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Sentinel Lymph Node Mapping with Radiocolloid in Malign Melanoma: Significance of Histopathological Findings in Follow up

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Abstract

The presence of metastasis in regional lymph nodes has an essential value on survival in patients with malign melanoma. This study aimed to evaluate our experience on sentinel lymph node (SLN) mapping with radiocolloid in malign melanoma patients using SPECT/CT and present follow-up findings. Conventional planar lymphoscintigraphy and SPECT/CT images of 66 patients with primary cutaneous melanoma who underwent SLN biopsy in addition to the local primary excision or reexcision were retrospectively reviewed. All detected lymph nodes were removed and evaluated histopathologically. The number and histopathological findings of SLNs were determined, and follow-up findings of patients with metastatic or nonmetastatic nodes were comparedA statistically significant difference was not found in the number of detected SLN between planar and SPECT/CT imaging. The difference of total numbers of the metastatic and benign lymph nodes was statistically significant. A total of 55/66 patients were followed up with 10 months of median follow-up time and the presence of metastatic SLN on initial histopathological assessment was found to have a high risk for further metastatic disease. In the follow-up findings of 8/10 patients in whom SLN could not be detected on both planar and SPECT/CT imaging could be reached, normal findings were detected in 4 patients, and common nodal-visceral metastases in 4 patients. We concluded that, patients with malignant SLN histopathology had a high risk of developing metastases and should be followed up more frequently. As determined high metastases rate in patients with non-visualized SLN on radiocolloid imaging, it is essential to follow up also these patients meticulously.

Keywords**:** *malign melanoma, lymphoscintigraphy, radiocolloid, SPECT/CT.*

Introduction

The presence of metastasis in regional lymph nodes has an essential value on survival in patients with malign melanoma (MM) (Morton et al., 2006). Five-year survival rates with and without nodal metastasis range between 40% - 78% and 53% - 97%, respectively (Balch et al., 2010).

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The first node receives lymphatic drainage directly from the tumor, defined as sentinel lymph node (SLN). SLN biopsy is a worldwide accepted procedure to limit morbidity of complete lymph node dissection in MM patients (Morton et al., 1992). Histopathological examination of selective SLN(s) allows deciding whether treatment of the whole lymphatic area is required. Peripheral injections of blue dye (isosulfan, methylene) and technetium-99m sulfur colloid are commonly performed methods to determine SLN for biopsy. The blue dye has some drawbacks, such as allergic and anaphylactic reactions and prolonged skin discoloration, which causes longer operation time (Pham et al., 2017). Preoperative conventional planar lymphoscintigraphy with radiocolloid as a noninvasive method is more sensitive than blu-dye in detecting SLN (Alazraki et al., 1997; Straver et al., 2010). Conventional planar technic has limitations in determining the exact anatomical localization of lymph nodes because of two-dimensional imaging. If the distance between the primary tumor and SLN(s) is short, the radioactivity of the primary injection site may obscure the SLN(s). Combining the conventional planar technic with three-dimensional technology of single-photon emission computed tomography (SPECT/CT) increases the sensitivity and accuracy of preoperative lymphoscintigraphy (Benke et al., 2018). Additional intraoperative gamma probe guidance allows higher SLN detection rates (Boland and Gershenwald, 2012).

This study aimed to evaluate our experience on sentinel lymph node mapping of malign melanoma patients using SPECT/CT and present follow-up findings.

Methods

Patients with primary cutaneous melanoma who underwent SLN biopsy in addition to the local primary excision or reexcision in Ondokuz Mayıs University Hospital from January 2019 to March 2023 were retrospectively reviewed. Patients with any additional known malignancy were excluded from the study due to the problems encountered in the differential diagnosis of metastases that may develop during follow-up. All procedures involving human participants were performed in accordance with the 2013 Helsinki Declaration in this retrospective study. Informed consent was obtained from all patients. On the same day of the surgery (2-4 h priorly), a total of 37-74 MBq of 99mTc-nanocolloid (Senti-Scint®; Hungary) in a total volume of 0.2-0.4 ml was injected around the lesion or scar of the primary excision area at the immediate proximity, at 2-4 points. After injection, planar images were acquired for 5-10 minutes and repeated every half an hour until the first lymph node was detected (max 2 hours). Immediately after the last planar image (at the end of 2. hours if there was no lymph node detected on planar images), SPECT/CT images were obtained without changing the patient's position. SPECT imaging was acquired with 128x128 matrix, 25 seconds/frame for 60 frames, and CT imaging with 40-60 mass, 130 KeV and 5 mm slice thickness parameters. Siemens Symbia True Point SPECT/CT gamma-camera system was used conventional planar lymphoscintigraphy and SPECT/CT imaging. Planar and SPECT/CT images were not interpreted separately; planar images were compared to SPECT/CT images concerning the number and location of detected SLN(s). SPECT/CT images were provided to the surgeon before surgery, marking the lymph node on transsectional images. The incision site was determined according to the SPECT/CT images. All radioactive lymph nodes identified with a hand-held intraoperative gamma probe were removed and evaluated histopathologically. The number and histopathological findings of SLNs were determined, and follow-up findings of patients with metastatic or nonmetastatic SLNs were compared.

