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Elderly Age Is Associated With More Conservative Treatment of Invasive Melanoma

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Abstract. *Background/Aim: Competing mortality risks complicate treatment of elderly melanoma patients potentially leading to conservative management, including no sentinel lymph node biopsy. As systemic immunotherapy offers justification for nodal evaluation, we examined treatment trends among elderly melanoma patients. Patients and Methods: We performed a National Cancer Database analysis of melanoma patients from 2004-2015. Patients were categorized by age (elderly ≥80-years-old). Multivariable logistic regression analyses were performed comparing characteristics and treatment by age. Results: Of 187,814 patients, 2.7% were 1-25, 11.6% were 26-40, 46.6% were 41-64, 28.8% were 65-79, and 10.3% were ≥80-years-old with clinicopathologic and treatment differences between age cohorts. Nodal surgery was least common among elderly patients (43.1% vs. 60.7-69.8%, p<0.0001). For stage III, immunotherapy was least common among the elderly (p<0.0001), but associated with greater survival (HR=0.52, 95%CI=0.32-0.84, p=0.008). Conclusion: Elderly melanoma patients were often treated conservatively, including no nodal evaluation, concerning for the potential undertreatment of this population.*

Treatment approaches for melanoma are rapidly changing with the advent of targeted systemic therapies, immunotherapies, and developments from clinical trials comparing approaches for nodal disease (1-3). This is of particular interest to the elderly, where melanoma is common and often present with advanced disease. Incidence rates of melanoma have been consistently increasing annually in older individuals, and in particular for men ≥85 years of age (4). Elderly patients frequently present with thick, ulcerated tumors with high mitotic activity (5, 6). Recent clinical trials have shown the benefits of systemic and regional immunotherapies in older adults and the elderly for metastatic and unresectable disease and in the adjuvant setting (3, 7, 8). Perier-Muzet *et al.* have shown improved progression-free survival in older patients (>65 years) treated with checkpoint inhibitor immunotherapy compared to younger cohorts (9). Despite the potential benefits of systemic therapies, patient comorbidities, frailty, and competing mortality risks complicate therapeutic decision-making in the elderly, potentially leading to less aggressive interventions in an effort to reduce morbidity and preserve patient quality of life (5, 10).

In light of the changing paradigms for the treatment of melanoma and the scarcity of research evaluating the application of current treatment guidelines in elderly patients, we sought to evaluate current trends in the management of melanoma among the elderly using the National Cancer Database (NCDB). As multimodal therapeutic approaches are recommended among stage III patients (1), we examined the implementation of multimodal therapy by age and clinicopathologic and treatment factors associated with improved survival among elderly patients (≥80 years old) with stage III disease.

Patients and Methods

We performed a retrospective analysis of 187,814 cutaneous melanoma patients using the NCDB between the years 2004-2015. The NCDB, a joint project by the American College of Surgeons and the American Cancer Society, collects data from all cancer patients seen at Commission on Cancer (COC) sites, capturing approximately 70% of all newly diagnosed cancer patients in the United States (11-13). As patient information was de-identified, the study protocol was exempt from the University of California, Davis Institutional Review Board approval.

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Key Words: Sentinel lymph node biopsy (SLNB), lymphadenectomy, immunotherapy, radiation, chemotherapy.

Table I. *Select patient demographics and clinicopathologic characteristics by age.*

