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Original Research

Impact of American Joint Committee on Cancer 8th edition classification on staging and survival of patients with melanoma



Theodora Kanaki ^a, Andreas Stang ^b, Ralf Gutzmer ^c, Lisa Zimmer ^a, Eleftheria Chorti ^a, Antje Sucker ^a, Selma Ugurel ^a, Eva Hadaschik ^a, Nikolai S. Gräger ^c, Imke Satzger ^c, Dirk Schadendorf ^a, Elisabeth Livingstone ^{a,*}

^a Department of Dermatology, University Hospital Essen, Essen, Germany and German Cancer Consortium of Translational Cancer Research (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany

^b Center of Clinical Epidemiology, Clo Institute of Medical Informatics, Biometry and Epidemiology (IMIBE), University Hospital Essen, Hufelandstr. 55, 45147 Essen, Germany

^c Skin Cancer Center Hannover, Department of Dermatology and Allergy, Hannover Medical School

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Abstract Objective: The American Joint Committee on Cancer (AJCC) 8th staging system introduced several revisions. To assess the impact of the 8th edition American Joint Committee on Cancer (AJCC8) staging system on subgrouping and survival, patients with melanoma from two tertiary skin cancer centres were classified according to both the 7th edition American Joint Committee on Cancer (AJCC7) and AJCC8.

Methods: A total of 1948 patients aged ≥ 18 years with cutaneous melanoma stage II-IV were included. The impact of sex and age on reclassification was assessed by log binomial models. The inverse probability of censoring weighting method was used to compute ROC curves from time-to-event data to assess the discriminatory ability of AJCC7 and AJCC8. Melanoma-specific survival (MSS) and overall survival (OS) were calculated, and age- and sex-adjusted MSS hazard ratios were estimated using Cox proportional hazards models.

Results: Of all, 23.5% of patients were assigned a different subgroup when classified according to AJCC8. Owing to upshifting to stage IIIC (AJCC7 24.8% vs. AJCC8 50.8%), patient numbers of stages IIIA and IIIB decreased from 28.7% to 16.2% and 46.5% to 28.3%. The prediction accuracy for AJCC7 and AJCC8 was comparable (integrated time-dependent area

* Corresponding author: Department of Dermatology, University Hospital Essen, Hufelandstrasse 55, 45147 Essen, Germany. Fax: +492017235434.

E-mail address: elisabeth.livingstone@uk-essen.de (E. Livingstone).

under the curve [AUC] of 0.75 and 0.74, respectively). Five-year MSS of IIB and IIC AJCC8 was poor and lower than that of IIIA AJCC8 (80%, 67% and 89%, respectively). Compared to results of the International Melanoma Database and Discovery Platform, 5-year MSS was 10–15% points lower for stages IIC, IIB and IIIC.

Conclusions: Upshifting affects primarily stage III subgroups, while effects in stage II are minor. Stage IIB/C (AJCC8) patients have 67–80% MSS and should be considered for adjuvant treatment, while in stage IIIA, the indication of adjuvant treatment is questionable.

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1. Introduction

Despite advances in immunotherapy and molecular targeted therapy, cutaneous melanoma still causes 55 000 cancer deaths annually worldwide [1]. Accurate melanoma staging is of great importance as it can aid in prognostic assessment and decision-making. In addition, clinical trial design and comparability of melanoma databases are greatly dependent on a reliable and universally accepted staging system.

In 2017, the 8th edition of the American Joint Committee on Cancer (AJCC8) melanoma staging was published [2]. Revisions of the tumour, node and metastasis categories and subsequently of stage subgroupings were based on the analysis of more than 46,000 patients with melanoma from 10 international institutions, the protocol-based International Melanoma Database and Discovery Platform (IMDDP) [2]. Major changes of AJCC8 affected the N category and subsequently stage III subgrouping. New N1, N2 and N3 categories were defined, with N1c, N2c and N3c representing satellite, microsatellite or in-transit metastases with 0, 1 or ≥ 2 associated positive nodes, respectively [3]. A further stage III subgroup (IIID) was introduced, and also substages IIIA–B differ from AJCC7 because of the new N categories and the inclusion of tumour thickness as a factor for stage III classification [2].

Based on the new staging classification, melanoma-specific survival (MSS) was calculated for stages I–III [2]. The better survival of stages I–II was argued to be a consequence of the widespread use of sentinel lymph node biopsy (SLNB); the requirement of SLNB for patients with T2 through T4 primary melanoma to be included in AJCC staging and, to a lesser extent, newer imaging technologies that improve the detection of clinically occult metastatic disease [2]. Also, for stages IIIA, B and C, melanoma survival drastically improved when compared with the corresponding stage groupings according to AJCC7 [4]. The more favourable survival was discussed to be a result of the better risk stratification according to the new stage III subcategories.

Precise prognosis assessment is important for indication of adjuvant therapy. Effective adjuvant therapies for stage III and IV melanoma are now available because of

the positive results of phase 3 trials [5–7]. Yet the health risks of acute and potentially late (and not yet discovered) toxicity, as well as the financial and psychological burden, must be weighed against the actual risk of recurrence when advising patients on adjuvant treatment.

In our clinical experience, the prognosis of patients with melanoma in stage II and III is worse than that reported for the IMDDP cohort [2]. As the IMDDP database included 10 international institutions with the four European centres located in Southern Europe but not in Germany, we aimed to assess the impact of AJCC8 classification on staging and survival in an independent German cohort of patients with melanoma. We therefore assessed (1) how many patients would be assigned a different subgroup when classified according to the 8th edition, (2) whether this improved risk stratification and (3) how this affected stage-specific survival probabilities in a large German melanoma cohort stage II–IV treated at two tertiary referral skin cancer centres.

