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# Outcomes and Risk Factors in Patients with Multiple Primary Melanomas

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## Abstract

The incidence and patient survival rates of melanoma have increased over the last several decades, with a growing population of patients who develop multiple primary melanomas (MPMs). To determine risk factors for developing MPMs and compare the survival of patients with MPMs to those with single primary melanomas, a prospective, multidisciplinary database of patients with melanoma at a single tertiary care institution was retrospectively reviewed. From 1985 to 2013, 6,963 patients with single primary melanomas and 305 patients with MPMs were identified. Mean follow-up was 8.3 ± 6.3 years for patients with single primary melanomas and 8.8 ± 5.9 years for patients with MPMs. Risk of developing multiple melanomas increased with age at diagnosis of first melanoma (hazard ratio [HR] = 1.20 for a 10-year increase in age, 95% confidence interval

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CONFLICT OF INTEREST

The authors state no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2018.07.009.

[CI] = 1.11–1.29, $P < 0.001$), male sex (HR = 1.44, 95% CI = 1.12–1.84, $P = 0.005$), and white race (HR = 3.07, 95% CI = 1.45–6.51). Patients with invasive MPMs had increased risk of melanoma-specific death both before (HR = 1.47, 95% CI = 1.0–2.2) and after adjusting for age, sex, site, race, family history of melanoma, personal history of other cancer, and Surveillance, Epidemiology, and End Results Program (SEER) stage (HR = 1.44, 95% CI = 0.95–2.2); however, this result did not reach statistical significance.

## INTRODUCTION

Melanoma is both more common and less deadly than it ever has been (Arnold et al., 2014; Erdmann et al., 2013; Linos et al., 2009). These trends have resulted in a growing population of melanoma survivors who are at high risk of developing subsequent primary melanomas (Spanogle et al., 2010; Whiteman et al., 2016). Understanding risk factors and prognosis for these patients is critical to clinical management and patient counseling.

There is limited literature regarding the prognosis for patients with multiple primary melanomas (MPMs) compared with those with single primary melanomas (SPMs) (Doubrovsky and Menzies, 2003; Kricker et al., 2013; Pardo et al., 2016; Youlden et al., 2016). Early reports appeared to suggest better survival in patients diagnosed with additional melanomas (Bower et al., 2010; Doubrovsky and Menzies, 2003; Kricker et al., 2013; Moseley et al., 1979; Rowe et al., 2015; Slingluff et al., 1993). However, these studies suffered from important statistical bias, either (i) bias against MPM patients when survival was measured from the last occurring melanoma or (ii) immortal time bias when survival was measured from the diagnosis of the first melanoma, because MPM patients by definition must live long enough to develop multiple melanomas. Two recent publications corrected for immortal time bias and concluded that MPM patients have worse overall survival (Pardo et al., 2016; Youlden et al., 2016). However, both of these studies were conducted in relatively homogeneous fair-skinned populations (Australia and the Netherlands) compared with the United States and in particular urban areas such as San Francisco (McEvoy et al., 2009; US Census Bureau, 2016; Weiner, 2015), were limited to invasive melanomas, and used population-based cancer registries following rules for registering MPMs that differ from the Surveillance, Epidemiology, and End Results Program (SEER) rules used in the United States (Weir et al., 2016). Because of the limited information available in population-based registries (Asgari, 2016), these prior studies did not account for family history of melanoma or personal history of internal cancer, factors that may adversely affect survival and have been strongly linked to occurrence of MPMs (Ford et al., 1995; Holland et al., 1999; Monzon et al., 1998; Spanogle et al., 2010).

In this study, we examined the risk factors for developing multiple melanoma and the survival of MPM patients compared with that of SPM patients. To overcome the limitations of previous studies, we used a time-varying analysis to avoid immortal time bias and included presence of melanoma in situ in our analysis because this is one of the most common presenting forms of melanoma. Finally, we adjusted for family history of melanoma and personal history of internal cancer to determine whether multiplicity of

melanoma is an independent prognostic factor, using detailed tumor and patient information available in our institutional database.