	Age Cohort (Years) (N=187,814)										
	Pediatric & AYA 1-25 N=5084		Early adult 26-40 N=21,857		Middle adult 41-64 N=87,494		Older adult 65-79 N=54,116		Elderly ≥80 N=19,263		
	N	%	N	%	N	%	N	%	N	%	*p*-Value
Female Gender	3,361	66.1%	13,033	59.6%	38,584	44.1%	19,383	35.8%	8,094	42.0%	<0.0001
Race											
Caucasian	4,893	96.2%	21,147	96.8%	85,075	97.2%	52,749	97.5%	18,793	97.6%	<0.0001
Black	45	0.9%	131	0.6%	515	0.6%	384	0.7%	147	0.8%	
Asian/Pacific Islander	31	0.6%	115	0.5%	288	0.3%	165	0.3%	61	0.3%	
Other	115	2.3%	464	2.1%	1,616	1.9%	818	1.5%	262	1.4%	
Charlson comorbidity index											
0	4,875	95.9%	20,842	95.4 %	78,453	89.7%	43,769	80.9%	15,218	79.0%	<0.0001
1	199	3.9%	938	4.3%	7,755	8.9%	8,332	15.4%	3,101	16.1%	
≥2	10	0.2%	77	0.3%	1,286	1.5%	2,015	3.8%	944	4.9%	
Income											
<$38,000	577	11.4%	2,413	11.0%	9,252	10.6%	6,572	12.1%	2,361	12.3%	<0.0001
$38,000-47,999	1,015	20.0%	4,462	20.4%	17,378	19.9%	11,709	21.6%	4,240	22.0%	
$48,000-62,999	1,404	27.6%	6,216	28.4%	23,757	27.2%	14,795	27.3%	5,294	27.5%	
≥$68,000	2,051	40.3%	8,631	39.5%	36,523	41.7%	20,628	38.1%	7,161	37.2%	
Unknown	37	0.7%	135	0.6%	584	0.7%	412	0.8%	207	1.1%	
Urban/Rural											
Metro	4,209	82.8%	18,040	82.5%	71,075	81.2%	43,150	79.7%	15,704	81.5%	<0.0001
Urban	649	12.8%	2,862	13.1%	12,213	14.0%	8,025	14.8%	2,508	13.0%	
Rural	77	1.5%	304	1.4%	1,483	1.7%	1,137	2.1%	352	1.8%	
Unknown	149	2.9%	651	3.0%	2,723	3.1%	1,804	3.3%	699	3.6%	
Insurance status											
Uninsured	253	5.0%	1,154	5.3%	3,735	4.3%	289	0.5%	66	0.3%	<0.0001
Private	4,130	81.2%	18,118	82.9%	72,428	82.8%	8,665	16.0%	1,645	8.5%	
Government	573	11.3%	2,138	9.8%	9,644	11.0%	44,235	81.7%	17,226	89.4%	
Unknown	128	2.5%	447	2.1%	1,687	1.9%	927	1.7%	326	1.7%	
Histology											
Superficial spreading	1,720	33.8%	8,643	39.5%	30,203	34.5%	14,767	27.3%	3,926	20.4%	<0.0001
Acral lentiginous	29	0.6%	197	0.9%	1,312	1.5%	1,035	1.9%	459	2.4%	
Lentigo maligna	15	0.3%	148	0.7%	2,601	3.0%	3,759	7.0%	1,566	8.1%	
Nodular	511	10.1%	2,197	10.1%	10,385	11.9%	7,123	13.2%	3,503	18.2%	
Desmoplastic	15	0.3%	149	0.7%	1,154	1.3%	1,244	2.3%	605	3.1%	
NOS	2,794	55.0%	10,523	48.1%	41,839	47.8%	26,188	48.4%	9,204	47.8%	
Site											<0.0001
Face	987	19.4%	3,285	15.0%	14,019	16.0%	14,802	27.4%	6,881	35.7%	
Trunk	1,851	36.4%	8,199	37.5%	31,569	36.1%	14,925	27.6%	3,666	19.0%	
Extremity	2,219	43.7%	10,242	46.9%	41,235	47.1%	23,886	44.1%	8,539	44.3%	
NOS	27	0.5%	131	0.6%	671	0.8%	503	0.9%	177	0.9%	
Breslow depth (median, IQR, mm)*	1.1	0.5-2.0	0.9	0.4-1.7	1.0	0.5-2.0	1.1	0.5-2.5	1.7	0.6-3.6	<0.0001
Ulceration	802	15.8%	3,490	16.0%	18,038	20.6%	13,412	24.8%	6,848	35.6%	<0.0001
T Classification											<0.0001
T1	2,239	44.0%	11,067	50.6%	39,502	45.2%	21,531	39.8%	5,562	28.9%	
T2	1,505	29.6%	6,062	27.7%	24,336	27.8%	14,249	26.3%	4,412	22.9%	
T3	838	16.5%	2,842	13.0%	13,078	15.0%	9,925	18.3%	4,449	23.1%	
T4	502	9.9%	1,886	8.6%	10,578	12.1%	8,411	15.5%	4,840	25.1%	
N Classification											
Nx	84	1.7%	342	1.6%	1,500	1.7%	1,108	2.1%	703	3.7%	<0.0001
N0	3,917	77.1%	17,734	81.1%	72,007	82.3%	45,780	84.6%	16,224	84.2%	
N1	670	13.2%	2,240	10.3%	8,019	9.2%	3,956	7.3%	1,142	5.9%	
N2	285	5.6%	1,041	4.8%	3,762	4.3%	1,997	3.7%	766	4.0%	
N3	128	2.5%	500	2.3%	2,206	2.5%	1,275	2.4%	428	2.2%	

Table I. *Continued*

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	Age Cohort (Years) (N=187,814)										
	Pediatric & AYA 1-25 N=5084		Early adult 26-40 N=21,857		Middle adult 41-64 N=87,494		Older adult 65-79 N=54,116		Elderly ≥80 N=19,263		
	N	%	N	%	N	%	N	%	N	%	*p*-Value
Stage											<0.0001
Stage I	3,154	62.0%	14,768	67.6%	55,211	63.1%	31,116	57.5%	8,491	44.1%	
Stage II	819	16.1%	3,163	14.5%	17,368	19.9%	15,056	27.8%	8,062	41.9%	
Stage III	1,053	20.7%	3,604	16.5%	13,104	15.0%	6,823	12.6%	2,226	11.6%	
Stage IV	58	1.1%	322	1.5%	1,811	2.1%	1,121	2.1%	484	2.5%	
Follow-up (median, IQR)	47	27-72	45	26-68	44	26-67	40	24-63	30	17-50	<0.0001

AYA: Adolescent and young adult; *missing data was excluded (n=183,585).

Patients were selected based on International Classification of Disease (ICD-03) site (C440-C449) and histology codes (8720-8723, 8730, 8740-8746, 8770-8774, 8780). Only patients with invasive disease and histologic/cytologic diagnostic confirmation were included. Patients with in-situ disease were excluded. Patients were categorized according to age: 1-25 years [pediatric, adolescent, and young adult (AYA)], 26-40 years (early adult), 41-64 (middle adult), 65-79 (older adult), and ≥80 years (elderly). Infants (<1 year) were excluded due the small number of patients in this cohort (n=41).

We abstracted patient demographics, clinicopathologic characteristics, treatment, and survival data from the NCDB. Patient medical comorbidities were assessed using the Charlson-Deyo comorbidity index (CDCI) (14). Staging was defined according to AJCC 6th and 7th criteria. Patients with missing/unknown staging (n=34,769) and T classification (n=69,483) information were excluded. Sentinel lymph node biopsy (SLNB) was defined as examination of 1-5 nodes and completion lymphadenectomy (CLND) was defined as ≥6 nodes, as previously described (15-17). Immunotherapy primarily consisted of interferon α-2b and IL-2 therapies, although a few patients may have also received a CTLA-4/PD-1 inhibitor (*i.e.* ipilimumab, pembrolizumab, nivolumab) based on involvement in clinical trials and/or FDA approval prior to December 2015. In addition to standard chemotherapeutics (*i.e.* dacarbzine, paclitaxel, *etc.*), BRAF/MEK inhibitors (*i.e.* dabrafenib, trametinib, vemurafenib) were also included in chemotherapy.

Statistical analysis. Patient demographics, clinicopathologic characteristics, and treatment modalities were compared between age cohorts using the Chi-square test, except for Breslow depth and follow-up for which the Kruskal-Wallis tests were performed. Missing data was included in analyses as 'unknown', with the exception of univariate analyses comparing Breslow depth (n=183,585) and surgical margins (n=183,805, surgical patients with known margin status) by age. A multivariable logistic regression model was performed to compare differences in odds of nodal evaluation (SLNB or CLND) based on age controlling for demographic and clinicopathologic differences. Model covariates included gender, race, CDCI, income, insurance status, T stage, composite stage, histology, site, and ulceration.

