Variations in Management of Stage I to Stage III Cutaneous Melanoma

A Population-Based Study of Clinical Practices in France

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Objective: To describe current management of cutaneous melanoma (CM) and identify factors accounting for disparities.

Design: Retrospective population-based study using survey of cancer registries and pathology laboratories, and questionnaires to physicians.

Setting: Five regions covering 19.2% of the French territory and including 8.2 million inhabitants.

Patients: Incident cases of patients with stage I to stage II (hereinafter, stage I-II) tumors staged according to the American Joint Committee on Cancer Staging guidelines and nodal stage III CM in 2004.

Main Outcome Measures: Modalities of diagnosis and excision, surgical margins, sentinel lymph node biopsy, adjuvant therapies and surveillance procedures, and their variations according to age, sex, residence, location of primary CM, Breslow thickness, type of physicians, modalities of decisions, and health care patterns.

Results: Clinical stage I-II CMs (n=710 cases) slightly predominated in females (53%), with a lower mean Breslow thickness (1.4 mm) than in males (1.9 mm). Initial excisions were most often performed by private dermatologists and wide excisions by surgeons. Narrow margins (8%) were associated with advanced age, higher Breslow thickness, and head location. Sentinel lymph node biopsy was performed in 34% of CMs thicker than 1.0 mm, depending on geographical regions, distance from reference centers, and health care patterns. Adjuvant therapies (mainly low-dose interferon) were proposed in 53% of thick CMs (≥1.5 mm), depending on the patient's age and geographical region. In contrast with French recommendations, surveillance procedures frequently included systematic medical imaging. Stage III nodal CMs (n=89 cases) predominated in males (62%). After lymphadenectomy, adjuvant therapies (including high-dose interferon in 32% of cases and chemotherapy in 24% of cases) were proposed in 68% of cases, depending on the patient's age and geographical region. A complete 1-year high-dose interferon regimen was administered in less than 10% of cases.

Conclusion: Large disparities still exist in the management of CM in France, depending to a greater extent on medical and geographical environment than on the characteristics of either patients or tumors.

Arch Dermatol. 2008;144(5):629-636
enhanced disparities in practice, little is known about their nature, extent, and causal factors. To date, studies on clinical practices have been rare and usually limited to specific topics (eg, surgical excision, \text{SLN dissection}, or surveillance procedures)\textsuperscript{24-26}. Most studies assessed practice intentions or physicians’ habits\textsuperscript{18-20,22-25,28} rather than actual practices, and very few were performed in a population-based setting\textsuperscript{7,24}. Last, data available to date mainly refer to the United States,\textsuperscript{18,20,22-25,27,28} and current practice patterns remain widely unknown in Europe.\textsuperscript{19,21} In France, only studies on intentions of practices related to the surveillance of localized CM are available.\textsuperscript{26} This prompted us to conduct a population-based descriptive and explicative analysis in a large geographic area of France on most aspects of the management of American Joint Committee on Cancer stage I to stage III CM, including modalities of diagnosis and excision, surgical margins, SLN dissection, adjuvant therapies, and surveillance procedures.

**METHODS**

**GEOGRAPHICAL SETTING**

The study was performed in the northeast of France, including the 5 regions of Alsace, Bourgogne, Champagne-Ardenne, Franche-Comté, and Lorraine, including 8.2 million inhabitants and covering 105,217 km\textsuperscript{2} (ie, 19.2\% of the total area of France). This area comprises 3 of the 11 French population-based general cancer registries, located in the départements of Haut-Rhin, Bas-Rhin, and Doubs, which include a total of 2.25 million inhabitants. The whole study area was therefore divided between type A areas, defined by the presence of a cancer registry, and type B areas, without registries, with different methods being used in both types for completing the data collection.

