Clinicopathologic characteristics and management trends of cutaneous invasive and *in situ* melanoma in older patients: a retrospective analysis of the National Cancer Data Base

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Abstract

Background: The incidence of melanoma in older patients is on the rise. Prior studies have shown disparities in surgical management and poor survival of older patients with melanoma.

Methods: This is a retrospective study of adult patients diagnosed with cutaneous invasive and *in situ* melanoma between 2000 and 2011 in the National Cancer Data Base. Characteristics and management of older patients (⩾60 years) were compared with younger patients (20–59 years) using χ^2 testing.

Results: Of 476,623 total cases, 54% (n = 258,153) were diagnosed among older patients. The reported cases in the older patients increased by 1.74-fold between 2000 and 2011. The majority were white (96%), men (65%), with early-stage disease (76% stage 0-II), and superficial spreading melanoma histology (39%). Older patients, compared with younger patients, were more likely to be men (65% *versus* 49%, $p < 0.0001$), and have *in situ* melanoma (28% *versus* 21%, $p < 0.0001$); less likely to have nodal metastases (7% *versus* 9%, $p < 0.0001$), receive care in academic centers (30% *versus* 35%, $p < 0.0001$), undergo wide excision or major amputation for stage I–III disease (68% *versus* 72%, $p < 0.0001$) and systemic therapy for stage III (18% *versus* 45%, $p < 0.0001$) and IV disease (30% *versus* 50%, $p < 0.0001$).

Conclusion: Older patients with melanoma are less likely to receive care in academic centers, undergo wide excision for stage I–III disease and receive systemic therapy for stage III–IV disease. Particularly, the utilization of systemic therapy is markedly low. This disparity is particularly important with the availability of less intense more effective therapies.

Keywords: academic medical center, age groups, cutaneous, melanoma, systemic therapy, wide excision

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Background

Surveillance, Epidemiology, and End Results (SEER) data indicates a rise in the incidence of cutaneous melanoma over the last two decades. The annual percentage increase in cutaneous melanoma is 2.4 between 1992 and 2010 in men, and 1.7 between 1997 and 2010 in women [Siegel *et al.* 2014]. Six decades of data from the Connecticut tumor registry also highlight increased incidence rates of melanoma of 17-fold in men and 9-fold in women between 1950 and 2007 [Geller *et al.* 2013]. Age being a risk factor for melanoma [Geller *et al.* 2013; Siegel *et al.* 2014], the rise is, at least partly, the consequence of an aging population. Indeed the incidence of melanoma in older patients has dramatically increased in the last few decades [Geller *et al.* 2007]. In addition, age has been shown to be an independent prognostic factor for disease-free survival [Austin *et al.* 1994], overall survival

[Balch *et al.* 2001] and disease-specific survival [Macdonald *et al.* 2011] in melanoma, albeit not consistently in all studies. For example, in one study, the 5-year disease-free survival of patients aged over 65 years with stage I and II melanoma was significantly worse than patients aged up to 65 years (55% *versus* 65%, $p = 0.007$). Age was a significant predictor of disease-free survival in a multivariate analysis [Austin *et al.* 1994]. The etiology for such disproportionately higher mortality rate in older patients is unclear. Such high incidence and mortality leads to substantial economic consequences of melanoma in older patients. A population-based analysis of the SEER Medicare data estimated an annual cost of $390 million for the management of melanoma in patients aged 65 years and over [Seidler *et al.* 2010].

As the baby boomers age, the incidence and mortality of older patients with melanoma, and the resulting economic burden are expected to further increase, thus highlighting the importance of understanding the biological behavior, and management trends of older patients with melanoma. We analyzed the clinicopathologic characteristics and management of patients with melanoma by age to identify the current trend.