To determine differences in multimodal treatment approaches, subset analysis was performed among patients with stage III disease. Rates of CLND, chemotherapy, immunotherapy, and radiation therapy by age were compared using Fisher's exact or Chi-square tests, as appropriate. We assessed demographic, clinicopathologic, and treatment approaches associated with overall survival among elderly (≥80 years) patients with stage III disease using the stepwise selection method (inclusion significance <0.25, exclusion >0.10) in a Cox proportional hazards model. As immunotherapy was associated with improved survival in elderly patients, a multivariable logistic regression model was performed to determine the odds of immunotherapy controlling for demographic and clinicopathologic differences among age cohorts. Statistical analyses were performed using SAS (version 9.4, SAS Institute, Cary, NC, USA). All tests were two sided. *p*-Values<0.05 were considered significant.

Results

Of the 187,814 patients with invasive melanoma, 5,084 (2.7%) were 1-25 years, 21,857 (11.6%) were 26-40 years, 87,494 (46.6%) were 41-64 years, 54,116 (28.8%) were 65-79 years, and 19,263 (10.3%) were ≥80 years. As shown in Table I, there were significant differences in gender, race, CDCI, income, urban/rural residence, insurance status, histology, site, Breslow depth, presence of ulceration, T and N classification, and stage between age cohorts. Pediatric and AYA and early adult patients were more frequently female compared to older patients (60.9% *vs*. 41.1%, $p<0.0001$). Breslow depth was greatest among elderly patients compared to younger cohorts (1.7 *vs*. 1.1, 0.9, 1.0, & 1.1 mm, $p<0.0001$), with corresponding higher rates of T3 and T4 disease ($p<0.0001$). Rates of ulceration were also higher for elderly patients compared to younger cohorts (35.6% *vs*. 15.8%, 16.0%, 20.6% and 24.8%, $p<0.0001$). Rates of nodal disease were lowest among elderly patients (12.1% *vs*. 21.3%, 17.3, 16.0%, and 13.4, $p<0.0001$) with corresponding lower rates of stage III disease ($p<0.0001$).

Table II. *Treatment approaches by age for patients with invasive melanoma.*

	Age cohort (Years) (N=187,814)										
	Pediatric & AYA 1-25 N=5,084		Early Adult 26-40 N=21,857		Middle Adult 41-64 N=87,494		Older Adult 65-79 N=54,116		Elderly ≥80 N=19,263		
	N	%	N	%	N	%	N	%	N	%	*p*-Value
Surgery											
None	24	0.5%	113	0.5%	649	0.7%	446	0.8%	321	1.7%	<0.0001
Local/gross excision	1,639	32.2%	7,176	32.8%	28,483	32.6%	17,637	32.6%	6,388	33.2%	
Mohs	96	1.9%	453	2.1%	1,922	2.2%	1,493	2.8%	586	3.0%	
Wide local excision	3,310	65.1%	14,058	64.3%	56,231	64.3%	34,373	63.5%	11,892	61.7%	
NOS/Unknown	15	0.3%	57	0.3%	209	0.2%	167	0.3%	76	0.4%	
Negative surgical margins*	4,888	97.7%	21,014	97.9%	83,432	97.4%	51,066	96.3%	17,345	92.9%	<0.0001
Lymphatic surgery											
None	1,503	29.6%	7,548	34.5%	29,703	34.0%	20,841	44.1%	10,761	55.9%	<0.0001
SLNB	2,434	47.9%	10,142	46.4%	42,980	49.1%	25,878	47.8%	6,816	35.4%	
CLND	1,113	21.9%	4,004	18.3%	14,118	16.1%	6,973	12.9%	1,491	7.7%	
Unknown	34	0.7%	163	0.8%	693	0.8%	424	0.8%	195	1.0%	
Immunotherapy**	543	10.7%	1,844	8.4%	5,792	6.6%	1,553	2.9%	165	0.9%	<0.0001
Chemotherapy***	136	2.7%	551	2.5%	2,114	2.4%	769	1.4%	150	0.8%	<0.0001
Radiotherapy	76	1.5%	378	1.7%	2,061	2.4%	1,578	2.9%	627	3.3%	<0.0001

AYA: Adolescent and young adult; SLNB: sentinel lymph node biopsy; CLND: completion lymphadenectomy. *Among those who underwent surgery and margins were known (n=183,805). **Primarily interferon α-2b and IL-2 therapies, with few receiving CTLA-4/PD-1 inhibitors. ***Including BRAF/MEK inhibitors.

Median follow-up for the entire cohort was 41 months (IQR=24-65).

Table II describes differences in treatment approaches by age cohort. Wide local excision was the most frequently employed surgical approach for all cohorts (63.8%). Elderly patients had the lowest rates of negative surgical margins (92.9% *vs.* 97.7%, 97.9%, 97.4%, and 96.3% $p<0.0001$). Elderly patients had the highest rates of no nodal surgery (including both SLNB and CLND) compared to younger cohorts (55.9% *vs.* 29.6%, 34.5%, 34.0%, and 44.1%, $p<0.0001$). In a multivariable model controlling for demographic and clinicopathologic differences between age groups, younger cohorts were associated with higher odds of nodal surgery compared to elderly cohorts [Pediatric & AYA adjusted OR (aOR)=5.88, 95%CI=5.37-6.45, $p<0.0001$; early adult aOR=5.32, 95%CI=5.01-5.65, $p<0.0001$; middle adult aOR=4.72, 95%CI=4.49-4.96, $p<0.0001$; older adult aOR=3.52, 95%CI=3.37-3.67, $p<0.0001$]. Elderly patients had the lowest rates of immunotherapy [0.9% *vs.* 10.7%, 8.4%, 6.6%, and 2.9%, $p<0.0001$ (*i.e.* primarily interferon α-2b and IL-2 therapies, with few receiving CTLA-4/PD-1 inhibitors)] and chemotherapy [0.8% *vs.* 2.7%, 2.5%, 2.4%, and 1.4%, $p<0.0001$ (including BRAF/MEK inhibitors)], but the highest rates of radiation therapy (3.3% *vs.* 1.5%, 1.7%, 2.4%, and 2.9%, $p<0.0001$). Desmoplastic histology was most frequently associated with radiation therapy among all patients (14.5% *vs.* 0.8-4.8%, $p<0.0001$) and among elderly patients (14.4% *vs.* 0.9-3.7%, $p<0.0001$).

