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Testing a new staging system for cutaneous melanoma proposed by the American Joint Committee on Cancer

S. Merkel[a,*], T. Meyer[a], T. Papadopoulos[b], G. Schuler[c], J. Göhl[a], W. Hohenberger[a], P. Hermanek[a]

[a]*Department of Surgery, University of Erlangen, Krankenhausstr. 12, D-91054 Erlangen, Germany*
[b]*Department of Pathology, University of Erlangen, Erlangen, Germany*
[c]*Department of Dermatology, University of Erlangen, Erlangen, Germany*

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Abstract

The American Joint Committee on Cancer (AJCC) recently proposed a new staging system for cutaneous melanoma. We tested its practicability and its prognostic value was compared with the currently used TNM classification. The data of 1976 melanoma patients were used for the testing. 1218 patients (61.6%) could be assigned to the proposed pT classification, 136 patients (90.1%) with lymph node metastases and/or in-transit metastases to the proposed pN classification and all 14 patients with distant metastases to the proposed pM classification. Proposed pathological staging was possible for 971 patients (49%). The number of pT1 patients (399 versus 230) and stage I patients (544 versus 393) was distinctly higher in the proposed classification. In proposed stage II and III groups, subgroups with different prognosis could be identified. The new staging system includes more detailed information on clinical and pathohistological findings. Nevertheless, it is practicable and enables more patients with excellent prognosis to be identified.

Keywords: Malignant melanoma; TNM classification; Staging system; Survival analysis

1. Introduction

The TNM classification of the International Union Against Cancer (UICC) [1] is a widely accepted staging system for malignant tumours. It is characterised by stability and continuity to collect data in a standardised way over a reasonable period of time. The classifications should remain unchanged until major advances in diagnosis or treatment require reconsideration of the current staging system. The current TNM classification of the UICC is identical to that published by the American Joint Committee on Cancer (AJCC) [2]. Recently, the AJCC proposed a new staging system for cutaneous melanoma [3]. This staging system was only approved in general, a validation of this proposed TNM classification and stage grouping criteria is missing.

The intent of our study was, to test the practicability of this proposed staging system and to compare the prognostic value of this proposal with the actual valid 5th edition of the TNM classification.

2. Patients and methods

This study is based on data of the Melanoma Registry of the University of Erlangen, Germany. In this registry all patients with cutaneous malignant melanoma treated at the Department of Surgery and/or at the Department of Dermatology are registered without selection. General epidemiological data, clinical findings, treatment data, histopathological findings and follow-up data are documented prospectively.

For this study, 1976 patients with the following inclusion criteria were selected:

- First manifestation of a solitary invasive cutaneous malignant melanoma (invasion at least of the stratum papillare, Clark Level II);

* Corresponding author. Tel.: +49-9131-853-3107; fax: +49-9131-853-2769.
E-mail address: susanne.merkel@chir.imed.uni-erlangen.de (S. Merkel).

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- first treatment between 1980 and 1997;
- no other previous or synchronous malignant tumour except squamous and basal cell carcinoma of the skin and carcinoma *in situ* of the cervix uteri;
- no residual tumour after primary treatment (R0 at clinical and pathohistological examination);
- pT classification defined (pT1-4) (86 patients with pTX excluded).

Patient and tumour characteristics are shown in Table 1. The median follow-up time period was 97 months (range 0–239 months). 16 patients (0.8%) were lost during follow-up. At the end of this study (31 December 1999), 583 patients (29.5%) had died.

Excision of the primary tumour was performed either at the Department of Surgery or the Department of Dermatology. In some cases, primary excision was performed by a dermatologist outside of the university and re-excision or lymph node dissection as part of primary treatment at the university hospital. 686 patients underwent lymph node dissection: 87 therapeutic dissections, 599 prophylactic dissections. In 25 patients, sentinel node biopsies were performed. The frequencies that lymph node dissection or sentinel lymph node biopsies were carried out depended upon the respective pT categories: pT1: 1.8% (8/453), pT2: 6.8% (34/503), pT3a: 61.6% (385/625), pT3b: 75.4% (89/118), pT4a: 69.6% (149/214), pT4b: 72.5% (29/40) and occult melanoma: 73.9% (17/23).

216 patients received hyperthermic isolated limb perfusion (196 prophylactic, 20 therapeutic).

The documentation of the detailed clinical and histopathological findings allowed the classification of the patients according to the 5th edition of the TNM classification of the UICC 1997 [1] (Tables 2 and 3). How many of these patients could be transformed into the proposed new staging system of the AJCC (Tables 2 and 3) and how many patients would change their staging group because of the new staging criteria was tested. In addition, Kaplan–Meier curves and survival rates were used to compare the prognostic value of the present TNM staging system and the proposed staging system.

Table 1
Patient and tumour characteristics

	n (%)
Age (median/range) (years)	53 (8–88)
Gender	
Male	843 (42.7)
Female	1133 (57.3)
Tumour site	
Head/neck	232 (11.7)
Trunk	653 (33.0)
Upper extremities	365 (18.5)
Lower extremities	703 (35.6)
Occult melanoma	23 (1.2)
Melanoma type	
Nodular melanoma	410 (20.7)
Superficial spreading melanoma	1252 (63.4)
Lentigo maligna melanoma	109 (5.5)
Acral lentiginous melanoma	98 (5.0)
Unclassified	107 (5.4)

2.1. Statistics

The Kaplan–Meier method was used to calculate 5- and 10-year rates of observed survival. Surgical mortality (7 patients within 90 days) was not excluded. For comparisons of survival the logrank test was used. The 95% confidence intervals (95% CI) were calculated according to Greenwood [4]. A P value of less than 0.05 was considered to be significant. All analyses were performed using the Statiscal Package for the Social Sciences (SPSS) for Windows Version 10 (SPSS, Inc., Chicago, IL, USA).

