Age as key factor for pattern, timing, and extent of distant metastasis in patients with cutaneous melanoma: A study of the German Central Malignant Melanoma Registry

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Background: Melanoma incidence rates rise as people age, but the impact of aging on distant metastasis is unclear.

Objective: To investigate how timing, pattern, and extent of distant metastasis is influenced by age.

Methods: Analysis of a single-center cohort of 1457 patients of the German Central Malignant Melanoma Registry with prospectively documented follow-up. Findings were compared with those for 1682 patients from 5 different institutions. All patients presented initially with stage IA to IIC and developed distant metastasis in their further disease course.

Results: The number of metastatic sites decreased with increasing age at melanoma diagnosis ($P < .001$). The rate of stage M1d disease decreased from 50.2% in patients aged 50 years or younger to 30.1% in patients older than 70 years, and the rate of stage M1b disease increased from 5.8% to 21.5%. The rate of lung metastases remained stable in all investigated age groups ($P = .54$). Distant metastases occurred earlier and were more synchronized in patients older than 70 years than in patients aged 50 years or younger. An age-dependent decrease in metastatic sites and stable rate of lung metastasis were found and confirmed by data on the multi-institutional cohort.

Limitations: The study was not population based.

Conclusion: Pattern, timing, and extent of distant metastasis change as people age. These findings may be considered when treating patients with melanoma of different ages. (J Am Acad Dermatol 2019;80:1299-307.)

Key words: age; brain metastasis; distant metastasis; melanoma; metastasis; metastatic disease; metastatic melanoma.

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Invasive cutaneous melanoma is one of the most common cancers among adolescents and young adults. Despite this, the demographic group that is at highest risk of receiving a diagnosis of melanoma and dying of this cancer is elderly people, notably white men.[1,2] Approximately 40% of persons in whom invasive malignant melanoma is diagnosed are older than 65 years.[3] Clinical experience shows that distant metastasis varies considerably between individual patients, but little is known about progression patterns related to age. Older age is recognized as an independent poor prognostic factor for relapse-free and melanoma-specific survival, but whether this association is due to a declining host defense, a changing tumor biology, or both remains unclear.[1] In this study, we sought to dissect patterns, timing, and extent of distant metastases related to age and discuss clinical implications of our findings.

CAPSULE SUMMARY

- Older age correlates with better response to immunotherapy in patients with stage IV melanoma, but the impact of aging on distant metastasis is unclear.
- This study found an inverse relationship between age at diagnosis and the number of metastatic sites; these findings may have implications for optimizing outcomes of patients with melanoma.

PATIENTS AND METHODS

Statistical analysis

Statistical calculations were performed with IBM SPSS software (version 23.0, IBM, Armonk, NY). Numeric variables were described by mean value and standard deviation if approximately normally distributed or by median value and interquartile range (IQR) if skewed. Proportions were presented with 95% confidence interval (CI).

The association between the number of metastatic sites and clinicopathologic characteristics was assessed with a univariate chi-square test. Significant parameters were further analyzed by multivariate binary logistic regression models using the number of sites as the dependent variable and clinicopathologic characteristics as covariates. The effect of age on the rate of metastatic sites was tested by using the Cochran-Armitage test. Survival rates were estimated according to the Kaplan-Meier method and compared with the log-rank test. Throughout the analysis, *P* values less than .05 were considered statistically significant.

Patients

Between 1976 and 2015, a total of 127,262 patients with melanoma were documented in the nationwide German Central Malignant Melanoma Registry after informed written consent had been obtained. More than 10% of these patients received their diagnosis and were treated at the Department of Dermatology of the University Hospital Tübingen (n = 13,994). Only patients with invasive cutaneous melanoma who presented with stage IA to IIC disease at primary diagnosis and developed stage IV disease in the further course of the disease were included in our analysis. Patients with unknown primary melanoma, known metastasis at the time of the initial diagnosis, and follow-up of less than 3 months were excluded. After application of inclusion and exclusion criteria, a total of 1457 patients could be included in the Tübingen cohort. The next 5 largest centers of the German Central Malignant Melanoma Registry were Wuerzburg (n = 564), Halle (n = 369), Erlangen (n = 305), Magdeburg (n = 283) and Dresden-Friedrichstadt (n = 161), which were analyzed together and referred to as the pooled cohort (n = 1682). The study period and inclusion and exclusion criteria were identical for both cohorts.

A standardized follow-up scheme, including physical examinations, imaging studies, and blood testing was performed according to the guidelines of the German Society of Dermatology and remained rather constant over time. Patients of the Department of Dermatology of the University Hospital Tübingen were prospectively documented in the German Central Malignant Melanoma Registry. Progression of the disease was documented in detail, and distant metastases were differentiated between M stage and visceral site. The date of occurrence of distant metastasis was recorded for each organ system. Tumor stages were classified according to the eighth edition of the American Joint Committee on Cancer cancer staging manual.[4]

The present study was approved by the ethics board of the University Hospital Tübingen (project number 543/2016BO2).

RESULTS

Table I shows the clinicopathologic characteristics of the Tübingen cohort. The median age of all patients at melanoma diagnosis was 57 years (IQR, 45-68) and the median follow-up 50 months (IQR, 28-88). The most common sites of distant metastasis were lung (64.2%), distant lymph nodes (45.8%), and central nervous system (CNS) (44.6%).

Abbreviations used:

CI: confidence interval
CNS: central nervous system
DMFS: distant metastasis–free survival
IQR: interquartile range

Figure 1 describes the association of age at melanoma diagnosis with the number of metastatic sites and different M categories in the further course of the disease. Increasing age was associated with a lower number of metastatic sites (Fig 1, *A*), a higher proportion of stage M1b disease, and a lower proportion of stage M1d disease (Fig 1, *B*). With the exception of lung metastasis, elderly patients had a decreasing rate of distant metastases in all of the investigated organs sites (Fig 2). Increasing age was associated with a shorter follow-up time after stage IV diagnosis (follow-up time of 8 months [IQR 3-17] for patients aged >60 years vs 10 months [IQR, 5-21] for patients aged ≤60 years] [Mann-Whitney U test, $P < .001$]), but there was no correlation between the length of follow-up and the number of metastatic sites (Spearman's rho, 0.029; $P = .28$).

