Skin Cancer of the Head and Neck

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ABSTRACT

The majority of skin cancers of the head and neck are nonmelanoma skin cancers (NMSC). Basal cell carcinoma and squamous cell carcinoma are the most frequent types of NMSC. Malignant melanoma is an aggressive neoplasm of skin, and the ideal adjuvant therapy has not yet been found, although various options for treatment of skin cancer are available to the patient and physician, allowing high cure rate and excellent functional and cosmetic outcomes. Sunscreen protection and early evaluation of suspicious areas remain the first line of defense against skin cancers.

KEYWORDS: Basal cell carcinoma, melanoma, Mohs' micrographic surgery, nonmelanoma skin cancer, squamous cell carcinoma

Skin cancer is the most common malignancy in the United States and makes up about one third of all cancers diagnosed. The common skin cancers include nonmelanoma skin cancers (NMSCs) and melanoma. The majority of skin cancers of the head and neck are NMSCs.¹ This article reviews NMSC and malignant melanoma separately.

NONMELANOMA SKIN CANCERS

Squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) are by far the most frequent pathologic types of NMSC; the ratio of BCC to SCC is ~3 to 4:1.¹

Etiology and Risk Factors

The most important factor involved in the pathogenesis of NMSC is the cumulative amount of exposure to ultraviolet radiation (UVR). UVR in the wavelength range 290 to 320 nm is the most carcinogenic.^{1,2} Other risk factors may contribute to the development of NMSC, including radiation exposure, long-term intake of arsenic, and fair-skinned people who tan poorly and

burn easily. In addition, NMSC may arise from preexisting conditions such as scars, chronic ulcers (Marjolin's ulcer), and sinuses.³

There are two types of people with rare genetic syndromes—xeroderma pigmentosa and nevoid basal cell carcinoma syndrome—who have an increased risk of developing NMSC. Xeroderma pigmentosa is an autosomal-recessive genetic disorder with reduced cell capacity to repair DNA damaged by UVR. It is associated with the development of many skin tumors, particularly SCC, but also BCC and melanoma, at a young age. Nevoid basal cell carcinoma syndrome is an autosomal-dominant genetic syndrome characterized by the presence or occurrence of multiple BCCs, cysts of the jaws, rib abnormalities, palmar and plantar pits, and calcification of the falx cerebri. The major treatment is early recognition, then ultraviolet shielding, and lifelong monitoring of the skin for development of malignancies.⁴

An increased incidence of NMSC, especially SCC, of the head and neck has also been found in transplant recipients.⁵ These SCCs are more likely to behave aggressively and have a high rate of metastasis.⁶

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Epithelial Skin Cancers

BASAL CELL CARCINOMA

The most common skin cancer is BCC, accounting for 70 to 75% of skin cancers. There are five clinical types of BCC:

1. noduloulcerative BCC, including rodent ulcer
2. superficial BCC
3. morpheaform BCC
4. pigmented BCC
5. fibroadenoma.

The first three of these are mentioned with the greatest frequency. The noduloulcerative lesions are the most common type, accounting for 75% of cases of BCC. The typical clinical appearance is a well-circumscribed nodule or plaque with pearly border and overlying telangiectasia and may be combined with rodent ulcer. Superficial BCC represents ~10% of BCC. The clinical presentation is discrete erythematous macules or plaques with scaly change and a thin rolled border.^{6,7}

BCC tends to share the common histopathologic features of a predominant basal cell type, peripheral palisading of lesional cell nuclei, and a mucinous stroma with artificial cleft between the epithelial island and the stroma. In addition, there are variable degrees of cytologic atypia and mitotic activity.⁷

The incidence of metastasis in BCC is very rare, occurring in 0.0028 to 0.1% of patients. Review of the literature shows that morpheaform, adenocystic, metatypical, and basosquamous types of BCC have a relatively high local recurrence rate. The affinity of aggressive BCCs for perineural invasion has also been reported.^{7,8}

SQUAMOUS CELL CARCINOMA

Review of several studies has shown that SCC may arise from precancerous lesions such as actinic keratosis (AK). The prevalence of AK in fair-skinned people ranges from 11 to 26%, and it was estimated that the risk of development of SCC from AK ranges between 6% and 10%.⁹ Bowen's disease is another pathologic entity that is thought to represent in situ SCC of the skin; it is commonly misdiagnosed as eczema or psoriasis. According to the literature, it becomes invasive SCC in 3 to 5% of patients, of whom ~13% will go on to develop metastases. Microscopically, Bowen's disease is characterized by full-thickness involvement of the epidermis and the pilosebaceous epithelium by atypical keratinocytes.¹⁰

SCC is the second most common skin cancer. Clinically, SCC of the skin most commonly consists of a shallow ulcer surrounded by a wide, elevated, indurated border on a sun-exposed area of the body. The ulcer is often covered by a crust with a granulated base. On histologic examination, irregular masses of epidermal

cells that proliferate downward into the dermis are noted. The tumor masses are composed in varying proportions of normal squamous cells and atypical squamous cells. According to the degree of keratinous differentiation, SCC can be subdivided into well differentiated, moderately differentiated, or poorly differentiated types. In general, with the more poorly differentiated change of the tumor, the fewer keratin pearls formed, the higher the nuclear/cytoplasmic ratio, and the more severe the nuclear atypia.⁷

There are certain clinical factors that correlate SCC with increased risk of local recurrence and metastasis. These include:

- size greater than 2 cm
- poor histologic differentiation
- involvement of sites such as the external ear or lip
- tumor arising from a previous scar
- perineural invasion
- occurrence in immunosuppressed patients.¹¹

Nonepithelial Skin Cancers

Apart from BCC or SCC, the remaining 5% of NMSCs develop from skin appendages, neuroendocrine cells, mesenchymal cells, or vascular structures.