Statistical analysis of the data was performed with SPSS 21.0 package program. The distribution of variables was evaluated with the Kolmogorov-Smirnov test. For categorical and continuous measurements, the Chi-square test and Mann Whitney U test were used. $p<0.05$ was considered significant for all tests.

Results

A total of 66 patients (35 M, 31 F) with a mean age of 53 years (±18 yrs) who underwent SLN biopsy in our institution and met the study criteria were retrospectively reviewed. Primary lesion excision was applied in 26/66 patients (39.4%), and reexcision was in 40/66 (60.6%) patients. The most common location of the primary lesion was head and neck (24 patients, 36.4%), followed by lower extremity (19 patients, 28.8%), trunk (14 patients, 21.2%), and upper extremity (9 patients, 13.6%) respectively. Superficial spreading melanoma was detected in 27/66 patients (41.0%) and was the most common pathological subtype. Characteristics of the patients and lesions were given in Table1.

Table 1. Data on patients and primary lesions.

Patient / lesion characteristics	Number	Percentage
Male/Female	35/31	53.0/47.0
Mean Age (Male/Female)	62/57	-
Primary Melanoma Location		
Head and Neck	24	36.4
Lower Extremity	19	28.8
Trunk (back, abdomen, gluteal)	14 (10,3,1)	21.2
Upper Extremity	9	13.6
Subtype of Melanoma		
Superficial Spreading Melanoma	27	41.0
Nodular Melanoma	22	33.3
Acral Lentiginous Melanoma	13	19.7
Unclassified	3	4.5
Nevoid Melanoma	1	1.5
Breslow Thickness (mm)(n=57)		
≤1.00	9	15.8
1.01-2.00	8	14.1
2.01-4.00	21	36.8
>4.00	19	33.3

At least one SLN was detected in 56/66 (84.8%) patients both on planar and SPECT/CT images. In the remaining 10 patients (15.2%), no radiotracer accumulation associated with SLN was detected. Primary lesion locations were head-neck in 6 patients, extremity in 2 patients, and trunk in 2 patients. Primary excision had been performed in 2/10 patients and reexcision in 8/10 patients.

The total number of detected nodes was 91 on planar imaging and 95 on SPECT/CT. A statistically significant difference was not found in the number of detected SLN between the two imaging modalities ($p>0.05$). SPECT/CT detected the same number of SLN(s) with planar imaging in 62/66 patients and provided better SLN visualization

and exact anatomical localization in all cases when compared to planar imaging. In 2 patients with one SLN on planar images, one additional lymph node per patient was noticed on SPECT/CT. Extra lymph nodes were very close to the other nodes and had slight radiotracer uptake seen on planar imaging. Primary lesion locations were head-neck and lower extremity. Planar and SPECT/CT images of these patients were represented in Figure 1. In one patient with a primary lesion on the lower extremity, 2 additional lymph nodes were determined on SPECT/CT. In one patient, a focus of radiotracer contamination was noticed on SPECT/CT, which was thought to be a SLN on planar imaging. Planar and SPECT/CT images of this patient were represented in Figure 2.