Among patients with stage III disease, as shown in Figure 1A-D, rates of CLND were lowest among elderly patients compared to younger cohorts for stage IIIA (40.6% *vs.* 73.1%, 75.1%, 69.2%, and 61.4%, $p<0.0001$), IIIB (31.0% *vs.* 76.4%, 75.3%, 68.4%, and 58.9%, $p<0.0001$), and IIIC disease (47.1% *vs.* 86.6%, 86.1%, 82.0%, and 71.7%, $p<0.0001$). Rates of chemotherapy were lower with increasing age for stage IIIA-C disease (IIIA: 8.0%, 6.5%, 6.2%, 2.8%, and 0.5%, $p<0.0001$; IIIB: 8.8%, 10.2%, 8.4%, 4.0%, and 1.9%, $p<0.0001$; IIIC: 12.7%, 14.1%, 11.5%, 8.6%, and 3.7%, $p<0.0001$). Rates of immunotherapy were also lower with increasing age (IIIA: 39.7%, 39.8%, 28.6%, 11.7%, and 0.7%, $p<0.0001$; IIIB: 48.8%, 39.6%, 33.7%, 14.4%, and 2.9% $p<0.0001$; IIIC 45.8%, 43.8%, 35.9%, 16.0%, and 4.0% $p<0.0001$). Radiation therapy was most common among older adult patients (but not elderly) for stage IIIA-C (IIIA: 3.8% *vs.* 1.2%, 1.6%, 2.1%, and 2.9%, $p=0.002$; IIIB: 9.4% *vs.* 2.4%, 4.5%, 5.7%, and 7.9%, $p<0.0001$; IIIC: 22.0% *vs.* 16.9%, 20.8%, 20.4%, and 14.3%, $p=0.03$).

Among elderly patients with stage III disease, female gender (HR=0.83, 95%CI=0.73-0.95, $p=0.006$) and income ≥$68,000 (HR=0.79, 95%CI=0.65-0.97, $p=0.02$) were associated with improved survival (Table III), while higher CDCI scores ($p\leq0.004$), T4 disease (HR=2.04, 95%CI=1.29-

