Melanoma and Tumor Thickness

Challenges of Early Diagnosis

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Objective: To test the basic assumption of campaigns for early diagnosis of melanoma, ie, prognosis is correlated with the delay in the diagnosis.

Design: Prospective study of the correlation between delays to diagnosis, assessed using a questionnaire, and the Breslow thickness as a prognosis marker.

Setting: Dermatology departments in France.

Patients: Five hundred ninety consecutive patients, referred within 12 weeks after resection of cutaneous melanoma.

Main Outcome Measures: Assessment of 5 successive time intervals from the first time the patients realized that they had a lesion until the resection of the melanoma, and results of the correlation between each time interval and tumor thickness (Breslow).

Results: There is a positive but weak correlation between tumor thickness and the delay to identify a lesion as suspicious ($r = 0.17; P = .009$). However, this delay tends to be short for the thickest tumors. There is a negative correlation between tumor thickness and the delay to seek medical attention ($r = -0.20; P < .001$). This delay was shorter for nodular melanoma. No correlation is found between melanoma thickness and physicians’ delays.

Conclusions: Poor prognosis can be accounted for by aggressive rapidly growing tumors rather than by delays. In well-informed populations, campaigns for early diagnosis of melanoma may thus no longer have a major impact on prognosis, unless they are focused on subgroups less accessible to information and medical care.

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The most accurate prognostic factor of primary melanoma has been shown to be the thickness of the lesion according to Breslow.

Campaigns for early diagnosis are based on the hypothesis that the tumor thickness is the consequence of the delay in the diagnosis, ie, patients’ delay in seeking medical attention and physicians’ delay in the detection of early melanoma. Information campaigns that increase population awareness about melanoma, training of physicians, and screening are expected to shorten these delays. Indeed, a decrease in Breslow thickness was observed in many countries where early detection was promoted.

For editorial comment see page 339

Although the correlation between the delay in the diagnosis and prognosis is admitted universally, it has never been established. Using thickness as a surrogate for prognosis, a few studies have addressed the question of whether tumor thickness is related to the delay. Unexpectedly, these studies failed to demonstrate a clear correlation between Breslow thickness and the delay in the diagnosis, thus suggesting that the link between the delay and prognosis may not be as strong as supposed. This weakness would have many implications on the validity and the cost-effectiveness ratio of screening and campaigns for early diagnosis of melanoma.

We thus designed a prospective study in a large population of patients with melanoma to assess correlation between the delay in the diagnosis and the Breslow thickness.

From January 1, 1995, through July 31, 1996, 590 consecutive patients were included. Three hundred forty were female (57.6%) and 250 were male (42.4%). Mean age was 51.2 years (range, 13-92 years;
PATIENTS AND METHODS

PATIENTS

Eighteen French dermatological departments of the public hospital system participated in the study. Consecutive patients referred for cutaneous melanoma in these centers entered the study when they fulfilled the following criteria: at least 12 years of age, histological confirmation of diagnosis of melanoma, and interview conducted within 12 weeks after melanoma resection. Patients were accepted only when the report forms were completed, a histological slide was available, and the diagnosis was confirmed by 2 experts. A total of 645 patients were entered by the centers, but only the 590 that fulfilled all these criteria were included in the analysis.

METHODS

Melanoma thickness was not reassessed, since we considered that the slide provided by the laboratories was not necessarily representative of the thickest component of the tumor. The following other histological characteristics were also recorded and checked: histological type, presence of ulceration and regression, and remnants of a nevus.

All patients were interviewed by a specially trained dermatologist in each center following a precise questionnaire, including 75 questions on patient characteristics, attitude of physicians before tumor resection, and tumor characteristics. Each patient was asked to recall the following 4 dates: when they first noticed a lesion (eg, a mole, a spot) on the site where the melanoma was diagnosed (D1), when they first believed that this lesion could be curious or potentially dangerous (D2), when this lesion was examined by a physician for the first time (D3), and when a physician first proposed removal (D4). A fifth date, when melanoma resection was performed (D5), was obtained from the files.