3. Results

3.1. Distribution according to pT, N/pN, M/pM and stage group

3.1.1. pT classification

1218 out of 1976 patients (61.6%) could be classified according to the proposed pT classification (occult melanoma not excluded, $n=23$). In 758 tumours (38.4%), this was not possible due to missing data on ulceration ($n=606$) or on tumour thickness in mm ($n=152$). In these cases, the tumour thickness was recorded only as class, e.g. 0.75–1.50 mm. In 489 patients (40.1%), the proposed pT category was lower than the standard pT category (Fig. 1). Most frequently, tumours of the categories pT2 and pT3a were reclassified as a lower pT category. In the category pT2, 154 patients (72%) were assigned to the lower proposed pT1 category. In the category pT3a, 302 patients (65%) were assigned to the proposed pT1 or pT2 category. A change to a higher proposed pT category was not observed.

3.1.2. N/pN classification

In 699 patients, both pN categories could be assigned, in 10 cases with satellites (no lymph node dissection performed), the pN category could be assigned in the proposed pN category only (Fig. 2). 15 patients could not be assigned to both pN categories: In 2 patients, the result of the pathohistological examination was unclear (pNX), in 2 patients, the number of involved lymph nodes was unknown, in 1 patient, the diameter of the lymph node metastases was undetermined and in 10 patients with lymph node metastases, data on the ulceration of the primary tumour were missing. 97 out

of 136 patients (71%) with lymph node metastases and/or in-transit metastases were assigned to a higher and 5 patients (4%) to a lower pN category. However, in the proposed pN classification there are three instead of two categories for lymph node-positive tumours.

3.1.3. M/pM classification

In 14 patients, distant metastases were observed at the time of first treatment: distant lymph node metastases in 10 patients and distant visceral metastases in 4 patients. All patients could be assigned to the proposed M/pM classification (Fig. 3), 6 patients to the categories M2 or M3.

3.1.4. Stage grouping

In the past, clinical assessment of regional lymph nodes was only documented as N0 (no lymph node metastases) or N+ (lymph node metastasis in at least one lymph node). Without the number of clinically involved lymph nodes, the subgroups of the proposed clinical stage III could not be defined.

Proposed pathological staging was possible for 971 patients (49.1%) (Fig. 4). It was impossible in 728 cases because there were no data on the proposed pT category (30 patients could be classified as the proposed stage IIIC despite missing data on pT), in 272 cases because of no pathological evaluation of their lymph nodes (demanded by the proposed classification for stage IB and higher) and in 5 cases because of missing pN classification. 243 patients (25.0%) were assigned to a lower, 3 patients to a higher stage of the proposed classification.

3.2. Survival analysis

Observed 5-year survival of all 1976 patients in our study was 82.2% (95% CI: 80.5–83.9%), observed 10-year survival was 71.5% (95% CI: 69.2–73.7%).

In 822 patients with localised melanoma (without satellites, in-transit metastases, lymph node metastases or distant metastases), 5-year survival was 85.9% (95% CI: 83.4–88.6%), 10-year survival was 76.5% (95% CI: 73.3–79.7%). Survival analysis of these patients showed similar results when the valid and the proposed pT categories were compared (Fig. 5). The difference in survival between pT1 and pT2 was small in the valid pT classification (96% versus 92% at 5 years and 89% versus 89% at 10 years, $P = 0.44$). However, in the proposed pT

Table 2
Valid and proposed TNM classification

Valid TNM classification		Proposed TNM classification	
pT classification[a]		pT classification	
pT1	⩽0.75 mm or Clark Level II	pT1a	⩽1.0 mm without ulceration
		pT1b	⩽1.0 mm with ulceration or level IV or V
pT2	0.76–1.5 mm or Clark Level III	pT2a	1.01–2.0 mm without ulceration
		pT2b	1.01–2.0 mm with ulceration
pT3a	1.51–3.0 mm or Clark Level IV	pT3a	2.01–4.0 mm without ulceration
pT3b	3.01–4.0 mm or Clark Level IV	pT3b	2.01–4.0 mm with ulceration
pT4a	>4.0 mm or Clark Level V	pT4a	>4.0 mm without ulceration
pT4b	>4.0 mm or satellite(s)	pT4b	>4.0 mm with ulceration
N/pN classification		N/pN classification[d]	
N1	Metastasis ⩽3 cm in any lymph node(s)	N1a	One lymph node, micrometastasis[e]
		N1b	One lymph node, macrometastasis[f]
N2a	Metastasis >3cm in any lymph node(s)	N2a	2–3 lymph nodes, micrometastasis[e]
N2b	In-transit met(s)[b,c]	N2b	2–3 lymph nodes, macrometastasis[f]
N2c	Metastasis >3 cm in any lymph node(s) and in-transit met(s)	N2c	In-transit met(s)/satellite(s) *without* metastatic lymph nodes
		N3	4 or >metastatic lymph nodes, matted lymph nodes, or combinations of in-transit met(s)/satellite(s), or ulcerated melanoma and metastatic lymph node(s)
M/pM classification		M/pM classification	
M1a	Metastasis in skin or subcutaneous tissue or lymph node(s) beyond the regional lymph nodes	M1	Distant skin, subcutis, or lymph node met(s) and normal LDH
M1b	Visceral metastasis	M2	Lung met(s) and Normal LDH
		M3	All other visceral and normal LDH or any distant met(s) and elevated LDH

LDH, lactate dehyrogenase; met(s): metastases.

