Enhanced Survival in Patients With Multiple Primary Melanoma

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Objective: To calculate survival probabilities of patients with 3 or more multiple primary melanomas.

Design: Retrospective cohort study of patients with primary melanoma.

Setting: Patients treated at a tertiary center (Sydney Melanoma Unit, Sydney, Australia) for stage I or II melanoma between 1983 and 1999.

Patients: From 5250 patients with primary melanoma, 264 (5.0%) had double and 34 (0.6%) had 3 or more primary melanoma lesions.

Results: The estimated 10-year risk for developing a second primary melanoma in these patients was 12.7% (95% confidence interval [CI], 10.5%-14.9%). For those patients who had 2 primary melanomas, the estimated 10-year risk of developing a third lesion was 27.7% (95% CI, 14.7%-36.7%). When controlling for known prognostic factors in a proportional hazards regression model, the number of primary melanomas was a significant favorable survival predictor when the thickest or the first tumor was modeled. In patients with 3 or more primary melanomas, 31 survived when 25 (95% CI, 22-27) were expected to survive. Patients who survive longer may have the opportunity to develop multiple primary melanomas. Patients who encountered all their primary lesions within 2 years may not be subject to this bias. Within the 3 or more melanoma set, 11 patients had all primary melanomas within 2 years. All survived, whereas 9 (95% CI, 8-10) were expected to survive.

Conclusions: Patients with 3 or more primary melanoma lesions survive longer than anticipated. Such enhanced survival in patients with 3 or more primary melanomas may be consistent with observations of an “immunization effect” in animals inoculated with multiple tumors.

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Occasionally, cancer is multicentric in nature. This may be due to an underlying genetic disposition, continuous initiation through exposure to carcinogenic stimuli, or by chance alone. Several cancers of the skin are often multicentric. Melanoma is no exception. Patients with melanoma are at greater risk of developing a second primary melanoma than the general population is at developing the first. The frequency at which patients with single primary melanoma develop additional primary melanomas has ranged from 1.12% to 6.38% of cases in several series. The development of 3 or more multiple primary melanomas occurred in 0.05% to 1.97% of these same patient populations. For patients with thin primary melanomas, the risk of developing a second primary tumor may be greater than the risk of developing a metastasis, particularly in populations from regions with heavy sun exposure and increasing survival from malignant melanoma.

Several studies have examined survival in multiple primary melanoma. In 3 studies, survival in patients with multiple primary melanoma has been shown to be no worse than in patients with a single lesion. In fact, in some studies, prognosis appears superior. However, with the exception of Burden et al, none of these studies controlled for crucial prognostic variables (eg, sex, age at diagnosis, thickness of the lesions, ulceration, and location) in determining survival. The 2 studies of Burden et al were limited by analysis of a small sample size of patients with 3 or more primary melanoma lesions (n=7 and 13, respectively). Our study was undertaken to evaluate the survival of a larger sample of patients with 3 or more primary melanomas. We controlled for known prognostic variables in determin-
ing survival and studied how the degree of tumor multiplicity affected survival.

In murine studies, inoculation with 3 or more different tumors can allow an immunization effect that is seen as rejection following subsequent challenge of a different tumor of the same tumor histological type and same inducing carcinogen. This tumor immunity is a response to putative common tumor antigens confined to that particular tumor type. Human melanoma has well-characterized common tumor antigens. However, little evidence exists for functional immune responses to these antigens in nature. If functional immunity to common tumor antigens can occur in patients with melanoma, then it may be predicted that patients with 3 or more primary melanomas will survive beyond expected rates. This would be consistent with Burnet’s proposal of tumor immunological surveillance.

**METHODS**

**POPULATION**

All patients who visit the Sydney Melanoma Unit (SMU), Sydney, Australia, are evaluated and registered prospectively on the SMU database. Melanoma disease status was classified according to the American Joint Committee on Cancer/TNM Staging System (AJCC/TNM) developed in 1983. In the present study, patients initially presenting with stage I or II disease (disease restricted to the primary lesion only, i.e., all had ulcerated lymph nodes), who appeared at the SMU within 1 year of their histological diagnosis of their first malignant melanoma between January 1983 and April 1999, were reviewed retrospectively. Patients who presented with metastatic disease on the first presentation were excluded to remove any referral bias. The pathological diagnosis of all melanomas in this chosen group of patients has been reviewed by the SMU. Cutaneous metastatic lesions were excluded with the combined use of clinical and histological criteria. Patients were followed up regularly, initially by the SMU and then by their local physician, from whom patient information was obtained. For patients who were unable to be contacted, the New South Wales Cancer Registry was surveyed for deaths due to melanoma. Their outcome and other data pertaining to their melanoma diagnosis and disease management were recorded on the SMU database. Death from malignant melanoma in the present study was considered the end point. Survival time was defined as the time between the initial histological diagnosis of primary melanoma and the date of the last follow-up or death from melanoma. Patients with causes of death other than malignant melanoma were censored at date of death due to melanoma. Their outcome and other data pertaining to their melanoma diagnosis and disease management were recorded on the SMU database. Death from malignant melanoma in the present study was considered the end point. Survival time was defined as the time between the initial histological diagnosis of primary melanoma and the date of the last follow-up or death from melanoma. Patients with causes of death other than malignant melanoma were censored at date of death. In patients with synchronous multiple primary melanoma, the thickest melanoma was considered the first. Synchronism was defined as the diagnosis of the second or subsequent lesions within 1 month of the diagnosis of the first lesion.