For each interval (D1-D2, D2-D3, D3-D4, and D4-D5), a list of questions investigated precisely what happened and what factors and causes were responsible for a short or a long delay. The questionnaire was conceived to fit each particular situation, ie, when the tumor was discovered by a physician (D1 and D2 irrelevant), when the patient believed immediately the lesion was suspicious (D1 = D2), or when the patient asked for removal (D4 irrelevant).

When the patient reported that the melanoma was diagnosed by a physician during routine clinical examination or during a visit for an unrelated problem, the melanoma was considered to be coincidentally diagnosed. Thus, D2 was missing in these cases, whereas D1 could have been defined by some patients who were aware of their lesion, but did not look at it. The remaining cases were considered to be self-detected.

To test the correlation between interval delays and Breslow thickness, the following 3 methods were used: assessment of correlation coefficient between each interval and Breslow thickness, comparison of delays in patients with increasing Breslow thickness, and comparison of Breslow thickness in patients with long and short delays. However, correlation of the D1-D2 (time to realize the lesion is potentially dangerous) and D2-D3 intervals (time before seeking medical attention) with Breslow thickness were only studied in self-detected melanoma, since they were irrelevant in patients with coincidentally diagnosed melanoma. In a de novo melanoma, D1-D2 interval is a good estimation of the time to identify an early lesion as potentially dangerous. In a melanoma developed on a preexisting nevus, D1 may be situated several years before the melanoma arises. In this case, D1-D2 interval is mainly an assessment of the precursor nevus history and not clearly an assessment of a delay in the diagnosis of melanoma. The correlation between D1-D2 interval and Breslow thickness was thus also studied in a subgroup of patients with D1-D2 interval of no longer than 5 years. This was the simplest way to reduce the proportion of uninformative D1-D2 intervals, assuming that in patients with very long D1-D2 interval (6-40 years), the lesion recognized on D1 was likely to be a preexisting nevus, and not the melanoma itself.

STATISTICS

All data were computerized and analyzed with parametric and nonparametric tests as appropriate, given the particular variables evaluated, using the Epi Info program (Epi Info version 6.04a; Centers for Disease Control and Prevention, Atlanta, Ga, and World Health Organization, Geneva, Switzerland) and SPSS program (SPSS Inc, release 6.1; SPSS Inc, Chicago, Ill). Correlation between intervals and Breslow thickness were assessed using the Spearman rank correlation test. For convenience of calculations, in situ melanomas were all standardized to 0.10-mm thickness. Mann-Whitney and Kruskal-Wallis tests were used to compare distribution values of time and Breslow thickness. To compare the distribution of qualitative variable, χ² test was used.

mean age of female patients, 48 years; mean age of male patients, 55 years).

MELANOMA CHARACTERISTICS

Median Breslow thickness was 1.19 mm (mean 2.3 mm; range, 0.1-99.0 mm). Breslow thickness was less than 1.5 mm in 336 (56.9%) of 590 lesions (Table 1). Histological signs of regression were noticed in 55 tumors (9.3%), ulceration in 112 (19.0%), and histological remnants of a nevus in 129 (21.9%). Fifty melanomas (8.5%) were achromic. Histological subtypes included 412 superficial spreading melanoma (SSM) (69.8%), 107 nodular melanoma (NM) (18.1%), 24 acral lentiginous melanoma (ALM) (4.1%), 21 lentigo melanoma (LM) (3.6%), and 26 unclassified (4.4%). Breslow thickness was lower in female than in male patients (median, 1.00 vs 1.54 mm; P<.001). A positive correlation was found between Breslow thickness and age (r = 0.19; n = 590; P<.001).