## RESULTS

### Study cohort

A total of 7,453 individuals were diagnosed with a first primary melanoma between 1985 and 2013. Of these, 185 patients were excluded (153 SPMs and 32 MPMs) on the basis of age (<18 years old) or because of incomplete records (Figure 1). The remaining 7,268 patients were included in our analysis: 6,963 (95.8%) with single melanomas (mean [standard deviation] age = 55.8 [16.2] years, 58.3% male) and 305 (4.2%) patients with MPMs (mean [standard deviation] age = 60.2 [15.2] years, 67.9% male). The mean follow-up for the SPM patients was 8.3 ± 6.3 years from the time of diagnosis of the first primary melanoma, and the mean follow-up for MPM patients was 8.8 ± 5.9 years. MPM patients were on average older, more likely to be male, and more likely to have a family history of melanoma—notably, 36.0% of MPM patients had a family history of melanoma versus 6.1% of SPM patients. Table 1 summarizes demographic characteristics of SPM and MPM patients.

A total of 694 tumors were identified in 305 MPM patients (mean = 2.3 melanomas per patient). The number of multiple primary lesions per patient ranged between 2 and 13. Two or more synchronous tumors were diagnosed in 68 patients at first presentation. Table 2 summarizes data on the multiplicity and chronology of melanomas in MPM patients. Seventy-seven percent of MPM patients developed their second melanoma within 5 years of the first malignancy, and 92% developed their second occurrence within 10 years after the first.

Patients with MPMs were more likely than patients with SPM to be diagnosed with other internal malignancies. Specifically, patients with MPMs had higher rates of liver, pleural, prostate, and bladder cancers (Table 3). The rates for these cancers in MPM patients were also higher compared with the general population. Other cancers that developed in both MPM and SPM patients but did not occur at a higher incidence rate compared with the general population are listed in Supplementary Table S1 online.

### Melanoma tumor characteristics

The anatomic distribution of MPM tumors differed from SPM tumors, with MPMs occurring more often on the head and neck, trunk, and upper extremities and SPMs occurring more often on the lower extremities ($P < 0.05$) (Table 4). Overall, the invasive MPM tumors were on average significantly thinner than the invasive SPM tumors (1.6 ± 2.0 vs. 2.2 ± 2.4, respectively; $P < 0.0001$). The first invasive melanoma in individuals with MPMs was on average the same thickness as melanomas of individuals with only SPM, both were on average 2.2 ± 2.4 mm ($P = 0.98$). Subsequent invasive melanomas in MPM patients were on average markedly thinner (1.1 ± 1.2 mm, $P < 0.0001$) than melanomas in SPM patients. Significantly, the thickest melanomas for each MPM patient had an average thickness (2.5 ± 2.0 mm, $P = 0.21$) similar in thickness to the melanomas in SPM patients. Overall, MPM

tumors were markedly more likely to be American Joint Committee on Cancer stage I or less compared with SPM tumors (79.6% vs. 56.2%). By SEER staging, overall, MPM tumors were more likely to be in situ or localized compared with SPM tumors (90.8% vs. 77.1%). Staging and thickness data are summarized in Table 5.

## Risk factors for developing multiple melanomas

We used a proportional hazards model to identify risk factors for developing a second primary melanoma in the presence of the competing risk of melanoma-specific mortality. Risk of developing multiple melanomas increased with age at diagnosis of primary melanoma (hazard ratio [HR] = 1.20 for a 10-year increase in age, 95% confidence interval [CI] = 1.11–1.29, $P < 0.001$), male sex (HR = 1.44, 95% CI = 1.12–1.84, $P = 0.005$), and white race (HR = 3.07, 95% CI = 1.45–6.51, $P = 0.003$). The site of the first primary melanoma was weakly predictive of developing future primary melanomas. Compared with a first primary melanoma on the trunk, the lip was associated with the highest risk of developing subsequent primary melanomas (HR = 2.92, 95% CI = 1.18–7.22, $P = 0.02$), and the eyelid was associated with the lowest risk (HR = 0.33, 95% CI = 0.05–2.36, $P = 0.27$). The results were very similar when the Fine-Gray proportional hazards model for the sub-distribution incidence functions was used as an alternative approach.

