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HYBRID IMAGING SPECT/CT IN SENTINEL LYMPH NODE DETECTION IN PATIENTS WITH MELANOMA

MASTER THESIS

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ΥΒΡΙΔΙΚΗΑΠΕΙΚΟΝΙΣΗSPECT/CT

ΣΤΗΝ ΑΝΙΧΝΕΥΣΗ ΤΟΥ ΛΕΜΦΑΔΕΝΑ ΦΡΟΥΡΟΥ ΣΕ

ΑΣΘΕΝΕΙΣ ΜΕ ΜΕΛΑΝΩΜΑ.

ΜΕΤΑΠΤΥΧΙΑΚΗ ΕΡΓΑΣΙΑ

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ABSTRACT

Introduction: Sentinel lymph node (SLN) biopsy and its preoperative localization consist of an important advancement in the surgical approach of melanoma patients.

Purpose: The purpose of this study is the evaluation of the diagnostic value and the clinical impact of hybrid tomographic imaging (SPECT/CT) technique with 16 slices in detecting and localizing SLN(s) in patients with melanoma vs planar dynamic and static radioisotopic lymphoscintigraphy (PLSs, PLSd).

Materials and Methods: From January 2019 to November 2021 82 patients with melanoma located in the head-neck area (n=20), the trunk (32), on the upper extremity (14) and the lower extremity (16) were included in our study. All of them initially underwent planar PLSs and PLSd after intradermally injection of radiolabeled nanocolloid albumin particles with99mTc. Subsequently, hybrid imaging, single-photon emission tomography combined with computerized tomography (SPECT/CT) was performed. Qualitative analysis was performed in order to evaluate the number and location of the sentinel lymph node(s) in both imaging techniques and to assess the additional clinical value of SPECT/CT vs planar lymphoscintigraphy (PLS). Statistical analysis was performed for both imaging methods having as gold standard the histopathological report.

Results: According to the histology report, sentinel nodes were harvested84 anatomical regions, including the axilla in 52 patients (62%) and the inguinal and the head and neck region each in 16 patients (19.0%). Planar imaging resulted in localization of lymph node in 68anatomical areas: 55 (80.9%), axillary, 9 (13.2%) inguinal and 4 (5.9%) in the head and neck area. Summing the results of SPECT-CT imaging, the 86 lymph node localizations per anatomical region were: 53 (61.9%) axillary, 17 (19.8%) inguinal and 16 (18.6%) in the head and neck area. Agreement in localization was

measured using kappa statistic between histology report and both imaging techniques. SPECT-CT showed higher agreement with histological reports (kappa=0.525, p<0.001). Agreement between both imaging techniques was less than moderate (kappa=0.394, p<0.001). The location of lymph nodes measured using histological examination and those observed at SPECT/CT imaging showed a higher correlation (r=0.743,rs=0.770) compared to PLS(r=0.331,rs=0.223). PLS underestimates the number of lymph nodes in comparison to histology examination. Additionally, the number of lymph nodes estimated using SPECT-CT were closer to respective numbers from the histology report.

Conclusion: Hybrid SPECT/ CT is an important diagnostic method with high impact in daily clinical practice offering a contribution in the more precise preoperative evaluation of the number and localization of sentinel lymph nodes. The clinical impact of SPECT/CT is to help to a better therapeutic decision making by reducing the false negative and false positive results, especially in difficult cases with unpredictable lymphatic drainage like in pts with head and neck and trunk melanoma. Moreover, SPECT/CT is very useful in more precise staging, treatment approach, and prognosis of the patients.

Key words: sentinel lymph node, melanoma, planar lymphoscintigraphy, SPECT/CT

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Figure 16: A patient with a trunk melanoma. A) PLS: no SLNs found (false negative), (B and C) SPECT/CT confirmed 2 SLNs located in the right and left axillary region. According to the histology report 1 lymph node in each axilla was removed.

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Abbreviations

SSM	superficial spreading melanoma
NM	nodular melanoma
LMM	Lentigno maligna melanoma
AJCC	American Joined Committee on Cancer
SLN	sentinel lymph node
SLNB	sentinel lymph node biopsy
NCCN	National Comprehensive Cancer Network
BT	Breslow thickness
CLND	complete lymph node dissection
PLSs	planar static lymphoscintigraphy
PLSd	planar dynamic lymphoscintigraphy
CT	computed tomography
SPECT	single photon emission computed tomography
SPECT/CT	single photon emission computerized tomography/ computerized tomography

GENERAL PART

1. INTRODUCTION

1.1 MELANOMA

Melanoma is a type of skin cancer that develops from the pigment-producing cells referred to as melanocytes. This malignancy typically occurs in the skin but on rare occasions it can occur in the mouth, intestines or in the eye (uveal melanoma). Cutaneous melanoma is considered as the deadliest form of skin cancer.The incidence of malignant melanoma is drastically increasing worldwide while no decrease in mortality is observed even with the new and advanced imaging techniques, diagnostic tests and therapies (better surgical management, new methods of chemotherapy)(Helgadottir et al., 2018)(Lowe et al., 2014)(Benvenuto-Andrade et al., 2005).

There are several risk factors for melanoma. Among them great impact have factors like age, sex, skin colour, sun exposure, occupation and positive family history of melanoma or other skin cancer on a 1st degree relative(Carr et al., 2020), (Markovic et al., 2007).

1.2 EPIDEMIOLOGY

Although the incidence of several malignant diseases decreases the incidence of malignant melanoma continues to increase dramatically. Less than a century ago malignant melanoma was a rare not commonly seen cancer but today it is the 14th most common malignancy of women and 18th most common in males in Greece. According to SEER (Surveillance, Epidemiology and End Result program) 1 in 63 Americans will develop melanoma during their lifetime(Prieto-Granada et al., 2016).

Incidence rates vary in Europe. The highest rate is observed in Scandinavian countries and in Mediterranean populations reaching up seven cases in 100.000 people. Parallel to the increase in melanoma incidence, there is an increase in melanoma mortality. According to Rigel et al., from 2003 to 2007 the median age of death from malignant melanoma in America was 68 years. Unlike other common solid tumours, melanoma has a higher chance to appear in young or middle-aged individuals with a median age at the time of diagnosis been 57 while the incidence linearly increases after the age 25 up to the age 50 and then decreases(Rigel et al., 2010). According to Marcovic etal., males are about 1.5 times more likely to develop melanoma than females and Caucasians about 10 times more than black(Markovic et al., 2007)(Ries et al.,2000).Other studies mention that age is a higher risk factor over gender.

1.3 RISK FACTORS

The most important risk factor for malignant melanoma is the exposure in UV radiation due to its genotoxic effects. According to Elwood et al. in the correlation between malignant melanoma and sun exposure concludes that intermittent sun exposure, sunburn, or history of sunburns in childhood are major determinant factors for melanoma development(Mark Elwood & Jopson, 1997)

The number of melanocytic nevi is an important parameter for melanoma development. Approximately 25% of melanoma cases occur in conjunction with a pre-existing nevus. Recent meta-analyses have concluded that patients with more than 100 nevi are in a 7-fold risk of developing this malignancy fact augmented by the greater size (>20cm)(Balch et al., 2009)(Gandini et al., 2005).

Tsao et al. studied families with inherited melanoma demonstrating the presence of a clear pattern of autosomal dominant inheritance with multiple family members affected in more than the first generation. The most common genetic abnormalities found in these families were mutations in cyclin dependent kinase inhibitor 2A (CDKN2A or p16), whereas mutation in cyclin-dependent kinase 4 (CDK4), was a more rare event (Tsao & Niendorf, 2004).Additionally, patients with family cancer syndromes, e.g. familial retinoblastoma, Li-Fraumeni syndrome and Lynch syndrome type II, show higher risk of developing melanoma (Markovic et al., 2007).

Several phenotypic characteristics such as red hair, fair skin, numerous freckles, light eye colour, sun sensitivity and an inability to tan, raise the risk of developing melanoma by approximately 50%(Titus-Ernstoff et al., 2005).

1.4CLASSIFICATION

Based on the clinical and histological features of the lesion, melanomas can be divided into 3 main subcategories: superficial spreading melanoma (SSM), nodular melanoma (NM) and lentigo maligna melanoma (LMM). Less common is the type of Spitzoid melanoma and desmoplastic melanoma(Helgadottir et al., 2018)(Balch et al., 2009).

Superficial spreading melanoma (SSM). SSM is the most common type of melanoma accounted for approximately 70%. It is related to intermittent sun exposure, and it is localized most often on the posterior side of the trunk and legs on both genders. SSMs may arise de novo or in conjunction with a nevus. From the clinical point of view, this cancer shows a variety of colours including tan, brown, grey, black, violaceus, pink and rarely blue or white. The lesion outline is usually sharply marginated

with one or more irregular peninsula-like protrusions. The surface may have a palpable papule or a nodule that extends several millimetres above the skin surface(McGovern et al., 1973).

Nodular melanomas(NM). It accounts for 5% of melanomas, most often occurs on the trunk and limbs of patients in the fifth or sixth decade of life and it is more common in males than females. NMs are often ulcerated, do not have a radial growth phase but only a vertical growth phase correlated with more rapid growth and higher rate of metastasis. Clinically, NMs have a relative uniform brown, black, or blue-black colour; they can present as a smoothly surfaced nodule, as an ulcerated polyp or as an elevated plaque with irregular outlines. In almost 50% of cases, NMs can be achromic. Their development is highly related to the intermittent exposure to the sun. Histologically, NMs are characterized by a predominance of dermal invasive tumour. An intradermal component may be present but directly overlies the invasive melanoma. The tumour is composed of small nests and aggregates of cancer cells that together form the overall malignant nodule (McGovern et al., 1973).

Lentigo malignamelanoma (LMM). LMM accounts for 4% to 15% of cutaneous melanomas and, unlike NM and SSM, correlates with long-term sun exposure and increasing age. This type of cancer has a slow progression and may evolve for decades before invading into the papillary dermis. Clinically, it shows a variety of colours black, brown, or brown on a tan background. It has irregular outlines and although the tumour is often relatively large and flat, a focus of invasion may be detected as a papule. It is located mainly at the neck and head. Histologically, it is characterized by a proliferation of cells that are localized to the basal layers of the epidermis (McGovern et al., 1973).

1.5 GRADING-STAGING

Cutaneous malignant melanoma is currently staged using the eighth edition of the AJCC staging system, which was implemented in the United States in January 2018. The staging is based on Tumour size(T), locoregional dissemination to the lymph nodes (N), and distant Metastasis (M) classification and grouping criteria(Medical et al., 2017)(Balch et al., 2009).

- **Tumour stage**

The tumour stage determination is based on Breslow thickness and the presence or absence of ulceration. Ulceration is determined based on histopathological examination and is defined as the full-thickness absence of epidermis above any portion of the primary tumour. Ulceration of the lesion is the parameter that helps us differentiate between the Ta and Tb group. Mitotic rate is no longer a T category criterion even though it is thought to have prognostic significance, and assessment of mitotic rate is recommended (McDivitt Duncan, 2009).

- **Node stage**

Node (N) stage identifies metastases to the regional or distal lymph nodes and non-nodal regional sites, including in-transit, micro-satellite, satellite, and subcutaneous metastases. Regional lymph nodes detected clinically or radiographically are designated as “clinically apparent,” while nodes detected only on sentinel lymph node biopsy are labelled “clinically occult.”

Satellite metastases include clinically evident cutaneous or subcutaneous metastases occurring discontinuous from and less than 2cm from the primary tumour, whereas micro-satellite and

satellite metastases refer to similar lesions but clinically non-evident and only detected microscopically. In-transit metastases include metastases discontinuous from and more than 2cm from the primary tumour. Two or more nodes adherent to one another detected, are classified as matted nodes. N categories are further subcategorized using descriptors for clinically occult (N1a, N2a, N3a), clinically apparent (N1b, N2b, N3b), and non-nodal locoregional metastases (N1c, N2c, N3c) (McDivitt Duncan, 2009).

- **Metastasis stage**

M stage designates distant metastasesfrom the location of the primary lesion is further stratified based on the site of metastases whether it is on soft tissues, organs or bony structures(McDivitt Duncan, 2009).

