Variation in the Diagnosis, Treatment, and Management of Melanoma In Situ

A Survey of US Dermatologists

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Objective: To assess current practices of US dermatologists regarding the diagnosis, treatment, and management of melanoma in situ (MIS).

Design: Survey.

Participants: A total of 1200 dermatologists randomly selected from the American Board of Medical Specialists Directory of Board Certified Medical Specialists.

Main Outcome Measures: Results based on 597 questionnaires returned.

Results: The overall response rate was 63% (597 of 945 eligible participants). To aid in clinical assessment, respondents reported using a magnifying lens (57.4%) and dermoscopy (17.4%). Most dermatologists preferred excisional and saucerization biopsies as the method of choice for sampling. A large percentage of physicians (78.9%) preferentially used dermatopathologists for the evaluation of the majority of pigmented lesions. Although most respondents would not unquestioningly accept a benign pathology diagnosis when there was a clinical suspicion of MIS, 16.1% would accept a pathologist’s diagnosis without further action. There was no consensus on the appropriate surgical margins or depth of excision for MIS. Of the respondents who characterized MIS as premalignant and malignant, 63.2% and 46.4%, respectively, did not know what percentage of MISs would progress to metastatic disease if left untreated.

Conclusions: Considerable variability exists in the clinical concept and management of MIS. Dermoscopy is underutilized. The true nature of the evolution of MIS is unknown. Surgical margins and depth of excision need to be standardized to help dermatologists manage disease. Further research in the specific area of MIS is warranted to develop clear guidelines in the management and prevention of further disease.

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The incidence of melanoma of the skin continues to rise. In 2005, 59,580 new cases of cutaneous melanoma and 7770 melanoma-related deaths are expected in the United States.1 In addition, it was anticipated that there would be another 46,170 cases of melanoma in situ (MIS) diagnosed in the United States in 2005.1 However, the combined total of 105,750 melanomas that were anticipated to develop in 2005 may actually have been an underestimate, since thin invasive melanomas and MIS are often treated in outpatient facilities and may not be reported to cancer registries.2 Furthermore, reporting delays may mask true incidence trends and actually give a false impression of declining incidence rates.3 It stands to reason that the true burden of melanoma on society and the medical system is much higher than that currently estimated.

Many studies have focused on the best possible methods of diagnosing and treating patients with invasive melanoma. However, despite the fact that the incidence of MIS continues to rise, few studies have addressed the entity of MIS. Dermatologists are frequently the first physicians to evaluate or perform biopsies of pigmented lesions suspected of being MIS. Subsequently, they often treat patients diagnosed as having MIS. However, there are differing views regarding the best methods to clinically evaluate and perform biopsies of lesions suggestive of MIS. In addition, opinions vary regarding optimal recommendations for the treatment of patients in whom this lesion is diagnosed. In response to the lack of uniformity in the approach toward patients with MIS, we surveyed a sample of US dermatologists to assess how they diagnose, treat, and manage MIS lesions.
A 3-page survey and a postage-paid return envelope were mailed to each of the 1200 physicians selected for the study in May 2001. Nonresponders were sent a second mailing 2 months later. After the second mailing, any survey returned because of an improper address or because the physician was no longer practicing at the address was further scrutinized (n=239). A Web-based physician search was conducted to update contact information for all the surveys returned as undeliverable. Any new contact information gleaned from the physician search was entered into the database contact list for the subsequent mailing. A third mailing was sent to all nonresponders and all physicians with new address information. To further increase response, a $3 incentive coupon from a well-known national coffee retailer was included in the third mailing.

The survey consisted of 28 questions and was designed to address medical and surgical management issues, as well as the diagnostic evaluation and clinical understanding of MIS.

**DATA ANALYSIS**

Descriptive frequencies were used to describe demographics and survey responses, and χ² tests were used to evaluate differences in survey responses according to demographic factors. The data were analyzed with SAS version 8.1 software (SAS Institute Inc, Cary, NC).

