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Ten-Year Survival after Multiple Invasive Melanomas Is Worse than after a Single Melanoma: a Population-Based Study

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The prognosis of melanoma patients who are diagnosed with multiple primary lesions remains controversial. We used a large population-based cohort to re-examine this issue, applying a delayed entry methodology to avoid survival bias. Of 32,238 eligible patients diagnosed between 1995 and 2008, 29,908 (93%) had a single invasive melanoma, 2,075 (6%) had two, and 255 (1%) had three. Allowing for differences in entry time, 10-year cause-specific survival for these three groups was 89% (95% confidence interval [CI] = 88–90%), 83% (95% CI = 80–86%), and 67% (95% CI = 54–81%), respectively. After adjustment for key prognostic factors, the hazard ratio of death within 10 years from melanoma was two times higher for those with two melanomas (hazard ratio = 2.01, 95% CI = 1.57–2.59; $P < 0.001$) and nearly three times higher when three melanomas were diagnosed (hazard ratio = 2.91, 95% CI = 1.64–5.18; $P < 0.001$) compared with people with a single melanoma. Melanoma-specific mortality remained elevated after adjusting for maximum thickness or ulceration of any melanoma regardless of the index tumor. After appropriately accounting for the interval between diagnosis of the first and subsequent melanomas, patients with multiple invasive melanomas have significantly poorer survival than patients with a single invasive melanoma.

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INTRODUCTION

Steady increases in the incidence of melanoma over past decades have been well documented in North America, Europe, Australia, and New Zealand (Erdmann et al., 2013; Nikolaou and Stratigos, 2014). Because of current high survival rates for melanoma overall (DeSantis et al., 2014; Nikolaou and Stratigos, 2014) combined with a large risk of developing a subsequent primary melanoma (Spanogle et al., 2010; Youlden et al., 2014), growing numbers of patients are consequently being diagnosed with more than one primary invasive cutaneous melanoma during their lifetime. Different studies have estimated that the chance of multiple primary melanomas occurring ranges from less than 1% to more than 10% of patients (Moore et al., 2015); we recently reported that 8% of patients in Queensland with a first primary invasive melanoma were diagnosed with a second primary invasive melanoma (Youlden et al., 2014).

Despite the scale of the problem of multiple primary melanomas, there is little understanding about how multiplicity affects survival compared with a single primary melanoma. This is largely because of the methodological challenges involved. In most previous studies, survival after multiple melanoma has usually been measured from the time of first diagnosis (Bower et al., 2010; Burden et al., 1994; Doubrovsky and Menzies, 2003; Moseley et al., 1979; Murali et al., 2012; Savoia et al., 2012; Scheibner et al., 1982; Slingluff et al., 1993); however, this method produces results that are biased toward improved survival for multiple melanomas (known as "survival bias"), as patients who live longer have greater opportunity to be diagnosed with additional melanomas (Bower et al., 2010; Doubrovsky and Menzies, 2003; Moseley et al., 1979). An alternate approach (Kricker et al., 2013; Rowe et al., 2015) has been to measure survival time from the diagnosis date of the most recent of the multiple primary melanomas, but this technique then biases outcome in the opposite direction because of disregarding the survival time between the first and last melanomas.

Here we examine melanoma-specific survival after multiple primary invasive melanomas in a large population-based cohort. To overcome the limitations of previous studies, we have used a methodology that appropriately incorporates the total period between diagnosis of the first and subsequent melanomas, without introducing a survival bias.

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Abbreviations: CI, confidence interval; HR, hazard ratio

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Table 1. Cohort characteristics of first primary invasive melanomas[1] by the presence of additional primary invasive melanomas, Queensland, 1995–2013[2]