The distribution of distant metastases in a single site versus in multiple concomitant sites is shown in Fig 3. Metastasis limited to a single site (solitary organ) occurred most commonly in patients with lung and CNS metastasis and in particular in elderly individuals. Solitary distant metastases in other sites were either rare or not associated with age at melanoma diagnosis. The time between development of the first and last organ site–containing metastasis was short and decreased with older age (Fig 4). Less than half of patients aged 50 years or younger (40.5%) but 63.0% of patients older than 70 years developed the final number of metastatic sites within 1 month after stage IV diagnosis (Fig 4, *B*).

Distant metastasis–free survival (DMFS) was shorter in older patients ($P < .001$) but did not differ overall between patients with stage M1a disease (37 months [95% CI, 25-49]), those with stage M1b disease (31 months [95% CI, 23-39]), those with stage M1c disease (33 months, [95% CI, 30-36]), and those with stage M1d disease (34 months, [95% CI, 31 – 37]) ($P = .190$) (Supplemental Fig 1 [available at http://www.jaad.org]).

Factors associated with the number of metastatic sites were explored in univariate and multivariate analyses (Fig 5 and Supplemental Table I [available at http://www.jaad.org]). Women (odds ratio, 0.75; 95% CI, 0.58-0.97; $P = .029$) and patients older than

Table I. Clinicopathologic characteristics of the Tübingen cohort (n = 1457)

Characteristic	n (% of total)
Sex	
Female	623 (42.8%)
Male	834 (57.2%)
Body site	
TANS	915 (62.8%)
Non-TANS	542 (37.2%)
Tumor thickness, mm	
≤1.00	255 (17.5%)
1.01-2.00	397 (27.2%)
2.01-4.00	483 (33.2%)
>4.00	322 (22.1%)
Median (IQR)	2.30 (1.25-4.00)
Histopathologic subtype	
SSM	668 (45.8%)
NM	442 (30.3%)
LMM	80 (5.5%)
ALM	117 (8.0%)
Other	149 (10.2%)
Unknown	1 (0.1%)
Ulceration	
Yes	468 (32.2%)
No	976 (67.0%)
Unknown	12 (0.8%)
Age at melanoma diagnosis, y	
Median (IQR)	57 (45-68)
≤50	518 (35.6%)
51-60	338 (23.2%)
61-70	312 (21.4%)
>70	289 (19.8%)
Distant metastasis	
Lung	936 (64.2%)
Distant nodes	668 (45.8%)
CNS	650 (44.6%)
Liver	597 (41.0%)
Bone	431 (29.6%)
Skin and subcutaneous tissue	341 (23.4%)
Intestine	147 (10.1%)
Others	541 (37.1%)
Staging (AJCC, eighth edition)	
M1a	91 (6.2%)
M1b	169 (11.6%)
M1c	547 (37.5%)
M1d	650 (44.6%)

M1a indicates distant metastasis to skin, soft tissue including muscle, and/or a nonregional lymph node; M1b indicates distant metastasis to lung with or without M1a sites of disease; M1c indicates distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease; and M1d indicates distant metastasis to the CNS with or without M1a, M1b, or M1c sites of disease.

AJCC, American Joint Committee on Cancer; *ALM*, acral lentiginous melanoma; *CNS*, central nervous system; *IQR*, interquartile range; *LMM*, lentigo maligna melanoma; *NM*, nodular melanoma; *SSM*, superficial spreading melanoma; *TANS*, thorax, upper arm, neck, scalp.

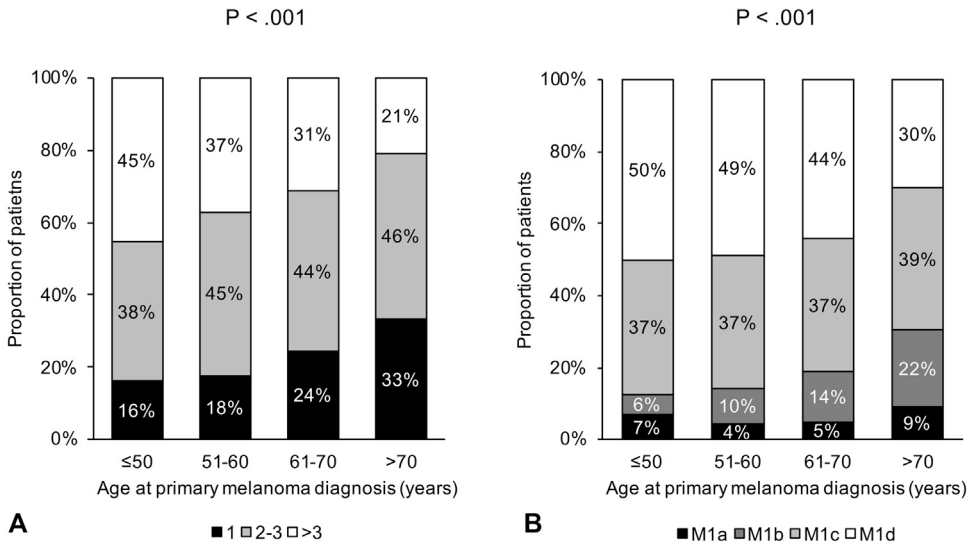

Fig 1. Extent of distant metastasis depends on age at melanoma diagnosis. **A**, Number of organ sites containing metastasis. **B**, Distribution of M categories. *P* values refer to results obtained with the Pearson chi-square test. The total number of patients was 1457. M1a indicates distant metastasis to skin, soft tissue including muscle, and/or a nonregional lymph node. M1b indicates distant metastasis to lung with or without M1a sites of disease; M1c indicates distant metastasis to non–central nervous system visceral sites with or without M1a or M1b sites of disease; and M1d indicates distant metastasis to the central nervous system with or without M1a, M1b, or M1c sites of disease.

