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A first prospective population-based analysis investigating the actual practice of melanoma diagnosis, treatment and follow-up

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ABSTRACT

Aim of the study: To describe the current management of patients diagnosed with cutaneous melanoma and melanoma in situ in Germany and assess for adherence with the existing German guideline in a first prospective population-based analysis.

Methods: Prospective and longitudinal population-based study using online questionnaires. Registration by practitioners and hospitals was open for all patients diagnosed with melanoma between April and June 2008 in Germany. For data analysis, patients with melanoma stages 0–III (AJCC 2002) were included.

Results: Data from 1081 patients registered by 106 different centres were available for analysis. Male patients were significantly older than female patients (61.4 years versus 55.8 years, $p < 0.0001$) and presented with thicker primary tumours (1.62 mm [median 0.9 mm] versus 1.48 mm [median 0.8 mm], $p = 0.01$). Excessive safety margin excisions were most often applied in melanoma in situ and in small centres. Insufficient excision margins (6.9%) were associated with head and neck localisation, geographical region and implementation of further staging procedures. Decision on sentinel lymph node biopsy complied with the German guideline in >85% of cases and was dependent on age and tumour localisation. Only 60% of patients received a complete lymph node dissection (CLND) after a positive SLNB, the rate of CLND was lowest in older patients. Adjuvant treatments were initiated in only 34% of patients formally qualifying for adjuvant treatment based on guideline recommendations. Approximately half of all staging procedures were done in no-risk/low-risk tumour patients.

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Conclusions: Management of melanoma in Germany did not show great dependency on centre size, geographical area or treating physician but rather on patient and tumour characteristics. The low rate of adjuvant treatment initiations reflects the need of treatment options in this patient group. Excessive initial staging procedures generate significant costs.

1. Introduction

Melanoma incidence is on a steady increase with some even calling it an epidemic. According to the World Health Organisation (WHO), the incidence of melanoma is increasing faster than any other cancer in the world. With an incidence rate of 68,130 for 2010, melanoma is currently the 5th most common cancer in men and the 7th most common cancer in women in the United States (US)[1] and thus poses a significant health issue and economic burden.

In the best interest of the patient as well as at a time of tight health budgets, the extent of diagnostic and therapeutic procedures undertaken in melanoma patients should be adapted to consensus-based guidelines which exist in many countries.[2–8] However, there are no universally accepted guidelines nor recommendations with regard to follow up frequency and duration and staging procedures differ considerably.

Investigations assessing the implementation of these guideline recommendations in the daily actual practice are limited. Especially in Europe, clinical practice assessments for melanoma are sparse, generally of retrospective nature and often only consider one aspect such as safety margin excision or sentinel lymph node biopsy (SLNB).[9,10] Only one extensive population-based study was conducted retrospectively in France; Grange et al. assessed and compared the clinical management of stages I–III melanoma patients in five French regions to the existing French guidelines in 2004.[11] The authors found that disparities in the management of melanoma depended to a great extent on medical and geographical neighbourhood rather than on the characteristics of either patients or tumours. Staging procedures often exceeded French recommendations.

The German melanoma guideline recommends comparatively extensive diagnostic procedures[5] with questionable benefit especially in low-risk melanoma. The detection rate of metastases in asymptomatic, low-risk patients is known to be quite low whereas the frequency of false-positive findings is high. Studies analysing the costs of initial and follow-up staging procedures in Germany have already demonstrated the expenses and low efficacy of these elaborate staging procedures.[12–14] These studies were, however, only restrospective monocentre evaluations.

The aim of this study was, therefore, to assess (i) the current practice of melanoma diagnosis, treatment and follow-up in Germany, (ii) the adherence of the actual melanoma management with the German melanoma guideline, (iii) if there are disparities of the actual management with regard to geographical area, centre size, insurance status, treating physician or patient and tumour characteristics and (iv) the costs generated by staging procedures at the time of initial diagnosis in stages I–III melanoma patients. As retrospective studies always yield a great risk of a recall bias, our investigation was designed as a prospective study, being the first prospective population-based analysis investigating the actual practice of melanoma diagnosis, treatment and follow-up in Germany. Patients were registered at the time of initial melanoma diagnosis and will be followed up for 4 years. For this investigation, data of patients with melanoma in situ and cutaneous melanoma stages I–III at registration were analysed.

2. Patients and methods

2.1. Study design

The study was initiated in Germany in April 2008 as a nationwide project (population = 82 million inhabitants [*source:* German Federal Statistical office, 2008], divided into 16 federal states). The study was a joint project of the *Arbeitsgemeinschaft Dermatoonkologie* (Dermatologic Cooperative Oncology Group, DeCOG), the *Deutsche Dermatologische Gesellschaft* (German Society of Dermatologists, *DDG*) and the *Berufsverband der Deutschen Dermatologen* (Professional Organization of German Dermatologists in Private Practice, *BVDD*). Ethics approval was attained from the ethic committee of the medical faculty Mannheim, University of Heidelberg, Germany. The study was sponsored by educational grants from Essex Pharma, Medac Onkologie, Bayer Health Care, Bristol-Myer Squibb and Swedish Orphan International.

Information on the project was sent out to members of the *DDG* and *BVDD* as well as announced at several national congresses. Physicians had to sign up for participation and were asked to anonymously register patients. Eligibility for participation was regardless of centre size or specialisation of treating physician. For every fully registered patient, the centres received a reimbursement of 30 €. Centres were divided into three groups according to registered patient numbers.

