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Similar survival of patients with multiple versus single primary melanomas based on Utah Surveillance, Epidemiology, and End Results data (1973–2011)

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Abstract

Background: Survival data are mixed comparing patients with multiple primary melanomas (MPM) to those with single primary melanomas (SPM).

Objectives: We compared MPM versus SPM patient survival using a matching method that avoids potential biases associated with other analytic approaches.

Methods: Records of 14,138 individuals obtained from the Surveillance, Epidemiology, and End Results registry of all melanomas diagnosed or treated in Utah between 1973 and 2011 were reviewed. A single matched control patient was selected randomly from the SPM cohort for each MPM patient, with the restriction that they survived at least as long as the interval between the first and second diagnoses for the matched MPM patient.

Results: Survival curves ($n = 887$ for both MPM and SPM groups) without covariates showed a significant survival disadvantage for MPM patients (chi-squared 39.29, $P < .001$). However, a multivariate Coxproportional hazards model showed no significant survival difference (hazard

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ratio 1.07, $P = .55$). Restricting the multivariate analysis to invasive melanomas also showed no significant survival difference (hazard ratio 0.99, $P = .96$).

Limitations: Breslow depth, ulceration status, and specific cause of death were not available for all patients.

Conclusions: Patients with MPM had similar survival times as patients with SPM. (J Am Acad Dermatol 2018;79:238–44.)

CAPSULE SUMMARY

- It is unclear whether patients with multiple primary melanomas (MPMs) have shorter survival than those with single primary melanomas (SPMs).
- MPM versus SPM patient survival were compared using a matching method that avoids potential biases associated with other analytic approaches.
- No survival difference was observed between MPM and SPM patients.

Keywords

melanoma; multiple primary; SEER; survival

An estimated 87,110 Americans will be diagnosed with invasive melanoma in 2017,¹ and melanoma incidence in the United States is projected to continue to increase at a rate of 3% annually.² Mortality rates have risen by 1.5% annually, with a current estimate that 9730 Americans will die from melanoma in 2017.¹ The risk of developing a second primary melanoma ranges from 6% to 12% in various studies^{3–5} and is increased in individuals with nevi, a family history of melanoma, and fair skin.⁶ The literature is divided concerning the prognosis of patients with multiple primary melanomas (MPMs) compared to those with a single primary melanoma (SPM). Multiple studies^{7–9} report longer survival in patients with SPM over MPM, while others report shorter^{10–14} or similar^{15–17} survival in SPM compared to MPM patients (Table I). Several groups have promulgated an “immunization” hypothesis,^{13,14} in which the first melanoma primes an immune response that controls the growth and metastasis of subsequent melanomas to explain their findings of longer survival in MPM compared to SPM patients. However, many potential confounding factors may affect survival analysis in patients with MPM. First, patients are more likely to be under closer skin surveillance after having SPM, so MPM are more likely to be detected at an earlier stage and therefore have a better prognosis. Indeed, an evaluation by Bradford et al¹⁸ of 9 cancer registries of the Surveillance, Epidemiology, and End Results (SEER) program from 1973 to 2006 that included 89,515 patients who survived 2 months after their initial melanoma diagnosis found that second melanomas were more likely to be thin compared to the first in MPM patients (depth <1.00 mm in 78% vs. 70%). Similarly, Murali et al¹⁹ reported that subsequent primary melanomas tended to be thinner than the first lesion. Second, in considering survival time starting from the first melanoma diagnosis, patients with MPM may exhibit improved survival as a consequence of living longer, therefore having a greater opportunity to develop additional melanomas. Third, in considering survival time from the most recent diagnosis in patients with MPM, patients with SPM may exhibit longer survival as a consequence of disregarding the survival time between the first and last melanomas.

Utah leads the nation in both melanoma incidence and mortality,²⁰ and therefore SEER data from Utah were analyzed to address the question of survival time after diagnosis in patients with MPM versus SPM. A novel patient-matching strategy was used that was designed to avoid the potential pitfalls of statistical approaches used in previous studies. After correction for multiple variables, no difference was observed in survival time after first diagnosis between patients with MPM and SPM.

