Chapter 25: Management of Head and Neck Melanoma

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Cutaneous melanoma is a capricious neoplasm characterized by a clinical behavior that can be considered archetypical of malignancy. The obscurity of its causes, the often unpredictable pattern of lymphatic and hematogenous metastases, the inscrutable differences between potentially curable and incurable lesions, and the often relentless progression of disease despite apparently adequate treatment all characterize this malignancy. The recognition of these characteristics led early cancer surgeons to adopt a philosophy of extensive surgical resections even for melanomas of the smallest size. Such dogma became a cornerstone in surgical oncology and in the treatment of melanomas.

Several important developments over the past 20 years, however, have provided new insight into the biology of melanoma and have led to a reassessment of its clinical management. This has been particularly true in the treatment of melanomas arising in the head and neck. The first development was the initiation of large, cooperative, multi-disciplinary efforts to study the epidemiologic, histopathologic, and clinical characteristics of melanomas arising from differing sites in the body. Much of the current data reviewed in this chapter are derived from such retrospective and prospective studies. A second major development was the recognition by pathologists, most notably Clark, McGovern, and Breslow, of an association between certain histologic patterns of melanoma and the clinical behavior of the neoplasm. And finally, it was recognized that melanoma, when diagnosed at its earliest stage of development, is as readily curable as many of its less aggressive cutaneous counterparts, such as basal cell and superficial squamous cell carcinomas.

These observations together with the facts that the incidence of melanoma is rapidly increasing (Greene et al, 1985) and that the detection of melanoma relies primarily on visual recognition, emphasize the importance of educational efforts directed at dissemination of appropriate high-quality diagnostic and therapeutic information to primary physicians and their patients.

Because the skin of the head and neck is one of the major exposed areas of the body, visual identification and early diagnosis of lesions suspected of being melanomas should lead to high cure rates. Classically, two thirds of melanomas were thought to arise from preexisting benign nevi, and malignant transformation was believed to be characterized by a change in the lesion - most commonly a change in size, color, surface elevation, or sensation (for example, the development of itching or tingling) (Wick et al, 1980). More recently, the most common forms of invasive melanoma are believed to arise from dysplastic nevi (atypical melanocytic hyperplasia) or de novo (melanoma in situ). It is inadvisable and logistically impossible to biopsy all pigmented cutaneous lesions, since all humans (except albinos) have a variable number of benign nevi. However, clinical signs - such as characteristic coloration (shades of red, white, or blue), irregular borders, or changes in either growth, color, or morphology - mandate the biopsy of such lesions. Furthermore, the cosmetic sequelae associated with major surgical resection of primary melanomas in the head and neck add importance to the early diagnosis of these lesions.

This chapter reviews the natural history of primary cutaneous melanomas of the head and neck, with a major emphasis on current management principles and changing trends in management that have challenged traditional concepts. Current concepts regarding microstaging and clinical decision making based on tumor site, histology, and depth of penetration are discussed as they specifically relate to the head and neck. Excluded from in-depth review are primary mucosal and ocular melanomas, which differ significantly from cutaneous melanomas in clinical and epidemiologic characteristics. Also excluded are acral lentiginous melanomas, because they do not occur as primary lesions in the head and neck.

Epidemiology

Melanomas arise from cells termed *melanocytes,* which have the ability to synthesize the pigment melanin. In humans, melanocytes are found in the basal layer of the epidermis near the dermal-epidermal junction. Typically, melanomas occur in individuals of fair complexion, particularly those with red or blonde hair, blue eyes and a tendency to sunburn or freckle easily after sun exposure (Beral et al, 1985). However, the relationship between melanoma development and sun exposure is not conclusive and is based primarily on epidemiologic studies that demonstrate higher rates of melanoma in regions where light-skinned individuals are exposed to intense and prolonged sunlight (such as Australia and Israel). These observations are further supported by geographic variations of rates (within regions) of melanoma, which increase directly with a population's proximity to the equator (Crombie, 1979b). Furthermore, lower rates of melanoma are typically reported in races having greater natural skin pigmentation, such as people of African or Asian descent (Crombie, 1979a). Sun exposure is also implicated in the development of melanomas in patients with xeroderma pigmentosum because the predilection for melanoma in these patients is limited to their sun-exposed skin. Of the various types of melanoma described in this chapter, lentigo maligna, which occurs most commonly on the face, is most closely associated with actinic exposure, whereas superficial spreading and nodular types are less so.

The incidence of cutaneous melanoma is increasing worldwide. In the USA, the age-adjusted incidence rates have more than doubled in the last 30 years (Deresa and Silverman, 1978). Recent data from the National Cancer Institute's Surveillance Epidemiology and End Results (SEER, 1984) system show an 80% increase in the incidence of melanoma between 1973 and 1980 (Greene et al, 1985). This increase is outpaced only by incidence rates for lung cancer. Despite this increase, overall 5-year survival rates for patients with melanomas have improved from 60% in 1963 to a current rate of 81% (National Cancer Institute, 1990). These improvements probably result from better recognition and earlier diagnosis of cutaneous melanoma rather than alterations in the biology of the neoplasm or refinements in treatment; however, the latter cannot be ruled out. Unfortunately, mortality rates in the USA have increased because of the rapidly rising incidence rates.

The incidence rates for head and neck melanomas are changing more slowly than those for cutaneous melanomas of other anatomic sites (Lee, 1985). The rates for other sun exposure-related skin cancers also appear to be increasing (Fears and Scotto, 1982), whereas rates for melanomas of sun-protected areas, such as the eye or pigmented skin, are not increasing (Hinds and Kolonel, 1983). Sunlight exposure appears to be the most important predisposing factor with ultraviolet B (280 to 320 nm) radiation believed to be the most critical component (Koh et al, 1990a; Sober, 1987). Some investigators have suggested that

excessive sun exposure in childhood or adolescence is a significant risk factor for later development of melanoma (Elwood et al, 1984; Holman et al, 1986; Lew et al, 1983). Some have speculated that early intermittent sun exposure and episodes of blistering sunburn may be more important than cumulative exposure. Whether increased recreational exposure to the sun or depletion of the earth's ozone layer and subsequent increase in the amount of ultraviolet light reaching the earth will lead to increases in melanoma in future years is unknown. Despite the increasing incidence, overall mortality for head and neck melanoma has declined somewhat because of a higher percentage of patients seeking treatment with localized disease and higher proportions of melanomas that are thinner, less invasive, and less ulcerated. As discussed later in this chapter, these features have prognostic significance.

Queensland, Australia, with a reported rate of 40 cases per 100.000 population, has the highest incidence of cutaneous melanoma in the world. The Australian figures represent over 7 times the incidence in the USA and 20 times that reported in the UK (Harris and Hinckley, 1983).

Primary melanomas of the head and neck account for 25% to 30% of all melanomas, even though the skin of the head and neck constitutes only 9% of the body surface area (Goldsmith, 1979). The skin of the head, face, and neck is second only to the skin of the extremities in the total incidence of melanoma. This predilection for the head and neck has been attributed to several factors, including actinic exposure and regional variations in the distribution of melanocytes in the skin. The epidermis of the cheek and forehead have two to three times as many melanocytes as other skin areas (Batsakis, 1979).

Natural history

The majority of patients with head and neck melanomas have a history of either recent change in a preexisting pigmented lesion or development of a new pigmented lesion. Generally 50% to 66% of melanomas arise from preexisting nevi (Batsakis, 1979; Goldsmith, 1979). McNeer and Das Gupta (1964) have reported that of 557 patients with a melanoma, 27% of those melanomas arose in a nevus considered to have existed since birth, and 39% arose in a nevus that existed for more than 5 years. The remaining 34% of patients thought that their melanomas developed in a nevus that had appeared within the previous 5 years.

No good evidence exists to prove that melanomas arising from preexisting nevi are clinically different in behavior than melanomas arising de novo. However, clinical and epidemiologic studies of a familial form of dysplastic nevus (B-K mole syndrome) have led to wider recognition of non-familial, or acquired, dysplastic nevi as potentially premalignant lesions. Familiarity with the natural history of common acquired nevi and the clinical characteristics of dysplastic nevi should enable one to diagnose and manage melanoma arising in an acquired dysplastic nevus much earlier in its natural history.