Merkel cell carcinoma is a rare and aggressive neuroendocrine dermal neoplasm. The classic appearance is a solitary red to violaceous nodule. Most of these tumors are typically less than 2 cm in size but can reach sizes as large as 10 cm. The majority of cases affect the head and neck and are thought to be caused by the actinic damage associated with sun exposure. The histopathology shows dense, small, blue round cells closely spaced in a trabecular pattern and sheets. Chromatin is delicate and uniformly distributed. Mitosis and nuclear fragments are regular features.¹² Treatment for Merkel cell carcinoma must be aggressive. Local recurrence after resection has been reported in as many as 44% of patients. Tumor resection with a 2- to 3-cm tumor-free margin is recommended in most studies, but this is often difficult to achieve in the head and neck. Adjuvant radiotherapy and chemotherapy are advocated for treatment of advanced disease, but their role remains unproven.¹³

Dermatofibrosarcoma protuberans (DFSP) is an intermediate malignancy that derives from dermal fibroblasts. It usually forms an indurated plaque with multiple reddish to purple nodules. It usually occurs on the trunk or the proximal extremities of young adults; only ~10 to 15% develop on the head and neck. The histopathology of DFSP shows compact, monomorphous spindle cells arranged in a storiform pattern from dermis to subcutaneous fat, and it usually shows a characteristic honeycomb pattern in the subcutis. Local recurrence is ~44%, but metastases occur in only 1 to 4% of patients. Several

studies have concluded that wide excision with a 2-cm tumor-free margin is necessary for adequate treatment. Because of functional and cosmetic concerns, Mohs' microsurgery (described later) is an alternative treatment of choice.¹⁴

Atypical fibroxanthoma (AFX) is a neoplasm of low-grade malignancy related to malignant fibrous histiocytoma. It usually presents as a solitary nodule less than 2 cm in diameter on the exposed skin of the head and neck or dorsum of the hand of elderly patients, often with a short history of rapid growth. The histopathologic finding usually shows an exophytic, dense cellular neoplasm with ulcerated surface. The classic tumor is composed of pleomorphic histiocyte-like cells and atypical giant cells, often with bizarre nuclei and numerous mitotic figures. Despite its apparently malignant histologic features—a small number of metastases have been reported—AFX usually follows an indolent or locally aggressive course. The recommended surgical treatment should include complete excision and margin control. In most instances, it seems unnecessary to use excisional margins greater than 1 cm to achieve a tumor-free margin.¹²

Sebaceous carcinoma is a malignant tumor derived from the adnexal epithelium of sebaceous glands. It may arise in ocular or extraocular sites and exhibit diverse clinical presentations. The most common presentation is a small, slowly enlarging, deep-seated nodule on the upper eyelid that clinically is indistinguishable from a chalazion. About 25% of all reported cases of sebaceous carcinoma are extraocular. Because it can occur in any site containing sebaceous glands, its incidence is highest in the head and neck region where sebaceous glands are most plentiful. Histologically, there are variable-sized, irregular lobules with undifferentiated cells and distinct sebaceous cells containing foamy cytoplasm. Many undifferentiated cells and sebaceous cells appear atypical; changes include nuclear pleomorphism or atypical mitosis. The clinical appearance of sebaceous carcinoma is not pathognomic, so the diagnosis is often delayed for months or years. Ocular sebaceous carcinoma quite frequently causes regional metastases, and the mortality rate is ~22%. In general, excision with wide (5 to 6 mm) surgical margins with frozen sections is the basis for treatment. Metastatic disease may be treated by excision and/or radiation and/or chemotherapy.¹⁵

Adnexal carcinoma may derive from eccrine glands, apocrine glands, and hair follicles. Most of these tumors are highly malignant. It is estimated that they account for 0.005% of all skin lesions and less than 1% of all head and neck skin cancers. Currently, many lesions are excised initially for diagnostic purposes. Because of the rare occurrence of these tumors, it is difficult to obtain a sufficient number of cases from a single institution to perform meaningful clinical trials of other therapeutic modalities.¹⁶

Staging

The tumor, node, metastasis (TNM) staging system for NMSC recommended by the American Joint Committee on Cancer Staging is based on retrospective data and uses the end points of recurrence and survival. For example, a T1 tumor is 2 cm or smaller, T2 lesions are larger than 2 cm but not larger than 5 cm, and T3 tumors are those that are larger than 5 cm. T4 tumors are characterized by invasion of adjacent structures such as cartilage, nerve, muscle, or bone. Only two categories are used to classify regional lymph node metastasis: N0 for no metastasis, and N1 for any positive lymph node regardless of size. If upon pathology evaluation the stage changes, the new stage is denoted with a "p" as a prefix (e.g., "pT4").¹⁷

Treatment

CURETTAGE AND ELECTRODESICCATION

The principle of curettage and electrodesiccation (C&D) is to use heat to kill residual tumor cells left after sharp curettage. This is the most widely used treatment for NMSC, in particular BCC. The indications for C&D include:

- primary BCC smaller than 1 cm
- well-demarcated and well-differentiated SCC
- anatomic sites at low risk for recurrence such as trunk, neck, and extremities.

