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Original Research

Melanoma-specific survival in patients with positive sentinel lymph nodes: Relevance of sentinel tumor burden

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KEYWORDS
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Abstract ***Background:*** The tumor burden within the sentinel lymph node (SLN) is not included in the 8th edition of the American Joint Committee of Cancer (AJCC) melanoma classification. Therefore, we analysed the prognostic relevance of the SLN tumor burden in the stage III subgroups.

Patients and methods: A total of 736 patients with melanoma with positive SLN and long-term follow-up (mean, 64.4 months; median, 59.0 months) were assessed. SLN tumor burden was evaluated by the maximum diameter of the largest deposit in all patients.

Results: By univariate Kaplan-Meier analyses, melanoma-specific survival (MSS) of patients in stage IIIA, IIIB and IIIC and lower sentinel tumor burden (cut-offs $\leq$0.5 mm and $\leq$1 mm) was significantly better than that in patients with higher sentinel tumor load (>0.5 mm and >1 mm).

By multivariate analysis using the Cox model, the maximum diameter of the largest deposit (cut-off $\leq$0.5 mm versus >0.5 mm and cut-off $\leq$1 mm as continuous variables) represented an independent prognostic parameter for MSS in stage III patients. Cut-off of 0.5 mm showed a slightly higher area under the receiver operating characteristic curve (AUC = 0.617) when than the cut-off of 1 mm (AUC = 0.599).

Conclusion: The prognosis of patients with stage III melanoma can be determined more precisely if the SLN tumor burden is considered, also within the existing AJCC subgroups. Thus, this parameter should be included in future classifications, and our study provides benchmarks

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in estimating prognosis and counselling patients with melanoma with positive sentinel nodes beyond the 8th AJCC Cancer Staging Manual. The optimal cut-off remains for SLN tumor burden remains to be determined, but our results suggest that a cut-off lower than 1 mm is preferable.

1. Introduction

Since 2018, adjuvant therapy of patients with melanoma in stage group III was revolutionised by the use of nivolumab, pembrolizumab and dabrafenib/trametinib [1–3]. Therefore, assessment of prognosis is crucial. This usually relies on a widely accepted classification, which in case of melanoma is the American Joint Committee of Cancer (AJCC) Cancer Staging Manual. The 7th edition of the American Association of Cancer Research (AACR) melanoma classification published in 2009 [4] was recently replaced by the 8th edition in 2017 [5]. This new edition implies major changes in allocation of patients in stage III to improve their discrimination and prognostication [6]. In addition to the number, sites and sizes of regional metastases (lymph nodes, in transit and satellite metastases, micrometastasis and macrometastasis) and the ulceration of the primary melanoma which were already used in the 7th AJCC edition, the 8th edition also included thickness of the primary melanoma to assign patients to stage IIIA-D.

However, no new parameters to improve the discrimination of prognostic groups were introduced. Tumor load in the sentinel lymph node (SLN) is an important prognostic parameter in stage III patients [7–10] but was not incorporated in the revised classification. The AJCC panel acknowledged the possible importance of the tumor load and proposed the incorporation in future classifications after further efforts to harmonise and standardise the assessment and reporting of SLN tumor burden [5]. We think that the tumor burden in the SLN defined by the maximum diameter of the largest deposit also is an important prognostic parameter. This parameter already is available today, can be measured reliably [11] and is helpful for prognostication of patients with stage III melanoma.

To provide further evidence, we analysed patients with melanoma, who had a primary melanoma ≥1 mm thickness and a positive SLN.

2. Material and methods

2.1. Patients

All patients met the following inclusion criteria: primary tumor thickness ≥1 mm, successful sentinel node biopsy with detection of tumor cells and no evidence of metastases in clinical and radiological assessments. SLN tumor burden was evaluated by the parameter of maximum diameter of largest deposit in all patients.

Patients were either from the DeCOG-SLT trial (Complete Lymph Node Dissection vs Watchful Waiting in Patients With Malignant Melanoma; Thickness of 1,0mm+ and Evidence of Metastases in the Sentinel Node, n = 432) or from the sentinel node database of the Skin Cancer Center Hannover (n = 304).

A total of 473 patients participated in the DeCOG-SLT trial, who were randomised to be treated additionally with completion lymph node dissection (CLND) − or without CLND [12]. The size of the SLN tumor load was not available for 41 of 473 patients; they were excluded from this study. All remaining 432 patients were included in this evaluation; in 171 of 432 patients (39.6%), CLND was performed.

Three hundred four patients were treated in our single centre (Skin Cancer Center Hannover) in the years 2000–2009, who did not participate in the DeCOG-SLT trial. All patients underwent initial surgical treatment of the primary melanoma in our department (Department of Dermatology and Allergy, Hannover Medical School, Hannover, Germany). As described previously, all patients underwent wide local excision of the primary melanoma with 1–2 cm safety margin and SLN biopsy [13]. If ulceration of the primary melanoma was not reported (n = 85), it was considered as absent. In 246 of 304 patients (80.9%), CLND after positive SLN biopsy was performed. CLND was not performed in 58 of 304 patients because of the following reasons: refusal by 53 patients after informed consent (in particular due to low tumor burden in 29 patients) and medical reasons prohibiting a major procedure in general anaesthesia in 5 patients.