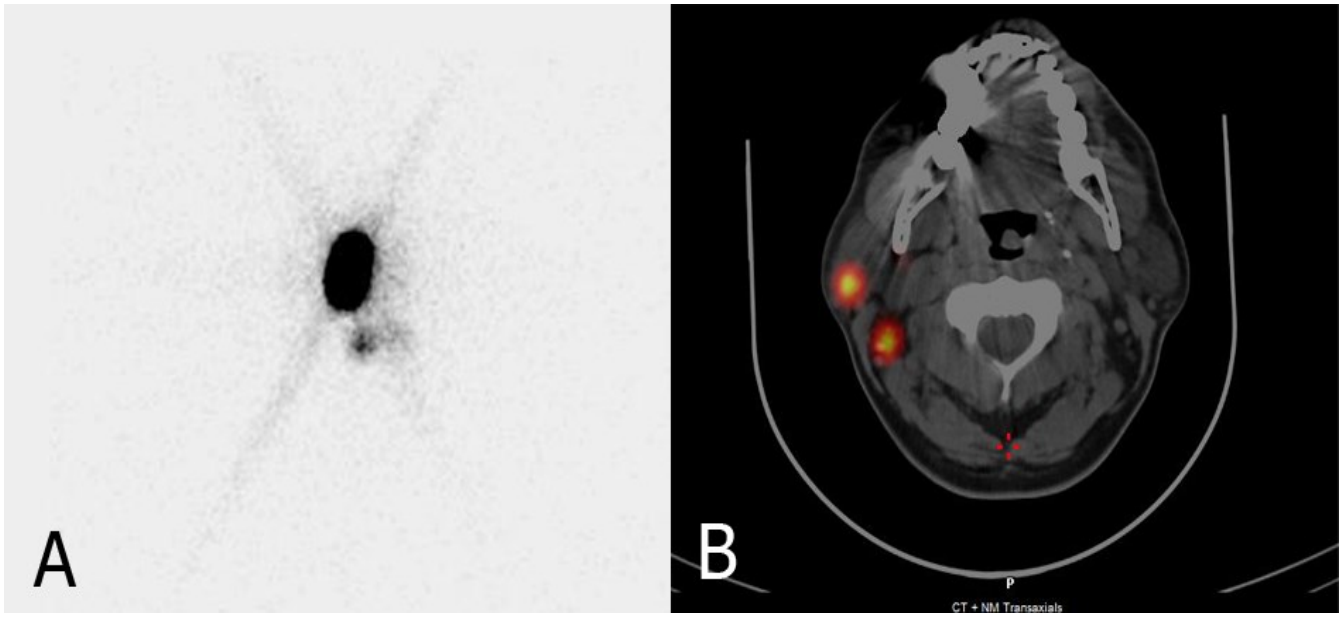

Figure 1: *A 49-year-old male patient underwent primary excision because of the pathological diagnosis of the lesion in the right ear helix determined as KL3 superficial spreading malignant melanoma. On planar lymphoscintigraphy images, radiotracer accumulation in the right cervical region inferior to the primary lesion area consistent with sentinel lymph node was observed (A). On SPECT/CT, in addition to the millimetric lymph node at the right cervical level 2B, there was a right intraparotideal lymph node, which is closely adjacent to the primary lesion (B). Both lymph nodes were excised during the operation, and histopathological examination was interpreted as reactive lymph nodes. In the patient's follow-up for 11 months, no finding in favor of recurrence or metastasis was detected.*