- **Clark level**

In the past in order to evaluate the staging of the melanocytic lesion, Breslow index and Clark levels should be evaluated, but nowadays Clark level is considered a poorly reproducible parameter. Clark level defines 5 different levels of infiltration of melanomas as referred to in 1969 Clark et al. (Ross, 2010)(McGovern et al., 1973).

1. Level I: all the tumor cells above the basement membrane (in situ melanoma).
2. Level II: the neoplastic cells have broken through the basement membrane and extended into the papillary dermis.
3. Level III: the neoplastic cells infiltrate the papillary dermis up to the interface with the reticular dermis.

4. Level IV: the neoplastic cells extend in depth among the bundles of collagen characteristic of the reticular dermis.
5. Level V: the cancer has spread into the subcutaneous tissue.

1.6 PROGNOSIS

Melanoma is considered a multifactorial disease that arises from a combination of genetic and environmental factors. The most important prognostic factors are the age, the performance status assessed by ECOG (Eastern Cooperative Oncology Group)(Azam et al., 2019) as well as the depth of the melanoma (measured by Breslow index) and the TNM staging. Moreover, detection of the sentinel lymph nodes (SLNs) by new imaging techniques such as hybrid SPECT/CT and PET/CT diagnostic modalities of nuclear medicine and proper treatment methods such as surgical approach, immunotherapy and chemotherapy are also especially important prognostic tools. All these parameters are particularly important for the therapeutic management and the improvement of quality of life (QOL) of patients with melanoma.

2. DIAGNOSIS

The diagnosis of melanoma requires a coordinated multidisciplinary effort involving surgeons, dermatologists, nuclear medicine physicians, and pathologists. Histopathological examination remains the gold standard diagnostic method. Early detection is the key in lowering its mortality rates and maximizing the prognosis potential.

- *Skin self-examination*: This diagnostic method has great potential for screening for melanomas or precancerous lesions. In the 80s melanomas were identified by their

macroscopic features and detected in advanced stage. The ABCD criteria were developed in 1985. The ABCD acronym stands for Asymmetry, Border irregularity, Color variegation, Diameter >6 mm. Later the letter "E" was added for Evolving, which is especially important for the diagnosis of nodular melanomas. The sensitivity for melanoma detection of this method ranges from 57 to 90%. Due to this range, there is the necessity of additional clinical diagnostic approaches to be developed in order to enhance the early and accurate diagnosis. For this purpose, Glasgow 7-point checklist was created which includes 3 major criteria (change in size, shape, color) and 4 minor criteria (sensory change, diameter of 7 mm or greater; and the presence of inflammation, crusting or bleeding)(Marsden et al., 2010).

- *Dermoscopy*: In order to properly diagnose a melanoma, assistive optical devices are necessary. Those devices include high-resolution dermoscopes or dermatoscopes or epiluminescent microscopes. Dermoscopy is a noninvasive diagnostic technique for in-vivo observation of the skin permitting visualization of structures not visible with the naked eye. Accuracy of melanoma detection of this method is higher than in simple skin self-examination because it renders early disease signs visible in the pigmented lesions much before clinical changes appear.
- *Total-body photographic images and short-term surveillance*: Some melanomas can be diagnosed neither with the naked eye (self-examination) nor dermoscopically. With total-body photographic images it is possible to create images that can be electronically captured, archived, retrieved and analyzed. In this way it is possible to detect minimal changes in the first stages of melanoma development. With this approach it is possible to follow the dynamic evolution of the melanocytic naevi over time (Neila & Soyer, 2011).

- *Reflectance Confocal Microscopy (RCM):*It is a valuable imaging tool in the diagnosis of malignant melanocytic lesions, allowing the non invasive examination of native skin in real-time at a nearly histologic resolution(Hofmann-Wellenhof et al., 2009).

3.SENTINEL LYMPH NODE CONCEPT

The regional lymph nodes are the most common site of metastatic dissemination from melanoma.However, randomized studies revealed no clear advantages when a prophylactic regional lymph node dissection was carried out. In 1992 Morton et al. described the concept of sentinel lymph node biopsy (SLNB) in 223 patients with melanoma(Morton et al., 1992). Melanoma first drains to a specific regional lymph node, the SLN or first echelon node, before involving other nodes, known as second echelon nodes. SLN is defined as a node receiving lymphatic drainage directly from the primary tumour. Tumour cells are present in the SLN before subsequent nodes in the regional basin become involved. Therefore, the tumour status of the SLN indicates the overall nodal status(Tew & Farlow, 2017). The SLN is not per se located in a typical regional lymph node basin, as the axilla, the inguinal region or the neck, but may at an unexpected site (Figure 1).

The classical SLNB concept implied that in the case of no SLN metastatic involvement the rest of the lymph nodes in the regional basin could be considered as disease-free as well as in the cases of unexpected lymph node site drainage, sparing these patients for a regional lymphadenectomy, which was reserved only for patients with SLN-containing metastases (Perissinotti et al., 2018). Long-term postsurgical complications like lymphedema of the lower limb after SLNB in the groin, are presented in up to 18% of cases, but are significantly less common than after (prophylactic) lymph node dissection(Perissinotti et al., 2018). The explanations for false negative SLNB are various and include inadequate preoperative SLN localization by lymphoscintigraphy.

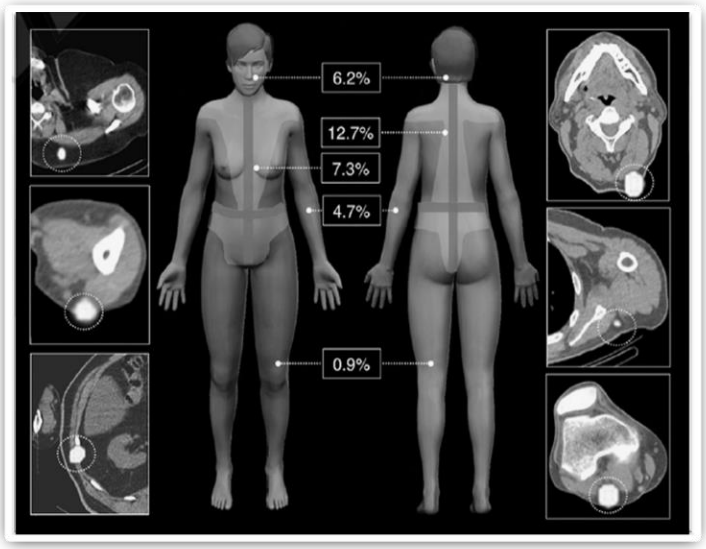

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Figure 1: Percentages of unexpected lymphatic drainage

SLNB is a validated technique that enables accurate staging with low morbidity. It is primarily used in patients with early-stage breast carcinoma and skin melanoma. SLNB has become the standard of care for patients with malignant melanoma and is now routine practice in the lymphatic staging of early melanoma. This procedure provides significant prognostic information and can identify those patients who should undergo lymphadenectomy immediately. The reported false negative rates (i.e., patients with positive non-SLNs or nodal recurrence after a negative SLNB divides by all patients with nodal disease, false negative and true positive) ranged up to 38%. The overall estimated risk of nodal recurrence after a negative SLNB was found to be 5% or less(Testori et al., 2009)(Nieweg, 2009).

The most important indication of SLNB is the disease staging. The National Comprehensive Cancer Network (NCCN) indication for SNB is Breslow thickness ≥0,8mm but also for thinner melanoma with risk factors like ulceration, high mitotic rate, lymphovascular invasion. However, 25 years after

its introduction in clinical practice, several questions still remain to be answered about SLNB in melanoma (Ferrara et al., 2018).

(i) Patients older than 70 years: in these patients the lower incidence of nodal metastasis and the higher 5-year mortality rate discourage SLNB (Ferrara et al., 2018);

(ii) Breslow thickness>4 mm (pT4) and/or micro and macro-satellitosis (pN2c): the high disease stage makes SNB just to achieve a palliative locoregional control of the disease.

(iii) Cases of regression: this may underestimate Breslow thicknessbut might be even a favorable prognostic factor.

(iv) Cases of desmoplastic subtype.

- Several questions arise also about the clinical prognostic impact of SLNB. The Multicentre Selective Lymphadenectomy Trial-1 (MSLT-1) compared the 5-year and 10-year outcome of patients with melanoma ≥1.20 mm thick who were randomly assigned to an SLNB arm (with complete lymph node dissection [CLND] if SLNB+) or an observation arm (elective lymph node dissection if clinical nodal relapse). After 10 years, the rate of nodal relapse after a negative SLNB was much lower than the nodal relapse rate in the observation arm (4% vs. 17.4%), thus confirming that SLNB is effective in selecting patients for CLND and locoregional disease control. More importantly, in intermediate thickness melanomas (1.2-3.5 mm Breslow thickness) SLN positive patients had a better 10-year melanoma-specific survival compared with the nodal relapsing patients of the observation group (62.1 ± 4.8 vs. 41.5 ± 5.60%)(Morton et al., 2014)(Ferrara et al., 2018). However, for the entire group of melanoma patients, including the entire group of all patients with intermediate thickness melanoma (irrespectively of the nodal status), no melanoma-specific survival benefit could be observed for SLNB and CLND. The role of CLND has become a topic of debate after publication of two recent randomized trials, the DeCOG-SLT and the MSLT-2 trial.

The first, underpowered, trial did not demonstrate improved outcome after CLND(Leiter et al., 2016) The MSLT-2 trial, which had however significant methodological flaws, demonstrated the prognostic significance of the status of the non-SLNs and improved locoregional disease control at the cost of increased surgical morbidity and the absence of overall survival benefit. Notably, in the control group patients were intensively followed with specific nodal sonography and underwent early lymph node dissection at nodal recurrence(Wong et al., 2018, Faries et al, 2017).

Current NCCN guidelines do not recommend routinely CLND for SLNB positive cases and the benefit of more prognostic data and improved locoregional disease control should be weighed against the costs and morbidity risk of CLND

Indications of SLNB in patients with melanoma

The various guidelines agree that it is appropriate to offer SLNB to those patients presenting a clinically localized melanoma with a significant risk of nodal involvement, depending on histopathologic characteristics of the melanoma(Chakera et al., 2009)(Ross, 2006). SLNB can be considered in patients with a clinically localized invasive melanoma of Breslow thickness >1 mm and in selected patients with a melanoma of Breslow thickness 0.8-1.0 mm, and regression with documented thickness of ≥1 mm or regression of more than 50–75 % of the whole pigmented lesion(Tew & Farlow, 2017).

In cases with Breslow thickness melanoma <0.8 mm, SLNB is generally not recommended, as the risk of lymph node involvement is very low. For Breslow thickness from 0.8 to 1 mm, some authors recommend SLNB since the risk for regional lymph node metastases is nearly 5%(Martínez Castillo et al., 2014). SLNB is offered to all patients with a melanoma lesion thickness from 1 to 4 mm due to the 8–30% risk of nodal metastasis (Bellew & Del Rosso, 2011). The indication in these patients

is warranted because of the need for staging and obtaining prognostic information, accordingly providing adequate adjuvant treatment. Patients with melanoma thicker than 4 mm present a possible nodal involvement in around 40% and a higher risk of distant metastasis; however, metastatic lymph nodes are usually clinically non palpable, so SLNB may constitute important prognostic information and may be relevant to prevent regional recurrence(Ceilley& Wilson, 2011).

Key Recommendations

- Thin melanomas: Routine SLN biopsy is not recommended for patients with melanomas that are T1a (nonulcerated lesions < 0.8 mm in Breslow thickness). SLN biopsy may be considered for T1b patients (0.8 to 1.0 mm Breslow thickness or < 0.8 mm Breslow thickness with ulceration) after a thorough discussion with the patient of the potential benefits and risks of harm associated with the procedure (Type of recommendation: evidence based; potential benefits outweigh risks of harm; Quality of evidence: low to intermediate; Strength of recommendation: moderate).
- Intermediate-thickness melanomas: SLN biopsy is recommended for patients with melanomas that are T2 or T3 (Breslow thickness of > 1.0 to 4.0 mm) (Type of recommendation: evidence based; potential benefits outweigh risks of harm; Quality of evidence: intermediate; Strength of recommendation: moderate).
- Thick melanomas: SLN biopsy may be recommended for patients with melanomas that are T4 (> 4.0 mm in Breslow thickness), after a thorough discussion with the patient of the potential benefits and risks of harm associated with the procedure (Type of recommendation: evidence based; potential benefits outweigh risks of harm; Quality of evidence: low to intermediate; Strength of recommendation: moderate).