The SMU database contained 10,410 patients who were diagnosed with their first primary malignant melanoma lesion after December 1982. To reduce selection bias affecting survival, patients who came to the SMU 1 year after their first diagnosis of melanoma were eliminated. There were 1,190 such cases. Patients who had in situ primary melanoma with no metastatic potential and those who first presented with metastatic disease (AJCC/TNM stage III or IV) were also removed. There were 1,451 of these cases. Finally, 2,519 patients with missing data in the variables thickness, ulceration, location, and diagnosis date of any primary melanoma, as well as date of birth, sex, status, and date of first and last visit to the SMU were removed. Ulceration was the most likely of these variables to be missing. Patients without a record of ulceration do not have a different rate of survival from those that do (data not shown). In effect, there were 5,250 patients in this study, and all patients with multiple primary melanoma came from the single primary melanoma data set.

**ANALYSIS AND STATISTICAL METHODS**

All analyses were performed using the SAS software package (SAS Institute Inc, Cary, NC) and Microsoft Excel (Microsoft Corp, Redmond, Wash). Graphical presentations of survival estimates were accomplished using SPSS statistical software (SPSS Inc, Chicago, Ill). Survival analysis on the selected patient data was carried out using Kaplan-Meier product-limit estimation of survival probabilities and Cox proportional hazards regression model, when appropriate. Survival distributions of product-limit estimates were compared using the log-rank test. Five variables were modeled. Three were categorical: sex (male or female), ulceration of the primary lesion (present or absent), and location of lesion (head and trunk [axial] or upper and lower limbs [extremities]); 2 were continuous: age at diagnosis (in years) and the Breslow thickness of the primary lesion (in millimeters). The variable thickness is heavily skewed in this data set because of a high proportion of thin malignant melanomas within the population. To normalize these data, the variable was log transformed. Interactions between variables were evaluated and included in a stepwise variable selection procedure when model building. The appropriateness of using any of the variables in the proportional hazards model was investigated by −2log(−logS[t]) plots. No variable violated the proportional hazards assumptions. All P values were 2-sided and were considered statistically significant at P < .05.

Among 5,250 cases of primary invasive melanoma selected for this study, 298 (5.7% of the patient population) had more than 1 primary melanoma lesion. The number of multiple primary lesions ranged from 2 to 5. Of the multiple melanoma cases, double primary melanoma made up 88.6%, triple melanoma made up 8.7%; and more than 3 melanomas made up 2.7%. Only 26.2% of patients with multiple melanoma had synchronous lesions, whereas the remaining 73.8% of these cases were asynchronous. Death due to malignant melanoma occurred in 501 patients (472 in patients with single primary melanoma, 26 in patients with double primary melanoma, and 3 in patients with triple or greater primary melanoma). Death due to other causes occurred in 189 patients (3.6% of the entire data set).

Comparisons between multiple and single primary melanoma patients are summarized in Table 1. Patients with 2 primary melanomas were significantly older at presentation of their first melanoma (mean age, 54.1 years) than patients with single melanoma (51.7 years). Furthermore, there was a notable male preponderance in patients with 3 or more primary melanomas (73.5%) compared with patients with single primary melanoma (54.0%).

Breslow thickness of melanoma is a critical prognostic indicator of disease survival, with survival inversely proportional to thickness, and can be used as an indicator of early vs late presentation. Subsequent lesions were thinner in patients with asynchronous multiple primary melanoma lesions. In patients with double
primary melanoma, 65.2% (122) of asynchronous patients had a second lesion that was thinner than the first. In patients with asynchronous triple or greater primary melanoma, 61.5% (16) of patients had thinner second lesions compared with the first. This increased to 73.1% (19) of patients with asynchronous triple or greater primary melanoma who had thinner third lesions compared with the first (Table 2).