Methods

This is a retrospective study of the National Cancer Data Base (NCDB) of patients with cutaneous melanoma diagnosed between 2000 and 2011 (the most recent available data). The NCDB, a joint program of the Commission on Cancer of the American College of Surgeons and the American Cancer Society initiated in 1989, contains oncology data from hospital cancer registries of more than 1500 accredited cancer programs in the United States and Puerto Rico. Approximately 70% of all newly diagnosed cases of cancer (including *in situ* carcinoma) in the United States, totaling about 29 million records, are reported to the NCDB. Certified tumor registrars at the Commission on Cancer-accredited cancer program registries collect and submit oncology data from patient charts using nationally standardized data item and coding definitions, and data transmission format specifications, in ways similar to SEER. All data are evaluated for data integrity, and undergo extensive quality monitoring [Bilimoria *et al.* 2008; American College of Surgeons 2013a].

Institutional review board waiver was obtained from the University of Nebraska Medical Center Institutional Review Board. All adults above the age of 20 years with melanoma were included in the study. Patients aged 60 years and above were categorized as older patients, which is the age cutoff frequently used by the United Nations to identify the older population [World Health Organization 2014]. In 2000, approximately 1330 hospitals reported cases of melanoma, which increased to approximately 1440 in 2011. The increase in the reported cancer cases (all types) from 2000 to 2011 was approximately 1.18-fold. Data abstracted in September 2013 included diagnosis year, age, gender, race, stage at diagnosis, histology, behavior, treatment received and hospital type. NCDB categorizes hospitals into community cancer centers (100–649 cancer cases annually, may need referral for a portion of therapy), comprehensive community cancer centers (⩾650 cases annually, may need referral for a portion of therapy), academic comprehensive centers (associated with university medical schools or designated as National Cancer Institute Comprehensive Cancer Care Programs) and others based on services offered and case volume [American College of Surgeons 2013b].

Statistical analysis

Descriptive statistics were used to calculate the frequency of distribution of cases according to age groups. χ^2 testing of independence was used to calculate any statistical difference in distribution between older and younger patients according to different patient-, disease- and treatment-related variables. Because data provided by the NCDB public website are pregrouped into age categories, we were unable to conduct any patient-level multivariate analyses.

Results

A total of 476,623 cases of invasive and *in-situ* cutaneous melanoma were diagnosed in NCDB hospitals between 2000 and 2011. Of these, 54.2% ($n = 258,153$) were diagnosed among patients over 60 years old (older population). Nearly three-quarters of these cases were invasive melanoma (71%). The majority of older patients were white (96%) and male (65%), and had early-stage disease [76% of all cases were stage 0–II; 81% of invasive melanoma (stages I–IV) were stage I–II]. The majority had Medicare insurance (64%) and received care in nonacademic centers (69%) (Table 1).

The new cases of melanoma in older patients reported to NCDB increased by 1.74-fold

Table 1. Characteristics of adult melanoma cases reported to National Cancer Data Base between 2000 and 2011.

Variable	20–59, *N* (%)	>60, *N* (%)	*p* value
N	215,078	258,153	
Man	106,420 (49.5)	169,019 (65.5)	<0.0001
Woman	108,658 (50.5)	89,134 (34.5)	
White	204,085 (94.9)	248,151 (96.1)	<0.0001
African American	1214 (0.6)	1599 (0.6)	
Hispanic	3523 (1.6)	2932 (1.2)	
Other/unknown	6256 (2.9)	5471 (2.1)	
Stage 0	42423 (19.7)	67,074 (26)	<0.0001
Stage I	100,259 (46.6)	92,047 (35.7)	
Stage II	21,627 (10.1)	37,797 (14.6)	
Stage III	19,279 (9)	18,528 (7.2)	
Stage IV	7364 (3.4)	10,960 (4.2)	
NA	1955 (0.9)	2423 (0.9)	
Unknown	22,171 (10.3)	29,324 (11.4)	
Malignant melanoma, NOS	129,589 (60.3)	148,663 (57.5)	<0.0001
Nodular melanoma	12,563 (5.8)	18,278 (7.1)	
Malignant melanoma in lentigo maligna	8632 (4)	34,285 (13.3)	
Superficial spreading Melanoma	56,082 (26.1)	43,302 (16.8)	
Other types	8212 (3.8)	13,625 (5.3)	
In situ	45,769 (21.3)	73,305 (28.4)	<0.0001
Invasive	169,309 (78.7)	184,848 (71.6)	
Not insured	8368 (3.9)	2510 (1)	<0.0001
Private/managed	178,856 (83.2)	67,124 (26)	
Medicaid	6732 (3.1)	2099 (0.8)	
Medicare	6231 (2.9)	167,526 (64.9)	
Other government	6858 (3.2)	11,184 (4.3)	
Unknown	8033 (3.7)	7710 (3)	
Academic comprehensive program* (*n* = 254)	34,801 (35.8)	40,005 (30.5)	<0.0001
Comprehensive community cancer program (*n* = 796)	47,841 (49.2)	64,171 (49)	
Community cancer program (*n* = 447)	10,173 (10.4)	13,328 (10.2)	
Other hospital (*n* = 112)	4516 (4.6)	13,443 (10.3)	

