Advantages of Sentinel Lymph Node Mapping by Single Photon Emission Computed Tomography/Computed Tomography in Early-Stage Malignant Head-and-Neck Skin Tumors

Abstract

Background: The aim of this study was to determine the advantages of preoperative sentinel lymph node mapping (SLNM) by single photon emission computed tomography/computed tomography (SPECT / CT) in patients with early-stage cutaneous head-and-neck malignancies. **Materials and Methods:** We conduct a 7-year and 6 months retrospective, cross-sectional study. Patients with early-stage malignant head-and-neck skin tumors and cutaneous adnexa who underwent SLNM by SPECT/CT from March 2012 and December 2019, were included in the study. **Results:** We retrospectively analyzed 28 patients: Melanoma was the most frequent tumor (64.2%), followed by squamous cell carcinoma (25%). The anterior cheek was the most common functional subsite (25%). Twenty-seven patients (96.4%) had a successful SLN detection with SPECT/CT. Neck lymph node dissection was performed in 23 patients (82.1%). According to the pathological specimen, lymph nodes were found in all of them; hence, the efficacy of the SPECT/CT for SLNM was 100%. At 7-year follow-up, systemic recurrence was found in one patient (3.6%), another had locoregional recurrence (3.6%), and the mortality rate was 3.6%. **Conclusions:** In early-stage malignant head-and-neck skin tumors, there is a high concordance between SLN found by SPECT/CT and the histopathological results. Preoperative SPECT/CT accurately detects the SLN, assesses unexpected lymph nodes and their drainage pathways, and facilitates their location by reliably showing the relationships between sentinel nodes and important anatomic structures. This allows to perform a clear preoperative evaluation, an accurate staging for all patients and to avoid excessive dissections that could result in cosmetic and functional deformities.

Keywords: *Head-and-neck hybrid imaging, lymphoscintigraphy, sentinel lymph node biopsy, single photon emission computed tomography*

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Introduction

Malignant head-and-neck skin tumors can metastasize early into regional lymph nodes, being the most relevant prognostic factor for the overall survival independently of the thickness of the primary lesion.[1] The unpredictable drainage patterns present a great challenge for sentinel lymph node mapping (SLNM).[2] The close proximity of the SLN to the primary cutaneous neoplasm represents a problem; the lymph node might be masked by the injection site of the radionuclide.[3]

Lymphoscintigraphy provides important information on the dynamic lymphatic drainage of the primary site and the location of the SLN. Planar lymphoscintigraphy (PL) is two-dimensional images that, even if they provide useful landmarks, the anatomical information is limited. Single photon emission computerized tomography (SPECT) facilitates the collection of emitted gamma radiation from multiple angles, allowing the generation of three-dimensional images of radiotracer accumulation and SLN location. However, anatomical resolution is still poor. The addition of conventional computerized tomography (CT) to the imaging protocol is considered a solution. Hybrid SPECT/CT provides anatomical details to the surgeon regarding the number and position of SLNs, a meaningful surgical "roadmap" can be created, which might also change surgical strategies. Accurate localization of SLNs with SPECT/CT has been shown to optimize incision planning and to reduce operative dissection time.[4]

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The aim of this study was to determinate advantages of preoperative SLNM by SPECT / CT in patients with early-stage cutaneous head-and-neck malignancies.

Materials and Methods

A 7½-year retrospective, cross-sectional study was carried out. We retrospectively analyzed the information of patients, over 18 years old, with early stages of skin and cutaneous adnexa neoplasms located in the head and neck, except basal cell carcinoma. All the diagnoses were previously confirmed with a biopsy. The patients underwent lymphatic mapping using SPECT/CT from March 2012 to December 2019.

We describe their baseline characteristics and the concordance of SLNM by SPECT/CT and the resulting surgical specimen.

The early-stage melanoma was defined according to the eighth edition of the American Joint Committee on Cancer,[5] as a lesion with a depth >0.76 mm and <2 mm on the Breslow scale, with or without ulceration, without clinical or radiological evidence of regional or distant metastases. For squamous cell carcinoma (SCC) and malignant tumors of the skin adnexa, the early stage is defined as a lesion of <4 cm in its largest diameter, without bone nor perineural invasion, with no evidence of regional or distant metastases and <6 mm of depth.

We adapted the classification by González-Ulloa, modified by Fattahi[6] for the description of the face-and-neck oncological subunits Table 1.

