Chapter 4

Detection of second primary cutaneous melanomas

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Chapter 4

ABSTRACT

Introduction
There have been few studies investigating the value of follow-up in the detection of second primary melanomas (SPMs) has not been undertaken, and there is scant information on the role of self-surveillance by the patient. The aim of this study was to assess the frequency of patient detection of both first primary melanomas (FPMs) and SPMs.

Methods
Patients were interviewed to determine who detected their FPM and SPM (in situ or invasive). The associations between clinical and pathological factors and the person who identified the FPM and SPM were examined using a multivariate analysis.

Results
112 patients with a recently diagnosed SPM were treated at the Sydney Melanoma Unit (Jul-'01 to Mar-'03). Patients detected 59% of the FPMs, compared with 46% of the SPMs. Female gender, greater Breslow tumour thickness (tt) and younger age were significant predictors for a patient-detected FPM (Odds Ratio: 4.9 (Confidence Interval 1.5-16.0) 3.2 (1.65-6.04), and 0.9 (0.9-1.0) respectively). Greater tt and readily visibility of the lesion to the patient were predicting factors for patient detection of a SPM (Odds Ratio: 1.9 (Confidence Interval 1.1-3.3) and 3.6 (1.4-9.1) respectively).

Conclusion
A history of melanoma does not increase the ability of patients to detect new or thinner primary melanomas themselves. Therefore, patients may benefit from regular clinical review by clinicians, who play an important role in the detection of new melanomas.
INTRODUCTION

Since the incidence of melanoma worldwide is steadily increasing, the design of follow-up programs for patients with melanoma is important. The increasing incidence has resulted in greater numbers of patients requiring follow-up.\textsuperscript{1,2} The financial burden for health care systems associated with follow-up programmes is a concern in many fields of cancer medicine, and particularly in melanoma.\textsuperscript{3,4} It is therefore important to strive for optimal cost-effectiveness in such programmes. The two main aims of melanoma follow-up are early detection of any recurrence of a first primary melanoma (FPM) and recognition of a second primary melanoma (SPM), if one should develop. Several groups have attempted to determine effective follow-up schedules, but no international consensus exists.\textsuperscript{5} Most follow-up schedules are based on the probability that recurrence will occur within a given time period for patients with different stages of melanoma. For patients with AJCC Stage I melanoma, their risk of developing a SPM (3-12%) is similar to their risk of developing a recurrence of the FPM (3-24%), although this is not the case for patients with higher disease stages (Stage III and IV: recurrence risk 60-72%).\textsuperscript{5} Few studies have evaluated the cost-effectiveness of follow-up schedules for the detection of SPMs. Brobeil et al concluded that follow-up every three months in the first two years after FPM diagnosis should be continued indefinitely, as it is the only way to detect SPMs at an early stage. In this retrospective study it was reported that 93% of the SPMs were detected by a physician at a routine follow-up visit.\textsuperscript{6} Garbe et al reported similar findings.\textsuperscript{7} Since we are not aware of any other specific studies that have been undertaken to determine who detects SPMs, or factors influencing this we planned a detailed study to examine factors related to SPM detection.

PATIENTS AND METHODS

Patient selection

All patients with cutaneous SPMs presenting to the Sydney Melanoma Unit (SMU) were prospectively identified from 1 July 2001 to 31 March 2003. Patients with both in situ and invasive melanomas were included. Excluded were patients who had multiple primary melanomas, developed a recurrence earlier than the SPM, had the FPM and SPM detected within 14 days of each other or were < 18 or > 85 years old at SPM diagnosis.
Interview process

A letter was sent to all selected patients advising them that they would be telephoned by one of the authors (ABF) and asking if they would be willing to answer questions in relation to their melanoma diagnoses. It was made clear that there was no obligation for them to participate, and prior to interview each patient’s approval for participation was obtained. A structured interview format was used to collect information relating to the detection of both the patient’s FPM and their SPM. This included the last follow-up interval before SPM diagnosis, and any instructions given by their doctor about skin self-examination at the time of their FPM diagnosis. (Figure 1)

Clinical and pathological features of first and second primary melanomas

Information on several features of both FPMs and SPMs was extracted from the prospectively set-up SMU database. Anatomical site of the melanoma was categorised as head/neck, trunk, upper or lower extremity. Melanomas regarded as readily visible to the patient were those on any anterior body area or on the posterior aspect of the forearm or leg. Patient age at the time of FPM and SPM diagnosis respectively was recorded. The interval between diagnosis of the FPM and the SPM and the time since the last melanoma follow-up visit or routine skin check was recorded in months.