[a] In case of discrepancy between tumour thickness and level, the pT category is based on the less favourable finding.

[b] In-transit metastasis involves skin or subcutaneous tissue more than 2 cm from the primary tumour, but not beyond the regional lymph nodes.

[c] With or without lymph node metastases ⩽3 cm in greatest dimension.

[d] No differences between N and pN.

[e] Micrometastases are diagnosed after elective or sentinel lymphadenectomy.

[f] Macrometastases are defined as clinically detectable lymph node metastases confirmed by therapeutic lymphadenectomy or when any lymph node metastasis exhibits gross extracapsular extension.

classification a trend was found (94% versus 91% at 5 years and 89% versus 83% at 10 years, $P=0.10$). In addition, the number of patients was distinctly higher in the proposed pT1 category (399 patients versus 230 patients) and distinctly lower in the proposed pT3 category (179 versus 339).

126 patients with regional lymph node metastases or in-transit metastases or both, but without distant metastases, could be compared with regard to the prognostic value of the pN category in both staging systems (Fig. 6). While in the valid pN classification survival was similar in the categories pN1 and pN2 (52% versus 45% at 5 years and 37% versus 35% at 10 years, $P=0.30$), in the proposed pN classification, Survival was similar in the categories pN1 and pN2 (65% versus 61% at 5 years and 60% versus 48% at 10 years, $P=0.31$).

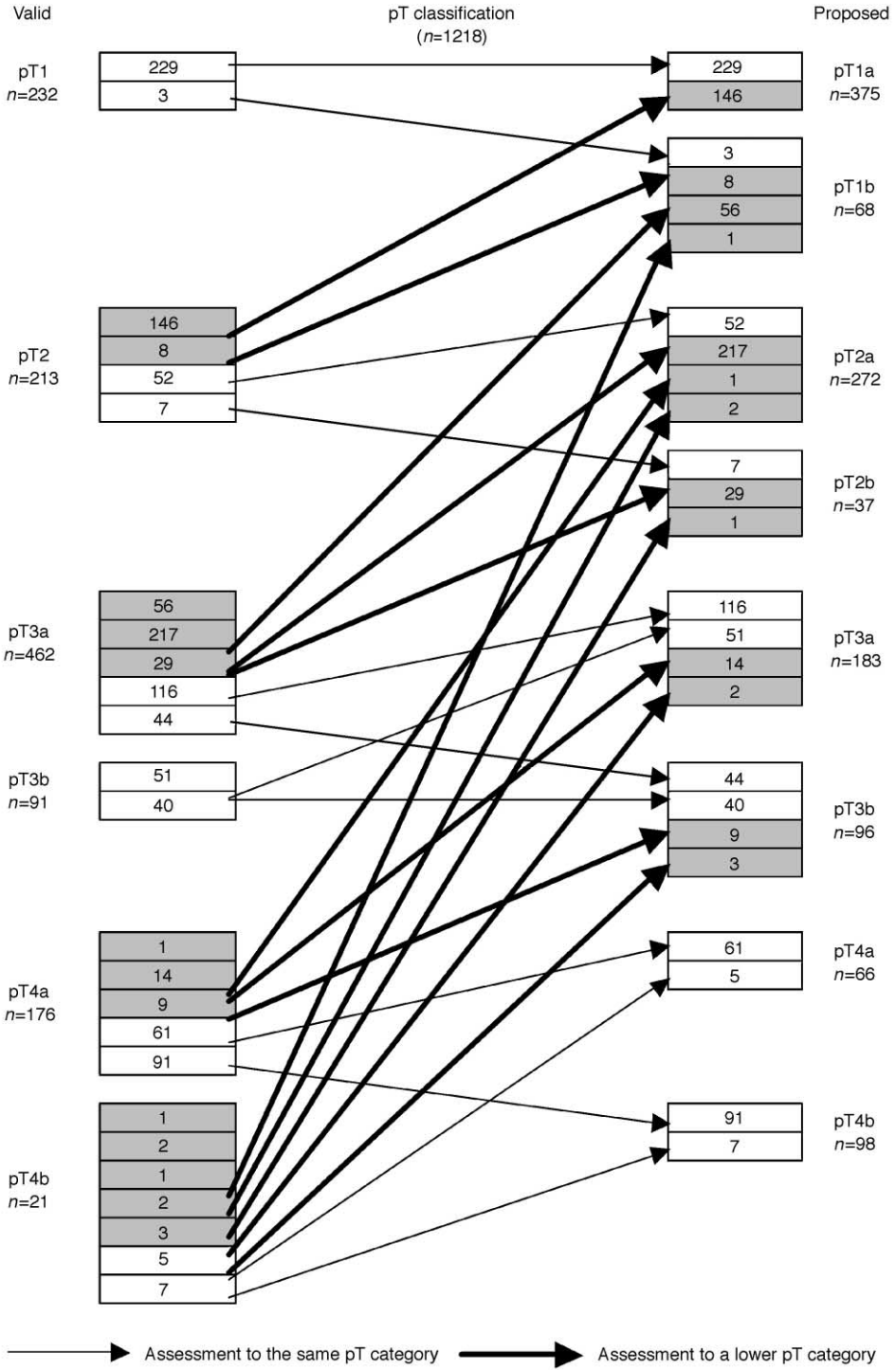

Fig. 1. pT category of the valid TNM classification and the proposed classification. Occult melanoma ($n=23$) not presented. Changes of the pT category are marked by shaded boxes.