The type of neck lymph node dissection (NLND) carried out in our patients was defined as follows:[7]
- Supraomohyoid neck dissection: Resection of level I, II, and III.
- Anterolateral neck dissection (ALND) includes levels I, II, III, and IV.
- Lateral neck dissection (LND) includes levels II, III, and IV.
- Posterolateral neck dissection (PLND) includes levels II, III, IV, and V.[2]
- Supraselective neck dissection (SND): Lymph nodes between one and two contiguous levels of the neck.,[2,5,6]
- SLN biopsy (SLNB) includes any lymphatic nodes documented previously with a perilesional injection, for our case, evidenced in a SLNM by SPECT/CT.

Image acquisition

A mean dose of 1–2 mCi of 99mTechnetium-nanocolloid (GE Healthcare, Eindhoven, The Netherlands) was injected intradermally in four deposits of 0.1 mL around the lesion or the scar of the primary excision. Conventional dynamic PL was performed immediately after injection followed by static imaging after 10 min and 2 h. Directly after the last conventional images, 2 h after injection of the radiopharmaceutical, SPECT and CT data were

Table 1: Oncological subunits of the head and neck	
Anatomical subunit	**Landmarks description**
Forehead	Superior margin from the hair implantation line, to the nasion and the eyebrows at the bottom and lateral to the sideburns
Nose	Superior from the nasion, lateral to the nasal slope and inferior to the implantation of the nasal wing and the columella
Eyelid	Superior from the lower edge of the eyebrow, down to the edge of the infraorbital rim, lateral and medial to the edge of the orbital wall
Anterior cheek	Superior from the infraorbital rim, medial from the nasal slope, passing through the nasolabial and melolabial sulcus; lateral a line that crosses from the external canthus to the mandibular line and inferior the mandibular line
Posterior cheek	Superior from zygomatic arch, lateral to preauricular fold, medial a line that crosses from the external canthus to the mandibular line. Lower to mandibular rim
Lips	The upper one from the columella to the interlabial sulcus and the lateral nasolabial sulcus. Inferior from the interlabial sulcus, inferior to the mentolabial sulcus and lateral from the mentolabial sulcus
Chin	Superior and lateral from the mentholabial sulcus to the mandibular rim and inferior to the submental fold
Ears	Includes both ears, from the preauricular fold, to the insertion of the shell in the temporal bone
Scalp	From the superior nuchal lines of the occipital bone to Superior margin from the hair implantation line. The scalp extends laterally over the temporal facia to the zygomatic arches and the sideburns
Neck	Superior from the mandibular line, inferior to the clavicles and the sternal fork, circumferentially

acquired using a hybrid camera (ecam, Siemens, Erlangen, Germany).

The SPECT (128×128 matrix, 60 frames, 25 s/frame) was performed using 4-angular steps in a 20–25 s time frame. For CT (140 kilovolt, 2.5 milliampere, B30s kernel), 5-mm slices were obtained.

After correction for attenuation and scatter, corresponding SPECT and CT axial 5-mm slices were generated using an Esoft 2000 application package (Siemens). Images were fused using a Carestream Dicom viewer in a Unix-based operating system (MAC OS X, MacPro; Apple, Cupertino, CA).

The images were analyzed by 2-dimensional orthogonal re-slicing in axial, sagittal, and coronal directions. A 3-dimensional presentation was generated with volume rendering to localize sentinel nodes in relation to anatomic structures. All images were available on a separate SPECT/CT screen in the operating room.
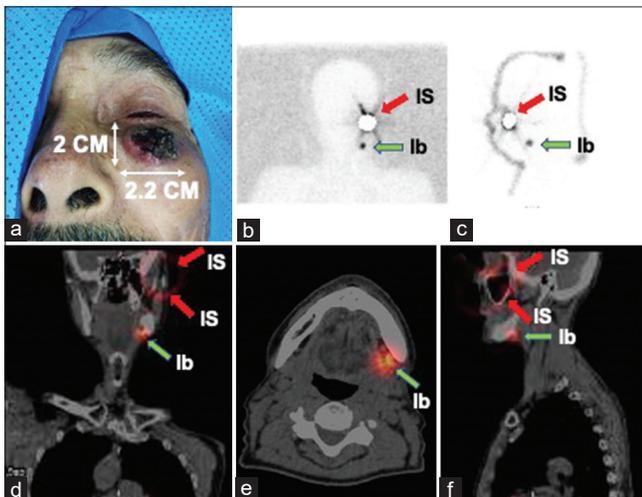
For interpretation of the images, the nodes with an afferent lymphatic vessel from the primary lesion site and nodes appearing first in each nodal basin were considered to be the sentinel nodes [Figure 1a-f].

