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Original

Value of planar lymphoscintigraphy (PL) versus SPECT/CT in evaluation of sentinel lymph node in trunk melanoma — one center, large series retrospective study

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Abstract

BACKGROUND: Localization and histopathological examination of sentinel lymph node is a standard of melanoma treatment. The first stage of identification of the SLN is the preoperative lymphoscintigraphy. The aim of this study was to assess and compare diagnostic value of planar lymphoscintigraphy and SPECT/CT in sentinel lymph node biopsy procedure performed in patients with cutaneous trunk melanoma.

MATERIAL AND METHODS: Between 2015 and 2016, patients with trunk melanoma (N = 255, F/M 95/160), aged from 17 to 88 after an excisional biopsy, with primary tumor ≥ pT1b (AJCC 2009, median Breslow thickness 2.0 ± 3.13) were included in the study. In all the patients PL was followed by SPECT/CT 1–3 hours after injection of ^{99m}Tc- colloid particles, and SLNB was performed the next day.

RESULTS: SPECT-CT revealed 78 (18.6%) SLN more than PL, and in 40 patients showed additional lymph drainage regions leading to surgical adjustments. In 18 patients (7.1%) SPECT-CT revealed SLN not visible in the PL (false-negative PL) and in 22 patients (8.6%), foci of uptake interpreted in PL as hot SLNs were found to be non-nodal sites of uptake when assessed on SPECT/CT (false positive PL). SPECT-CT vs. PL mismatch was observed in 31 patients (12.2%) and was the most common in patients with primary lesions located in the anterior inferior medial region (75%).

CONCLUSIONS: Results of the presented study indicates the high diagnostic value of SPECT-CT in assessment of SLNs and proved that SPECT-CT increases the sensitivity and accuracy of SLN identification as compared to PL even in very experienced hands.

KEY words: sentinel node, SPECT/CT, trunk melanoma, planar lymphoscintigraphy

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Introduction

Skin melanoma is the leading cause of death from cutaneous malignancies, and the incidence rate in the last three decades has almost triplicated [1]. Radioisotopic evaluation of lymphatic drainage as a potential pathway for tumor spreading and a sentinel lymph node (SLN) search is a contemporary oncological standard in management of skin melanoma patients without clinical features of lymph node involvement and distal metastases [2].

The sentinel lymph node (SLN) is defined as the first lymph node(s) receiving direct lymphatic drainage from the primary tumour. The concept and definition of SLN is derived from Gould's works and its wider clinical application was published in the 1970s by Cabanas. [3, 4] However, only in the nineties of the last century has this procedure been introduced into clinical practice. Krag's and Alex's studies published at that time present an extensive use of planar lymphoscintigraphy (PL) in search of SLN in skin melanoma and breast cancer [5].

In skin melanoma patients, lymphatic drainage from primary lesions located in the trunk can be multidirectional and may include different basins [6].

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Sentinel lymph node biopsy (SLNB) procedure, so called triple technique, consists of preoperative lymphoscintigraphy, intraoperative administration of dye (patent blue, isosulfan blue, methylene blue, indocyanine green) and finding the sentinel node in the operation area using handheld scintillation probe and visualization ("hot and blue") then histopathological examination (serial examination with immunohistochemical staining).

Finding metastatic cells in a SLN in histopathological examination is, according to the current oncological standards, an indication for the radical lymph node dissection. In order to determine extent of surgical procedure and to minimize the risk of complications in therapeutic management in skin melanoma patients, it is necessary to locate and examine SLNs. Triple technique is a routine oncological practice at the Maria Sklodowska-Curie Institute — Oncology Center in Warsaw. The first stage of identification of the SLN is the preoperative lymphoscintigraphy, then intraoperative handheld probe verification and dye administration just before the operation (usually Patent Blau®). This technique allows to visualize the direction of the lymphatic drainage, determine the location and estimate the number of SLN, and visualize the SLN located outside of the anatomically defined regional lymphatic basin [7, 8].

Application of combined SLN identification techniques increases the sensitivity and efficiency of the procedure. According to different authors, using only the dye in the search of the SLN has a sensitivity of 80 to 83%. The use of radiopharmaceutical only has sensitivity 90–94%, whereas, the combination of both methods increases the sensitivity to 97–99% [9, 10]. The optimal accomplishment of the procedure requires close cooperation between the nuclear medicine specialist, the operating surgeon and the pathologist [11].