*Only those patients, who received all or part of first course treatment in the hospital where they were diagnosed, were utilized to determine hospital-type.
NA, not available; NOS, not otherwise specified.

(Figure 1), from 15,910 cases in 2000 to 27,669 cases in 2011 (Table 2), compared with an increase of 1.18-fold in younger patients. A significant increase was observed in all subgroups by sex, race, stage and behavior (*in situ versus* invasive), but the greatest increase was noted in men (79%), white patients (74%), Hispanic patients (88%), stage 0 (96%), I (113%) and IV disease (123%).

Older patients, compared with younger patients, were more likely to be male (65% *versus* 49%, $p < 0.0001$), have *in situ* melanoma (28% *versus* 21%, $p < 0.0001$) and lentigo maligna (13% *versus* 4%, $p < 0.0001$). They were less likely to have superficial spreading melanoma (16% *versus* 26%, $p < 0.0001$), and nodal metastases (7% *versus* 9%, $p < 0.0001$), receive care in academic centers (30% *versus* 35%, $p < 0.0001$), undergo wide excision (>1 cm margin) or major amputation for stage I–III disease (68% *versus* 72%, $p < 0.04$) (Table 3) and receive systemic therapy, including chemotherapy or immunotherapy for stage III (18% *versus* 45%, $p < 0.0001$) and IV disease (30% *versus* 50%, $p < 0.0001$) (Table 4).

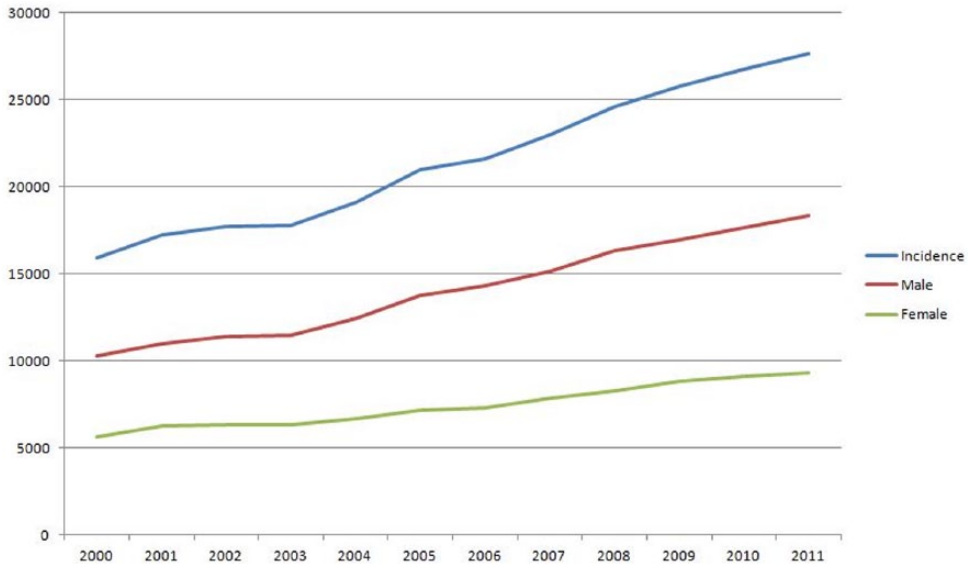

Figure 1. Incidence Reported cases of melanoma in older patients.