Breslow tumour thickness was recorded for all lesions. In situ melanomas were analysed as a separate group and considered to have a tumour thickness of 0.0 mm for statistical purposes.\(^8\)

First and second melanoma detection

The person detecting the FPM or SPM was assigned to one of three groups: 1. patient, or any person related to the patient (e.g. partner, sibling, parent), 2. doctor (at follow-up skin check or a non-skin related visit), 3. any other person. Lesions were considered to be patient-detected if the identification had resulted in a (patient initiated) medical consultation within several weeks, or the patient had specifically identified the lesion to the doctor at the scheduled follow-up consultation.

Statistical analysis

For statistical analyses patients with a melanoma that was not detected by the patient (or related person) or a doctor were excluded (FPM n=11, SPM n=3). The paired sample t-test was used to compare tumour thickness for FPMs and SPMs. Univariate tests were used (Chi square, Fisher’s exact and independent sample t-test where appropriate) to find a statistical relation between the person detecting
Detection of second primary melanomas

The melanoma and multiple variables (FPM and SPM: gender, age at diagnosis, anatomical site of the melanoma, ready visibility to the patient). The person identifying the FPM, instruction of self-detection at the time of FPM diagnosis and the interval between FPM and SPM were additionally compared to the person identifying the SPM. All variables that were statistically significant in the univariate analysis were included in a multivariate logistic regression model for FPM and SPM.

Figure 1. Structured interview regarding first and second melanoma detection

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FIRST AND SECOND MELANOMA

Patient name: ..................................

PIN no: ..................................

Person detecting second melanoma

patient
partner
family doctor (specify reason for visiting)
other doctor (specify)
SMU doctor
other (specify)

How was the melanoma detected?

(specify event)

Symptom(s) (if any): ..................................

Date of diagnosis of first/second melanoma

(or time interval)

Person detecting first melanoma

patient
partner
family doctor (specify reason for visiting)
other doctor (specify)
SMU doctor
other (specify)

Did anyone tell you where you had to look out for in the future, at diagnosis of the first melanoma? How to check your skin and lymph node fields?

Yes

Who: ..................................

No

Who was the last doctor you visited before the second melanoma was detected? (date): ..................................

What frequency of follow-up would you prefer?

every month
every 3 month
every 6 month
every year
less than every year
only at the time I have complains

Date interview: ..................................

Any comments: ..................................

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the melanoma and multiple variables (FPM and SPM: gender, age at diagnosis, anatomical site of the melanoma, ready visibility to the patient). The person identifying the FPM, instruction of self-detection at the time of FPM diagnosis and the interval between FPM and SPM were additionally compared to the person identifying the SPM. All variables that were statistically significant in the univariate analysis were included in a multivariate logistic regression model for FPM and SPM.
detection respectively. Statistical significance was considered to exist in all tests if a p-value of <0.05 was obtained.

RESULTS

The selection criteria were met by 112 patients. The median ages at FPM and SPM diagnosis were 55 years (range 18-81) and 61 years (range 26-85) respectively. The median interval between FPM and SPM diagnosis was 3.8 years (range 2 weeks-20 years). The median time interval between the last follow-up visit and date of SPM diagnosis was 6 months (range 2 weeks - >10 years). Seventy percent had their last follow-up check at the SMU, their local doctor or a dermatologist within the previous 12 months.