The pathology workup was similar within the DeCOG study [12] and Skin Cancer Center Hannover [14]. Histopathological analysis of SLNs was performed in slices of 1–2 mm thickness of the respective nodes, which were separately paraffin-embedded and stained in serial sections with haematoxylin and eosin and immunohistochemical stains for S-100 protein, HMB-45, and Melan-A. Because the S-100 did not provide additional information, this staining was dispensed during the course of the patient collection and not available since 2007 for lymph nodes from the Skin Cancer Center Hannover.

Table 1
Characterisation of 736 melanoma patients with positive SLN.

Characteristic	SLN-positive maximum diameter largest deposit ≤0.5 mm	SLN-positive maximum diameter largest deposit >0.5–1.0 mm	SLN-positive maximum diameter largest deposit >1.0 mm	*p-value*
No.	335	195	206	
Age (years)				
Median (IQR, 23)	56	58	59	0.002
Sex				
Male (%)	182 (54.3)	117 (60.0)	134 (65.0)	0.004
Female (%)	153 (45.7)	78 (40.0)	72 (35.0)	
Site of primary tumor				
Head/Neck	16 (4.8)	0 (0.0)	5 (2.4)	0.053
Trunk	154 (46.0)	89 (45.6)	100 (48.5)	
Upper extremity	47 (14.0)	35 (17.9)	24 (11.7)	
Lower extremity	115 (34.3)	71 (36.4)	75 (36.4)	
Unknown	3 (0.9)	0 (0.0)	2 (1.0)	
Thickness of primary melanoma (mm)				
Median (IQR 2.06)	2.2	2.6	3.05	<0.001
Ulceration of primary melanoma				
Yes (%)	123 (36.7)	77 (39.5)	97 (47.1)	<0.001
No (%)	188 (56.1)	81 (41.5)	85 (41.3)	
Unknown (%)	24 (7.2)	37 (19.0)	24 (11.7)	
Pathological stage group according to 8th edition [5]				
IIIA (%)	130 (38.8)	54 (27.7)	46 (22.3)	<0.001
IIIB (%)	87 (26.0)	52 (26.7)	48 (23.3)	
IIIC (%)	118 (35.2)	89 (45.6)	109 (52.9)	
IIID (%)	0 (0)	0 (0)	3 (1.5)	
Recurrence				
Yes (%)	101 (30.1)	79 (40.5)	104 (50.5)	<0.001
No (%)	234 (69.9)	116 (59.5)	102 (49.5)	
Yes, IIIA	20	15	15	0.588
Yes, IIIB	20	16	20	
Yes, IIIC	61	48	66	
Yes, IIID	0	0	3	
Distant metastases				
Yes (%)	78 (23.3)	63 (32.3)	83 (40.3)	<0.001
No (%)	257 (76.7)	132 (67.7)	123 (59.7)	
Yes, IIIA	15	11	10	0.454
Yes, IIIB	16	11	14	
Yes, IIIC	47	41	56	
Yes, IIID	0	0	3	
Deceased				
Yes, melanoma (%)	59 (17.6)	60 (30.8)	87 (42.2)	<0.001
Yes, other (%)	21 (6.3)	8 (4.1)	11 (5.3)	
No (%)	255 (76.1)	127 (65.1)	108 (52.4)	
Yes, melanoma, IIIA	11	9	10	0.578
Yes, melanoma, IIIB	12	13	15	
Yes, melanoma, IIIC	36	38	59	
Yes, melanoma, IIID	0	0	3	
CLND				
Yes, positive NSLN	22 (6.6)	15 (7.7)	39 (19.0)	<0.001
Yes, negative	172 (51.5)	78 (40.0)	89 (43.4)	
No	140 (41.9)	102 (52.3)	77 (37.6)	
Yes, positive NSLN, IIIA	2	2	4	0.913
Yes, positive NSLN, IIIB	6	3	8	
Yes, positive NSLN, IIIC	14	10	24	
Yes, positive NSLN, IIID	0	0	3	

IQR, interquartile range; CLND, completion lymph node dissection; SLN, sentinel lymph node; NSLN, non sentinel lymph node.

In the DeCOG trial, the maximum diameter of the largest deposit was assessed prospectively by local (dermato)pathologists and categorised into ≤0.5 mm, 0.51 mm–1 mm, 1.01–2 mm, 2.01–5 mm and >5 mm. In the Skin Cancer Center Hannover, all slides from the positive SLNs were retrospectively assessed, and the maximum diameter of the largest deposit was assessed as the continuous variable.

Patients were followed up according to German guidelines [15]; the median and mean follow-up times were 59.0 and 64.4 months, respectively. Melanoma-specific survival (MSS) was defined as death due to melanoma; deaths due to other causes or unclear causes were censored.

2.2. Statistics

The software SPSS, version 25, was used for statistical analyses. For univariate analyses, chi-squared tests and Kaplan-Meier tests were performed. A backwards step-wise Cox multivariate analysis was performed including parameters that were significant by univariate analysis.

