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ORIGINAL ARTICLE – MELANOMAS

Older Age is Associated with a Higher Incidence of Melanoma Death but a Lower Incidence of Sentinel Lymph Node Metastasis in the SEER Databases (2003–2011)

Margaret W. Cavanaugh-Hussey, MD, MPH[1], Euphemia W. Mu, MD[2], Sewon Kang, MD, MPH[3], Charles M. Balch, MD[4], and Timothy Wang, MD[3]

[1]Department of Dermatology, Brigham and Women's Hospital, Boston, MA; [2]Department of Dermatology, New York University, New York, NY; [3]Department of Dermatology, Johns Hopkins Medical Institutions, Baltimore, MD; [4]Division of Surgical Oncology, University of Texas Southwestern Medical Center, Dallas, TX

ABSTRACT

Purpose. Elderly melanoma patients are known to have lower survival rates than younger patients with melanoma. Paradoxically, a few recent studies have shown a lower frequency of sentinel lymph node (SLN) positivity in older individuals. This is the first analysis of a large national sample to examine the relationship between SLN metastasis and melanoma death across all age groups.

Methods. The U.S. Surveillance Epidemiology and End Results (SEER) Databases were queried to examine SLN biopsy and mortality outcomes in 158,813 melanoma cases reported from 2003 to 2011, the most current data available in SEER.

Results. In bivariate analyses of the 47,577 cases with coded tumor depths and nodal surgery, increasing age varied directly with melanoma death and inversely with SLN positivity, for tumor depths >1 mm ($P < 0.001$). In multivariate regression analyses, 60–79 year-olds were more likely to die of melanoma compared with 20–39 year-olds [odds ratio (OR) 1.83, 95 % confidence interval (CI) 1.64–2.05], but they were less likely to be SLN-positive (OR 0.62, 95 % CI 0.57–0.68). The inverse association between melanoma mortality and SLN positivity was most pronounced at the extremes of age.

Discussion. The finding that increasing age is associated with a higher incidence of melanoma death but a lower incidence of SLN metastasis highlights the need for further study into age-related differences in melanoma biology, immunological surveillance, and host response. It also questions whether the 5- and 10-year survival rates associated with the current melanoma staging system should be stratified by age to predict outcomes more accurately for melanoma patients.

Age is known to be an important predictor of melanoma mortality. Several studies have shown that elderly melanoma patients have worse survival outcomes than younger patients with melanoma, regardless of the clinical and histological characteristics of the primary tumor.[1–6] Not only has age been shown to be an independent prognostic factor with respect to melanoma survival, but a consistent decline in survival is seen with each increasing decade of life.[2]

Whereas older patients are more likely to die of melanoma, a few studies have counter-intuitively shown a lower frequency of sentinel lymph node (SLN) positivity in the elderly.[7–11] In a single-institution analysis utilizing a prospective database of >1100 patients at the University of Michigan, the odds ratio for SLN positivity declined with each decade of advancing age.[9] In this sample, it was estimated that a 20-year-old patient had a threefold higher risk of SLN positivity than a 50-year-old, when all other clinical and histological variables were controlled. This finding was supported in the multi-institutional Sunbelt Melanoma Trial, involving >3000 patients. In this population, SLN metastases were almost twice as frequent in patients who were <30 years of age than in patients >60 years of age (23.1 vs. 12 %).[7]

More recently, Balch et al. had similar findings using a cohort of 7756 melanoma patients undergoing SLN biopsy

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M. W. Cavanaugh-Hussey, MD, MPH
e-mail: mcavanaugh-hussey@partners.org

from the expanded American Joint Committee on Cancer melanoma staging database. The authors found that although older patients had primary melanomas with features associated with more aggressive biology, there was a significant decrease in the incidence of SLN positivity with increasing patient age. The incidence of SLN metastasis was 25.8 % for patients younger than 20 years compared with 15.5 % in patients >80 years of age.[12]

The paradox of decreased SLN involvement and increased mortality in the elderly is important to explore further, because the 5- and 10-year survival rates associated with the current melanoma staging system are influenced significantly by the presence or absence of nodal disease. The prognostic capacity of the system is limited if both an elderly patient and a young patient are assigned the same stage of melanoma, but the elderly patient is more likely to die from the disease. In addition, the paradox raises interesting questions about age-related differences in melanoma biology and host response that need to be further examined.

