Role of Dermatologists in Treating Melanoma

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ABSTRACT

Melanoma is a major focus of dermatology training and practice, with dermatologists playing a central role in managing melanoma through primary prevention, secondary prevention, diagnosis, and treatment of thinner tumors. Dermatologists have led public health efforts to raise melanoma awareness, promulgate the early warning signs of melanoma, and promote melanoma prevention through sun protection. Dermatologists have unique expertise in melanoma risk assessment and the clinical diagnosis of melanoma through visual inspection and the use of diagnostic aids, including dermoscopy and photographically assisted follow-up. Increasing incidence of melanoma, earlier melanoma detection, narrower excision margins, and improved surgical training in dermatology have recently combined to enhance the role of dermatologists in melanoma care. For patients with thin primary melanomas, dermatologists are increasingly assuming complete care, including wide local excision and long-term surveillance for both disease recurrence and detection of new primary melanoma. Conversely, the advent of sentinel lymph node biopsy and adjuvant therapy has made melanoma management more complex and has intensified the need for a multidisciplinary approach to the disease. In this context, dermatologists contribute significantly to the formation, administration, and implementation of multidisciplinary melanoma programs. (JNCCN 2006;4:695–702)

Despite significant progress in the past few decades, treating melanoma remains a challenge to physicians worldwide. The incidence of cutaneous melanoma in Caucasian populations is increasing. Melanoma ranks among the top 6 cancers in both men and women in the United States and Australia. This increased incidence has been variably attributed to a true increase in incidence or an increased detection of biologically indolent disease through enhanced screening efforts and higher skin biopsy rates. The rising incidence has been accompanied by a less dramatic, albeit significant, increase in mortality (e.g., Netherlands [24% in 1989–1998], United Kingdom [20% in 1991–2001]), supporting a true increase in incidence.

Melanoma treatment encompasses many different clinical specialties. Dermatologists have been playing an increasingly important role in the management of melanoma. The key to effective melanoma management is early diagnosis. Public health campaigns have raised awareness of the importance of seeing a physician experienced in diagnosing melanoma (i.e., a dermatologist) as early as possible. Clinicians in the United Kingdom highly recommend that patients with potential melanoma be referred to pigmented lesion clinics and be seen within 2 weeks of receiving a referral letter. Dermatologists have a central role in caring for these patients. Pigmented lesion clinics have also gained popularity in Italy and, to a lesser extent, the United States. In the United States, many patients newly diagnosed with melanoma are self-referred to a dermatologist.

The role of dermatologists in melanoma care varies widely in different countries. In the United States, dermatologists are involved in the prevention, detection, and treatment of low-risk melanoma and directing the patient with advanced melanoma through the system of specialized care. Dermatologists do not routinely perform sentinel lymph node biopsies (SLNBs) or administer adjuvant therapy for patients with high-risk melanoma. In Germany, SLNBs are reported to be performed routinely by dermatologists. In the United States, dermatologists do not routinely administer chemotherapy, whereas in other countries (e.g., Italy) chemotherapy is routinely administered in some dermatology departments.

Over the past decade, the dermatologists’ role in managing cutaneous melanoma has undergone a paradigm shift. This is partly because of the increasingly surgical
orientation of the specialty coupled with the trend toward narrower excision margins, especially for thin melanomas. A growing number of dermatologists are performing initial biopsies and wide excisions and playing a key role in coordinating the care of patients with melanoma. In the increasingly specialized medical environment, multispecialty melanoma clinics are gaining popularity for managing patients with complex melanoma, with dermatologists playing an increasingly important role. This article discusses the role of the dermatologist throughout the spectrum of melanoma care.

**Melanoma Prevention**

Without highly effective treatment for advanced melanoma, prevention and early detection are of paramount importance. Successful prevention depends on an understanding of the origin of melanoma and finding possible ways to interrupt its evolution.