Patients were eligible for inclusion if they were diagnosed with melanoma between April 1st and June 30th, 2008 and signed an informed consent for study participation. An extensive online questionnaire (e-CRF) had to be filled out by the physician registering the patient asking for data regarding diagnosis, management and surveillance. Initials, date of birth as well as tumour specific data were used for excluding duplicate entries. For the current analysis, only patients with cutaneous melanoma in situ and melanoma stages I–III were included, patients with unknown primary, primary other than cutaneous, unknown tumour thickness, distant metastases and unclassifiable tumour stage were excluded in order to achieve a homogenous patient population with comparable datasets. Additional requirements for analysis inclusion were a completed questionnaire and signed informed consent. Registration of patients was open until September 30th, 2008.

Exhaustiveness rate calculation was based on the incidence rate of the cancer registry of the state of Saarland, Germany, for the year 2008 (Saarland Cancer Registry 2008: 23.9/100,000, http://www.krebsregister.saarland.de/datenbank/datenbank.html) and on the German population in 2008 (German Federal Statistic Office 2008: 82,002,400, http://www.destatis.de/jetspeed/portal/cms/Sites/destatis/Internet/DE/Navigation/Statistiken/Bevoelkerung/Bevoelkerungsstand/Bevoelkerungsstand.psml) and adjusted for the registration period (3 months).

2.2. Data collection

The following data were collected for all patients: age; sex; date of initial diagnosis; insurance status; comorbidities; ECOG; clinical and histological characteristics of the tumour; modalities of surgery (including initial excision, definitive surgery; safety margin excision; amputation of fingers and toes; sentinel biopsy and complete lymphadendectomy); results of sentinel biopsy and complete lymphadectomy; medical diagnostic imaging; adjuvant treatment (including further specification of treatment, inclusion in study treatments, admission to hospital for initiation of therapy and time from initial diagnosis to treatment initiation); and specification of treating physicians (with regard to specialty of physician performing surgical, surveillance and therapy procedures). Health care centres were subdivided into three groups according to the number of patients registered: (1) small centres: centres with 1–9 registered patients, (2) medium centres: centres with 10–29 registered patients and (3) large centres: centres with $\geqslant$30 registered patients.

2.3. Statistical analysis

All data were analysed in a descriptive and explicative manner. Missing data were not substituted; implausible data were recorded as 'missing'. The chi-square test was used to investigate the dependency of two categorial variables, the Wilcoxon test was used to assess whether the value of continuous variables differ between individual groups. Multivariate logistic regression analyses were performed to investigate factors associated with the following variables: adequacy of definitive margin excision, SLNB, CLND and adjuvant therapy. For each analysis, factors tested for explicative value belonged to the following: age (<60 years versus $\geqslant$60 years), sex, federal state, region (former East versus West Germany), centre size, insurance status, tumour thickness ($\leqslant$1 mm versus >1 mm), location of the tumour, implementation of further staging procedures, specialisation of physician performing initial excision, specialisation of physician performing definitive margin excision and specialisation of physician performing SLNB. Factors significant at the $p = 0.20$ level in univariate analyses were included in stepwise regression multivariate analyses. All analyses were performed using SAS statistical software (SAS Inc., Cary, North Carolina).

3. Results

Patients (1360) were registered in the database, informed consent was obtained in 1271 cases. After correction for duplicate cases, a total of 1264 cases remained leading to an exhaustiveness rate of 0.26. Additionally, patients with unknown primary, primary other than cutaneous, unknown tumour thickness, distant metastases and unclassifiable tumour stage were excluded, leaving 1081 cases from 106 different centres for complete analysis. 20% of all patients were registered by 73 small centres, 26.5% by 20 medium centres and 53.6% by 13 large centres.

The tumour characteristics are shown in Table 1, patient characteristics are depicted in Table 2. Mean age at initial diagnosis was 58 years (median age 61 years, ranging from 17 to 92 years), men were significantly older than women (61.4 years versus 55.8 years, $p < 0.0001$). Mean tumour thickness was 1.55 mm (median 0.82 mm), the tumour thickness was higher in males than in females (1.62 mm [median 0.9 mm] versus 1.48 mm [median 0.8 mm], $p = 0.01$), men and women were equally affected (50.5% and 49.5%, respectively). The predominant location in males was the back (34.1% males versus 15.7% females), in contrast to the lower extremity in females (41.3% females versus 15.9% males).

One hundred and seven patients (9.9%) were diagnosed with melanoma in situ. Approximately 50% of melanoma in situ (pTis) patients were registered by small centres; in all other categories, more than half of patients were registered by large centres (Table 3). The majority of patients presented with stage I disease (65%) according to the American Joint Committee on Cancer classification (AJCC 2002), in only 9.1% spreading to local lymph nodes or satellite/intransit metastases were detected.

85.3% of patients had public insurance cover, 11.9% private insurance cover and 2.5% public insurance cover with private insurance cover for hospital stays. Comorbidities were documented in 8.4% of cases; cardiovascular diseases domineered (60.7%) followed by additional cancers (16.8%) and diabetes (16.9%) (Table 2). In 12.9% of patients comorbidities affected the choice of therapy procedures in the opinion of the treating physician. 80.2% of patients had an ECOG performance status of 0.

Almost all patients were documented as participating in regular follow-up schemes (99.4%) predominantly under the surveillance of dermatologists (98.5%). Only 9 and 4 cases were to be followed up by general practitioners and oncologists, respectively.