**INCLUSION OF CASES AND ASSESSMENT OF EXHAUSTIVENESS**

The study was approved by the French National Commission Informatique et Liberté, and by scientific committees of the Fondation de France and the French Dermatologic Society. Cases eligible for the study were either (1) incident cases of clinical stage I-II invasive CM diagnosed from January 1 to December 31, 2004, in residents of the study area, or (2) incident cases of regional lymph node metastases (stage III) in 2004, regardless of when the diagnosis of the primary tumor was made. Patients with in situ CM, patients with in-transit metastases, and those with distant metastases at initial evaluation were excluded.

In the whole study area (types A and B), most eligible cases were identified by an initial systematic survey of private and hospital dermatologists (survey 1). A questionnaire was mailed in June 2005 to all of them, asking for an anonymous report of eligible cases. Data regarding diagnosis, management, and surveillance were collected using 2 specific models of questionnaires, for clinical stage I to stage II (hereinafter stage I-II) and stage III CMs, respectively. Participating physicians could request the assistance of a clinical research associate, either by telephone or on site. Those who did not respond were contacted again by telephone and/or mail.

Because it was anticipated that a notable proportion of eligible cases would be unreported by dermatologists, a complementary population-based survey (survey 2) was conducted for stage I-II CM, relying on cancer registries in type A areas and on private and public pathology laboratories in type B areas. When additional eligible cases were so identified, corresponding physicians were asked for information, using similar data forms. Initials and date of birth were used for excluding duplicate entries. Eligible cases were included for analysis when a completed questionnaire was obtained.

For stage I-II CM, an exhaustiveness rate was calculated, defined as the ratio of included cases to eligible cases. In type A areas, the number of eligible cases was provided by cancer registries, which have been exhaustively collecting incident cases of cancers for many years. In type B areas, without previous habits of exhaustive registration, it was supposed that the real number of eligible cases should be higher than that identified by the survey of pathology laboratories. Therefore, the number of eligible cases was evaluated using the hypothesis that the survey of dermatologists (survey 1) would lead to the inclusion of the same proportion of eligible cases in both areas. The ratio of cases included by survey 1 to eligible cases, as calculated in type A areas, was applied to type B areas, giving the estimated number of eligible cases and thereafter the exhaustiveness (ratio of included cases to estimated cases) in type B areas.

**DATA COLLECTION**

For clinical stage I-II CM, the following data were collected for each patient: age; sex; geographic region; area of residence (urban vs rural) and distance to a reference center, as defined by the presence of a multidisciplinary decision committee (MDC) for skin cancers; circumstances of diagnosis; clinical and histological characteristics of the tumor; modalities of surgery (including excisional biopsy, definitive surgery, and total margins); SLN biopsy; presentation to an MDC for decision of management, as recommended by the French Cancer Plan; medical imaging for staging; adjuvant therapies; and surveillance procedures. In view of the whole questionnaire, 3 health care patterns were defined, involving: (1) private physicians only, without resort to public hospitals or regional cancer centers; (2) public (university or nonuniversity) hospitals; or (3) regional cancer centers.

For regional lymph node metastases (stage III), the same data were collected, including circumstances of discovery and surgical and medical management. Clinical stage I-II cases that were reevaluated as stage III by SLN biopsy were analyzed within the stage I-II group for their management preceding SLN analysis, and within the stage III group for further management.

**STATISTICAL ANALYSIS**

Stage I-II and stage III cases were studied separately with descriptive and explicative analyses. Explicative analyses were performed using univariate and multivariate logistic regression models to investigate factors associated with the following variables: time from initial excision to definitive surgery, adequacy of total margins with current recommendations, presentation to an MDC, SLN biopsy, proposition and then institution of adjuvant therapies, and level of surveillance procedures. For each analysis, factors tested for explicative value (when pertinent) belonged to the following: age, sex, area of residence (rural vs urban), geographic region of residence, distance from residence to the nearest reference center, presentation to MDCs, location of the tumor, Breslow thickness, qualification of physicians performing excisions (surgeons vs dermatologists), and health care pattern. Factors significant at the P = .20 level in univariate analyses were included in stepwise regression multivariate analyses. All analyses were performed using SAS statistical software (SAS Inc, Cary, North Carolina). In view of the number of explicative analyses performed, only results of multivariate analyses are presented.
RESULTS