Typically, common acquired nevi (that is, junctional, compound, or dermal) that are found in the skin of most white adults develop during the early years of childhood and may number from 10 to 40 lesions per person (Greene et al, 1985). They are generally round or oval, with smooth borders sharply demarcating them from the surrounding skin. Pigmentation may vary from uniform tan or brown to less common mottled variations of these colors. They are small: generally less than 6 mm. Over a period of years the nevus characteristically

undergoes a predictable series of changes. These include a change from a macular (junctional nevus) form to an elevated (compound nevus) stage, which corresponds histologically to the descent of nevus cells into the underlying dermis. These larger papular lesions are rarely black. With further descent of nevus cells into the dermis, the lesion becomes pink or flesh colored (dermal nevus) and the lesion may involute or slough. The phases of this natural evolution may be arrested at any point for a given nevus. The clinical appearance of any nevus that cannot be clinically attributed to a phase of the normal evolutionary sequence of a common acquired nevus should raise suspicions of a dysplastic nevus (Greene et al, 1985).

Dysplastic nevi are typically larger (6 to 15 mm in diameter) than common moles and have irregular borders and irregular tan, brown, or pink coloration. Margins tend to be indistinct and fade into the surrounding skin, virtually always maintaining some flat or macular component. The surface is usually varied, often with a central or eccentric papule surrounded by macular or nearly macular pigmentation. The development of black areas within such a lesion should prompt an excision to rule out melanoma (Greene et al, 1985). Acquired dysplastic nevi must be carefully followed, frequently with photographic documentation. Certainly nevi that are changing or otherwise suspicious or are located in places where monitoring is difficult (such as the scalp) should be excised. Although the magnitude of the risk of melanoma in nonfamilial dysplastic nevi is unknown, it has been estimated that as many as 4 million persons in the USA have one or more of these acquired pre-neoplastic nevi (Kraemer et al, 1983).

Age

The peak incidence of head and neck melanoma occurs in the fourth through the seventh decades (Conley and Hamaker, 1977; Gussack et al, 1983; Harris and Hinckley, 1983). This peak is somewhat later than that for melanoma in general. In a review of 399 cases of melanoma of the head and neck, Gussack and associates (1983) found the average age of patients at the time of diagnosis was 52 years, with a range of 16 to 93 years. This compares with an average age of 48 years for patients with stage I melanoma reported from centers worldwide (Balch et al, 1985a). The prevalence of Hutchinson's melanotic freckle in the older population and prolonged exposure to sunlight may account for this variation in distribution with age. Melanomas are quite uncommon in childhood or in the immediate postpubertal period. In the past, melanomas in children were thought to be associated with a favorable prognosis, however, this concept was the result of including in survival data children with certain benign nevi (Spitz nevus) that simulated malignancy histologically. Of the 41 cases of melanoma in children reported before 1966, only 11 arose from the skin of the head and neck (Batsakis, 1979). It is currently thought that the survival rates for children are similar to those for adults.

Sex

Men tend to have a slightly higher incidence of head and neck melanomas than women. Most studies report male:female ratios of 1.5:1.0 (Gussack et al, 1983; Storm et al, 1978). In a retrospective review of 660 cases Conley and Hanamaker (1977) confirmed this male predominance but also noted that cheek melanomas tended to predominate in females.

Site

The anatomic location of a primary melanoma affects the prognosis. Patients with cutaneous melanoma of an extremity have a better prognosis in general than those with melanomas rising on the trunk or skin of the head and neck. Within the head and neck region, patients with scalp melanomas have a worse prognosis than those with lesions on the face or neck (Fig. 25-1) (Balch et al, 1985b). These differences persist even after accounting for differences in sex or tumor thickness. Recently Day and associates (1982a) defined the upper back, upper outer arm, neck, and scalp as four specific sites associated with poor prognosis and coined the acronym BANS to help identify these sites. A recent review of prognostic factors in 4000 patients with cutaneous melanomas did not confirm a worse prognosis for these compared with other anatomic sites (except for scalp melanomas) (Balch et al, 1985b).

The cheeks, scalp, and skin of the neck, in accordance with melanocyte distribution, are the cutaneous sites in the head and neck most often involved by primary melanoma. Of 399 cases Gussack and associates (1983) reported, 46% had primary melanomas of the scalp and neck, and 43% had primary lesions located on the face and nose. Only 11% had ear involvement. However, in the Queensland experience, scalp and lip lesions were relatively uncommon, and most melanomas occurred in the skin of the cheek, temple, or neck (Fig. 25-2) (Harris and Hinckley, 1983). In 857 patients reported by Fisher (1989), face and neck account for 62% of melanoma, scalp 26%, ear 9%, and nose 4%. O'Brien (1991) found that the most common primary site was face (47%), followed by neck (295), scalp (14%), and ear (10%) in a study of 998 patients.

A melanoma arising on the mucosal surface of the upper aerodigestive tract is an uncommon event. Mucosal melanomas generally represent 2% to 3% of all melanomas (Shah et al, 1977; Snow et al, 1978). The majority arise in the nasal cavity or paranasal sinuses (McKinnon et al, 1989; Stern et al, 1991). In the oral cavity, the areas most often involved, in descending order of frequency, are the following: palate, upper alveolar ridge, buccal mucosa, lower alveolar ridge, lip, tongue, and floor of mouth with a predilection for the upper jaw (Batsakis, 1979). The age, sex, and racial distribution of patients with mucosal melanomas are similar to those for patients with melanomas elsewhere in the head and neck.

Mucosal melanomas tend to be more aggressive lesions and to have a much poorer prognosis that their cutaneous counterparts. They develop from melanocytes residing in mucous membranes and most commonly have an adjacent lentiginous component. It is unclear whether the poor prognosis associated with mucosal melanomas results from a different biological behavior or from their location in areas where blood vessels and lymphatics are much closer to the site of origin. The poor prognosis for patients with mucosal melanomas may also be explained by other factors. The relatively hidden location of most mucosal melanomas of the head and neck contributes to delay in both patient presentation and diagnosis. Histologic staging based on the depth of invasion of primary mucosal melanoma has little prognostic utility. Histologic differences from cutaneous melanomas - such as higher frequency of mitosis, blood vessel and lymphatic invasion, and inaccuracy in determining the level of invasion - have also been reported as reasons for the poor prognosis of mucosal melanomas (Snow et al, 1978).

Primary melanomas arising in a neck node or metastatic from an unknown primary site are rare. Chang and Knapper (1982) reported a 4.4% incidence of malignant melanoma appearing in lymph nodes in the absence of an apparent cutaneous or mucosal primary lesion. One fourth of these cases occurred in neck lymph nodes. Spontaneous regression of the primary melanoma or de novo development in the parenchyma of a lymph node have been offered as explanations for this rare clinical event. However, the true cause remains obscure. A peak incidence in the fifth decade is consistent with that reported for primary cutaneous or mucosal melanomas (Batsakis, 1979; Chang and Knapper, 1982). Treatment consists of radical neck dissection. If treated promptly (within 3 months), these patients appear to have better 10-year survival rates than either patients with nodal metastases from known primaries or patients receiving delayed (greater than 3 months) radical lymphadenectomy for metastases from an unknown primary (Chang and Knapper, 1982; Velez et al, 1991).

Diagnosis and Classification

The clinical characteristics of a melanoma are varied but consistent enough to make the diagnosis of a suspicious lesion fairly straightforward. The cardinal feature is change in a preexisting skin lesion or appearance of a new lesion that generally takes place over a period of months. Rapidly appearing lesions that have a duration of only days to weeks usually represent an inflammatory condition, such as a pyogenic granuloma. Lesions that have not changed over several years are unlikely to be melanomas. The differential diagnosis includes a variety of pigmented skin lesions (Table 25-1) and is discussed in more detail in Chapter 24. A variety of vascular lesions, including pyogenic granuloma and hemangioma, can also look like melanoma. Kaposi's sarcoma deserves special mention because it is increasingly seen in patients with AIDS and can appear as a cutaneous red, blue, or violet papule or nodule.