Table 1: Indications of SLNB in patients with melanoma according to ASCO and SSO guidelines (Wong et al., 2018).

SLNB is a procedure that involves a multidisciplinary team requiring a close cooperation between nuclear medicine physicians, surgical specialists, and pathologists. It is very useful in selecting patients for a better locoregional disease control and is considered nowadays the standard of care in the majority of clinical guidelines.

4.RADIOISOTOPIC TECHNIQUES FOR SLN DETECTION

The detection of SLNs is performed before the SLNB (preoperative detection) and during surgery (intraoperative detection). Preoperative detection is based on radioisotopic techniques and intraoperative detection can be performed with radioisotopic and/or non radioisotopic methods. Radioisotopic detection techniques are advantageous. The reason is because the localization of the sentinel lymph node can be achieved preoperatively even before the first incision and confirming the location also during the surgery (intraoperative). Those methods allow us to evaluate the exact location and number of sentinel lymph nodes and reduce the need for an extended lymph node resection in search of SLN and all the side effects an extensive surgery could be associated with.

For both pre and intraoperative detection a radiotracer, a substance labelled with an isotope, is used. Nanocolloid particles labelled with 99mTc are administered intradermally (2-4 injections) around the site region of primary or excised lesion. These nanocoloid particles are transferred through the lymphatic system to the lymph node and because they have the proper size and affinity and then they are trapped by macrophages of lymph nodes by the process of phagocytosis.

RADIOTRACERS

Various radiotracers, primarily 99mTc-based agents (t½=6 h), have been used for lymphatic mapping in melanoma worldwide. The radiotracer drains from the injection site via lymphatic vessels and is accumulated in the SLN by phagocytosis of macrophages or retention due to particle size. Often, a fraction of the radiopharmaceutical moves on to second- and third-echelon nodes downstream. Smaller particles are drained more quickly to the SLN but also tend to accumulate in non-SLNs. Large particles migrate more slowly and are retained in the SLN. There are no

documented differences in the clinical outcome with different particle sizes (Tew & Farlow, 2017). The choice of the ideal radiotracer is usually based on availability: 99mTc-albumin nanocoloids in Europe, 99mTc-antimony trisulphide in Australia and Canada and 99mTc-sulphur colloid in the US. Small particles such as 99mTc-antimony trisulphide (mean size 5 – 30 nm) drain quickly, and imaging is usually completed 1 – 3 h after administration. When medium-sized particles (50 – 200 nm) are used, nodes may not be clearly visible after 1 – 2 h and additional images should be acquired after 4 – 6 h or even the next day. This must be taken into consideration in a 1-day protocol. In Europe, small or medium-sized colloids are commonly used (Nanocoll®, human serum albumin nanocolloid, 5 – 80 nm; Nanocis®, rhenium sulphide nanocoloid, 50 – 200 nm). Particles >200 nm move slowly and remain predominantly at the injection site. Therefore, 99mTc-sulphur colloid, with a maximum size of 350 – 5, 000 nm, should be filtered with a 100- to 200-nm membrane filter after preparation of the radiopharmaceutical to select smaller particles. A further radiotracer was approved by the US Food and Drug Administration (FDA) in 2013 and received a positive statement from the European Medicines Agency in 2014: 99mTc-tilmanocept (Lymphoseek®), which is a mannosyl diethylene triamine penta-acetate (DTPA) dextran that targets the CD206 receptor. The molecular size is 7 nm, but accumulation in SLNs is not dependent on particle size as with the other colloids. Tilmanocept binds to mannose receptors expressed by reticuloendothelial tissue including macrophages and dendritic cells in lymph nodes, which present it to T-cell lymphocytes in lymph nodes. The advantages of this tracer include rapid clearance from the injection depot and low accumulation in second-echelon nodes. This novel radiotracer might be of utility in patients with head and neck melanoma. Labelling, injected activity and volume Labelling should be performed according to the product information provided by the manufacturer. The commonly used radiotracers are labelled with 99mTc-pertechnetate and a radiochemical purity of ≥90 – 95 % should be confirmed before injection. 99mTc labelling of human serum albumin colloid proceeds within 10

min at room temperature while sulphide, rhenium, and antimony colloids require heating. It is important to pay attention to the specific activity (number of decays per second per amount of substance) and the number of particles administered. Based on the assumption of a limited clearing capacity of the macrophages in the SLN, it has been suggested that the maximum activity of 99mTc should be loaded onto the smallest number of particles. Labelling at higher specific activities has been demonstrated to result in higher nodal count rate for the same administered activity. Although the kit reconstitution instructions allow the addition of 185 to 5,550 MBq in a volume of 1 to 5 ml (Tew & Farlow, 2017), it is recommended that 99mTc-human serum albumin colloid be prepared at a minimum activity concentration of 100 MBq/ml (i.e. to deliver 20 MBq in 0.2 ml) at the time of injection and, wherever possible, the maximum reconstitution volume be used (e.g. ≥500 MBq in 5 ml). Colloids are suspensions and may therefore settle by gravity if the syringe is not moved for more than a few minutes. Before injecting the radiopharmaceutical, the syringe therefore must be tilted, but not shaken, to distribute the tracer in the suspension homogeneously. Until now, no consensus on the injected activity has been reached. The administered activity depends on the time between lymphoscintigraphy and operation (1-day or 2-day protocol) and varies among published studies (from approximately 5 MBq up to 120 MBq).

Radiolabelled nanocolloid has been combined with ICG (ICG-99mTc-NanocollR) to assist the intraoperative identification of SNs located in areas of difficult surgical access such as pelvic nodes from prostate and vulvar cancer or lymph nodes situated in complex locations as in cases of head and neck cancer. These hybrid agents for bimodal imaging combine radioactivity and fluorescence in one signature. It can be also used for SPECT/CT imaging.

The radiotracer is intradermally injected around the primary lesion or the scar of the excised melanoma. The number of injections depends on the size of the lesion/scar and on the anatomical

region. The radiotracer is injected around the primary tumour or on each side of the centre of the excision biopsy scar, usually in four or more aliquots. Fewer deposits may be injected if appropriate (Tew & Farlow, 2017). In head and neck melanoma, the radiopharmaceutical should be injected in four equal deposits (3, 6, 9, 12 h) around a primary lesion because of the often-complex lymphatic drainage to multiple lymph nodes. In trunk melanoma, at least four separate tracer injections might be preferred. In melanoma of an extremity, at least an injection medial and lateral to the tumour must be performed to mimic lymphatic drainage from the tumour. The injected volume is 0.1 – 0.2 ml per aliquot, depending on the location of the primary tumour. The volume needs to be small because of the intradermal injection of radiocolloid. If the volume is too large, lymphatics may collapse or the wheal on the skin surface may rupture. Subcutaneous injection should be avoided because it may not reflect the lymphatic drainage from the cutaneous melanoma. The distance from the injection site to the scar or tumour should not exceed 1 cm. The injected dose depends on the injected radiopharmaceutical.

PREOPERATIVE DETECTION OF SLN(s)

Preoperative detection of SLN(s) is based primarily on ***planar static (PLSs)*** and ***dynamic (PLSd) lymphoscintigraphy***techniques.Recently, hybrid imaging methods such as **SPECT/CT** seems to have an important role on SLNs preoperative detection. The hybrid SPECT/CT imaging technique is the preferred method of sentinel lymph node detection due to its ability to give us not only anatomical but also functional information. The usefulness of this diagnostic technique is more prominent in the cases of an unexpected SLN drainage of the lesion and in cases that a single lesion has more than one SLN.

Planar lymphoscintigraphy

Lymphoscintigraphy for lymphatic mapping in the SLNB procedure was incorporated in the early 1990s. Preoperative planar lymphoscintigraphy (PLS) can depict all lymph node locations that might be at risk for metastases, providing a roadmap to guide the intervention. PLS is performed by using conventional gamma cameras. Gamma rays emitted by the radiotracer (radiolabeled nanocoloid particles) given by subdermal injections to the patient, travel through the holes in the collimator to strike the radiation-sensitive crystal(**Figure 2**).

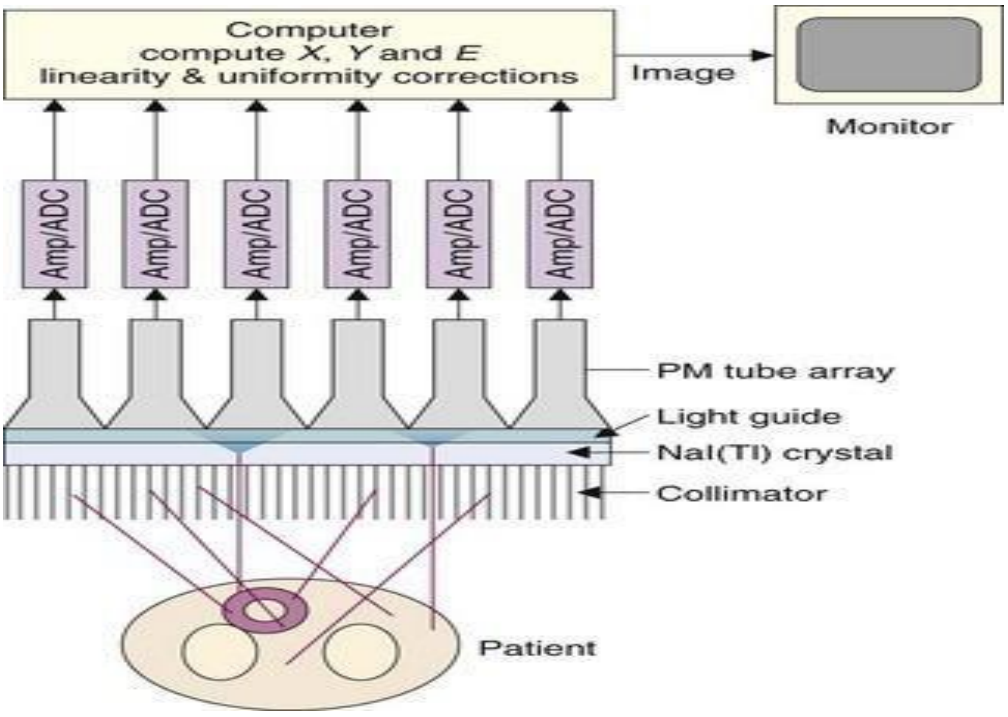


Figure 2: Conventional γ-camera

Early planar dynamic lymphoscintigraphy (PLSd) is recommended as it allows the visualization of the radiotracer's passage through the lymphatic ducts and its arrival and trapping in the first SLN(s). Subsequently, early, and late planar static lymphoscintigraphy (PLSs) is performed.