3.1. Adequacy of definitive margin excision

Adequate definitive margin excision was defined as 0.5 cm in melanoma in situ, 1 cm in melanoma with a tumour thickness $\leqslant$ 2 mm and 2 cm in melanoma with a tumour thickness > 2 mm according to the German melanoma guideline[5]. Initial excisions and definitive margin excisions were predominantly performed in private dermatological practices and departments of dermatology (Table 4).

Adequacy of definitive margin excision generally complied with the German guideline in 84% of all tumour thicknesses. Insufficient margin excisions occurred in 6.9%, excessive margin excisions in 9.1%. Safety margin excisions were most often applied correctly in patients with melanoma <1 mm (89%) (Table 5). Incorrect excision margins (margins either insufficient or exceeding recommendations) were found most often in the melanoma in situ-group (28.2%). In 18.4% of

Table 1 – Tumour characteristics of study cohort and central German melanoma registry.

Melanoma characteristics	All cases (n = 1081)	%	Central cancer registry Tübingen 2008 (n = 4719)[a]	%
Tumour thickness, mm				
Mean	1.55	n.a.	1.77	n.a.
Median	0.82	n.a.	0.9	n.a.
Male, mean (median)	1.62 (0.9)	n.a.	1.88 (0.9)	n.a.
Female, mean (median)	1.48 (0.8)	n.a.	1.58 (0.8)	n.a.
Histological subtype				
Superficial spreading melanoma	575	59.0	2160	45.8
Nodular melanoma	153	15.7	661	14.0
Lentigo maligna melanoma	82	8.4	465	9.9
Acrolentiginous melanoma	34	3.5	170	3.6
Not specified/unknown/others	130	13.3	1263	26.8
Melanoma in situ[b]	107	n.a.	n.d.	n.d.
Stage (AJCC 2002)[c]				
0	107	9.9	n.d.	n.d.
IA	480	44.4	1363	42.1
IB	223	20.6	815	25.2
IIA	89	8.2	306	9.5
IIB	65	6.0	241	7.4
IIC	19	1.8	144	4.4
IIIA	41	3.8	114	3.5
IIIB	44	4.1	165	5.1
IIIC	13	1.2	89	2.7
Localisation (%)				
Back	270	25.0	1123	23.8
Lower leg	131	12.1	493	10.5
Upper leg	129	11.9	450	9.5
Upper arm	117	10.8	566	12.0
Face	102	9.5	470	10.0
Chest	85	7.9	448	9.5
Abdomen	61	5.6	112	2,40
Lower arm	60	5.6	208	4.40
Foot	48	4.4	194	4.10
Head (location other than face)	34	3.2	223	4.7
Neck	18	1.7	108	2.3
Backside	14	1.3	52	1.1
Hand	10	0.9	44	0.9
Penis/scrotum	1	0.1	12	0.3
Other	1	0.1	57	1.2
Unknown	–	–	159	3.4

Abbreviations: AJCC, American Joint Committee on Cancer; n.a., not applicable; n.d., not documented.
Due to rounding, percentage may not equal 100.
[a] Data on melanoma in situ not collected by central cancer registry.
[b] Melanoma in situ excluded from percentage as no histological subtype of melanoma.
[c] 1482 entries from the Central cancer registry missing due to invalid information in the reporting forms making it impossible to calculate the tumour stage.

patients with melanoma in situ, safety margin excision exceeded the requirements in contrast to only 2.6% for melanoma $\leqslant$1 mm and 9.7% for melanoma >1 mm. Definitive margin excision was insufficient in 17.5% of patients with melanoma >2 mm, but only in 6.7% for melanoma $\leqslant$2 mm and 9.1% of melanoma in situ. Definitive margin excision was most often performed correctly in large centres (88.2%); compliance was least in small centres (74.8%); (medium centres 82.3%). In small centres, definitive margin excision was chosen too small or excessive in equal proportions (12.9% and 12.4%, respectively). Correct safety margin excisions were used in 80.4% of patients >60 years (patients $\leqslant$60 years: 87.7%) and in only 67.8% of tumours localised on the head and neck in contrast to 89.7%, 87.7% and 74.3% of tumours localised on the extremities, the trunk and other localisations, respectively.

Multivariate analyses showed that excessive safety margin excision was independently associated with tumour thickness $\leqslant$ 1 mm (OR 0.2, 95%-CI 0.09–0.35, $p < 0.0001$) and centre size (12.4% small centres, 8.5% medium centres, 4.1% large centres, $p = 0.0046$); insufficient safety margin excision was independently associated with tumour localisation (head and neck 31.7% versus extremities 5.0%, trunk 5.2%, others 15.6%, $p < 0.0001$), implementation of further staging proce-

Table 2 – Patient characteristics of study cohort and central German melanoma registry.