DELAYS

There was no difference in any delay components according to sex. A negative correlation was found between D2-D3 interval and age (r = −0.15; n = 418; P = .02), with D2-D3 interval shorter in older people. The D2-D3 interval was shorter in patients with NM than in patients with SSM (median, 46 vs 78 days; P = .03).
COMPARISON OF COINCIDENTALLY DIAGNOSED AND SELF-DETECTED MELANOMA

Mean age was significantly higher in the 172 coincidently diagnosed (29.2%) than in the 418 self-detected melanomas (70.8%) (55.8 vs 49.3 years; P < .001). Melanoma was more often self-detected in female than in male patients (P = .05). Tumor thickness was lower in coincidentally diagnosed than in self-detected melanoma (median, 0.9 vs 1.3 mm; P < .001). The distribution of histogenetic types was significantly different in coincidentally diagnosed and self-detected melanoma (Table 1), with more LM in coincidently diagnosed melanoma and more SSM, NM, and ALM in self-detected melanoma (x², P < .001). The D3-D4 (time to propose resection) and D4-D5 intervals (time to remove the lesion) were not different (P = .47) in coincidentally diagnosed and self-detected melanoma (Table 1).

RELATIONSHIP BETWEEN DELAYS AND MELANOMA THICKNESS

D1-D2 Interval Delay

In patients with self-detected melanoma, no significant correlation could be found between the D1-D2 interval and Breslow thickness distribution (Table 2). The D1-D2 interval was not different in each thickness subgroup (<0.75, 0.75-1.49, 1.50-2.99, and ≥3 mm) (Table 3). In the subgroup of patients with D1-D2 interval of no longer than 5 years, a positive and significant correlation was found between Breslow thickness and D1-D2 interval (Table 2). This correlation remained significant in SSM (r = 0.21; n = 166; P = .007) but not in NM (r = −0.07; n = 56; P = .60). The D1-D2 interval significantly increased with Breslow thickness, up to 3 mm (Table 3), but was shorter in melanoma of at least 3.00 mm than in tumors from 1.50 to 2.99 mm. Moreover, using the median D1-D2 interval (4 months) as a limit between short and long D1-D2 interval, Breslow thickness was found to be higher in patients with long delay (Table 4).

D2-D3 Interval Delay

In self-detected melanoma, a negative correlation was found between Breslow thickness and D2-D3 interval (Table 2). However, the correlation in each histopathological type was not significant (SSM, r = −0.11 [n = 293; P = .06]; NM, r = −0.15 [n = 82; P = .40]). The D2-D3 interval was shorter in patients with thick tumors than in those with thin tumors (Table 3). Using the median of D2-D3 interval (2 months) as a limit between short and long interval, Breslow thickness was higher when D2-D3 interval was no longer than 2 months than when it was longer than 2 months (Table 4).

D3-D4 and D4-D5 Interval Delay

In patients with coincidently diagnosed melanoma, there was a positive correlation between Breslow thickness and D3-D4 interval (Table 2), and the D3-D4 interval tended

### Table 1. Histological Characteristics of Tumors and Delays in the Diagnosis in Patients With Self-Detected and Coincidentally Diagnosed Melanoma

<table>
<thead>
<tr>
<th>Patients</th>
<th>Breslow Thickness, Median/Mean mm</th>
<th>Delays, Median/Mean (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>D1-D2</td>
</tr>
<tr>
<td>All (n = 418)</td>
<td>1.30/2.61</td>
<td>25 mo/122 mo (0 d-642 mo)</td>
</tr>
<tr>
<td>Patients with D1-D2 ≤5 y (n = 247)†</td>
<td>1.10/2.20</td>
<td>4 mo/12 mo (0 d-57 mo)</td>
</tr>
<tr>
<td>All (n = 172)</td>
<td>0.93/1.54</td>
<td>. . .</td>
</tr>
</tbody>
</table>

*Abbreviations are explained in the “Methods” subsection of the “Patients and Methods” section. Ellipses indicate not applicable.
†Indicates after exclusion of patients with probably irrelevant assessment of D1-D2 interval.

