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 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., had all uninvolved 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. Patients who presented with stage III or IV disease (AJCC/TNM stage III or IV) were also removed. There were 5250 patients in 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 developing a second primary lesion was 12.7% (95% CI, 10.5%-14.9%). For the entire data set (N = 5250), the 10-year risk of developing an additional primary melanoma for those who developed further primary melanoma lesions was then 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 (log rank for trend, 6.08; P = .01).

A Cox proportional hazards regression model was then created from previously known variables of significance.23 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

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**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>
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<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>54.1/55.3</td>
<td>54.6/55.5</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 Melanomas, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double primary melanoma</td>
<td>187</td>
<td>122 (65.2)</td>
</tr>
<tr>
<td>Second melanoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triple or greater primary melanoma</td>
<td>26</td>
<td>16 (61.5)</td>
</tr>
<tr>
<td>Second melanoma</td>
<td>26</td>
<td>19 (73.1%)</td>
</tr>
<tr>
<td>Third melanoma</td>
<td>26</td>
<td></td>
</tr>
</tbody>
</table>

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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).

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...
with multiple melanoma calculated by the multiplication of the baseline survival probabilities for each of their melanomas showed significantly increased observed survival compared with expected survival. To control for any “survival bias” in patients with multiple melanomas, we analyzed those patients who had all of their melanomas in the relatively short time interval of less than 2 years. If increased survival in patients allowed the development of multiple lesions, rather than multiple lesions causing increased survival, one would expect that these patients with lesions diagnosed within 2 years would be relatively free of such bias. Improved survival was observed in patients with 3 or more primary lesions who presented with all their lesions within 2 years. In contrast, those patients with double primary melanoma survived as expected.

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 al6 described them as 83% to 78% (data derived from graph) in their 1994 publication. In the Burden et al16 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 al14 reported on 90 patients with multiple primary melanoma from 1951 to 1982 and found that for men the 5-year survival rate in patients with multiple lesions was 88.9% and 66.8% for patients with a single lesion. But for women, no difference was found, with 86.5% of patients with single and 82.7% of patients with multiple primary melanoma surviving 5 years. Except for the latter, the 5-year survival of patients with a single primary melanoma was less than 80%

In our study, the 5-year survival rate had improved to 86.5% in all patients with single primary melanoma. Thus in this group of patients, there is a reduction in the bias that early death from melanoma inhibited patients from developing multiple lesion as fewer patients were removed from the study owing to death.

The prevalence of multiple primary melanoma in other series ranged from 1.1% to 6.4% of patients with a single primary lesion.1,15 In our study, the prevalence of multiple primary melanoma in this group was 5.6%. This was similar to a population-based study on multiple primary melanoma from Australia on 14 560 patients, of which 4.5% developed a second primary melanoma.8 Hence, we believe that our sample is representative of the wider population. Regions with a high and rising background incidence of melanoma, such as New South Wales, Australia, may have higher risks of developing multiple primary melanoma. In this study, at 10 years almost 13% of patients with a single primary melanoma would have developed a second primary melanoma and 28% of patients with double primary melanoma would have developed a third.

The proportion of men increased with the number of primary melanomas removed. This male predominance has been noted before in other studies3,4,7 but unlike other studies,4,10 patients with multiple lesions were not younger at first diagnosis; in fact, the trend suggested that they may be older. Second melanomas were, in approximately 60% of asynchronous cases, thinner than the first. Third melanomas were even more likely (72% of cases) to be thinner. This is a probable result of increased surveillance and earlier detection of subsequent primary melanomas in this population.

Why should survival be superior in patients with 3 or more primary melanomas? Resistance to a second tumor has been shown in carcinogen-induced tumors in animal models. Two mechanisms have been described.20 Concomitant resistance is the failure of a second tumor to grow in an animal already bearing a different tumor of the same histological type. The inhibition of the second tumor is dependent on the size difference between the 2 tumors.20 Its effect is nonspecific and has been shown to involve both immunological and nonimmunological processes.20 Sinecomitant immunity is the immunological resistance of the host to a second (or subsequent) tumor challenge after the surgical removal of a previously growing tumor. It is weaker, reliant on a functional immune system, and is evident only after the removal of the first tumor.26 Its strength is dependent on the immunogenicity of the tumors and the size of the original tumor (smaller tumors result in stronger growth inhibition).26 There is no evidence in murine studies that sinecomitant tumor immunity (from multiple nonviral induced tumor immunizations) protects against the appearance of new primary tumors. Rather, it protects against growth of an established tumor (tumor challenge).26

In recent years, many common tumor antigens have been described in human melanoma.18 While successful immunization using these antigens has occurred in a therapeutic setting, their role as immunological surveillance recognition antigens is unclear. Observations in experimental animal models of UV radiation or chemical carcinogen-induced tumors suggest that recognition of common tumor antigens require multiple (usually 3) immunizations.17 In such models, serial transplantation of 3 tumors of the same histological type and induced by the same carcinogen can lead to rejection following challenge of a different tumor, also induced by the same carcinogen and of the same histological type. Single immunizations are ineffective in inducing functional immunization against these putative common tumor antigens. Such observations may predict that patients with 3 or more primary melanomas may develop a functional “immunization” to common melanoma tumor antigens, which may lead to enhancement in survival. Indeed, our study showed such enhanced survival.

While an immunization effect may induce enhanced survival in patients with multiple primary melanomas, ...
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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