Characteristics of first primary invasive melanoma	Patients with a single primary invasive melanoma	Patients with two primary invasive melanomas	Patients with three or more primary invasive melanomas	*P*
Eligible patients (n)	29,908	2,075	255	
Median follow-up (y)	9.2	9.8	9.9	<0.001
Median age at diagnosis (y)[3]	57	63	65	<0.001
	Col %	Col %	Col %	
Mortality status 10 y after diagnosis[3]				0.041
Alive	77.2	75.6	74.9	
Melanoma-specific death	8.6	9.9	12.5	
Nonmelanoma death	14.2	14.5	12.5	
Sex[3]				<0.001
Males	56.8	69.8	83.1	
Females	43.2	30.2	16.9	
Body site[3]				<0.001
Head and neck	15.5	15.6	13.7	
Trunk	34.7	38.3	40.0	
Upper limbs and shoulders	23.8	24.1	26.7	
Lower limbs	21.6	19.9	18.0	
Not specified	4.5	2.2	1.6	
Morphology[3]				0.011
Nodular melanoma	8.1	8.2	11.4	
Melanoma in naevus	2.2	2.6	3.9	
Lentigo maligna melanoma	5.5	7.1	6.3	
Superficial spreading melanoma	53.8	53.7	50.6	
Other specified melanoma	4.0	3.3	4.7	
Not otherwise specified	26.5	25.2	23.1	
Thickness[3]				<0.001
<1mm	68.8	69.1	64.3	
1 mm to <2 mm	12.8	14.2	17.3	
≥ 2 mm	11.4	13.2	15.7	
Not recorded	7.0	3.6	2.8	
Ulceration[3]				0.002
No	56.5	57.5	59.2	
Yes	8.8	9.6	14.1	
Not recorded	34.8	32.9	26.7	

[1]Characteristics shown are for first primary melanoma only.
[2]First primary invasive melanomas were diagnosed between 1995 and 2008, with follow-up to 31 December 2013 for diagnosis of subsequent primary invasive melanomas (maximum of 10 y of follow-up from the date of diagnosis of the first primary invasive melanoma).
[3]*P*-values based on chi-squared tests for categorical variables and nonparametric *k*-sample tests for medians.

RESULTS

Study cohort

A total of 32,861 individuals were diagnosed with a first primary invasive melanoma in Queensland between 1995 and 2008. Of these, 488 were excluded on the basis of being younger than 15 or older than 89 at the time of diagnosis, 49 were omitted because of coding issues such as the date of death being the same as the date of diagnosis or the basis of diagnosis being either autopsy or death certificate only, and a further 86 were ineligible due to four or more primary invasive melanomas being diagnosed within 10 years of the first melanoma, leaving 32,238 patients (98%) in the study cohort.

The majority (n = 29,908, 93%) of eligible patients were diagnosed with a single primary invasive melanoma, 2,075 (6%) had two primary invasive melanomas, and 255 (1%) were diagnosed with three primary invasive melanomas within 10 years of the index melanoma. For patients with two melanomas, 164 (8%) were synchronous, whereas 5 patients (2%) with three melanomas had them all diagnosed on the same day. Median follow-up across the entire cohort was 9.3 years.

Overall, 9% of patients died from melanoma within 10 years of the first diagnosis (Table 1), but the proportion of melanoma-specific deaths was higher (13%) when three melanomas were recorded ($P = 0.04$). Those with multiple melanomas tended to be older at first diagnosis ($P < 0.001$), with a median age of 65 years for the group with three melanomas compared with 57 years for those with a single melanoma, although this age disparity was more apparent for males (67 and 59 years old, respectively) than for females (55 and 53 years old, respectively). Males outnumbered females in the cohort, with the proportion of males increasing from 57% for a single melanoma to 84% among patients with three invasive melanomas.

Melanoma tumor characteristics

Characteristics of the first melanoma varied significantly according to the number of melanomas diagnosed (Table 1).

Table 2. Characteristics of second and third primary invasive melanomas compared to corresponding first primary invasive melanoma, Queensland, 1995–2013[1]

	First primary invasive melanoma	Second primary invasive melanoma	First primary invasive melanoma	Third primary invasive melanoma
Eligible patients (n)	2,330		255	
Median time from diagnosis of first primary melanoma (y)	n.a.	3.1	n.a.	5.1
Median age at diagnosis (y)	63	67	65	70
	Col %		Col %	
Body site[2]				
Head and neck	15.4	18.1	13.7	16.9
Trunk	38.5	38.3	40.0	42.0
Upper limbs and shoulders	24.3	24.9	26.7	22.4
Lower limbs	19.7	18.1	18.0	18.4
Not specified	2.1	0.6	1.6	0.4
	$P = 0.053$		$P = 0.545$	
Morphology[2]				
Nodular melanoma	8.5	7.9	11.4	7.1
Melanoma in junctional naevus	2.8	2.8	3.9	3.5
Lentigo maligna melanoma	7.0	7.9	6.3	9.0
Superficial spreading melanoma	53.4	52.5	50.6	51.8
Other specified melanoma	3.4	4.7	4.7	4.3
Not otherwise specified	24.9	24.3	23.1	24.3
	$P = 0.220$		$P = 0.492$	
Thickness[2]				
<1mm	68.5	70.5	64.3	72.2
1 mm to <2 mm	14.5	12.9	17.3	12.2
≥2 mm	13.5	13.8	15.7	13.7
Not recorded	3.5	2.8	2.8	2.0
	$P = 0.200$		$P = 0.143$	
Ulceration[2]				
No	57.6	64.2	59.2	70.2
Yes	10.1	9.8	14.1	10.6
Not recorded	32.2	26.1	26.7	19.2
	$P = 0.138$		$P = 0.084$	