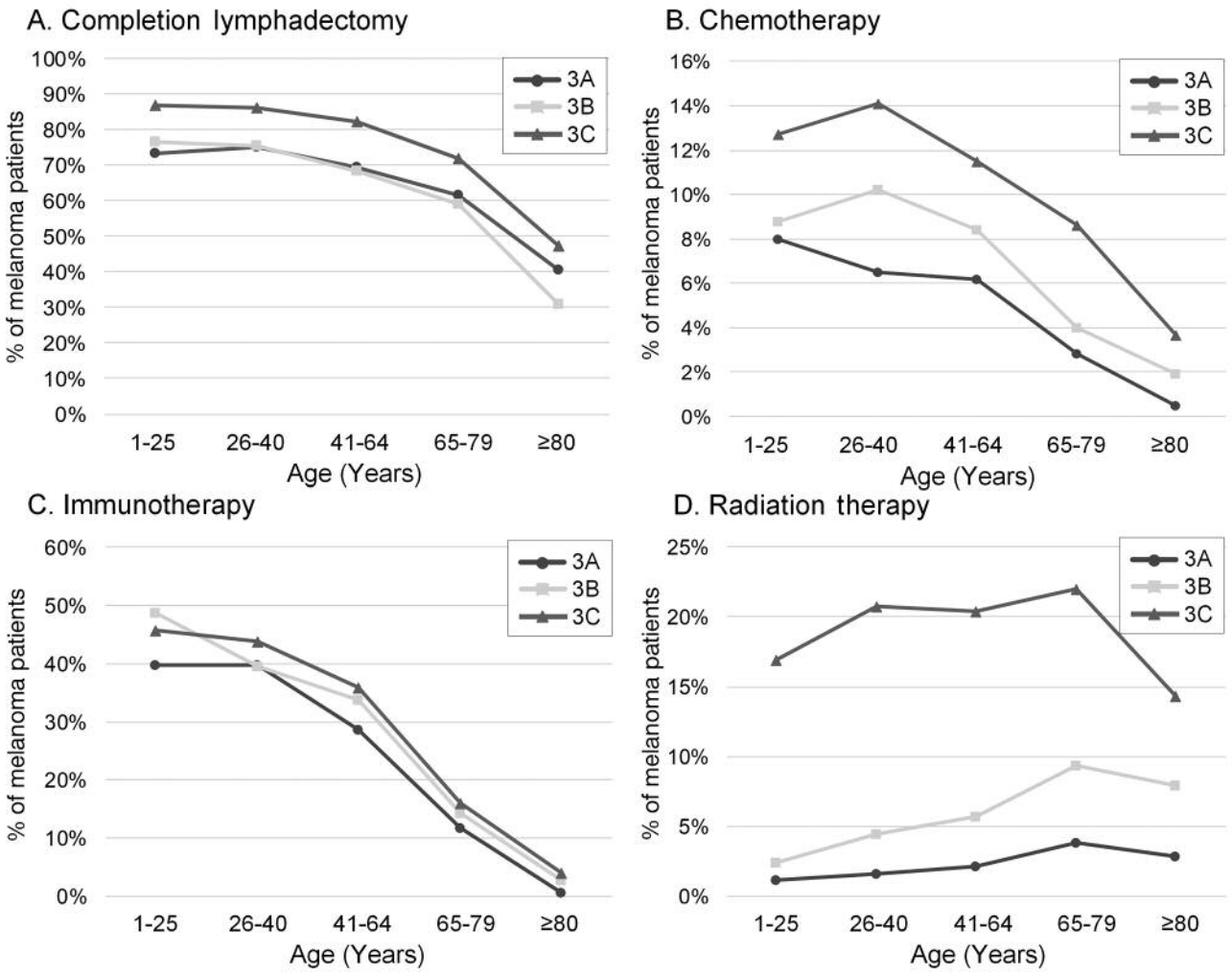

Figure 1. *Rates of (A) completion lymphadenectomy, (B) chemotherapy, (C) immunotherapy, and (D) radiation therapy among stage IIIA, B and C patients by age. There were significant differences in rates of (A) completion lymphadenectomy (stage IIIA, B, & C disease, p<0.0001), (B) chemotherapy (stage IIIA, B, & C disease, p<0.0001), (C) immunotherapy (stage IIIA, B, & C disease, p<0.0001), and (D) radiotherapy (stage IIIA, B & C disease p≤0.03) by age. Chemotherapy included BRAF/MEK inhibitor therapies.*

3.21, $p<0.0001$), higher N classification (N2 HR=1.18, 95%CI=1.004-1.38, $p=0.04$; N3 HR=1.78, 95%CI=1.41-2.23, $p<0.0001$), ulceration (HR=1.35, 95%CI=1.17-1.57, $p=0.0001$), and stage IIIC disease (HR=1.40, 95%CI=1.09-1.79, $p=0.009$) were associated with worse survival. Primary site surgery ($p\leq0.04$), CLND (HR=0.72, 95%CI=0.58-0.90, $p=0.004$), and immunotherapy (HR=0.52, 95%CI=0.32-0.84, $p=0.008$) were associated with improved overall survival.

As immunotherapy was associated with improved survival among elderly patients with stage III disease, a multivariable model was performed (Table IV). All younger age cohorts were associated with greater odds of receiving immunotherapy compared to elderly patients ($p<0.0001$ all). Additionally, African American race and higher CDCI scores were associated with lower odds of immunotherapy ($p<0.05$), while higher income, private insurance, higher T and composite stage were associated with higher odds of immunotherapy ($p<0.05$ for all).

Discussion

In the present study, we identified significant demographic, clinicopathologic, and treatment differences among melanoma patients based on age, which were most pronounced in elderly patients. Consistent with previous research, elderly patients presented with thicker tumors with higher rates of ulceration, but lower rates of nodal disease when compared to younger patients (18-22). Importantly, we

Table III. *Predictors of overall survival among elderly patients with stage III disease*.*

	HR	95%CI		*p*-Value
Gender				
Male	Reference			
Female	0.83	0.73	0.95	0.006
Income				
<$38,000	Reference			
$38,000-$47,999	0.87	0.71	1.07	0.19
$48,000-$67,999	0.90	0.74	1.09	0.27
≥$68,000	0.79	0.65	0.97	0.02
CDCI				
0	Reference			
1	1.25	1.07	1.46	0.004
2	1.87	1.38	2.53	<0.0001
T classification				
T1	Reference			
T2	1.27	0.79	2.05	0.32
T3	1.45	0.91	2.29	0.12
T4	2.04	1.29	3.21	<0.0001
N Classification				
N1	Reference			
N2	1.18	1.004	1.38	0.04
N3	1.78	1.41	2.23	<0.0001
Ulceration	1.35	1.16	1.57	0.0001
Stage				
3A	Reference			
3B	1.16	0.97	1.40	0.11
3C	1.40	1.09	1.79	0.009
Primary Site Surgery				
None	Reference			
Local/Gross excision	0.33	0.15	0.73	0.006
Moh's	0.38	0.15	0.97	0.04
Wide local excision	0.31	0.14	0.68	0.003
Lymph node surgery				
None	Reference			
SLNB	0.88	0.71	1.09	0.24
CLND	0.72	0.58	0.90	0.004
Immunotherapy**	0.52	0.32	0.84	0.008

Elderly defined as age ≥80 years (n=1,576); CDCI: Charlson Deyo comorbidity index; SLNB: sentinel lymph node biopsy; CLND: completion lymphadenectomy. *Using stepwise selection method with inclusion criteria of significance at 0.25 and exclusion of 0.10. Among elderly patients, race, insurance status, urban/rural residence, tumor site, histology, chemotherapy, and radiotherapy failed to meet significance in the model. **Primarily interferon α-2b and IL-2 therapies, with few receiving CTLA-4/PD-1 inhibitors.

Table IV. *Odd of immunotherapy* treatment in melanoma patients with stage III disease.*

	Odds Ratio	95%CI		*p*-Value
Age				
Elderly (>80 years)	Reference			
Older adult (65-79)	5.96	4.37	8.13	<0.0001
Middle adult (41-64)	15.05	11.03	20.54	<0.0001
Early adult (26-40)	22.57	16.43	31.00	<0.0001
Pediatric and AYA (1-25)	25.87	18.43	36.30	<0.0001
Gender				
Male	Reference			
Female	1.05	0.98	1.13	0.16
Race				
Caucasian	Reference			
Black	0.68	0.49	0.93	0.02
Asian/Pacific Islander	1.01	0.66	1.53	0.98
American Indian/ Alaskan Native	0.83	0.42	1.64	0.58
Other/Unknown	0.96	0.72	1.28	0.77
Income				
<$38,000	Reference			
$38,000-$47,999	1.09	0.98	1.23	0.13
$48,000-$67,999	1.22	1.10	1.37	0.0003
≥$68,000	1.14	1.03	1.27	0.02
Insurance status				
None	Reference			
Private	1.31	1.13	1.52	0.0004
Government	0.99	0.84	1.17	0.94
CDCI				
0	Reference			
1	0.93	0.84	1.03	0.18
≥2	0.63	0.49	0.81	0.0003
Site				
Face	Reference			
Trunk	1.18	1.07	1.30	0.001
Extremity	1.12	1.02	1.24	0.02
T classification				
T1	Reference			
T2	1.20	1.04	1.38	0.01
T3	1.34	1.16	1.55	<0.0001
T4	1.32	1.14	1.53	0.0003
Histology				
Superficial spreading	Reference			
Acral lentiginous	1.24	1.02	1.51	0.04
Nodular	1.09	0.99	1.20	0.08
Desmoplastic	1.02	0.67	1.55	0.92
NOS	0.95	0.87	1.03	0.22
Ulceration	1.01	0.93	1.10	0.85
Stage				
3A	Reference			
3B	1.22	1.12	1.34	<0.0001
3C	1.40	1.26	1.54	<0.0001

