

Association Between Sentinel Lymph Node Excision With or Without Preoperative SPECT/CT and Metastatic Node Detection and Disease-Free Survival in Melanoma

Ingo Stoffels, MD

Christian Boy, MD

Thorsten Pöppel, MD

Jasna Kuhn, MD

Kerstin Klötgen, MD

Joachim Dissemond, MD

Dirk Schadendorf, MD

Joachim Klode, MD

MELANOMA HAS BECOME an increasing interdisciplinary public health challenge worldwide. According to the World Health Organization, the incidence of melanoma is increasing faster than any other cancer in the world. Melanoma is the third most common cancer in Australia and the fifth most common cancer in the United States. The American Cancer Society estimated that approximately 70 230 new melanomas were diagnosed in the United States during 2011, resulting in approximately 8790 deaths.¹ However, melanoma accounts for less than 5% of skin cancer cases, yet it causes more than 75% of skin cancer deaths² and thus poses a significant health issue and economic burden.³ Because melanoma, depending on tumor depth, metastasizes early into regional lymph nodes,^{4,5} sentinel lymph node excision (SLNE) is probably the most important diagnostic and potentially therapeutic procedure for patients with melanoma.^{6,7} The histological

Context Malignant melanoma has become an increasing interdisciplinary public health challenge worldwide. Sentinel lymph node excision (SLNE) is considered the most sensitive and specific staging test for the detection of micrometastatic melanoma in regional lymph nodes.

Objective To compare metastatic node detection and disease-free survival using single-photon emission computed tomography/computed tomography (SPECT/CT)-aided SLNE vs standard SLNE in patients with melanoma.

Design, Setting, and Patients A prospective, computerized melanoma patient database at the University Hospital Essen, Skin Cancer Center, Essen, Germany, was used to identify a cohort of 464 patients eligible for SLNE between March 2003 and April 2011. A total of 403 patients with clinically negative lymph nodes, who underwent SLNE with or without preoperative SPECT/CT, qualified for subsequent analysis.

Main Outcome Measures Metastatic node detection and disease-free survival.

Results Between March 2003 and October 2008, 254 patients underwent the standard SLNE technique. After November 2008, 149 patients underwent the SPECT/CT technique. Patients who did not receive SLNE in both intervals (46/300 [15.34%] for standard cohort vs 15/164 [9.15%] for SPECT/CT cohort; $P=.06$) did not differ in either age (difference, 69.20 years; 95% CI, 62.84-72.07 years; $P=.38$), tumor depth (difference, 2.90 mm; 95% CI, 2.87-4.54 mm; $P=.54$), or ulceration of the primary tumor (difference, -8.00%; 95% CI, -35.74% to 19.81%; $P=.59$). However, using SPECT/CT allowed SLNE in the head and neck area more frequently (2.0% for standard vs 23.5% for SPECT/CT; difference, 21.1%; 95% CI, 14.1%-28.2%; $P<.001$). In the SPECT/CT cohort, more sentinel lymph nodes per patient were detected than in the standard cohort (2.40 vs 1.87; 95% CI, 1.93-2.18; $P<.001$). The number of positive sentinel lymph nodes per patient was significantly higher in the SPECT/CT cohort than in the standard cohort (0.34 vs 0.21; 95% CI, 0.21-0.31; $P=.04$). The local relapse rate in the SPECT/CT cohort was lower than in the standard cohort (6.8% vs 23.8%, $P=.03$), which prolonged 4-year disease-free survival (93.9% vs 79.2%; $P=.02$).

Conclusion Among patients with clinically lymph node-negative melanoma, the use of SPECT/CT-aided SLNE compared with SLNE alone was associated with a higher frequency of metastatic involvement and a higher rate of disease-free survival.

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Author Affiliations: Departments of Dermatology, Venerology, and Allergology (Drs Stoffels, Kuhn, Klötgen, Dissemond, Schadendorf, and Klode), and Nuclear Medicine (Drs Boy and Pöppel), University of Essen-Duisburg, Essen, Germany.

Corresponding Author: Joachim Klode, MD, Departments of Dermatology, Venerology, and Allergology, University School of Medicine Essen-Duisburg, Hufelandstrasse 55, 45122 Essen, Germany (joachim.klode@uk-essen.de).

status of the sentinel lymph node (SLN) is the most relevant prognostic factor for overall survival in patients with melanoma, independent of primary tumor thickness.⁸⁻¹⁰

Recommendations for the use of SLNE for primary melanoma are therefore included in the current American Joint Committee on Cancer guidelines.¹¹ However, SLNE has a high false-negative rate of up to 44%.¹² The current gold standard for SLN detection and targeted extirpation is preoperative lymphoscintigraphy. The recently introduced hybrid single-photon emission computed tomography/computed tomography (SPECT/CT) technique could help overcome the above-mentioned difficulties by providing additional anatomical information to the surgeon.¹³⁻¹⁵ Therefore, the preoperative 3-dimensional SLN mapping by means of hybrid SPECT/CT is gaining significance.¹⁶ The goal of our study was to compare the association between SLNE with vs without preoperative SPECT/CT imaging and metastatic node detection and disease-free survival in patients with cutaneous melanoma.