Table 2. Trends of reported cutaneous invasive and *in situ* melanoma cases in older patients.

Variables	2000	2011	Percentage increase between 2000 and 2011
Incidence	15,910	27,669	74%
Behavior			
In situ	4442 (28%)	7976 (29%)	80%
Invasive	11,468 (72%)	19,693 (71%)	72%
Sex			
Men	10,269 (65%)	18,362 (66%)	79%
Women	5641 (35%)	9307 (34%)	65%
Race			
White	15,290 (98%)	26,592 (98%)	74%
African American	103 (1%)	154 (1%)	50%
Hispanic	171 (1%)	322 (1%)	88%
Stage			
Stage 0	4037 (30%)	7902 (31%)	96%
Stage I	4886 (36%)	10,407 (40%)	113%
Stage II	2421 (18%)	4267 (16%)	76%
Stage III	1692 (12%)	2009 (8%)	19%
Stage IV	598 (4%)	1331 (5%)	123%

Patients with unknown race or stage were excluded from the analysis.

Table 3. First course surgery in stage I to III melanoma reported to National Cancer Data Base between 2000 and 2011.

Variable	20–59, *N* (%)	>60, *N* (%)	*p* value
Wide excision >1 cm margin or major amputation	102,530 (72.6)	102,107 (68.8)	0.0419
Other surgery*	36,957 (26.2)	44,282 (29.9)	
No surgery	1670 (1.2)	1968 (1.3)	
Unknown if surgery performed	8 (0)	15 (0)	

*This included gross excision, unspecified local excision, surgery and local tumor destruction.

Table 4. Systemic therapy use in melanoma reported to National Cancer Data Base between 2000 and 2011.

Variable	20–59, *N* (%)				>60, *N* (%)				
	None	Chemo	Immuno	C/I	None	Chemo	Immuno	C/I	
Stage 0	41,594 (99.6)	24 (0.1)	106 (0.3)	2 (0)	65,741 (99.5)	52 (0.1)	303 (0.4)	0 (0)	$p<0.0001$
Stage I	97,921 (99.5)	140 (0.1)	367 (0.4)	13 (0)	90,262 (99.6)	133 (0.2)	209 (0.2)	5 (0)	
Stage II	19,154 (90.8)	364 (1.7)	1530 (7.3)	53 (0.2)	35,854 (96.7)	322 (0.9)	851 (2.3)	29 (0.1)	
Stage III	10,183 (54.6)	1515 (8.1)	6480 (34.7)	483 (2.6)	14,714 (81.6)	889 (4.9)	2324 (12.9)	105 (0.6)	
Stage IV	3513 (49.4)	2383 (33.5)	752 (10.6)	461 (6.5)	7396 (69.6)	2492 (23.4)	548 (5.2)	192 (1.8)	
NA	1674 (87.9)	70 (3.7)	132 (6.9)	28 (1.5)	2253 (94.6)	55 (2.3)	65 (2.7)	8 (0.4)	
Unknown	19,859 (92.6)	542 (2.5)	919 (4.3)	128 (0.6)	27,295 (95.9)	574 (2)	535 (1.9)	62 (0.2)	

Patients with unknown age, with missing information and who received unspecified or other categories of systemic therapy (n = 9574) were excluded.
C/I, chemotherapy and immunotherapy; chemo, chemotherapy; immuno, immunotherapy; NA, not available.