2. Material and methods

2.1. Patient selection

Patients ≥ 18 years with cutaneous melanoma stage II–IV at the time of initial melanoma presentation who were documented within the tumour registries of the Department of Dermatology Essen, Germany, were eligible for this retrospective cohort study (Fig. 1). The Department of Dermatology Essen is a tertiary centre specialised on skin cancer. Because SLNB was not routinely performed before 2003, the inclusion of patients was restricted to patients diagnosed after 2003 and up to January 31st, 2018. Data on sex, age and date of diagnosis, histological subtype, location, Breslow thickness, ulceration, mitotic rate, wide margin excision, SLNB and lymph node dissection (LND) including nodes examined/positive, results of imaging staging at diagnosis, date of last follow-up, vital status and cause of death were retrieved from the local clinical cancer registry and patient records. The most recent follow-up on vital status was performed on October 9th, 2018, by the follow-up centre of the local clinical cancer registry. The follow-up centre receives vital status information

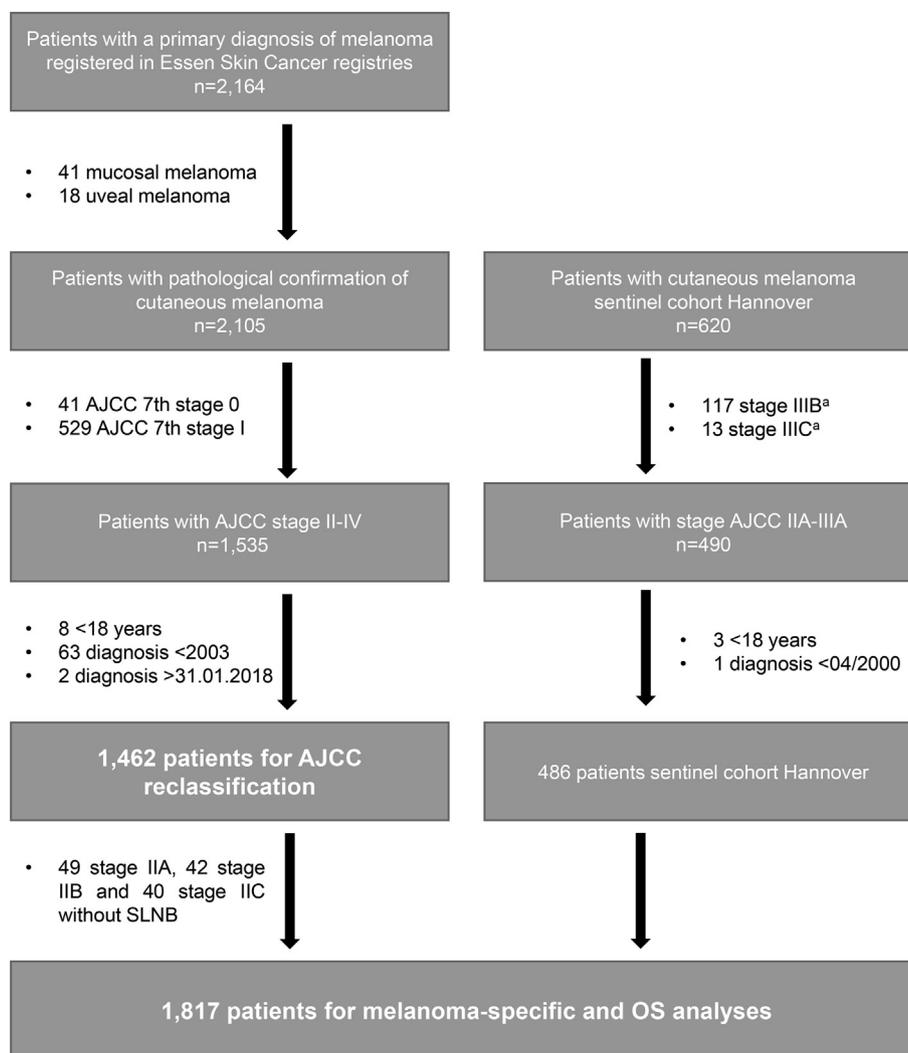


Fig. 1. Flowchart for the selection of the study population. ^aOnly stage IIA-IIC and IIIA patients were pooled with our cohort as patients with macrometastases or in-transit metastases were missing in stages IIIB-C of the Hannover cohort. AJCC, American Joint Committee on Cancer; SLNB, sentinel lymph node biopsy.

including date of death from the German Resident's Registration Offices and from Essen University Hospital medical records. Cause of death was ascertained from patient records, and if uncertain, general practitioners and relatives were contacted.

For the survival analyses, we enriched our cohort by a cohort from the Skin Cancer Center, Department of Dermatology and Allergy, Hannover Medical School, Germany, to increase statistical power. This well-described cohort [8] exclusively encompasses patients with melanoma who underwent SLNB between April 2000 and December 2009. Only stage IIA-IIC and IIIA patients were pooled with our cohort because patients with macrometastases or in-transit metastases were missing in stages IIIB-C of the Hannover cohort. Vital status for this cohort was updated in 2016 through linkage with ONkeyLINE, a Web-based cancer registry (described herein [9]) for all patients who were not in

regular follow-up and for whom vital status was unknown.

All patients were assessed and categorised according to the criteria of the 7th AJCC staging edition [10] and reclassified according to the 8th AJCC staging edition [2]. The study was approved by the institutional ethics committee of the University Duisburg-Essen (BO-18-8111) and Hannover Medical School (1612–2012).

2.2. Statistical analysis

The changes of AJCC8 were evaluated by calculating the proportions of patients reclassified in higher and lower staging groups as compared with AJCC7. Log binomial models were used to estimate the impact of sex and age on reclassification by relative risks and 95% confidence intervals (95% CIs). We estimated age- and sex-adjusted MSS hazard ratios and 95% CI for the

AJCC stages using Cox proportional hazards models. Stage IIA was defined as the reference group. To assess the discriminatory ability of AJCC7 and AJCC8, we used the inverse probability of censoring weighting (IPCW) method to compute the ROC curves adjusted for age and sex and the pointwise confidence limits for the area under the curve (AUC) curves based on the Cox proportional hazards regression models [11,12].