METHODS

Patients

A prospective, computerized melanoma patient database at the University Hospital Essen, Skin Cancer Center, Essen, Germany, was used to identify a cohort of 464 patients eligible for SLNE between March 2003 and April 2011. A patient was defined as clinically lymph node negative if neither in clinical examination nor in preoperative ultrasound a metastasis was detected.¹¹ The study was approved by the institutional review board and all patients had given either written or oral consent to be entered into the database.

From the initial cohort, 403 patients with melanoma who underwent SLNE between March 2003 and April 2011 were evaluated. Between March 2003 and October 2008, 254 patients with melanoma received SNLE without preoperative SPECT/CT. Between

November 2008 and April 2011, all sentinel node scintigraphies were performed as SPECT/CT in 149 patients. Obesity was analyzed because it has been reported as a cause for the non-visualization of SLNs on preoperative planar lymphoscintigraphy.¹⁷ Both cohorts were treated with the same therapy according to the guidelines of the Deutsche Dermatologische Gesellschaft (German Association of Dermatology).¹⁸

With a negative SLN (stages I-II), the follow-up in both cohorts was the same and based on the guidelines of the German Association of Dermatology. Patients in both cohorts with a negative SNL but stage IIC disease were offered low-dose interferon therapy. With a positive SLN, the standard treatment was regional lymph node dissection in both cohorts. Patient of both cohorts with stage IV disease received treatment with the chemotherapy gold standard dacarbazine. After 2010, 8 patients with stage IV melanoma in the SPECT/CT cohort were treated with study medications, such as BRAF inhibitors, MEK inhibitors, or CTLA-4 antibodies.

Sentinel Node Scintigraphic Technique and SPECT/CT

Two cohorts were formed according to the scintigraphic imaging technique used: examinations in which planar imaging and a SPECT/CT were accomplished formed the SPECT/CT cohort and examinations in which SPECT/CT was not available formed the standard cohort with standard planar imaging alone.

Lymphoscintigraphy was performed with either 16 MBq or 80 MBq of Tc-99m-nanocolloid (Nanocoll, GE Healthcare Buchler GmbH & Co KG) depending on the schedule of the surgical procedure—same day vs following day. The colloid was injected with a total volume of 0.4 mL in 4 intradermal deposits of 0.1 mL each, which were located at the borders of the primary tumor site, or were located on both sides of the excisional scar, if the primary tumor had been removed. Dy-

namic images of the corresponding anatomical region and their adjacent lymphatic basins were acquired at 30 seconds per frame for 5 minutes with a total of 10 frames. Afterwards, anterior, lateral, and oblique projections were acquired for 5 minutes each, using a dual-detector gamma camera with a mounted 2 row multidetector CT scanner (Symbia T, Siemens Healthcare).

Because the SPECT/CT technique became available in November 2008, SPECT/CT images of the region in which an SLN was visualized were obtained immediately after the planar images showing an SLN (SPECT: 128 × 128 matrix, 128 frames, 25 seconds per frame, OSEM algorithm with 8 iterations and 4 subsets, correction for attenuation and scatter; CT: 130 kV, 17 mAs, 5 mm slices, image reconstruction in a medium smooth kernel). The reconstructed data were displayed as sagittal, coronal, and axial slices. Inherent image fusions were generated from the coregistered SPECT and low-dose CT images using the E.soft 2007 application package (Siemens Healthcare). Minor misregistrations were corrected manually. Delayed planar images were acquired 2 hours after colloid injection, followed by SPECT/CT if an SLN was only then visualized. If no SLN was visualized in these images, another set of planar images was acquired 2 hours later. No further imaging was performed if no SLN could be identified in the latter set of images.

After an SLN was visualized, a hand-held probe (C-Trak, Care Wise Medical Products Corporation) was used to identify the site with the highest counts. This site was marked on the skin with permanent ink as a first guide to the supposed location of an SLN. The same hand-held probe was used during surgery. After SLNE, ex-vivo counting was performed followed by probing of the lymphatic basin in search of additional nodes with high counts.