70 years (odds ratio, 0.39; 95% CI, 0.28-0.55; $P < .001$) had a significantly lower risk for multiple metastatic sites compared with men and patients aged 50 years or younger.

In the second part of our analysis, findings from the Tübingen cohort were compared with the pooled data on 1682 patients with stage IV melanoma from 5 different institutions (Supplemental Table II [available at http://www.jaad.org]). The median age of these patients was 58 years (IQR, 45-68), and the median follow-up was 41 months (IQR, 23-74). The age-dependent decrease in the number of metastatic sites ($P < .001$) was confirmed by the data on the pooled cohort (Supplemental Figs 2 and 3 and Supplemental Table III [available at http://www.jaad.org]). Increasing age was further associated with a decreasing rate of brain metastases ($P = .023$), in contrast to the stable incidence of lung metastases ($P = .107$) (Supplemental Fig 4 [available at http://www.jaad.org]).

DISCUSSION

Metastasis is a multistep process that requires cancer cells to invade the surrounding tissue, enter the circulation, seed at distant sites, and grow.[5,6] In the last few decades, it has become increasingly evident that tumor progression is not solely determined by cell-intrinsic mechanisms but also by factors and nonmalignant cells in the tumor microenvironment that can exert inhibitory or promoting effects on metastasis formation and underlie age-related changes.[7]

Older age at cancer diagnosis has been linked to a decreasing rate of positive sentinel lymph node biopsy results in patients with melanoma[8] and to a less aggressive phenotype in breast cancer,[9,10] colorectal cancer,[11] and renal cell carcinoma.[12] However, the impact of age on pattern and extent of distant metastasis in patients with cutaneous melanoma remains unclear.

Our study identified age at melanoma diagnosis as key factor for timing, pattern, and extent of distant metastasis. Elderly patients with melanoma had a shorter DMFS but a lower number of metastatic sites compared with younger patients. In the Tübingen cohort, one-third of patients older than 70 years presented with distant metastases limited to a solitary organ compared with 16.4% of patients aged 50 years or younger. The high rate of organ sites containing metastasis is close to that reported in autopsy cases and underscores the accuracy of staging examinations and documentation.[13] The relatively small number of patients in the pooled cohort and their lower number of distant metastases can be explained by the shorter follow-up time. This leads to an underrepresentation of metastases with late occurrence, such as CNS or intestinal metastases, and limits the value of this cohort as validation set.

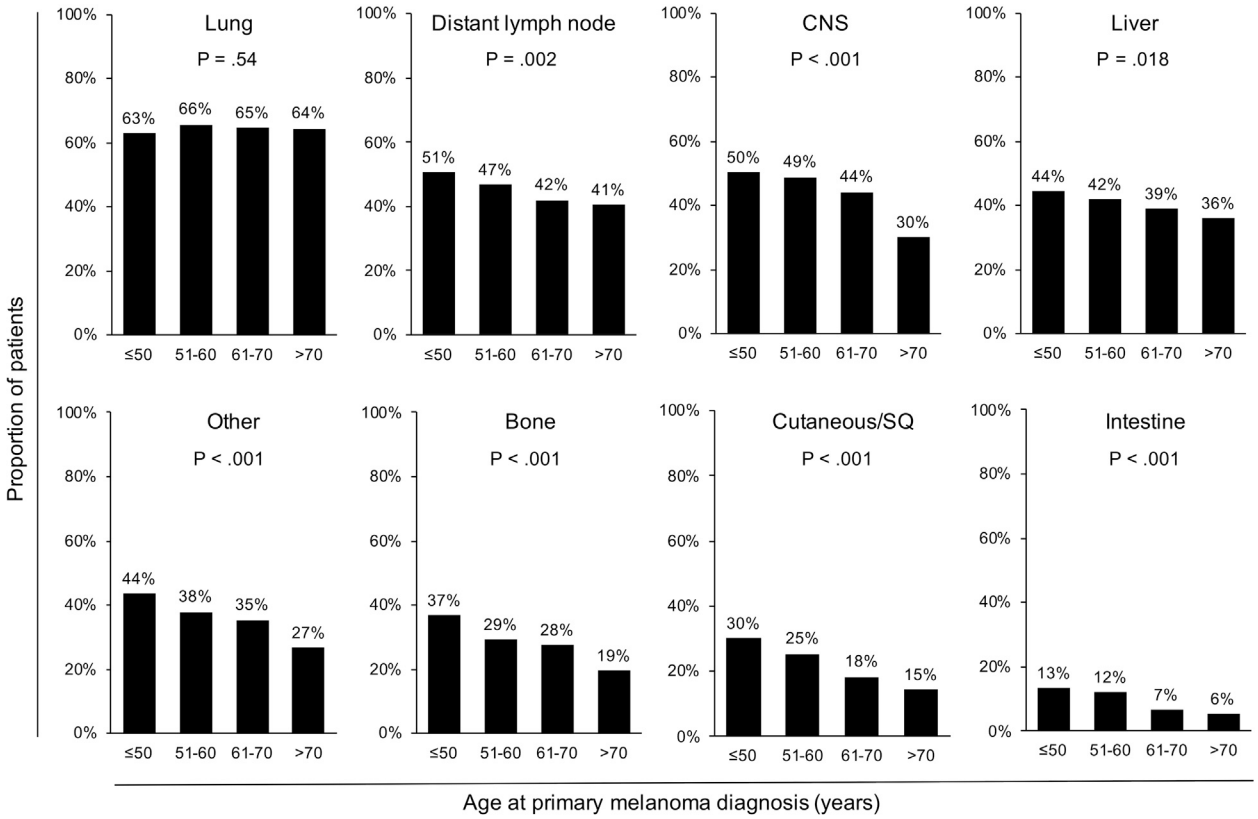

Fig 2. Age-dependent distribution of metastatic sites. The total number of patients was 1457. *P* values refer to results obtained with the Cochran-Armitage test. *CNS*, Central nervous system; *SQ*, subcutaneous.