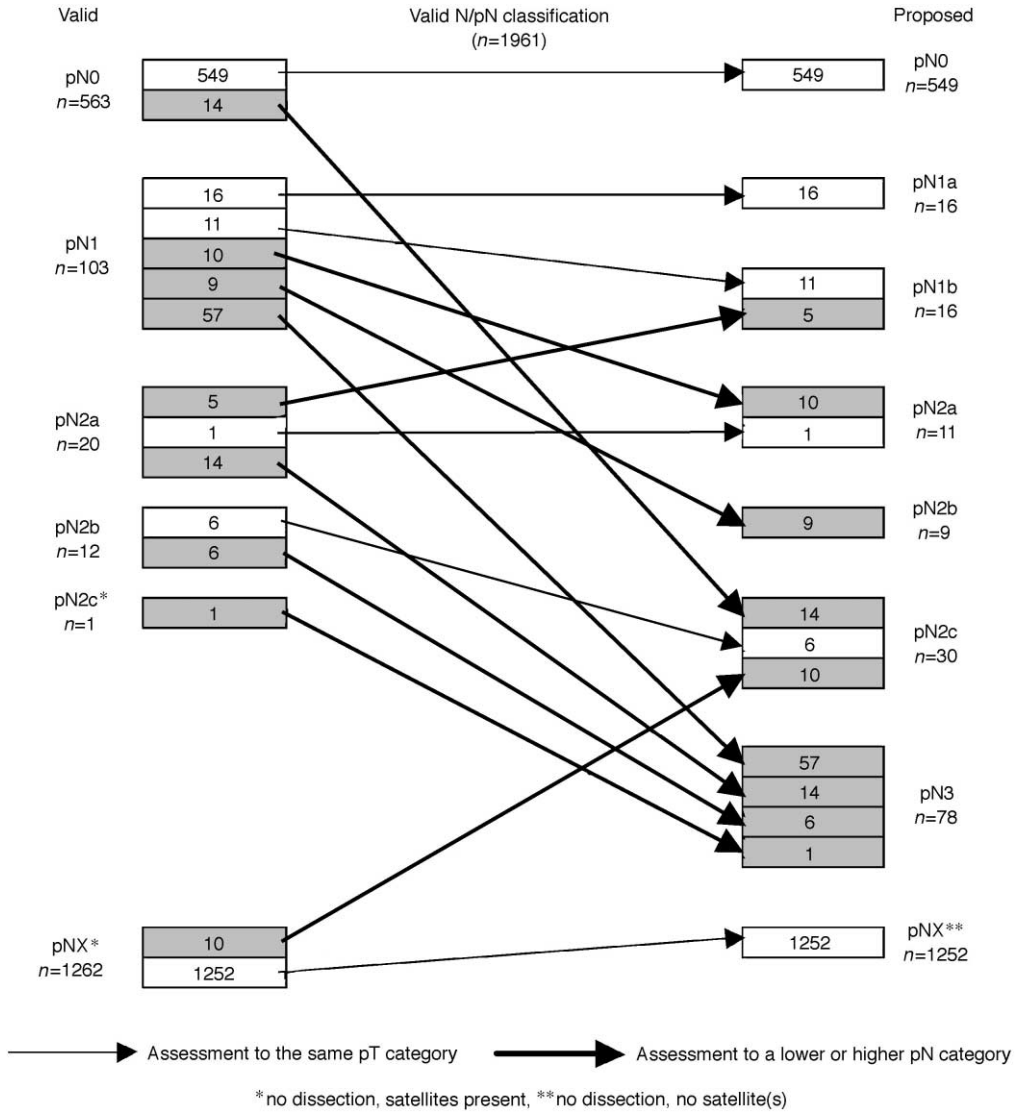

Fig. 2. N/pN category of the valid TNM classification and the proposed classification. Changes of the N/pN category are marked by shaded boxes.

In Fig. 7, survival with regard to the pathological stage is shown. The observed 5-year survival rate of 971 patients, who could be assigned to the valid as well as to the proposed pathological staging system, was 79.9% (95% CI: 77.3–82.5%), the 10-year survival rate was 69.7% (95% CI: 66.5–72.9%). In both staging systems, significant differences between the staging groups I–IV were found. In stage I, survival rates were nearly identical in both classification systems, 94% (at 5 years) and 89% (at 10 years) in the valid and 94% (at 5 years) and 87% (at 10 years) in the proposed staging system. However, the number of patients assigned to stage I was distinctly higher in the proposed staging system (544 versus 393). Therefore, stage II and III survival rates were higher in the valid classification system than in the proposed one (stage II: 83% versus 71% at 5 years, and 72% versus 58% at 10 years, stage III: 56% versus 51% at 5 years, and 42% versus 37% at 10 years). In stage IV, survival was identical as the same patients were considered in the analysis. In the survival analysis of the proposed substages (Table 4), no significant differences were found between the substages IA and IB. In stage II, as well as in stage III, survival was significantly worse in the substage C when compared with substages A and B.