Until recently, in the skin melanoma patients with primary lesion located on the trunk, radioisotope search for a SLN performed only by PL technique (anterior and posterior acquisition) was believed sufficient. Additional oblique projections were also considered, as allowing better anatomical localization of visualized lymph nodes [12].

Currently, according to the latest recommendations of the leading scientific societies in the field (European Association of Nuclear Medicine (EANM), the European Society of Surgical Oncology (ESMO), the American Society of Clinical Oncology (ASCO) and the Society of Surgical Oncology (SSO)) in patients with skin melanoma located on the trunk, as well as on the head and neck, it is necessary to supplement the planar imaging with single-photon emission computed tomography (SPECT-CT) and three-dimensional reconstruction [13, 14]. This allows for much greater accuracy of anatomical localization and provides more information relevant for SLNB, making it the "gold standard" in skin melanoma and breast cancer diagnostic process [11, 15, 16]. Nevertheless the number of publications comparing both techniques (PLvs SPECT-CT lymphoscintigraphy) on large groups of patients is limited, especially single-centered.

Objective

The aim of this study was to assess and compare diagnostic value of PL and SPECT/CT in SLNB procedure performed in patients with cutaneous melanoma located on the trunk.

Material and methods

The study includes patients with skin melanoma located on the trunk, hospitalized in Maria Sklodowska-Curie Institute — Oncology Center (MSCI) in Warsaw — operated in the Department of Soft Tissue/Bone Sarcoma and Melanoma and diagnosed in the Department of Endocrinological Oncology and Nuclear Medicine. During two years (2015–2016), 255 patients (95 women, 160 men), aged from 17 to 88 (median age 61) after an excisional biopsy, in stage of primary tumor ≥ pT1b (median Breslow thickness 2.0 ± 3.13 [Me ± SD]) according to AJCC 2009 classification, were included in the study. The localization of the primary tumor at the trunk was categorized according to 12 anatomical regions, as presented and explained in Figure 1.

All patients included in the study underwent sentinel lymph node biopsy (SLNB). In the studied group radioisotope examinations were carried out routinely using both imaging PL and SPECT-CT (single-photon emission computed tomography with multidetector 16 row CT fusion) with a three-dimensional reconstruction of the image. Radiopharmaceutical used in the preoperative lymphoscintigraphy was nanoalbumin (Nanocoll, GE Healthcare, Little Chalfont, GB) labeled with a technetium isotope (^{99m}Tc). The data was obtained using SPECT-CT (Discovery NM/CT 670 GE Healthcare), as well as dynamic and static phase of PL, immediately following intradermal administration of radiocolloid with 5–20 MBq activity in 2–6 injections around the scar after the excisional biopsy. PL data acquisition was performed using a two-head gamma camera with low-energy high-resolution collimator on a 128 x 128 or 256 × 256 matrix. The energy window was adjusted to ^{99m}Tc (140 keV) with a tolerance of 15 ± 5%. The data was compiled using dedicated computer applications on workstations (Xeleris 3.1, GE Healthcare). The SLNB procedure was performed in accordance with the two-day protocol used in MSCI. The radioisotope was administered 16–20 hours prior to surgery.

In the statistical analysis of the results obtained, data compatibility with the normal distribution was checked using the Shapiro-Wilk test. Parametric variables fulfilling normal distribution assumptions were analyzed by the t-test for dependent variables. In case of data inconsistency with normal distribution, the Mann-Whitney-Wilcoxon test was used after ranking. To assess the impact of one grading factor (divided into multiple levels) on values of a tested measurable characteristic ANOVA variance analysis was used, or when breaking the assumptions, the Kruskal-Wallis test was applied. The threshold of statistical significance assumed was $p \leq 0.05$. Percentages were rounded to the nearest integers. Calculations were performed using Statistica 12.5 (Tibco, Palo Alto, CA, USA), PQstat (PQStat Software, Poznan, Poland), and Microsoft Excel 2007 (Microsoft Inc, Redmond, WA, USA) software.