The following histopathologic features of patient characteristics, the primary melanoma and SLN were analysed in different combinations with two different cut points given: age (cut-off value 60 years), Breslow thickness, ulceration of the primary melanoma (absent versus present) and maximum diameter of the largest deposit (with cut-off values ≤ 0.5 mm vs > 0.5 mm or ≤1 mm vs > 1 mm as the continuous variable). Multivariate analysis including tumor burden as the continuous variable could only be conducted on patients from our single centre (Skin Cancer Center Hannover) because in the DeCOG database, the tumor burden (maximum diameter of the largest deposit) was not specified as a continuous variable. Sensitivity and specificity values with area under the receiver operating characteristic (ROC) curve (AUC) for maximum diameter of the largest deposit regarding MSS were calculated. P-values and confidence intervals are given. In case of a p-value <0.05, the result was considered statistically significant.

3. Results

In total, 736 patients were eligible for this study.

We grouped the 736 SLN-positive patients in the stage III categories according to the 8th AJCC Cancer Staging Manual. Two hundred thirty patients (31.3%) were grouped in stage IIIA, 187 patients (25.4%) in stage IIIB, 316 patients (42.9%) in stage IIIC and 3 patients (0.4%) in stage IIID. Assessing the tumor burden of the SLN in these subgroups, the tumor burden showed an increase from stage IIIA to IIID (Table 1). The 8th AJCC classification provided excellent differentiation between stage IIIA, IIIB and IIIC patients in univariate Kaplan-Meier analyses (Fig. 1).

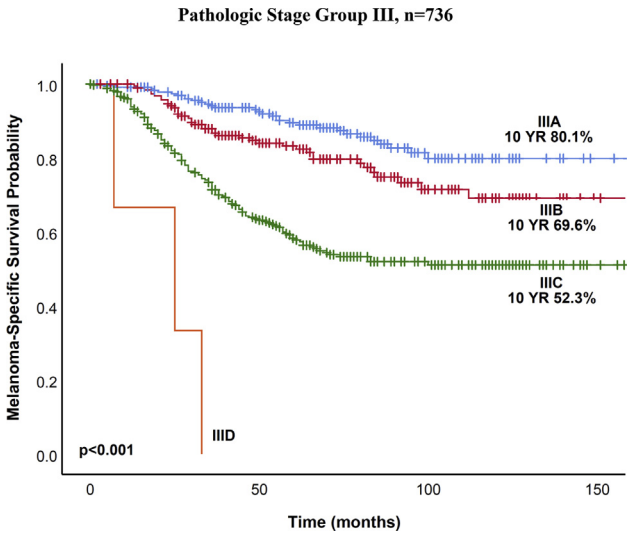

Fig. 1. Survival rates of 736 melanoma patients with positive SLN stratified by the 8th edition of the AJCC classification. AJCC, American Joint Committee of Cancer; SLN, sentinel lymph node.

Then, we selected three cut-off values of the SLN tumor burden (maximum diameter of the largest deposit ≤ 0.5 mm versus >0.5 mm, ≤1 mm versus >1 mm and ≤2 mm versus >2 mm) based on the data in the DeCOG-SLT trial as well as the cut-off value of >1 mm in 2 recent adjuvant melanoma studies [2,3,12].

3.1. Kaplan-Meier analysis

By univariate Kaplan-Meier analysis, patients in stage IIIA, IIIB and IIIC had a significant better prognosis with a lower maximum diameter of the largest deposit (≤0.5 mm and ≤1 mm, respectively) than those with a higher tumor burden (>0.5 mm and >1 mm, respectively, Fig. 2) and the 10-year MSS rates were significantly higher for all stage IIIA, IIIB and IIIC patients with SLN tumor deposits ≤0.5 mm and ≤1 mm (Fig. 2). MSS of stage IIIA patients differed not significantly when stratified by the cut-off of 2 mm, whereas prognosis was significantly better with tumor burden <2 mm in stage IIIB ($p < 0.001$) and IIIC ($p = 0.002$) patients (data not shown).

3.2. Receiver operating characteristic curve analysis

ROC curve analysis was used to compare the sensitivity and specificity of different cut-offs (0.5 mm, 1 mm and 2 mm) to predict the prognosis of melanoma patients in stage III. Cut-off of 0.5 mm showed the highest area under the ROC curve (AUC = 0.617) when compared with the cut-off of 1 mm (AUC = 0.599) and 2 mm (AUC = 0.556; Fig. 3a). In subgroup analyses of stages IIIA, IIIB and IIIC, the cut-off of 0.5 mm was also superior compared with 1 mm and 2 mm (Fig. 3b–d).