The contraindications for C&D include:

- neoplasm located in areas at high risk for recurrence, such as nose, ear, and periorcular and perioral areas
- pathology reported as melanoma.

The advantages of C&D include rapidity of treatment, low cost, ease of treatment, and cure rates in excess of 90%. The disadvantage is that this method may induce hypopigmented or hypertrophic scars. Also, no specimen is available for histologic review of the margins after treatment.^{6,18}

CRYOSURGERY

Cryosurgery is performed with freezing temperatures to selectively destroy skin cancers. The most common method is to use liquid nitrogen via spray or metal probe. In general, a double freeze-thaw cycle with a tissue temperature of -50°C is required to ensure the destruction of most neoplastic tissue. This method has similar indications and limitations to those of C&D. Compared with procedures such as C&D, the major disadvantage of cryosurgery is that effective treatment requires more skill and experience; also, it may be associated with more morbidity such as swelling, blistering, weeping, and oozing over the treated area. Caution should be used

when treating lesions on the lip, nasal ala, or eyelid, because wound contraction can lead to retraction of free margins and asymmetry. The cure rates for neoplasms treated with cryosurgery range from 94 to 99%.⁶

SURGICAL EXCISION

Surgical resection is the most common method of treatment for skin cancer of the head and neck. The physician should keep four goals in mind:

1. total removal or destruction of the tumor
2. maximal preservation of normal tissue
3. preservation of function
4. optimal cosmesis.

The most important principle of treatment is complete tumor excision because if this goal is not achieved, the other goals cannot be achieved.

Adequate margins of resection are necessary to achieve clear margins. For the majority of BCC and SCC cases, 4-mm margins are sufficient for lesions smaller than 2 cm in diameter. However, if the tumor is 2 cm or greater, is in high-risk areas, is invading fat, or is not well differentiated, 6-mm margins of excision are required.¹⁹ In addition, care must be taken to take appropriate deep margins. Although sentinel node excision is not routinely practiced for NMSC, local and regional metastasis must be evaluated when present.

Reconstruction of the defect depends on the size of the defect and the nature of the tumor excised. For smaller lesions, primary closure and healing by secondary intention are appropriate options. Intermediate defects may need a skin graft or local advancement of a rotational flap for adequate closure. For large defects, regional or distant pedicled flaps or free flaps are used. Therefore, careful preoperative assessment, including diagnostic imaging and consultation with an experienced reconstructive surgeon, is essential if use of rotational flaps or free flaps is needed.

MOHS' MICROGRAPHIC SURGERY

Mohs' micrographic surgery (MMS) is a specialized type of surgical technique that maximally preserves healthy tissue. Frederic E. Mohs developed the procedure in the 1930s. After modification of the method in the following years, the current procedure is first to use local anesthesia to outline the tumor with a 1- to 3-mm margin. Then a curette is used to debulk the tumor with excision begun at a 45-degree angle to the skin. Before complete excision of the tumor, the initial etching incision should include asymmetric marks to enable accurate marginal tumor mapping. The tissue specimen is oriented and divided into four sections to permit processing of horizontal frozen sections and histologic examination of the entire tumor margin. This cycle of

resection and pathologic examination is repeated until the margins are tumor-free.

Compared with other treatment modalities, MMS offers a high cure rate of skin cancer in selected settings. Overall 5-year cure rates of greater than 99% are achieved in the excision of primary BCC, and 96% are attained for recurrent BCC. On the other hand, for SCC treated with MMS, the 5-year cure rate of patients with metastases was 16% compared with the 5-year cure rate of 98% in those without metastases. The major disadvantages of MMS are prolonged procedure, special equipment (cryostat), and a highly trained surgical team (histotechnologist, Mohs' surgeon, and dedicated pathologist).²⁰

RADIOTHERAPY

Although radiation therapy is now used much less than previously for the primary management of NMSC, it is estimated that 90% of lesions smaller than 3 cm can be controlled using radiotherapy. Surgical excision may cause severe functional or cosmetic deficits, thus primary radiotherapy is an important option. Indications for postoperative radiotherapy include large or recurrent primary lesions, close or positive tumor margins and/or perineural invasion, or radiosensitive neoplasms such as Merkel cell carcinoma.^{21,22}

There are several points of caution. Dosages are carefully calculated to minimize damage to surrounding tissue, and any radiosensitive organ should be shielded if the tumor is near it. The contraindication of radiotherapy is nevroid basal cell carcinoma syndrome.⁶

TOPICAL 5-FLUOROURACIL TREATMENT

5-Fluorouracil (5-FU) is a structural analogue of thymine that inhibits thymidylate synthetase, thereby interfering with DNA synthesis in dividing cells and causing cell death. Topical 5-FU therapy can result in cure rates of 92% for SCC in situ and 95% for superficial BCC. The disadvantage of topical 5-FU treatment is significant inflammation and irritation during treatment.⁶

LASERS

Lasers play a limited role in the management of NMSC. The carbon dioxide laser can be used in the focus mode to excise lesions or in the defocused mode to vaporize lesions. It may be a choice of treatment for precancerous lesions.