For MSS and OS analyses, the combined cohort from Essen and Hannover was considered, but stage II patients were only included if they had undergone SLNB (for selection of patients Fig. 1). Survival was calculated from date of diagnosis of melanoma to date of death and was censored on the last date the subject was known to be alive or at 10 years of follow-up, whichever occurred first. For MSS analyses, patients were additionally censored at the date of death if they had died from reasons other than melanoma. Survival analyses were conducted using the Kaplan-Meier method. To assess if the new subgroups in stage III lead to a better risk stratification, patients staged IIIA according to AJCC7 were reclassified according to AJCC8 and MSS was estimated for the various staging groups.

All statistical analyses were performed using IBM SPSS Statistics software (version 25.0; International Business Machines, Armonk, NY, USA) or SAS (edition 9.4; SAS Institute, Cary, North Carolina, USA). Instead of reporting p-values, CIs were calculated and reported to assess the precision of estimates [13].

3. Results

3.1. Patient population

Overall, 1,462 patients with cutaneous melanoma were included for reclassification according to AJCC8 (Fig. 1). For the MSS and OS analyses, patients without SLNB result in stage II were excluded and the cohort was enriched by 486 stage IIA-III A patients from Hannover (total $N = 1,817$; for selection of patients Fig. 1). Clinicopathological characteristics of the cohorts are depicted in Table 1 and Suppl. Table 1. The median age at diagnosis was 60 years (10th, 90th percentile: 36, 79 years); 58.5% ($N = 856$) were male. At a median follow-up time of 3.3 years, 41.7% ($n = 609$) of patients had died, and melanoma was the cause of death in 438 patients (71.9%).

3.2. Stage shift from AJCC7 to AJCC8

At the time of melanoma diagnosis, 44.0% of patients had AJCC7 stage II, 49.3% stage III and 6.7% stage IV disease (Table 1). The stage shifting that occurred after reclassification according to AJCC8 is illustrated in Fig. 2 and Suppl. Table 2. In total, 343 patients of stage II/III patients (23.5%) were assigned a different

Table 1

Clinicopathological characteristics of patients with cutaneous melanoma stage II-IV from the Department of Dermatology, Essen ($N = 1462$).

Median age at diagnosis (10th, 90 th percentile)	60 years (36, 79)
Median follow-up time (interquartiles)	3.3 years (1.8, 5.7)
Sex	
Male	856 (58.5%)
Female	606 (41.5%)
Deceased	609 (41.7%)
Melanoma-specific death	438 (71.9%)
Location of primary melanoma	
Trunk	440 (30.1%)
Lower extremity	279 (19.1%)
Upper extremity	222 (15.2%)
Head/neck	211 (14.4%)
Acral	140 (9.6%)
Unknown/other	170 (11.6%)
Histological subtype	
SSM	238 (16.3%)
NMM	392 (26.8%)
ALM	65 (4.4%)
LMM	17 (1.2%)
Desmoplastic	10 (0.7%)
Amelanotic	50 (3.4%)
Other	104 (7.1%)
Unknown	586 (40.1%)
Stage at diagnosis (AJCC 7th edition)	
IIA	290 (19.8%)
IIB	230 (15.7%)
IIC	124 (8.5%)
IIIA	207 (14.2%)
IIIB	335 (22.9%)
IIIC	179 (12.2%)
IVM1a	14 (1.0%)
IVM1b	19 (1.3%)
IVM1c	64 (4.4%)

AJCC, American Joint Committee on Cancer; SSM, superficial spreading melanoma; NMM, nodular malignant melanoma. ALM, acral lentiginous melanoma; LMM, lentigo malignant melanoma.

stage with most patients being upshifted ($N = 324$, 94.5%). Stage IIIA/B patients were mostly reclassified to the higher risk substage IIIC ($N = 228$, 70.4% of patients with upshifting). Only few shifts occurred in stage II with three patients falling into lower staging subgroups (2 patients from IIA to IA, 1 patient from IIB to IIA) because of rounding of tumour thickness to only one decimal. In stage IV, 19 patients (19.6%) had brain metastases at initial diagnosis of melanoma and were therefore allocated to the new stage IV M1d. As most stage shifting occurred in stage III, the effect of age and sex on reclassification was assessed exclusively for this patient group. Female patients were less often reclassified than male patients (risk ratio [RR]: 0.89; 95% CI: 0.76–1.05); reclassification was independent of age (for every 10 years of age, RR: 0.98; 95% CI: 0.94–1.03).

The age- and sex-adjusted AUC of AJCC7 and AJCC8 presented barely any difference (Fig. 3). When