Age-related changes in distant metastasis have also been found in previous reports. Two studies investigating the impact of age on outcomes with immunotherapy for patients with melanoma reported a higher rate of stage M1b disease (34% vs 13%) and a lower rate of stage M1c disease (53% vs 69%) in patients older than 65 years compared with in patients aged 65 years or younger (staging according to the seventh edition of the American Joint Committee on Cancer staging manual).[14] Moreover, brain metastases were reported in 29.8% of patients aged 50 years or younger but in only 14.9% of patients aged 75 years or older.[15]

This surprising association raises the question of how increasing age can protect from metastasis. In preclinical animal models, B16 melanoma cells formed smaller and less vascularized tumors in older mice than in younger mice[16] and the age-associated restrained tumor growth could be transferred into young mice by old-to-young bone marrow transplantation.[17] Bojovic and Crowe investigated the impact of aging on chemically induced squamous cell carcinoma formation and observed shorter tumor latency periods but fewer cervical lymph node metastases and a reduced intratumoral microvessel density in old mice compared with that in young mice.[18] The lower rate of distant metastases in elderly patients with melanoma may be explained by the failure of micrometastases to grow because of a lack of vascularization, a phenomenon that has been termed *angiogenic dormancy*.[5,19,20] Alternative reasons behind the decrease in distant metastases include different tumor metabolism and age-related changes in the host tissue, such as in the extracellular matrix and stromal cells.[21] The stable rate of lung metastasis in all age groups could be explained by vascular co-option (ie, the incorporation of preexisting vessels from surrounding tissue instead of utilization of angiogenesis). It has been shown recently that vessel co-option is common in human lung metastases and mediates resistance to antiangiogenic therapy in preclinical lung metastasis models.[22]

Another interesting finding of our study is the synchronized occurrence of distant metastases years after primary melanoma diagnosis. Experimental studies suggest that the reactivation of dormant cancer cells is governed by complex interactions

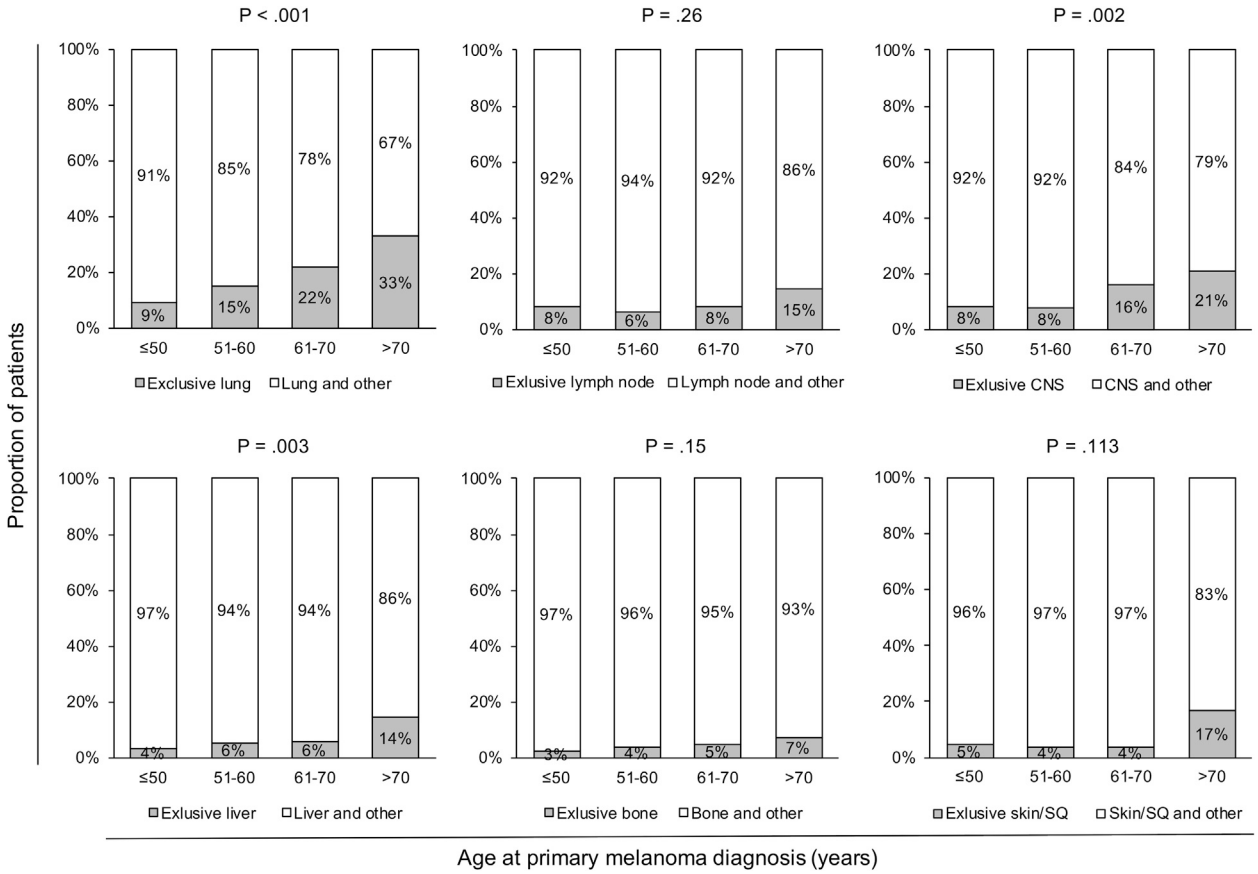

Fig 3. Distribution of metastases in a single site versus in multiple concomitant sites. The most common organ sites containing metastasis were stratified according to age categories. The total number of patients was 1457. *P* values refer to results obtained with the Cochran-Armitage test. *CNS*, Central nervous system; *SQ*, subcutaneous. Age at primary melanoma diagnosis (years)

between metastasis-initiating cells and the microenvironment of the target organ.[23] The occurrence of multiple, robustly growing metastases may be explained by the simultaneous reactivation of dormant tumor cells in response to niche signals, which are similar to those that affect normal adult stem cells.[23] For example, vitamin A—retinoic acid signaling controls hematopoietic stem cell dormancy via regulation of c-Myc.[24]