The medical records were registered in the electronic system (SAP®) and the case report form on RedCap. All patients gave their consent for the use of their data for clinical research. Baseline characteristics were described using summary measures (mean, medians, standard deviation, ranges, minimum and/or maximum, and proportions); data were analyzed using IBM SPSS Statistics, version 19 licensed to National Cancer Institute with some variable crossings using the dynamic tables function. We report descriptive, continuous, and categorical variables with medians, ranges, and percentages respectively.

Routine follow-up consisted of history taking and a physical examination that included the face, the scalp, the neck, and regional nodal basins at 3-month or 6-month intervals, combined with annual ultrasonography of the neck. Other imaging studies were performed only when indicated by symptoms or physical examination findings.

First sites of recurrence were classified as local, regional, or systemic. Isolated skin recurrences were considered local, and isolated regional lymph node metastases were classified as regional.

Written approval was obtained from the institutional review board for a retrospective chart review study. This research protocol follows the guidelines established at the Declaration of Helsinki of the year 2013 and the ethical guidelines for biomedical research prepared by the Council of International Organizations of Medical Sciences.
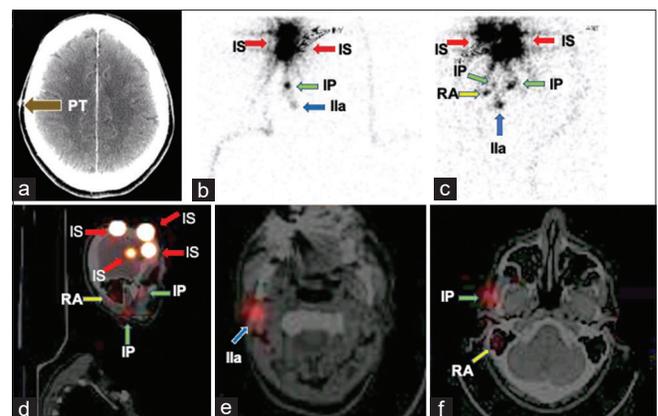
Results

From March 2012 to December 2019, 38 patients underwent SLNM by SPECT/CT as a part of the assessment for early-stage skin tumor of the head and neck. Of those, 28 were included: 15 women (53.6%) and 13 men (46.4%), with a mean age of 68 years (range: 30–85) and 10 patients were excluded because they did not meet inclusion criteria. Melanoma was the most frequent tumor found in 18 patients (64.2%), followed by SCC with 7 patients (25%), the remaining three had other histological types (Meckel cell tumor, hidradenocarcinoma, and sebaceous cell carcinoma). According to the Breslow scale, 12 patients (42.9%) presented a thickness between 1.51 and 4 mm (Breslow III), 8 patients (28.6%) more than 4 mm (Breslow IV), 7 patients between 0.76 and 1.5 mm (Breslow II), and one patient <0.75 mm (Breslow I).

Of the 28 patients injected at first, 27 had a successful lymph node detection with SPECT/CT and at least one SLN was identified. In one patient, no migration of the radiotracer was seen in any lymph node basin.

The anterior cheek was the most common anatomic subsite with seven cases (25%), followed by the ear with 4 cases (14.3%), eyelid with 4 cases (14.3%), and scalp with 4 cases (14.3%). In the posterior cheek, we found three cases (10.7%) and in the lip 3 cases as well (10.7%). Furthermore, there were two cases in the forehead (7.1%) and finally one in the nose (3.6%), no cases were seen in the neck nor in the chin [Table 2].

The lymphatic drainage pattern of the cheek trends toward the nodes of the high echelon: levels I, II, III, and V, including the parotid gland in all of the patients. The forehead shares this pattern, without draining to the Level I. The scalp not only has a tendency to follow this pattern

Figure 1: Preoperative node mapping with single photon emission computed tomography/computed tomography. (a) A 69-year-old patient with a Stage II squamous cell carcinoma squamous cell carcinoma of the lower eyelid. (b-c) Site of injection in planar imaging in lymphoscintigraphy (red arrows) and the sentinel lymph node (green arrows). (d-f) Single photon emission computed tomography/computed tomography images shows the site of injection (red arrows) and the location of the sentinel lymph node related to a lymph node on the Group II (green arrows)

