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Implications of age and conditional survival estimates for patients with melanoma

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Abstract

Objective—Overall cancer incidence is decreasing while melanoma cases increase. Conditional survival estimates offer a more accurate prognosis for patients as they survive past diagnosis. It is unknown the effect age and stage has on a melanoma patient's conditional survival estimate.

Methods—Surveillance, Epidemiology, End Results (SEER) data was utilized, identifying new diagnosis cutaneous melanoma patients (N=95,041), from 1998–2005, with up to 12 year follow up. Estimates of disease-specific survival by stage and age were determined by Cox regression and transformed to estimate conditional five-year survival.

Results—Localized melanoma patients have an excellent five-year survival at diagnosis and subsequent years. For patients with localized and regional disease, an age effect is present for disease-specific mortality when comparing older patients (70–79 years) to younger patients (<30 years): hazard ratio (HR) for mortality 3.79 (95% confidence interval (CI) 3.01–4.84) and HR 2.36 (95% CI 1.93–2.91), respectively. No age effect difference is observed in disease-specific survival

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for advanced disease: HR 1.14 (95% CI 0.87–1.53). Over time conditional survival estimates improve for older patients with localized and regional disease. This improvement is not seen in distant disease nor is the age gradient.

Conclusions—Disease-specific mortality and conditional survival for patients with localized and regional melanoma is initially impacted by older age with effects dissipating over time. Age does not affect survival in patients with advanced disease. Understanding the conditional five-year disease-specific survival of melanoma based on age and stage can help patients and physicians, informing decision making about treatment and surveillance.

Keywords

cutaneous melanoma; age; stage; conditional survival

Introduction

Though the overall incidence of cancer has been decreasing over the past 35 years, the incidence of melanoma has shown a nearly 200% increase over the same time period [1–4]. Recent data demonstrate that the greatest increases in melanoma incidence have occurred in younger women and older men, with a commensurately increasing risk of mortality, especially in older men [2, 4–7]. Cancer stage is considered the most important prognostic factor for melanoma patients, but there is a fair amount of heterogeneity within stage groupings. As such, the natural history of melanoma is incompletely defined, with some patients having an excellent likelihood of long-term survival and others having an increased risk of death secondary to a tumor with similar clinicopathologic features [1, 5–6].

Although the five- and ten-year survival rates at time of diagnosis are well described [1], conditional survival estimates, or the likelihood of survival based on how long a patient has already survived, remain understudied [8]. Conditional survival estimates may be particularly informative for older patients with melanoma since there appears to be an inverse relationship between increasing age and the incidence of sentinel node positivity [9–10] even though older patients have higher overall mortality rates. A better understanding of conditional survival is important for both patients and providers as it may offer useful information for treatment planning and long-term management strategies.

In this study, we determined conditional five-year disease-specific survival for melanoma based on stage and age. The specific effect of age and stage on longer-term melanoma survival is unknown and increasingly important given an increasing incidence of melanoma in an aging population. We hypothesize that age at diagnosis is an important consideration in conditional survival and that treatment planning as well as surveillance strategies for older patients with melanoma will be better informed by our findings.

Methods

Data Source and Study Population

We used Surveillance, Epidemiology, and End Results (SEER) data to study patients diagnosed with melanoma (N=95,041) between 1998–2005. Only new cases of cutaneous

melanoma were included in this analysis; melanoma in-situ cases and patients presenting with distant disease from unknown primary sites were excluded. Follow up data were available for up to 12 years, with a median follow up time of 6.3 years. We used SEER-defined tumor stages in the analysis: localized, regional and distant disease. Age was categorized by decades, as <30, 30–39, 40–49, 50–59, 60–69, 70–79 and 80 years.

Since this study uses publically available data that cannot be tracked to human subjects, we did not need Institution Review Board (IRB) approval based on an exemption from the University of Michigan IRB.

Statistical Analysis

Using Cox regression, we estimated the disease-specific survival function for each SEER stage. To simplify the presentation of our figures, we initially included age but not sex as a covariate in our models. We later incorporated sex for the purpose of estimating hazard ratios.

The conditional five-year survival function is defined as $CS_5(t) = \Pr(T > 5+t | T > t)$, where T represents a patient's true survival time in years from diagnosis. That is, given that a patient has survived t years past diagnosis, $CS_5(t)$ is the probability that he or she will survive an additional five years. Applying the definition of conditional probability, we can write $CS_5(t) = \Pr(T > 5+t) / \Pr(T > t) = S(5+t) / S(t)$ where S is the survival function. Using this equation, we estimated $CS_5(t)$ by first estimating $S(5+t)$ and $S(t)$ via Cox regression.