METHODS

Patients

The Utah Cancer Registry (UCR) established statewide required reporting of primary cancers diagnosed or treated in Utah in 1966 and became one of the original National Cancer Institute SEER cancer registries in 1973. Melanomas recorded in the UCR represent histologically confirmed, independent primary cancers, including both in situ and invasive lesions. The analysis reported here reviewed 18,753 records of 14,138 individuals obtained from the SEER registry of melanomas diagnosed or treated in Utah between 1973 and 2011. A total of 887 MPM patients, defined as having 2 primary melanomas diagnosed 1 year from each other (to exclude multiple synchronous primary melanomas), and 9984 SPM patients were identified. To eliminate potential survival bias wherein SPM patients may not survive long enough to have a second primary melanoma a single matched control was selected randomly from the SPM cohort for each MPM patient, with the restriction that they survived at least as long as the interval between the first and second diagnoses for the matched MPM patient. Each control case was used only once. This study was approved by the University of Utah Institutional Review Board.

Statistical analysis

Survival time in months was calculated from the first diagnosis for both MPM and matched SPM patients until either date of death (any cause) or December 31, 2011 (censor date). Available variables were compared between the matched MPM and SPM patients. Breslow depth and ulceration status were not available for many patient tumors and therefore were not included in the multivariate survival analysis. A Mantel–Cox chi-squared test was used to compare categorical variables and Student *t* tests were used to compare continuous variables. Kaplan–Meier survival analysis was carried out to compare survival curves between patients with MPM and SPM without respect to covariates. A multivariate Cox proportional hazards model was built using diagnosis age, diagnosis year, sex, invasive (yes or no), location (hip and lower extremity), and location (face) as covariates. SPSS statistical software (version 24.0; IBM Corporation, Armonk, NY) was used for the analyses.

RESULTS

A total of 887 MPM/SPM pairs were successfully matched and included in the initial analyses. The 2 groups differed significantly by sex, living status, site, stage, and histologic subtype; MPM patients exhibited female predominance, a higher death rate, a proclivity for the face and not the lower extremities, a greater proportion of lentigo maligna subtype and more in situ tumors, while ulceration status was not different (Table II). The MPM cohort

was significantly older and the diagnosis year was later than the SPM cohort. Breslow thickness for the first melanoma was not significantly different between the 2 groups (Table III). The mean follow-up time was 173.9 months (14.5 years). Unadjusted Kaplan–Meier survival analysis comparing matched MPM and SPM patients showed a significant survival disadvantage for MPM patients with a chi-squared valued of 39.29 ($P < .001$), as shown in Fig 1. Because multiple factors differed significantly in SPM and MPM matched patients (Tables II and III), a multivariate Cox proportional hazards model was built with diagnosis age, diagnosis year, sex, invasive, and location (hip and lower extremity, face) as covariates. As shown in Fig 2, this analysis showed no significant survival difference between MPM and matched SPM patients with a hazard ratio (HR) of 1.07 (95% confidence interval [CI] 0.87–1.31; $P = .55$). We repeated the analysis with only diagnosis year and diagnosis age as covariates (because the former was nearly significant and the latter was significant in the larger model). The HR was 1.08 (95% CI 0.88–1.32; $P = .48$). A summary of the statistics for the Cox model incorporating multiple variables is shown in Table IV.