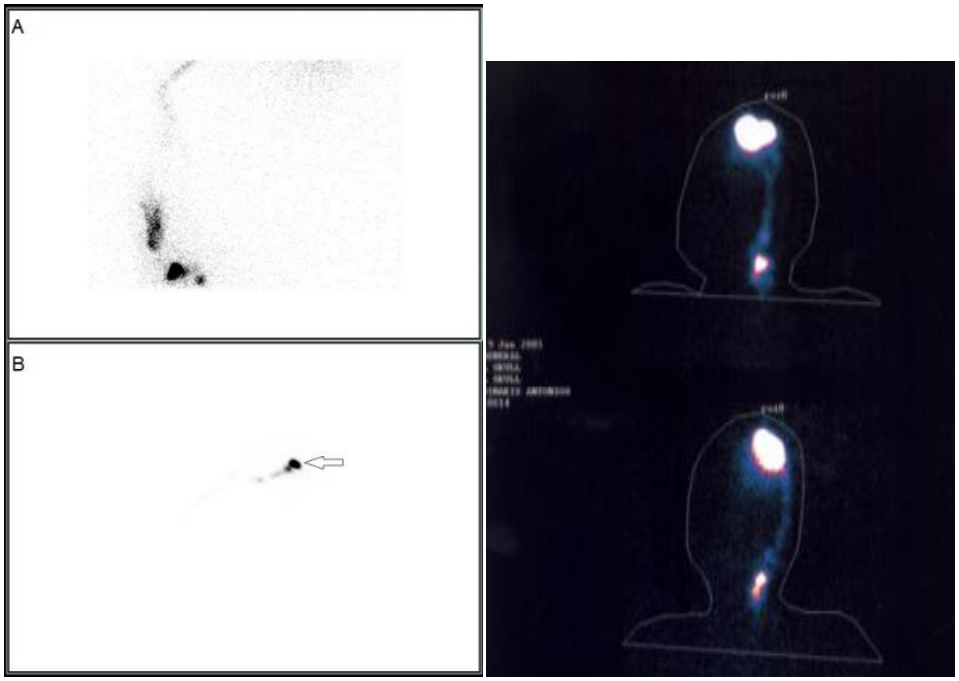


Figure 3. Planar dynamic lymphoscintigraphy (PLSd)

Early images help to discriminate true SLNs from the second-echelon nodes that are often observed. Static images are obtained in several anatomic regions depending on the site of the primary melanoma and the possible lymphatic drainage basins.

The additional use of dynamic imaging is essential for melanomas due to the unpredictable lymphatic drainage mostly for head and neck melanomas and for trunk melanomas. Lymphatic drainage in these cases tends to have uncertain patterns, whereas drainage from the limbs tends to be more consistently into the axillary or inguinal anatomic regions. PLSd imaging is also useful to distinguish any true SLN from a second-tier node, which can be falsely interpreted as true SLN on PLSs imaging.

There is a learning phase for a lymphatic mapping team. A recent study at a specialized melanoma centre showed a 5.7 % false-negative rate over a 15-year period, but the rate was 29.4 % in the first year (Tew & Farlow, 2017).

Causes of false negative results may be imaging of the wrong nodal basin, or failure to depict all potential drainage basins, failure to visualize the afferent lymph vessel, or failure to detect SLN(s) in an unusual anatomical region. Furthermore, metastases in the SLN(s) inhibit tracer accumulation in these nodes. Sometimes, the time between lymphoscintigraphy and the surgery, is so long that the radioactive node can no longer be traced. If this occurs, the patient can be reinjected before the surgical procedure is started (Tew & Farlow, 2017).

False positive findings should be due to skin contamination arising from the injection or urinary contamination may be misinterpreted as a lymph node, while second-echelon nodes may be misinterpreted as SLNs if no early dynamic or static images are acquired.

Hybrid imaging modalities in the preoperative detection of SLN(s) in patients with melanoma. PET/CT and SPECT-CT lymphoscintigraphy

Nuclear medicine procedures for SLNB such as PET/CT and SPECT/CT have remarkably improved the accuracy of melanoma staging. The contribution of nuclear medicine to management of melanoma patients is increasing. Among the preoperative techniques the most essential role has the radioisotopic PLSd and PLSs and the most recent hybrid imaging single photon emission computerized tomography/computerized tomography (SPECT/CT). Preoperative lymphoscintigraphy transformed the original 'open and see' paradigm into a **'see and open'** approach offering the possibility to visualize the melanoma's lymphatic drainage pattern, thus helping the surgical plan (Perissinotti et al., 2018).

Imaging modalities, including contrast-enhanced computed tomography (CT) and 18F-fluorodeoxyglucose (18F-FDG) PET/CT, have a much lower sensitivity for the detection of small lymph node metastases compared with SLN SPECT/CT imaging. This is because of the limited value

of CT in characterizing a metastatic lymphnode due to the size criteria(Wagner et al., 2013)(Perissinotti et al., 2018).

Moreover, PET has several limitations: small lymph node metastases are either not resolved on PET because of reduced spatial resolution. However, 18F-fluorodeoxyglucose PET/CT is useful in clinical staging and treatment decision as well as in the evaluation of therapy response. Positron emission tomography, as diagnostic modality, can depict metabolic changes that precede anatomic alterations. The most used radiotracer for PET in oncology is FDG because of its capability to represent the neoplastic hypermetabolism due to the incremented glucose consumption of cancerous lesions. Melanoma lesions are highly avid for FDG, allowing the use of FDG-PET/CT in selected melanoma patients. PET/CT with 18F-FDG may play an important role in determining which lesions should be surgically removed in cases of lymph node metastases in stage III patients and in cases of oligometastatic disease in stage IV patients(Perissinotti et al., 2018).

Since 1990s important technical advances like single-photon emission computed tomography images with integrated computed tomography (SPECT/CT) and intraoperative portable imaging devices participate in routine clinical practice.SLN SPECT/CT provides complementary functional and anatomical information and seems to be superior to PLSs in several indications. Although SPECT can improve the possibility of localizing a lesion with increased uptake, normal activity on structures maybe more difficult to be identified. Recently, a new imaging device combining a dual-head gamma camera with low-dose CT has been introduced, thus permitting attenuation correction and correct fusion of SPECT and CT images taken during the same session without moving the patient or using external markers and difficult mathematical algorithms.

SPECT/CT hybrid diagnostic imaging can provide additional information that improves the diagnostic accuracy and confidence of planar and SPECT interpretation and leads to changes in therapeutic options in about 37% of patients(Quartuccio et al., 2020).

PLSs and PLSd cannot give accurate anatomic information about the exact localization of SLNs. The introduction SPECT/CTdiagnostic imaging method offering a 3D imaging seems to have an essential role in the concept of SLNB. SPECT/CT seems to have several advantages over PLS. Modern gamma cameras can acquire SPECT/CT and fuse the functional SPECT images with the anatomical data from CT in three dimensions(Perissinotti et al., 2018). This modality implements higher resolution images that significantly enhance the 'see and open' approach. They provide better anatomical localization and can modify the evaluation of PLSs and PLSd in terms of number and localization of SNs. Furthermore, SPECT/CT can discriminate precisely the activity arising from two closely placed nodes that are usually depicted as a single hot spot on PLS. Hybrid imaging with SPECT and CT including anatomical information improves the localization of SLNs and reduces misinterpretation of images.

Images obtained by SPECT/CT are three-dimensional and have better contrast and spatial resolution than planar images. For SPECT/CT, a higher overall SLN detection rate and better detection of SLNs located next to the injection site have been reported, and in addition there is a significant cost reduction. SPECT/CT should be performed in head and neck melanoma owing to the complex anatomy. Moreover, SPECT/CT is highly recommended for the groin area and recommended for the axillary area because it facilitates the detection of in-transit nodes and aberrant lymphatic drainage stasis in lymph vessels and consequently facilitates the surgical procedure(Tew & Farlow, 2017)(Quartuccio et al., 2019).

SPECIAL PART

1. Purpose

The main purposes of this study are: a) to evaluate the role of a new hybrid imaging modality SPECT/CT 16 slices in detecting the sentinel lymph nodes (SLNs) preoperatively and during the surgery and b) to compare the hybrid imaging SPECT/CT with the PLSs and PLSd imaging methods and

2. Materials and methods

2.1 Patients

All patients admitted to this study derived from the University Hospital of Heraklion, Crete and the study was approved by the hospital ethics committee. Between January of 2019 and December of 2021, a total of 82 patients (31female and 51male) with mean age (years 63.5 $\pm$ 15.5) with different types of histopathologically proven cutaneous melanoma (upper limb 14, lower limb 16, trunk 32, head and neck 20) were prospectively recruited to the department of Nuclear Medicine.

Inclusion criteria were: patients with histological examination report of melanoma who fulfilled the criteria for surgical excision of primary lesion and SLNB and patients who have already excised melanoma.

All patients underwent PLSs, PLSd and hybrid SPECT/CT imaging with 99mTc nanocolloid.

Number of patients	82
Mean age (years)	63.5 ± 15.5 (33-90)
Sex	
Males	51(62.8%)
Females	31 (37.8%)
Localization of melanoma	
Head-neck	20
Trunk	32
Upper extremity	14
Lower extremity	16

Table 2: Demographic characteristics of patients and localization of melanoma.

2.2 Methods

All patients underwent:

a) Dynamic and static planar radioisotopic lymphoscintigraphy (PLSd and PLSs)

b) Hybrid SPECT/CT with 16 slices CT

after intradermal administration of 2-4 mCi^{99m}Tc-nanocolloid injections around the primary or excised lesion. Interpretation was based on qualitative analysis by evaluating the number and anatomical localization of SLNs detected on each imaging method.

2.2.1 PLSd, PLSs and SPECT/CT lymphoscintigraphy

Patients were intradermally injected with 2-4mCi of Tc-99m nanocoloid around the area of the melanocytic lesion. Based on the size of the melanoma, the radioactive substance is administered in 2-4 separate injections of 1mCi each. A dual head tomographic γ camera (Philips Forte Jet Stream)and a SPECT/CT (GE Medical System, Discovery NM/CT670) equipped with a high resolution, low energy parallel hole collimatorswas used.

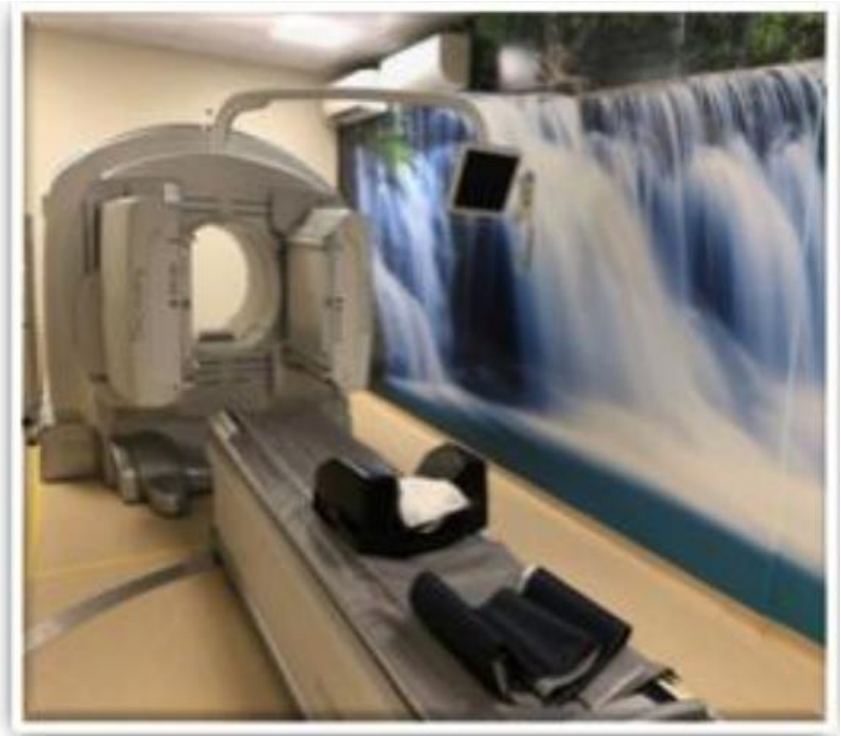


Figure 4: SPECT/CT γ-camera

PLSd and PLSs imagingaccording to the location of the lesion (anterior, posterior and/or lateral views) were obtained immediately after injecting the radiotracer. The energy window was centred on the photon energy peak for 99m-Tc at 140kEv with a window width of 20%.

Immediately after, all patients underwent a SPECT/CT imaging in designated areas. The following SPECT protocol involved the following parameters: 15 s per frame, step and shoot acquisition, 64 projections with 180 degrees rotation for each camera head, and a 128 X 128 matrix. A low-dose CT scan was performed immediately after SPECT acquisition with the patient in the same position. For CT imaging, the following acquisition parameters were used: 50–200 mAs, 120 kV, and slice thickness of 3.75 mm and pitch of 1.25. A low dose technique was used. No intravenous contrast agent was given.

2.2.2 Interpretation

Image analysis was performed on a dedicated functional workstation (Xeleris 4Workstation, GE Medical Systems, Milwaukee, WI) equipped with DICOM viewing software for imaging reconstruction. SPECT data were reconstructed using the GE's software.