### Table 2. Correlation Between Delays to Diagnosis and Thickness of Melanoma

<table>
<thead>
<tr>
<th>Delays</th>
<th>Correlation Coefficient r</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients With Self-detected Melanoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D1-D2 (n = 395)</td>
<td>0.05</td>
<td>.32</td>
</tr>
<tr>
<td>D2-D3 (n = 418)</td>
<td>−0.20</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>D3-D4 (n = 418)</td>
<td>0.004</td>
<td>.90</td>
</tr>
<tr>
<td>D4-D5 (n = 418)</td>
<td>0.02</td>
<td>.70</td>
</tr>
<tr>
<td>D1-D5 (n = 418)</td>
<td>−0.004</td>
<td>.90</td>
</tr>
<tr>
<td>After exclusion of patients with probably irrelevant assessment of D1-D2†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D1-D2 (n = 247)†</td>
<td>0.17</td>
<td>.009</td>
</tr>
<tr>
<td>D1-D5 (n = 247)</td>
<td>0.04</td>
<td>.50</td>
</tr>
<tr>
<td>Patients With Coincidentally Diagnosed Melanoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D3-D4 (n = 172)</td>
<td>0.25</td>
<td>≤.001</td>
</tr>
<tr>
<td>D4-D5 (n = 172)</td>
<td>0.13</td>
<td>.08</td>
</tr>
</tbody>
</table>

*Abbreviations are explained in the “Methods” section of the “Patients and Methods” section. Correlations were assessed using the Spearman rank correlation test.
†Indicates patients with D1-D2 interval of ≤5 years.
COMMENT

To our knowledge, we have presented the largest prospective study of the relation between the delay in the diagnosis of cutaneous melanoma and melanoma thickness. The basic assumption for screening and early diagnosis campaigns is that the longer the delay, the thicker the melanoma, and the poorer the prognosis. In contrast to the 5 previous studies, we were able to find correlation between delay in the diagnosis of cutaneous melanoma and Breslow thickness, probably because our investigation of the delays was more precise, and because we included a higher number of patients.

Reviewing the charts of 245 patients during a 6-year period, Cassileth et al did not find any correlation between Breslow thickness and the length of time from the appearance of new lesions or the change in preexisting lesions to diagnosis. Temoshok et al, in a prospective study of 59 patients, did not find a significant correlation between Breslow thickness and an interval corresponding to our definition of D2-D3 interval (P < .10). In a 1991 prospective study of 250 patients, Krige et al did not find any correlation between a period corresponding to D1-D2 or D2-D3 interval, according to our definition, and Breslow thickness. In a 1997 prospective study of 102 patients, Baccard et al did not find any significant correlation between the thickness of melanoma and time to diagnosis (P > .05). Only 1 study, using a definition of delays that seemed to correspond to our D2-D3 or D2-D4 interval, found in 106 patients a positive correlation between the delay and Breslow thickness. However, this correlation was demonstrated only in NM and self-detected SSM.

The imprecisions in the assessment of the delays are certainly the major drawback of this type of study. They can be due to incomplete patient recall of the date the lesion was first noticed and to difficulties in defining reference dates. To minimize this bias in our study, patients were questioned immediately after resection, when they were best able to recall the history of their melanoma, and we defined 5 reference dates, easy to understand for any patient, that were investigated separately. Finally, we tried to limit the proportion of cases in which the assessment of an interval probably did not provide relevant information about actual melanoma history and
delays. Therefore, we calculated correlations between D1-D2 interval and Breslow thickness in a subgroup of patients with D1-D2 interval of no longer than 5 years.

The delay in D1-D2 interval probably depends on many factors, such as sex, age, the patient’s awareness about melanoma, accessibility of the tumor to the view, clinical appearance of the tumor, and perhaps the familial and social context of the patient. The delay in D2-D3 interval may depend on patient awareness about melanoma but also on the psychological profile of the patient. The delay in D3-D4 interval depends on physician competence. The delay in D4-D5 interval is probably the result of physician message, psychological profile of the patient, and health system organization.

All median intervals from D2 to D5 were short (1 week to 2 months), although the upper values were very long. These results were expected in a country with a good awareness about melanoma. The median D1-D2 and D2-D3 intervals were much longer than the median D3-D4 and D4-D5 intervals (4 months, 2 months, 0 days, and 1 week, respectively), suggesting that the medical delay generally had little impact on tumor thickness.

We showed a correlation between Breslow thickness and the delay in D1-D2 interval. However, this correlation was found only in the subgroup with D1-D2 interval of no greater than 5 years. Indeed, in the other subgroup (D1-D2 interval > 5 years), D1-D2 interval that often included the history of a preexisting nevus was probably not a good surrogate for the delay to identify an early lesion as potentially dangerous.