The public health implications of age-related differences in melanoma outcomes are far reaching. The number of people in the United States who are aged 65 or older is expected to increase from 35 million to 86.7 million between 2000 and 2050.[13] Men have a 1 in 157 probability of being diagnosed with melanoma between the ages of 40 and 59, whereas they have a 1 in 54 probability of being diagnosed with melanoma from age 70 years to the end of life. For women, the probabilities of being diagnosed with melanoma are 1 in 181 and 1 in 123, for the same respective age intervals.[14] The finding that older individuals are more likely to die of melanoma, regardless of nodal involvement, will have increasing sociologic and economic impact in the years to come.

To date, no large population-based study has compared SLN positivity and melanoma mortality across all age groups. For the present study, the most current data available through the Surveillance Epidemiology and End Results (SEER) Databases was systematically analyzed to assess the effect of age on nodal involvement and melanoma death. This large pool of melanoma data provides important, current information to better characterize age-related differences in melanoma outcomes.

MATERIALS AND METHODS

Database

The US Surveillance Epidemiology And End Results (SEER) Databases were queried to examine the most recent melanoma data on file, cases from 2003 to 2011. Organized by the National Cancer Institute (NCI) in 1973, SEER contains data on the prevalence, incidence, and survival of every case of cancer recorded from 20 tumor registries in the United States. These databases represent approximately 28 % of the United States population.[15] This study analyzed cases diagnosed in and after 2003, the years for which lymph node procedures were most accurately and consistently coded.

Case Identification

SEER*Stat Version 8.1.5 (National Cancer Institute, Bethesda, MD) was used to identify all patients diagnosed with invasive melanoma based on the International Classification of Diseases for Oncology, Third Edition melanoma codes (M8720-8790). The coding for melanoma was designated by pathologists and excluded melanocytic tumors of uncertain malignant potential (MelTUMPs), atypical Spitz nevi, and severely atypical melanocytic tumors. Data extracted on each case include age, gender, year of diagnosis, extent of disease, tumor thickness, ulceration, primary site, histology, race, survival in months, vital status, scope of regional lymph node surgery, and lymph node positivity.

Lymph Node Procedure

In SEER, the regional lymph node surgery variable (code 2003+) documents both SLN biopsies and complete lymph node dissections (CLNDs). The regional node positive variable (code 1988+) records evidence of positive lymph node metastasis from regional lymph node procedures. Data from 1973 to 2002 were omitted from this study, because CLNDs replaced codes of SLN biopsies prior to 2003.

Analysis

Further analysis of extracted cases and associated data was conducted in Intercooled Stata 11.0 for Mac (Stata Corp, College Station, TX). Baseline characteristics were compared by the χ^2 test or ANOVA for categorical variables and Student's t test for continuous variables. Age categories were divided by 20-year intervals (<20, 20–39, 40–59 years, 60–79, 80+ years). Controlling for tumor depth, prevalence rates of sentinel lymph node involvement and melanoma death were assessed for all age groups. Only patients who had sentinel lymph node procedures performed and coded tumor depths were included in the analysis. The associations between age, nodal status, and melanoma mortality were then estimated using linear logistic regression analyses, controlling for tumor depth, ulceration, primary tumor site, histological subtype, and lymph node surgery.

RESULTS

There were 158,813 cases of melanoma recorded in the SEER Databases from 2003 to 2011. The median time of follow-up for all patients was 45 months.

Patient Characteristics

Baseline characteristics of the sample population are provided in Table 1. Of the 158,813 melanoma cases, 67,267 (42.4 %) were reported in females and 91,546 (57.6 %) were reported in males. Females were more frequently represented in the <40-year-old demographic (62.7 %, $P < 0.001$), whereas males were more commonly represented in the ≥40-year-old demographic (60.4 %, $P < 0.001$). A total of 149,722 (94.4 %) patients self-identified as Caucasian.