**RESULTS**

A total of 1200 surveys were sent. Of these, 171 were returned because of incorrect addresses, and 84 were considered ineligible because the physician was deceased (n=5), no longer practicing dermatology (n=14), or retired (n=65). The final study sample was composed of 597 completed surveys, for an overall response rate of 63% (597/945 eligible recipients). Low response rates for physician-based surveys are common, with a mean response rate of 54%. We recognize that this response rate raises the possibility of reporting bias and limited generalizability of our results. A comparison of the characteristics of respondents and nonrespondents suggested that our sample was representative (data not shown). Sex, practice location, and years in practice were similar for responders, nonresponders, and the dermatologists who failed to meet inclusion criteria. Characteristics of the survey respondents are presented in Table 1.

**DIAGNOSIS OF MIS (EXCLUDING LENTIGO MALIGNA OF THE FACE)**

**Clinical Diagnosis**

The use of diagnostic tools in the evaluation of suspicious pigmented lesions was investigated. The most common tool used was the magnifying lens (57.4%), and this varied according to the number of years of dermatology practice. Dermatologists in practice for longer than 17 years were more likely to use a magnifying lens for the clinical diagnosis of MIS (67.2% vs 47.8%; P<.001). Also, 104 physicians (17.4%) used a dermoscope to evaluate lesions suggestive of MIS, and its use varied according to practice type. Physicians practicing in a group or solo practice used the dermoscope less than those in an academic setting (15.9% vs 29.4%, respectively; P=.01). How-

<table>
<thead>
<tr>
<th>Table 1. Description of 597 Survey Respondents and Frequency of MIS in Practice</th>
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<tr>
<td><strong>Variable</strong></td>
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<td>Years in practice, mean ± SD</td>
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<tr>
<td>Sex</td>
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<td>Female</td>
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<td>Male</td>
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<td>Practice type</td>
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<tr>
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<tr>
<td>≤50%</td>
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<tr>
<td>Surgical</td>
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<td>Practice location</td>
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<td>Suburban</td>
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<tr>
<td>Rural</td>
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<tr>
<td>No. of histologically confirmed MISs diagnosed during past year</td>
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<tr>
<td>≤10</td>
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<tr>
<td>11-20</td>
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<td>21-30</td>
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<td>31-40</td>
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<td>41-50</td>
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<td>&gt;50</td>
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<tr>
<td>Trend in No. of MIS cases during past 5 y</td>
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<td>Increased</td>
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<td>Decreased</td>
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<tr>
<td>Remained the same</td>
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<td>Unknown</td>
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Abbreviation: MIS, melanoma in situ.

*Some categories do not total 100% because of missing or incomplete responses.
ever, dermoscope use did not differ with respect to the number of years in practice. The biopsy methods most commonly used by the respondents were excision (38.7%), deep shave or saucerization (34.1%), punch (19.0%), shave (7.8%), and other (0.4%).

**Histopathologic Diagnosis**

The survey showed that 384 respondents (64.3%) believed that the threshold for histologic diagnosis of MIS varied significantly among pathologists (Table 2). A majority of the respondents (78.9%) reported sending more than 50% of pigmented lesion biopsy specimens directly to a dermatopathologist. However, when the pathology report returned with a benign diagnosis but there was a clinical suspicion of MIS, most respondents would take further action (Table 2). Only 96 respondents (16.1%) would accept the diagnosis without further evaluation.

**SURGICAL TREATMENT**

Clinical margins used by respondents for the resection of MIS were elicited (Table 3). Fifty-five percent of respondents (n=327) used clinical margins of 5 mm or less for MIS not on the face, and 57.0% (n=340) did so for MIS or lentigo maligna on the face. Furthermore, 19 respondents (3.2%) believed that MIS should be excised to the level of the dermis; to the superficial fat, 219 (36.7%); to the deep fat, 175 (29.3%); to the superficial fascia, 59 (9.9%); including the superficial fascia, 1 (0.2%); and other, 7 (1.2%). Surgical treatment of MIS was also assessed by questions regarding the practice of Mohs surgery for lentigo maligna or MIS on the face. Furthermore, 19 respondents (n=327) used clinical margins of 5 mm or less for MIS not on the face, and 57.0% (n=340) did so for MIS on the face. Mohs surgery was used at least occasionally by 56.3% of all respondents for facial lesions, while most physicians (82.2%) would not attempt Mohs surgery for nonfacial lesions.