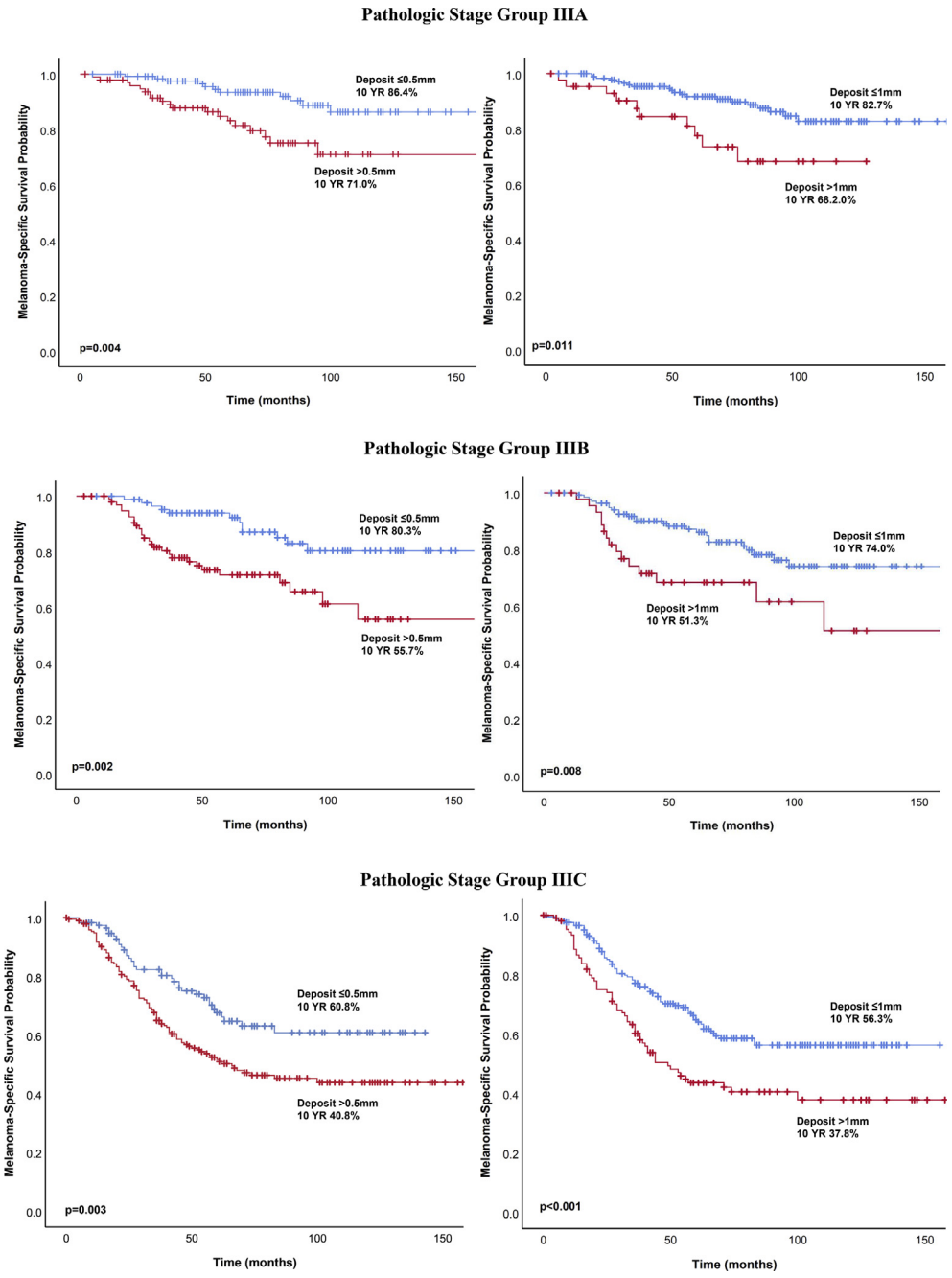

Fig. 2. Kaplan-Meier analysis of melanoma-specific survival in stage IIIA (Fig. 2a), IIIB (Fig. 2b) and IIIC patients (Fig. 2c) with malignant melanoma divided between patients with positive SLN with a maximum diameter of the largest deposit in the SLN ≤0.5 mm versus >0.5 mm and ≤1 mm versus >1 mm. Ten-year survival rate (10 YR) was significantly improved in patients with maximum diameter of the largest deposit ≤0.5 mm and ≤1 mm in stages IIIA, IIIB and IIIC when compared with patients with maximum diameter of the largest deposit >0.5 mm and >1 mm, respectively. SLN, sentinel lymph node.

However, the AUC values for 0.5 mm were only slightly better than those for 1 mm and 2 mm.

3.3. Multivariate analysis

To determine independent prognostic parameters of patient characteristics, primary melanoma and SLN tumor burden, we performed a backwards stepwise Cox multivariate analysis including the potential prognostic parameters. SLN tumor burden was tested with two cut-offs (>0.5 mm and >1 mm) in all patients.

The four significant parameters determined in this analysis were age (>60 years), Breslow thickness, ulceration of the primary melanoma (present) and SLN tumor burden (maximum diameter of the largest deposit >0.5 mm and maximum diameter of the largest deposit >1 mm, respectively; Table 2a and 2b).