Sentinel Lymph Node Excision

The SLNE was performed as a standard procedure at the Department of Dermatology, University Hospital Es-

sen, Essen, Germany, according to the guidelines of the German Association of Dermatology.¹⁸ The procedure was conducted in patients with melanoma and having American Joint Committee on Cancer stages I and II (tumor depth, ≥ 1.0 mm).

Subsequent SLNE was performed either under local anesthesia or general anesthesia.^{19,20} Preparation and subsequent excision of all marked lymph nodes was performed via an incision over the area with the highest activity indicated by a mobile manual scintillation measuring probe (C-Trak, Care Wise Medical Products Corporation) in the control cohort or by preoperative marking on the skin according to the additional information obtained from SPECT/CT in the SPECT/CT cohort. Surgery was terminated as soon as no further radioactive foci could be detected in the surgical field. The surgical technique was identical in both cohorts. Dyes, such as patent blue, were not used because of potential allergic reactions and the risk of a permanent tattoo.²¹

Histology

The dissected tissue containing the SLN was placed in 4% formalin solution. Frozen slide analysis was not performed. The SLNs were separated from surrounding adipose tissue, bisected, lamellated, and embedded. Subsequent serial sections were made. Conventional staining with haematoxylin and eosin staining, as well as immunohistological staining with antibodies to S100, MelanA, and Human Melanoma Black 45 for melanoma were performed on all specimens.^{22,23}

False-Negative Sentinel Node

The SLNE was considered false negative if a primary recurrence developed within 12 months after SLNE in the lymph node basin from which a tumor-free SLN had been removed.²⁴ The false-negative rate was defined as the ratio of false-negative results to the total number of positive nodes (false-negative nodes plus true-positive nodes).²⁵

Statistical Evaluation

The statistical analysis was performed with SPSS version 19 (SPSS Inc). The χ^2 test or Fisher exact test were used to evaluate relationships between categorical variables. Kaplan-Meier curves and the log-rank test were used to evaluate the relationship between the SLNE techniques (standard control vs SPECT/CT) and outcome from the operation date of the SLNE to the date of first-disease recurrence or the date of death or the last follow-up, whichever came first. The association between SPECT/CT, histology, sex, localization of the pri-

mary, age, Breslow thickness, ulceration, and SLN status as prognostic factors was analyzed for the clinical outcome by univariate analysis and stepwise multivariate Cox proportional hazards regression model analysis. Hazard ratios (HRs) and 95% CIs were calculated from the Cox proportional hazards regression model, including all factors for multivariate analysis as a 2-sided test. Differences were regarded statistically significant at $P < .05$.

Because SPECT/CT was performed only after November 2008, the follow-up of both cohorts was set at 48

Table 1. Patient Characteristics of the SPECT/CT Cohort vs Standard Cohort of Lymphoscintigraphy

Characteristics	Total (N = 403)	Standard Cohort (n = 254)	SPECT/CT Cohort (n = 149)	P Value
Age, y				
Mean (SD)	58.62 (15.95)	58.11 (15.52)	59.48 (16.70)	.25
Median	62.00	62.00	62.00	
Sex, No. (%)				
Male	244 (60.5)	151 (59.4)	93 (62.4)	.60
Female	159 (39.5)	103 (40.6)	56 (37.6)	.34
Tumor depth, mm				
Mean (SD)	2.69 (2.18)	2.71 (2.08)	2.66 (2.38)	.16
Median	1.90	1.93	1.80	
Primary localization, No. (%)				
Head or neck	38 (9.4)	6 (2.4)	32 (21.5)	<.001
Torso	175 (43.4)	110 (43.3)	65 (43.6)	>.99
Extremity	169 (41.9)	123 (48.4)	46 (30.9)	<.001
Hand or foot	21 (5.2)	15 (5.9)	6 (4.0)	.49
Ulceration of primary tumor, No. (%)	114 (28.3)	83 (32.7)	30 (20.0)	.005
Localization of SLNs, No. (%)				
Head or neck	41 (10.2)	6 (2.0)	35 (23.5)	<.001
Axilla	191 (47.4)	123 (48.4)	68 (45.6)	.61
Groin	166 (41.2)	122 (48.0)	44 (29.5)	<.001
Pectoral	2 (0.5)	1 (0.4)	1 (0.7)	>.99
Popliteal	3 (0.7)	2 (0.8)	1 (0.7)	>.99
SLNs				
SLNs per patient	2.07 (833/403)	1.87 (475/254)	2.40 (358/149)	<.001
Median (range)	2.00 (0-9)	2.00 (0-9)	2.00 (0-9)	
Positive SLNs				
Patients, No. (%)	99 (24.57)	48 (18.9)	41 (27.5)	<.001
SLNs per patient	0.26 (105/403)	0.21 (54/254)	0.34 (51/149)	.04
Median (range)	0.00 (0-3)	0.00 (0-2)	0.00 (0-3)	
Obesity (BMI >30)				
Patients, No. (%)	31 (7.7)	24 (9.4)	7 (4.7)	.05
SLNs per patient	2.05 (64/31)	1.82 (44/24)	2.86 (20/7)	.07
Positive SLNs per all SLNs	0.14 (9/64)	0.09 (4/44)	0.25 (5/20)	<.001
Positive SLNs per patient	0.29 (9/31)	0.16 (4/24)	0.71 (5/7)	<.001