[1]Includes second and third primary invasive melanomas that were diagnosed within 10 y from the date of diagnosis of the first primary invasive melanoma.
[2]*P*-values based on chi-squared statistic that was converted into an *F* statistic after correcting for clustering of melanomas by patients. Test statistics exclude the category "not specified" or "not recorded."

The first melanoma for patients with three primary invasive melanomas was more likely to occur on the trunk (40% vs. 35% for patients with a single melanoma; $P < 0.001$ for body site), have nodular morphology (11% vs. 8%; $P = 0.011$), be at least 2 mm thick at diagnosis (16% vs. 11%; $P < 0.001$), and have reported ulceration (14% vs. 9%; $P = 0.002$). When the features of the second and third invasive melanomas were compared with the first melanoma for patients who had multiple melanomas (Table 2), no significant differences in regard to the distributions of body site, morphology, thickness category, or ulceration were found.

Survival

Using the delayed entry method, unadjusted 10-year cause-specific survival (corrected for entry time only) was highest (89%) for patients with a single primary invasive melanoma, intermediate (83%) for those with two melanomas, and lowest (67%) in patients who had three primary melanomas diagnosed within 10 years (Table 3 and Figure 1a). After adjusting for the characteristics of the index melanoma (Figure 1b), the survival point estimate in patients with three melanomas was closer to the other categories (79% vs. 89% for one melanoma and 84% for two melanomas) essentially reflecting the poor prognosis attributes of the first melanoma in this group of patients. Even so, these differences were highly significant, with the likelihood of death from melanoma within 10 years of first diagnosis being twice as high for individuals with two melanomas (hazard ratio [HR] = 2.01, 95% confidence intervals [CI] = 1.57–2.59; $P < 0.001$) and nearly three times higher when three melanomas were recorded (HR = 2.91, 95% CI = 1.64–5.18; $P < 0.001$). Although the survival advantage for patients with a single melanoma was further attenuated when the thickness category and ulceration of the first melanoma were replaced in the multivariate model by the maximum thickness category and positive ulceration status of the second or third melanomas, variation in the estimates remained significant (Table 3 and Figure 1c).

When the analysis was repeated using other definitions for survival time, no significant differences in outcome could be observed according to the number of melanomas diagnosed ($P = 0.183$ for the overall effect) when survival time was accrued from the date of diagnosis for the first invasive melanoma (Supplementary Table S1 online). Alternatively, compared with those with a single invasive melanoma,

Table 3. Ten-year adjusted cause-specific survival estimates and hazard ratios by number of primary invasive melanomas, Queensland, 1995–2013[1]

Number of primary invasive melanomas	n	Ten-year cause-specific survival estimates[2] (95% CI)	Excess hazard ratios (95% CI)	*P*
Unadjusted Model[3]				
Single	29,908	88.9 (88.3–89.6)	1.00	
Two	2,075	82.7 (79.8–85.6)	1.49 (1.25–1.77)	<0.001
Three	255	67.0 (53.6–80.5)	2.69 (1.81–4.00)	<0.001
Overall effect: $P < 0.001$				
Adjusted Results—Model 1[4]				
Single	29,908	89.2 (88.8–89.7)	1.00	
Two	2,075	83.5 (81.4–85.7)	2.01 (1.57–2.59)	<0.001
Three	255	78.9 (71.7–86.1)	2.91 (1.64–5.18)	<0.001
Overall effect: $P < 0.001$				
Adjusted Results—Model 2[5]				
Single	29,908	89.1 (88.6–89.5)	1.00	
Two	2,075	86.1 (84.2–88.1)	1.49 (1.14–1.96)	0.004
Three	255	82.9 (76.6–89.2)	2.08 (1.09–3.97)	0.026
Overall effect: $P = 0.008$				