STAGE I-I I CM CASES

A total of 710 clinical stage I-II CM cases were included, 600 at the term of survey 1 and 110 at the term of survey 2, 256 (36%) from type A areas and 454 (64%) from type B areas, leading to an exhaustiveness rate of 80% in type A areas and 81% in type B areas. These CMs occurred in 373 females (53%) and 332 males (47%), ranging in age from 14 to 97 years (mean age [SD], 58 [17] years; median age, 58 years). The mean age of onset was similar in males (58 years) and females (57 years). Patients were living in an urban area in 61% of cases and in a rural one in 39% and originated from the geographical regions of Alsace, Lorraine, Bourgogne, Champagne-Ardenne, and Franche-Comté in 29%, 27%, 16%, 15%, and 13% of cases, respectively. Five patients had 2 primary CMs in 2004. In these patients, the management of each tumor was analyzed separately.

The clinical and histological characteristics of CM cases are shown in Table 1. The mean Breslow thickness was higher in men (1.9 mm [median, 0.91 mm]) than in women (1.4 mm [0.7 mm]) (P = .03).

The CMs were included in the study by private dermatologists (PDs), hospital dermatologists (HDs), or oncologists in 55%, 41%, and 5% of cases, respectively. Among cases reported by PDs, patients consulted for their tumor by themselves in 48% of cases and were referred by general practitioners (GPs) or other specialists in 20% and 4% of cases, respectively. In other cases, they were either prospectively followed for their nevi (10%) or diagnosed as having CMs on systematic cutaneous examination when consulting PDs for other diseases (17%). Among cases reported by HDs, 76% were referred by PDs and 10% by GPs. Overall, at least 17% of cases were first suspected by GPs, 85% were diagnosed or confirmed by PDs, and 11% by HDs.

Initial excisions (usually excisional biopsies for diagnosis) were performed by PDs, surgeons, HDs, and other physicians in 70%, 19%, 8%, and 3% of cases, respectively. Wide definitive excisions were performed by surgeons, PDs, and HDs in 63%, 21%, and 16% of cases, respectively. Time to definitive surgery ranged from 0 (for 1-step large excision) to 374 days (median, 28 days). The CMs were presented to MDCs in reference centers, as recommended by the French Cancer Plan, in 29% of cases. These percentages were 23%, 44%, and 57% for cases with a Breslow thickness lower than 1.5 mm, 1.5 to 3.0 mm, and higher than 3.0 mm, respectively. Information regarding total excision margin, SLN biopsy, initial staging, adjuvant therapies, modalities of follow-up, and global health care patterns in the whole series and according to Breslow thickness is shown in Table 1.

An adjuvant therapy was proposed in 3% of CMs with a Breslow thickness of 1.5 mm or lower and in 53% of those exceeding 1.5 mm. The proposed adjuvant therapy was low-dose interferon, as approved in France (3 million IU, 3 times a week for 18 months), in 66% of cases. In 11% and 8% of cases, it consisted in interferon alfa-2 or a vaccination within a clinical trial, respectively. High-dose interferon, according to Kirkwood et al, was proposed in 7% of cases and other, undescribed, therapies in 7%. The adjuvant therapy was actually instituted in 67% of cases. It was completed in 62% of these cases and was withdrawn in 38% after a mean time of 3.5 months (range, 0.1-12 months), owing to poor tolerance (50%), recurrence or metastasis (18%), or miscellaneous reasons (32%).