Results

In the study group, melanoma was more common in men ($p = 0.0464$). In 59.6% (152 patients) skin melanoma was found on the posterior surface of the trunk. As shown in Figure 1, 190 primary lesions were located on the upper part of the trunk and 65 in the lower part. On the right side of the trunk, the lesions were found in 96 subjects, in the medial part of the body there were 46 lesions, and in the left side of the body 113 lesions. There were no

Table 1. SPECT-CT located significantly more SLN in a larger group of patients and the average number of lymph nodes detected in one patient was significantly higher when SPECT-CT was performed. Analysis of PL revealed 95.1% sensitivity (P < 0.05, CI 90–95.1%) and positive predictive value (PPV) of 95.6% (p < 0.05, CI 93.4–97.3%). Accuracy (ACC) was 89.4% (p < 0.05, CI 86.5–91.9%). For the SPECT-CT test the sensitivity of the method was 98.6% (p < 0.05, CI 97.1–99.4%), positive predictive value 99.8% (p < 0.05 CI 98.9–99.9%) and accuracy at 98.4% (p < 0.05, CI 96.8–99.3%)

	PL	SPECT/CT
Number of SLN/number of patients	419/236	497/253*
Average nodes/patient	1.66	1.96*
Sensitivity	95.1	98.6*
Accuracy	89.4	98.4*
PPV	95.6	99.8*

*p < 0.05 vs. PL

differences in primary lesion localization neither between sexes, nor among the age groups.

Preoperative PL and SPECT-CT was conducted in all 255 patients included in the study. It allowed to assess the localization and number of SLN, directions of lymphatic flow and also the anatomical regions of lymphatic basin. In PL, there were 419 sentinel nodes revealed in 236 patients. The number of lymph nodes detected in one patient ranged from 1 to 7, with an average of 1.66 (Table 1). In the remaining 18 subjects (7%), there were no SLN revealed by this imaging modality. PL also defined directions of lymphatic drainage from the scar after primary lesion excision. In 156 patients (61.2%), there was one region of lymphatic drainage, and in 75 patients (29.4%) there were two regions. In 3 patients, lymphatic drainage and sentinel nodes were observed in three anatomical regions. Four different lymphatic drainage directions were detected in only 2 patients.

Lymphoscintigraphy performed by SPECT-CT revealed 497 sentinel nodes in 253 patients. The number of lymph nodes located in one patient ranged from 1 to 6, with an average of 1.96 (Table 1). Only in 2 patients (0.7%) SLN was not revealed by SPECT/CT.

The SPECT-CT study also determined the pathways of lymphatic drainage from the area of the primary lesion. Sentinel nodes in one anatomical region were located in 153 cases (60%). Two lymphatic regions were sighted in 85 patients (33.3%). In the studied group, there were 3 patients who had lymphatic drainage to four anatomical regions in the SPECT-CT study. In these patients, the scar after the biopsy of the tumor was located in the upper part of the back in the midline. In another 11 patients (4.3%), three regions of lymphatic drainage were revealed. In this group, only two of primary lesions were located on the frontal surface of the trunk and the other 9 on the back of the midline or left side (7 and 2 patients respectively).

Differences in the number of visible lymph nodes detected with PL and/or SPECT-CT between sexes and age groups were not statistically significant (p = 0.306).

SPECT-CT showed 497 sentinel nodes — 78 (18.6%) more than PL. In 40 patients additional lymph drainage regions (including nuchal, cervical, clavicular, iliac nodes) were located, not shown by planar imaging. In 18 patients (7.1%) SPECT-CT revealed sentinel nodes not visible in the PL (false-negative PL).

Particularly noteworthy is the group of 22 patients (8.6%), who had foci of enhanced activity in the PL, suggesting the presence of lymph nodes, that was not confirmed by the SPECT-CT. In three of these cases, the hot spot was identified as contamination of the skin, two of them were defined as a pathway of lymphatic drainage, and in the other 17 cases SPECT-CT images showed that the visible focus of increased activity interpreted as a sentinel node was a lymphatic vessel confluence (false positive PL).