Strong evidence shows that sunlight exposure in predisposed individuals increases their risk for developing melanoma. This effect is best supported by epidemiologic studies of severe episodic sunburn in early life. Although episodic sunburn is associated with superficial spreading and nodular melanoma, long-term cumulative sun exposure is more closely linked with the development of lentigo maligna melanoma. Recognition of anatomically, histologically, and molecularly differing subsets of melanoma with epidemiologically varied associations with sun exposure and nevus phenotype has led to the concept of divergent pathways in the pathogenesis of melanoma. This proposes that sunlight induces melanocytes of nevus-prone individuals to proliferate and become neoplastic with little further requirement for sun exposure. Melanomas are more likely to arise on the backs of these individuals, where increased numbers of ontogenetically unstable melanocytes are present. On the other hand, individuals who are less prone to nevi require ongoing sunlight exposure for melanomas to develop. Melanomas in these individuals tend to arise on chronically sun-exposed areas.

Ultraviolet (UV)-A and UV-B rays have been implicated in the pathogenesis of melanoma. Experts speculate that UV radiation causes melanoma from both direct and indirect DNA damage, immunosuppression, and stimulation of growth factors in skin.

**Genetic Factors**

Knowledge of the genetic basis of melanoma is increasing but does not yet practically apply to efforts in prevention and management. Germline mutations in 3 highly penetrant gene products have been associated with familial melanoma: p16, p19, and cyclin-dependent kinase 4. Patients with familial melanoma constitute a very small proportion of the overall population of patients with melanoma, and penetration in these families depends on geographic location and skin phototype. Currently, routine genetic testing for melanoma susceptibility genes is not advised. Acquired mutations in BRAF and other genes in the MAP kinase, RB, and p53 pathways are associated with nevogenesis and melanoma. Targeted therapies designed to capitalize on these observations are being studied.

**Identifying Patients at Risk**

Several clinical risk factors for melanoma have been identified, including family history of melanoma, personal history of melanoma, multiple nevi, dysplastic (atypical) nevi, and immunosuppression. Individuals with type I skin (i.e., those who burn easily, tan poorly), freckling, blue eyes, and red hair are at increased risk for developing melanoma. This sun-sensitive phenotype is genetically linked to polymorphisms in the melanocortin receptor 1 (MC1R). Dysplastic nevi are among the strongest risk factors for melanoma and complicate attempts at detection because they may demonstrate the ABCD clinical warning signs of melanoma: asymmetry, border irregularity, color variation, and large diameter.

Dermatologists are specially trained in identifying individuals at increased risk for melanoma and in detecting early melanoma. Because of a growing understanding of the complexity of UV carcinogenesis, photoaging, and vitamin D metabolism, dermatologists are uniquely qualified to counsel patients in skin cancer prevention.

**Melanoma Screening and Surveillance**

Although experts agree that early detection has the greatest immediate potential for preventing deaths from melanoma, the impact of screening on mortality has not been formally studied and thus can be debated. Recent trends toward the diagnosis of thin melanoma can be attributed to increased public awareness and, to a lesser extent, screening. In the United
States, the American Academy of Dermatology (AAD) sponsors annual free skin cancer screenings. The AAD conducted 1,024,350 skin cancer screenings between 1985 and 1999, with an estimated 800,000 individuals undergoing at least 1 free screening (Figures 1 and 2). A report analyzing the AAD campaign from 1992 through 1994 noted that the screenings detected mostly thin stage 1 localized melanoma with associated good prognosis and imparted a broad skin cancer educational message. The report also noted that 39% of the patients in whom melanoma was detected would not have undergone skin examination if not for the free screenings. Aitken et al. studied a community-based melanoma screening program in Australia as part of a large-scale randomized control trial. Primary care physicians, specially trained by a dermatologist, conducted the skin cancer screenings. The clinical detection rate for suspected melanoma was 1.3 per 100 patients screened, and 0.2 per 100 patients had a histologically confirmed melanoma. The specificity of whole body skin examination for melanoma detection was found to be comparable to other screening tests for cancer, including mammography.