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; SLNs, sentinel lymph nodes; SPECT/CT, single-photon emission computed tomography/computed tomography.

Table 2. Patient Characteristics of the SPECT/CT vs Standard Cohorts in the Dropout Group

Characteristics	Total (N = 464)	Dropout Group		P Value
		Standard Cohort (n = 300)	SPECT/CT Cohort (n = 164)	
Dropouts, No. (%)	61 (13.14)	46 (15.34)	15 (9.15)	.06
Age, y				
Mean (SD)	66.98 (17.74)	66.17 (18.02)	69.47 (17.18)	.38
Median	69.00	68.50	70.00	
Sex, No. (%)				
Male	36 (59.0)	29 (63.0)	7 (46.7)	.03
Female	25 (41.0)	17 (37.0)	8 (53.3)	.82
Tumor depth, mm				
Mean (SD)	3.72 (3.13)	3.70 (3.36)	3.76 (2.45)	.54
Median	2.70	2.65	3.10	
Primary localization, No. (%)				
Head or neck	20 (32.8)	17 (37.0)	3 (20.0)	<.001
Torso	19 (31.1)	13 (28.3)	6 (40.0)	.80
Extremity	18 (29.5)	13 (28.3)	5 (33.3)	>.99
Hand or foot	4 (6.6)	3 (6.4)	1 (6.7)	>.99
Ulceration of primary tumor, No. (%)	24 (39.3)	19 (41.3)	5 (33.3)	.59
Reason for not carrying SLNE, No. (%)				
Patient refuses	18 (29.9)	10 (21.7)	8 (53.3)	
Not offered	25 (41.0)	25 (54.3)	NA	
Ultrasonography positive	10 (16.4)	6 (13.0)	4 (26.7)	
Primary neck dissection	4 (6.6)	3 (6.5)	1 (6.7)	
No detection in lymphoscintigraphy	1 (1.6)	1 (2.2)	NA	
Allergy to albumin colloid	1 (1.6)	NA	1 (6.7)	
Unknown	2 (3.3)	1 (2.2)	1 (6.7)	

Abbreviations: NA, not available; SLNE, sentinel lymph node excision; SPECT/CT, single-photon emission computed tomography/computed tomography.

months to make the results comparable. Data from the univariate and multivariate analyses indicate that the study is adequately powered.

RESULTS

Patient Characteristics

From the initial cohort of 464 patients, 403 with clinically lymph node-negative data qualified for subsequent analysis between March 2003 and April 2011. Between March 2003 and October 2008, 254 patients with melanoma underwent SNLE without preoperative SPECT/CT. Between November 2008 and April 2011, all sentinel node scintigraphies were performed as SPECT/CT in 149 patients. We compared the 2 study cohorts and found no difference in sex, age, and especially not in the well-established predictive factor tumor thickness. There was no difference in scope or type of testing. After November 2008,

SPECT/CT was performed in all patients.

Baseline characteristics, including analysis of overweight patients, are shown in TABLE 1. Melanomas with a Breslow thickness of at least 1.0 mm were included. Breslow thickness varied between 1.0 mm and 13.0 mm (mean, 2.69 mm; median, 1.90 mm). A total of 114 patients (28.3%) had melanomas that showed an ulceration of the primary tumor. Thirty-eight patients (9.4%) had melanomas that were localized on the head or neck area, 169 (41.9%) had melanomas localized on the extremities, 175 (43.4%) had melanomas localized on the torso, and 21 (5.2%) had melanomas localized on the hand or foot. Using SPECT/CT allowed SLNE in the head and neck area more frequently (2.0% for standard vs 23.5% for SPECT/CT; difference, 21.1%; 95% CI, 14.1%-28.2%; $P < .001$).