Product-limit failure estimates were used to determine the risk of developing additional lesions in patients with primary melanoma (Figure 1). Development of an additional primary melanoma was treated as the event. Follow-up time was from the date of pathological diagnosis of the last primary lesion to when the patient was last seen at the SMU or until death for censored individuals or until the date of pathological diagnosis of an additional primary melanoma for those who developed further primary melanoma lesions. For the entire data set (N = 5250), the 10-year risk of developing a second primary lesion was 12.7% (95% CI, 10.5%-14.9%). For the multiple data set (n = 298), the 10-year risk of a third primary lesion was 27.7% (95% CI, 10.5%-14.9%). For the entire data set (N = 5250), the 10-year risk of developing additional primary melanoma lesions was then created from previously known variables of significance.25 These were sex, age at diagnosis, Breslow thickness of the primary lesion (log e transformed), location of the primary lesion, which is controlled for. In this study only, survival time is defined from the diagnosis of the lesion, which is controlled for until last known follow-up or death. This was the first lesion when the disease began; the thickest lesion that was most likely to result in death; or the last

Table 1. Comparison of Patients With Single, Double, and Triple or Greater Primary Melanoma*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Single</th>
<th>Double</th>
<th>Triple or Greater</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>4952</td>
<td>266</td>
<td>34</td>
</tr>
<tr>
<td>Deaths</td>
<td>472 (9.5)</td>
<td>26 (9.8)</td>
<td>3 (8.8)</td>
</tr>
<tr>
<td>Male sex</td>
<td>2677 (54.0)</td>
<td>163 (61.7)</td>
<td>25 (73.5)</td>
</tr>
<tr>
<td>Age at first diagnosis, y</td>
<td>51.7/51.9</td>
<td>54.1/55.5</td>
<td>54.8/55.5</td>
</tr>
<tr>
<td>Follow-up time from first melanoma, y</td>
<td>3.7/3.0</td>
<td>5.7/5.0</td>
<td>7.0/5.9</td>
</tr>
<tr>
<td>Asynchronous patients</td>
<td>4952</td>
<td>187</td>
<td>26</td>
</tr>
<tr>
<td>Thickness of first primary melanoma, mm</td>
<td>1.8/1.1</td>
<td>1.7/1.0</td>
<td>1.8/1.6</td>
</tr>
<tr>
<td>Ulceration present in first primary melanoma</td>
<td>1112 (22.5)</td>
<td>34 (18.2)</td>
<td>3 (11.5)</td>
</tr>
<tr>
<td>First primary melanoma located on limb</td>
<td>2577 (52.0)</td>
<td>76 (40.6)</td>
<td>14 (53.8)</td>
</tr>
</tbody>
</table>

*Data are number (percentage) or mean/median unless otherwise specified.
†Significantly different between both the single and double primary melanoma groups (χ² = 5.30, P = .02) and the single and triple or more groups (χ² = 5.16, P = .02).
‡Mean age at first diagnosis is significantly different between single and double primary melanoma groups (t = 2.43, P = .03).

Table 2. Change in Thickness, Ulceration, and Location in Subsequent Primary Melanomas in Patients With Asynchronous Multiple Primary Melanoma

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Total No. of Patients</th>
<th>Patients With Thicker First Melanoma, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double primary melanoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second melanoma</td>
<td>187</td>
<td>122 (65.2)</td>
</tr>
<tr>
<td>Triple or greater primary melanoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second melanoma</td>
<td>26</td>
<td>16 (61.5)</td>
</tr>
<tr>
<td>Third melanoma</td>
<td>26</td>
<td>19 (73.1%)</td>
</tr>
</tbody>
</table>

Survival curves for each of the 3 groups of patients (single, double, and triple or greater primary melanoma) were generated by the Kaplan-Meier method.23 Patients with 3 or more primary melanomas survived longer than those in the other 2 groups (Figure 2). The difference between the 3 groups was tested for trend and was significant (log rank for trend, 6.08; P = .01).

A Cox proportional hazards regression model was then created from previously known variables of significance.25 These were sex, age at diagnosis, Breslow thickness of the primary lesion (log transformed), location of lesion, and presence of ulceration. All variables were significant on a univariate analysis (data not shown), but when combined in a multivariate analysis, sex failed to be significant. The inclusion of the 2-way interaction term between sex and thickness returned the significance of sex as a variable. This model is outlined in Table 3. The number of primary melanoma lesions was then investigated as a variable of significance in the Cox proportional hazards regression model detailed previously.