## Mortality outcomes

In an unadjusted model of cause-specific (i.e., melanoma-specific) survival with the presence of multiple melanomas included as a time-dependent covariate, no statistically significant increase in risk of death was found for patients with MPMs, including those with only melanoma in situ, compared with those with SPM (HR = 1.17, 95% CI = 0.86–1.59). This result held even after adjusting for age, sex, site, race, family history of melanoma, personal history of other cancer, and SEER stage (HR = 1.27, 95% CI = 0.93–1.73). Results were similar when calculated for overall survival. Analysis of patients with invasive melanomas found an increase in risk of death from melanoma among patients with multiple invasive primary melanomas compared with those with single invasive melanomas (HR= 1.47, 95% CI = 1.00–2.20). However, this effect lost statistical significance after adjustment for age, sex, site, race, family history of melanoma, personal history of other cancer, and SEER stage (HR = 1.44, 95% CI = 0.95–2.20) (Table 6). In the subgroup of patients with in situ melanomas only, in situ MPMs did not change overall survival. Melanoma-specific survival could not be calculated because there were no melanoma-specific deaths in this group.

The impact of statistical methods on these comparisons is apparent if alternative definitions of survival are used. Unadjusted cause-specific survival calculated from the date of first melanoma diagnosis showed lower risk of melanoma-specific death in MPM patients compared with SPM patients (HR = 0.78, 95% CI = 0.59–1.04), with the difference from the estimates given earlier due directly to immortal time bias.

## DISCUSSION

This study of survival in patients with multiple primary melanomas includes melanoma in situ, uses appropriate statistical techniques to account for immortal time bias, and comprehensively controls for the many confounding factors that affect melanoma outcomes. We identified age, male sex, and white race as important risk factors for developing subsequent melanomas after the diagnosis of an initial melanoma. Our data show that patients with MPMs (i) have a significantly increased family history of melanoma (36.0% vs. 6.1% in SPM patients); (ii) have a significantly increased risk of internal cancers; (iii) have their thickest tumors similar in thickness to that of SPM, with subsequent tumors thinner than the first, and (iv) develop their second melanoma within 10 years of their first (92.3% of MPM patients). In addition, those MPM patients with only MIS have better outcomes compared with patients with a single MIS. Our results suggest that, overall, patients with multiple primary invasive melanomas are at increased risk of death compared with patients with single primary invasive melanomas, but in our population, multiplicity appears to be a weaker predictor of mortality than previously reported.

Our data are similar to results from recent publications that also account for immortal time bias; however, our study highlights important factors leading to a decreased effect size (Pardo et al., 2016; Youlden et al., 2016). First, previous studies differed from ours in the adjustments made for possible confounding factors. Here, we have controlled for race, family history of melanoma, personal history of internal malignancy, site, and nodal and metastatic status; neither of the previous studies controlled for all of these factors, each of which have been shown to influence melanoma outcomes (Dawes et al., 2016; Ford et al., 1995; Holland et al., 1999; Lachiewicz et al., 2008; Lasithiotakis et al., 2008; Mahendraraj et al., 2017; Monzon et al., 1998; Spanogle et al., 2010; Zell et al., 2008). The Youlden study did not adjust for nodal or metastatic status; in contrast, Pardo et al. did adjust for these factors, which resulted in a significantly decreased HR of 1.32 (95% CI = 1.17–1.50) compared with the HR of 2.10 (95% CI = 1.57–2.59) reported by Youlden et al. Adjusting for additional relevant confounders in our study resulted in a similar HR as in the Pardo et al. study but a loss in statistical significance. These additional risk factors (personal history of malignancy and family history) shifted the hazard ratio slightly, which may be important given recent evidence that genetic factors are important in prognosis for patients with multiple melanoma (Helgadottir et al., 2017), although our study may not be statistically powered to conclusively show this. Second, our population is distinct both in genetic and environmental background. The studies by Youlden et al. and Pardo et al. were conducted in a relatively homogenous fair-skinned population; it is important to assess outcome results in different populations (McEvoy et al., 2009; US Census Bureau, 2016; Weiner, 2015). The study population in Pardo et al. differed from that in the Youlden et al. study and our study by having a greater proportion of females to males, which may explain the lower risk found by Pardo et al., because women have better outcomes compared with men (Nosrati and Wei, 2014). Pardo et al. also had a higher proportion of younger patients in the multiple melanoma patient group compared with single melanoma patients, whereas the multiple melanoma patients in the Youlden et al. study and ours were older on average than the single melanoma patients. Finally, in our MPM group, the average thickness of