FACTORs INFLUENCING PRACTICES

Surgical Margins

Factors independently associated with insufficient surgical margins (as opposed to adequate or excessive margins) were an advanced age (>60 years; odds ratio [OR], 4.0; 95% confidence interval [CI], 1.8-9.0; P = .001), Breslow thickness higher than 1.5 mm (OR, 4.8; 95% CI, 2.3-9.9; P < .001) and location on the head and neck (OR, 3.5; 95% CI, 1.6-7.4; P = .001). Factors independently associated with excessive margins (as opposed to adequate or insufficient) were the health care pattern 1 (OR, 4.9; 95% CI, 1.5-4.0; P < .001) and certain geographic regions (P = .03). Sex, area of residence (rural vs urban) and distance to a reference center, presentation to MDCs, and qualification of the physician performing the definitive excision (surgeon vs PD or HD) had no effect on surgical margins.

Time From Initial Excision to Definitive Surgery

Time to definitive excision exceeded 6 weeks in 24% of cases. Factors associated with a long delay (>6 weeks) to definitive surgery were excision by a surgeon (vs PDs or HDs; OR, 4; 95% CI, 2.3-6.8; P < .001) and certain geographic regions (P = .02). Sex, area of residence and distance from residence to a reference center, presentation to MDCs, and health care pattern had no effect on the delay for definitive surgery.

SLN Biopsy

An SLN biopsy was performed in 19% of all clinical stage I-II CMs, including 7% and 34% of those with a Breslow thickness lower than 1.0 mm and 1.0 mm or higher, respectively. The SLN biopsy finding was positive in 25 of 132 cases analyzed (19%). These cases were therefore reclassified as (microscopic) stage III CM.

Factors independently associated with SLN biopsy in cases with a Breslow thickness higher than 1 mm were health care patterns 2 and 3 (OR, 17; 95% CI, 5.5-55.0; P < .001), distance greater than 60 km to a reference center (OR, 3.6; 95% CI, 1.8-7.6; P < .001) and certain geographic regions (P < .001). Age, sex, area of residence, presentation to MDCs, location of primary CM, Breslow thickness (when ≥1.0 mm), and health care pattern did not influence the use of SLN biopsy.

Adjuvant Therapy

Factors independently associated with the proposal of adjuvant therapies in cases with a Breslow thickness higher than 1.5 mm were a younger age (≤60 years; OR, 7.4;
Table 1. Management of 710 Stage I-II CMs in the Study Area in 2004