Discussion

NCDB, which captures approximately 70% of all new cancer diagnoses, demonstrated a 1.74-fold increase in the reported cases of melanoma (invasive and *in situ* combined) in older patients in the last decade. This rapid increase is only partly related to the increase in the number of reporting hospitals, since the increase in younger patients as well as the increase in all types of reported cancer cases from 2000 to 2011 was only 1.18-fold. A significant increase in melanoma in older patients was observed in all subgroups. The highest absolute rise was observed in white men. Although the early-stage disease comprised the majority of upsurge, the percentage increase in metastatic disease was also dramatic.

Older patients accounted for more than half of all melanoma cases and disproportionately affected men and white patients. The increase in the reported cases is consistent with the results from the SEER database [Geller *et al.* 2007] and Connecticut tumor registry [Geller *et al.* 2013]. Between 1973 and 2002, the incidence of melanoma increased by threefold in non-Hispanic white patients aged 65 years and over, and fivefold in non-Hispanic white men aged 65 years and over [Geller *et al.* 2007].

Older patients with invasive melanoma frequently presented with early-stage disease (81% stage I–II), which is consistent with results from the SEER database. According to the SEER database, between 2003 and 2009, 84% of melanoma cases presented at a localized stage [Siegel *et al.* 2014]. Superficial spreading melanoma was the most common histology irrespective of age [Linos *et al.* 2009; Tsai *et al.* 2010; Ciocan *et al.* 2013]. Although there were differences in histology of older patients with melanoma, compared with the younger patients, in our study, the majority of histology was categorized as melanoma not otherwise specified in NCDB, thus limiting the comparison. Older patients were more likely to have *in situ* disease and less likely to have nodal metastases at presentation. Prior studies have shown that older patients with melanoma are more likely to have adverse prognostic features such as elevated mitotic rate and tumor thickness, histologic ulceration, nodular subtype, head and neck location, but less likely to have lymph node metastases [Tsai *et al.* 2010; Ciocan *et al.* 2013]. Altered lymphatic flow with age may account for decreased lymph node metastases [Conway *et al.* 2009].

Older patients were less likely to have private or managed insurance and more likely to have Medicare, as expected. They were also less likely to receive care in academic centers. A previous NCDB analysis using 2003–2007 data reported only as an abstract had shown similar results [Tsai *et al.* 2011]. This is important since the insurance and hospital types, geographic area of treatment and oncology background of surgeons have been shown to influence compliance with National Comprehensive Cancer Network (NCCN) treatment guidelines for melanoma [Erickson *et al.* 2008; Bilimoria *et al.* 2009]. Medicaid or Medicare insurance, hospitals other than NCCN/National Cancer Institute designated hospitals, Northeast, South or West geographic area of treatment [Bilimoria *et al.* 2009] as well as non-oncology background of surgeons [Erickson *et al.* 2008] were factors associated with poor compliance with NCCN guidelines in a study.

Although the majority of older patients were diagnosed with potentially curable localized disease, the use of wide excision in stage I–III disease was somewhat less common. Prior analysis has also shown that older patients are less likely to undergo wide local excision, sentinel lymph node biopsy for clinically node-negative melanoma over 1 mm thick, and regional lymphadenectomy for stage III disease [Tsai *et al.* 2011]. Delay in definitive excision of over 6 weeks [Ciocan *et al.* 2013] and poor surgical management have also been reported in other studies [Bilimoria *et al.* 2009; Tsai *et al.* 2010; Ciocan *et al.* 2013]. Although a less aggressive approach may be appropriate in select older patients with poor life expectancy from other comorbidities, fit patients should have an adequate resection to improve outcomes.