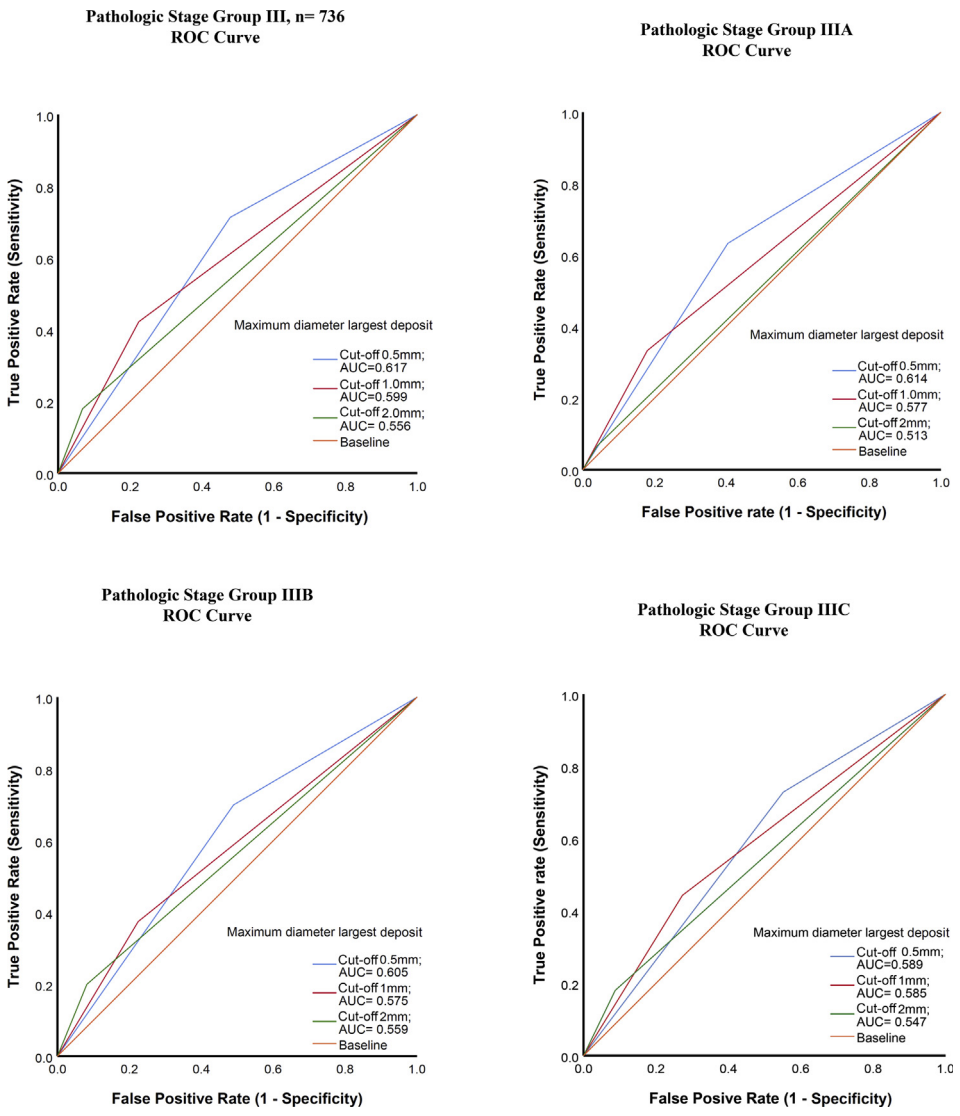

Fig. 3. Receiver operating characteristic curves for SLN tumor burden with two different cut-offs (0.5 mm and 1 mm) in 736 patients with stage III melanoma (Fig. 3a). Sensitivity and specificity define prognosis in patients with stage IIIA (Fig. 3b), stage IIIB (Fig. 3c) and stage IIIC melanoma (Fig. 3d). Area under the area under the receiver operating characteristic curve (AUC) values is given in the right lower corner of each plot. SLN, sentinel lymph node.

Table 2a
Backwards stepwise Cox multivariate analysis of parameters of the primary melanoma, patient characteristics and SLN tumor burden (cut-off ≤0.5 mm versus >0.5 mm) with regard to the prediction prognosis of 736 stage III patients.

Characteristic		p-value	Hazard ratio	−95% CI	+95%
Maximum diameter largest deposit Sentinel tumor burden	>0.5 mm	<0.001	2.324	1.702	3.171
Breslow thickness of primary melanoma	Continuous variable	0.001	1.053	1.022	1.084
Ulceration of primary melanoma	Yes	<0.001	1.867	1.385	2.516
Age	>60 years	<0.001	1.712	1.283	2.284
Sex	Male	0.182	1.227	0.909	1.656

3.4. Sentinel lymph node tumor burden as a continuous variable in multivariate analysis and receiver operating characteristic curve analysis

Maximum diameter of the largest deposit as a continuous variable was also an independent significant parameter when included into multivariate analysis (Table 2c). ROC curves for SLN tumor burden as the continuous variable revealed an AUC value of 0.674 to predict prognosis in stage III patients (Fig. 4).

Table 2b
Four parameters yielded significant results. Using the different cut-off (≤1 mm versus >1 mm) the same four parameters were also significant.