<table>
<thead>
<tr>
<th>CM Characteristic and Management</th>
<th>All Cases (n=710)</th>
<th>Cases With Breslow Thickness ≤1.5 mm (n=474)</th>
<th>Cases With Breslow Thickness &gt; 1.5 mm (n=198)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location (n=710), %&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head and neck</td>
<td>14</td>
<td>NCR</td>
<td>NCR</td>
</tr>
<tr>
<td>Upper limb</td>
<td>19</td>
<td>NCR</td>
<td>NCR</td>
</tr>
<tr>
<td>Trunk</td>
<td>36</td>
<td>NCR</td>
<td>NCR</td>
</tr>
<tr>
<td>Lower limb</td>
<td>32</td>
<td>NCR</td>
<td>NCR</td>
</tr>
<tr>
<td>Breslow thickness (n=672), mm&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>1.61</td>
<td>NCR</td>
<td>NCR</td>
</tr>
<tr>
<td>Median</td>
<td>0.8</td>
<td>NCR</td>
<td>NCR</td>
</tr>
<tr>
<td>Ulceration (n=633), %&lt;sup&gt;c&lt;/sup&gt;</td>
<td>18</td>
<td>NCR</td>
<td>NCR</td>
</tr>
<tr>
<td>Health care pattern (n=710), %&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pattern 1 (private physicians only)</td>
<td>42</td>
<td>52</td>
<td>20</td>
</tr>
<tr>
<td>Pattern 2 (public hospitals)</td>
<td>52</td>
<td>43</td>
<td>75</td>
</tr>
<tr>
<td>Pattern 3 (regional cancer centers)</td>
<td>6</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Total excision margin (n=570), %&lt;sup&gt;c,d,e&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Adequate</td>
<td>76</td>
<td>78</td>
<td>72</td>
</tr>
<tr>
<td>Narrow</td>
<td>8</td>
<td>4</td>
<td>18</td>
</tr>
<tr>
<td>Excessive</td>
<td>16</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>Sentinel node dissection (n=710), %&lt;sup&gt;d&lt;/sup&gt;</td>
<td>81</td>
<td>88</td>
<td>65</td>
</tr>
<tr>
<td>Performed (% positive)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>19 (19)</td>
<td>12 (7)</td>
<td>35 (29)</td>
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<tr>
<td>Adjuvant therapy (n=666), %&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Proposed&lt;sup&gt;d&lt;/sup&gt;</td>
<td>16</td>
<td>3</td>
<td>53</td>
</tr>
<tr>
<td>Proposed and instituted&lt;sup&gt;d&lt;/sup&gt;</td>
<td>11</td>
<td>1.75</td>
<td>36</td>
</tr>
<tr>
<td>Instituted and completed&lt;sup&gt;d&lt;/sup&gt;</td>
<td>7</td>
<td>1.5</td>
<td>21</td>
</tr>
<tr>
<td>Initial staging (n=662), %&lt;sup&gt;a,c,d&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical examination only</td>
<td>17</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>Including chest radiography and abdominal US</td>
<td>52</td>
<td>60</td>
<td>32</td>
</tr>
<tr>
<td>Including CT scan</td>
<td>27</td>
<td>20</td>
<td>51</td>
</tr>
<tr>
<td>Including FDG-PET</td>
<td>3</td>
<td>2</td>
<td>5</td>
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<tr>
<td>Follow-up&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
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<tr>
<td>Frequency of follow-up visits (n=685), %&lt;sup&gt;a,c,d&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>3-mo interval</td>
<td>43</td>
<td>36</td>
<td>57</td>
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<tr>
<td>6-mo interval</td>
<td>43</td>
<td>55</td>
<td>10</td>
</tr>
<tr>
<td>Other or NP</td>
<td>14</td>
<td>9</td>
<td>34</td>
</tr>
<tr>
<td>Modalities of surveillance (n=626), %&lt;sup&gt;a,c,d,h&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical examination only</td>
<td>54</td>
<td>62</td>
<td>30</td>
</tr>
<tr>
<td>Including chest radiograph and abdominal US</td>
<td>32</td>
<td>31</td>
<td>36</td>
</tr>
<tr>
<td>Including CT scan</td>
<td>13</td>
<td>7</td>
<td>34</td>
</tr>
<tr>
<td>Including FDG-PET</td>
<td>0.5</td>
<td>0.2</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: CM, cutaneous melanoma; CT, computed tomographic; FDG-PET, positron emission tomography–computed tomography with fluorodeoxyglucose F 18; NCR, not clinically relevant; NP, not performed; US, ultrasonography.

<sup>a</sup> Because of rounding, percentages may not total 100%.

<sup>b</sup> Breslow thickness was undetermined or not specified in 38 cases (5%).

<sup>c</sup> Owing to nonspecified data, the total numbers of cases may differ from 710.

<sup>d</sup> Compared with French recommendations (Consensus Conference<sup>1</sup> and Agence Nationale pour le Développement de l’Evaluation Médicale<sup>29</sup>).

<sup>e</sup> For further management, cases with positive sentinel lymph node or regional nodal metastases diagnosed concomitantly with the primary tumor were excluded from Table 1 and analyzed within the stage III group (Table 2).

<sup>f</sup> Follow-up was planned in the absence of recurrence or metastasis. French recommendations were clinical follow-up visits at 6-month intervals for CMs with a Breslow thickness 1.5 mm or lower and at 3-month intervals for CMs with a Breslow thickness higher than 1.5 mm.