Although increasing age had been recognized as a negative prognostic factor for melanoma-specific survival in the past, this dogma seems to be challenged in the era of modern systemic therapies. In a multivariate Cox proportional hazards model of patients treated with B-Raf proto-oncogene, serine/threonine kinase and mitogen-activated protein kinase/ERK kinase inhibitors, older age was associated with an improved hazard ratio for progression-free survival and overall survival (for an increment of 10 years: 0.90 [95% CI, 0.83-0.97] and 0.89 [95% CI, 0.81-0.98], respectively).[25] Similarly, retrospective cohort studies of patients with melanoma treated with immunotherapy in a real-life setting found an equal or even better clinical outcome in elderly patients.[14,15,26] The exact reasons for these findings remain to be elucidated, but the lower number of metastatic sites and regulatory T cells in elderly patients could explain an improved response to immunotherapeutic agents and pharmacologic inhibition of the mitogen-activated protein kinase pathway.[26] Moreover, genetic analyses have shown that the tumor mutational burden increases with age and that a higher mutational load is associated with enhanced sensitivity to immune checkpoint inhibitors.[27]

Our findings have important clinical implications. First, the synchronized occurrence of distant metastasis in elderly patients enables an early assessment of the final disease stage and provides a good basis for decision making regarding treatment. Second, young patients almost invariably progress to stages M1c and M1d during their disease course independently of the initial manifestation in stage IV. Understanding these different progression patterns

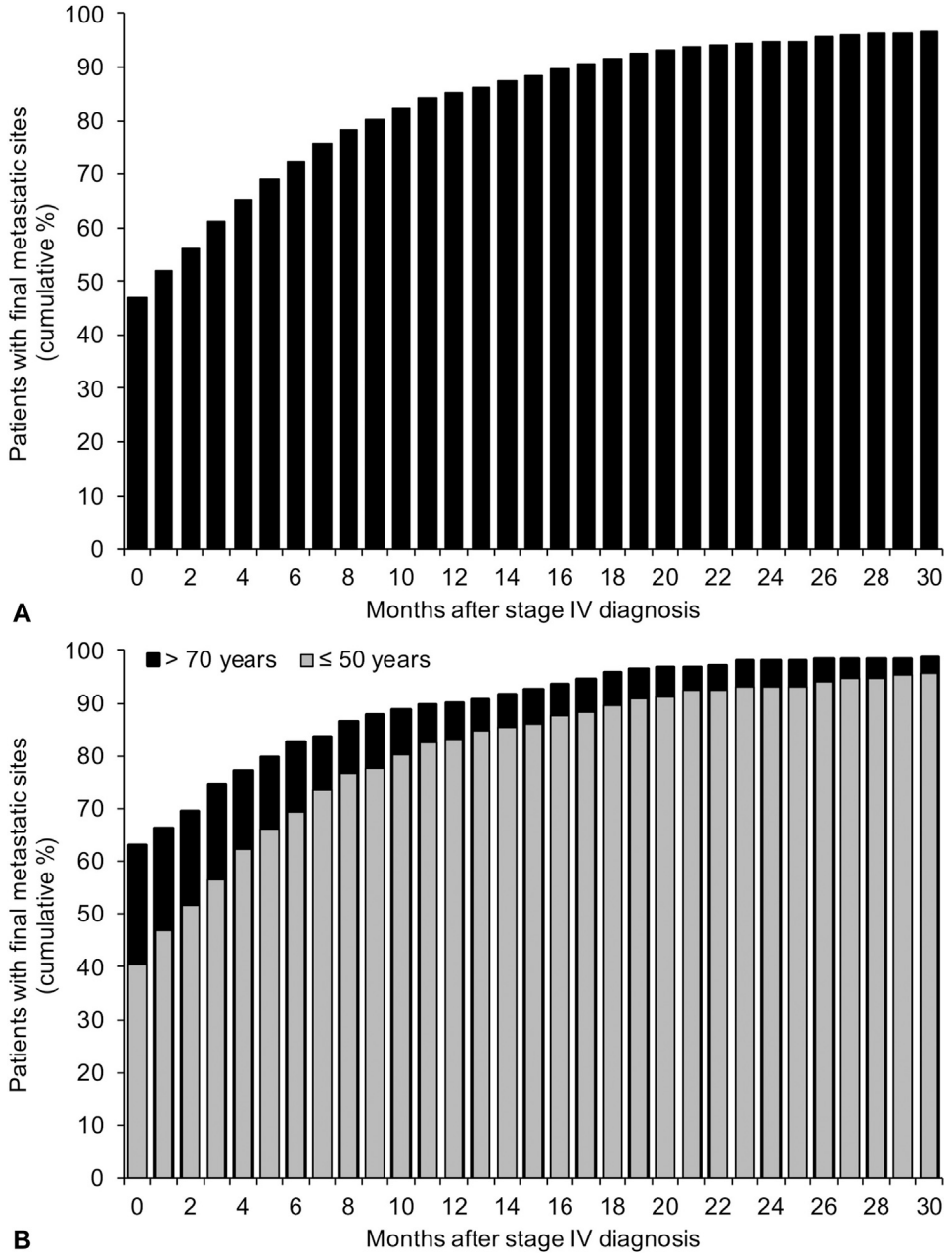

Fig 4. Time between development of the first and last organ site—containing metastasis. **A**, Total study population of the Tübingen cohort. Of the 1457 patients, 317 (21.8%) had only 1 metastatic site **B**, Comparison of patients older than 70 years and patients aged 50 years or younger. Of the 289 patients older than 70 years, 96 (33.2 %) had only 1 metastatic site, and of the 518 patients aged 50 years or younger, 85 (16.4 %) had only 1 metastatic site ($P < .001$, log-rank-test).