In the analyzed group also the inconsistencies in the visualization of lymphatic basins in PL and SPECT-CT were assessed (PS and SPECT-CT territory mismatch). SPECT-CT and PL outcomes were different in 31 patients (12.2%). SPECT-CT vs. PL mismatch was the most common in patients with primary lesions located in the anterior inferior medial region (75%) and the smallest in the posterior inferior medial area (0%). Data considering sensitivity, accuracy and PPV of both techniques are presented in the Table 1. In histopathological assessment of the SNB a total number of 637 lymph nodes were analysed. Melanoma metastases in histopathological examination were found in 83 lymph nodes (13%) in 64 patients (25.1%). There was a statistically significant difference in the incidence of metastases in individual age groups (p = 0.027709). The highest number of metastatic lesions was found for the age range 66–75 years (32%), the smallest for the age group ≥ 75 (4%). There was also a statistically significant difference in the incidence of metastatic nodes depending on the location of the primary lesion (p = 0.002218), with the highest prevalence of metastases occurred for the patients with primary focus in the anterior inferior medial area (50%), while the lowest occurred in the posterior superior right region (16%).

The localization of primary melanoma lesions and the data on relative risk ratio for metastases from them are presented in Figure 1.

Discussion

Already in the eighties of the last century attention was paid to the multidirectional lymphatic drainage in cases of cutaneous melanoma located on the trunk [17]. The basis for analyzing the pathways of lymphatic drainage is to determine the anatomical region in which primary cancer is located. The most complex regional division of the body surface was proposed by Reynolds in 2010. For statistical purposes, he defined over 30 anatomical regions [18]. In our opinion, such a complicated division has no significant clinical relevance and therefore our working definition of regions is based on commonly used anatomical terms, distinguishing twelve topographical areas. The simplest division into four anatomical regions was performed in 1993 by Uren, analyzing a group of 209 skin melanoma patients with primary lesions on the trunk [19]. Twenty-two of them had lymphatic drainage to three or more anatomical regions in a planar study, but the largest group of patients with melanoma located on the trunk was analyzed by this author in 2003 [20]. His study assessed the direction of lymphatic drainage in 211 patients with melanoma on the anterior surface and 1057 with melanoma on the posterior surface of the trunk. In this group, in 1164 patients, the tumor was in the upper trunk and in the remaining 104 below the transverse line of the trunk. In the entire study group, more than 25% patients had multidirectional lymph drainage, including cervical, retroperitoneal, perirenal and rib node [20].