AYA: Adolescent and young adult; CDCI: Charlson Deyo comorbidity index; SLNB: sentinel lymph node biopsy; CLND: completion lymphadenectomy; NOS: not otherwise specified. *Primarily interferon α-2b and IL-2 therapies, with few receiving CTLA-4/PD-1 inhibitors.

identified significant disparities in nodal evaluation and multimodal treatment among elderly patients compared to younger cohorts. Elderly patients had the lowest rates of negative margin resection, more frequently did not undergo any nodal evaluation, and less frequently underwent systemic therapy compared to younger cohorts. These results highlight that although elderly melanoma patients often present with more advanced disease, this population appears to be treated more conservatively by clinicians than younger cohorts.

SLNB was least commonly performed among elderly patients compared to younger age cohorts. Such findings suggest that despite the benefits of SLNB as a prognostic tool to help guide treatment decisions, SLNB appeared to be

performed more conservatively in the elderly population (1, 18, 20-23). This conservative use of SLNB in the elderly is likely multifactorial. Although elderly patients present with more advanced primary tumors, multiple studies have shown that sentinel lymph node positivity is less common in this age group, which may influence treatment decisions (18, 20-22). For T2 melanomas, Egger *et al*. found that age was inversely associated with SLNB positivity (20). However, elderly patients 'low-risk' for positive SLNB, defined as 4.9% risk, only included those with a melanoma thickness of 1.2 mm or less and without lymphovascular invasion. Similarly, Song *et al*. identified a cohort of 'low-risk' patients (*i.e*. <5% risk) with T4 melanomas, which only included those ≥80 years of age with no high-risk tumor features including ulceration, mitoses, or lymphovascular invasion. Therefore, the low rate of SLNB observed in elderly patients may partially reflect selective use of SLNB due to the inverse relationship between age and SLNB positivity. However, it is important that clinicians are aware that age alone does not make elderly patients low-risk for nodal positivity, but clinical factors including ulceration, mitoses, and lymphovascular invasion are also important and need to be incorporated in the decision-making. Furthermore, as patient frailty, medical comorbidities, and competing mortality risks are of importance in elderly patients, SLNB may not be recommended in elderly patients who are not thought to be candidates for adjuvant therapies despite positive nodal disease. This paradigm in particular is actively changing as the application of PD-1 inhibitor therapies has been proven safe, tolerable and efficacious in the elderly population and affords significant survival benefit (3, 9). Regardless, this finding highlights the need for clinicians to be aware of potential biases leading to the underutilization of SLNB in older individuals as SLNB remains an important prognostic tool to identify those who may benefit from adjuvant therapy.

In addition to lower rates of evaluation of nodal disease in the elderly, we identified additional important treatment disparities among elderly patients with known nodal disease. In both univariate and multivariable analyses, elderly patients with stage IIIB/C disease were less frequently treated with immunotherapy, despite immunotherapy being associated with greater overall survival. Although we acknowledge that these findings are impacted by selection bias with unmeasured confounders (as these elderly patients may have not been candidates for previous immunotherapeutic agents based on competing risks of death and functional status), this finding remains noteworthy as it suggests a potential clinical and/or prognostic benefit associated with immunotherapy in the elderly. Future research is needed in the present era of PD-1 inhibitor therapies to evaluate if this age-related treatment disparity continues to persist despite both clinical trials and cohort studies showing improved prognosis in elderly patients treated with PD-1 inhibitors (3, 7-9).

We do acknowledge the limitations of this study. Importantly, the cohort consists of patients diagnosed from 2004 to 2015 and, therefore, few patients likely received checkpoint inhibitor therapy (*i.e*. ipilimumab, pembrolizumab, nivolumab). As these systemic therapies have become the standard of care for stage III and IV disease (1), future research is needed to further evaluate age-related diagnostic and treatment disparities. Additionally, NCDB is limited with respect to detailed treatment information and prognostic outcomes. As such, we were not able to ascertain the reasons leading to the treatment decisions observed (including patient frailty or functional status) or the specific systemic chemotherapy and immunotherapy regimens utilized. Furthermore, we were not able to evaluate important outcomes including disease-specific or recurrence-free survival. Additionally, NCDB lacks centralized pathologic review, with implications of the potential misdiagnosis of Spitzoid nevi as melanoma in the pediatric and AYA cohort (24, 25). Regardless of these limitations, NCDB does possess multiple strengths including a rigorous audit process to facilitate accurate, complete documentation of patient records and collection of data from approximately 70% of all newly diagnosed cancer patients in the U.S, which is important when investigating national trends in diagnosis and treatment of melanoma in the elderly (11, 12).

Conclusion

In this multi-institutional analysis of melanoma patients, we identified significant clinicopathologic, treatment, and prognostic differences based on age, particularly for the elderly. Although elderly patients more commonly presented with advanced disease, they were often treated conservatively, with lower rates of nodal evaluation, higher rates of positive margins, and lower rates of systemic therapies. Among those with known nodal disease, less aggressive treatment approaches including lower rates of immunotherapy were common among elderly patients. Although these findings may largely reflect thoughtful clinical decision-making and deliberation, weighing of the risks and benefits of aggressive interventions in this potentially vulnerable population, these findings may also potentially reflect the undertreatment of elderly melanoma patients.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

Sarah B. Bateni: conception and research design, acquisition of data, data analysis and interpretation, drafting and revisions of manuscript, final approval. Alexandra J. Johns, Alicia A. Gingrich, Sepideh Gholami, Richard J. Bold, & Robert J. Canter: conception,

data interpretation, drafting and revisions of final manuscript, final approval. Amanda R. Kirane: conception and research design, acquisition of data, data interpretation, drafting and revisions of manuscript, final approval.