Results

Clinicopathologic characteristics of the study population are shown in Table 1. The gender distribution is roughly equal (43.5% female and 56.5% male) but melanoma is more common in white patients, accounting for 95.4% of all melanoma diagnoses. Nearly 30% of all patients are age 70 or older. A large proportion (84.2%) of patients has localized disease. Only 3.8% of all melanoma patients have distant metastases at time of initial diagnosis. Because of this, the overall prognosis for melanoma is generally good, and, at time of censoring, only 10% of all melanoma patients had died from their cancer.

Disease-specific mortality is influenced by age and gender. Increasing age is associated with a worse prognosis. There is a linear relationship between age and disease-specific mortality. The effect of age (grouped by decade of age) is seen in every stage, though the strongest association with mortality is seen in the oldest patients with localized disease. For example, the hazard ratio (HR) for mortality is 3.79 (95% confidence interval (CI) 3.01–4.84) for patients age 70–79 compared to patients under age 30 with localized disease. For regional disease, there is a slight age association with mortality: HR 2.36 (95% CI 1.93–2.91) for patients age 70–79 compared to patients under age 30. The age effect is least pronounced in distant disease and the relationship between age and mortality does not reach statistical significance: HR 1.14 (95% CI 0.87–1.53) for patients age 70–79 compared to patients under age 30. Male patients with melanoma have a slightly worse prognosis than female patients regardless of SEER stage: localized (HR 1.62 (95% CI 1.51–1.74)), regional (HR 1.33 (95% CI 1.24–1.43)), and distant (HR 1.11 (95% CI 1.02–1.22)) (Table 2).

Figure 1 illustrates the conditional five-year disease-specific survival of patients with localized melanoma by age group. At the time of diagnosis there is a small age gradient observed between the groups, with better overall survival for younger patients. Over time, younger patients maintain excellent conditional 5-year survival. Initially, older patients have a worse prognosis, but after the first year of diagnosis, their likelihood of surviving the next five years improves. Further, the longer an older patient survives, there continues to be gains in their 5-year conditional survival. With the passage of time the survival difference based on age decreases with a narrowing of the age gradient, and age becomes less of an influence on survival.

Figure 2 shows the conditional five-year disease-specific survival of patients with regional melanoma, noting a clear age gradient. Here, younger patients clearly have better survival rates than older patients at time of diagnosis. However, as time goes on (years past the time of initial diagnosis), there is a decrease in the survival gradient between the age groups. Interestingly, survival for older patients approaches that of the younger patients, with age becoming less of a survival factor over time. The findings demonstrate the longer an older patient survives, the higher the likelihood that they will survive another five years, even when compared to younger patients with similar stage of disease.

The conditional 5-year disease-specific survival of patients with distant disease show that the longer melanoma patients survive, the better the likelihood that they will survive another five years (Figure 3). Despite an initially poor prognosis in patients with distant disease, conditional 5-year survival improves more rapidly with time than in patients with regional disease. Interestingly, age does not differentially impact survival in melanoma patients with distant metastases over time and no age gradient is seen between older and younger patients. Similar to the findings with traditional estimates of disease-specific mortality (Table 2), there is no significant association between age and conditional survival for patients with distant metastases.

Discussion

The results of this study provide information to patients and providers regarding the conditional five-year disease-specific survival of patients with melanoma. We found that increasing age at time of diagnosis was associated with worse disease-specific mortality in localized and regional melanoma. The conditional five-year disease-specific survival of localized melanoma was generally excellent, but importantly, patients with regional and distant melanoma demonstrated improvements in conditional survival with time. In regional disease, older patients appeared to have greater gains in conditional survival compared to younger patients. Interestingly, patients with distant disease gained the most survival benefit with time, and there did not appear to be survival differences based on age.

Although conditional survival has been studied in melanoma, to date, studies have not focused on the specific implications of age and stage [8, 11–13]. The incidence of melanoma is rising [1,2,4] and is now the fifth most common cancer in the United States, mostly attributed to an increase in diagnosis in younger women and older men [2,6]. Treatment decisions for older patients are somewhat controversial, and there appears to be

underutilization of sentinel node biopsy and completion lymph node dissection and systemic agents (as adjuvant treatment in regional disease or as directed treatment in advanced disease) in the elderly population [7,14–17]. While a melanoma diagnosis is generally associated with excellent outcomes, more advanced stages of disease carry a far worse prognosis [6]. With advances in multimodal treatment options for advanced melanoma, it is becoming increasingly important to understand the implications of advancing age on longer term survival, as estimated by conditional survival probabilities.