Qualitative analysis was performed first on PLSd and PLSs images, followed by SPECT/CT imaging. SPECT/CT images were evaluated in all three planes: coronal, sagittal and transverse axis. Findings from SPECT/CT were compared with PLSd and PLSs. A statistical analysis was performed.

Associations of detected SLNs were measured using Pearson's or Spearman's coefficient. Scatter plots, agreement plots and Bland and Altman plots were applies for measuring the concordance between detected SLNs from imaging methods and histology. For qualitative data categories, agreement was measured using kappa statistics.

Data were recorded in an EXCEL 365 spreadsheet and its analysis and graphical representation was

made using EXCEL 365, IBM SPSS Statistics 24.0. A p-value=0.05 was set as level of significance.

3.Results

A total of 82 patients with melanoma have been investigated for the detection of SLNs. Among those 82 patients, 51 (62.2%) were males. The mean age of participants was 63.5 ± 15.5 within a range of 33 to 90. Females showed a mean of 66.2 ± 16.4 years of age significantly not different from males'age 61.9 ± 15.0 years old (p=0.351) (**Table 2**).

Agreement on localization of sentinel lymph nodes

Three different types of lymph detection were provided: a) a histologicalreport (considered as a gold standard), b) planar imaging and c) SPECT/CT Imaging.

Summing the results of histological reports of the surgically removed SLNs, the 84 localizations of the SLNs per anatomical region are axillary in 62%, inguinal in 19% and head and neck in 19%(**Figure 5 and Figure 6**).

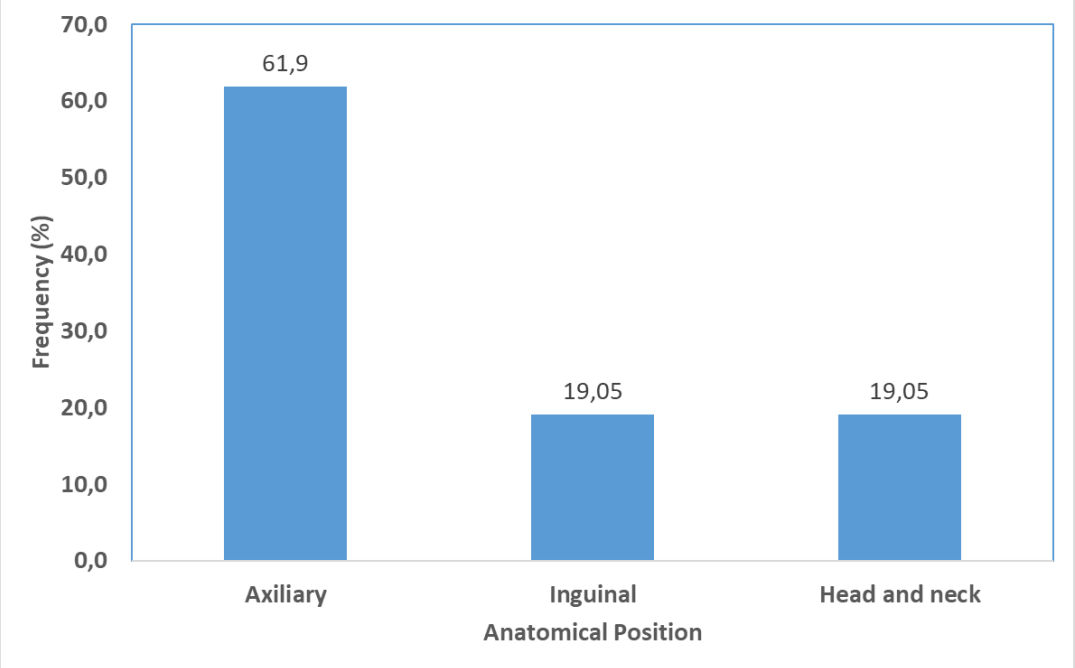
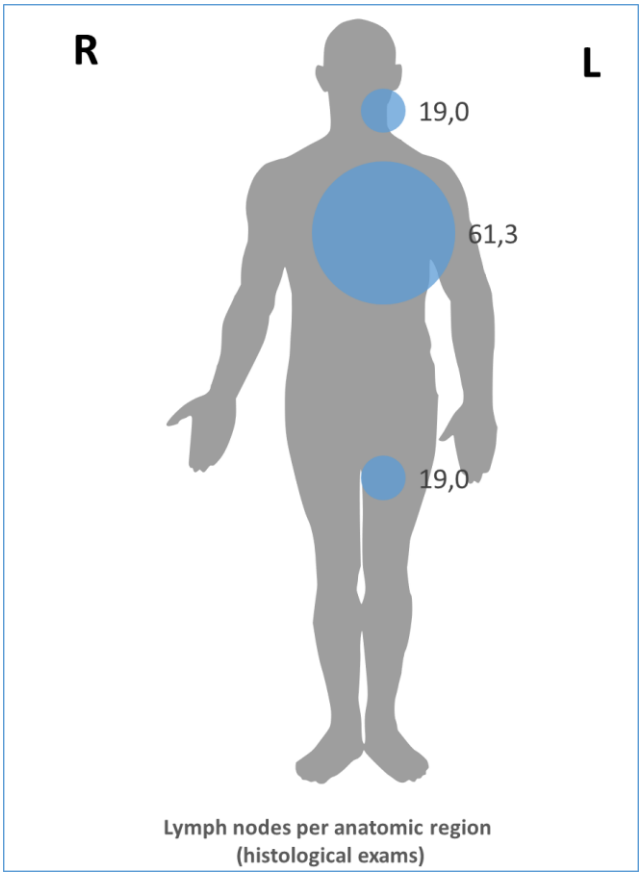


Figure 5. Position and frequencies of total lymph nodes as resulted from histological reports



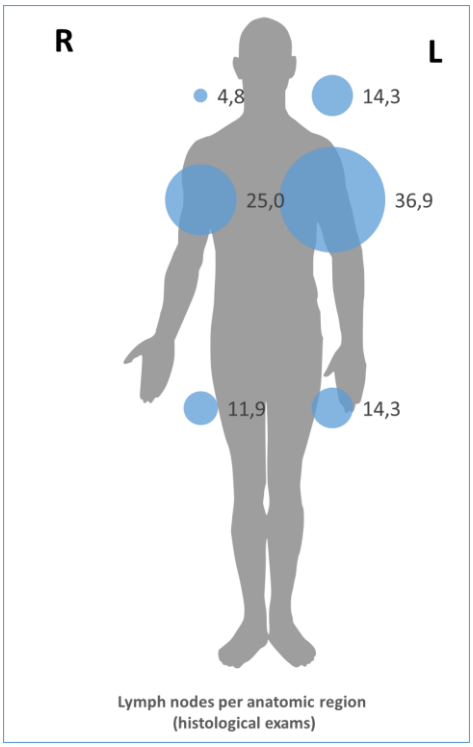


Figure 6: Crude position of lymph nodes based on histological reports

Summing the results of planar imaging, the 68 localizations of the lymph nodes per anatomical region are axillary in 80.9%, inguinal in 13.2% and head and neck in 5.9**% (Figure 7 and Figure 8)**.

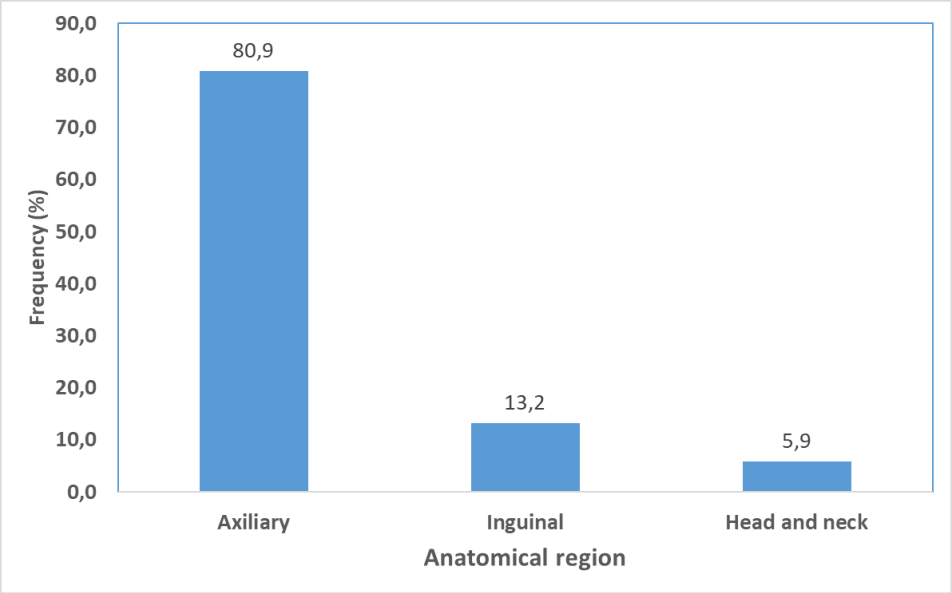
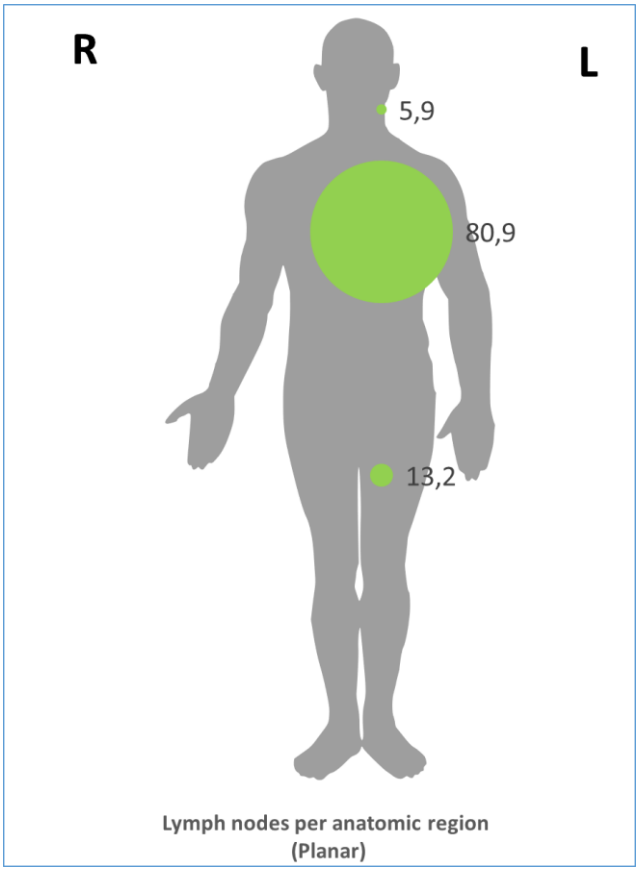


Figure 7: Position and frequencies of total lymph nodes as resulted from planar imaging



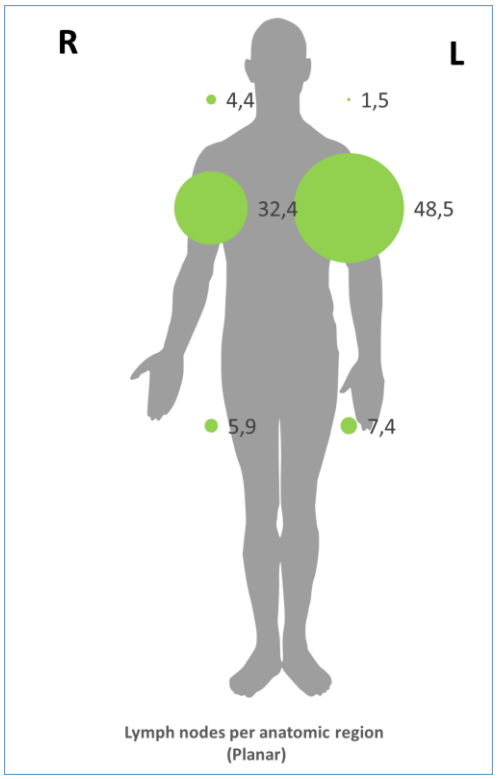


Figure 8: Crude position of lymph nodes based on PLSd and PLSs

Summing the results of SPECT-CT imaging, the 86 lymph node localizations per anatomical

region are axillary in 61.6%, inguinal in 19.8% and head and neck in 18.6%.(**Figure 9 and Figure 10**)