Disclosures

The National Cancer Database (NCDB) is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The CoC's NCDB and the hospitals participating in the CoC NCDB are the source of the de-identified data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the Authors.

Data Availability

The data that support the findings of this study are available from the National Cancer Database. Restrictions apply to the availability of these data, which were used under license for this study. Data are available at https://www.facs.org/quality-programs/cancer/ncdb with the permission of the National Cancer Database.

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References

1 Swetter, SM, Thompson, JA, Coit, DG, Albertini, MR, Barker, C, Boland, G, Carson, WE, Daniels, GA, DiMaio, D, Durham, A, Fields, RC, Fleming, MD, Galan, A, Gastman, B, Grossmann, K, Guild, V, Johnson, D, Joseph, RW, Karakousis, G, Lange, JR, Margolin, K, Nath, S, Olszanski, AJ, Ott, PA, Ross, MI, Salama, AK, Skitzki, J, Sosman, J, and Wuthrick, E. National comprehensive cancer network NCCN guidelines in oncology cutanesous melanoma. Version 2.2020, 2020. Available at: https://www.nccn.org/professionals/physician_gls/PDF/melanoma.pdf [Last accessed on April 9, 2020]

2 Faries MB, Thompson JF, Cochran AJ, Andtbacka RH, Mozzillo N, Zager JS, Jahkola T, Bowles TL, Testori A, Beitsch PD, Hoekstra HJ, Moncrieff M, Ingvar C, Wouters M, Sabel MS, Levine EA, Agnese D, Henderson M, Dummer R, Rossi CR, Neves RI, Trocha SD, Wright F, Byrd DR, Matter M, Hsueh E, MacKenzie-Ross A, Johnson DB, Terheyden P, Berger AC, Huston TL, Wayne JD, Smithers BM, Neuman HB, Schneebaum S, Gershenwald JE, Ariyan CE, Desai DC, Jacobs L, McMasters KM, Gesierich A, Hersey P, Bines SD, Kane JM, Barth RJ, McKinnon G, Farma JM, Schultz E, Vidal-Sicart S, Hoefer RA, Lewis JM, Scheri R, Kelley MC, Nieweg OE, Noyes RD, Hoon DSB, Wang HJ, Elashoff DA and Elashoff RM: Completion dissection or observation for sentinel-node metastasis in melanoma. N Engl J Med *376(23)*: 2211-2222, 2017. PMID: 28591523. DOI: 10.1056/NEJMoa1613210

3 Eggermont AMM, Blank CU, Mandala M, Long GV, Atkinson V, Dalle S, Haydon A, Lichinitser M, Khattak A, Carlino MS, Sandhu S, Larkin J, Puig S, Ascierto PA, Rutkowski P, Schadendorf D, Koornstra R, Hernandez-Aya L, Maio M, van den Eertwegh AJM, Grob JJ, Gutzmer R, Jamal R, Lorigan P, Ibrahim N, Marreaud S, van Akkooi ACJ, Suciu S and Robert C: Adjuvant pembrolizumab versus placebo in resected stage III melanoma. N Engl J Med *378(19)*: 1789-1801, 2018. PMID: 29658430. DOI: 10.1056/NEJMoa1802357

4 American Cancer Society: Cancer facts and figures, 2019. Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf [Last accessed May 25, 2019]

5 Rees MJ, Liao H, Spillane J, Speakman D, McCormack C, Donahoe S, Pohl M, Webb A, Gyorki D and Henderson MA: Melanoma in the very elderly, management in patients 85years of age and over. J Geriatr Oncol 4: 488-493, 2018. PMID: 29398454. DOI: 10.1016/j.jgo.2018.01.001

6 Balch CM, Soong SJ, Gershenwald JE, Thompson JF, Coit DG, Atkins MB, Ding S, Cochran AJ, Eggermont AM, Flaherty KT, Gimotty PA, Johnson TM, Kirkwood JM, Leong SP, McMasters KM, Mihm MC, Jr., Morton DL, Ross MI and Sondak VK: Age as a prognostic factor in patients with localized melanoma and regional metastases. Ann Surg Oncol *20(12)*: 3961-3968, 2013. PMID: 23838920. DOI: 10.1245/s10434-013-3100-9

7 Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, Hassel JC, Rutkowski P, McNeil C, Kalinka-Warzocha E, Savage KJ, Hernberg MM, Lebbe C, Charles J, Mihalcioiu C, Chiarion-Sileni V, Mauch C, Cognetti F, Arance A, Schmidt H, Schadendorf D, Gogas H, Lundgren-Eriksson L, Horak C, Sharkey B, Waxman IM, Atkinson V and Ascierto PA: Nivolumab in previously untreated melanoma without braf mutation. N Engl J Med *372(4)*: 320-330, 2015. PMID: 25399552. DOI: 10.1056/NEJMoa1412082

8 Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, Daud A, Carlino MS, McNeil C, Lotem M, Larkin J, Lorigan P, Neyns B, Blank CU, Hamid O, Mateus C, Shapira-Frommer R, Kosh M, Zhou H, Ibrahim N, Ebbinghaus S, Ribas A and investigators K-: Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med *372(26)*: 2521-2532, 2015. PMID: 25891173. DOI: 10.1056/NEJMoa1503093

9 Perier-Muzet M, Gatt E, Peron J, Falandry C, Amini-Adle M, Thomas L, Dalle S and Boespflug A: Association of immunotherapy with overall survival in elderly patients with melanoma. JAMA Dermatol *154(1)*: 82-87, 2018. PMID: 29214290. DOI: 10.1001/jamadermatol.2017.4584