Surveillance Procedures

Systematic surveillance procedures were clinical examination only in 54% of cases, chest radiography and/or abdominal US in 32%, and included computed tomographic (CT) scans in 13%. Factors independently associated with the systematic use of CT scans for surveillance were presentation to MDCs (OR, 4.5; 95% CI, 2.4–8.7; P < .001), Breslow thickness higher than 1.5 mm (OR, 5.6; 95% CI, 4.0–10.0; P < .001) and certain geographic regions.
A total of 89 stage III CM cases were included, originating from Alsace, Bourgogne, Champagne-Ardenne, Lorraine, and Franche-Comté in 26%, 25%, 20%, 19%, and 10% of cases, respectively. The ratio of stage III to stage I-II cases diagnosed in 2004 was 89:710 (12.5%). Thirty-five patients had primary tumors and regional lymph node metastases diagnosed within the same year. Regional lymph node metastases occurred in 55 men (62%) and 34 women (38%), aged 27 to 84 years (mean age [SD], 59.8 [15.1] years; median age, 61 years). Characteristics of corresponding primary tumors are shown in Table 2. The time from diagnosis of primary tumors to regional metastases ranged from 0 (concomitant diagnosis) to 149 months (mean time, 21.9 months; median time, 5 months). Seventy-two percent of stage III cases were presented to MDCs. Circumstances of diagnosis of nodal metastases and information regarding staging procedures and follow-up are shown in Table 2. After diagnosis of nodal metastases, a complete lymphadenectomy was performed in 82 cases (92%). Among the other 7 patients (8%), 4 had regional metastases considered inextirpable and were first treated by chemotherapy alone (3 cases) or associated with radiotherapy (1 case); 1 had only a focal micrometastasis less than 0.2 mm in diameter of the SLN; 1 refused lymphadenectomy; and the last patient did not undergo lymphadenectomy for an unknown reason.

After lymphadenectomy, adjuvant therapies were proposed in 56 cases (68%). Factors associated with adjuvant therapy being proposed were certain geographic regions of residence (P = .02) and a younger age (≤60 years; OR, 2.6; 95% CI, 0.9-7.0; P = .06).

In 26 of 56 cases (46%), the proposed adjuvant therapy was high-dose interferon as approved in France and the United States.31 After being proposed, adjuvant high-dose interferon was actually instituted in 20 of 26 cases. Five patients declined to take the treatment, and 1 patient developed distant metastases before outset. Among 20 patients who did start adjuvant high-dose interferon therapy, only 8 received a complete 1-year course. In other cases, interferon treatment was withdrawn 1 to 10 months after initiation (median time, 3 months), either for poor tolerance (6 cases) or for recurrence or metastases (6 cases).

A chemotherapy (most often dacarbazine, fotemustine, or temozolomide) was proposed as an adjuvant therapy in 20 of 56 cases (36%). Other proposed adjuvant therapies were interferon within a clinical trial (3 of 56 cases), low-dose interferon (1 of 56 cases), dacarbazine plus low-dose interferon (2 of 56 cases), vindesine plus radiotherapy (1 of 56 cases), and radiotherapy (3 of 56 cases).

In this population-based study, we collected comprehensive information on the management of 710 stage I-II CMs and 89 nodal stage III CMs diagnosed in 2004 in a large geographic area covering roughly 20% of France. Using databases of cancer registries and pathology laboratories, we evaluated the exhaustiveness of inclusions as 81% of all incident stage I-II cases in the study area. Because the ratio of nodal stage III to stage I-II cases (89:710[12.5%]) was in accordance with the natural history of CM in France, it may be assumed that a similar exhaustiveness rate was reached for stage III cases. The slight predominance of primary CM in female patients (sex ratio, 1:1.2) contrasted with higher Breslow thicknesses (median thickness, 0.91 mm vs 0.7 mm; P = .03) and more frequent regional lymph node metastases (sex ratio, 1:6) in males. These results confirm and extend na-
tional epidemiologic data on CM available in France and provide the first population-based assessment of nodal metastases.