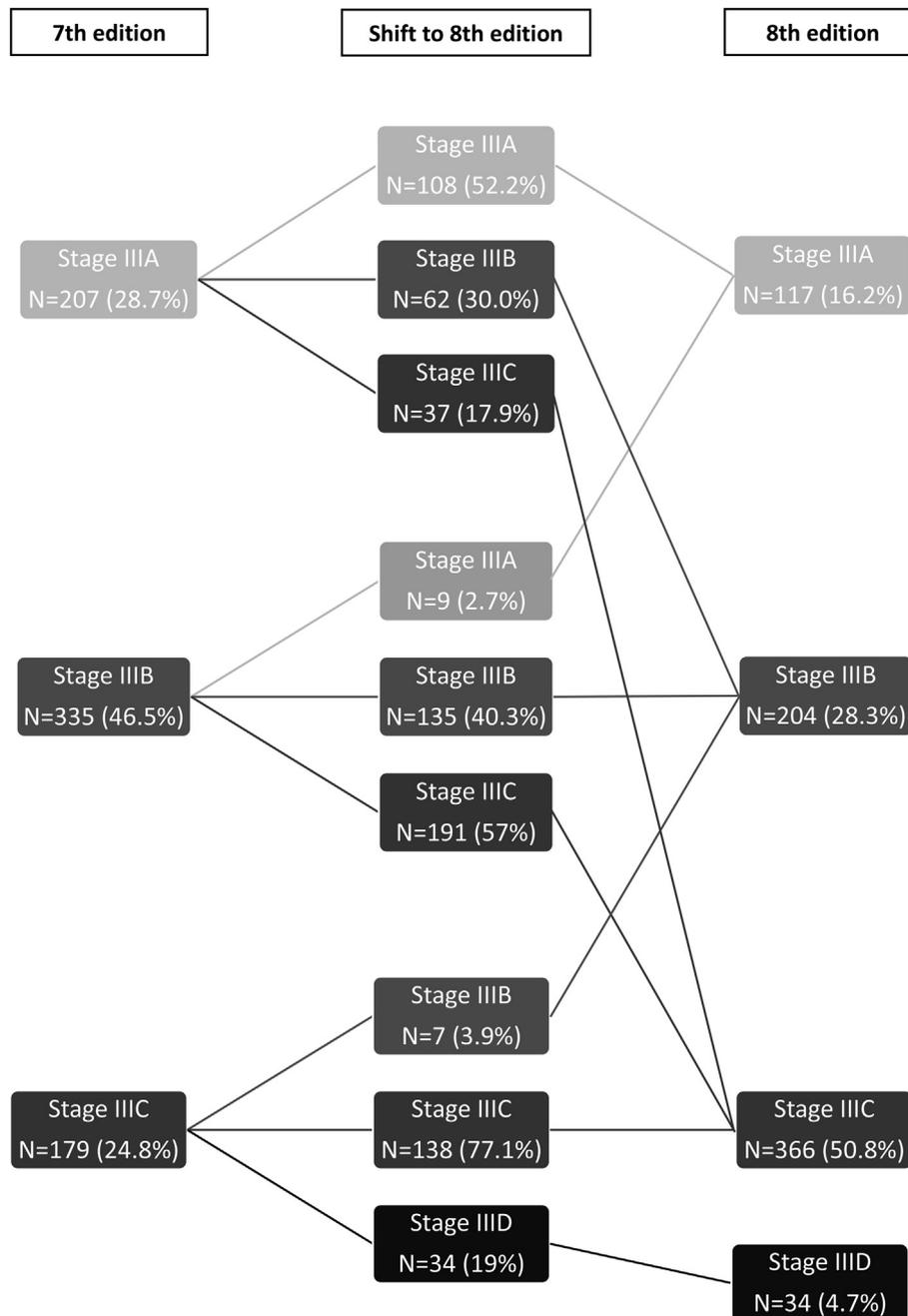


Fig. 2. Classification of stage III patients ($N = 721$, 49.3% of Essen cohort) according to AJCC7 and AJCC8. AJCC, American Joint Committee on Cancer.

applying AJCC8, the Cox model showed that hazard ratios (HRs) tended to increase by stages except for stage IIIA which showed an HR below one, indicating a higher MSS than that for the reference group stage IIA (Table 2). However, when applying AJCC7, the MSS of stage IIIA was above one, indicating a lower MSS than that for stage IIA. The introduction of subgroup IIID led to a decreased HR, specifically for stage IIIC AJCC8 (IIIC vs. IIA HR: 2.72; 95% CI: 2.00–3.70) compared with stage IIIC AJCC7 (IIIC vs. IIA HR: 4.04; 95% CI: 2.87–5.67).

3.3. Melanoma-specific survival

When classified according to AJCC8, 5- and 10-year MSS resulted in higher survival probabilities for subgroups IIIA, B and C than for the corresponding subgroups of AJCC7 (Fig. 4, Table 3). Owing to few shifts, MSS probabilities did not change in stage II subgroups. Five-year MSS of AJCC8 stage IIIA patients (89%) was comparable with that of stage IIA patients (88%) and superior to stage IIB (80%) and IIC patients (67%). For