and the extent of distant disease may assist in choosing the best treatment options and optimizing outcomes of patients with melanoma. Third, the shift from stage M1d to M1b and a decreasing number of metastatic sites in elderly patients provides a rationale for choosing less aggressive treatment options in this subset of individuals. It has been shown that the utilization of systemic therapies in stage III and IV disease is markedly low in elderly patients with melanoma, and the availability of less intense and more effective therapies could help to overcome this disparity.[28]

The present study is not devoid of limitations. Elderly patients have a more limited life span than younger patients do, and this confounding factor inevitably contributes to shorter DMFS. Moreover,

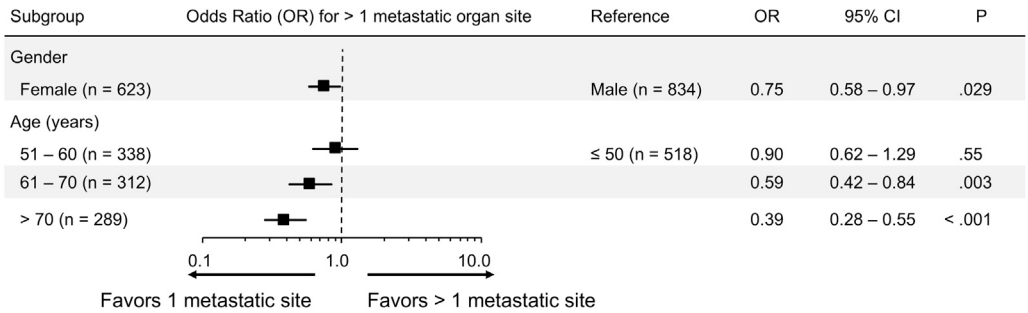

Fig 5. Factors prognostic for single or multiple metastatic sites. Results of a multivariate binary logistic regression analysis. The total number of patients was 1457. *CI*, Confidence interval; *OR*, odds ratio.

uncommon metastatic sites were summarized under the term *other metastasis* and not further discriminated in the registry data. This leads to a loss of information in a subset of the analyzed patients (37.1% [n = 541 of 1457]). Owing to the long study period, treatment schemes have changed over time, which may have affected progression patterns in general but not affected age-related patterns as much. Finally, the study is not population based, which limits generalization of our findings. On the other hand, the chosen study design provides excellent follow-up and detailed information about the disease course of the patients. Both aspects were prerequisites for the present study. Moreover, the study has been strengthened by the prospective documentation of follow-up examinations, by the validation of our findings thanks to use of a pooled cohort from 5 different institutions, and by the large sample size.

In conclusion, this study demonstrates that the pattern, timing, and extent of distant metastasis changes as people age. Elderly patients present with a lower number and prognostically more favorable metastatic sites. These findings may have clinical implications for the treatment of patients with melanoma of different ages.

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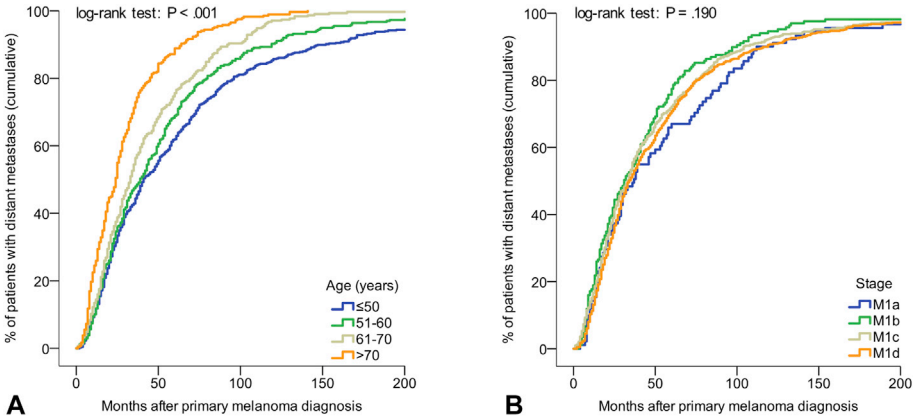
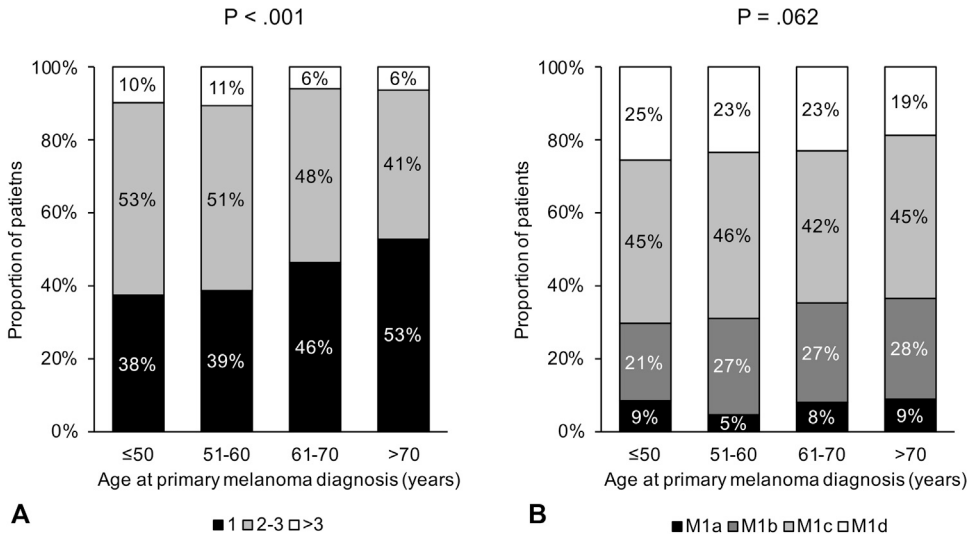
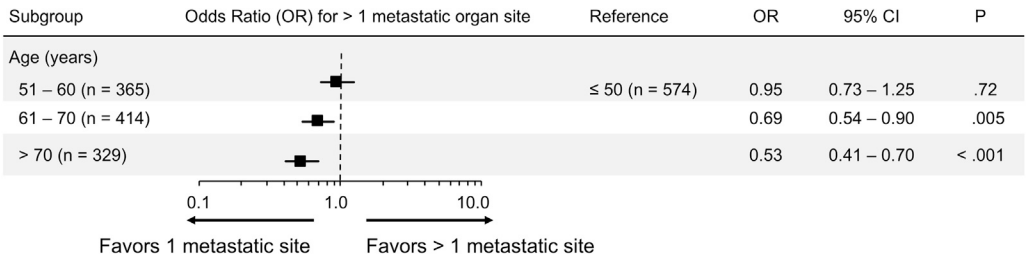