PHOTODYNAMIC THERAPY

Photodynamic therapy (PDT) is a treatment modality involving the administration of a photosensitizing compound and the accumulation of the sensitizer molecules in the target cells, followed by selective irradiation of the lesion with visible light. The procedure results in tumor necrosis. Hematoporphyrin is the first systemically studied photosensitizer for clinical PDT. The cutaneous

accumulation of photosensitizer and its slow clearance from the skin leads to long-lasting cutaneous photosensitivity, up to 4 to 6 weeks, and an approach (topical PDT) to avoid this side effect has been developed. The standard procedure for topical PDT for a skin tumor is application of 20% δ -aminolevulinic acid (ALA) over lesional skin; the lesions are then exposed to light at 630 to 635 nm for 3 to 6 hours after ALA application. Based on a literature review, the procedure is safe and efficacious for treatment of cutaneous precancer and cancer, and encouraging results have been reported in treating AK, Bowen's disease, and superficial BCC and SCC.

In contrast with many conventional therapeutic modalities, PDT has comparatively insignificant side effects such as burning pain, stinging, or itching restricted to the illuminated areas. The most frequent cosmetic problem is residual hyper- and hypopigmentation induced by PDT. There are still some problems with PDT, including the cost, consumption of time, and the need for special, expensive equipment.²³

INTERFERON

Interferons (IFNs) are a group of naturally occurring cytokines that have multiple biologic effects, including control of cell growth and differentiation, modulation of immune responses, and antiviral activity. The intralesional administration of IFN- α has shown promise in the treatment of superficial and nodular BCCs, producing cure rates of more than 80%.^{24,25} Further studies are needed to determine the amount of IFN and the duration of therapy.

RETINOIDS

Vitamin A and its physiologic metabolites and synthetic derivatives (retinoid) have been shown to have protective effects against the development of certain types of cancer. Clinically, isotretinoin (13-*cis*-retinoic acid) significantly decreases the incidence of second primary tumor in patients with head and neck cancer and reduces the appearance of NMSC in patients with xeroderma pigmentosum. Generally speaking, they are more effective as chemopreventive agents than as chemotherapeutic agents.²⁶

Conclusion

NMSC of the head and neck is quite common. Once a diagnosis of NMSC is considered, a complete history, review of systems, and physical examination should be performed. Because of the variety of surgical and non-surgical options that are available for the treatment of NMSC, careful preoperative assessment, including diagnostic imaging and consultation with an experienced reconstructive surgeon, radiologist, or oncologist, may be needed.

MALIGNANT MELANOMA

Malignant melanoma is an aggressive neoplasm of skin. Although it is less common than NMSC, it has been estimated to be the seventh most frequent cancer in whites in the United States. Because one third of melanomas arise in the head and neck, a surgeon should have a thorough working knowledge of the disease. The lifetime risk of an individual developing malignant melanoma in the United States was expected to climb to 1 in 75 by the year 2000; during the past decade, the annual increase in malignant melanoma was ~5 to 6% per year, the most rapidly increasing rate for any cancer in America.¹

Malignant melanoma is a lethal cancer but is not uniformly fatal. Although melanoma comprises only 5% of all skin cancers, more than three of four deaths from skin cancer are due to melanoma. Owing to earlier detection, the case fatality rate for melanoma has been dropping in recent decades.^{1,27}

Etiology and Risk Factors

Similar to NMSC, there is a strong correlation between sun exposure and the development of malignant melanoma. In contrast with NMSC (SCC and BCC), whose development correlates with chronic sun exposure, the development of malignant melanoma correlates better with intermittent intense exposure to UV radiation.

Individuals who suffered blistering or other severe sunburn during childhood or adolescence appear to be at increased risk for developing a melanoma later in life. Fair-skinned persons who have blue eyes, red or blond hair, light complexion, and freckling tendency are at increased risk for the development of melanoma. This observation emphasizes the importance of educating this population, and protection from the sun should begin at an early age.^{1,28}

Most malignant melanomas (70% or more) arise in normal skin rather than from a preexisting melanocytic lesion.¹ At least three types of lesion are known to be precursors to malignant melanoma. In a literature review, the percentage of histologically associated malignant melanomas with large numbers of *melanocytic nevi* (including common melanocytic nevi and dysplastic nevi) varied between 4% and 72% and the maximal frequency between 20% and 30%.²⁹ *Congenital melanocytic nevi* (CMN), which are present at birth, may give rise to melanoma. A significant increased risk of melanoma in patients with giant CMN (>20 cm in diameter) from 5 to 40% has been reported.³⁰ *Lentigo maligna* (LM) is regarded as a form of melanoma in situ; the exact percentage of LM that progress to lentigo maligna melanoma (LMM) is unknown. The lifetime risk of LMM developing from LM is estimated to be 4.7% at 45 years of age and 2.2% for a person 65 years old.²⁸