Table 1. Anatomic site, visibility of site by the patient and Breslow tumor thickness for first and second primary melanoma

<table>
<thead>
<tr>
<th></th>
<th>FPM</th>
<th>SPM</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Anatomic site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head and neck</td>
<td>11</td>
<td>10</td>
<td>21</td>
</tr>
<tr>
<td>Trunk</td>
<td>62</td>
<td>55</td>
<td>42</td>
</tr>
<tr>
<td>Upper extremity</td>
<td>18</td>
<td>16</td>
<td>24</td>
</tr>
<tr>
<td>Lower extremity</td>
<td>21</td>
<td>19</td>
<td>25</td>
</tr>
<tr>
<td>Total</td>
<td>112</td>
<td></td>
<td>112</td>
</tr>
<tr>
<td>Visibility of site by patient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Readily visible</td>
<td>58</td>
<td>52</td>
<td>71</td>
</tr>
<tr>
<td>Poorly visible</td>
<td>54</td>
<td>48</td>
<td>41</td>
</tr>
<tr>
<td>Total</td>
<td>112</td>
<td></td>
<td>64</td>
</tr>
<tr>
<td>Breslow tumor thickness (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>melanoma in situ</td>
<td>15</td>
<td>15</td>
<td>36</td>
</tr>
<tr>
<td>T1: &lt;1.0</td>
<td>53</td>
<td>52</td>
<td>56</td>
</tr>
<tr>
<td>T2: 1.01-2.0</td>
<td>16</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>T3: 2.01-4.0</td>
<td>13</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>T4: &gt; 4.0</td>
<td>4</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
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<td>11</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>total</td>
<td>112</td>
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</tr>
<tr>
<td>mean</td>
<td>1.1</td>
<td></td>
<td>0.7</td>
</tr>
<tr>
<td>median</td>
<td>0.7</td>
<td></td>
<td>0.5</td>
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<tr>
<td>minimum (in situ melanomas)</td>
<td>0.0</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>maximum</td>
<td>7.3</td>
<td></td>
<td>6.1</td>
</tr>
</tbody>
</table>

FPM: first primary melanoma
SPM: subsequent primary melanoma
* wilcoxon test
Clinical and pathological features

Clinical and pathologic details regarding the FPMs and SPMs are given in Table 1. The Breslow thicknesses of SPMs were statistically less than those of FPMs.

Detection of first primary melanomas and second primary melanomas

Table 2 records the persons detecting the patients’ FPMs and SPMs. Only Breslow tumour thickness, age at FPM diagnosis, gender, readily visibility of the lesion to the patient and site of the FPM had a statistically significant relationship to the person detecting the FPM the univariate analysis. Using multivariate analysis, greater Breslow tumor thickness, female gender and younger age were predictors for patient detected FPMs (Table 3). Included in the multivariate logistic regression model for SPM detection were primary tumour site, Breslow tumour thickness, disease free interval and readily visibility of the lesion to the patient. Greater Breslow tumor thickness and ready visibility of the melanoma to the patient were revealed as significant predictors for patient detection of a SPM (Table 3). Although patient-detected melanomas tended to be thicker, 24% of in situ FPMs and 32% of in situ SPMs were patient-detected. Fifty percent of patients did not recall receiving instruction regarding self-examination at the time of FPM diagnosis (although it is routine practice at the SMU to provide such advice). This reporting was equally distributed amongst gender and age groups and was not related to the person identifying the SPM. Among the 56 patients who indicated that they were instructed, 5 stated that they received information from their family physician, 18 from a non-SMU specialist (dermatologist or surgeon) and 33 from a SMU doctor.

Table 2. Person who detected first and second primary melanomas

<table>
<thead>
<tr>
<th>Person who detected melanoma</th>
<th>FPM</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>patient</td>
<td>55</td>
<td>49</td>
<td>41</td>
<td>37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>partner</td>
<td>11</td>
<td>10</td>
<td>12</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>general practitioner (family physician)</td>
<td>15</td>
<td>13</td>
<td>9</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>specialist</td>
<td>20</td>
<td>18</td>
<td>47</td>
<td>42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>other</td>
<td>11</td>
<td>10</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>total</td>
<td>112</td>
<td>100</td>
<td>112</td>
<td>100</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FPM: first primary melanoma
SPM: subsequent primary melanoma
DISCUSSION

A surprising finding in this study was that a melanoma history did not increase the likelihood that a patient would detect a SPM. Compared with melanomas detected by others, patient-detected FPMs were mainly of greater Breslow tumor thickness, detected by women and in younger patients. Second patient-detected melanomas were mainly of greater Breslow's tumor thickness and localised at readily visible body sites for the patient. On the basis of the results of this study, we conclude that periodic clinical review by clinicians plays an important role in the detection of new and thinner melanomas in patients who have had a previous primary melanoma.