Changes in growth or color are the most commonly recognized symptoms of a melanoma. A melanoma's growth characteristically takes two forms, most commonly an initial horizontal or radial direction of growth as the lesion spreads superficially, followed by an invasive nodular or vertical growth phase. Infrequently, vertical growth begins de novo. Awareness of the natural history and recognition of the clinical characteristics of ordinary common nevi should allow suspicion of dysplasia or melanoma in any lesion that does not conform to the size, growth pattern, or clinical appearance of an acquired common benign nevus.

Regardless of whether there is a history of an antecedent nevus, cutaneous melanoma develops in one of three patterns that have distinct clinical and histologic characteristics: (1) melanoma arising in Hutchinson's melanotic freckle (associated with lentigo maligna melanoma); (2) superficial spreading melanoma; and (3) nodular melanoma. Each pattern is associated with an individual clinical behavior and prognosis. Nodular melanoma is the most aggressive form, and melanoma arising in Hutchinson's melanotic freckle tends to be the least aggressive form. Melanoma is classified according to its noninvasive component because the invasive portions look similar in each type of melanoma. Those lacking an adjacent noninvasive area are called nodular melanomas; the other types are distinguished by determining whether the adjacent component is of the superficial spreading or lentigo maligna type.

Hutchinson's melanotic freckle

Hutchinson's melanotic freckle (HMF) is a premalignant, spreading, macular pigmentation that occurs most commonly in the skin of the temple or on the malar regions in elderly patients. It may also occur on other exposed areas of the face and neck, which characteristically show severe solar degeneration. An HMF is an extensively pigmented lesion with grossly irregular borders, indicating regression or migration of the pigment cells. It characteristically has a smooth surface; however, malignant degeneration to a lentigo maligna melanoma is usually associated with the development of a very noticeable thickened or elevated nodule within the freckle. The proportion of HMF that develops into melanoma is probably less than 5%. The histologic distinction between the benign phase of HMF and in situ lentigo maligna melanoma is extremely difficult to make.

Table 25-1. Differential diagnosis of cutaneous melanomas

Lesion	Clinical characteristics
Seborrheic keratosis	Multiple, waxy; has long history
Nevi	
Junctional	Macular, nonpalpable, usually < 1 cm, pale to dark brown, orderly color, skin markings preserved; has very slow history of change in growth
Compound	Palpable, dark brown; may occur with junctional type, may have depigmented halo
Dermal	Dome shaped, lacks pigment; has distorted skin markings
Hemangioma	Blue-black to red, slow growing; blanches with pressure unless thrombosed
Blue nevus	Usually < 0.5 cm, blue-black, palpable, slow growing; rarely undergoes malignant degeneration
Pyogenic granuloma	Form of rapidly developing hemangioma; surrounded inflammation
Spitz nevus	Small, < 2 cm, flat reddish, rarely ulcerated
Pigmented basal cell carcinoma	Common, slow growing; rarely bleeds, has mottled appearance, needs biopsy to differentiate from melanoma
Squamous cell carcinoma	Rarely confused with melanoma, nonpigmented; has prominent keratin formation or ulceration.

Lentigo maligna melanoma

Lentigo maligna melanoma (LMM) (see Plate 5, A) is the least common of the three major forms of cutaneous melanoma. It accounts for about 6% to 10% of all cases (Wick et al, 1980). It is characterized by a slow radial growth phase that may progress for years. McGovern reported 33 cases of lentigo maligna melanoma that took from 15 months to 40 years to develop, with an average developmental period of 9 years (Goldsmith, 1979). They are very slow to invade deeply and consequently have a much better prognosis than do other forms of melanoma. Survival statistics approaching 100% have been reported (McGovern et al, 1980). LMM best exemplifies the concept of the two growth phases for melanoma popularized by Clark et al (1975), which consists of a radial phase of proliferation of

melanocytes in the epidermis followed by development of a dermal invasion or a vertical growth phase. Nodular melanomas do not display these distinct growth phases.

Superficial spreading melanoma

Melanomas with an adjacent component of the superficial spreading type are the most common melanoma, comprising approximately 75% of all cases. They are usually more circumscribed than LMM and start as a superficial spreading pigmentation (radial growth phase), which is seldom larger than 2 cm in diameter before ulceration and bleeding develop. Ulceration and bleeding herald dermal invasion (vertical growth phase) and are associated with a much worse prognosis. The major clinical feature of a superficial spreading melanoma is a kaleidoscopic variety of colors, ranging from tan-black, brown, and blue-gray to violaceous pink (see Plate 5, E). In a study of 786 cases of superficial spreading melanoma Wick and associates (1980) reported that an increase in size and the presence of color changes are the most useful early clinical signs noted by patients and are present in 71% of superficial and more easily curable lesions.

The radial growth portion of a superficial spreading melanoma may consist of melanoma in situ or nonmalignant melanocytic dysplasia. Areas of spontaneous regression are also common. Lesions tend to demonstrate radial growth for 1 to 7 years before becoming deeply invasive. During this critical period of radial growth, superficial spreading melanomas are highly curable. As closer attention is paid to the significant features of early superficial spreading melanomas, the diagnosis will be substantiated earlier and result in improved survival rates.

Nodular melanoma

Fortunately, nodular melanomas comprise only 10% to 15% of all melanomas. They tend to be much more aggressive than either the superficial spreading or the lentigo maligna types. Both exposed and unexposed skin surfaces are affected: generally, nodular melanomas develop in patients who are around 50 years of age.

The color of a nodular melanoma is characteristically a shade of blue: blue-black, blue-gray, or reddish blue. A nonpigmented form of nodular melanoma exists. These lesions can be extremely difficult to diagnose by color, but occasionally small, dark specks of pigmentation appear at the base of the lesion. The majority of mucosal melanomas tend to be of the nodular type, which is consistent with their poor prognosis.

Nodular melanomas are invasive from the beginning. Unlike lentigo maligna and superficial spreading melanomas, they are characterized by an early vertical growth phase, which may progress so rapidly that early surface ulceration occurs. Regardless of whether nodular melanomas arise de novo or from a preexisting nevus, there is no preliminary radial growth stage or peripheral spreading pigmentation. Because of its early invasive characteristics, nodular melanoma has a very poor prognosis, and survival rates tend to correlate inversely with the depth of invasion.

Table 25-2. American Joint Committee on Cancer staging for melanoma

Classification		Criteria

Primary tumor (pT)

pT0		No evidence of primary tumor
pTis		Melanoma in situ (atypical melanocytic hyperplasia (Clark's level I) not an invasive lesion
pT1		Invades papillary dermis (level II) or 0.75 mm or less thick*
pT2		Invades papillary-reticular dermis interface (level III) or 0.76 mm to 1.5 mm thick*
pT3		Invades reticular dermis (level IV) or 1.51 mm to 4.0 mm thick*
	pT3a	Tumor 1.51 to 3.0 mm thick
	pT3b	Tumor 3.01 to 4.0 mm thick
pT4		Invades subcutaneous tissue (level V) or more than 4.0 mm thick or satellite within 2 cm of the primary*
	pT4a	Tumor greater than 4.0 mm and/or invades subcutaneous tissue
	pT4b	Satellites within 2 cm of primary tumor

Nodal involvement (N)

N0		No regional lymph node involvement
N1		Metastasis 3 cm or less in greatest dimension
N2		Metastasis greater than 3 cm in any regional node and/or in-transit metastasis
	N2a	Metastasis greater than 3 cm
	N2b	In-transit metastasis&
	N2c	Both N2a and N2b

Distant Metastasis (M)

M0		No distant metastasis
M1		Distant metastasis
	M1a	In skin or subcutaneous tissue or lymph nodes beyond the regional nodes
	M1b	Visceral metastasis

* When thickness and level of invasion criteria do not coincide, the lesion is assigned to the higher pT classification (that is, least favorable finding).
& In-transit metastasis involves skin or subcutaneous tissue more than 2 cm from the primary tumor but not beyond the regional lymph nodes.