[1]First primary invasive melanomas were diagnosed between 1995 and 2008, with follow-up to 31 December 2013 for diagnosis of subsequent primary invasive melanomas (maximum of 10 y of follow-up from the date of diagnosis of the first primary invasive melanoma).
[2]Survival time was calculated from the date of diagnosis of the first primary invasive melanoma with delayed entry when subsequent melanomas were diagnosed.
[3]Model is adjusted for entry time only.
[4]Adjusted for entry time, sex and the following variables relating to the first primary invasive melanoma: age at diagnosis, body site, morphology, thickness category and ulceration.
[5]Adjusted for entry time, sex, thickness category of the thickest melanoma, presence of ulceration in any melanoma and the following variables relating to the first primary invasive melanoma: age at diagnosis, body site, and morphology.

survival was significantly poorer for patients with either two (HR = 2.35, 95% CI = 2.02–2.72; $P < 0.001$) or three invasive melanomas (HR = 3.51, 95% CI = 2.57–4.80; $P < 0.001$) in the situation where survival time commenced from the date of last primary invasive melanoma diagnosis.

DISCUSSION

Uncertainty currently surrounds the long-term survival of patients with multiple compared with single primary cutaneous melanomas. We used a population-based cohort to compare melanoma-specific survival in groups of patients with one, two, or three primary invasive tumors over a 10-year follow-up period. Our results clearly demonstrate that, after making appropriate allowances for the time to diagnosis between first and subsequent melanomas by adopting a delayed entry analysis, survival from the time of first diagnosis of melanoma was significantly poorer for patients diagnosed with multiple primary invasive melanomas compared with a single primary invasive melanoma.

The American Joint Committee on Cancer has adopted a pragmatic approach regarding prognostic criteria for patients with more than one melanoma, with their guidelines focusing solely on the most "severe" tumor (Balch et al., 2009). Our analysis reveals that the number of melanomas diagnosed also needs to be considered. Taking into account thickness and ulceration (as American Joint Committee on Cancer criteria) from either the first or "most severe" melanoma and also age, sex, morphology, and body site, we were able to show that multiple melanomas have a major influence on patient survival even after adjusting for these key demographic and clinicopathological criteria.

Our findings differ markedly from most previous studies on this topic, which have reported that being diagnosed with multiple melanomas has a protective influence (Bower et al., 2010; Burden et al., 1994; Doubrovsky and Menzies, 2003; Moseley et al., 1979; Murali et al., 2012; Savoia et al., 2012; Scheibner et al., 1982). However, in each of these studies, survival was analyzed from the time of diagnosis of the first melanoma. It is therefore probable that the perceived improvement in survival for patients with two or more melanomas was attributable to survival bias, given that the longer a patient survives, the more likely they are to be diagnosed with additional melanomas (Bower et al., 2010; Doubrovsky and Menzies, 2003; Moseley et al., 1979).

Two other studies found little difference in survival for people with single or multiple melanomas (Kricker et al., 2013; Slingluff et al., 1993), whereas Rowe et al. (2015) recently reported that multiple invasive melanomas were associated with poorer survival when measured from the date of diagnosis of the last melanoma. The outcome was not statistically significant, however, when survival was assessed from the time of diagnosis of the first invasive melanoma (Rowe et al., 2015). The authors acknowledged that choosing the last melanoma as the index for survival interval calculation biased the study toward poorer survival in those with multiple melanomas (Rowe et al., 2015).

The use of the delayed entry method is an appropriate technique to compare survival between patients with a single invasive melanoma versus those with multiple invasive melanomas as it avoids the inherent biases associated with simply measuring survival time from either the first or last diagnosis. Delayed entry is commonly used in studies on