Characteristic		p-value	Hazard ratio	−95%	+95%
Maximum diameter largest deposit Sentinel tumor burden	>1 mm	<0.001	2.214	1.654	2.963
Breslow thickness of primary melanoma	Continuous variable	0.006	1.044	1.013	1.076
Ulceration of primary melanoma	Yes	<0.001	1.996	1.481	2.690
Age	>60 years	<0.001	1.743	1.307	2.325
Sex	Male	0.155	1.243	0.921	1.677

Table 2c
Multivariate analysis including SLN tumor burden as a continuous variable could be performed on the 304 of 736 patients treated in our single centre (Skin Cancer Center Hannover), as the tumor thickness was assessed in categories in the DeCOG study. The maximum diameter of the largest deposit (as a continuous variable) and the ulceration of the primary melanoma yielded significance.

Characteristic		p-value	Hazard ratio	−95%	+95%
Maximum diameter largest deposit Sentinel tumor burden	Continuous variable	<0.001	1.245	1.102	1.406
Breslow thickness of primary melanoma	Continuous variable	0.258	1.069	0.952	1.201
Ulceration of primary melanoma	Yes	<0.001	3.353	1.920	5.857
Age	>60 years	0.822	1.068	0.603	1.890
Sex	Male	0.078	1.658	0.945	2.909

4. Discussion

4.1. Tumor load as an important prognostic parameter

By introducing the 8th edition of the AJCC Cancer Staging Manual, we have learned that also in the stage of regional metastases (stage III), the thickness of the melanoma is a prognostically relevant parameter. We analysed in this study whether the SLN tumor burden can add another relevant variable to the prognostically complex model in patients with stage III melanoma. First, we tested the discriminatory power of the new AJCC Cancer Staging Manual in our patient cohort of 736 SLN-positive patients. Three significantly different groups could be identified ($p < 0.001$; Fig. 1). In a second step, we compared the MSS of patients with an SLN low tumor load with the MSS of patients with a higher SLN tumor load in the respective substages IIIA, IIIB and IIIC. We used the parameter of maximum diameter of the largest deposit with three different cut-offs, 0.5 mm, 1.0 mm and 2 mm. The 1.0-mm cut-off was previously used to classify patients into adjuvant studies and in the DeCOG-SLT trial [2,3,12]. In all three groups (stage IIIA, stage IIIB and stage IIIC), significant prognostic differences could be demonstrated when stratified for SLN tumor load by cut-offs 0.5 mm and 1 mm. In ROC curves, the cut-off of 0.5 mm was found to be superior, but the difference was only modest. Moreover, the tumor load of the SLN (cut-offs 0.5 mm and 1 mm as the continuous variable) was an independent prognostic parameter in the multivariate analyses. Our findings are in line with those of two recent studies by Madu *et al.* [16] and Verver *et al.* [17]. Madu *et al.* [16] analysed 640 patients with stage III melanoma of the Dutch NKI-database with regional lymph node metastases (both macrometastasis and micrometastasis) as well as locoregional cutaneous metastases. In the patients with stage IIIA melanoma according to the AJCC 8th edition ($n = 77$), maximum diameter of the largest deposit (cut-off 1 mm) was used to group these patients with stage IIIA melanoma. MSS of patients with maximum diameter of the largest deposit ≤1 mm was significantly longer ($p = 0.02$) than MSS of patients with maximum diameter of the largest deposit >1 mm (91% versus 72%).

Verver *et al.* [17] stratified 1015 SLN-positive melanoma patients from 9 European Organisation for Research and Treatment of Cancer (EORTC) Cancer Centers by ulceration and SLN tumor burden and were able to identify four different prognostic risk groups using these two parameters. They focused their analysis on the relevance of CLND for correct staging of patients with melanoma with positive node rather than the relevance of SLN tumor load on AJCC substages.

While the maximum diameter of the largest deposit cut-off value of 1 mm is used in several studies [16,2,3], we analysed 3 cut-offs (0.5 mm, 1 mm and 2 mm), which were used in the DeCOG-SLT trial [12]. The cut-offs of 0.5 mm and 1 mm revealed significant differences in all stage III patients, while the cut-off of 0.5 mm showed a slightly higher AUC in the ROC curve analysis than 1 mm. Thus, the SLN tumor load is of prognostic importance, but the ideal cut-off needs to be determined, and our data point towards a cut-off lower than 1 mm.

The most probable scenario is that prognosis deteriorates continuously with increasing maximum diameter of the largest deposit.