the thickest invasive melanomas did not differ from the average thickness of the invasive melanomas in the SPM group, and subsequent tumors were significantly thinner compared with the initial MPM tumor, similar to findings by others (Bower et al., 2010; Menzies et al., 2017; Moore et al., 2015) and consistent with our findings that the outcomes were not significantly different in the MPM vs. SPM groups. In the Youlden et al. cohort, the MPM tumors were thicker than those in their SPM group and more likely to be ulcerated, and the subsequent melanomas were thicker than the initial MPM; these key differences in tumor characteristics likely contributed to the worsened outcome seen in their MPM cohort.

We corrected for immortal time bias using an appropriate time-varying survival model and directly compared the time-varying survival model to the classic model using the first melanoma as the index tumor. The correction for immortal time bias is critical, as can be seen by the difference in results presented in Table 6. Using the first melanoma as the index tumor to calculate survival erroneously suggests that patients with multiple melanoma have decreased mortality. Our results support current clinical recommendations by the American Joint Committee on Cancer, which focus on prognostication using the most severe melanoma with less emphasis on multiplicity of melanomas (Gershenwald et al., 2017).

There are several additional hypotheses to explain the decrease in effect size observed in our patients with multiple primary melanomas. Some authors have suggested that sinecomitant immunity may develop in patients with multiple melanomas, effectively immunizing them to progression of their tumors (Doubrovsky and Menzies, 2003). In addition, the biology of tumors from patients with multiple melanoma may be distinct (Bower et al., 2010), possibly linked to the significantly increased percentage of positive family history in these patients (36.0%) compared with patients with only one melanoma (6.1%), suggesting significant genetic differences; a previous study found that 19% of MPM patients had germline mutations in *CDKN2A* compared with 4.4% of patients with SPM (Bruno et al., 2016). Furthermore, once a patient has a diagnosis of the first melanoma, medical and personal surveillance likely increases, and sun-seeking behavior may be curbed, resulting in subsequent melanomas that are thinner than the first; this is supported by our and others' findings (Bower et al., 2010; Menzies et al., 2017; Moore et al., 2015) that average thickness of subsequent tumors is significantly thinner than the first tumor in MPM patients.

There were several limitations of this study. Our patients were drawn from a single academic tertiary referral center, the cohort was not population based, and our study is smaller than other recent studies. A further limitation is that the standard of treatment for patients at early time points in our data set may not reflect current treatment strategies. However, our study adjusts for several relevant confounding factors, including race, family history of melanoma, personal history of internal malignancy, site, and nodal and metastatic status, which were lacking in earlier studies. Larger studies, with the inclusion of these covariates, are needed to corroborate our survival results.

Rising incidence of melanoma and increased survival have led to a growing population of patients with multiple melanomas. It is therefore critical that accurate prognostic information is available to guide patient counseling and clinical management. Our data

indicate that patients with multiple melanomas should be considered for genetic counseling, as guided by the family history; that clinicians should be aware of the increased risk of multiple internal cancers; that most of the second melanomas will occur within 5 years of the first; and that the vast majority of patients will have their second melanoma within 10 years of the first. Further genetic studies may shed light on the relationship between family history and melanoma multiplicity.