Several additional analyses were performed to address different analytical methods used in previous studies. First, to address the possibility that using all patients and survival time from the first diagnosis would agree with previous papers that showed a survival time advantage for MPM patients, the same multivariate analysis used with our matched cases was applied to all patients without matching. The results showed significantly longer survival time for MPM patients (HR 0.632 [95% CI 0.56–0.71]; $P < .001$), consistent with a longer survival time bias favoring MPM with this approach. Second, all patients were included, and survival time was counted from the second melanoma occurrence for MPM patients (with the restriction that the second diagnosis not be synchronous). Applying the same multivariate Cox regression model, there was a significantly shorter survival time for patients with MPM (HR 1.25 [95% CI 1.08–1.43]; $P = .002$), consistent with a shorter survival time bias favoring SPM with this approach. In addition, because the MPM cohort contained more in situ melanomas, we restricted the corrected analysis to only invasive melanomas among the matched MPM and SPM patients (SPM, $n = 615$; MPM, $n = 504$), and observed no survival difference between MPM and matched SPM patients (HR 0.99 [95% CI 0.76–1.29]; $P = .96$), suggesting that statistical control for this variable was adequate. Finally, because diagnosis age was the only significant variable in the Cox model (Table IV), survival analysis was repeated using only this variable, resulting in a nonsignificant difference in survival between the 2 groups (HR 1.11 [95% CI 0.91–1.37]; $P = .30$). Therefore, age at diagnosis alone explains most of the difference between the unadjusted Kaplan–Meier and corrected Cox regression results.

DISCUSSION

Conflicting conclusions regarding differences in survival time for MPM versus SPM patients evident in the literature (Table I) likely stem from different statistical approaches used. Many previous studies^{10–15} measured survival from the time of the first diagnosis, which results in a survival bias toward improved survival for multiple melanomas, because individuals having a greater opportunity to develop additional melanomas have generally lived longer. Indeed, Cox regression analysis performed with our entire MPM and SPM cohorts with no correction or matching showed a significant survival advantage for MPM patients (not

shown). In other studies,^{16,17} survival was calculated from the date of the most recently diagnosed MPM. This method biases toward decreased survival time estimates for MPM patients, because the time between the first and second primary melanomas is not taken into account. Youlden et al⁸ used a delayed-entry method, also known as left truncation, which incorporates the time between the diagnosis of the first and second melanomas, but only time after the second melanoma contributes to the survival analysis.

The approach presented here differed from those discussed above, in that SPM controls were matched by ensuring they survived at least as long as the time between development of first and second melanomas in MPM patients. This method mitigates survival bias seen if SPM patients do not survive long enough to have a second diagnosis, or an opposite survival bias introduced by starting the survival time at the second melanoma diagnosis for MPM patients. After controlling for the multiple differences between the MPM and matched SPM patients, no significant survival difference existed between the groups (Fig 2, Table IV). These results are consistent with 3 previous studies^{15–17} that used various statistical approaches.

An “immunization” hypothesis—in which the first melanoma primes an immune response that controls the growth and metastasis of subsequent melanomas—has been promulgated by several groups^{13,14} to explain their findings of increased survival in MPM patients. Rather, it seems more likely that patients with a high-risk first melanoma are less likely to survive long enough to have multiple melanomas, and that patients are subjected to more intense surveillance after their first melanoma.

The patients in the Utah MPM cohort were older and female, with a predominance of lentigo maligna subtype on the face, compared to matched SPM patients (Table II). Most previous studies found that patients with MPM were older males,^{7,8,12,14,17,21–23} while 2 studies did not find a sex difference.^{11,12} One report noted that subsequent melanomas were more likely to be located on the head and neck and to be of the lentigo maligna subtype,²³ similar to the Utah findings; however, most previous studies reported that MPM cohorts tend to develop subsequent melanomas in similar distribution sites to their initial melanoma,^{13,16,21} most commonly on the trunk,^{7–9,11} and of the superficial spreading subtype followed by the nodular subtype.^{7,10,16}

A limitation of our study, as in all registry-based studies, was that not all information was available for all the patients. Specifically, Breslow depth and ulceration were missing from approximately 85% and 75% of the patients, respectively, because this particular information was not collected by the UCR before 2004. While these factors are major contributors to tumor stage, we did address tumor stage differences between the 2 groups by including in situ versus invasive status in our multivariate analysis. In addition, we did not have melanoma specific cause of death information and used death from any cause. It seems unlikely that specific cause of death would be different between patients with MPM and SPM.