Figure 2: Preoperative imaging: A 60-year-old patient with a Stage I melanoma of the scalp. (a) Computed tomography scan shows the lesion on the parietal right side (Primary tumor). (b-c) Planar images in scintigraphy show the injection site (red arrows), and the draining location: Group IIa (IIa) (blue arrows), intraparotid gland (IP) (green arrow), and retroauricular nodes (RA) (yellow arrow). (d-f) Single photon emission computed tomography/computed tomography images show the site of injection (red arrows) and the relation of the draining location with the parotid gland (green arrow), the Group II (blue arrow), and the retro auricular nodes (yellow arrows)

Table 2: Number of cases per oncological subunits

Subsite	Histology					Total
	Melanoma	SCC	Meckel cell carcinoma	Sebaceous carcinoma	Hidradenocarcinoma	
Forehead	2	0	0	0	0	2
Nose	1	0	0	0	0	1
Eyelid	2	1	0	1	0	4
Anterior cheek	5	1	1	0	0	7
Posterior cheek	3	0	0	0	0	3
Lips	0	3	0	0	0	3
Ear	3	1	0	0	0	4
Chin	0	0	0	0	0	0
Neck	0	0	0	0	0	0
Scalp	2	1	0	0	1	4

SCC: Squamous cell carcinoma

as well but also has a posterior drainage to the suboccipital nodes. All the anatomical subsites shared the level II as a common drain pattern, except the nose and lips that drained exclusively to the Level I. The ear went straight to level II and the suboccipital echelon. The sites and levels of drainage are listed on Table 3.

Twenty-three patients underwent NLND: 9 patients underwent SND, 5 SLNB, and the remaining 9 came in for selective neck dissection (4 to ALND, 4 to LND, and 1 to PLND), 19 of the 23 patients had a resection of the primary lesion as well. From these 23 patients, only six were re-injected in the same day of the procedure. Of those, five had a SLNB, the remaining drained to more than two contiguous lymphatic levels, and therefore a SND was carried out.

Seven patients with radiological involvement of the parotid level by SPECT/CT underwent a superficial parotidectomy [Figure 2a-f].

Four of the 28 patients injected at first were not operated: one where SLN was not detected, two had several comorbidities, and the last one was treated in other institution.

According to the pathological specimen, there were lymph nodes in the 23 patients who underwent NLND; hence, the effectiveness of the SPECT/CT for SLNM was 100%. Of the 28 biopsies from the primary lesion, 12 had a thickness between 1.51 and 4 mm (42.9%) and 8 patients (28.6%) more than 4 mm, only 7 patients had a thickness between 0.76 and 1.5 mm, and 1 patient <0.75 mm.

The patients were followed from the date of surgery, through clinical controls, and telephone contact. The median follow-up was 31.5 months and one patient had a maximum follow-up of 90.7 months. Recurrence rates at 7-year follow-up were 3.6% for systemic recurrence (pulmonary and bone metastasis), 3.6% for locoregional recurrence, and 3.6% for mortality. The patient with systemic recurrence was the same that passed away.

Table 3: Drainage of each oncological subunit of the head and neck to the lymphatic groups

Subsite	Drainage group						
	I	II	III	IV	V	Parotid	Suboccipital
Forehead	-	X	X	-	X	X	-
Nose	X	-	-	-	-	-	-
Eyelid	-	X	-	-	-	-	-
Anterior cheek	X	X	X	-	X	X	-
Posterior cheek	-	X	X	-	X	X	-
Lips	X	-	-	-	-	-	-
Ear	-	X	-	-	-	-	X
Chin	-	-	-	-	-	-	-
Neck	-	-	-	-	-	-	
Scalp	-	X	-	X	X	-	X

Discussion

SLN detection using lymphoscintigraphy planar imaging and the injection of isosulfan blue dye, in patients with early stage skin tumors of the head-and-neck region, it is considered difficult despite the advances on imaging in recent years.[2-8] The reasons are that the head-and-neck region contains a network of more than 350 lymph nodes and the tumors do not always follow a standard lymphatic drainage pathway.[8,9] This region has similar drainage pathways shared by the different topographical regions and has several overlapping networks of lymphatic vessels that may cross to the contralateral side for midline tumors (according to the distance of the primary lesion to the midline).[10,11] Finally, almost 21% of aberrant sentinel nodes may be localized outside a recognized lymphatic field.[12] Instead, SLNM by SPECT/CT helps provide a much clear road map by defining the drainage pathway for a given location and the sentinel node of every individual tumor, with a strong positive predictability value, helping to reduce the chance of false negatives biopsies.[13,14]