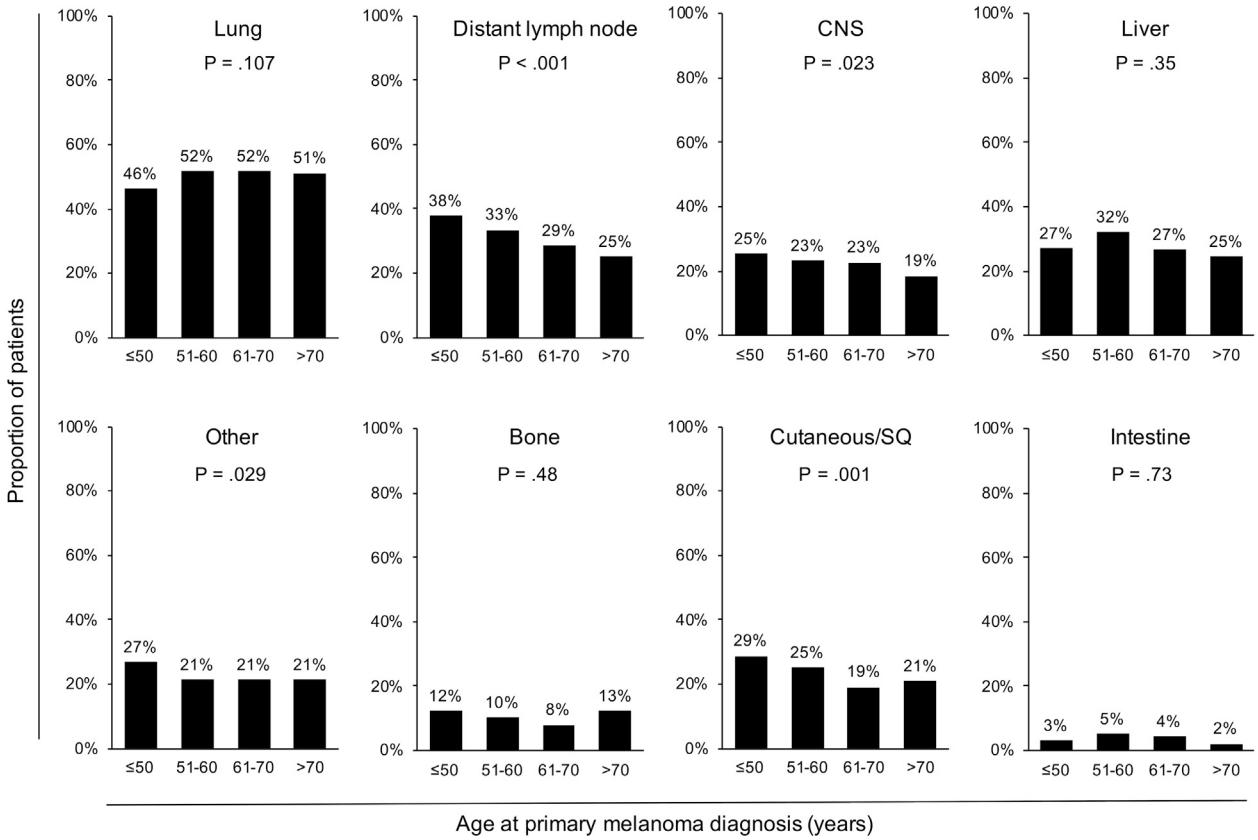
Supplemental Fig 1. Prognostic factors for distant metastasis–free survival in the Tübingen cohort. Kaplan-Meier curves for age at melanoma diagnosis (**A**) and M categories according to the eighth edition of the American Joint Committee on Cancer cancer staging manual (**B**). The total number of patients was 1457. M1a indicates distant metastasis to skin, soft tissue including muscle, and/or a nonregional lymph node. M1b indicates distant metastasis to lung with or without M1a sites of disease; M1c indicates distant metastasis to non–central nervous system visceral sites with or without M1a or M1b sites of disease; and M1d indicates distant metastasis to the central nervous system with or without M1a, M1b, or M1c sites of disease.



Supplemental Fig 2. Extent of distant metastasis in the pooled cohort. **A**, Number of organ sites containing metastasis. **B**, Distribution of M categories. *P* values refer to results obtained with the Pearson chi-square test. The total number of patients was 1682. M1a indicates distant metastasis to skin, soft tissue including muscle, and/or a nonregional lymph node; M1b indicates distant metastasis to lung with or without M1a sites of disease; M1c indicates distant metastasis to non—central nervous system visceral sites with or without M1a or M1b sites of disease; and M1d indicates distant metastasis to the central nervous system with or without M1a, M1b, or M1c sites of disease.



Supplemental Fig 3. Factors prognostic for single or multiple metastatic sites in the pooled cohort. Results of a binary logistic regression analysis. The total number of patients was 1682. *CI*, Confidence interval; *OR*, odds ratio.



Supplemental Fig 4. Age-dependent distribution of metastatic sites in the pooled cohort. *P* values refer results obtained with the Cochran-Armitage test. The total number of patients was 1682. *CNS*, *C*entral nervous system; *SQ*, subcutaneous.