FPM and SPM and follow-up

As far as we are aware, this is the first study that has investigated the role of patients in the detection of both FPMs and SPMs. The relatively large number of second melanomas has never been described in this context before. Especially in patients with multiple melanomas, in situ melanoma is an important entity. Therefore, inclusion of these pre-malignant lesions was of additional value.

The median interval between FPM and SPM detection in this study is similar to that reported by others. The interval between scheduled follow-up visits increased over time for most patients in the study and 20 patients did not have any routine follow-up visits scheduled at the time of SPM diagnosis.

The reliability of the information regarding second melanoma detection was likely to be high, because these data were obtained directly from patients and not retrieved indirectly from medical records. Clinical and pathologic data were extracted from the SMU's prospectively set up database and therefore were also

### Table 3. Multivariate logistic regression analysis of first and second primary melanoma in relation to the person detecting the melanoma

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>p-value</th>
<th>95%-confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>First primary melanoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>gender</td>
<td>4.9</td>
<td>&lt;0.01</td>
<td>1.48 - 15.98</td>
</tr>
<tr>
<td>age at first melanoma diagnosis</td>
<td>0.9</td>
<td>&lt;0.01</td>
<td>0.91 - 0.99</td>
</tr>
<tr>
<td>Breslow's tumor thickness</td>
<td>3.2</td>
<td>&lt;0.01</td>
<td>1.65 - 6.04</td>
</tr>
<tr>
<td>anatomical site</td>
<td>0.7</td>
<td>0.39</td>
<td>0.37 - 1.47</td>
</tr>
<tr>
<td>readily visibility</td>
<td>2.0</td>
<td>0.26</td>
<td>0.61 - 6.41</td>
</tr>
<tr>
<td>Second primary melanoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>readily visibility</td>
<td>3.58</td>
<td>&lt;0.01</td>
<td>1.41 - 9.09</td>
</tr>
<tr>
<td>Breslow's tumor thickness</td>
<td>1.90</td>
<td>0.02</td>
<td>1.10 - 3.28</td>
</tr>
<tr>
<td>anatomical site</td>
<td>1.38</td>
<td>0.12</td>
<td>0.92 - 2.06</td>
</tr>
<tr>
<td>disease free interval</td>
<td>1.00</td>
<td>0.85</td>
<td>1.00 - 1.00</td>
</tr>
</tbody>
</table>
likely to be of high validity. On the other hand, certain information regarding the first melanoma, which was in some cases diagnosed many years earlier, may have been subject to recall bias. Most patients in this study received their initial treatment outside the SMU. First melanoma clinical information or information regarding follow-up before the second melanoma diagnosis was not available in some cases. Conclusions related to follow-up in these cases cannot be made with complete confidence from the current study.

Detection of FPM and SPM in relation to previous studies

In agreement with previous studies focusing on detection of primary melanomas, female patients in this SMU series were more likely to have detected a first melanoma. This might be due to the fact that women are more aware of their skin than men. However, for second melanoma, this finding is not consistent in the literature and was not confirmed by our data. Younger age at first melanoma diagnosis was found to be related to the person detecting the first melanoma, a finding supported by other studies. Nevertheless, the effect of age was marginal, and we could not confirm this effect for the SPMs.

The majority of the FPMs in our study were patient-detected. These findings are comparable with previous studies. Surprisingly, fewer SPMs were patient-detected, although the number was much higher than previously described. This could be explained by the fact that lesions classified as “patient”-detected in this study consisted not only of true patient-detected lesions, but also included lesions detected by a person related to the patient (e.g. partner or relative). The exact description of a patient-detected lesion was not provided in either of the previous publications. Another explanation could be that 82% of the patients had routine follow-up visits in or outside the SMU. Not only at the SMU, but also at other medical practices in Australia, instructions for self-examination might have been more thorough. Also patient awareness might have been greater than elsewhere in the world, because of the much higher incidence of melanoma.