Recent work has demonstrated an important role for age as a prognostic variable, with investigators citing much poorer outcomes for elderly patients [4–5]. Indeed, age is an important factor in conditional five-year survival in localized and regional melanoma. Here, we show similar trends, with worse initial estimates of survival with advancing age. However, with time, the conditional survival estimates demonstrate that the age gradient, or negative impact of age, narrows with time in patients with localized and regional disease. Prior studies have used age 50 as a binomial cut point, obscuring the effects of more advanced age at diagnosis [18–19]. One European study did demonstrate an improvement in conditional survival estimates by age, with a narrowing of the age gradient for melanoma patients, but this was not further analyzed by stage [12].

By evaluating increasing age by decade, our results demonstrate the importance of considering conditional survival rates in elderly patients since those who continue to survive after their initial diagnosis actually do very well. And in fact, elderly patients with regional disease seem to have the most to gain over time since their conditional survival rates actually improve more than in younger patients. This has important implications for decision making about treatment options for older patients, supporting a role for appropriate use of wide excision and sentinel node biopsy when clinically indicated [17]. Going forward, these findings may inform the use of adjuvant therapies, even in older populations.

Interestingly, there is no noted age gradient in survival rates for patients with distant melanoma. Here, elderly patients who survive after their initial diagnosis actually do just as well as their younger counterparts. Because of the increasing incidence of high risk melanoma in older men, our findings have important implications for decision making regarding patient selection for potentially effective systemic treatments. Many studies have restricted the use of immunotherapy in older patients because of toxicity concerns, but the current data suggest that older patients may in fact have as much to gain (if not more to gain) from treatment as younger patients. Strong consideration should be given to use of systemic treatment based on performance status and comorbidities rather than age alone. Further, our results support the need for continued studies on tumor biology and host response in elderly patients with melanoma.

This study's findings are relevant to both physicians and patients. Understanding the conditional five-year disease-specific survival allows physicians to create appropriate management plans and allows patients to have a more accurate assessment of their life expectancy. A melanoma patient with regional or distant disease who survives three years after diagnosis has a very different five-year life expectancy than what they had at time of diagnosis, representing "credit for time served." Our results also highlight the importance of

appropriate treatment (surgical treatment for localized/regional disease and systemic treatment for distant disease) even in more elderly age groups.

There are limitations to this study. SEER data are limited in reporting of comorbid conditions and receipt of systemic treatment. However, SEER is a population-based dataset and likely very reflective of generalizable national outcomes. Another limitation is that SEER does not include information about systemic treatments. Though newer therapeutics (e.g., vemurafenib, dabrafenib, trametinib, ipilimumab, pembrolizumab, and nivolumab) must be considered in contemporary discussions about survival with advanced melanoma, there were no meaningful treatments during the time span of this study cohort (1998–2005). Increasing use of effective systemic treatments will likely change point estimates of disease-specific survival, but their impact on future estimates of conditional survival are currently unknown. Another potential limitation is that although disease-specific survival rates are standard outcome measures, they can underestimate actual cancer-related deaths [20]. This would have the possible effect of slightly overestimating our results in the context of how conditional survival influences long-term outcomes.

The results of this study provide information regarding the conditional five-year disease-specific survival for melanoma based on age and stage, which gives a more pertinent survival estimation the further a patient is from time of diagnosis. Initially, older age is associated with a poorer prognosis. However, in localized and regional disease, age becomes less of a detrimental factor in conditional survival estimates as time goes on. Interestingly, patients with distant disease gained the most survival benefit with time, and there did not appear to be conditional survival differences based on age at all. Since the number of older patients diagnosed with advanced stage melanoma continues to increase, management of these patients will continue to be a challenge. Our findings help inform clinical decision making, suggesting that we should be more cognizant of age bias in treatment decisions.

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Figure 1.
Conditional 5 Year disease-specific survival for localized melanoma patients by age group.

Figure 2.
Conditional 5 Year disease-specific survival for regional melanoma patients by age group.

Figure 3.
Conditional 5 Year disease-specific survival for distant melanoma patients by age group.