Patients who received no SLNE between March 2003 and April 2011 (dropout groups), although the inclusion criteria were met, are shown with baseline characteristics in TABLE 2. The dropout rate in the SPECT/CT cohort was 9.15% (15/164 patients) and 15.34% in the standard cohort (46/300 patients; $P = .06$). Patients who did not receive SNLE in both intervals did not differ in either age (difference, 69.20 years; 95% CI, 62.84-72.07 years; $P = .38$), tumor depth (difference, 2.90 mm; 95% CI, 2.87-4.54 mm; $P = .54$), or ulceration of the primary tumor (difference, -8.00%; 95% CI, -35.74% to 19.81%; $P = .59$).

No major complications occurred; especially no nerve injury was reported. There were no operative fatalities in either group. There were no significant statistical differences in complication rates between the 2 groups. Complications occurred in 6 of 149 patients (4.0%) in the SPECT/CT cohort and 20 of 254 patients (7.9%) in the standard cohort (difference, 3.8%; 95% CI, -0.73% to 8.41%; $P = .21$). In the SPECT/CT cohort, the surgical approach was changed based on SPECT/CT information in 33 of 149 patients (22.1%). In 24 of these cases (72.73%), the skin incision was performed at a different localization in comparison with the lymphoscintigraphy and in 9 cases (27.27%), the skin incision was smaller.

In 68 of 89 patients (76.4%) with positive SLN, a complete lymphadenectomy was performed according to national guidelines. The remaining 21 patients who had a positive SLN refused the recommended lymphadenectomy and decided to have a guidelines-oriented follow-up with clinical examinations and ultrasonography.¹⁸

Sentinel Lymph Node

A total of 254 patients (63.0%) underwent lymphoscintigraphy with the standard cohort technique and 149 patients (37.0%) underwent surgery with the SPECT/CT technique. A total of 833 SLNs were removed from 403 patients. We found 2.40 SLNs per pa-

tient (out of 358 SLNs) in the SPECT/CT cohort and 1.87 SLNs per patient (out of 475 SLNs; 95% CI, 1.93-2.18) in the standard cohort (0.52 SLNs per patient; 95% CI, 0.28-0.79; $P < .001$). Fifty-one of 358 excised SLNs (14.2%) in the SPECT/CT cohort and 54 of 475 SLNs (11.4%) in the standard cohort showed metastatic involvement (-2.90%; 95% CI, -7.45% to -1.72%; $P = .02$). With respect to the 2 groups, we were able to identify 41 patients (27.5%) with positive SLNs in the SPECT/CT cohort and 48 (18.9%) with positive SLNs in the standard cohort ($P < .001$). The number of positive SLNs per patient was significantly higher in the SPECT/CT cohort than in the standard cohort (0.34 vs 0.21; 95% CI, 0.21-0.31; $P = .04$) (Table 1).

Disease-Free Survival

Patient follow-up was between 0 and 93 months (mean, 28.8 months; median [SD], 22.00 [23.77] months). The SPECT/CT cohort was observed for 13.32 months (median [SD], 11.00 [11.37] months) and the standard cohort was observed for 37.69 months (median [SD], 35.00 [24.48] months). The false-negative SLN rate was 6.8% (3/41 patients) in the SPECT/CT cohort and 23.8% (15/48 patients) in the standard cohort ($P = .03$).

TABLE 3 provides a summary of prognostic factors for disease-free survival by univariate and multivariate methods. The univariate analysis for SPECT/CT (HR, 3.21; 95% CI, 1.14-9.06; $P = .03$), Breslow thickness of 1.0 mm or more (HR, 1.26; 95% CI, 1.15-1.38; $P < .001$), histologically positive SLNs (HR, 5.02; 95% CI, 2.79-9.03; $P < .001$), and ulceration of the primary melanoma (HR, 3.69; 95% CI, 2.04-6.67; $P < .001$) were statistically significant. Significant indicators of disease-free survival by multivariate analysis were the following for SPECT/CT (HR, 4.11; 95% CI, 1.25-13.51; $P = .02$), histologically positive SLNs (HR, 4.14; 95% CI, 2.14-7.98; $P < .001$), Breslow thickness of 1.0 mm or more (HR, 1.16; 95% CI, 1.02-1.32; $P = .02$), male sex (HR, 0.44; 95% CI, 0.22-0.92; $P = .03$),

Table 3. Factors Associated With Disease-Free Survival for Patients With Melanoma Who Underwent SLNE Aided by Preoperative SPECT/CT