Targeting the population at the greatest risk of dying from melanoma would optimize the cost-effectiveness of mass screening for the disease. Surveillance, Epidemiology, and End Result (SEER) data from the United States National Center for Health Statistics show that melanoma mortality increases significantly with age and is considerably higher in men, especially in older age groups. This is consistent with findings from the American Academy of Dermatology National Skin Cancer Screening Program, which showed that the highest yield of melanomas occurred among male participants older than 50 years who reported a changing mole or had skin types I and II. Some experts have therefore suggested that screening programs should be targeted to men older than 50 years. Others have challenged this strategy by underscoring the greater impact on years of life lost through melanoma detection at a young age, and the possibility that the nodular melanomas more commonly encountered in older men may defy detection at an early curable stage.

Self–skin examination (SSE) is an important method for detecting suspected melanoma and generating public awareness of the warning signs of melanoma. In an Italian study, 40.6% of patients detected their own melanomas. Brady et al. studied the detection pattern among 471 patients newly diagnosed with melanoma, finding that 57% detected their own melanomas and that women were more likely to self-detect than men. Teaching interventions and digital cutaneous photography can enhance patients’ adherence to SSE. Although primary care physicians have the greatest opportunity to screen patients for skin cancer and instruct patients in the performance of SSE, these activities remain primarily in the domain of dermatologists. Patients at especially high risk for melanoma are those with dysplastic nevi and a personal or family history of melanoma. These individuals often have a complex nevus pattern that complicates melanoma detection. These individuals are suggested to benefit from periodic expert dermatologic examination for the detection of early malignant melanoma.
Melanoma Diagnosis

Simple visual examination has an estimated sensitivity of approximately 70% for detecting melanoma.\(^{34,35}\) Although traditional visual examination remains the primary method of melanoma detection, use of newer diagnostic aids is increasing in clinical practice. Dermoscopy and whole body photography are the primary diagnostic aids used by some dermatologists. The dermatoscope is a handheld device that is equipped with a transilluminating light source and standard magnifying optics. Imaging of subsurface features is accomplished using either a liquid interface and glass contact plate or polarized light. For experienced users, dermoscopy has been shown to improve the accuracy of melanoma diagnosis when compared with routine clinical examination. This is reflected in the increasing number of PubMed citations on dermoscopy over the past 20 years (Figure 3). Kittler et al.\(^{36}\) reported a meta-analysis of 27 published studies comparing the diagnostic accuracy for melanoma with or without dermoscopy. The mean odds log ratio was significantly higher for melanoma diagnosis with dermoscopy than without (3.4 [2.9–3.9] vs. 2.5 [1.9–3.1]; \(P = .03\)), with a 49% improvement in diagnostic accuracy by experienced dermatoscopists. Although dermoscopy is widely used in Europe, it has only recently gained acceptance among dermatologists in the United States.\(^{37}\) In a 2001 survey of U.S. academic dermatology groups, researchers found that 51% of the respondents used dermoscopy and that most believed it helped to more accurately detect early melanoma.\(^{38}\) Advancements in information technology and digital imaging caused the field of tele-dermoscopy to be established, which allows access to dermoscopy expertise from a distant location. Patients’ clinical and dermoscopic images and relevant clinical data are sent to the tele-dermoscopy consultant in a store-and-forward fashion. Tele-dermoscopy has been shown to be feasible, reasonably accurate, and comparable to on-site consultation.\(^{39,40}\)

Dermatologists play a primary role in the evaluation and surveillance of patients with dysplastic nevus syndrome who require expert examinations to detect early melanomas in a background of numerous atypical nevi. Baseline whole-body cutaneous photography permits an objective assessment at subsequent visits for the detection of new and changing lesions. Rapidly evolving digital imaging systems permit efficient monitoring for subtle changes in the clinical and dermoscopic appearance of individual atypical nevi. This technique has been increasingly incorporated into clinical practice. A 2001 survey of academic centers in the United States found that 63% used whole-body photography in a subset of patients.\(^{41}\)