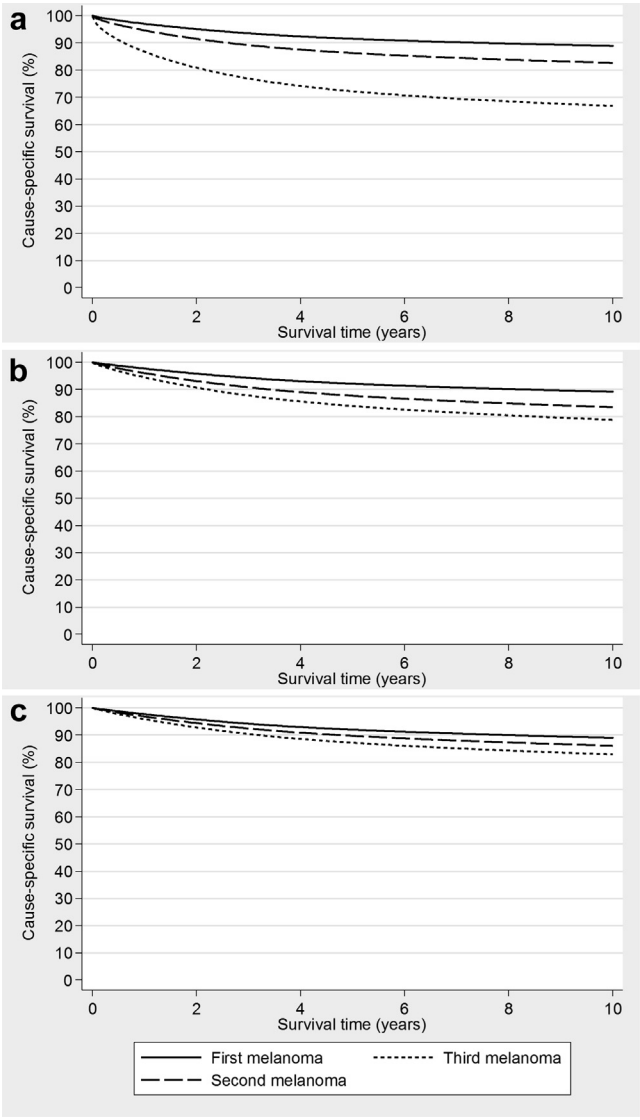

Figure 1. Unadjusted and adjusted cause-specific survival for single and multiple primary invasive melanomas, Queensland, 1995–2013. **(a)** The survival curves were adjusted for entry time only. **(b)** The survival curves were adjusted for entry time, sex, and the following variables relating to the first primary invasive melanoma: age at diagnosis, body site, morphology, thickness category, and ulceration. **(c)** The survival curves were adjusted for entry time, sex, thickness category of the thickest melanoma, presence of ulceration in any melanoma, and the following variables relating to the first primary invasive melanoma: age at diagnosis, body site, and morphology.

survival (Campbell et al., 2015; Li et al., 2013) or the occurrence of second cancers (Brewster et al., 2004) to account for the lag between initial cancer diagnosis and study enrollment. These situations are analogous to the present investigation, in that patients with multiple melanomas can be considered to have been "enrolled" (included) in our study from the date of diagnosis of either their second or third melanoma.

When we replicated our study based on follow-up from the time of diagnosis of the first melanoma, the number of invasive melanomas diagnosed had no bearing on survival in accordance with some previous reports (Kricker et al., 2013; Slingluff et al., 1993). Also similar to another paper, multiple invasive melanomas were a hazard if survival time was accumulated from the date of diagnosis of the last melanoma (Rowe et al., 2015). Therefore, the population cohort studied here allows replication of previous reports on survival of multiple melanomas. Only the delayed entry method avoids the biases inherent to both of these other models while still pointing to a survival disadvantage for patients with multiple invasive melanomas.

Unlike the recent study by Kricker et al. (2013), we considered invasive melanomas only, having previously demonstrated that diagnosis of an additional in situ melanoma is inconsequential in terms of influencing the prognosis for patients with an invasive melanoma (Youlden et al., 2016). Counting in situ lesions as contributing to melanoma multiplicity for the purposes of survival estimation thus has the potential to dilute any survival disparities toward the null. This may then explain the lack of difference in outcome reported by Kricker et al. (2013), despite the fact that they attempted to overcome the bias toward improved survival for multiple melanomas by measuring survival time from the tumor that was diagnosed last.