Variable	No. (%) of Patients	Univariate Analysis		Multivariate Analysis	
		HR (95% CI)	P Value	HR (95% CI)	P Value
SPECT/CT					
Yes	149 (36.9)	1 [Reference]		1 [Reference]	
No	254 (63.1)	3.21 (1.14-9.06)	.03	4.11 (1.25-13.51)	.02
Histology					
SSM	165 (40.9)	1 [Reference]		1 [Reference]	
NM	141 (35.0)	2.88 (1.43-5.81)	.003	1.41 (0.03-3.12)	.40
Other	97 (24.1)	1.48 (0.57-3.81)	.42	1.43 (0.51-4.04)	.49
Sex					
Female	159 (39.5)	1 [Reference]		1 [Reference]	
Male	244 (60.5)	0.80 (0.44-1.43)	.45	0.44 (0.22-0.92)	.03
Primary localization					
Head or neck	38 (9.4)	1 [Reference]		1 [Reference]	
Hand or foot	21 (5.2)	0.51 (0.05-4.95)	.56	0.15 (0.13-1.70)	.13
Torso	175 (43.3)	1.34 (0.40-4.49)	.63	0.91 (0.23-3.51)	.89
Extremity	169 (41.9)	1.24 (0.37-4.21)	.73	0.34 (0.08-1.41)	.14
Age, per y		1.01 (0.99-1.03)	.45		>.99
Breslow thickness, per mm	403 (100)	1.26 (1.15-1.38)	<.001	1.16 (1.02-1.32)	.02
Ulceration					
Absent	289 (71.7)	1 [Reference]		1 [Reference]	
Present	114 (28.3)	3.69 (2.04-6.67)	<.001	2.07 (1.07-3.99)	.03
Sentinel node status					
Negative	314 (77.9)	1 [Reference]		1 [Reference]	
Positive	89 (22.1)	5.02 (2.79-9.03)	<.001	4.14 (2.14-7.98)	<.001

Abbreviations: HR, hazard ratio; NM, nodular melanoma; SLNE, sentinel lymph node excision; SPECT/CT, single-photon emission computed tomography/computed tomography; SSM, superficial spreading melanoma.

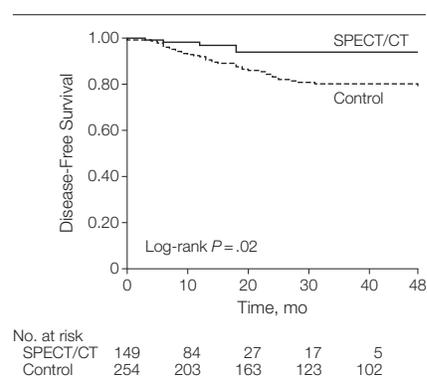
and ulceration of the primary melanoma (HR, 2.07; 95% CI, 1.07-3.99; $P = .03$).

The calculated 4-year disease-free survival rates were 93.9% in the SPECT/CT cohort vs 79.2% in the standard cohort ($P = .02$) (FIGURE 1). The overall survival rates were 95.9% in the SPECT/CT cohort and 92.1% in the standard cohort ($P = .80$).

Overweight Patients

Patients with body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) of 30 or higher were considered obese. Thirty-one patients (7.6%) in the study population were found to have BMI values equal to or higher than 30 (mean, 31.48; median, 31.00). Among this subgroup of patients, we detected 5 positive SLNs out of 20 (25%) in 7 obese patients in the SPECT/CT cohort. In the standard cohort, we found 4 positive SLNs out of 44 (9.1%) in 24 obese patients ($P < .001$) (Table 1).

Figure 1. Kaplan-Meier Curve With the SPECT/CT-Specific Disease-Free Survival Over 48 Months



SPECT/CT indicates single-photon emission computed tomography/computed tomography.