Treatment of Early-Stage Melanoma

As more melanomas are being diagnosed at an early stage, the role of the dermatologist in managing melanoma is increasing. Dermatologists are best suited to make the clinical diagnosis and perform an optimal biopsy that considers the pretest probability of melanoma and the histologic considerations of tissue sampling and assignation of prognostic attributes. Initial staging of melanoma is primarily dependent on the Breslow tumor thickness and presence or absence of an ulcer, which indicates whether the patient is a candidate for SLNB. A multicenter international (MSLT-1) trial found SLNB to be safe and accurate for patients with melanoma.\(^{42}\) SLNB has been recommended as a staging procedure for patients with primary melanoma 1.0 mm or more thick and for melanoma less than 1.0 mm with associated adverse histologic factors (i.e., ulceration, extensive regression, or Clark level IV/V invasion). In the United States, many dermatologists perform wide local excisions and assume complete care for patients with melanomas less than 1.0 mm thick who are not deemed candidates for SLNB or adjuvant therapy.

Dermatology is becoming an increasingly surgically oriented specialty with a growing number of subspecialized dermatologic surgeons. The number of skin cancer treatment procedures performed by dermatologic surgeons in the United States, including for...
non-melanoma, has increased recently (Figure 4).\textsuperscript{41} MacKie et al.\textsuperscript{41} noted that in the west of Scotland, 40\% of melanomas were removed by dermatologists in 1998, compared with only 3\% in 1979. The focus on a narrower excision margin has contributed to this trend (Table 1). Melanoma management guidelines from the United Kingdom, United States, and Switzerland recommend an excision margin of 0.5 cm for in situ melanoma, and a 1.0-cm margin for melanoma with Breslow thickness of up to 2.0 mm.\textsuperscript{6,45,46}

These excisions are readily accomplished by most dermatologists in the outpatient setting. Subspecialty dermatologic surgeons are becoming expert and experienced in managing large wounds in surgically-sensitive anatomic sites requiring complex repairs.

The skills of dermatologists are especially well suited to managing lesions with an extensive in situ component or poorly circumscribed margins. These lesions are often of the lentigo maligna (LM) type occurring on chronically sun-damaged skin. LM is found most commonly on the face of elderly patients, where it develops slowly as an asymmetric macule with brown to black pigmentation and an irregular scalloped border. Dermatologic assessment aided by the use of dermoscopy leads to the earlier recognition of LM.\textsuperscript{47} Complete surgical excision of LM is advised to avoid local recurrence, but it is often difficult to delineate the optimal surgical margin clinically. Aided by Wood’s lamp examination and dermoscopy, a margin can often be detected for lesions with clinically inapparent margins. Mohs’ micrographic surgery (MMS), a technique performed exclusively by specially-trained dermatologic surgeons, has been used to optimize margin control and conserve normal tissue. The Mohs’ surgical technique involves a staged excision with intraoperative histologic assessment of the entire resection margin using frozen tissue technique after each stage of the excision. Modifications of the technique, including the use of immunohistochemistry and paraffin embedded routine histology with delayed closure, have been used to address the common difficulty of determining the histologic margin of LM on frozen section pathology.\textsuperscript{48} Single-center series have reported MMS to result in low rates of recurrence and good cosmetic results.\textsuperscript{49}

Regardless of the surgical modality, LM has a significant risk for local recurrence. Surgery for these lesions may also be relatively contraindicated based on patient age, the low risk for progression to metastatic disease, and the cosmetic/functional consequences of surgery. Therefore, alternatives to surgery are needed, such as radiation therapy and topical therapies. Although not an approved therapy, some dermatologists have recently expressed interest in the off-label use of topical imiquimod for treating LM melanoma in situ in poor surgical candidates.

