoeckli SJ, Haerle SK, et al: Sentinel European Node Trial (SENT): 3-year results of sentinel node biopsy in oral cancer. *European Journal of Cancer* 51:2777-2784, 2015

- [103] Moya-Plana A, Aupérin A, Guerlain J, et al: Sentinel node biopsy in early oral squamous cell carcinomas: Long-term follow-up and nodal failure analysis. *Oral Oncology* 82:187-194, 2018
- [104] Murer K, Huber GF, Haile SR, et al: Comparison of morbidity between sentinel node biopsy and elective neck dissection for treatment of the n0 neck in patients with oral squamous cell carcinoma. *Head Neck* 33:1260-1264, 2011
- [105] Tartaglione G, Rubello D, Colletti PM: The Progressive Advances of Sentinel Lymph Node Biopsy Technique in Head and Neck Cancer. *Clin Nucl Med* 42:100-103, 2017
- [106] Marcinow AM, Hall N, Byrum E, et al: Use of a Novel Receptor-Targeted (CD206) Radiotracer, ^{99m}Tc-Tilmanocept, and SPECT/CT for Sentinel Lymph Node Detection in Oral Cavity Squamous Cell Carcinoma: Initial Institutional Report in an Ongoing Phase 3 Study. *JAMA Otolaryngol Head Neck Surg* 139:895-902, 2013
- [107] Agrawal A, Civantos FJ, Brumund KT, et al: [^{99m}Tc]Tilmanocept Accurately Detects Sentinel Lymph Nodes and Predicts Node Pathology Status in Patients with Oral Squamous Cell Carcinoma of the Head and Neck: Results of a Phase III Multi-institutional Trial. *Ann Surg Oncol* 22:3708-3715, 2015
- [108] KleinJan GH, van Werkhoven E, van den Berg NS, et al: The best of both worlds: a hybrid approach for optimal pre- and intraoperative identification of sentinel lymph nodes. *Eur J Nucl Med Mol Imaging* 45:1915-1925, 2018
- [109] van den Berg NS, Brouwer OR, Klop WMC, et al: Concomitant radio- and fluorescence-guided sentinel lymph node biopsy in squamous cell carcinoma of the oral cavity using ICG-^{99m}Tc-nanocolloid. *Eur J Nucl Med Mol Imaging* 39:1128-1136, 2012
- [110] Heuveling DA, van Weert S, Karagozoglu KH, et al: Evaluation of the use of freehand SPECT for sentinel node biopsy in early stage oral carcinoma. *Oral Oncology* 51:287-290, 2015
- [111] Bluemel C, Matthies P, Herrmann K, et al: 3D scintigraphic imaging and navigation in radioguided surgery: freehand SPECT technology and its clinical applications. *Expert Rev Med Devices* 13(4):339-51, 2016
- [112] Garneau JC, Bakst RL, Miles BA. Hypopharyngeal cancer: A state of the art review. *Oral Oncol.* 2018;86:244–250.
- [113] Chen W-C, Chuang H-C, Lin Y-T, et al. Clinical impact of human papillomavirus in laryngeal squamous cell carcinoma: a retrospective study. *PeerJ.* 2017;5:e3395.