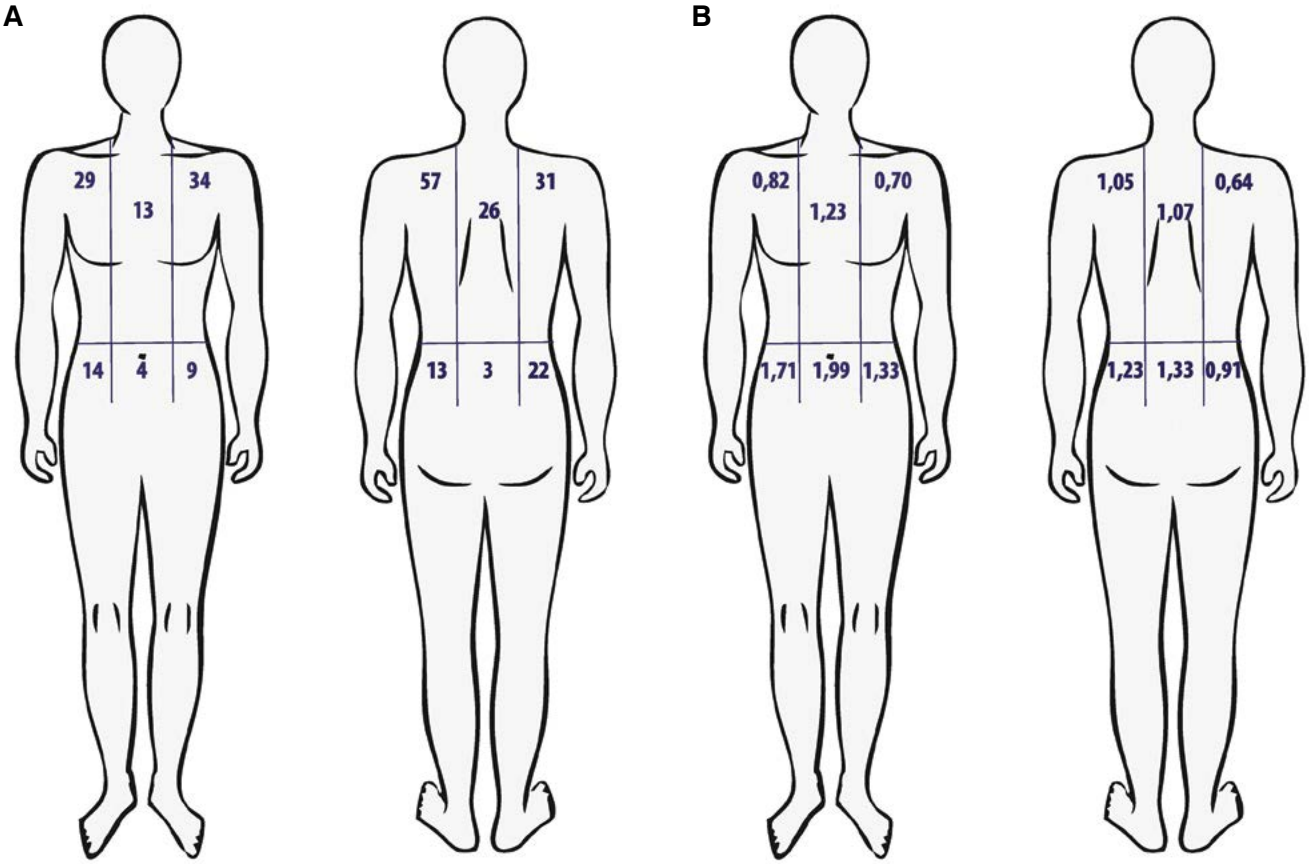

Figure 1. Localization of primary tumour (**A**) and relative risk of metastasizing depending on region where the primary tumour is located (**B**). The trunk is divided into 12 areas as follows: **anterior area** — part of abdomen and thorax delimited laterally by midaxillary lines: **anterior superior and anterior inferior areas** delimited by abdominal transverse line (horizontal line passing through umbilicus), **anterior lateral right and anterior lateral left areas** delimited medially by parasternal lines, **anterior medial area** between both parasternal lines, **posterior area** — dorsal area delimited laterally by midaxillary lines: **posterior superior and inferior areas** delimited by extention of abdominal transverse line, **posterior lateral right and posterior lateral left regions** delimited medially by paravertebral line **posterior medial area** between both paravertebral lines

In the recent work of El Muntasar examined group of 212 patients and reported melanoma on the posterior surface of the trunk in 73% cases, and on the right side in 57%, however, he did not distinguish the central location [21]. The most extensive analysis of the lateralization of melanoma was conducted by Brewster in 2007. This author, by analyzing the data of 98221 patients from 6 European countries, reported a higher incidence of this tumor on the left side (RR 1.10, 95% CI 1.08–1.11) and presented the hypothesis explaining the phenomenon [22]. In our group of 255 patients in 152 (59.6%) the primary lesion was located on the posterior surface of the trunk and the remaining 103 on the anterior surface. In the upper part of the trunk 190 (74.5%) of lesions were found, and in the lower 65. In 96 (37.6%) patients, the primary lesion was present on the right site whereas 113 on the left site, and 46 (18%) in the medial region. The differences observed in the distribution of primary lesions may be due to the geographic regions in which the studies were conducted, varying exposure to sunlight, and different patterns of patient behavior [22].

With the development of hybrid imaging techniques, first proposals to supplement PL with SPECT-CT were made in the year 2003 [23]. In publications from this period it was stated that the SPECT-CT technique could be useful in determining the exact location of sentinel nodes in regions with complex anatomical structures [24]. In 2009, van der Ploeg demonstrated the benefits of SPECT-CT in the group of patients with difficulty in interpreting planar studies, stating that in 85 melanoma patients, including 31 cases of melanoma on the trunk, the SPECT-CT study revealed an additional 12 lymph nodes in 7 patients. The author assessed that the SPECT-CT technique did not yield any additional information in only 42% of the patients [25].