4. Discussion

4.1. Differences, practicability and changes of the present and the proposed staging system

4.1.1. pT classification

The currently used pT classification requires data on tumour thickness, Clark level and the presence or absence of satellites to classify the primary tumour of

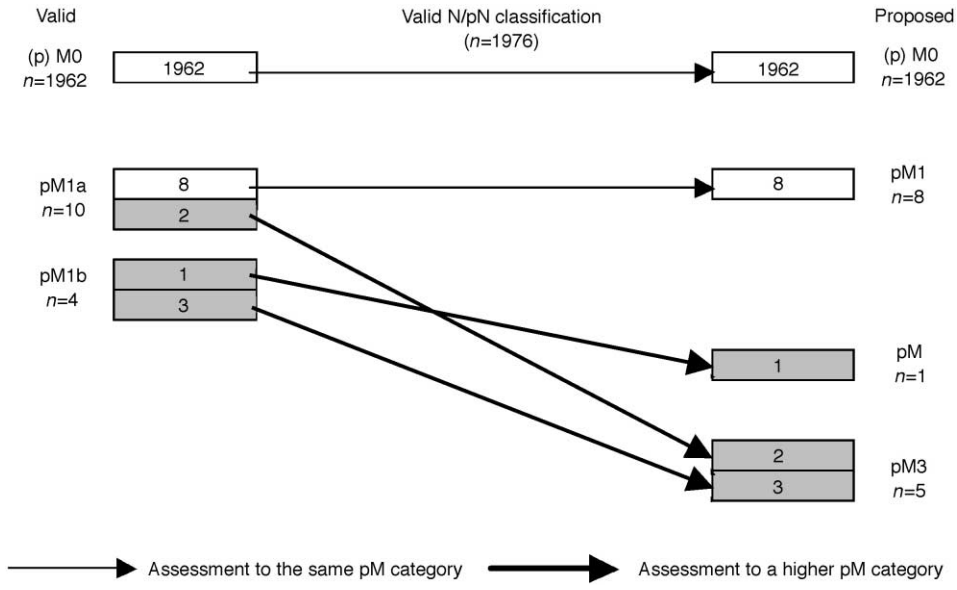

Fig. 3. M/pM category of the valid TNM classification and the proposed classification. Changes of the M/pM category are marked by shaded boxes.

Table 3
Stage groupings for cutaneous melanoma

Valid staging				Proposed staging							
				Clinical staging[a]				Pathological staging[b]			
I	pT1	N0	M0	IA	pT1a	N0	M0	IA	pT1a	N0	M0
	pT2	N0	M0	IB	pT1b	N0	M0	IB	pT1b	N0	M0
					pT2a	N0	M0		pT2a	N0	M0
II	pT3	N0	M0	IIA	pT2b	N0	M0	IIA	pT2b	N0	M0
					pT3a	N0	M0		pT3a	N0	M0
				IIB	pT3b	N0	M0	IIB	pT3b	N0	M0
					pT4a	N0	M0		pT4a	N0	M0
				IIC	pT4b	N0	M0	IIC	pT4b	N0	M0
III	pT4	N0	M0	IIIA	Any pT1-4a	N1b	M0	IIIA	pT1-4a	N1a	M0
	Any pT	N1, N2	M0	IIIB	Any pT1-4a	N2b	M0	IIIB	pT1-4a	N1b	M0
									pT1-4a	N2a	M0
				IIIC	Any pT	N2c	M0	IIIC	Any pT	N2b, N2c	M0
					Any pT	N3	M0		Any pT	N3	M0
IV	Any pT	Any N	M1	IV	Any T	Any N	Any M	IV	Any T	Any N	Any M

[a] Clinical staging includes microstaging of the primary melanoma and clinical/radiological evaluation for metastases; by convention, it should be used after complete excision of the primary melanoma with *clinical* assessment for regional and distant metastases.

[b] Pathological staging includes microstaging of the primary melanoma and pathological information about the regional lymph nodes after partial or complete lymphadenectomy, except *for pathological stage IA patients, who do not need pathological evaluation of their lymph nodes.*

the malignant melanoma. In the proposed pT classification, tumour thickness and the presence or absence of ulceration are necessary criteria to assess the pT category whereas Clark level is only necessary in cases with tumour thickness up to 1 mm. The presence of satellites is considered in the N/pN category. Therefore, the pT classification is simplified.

In various studies [6–12], tumour thickness has been shown to be the most important single prognostic factor, especially in localised melanoma, and to be more relevant than the level of invasion (Clark level) [9]. Buzaid and colleagues [10] reported a significant influence of the level of invasion on survival only for patients with a tumour thickness up to 1 mm. In the currently used TNM classification, the level of invasion was regarded as helpful in tumours with ulceration, when tumour thickness would underestimate the aggressive potential of the tumour [5]. The introduction of the prognostic factor 'ulceration' [6,7,10–13] into the new proposed staging system considers this problem. The presence of clinical or microscopic satellites, in the current TNM classification assigned to pT4b, is assigned to