Patient characteristics	All cases (n = 1081)	Central cancer registry Tübingen (2007)
Age (mean)	58	60
Male	61.4	62
Female	55.8	58
Gender (%)		
Male	50.5	50.5
Female	49.5	49.5
Comorbidities[a]		
Cardiovascular diseases	310	n.d.
Other malignancies	91	n.d.
Diabetes	86	n.d.
Active autoimmune diseases	18	n.d.
Immunosuppression	6	n.d.
ECOG status		
0 (=Karnofsky 100%)	867	n.d.
1 (=Karnofsky 80–90%)	106	n.d.
2 (=Karnofsky 60–70%)	15	n.d.
3 (=Karnofsky 40–50%)	2	n.d.
4 (=Karnofsky 10–30%)	1	n.d.
Not specified	90	n.d.
Insurance status, No. (%)		
Public health insurance	922 (85.3%)	n.d.
Private health insurance	129 (11.9%)	n.d.
Public health insurance with private health insurance cover for hospital stays	27 (2.5%)	n.d.
No insurance cover	3 (0.3%)	n.d.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; n.d., not documented.
Due to rounding, percentage may not equal 100.
[a] Multiple entries allowed.

dures (performed, OR 0.4, 95%-CI 0.18–0.69, $p = 0.0021$) and region (East versus West Germany, OR 4.7, 95%-CI 1.61–13.72, $p = 0.0046$). Sex, federal state, insurance status, specialisation of physician performing initial excision and specialisation of physician performing safety margin excision had no effect on safety margin excision.

3.2. *Sentinel lymph node biopsy*

Sentinel node biopsy is recommended for tumours >1 mm and can be considered in patients with thinner tumours and Clark level IV/V and ulceration of primary tumour (T1b, AJCC 2002) according to the German melanoma guideline.[5] A total of 401 patients (37.1%) underwent SLNB of which 89 were positive (22.2%) (Table 5). In general, decision of SLNB complied with the German guideline recommendations in 87.8%, when subanalysing for centre size, no great variation was seen (compliance in 89.8%, 89.5% and 86.2% of cases for small, medium and large centres, respectively). SLNB was generally performed in departments of dermatology (Table 4). In 35 cases a SLNB was performed in melanoma in situ and T1a stage. None of the sentinel nodes in melanoma in situ were positive, but 4 out of 32 in T1a. In T4b stage, only 70% of patients underwent SLNB.

Factors independently associated with SLNB in cases with a tumour thickness $\geqslant$ 1 mm were younger age ($\leqslant$60 years, OR 2.7, 95%-CI 1.35–5.42, $p = 0.005$), implementation of further staging procedures (performed, OR 7.8, 95%-CI 1.27–47.80, $p = 0.026$), tumour localisation (head and neck 59.1% versus extremities 91.6%, trunk 86.3%, others 80%, $p < 0.0001$) and physician performing safety margin excision (private dermatological practice 33.3% versus department of dermatology 85.5%, others 89.7%, $p = 0.018$). Sex, federal state, region (East versus West), centre size, insurance status, specialisation of physician performing initial excision and specialisation of physician performing SLNB had no effect on SLNB.

3.3. *Complete lymph node dissection*

Complete lymph node dissection of the affected lymph node basin is recommended in patients with microscopic and macroscopic nodal involvement according to the German melanoma guideline.[5] Sixty-five patients received a complete lymph node dissection (CLND) either after proven metastasis in the sentinel lymph node or because of macroscopic lymph node involvement (3 patients). In 38.5% (25 patients) CLND showed further tumour cell invasion.

CLND after positive SLNB followed in only 60% of cases; 18.9% of patients <60 years and about 55.8% of patients $\geqslant$60 years did not undergo CLND despite positive sentinel lymph node. Patients under 60 years who did not undergo CLND despite positive SLNB were reassessed (7 cases); in 3 patients the sentinel showed only micrometastasis, the treating physicians discussed the significance of micrometastasis

Table 3 – Patient and melanoma characteristics adjusted for melanoma in situ, melanoma with tumour thickness < 1 mm and ⩾1 mm.

Patient and melanoma characteristics in relationship to tumour thickness	All cases, $n = 1081$ (%)	Melanoma in situ, $n = 107$ (%)	Breslow index <1 mm, $n = 555$ (%)	Breslow index ⩾1 mm, $n = 419$ (%)
Gender				
Male	546 (50.5)	50 (9.2)	266 (48.7)	230 (42.1)
Female	535 (49.5)	57 (10.7)	289 (54.0)	189 (35.3)
Insurance status				
Public insurance	922 (85.3)	88 (9.5)	487 (52.8)	347 (37.6)
Private insurance	129 (11.9)	15 (11.6)	60 (46.5)	54 (41.9)
Public insurance with private insurance cover for hospital stays	27 (2.5)	18 (66.7)	7 (25.9)	18 (66.7)
No insurance cover	3 (0.28)	2 (66.7)	1 (33.3)	0 (0)
Centre size				
Small centre (1–9 registered patients)	216 (20.0)	46 (21.3)	124 (57.4)	46 (21.3)
Medium centre (10–29 registered patients)	286 (26.5)	19 (6.6)	143 (50.0)	124 (43.4)
Large centre (>30 registered patients)	579 (53.6)	42 (7.3)	288 (49.7)	249 (43.0)
Location				
Head and neck	154 (14.2)	24 (15.6)	79 (51.3)	51 (33.1)
Upper extremity	187 (17.3)	18 (9.6)	95 (50.8)	74 (39.6)
Trunk	432 (40.0)	40 (9.3)	234 (54.2)	158 (36.6)
Lower extremity	308 (28.5)	25 (8.1)	147 (47.2)	136 (44.2)

Due to rounding, percentage may not equal 100.

Table 4 – Surgical procedures adjusted for performing institution.