**MANAGEMENT AND FOLLOW-UP**

Physicians were asked questions regarding the proper management and follow-up for histologically confirmed MIS lesions. The majority of physicians (77.1%) did not order additional tests after the diagnosis of MIS had been established. Of those who ordered additional tests, 12.7% ordered complete blood cell counts, 14% liver function tests, 8.7% lactate dehydrogenase measurement, and 18.3% chest x-rays. Overall, 493 (86.8%) of the respondents reported recommending lifelong dermatologist-performed total-body skin examinations on patients with MIS, while 447 (79.5%) recommended that family members of patients receive skin cancer screening examinations. This screening should begin at age 11 to 20 years according to 189 respondents (43.8%), at 10 years old or younger by 121 (28.1%), and at older than 20 years by 121 (28.1%).

**CLINICAL CONCEPT OF DISEASE**

The respondents’ clinical concept of MIS is shown in Table 4. Although 499 respondents (83.6%) believed that MIS is a malignancy, 166 respondents (27.8%) reported not knowing what percentage of MIS would progress to invasive growth phase if left untreated, while an even greater number of respondents (262 [43.9%]) reported not knowing what percentage of MIS would metastasize if left untreated. Of the respondents who characterized MIS as premalignant and malignant, 63.2% and 46.4%, respectively, did not know what per-
The results of this survey of a cross-sectional population of US dermatologists indicate that there is variability concerning the entity of MIS and its diagnosis, treatment, and management. The need for a more uniform approach is underlined by an increasing incidence of MIS in the United States.

CLINICAL METHODS OF DIAGNOSIS

Early melanoma can be difficult to differentiate clinically from other pigmented lesions. In our survey we found that, although many respondents (32%) did not use any diagnostic tools to aid them in the evaluation of lesions suggestive of MIS, the majority (57%) used a magnifying lens. In addition, respondents who had practiced for more than 17 years were more likely to use magnifying lenses. It is unclear whether this increase in magnifying lens use among the more experienced dermatologists was a function of the nature of the training they received, or merely the fact that these dermatologists were compensating for age-related decreased visual acuity. These findings are of interest since there is a paucity of literature regarding the use of the magnifying lens for assistance in diagnosing skin cancer. The addition of dermoscopy to the visual examination, on the other hand, has been reported to improve the diagnostic accuracy of melanoma and has even been suggested by some to be the cornerstone of such a diagnosis. However, only 17% of the respondents in our study reported the use of the dermoscope, with physicians working in an academic setting more likely to use it than those in private practice. A likely explanation for the limited use of dermoscopy is the lack of training. Currently, it is estimated that about half of US dermatology residency programs use dermoscopy in the evaluation of pigmented lesions. Although not addressed in this study, it has been shown that the use of dermoscopy led to a decrease in the number of biopsies of benign lesions without compromising the sensitivity of melanoma diagnoses.

BIOPSY METHODS

Concerning the most commonly used biopsy method for clinically suspected MIS excluding the face, most dermatologists reported the use of excisional surgical techniques. Excisional and saucerization biopsies are the best approaches for obtaining an accurate histologic diagnosis. Incisional biopsy specimens of lentigo maligna often fail to show the areas with the most advanced histologic changes. Consequently, inaccurate microstaging can occur because of sampling errors within clinically heterogeneous lesions. On the other hand, an excisional biopsy may be impractical in lesions that are large or in areas of cosmetic concern. In these select cases, a partial biopsy may be the most reasonable approach to obtain a diagnosis.