      A wide variety of clinical staging systems for melanoma have been devised, by both single institutions and groups of investigators. However, the resulting variation in clinical staging has significantly impaired data interpretation and standardization by which survival results or treatment methods can be compared among different institutions. The simplest and most widely used system consists of three categories representing clinically localized disease

(stage I), regional node or in-transit metastases (stage II), and disseminated melanoma (stage III). A shortcoming of this system is the fact that the majority (70 to 85%) of patients are classified as being in stage I, which does not distinguish those patients with stage I disease who have a poor prognosis. This staging system has recently been expanded to include four stage groupings (see Tables 25-2 and 25-3). Clark's introduction of histologic microstaging with five levels of tumor involvement and the demonstration of the prognostic importance of invasion depth has allowed separation of patients with localized disease into groups having different prognoses and risks of metastasis.

Clark demonstrated that depth of invasion is clearly the most important characteristic in the histologic staging of melanoma (Clark et al, 1969). Clark's microstaging classification has become widely accepted as a useful method for classifying melanomas (Fig. 25-3). Breslow further refined Clark's classification, relating the prognosis of a melanoma to its actual measured depth (thickness) of invasion, as determined with an ocular micrometer (Breslow, 1970). According to this schema, lesions are divided into thin (0.75 mm or less), intermediate (0.76 to 1.5 mm), and thick (greater than 1.5 mm) lesions (Fig. 25-4).

Table 25-3. American Joint Committee on Cancer stage groupings for melanoma

Stage	**Criteria**
I	pT1, N0, M0
	pT2, N0, M0
II	pT3, N0, M0
	pT4, N0, M0
III	any pT, N1 or N2, M0
IV	any pT, any N, M1.

Breslow's thickness and Clark's depth of invasion of cutaneous melanoma are independent prognostic variables for survival. They are relatively congruent in levels II and V but not in levels III and IV (Breslow, 1975) because of the great variability in the thickness of lesions that are Clark's level III or IV (Fig. 25-5). Because the chance of developing recurrent disease appears to be directly proportional to tumor thickness and the mean survival after surgery appears to be inversely proportional to tumor thickness, the heterogeneity within level III and IV melanomas is a serious shortcoming, if level of invasion alone is used as a guide to therapy (Batsakis, 1979).

Although there are weaknesses associated with each form of histologic microstaging, the combined Breslow-Clark classification is a useful means of relating patient prognosis with a primary melanoma's depth of invasion. It is generally accepted that level I and II lesions are less than 0.75 mm thick and that lesions more than 1.5 mm thick are comparable to those in Clark's levels IV and V. Clark's level III lesions fall roughly between 0.75 and 1.5 mm in thickness (Goldsmith, 1979; Harris and Hinckley, 1983) (Fig. 25-3). Thin lesions are associated with a very low metastatic risk. Intermediate levels (0.75 mm to 3.99 mm) have a 50% to 60% risk of regional metastases and a 10% to 20% risk of distant metastases, whereas thick lesions (those greater than 4 mm) are associated with a distant metastatic rate of 60% to 80% (Franklin et al, 1976; Goldsmith, 1979; Harris and Hinckley, 1983).

These observations and the shortcomings of a purely clinical staging system have resulted in the proposal of a new TNM four-stage classification system by the American Joint Committee on Cancer (AJCC) (Beahrs et al, 1988). In this system (Table 25-2) both the level of invasion and the maximal measured thickness determine the T classification. Primary tumors with satellite lesions or nodules within 2 cm of the primary tumor are characterized as T4 in the AJCC classification. Satellite lesions or nodules at a greater distance, but not beyond primary lymph node drainage, are considered in-transit metastases and are included under the N categories. The AJCC stage grouping (Table 25-3) reflects the differing prognoses for patients with localized disease according to histologic microstaging. This grouping delineates groups of patients who are more evenly divided prognostically.

Other factors that influence the results of melanoma treatment have been identified. These include age, sex, presence of ulceration, and various histologic parameters, such as vascular invasion, mitotic activity, and differentiation. Several other factors pertinent to head and neck melanomas also correlate with prognosis, such as the site of the melanoma and the lymph node status. These are discussed later in this chapter. The complete prognostic index must include all of the factors noted above as well as general patient factors. Given this multivariate index, the outcome of most cutaneous melanomas can be predicted.

Surgical Management

General principles

Successful treatment of a melanoma depends on the early recognition and accurate surgical excision of the lesion. As with most solid malignancies, the best chance to cure a melanoma is at its initial presentation, and that chance should be used to remove all malignant cells. Traditionally this has meant wide excisions with margins of 3 to 5 cm. These excisions are cosmetically and functionally unacceptable in the head and neck. Accumulated experience with less radical excisions of primary head and neck melanoma together with the increasing percentage of patients diagnosed with earlier lesions (Bagley et al, 1981; Harris and Hinckley, 1983) and the low recurrence and metastasis rates associated with thin lesions have resulted in an appreciation that wide resections are not necessary in most instances (Cosimi et al, 1984; Day et al, 1982b; Shafir et al, 1982; Urist et al, 1985). These observations have now been confirmed in a prospective randomized trial by Veronesi et al (1988). Only three recurrences were reported in 305 patients with trunk extremity melanomas who underwent narrow (1 cm) excision margins. No recurrences were reported in 185 of these patients who had lesions less than 1.0 mm in thickness (Veronesi et al, 1988, 1991).

It is axiomatic that accurate surgical planning depends on adequate staging, and that for localized melanomas this requires optimal biopsy and skilled histologic interpretation. Other factors that influence planning include the size and location of the lesion, patterns of regional lymphatic drainage, type of melanoma, and age and condition of the patient. Because of these factors, the biopsy of suspicious lesions is best managed by the surgeon who will be responsible for the patient's definitive care. This allows not only adequate planning for the resections of large lesions but also shorter time intervals between biopsy and resection and often more complete histologic microstaging.

For the surgeon, key considerations in decision making for a localized melanoma include the type and timing of the biopsy, extent of local excision, type of closure, need for lymph node dissection, and potential that further treatment with adjuvant therapy may be warranted. For patients with clinically positive regional nodes, therapeutic node dissection is indicated, since significant benefit is frequently derived from local and regional tumor control, even if regional node metastases portend distant dissemination in the vast majority of such patients (Roses et al, 1980). Locally recurrent lesions are generally managed with surgical excision when feasible or radiation therapy.

Biopsy

Any lesion suspected of harboring a melanoma should be biopsied. Shave excision or curettage biopsy of pigmented lesions is contraindicated (Drzewiecki, 1982), since those methods do not remove the entire depth of the lesion and are incompatible with accurate microstaging. Dermal punch biopsy, if obtained from the area of deepest skin invasion, gives accurate staging information. No documented evidence shows that either dermal punch biopsy or incisional biopsy of a melanoma lesion is associated with an increased risk of local recurrence, nodal metastases, or death from disease (Bagley et al, 1981; Perzik, 1981). In the head and neck particularly, where excisional biopsy leaves a large defect or causes disfigurement, an incisional biopsy or punch biopsy can provide adequate tissue for diagnosis if the deepest and most representative areas are sampled.

Regardless of technique, biopsies must be full thickness into the subcutaneous tissue to permit microstaging. Smaller lesions (less than 1.5 cm), especially those located on the face, can be completely excised with only a small margin (2 mm) of normal skin, so that the resulting deformity is minimal if the lesion is benign (Goldsmith, 1979; Gumport et al, 1981). Associated satellite lesions should be removed at the time of definitive surgical procedure. The initial biopsy incision should interrupt the proximal lymphatics draining to the first regional lymph node station, theoretically minimizing the opportunity for tumor cells within the lymphatics to be milked toward the regional lymph nodes during the surgical procedure. Most surgeons leave the underlying fascia intact. If a biopsy shows an in situ melanoma, the lesion should still be excised even if it is benign, since it frequently recurs as an in situ or invasive melanoma.