## METHODS

### Design and Setting

A prospective, single-institution, multidisciplinary database of patients seen at the University of California, San Francisco with melanoma was retrospectively reviewed. Patients with a diagnosis of melanoma of any type were included. Data extraction was supervised by a certified tumor registrar in accordance with the American College of Surgeons, Commission on Cancer per the *Facility Oncology Registry Data Standards Manual* (https://www.facs.org/quality-programs/cancer/ncdb/registrymanuals/cocmanuals/fordsmanual). Patients with multiple primary melanomas were defined as those with two or more primary melanomas based on the Surveillance, Epidemiology, and End Results multiple primary histology guidelines (Johnson et al., 2007). Synchronous melanomas were defined as those diagnosed on the same date. The study was approved by the University of California, San Francisco Institutional Review Board; the requirement for written consent was waived because many subjects are no longer being followed at the institution or are deceased and the large number of records required made it impracticable to contact all potential subjects.

### Measures

Outcomes were overall survival and melanoma-specific survival. A search for vital status (most recent date alive vs. date of death) was performed at least yearly for all melanoma patients. Sources for vital status information included both active and passive follow-up processes such as searching the University of California, San Francisco electronic medical record; direct patient contact; contacting patient's family; contacting patients' physicians; other treating facilities; and/or matching to state registry death certificate files, Department of Motor Vehicles registration, or voter registration. In addition, for all patients who are lost to follow-up for more than 1 year, yearly internal and online confirmation of alive or dead status was done. In all cases, cause of death reflects information from a death certificate.

### Statistical analysis

Continuous variables were described using means and standard deviations, and proportions were calculated for categorical variables. We compared groups using either the Kruskal-Wallis test or chi-square test as appropriate. Proportional hazards regression models were used for mortality, with MPM/SPM status entered as a time-varying covariate. Individuals with synchronous melanomas were classified as MPM throughout follow-up. This allowed the calculation of HRs comparing the MPM and SPM groups, adjusted for a prespecified set of possible confounders (Levesque et al., 2010). Patients were censored at the end of follow-up, which we defined as the date of last known contact. To identify independent significant risk factors for the occurrence of MPMs, correcting for all other possible risk factors, a

cause-specific proportional hazards model was used in a competing risk framework (with melanoma-specific mortality as the competing risk) (Kalbfleisch and Prentice, 2002). When data on competing risk factors such as family history of melanoma were missing from the record, they were coded as unknown but still included in the analysis. For comparison, a competing risk proportional hazards model for the subdistribution functions was also used (Fine and Gray, 1999). It is inappropriate to treat death as a censoring event when considering the risk of developing an MPM because time to death is unlikely independent of time to an MPM. All analyses were run using SAS, version 9.4.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Abbreviations:

| | |
|---|---|
| **CI** | confidence interval |
| **HR** | hazard ratio |
| **MPM** | multiple primary melanoma |
| **SEER** | Surveillance, Epidemiology, and End Results Program |
| **SPM** | single primary melanoma |