Surgical modalities	Primary excision, %	Safety margin excision, %	Sentinel lymph node biopsy, %
Private dermatological practice	59.5	15.3	0
Department of dermatology	31.3	80.5	91.3
Department of surgery	2.4	3.0	7.0
Department of maxillofacial surgery	0.2	0.1	0.3
Other/unknown	6.7	1.2	1.5

with the patients, and CLND was subsequently rejected by the patients. In 3 cases no further information could be given, in 1 case it was decided to refrain from a CLND due to the anatomical site of the sentinel lymph node (subscapular).

The factor independently associated with CLND in sentinel node positive cases in whom a CLND would be indicated was age (⩽60 years, OR 6.9, 95%-CI 2.42–19.86, $p = 0.0003$). Sex, federal state, region (East versus West), centre size, insurance status, location of tumour, implementation of further staging procedures, specialisation of physician performing initial excision, specialisation of physician performing safety margin excision and specialisation of physician performing SLNB had no effect on CLND.

3.4. *Adjuvant therapy*

Adjuvant therapy is recommended for patients with an increased risk of tumour progression and should be discussed for patients with a tumour thickness ⩾ 1.5 mm and in patients with lymph node metastasis without evidence of distant metastases according to the German guideline.[5] Adjuvant therapies were initiated in 114 cases of 330 patients formally qualifying for adjuvant treatment, 3 patients received adjuvant treatment although not recommended. Even in stage III melanoma, adjuvant treatment was started in only 54.1% of patients. Interferon (low dose, intermediate and high dose) was the predominantly administered therapy; Table 6 provides an overview of all therapy regimens. Overall, therapy administration and supervision were overseen predominantly by dermatologists (95%), oncologists accounted for 3.4% and others for 1.7%. 63.9% of patients were admitted to hospital for the initiation of their therapy, mean time for the hospital stay was 3.9 days (SD 3.38 days, min. 1 day, max. 22 days). Mean time lag between initial diagnosis and treatment initiation was 64.2 days (SD 32.5 days, min. 4 days, max. 181 days). The longest time lag was observed in medium sized centres (mean 76.4 days), the greatest variation of time lag was seen in patients referred from small centres (min. 13 days, max. 181 days).

Factors independently associated with the initiation of an adjuvant therapy for patients with a tumour thickness > 1.5 mm in whom an adjuvant therapy should be discussed according to the German guideline were younger age (⩽60 years, OR 3.7, 95%-CI 2.15–6.19, $p < 0.0001$) and insurance

Table 5 – Management of 1081 melanoma and melanoma in situ cases in Germany adjusted for melanoma in situ, melanoma with tumour thickness < 1 mm and >1 mm.

Disease management in relationship to tumour thickness	All cases	Melanoma in situ (n = 107)	Breslow index <1 mm (n = 555)	Breslow index ⩾1 mm (n = 419)
Definitve margin excision (n = 1042)				
Correct	875 (84.0%)	74 (71.8%)	478 (89.0%)	323 (80.3%)
Insufficient	95 (9.1%)	10 (9.7%)	45 (8.4%)	40 (10.0%)
Excessive	72 (6.9%)	19 (18.4%)	14 (2.6%)	39 (9.7%)
Sentinel node biopsy (n = 1081)				
NP	680 (62.9%)	104 (97.2%)	501 (90.3%)	75 (17.9%)
Performed	401 (37.1%)	3 (2.8%)	54 (9.7%)	344 (82.1%)
Positive sentinel	89 (22.2%)	0 (-%)	6 (11.1%)	83 (24.1%)
Therapy situation (n = 1081)				
Adjuvant therapy	117	0 (0%)	4 (0.7%)	113 (27.0%)
Initial staging, multiple entries possible, total number (n = 1081)	3867	122	1756	1989
Lymph node US	801	37 (34.6%)	414 (74.6%)	350 (83.5%)
S100	630	24 (22.4%)	281 (50.6%)	325 (77.6%)
Abdominal ultrasound	678	25 (23.4%)	391 (70.6%)	262 (62.5%)
Chest radiography	687	21 (19.6%)	389 (70.1%)	277 (66.1%)
CT/MRI head	193	0 (0%)	24 (4.3%)	169 (40.3%)
CT/MRI thorax	198	2 (1.9%)	30 (5.4%)	166 (39.6%)
CT/MRI abdomen	199	1 (0.9%)	28 (5.0%)	170 (40.6%)
Bone scintigraphy	41	0 (0%)	12 (2.2%)	29 (6.9%)
PET	27	0 (0%)	1 (0.2%)	26 (6.2%)
Other blood tests	413	12 (11.2%)	186 (33.5%)	215 (51.3%)

Abbreviations: NP, not performed; US, ultrasound; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.
Due to rounding, percentage may not equal 100.

Table 6 – Adjuvant therapy regimens initiated in all patients.

Adjuvant therapy, %	
Low-dose IFN (3x3 M IU)	75.6
Intermediate-dose IFN (5 × 9 M IU, 3 × 5 Mio IU)	3.3
Kirkwood scheme IFN	9.8
pegylated IFN	4.9
DTIC	1.6
Other	4.9

Abbreviations: IFN, interferon; DTIC, dacarbazine.

status (public insurance, OR 2.4, 95%-CI 1.02–5.41, p = 0.044). Sex, federal state, region (East versus West), centre size, insurance status, location of tumour, implementation of further staging procedures, specialisation of physician performing initial excision, specialisation of physician performing safety margin excision and specialisation of physician performing SLNB had no effect on adjuvant therapy.