Controversy exists as to whether initial biopsy followed by later reexcision is less efficacious than frozen-section biopsy and immediate excision if the biopsy is positive. Because correct intraoperative diagnosis and assessment of thickness are crucial for an effective surgical approach, reliance on frozen sections requires the skills of a pathologist experienced in the interpretation of such biopsies. Several authors report a 98% accuracy rate using frozen sections for both level of invasion and thickness (Harris and Hinckley, 1983; Jansen and Westbrook, 1981; Shafir et al, 1983). However, measurement of skin melanoma thickness can vary by technique. Thickness on frozen sections has been reported to be 0.1 to 0.4 mm more than that measured on paraffin sections of the same specimens (Shafir et al, 1983). This difference in thickness may be caused by shrinkage during the process of fixation and embedding in paraffin. It has been suggested that tumors measuring up to 0.85 mm on frozen section should be included in the group of thin melanomas. It has also been found that maximal depth of invasion is generally found to be greater when techniques of serial sectioning are used (Solomon et al, 1983). The tumor specimen must be bisected through the

point of maximal elevation or through the area of the most intense pigmentation to measure the thickness and level of invasion accurately. The total height of the lesion - vertical at the point of maximal thickness - must be measured. For ulcerative lesions measurements are made from the base of the ulcer crater to the maximal depth of invasion (Balch, 1982). In cases of regressing melanomas, multiple sections are often required to substantiate the diagnosis and determine thickness accurately. Therefore final assessment often must await the paraffin sections.

Many surgeons prefer first to excise suspicious lesions within narrow margins (2 mm) and then to perform elective reexcision of the scar as soon as possible after diagnosis and microstaging are complete. This two-step approach allows adequate time for counseling the patient and planning definitive treatment. Time is also available for obtaining lymphoscintigraphy if lymphatic drainage patterns are unclear. Although there is a theoretic risk of tumor dissemination at the time of biopsy, there is no evidence that these methods alter prognosis (Eldh, 1979; Epstein, 1971).

Primary tumor margins

Much of the dogma concerning the adequacy of resection margins for localized cutaneous melanomas arose from Handley's 1907 Hunterian lectures (Day et al, 1982b). However, Handley's recommendations for wide margins were based on a single autopsy study of the distribution of tumor in the lymphatics surrounding cutaneous metastases, not primary tumors. Furthermore, Handley did not actually specify 5.0 cm margins, which have been the standard practice for many years, but rather that the resection should be performed about an inch from the edge of the tumor. Particularly in the head and neck, it is important to preserve as much of the normal tissue as possible, and wide margins may be impossible without causing significant cosmetic or functional disability.

Recent studies using primary tumor thickness as a correlate of survival have shown that the magnitude of surgical margins has no effect on the incidence of local recurrence or mortality (Urist et al, 1985). Although this question is still open to scientific debate, clearly the risk of recurrence correlates more with thickness of the lesion than width of the resection margins. Particularly for thin lesions, guidelines for minimal safe margins have not yet been established, since local recurrence is exceedingly rare even with margins of 1 cm or less. It is generally recommended that 1 to 2 cm margins are acceptable for thin lesions or for lentigo maligna melanomas.

The World Health Organizaton (WHO) reported that survival was not influenced by the size of the resection margin even after compensating for the expected higher mortality with thicker melanomas (Cascinelli et al, 1980). Of 593 patients with stage I disease in the WHO study, 36 had margins of less than 1 cm, and 60 had margins greater than 1 cm but less than 2 cm. No local recurrences occurred in any of these patients with thin lesions, and only 4 local recurrences were noted in those with lesions of intermediate thickness. Cosimi and associates (1984) reported similar data. Of 49 patients with level II or III melanomas, more than half were treated with margins of less than 2 cm. No local recurrences were noted in any patient treated with limited excision.

As a result of a retrospective review of 147 patients at the Lahey Clinic over 25 years, Bagley and associates (1981) recommended resection margins of clinically uninvolved skin measuring twice the diameter of the primary melanoma, although narrower margins might be used in low-risk melanomas. In that study, the risk of in-transit, nodal, or systemic metastases was shown to be independent of margins: it was only a function of the risk status of the melanoma.

In a recent study of 586 patients with head and neck melanomas, surgical margins of less than 2 cm were used in over 80% of the patients. The overall local recurrence rate was only 4%. It was believed that these local recurrences could be accounted for by factors other than margins, such as tumor thickness, ulceration, and patient age (Urist et al, 1985).

One prospective randomized study (Veronesi et al, 1988) has examined 1 cm versus 3 cm excision margins in patients with trunk and extremity melanoma that were 2 mm or less in thickness. In 612 evaluated patients, no differences in overall or disease-free survival were found between groups according to resection margins. Only three local recurrences occurred; all in the narrow resection group. No local recurrences were reported in either group when the lesion measured less than 1.0 mm in thickness.

The limited surgical defects created by narrower margins around a primary melanoma permit most excisions to be closed primarily or by local rotational transposition or advancement flaps, with excellent cosmetic results. Skin grafting is seldom required. The closure method does not appear to alter prognosis (Bagley et al, 1981; Cosimi et al, 1984).

Regional lymph nodes

No area in the treatment of head and neck melanomas is surrounded by more controversy than the management of the regional lymphatics. The regional lymph nodes are the most common site of metastases from cutaneous melanomas (Patel et al, 1978). Treatment concepts in the overall management of melanoma must therefore acknowledge the risk of occult metastases in patients with clinically localized disease and take into account the prognosis when clinically evident regional metastases exist.

Surgeons have little disagreement that a patient with a melanoma of the head or neck and clinically involved regional nodes should have a regional lymph node dissection. Overall survival rates for these patients are dismal, since 70% to 85% of patients with clinically evident nodal disease die of disseminated melanoma. Although metastases to the lymph nodes of the neck seriously alter the prognosis of the patient, therapeutic dissection improves local and regional tumor control and benefits those few patients who may never develop disseminated melanoma. This include those rare patients with regional lymph node metastases from an unknown primary (Velez et al, 1991). Adequate resection may achieve a 25% 5-year survival rate, which is superior to the results of either radiation therapy or chemotherapy. Also, since untreated regional tumor growth can be disfiguring and emotionally disabling for the patient, resection of nodal disease even in the face of systemic dissemination can improve the patient's quality of life.

Confusion exists in the current literature, however, as to whether immediate (prophylactic or elective) or delayed (when nodes become positive) lymphadenectomy for occult lymph node metastases is more beneficial. This confusion is related to the fact that survival data for wide local excision (WLE) versus WLE with elective neck dissection are derived from retrospective reviews of small numbers of treated patients in which differences in important prognostic factors (such as lesion thickness, tumor site, and presence of ulceration) have not been adequately considered. Furthermore, most studies of the value of regional dissections involve patients with extremity melanomas, and those results may not be directly applicable to head and neck melanomas, where overall prognosis is poorer and lymphatic drainage is more variable.

The rationale for elective neck dissection (END) is based on the assumption that the growth and natural history of a melanoma is in some respects orderly and that microscopic metastases disseminate first to the regional lymph nodes, then to distant sites. Removal of micrometastases before distant dissemination has occurred is thus beneficial, and the decision to perform an elective dissection is based on the risk of occult metastases being present in a given patient. There is an obvious theoretic advantage in removing occult metastases (minimal tumor burden) over waiting until metastases become evident (billions of metastatic cells), since distant dissemination is less likely. This conjecture is supported by the poor 5- and 10-year survival rates (less than 25%) reported for delayed lymph node dissection (Balch et al, 1981; Fortner et al, 1977; Simons, 1972). Furthermore, significantly poorer survival rates are reported as the number of involved lymph nodes increases (Balch et al, 1981; Day et al, 1981; Fortner et al, 1977; Olson et al, 1981). Recent data both support (Loree and Spiro, 1989) and refute (Fisher, 1989) the benefits of elective node dissection in patients with head and neck cutaneous melanoma. Resolution of this controversy awaits completion of ongoing prospective randomized trials (Balch, 1988; Cady, 1988).

The major disadvantage of elective dissection is that some patients are subjected to unnecessary surgery. There is also a theoretic concern that dissection itself may encourage the dissemination of melanoma cells. In addition, some surgeons think that because rates of distant dissemination are so high once regional metastases have occurred, immediate END is a palliative procedure at best and should be withheld until the development of positive nodes identifies those patients who may need regional disease palliation.

Regardless of surgical philosophy, accumulated experience and newer concepts of histologic microstaging have provided data useful in the decision-making process relating to an elective neck dissection. Factors to be considered include lesion thickness, melanoma type, tumor site, and presence of ulceration as they relate to the risk of occult metastases.