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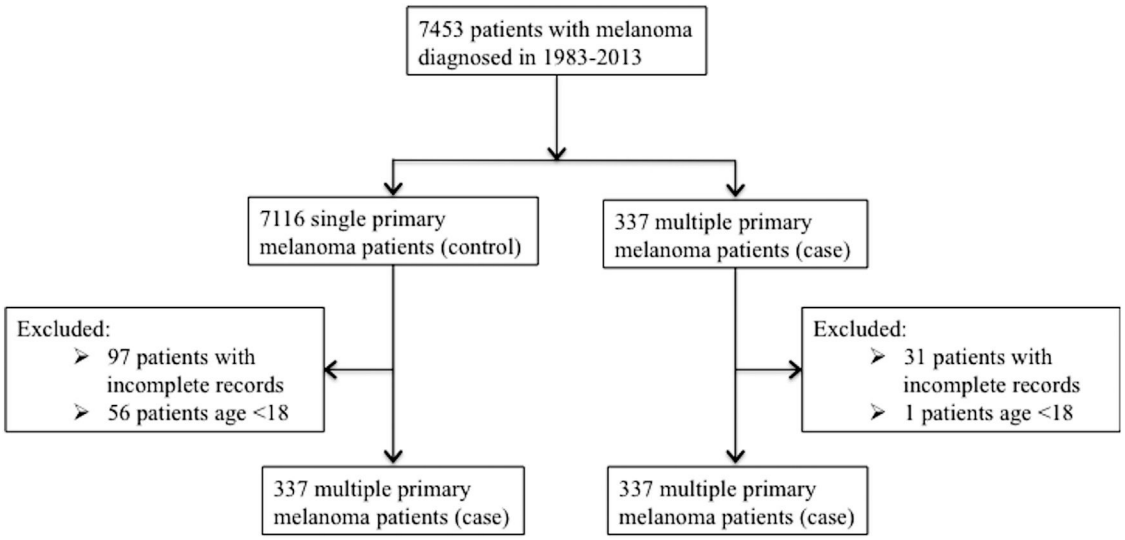


**Figure 1. Consolidated Standards of Reporting Trials (CONSORT) diagram.**
Schematic decision tree depicting study subject inclusion and exclusion criteria.

**Table 1.**

Patient characteristics

| Patient Characteristics | SPM (n = 6,963) | MPM (n = 305) | *P*-Value |
|---|---|---|---|
| Age in years[1] | | | <0.0001 |
| Mean ± SD | 55.8 ± 16.2 | 60.2 ± 15.2 | |
| Sex, n (%) | | | <0.0001 |
| Male | 4,062 (58.3) | 207 (67.9) | |
| Female | 2,901 (41.7) | 98 (32.1) | |
| Race, n (%) | | | <0.05 |
| White | 6,440 (92.5) | 298 (97.7) | |
| Asian | 82 (1.2) | 0 (0) | |
| Black | 34 (0.5) | 0 (0) | |
| Hispanic | 207 (3) | 3 (1) | |
| Native American | 6 (0.1) | 0 (0) | |
| Other | 44 (0.6) | 0 (0) | |
| Unknown | 150 (2.2) | 4 (1.3) | |
| Family history of melanoma, n (%) | n = 1,965 | n = 141 | <0.0001 |
| No | 1,845 (93.9) | 90 (64.0) | |
| Yes | 120 (6.1) | 51 (36.0) | |
| Follow-up time, years, mean ± SD | 8.3 ± 6.3 | 8.8 ± 5.9 | |
| Overall deaths | 2,973 (42.6) | 101 (33.2) | |
| Melanoma-specific deaths | 1,444 (20.7) | 50 (16.4) | |
| 5-year survival rate, % (95% CI) | 72 (71–73) | 65 (58–74) | |
| 10-year survival rate, % (95% CI) | 58 (57–60) | 49 (40–61) | |

Abbreviations: CI, confidence interval; MPM, multiple primary melanoma; SD, standard deviation; SPM, single primary melanoma.

[1]At time of first melanoma diagnosis.

**Table 2.**

Multiple melanoma characteristics

| Patient Characteristics | MPM (n = 305) |
|---|---|
| Number of melanomas, n (%) | |
| 2 | 260 (85) |
| 3 | 30 (10) |
| >4[1] | 15 (5) |
| Time interval between first and second melanomas in years, n (%)[2] | |
| <1 | 111 (43.7) |
| 1–2 | 35 (13.7) |
| 2–5 | 50 (19.6) |
| 5–10 | 39 (15.3) |
| ≥10 | 19 (7.4) |
| Median time in years (95% CI) to second tumor | 1.4 (1.0–1.9) |

Abbreviations: CI, confidence interval; MPM, multiple primary melanoma.

[1] Highest number of melanomas was 13.

[2] Patients with asynchronous melanomas only (n = 254).