Disease Characteristics

Among cases with coded histological subtype, superficial spreading melanomas were most common (45,080 cases, 60.2 %). Coded cases of nodular melanomas were more common in patients aged ≥60 years (6642 cases, 8.8 %) than in patients aged <60 years (3853 cases, 5.1 %; $P < 0.001$). The incidence of histological ulceration was higher in patients aged ≥60 years (12.8 %) than in patients aged <60 years (7.8 %; $P < 0.001$). Compared with younger patients, individuals aged ≥60 years more frequently presented with melanoma of the face, head, and neck (27 vs. 13 %, $P < 0.001$).

Disease Extent and Mortality

Individuals younger than aged 20 years had a higher incidence of regional lymph node involvement than patients aged ≥20 years (16.6 vs. 9.2 %, $P < 0.001$). However, distant metastases were more common in patients aged ≥20 years (4.2 %) than in patients aged <20 years (2.5 %; $P < 0.001$). Sentinel lymph node biopsy and complete lymph node dissection were more frequently reported in patients aged <20 years (34.8 and 11.3 %, respectively) than in patients aged >20 years (23.4 and 7.3 %; $P < 0.001$). Overall, death from melanoma was more prevalent in patients aged >60 years (8420 deaths; 10.0 % of patients) than in patients aged <60 years (4322 deaths; 5.9 % of patients; $P < 0.001$).

Tumor Thickness Subset Analysis

To explore differences in sentinel lymph node involvement and melanoma mortality by age, we systematically evaluated subsets of patients according to histological tumor thickness. Only the 47,577 patients who had sentinel lymph node biopsies performed with coded tumor depths were included in the analysis. For tumor thickness subsets >1 mm—the thickness parameter for which sentinel lymph node procedures are recommended—younger patients were more likely than older patients to have positive regional lymph nodes ($P < 0.001$; Table 2). This was an inverse association across each incremental age group (Fig. 1a). For each thickness subset, however, older patients were more likely than younger patients to die of melanoma ($P < 0.001$; Table 3). This was a positive association across each incremental age group (Fig. 1b).

Multivariate Regression Analysis

Controlling for tumor thickness, ulceration, primary tumor site, and histological subtype, patients were less likely to have positive sentinel lymph nodes with each increasing age category. At the age extremes, the odds of someone aged >80 years having a positive sentinel node was 0.38 that of someone aged 0–20 years [95 % confidence interval (CI) 0.26–0.54]. However, when controlling for the above variables, in addition to lymph node surgery, age varied positively with melanoma death. In this case, the odds of someone aged >80 years dying of melanoma was 6.60 that of someone aged 0–20 years (95 % CI 3.44–12.69).

The inverse correlation between melanoma death and SLN metastasis was seen not only at the extremes of age (Fig. 2). When using patients aged 20–39 years as a referent, 60–79 years olds were more likely to die of melanoma [odds ratio (OR) 1.83, 95 % CI 1.64–2.05]. Yet, patients aged 60–79 years were less likely to be node-positive compared with 20–39 years olds (OR 0.62, 95 % CI 0.57–0.68).

DISCUSSION

In this large national sample, older patients had a higher incidence of melanoma death compared with younger individuals, despite a lower incidence of sentinel lymph node metastasis. Our findings in the SEER Databases support previous hypotheses that melanoma behaves differently in individuals as they age.[5,16,17]

Although age is known to be an important predictor of melanoma outcomes, it is not included in our current staging system for melanoma, which was most recently revised by the American Joint Committee on Cancer (AJCC) in 2010. The current tumor, node, and metastasis (TNM) staging system has significant predictive capabilities for patient prognosis and survival.[18] However, our analysis raises the question as to whether the survival rates

TABLE 1 Characteristics of all patients with invasive melanoma in the SEER databases: 2003–2011