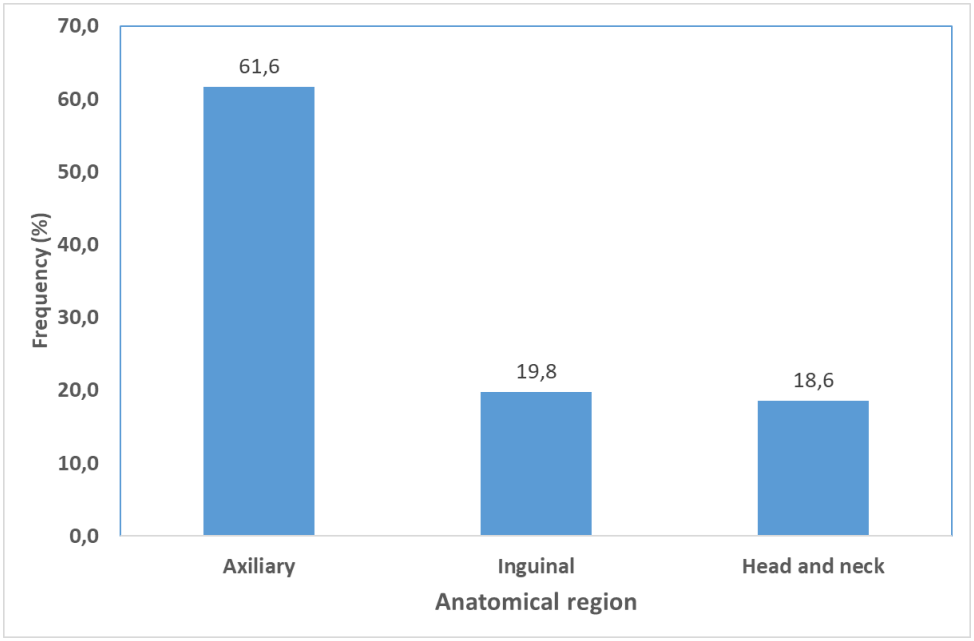
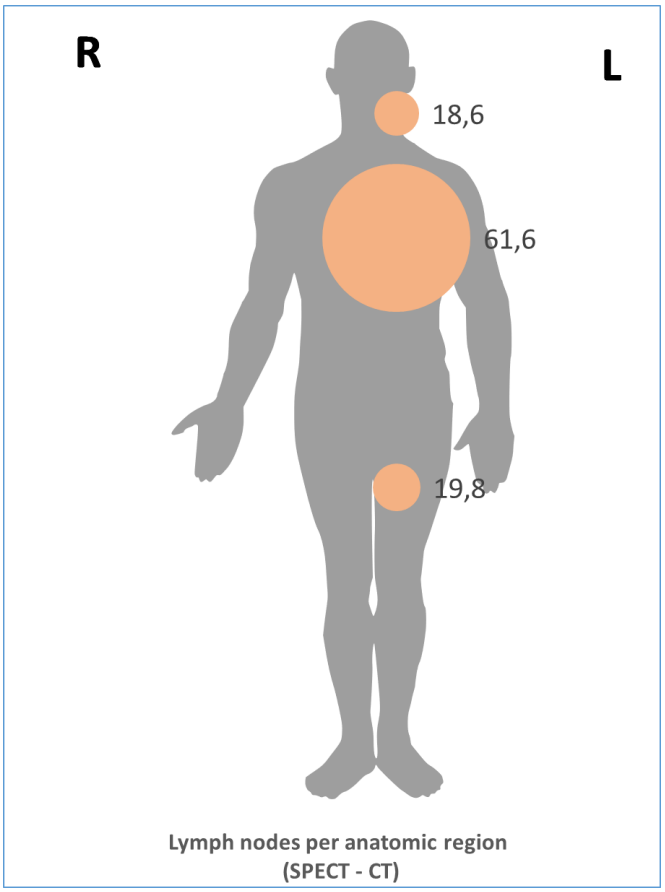


Figure 9: Position and frequencies of total lymph nodes as resulted from SPECT/CT imaging



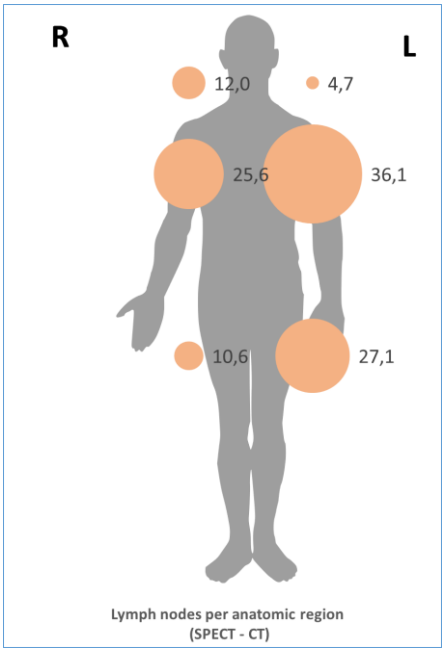


Figure 10: Crude position of lymph nodes based on SPECT-CT findings

Agreement in localization was measured using kappa statistic between the three techniques. SPECT-CT showed higher agreement with histological exams (kappa=0.525, p<0.001). Agreement between both imaging techniques was less than moderate (kappa=0.394, p<0.001) **(Table 3).**

Table 3: Measure of agreement regarding SLN location between histological report, PLS and SPECT/CT (kappa statistics)

	Exam 1	**Exam 2**	**kappa**	**P**
Total	Histological report	Planar	0.316	<0.001
	Histological report	SPECT-CT	0.525	<0.001
	Planar	SPECT-CT	0.394	<0.001

<u>Agreement onthe number of sentinel lymph nodes</u>

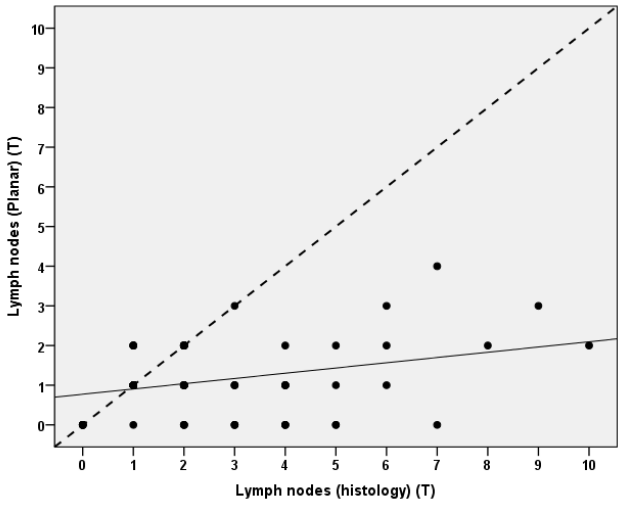
Table 4 summarises the Pearson's r (r), Spearman's r (r_s) correlation coefficients and the linear regression coefficients (R^2, a, b). It can be seen that SPECT/CT imaging showed higher correlation coefficients for number of lymph nodes when compared with the number of lymph nodes noted in the histological report: total: r=0.743,rs=0.770. Between the two imaging methods, a lower coefficient for total lymph nodes (r=0.414, rs=0.491) was shown.

Method	1	2				Linear Regression			
	X	**Y**	**R**	**Rs**	**R^2**	**a**	**B**	**R^{2*}**	**b***
Total	**Histological report**	**Planar**	0.331	0.223	0.110	0.773	0.132	0.541	0.315
	Histological report	**SPECT/CT**	0.743	0.770	0.552	0.651	0.441	0.809	0.595
	Planar	**SPECT/CT**	0.414	0.491	0.171	1.058	0.614	0.629	1.224

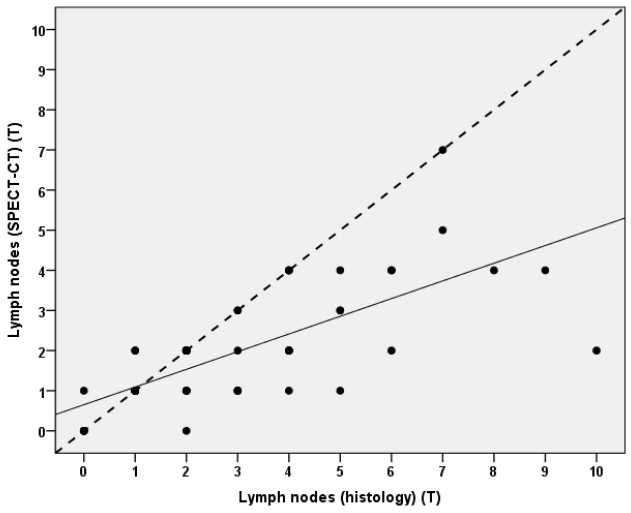
*Asterisk indicate linear equation without constant

Table 4. Correlation and linear regression coefficients between estimated number of nodes

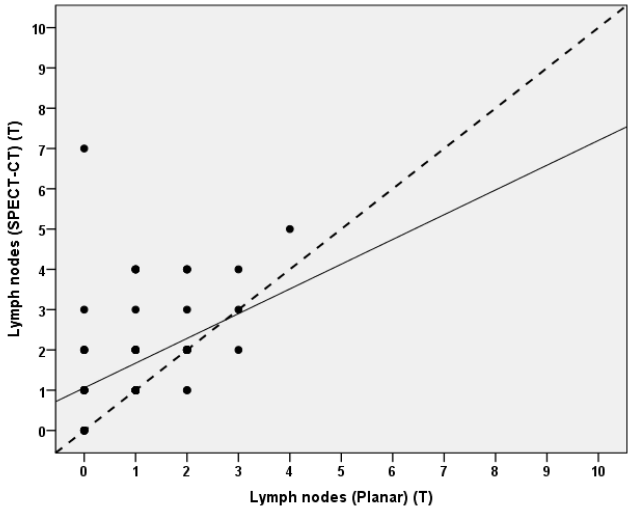
Agreement plots of total number of SLNs between histological report and imaging techniques were shown in **Figures 11 (a to c)**.



(a)



(b)



(c)

Figure 11 (a-c). Agreement plots for the total number of lymph nodes: a) histology vs PLS, b) histology vs SPECT-CT and c) PLSvs SPECT-CT.

In **Figure12,** Bland and Altman plots were applied to present the differences in lymph nodes detection between the two imaging methods vs their average lymph nodes detection. Such diagrams were used to predict the agreement of both imaging tools. The mean of differences is near 0 (0.63 total). Only one was over the confidence zone.

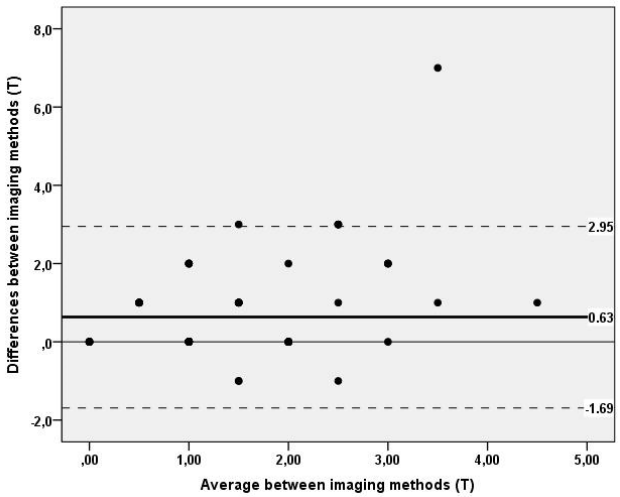


Figure 12. Bland and Altman plots for the measurement of agreement of measures between PLS and SPECT/CT for the total number of lymph nodes.

Moreover, in 28 patients, SPECT/CT revealed 48 additional nodes over those detected on planar imaging. There were 12 cases in which planar images could not demonstrate a SLN. Sensitivity, specificity, positive predictive value and negative predictive value are shown in Table 5.