**Table 3.**

Internal malignancies in SPM patients, MPM patients, and the general population

| Other Internal Cancers | Patients with SPMs, n (%) (n = 6,963) | Patients with MPMs, n (%) (n = 305) | *P*-Value | Cancer Prevalence in General Population (SEER), % |
|---|---|---|---|---|
| Liver | 1 (0.01) | 1 (0.32) | 0.001 | 0.01 |
| Pleura | 2 (0.02) | 1 (0.32) | 0.01 | 0.0013 |
| Prostate | 127 (1.82) | 11 (3.60) | 0.02 | 1.52 |
| Bladder | 21 (0.30) | 3 (0.98) | 0.03 | 0.13 |
| Breast | 71 (1.01) | 3 (0.98) | 0.99 | 0.72 |
| Colon | 23 (0.33) | 2 (0.65) | 0.32 | 0.29 |
| Kidney | 18 (0.25) | 2 (0.65) | 0.18 | 0.09 |
| Brain | 17 (0.24) | 1 (0.32) | 0.75 | 0.03 |
| Leukemia | 22 (0.31) | 1 (0.32) | 0.95 | 0.08 |
| Non-Hodgkin’s Lymphoma | 44 (0.63) | 2 (0.65) | 0.93 | 0.14 |
| Rectum | 19 (0.26) | 1 (0.32) | 0.84 | 0.29 |
| Thyroid | 20 (0.28) | 1 (0.32) | 0.88 | 0.13 |
| All Internal Malignancies | 437 (5.8) | 27 (8.8) | | |

Abbreviations: MPM, multiple primary melanoma; SEER, Surveillance, Epidemiology, and End Results Program; SPM, single primary melanoma.

**Table 4.**

Tumor site

| Tumor Characteristics | SPM (n = 6,963) | MPM (n = 694) | *P*-Value |
|---|---|---|---|
| Anatomic site, n (%) | | | <0.05 |
| Head and neck | 1,942 (27.8) | 211 (30.4) | |
| Trunk | 1,814 (26) | 195 (28) | |
| Upper extremity | 1,347 (19.3) | 162 (23.3) | |
| Lower extremity | 1,450 (20.8) | 116 (16.7) | |

Abbreviations: MPM, multiple primary melanoma; SPM, single primary melanoma.

**Table 5.**

Tumor depth, SEER staging, and AJCC staging for multiple melanomas and subgroups compared with single melanomas

| Tumor Characteristics | SPM | MPM | First Tumor among MPMs | Subsequent Tumors among MPMs | Thickest Tumor among MPMs |
|---|---|---|---|---|---|
| Breslow depth in mm, n (%) | n = 2,729 | n = 677 | n = 293 | n = 304 | n = 293 |
| Mean[1] ± SD (*P*-value[2]) | 2.2 ± 2.4 | 1.6 ± 2.0 (<0.0001) | 2.2 ± 2.4 (0.98) | 1.1 ± 1.2 (<0.0001) | 2.5 ± 2.0 (0.21) |
| 0, MIS | 411 (15.1) | 263 (38.8) | 69 (23.6) | 151 (49.7) | 36 (12.3) |
| 0.1–1.0 | 757 (27.7) | 239 (35.4) | 104 (35.5) | 106 (34.9) | 118 (40.3) |
| 1.1–2.0 mm | 758 (27.8) | 74 (10.9) | 55 (18.8) | 16 (5.3) | 55 (18.8) |
| 2.1–4.0 mm | 491 (18.0) | 74 (10.9) | 41 (13.9) | 28 (9.2) | 59 (20.1) |
| >4.0 mm | 312 (11.4) | 27 (4.0) | 24 (8.2) | 3 (1.0) | 25 (8.5) |
| Distribution *P*-value[3] | — | <0.0001 | <0.0001 | <0.0001 | 0.0009 |
| AJCC staging, n (%) | n = 5,462 | n = 674 | n = 275 | n = 272 | n = 275 |
| 0 | 1,064 (19.5) | 264 (39.2) | 64 (23.3) | 142 (52.2) | 39 (14.2) |
| 1 | 2,006 (36.7) | 272 (40.4) | 121 (44.0) | 97 (35.7) | 128 (46.6) |
| 2 | 1,183 (21.7) | 86 (12.8) | 55 (20.0) | 24 (8.8) | 65 (23.6) |
| 3 | 856 (15.7) | 42 (6.2) | 30 (10.9) | 6 (2.2) | 35 (12.7) |
| 4 | 353 (6.5) | 10 (1.5) | 5 (1.8) | 3 (1.1) | 8 (2.9) |
| Distribution *P*-value[3] | — | <0.0001 | 0.0001 | <0.0001 | 0.006 |
| SEER staging, n (%) | n = 6,321 | n = 685 | n = 300 | n = 320 | n = 297 |
| In situ | 1,051 (16.6) | 263 (38.4) | 70 (23.3) | 164 (51.3) | 39 (13.3) |
| Local | 3,827 (60.5) | 359 (52.4) | 189 (63.0) | 140 (43.8) | 204 (68.7) |
| Regional | 1,067 (16.9) | 49 (7.2) | 32 (10.7) | 13 (4.1) | 44 (14.8) |
| Distal | 376 (5.9) | 14 (2.0) | 9 (3.0) | 3 (0.9) | 10 (3.4) |
| Distribution *P*-value[3] | — | <0.0001 | 0.0003 | <0.0001 | 0.02 |