	Age <20 years (n = 1046)		20–39 years (n = 17,726)		40–59 years (n = 54,576)		60–79 years (n = 62,363)		80+ years (n = 23,102)		P*
	No.	%	No.	%	No.	%	No.	%	No.	%	
Extent of disease											<0.001
Localized	799	76	15,347	87	46,237	85	51,076	82	17,853	77	
Regional	174	17	1369	8	4580	8	5792	9	2821	12	
Distant	26	3	412	2	1979	4	3068	5	1140	5	
Unstaged	47	4	598	3	1780	3	2427	4	1288	6	
Gender											<0.001
Female	607	58	11,161	63	25,452	47	21,316	34	8731	38	
Male	439	42	6565	37	29,124	53	41,047	66	14,371	62	
Race/ethnicity											<0.001
White	959	92	16,315	92	51,010	93	59,305	95	22,133	96	
Black	12	1	89	1	234	1	341	1	139	1	
Other	27	2	187	1	442	1	503	1	170	1	
Unknown	48	5	1135	6	2890	5	2214	4	660	3	
Histology											<0.001
Superficial spreading	324	31	6797	38	17,962	32	15,724	25	4273	19	
Nodular	60	6	815	5	2978	5	4251	7	2391	10	
Other	103	10	912	5	4569	8	9326	15	4341	19	
NOS	559	53	9202	52	29,067	53	33,062	53	12,097	52	
Thickness (mm)											
Median (IQR)	1.4 (0.4–1.5)		0.9 (0.3–0.9)		1.0 (0.3–1.0)		1.2 (0.3–1.3)		1.7 (0.4–2.1)		
<1.01	590	56	12,750	72	37,244	68	38,869	62	11,659	50	<0.001
1.01–2	154	15	2135	12	7052	13	8248	13	3200	14	
2.01–4	100	10	907	5	3344	6	5064	8	2804	12	
>4 mm	73	7	507	3	2069	4	3534	6	2428	11	
Unknown	129	12	1427	8	4867	9	6648	11	3011	13	
Ulceration											<0.001
No ulceration	733	70	13,386	76	40,285	74	44,048	71	14,585	63	
Ulcerated	82	8	1127	6	4487	8	6788	11	4136	17	
Unknown	231	22	3213	18	9804	18	11,527	18	4381	19	
Primary site											<0.001
Extremities	410	39	8166	46	24,928	46	24,075	40	8392	36	
Torso	370	35	6863	39	29,023	37	18,858	30	4728	20	
Face, head, neck	230	22	2143	12	7287	13	14,784	24	8274	36	
Other	36	3	554	3	2338	4	3646	6	1708	7	
Treatment											<0.001
No LN surgery	543	52	11,477	65	35,146	64	41,644	67	17,754	77	
SLN biopsy only	364	34	4598	26	14,197	26	14,723	24	3446	15	
LN dissection	118	11	1349	8	4263	8	4713	8	1228	5	
Unknown	21	2	302	2	970	2	1283	2	674	3	
Vital status											<0.001
Alive	996	95	16,838	95	49,486	91	50,052	80	12,774	55	
Melanoma deaths	42	4	723	4	3557	6	5655	9	2765	12	
Other deaths	8	1	165	1	1533	3	6656	10	7563	33	

IQR interquartile range

* Groups compared by the χ^2 test except for continuous variables

TABLE 2 Depth-for-depth analyses of nodal status for all age categories: 2003–2011

Thickness (mm)	Age <20 years (n = 458)		20–39 years (n = 5782)		40–59 years (n = 17,880)		60–79 years (n = 18,836)		80+ years (n = 4621)		P*
	No.	%	No.	%	No.	%	No.	%	No.	%	
<1.01											<0.001
LN negative	126	76	2429	87	6477	85	5473	83	894	76	
LN positive	25	15	223	8	663	9	590	9	143	12	
Unknown	15	9	147	5	491	6	508	8	148	12	
1.01–2 mm											<0.001
LN negative	99	72	1438	80	4823	83	5142	85	1094	85	
LN positive	36	26	319	18	846	15	709	12	134	10	
Unknown	3	2	33	2	154	3	187	3	54	5	
2.01–4 mm											<0.001
LN negative	50	56	452	59	1847	66	2820	74	941	78	
LN positive	38	43	310	40	898	32	875	23	218	18	
Unknown	1	1	11	1	62	2	104	3	45	4	
>4 mm											<0.001
LN negative	25	38	168	40	809	50	1468	61	572	60	
LN positive	38	59	230	55	742	46	880	36	319	34	
Unknown	2	3	22	5	68	4	80	3	59	6	