In our analysis, attributes of second and third melanomas did not markedly differ from the first tumor for patients with multiple melanomas. Interestingly, however, characteristics of the first invasive melanoma differed among patients with subsequent invasive melanomas compared with those who had a single invasive melanoma only. In particular, for patients with multiple invasive melanomas, initial tumors were thicker and more likely to be ulcerated or nodular, all being associated with poorer outcome (Baade et al., 2015). These differences being already present at the first invasive melanoma may point to a propensity in these patients to develop more aggressive disease, adding further support to our findings. Indeed, melanoma survival has been suspected to have an inherited component as reflected by familial clustering of fatal melanomas (Brandt et al., 2011). The older age at first diagnosis for those with multiple melanomas may also account for at least some of the differences in the characteristics of the initial invasive lesion; for instance, older people are more likely to present with nodular or ulcerated melanomas (Lasithiotakis et al., 2010). A possible alternative may be that patients with multiple melanomas do not have the required awareness of their melanoma risk and delay surveillance and treatment.

Besides our use of the delayed entry method to counter the biases present in earlier studies on survival for multiple melanomas, another advantage of this study over previous studies was the much larger cohort size, giving us added power to detect differences in survival. In terms of limitations, the precision of cause of death coding is subject to some uncertainty, particularly for older patients when several possible causes may coincide. Information from hospital records, death certificates, autopsy reports, and pathology records was used by the Queensland Cancer Registry to ensure that cause of death was assigned as accurately as possible. A further limitation was that information on other clinical indicators, such as sentinel node status, was unavailable from routinely collected registry data, and so we could not adjust the results for these additional prognostic variables. Similarly, information on family history of melanoma was not available.

Given increasing melanoma incidence and prolonged survival for most patients, it is vital that reliable prognostic

information is available for patients with multiple invasive lesions and for their clinicians. Contrary to existing evidence, our findings overwhelmingly point toward poorer outcomes in patients with multiple invasive melanomas. This in turn emphasizes the need for adequate recording of past disease in melanoma patients. Knowledge of a patient's history of multiple melanomas should prompt careful surveillance to detect new or recurrent disease.

MATERIALS AND METHODS

Data

Deidentified records for cases of invasive melanoma (ICD-O-3 code C44 and morphology M872–M879) diagnosed between 1995 and 2013 were obtained from the Queensland Cancer Registry in accordance with ethics guidelines and approvals. The Queensland Cancer Registry is a population-based collection with virtually complete ascertainment of all diagnoses within the state of Queensland in Australia. Notification of all cancer diagnoses is required by law, apart from basal and squamous cell carcinomas of the skin (Queensland Cancer Registry and Cancer Council Queensland, 2014). Variables in the data extract included sex, age at diagnosis, tumor behavior, body site, morphology, Breslow thickness, ulceration, date of diagnosis, and date and cause of death (where applicable). Mortality status as at 31 December 2013 was ascertained by linkage with the Queensland Registry of Births, Deaths and Marriages, and the National Death Index of Australia.

The study cohort comprised all Queensland residents aged 15–89 years who were diagnosed with a first primary invasive melanoma between 1995 and 2008, thus allowing a minimum follow-up of 5 years. Where relevant, records for second and third primary invasive melanomas that occurred within 10 years of the index melanoma were connected through unique patient numbers. Subsequent primary melanomas that were diagnosed more than 10 years after the first diagnosis were not considered. In situ melanomas (Youlden et al., 2016) and recurrent disease or cutaneous metastases based on pathology findings were also disregarded. Patients were excluded from the cohort if they were diagnosed with four or more primary invasive melanomas within 10 years, when the date of diagnosis was the same as the date of death, or where the basis of diagnosis was either autopsy or death certificate only.

Analysis

The cohort was stratified according to the number of invasive primary melanomas diagnosed (up to a maximum of three). If two or more melanomas were diagnosed on the same day, the order was determined according to the sequence in which they were registered.

Key demographic and clinical characteristics for the first primary invasive melanoma were compared across these three strata using chi-squared tests for categorical variables and nonparametric *k*-sample tests for the equality of median values. For persons with multiple melanomas, the features of the first melanoma were also compared with the corresponding characteristics of the second and third melanomas, with differences in the distribution for categorical variables evaluated by estimating variance based on Taylor linearization to account for clustering.

Cause-specific survival time accumulated from the date of diagnosis of the first primary invasive melanoma to either the date of death, the end of the study period (31 December 2013) or 10 years from the date of initial diagnosis, whichever occurred first. Censoring was applied if patients remained alive at the end of the follow-up period, or if they died and the cause of death was not coded as melanoma.