Recently many case reports from different centers have been published in which SPECT-CT was used to verify the results of PL [26–30]. Also, several studies that evaluated the number of additional lymph nodes and the benefits of SPECT-CT imaging in the skin-melanoma population in different locations have been published. In the Kraft's study of 113 patients (including 55 with trunk localization), SPECT-CT showed 334 sentinel nodes, compared with 253 detected in PL (36% more), and revealed lymph nodes in 8 (7.1%) patients with negative PL [15]. Similarly, Doepker analyzed a group of 351 skin malignancies patients (including 300 with melanoma of different locations) in 172 (49%) of them reported additional lymph nodes not shown in PL [31]. Also Veenstra [32], evaluating a small group of 35 patients, stated that the SPECT-CT technique allowed for additional information in 16 of them [32].

In our own material of SPECT-CT technique, 497 sentinel nodes were seen — 78 (18.6%) more than in the planar study. This number is almost two times smaller than that in the recent publications. The cause for such a difference may be a homogenous group of our patients and a large experience of the center in interpretation of PL images in search of SLNs. Similar results were obtained in a recent multicenter study, where the number of lymph nodes shown in the SPECT-CT study was only 13.1% greater than in PL [16].

In our analysis, 40 patients (15.7%) had additional lymph drainage regions not shown in planar imaging and in 18 (7.1%) cases SPECT-CT revealed SLNs not visualized by planar analysis. In 153 patients (60%) sentinel nodes were located in one anatomical region, in 85 (33.3%) in two regions, in 11 (4.3%) patients in three regions of the lymphatic drainage. There were 3 patients in the studied group, in which the SPECT-CT technique showed lymphatic flow to four anatomical regions. The number of patients diagnosed with multidirectional drainage is significantly higher than in some previous studies (40% in our group vs. 23.2% in e.g. Mc Hugh's) [33]. However, the results we observe are similar to those published by Fitzgerald, who analyzed a group of 214 skin melanoma patients and reported lymphatic drainage to single anatomical region in only 59.9% of patients with a primary lesion located on the trunk [34].

According to our knowledge, our study is one of the few done on such a homogeneous group of patients. The study included only patients with cutaneous melanoma located on the trunk after a biopsy of primary lesion. In the entire group analyzed, PL and SPECT-CT was performed in one center with extensive experience in performing radioisotope studies using the same protocol [35]. More common trunk melanoma in men (63%) and asymmetry in frequency of primary lesions occurrence (59.6% in the posterior area of the trunk, 44% in the left, 37.3% in the right and 18.7% in the medial region) was confirmed. It was also confirmed that in a significant group of patients (39.6%) the lymph flow was omnidirectional, incompatible with the predicted "anatomical" direction of the lymph nodes. Also, the mismatches found in various test techniques were assessed and described above.

In our study a total of 637 lymph nodes were collected and melanoma metastases were found in 83 nodes (13%) in 64 patients (25.1%). We established differences in the incidence of metastases, in particular due to various age groups and locations of primary change — the highest prevalence of metastases was found for the age range 66–75 (32%) and for the anterior inferior medial area (50%), the lowest for the age group ≥ 75 (4%) and the posterior superior right site (16%). These results are similar to those presented in the literature [35].

Recently, it is believed that in skin melanoma patients, the visualization of as many lymphatic drainage lines and sentinel nodes as possible may have significant prognostic implications. It is also believed that patients with multiple basins lymphatic drainage, with no metastases confirmed, have a better prognosis, however, the prognostic significance of multiple draining basins remains controversial [36]. The precise three-dimensional localization of the lymph nodes in the SPECT-CT study reduces the number and extent of radical lymphadenectomy and often changes the scope of surgery, shortens its duration, thus reducing the number of possible surgical complications and shortening the duration of hospital stay [2, 37].

Results of the presented study indicates the high diagnostic value of hybrid techniques in assessment of sentinel nodes. The addition of SPECT-CT to preoperative diagnostics allowed not only to visualize a greater number of lymph nodes in relation to routine PL and additional lymphatic drainage regions, but also to detect foci of enhanced activity that were not sentinel nodes. Thus SPECT-CT imaging modality increases the sensitivity and accuracy of SLN identification in comparison to PL, even in very experienced hands.

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