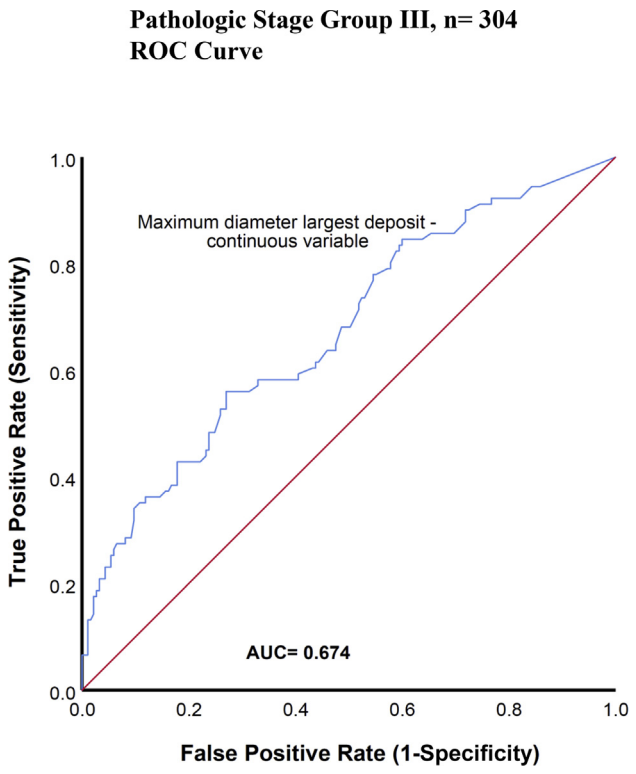

Fig. 4. Receiver operating characteristic curve for SLN tumor burden as a continuous variable in 304 patients with stage III melanoma of our single centre (Skin Cancer Center Hannover). SLN, sentinel lymph node.

4.2. Comparability of the patient cohorts

The AJCC cohort shows significantly better survival rates in stage IIIA, IIIB and IIIC patients than our cohort. In stage IIIA, we observed a 10-year MSS of 80% (AJCC 88%), in stage IIIB of 70% (AJCC 77%) and in stage IIIC of 52% (AJCC 60%). This is surprising because our study included only patients with positive sentinel node, while the AJCC included also patients with macrometastases in stage IIIB and IIIC.

Madu *et al.* [16] reported 5-year MSS rates, which were also considerably worse than AJCC: in stage IIIA 86% (AJCC 93%), in stage IIIB 78% (AJCC 83%), in stage IIIC 57% (AJCC 69%) and in stage IIID 19% (AJCC 32%).

The obviously better outcome of the patients in the AJCC cohort could be due to a possibly shorter follow-up time, which is not given in the AJCC classification [5]. It is also possible that in large international cohorts, such as the AJCC cohort, deaths could not always be precisely attributed to melanoma or other causes, which would result in an underestimation in MSS. The follow-up determination in our single skin cancer centre and in a study such as the DeCOG-SLT trial could be more intensive and thorough. However, due to lack of data in the AJCC classification, this is speculation at this point of time.

4.3. Sentinel lymph node tumor load and adjuvant treatment

In recent adjuvant clinical trials, such as the COMBI-AD trial [2] and the Keynote-54 trial [3], the maximum diameter of the largest deposit was already incorporated in the inclusion criteria. Stage IIIA patients (according to the 7th edition of the AJCC Cancer Staging Manual) were eligible with maximum diameter of the largest deposit of >1 mm. Recently, the impact of adjuvant therapy in stage III patients according to the 8th AJCC classification was investigated in two retrospective calculations of the COMBI-AD [18] and the Keynote-54 [19] trial. While in the Keynote-54 trial, the follow-up time was not sufficient yet, the COMBI-AD trial showed an impact of dabrafenib + trametinib on recurrence-free survival of stage IIIA patients. Seventy percent of placebo-treated patients in stage IIIA (n = 39) had not relapsed after 3 years, while 83% of patients treated with dabrafenib + trametinib (n = 50) were without recurrence.

This furthermore emphasises the practical relevance of SLN tumor load in the interpretation of clinical trials, possibly also for the registration of adjuvant therapies and for counselling of patients.

5. Conclusion

Taken together, our data point towards a crucial prognostic relevance of the SLN tumor load in stage IIIA, IIIB and IIIC in the 8th edition of the AJCC Melanoma Staging Manual. Thus, we recommend incorporating the parameter of maximum diameter of the largest deposit in an updated melanoma classification. However, the optimal cut-off point needs to be determined in a larger patient cohort.

Conflict of interest statement

I.S. has received honoraria from GSK, Roche, MSD, BMS and Novartis; U.L. from Roche, MSD, Novartis and Sanofi; N.G. from Novartis; C.G. from Amgen, BMS, MSD, NeraCare, Novartis, Philogen, Pierre Fabre, Roche, SUN Pharma and Sanofi and R.G. from Roche, BMS, MSD, Novartis, Pfizer, Amgen, Merck Serono, Almirall Hermal, SUN Pharma, Sanofi and Pierre Fabre. I.S. has served consultant or advisory role in GSK, Roche, MSD, BMS and Novartis; U.L. in Roche, MSD, Novartis and Sanofi; C.G, in Amgen, BMS, MSD, NeraCare, Novartis, Philogen, Pierre Fabre, Roche, SUN Pharma and Sanofi and R.G. in BMS, Roche, Novartis, Almirall Hermal, MSD, Amgen, Incyte Corporation, 4SC, Sun Pharma, Sanofi, Merck Serono and Pierre Fabre. C.G. has received research funding from BMS, NeraCare, Novartis, Roche and Sanofi; I.S. from Novartis and Pfizer and

R.G. from Novartis, Pfizer, Johnson & Johnson, Amgen and Merck Serono. R.G. has received travel and accommodation expenses from Roche, BMS, Pierre Fabre and Merck Serono. U.K. reports no conflict of interest.