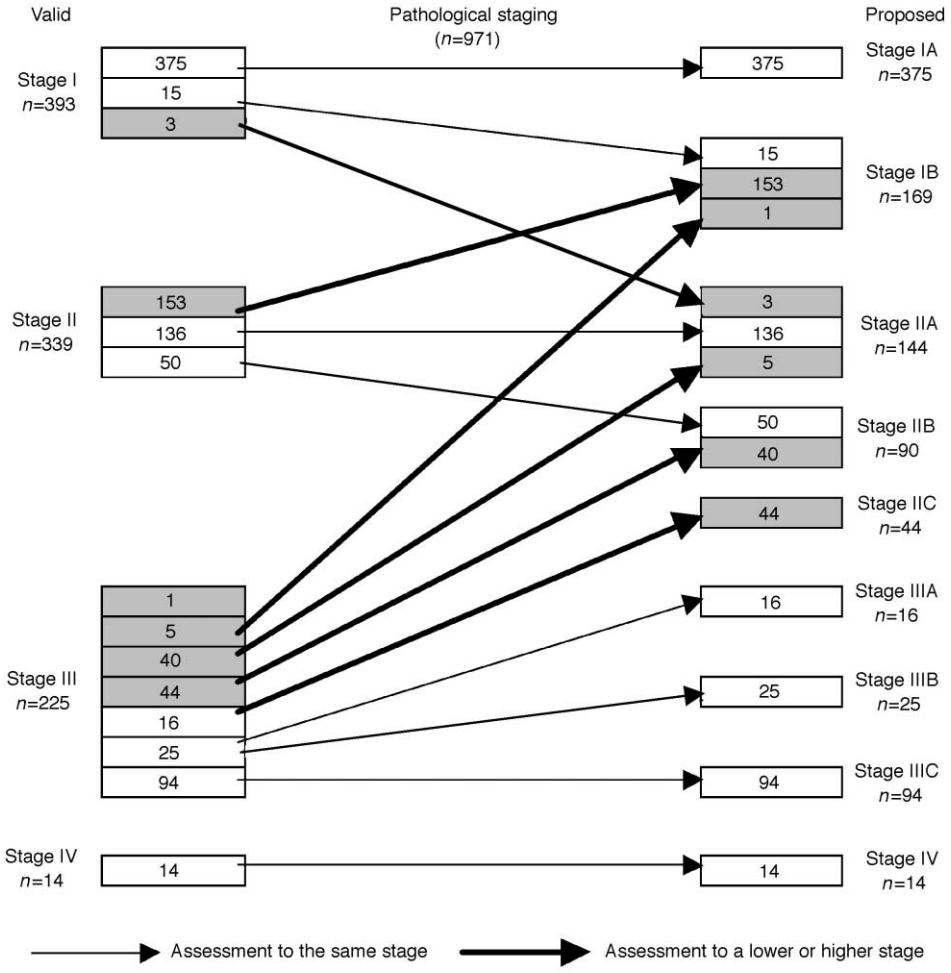

Fig. 4. Pathological stage groupings of the valid TNM classification and the proposed classification. Changes of the stage groupings are marked by shaded boxes.

Table 4
Survival analysis: proposed pathological substaging

	n	5-year survival observed (%) with 95% CI (%)	10-year survival observed (%) with 95% CI (%)	*P* value
Stage IA	375	94.4 (91.8–97.0)	88.5 (84.5–92.6)	0.2541 (IA versus IB)
Stage IB	169	92.8 (88.8–96.7)	84.6 (78.8–90.3)	0.0003 (IB versus IIA)
Stage IIA	144	76.7 (69.7–83.6)	65.0 (56.8–73.2)	0.6247 (IIA versus IIB)
Stage IIB	90	74.9 (65.7–84.0)	61.8 (51.2–72.3)	<0.0001 (IIB versus IIC)
Stage IIC	44	46.0 (30.8–61.1)	30.1 (15.8–44.4)	0.1783 (IIC versus IIA)
Stage IIIA	16	62.5 (38.8–86.2)	54.7 (29.5–79.9)	0.4131 (IIIA versus IIIB)
Stage IIIB	25	75.4 (58.2–92.5)	62.2 (40.3–84.1)	0.0019 (IIIB versus IIIC)
Stage IIIC	94	42.6 (32.4–52.8)	25.7 (16.2–35.1)	0.0342 (IIIC versus IV)
Stage IV	14	14.3 (0–32.6)	7.1 (0–20.6)	

(p)N2c/(p)N3 in the proposed TNM classification. However, in both staging systems tumours with satellites are finally assigned to stage III.

As tumour thickness with new cut-off points [9] is the predominant factor of the proposed pT classification, 40.1% of the 1218 patients were reclassified to a lower pT category, most frequently from the current pT2 and pT3a categories (72 and 65%, respectively).

4.1.2. N/pN classification

The assessment of the N/pN category in the currently used classification considers the size of regional lymph nodes metastases and the presence or absence of in-transit metastases. Clinical and pathological assessment are performed separately. The proposed system includes predominant prognostic factors as follows: the number of involved lymph nodes [13–20], the