Sample size includes all patients undergoing lymph node surgery with coded tumor depths

* Groups compared by the χ^2 test

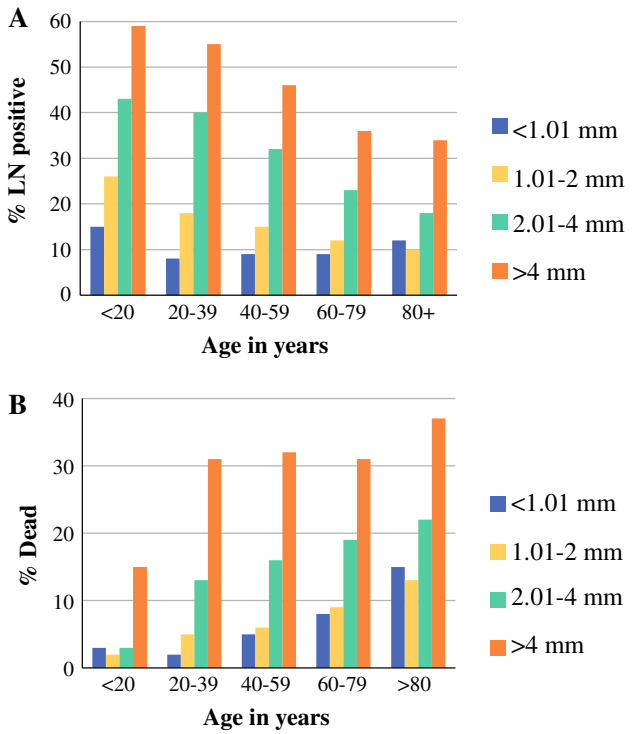

FIG. 1 **a** Lymph node positivity by tumor thickness and age. **b** Mortality due to melanoma by tumor thickness and age

associated with the AJCC staging system should be stratified by age to more accurately estimate melanoma outcomes, similar to some current electronic prediction tools which estimate individualized 5- and 10-year survival rates for localized melanoma.[18,19] Accurate prediction of melanoma prognosis is essential, because it weighs heavily on the decisions physicians make with their patients regarding plans for treatment and clinical follow-up.

Our understanding of the mechanisms underlying melanoma heterogeneity by age is limited. It is still unclear whether age differences in melanoma death and lymph node metastasis are due to the biology of the tumor itself or variations in host response over time. With advancing age, matrix degrading metalloproteinase levels are markedly elevated in human skin.[20] Such an alteration in the skin of an older host may facilitate local tumor invasion and even distant metastases of primary melanomas. In addition, elderly patients have decreased immunologic function compared with younger individuals. Some authors support that there are age-related changes to immunologic surveillance, including decreased lymphatic flow to nodes and/or nodal involution.[21–23] Others hypothesize that SLN biopsies may detect a greater proportion of micrometastases, which younger, more competent immune systems can eliminate before they develop clinical significance.[7] Alternatively, some authors suggest that there is a decreased uptake of radioactive dye with age, which makes falsely negative SLN biopsies more likely in the elderly.[24]

In addition, while our findings in SEER support that differences in melanoma outcomes are most pronounced at the extremes of age, there are inherent limitations when

TABLE 3 Depth-for-depth analyses of mortality due to melanoma for all age categories: 2003–2011

Thickness (mm)	Age <20 years (n = 455)		20–39 years (n = 5724)		40–59 years (n = 17,373)		60–79 years (n = 18,107)		80+ years (n = 3442)		P*
	No.	%	No.	%	No.	%	No.	%	No.	%	
<1.01											<0.001
Alive	160	97	2716	98	7102	95	5578	92	739	85	
Dead	5	3	70	2	361	5	470	8	132	15	
1.01–2 mm											<0.001
Alive	134	98	1693	95	5372	94	5042	91	841	87	
Dead	3	2	85	5	315	6	484	9	129	13	
2.01–4 mm											<0.001
Alive	85	97	651	87	2265	84	3547	81	696	78	
Dead	3	3	100	13	444	16	827	19	201	22	
>4 mm											<0.001
Alive	55	85	284	69	1028	68	1484	69	457	65	
Dead	10	15	125	31	486	32	675	31	247	35	