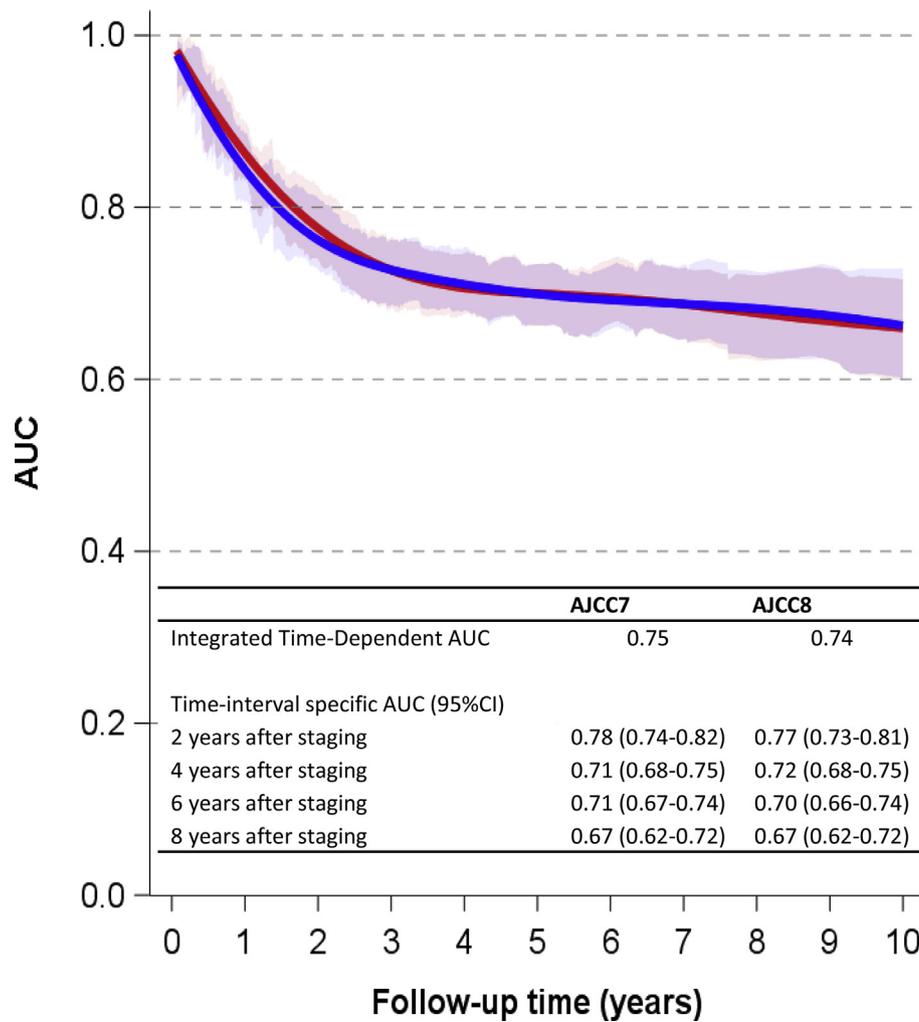


Fig. 3. Time-dependent areas under the curve (AUCs) for assessing the predictive accuracy of AJCC7 and AJCC8 to predict melanoma death ($N = 1,462$, Essen cohort). AJCC7 (red) and AJCC8 (blue); thick lines represent estimated AUCs, coloured areas indicate pointwise 95% CI limits. AJCC, American Joint Committee on Cancer; CI, confidence interval.

Table 2

Age- and sex-adjusted MSS hazard ratios of melanoma death and 95% CI for the AJCC stages using Cox proportional hazards models ($N = 1,462$, Essen cohort).

Stage according to AJCC 7th edition	<i>N</i>	Hazard ratio (95% CI)	Stage according to AJCC 8th edition	<i>N</i> ^a	Hazard ratio (95% CI)
IIA (reference)	290	—	IIA (reference)	289	—
IIB	230	1.33 (0.92–1.93)	IIB	229	1.34 (0.93–1.94)
IIC	124	1.83 (1.21–2.78)	IIC	124	1.83 (1.20–2.77)
IIIA	207	1.35 (0.93–1.97)	IIIA	117	0.84 (0.50–1.41)
IIIB	335	1.91 (1.39–2.64)	IIIB	204	1.78 (1.23–2.52)
IIIC	179	4.04 (2.87–5.67)	IIIC	366	2.72 (2.00–3.70)
—			IIID	34	4.39 (2.35–8.20)
IV	97	5.96 (4.06–8.76)	IV	97	5.94 (4.05–8.73)

AJCC, American Joint Committee on Cancer; CI, confidence interval.

^a Two patients reclassified as stage IA according to AJCC8 were omitted in the AJCC8 analyses.

AJCC8 stage IIIB patients, 5- and 10-year MSS (5 y 73%; 10 y 55%) was inferior to that of stage IIB patients (5 y 80%; 10 y 65%) but superior to stage IIC patients (5 y 67%; 10 y 47%). The Kaplan-Meier graph shows an initial steep MSS drop of stage IIID patients with a course of the curve parallel to stage IV patients. Owing

to small patient numbers in stage IIID, only few patients were still at risk after 3 years and therefore render our analysis on 5- and 10-year MSS probability for stage IIID uninformative.

MSS survival probabilities of our cohort were generally lower than the reported probabilities of the

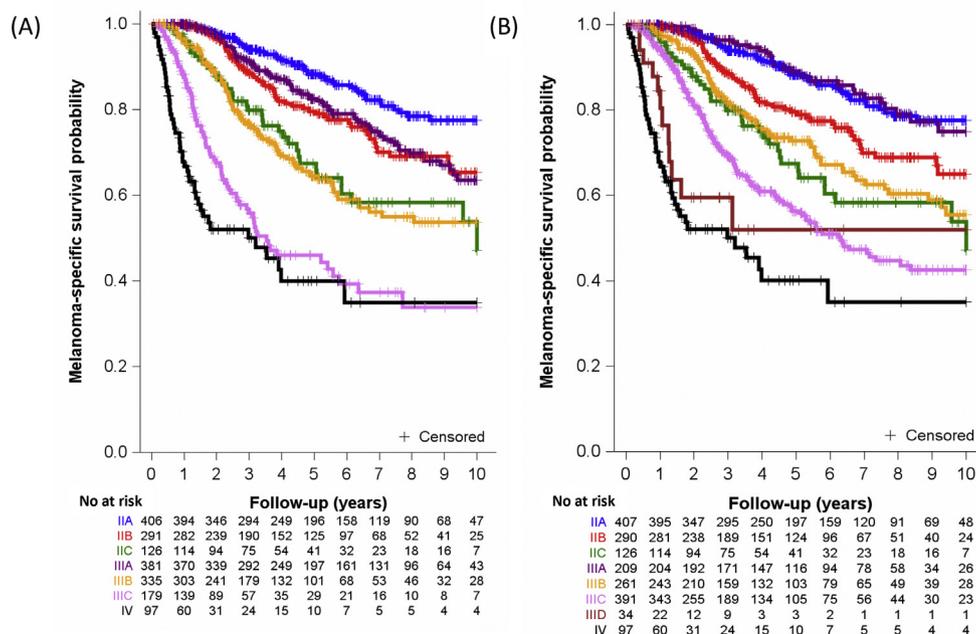


Fig. 4. Melanoma-specific survival of the combined cohorts from Essen and Hannover ($N = 1,817$) according to (A) AJCC7 and (B) AJCC8. Patients without successful SLNB in stage II were excluded. Two patients reclassified as stage IA according to AJCC8 were excluded to prevent additional stage IA survival curve in Fig. 4B. AJCC, American Joint Committee on Cancer; SLNB, sentinel lymph node biopsy.

IMDDP cohort [2] (Table 3). Discrepancies were largest for stage IIC, IIIB and IIIC; in these subgroups, 5-year MSS was about 10–15 percentage points lower than that in the IMDDP cohort.