Another important constitutional risk factor for melanoma is a family history of melanoma (particularly if associated with a personal and family history of dysplastic nevi). The patients with familial dysplastic nevus syndrome and sporadic dysplastic nevi are at significantly greater risk for malignant melanoma than the general population. It is important to establish accurate baseline photographs and maintain close clinical follow-up. Biopsies are reserved for the initial diagnosis of dysplastic nevi and for lesions suspected of being malignant melanoma. Xeroderma pigmentosa is a genetic syndrome associated with melanoma.⁴

Clinical Evaluation

To summarize the important risk factors, Dr. T.B. Fitzpatrick proposed the acronym MMRISK: M = Moles: atypical; M = Moles: common; R = Red hair and freckling; I = Instability to tan: skin phototypes I and II; S = Sunburn: severe sunburn before age 14 years; K = Kindred: family history of melanoma.²⁸

On physical examination, the mnemonic ABCD developed years ago to aid in the diagnosis of melanoma is helpful in assessing a patient with a pigmented lesion. The ABCD of melanoma is as follows: Asymmetry: the melanoma is not symmetrical; Border: note the highly irregular and uneven border; Color: the color is variegated with different shades of brown, black, and tan; Diameter: the diameter is usually >6 mm.²⁸

Aids to clinical diagnosis include a Wood's lamp, dermatoscopy, and photography. The ultimate diagnosis of a melanoma depends on the biopsy. In general, the lesion should be excised with narrow margins whenever possible. Otherwise, an incisional biopsy is appropriate when the suspicion for melanoma is low, the lesion is large, or it is impractical to perform an excision. Needle and shave biopsies of primary lesions are discouraged because they do not adequately assess thickness.³¹

Classification and Histopathology of Cutaneous Malignant Melanoma

Melanoma results from the malignant transformation of melanocytes. According to their gross and microscopic characteristics, melanoma can be classified into four main growth patterns:

- lentigo maligna
- superficial spreading
- nodular
- acral lentiginous melanoma.

LENTIGO MALIGNA

The clinical manifestation of lentigo maligna (LM) is an irregularly mottled pigmented macule or patch on sun-exposed areas. It occurs most often in elderly patients

with sun-damaged atrophic skin. Histopathologically, the epidermis usually shows atrophic change with thinning and loss of rete ridges and an increased number of atypical melanocytes in the basal cell layer. The melanocytes vary in appearance, size, and shape and show atypical changes in the nuclei.^{28,32}

LENTIGO MALIGNA MELANOMA

Lentigo maligna melanoma (LMM) is the least common type of melanoma (usually 4 to 15% of all types). It is almost exclusively located on sun-exposed skin of the head and neck, with the nose and cheeks the most common sites. The clinical appearance is a flat patch with irregular borders, with or without a papulonodular portion. The color is variegated and may include tan, brown, black, blue-gray, and white. The histopathology of LMM is extensive hyperplasia of typical melanocytes along the dermal-epidermal junction and nesting of atypical melanocytes invading the papillary dermis. In addition, there is always severe solar elastotic degeneration in the upper dermis.^{28,32}

SUPERFICIAL SPREADING MELANOMA

Superficial spreading melanoma (SSM) represents ~70% of all melanomas and is the most common type of cutaneous melanoma. SSM may present as a deeply pigmented macule or plaque with pigment variegation. The most common sites of SSM are the legs of women and the backs of men. The histopathology of SSM is irregular epidermal hyperplasia with a pagetoid distribution of large melanocytes. These large cells may occur singly or in nests and have uniform cytologic atypia.^{28,32}

NODULAR MELANOMA

The second most common subtype of melanoma is nodular melanoma (NM), with a frequency of 15 to 30% of all types. NM presents as a uniform dark blue-black nodule on the trunk, head, and neck. Early recognition of NM can be difficult because it lacks many of the conventional clinical features of melanoma. But NM is remarkable for its rapid evolution within several weeks to months. The histopathology of NM is contiguous proliferation of neoplastic melanocytes in the dermis, forming a tumor mass that is larger than the largest nest in the overlying epidermis. Pagetoid spreading of the epidermis with neoplastic melanocytes may be absent or may be limited to that portion overlying the dermal mass.^{28,32}

ACRAL LENTIGINOUS MELANOMA

Acral lentiginous melanoma (ALM) occurs relatively infrequently in light-skinned whites but represents the most common form in those of darker complexion. The histopathology shows proliferation of neoplastic melanocytes with heavily pigmented granules along the dermal-epidermal junction. As the name implies,

ALM always occurs on acral parts, the most common site being the sole of the foot. We will not therefore discuss ALM here.^{28,32}

Staging

Once the diagnosis of a melanoma is confirmed, the history should be reviewed. This should include a review of systems and a family history of atypical moles and melanoma. A thorough physical examination should be performed. The requirement of sentinel lymph node biopsy and extensive laboratory investigation should be evaluated.

The American Joint Committee on Cancer (AJCC) Tumor Node Metastasis Committee has approved a new melanoma staging system, which was implemented in 2002.³³ Tables 1 and 2 present the TNM categories and staging groups, respectively. There are three prognostic factors included in AJCC staging system:

1. tumor thickness
2. ulceration
3. level of invasion (Clark's level).