In summary, no survival difference was observed between MPM and matched SPM patients in the Utah SEER data. Given the increased likelihood of improved surveillance resulting in

thinner subsequent melanomas in patients following their initial diagnosis,^{18,19} it is likely that the most important factor in long-term survival for MPM patients is the nature of their first melanoma. These results suggest agreement with Grob²⁴ that MPM is not a distinct biologic entity, and that long-term prognosis for individuals who survive their first melanoma is more dependent on compliance with self-skin examinations and frequent skin surveillance by an experienced provider to facilitate earlier detection of subsequent melanomas.

In conclusion, using a novel matching approach, a survival difference in patients with MPM versus those with SPM was not observed.

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Abbreviations used:

HR	hazard ratio
MPM	multiple primary melanoma
SPM	single primary melanoma
SEER	Surveillance, Epidemiology, and End Results

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Fig 1. Univariate survival analysis. Survival curves of 887 patients with multiple primary melanoma (MPM) and 887 matched patients with single primary melanoma (SPM). Chi-squared = 39.29, $P < .001$.

Fig 2.

Multivariate survival analysis. Survival curves of 887 patients with multiple primary melanoma (MPM) and 887 matched patients with single primary melanoma (SPM) using a Cox proportional hazards model with diagnosis age, diagnosis year, sex, invasive (yes or no), and location (hip and lower extremity, face) as covariates. The hazard ratio for MPM was 1.07 (95% confidence interval 0.87–1.31; $P = .55$).

Table I.

Summary of previous survival studies in patients with multiple primary melanomas

Study, year	Data source, study period	No. of MPMs (no. of patients)	Median follow-up (y)	Stages included	Entry point for analysis	Results (MPM vs SPM)	Survival
Rowe et al, ⁷ 2015	Queensland Study of Melanoma, 1982–2004	190 (1068)	24.4	Stages I and II	Model 1: first tumor; model 2: most recent MPM	Model 1: HR 1.8, NS; model 2: HR 2.76; $P = .017$	SPM > MPM
Youlden et al, ⁸ 2016	Queensland Cancer Registry, 1995–2008	2330 (32,238)	9.3	Invasive and NOS	Delayed-entry model	2 MPM HR2.01, $P < .001$; 3 MPM HR 2.91, $P < .001$	SPM > MPM
Utjes et al, ⁹ 2017	Swedish Melanoma Register, 1990–2007	700 (27,235)	8.6	Stages I, II, III, and IV	Date of second tumor	HR 1.48, $P < .001$	SPM > MPM
Burden et al, ¹⁵ 1994	Scottish Melanoma Group, 1979–1991	45 (3818)	Not reported	Invasive and NOS	First tumor	NS, $P = .058$	MPM = SPM
Hwa et al, ¹⁶ 2012	Melanoma Database at New York University, 2002–2008	61 (788)	3.2 (SPM), 3.7 (MPM)	Stages I, II, and III	Most recent MPM	HR 1.01, NS	MPM = SPM
Kricker et al, ¹⁷ 2013	Cancer registries in Australia, Canada, Italy and U.S., 1998–2003	1206 (3578)	7.6 overall; 8 (SPM) and 6.6 (MPM)	Stages 0, I, II, III, and IV	Most recent MPM	HR 1.24, NS	MPM = SPM
Scheibner et al, ¹⁰ 1982	Sydney Hospital, 1951–1980	90 (3128)	Not reported	Stage I	First tumor	Men: 88.9% vs 66.8%, $P = .05$; women: 86.5% vs 82.7%, NS	MPM > SPM (men only)
Slingluff, Jr et al, ¹¹ 1993	Duke Cancer Center, 1972–1993	283 (7530)	3.7 (SPM), 4.8 (MPM)	Invasive and NOS	First tumor	Improved survival, $P = .003$	MPM > SPM
Dobrovsky and Menzies, ¹⁴ 2003	Sydney Melanoma Unit Database, 1983–1999	298 (5250)	3.7 (SPM), 5.7 (2), and 7.0 (3+)	Stages I and II	First tumor	Patients with >3 tumors survived longer than those with 1 or 2 tumors, $P = .01$	MPM > SPM
Bower et al, ¹² 2010	Sunbelt Melanoma Trial, 1997–2003	48 (2506)	5.5	Stages I (1 mm) and II	First tumor	Similar DFS, but better OS (5-year 95.3% vs 80%, $P = .005$)	MPM > SPM
Savoia et al, ¹³ 2012	Centra Melanomi of University of Turin, 1975–2009	270 (4292)	Not reported	Stages 0, I, and II	First tumor	OS HR0.55, $P = .001$; DFS HR 0.7, $P = .010$	MPM > SPM