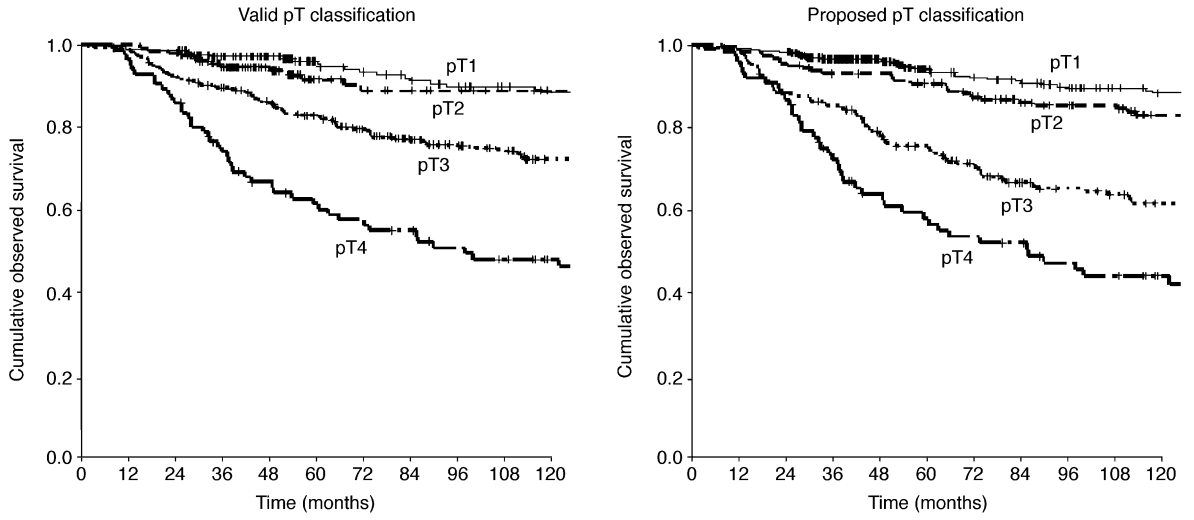

Fig. 5. Observed survival according to the valid and proposed pT classification in localised melanoma. Valid pT classification: pT1: $n=230$ (28%), pT2: $n=163$ (20%), pT3: $n=339$ (41%), pT4: $n=90$ (11%). Proposed pT classification: pT1: $n=399$ (49%), pT2: $n=167$ (20%), pT3: $n=179$ (22%), pT4: $n=77$ (9%).

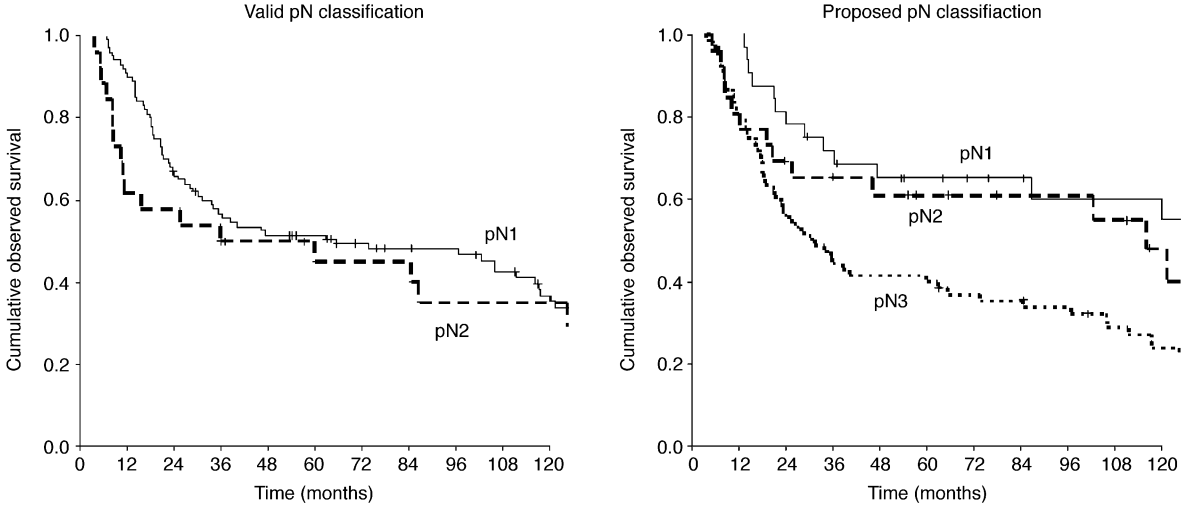

Fig. 6. Observed survival according to the valid and proposed pN classification in melanoma with regional lymph node metastases and/or in-transit metastases, but without distant metastases. Valid pN classification: pN1: $n=100$ (79%), pN2: $n=26$ (21%). Proposed pN classification: pN1: $n=32$ (25%), pN2: $n=26$ (21%), pN3: $n=68$ (54%).

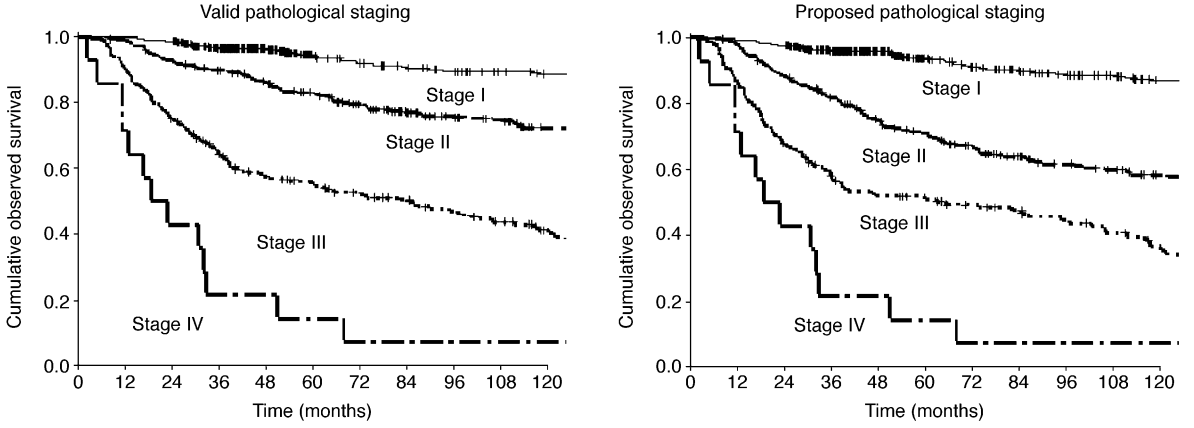

Fig. 7. Observed survival according to the valid and proposed pathological staging. Valid TNM: stage I: $n=393$ (40%), stage II: $n=339$ (35%), stage III: $n=225$ (23%), stage IV: $n=14$ (1%). Proposed TNM: stage I: $n=544$ (56%), stage II: $n=278$ (29%), stage III: $n=135$ (14%), stage IV: $n=14$ (1%).