In the AJCC staging system, tumor thickness is the most powerful independent prognostic factor for patients with primary cutaneous melanoma. Melanoma thickness is measured from the granular layer of the epidermis to the greatest depth of tumor invasion. This was originally described by Breslow. Now it is correlated with a thickness of ≤ 1 mm (T1), 1.01 to 2 mm (T2), 2.01 to 4 mm (T3), or ≥ 4 mm (T4). Ulceration is the second most powerful factor for poor prognosis.

The anatomic level of invasion (Clark's level) is an independent factor only for thin melanomas (< 1 mm, or category T1). It is classified into levels I to V. Level I indicates melanoma confined to the epidermis. Level II indicates tumor cell extended into the papillary dermis but not reaching the papillary-reticular dermal interface. Level III indicates invasion of neoplasm to fill and expand the papillary dermis but not penetrating the reticular dermis. With level IV, there is a clear extension of tumor cells into the reticular dermis. Finally, level V indicates subcutaneous invasion.³³

The other prognostic factors also significantly correlate with survival. The worse prognostic factors

Table 1 TNM Classification of Melanoma

T Classification	Thickness	Ulceration Status
T1	≤ 1.0 mm	a: without ulceration and level II/III b: with ulceration or level IV/V
T2	1.01–2.0 mm	a: without ulceration b: with ulceration
T3	2.01–4.0 mm	a: without ulceration b: with ulceration
T4	> 4.0 mm	a: without ulceration b: with ulceration
N Classification	Number of Metastatic Nodes	Nodal Metastatic Mass
N1	1	a: micrometastasis* b: macrometastasis†
N2	2–3	a: micrometastasis* b: macrometastasis† c: in-transit metastases/satellite(s) without metastatic nodes
N3	Four or more metastatic nodes, or matted nodes, or in-transit metastases/satellite(s) with metastatic node(s)	
M Classification	Site	Serum Lactate Dehydrogenase
M1a	Distant skin, subcutaneous, or nodal metastasis	Normal
M1b	Lung metastasis	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

*Micrometastases are diagnosed after sentinel or elective lymphadenectomy.

†Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension.

Table 2 Proposed Staging Groups for Cutaneous Melanoma

	Clinical Staging*			Pathologic Staging†		
	T	N	M	T	N	M
0	Tis	N0	M0	Tis	N0	M0
IA	T1a	N0	M0	T1a	N0	M0
IB	T1b	N0	M0	T1b	N0	M0
IIA	T2a	N0	M0	T2a	N0	M0
	T2b			T2b		
IIB	T3a	N0	M0	T3a	N0	M0
	T3b			T3b		
IIC	T4a	N0	M0	T4a	N0	M0
	T4b			T4b		
III‡	Any T	N1	M0			
		N2				
		N3				
IIIA				T1 to 4a	N1a N2a	M0
					N2a	
					T1-4a	
IIIB				T1 to 4b	N1a	M0
				T1 to 4b	N12a	M0
				T1 to 4a	N1b	M0
				T1 to 4a	N1b	M0
				T1 to 4a/b	N2c	M0
IIIC				T1 to 4b	N1b	M0
				T1 to 4b	N2b	M0
				Any T	N3	M0
IV	Any T	Any N	Any M1	Any T	Any N	Any M1

*Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastasis. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastasis.

†Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy. Pathologic stage 0 or stage 1A patients are the exception; they do not require pathologic evaluation of their lymph nodes.

‡There are no stage III subgroups for clinical staging.

include increasing age, male tumor on head and neck, increasing mitotic rate, diminished tumor-infiltrating lymphocytes, microscopic metastasis, and vascular invasion.^{28,34}

Treatment

SURGICAL EXCISION

The standard treatment for cutaneous melanoma is complete surgical excision of the primary lesion. The current American Academy of Dermatology (AAD) guidelines of care for cutaneous melanoma recommends an 0.5-cm margin for melanoma in situ, a 1-cm margin for invasive melanomas <2 mm thick, and 2-cm margins for melanomas >2 mm thick.³¹

It is important to note that strict guidelines should not be routinely recommended in the surgical management of cutaneous primary melanoma. Melanoma excision at special sites, such as ear, nose, or other site of head and neck, also requires separate surgical, functional, and cosmetic consideration. In addition, the

surgeon must think in three dimensions; that is, how best to obtain a deep margin as well as lateral margins (e.g., whether or not resection of muscle and facial bones is required for adequate margins). When tissue conservation is important, intraoperative frozen section analysis may be helpful.

MOHS' MICROGRAPHIC SURGERY

Mohs surgery has been advocated for the treatment of primary cutaneous melanoma, especially those located on the head, neck, hands, and feet.³¹ The other selective criteria of Mohs' micrographic surgery (MMS) are desmoplastic melanoma with invisible extensions from perineural invasion, locally recurrent melanoma, and melanoma located in areas in which tissue preservation is mandatory.^{21,35}

SENTINEL LYMPH NODE BIOPSY AND ELECTIVE LYMPH NODE DISSECTION

The sentinel lymph node is the first node or nodes to drain a primary neoplasm. Sentinel lymph node biopsy is performed to determine whether regional metastases are

present. The head and neck area is notorious for being harder to map. The previously reported success rate was 70 to 80%, but, by using two mapping techniques, the success rate is increased to 95%.