Occult metastases occur with primary head and neck melanomas in 14% to 44% of cases (Goldsmith, 1979; Olson et al, 1981; Storm and Eilber, 1981). The risk of occult metastases varies directly with the thickness of the primary lesion. For melanomas of all sites the risk of regional metastases varies from virtually no risk for lesions less than 0.75 mm, to 25% for lesions 0.76 to 1.49 mm, to 57% for lesions 1.5 to 3.99 mm, and to 62% for lesions greater than 4.0 mm in thickness (Balch, 1980; Harris and Hinckley, 1983; Simons et al, 1972). Similar estimated risks have been reported for axial (head, neck, trunk) locations (Balch et al, 1985c). Thus for patients with thin melanomas (less than 0.75 mm) END offers no significant benefit. Similarly, occult nodal metastases are also unlikely in patients with

lentigo maligna melanoma; END is not indicated for this type of melanoma, which is highly curable with local resection alone.

For superficial spreading or nodular melanomas in the head and neck, lesions of intermediate thickness (0.75 to 4.00 mm) have increasingly higher rates of occult metastases (14% to 44%) (Olson et al, 1981; Storm and Eilber, 1981). These rates have been determined by histologic analysis of END specimens. These figures, however, may be underestimations of the actual metastatic rate, since they are less than the 50% to 60% rate at which subsequent clinical nodal metastases develop when elective dissections are not performed for intermediate-thickness lesions (Balch, 1980). These observations argue for ENDs in localized, intermediate-thickness melanomas if one believes that removal of microscopic metastases is beneficial.

A number of authors have suggested an improved survival with END for deeply invasive head and neck melanomas (Ames et al, 1976; Balch et al, 1982; Das Gupta, 1977; Olson et al, 1981; Simons, 1972). Others, however, have argued that 5-year survival rates are similar when regional metastases have occurred regardless if they are occult or clinically evident, and that immediate END offers no major advantage over dissections delayed until metastases become evident (Crowley and Seigler, 1990). This has been supported by the results of two randomized trials of WLE alone compared with WLE with END of melanomas in sites other than the head and neck (Sim et al, 1978; Veronesi et al, 1982b). However, the follow-up period in these trials was short, and it has been shown in at least one large prospective trial that the risk of failure from a WLE of a localized melanoma persists even 5 to 10 years after treatment. Balch and associates (1985c) have demonstrated significantly lower 10-year survival rates for axial melanoma (0.76 to 4.0 mm thick) treated with WLE alone, compared with WLE with regional node dissection. This analysis included 430 patients and showed 80% survival with node dissection compared to 56% with WLE alone for lesions 0.76 to 1.49 mm thick, and 64% survival compared to 33% survival for lesions 1.50 to 3.99 mm thick.

Day and associates (1981) have also suggested that a good prognosis (80% survival over 5 years) can be expected in a subgroup of patients with melanomas less than 3.5 mm thick in whom END shows less than 20% of the nodes involved with melanoma. Likewise, Olson and associates (1981) reported 5-year survival rates of better than 50%, which were similar among patients receiving END for a head or neck melanoma in whom the histologic findings were either negative or showed only one or two positive nodes. This compared with a 15% survival rate for those with 3 or more positive nodes. It should also be noted that most studies of patients with head and neck melanomas report dismal long-term survival rates for patients treated with delayed neck dissection for metachronous regional metastases (Conley and Pack, 1963; Fortner et al, 1977; Fisher, 1989; Hoyt and Fisher, 1989).

Thus strong theoretic rationale exists for considering END for patients with lesions of intermediate thickness. However, the quantitative risk of occult regional metastases is not only factor that may influence the decision to perform END, since the metastasis rate may be low in relatively thin (0.75 to 1.50 mm) intermediate lesions and thus not justify the morbidity of dissection. Primary tumor location in localized melanomas is also an important prognostic variable. The combination of specific location and measurement of thickness predicts recurrence and death from melanoma better than any other known combination of two

variables.

In looking at prognostic variable in "thin" intermediate-thickness lesions, Day and associated (1982a) reported that localized head and neck melanomas of 0.85 to 1.69 mm in thickness arising on the face and anterior neck have a survival rate greater than 95%, which is similar to that for thin melanomas. Equally thick melanomas located on the scalp or posterior and lateral neck (BANS areas) are associated with higher occult metastatic rates and a poorer prognosis. The skin overlying the mandible has also been reported to be a high-risk location (Rogers et al, 1983). For these high-risk sites, the benefit of END for lesions 0.75 to 1.5 mm thick may be greater than for other head and neck sites.

Ulcerated melanomas also have a poorer prognosis and higher metastatic rates. Balch and associates (1985b) reported 10-year survival rates of 60% to 70% for nonulcerated axial melanomas, compared with 25% survival for ulcerated lesions. Neck dissection should be considered for thinner lesions (0.75 to 1.5 mm) that are ulcerated.

Another important consideration is the likelihood that the patient will return for routine follow-up examinations after WLE of a localized melanoma. If reliable follow-up period is uncertain, immediate node dissection may be advisable rather than a watch-and-wait plan regarding regional metastases.

A corollary to the theoretic considerations in elective neck dissections is the concept that many lesions on the face, scalp, or neck may have ambiguous lymphatic drainage patterns. The boundaries of elective neck dissection should encompass all lymphatics at risk if the dissection is to be beneficial. Traditional dissection approaches may underestimate lymphatic drainage patterns for specific lesions. Preoperative lymphoscintigraphy has proven to be beneficial in predicting lymphatic drainage patterns (Lock-Anderson et al, 1989; Norman, 1991). Norman and associates (1991) have shown that traditional lymph node dissections for trunk or head and neck primaries may be inadequate in up to 60% of cases. Unexpected drainage to anterior cervical nodes from shoulder/posterior neck lesions and to posterior cervical nodes from shoulder, back, and neck was noted. For the posterior base of neck, drainage was possible to six separate nodal basins including axillary sites. Such scanning techniques should be considered in all patients undergoing preoperative assessment for elective node dissection where lymphatic drainage patterns are not certain. The studies by Norman (1991) suggest that lymphatic drainage overlap is so frequent with head and neck sites that routine lymphoscintigraphy may be warranted.

A final consideration is the age and sex of the patient and the morbidity of neck dissection. For women with melanomas, overall prognosis is better and the risk of metastases is slightly less. Younger patients appear to have a better prognosis than elderly patients have. In all cases the overall benefit of dissection must be weighed against the morbidity of the procedure, taking into account the thickness of the lesion, type of melanoma, location, and other prognostic characteristics.

With these accumulated data, justification for END can be established in situations with a high risk of occult regional metastases in which the pattern of lymphatic drainage can be predicted. That includes patients with lesions 1.5 to 4.0 mm thick (T3 or level IV or V) arising from most sites in the head and neck. Consideration should be given to preoperative

lymphoscintigraphy, particularly in scalp, ear, and facial lesions. The decision to perform an END for patients with lesions 0.75 to 1.5 mm thick (T2 or level III) needs to be individualized, with dissection advisable in most situations, if any one of the following conditions exist: thickness approaching 1.5 mm, ulceration, nodular type, or location at a high-risk site (see box).

Box: Indications for elective neck dissection in patients with head and neck melanoma

Melanomas 0.75 to 1.5 mm thick in BANS areas or other high-risk sites.

Ulcerated or nodular melanomas 0.75 to 1.5 mm thick.

Melanomas 1.5 to 4.0 mm thick in any site with predictable lymphatic drainage.

Thick melanomas (greater than 4.0 mm) for local and regional tumor control.

Any melanoma more than 0.75 mm thick when inadequate patient follow-up is expected.

For patients with thick (greater than 4.0 mm) melanomas of the head and neck, prognosis is poor because of the high rates of distant metastases associated with these lesions. Balch and associates (1985c) have estimated that the risk of occult distant and regional metastases approaches 80%. In these patients, END is unlikely to alter the overall prognosis but does offer the opportunity of providing benefit in terms of local and regional tumor control and providing staging information that may be useful in planning adjuvant treatment strategies.