3.4. Impact of reclassification on stage IIIA patients

Of the 381 patients of the combined Essen and Hannover cohort classified IIIA according to AJCC7, 200 (52.5%) remained in stage IIIA according to AJCC8, 119 (31.2%) were upshifted to IIIB and 62 (16.3%) to IIC (Suppl. Fig. 1). MSS of the three subgroups differed remarkably (Fig. 5); patients who remained in stage IIIA had a better MSS than patients who were upshifted to stage IIIB and IIC (5-year MSS of stage IIIA 89%, IIIB 81% and IIC 64%, respectively). The 5-year MSS probabilities of the upshifted IIIB and IIC patients were higher than those of all stage IIIB (73%) and all stage IIC patients (56%).

4. Discussion

The AJCC8 melanoma staging system introduced substantial changes in the subgrouping of disease stages. Since its implementation, it has been used worldwide in clinical practice and in melanoma trials. Physicians commonly use the stage-specific survival data reported by Gershenwald *et al.* [2] as a benchmark for treatment decisions and the conception of new trials. However, it was also suggested that the update of the melanoma

staging system came too early, which did not allow the effects of therapeutic advances and emerging prognostic biomarkers to be integrated [17].

While stage II and IV patients were relatively unaffected by the AJCC8 classification system, a relevant stage shift could be noted in stage III patients in our cohort. Overall, 23.5% of all patients were reclassified; the majority was upshifted within stage III. Our results for shifting in stage III patients are in line with the results of Madu *et al.* [14] from the Netherlands, Tarhini *et al.* [15] from the United States and the IMDDP cohort itself [2]. In contrast to AJCC7, twice as many patients were classified as stage IIIC (24.8% vs. 50.8%), while proportion of stages IIIA and IIIB decreased from 28.7% to 16.2% and 46.5% to 28.3%, respectively. In view of the results of all investigations, approximately half of stage III patients in the Western world will pertain to the high-risk stage IIIC group when staged according to AJCC8. The newly designated stage IIID encompasses only a very small group of patients of about 5%.

In stage III, reclassification affected fewer women than men, while age showed a minor impact. The prediction accuracy for AJCC7 and AJCC8 was comparable (integrated time-dependent AUC of 0.75 and 0.74, respectively) with two special features. First, the risk of dying from melanoma (in an age- and sex-adapted model) is comparable or even slightly lower for stage IIIA AJCC8 than for stage IIA AJCC8, while it is higher for IIIA AJCC7 than for IIA AJCC7. Second, as several of the previous stage IIIC patients were upshifted to the

Table 3

Median, 5- and 10-year overall and melanoma-specific survival probabilities for the combined Essen and Hannover cohort^a and for the IMDDP cohort [2].

Overall survival									
	AJCC 7th								
	Stage II			Stage III			Stage IV		
	IIA	IIB	IIC	IIIA	IIIB	IIIC	IV		
Median; years (95% CI)	n.r.	n.r.	5.1 (4.1-9.2)	n.r.	5.9 (5.3-8.1)	2.9 (2.2-3.6)	2.8 (1.3-4.0)		
5-year	82%	71%	52%	76%	58%	36%	37%		
10-year	64%	52%	30%	56%	41%	21%	32%		
	AJCC 8th								
	Stage II			Stage III				Stage IV	
	IIA	IIB	IIC	IIIA	IIIB	IIIC	IIID	IV	
Median; years (95% CI)	n.r.	n.r.	5.1 (4.1-9.2)	n.r.	8.9 (6.7-n.r.)	4.5 (3.6-5.6)	2.7 (1.1-n.r.)	2.8 (1.3-4.0)	
5-year	82%	71%	52%	84%	68%	47%	40%	37%	
10-year	64%	51%	30%	65%	47%	31%	40%	32%	
Melanoma-specific survival									
	AJCC 7th								
	Stage II			Stage III			Stage IV		
	IIA	IIB	IIC	IIIA	IIIB	IIIC	IV		
Median; years (95% CI)	n.r.	n.r.	10.0 (5.8-n.r.)	n.r.	n.r.	3.5 (2.6-5.8)	3.2 (1.3-5.9)		
5-year	88%	80%	67%	82%	64%	46%	40%		
10-year	78%	65%	47%	64%	54%	34%	35%		
	AJCC 8th								
	Stage II			Stage III				Stage IV	
	IIA	IIB	IIC	IIIA	IIIB	IIIC	IIID	IV	
Median; years (95% CI)	n.r.	n.r.	10.0 (5.8-n.r.)	n.r.	n.r.	6.3 (5.1-8.4)	n.r.	3.2 (1.3-5.9)	
5-year	88%	80%	67%	89%	73%	56%	52%	40%	
10-year	78%	65%	47%	75%	55%	43%	52%	35%	
IMDDP cohort									
	AJCC 8th								
	Stage II			Stage III				Stage IV	
	IIA	IIB	IIC	IIIA	IIIB	IIIC	IIID	IV	
Median; years (95% CI)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	
5-year	94%	87%	82%	93%	83%	69%	32%	n.a.	
10-year	88%	82%	75%	88%	77%	60%	24%	n.a.	

^a Patients without successful SLNB in stage II were excluded.

new subgroup IIID, the risk of melanoma-specific death improved for stage IIIC AJCC8.