	PLS	**SPECT/CT**
Sensitivity	85.0%	100%
Specificity	71.4%	85.7%
Positive predictive value	97.0%	98.8%
Negative predictive value	29.4%	100%

Table 5: Sensitivity, specificity, positive predictive value and negative predictive value for PLS and SPECT/CT

Figures 13: A patient with an eye melanoma. A) PLS showed 2 possible SLNs but without specific anatomical location. B) SPECT/CT showed a parotid lymph node. During surgery a parotid lymph node was found as confirmed by the histological report.

a)

b)

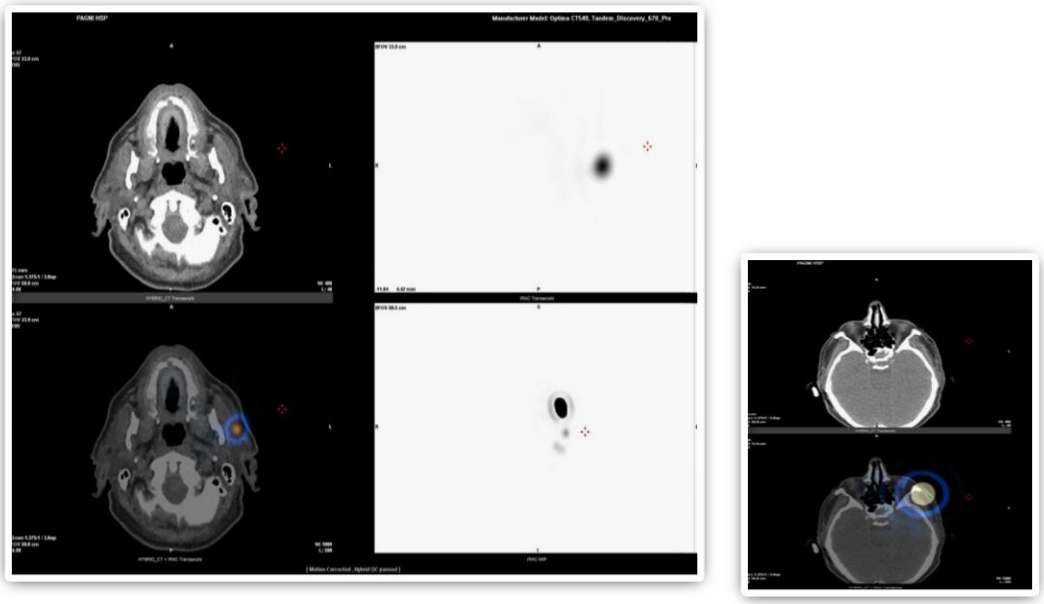


Figure 14:A patient with a melanoma of the scalp. A) PLS showed a 1 possible SLN but without clear information about the anatomical region. B) SPECT/CT showed 2 SLNs (1 postauricular and 1 jugular SLN). During surgery 2 SLNs were found and confirmed by the histological report.

a)

b)

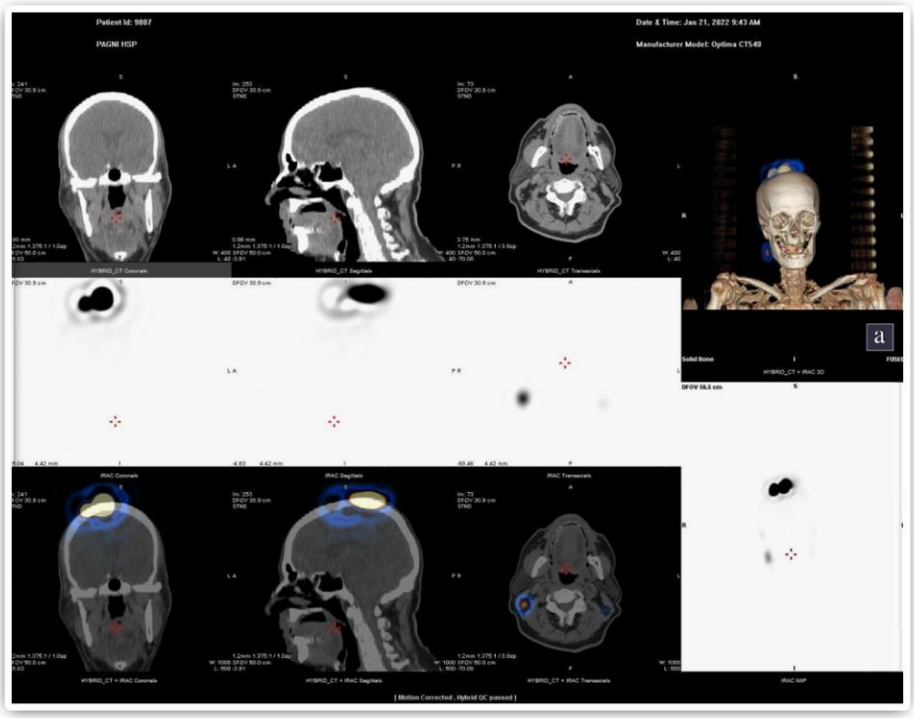
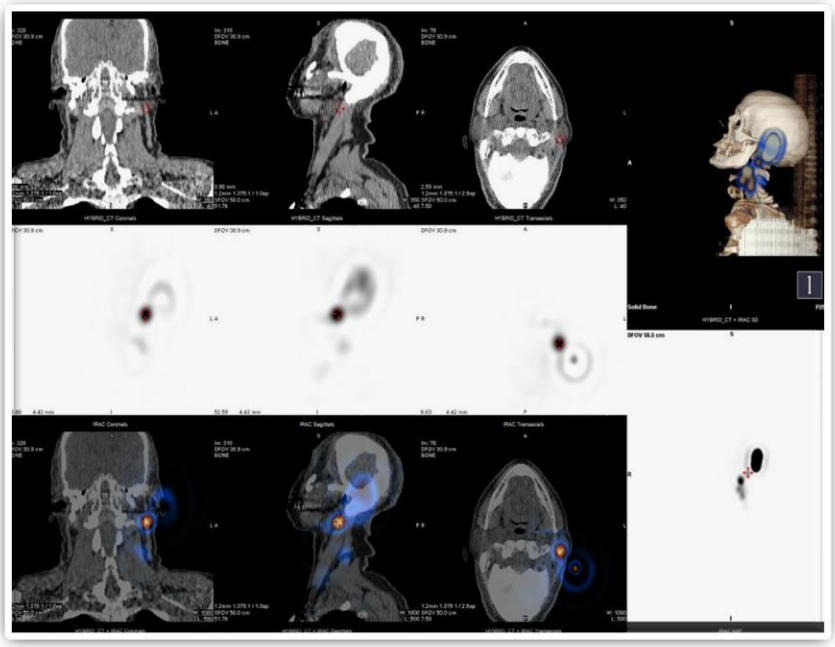


Figure 15: A patient with an auricular melanoma. A) PLS showed the lymphatic drainage with possible SLN(s) but without clear information about the number and exact location of SLN(s).(B and C) SPECT/CT showed very clearly 2 SLNs (1 submandibular and 1 jugular). According to the histological report 2 SLNs had been removed.

a)

b)



c)

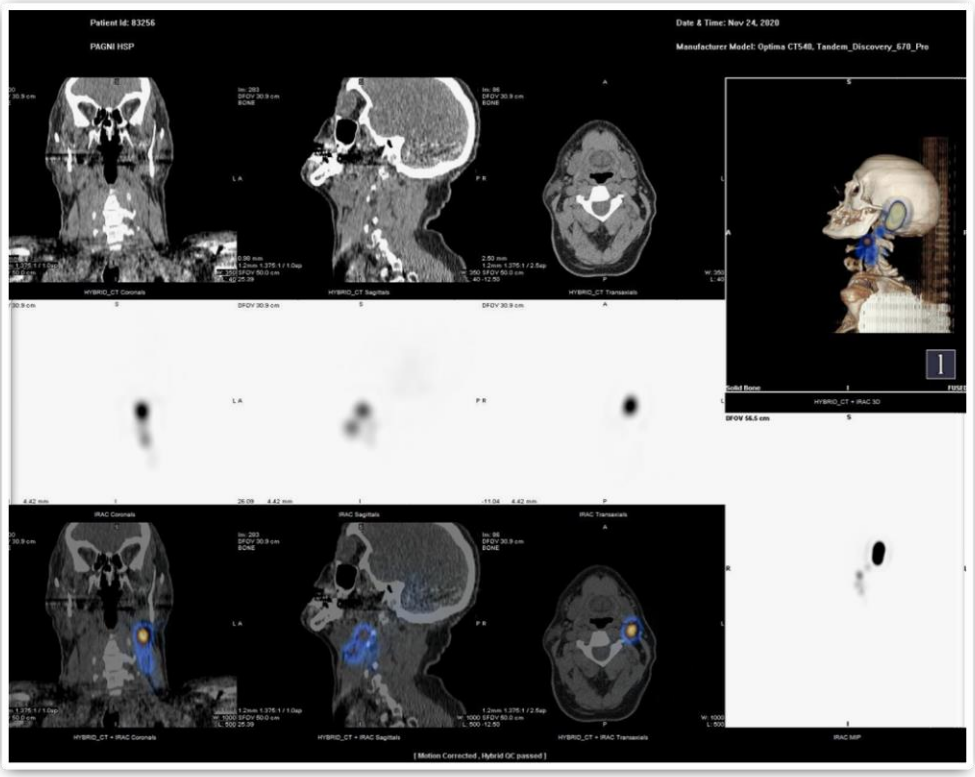
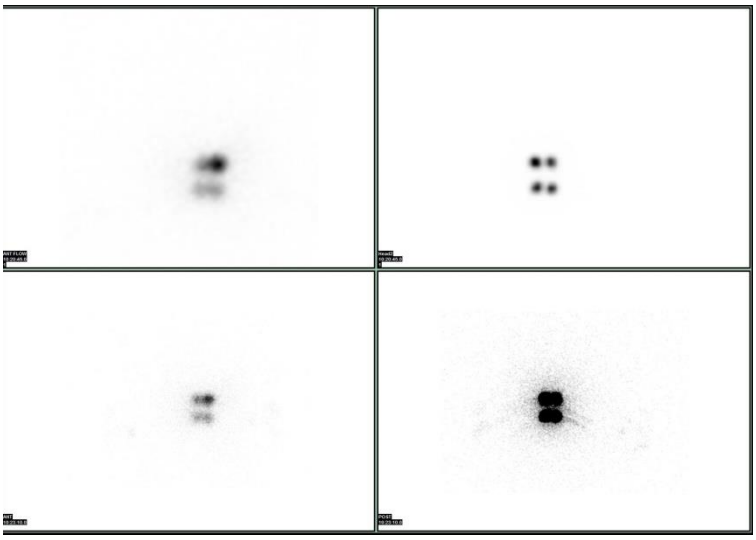
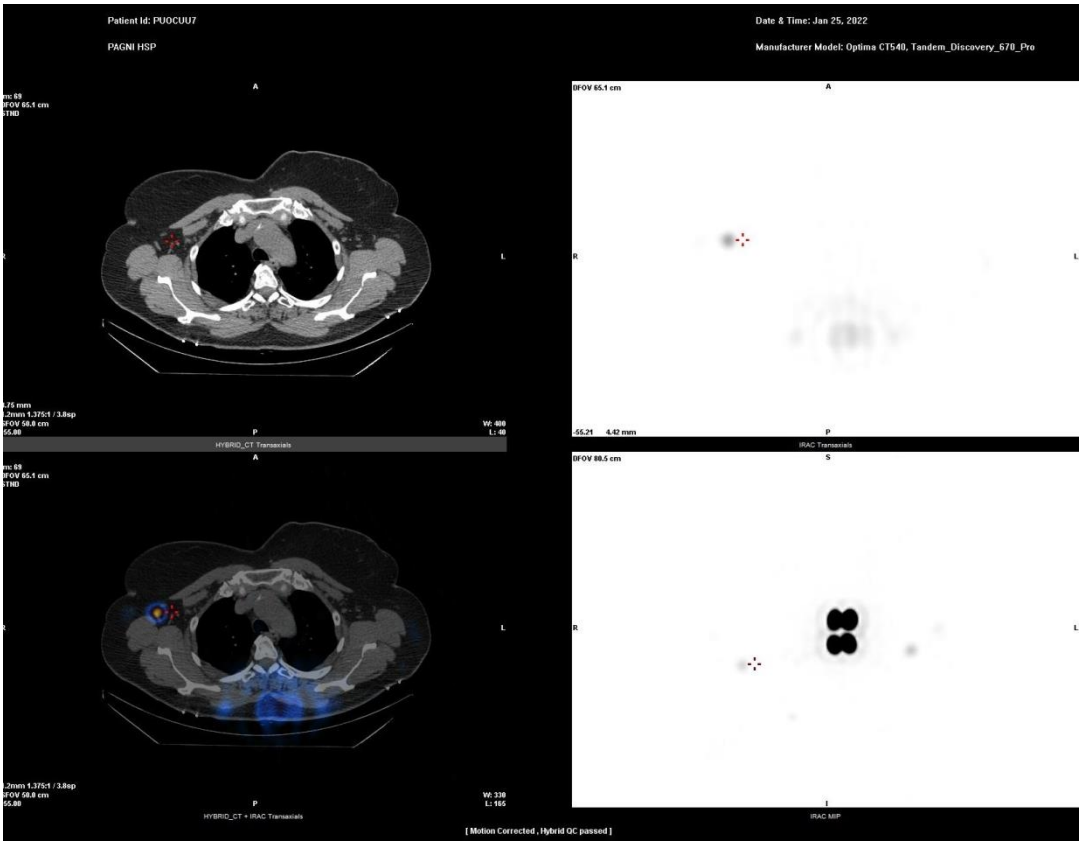
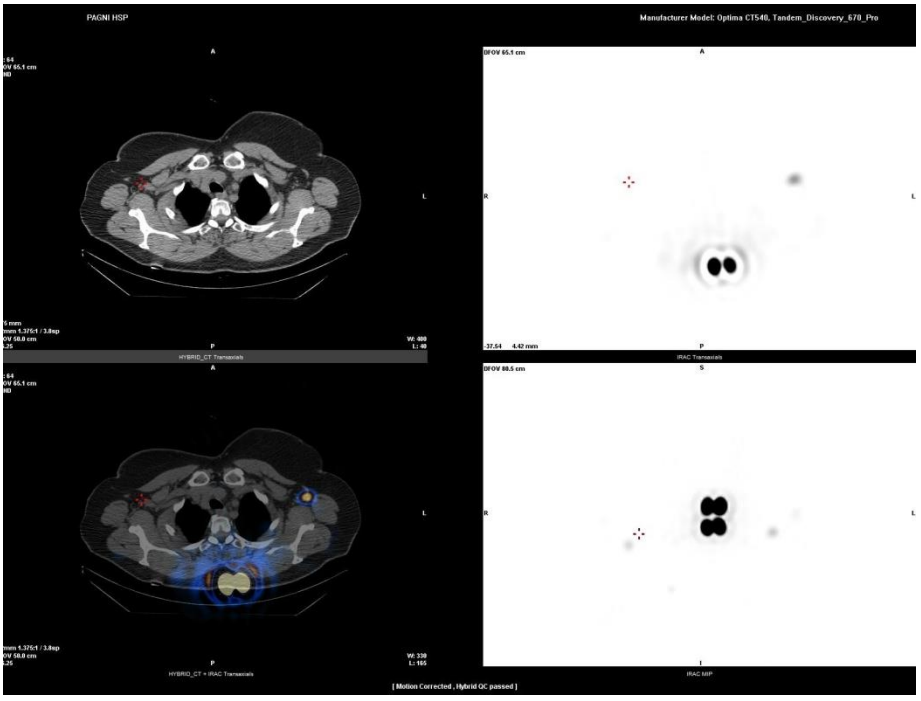