The results thus indicate that a history of a previous melanoma will not necessarily improve the effectiveness of a patient’s ability to detect a second melanoma. Also, a patient-detected FPM was not a predictor for a patient detection of a SPM. Richard et al examined patient delay in melanoma diagnosis (mainly first melanoma), and reported findings similar to those of the SMU, particularly a greater number of first than second melanomas being patient-detected. In accordance with previous studies we found a statistically significant difference between first and second melanoma thickness within the individual patients, with second melanomas being
consistently thinner.\textsuperscript{6,10,19} We consider this likely to be a result of regular follow-up visits, which were initiated for most patients after their first melanoma diagnosis. However, improved patient awareness after FPM diagnosis might also have played a role, because the proportion of patient-detected in-situ melanoma increased. Correlation between the person identifying the melanoma and Breslow tumour thickness has been investigated previously only for first melanomas. Our findings reflect the results of these other studies, in which most thinner melanomas were detected by physicians.\textsuperscript{12,17} Although early stage melanomas may be difficult to recognise, 24\% of in situ melanoma first melanomas and 32\% of in situ melanoma second melanomas were patient-detected. To increase patient-detected early melanoma, improved skills allowing the identification of thin (invasive) melanomas and melanoma in situ are required by both patients and their partner.

Detection of melanoma and self-surveillance

It is possible that patients with a melanoma history who are not diligent in self-surveillance of their skin tend to rely on their follow-up visits, where they expect to receive a thorough examination by their doctor for the detection of new lesions. Although this assumption would require separate investigation, it is supported by a previous study that examined patient delay in first melanoma diagnosis, in which it was found that significantly more patients who did not detect their first melanoma themselves had consulted a dermatologist or a family physician in the previous year.\textsuperscript{11} Furthermore, it is likely that a relatively large proportion of the patient population developing a SPM will have the dysplastic naevus syndrome,\textsuperscript{9,10} one of the main predictive factors for developing multiple melanomas.\textsuperscript{20} Since these patients often have scores or even hundreds of naevi, detection of early melanomas amongst an often large number of borderline suspicious lesions becomes more difficult. Unfortunately, the number of patients with this syndrome was not recorded in our study.

Previous studies have shown that promoting increased awareness and encouraging regular self-examination may be useful and inexpensive methods of reducing the incidence of advanced melanoma and may also increase the early detection of second melanoma.\textsuperscript{11,21-23} If self-examination were to be successful, follow-up visits could be reduced. This reduction is very important in terms of resource allocation and cost containment, especially in countries such as Australia with its high melanoma incidence. Currently, no international consensus has been reached about the optimal frequency of follow-up visits for melanoma patients. The aims of follow-up are multiple. Not only does the detection of new primary melanomas play an important role, but detection of recurrences, patient reassurance and medical audit for clinical research purposes are additional goals. If more effective instruction
on self-examination was provided, the recommended follow-up frequency might be reduced for patients with in-situ and Stage I melanoma. However, on the basis of this study, reduction of the follow-up frequency for the detection of subsequent primary melanoma is not warranted, since patient detection was shown to be less effective than physician check-ups. This finding might be in contrast with earlier statement of Kroon and Nieweg who claimed that frequent follow-up does not improve survival. Recommendations regarding the optimal frequency of follow-up visits have been investigated by the same authors and will be published elsewhere in the near future.

Future research
Several questions remain to be answered by future research. The cost-effectiveness of follow-up for melanoma patients is unclear in terms of quality adjusted life years. Also, the exact role of self-examination, and how to establish this, needs further investigation.

Summary
In summary, it is clear from the results of this study that more effective education is required to improve the rate of detection of SPMs by patients or their partners. Any individual who has had a melanoma is at risk (3-12%) of developing a second primary tumour, so attention to this education process is likely to be well worthwhile. The results of this study also highlight the importance of ongoing, long-term medical supervision of all patients who have had a melanoma, because many SPMs are unlikely to be detected at any early stage by patients or their partners. The ultimate goal of follow-up and recurrence detection is improvement of survival, but this has not been demonstrated for FPMs and has not been investigated for SPMs.
Chapter 4

References


Detection of second primary melanomas