The description of oncological subunits of the skin of the head-and-neck region was needed, so we adapted the esthetical units described by Fattahi, Morton *et al*., and
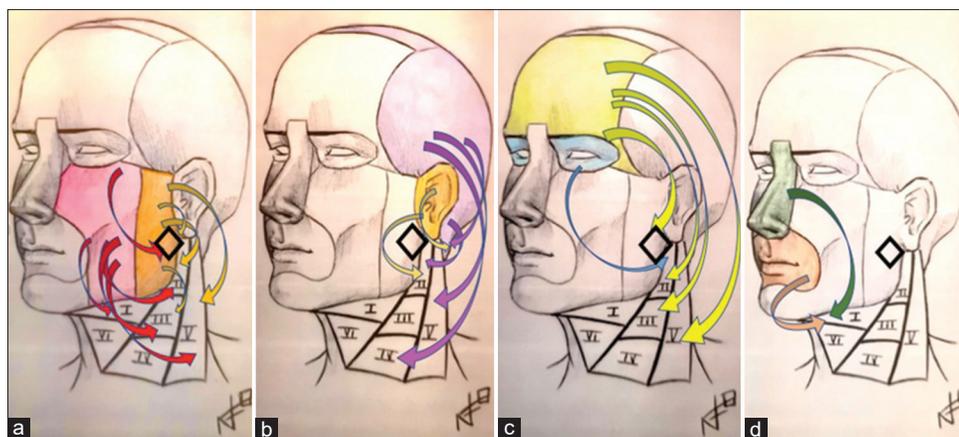
Figure 3: Lymphatic drainage per oncological subunits. (a) Anterior cheek (red, red arrows): groups I, II, III, V and parotid gland (◊). Posterior cheek (orange, orange arrows): Groups II, III, V, parotid gland. (b) Scalp (purple, purple arrows): Groups II, IV, and V and suboccipital. Ear (yellow, yellow arrows): Groups II, suboccipital. (c) Forehead (pale yellow, pale yellow arrows): Groups II, III, and V, parotid gland). Eyelids (blue, blue arrows): Group II. (d): Lips (orange, orange arrows): Group I Nose (green, green arrows): Group I

Uren.[2,6,15] This helped us to unify criteria on the lymphatic drainage of each cutaneous area of head-and-neck region and to derivate from our experience of analyzing the data obtained [Table 3].

We observed in our study that lateral subunits (anterior cheek, posterior cheek, ear, scalp, and eyelids) share a trend toward the level II in 60%, but Vauterin *et al*. reported a 79%[8] [Figure 3]. This demonstrates a common pathway of the skin tumors of lateral location. We did not find contralateral drainage on lateral subunits either which proves that the drainages do not cross the midline in early stages; therefore, any prophylactic dissection is dismissed. Consequently, we recommend to observe closely the level II with lesions thicker than 0.7 mm for melanoma or 4 mm for SCC, as it behaves as the common pathway of the lateral subunits.

The anterior cheek represented the majority of the cases (7 of 28), this subsite drained to the levels I, II, III, and V and to the parotid gland. We believe it is important to remark the parotid gland as a part of the usual echelons at the moment of the lymphatic screening. Suton *et al*. found 16.1% of metastatic compromise of the gland on skin melanomas with a thickness >0.7 mm and 86% for a thickness >4 mm.[16] Furthermore, Vauterin *et al*. and Suton *et al*. described occult metastasis with parotid involvement in 35% of patients with unfavorable SCC with a size >2 cm or thickness >4 mm.[8] Patients with parotid and neck involvement demonstrated poorer prognosis than patients with neck involvement alone, with almost a 40% of occult metastasis.[17]

It is important to be aware that intraparotid lymphatic nodes are frequently affected from metastatic spread of tumors from the lateral head subunits suggesting the need for a superficial parotidectomy along with a neck dissection, like we found in our study, especially in the cheek and forehead. Suton *et al*. recommend that patients

with cutaneous head-and-neck melanoma undergoing neck dissection for primaries originating in the face, forehead, coronal scalp, periauricular area, and upper neck should be considered for parotidectomy.[16] If the SPECT/CT shows positive findings, we suggest performing a superficial parotidectomy for skin tumors with a Breslow thickness >0.7 mm for melanoma, and >4 cm for SCC with clinically negative necks for the anterior cheek and forehead, but in the absence of positive of SLNM of the parotid, no parotidectomy is recommended.