MSS of stage II subgroups staged according to AJCC7 or AJCC8 did not differ as only two patients were downshifted. When comparing MSS curves within AJCC8, the disease course of patients with stage IIB and IIC was inferior to patients with stage IIIA (Fig. 4) with a 5-year MSS probability of 80%, 67% and 89%, respectively, while curves for stage IIA and IIIA ran closely together. The poorer outcomes of patients with stage IIB/C melanoma than patients with stage IIIA melanoma is well known and was shown by the IMDDP cohort itself [2]. Yet when the AJCC melanoma staging groups were revised, the better prognosis of patients with thin primaries but positive sentinel biopsies did not lead to classification of this patient group into a lower

tumour stage. The detection of a sentinel micrometastasis alone still results in upshifting to stage III in AJCC8. We feel that the current stage IIIA AJCC8 subgroup is of little impact on clinical decision-making and is even misleading; a higher stage should imply a worse prognosis which is not the case. Abdel-Rahman [16] suggested a modified AJCC8 classification where stage IIIA is classified as IIB, IIB as IIC, IIIB as IIIA and IIC as IIIB. However, rather than just re-naming subgroups, we agree with Grob *et al.* [17] that additional prognostic biomarkers (e.g. molecular, genetic, immunological, histological) should be considered in future AJCC classifications for more precise risk stratification and stage grouping, but it will take years to validate these. In this light, the significance of SLNB itself also needs to be questioned, particularly in patients

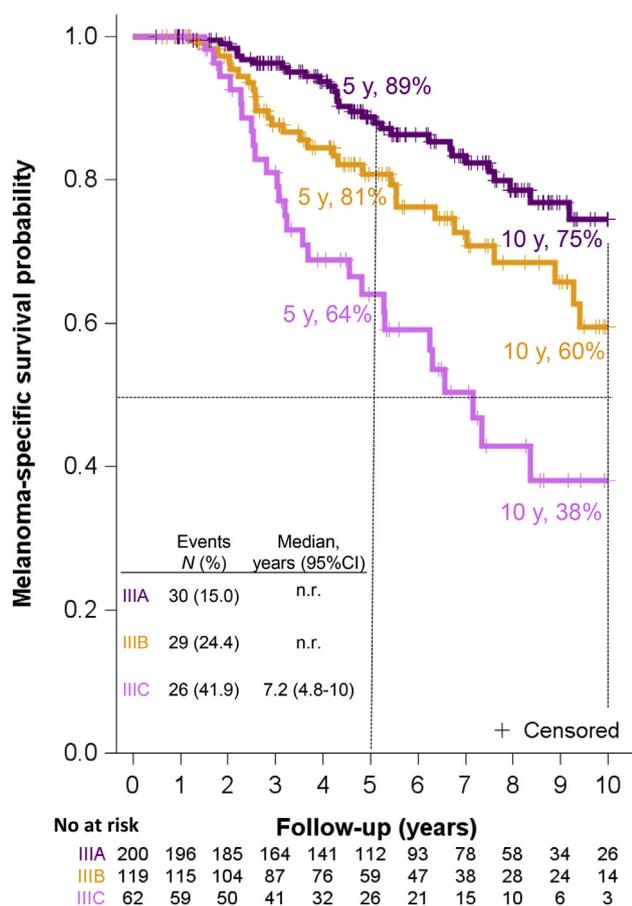


Fig. 5. Melanoma-specific survival of patients who were assigned stage IIIA subgroup (combined cohorts from Essen and Hannover, $N = 381$) according to AJCC 7th edition stratified for stage according to AJCC 8th edition. AJCC, American Joint Committee on Cancer; CI, confidence interval.

with pT1a, pT1b and pT2a tumours. First, the SLNB positivity rate in these patient groups is very low [18–21]. Second, even if the lymph nodes are microscopically involved, we know that prognosis is good. Recent data also show a 10% rate of false-positive sentinel rate in stage IIIA patients misdiagnosing capsular nevi and melanophages as melanoma metastasis [22]. Before patients with primaries up to pT2a are spared SLNB, it has to be considered that they will subsequently be classified as IA/IB but may not share the same prognosis as patients with biopsy-proven negative sentinel nodes. Until other biomarkers delineating patients at increased risk of progression are validated, there must be a differentiated discussion with the individual patient on the omission of SLNB in primary tumours up to pT2a. If the patients opt to undergo SLNB, additional factors such as sentinel tumour burden [14] and location of the metastasis [23] should be considered for adequate prognosis assessment and decision on further management, such as intensity of follow-up and adjuvant treatment.

Targeted therapy and immunotherapy are approved for adjuvant treatment of stage IIIA. As patients with stage IIIA and a micrometastasis in the sentinel node <1 mm were excluded from the adjuvant trials [5–7], the true benefit of adjuvant therapy for these patients is unknown. For two of the adjuvant trials, the COMBI-AD trial and the EORTC1325, the investigators re-stratified patients according to AJCC8 [24,25]. The benefit of adjuvant dabrafenib plus trametinib as well as pembrolizumab was still seen for all subgroups, yet in stage IIIA, patient numbers became very small, confidence intervals became wide and the relapse-free survival advantage decreased considerably (adjuvant Dabrafenib plus Trametinib in Stage III *BRAF*-Mutated Melanoma (COMBI-AD) AJCC7 HR: 0.44, 95% CI: 0.23–0.84 vs. AJCC8 HR: 0.63, 95% CI: 0.26–1.56; Keynote-054, adjuvant pembrolizumab versus placebo after Complete resection of high-risk stage III melanoma (EORTC1325) AJCC7 HR: 0.32, 95% CI: 0.09–1.23 vs. AJCC8 HR: 0.76, 95% CI: 0.11–5.43). Conversely, patients with stage IIB/C are at a much higher need for adjuvant treatment. A current trial of adjuvant treatment with pembrolizumab vs. placebo in stage IIB/C (NCT03553836) is addressing this need; other trials will follow soon. Making the decision of adjuvant treatment only dependent on AJCC stage, however, will not help identify all patients with an aggressive melanoma primary and thus a rapid disease course. Grob *et al.* [26] recently differentiated between two different concepts of adjuvant therapy: early adjuvant strategies, with the objective of treating the cancer before it becomes overtly metastatic, and late adjuvant treatment in overt metastatic disease, where a medical intervention is started once the detectable component of the metastatic disease (nodal or visceral) has been surgically resected. Based on these concepts, stage IIIA AJCC8 represents an ambiguous patient group as this cancer could be assumed to be either only a primary melanoma with an immunological conflict around a few tumour cells in the first nodal relay or as an already active metastatic disease [26]. New individual biomarkers are needed to detect aggressive primary melanomas more reliably than SLNB. To better address the question of the necessity of adjuvant therapy in stage IIIA, the AJCC Melanoma Expert Panel has mobilised the IMDDP consortium to explore the role of adjuvant treatment in stage IIIA AJCC8 [27].