Our study also provides population-based information on the respective role of patients, GPs, dermatologists, and surgeons in the diagnosis and initial management of CM in France. Although at least 17% of CM cases were first suspected by GPs, many patients first consulted a dermatologist (most often a PD) by themselves for their tumor. Finally, 85% of CMs were diagnosed or confirmed by PDs and 11% by HDs. The initial excision was most often performed by PDs (70%) and the definitive excision by surgeons (63%). Considering the relatively low median Breslow thickness (0.8 mm) in our study population, these observations emphasize the crucial importance of the awareness of CM among both the general population and GPs, and the central role of PDs in early diagnosis and excision in France. The respective role of dermatologists and surgeons is in accordance with previous observations in other western countries. In Canada, a national survey of surgical practice showed a high involvement of dermatologists in surgery of skin cancers. Similar to our study, a survey of dermatologists in the United States showed that most of them performed initial excisional biopsies before referring patients to surgeons for wide definitive excisions.

We observed a large variability in the management of CM. This variability, as measured in about 80% of incidental cases in a limited geographic area, probably underestimated the actual heterogeneity in management of CM in France as a whole. However, to our knowledge, our results provide for the first time comprehensive information about the nature, extent, and causal factors of disparities. Notable variations were observed at all steps of management, including excision and total margins, sentinel node dissection, presentation to MDCs, initial staging, adjuvant therapies, and surveillance procedures. Factors accounting for this variability were not only related to patients and their tumors (ie, age, anatomical location, Breslow thickness), but also to their medical and geographical environment (ie, geographical region, distance from residence to reference centers, physicians performing excisions, presentation to MDCs, and health care pattern). Factors most regularly affecting practices were the geographical region and the health care pattern. The region had independent significant effects at almost all steps of CM management, including surgical margins, time to definitive surgery, SLN analysis, and adjuvant therapies.

French recommendations for total margins in 2004 were 1 cm for CMs with a Breslow thickness 1.0 mm or lower, 1 to 2 cm for a Breslow thickness 1.0 to 2.0 mm, and 2 to 3 cm for a Breslow thickness higher than 2.0 mm. Practices were in accordance with these recommendations in 76% of cases. Excessive margins (as routinely recommended in the past) were more frequent (16%) than insufficient margins (8%). Factors significantly accounting for insufficient margins were advanced age, elevated Breslow thickness, and the location on head and neck. These results may be explained by technical and/or esthetic limitations encountered with thick CMs, particularly when located on the face, and by limitations to general anesthesia or noncompliance to reexcision in elderly patients. The role of age is in accordance with previous studies in the United States and the Netherlands. Dutch investigators showed that advanced age was the most important determinant of noncompliance for reexcision. However, they did not observe any significant effect of compliance on survival. In addition to previous studies supporting French recommendations for surgical margins before 2004, a large, randomized, subsequent study showed that a narrow 1-cm margin for CMs 2 mm or greater in thickness did not modify the overall survival rate, compared with a 3-cm margin. Because this study was published in early 2004 in a journal with a large impact factor, it may have influenced practices in the present study and thereafter.