COMMENT

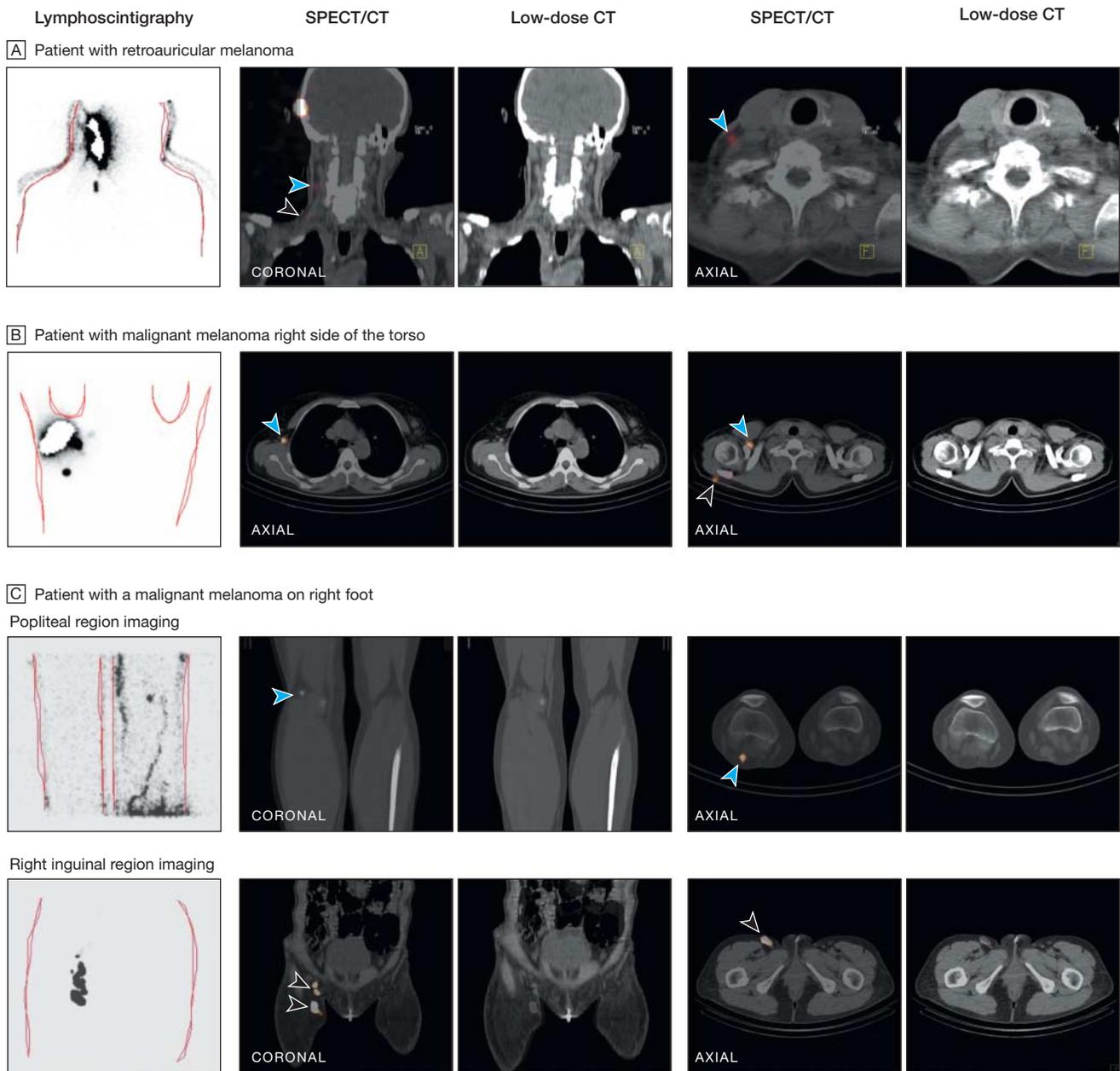
To our knowledge, this is the largest study performed to study the potential benefit of preoperative lymphoscintigraphy with SPECT/CT when compared with standard SLNE without

SPECT/CT in patients with melanoma. Our study confirms the improved identification of SLNs in overweight patients with melanoma (Table 1)¹⁷ as well as those with tu-

mors in the head and neck area.^{20,26} In the head and neck area, we used smaller incisions as well as alternative entry points due to the exact anatomical localization of the SLN. For example, if

SPECT/CT demonstrates that the SLN is not under the sternocleidomastoid muscle but on the dorsal margin of the muscle, the surgeon is able to choose a different surgical entry point

Figure 2. Preoperative Lymphoscintigraphy, SPECT/CT, and Low-Dose CT Imaging of 3 Representative Study Patients



SPECT/CT indicates single-photon emission computed tomography/computed tomography. The red lines indicate patients' body contour. A, Patient with a retroauricular melanoma. SPECT/CT in the coronal and axial planes shows 1 cranial sentinel lymph node (SLN) (blue arrowheads) and 1 caudal SLN (black arrowhead). B, Patient with a malignant melanoma on the right side of the torso. SPECT/CT in the axial plane of the axillary region shows 1 SLN (blue arrowhead). SPECT/CT in axial plane of the scapular region shows 1 SLN next to the coracoid (black arrowhead) and another SLN in the cranial axillary region (blue arrowhead). C, Patient with a malignant melanoma on the right foot. SPECT/CT in the coronal and axial planes of the popliteal region shows 1 SLN (blue arrowheads). SPECT/CT in the coronal and axial planes of the inguinal region shows 4 SLNs (black arrowheads).