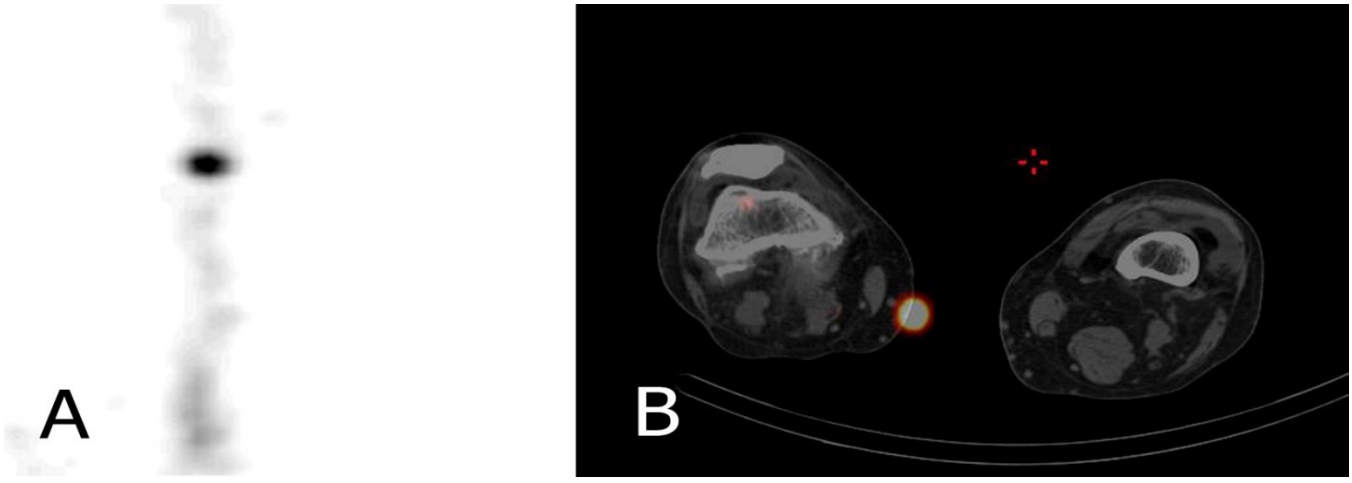

Figure 2: *An 86-year-old male patient underwent primary excision with the pathological diagnosis of the lesion on the right sole, which was determined as KL3 acral lentiginous malignant melanoma. On planar lymphoscintigraphy images, radiotracer accumulation was observed in the right popliteal region, which was thought to be compatible with the sentinel lymph node (A). On SPECT/CT, the accumulation observed in the right popliteal area was consistent with artifact secondary to radioactive material contamination (B). In the patient's follow-up for 7 months, no finding in favor of recurrence or metastasis was detected*.

Total numbers and locations of SLNs were decided according to SPECT/CT findings in 56 patients and reported to the surgeon preoperatively with printed SPECT/CT figures in order to offer detailed location. All 95 lymph nodes in 56 patients were removed in operation and analyzed histopathologically. 73/95 SLNs in 45 patients were only benign, and 14/95 SLNs in 8 patients were only malign. In 3 patients, one benign SLN per patient was reported in addition to at least one (5 in total) malign SLN.

The total numbers of metastatic and benign lymph nodes were 19/95 (20.0%) and 76/95 (80.0%), respectively, and the difference was statistically significant ($p<0.05$). Additional 4 lymph nodes detected only on SPECT/CT images had the same histopathological findings with lymph nodes detected on planar imaging.

A total of 55/66 patients were followed up with at least one imaging modality, including PET/CT, MR, USG, and CT. The Median follow-up time was 10 months (range 3-35 months). Preoperative imaging could not identify SLN in 8/55 patients. In 47 patients, histopathological diagnosis of SLNs was metastatic in 9/47 (19.1%) and benign in 38/47 (80.9%). According to the follow-up data, regional and/or distant metastases were observed in 4 /9 patients (44,4%) with at least one metastatic SLN (2 patients visceral metastases and 2 patients multiple nodal-visceral metastases) and 1/38 patient (2,6%) with benign SLN (visceral metastasis) (Table 2). The presence of metastatic SLN on initial histopathological assessment was found to have a high risk for further metastatic disease ($p<0.05$).

Follow-up findings of 8/10 patients in whom SLN could not be detected on both planar and SPECT/CT imaging could be reached. Normal findings were detected in 4 patients, and common nodal-visceral metastases in 4 patients.

During the follow-up period, 3 patients died due to metastatic disease. Primary lesion locations were trunk and head–neck in 2 patients with detected metastatic SLN and head–neck in one patient in whom SLN could not be detected by either method.

Table 2. Numbers and percentages of SLN detected and nondetected patients with regional and/or distant metastases on follow-up.

	Regional and/or distant metastases on follow-up n (%)	
	Yes	No
SLN detected		
Malign	4 /9 (44.4%)	5/9 (55.6%)
Benign	1/38 (2.6%)	37/38 (97.4%)
SLN nondetected	4/8 (50.0%)	4/8 (50.0%)