Some of the controversy surrounding END has been stimulated by concern on the part of surgeons and patients regarding the morbidity and deformity associated with classic radical neck dissection. Because of the increasing recent proof for the efficacy of modified neck dissection in control of regional micrometastases from head and neck squamous carcinomas (Bocca et al, 1984; Lingeman et al, 1977; Molinari et al, 1980) and selected melanomas (Byers et al, 1980), complete lymphatic dissections that preserve nonlymphatic neck structures (such as the spinal accessory nerve, sternocleidomastoid muscle, and internal jugular vein) may be an alternative consideration. Such dissections offer the potential for securing a favorable functional and cosmetic result yet eradicating microscopic tumor deposits that, if allowed to multiply, could jeopardize long-term prognosis.

Reliable statistical data substantiating the benefit of END in head and neck melanomas are currently lacking. Such data can be derived only from prospective randomized trials comparing WLE alone to WLE with END, in which treatment groups are balanced with respect to tumor thickness and other known prognostic variables. Until the results of such trials are known, the role of END will undoubtedly remain controversial.

In-transit metastases

In-transit metastases result from melanoma cells trapped in lymphatics and represent subcutaneous or intracutaneous metastases. As such they are associated with regional lymph nodal involvement and have a similar poor prognosis. This is reflected by the inclusion of in-transit metastases in the American Joint Committee (AJC) staging system classification for nodal involvement (see Table 25-2). Optimal treatment has not been defined but varies according to the number and location of the metastases. When feasible, local aggressive surgical resection is more effective than systemic chemotherapy. Surgical excision, either in continuity with primary resection and node dissection or as a separate procedure for recurrent lesions, should be considered when the number of metastases is small and their location is amenable to resection. Other methods of treatment used in the past have included radiation therapy, intralesional immunotherapy with agents such as bacillus Calmette-Guerin (BCG) or dinitrochlorobenzene (DNCB), cryotherapy, and systemic or regional chemotherapy infusions.

Selected sites

External ear

The ear is an uncommon site for a melanoma. Of the 399 patients with melanomas reported by Gussack and associates (1983), only 11% had primary melanomas of the ear, which is similar to both the UCLA (Storm et al, 1978) and the NYU experiences (Roses et al, 1980). Conley has reported 16% incidence of ear melanoma among 223 patients with head and neck melanoma (Conley, 1991). Lesions of the helical rim are the most common and have a much better prognosis than more central ear lesions have. Modified wedge excision is generally adequate for this rim lesions and achieves a better cosmetic result than does an auriculectomy (Storm et al, 1978). Lesions more than 1.5 mm thick (levels IV and V) are frequently nodular or ulcerated and generally require at least a partial auriculectomy. Preservation of a portion of the upper helix is beneficial in patients who wear eyeglasses. It also aids in the stabilization of a prosthesis; however, a total auriculectomy allows the fitting of a cosmetically acceptable total auricular prosthesis. Central ear lesions (of the canal, concha, tragus, and antitragus) have a poorer prognosis (Gussack et al, 1983), and because of their location they frequently necessitate wide cartilage resection and skin grafting or total auriculectomy.

Decision making for therapeutic or elective dissection of the regional lymph nodes should take into consideration the regional lymphatic drainage of the various portions of the ear and the prognostic risk associated with the lesion (Fig. 25-6). Lymphoscintigraphy should be utilized preoperatively for lesions with ambiguous drainage. The incidence of nodal metastases varies from 20% to 60%, depending on the lesion's thickness (Byers et al, 1980). The lymphatics from the external ear drain anteriorly to the preauricular and periparotid nodes, posteriorly to the postauricular lymph nodes, and inferiorly to the subdigastric lymph nodes. Dissection of these lymph node groups in continuity with neck dissection is recommended and generally involves a superficial parotidectomy with facial nerve preservation (Harris and Hinckley, 1983). If involvement of parotid lymph nodes is evidence, the deep lobe of the parotid should also be removed. In any case, if an END is performed, the periparotid lymph nodes should be included, since they are a primary nodal station and the accurate preoperative clinical assessment of positive parotid nodes is poor (Byers et al,

1980).

Scalp

After the face, the scalp and neck are rated as the most common areas for head and neck melanomas (Batsakis, 1979; Conley, 1991; Gussack et al, 1983). Tumors arising in these areas, particularly those arising in the BANS areas, are relatively aggressive tumors and may go undetected for long periods of time, particularly in men with abundant hair coverage. Scalp melanomas are associated with high occult metastatic rates and a poor prognosis, and an END should be considered for any lesion more than 0.75 mm thick. Conley (1963) reported a 14% 5-year survival for patients with scalp melanoma who were treated with delayed neck dissection, compared with 25% survival for those treated with elective dissection.

The lymphatic drainage for scalp lesions anterior to the pinna includes parotid, submandibular, submental, and upper jugular lymph nodes. Lesions posterior to the pinna drain to occipital, postauricular, and posterior cervical or jugular nodes. The lymphatics do not pass through the pinna, and therefore auriculectomy is not required (Franklin et al, 1976).

The posterior scalp lesions are difficult to manage because lymphatic drainage can be either ipsilateral or bilateral (Fisher et al, 1983; Goepfert et al, 1980). Bilateral posterior neck dissection with WLE may be necessary for midline lesions. Thin (0.75 mm or less) temporal and parietal scalp lesions are treated like other areas - with WLE alone. Temple lesions more than 0.75 mm thick require wide excision in combination with a superficial parotidectomy and in-continuity neck dissection (Harris and Hinckley, 1983). Melanomas arising from the posterior or lateral neck skin are also candidates for an END, since their prognosis is poor and the neck lymphatics are immediately available for dissection at the time of primary excision. For scalp or neck lesions located near the midline or those with ambiguous drainage, lymphoscintigraphy should be used to delineate regional node stations that drain the primary tumor (Bennett and Lago, 1983; Normal, 1991; Wanebo et al, 1985).

Face

Of over 800 patients with head and neck melanoma reported by Conley (1991), over 30% had lesions arising on the face. Lesions of the face require adequate surgical control with minimal cosmetic disfigurement. Wide local excision with primary closure is possible in many cases. Of significant importance have been the recent observations that excessively wide margins are unnecessary in most primary excisions. Margins of 1 to 2 cm are generally adequate and leave satisfactory cosmetic results. Regional node dissection can be considered for thin (0.75 to 1.5 mm) intermediate-thickness lesions when the lymphatic drainage can be predicted. In most cases node dissection is reserved for lesions more than 1.5 mm thick, with the addition of a superficial parotidectomy for preauricular and malar lesions (Gussack et al, 1983). Resection of the deep lobe of the parotid and in-continuity neck dissection are recommended if clinically obvious superficial parotid metastases exist. Local flaps are generally used to reconstruct large facial defects because they provide better color and texture match than do skin grafts.

Nose

The nose is an uncommon site for a melanoma, making up only 2% to 5% of head and neck melanoma (Conley, 1991). Metastases may spread bilaterally to facial, parotid, or cervical lymph nodes. Of 17 patients who were followed over a 34-year period, 29% survived 5 years (Byers et al, 1982). Only 20% of the patients developed histologically positive lymph nodes, and all died of the disease. Lesions up to 1.5 mm thick require wide excision that includes the underlying cartilage but leaves the inner lining intact. Thicker lesions should be treated with full-thickness excision and local flap reconstruction. Because of unpredictable lymphatic drainage patterns, a neck dissection and/or superficial parotidectomy is reserved for subsequent nodal metastases (Byers et al, 1982).

Eyelid

For all but thick lesions, excision of full-thickness skin down to the tarsal plate or orbital septum is recommended. Lid margins should be preserved (provided that they are not involved) and the defect repaired with a full-thickness graft (Harris and Hinckley, 1983). Wedge excision with 1.0 cm skin margins is sufficient if the lid margin is involved. Lesions more than 1.5 mm thick require excision of the eyelid to the orbital rim. Extension through the full thickness of the eyelid into the periorbital fat is sometimes seen in advanced lesions and usually requires exenteration of the orbit (Harris and Hinckley, 1983).

Mucosal

In general, the treatment of mucosal melanoma has not been uniform, therefore treatment results are difficult to interpret. Most published reports suggest a dismal 5-year survival rate of 10% to 15% (Conley, 1989; Hoyt et al, 1989; Stern et al, 1991). The majority of head and neck melanoma patients seek treatment with localized disease, however, 12% to 24% of patients have regional node metastases when they seek treatment (Hoyt et al, 1989; Stern et al, 1991). The only clinical finding that has definite prognostic significance is the presence of the distant metastases at the time of diagnosis.