Our study also revealed that the use of systemic chemotherapy or immunotherapy in stage III and IV disease was less common in older patients. In a population-based French study, adjuvant interferon therapy was less frequently proposed (18% *versus* 58%, $p < 0.001$), started (9% *versus* 36%, $p < 0.001$) and completed (36% *versus* 65%, $p = 0.004$) in patients aged 70 years and over compared with younger patients. The development of adverse effects (50%), disease progression (30%) and patient's choice or unspecified reasons (20%) were the reasons for discontinuation of adjuvant therapy in older patients [Ciocan *et al.* 2013]. Another prospective population-based study in Germany showed age up to 60 years (odds ratio 3.7) and insurance type (odds ratio 2.4) were the only independent factors associated with the initiation of adjuvant therapy [Livingstone *et al.* 2011]. The modest benefit of adjuvant therapy and anticipated poor tolerance in older patients are considered the reasons for low utilization of adjuvant therapy. A recent analysis of a prospectively collected database, however, revealed comparable safety and efficacy profile of high-dose interleukin 2 in patients aged 65 years and over ($n = 22$) compared with younger patients ($n = 82$) [Clark *et al.* 2013]. Although selection bias may be at play, this study illustrates that the use of systemic therapy may be appropriate for older patients with good performance status. Older patients with comorbidities may not be able to tolerate conventional chemotherapy and immunotherapy; however, with the availability of less intense more effective therapies, systemic therapy should not be underutilized. Importantly, these patients should be offered enrollment in clinical trials of novel therapeutic options.

Even though older patients are more likely to have adverse prognostic features, such as elevated mitotic rate, thick tumors and ulceration, nodal metastases are less frequent [Tsai *et al.* 2010; Ciocan *et al.* 2013]. Despite these differences, age has been shown to be an independent prognostic factor for disease-free survival [Austin *et al.* 1994] overall survival [Balch *et al.* 2001] and disease-specific survival [Macdonald *et al.* 2011], albeit not in all studies. The reasons for poor survival in older patients is unclear but speculated to be related to the differences in tumor biology, host biology, healthcare discrepancies [Tsai *et al.* 2010] or competing causes of death. The poor utilization of potentially curative wide excision, as well as systemic therapy, as shown in our study, may possibly contribute to poor survival in older patients with melanoma; however, other factors including the presence of comorbidities can certainly play an important role.

Limitations and strengths

There are several limitations of a study utilizing a database, which include retrospective design, possibility of administrative errors in entering data and lack of availability of information on possible confounders. The data collection of NCDB is similar to SEER; all data are evaluated for data integrity and undergo extensive quality monitoring [Bilimoria *et al.* 2008], hence the accuracy of the NCDB is reliable. The rise in cases of older patients with melanoma may be related to increased reporting; however, the rise was substantially higher than younger patients, thus suggesting an actual increase. Both invasive and *in situ* melanoma were lumped into one category for calculation of the trend; however, as illustrated in table 2, the trend of invasive melanoma has also increased. Although some of the differences between the two groups such as wide excision are statistically significant, the actual clinical difference may be small. We acknowledge such findings are noticeable in studies with very large sample size. Patient-level data allow a more detailed analysis of different factors associated with the disparities identified. Since the publicly accessible NCDB through its website provides data pregrouped by different categories, we were unable to perform a patient-level multivariate analysis. However, the current study is the largest study, to our knowledge, to provide a focused analysis of clinicopathologic and management trends in older patients with melanoma using a large database. The majority of the previously published

studies included a population size of a few thousand or less. Additionally, this is the first population-based US study, to our knowledge, to compare systemic therapy use between older and younger patients. The healthcare disparities are very relevant as we move from intensive but less effective systemic therapy to better tolerated and more effective therapy options.

In conclusion, older patients with melanoma comprise more than half of all cases of adult melanoma, and are less likely to receive care in an academic center, undergo wide excision for stage I–III disease and receive systemic therapy for stage III–IV disease. In particular, the utilization of systemic therapy is markedly lower. These healthcare discrepancies should be monitored and changed as we move to an era of highly effective and better tolerated therapy options.

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Conflict of interest statement

AKG reports serving as a consultant for Boehringer Ingelheim and Otsuka Pharmaceuticals. PTS reports receiving payment for lectures from Bristol Myers and Celgene in the past. There are no conflict of interest for any other authors.

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