DFS, Disease-free survival; HR, hazard ratio; MPM, multiple primary melanoma; NOS, not otherwise specified; NS, not significant; OS, overall survival; SPM, single primary melanoma.

Table II.

Comparison of categorical variables for patients with multiple primary melanoma and matched patients with single primary melanoma

Variable	MPM, n	SPM, n	Chi-squared*	p value
Sex				
Female	588	437	52.7	<.001
Male	299	450		
Death				
No	650	727	19.2	<.001
Yes	237	160		
Site				
Face	326	202	60.3	<.001
Scalp, neck	88	62		
Trunk	187	221		
Upper limb, shoulder	173	212		
Lower limb, hip	99	166		
NOS	14	24		
Stage				
In situ	383	272	28.9	<.001
Localized	441	528		
Regional	37	40		
Distant	3	8		
Histologic subtype (<i>ICD-O-3.1</i> code)				
Melanoma in situ (8720/2)	95	93	0.02	.94
Lentigo maligna (8742/2)	539	682	53	<.001
Invasive melanoma				
Lentigo maligna melanoma (8742/3)	79	53	5.1	.02
Nodular (8721)	31	40	1.2	.33
Superficial spreading (8743)	182	255	15.7	<.001
NOS, other [†]	212	267	8.3	.004
Ulceration [‡]				
Absent	234	176	0.39	.25
Present	22	12		

ICD-O-3.1, International Classification of Diseases for Oncology, version 3.1; MPM, multiple primary melanoma; NOS, not otherwise specified; SPM, single primary melanoma.

* Used to compare categorical variables.

[†] Includes amelanotic, nevus-derived, acral lentiginous, desmoplastic, and spindle cell melanoma subtypes.

[‡] Ulceration status was unavailable for 631 patients with MPM and 699 patients with SPM.

Table III.

Comparison of continuous variables for patients with multiple primary melanoma and matched patients with single primary melanoma

Variable	N	Mean (SD)	P value *
Survival, months			
MPM	887	143.8 (96.9)	<.001
SPM	887	172.3 (110.2)	
Diagnosis year			
MPM	887	1997.9 (8.6)	<.001
SPM	887	1995.1 (9.9)	
Diagnosis age, y			
MPM	887	60.8 (15.4)	<.001
SPM	887	49.7 (18.0)	
Breslow thickness, mm [†]			
MPM	142	1.06 (1.27)	.52
SPM	123	0.96 (1.42)	

MPM, Multiple primary melanoma; SD, standard deviation; SPM, single primary melanoma.

* Student *t* tests were used to compare continuous variables.

[†] Breslow depth was unavailable for 745 patients with MPM and 764 patients with SPM.

Table IV.

Summary of multivariate Cox proportional hazards model

Variable	HR (95% CI)	P value
Diagnosis age	1.110 (1.099–1.121)	.000
Diagnosis year	1.017 (1.000–1.036)	.055
Sex	0.930 (0.747–1.158)	.518
Invasive	1.188 (0.955–1.476)	.121
Hip and lower extremity	0.945 (0.643–1.387)	.772
Face	0.867 (0.688–1.093)	.228
Patient (MPM, SPM)	1.067 (0.866–1.314)	.545

CI, Confidence interval; *HR*, hazard ratio; *MPM*, multiple primary melanoma; *SPM*, single primary melanoma.