Furthermore, we noticed that the scalp and the ear drained down to levels II and suboccipital, joining both paths on a common way, leading to the deep jugular lymph nodes. This confronts the theory of an anterior and posterior drainage pathways, divided by a line crossing along the two external auditory meatus, previously described in the studies of O'Brien *et al*. in 1995.[2,18] This supports the concept proposed by Pan *et al*. of a functional drainage based on groups (Scalp, Face, and Anterior Neck), where the lymphatic capillaries join sequentially. At first, to form a lymphatic vessel and end at a first level lymph node, combining anastomosis between the groups, in some cases bypassing the anatomical order.[10] Like Pan *et al*. we observed that scalp, forehead, anterior, and posterior cheek share a common echelon to level V,[10] supporting the advantage of SLNM by SPECT/CT in early stages of cutaneous tumors of head and neck.

The nose and lips drained to levels Ia and Ib exclusively, due to the proximity to the midline of this subsite; the contralateral level Ia should be observed if the lesion cross midline, where occult metastasis might appear [Figure 3]. If the primary lesion is located on the nose or on the lips, Group I should be included in the NLND.

Our study did not include patients with lesions on or near the midline, because they may have drainage on both sides of the neck.[9,12,19] Therefore, SLNM is not recommended in

these cases because lymphatic drainage can be bilateral and extended bilateral neck dissections increase morbidity with no evidence of a real benefit for the patients. Furthermore, there is a high probability of bilateral parotid drainage, forcing bilateral parotid dissection.[16,20] Lavelli *et al*. also recommend to avoid inappropriate or excessive neck dissection that could represent esthetic or/and functional limitations.[9,21]

Nearly 66% of the 24 patients with early tumor had a deeper Breslow in the final pathology. Probably because in the preoperative biopsy the sample was taken from the superficial tissue. Thompson *et al*. (*n* = 17.248) report a risk ratio of metastasis for SCC of 9.64 (1.30–71.52) (95% confidence interval) and 7.13 (3.04–16.72) for Breslow >2 mm and >6 mm, respectively.[22] Other authors inform that the risk of metastasis for melanoma is below 5% for a thickness of <0.8 mm and between 12% and 15% for lesions of 0.8–1 mm.[15,16] We found locoregional recurrence in a tumor thickness >1.50 mm.

We reinjected six patients before surgery. The SLNM before surgery helps the surgeon to take a better decision on SLNB or a selective/supraselective node dissection. This depends on the findings and allows more accurate incisions in node dissection, especially in complicated or difficult to approach locations, reducing the rate of neurovascular injury, and the operating time.[23,24]

The concordance between SLNM by SPECT/CT and final pathology of the 23 patients was 100%, which confirms that this preoperative diagnostic test is recommended for early-stage head-and-neck skin tumors.

Our preliminary results suggest that NLND following SLNM is an effective procedure and that SLN may be successfully identified and harvested in the majority of patients.

Our results have a big internal validity, but we cannot generalize them due to small sample size, this matter can be addressed in a future research through a controlled research including the disparity of the initial tumor locations and the low number of cases represented for most of them.

In addition, we believe that reinjecting all patients before surgery could have improved our results. Our institution is a reference center for oncological pathology in advanced conditions which results in a low number of cases in early stages.

Conclusions

Satellite lymph node detection, with conventional lymphoscintigraphy and planar imaging in head and neck, can be very difficult for precisely locate lymph node without anatomical landmarks. Due to unpredictable drainage, preoperative SPECT/CT is very useful to detect SLNs. SPECT/CT is important in the assessment of unexpected lymph nodes; it helps the study not only of the lymph node

drainage pathway but also the anatomical region. SLNM by SPECT/CT determines the exact anatomical location of the SLN, especially when injection site is close to the SLN.

This helps to perform a clear preoperative evaluation, an accurate staging for all patients and to avoid excessive dissections that could result in cosmetic and functional deformities.

There is also a high concordance between SLNs found by SPECT/CT and the histopathological results in early-stage malignant head-and-neck skin tumors.

We believe this data may be validated with a larger cohort, increasing the cases of early-stage tumors in order to complement the findings of this study.

Conflicts of interest

There are no conflicts of interest.

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