Delayed entry (also known as left truncation) (Cleaves et al., 2008) was used to counter the inherent bias toward longer survival times among those diagnosed with a subsequent melanoma. For people with a single melanoma, the survival time is measured from the date of diagnosis of that index melanoma. Typically, most previous studies have used this same approach when considering people with two or more melanomas, that is, calculating the survival time from the date the index melanoma was diagnosed and using all that time in the analysis (Figure 2, Group A). Other studies have started the survival time from when the last melanoma was diagnosed (Figure 2, Group B). However, under the delayed entry approach, although the survival time for patients with multiple melanomas starts at the date of diagnosis of the index melanoma, it only contributes to the analysis from the time when their last melanoma (second or third) was diagnosed (Figure 2, Group C), and is not reset to zero, as would occur if the subsequent melanoma were used as the index rather than the initial melanoma (Kricker et al., 2013; Rowe et al., 2015). For example, if an individual was diagnosed with two melanomas 3 years apart, their survival time would only contribute to the calculations from the third year onwards. Similarly, if a third melanoma was diagnosed 5 years after the first, then survival time would only accrue from the fifth year, ignoring the date of diagnosis of the second melanoma.

Unadjusted 10-year survival was calculated using the Kaplan-Meier method. Flexible parametric survival models (Royston and Lambert, 2011) were then applied to the data. The baseline survival distribution is represented as a restricted cubic spline function in flexible parametric survival models, allowing non-proportional effects in the underlying hazard function to be

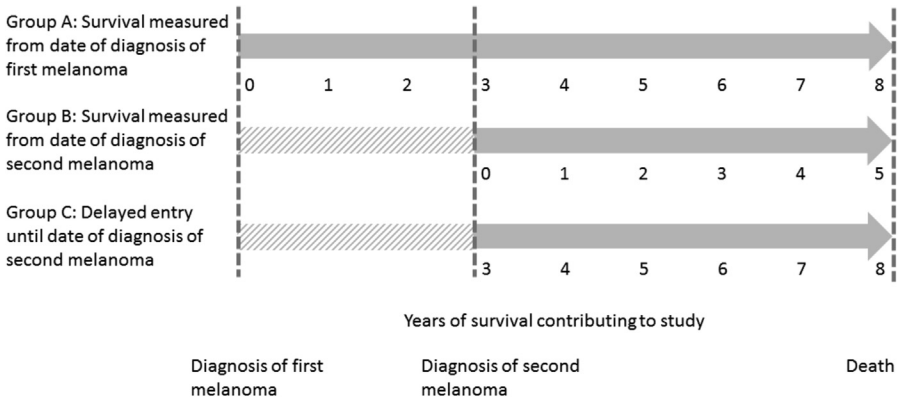

Figure 2. Comparison of methods used to measure survival time.

estimated more readily compared with the simpler linear function in traditional Cox proportional hazard models. After assessing various options for the scale parameter and the number of internal knots for the cubic spline function according to the Bayes information criterion statistic, the model providing the best fit was on the normal scale with three internal knot points.

The multivariate models were adjusted for sex, age at diagnosis, body site, melanoma morphology, thickness category and ulceration, with body site and thickness included as time varying variables. Melanoma thickness was fitted in the flexible parametric survival models as a categorical rather than a continuous variable allowing more stable estimates with minimal effects on the model outcomes (comparative results not shown).

Two models were fitted; the first model was based solely on the characteristics of the first primary melanoma, whereas the second model applied the characteristics of the melanoma at highest risk of recurrence in terms of thickness category and ulceration for patients who were diagnosed with multiple melanomas. Given that delayed entry was only applied to patients with multiple invasive melanomas, we could not assume independence between the entry and failure events, and so entry time was also incorporated as a covariate in the models (including the "unadjusted" results) to avoid the possibility of introducing late entry bias (Matsuura and Eguchi, 2005). Results were expressed in terms of excess HRs along with corresponding 95% CIs.

Finally, to allow comparison of different methods of estimation of the survival interval, our model (first model) using delayed entry (Figure 2, Group C) was compared with two alternative definitions of survival, that is, including all follow-up time from the date of diagnosis of the first melanoma (Figure 2, Group A) and considering survival commencing from the date of diagnosis of the final melanoma only (Figure 2, Group B).

All analyses were conducted using Stata/SE version 14.1 for Windows (College Station, TX). The "stpm2" command (Royston and Lambert, 2011) was used to fit the flexible parametric survival models.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at http://dx.doi.org/10.1016/j.jid.2016.03.014.

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