All patients were included in this analysis (N = 5250). Only 1 lesion in the patients with multiple melanomas could be controlled for. In this study only, survival time is defined from the diagnosis of the lesion, which is controlled for until last known follow-up or death. This was the first lesion when the disease began; the thickest lesion that was most likely to result in death; or the last
Finally, survival probabilities of patients with multiple lesions were calculated using the Cox proportional hazards regression model developed previously (Table 3). Baseline survival probabilities for the occurrence of each multiple primary melanoma were calculated from the 4952 single-lesion data set. The 95% CIs were calculated from the linear predictor estimate and its standard error. In this analysis, the effect of known significant variables were controlled for. The overall probability of survival for each multiple melanoma patient was calculated by the multiplication of the baseline survival probabilities for each of their primary melanoma lesions. The survival probabilities and their 95% CIs and observations in patients with melanoma with 2 or 3 or more primary lesions is shown in Table 5. In patients with 3 or more primary melanomas, we observed 31 surviving patients, whereas only 25 (95% CI, 22-27) were expected to survive. The results of improved survival in patients with 3 or more primary melanomas could be explained by a “survival bias” (ie, longer survivors are more likely to develop multiple lesions than those who die earlier from their single melanomas). This bias can be severely reduced by analyzing those patients with multiple melanomas who have all of their melanomas in the relatively short time interval of less than 1 or 2 years. For the 12 patients who had their 3 or more primary melanomas within 2 years of first diagnosis, 11 survived. The expected survival was 9 (95% CI, 8-10) patients.

As seen in patients with 3 or more primary lesions, the observed survival of patients with 2 primary lesions was better than predicted from the single primary melanoma survival estimates. There were 238 surviving patients of 264 in the group. Expected survival was 224 (95% CI, 209-236) (Table 5). However, in contrast to patients with 3 or more lesions, the survival advantage disappeared for those patients who had both lesions excised within a 2-year period (Table 5).

Survival time is significantly longer in patients with 3 or more lesions in comparison with those with a single lesion (Table 1). Patients who develop additional disease, whether it be a metastases or another primary lesion, will return for further treatment. For patients who had all lesions diagnosed within 2 years, mean survival times were not significantly different (4.9 years in patients with ≥3 primary melanomas and 4.2 years in those with double primary melanoma) from single-lesion patients (3.7 years) (t = −1.44; P = .15)

**COMMENT**

Our results showed that survival of patients with multiple melanomas is superior to the survival of patients with 1 primary tumor when no prognostic factors are controlled for under the product-limit method of survival analysis. When controlling for all known prognostic factors in a Cox proportional hazards regression model, the number of primary melanomas was a significant favorable survival indicator when the thickest tumor (most likely cause of death) or the first tumor were modeled. Furthermore, when controlling for all prognostic factors, the overall probability of survival for each patient lesion to appear. Table 4 summarizes the results from this analysis. The number of primary melanomas was a significant favorable survival indicator when the first melanoma or the thickest melanoma was controlled for. When the last melanoma was controlled for, increasing melanoma number now resulted in a significant increasing hazard rate. This later finding was not unexpected, since the early melanomas, which are generally thicker in multiple primary melanoma (Table 2), are ignored in this survival analysis.

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All but 2 studies on multiple primary melanoma survival failed to control for known prognostic factors. The exceptions were the studies by Burden et al,2,16 who matched by age, sex, thickness, and body site of the first melanoma in multiple lesion patients to single-lesion patients. These 2 studies were limited by the small sample of patients with 3 or more primary melanomas (n = 7 and 13, respectively). Neither study showed significant survival for patients with multiple primary melanoma compared with patients with a single lesion. A study by Moseley et al10 found that after 5 years, 100% of patients with multiple lesions were still alive compared with the 55% of patients with a single lesion (data derived from graph). Slingluff et al17 reported these rates as 82% to 70% (data derived from graph) and Burden et al18 described them as 83% to 78% (data derived from graph) in their 1994 publication. In the Burden et al18 publication from 1999, no significant difference in survival was observed between single and multiple primary melanoma groups in a matched study nor in a proportional hazards analysis. Only 13 patients had more than 2 primary melanomas compared with 34 patients in our study. Previously within the SMU, Scheibner et al6 reported on 90 patients compared with 34 patients in our study. Previ-
noma, other mechanisms may be involved. In particular, patients with defined genetic mutations, particularly in CDKN2A encoding the p16 protein, have a propensity to get multiple primary lesions.\textsuperscript{16,27} Furthermore, the most important risk factor for a patient with melanoma of developing a second primary is a family history of melanoma.\textsuperscript{16} It is therefore conceivable that a genetic predisposition enhancing the risk for primary melanoma may also affect other biological tumor characteristics such as metastatic potential. Because of this, we have investigated evidence for a functional immune response in patients with multiple primary melanoma. These studies show increased histological regression correlating with cytotoxic lymphocyte production to the common melanoma tumor antigen melan-A/MART-1 and MART-1 tumor-loss variants in the last primary tumor.\textsuperscript{19} Such observations are consistent with Burnet's\textsuperscript{20} proposal of immunological surveillance whereby the normal function and primary evolutionary adaptive influence of the cellular immune system is to recognize and destroy malignant cells early in tumorigenesis. While many corollaries of this theory have failed scrutiny,\textsuperscript{28} such evidence suggests that in patients with multiple primary melanoma, immunological surveillance may be significant.

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