Sample size includes patients who underwent lymph node surgery with coded tumor depth and melanoma-specific mortality

* Groups compared by the χ^2 test. $P < 0.001$ for comparison by two-sided t test of patients aged <20 years and patients aged >80 years

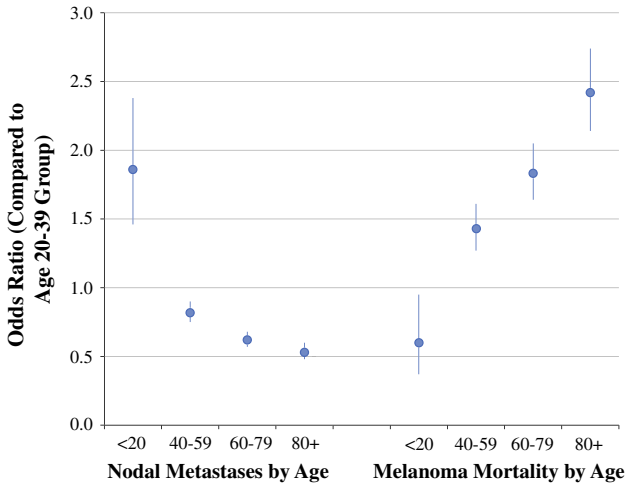

FIG. 2 Odds ratios for sentinel lymph node metastases and mortality due to melanoma in patients diagnosed with malignant melanoma from 2003 to 2011. Model controls for tumor thickness, ulceration, primary tumor site, and histological subtype. Reference group 20–39 years olds

analyzing these groups, including a smaller number of patients in the <20 year-old and 80+ year-old subsets, the likely inclusion of tumors with less aggressive behavior in the younger population (e.g., Spitz tumors and MelTUMPs) and competing mortality in the elderly. Furthermore, the incidence of lymph node surgery (SLN biopsy and/or nodal dissection) decreases with age (45 % of <20 year-old group, 34 % of 20–39 year-old group, 34 % of 40–59 year-old group, 32 % of 60–79 year-old group, and 20 % of 80+ year-old group). Not only are older patients disproportionately excluded from the analysis of SLN involvement, but differences in rates of lymph node procedures may affect treatment decisions and melanoma mortality at the extremes of age.

Additional research is needed to explore age-related differences in melanoma biology, immunological surveillance, and host response. In addition, other confounding factors need to be studied, such as limited physiologic reserve in the elderly, poorer access to care, and potential physician inclination towards fewer aggressive treatment interventions.[16]

In comparing rates of lymph node involvement and melanoma survival across age groups, the SEER Databases provide a large sample of uniformly collected data, which is largely representative of melanoma cases across the United States. The 2003–2011 data were selected in this study, because 2003 marks the year in which the histological features of melanoma and lymph node status for individual cases were more consistently and completely coded. However, there remain a number of cases with uncoded variables, which limits validity. Some other potential limitations in SEER data include: (1) lack of information on chemotherapy and other adjuvant treatments for melanoma, (2) lack of central histological review, and (3) lack of information on comorbidities.[25] Studies with more robust coded data and >45-month follow-up are needed to determine the lifelong risk of melanoma mortality, particularly for the young, who may be at risk for late events.

These noted limitations in SEER are common to most large epidemiological databanks, and they have been well addressed in the literature. Despite its limitations, SEER remains a valuable resource of population-based data for analyzing patterns and trends in patient characteristics, cancer treatments, and outcomes.[26,27]

CONCLUSIONS

Older patients in the SEER Databases have higher rates of melanoma death than younger patients, but they are less likely to have positive sentinel lymph nodes. This paradoxical association is seen across each incremental age group, even when controlling for relevant clinical and histological features. This population-based study highlights the need for further investigation into age-related differences in melanoma biology and host response. It also raises the question about whether the 5- and 10-year survival rates associated with the melanoma staging should be age stratified to estimate melanoma prognosis more accurately.

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CONFLICT OF INTEREST All authors disclose no conflict of interest.

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