RELIABILITY OF HISTOLOGIC DIAGNOSIS

Histologic examination of biopsy specimens of pigmented skin lesions is used to reach an exact diagnosis. However, several studies have shown that there is variability between pathologists in the interpretation of pigmented skin lesions. Accordingly, a majority (64.3%) of respondents in our study believed that there is significant variability in the threshold for histologic diagnosis of MIS. Furthermore, recent literature has questioned the reliability of the histologic diagnosis of lesions such as MIS with routine stains such as hematoxylin-eosin. Megahed et al performed immunohistochemical analysis with the melanocytic marker melan-A/MART-1, a reliable marker for melanoma. They found invasive melanoma in 29% of 104 cases that were originally deemed to be MIS with routine hematoxylin-eosin staining. Although most trained pathologists can perform immunohistochemistry, a dermatopathologist may be more likely to use these more specific techniques to render a more precise analysis of diagnostically challenging melanocytic lesions. In our study, most respondents demonstrated greatest confidence in the diagnostic abilities of dermatopathologists for obtaining accurate diagnoses. This was evidenced by the fact that almost 80% of respondents reported sending more than half of pigmented lesion biopsy specimens directly to a dermatopathologist as opposed to a general pathologist, although limitations such as access may play a part in the remaining 20%. Clinical impressions, however, tempered reliance on histologic diagnosis. When a clinically suspicious MIS returned with a benign histologic diagnosis, 84% of the respondents would take additional measures to re-evaluate the lesion.

TREATMENT OF MIS

Optimal Margin Control

Although other therapies have been used, excisional surgery remains the standard of care for definitive treatment of histologically proved MIS lesions. However, great controversy exists over the optimal...
resection margin appropriate for MIS. When Breslow and Macht\textsuperscript{33} established the theory that prognosis was directly associated with tumor thickness more than 2 decades ago, the international consensus was that 1-cm margins were safe for thin cutaneous melanoma tumors. In 1992, the National Institutes of Health Melanoma Consensus Conference considered 5-mm margins effective for treating MIS.\textsuperscript{13} These narrow margins are likewise recommended internationally.\textsuperscript{34} Although margins of as little as 3 mm have also been recommended,\textsuperscript{35} many subsequent studies using Mohs micrographic surgery have shown that narrow margins may not be adequate.\textsuperscript{36-41} The optimal-margin controversy stems from the fact that no large-scale prospective controlled studies have examined margins for MIS. It is not surprising that the respondents in our study were divided between supporting a surgical margin of 5 mm or less (57.0%) and greater than 5 mm (33.3%) for MIS. It is clear that further prospective research is required to address the optimal surgical margins for MIS, with long-term follow-up to determine local recurrence rates as well as disease-free and melanoma-related survival.

\textbf{Depth of Excision}

As with surgical margins, there are few data to support the appropriate depth to which MIS should be definitively excised. Currently, there are no widely accepted guidelines for the depth of excision of MIS. Neither the American Academy of Dermatology nor the National Comprehensive Cancer Network mentions depth of excision for MIS in its melanoma treatment guidelines. This fact may explain the variability in the responses in our survey. The majority of respondents reported removal of lesions at least down to the superficial fat. This surgical practice may stem from the fact that it is generally necessary to excise at least to the level of the subcutaneous fat for primary wound closure.

\textbf{Mohs Micrographic Surgery}

The present survey also addressed the issue of Mohs micrographic surgery for the treatment of MIS. Although controversial, the Mohs technique offers an alternative to excisional surgery, with complete examination of all margins and possible tissue conservation. Case series have supported the efficacy of Mohs surgery for MIS, with long-term cure rates equaling or exceeding historical cure rates with conventional wide local excision.\textsuperscript{42-44} In our study, more than half of all respondents reported the use of Mohs micrographic surgery in the surgical treatment of facial MIS, whereas most respondents favored traditional surgical excision for nonfacial lesions. This differential practice in treating facial vs nonfacial MIS is likely due to the finding that recurrence rates on the head and neck are especially high after local excision.\textsuperscript{45} This high recurrence rate has been attributed to subclinical extensions of the primary tumor that may be missed by the random histologic examination of the surgical margins. Other explanations include a residual “field effect,” where the histologically normal-appearing melanocytes in a given area share a developmental or environmentally acquired susceptibility to malignant transformation.