type of metastasis (clinically-negative nodes versus clinically-positive nodes, pathologically confirmed) [13,16,17,21], gross extracapsular extension [17], in-transit metastasis, satellites and ulceration of the primary tumour [14]. Three different N/pN categories with two subcategories in pN1 and three subcategories in pN2 lead to a more complicated system. A strict separation of N and pN is not required. In summary, more staging criteria are demanded, but these parameters are recorded easily.

Because the new N/pN category includes three instead of two categories, approximately three-quarters were reclassified from pN1 or pN2 to a higher pN category. 24 patients changed from the present N0/pN0 category to the proposed N/pN2c category because of the presence of satellites.

4.1.3. M/pM classification

In the assessment of the M/pM category, the metastatic site is more specified in the proposed classification. While the valid M/pM classification distinguishes between non-visceral and visceral distant metastases, the proposed M/pM classification considers the lung as a site of distant metastases separately [13,17,22–24] and introduces serum lactate dehydrogenase (LDH) [23,25,26] in its subclassification. Knowledge of the LDH level, a routinely examined parameter, is a reasonable additional effort for the clinician or pathologist.

4.1.4. Stage grouping

Clinical and pathological staging is separated in the proposed classification system. Additional substaging allows the classification of patients into more detailed subgroups. According to the philosophy of the TNM system staging, "It has to be simple enough for universal use in both highly developed and developing countries and sufficiently uncomplicated so that medical professionals are not discouraged from using the system. Furthermore, for specialised institutions and for investigational purposes, a relatively simple staging system is not sufficient and runs the risk of not being used" [27].

However, there are some problems when patients already registered have to be reclassified according to the new system. Tumour thickness has to be documented in mm (classes are not sufficient). For N/pN classification, the various parameters have to be recorded. For pathological staging sentinel lymph node biopsy (at least) is necessary (except for pathological stage IA patients) and, finally, for the M classification LDH levels have to be registered. Only a careful collection of raw data enables patients to be changed to this (or another) new classification and for existing and new staging systems to be improved and developed. Pathological staging was possible in 49.1% of the registered patients. This low rate was not only caused by missing data for the pT or N/pN categories, but also by the requirement of at least a sentinel node biopsy for patients classified as stage IB and above. Two different strategies of pathological lymph node staging in patients with clinically-negative lymph nodes have been performed at our surgical department. In most patients with a tumour thickness of 1.5 mm or more, elective lymph node dissection was performed. Recently, sentinel lymph node biopsy has been introduced.

The proposed staging system includes more patients classified as stage I and, consequently, fewer stage II and III patients. This was observed, because in the proposed staging system a large number of patients changed to a lower pT category and pT4 tumours without lymph node metastases were no longer categorised as stage III. Therefore, nearly 45% of the present stage II patients were reclassified to the proposed stage I and 40% of the present stage III patients were reclassified to the proposed stages I or II.

4.2. Comparison between the present and the proposed staging systems with respect to survival

Comparing survival of localised melanoma, we found nearly identical 5- and 10-year survival rates for pT1 tumours in both staging systems (valid TNM: 96 and 89%, proposed TNM: 92 and 89%). However, in the valid pT classification, 28% ($n=230$) of the patients were assigned to pT1, whereas in the proposed pT classification 49% ($n=399$) of the patients were categorised as pT1. This phenomenon was also observed in the stage grouping. In stage I, 5- and 10-year survival rates of both staging systems were identical (valid TNM: 94 and 89%, proposed TNM: 94 and 87%), but the number of patients assigned to stage I was distinctly higher in the proposed staging system ($n=544$, 56%) than in the actual valid system ($n=393$, 40%). Thus, the proposed pT classification identifies more patients with excellent prognosis and enables subgroups of different prognosis in stage II to be distinguished. In patients with synchronous lymph node metastasis and/or in-transit metastasis, similar 5- and 10-year survival rates were found for pN1 and pN2 defined by the currently used pN classification (pN1: 52 and 37%, pN2: 45 and 35%). However, in the proposed N/pN classification, a distinctly lower survival rate for patients with pN3 tumours was found when compared with pN1 and pN2 tumours (pN1: 65 and 60%, pN2 61 and 48%, pN3: 40 and 24%, $P=0.13$). This new pN classification enables subgroups of patients with lymph node metastasis that differ in survival to be identified.

The prognosis of patients with distant metastasis was poor. The small number of patients with distant metastases as a primary tumour manifestation ($n=14$) operated upon for cure did not allow a subgroup analysis.

4.3. Summarising the assessment of the proposed staging system

Although additional staging criteria are required, the new staging system for cutaneous melanoma proposed by the AJCC seems to be practicable. Comparing the proposed classification system with the currently used TNM classification, it seems to be superior in predicting survival. More patients with excellent prognosis were identified with localised melanoma. In stages II and III, it was possible to distinguish between subgroups with a better and worse prognosis. For advanced melanoma with distant metastases, the number of patients of the Erlangen Melanoma registry was too small to assess the prognostic value of the new substaging.

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