3.5. *Diagnostic staging procedures*

According to the German melanoma guideline,[5] lymph node sonography, laboratory work up including S100 protein level in serum, abdomen ultrasound and chest X-ray should be performed as routine staging in tumours thicker than 1 mm and can be performed in thinner tumours. Staging procedures (including S100 serum levels, other blood tests and systematic medical imaging) were done in 85.3% of all registered patients and were primarily organised by the centre registering the patient (60.1%). Applying the strict rule of only carrying out further staging procedures in patients with tumours thicker than 1 mm, the implementation of staging procedures exceeded the recommendations in 55.4%. Especially in small centres, recommendations were often not heeded (70.8%, 49.2% and 54.1% for small, medium and large centres, respectively; p = 0.001). The total sum of diagnostic procedures undertaken in all patients at the time of initial melanoma diagnosis accumulated to 3867 with lymph node ultrasound being the most common procedure (20.7%) followed by abdominal ultrasound (17.8%) and chest X-ray (17.5%). A total of 1878 (48.6%) staging procedures were done in melanoma in situ and melanoma <1 mm (Table 5) without any melanoma-specific death risk. 98 CT, MRI and positron emission tomography (PET) and bone scans were done in melanoma in situ and T1a/b.

The calculation of costs that the different procedures caused is based on the official scale of medical reimbursement charges in Germany (*Gebührenordnung für Ärzte*, *GOÄ*) (Table 7). As no differentiation between CT and MRI scan was made in the e-CRF, costs for the less expensive CT scans were used for calculations. In total, 52,398.77€ were solely spent on initial staging procedures in 662 patients with melanoma in situ and melanoma <1 mm tumour thickness. As approximately 12,000 patients were diagnosed with melanoma in situ and melanoma <1 mm tumour thickness in 2008 in Germany, roughly 1,000,000€ (1,327,100.00 US$) can be estimated to have been spent for this patient group based on our study results. In our patient collective, 129,754.14€

Table 7 – Costs of initial staging procedures in different tumour stages.

Revenues for staging procedures according to GOÄ	Medical reimbursement numbers	Charges in Euro	Amount of examinations in melanoma in situ, pT1a and pT1b patients (AJCC 2002)	Total costs	Amount of examinations in melanoma stages 0–IIC patients (AJCC 2002)	Total costs
Lymph node sonography	GOÄ 410, 420	16.32€	451	7360.32	719	11734.08
Chest x-ray	GOÄ 5137	26.23€	410	10754.30	626	16419.98
Abdominal ultrasound	GOÄ 410, 420	16.32€	416	6789.12	621	10134.72
Protein S100 ligand assay	GOÄ 3901 H3	26.23€	305	8000.15	555	14557.65
Standard blood tests	GOÄ 250, 3541H	30.31€	198	6001.38	358	10850.98
CT abdomen[a]	GOÄ 5372	151.55€	29	4394.95	140	21217.00
CT thorax[a]	GOÄ 5371	134.06€	32	4289.92	136	18232.16
CT head[a]	GOÄ 5370	116.57€	24	2797.68	136	15853.52
Bone scintigraphy	GOÄ 5425	131.15€	12	1573.80	32	4196.80
PET	GOÄ 5489	437.15€	1	437.15	15	6557.25
Total				52,398.77		129,754.14

Abbreviations: GOÄ, *Gebührenordnung für Ärzte* (medical reimbursement charges in Germany); CT, computed tomography; PET, positron emission tomography; AJCC, American Joint Committee on Cancer.

[a] As no differentiation between CT and MRI scan was made in the e-CRF, calculation is based on the less expensive CT scan cost.

were spent on patients without locoregional metastases (stages 0–IIC) equalling 132.00€/patient. As no patients with distant metastases were included in this analysis, it can be concluded that no distant metastases were detected by the extensive staging procedures carried out.

4. Discussion

Our prospective data analysis of 1081 patients diagnosed with stages I–III melanoma from April to June 2008 in Germany investigated the actual clinical practice of melanoma management and whether variations of melanoma management were dependent on geographic, demographic or tumour specific characteristics.

Overall, demographic data were consistent with those of the largest German melanoma register in Tübingen, Germany (Tables 1 and 2). There was no sex preponderance, but men were significantly older than women (61.4 years versus 55.8 years, $p < 0.0001$). The mean tumour thickness was 1.55 mm (median 0.82 mm), and tumour thickness was significantly higher in men than in women (1.62 mm [median 0.9 mm] versus 1.48 mm [median 0.8 mm], $p = 0.01$). The majority of patients were diagnosed with stage IA and IB disease (65%). More than half of all patients were registered by large centres, the majority of melanoma in situ were registered by small centres indicating that no-risk/low-risk melanoma is generally treated by dermatologists in private practices whereas higher-risk melanoma get referred to specialised centres.

Surgical procedures including primary excision, safety margin excision and SLNB were primarily performed by dermatologists, either in a private dermatological practice or in a hospital setting underlining the central role dermatologists play in diagnosis and also treatment of melanoma in Germany. Safety margin excision as defined by the German guidelines for melanoma[5] was applied correctly in most cases (84%), especially in large centres (88.2%). Insufficient excisions (9.1%) were used slightly more often than excessive excisions (6.9%). Factors correlated with insufficient safety margins were tumour localisation especially in the head and neck area and patients treated in the Eastern German region. The implementation of further staging procedures was negatively related. Insufficient safety margins in tumours of the head and neck have already been shown by other investigators[11,15,16] and most commonly result from anatomically or aesthetically restrained and thus limited surgery. Inadequate excision margins are associated with an increased risk of locoregional recurrence and in-transit metastases,[17,18] the impact of an inadequate safety margin on survival, however, is uncertain. A Dutch study did not observe any significant effect of compliance on survival,[10] whereas a United Kingdom (UK) study of 900 melanoma patients with tumour thicknesses > 2 mm who where randomised to either 1- or 3-cm margin excisions showed a 20% higher melanoma-related death rate in patients treated with the narrower margins.[17] Especially comorbidities, resulting morbidity from re-excision, life-expectancy and the patient's wish are reasons that need to be considered when the decision about safety margin excision is being made. Tumour location in the head/neck area can be argued as a reasonable exemption from the guideline recommendations and demonstrates that individual decisions are warranted in certain cases.