Figure 16: A patient with a trunk melanoma. A) PLS no SLNs found (false negative), (B and C) SPECT/CT confirmed 2 SLNs located in right and left axillary region. According to the histology report 1 lymph node in each axilla was removed.

A)




Patient Id: PUOCUU7
PAGNI HSP
Date & Time: Jan 25, 2022
Manufacturer Model: Optima CT540, Tandem_Discovery_670_Pro
DFOV 65.1 cm
DFOV 80.5 cm
HYBRID_CT Transaxials
IRAC Transaxials
HYBRID_CT + IRAC Transaxials
IRAC MIP
[Motion Corrected , Hybrid QC passed]


PAGNI HSP
Manufacturer Model: Optima CT540, Tandem_Discovery_670_Pro
DFOV 65.1 cm
DFOV 80.5 cm
HYBRID_CT Transaxials
IRAC Transaxials
HYBRID_CT + IRAC Transaxials
IRAC MIP
[Motion Corrected , Hybrid QC passed]

B,C)

4. DISCUSSION

The clinical impact of SPECT/CT hybrid imaging on SLN(s) studies was prospectively assessed in 82 patients diagnosed with malignant melanoma in order to evaluate the extent of disease and thus obtain guidance for the patients' future management and surgical approach.

Our study showed that SPECT/CT has an additional value in patients with melanoma by detecting more SLNs and SLNs located on different anatomical sites than expected as well as by helping the precise excision of the true SLN(s).Regarding the SLN location, SPECT/CT had a higher agreement with the histology reports, compared to PLSs and PLSd(kappa=0.525, $p<0.001$).Moreover, agreement between the imaging techniques was less than moderate (kappa=0.394, $p<0.001$). Additionally, the number of lymph nodes estimated using SPECT-CT were closer to respective numbers from the histology reports. PLS underestimates the number of lymph nodes in comparison to the histology reports. SPECT-CT showed a better prediction on number of lymph nodes in comparison to PLS.

In accordance to our results, several studies highlighted the usefulness of SPECT/CT. In a prospective multicenter trial, recommend performing SPECT/CT in all patients with melanoma of the head and neck and trunk and in all melanoma patients with unexpected drainage on planar images. In this study, SPECT/CT information not only led to the detection of more SLNs, but also to a 37% surgical adjustment (Wagner et al., 2013).

Doepker et al. performed PLS and SPECT/CT in 351 pts with melanoma. The mean number of hot spots visualized on SPECT/CT was significantly higher vs PLS. PLS was unable to identify any hot spots in 8.3 % of patients. SPECT/CT also demonstrated additional sites additional nodal basins in 29.4 % of patients not seen on PLS(Doepker et al., 2017).

Alvarez Paez et al. stated that in 50% of patients with melanoma of the trunk, SPECT/CT hybrid-fused images provided clinically relevant information and visualized additional SNs in 23% of the cases. Moreover, the surgical approach was modified in 35% of such patients by demonstration of metastases in SNs depicted exclusively by the SPECT/CT, contributing to a more accurate staging and a reduction of potential false-negative results (Alvarez Paez et al., 2012)

Several studies have also shown that SPECT/CT has a higher sensitivity by identifying more SLNs than does conventional planar imaging (dynamic and delayed planar) alone. SPECT/CT is particularly useful in detecting SLNs that are close to the injection site, by limiting the shine through effect and may be missed on planar images because of scatter. SPECT/CT identified SLNs in 9/21 (43%) patients with a primary melanoma in the head and neck or truncal region that were missed on planar images (two of these patients had nodes involved with tumour). Out of these nine patients, three had SLNs that were located close to the injection site, two had in-transit nodes and another four had SLNs identified in a separate drainage basin(Even-sapir et al., 2003).Other studies have shown similar findings. SPECT/CT managed to identify an additional SLN in 16% of patients (Veenstra et al., 2012). Moreover, SPECT/CT was particularly accurate in identifying SLNs near the injection site and distinguishes any skin contamination from nodal uptake. Another study found additional SLNs in 2/18 (11%) patients.(Mucientes Rasilla et al., 2009). Moreover, Tew et al. showed a high rate of SLN identification by using SPECT/CT. It was most frequently helpful when the primary melanoma was located in the head, neck and trunk. Another study compared PLSd images with PLSs images. 38/220 had an SLN metastasis, three (8%) of which were not identified on delayed planar imaging (one in the neck and two in the axillae)(Nielsen et al., 2011)(Tew & Farlow, 2017).

Benke et al. showed that SPECT/CT revealed more SLNs, determined with accuracy the drainage pathway, provided accurate anatomical information and a higher sensitivity, specificity, accuracy and PPV vs PLS (Benke et al., 2018).

Moreover, in our study we showed that SPECT/CT was able to accurately evaluate the exact anatomical region of SLNs and modify the surgical approach. In accordance to our results, several studies showed that SPECT/CT can accurately depict lymph nodes placed in the vicinity of the injection site where visualization is often hampered by the scatter activity. Additionally, SPECT/CT can contribute to the recognition of non-nodal tracer uptake and provide important information in cases of unclear drainage patterns with inconclusive interpretation from the conventional images (e.g., no visualization or unclear location of the nodes). SPECT/CT is of special value in cases where PLS is not able to discriminate an interval SN vs lymphatic lake, lymphangioma or contamination of the skin. SPECT/CT facilitates the appraisal of the number and size of SNs allowing correlation of focal uptakes to morphological structures. This facilitates the SN resection by allowing a proper planning of the localization and size of the surgical incision and provides a better understanding of the lymphoscintigraphic information(Vidal-Sicart et al., 2011)(Uren, 2009).

Stoffels et al. revealed that in the head and neck area and in obese patients with melanoma, the identification of the SNs was improved by the SPECT/CT when compared with conventional PLS. They showed that higher frequency of metastasis and a higher rate of disease-free survival were associated with the use of SPECT/CT. SPECT/CT advantages overcome the disadvantages such as the increased radiation dose, additional costs acquisition and interpretation time).Chapman et al. showed that by using hybrid imaging SPECT-CT in addition to PLS was significantly associated with an increased likelihood of positive SLN(s)(Stoffels et al., 2012)(Chapman et al., 2016).

Another important advantage of SPECT/CT imaging is the possible change of the therapeutic management. Many studies suggest the clear impact of SPECT/CT on the surgical approach of patients' management. Several studies showed that there was a clear or questionable benefit of SPECT/CT in all head and neck tumours, 71% of midline truncal melanomas and 27% of lower-limb melanomas (particularly for deep SLNs) providing accurate anatomical information. This leads to alteration of the surgical approach in 4/18 (22%) and 10/35 (29%) patients, respectively(Veenstra et al., 2012)(Mucientes Rasilla et al., 2009).

Berger et al. confirmed that the use of SPECT/CT led to a higher number of identified SNs without an increase in overall operation time. Operation time per harvested SLN decreased(Berger et al., 2021).

Moncrief et al.confirmed the increased accuracy of SPECT/CT for identifying SLN metastases, which would appear to have a significant therapeutic benefit (Moncrieff et al., 2021).

Moreover, other advantages of SPECT/CT seem to be the role in cosmetic results, better QOL, smaller operating time and lower cost(Klode et al., 2011).

Despite all its advantages, SPECT/CT should always be performed in combination with PLS lymphoscintigraphy. SPECT/CT alone is not able to replace the sequential information of PLSd, which is the standard technique in SLNB(Perissinotti et al., 2018).

5. CONCLUSIONS

SPECT/CT is a hybrid imaging technique, which combines the benefits of the functional information from SPECT with the detailed anatomical data provided by CT.The increasing availability of hybrid SPECT/CT devices offers higher accuracy for localization and number of SLNs in comparison with

PLSs and PLSd.

The results of this study indicate that the hybrid SPECT/CT system provides improved localization of scintigraphy findings in most of the patients, defined as a more precise interpretation of the anatomical site of radiopharmaceutical uptake. It can improve staging of patients with malignant cutaneous melanoma by more precise localization of the SLNs, making it possible to assist optimally SLNB and to decrease its false negative rate, which consequently may provide increased disease-free survival and higher quality of life.

SPECT/CT provides incremental diagnostic value and greater reader confidence. Also changes the clinical management in a significant percentage of patients and should therefore always be performed if available.

6. LITERATURE

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