\textbf{FURTHER TESTING AND FOLLOW-UP}

The present survey also assessed the dermatologists’ propensity to order additional laboratory tests and imaging studies in patients diagnosed as having MIS. Most respondents (77.1\%) did not order additional tests after a diagnosis of MIS was made and definitive excision was performed. This conservative approach for the follow-up of patients with histologically proved MIS is in keeping with the Melanoma Consensus Conference of 1992.\textsuperscript{13} This conference considered only early melanomas (MIS and invasive lesions <1 mm thick) and concluded that a staging workup was not indicated for this group of patients.

It is well known that patients with a history of melanoma are at a higher risk than the general population for developing additional melanomas and nonmelanoma skin cancers. It is therefore not surprising that clinical follow-up of patients with MIS was deemed important by respondents. Most respondents (86.8\%) believed that patients should have lifelong follow-up with dermatologist-assisted total-body skin examination after an initial diagnosis of MIS. This is in accord with the guidelines from the National Comprehensive Cancer Network for pigmented lesions suggestive of MIS.\textsuperscript{46} Indeed, reports have described recurrences of MIS that have led to invasive lesions with severe morbidity or fatal outcomes.\textsuperscript{47-51} Furthermore, a study done in Sweden concluded that the relative risk for later developing invasive melanoma among patients with MIS was increased more than 20-fold compared with the general population and that there was a statistically increased risk of developing invasive cutaneous melanoma at least up to 14 years after diagnosis of MIS.\textsuperscript{32}

Overall, respondents were also inclined to promote the screening of family members of patients with MIS. Increasing evidence for the genetic basis of melanoma\textsuperscript{33} may underlie this relative consensus for familial screening. Variation occurred, however, in the age at which to begin screening, with most recommending screening in the pubertal years of 11 to 20.

\textbf{CLINICAL CONCEPT OF MIS}

Finally, some of the most telling, yet inconsistent, responses were those dealing with the clinical concept of MIS. To date, there remains considerable uncertainty regarding the histologic predictive value for biological behavior with regard to MIS. In vitro studies have demonstrated that in situ lesions are biologically unable to produce immortal cell lines in tissue culture.\textsuperscript{49} Nonetheless, the overwhelming majority of dermatologists (83.6\%) believe MIS to be a true malignancy, and approximately the same percentage (78.2\%) relay this sentiment to their patients (Table 4). However, a significant proportion of respondents (27.8\%) reported not knowing what percentage of MIS would progress to invasive growth phase if left untreated. In addition, 43.9\% reported not knowing what percentage of MIS
would metastasize if left untreated. These numbers reflect the uncertainty that exists among dermatologists with regard to the natural course and potentially fatal outcomes associated with MIS. Further research such as genomic profiling needs to be undertaken to gain a better understanding of the biological behavior of MIS.

CONCLUSIONS

This study gives some indication as to how US dermatologists are currently diagnosing and managing MIS. Responses to this survey affirm the diversity of beliefs and practices of dermatologists with regard to MIS. The low percentage of respondents using dermoscopy underscores the need for more teaching in this area. Excision and saucerization are acceptable means of making a diagnosis. The majority of respondents preferentially use dermatopathologists but do not blindly accept a benign histologic diagnosis when there is a clinical suspicion of MIS. There is a great need for further studies to investigate appropriate margins, which may differ for lesions on the torso and face. While the overall approach demonstrated by the respondents of this survey seems to identify MIS as a true malignancy, the uncertainty regarding its invasive potential if left untreated warrants additional studies of the biology and the natural course of this disease. Further research in the specific area of MIS is warranted to develop clear guidelines in the management and prevention of further disease.

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