Excessive safety margin excisions occurred in our dataset in only 6.9% in contrast to 16% of all patients in the study by Grange et al.[11] Excessive safety margin excisions were used most often in melanoma in situ and in small centres. In only 6 patients safety margin excisions of 3 cm were chosen. Very wide margin excisions have not demonstrated a benefit on overall survival (OS) and disease free survival (DFS)[19–22] and should, therefore, be omitted. The most recent recommendations[23,24] are consistent with the German National guidelines although there is still ongoing discussion about optimal excision margins for all types of melanoma.[25,26]

In this study, implementation of SLNB was in accordance with the national guideline in 87.8% of all cases and thus much higher than the rate reported by others.[11,27–29] In the French data analysis[11], SLNB was done in only 34% of patients with a tumour thickness > 1 mm (at the time of data documentation, French guidelines did not include SLNB recommendations). Bilimoria et al.[27] found that fewer than half of patients with clinically node-negative stage IB/II melanoma underwent SLNB as part of first course treatment in the USA five years after integration of SLNB into National Comprehensive Cancer Network (NCCN) clinical practice guidelines. Factors independently associated with SLNB implementation in our study were tumour location, age and physician performing the safety margin excision. Whereas SLNB was done in >80% of tumours located on sites other than the head and neck, patients with head and neck melanoma underwent SLNB in only approximately 60%. SLNB of the axilla and inguinal lymph node basins is a routine procedure at most departments of dermatology in Germany, for SLNB in the head/neck, patients often need to be referred to ENT specialists or maxillofacial surgeons. Also, the value of SLNB in head and neck tumours is being discussed controversially as the false-negative rate is high and depends to a greater part on practical and technical procedures than in other lymphatic areas.[30,31] The two alternatives, watchful waiting and elective lymphadenectomy, are not attractive alternatives. Morton's study[32] showed progression of disease in the watch-and-wait group for patients with positive SLNB versus those who were watched and developed regional metastases. Elective lymphadenectomy on the other hand leads to many unnecessary dissections with considerable morbidity. New advances in SLNB of the head and neck area such as the usage of single photon emission computed tomography/computed tomography (SPECT/CT) for presurgical detection and marking of the sentinel node make the procedure more accurate[33] and will hopefully help to establish SLNB as a valuable routine procedure also in the head and neck area in the future.

Underusage of SLNB in older patients has been demonstrated by others[27,28] and is likely attributable to the factors also mentioned for non-reexcision of melanoma in older patients. As for reexcision, decision on SLNB in older patients should be made on an individual basis with special emphasis on (a) the patient's general state and (b) the fact that SLNB is considered a diagnostic tool that should lead to subsequent CLND if the sentinel is positive.

Only one third of patients eligible for SLNB who underwent safety margin excision in a private dermatological practice (total of 6 eligible patients) received a SLNB. Due to the small number of 6 patients, no reliable interpretation can be made, the assumption of nodal undertreatment of patients who do not get referred to hospitals for safety margin excisions where a SLNB is subsequently organised has to be made with caution.

In 35 cases, SLNB was performed in melanoma in situ and pT1a stage. Reasons for decision on SLNB in these no-risk/low-risk patients are uncertain. In some cases tumour thickness might have been assumed higher pre-surgically and primary excision of melanoma was carried out at the same time as SLNB, in other cases regression within the tumour or tumour thicknesses close to 1 mm was stated. Otherwise, as melanoma in situ per definition cannot metastasize and cure rate is >90% in melanoma <1 mm,[34] there is no indication for SLNB in these patients. However, no pattern of increased SLNB rates in certain regions or centres could be noted, thus the inordinate performance of SLNB in these patients was evaluated as being of no greater significance (only 2.8% of all melanoma in situ and 6.6% of all T1a patients). In pT4b stage, only two-thirds underwent SLNB. As stated by others, SLNB should not be omitted in patients with a primary thick melanoma without evidence of distant metastases.[35] To be accurately informed about a patient's prognosis and to decide whether subsequent completion lymph node dissection is indicated, SLNB is necessary also in this high risk patient collective and cannot be replaced by other staging procedures.

Compared to the high rate of SLNB in Germany, the rate of CLND after sentinel positivity was surprisingly low (59.6%), but reflects the findings of Erickson et al.[15] Especially older patients (>60 years) did not routinely undergo CLND albeit indicated. In younger patients, the detection of only micrometastasis in the sentinel node was the most common reason to refer from CLND. As of yet, there is no consensus as to whether micrometastasis in the sentinel lymph node demonstrates an acceptably low risk allowing forgoing of CLND. Recent studies reported that isolated metastases of <0.1 mm[36,37] or <0.2 mm[38] have a prognosis similar to patients with negative sentinel lymph nodes. Another study, however, stated that patients with micrometastases of $\leqslant$0.2 mm have a 12% rate of further metastases upon CLND and a significantly less 5-year survival rate compared to sentinel node negative patients.[39] The significance of micrometastasis has gained even more importance with the implementation of the AJCC 2009 classification according to which immunohistochemical staining of single cells alone with malignant morphologic features will be accepted to classify a sentinel node as positive.[34] Only long-term follow-up will eventually determine the real significance of microscopic nodal invasion with regard to locoregional recurrence and overall survival. Until then, CLND should be discussed thoroughly with patients with proven micrometastasis.