Imiquimod is an immune response modifier that stimulates cytotoxic T-cell mediated immune response and may also act directly on melanoma cells to cause apoptosis. The immunostimulatory effects of imiquimod are mediated through activation of Toll-like receptors (TLR), especially TLR-7. TLRs are expressed on neutrophils, macrophages, dendritic cells, dermal endothelial cells, mucosal epithelial cells, B cells, and T cells, and play an important role in the augmentation of both innate and acquired immune response by

**Table 1 Primary Cutaneous Melanoma**

<table>
<thead>
<tr>
<th>Tumor Thickness</th>
<th>Recommended Clinical Margin</th>
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<tbody>
<tr>
<td>In situ</td>
<td>0.5 cm</td>
</tr>
<tr>
<td>≤ 1.0 mm</td>
<td>1.0 cm (category 1)</td>
</tr>
<tr>
<td>1.01–2.0 mm</td>
<td>1.0–2.0 cm (category 1)</td>
</tr>
<tr>
<td>2.01–4.0 mm</td>
<td>2.0 cm (category 1)</td>
</tr>
<tr>
<td>&gt; 4.0 mm</td>
<td>2.0 cm</td>
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- Margins may be modified to accommodate individual anatomic or cosmetic considerations.
- For in situ melanomas, pathologic confirmation of a negative peripheral margin is important (category 2B).


producing cytokines and growth factors.\textsuperscript{50} Imiquimod also induces Langerhans cell migration.\textsuperscript{51,52} Five percent imiquimod cream has been applied to LM, with regimens ranging from 3 times per week to daily with varying lengths of therapy (5–13 months). Multiple small studies have noted complete clinical and histopathologic remission in most patients.\textsuperscript{53,54} Although this is not an approved or recommended therapy, the use of imiquimod for LM highlights the dermatologist’s role in the study and use of innovative topical approaches for melanoma prevention and treatment.

Follow-up and Surveillance
Clinical follow-up of patients with melanoma is designed to detect disease recurrence and additional primary melanomas and to provide psychosocial support. The estimated risk for second primary melanoma ranges from 0.2% to 8.6%.\textsuperscript{55,56} The incidence of multiple primary melanomas is higher in patients with a family history of melanoma or a history of dysplastic nevi.\textsuperscript{56} Patients diagnosed with LM melanoma have a significant risk for developing another cutaneous malignancy within 5 years.\textsuperscript{57} Experts recommend that patients with melanoma be followed-up 1 to 4 times per year for 2 years after diagnosis, and 1 to 2 times per year thereafter. The frequency of follow-up is determined by tumor thickness, stage of disease, history of multiple primary melanomas, presence of clinically atypical nevus, family history of melanoma, patient anxiety, and patient awareness/ability to recognize signs and symptoms of disease.\textsuperscript{40} The thorough skin examination, lymph node examination, and symptom-directed evaluation required at each follow-up visit fall within the clinical purview of the dermatologist. During the follow-up visits, patients should be counseled and instructed in self-examination, because patients discover most recurrences and metastases, even when they undergo routine professional follow-up.

Multidisciplinary Melanoma Clinics
Melanoma treatment benefits from a multidisciplinary approach, which many centers have advanced by creating multidisciplinary melanoma clinics (MDMCs). The core team of dermatologists and medical and surgical oncologists is supplemented by dermatopathologists, plastic surgeons, radiation oncologists, otorhinolaryngologists, obstetrician/gynecologists, ophthalmologists, nuclear medicine specialists, psychiatrists, geneticists, and social workers.\textsuperscript{58} Many MDMCs are administratively anchored in departments of dermatology. In the MDMC model, the patients benefit from highly coordinated subspecialty care and the participating physicians gain a broader expertise in melanoma across all stages. MDMCs also present a unique opportunity for the assembly of large clinically accurate databases for melanoma research. Expert dermatopathologists play a central role in the clinical and academic programs of the MDMC.

Summary
Melanoma is a major focus of dermatology training and practice, and the dermatologist plays a central role in managing melanoma in the realms of public health and patient care.

References
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