MSS of stage IIIA AJCC7 patients who were upshifted to IIB and IIC according to AJCC8 was markedly lower than that of patients who remained in subgroup IIIA. This underlines the role of tumour thickness as a risk factor even if locoregionary micrometastasis has already occurred. Interestingly, 5-year MSS probabilities of patients with micrometastases who were upshifted to stage IIB and IIC (81% and 64%) were more in line with stage IIB and IIC patients (80%

and 67%) than with all stage IIIB and IIIC patients (73% and 56%). The utility of SLNB in patients with a higher tumour thickness and inconspicuous lymph nodes on ultrasound therefore also needs to be reconsidered alongside other biomarkers and therapeutic strategies in a future AJCC revision.

Despite excluding patients without SLNB results, MSS probabilities of stage II patients of our cohort was below that of the IMDDP cohort (our cohort: IIA 88%, IIB 80% and IIC 67%, IMDDP cohort IIA 94%, IIB 87% and IIC 82%) [2]. The difference was particularly evident for stage IIC patients where MSS was 15 percentage points lower. Similar to stage II, our survival probabilities for IIIB and IIIC are approximately 10 percentage points below those of the IMDDP cohort – a discrepancy that was also seen in the Dutch cohort [14]. In an Australian cohort, even lower 5-year MSS probabilities were found when adjusted for patient sex and age [28]. Reasons for these differences are difficult to determine; centres of the IMDDP as well as Essen and Hannover are tertiary and quaternary centres with easy access to staging modalities, modern therapies and clinical trials. Unfortunately, demographic (e.g. age, sex), tumour-specific data (e.g. localisation and histology of the primary) and details of the follow-up period (e.g. follow-up duration, percentage of loss of follow-up or characterisation of lost patients in comparison with patients still in follow-up) of the different subsets of the IMDDP cohort were not reported by Gershenwald *et al.* [2], making the study of reasons for the differences difficult. The MSS differences seem too large to be dependent on only demographics and tumour characteristics. Particularly the length of follow-up and the proportion of patients who died due to melanoma versus due to other causes (and the intensity how the cause of death was ascertained) are important factors that may explain differences in MSS between our cohort and IMDDP. The IMDDP working group is actively trying to further improve and update their data set and is currently investigating a second phase of an even expanded, international data collection and analysis, including assessment of relapse-free survival outcomes [27]. It would be helpful if demographic, tumour-specific and follow-up information of this new cohort was published to allow for comparison with other cohorts.

Our patients are – as in other studies investigating patient data from tertiary, specialised skin cancer centres – selected in terms of tumour characteristics or courses of disease. Patients with tumour progression will be referred to tertiary centres leading to a selection of patients with worse prognosis. Generalisability of results to all patients with melanoma of the studied stages may therefore be limited. To enhance the quality of health-care for patients with melanoma in general, it would be useful to set up an international registry similar to the Dutch Melanoma Treatment Registry, which constitutes

a collaboration of all stakeholders involved in care of patients with melanoma [29].

5. Conclusion

The 8th AJCC classification for melanoma leads to an up-classification of 44.9% of patients within stage III while re-classifications in stage II are rare. The introduction of subgroup IIID, the new N classification and the consideration of tumour thickness results in higher MSS probabilities for subgroup IIIA-C, albeit in our cohort lower than calculated for the IMDDP cohort. Stage IIB/C patients have a poor MSS and urgently require adjuvant treatment options. The benefit of adjuvant treatment in stage IIIA patients (AJCC8) is questionable as melanoma progression risk is very low, and sentinel tumour burden might be an important tool to identify patients with higher risk.

Conflict of interest statement

T.K. reports receiving travel grants from Novartis, Amgen, Celgene, Lilly and Pierre Fabre. A.St. reports no conflict of interest. R.G. reports receiving research support from Novartis, Pfizer, Johnson & Johnson, Amgen, Merck Serono as well as speakers and advisory board honoraria from Roche Pharma, Bristol-Myers Squibb (BMS), GlaxoSmithKline, Novartis, Merck Serono, MSD, Almirall Hermal, Amgen, Pierre Fabre, Sanofi, Leo Pharma, Amgen, Pfizer, Roche-Posay, Incyte, Merck Serono, 4SC and Takeda. L.Z. has served as a consultant and/or has received honoraria from Roche, BMS, Merck Sharp & Dohme (MSD), Novartis, Pierre Fabre and Sanofi and travel support from MSD, BMS, Amgen, Pierre Fabre and Novartis. E.C. has received travel support from BMS, MSD and Novartis. A.Su. reports receiving advisory board honoraria from Novartis. S.U. reports receiving research support from BMS and Merck Serono; speakers and advisory board honoraria from BMS, MSD, Merck Serono, Novartis and Roche as well as travel support from BMS and MSD. E.H. reports no conflict of interest. N.S.G. received travel support from Novartis. I.S. has received research funding from Pfizer and Novartis; reports receiving honoraria from BMS, Roche Pharma, Novartis; has served as a consultant/advisory role for Sanofi, Regeneron, Novartis, Roche Pharma and BMS and has received travel grants from BMS and Novartis. D.S. has received research funding from Novartis and BMS, has served as a consultant or/and has received honoraria from Amgen, Leo Pharma, Roche, BMS, MSD, Novartis, Incyte, Regeneron, 4SC, AstraZeneca, Immunocore, Pierre Fabre, Merck EMD, Pfizer, Philogen, Sanofi, Inflarx, 4SC, Neracare and Array and travel support from Novartis, BMS, MSD, Roche and Pierre Fabre. E.L. has

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejca.2019.06.011>.

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