From a review of literature, it is considered that a sentinel lymph node biopsy should be performed on patients with a melanoma greater than 1 mm thick; the staging information can then be used to plan elective lymph node dissection and adjuvant therapy. This technique can be used to make the surgical care of the melanoma patient more conservative, so that only those patients with evidence of regional node metastasis are subjected to the morbidity and expense of a complete node dissection and the toxicity of adjuvant therapy.³⁶

INITIAL DIAGNOSTIC WORKUP AND ONGOING

FOLLOW-UP

The current AAD guidelines for care of primary cutaneous melanoma recommend that routine laboratory tests and imaging studies are not required for initial staging or follow-up in asymptomatic patients with primary cutaneous melanoma that is 4 mm or less in thickness. Indications for such studies are directed by a thorough medical history and physical examination.

The goal of follow-up of patients with melanoma is to reduce morbidity and mortality through the detection of asymptomatic metastases and additional primary melanomas. Although there is no evidence to support a specific follow-up interval, the AAD recommends follow-up one to four times a year for 2 years after diagnosis, depending on the risk factors, and one to two times a year thereafter. The risk factors include tumor thickness, patient with multiple melanomas, presence of clinically atypical nevi, family history of melanoma, and patient anxiety or awareness/ability to recognize signs and symptoms of disease.³¹

ADJUVANT THERAPY

The ideal adjuvant therapy has not yet been found. A recent study shows a significant increase in disease-free survival for high-risk patients with melanoma receiving high-dose IFN- α . The regimen is first intravenous IFN- α (20×10^6 IU/m² per day, 5 days per week for 4 weeks), followed by subcutaneous IFN- α (10×10^6 IU/m² per day, 3 days per week for 11 months). Because of the considerable side effects associated with high-dose IFN- α , low-dose IFN- α has been found to have better immunologic activity in in vitro studies; a more recent study is using the treatment with low-dose subcutaneous IFN- α for 2 years. No definitive results of these studies have been published.³⁷

Chemotherapy has traditionally had two major uses: as adjuvant therapy in high-risk patients and as palliative therapy in patients with stage IV disease. To date, no prospective randomized trials have supported the use of chemotherapy as adjuvant treatment for

cutaneous melanoma. The chemotherapeutic agent most commonly used to treat disseminated melanoma is dacarbazine, which produced 20 to 25% response rates in treated patients with metastatic or recurrent disease.^{37,38}

Melanoma is considered to be relatively radio-resistant, thus limiting the role of radiation therapy in its management. The optimal dose fraction is unclear. Based on encouraging results with a few large-dose fractions, the Radiation Therapy Oncology Group began a prospective randomized trial of regional adjuvant radiotherapy after lymphadenectomy in patients with node-positive head and neck melanoma.³⁷

CONCLUSION

The rate of malignant melanoma is currently rising faster than that of any other cancer, and it has become an important public health problem. Most melanomas are amenable to cure with early diagnosis and appropriate treatment. Several options for the treatment of skin cancer are available to the patient and physician, allowing high cure rates and excellent functional and cosmetic outcomes. Until further research yields a cure for advanced malignant melanoma, sunscreen protection and early evaluation of suspicious areas remain the first line of defense in the fight against malignant melanoma.^{6,27}

REFERENCES

1. Marks R. An overview of skin cancers. Incidence and causation. *Cancer* 1995;75(2 Suppl):607-612
2. Buzzell RA. Effects of solar radiation on the skin. *Otolaryngol Clin North Am* 1993;26:1-11
3. Johnson TM, Rowe DE, Nelson BR, Swanson NA. Squamous cell carcinoma of the skin (excluding lip and oral mucosa). *J Am Acad Dermatol* 1992;26(3 Pt 2):467-484
4. Shumrick KA, Coldiron B. Genetic syndromes associated with skin cancer. *Otolaryngol Clin North Am* 1993;26:117-137
5. Gourin CG, Terris DJ. Head and neck cancer in transplant recipients. *Curr Opin Otolaryngol Head Neck Surg* 2004;12:122-126
6. Padgett JK, Hendrix JD Jr. Cutaneous malignancies and their management. *Otolaryngol Clin North Am* 2001;34:523-553
7. Kirkum N. Tumors and cysts of the epidermis. In: Elder DE, Elenitsas R, Murphy GF, et al., eds. *Lever's Histopathology of the Skin*. 9th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2005:805-866
8. Lo JS, Snow SN, Reizner GT, Mohs FE, Larson PO, Hruza GJ. Metastatic basal cell carcinoma: report of twelve cases with a review of the literature. *J Am Acad Dermatol* 1991;24(5 Pt 1):715-719
9. Salasche SJ. Epidemiology of actinic keratoses and squamous cell carcinoma. *J Am Acad Dermatol* 2000;42(1 Pt 2):4-7
10. Kao GF. Carcinoma arising in Bowen's disease. *Arch Dermatol* 1986;122:1124-1126
11. Rowe DE, Carroll RJ, Day CL Jr. Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell

- carcinoma of the skin, ear, and lip. Implications for treatment modality selection. *J Am Acad Dermatol* 1992;26:976-990
12. Brown MD. Recognition and management of unusual cutaneous tumors. *Dermatol Clin* 2000;18:543-552
 13. Lawenda BD, Thiringer JK, Foss RD, Johnstone PA. Merkel cell carcinoma arising in the head and neck: optimizing therapy. *Am J Clin Oncol* 2001;24:35-42
 14. Gloster HM Jr. Dermatofibrosarcoma protuberans. *J Am Acad Dermatol* 1996;35(3 Pt 1):355-374; quiz 375-376
 15. Nelson BR, Hamlet KR, Gillard M, Railan D, Johnson TM. Sebaceous carcinoma. *J Am Acad Dermatol* 1995;33:1-15; quiz 16-18
 16. Marendra SA, Otto RA. Adnexal carcinomas of the skin. *Otolaryngol Clin North Am* 1993;26:87-116
 17. Greene FL, Page DL, Fleming ID, et al. *AJCC Cancer Staging Manual* 6th ed. Chicago, IL: American Joint Committee on Cancer; 2002
 18. Salasche SJ. Status of curettage and desiccation in the treatment of primary basal cell carcinoma. *J Am Acad Dermatol* 1984;10(2 Pt 1):285-287
 19. Brodland DG, Zitelli JA. Surgical margins for excision of primary cutaneous squamous cell carcinoma. *J Am Acad Dermatol* 1992;27(2 Pt 1):241-248
 20. Shriner DL, McCoy DK, Goldberg DJ, Wagner RF Jr. Mohs micrographic surgery. *J Am Acad Dermatol* 1998;39:79-97
 21. Halpern JN. Radiation therapy in skin cancer. A historical perspective and current applications. *Dermatol Surg* 1997;23:1089-1093
 22. Morrison WH, Garden AS, Ang KK. Radiation therapy for nonmelanoma skin carcinomas. *Clin Plast Surg* 1997;24:719-729
 23. Kalka K, Merk H, Mukhtar H. Photodynamic therapy in dermatology. *J Am Acad Dermatol* 2000;42:389-413; quiz 414-416
 24. Tucker SB, Polasek JW, Perri AJ, et al. Long-term follow-up of basal cell carcinomas treated with perilesional interferon alfa 2b as monotherapy. *J Am Acad Dermatol* 2006;54:1033-1038
 25. Edwards L, Tucker SB, Perednia D, et al. The effect of an intralesional sustained-release formulation of interferon alfa-2b on basal cell carcinomas. *Arch Dermatol* 1990;126:1029-1032
 26. Niles RM. Recent advances in the use of vitamin A (retinoids) in the prevention and treatment of cancer. *Nutrition* 2000;16:1084-1089
 27. Rigel DS. Epidemiology and prognostic factors in malignant melanoma. *Ann Plast Surg* 1992;28:7-8
 28. Langley RGB, Barnhill RL, Mihm MC Jr. Neoplasms: cutaneous melanoma. In: Freedberg IM, Eisen AZ, Wolff K, et al., eds. *Fitzpatrick's Dermatology in General Medicine*. 6th ed. New York, NY: McGraw-Hill; 2003:917-947
 29. Stolz W, Schmoeckel C, Landthaler M, Braun-Falco O. Association of early malignant melanoma with nevocytic nevi. *Cancer* 1989;63:550-555
 30. Tannous ZS, Mihm MC Jr, Sober AJ, Duncan LM. Congenital melanocytic nevi: clinical and histopathologic features, risk of melanoma, and clinical management. *J Am Acad Dermatol* 2005;52:197-203
 31. Sober AJ, Chuang TY, Duvic M, et al; Guidelines/Outcomes Committee. Guidelines of care for primary cutaneous melanoma. *J Am Acad Dermatol* 2001;45:579-586
 32. Elder DE, Elenitsas R, Murphy GF, Xu X. Benign pigmented lesions and malignant melanoma. In: Elder DE, Elenitsas R, Murphy GF, et al., eds. *Lever's Histopathology of the Skin*. 9th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2005:715-803
 33. Balch CM, Buzaid AC, Soong SJ, et al. Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. *J Clin Oncol* 2001;19:3635-3648
 34. Rigel DS, Friedman RJ, Kopf AW, Silverman MK. Factors influencing survival in melanoma. *Dermatol Clin* 1991;9:631-642
 35. Zitelli JA, Brown CD, Hanusa BH. Mohs micrographic surgery for the treatment of primary cutaneous melanoma. *J Am Acad Dermatol* 1997;37:236-245
 36. Wells KE, Rapaport DP, Cruse CW, et al. Sentinel lymph node biopsy in melanoma of the head and neck. *Plast Reconstr Surg* 1997;100:591-594
 37. Barth A, Morton DL. The role of adjuvant therapy in melanoma management. *Cancer* 1995;75(2 Suppl):726-734
 38. Hill GJ II, Moss SE, Golomb FM, et al. DTIC and combination therapy for melanoma: III. DTIC (NSC 45388) Surgical Adjuvant Study COG PROTOCOL 7040. *Cancer* 1981;47:2556-2562