Supplemental Table I. Patient and tumor characteristics for patients of the Tübingen cohort with 1 versus more than 1 metastatic site

Characteristic	1 metastatic site (n = 317)	>1 metastatic site (n = 1140)	*P* value
Sex			.035
Female	152 (47.9 %)	471 (41.3 %)	
Male	165 (52.1 %)	669 (58.7 %)	
Body site			.90
TANS	200 (63.1 %)	715 (62.7 %)	
Non-TANS	117 (36.9 %)	425 (37.3 %)	
Breslow thickness, mm			.80
≤1.00	59 (18.6 %)	196 (17.2 %)	
1.01-2.00	89 (28.1 %)	308 (27.0 %)	
2.01-4.00	98 (30.9 %)	385 (33.8 %)	
>4.00	71 (22.4 %)	251 (22.0 %)	
Histopathologic subtype*			.50
SSM	145 (45.9 %)	523 (45.9 %)	
NM	99 (31.3%)	343 (30.1 %)	
LMM	22 (7.0 %)	58 (5.1 %)	
ALM	24 (7.6 %)	93 (8.2 %)	
Others	26 (8.2 %)	123 (10.8 %)	
Ulceration†			.78
Yes	104 (33.1 %)	365 (32.3 %)	
No	210 (66.9 %)	766 (67.7 %)	
Age at melanoma diagnosis, y			<.001
≤50	85 (26.8 %)	433 (38.0 %)	
51-60	60 (18.9 %)	278 (24.4 %)	
61-70	76 (24.0 %)	236 (20.7 %)	
>70	96 (30.3 %)	193 (16.9 %)	

P values refer to results obtained with the Pearson chi-square test.
ALM, Acral lentiginous melanoma; *LMM*, lentigo maligna melanoma; *NM*, nodular melanoma; *SSM*, superficial spreading melanoma; *TANS*, thorax, upper arm, neck, scalp.
*Data missing for 1 patient.
†Data missing for 12 patients.

Supplemental Table II. Clinicopathologic characteristics of the pooled cohort (n = 1682)

Characteristic	n (% of total)
Sex	
Female	667 (39.7%)
Male	1015 (60.3%)
Body site	
TANS	1080 (64.2%)
Non-TANS	602 (35.8%)
Tumor thickness, mm	
≤1.00	233 (13.9%)
1.01-2.00	436 (25.9%)
2.01-4.00	535 (31.8%)
>4.00	478 (28.4%)
Median (IQR)	2.50 (1.50-4.50)
Histopathologic subtype	
SSM	653 (38.8%)
NM	556 (33.1%)
LMM	51 (3.0%)
ALM	108 (6.4%)
Others	51 (3.0%)
Unknown	263 (15.6%)
Ulceration	
Yes	583 (34.7%)
No	825 (49.0%)
Unknown	274 (16.3%)
Age at melanoma diagnosis (years)	
Median (IQR)	58 (45-68)
≤50	574 (34.1%)
51-60	365 (21.7%)
61-70	414 (24.6%)
>70	329 (19.6%)
Distant metastasis	
Lung	836 (49.7%)
Distant nodes	540 (32.1%)
CNS	386 (22.9%)
Liver	464 (27.6%)
Bone	183 (10.9%)
Skin and subcutaneous tissue	405 (24.1%)
Intestine	61 (3.6%)
Others	391 (23.2%)
Staging (AJCC eighth edition)	
M1a	128 (7.6%)
M1b	422 (25.1%)
M1c	746 (44.4%)
M1d	386 (22.9%)

M1a indicates distant metastasis to skin, soft tissue including muscle, and/or a nonregional lymph node; M1b indicates distant metastasis to lung with or without M1a sites of disease; M1c indicates distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease; and M1d indicates distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease.

AJCC, American Joint Committee on Cancer; *ALM*, Acral lentiginous melanoma; *CNS*, central nervous system; *IQR*, interquartile range; *LMM*, lentigo maligna melanoma; *NM*, nodular melanoma; *SQ*, subcutaneous; *SSM*, superficial spreading melanoma, *TANS*, thorax, upper arm, neck, scalp.

Supplemental Table III. Patient and tumor characteristics for patients of the pooled cohort with 1 versus more than 1 metastatic site

Characteristic	1 metastatic site (n = 722)	>1 metastatic site (n = 960)	*P* value
Sex			.82
Female	284 (39.3 %)	383 (39.9 %)	
Male	438 (60.7 %)	577 (60.1 %)	
Body site			.71
TANS	460 (63.7 %)	620 (64.6 %)	
Non-TANS	262 (36.3 %)	340 (35.4 %)	
Breslow thickness, mm			.26
≤1.00	93 (12.9 %)	140 (14.6 %)	
1.01-2.00	182 (25.2 %)	254 (26.5 %)	
2.01-4.00	248 (34.3 %)	287 (29.9 %)	
>4.00	199 (27.6 %)	279 (29.1 %)	
Histopathologic subtype*			.093
SSM	256 (42.3 %)	397 (48.8 %)	
NM	251 (41.5%)	305 (37.5 %)	
LMM	27 (4.5 %)	24 (2.9 %)	
ALM	51 (8.4 %)	57 (7.0 %)	
Other	20 (3.3 %)	31 (3.8 %)	
Ulceration†			.43
Yes	266 (42.6 %)	317 (40.5 %)	
No	359 (57.4 %)	766 (59.5 %)	
Age at melanoma diagnosis, y			<.001
≤50	215 (29.8 %)	359 (37.4 %)	
51-60	141 (19.5 %)	224 (23.3 %)	
61-70	192 (26.6 %)	222 (23.1 %)	
>70	174 (24.1 %)	155 (16.1 %)	

P values refer to results obtained with the Pearson chi-square test. *ALM*, acral lentiginous melanoma; *LMM*, lentigo maligna melanoma; *NM*, nodular melanoma; *SSM*, superficial spreading melanoma; *TANS*, thorax, upper arm, neck, scalp.

*Data missing for 263 patients.

†Data missing for 274 patients.