The correlation between D1-D2 interval and Breslow thickness was not as strong as could be expected ($r = 0.17$; $n = 247$; $P = .009$). This can be accounted for by the apparent bimodal relationship between Breslow thickness and the delay. Whereas increasing median thickness was associated with an increasing D1-D2 interval to a Breslow thickness of 3 mm (Table 3), the median D1-D2 interval was surprisingly 2 times shorter in melanoma thinner than 3 mm than in melanoma from 1.5 to 3 mm (123 vs 365 days). Aggressive melanoma may grow more quickly but may also have more spectacular symptoms and draw patient attention more rapidly. In other words, despite a rapid reaction of patients, these aggressive tumors may however be thick when removed. They may represent a large part of melanoma thicker than 3 mm and account for the apparently paradoxical shorter delay in thick tumors (Table 3).

Surprisingly enough, tumor thickness tended to be lower when D2-D3 interval was higher ($r = -0.20$; $n = 418$; $P < .001$). Again, melanoma with the most aggressive behavior grows more quickly but may induce anxiety more rapidly (shorter D2-D3 interval) than another melanoma. Despite a more rapid visit to a physician, they are usually more deeply invasive. This hypothesis is supported by the comparison of NM with SSM. Nodular melanomas, which are usually considered to be rapidly growing tumors, had a higher mean Breslow thickness than SSM (1.41 vs 5.67 mm), although they tended to be associated with a shorter D2-D3 interval than SSM.

In patients with self-detected melanoma, no correlation was found between D3-D4 or D4-D5 interval and Breslow thickness, suggesting that medical delays have little influence on prognosis. These results suggest that minimizing the delay between the patient presenting to the general practitioner and the excision in the hospital would probably have little impact on prognosis in most patients. Conversely, in patients with melanoma discovered by chance during a physical examination, the impact of the delays in D3-D4 and D4-D5 intervals on Breslow thickness became detectable. Breslow thickness was significantly correlated with D3-D4 interval, and there was a trend in favor of a correlation with D4-D5 interval.

As already noticed in previous studies, Breslow thickness was lower and thus the prognosis was more favorable in coincidentally diagnosed than in self-detected melanoma. Quickly growing aggressive melanoma is more likely to draw the attention of the patient, whereas the slowly growing types are more likely to go unnoticed until a systematic examination. In this regard, we must underline that there was an excess of NM in self-detected tumors and an excess of LM in coincidentally diagnosed tumors. The proportion of male patients with self-detected was lower than that with coincidentally diagnosed melanoma. This suggests a need for targeted publicity campaigns at self-detection in male patients. Moreover, frequency of visits to physicians being similar between men and women in our study ($P = .09$; $\chi^2 = 4.73$), the following hypotheses may account for this sex-related difference: melanomas in men are often invisible (on the back), and men pay little attention to their skin.

Our data underline that the Breslow thickness of melanoma results not only from the delay in the diagnosis but also from the biological aggressiveness of the tumor. The respective impact of the delay and the biological behavior of the melanoma on the final thickness of the tumor may depend on the population studied. In an uninformed population, the delay in the diagnosis is very long and is probably the main factor responsible for the tumor thickness. Education campaigns are thus useful. Conversely, in a well-informed population, tumor thickness may be correlated more strongly with biological behavior of the tumor, than with delay in the diagnosis that is generally short. Indeed, despite a very early diagnosis, a number of aggressive and rapidly growing melanomas are already thick at the time of resection, whereas a number of slowly growing tumors are still thin even when they are detected late in a well-informed population. The major factor accounting for poor prognosis may thus no longer be the delay but the biological aggressiveness of the tumor, which is unfortunately not preventable. These data suggest that shortening the delay in the diagnosis by intensifying education and screening of the whole population may not lead any longer to a strong improvement of prognosis. However, our study also shows that delays are still very long in some cases, which highlights the need to identify the individuals who are probably less accessible to information or medical care. Screening and education campaigns should be focused on these groups at risk for having a very long delay in the diagnosis.

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