French guidelines available in 2004 did not include recommendations concerning SLN biopsy. In the present study, we found that SLN biopsy was performed in 34% of patients with a CM at least 1 mm in thickness. This percentage was similar (35%) when only CMs higher than 1.5 mm were considered. Factors influencing SLN biopsy for CMs greater than 1 mm in thickness were independent of characteristics of either patients or tumors and were only related to their medical and geographical environment. No previous comparable study was available in France. To our knowledge, only 1 population-based study of SLN practices has been published to date. This study showed that SLN biopsies were performed in 50% of stage IB CMs and 47% of stage II CMs in the United States in 2001. Because this study also demonstrated an important increase of SLN biopsies over the previous 4 years and this procedure has been encouraged by the National Comprehensive Cancer Network clinical guidelines, it is probable that the current use of SLN biopsies in the United States is much higher than that observed in our study. In a recent survey conducted in Oregon, 76% of respondent surgeons stated that they used SLN biopsy in their practice. In Europe, the introduction of SLN biopsy into clinical practice has been poorly evaluated but seems to be inconsistently used. Although recent reports seem to indicate a relatively wide use in Germany, a survey performed in 2001 in the United Kingdom showed that only 15 of 49 surgical units (31%) that treated patients with CM used SLN analysis. Our study showing intermediate use of SLN biopsy in France was performed before the publication of the new French guidelines, which did not set SLN analysis as a standard of care, and before the recent publication of the Multicenter Selective Lymphadenectomy trial. In view of the considerable debate and controversy that this publication sparked in France and worldwide, it is still unclear how these results will influence practice in a near future.

In France, only low-dose interferon alfa-2a and high-dose interferon alfa-2b have been approved as adjuvant therapies for CMs 1.5 mm or higher in thickness and those at high risk of recurrence (mainly stage III), respectively. Overall, we found that an adjuvant therapy was proposed in 53% of stage I-II CMs thicker than 1.5 mm.
and 68% of stage III cases but actually was initiated in only 36% and 54% of cases, respectively. In most stage I-II cases, this adjuvant therapy was low-dose interferon as approved in France, or variable therapies within clinical trials. In contrast, a substantial proportion of patients with stage III CM received (nonapproved) chemotherapies, radiotherapy, or combined therapies. High-dose interferon, as approved in France and in the United States, was proposed in 26 of 82 stage III cases, but actually instituted and completed in only 20 of 82 and 8 of 82 cases, respectively. Therefore, adjuvant high-dose interferon does not seem to be a standard of care in real-life practice in France.

As in previous studies, we observed little variability and global compliance with French recommendations concerning the frequency of clinical follow-up visits and skin examinations. In contrast, surveillance procedures showed large geographic variations and frequently included systematic medical imaging, which was not in compliance with French guidelines published both before and after the period of the present study. Paradoxically, presentation to MDCs in reference centers was associated with more intensive surveillance procedures, that is, less compliance with French guidelines. This may be explained by the low grade of evidence of such recommendations, which to date rely mainly on retrospective and descriptive studies. Besides, many physicians are increasingly familiar with new imaging techniques, including lymph node US, CT scans, magnetic resonance imaging, and FDG-PET, which clearly improve the early identification of recurrences and metastases. Furthermore, a recent prospective study using stage-specific follow-up procedures suggested that early detection of recurrences was associated with a survival benefit in patients with stage I to stage III CM. However, intensive follow-up strategies have not been compared with less intensive ones in prospective randomized trials, as previously performed in breast and colorectal cancer, and such studies are still needed to improve consensus on surveillance in CM.

In summary, our study showed large and notable disparities in the management of CM in France and discrepancies with current practice guidelines. The present identification of factors accounting for variations could lead to future homogenization and improvements. Repeated clinical guidelines and new advances for the management of CM should be confronted with real-life practice. Because studies of practice provide important information in terms of public health, they should be extended over countries most heavily affected by CM and repeated over time.

Accepted for Publication: September 10, 2007.

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Financial Disclosure: None reported.

Funding/Support: This study was supported by grants from the Société Française de Dermatologie and the Fondation de France.

Additional Contributions: We thank the physicians and dermatologists who provided data for this study and the following associations of dermatologists: Association d’Enseignement Post-Universitaire en Dermato-Vénéréologie de Champagne-Ardenne, Association des Dermatologues de Bourgogne, Association d’Information Post-Universitaire des Dermato-Vénéréologues de Strasbourg, Association de Formation des Dermatologues de Franche-Comté, and Association Lorraine Post-Universitaire de Dermatologie.

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