- [114] Groome PA, O'Sullivan B, Irish JC, et al. Management and outcome differences in supraglottic cancer between Ontario, Canada, and the Surveillance, Epidemiology, and End Results areas of the United States. *J Clin Oncol Off J Am Soc Clin Oncol*. 2003;21:496–505.
- [115] Kotwall C, Sako K, Razack MS, et al. Metastatic patterns in squamous cell cancer of the head and neck. *Am J Surg*. 1987;154:439–442.
- [116] Steuer CE, El-Deiry M, Parks JR, et al. An update on larynx cancer. *CA Cancer J Clin*. 2017;67:31–50.
- [117] Lewis-Jones H, Colley S, Gibson D. Imaging in head and neck cancer: United Kingdom National Multidisciplinary Guidelines. *J Laryngol Otol*. 2016;130:S28–S31.
- [118] Van den Brekel MW, van der Waal I, Meijer CJ, et al. The incidence of micrometastases in neck dissection specimens obtained from elective neck dissections. *The Laryngoscope*. 1996;106:987–991.
- [119] Zhang B, Xu Z-G, Tang P-Z. Elective lateral neck dissection for laryngeal cancer in the clinically negative neck. *J Surg Oncol*. 2006;93:464–467.
- [120] Colevas AD, Yom SS, Pfister DG, et al. NCCN Guidelines Insights: Head and Neck Cancers, Version 1.2018. *J Natl Compr Cancer Netw JNCCN*. 2018;16:479–490.
- [121] Tamaki A, Miles BA, Lango M, et al. AHNS Series: Do you know your guidelines? Review of current knowledge on laryngeal cancer. *Head Neck*. 2018;40:170–181.
- [122] Hall SF, Groome PA, Irish J, et al. Radiotherapy or surgery for head and neck squamous cell cancer: establishing the baseline for hypopharyngeal carcinoma? *Cancer*. 2009;115:5711–5722.
- [123] Chung E-J, Lee S-H, Baek S-H, et al. Pattern of cervical lymph node metastasis in medial wall pyriform sinus carcinoma. *The Laryngoscope*. 2014;124:882–887.
- [124] Ho AS, Kim S, Tighiouart M, et al. Association of Quantitative Metastatic Lymph Node Burden With Survival in Hypopharyngeal and Laryngeal Cancer. *JAMA Oncol*. 2018;4:985–989.
- [125] Kontio R, Leivo I, Leppänen E, et al. Sentinel lymph node biopsy in oral cavity squamous cell carcinoma without clinically evident metastasis. *Head Neck*. 2004;26:16–21.
- [126] Kuriakose MA, Trivedi NP. Sentinel node biopsy in head and neck squamous cell carcinoma. *Curr Opin Otolaryngol Head Neck Surg*. 2009;17:100–110.
- [127] Esposito ED, Motta S, Cassiano B, et al. Occult lymph node metastases in supraglottic cancers of the larynx. *Otolaryngol--Head Neck Surg Off J Am Acad Otolaryngol-Head Neck Surg*. 2001;124:253–257.

- [128] Alkureishi LWT, Burak Z, Alvarez JA, et al. Joint practice guidelines for radionuclide lymphoscintigraphy for sentinel node localization in oral/oropharyngeal squamous cell carcinoma. *Eur J Nucl Med Mol Imaging*. 2009;36:1915–1936.
- [129] Werner JA, Dünne A-A, Ramaswamy A, et al. Sentinel node detection in N0 cancer of the pharynx and larynx. *Br J Cancer*. 2002;87:711–715.
- [130] Lawson G, Matar N, Nollevaux M-C, et al. Reliability of sentinel node technique in the treatment of N0 supraglottic laryngeal cancer. *The Laryngoscope*. 2010;120:2213–2217.
- [131] Tomifuji M, Shiotani A, Fujii H, et al. Sentinel node concept in clinically n0 laryngeal and hypopharyngeal cancer. *Ann Surg Oncol*. 2008;15:2568–2575.
- [132] Hu G, Zhong S, Xiao Q, et al. Radiolocalization of sentinel lymph nodes in clinically N0 laryngeal and hypopharyngeal cancers. *Ann Otol Rhinol Laryngol*. 2011;120:345–350.
- [133] Veij Mestdagh PD, Walraven I, Vogel WV, et al. SPECT/CT-guided elective nodal irradiation for head and neck cancer is oncologically safe and less toxic: A potentially practice-changing approach. *Radiotherapy and Oncology* 147:56-63, 2020.
- [134] [HTTPS://clinicaltrials.gov/ct2/show/NCT03010553](https://clinicaltrials.gov/ct2/show/NCT03010553) website lastly consulted on June 17 2020.

Figures

Figure 1

A 51 years old male underwent pre-surgery lymphoscintigraphy for a left periauricular melanoma, Breslow thickness 1.1 mm, Clark Stage 3. After lymphoscintigraphy, (A: SPECT volume rendering, B: Fused SPECT/CT volume rendering) the sentinel node identified in the second level was removed, no sign of metastatic involvement was detected at histopathologic analysis. No regional recurrence was observed during 30 months follow up.

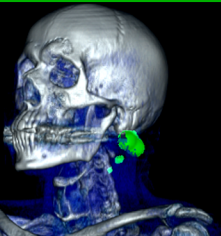
Figure 2

A 73-year-old woman underwent pre-surgery lymphoscintigraphy for a Merkel Cell Carcinoma of the dorsum nasi. After lymphoscintigraphy, (A: SPECT volume rendering, B: Fused SPECT/CT volume rendering) the sentinel nodes identified in the first level, bilaterally, were removed, but no sign of metastatic involvement was detected at histopathologic analysis. No regional recurrence was observed during 47 months follow up.

A



B



A



B