(FIGURE 2). In 33 of 149 patients (22.1%), the surgical approach was changed based on SPECT/CT findings, which is in line with previous study results.^{15,26} In the current literature, preoperative SPECT/CT is not recommended for patients with torso or extremity melanoma.^{15,27} In the axilla and groin, however, the reported false-negative rate is very high and varies between 5.7% and 32.0%, respectively.^{24,28} In our study, we were able to demonstrate the reliability and effectiveness of preoperative SPECT/CT imaging for all SLNE without preselection by anatomical site (Table 1 and Figure 2, with an example for cervical, axillary, popliteal, and inguinal SLN). With the SPECT/CT-guided SLNE, we removed more SLNs (2.40 SLNs per patient) than in the standard cohort (1.87 SLNs per patient, $P < .001$), which is consistent with previous studies.^{20,26,29} This finding can be explained by excised nodes near the injection site, which are more clearly visualized with SPECT/CT and the detection of SLN with a weak tracer signal. The additional SLNs excised in the SPECT/CT cohort resulted in no increase in morbidity. On the contrary, in the SPECT/CT cohort, we demonstrated a lower morbidity than in the standard cohort (4.0% vs 7.9%, $P > .05$). The metastatic involvement rate of the SLN was significantly higher in the SPECT/CT cohort than in the standard cohort (34% vs 21%, $P = .04$). Accordingly, the rate of local relapses in the SPECT/CT cohort was significantly lower than in the standard cohort (6.8% vs 23.8%, $P = .03$), which subsequently prolonged the disease-free survival (4-year rates were 93.9% in the SPECT/CT cohort vs 79.2% in the standard cohort, $P = .02$) (Figure 1).

Our study confirms that the SLN status is a significant prognostic factor ($P < .001$) for a prolonged disease-free survival.³⁰⁻³³ The multivariate analysis revealed that SPECT/CT is also a significant prognostic factor for prolonged disease-free survival (Table 3). We could not detect a significant difference in overall survival, although the ulceration rate

in the standard cohort was higher than in the SPECT/CT cohort (Table 1), an indicator for very poor survival. Conversely, location of the primary node in the SPECT/CT cohort was significantly higher on the head and neck where survival is much poorer. These negative effects on overall survival in each cohort may theoretically offset each other, so that no difference can be detected. However, it is more likely that these results are due to the limited median follow-up of 28.8 months, which is too short to detect a difference with respect to overall survival.

According to the observations by Morton et al,⁷ SLNE leads to an improvement of life years and quality adjusted life years. Moreover, some merits of SLNE in the SPECT/CT technique in local anesthesia include sparing patients the common risks and adverse effects of general anesthesia, such as nausea, vomiting, dizziness, and lethargy, further minimizing the risks of aspiration pneumonitis and adverse effects of tracheal intubation, such as sore throat, croup, and hoarseness.³⁴

Limitations of our study include the design and in particular the temporal separation of the 2 cohorts. This could lead to a bias for the time-dependent end points. However, this does not affect the time-independent variables such as the count of excised SLNs and the quantity of excised positive SLNs. Time-dependent consequences of a significantly higher identified metastatic involvement rate of SLNs in the SPECT/CT cohort should result in a lower rate of local relapses and a prolonged disease-free survival as described in our results. Therefore, our results are credible and the generation of a time-dependent bias is very unlikely. Nevertheless, our results demonstrate clear advantages of adding the described preoperative SLN imaging by SPECT/CT to the current practice of preoperative lymphoscintigraphy in patients with melanoma. These advantages also lead to lower dropout rates (Table 2).

In conclusion, the preoperative visualization of SLN with SPECT/CT is

technically feasible and facilitates the detection of additional positive SLNs. The use of this technique offers the physician the preoperative possibility of determining the exact location and visualization of the SLN, especially if the tracer signal is too weak for detection by the handheld gamma probe alone or the SLN is in the immediate vicinity of the remaining tracer depot. In patients with cutaneous melanoma, the use of SPECT/CT-aided SLNE compared with SLNE alone was associated with higher detection of metastatic involvement and a higher rate of disease-free survival.

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Study concept and design: Boy, Klode.

Acquisition of data: Stoffels, Boy, Pöppel, Kuhn, Klötgen, Klode.

Analysis and interpretation of data: Stoffels, Boy, Dissemond, Schadendorf, Klode.

Drafting of the manuscript: Stoffels, Pöppel, Kuhn, Klötgen, Dissemond, Klode.

Critical revision of the manuscript for important intellectual content: Stoffels, Boy, Schadendorf, Klode.

Statistical analysis: Stoffels, Boy, Klode.

Administrative, technical, or material support: Stoffels, Boy, Pöppel.

Study supervision: Stoffels, Boy, Schadendorf, Klode.

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