Author contributions

I.S. and R.G. contributed to study concepts and design. I.S., R.G. and U.L. contributed to data acquisition. I.S., R.G., U.L., U.K. and C.G. contributed to quality control of data and algorithms. I.S. and R.G. contributed to data analysis and interpretation. I.S., R.G., N.G. and U.L. (for DeCOG) and U.K. (for DeCOG) contributed to statistical analysis. I.S., N.G., R.G., U.L., C.G. and U.K. prepared the manuscript. I.S., R.G. and U.L. edited the manuscript.

References

[1] Weber J, Mandala M, Del Vecchio M, et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. N Engl J Med 2017 Nov 9;377(19):1824–35.

[2] Long GV, Hauschild A, Santami M, et al. Adjuvant dabrafenib plus trametinib in stage III BRAF-mutated melanoma. N Engl J Med 2017 Nov 9;377(19):1813–23.

[3] Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma. N Engl J Med 2018;378:1789–801.

[4] Balch CM, Gershenwald JE, Soong S, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol 2009 Dec 20;27(36):6199–206.

[5] Gershenwald JE, Scolyer RA, Hess KR, et al. Evidence based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin 2017 Nov;67(6):472–92.

[6] Grob JJ, Schadendorf D, Lorigan P, et al. Eighth American Joint Committee on Cancer (AJCC) melanoma classification: Let us reconsider stage III. Eur J Cancer 2018 Mar;91:168–70.

[7] Starz H, Balda BR, Kramer KU, et al. A micromorphometry-based concept for routine classification of sentinel lymph node metastases and its clinical relevance for patients with melanoma. Cancer 2001;91:2110–21.

[8] van der Ploeg AP, van Akkooi AC, Rutkowski P, et al. Prognosis in patients with sentinel node-positive melanoma is accurately defined by the combined rotterdam tumor load and dewar topography criteria. J Clin Oncol 2011 Jun 1;29(16):2206–14.

[9] Van der Ploeg AP, van Akkooi AC, LU Haydu, et al. The prognostic significance of sentinel node tumor burden in melanoma patients: an international, multicenter study of 1539 sentinel node-positive melanoma patients. Eur J Cancer 2014 Jan; 50(1):111–20.

[10] Satzger I, Meier A, Voelker B, et al. Parameters predicting prognosis in melanoma sentinel nodes. J Clin Oncol 2011;29(26): 3588–90. Sep. 10.

[11] Murali R, Cochran AJ, Cook MG, et al. Interobserver reproducibility of histologic parameters of melanoma deposits in sentinel lymph nodes: implications for management of patients with melanoma. Cancer 2009. Nov 1;115(21):5026–37.

[12] Leiter U, Stadler R, Mauch C, et al. Complete lymph node dissection versus no dissection in patients with sentinel lymph node biopsy positive melanoma (DeCOG-SLT): a multicentre, randomised, phase 3 trial. Lancet Oncol 2016 Jun;17(6):757–67.

[13] Satzger I, Meier A, Zapf A, et al. Is there a therapeutic benefit of complete lymph node dissection in melanoma patients with low tumor burden in the sentinel node? Melanoma Res 2014 Oct; 24(5):454–61.

[14] Meier A, Satzger I, Völker B, et al. Comparison of classification systems in melanoma sentinel lymph nodes–an analysis of 697 patients from a single center. Cancer 2010 Jul 1;116(13):3178–88.

[15] Pflugfelder A, Kochs C, Blum A, et al. S3-guideline "diagnosis, therapy and follow-up of melanoma" – short version. J Dtsch Dermatol Ges 2013 Jun;11(6):563–602.

[16] Madu MF, Franke V, Van de Wiel B, et al. External validation of the 8th Edition Melanoma Staging System of the American Joint Committee on Cancer (AJCC): effect of adding EORTC sentinel node (SN) tumor burden criteria on prognostic accuracy in stage III. J Clin Oncol 2018;36. suppl; abstr 9500.

[17] Verver D, van Klaveren D, van Akkooi ACJ, et al. Risk stratification of sentinel node-positive melanoma patients defines surgical management and adjuvant therapy treatment considerations. Eur J Cancer 2018 Jun;96:25–33.

[18] Larkin J, Hauschild A, Santinami M, et al. Dabrafenib plus trametinib (D + T) as adjuvant treatment of resected BRAF-mutant stage III melanoma: findings from the COMBI-AD trial analyzed based on AJCC 8 classification. J Clin Oncol 2018;36. suppl.; abstr 9591.

[19] Eggermont AMM, Blank CU, Mandala M, et al. Prognostic and predictive value of AJCC-8 staging in the phase 3 EORTC 1325/Keynote-054 trial of pembrolizumab vs. placebeo in resected high-risk stage III melanoma. Eur J Cancer 2019 Jul;116:148–57.