Table 1

Clinicodemographic characteristics of patients with melanoma, 1998–2005.

Cancer	Melanoma			
	Localized N (%)	Regional N (%)	Distant N (%)	Total N (%)
Stage	80,018 (84.2)	11,371 (12.0)	3,652 (3.8)	95,041 (100.0)
Patient Characteristics				
Age				
< 30	4,421 (5.5)	558 (4.9)	84 (2.3)	5,063 (5.3)
30 – 39	8,266 (10.3)	857 (7.5)	189 (5.2)	9,312 (9.8)
40 – 49	14,252 (17.8)	1,686 (14.8)	469 (12.8)	16,407 (17.3)
50 – 59	16,343 (20.4)	1,986 (17.5)	690 (18.9)	19,019 (20.0)
60 – 69	14,147 (17.7)	2,047 (18.0)	758 (20.8)	16,952 (17.8)
70 – 79	14,018 (17.5)	2,288 (20.1)	868 (23.8)	17,174 (18.1)
80	8,571 (10.7)	1,949 (17.1)	594 (16.3)	11,114 (11.7)
Sex				
Female	35,841 (44.8)	4,345 (38.2)	1,156 (31.7)	41,342 (43.5)
Male	44,177 (55.2)	7,026 (61.8)	2,496 (68.3)	53,699 (56.5)
Race				
White	76,160 (95.2)	10,992 (96.7)	3,503 (95.9)	90,655 (95.4)
Black	283 (0.4)	123 (1.1)	62 (1.7)	468 (0.5)
Other	568 (0.7)	171 (1.5)	79 (2.2)	818 (0.9)
Unknown	3,007 (3.8)	85 (0.7)	8 (0.2)	3,100 (3.3)
Year of diagnosis				
1998	4,794 (6.0)	633 (5.6)	216 (5.9)	5,643 (5.9)
1999	5,002 (6.3)	704 (6.2)	208 (5.7)	5,914 (6.2)
2000	10,262 (12.8)	1,557 (13.7)	447 (12.2)	12,266 (12.9)
2001	11,248 (14.1)	1,809 (15.9)	515 (14.1)	13,572 (14.3)
2002	11,228 (14.0)	1,894 (16.7)	507 (13.9)	13,629 (14.3)
2003	10,951 (13.7)	2,027 (17.8)	552 (15.1)	13,530 (14.2)
2004	12,686 (15.9)	1,355 (11.9)	608 (16.6)	14,649 (15.4)
2005	13,847 (17.3)	1,392 (12.2)	599 (16.4)	15,838 (16.7)

Cancer	Melanoma			
	Localized N (%)	Regional N (%)	Distant N (%)	Total N (%)
Disease-specific survival				
Dead	3,384 (4.2)	3,703 (32.6)	2,421 (66.3)	9,508 (10.0)
Censored	76,634 (95.8)	7,668 (67.4)	1,231 (33.7)	85,533 (90.0)
Overall survival				
Dead	14,587 (18.2)	5,983 (52.6)	3,221 (88.2)	23,791 (25.0)
Censored	65,431 (81.8)	5,388 (47.4)	431 (11.8)	71,250 (75.0)

Table 2

Disease-specific mortality of melanoma stages by age and sex

Cancer	Melanoma (N=95,041)		
Stage	Localized HR (95%CI)	Regional HR (95%CI)	Distant HR (95%CI)
Patient Characteristics			
Age			
< 30	1.00	1.00	1.00
30 – 39	1.08 (0.83, 1.43)	1.43 (1.13, 1.81)	1.03 (0.75, 1.42)
40 – 49	1.57 (1.24, 2.03)	1.71 (1.39, 2.13)	1.14 (0.86, 1.53)
50 – 59	1.82 (1.44, 2.34)	2.09 (1.71, 2.58)	1.11 (0.84, 1.49)
60 – 69	2.45 (1.94, 3.13)	2.07 (1.69, 2.55)	1.15 (0.88, 1.55)
70 – 79	3.79 (3.01, 4.84)	2.36 (1.93, 2.91)	1.14 (0.87, 1.53)
80	6.30 (5.00, 8.07)	3.11 (2.54, 3.84)	1.17 (0.89, 1.58)
Sex			
Female	1.00	1.00	1.00
Male	1.62 (1.51, 1.74)	1.33 (1.24, 1.43)	1.11 (1.02, 1.22)

Note: CI, Confidence interval; HR, Hazards ratio