10 Orloff M: Melanoma immunotherapy in the elderly. Curr Oncol Rep *20(2)*: 20, 2018. PMID: 29500787. DOI: 10.1007/s11912-018-0656-3

11 Boffa DJ, Rosen JE, Mallin K, Loomis A, Gay G, Palis B, Thoburn K, Gress D, McKellar DP, Shulman LN, Facktor MA and Winchester DP: Using the national cancer database for outcomes research: A review. JAMA Oncol *3(12)*: 1722-1728, 2017. PMID: 28241198. DOI: 10.1001/jamaoncol.2016.6905

12 Bilimoria KY, Bentrem DJ, Stewart AK, Winchester DP and Ko CY: Comparison of commission on cancer-approved and -nonapproved hospitals in the united states: Implications for studies that use the national cancer data base. J Clin Oncol *27(25)*: 4177-4181, 2009. PMID: 19636004. DOI: 10.1200/JCO.2008.21.7018

13 Mallin K, Browner A, Palis B, Gay G, McCabe R, Nogueira L, Yabroff R, Shulman L, Facktor M, Winchester DP and Nelson

H: Incident cases captured in the national cancer database compared with those in U.S. Population based central cancer registries in 2012-2014. Ann Surg Oncol *26(6)*: 1604-1612, 2019. PMID: 30737668. DOI: 10.1245/s10434-019-07213-1

14 Charlson ME, Pompei P, Ales KL and MacKenzie CR: A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis *40(5)*: 373-383, 1987. PMID: 3558716. DOI: 10.1016/0021-9681(87)90171-8

15 Lorimer PD, White RL, Walsh K, Han Y, Kirks RC, Symanowski J, Forster MR, Sarantou T, Salo JC and Hill JS: Pediatric and adolescent melanoma: A national cancer data base update. Ann Surg Oncol *23(12)*: 4058-4066, 2016. PMID: 27364504. DOI: 10.1245/s10434-016-5349-2

16 Roaten JB, Partrick DA, Pearlman N, Gonzalez RJ, Gonzalez R and McCarter MD: Sentinel lymph node biopsy for melanoma and other melanocytic tumors in adolescents. J Pediatr Surg *40(1)*: 232-235, 2005. PMID: 15868590. DOI: 10.1016/j.jpedsurg.2004.09.022

17 Bateni SB, Davidson AJ, Arora M, Daly ME, Stewart SL, Bold RJ, Canter RJ and Sauder CAM: Is breast-conserving therapy appropriate for male breast cancer patients? A national cancer database analysis. Ann Surg Oncol *26(7)*: 2144-2153, 2019. PMID: 30761438. DOI: 10.1245/s10434-019-07159-4

18 Balch CM, Thompson JF, Gershenwald JE, Soong SJ, Ding S, McMasters KM, Coit DG, Eggermont AM, Gimotty PA, Johnson TM, Kirkwood JM, Leong SP, Ross MI, Byrd DR, Cochran AJ, Mihm MC Jr., Morton DL, Atkins MB, Flaherty KT and Sondak VK: Age as a predictor of sentinel node metastasis among patients with localized melanoma: An inverse correlation of melanoma mortality and incidence of sentinel node metastasis among young and old patients. Ann Surg Oncol *21(4)*: 1075-1081, 2014. PMID: 24531700. DOI: 10.1245/s10434-013-3464-x

19 Sabel MS, Kozminski D, Griffith K, Chang AE, Johnson TM and Wong S: Sentinel lymph node biopsy use among melanoma patients 75 years of age and older. Ann Surg Oncol *22(7)*: 2112-2119, 2015. PMID: 25834993. DOI: 10.1245/s10434-015-4539-7

20 Song Y, Azari FS, Metzger DA, Fraker DL and Karakousis GC: Practice patterns and prognostic value of sentinel lymph node biopsy for thick melanoma: A national cancer database study. Ann Surg Oncol 26: 4651-4662, 2019. PMID: 31485823. DOI: 10.1245/s10434-019-07783-0

21 Egger ME, Stevenson M, Bhutiani N, Jordan AC, Scoggins CR, Philips P, Martin RCG 2nd and McMasters KM: Age and lymphovascular invasion accurately predict sentinel lymph node metastasis in t2 melanoma patients. Ann Surg Oncol *26(12)*: 3955-3961, 2019. PMID: 31392528. DOI: 10.1245/s10434-019-07690-4

22 Sinnamon AJ, Neuwirth MG, Yalamanchi P, Gimotty P, Elder DE, Xu X, Kelz RR, Roses RE, Chu EY, Ming ME, Fraker DL and Karakousis GC: Association between patient age and lymph node positivity in thin melanoma. JAMA Dermatol *153(9)*: 866-873, 2017. PMID: 28724122. DOI: 10.1001/jamadermatol.2017.2497

23 Morton DL, Thompson JF, Cochran AJ, Mozzillo N, Nieweg OE, Roses DF, Hoekstra HJ, Karakousis CP, Puleo CA, Coventry BJ, Kashani-Sabet M, Smithers BM, Paul E, Kraybill WG, McKinnon JG, Wang HJ, Elashoff R, Faries MB and Group M: Final trial report of sentinel-node biopsy versus nodal observation in melanoma. N Engl J Med *370(7)*: 599-609, 2014. PMID: 24521106. DOI: 10.1056/NEJMoa1310460

24 Dika E, Ravaioli GM, Fanti PA, Neri I and Patrizi A: Spitz nevi and other spitzoid neoplasms in children: Overview of incidence data and diagnostic criteria. Pediatr Dermatol *34(1)*: 25-32, 2017. PMID: 27874206. DOI: 10.1111/pde.13025

25 Ludgate MW, Fullen DR, Lee J, Lowe L, Bradford C, Geiger J, Schwartz J and Johnson TM: The atypical spitz tumor of uncertain biologic potential: A series of 67 patients from a single institution. Cancer *115(3)*: 631-641, 2009. PMID: 19123453. DOI: 10.1002/cncr.24047

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