Interferon α is still the only therapy approved in the adjuvant setting in Germany; other treatment options are only available within clinical trials. Of the 330 patients with a tumour thickness $\geqslant$ 1.5 mm and no evidence of distant metastasis, only 117 (35.5%) received an adjuvant therapy. Even in stage III only approximately half of patients started adjuvant treatment. These figures are even lower than those of Grange et al.[11] who found that in 36% of cases with stages I–II melanoma >1.5 mm and 68% cases of stage III melanoma an adjuvant therapy was initiated. The low rate of adjuvant therapy initiations in Germany in 2008 is firstly most likely due to the extensive discussions of the true value of interferon α treatment as interferon α has so far only demonstrated a clear benefit in terms of prolonged relapse-free survival but not overall survival[24] and secondly to the lack of alternative treatment options in clinical trials at the time this study was conducted. The low rate of adjuvant treatment initiations is a clear indicator for the need of alternative treatment options in the adjuvant setting. Again, older age ($\geqslant$60 years) was negatively related with the implementation of an adjuvant therapy. Due to the significant side-effects of interferon treatment, indication of interferon therapy in older patients

needs to be thoroughly evaluated and the benefit gained weighed against the possible side effects especially in older patients. The time lag between the initial diagnosis and therapy initiation was more than 2 months; reasons for the time lag were not given but are most likely attributable to recovery from surgery and additional examinations required before therapy initiation. Time lag did not differ significantly between centre sizes and, therefore, indicates that general improvement across all centres is needed.

The German melanoma guideline recommends intense staging procedures even in asymptomatic patients at the time of initial diagnosis[5] in contrast to many other guidelines.[3,6,7,40] Nevertheless, the actual amount of staging procedures undertaken in our patient population exceeded our expectations by far. Almost half of all staging procedures were done in low risk melanoma (tumour thickness < 1 mm) and melanoma in situ (total of 3867 procedures) accumulating to 52,398.77€ in 662 patients. 85.3% of patients received at least one staging procedure, costs totalled at 167,580.76€ for all patients ($n = 1081$) of which none led to the detection of distant metastases. Especially in small centres, which primarily treat low-risk melanoma, comparatively more staging procedures, particularly costly procedures such as CT/MRI scans and bone scintigraphy were used.

Baseline staging for distant metastases is known to have a low diagnostic yield with a high rate of false-positive findings.[13,41–46] Especially in low-risk melanoma (tumour thickness < 1 mm) with a cure rate of >90%, the likelihood of detecting asymptomatic metastases at the time of primary diagnosis is virtually zero[47]; imaging work-up can, therefore, not generally be recommended. As 60% of first recurrences of melanoma are locoregional metastases,[48,49] imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) scans of thorax and abdomen yield no advantage in detecting metastases over less costly examinations such as clinical follow-up and lymph node ultrasound.[12–14,50] Hofman et al. concluded from their evaluation of 661 melanoma patients that only the inexpensive lymph node ultrasound and clinical examination should be included in the routine work-up at initial staging.[13] For many physicians in Germany, one justification for imaging work-up in this patient population other than meeting their patients' wish is that it can serve as baseline information for future comparison. The costs generated by the excessive staging procedures, the resulting false feeling of security and the psychological distress patients experience due to a false-positive finding are important factors also requiring consideration.

Some limitations of this study have to be noted. The majority of centres participating in this study were dermatological centres. Underreporting of patients solely treated by, e.g. general practitioners, oncologists and surgeons might have occurred. No valid statement can, therefore, be made as to whether treatment by non-dermatologists differed from our findings. However, melanoma patients of all tumour stages are primarily under the care of dermatologists in Germany which is confirmed by the high patient registration rate of this study. Another limitation might be that the data reported reflect the care of patients from centres with a higher level of cancer specialisation where melanoma treatment algorithms are well implemented. As approximately half of all patients were registered by small and medium sized centres with small centres very often only registering one patient, we can assume a great diversity of participating centres with different levels of cancer specialisation representing the actual patient care in Germany.

Overall, compliance with German melanoma guidelines for safety margin excision and SLNB was satisfactory reaching a compliance rate of more than 80%. No great variation was noted between different centre sizes, geographical regions, health care cover and physician performing surgical procedures. Compliance with recommendations for surgical procedures was less in older patients (⩾60 years) and tumours located in the head and neck area. Also, SLNB rate in high-risk melanoma and CLND after positive SLNB was low. The true implications, which these deviations from the surgical treatment guidelines will have on patient outcome will be seen in the study's follow-up data 2 and 4 years after initial diagnosis. The adjuvant treatment situation in Germany needs improvement at centres of all sizes primarily with regard to the treatment alternatives as well as the long delay between initial diagnosis to therapy initiation. The greatest concern is the current practice of initial staging procedures which showed ineffective diagnostic procedures especially in low-risk melanoma posing a significant financial issue.

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Conflict of interest statement

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