Abbreviations: AJCC, American Joint Committee on Cancer; MPM, multiple primary melanoma; SEER, Surveillance, Epidemiology, and End Results Program; SPM, single primary melanoma.

[1] Invasive melanomas only, excludes melanoma in situ.

[2] *P*-values denote comparison of mean to that of SPM by *t* test or by generalized linear model in the case of subsequent tumors among MPM.

[3] *P*-values denote comparison of distributions to that of SPM by chi-square test.

**Table 6.**

Hazard ratios for mortality of patients with multiple versus single primary melanomas

| Mortality Analysis MPM versus SPM | HR (95% CI), All Cause Death | Patients | Events | Follow-Up[1] | HR (95% CI), Melanoma Related Death | Patients | Events | Follow-Up[1] |
|---|---|---|---|---|---|---|---|---|
| All melanomas | | | | | | | | |
| Unadjusted Model | 1.16 (0.94–1.43) | 6,300 | 2,335 | 53,153 | 1.17 (0.86–1.59) | 6,300 | 1,086 | 53,153 |
| Adjusted Model[2] | 1.09 (0.87–1.34) | 6,300 | 2,335 | 53,153 | 1.27 (0.93–1.73) | 6,300 | 1,086 | 53,153 |
| First Tumor as Index | 0.73 (0.60–0.89) | 7,266 | 3,070 | 60,183 | 0.78 (0.59–1.04) | 1,493 | 1,493 | 7,247 |
| Invasive only | | | | | | | | |
| Unadjusted model | 1.33 (0.99–1.79) | 5,497 | 2,360 | 44,562 | 1.47 (1.0–2.2) | 5,497 | 1,227 | 44,563 |
| Adjusted model[2] | 1.21 (0.87–1.67) | 5,497 | 2,360 | 44,562 | 1.44 (0.95–2.2) | 5,497 | 1,227 | 44,563 |
| MIS only | | | | | | | | |
| Unadjusted model | 1.19 (0.56–2.5) | 1,117 | 198 | 9,578 | NA | NA | NA | NA |
| Adjusted model[2] | 0.81 (0.4–1.62) | 1,117 | 198 | 9,578 | NA | NA | NA | NA |

Abbreviations: CI, confidence interval; HR, hazard ratio; MIS, melanoma in situ; MPM, multiple primary melanoma; NA, not applicable; SPM, single primary melanoma.

[1]Follow-up time in person-years.

[2]Adjusted for sex, age, ethnicity, site, SEER stage, family history of melanoma, and personal history of malignancy.