Discussion

In the early stage of malignant melanoma, metastasis in lymph nodes is the most important prognostic factor for survival (Balch et al., 2010). For monitoring and therapy management, identifying lymph node metastasis is very crucial (Wong et al., 2012). Preoperative planar lymphoscintigraphy is a worldwide used radionuclide imaging technic in identifying SLN(s), but it has limitations, especially in localizing exact anatomical territories (Thompson et al., 1999). SPECT/CT, a relatively new imaging modality, provides more detailed information with presenting morphological and functional data together. This study aimed to evaluate our experience on malign melanoma patients about sentinel lymph node mapping using SPECT/CT and present follow-up findings of patients concerning histopathological assessment. The presence or absence of nodal metastatic disease is the most important prognostic factor in early-stage melanoma patients. Studies showed that metastatic SLN(s) decreases 5-year survival to 20-70% (Howlader et al., 2017). A complete lymph node dissection had some complications, such as lymphedema, hematoma, infection, and nerve dysfunction, and several studies showed that a complete lymph node dissection had not improved survival (Balch et al., 2009; Sim et al., 1978). As the histopathological assessment of SLN was essential for managing patients, radionuclide agents, blue dyes, or both were used for imaging SLN. Blue dye technic was first developed by Morton and had an identification rate of 82% (Morton et al., 1992). Later, radionuclide agents, including 99mTc-sulfur colloid, 99mTc-nanocolloid and 99mTc-antimony trisulfide was used to identify SLN (Niebling et al., 2016). Preoperative planar lymphoscintigraphy had a relatively low SLN(s) identification rate with 81% because of superimposition of lymph nodes or shine-through from the primary injection site in addition to the low image resolution of planar imaging itself (Jansen et al., 2000; Doepker et al., 2017). SPECT/CT fusion imaging technic had shown to be superior to the planar method to detect SLN(s) by providing functional and morphological information together. Technic offered more accurate anatomical localization and more SLN(s) detection rate than planar imaging and reduced misinterpretation of images mainly caused by contamination with radiotracer (Stoffels et al., 2012). It had been

reported that the contribution of the SPECT/CT method is essential, especially in the head and neck region because of the superposition risk of small-sized and closely adjacent lymph nodes in two-dimensional planar images (Tardelli et al., 2016). In our study, although there was no significant difference in the number of additional SLN(s) detected by SPECT/CT, the method contributed to the surgeon by providing important anatomical detail in all patients. A total of 4 extra lymph nodes in 3 patients were detected on SPECT/CT. However, the histopathological examination findings of these lymph nodes were the same as the lymph nodes detected on planar examination. Therefore, SPECT/CT did not cause any change in these patients' diagnoses or treatment approaches. In another patient, a focus of radiotracer contamination, which was evaluated as lymph node on planar method, was noticed on SPECT/CT images. In our study, the percentage of patients with malign histopathological findings in sentinel lymph nodes was 20%; it was generally similar to the literature (Hudak et al., 2015). Histopathological findings of SLN(s) provide important information in determining prognosis in patients, especially with localized intermediate thickness cutaneous malign melanoma (Gonzalez 2018). In the follow-up of our patients with malignant and benign/reactive SLN(s), regional and/or distant metastases developed in 44.4% and 2.6% of patients, respectively and the results supported the literature. The significantly higher probability of detecting metastatic disease in patients with malignant SLN(s) will guide the follow-up of these patients. There were 10 patients whom SLN could not visualize with either planar or SPECT/CT method in our study. The primary lesion area was head and neck in 6 of these patients, and reexcision surgery was performed in 8 patients. Of these 10 patients, follow-up data could be obtained in 8 patients, and metastatic disease was detected in 4 patients (50%) during follow-up. Problems were reported for SLN imaging, especially after reexcision surgery and in the head and neck region (Erman et al., 2012; Miller et al., 2011). The detection rate of metastatic disease in the follow-up of patients with non-visualized lymph nodes was also high in our study. Therefore, non-detected metastases should be in mind for non-visualized lymph nodes, especially in patients with head-neck lesions and reexcision surgery. It was thought that follow-up of patients with non-visualized SLN on radiocolloid should be more frequent and meticulous to detect possible metastases earlier.

Although there were some limitations in our study, such as the small sample size and the short median follow-up period, our findings supported the literature. We concluded that histopathological examination of SLN(s) imaged with radiocolloid and SPECT/CT technique was crucial in determining the prognosis of patients with malignant melanoma. Since patients with malignant SLN histopathology had a high risk of developing metastases, these patients should be followed up more frequently. High metastases rate determined in patients with non-visualized SLN on radiocolloid imaging was also another important finding. Therefore, it is essential to follow up also these patients meticulously.

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Authorship Contributions

Concept: S.U.S., B.K., **Design:** S.U.S., B.K., **Supervision:** S.U.S., B.K, **Data Collection and/or Processing:** S.U.S. **Analysis and/or Interpretation:** S.U.S., **Literature Review:** S.U.S., **Writer:** S.U.S.

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