The vast majority of patients with local disease undergo surgery as the initial treatment. In the past, radiation therapy was used only in patients with uncertain surgical margins or with locally recurrent or unresectable disease. It has been documented that local control may be increased by adjuvant radiation therapy, especially in patients with questionable surgical margins (Snow et al, 1978).

Not surprisingly, the issue of node dissection for the control of subclinical regional disease in cases of mucosal melanoma of the head and neck remains unclear. As the status of the regional lymph nodes does not appear to affect survival, elective dissection of the neck is probably not warranted (Stern et al, 1991). Surgery plus adjuvant radiation therapy provide the greatest benefit to patients with either regional metastases or large bulky primary disease. Chemotherapy has generally been reserved for patients with systemic disease and has not enhanced survival or local-regional control rates.

Patients with mucosal melanoma usually die of a combination of local recurrence and distant metastases (Hoyt et al, 1989). Distant disease is associated with local recurrence in greater than 90% of the cases (Blatchford et al, 1986). The average time to first local recurrence is usually 9 to 12 months; once local disease recurs, distant metastases are usually diagnosed within 3 months.

Other Treatment Modalities

Data regarding adjuvant treatment approaches for melanomas are contradictory and difficult to interpret. This is because few studies have been prospective randomized trials, and treatment regimens consisting of chemotherapy, immunotherapy, or chemoimmunotherapy have varied greatly among studies. However, because histologic tumor thickness and pathologic staging of neck disease can identify groups of patients at high risk for recurrence, interest in adjuvant treatment strategies remain high.

Adjuvant chemotherapy

The lack of effective drugs has limited the development of effective adjuvant chemotherapy. The most active drug has been dacarbazine, which has a response rate of only 20% to 30%. The use of other drugs such as the vinca alkaloids and the nitrosoureas in combination with dacarbazine has failed to improve response rates substantially (Luce, 1975).

Initial trials of adjuvant chemotherapy or chemoimmunotherapy had encouraging results in patients at high risk of relapse (Mastrangelo et al, 1979; Wood et al, 1978). However, these trials either used historical control groups or consisted of too few patients to allow reliable interpretation. The results of adjuvant chemotherapy reported from large, prospective randomized trials have been uniformly disappointing (Balch et al, 1984; Fisher et al, 1981; Hill et al, 1981; Jacquillat et al, 1982; Veronesi et al, 1982a). In fact, in a well-done randomized trial conducted by the Central Oncology Group, survival and disease-free intervals were significantly worse in patients receiving adjuvant dacarbazine compared with controls (Hill et al, 1981). The lack of benefit from adjuvant chemotherapy reported in prior trials has been consistent even when subgroups of patients categorized by various known prognostic variables were analyzed. Until newer drugs or regimens with higher rates of tumor response are developed, adjuvant chemotherapy approaches should be reserved for investigational protocols or carefully designed clinical trials. Current survival data do not support routine use in patients with limited resectable disease.

This viewpoint is further supported by the observation that resectable disease is frequently associated with relatively long disease-free intervals. The toxicity and morbidity that frequently accompany rigorous chemotherapy argue against prolonged adjuvant chemotherapy, since the potential benefit is doubtful and further impairment in quality of life is highly undesirable.

Chemotherapy for advanced disease

Once a melanoma has disseminated, the prognosis is dismal. If solitary metastases can be resected, a median survival of 8 months can be expected (Fuen et al, 1982). However systemic dissemination or unresectable disease is associated with a survival of less than 6

months (Balch et al, 1983; Fuen et al, 1982).

The role of chemotherapy in the management of disseminated disease is limited. Because response rates with existing drugs and combination regimens are poor, a major consideration must be patient quality of life and palliation of symptoms. Outcome is not altered by intensive chemotherapy, and therefore decision making must take into account drug toxicity versus objective benefit. In general, asymptomatic patients need not be treated; however, when symptoms occur, a trial of drug therapy may be warranted.

Several factors are useful in predicting tumor response to chemotherapy. The sites of metastases are important, since skin and soft tissue disease responds more favorably than visceral tumor involvement. Female sex and good patient performance status have also been suggested as favorable prognostic factors for response to chemotherapy, but a recent review indicates that these factors are more closely associated with survival than tumor response (Presant and Bartolucci, 1982). Prior treatment with chemotherapy significantly reduces the probability of subsequent tumor response. Although it has been reported that responders to chemotherapy survive longer than nonresponders do (Constanza et al, 1977), the overall impact of chemotherapy on survival is minimal, and these differences probably reflect differences in tumor biology and other prognostic variables rather than any effect of chemotherapy. A major question has been whether any combination of drugs yields better results than the best single agent (dacarbazine) alone. Recently, the addition of tamoxifen to drug regimens, dose intensification, chemotherapy combined with hyperthermic perfusion, and combinations of chemotherapy with alpha interferon and interleukin 2 have shown improved response rates, although duration of response has generally not increased substantially.

Because a great need exists for development of newer, more active drugs, and because standard drugs yield such poor results, some rationale exists for trials of new agents in previously untreated patients. Patients with disseminated melanomas represent a valuable resource for new drug development, and this consideration, along with the patient's wishes and the clinical setting may be important in deciding whether to use chemotherapy.

Adjuvant radiation therapy

Melanomas have traditionally been considered resistant to radiation therapy. However, much of the historical data supporting this opinion have lacked a scientific basis. Not until the late 1950s, when Dickinson (1958) reported increased survival rates with postoperative high-dose radiation therapy, was the potential benefit of adjuvant therapy of melanoma suggested. Most of the prior data regarding the radioresistance of melanoma were based on treatment experiences with conventional fractionation schemes in patients with advanced disease. In the early 1970s work with melanoma cell lines in tissue culture indicated that the observed radioresistance of melanomas was the result of a broad shoulder on the cell survival curve (Harwood and Cummings, 1981). It was subsequently shown that large-dose/fraction radiation therapy could produce higher response rates than conventional 200-cGy daily fractions (Johanson et al, 1983). Furthermore, melanoma cells are believed to have a large capacity for repair of sublethal radiation damage, and this may partly explain prior reports of radioresistance for these tumors.

In recent years a number of reports have demonstrated tumor regression with large-dose/fraction radiation therapy for cutaneous and distant melanoma metastases (Brascho, 1985). Overgaard (1980) reported increased response rates in patients with stage I and II melanomas using fraction sizes greater than 800 cGy as compared with less than 400 cGy/fraction. Responses, however, did not correlate with the total radiation dose. Doss and Memula (1982) reviewed radiation response rates for stage III melanomas. Bone and cerebral metastases were the most common sites treated. Although the overall complete response rate was only 37%, a 67% response rate was noted with regimens of more than 400 cGy/fraction. Harwood and Cummings treated 54 patients with high-dose/fraction radiation therapy on days 0, 7, and 21, using a daily dose fraction of 800 cGy (Johanson et al, 1983). They divided their patient population into three clinical categories of disease: microscopic residual melanoma following surgery, gross residual melanoma after surgery, and recurrent melanoma. Local control rates were improved by irradiation; however, a high rate of systemic failure at other sites was noted, which emphasizes the need for more effective systemic therapy for melanoma.

Although recent reports of improved survival with radiotherapy for melanomas have been encouraging, the only published trial of adjuvant radiation therapy had negative results. Creagan and associates (1979) showed no survival benefit for adjuvant radiation therapy after tumor resection in a retrospective study of patients with head and neck melanomas. Similarly, no benefit was demonstrated in patients with minimal residual melanomas, and furthermore, there were no survival differences between patients with gross residual tumor and those with no clinical evidence of disease at the start of radiation therapy. Unfortunately, in this study the dose per fraction of radiation was 200 cGy and the lack of benefit may have been related to the low dose/fractions used.

Most reported studies consist of selected patients in whom the anatomic site, tumor extent, or risk of operation prohibited complete resection of the melanoma. In such instances local excision followed by large-dose/fraction radiation treatments might be considered when wide excision is either hazardous or grossly mutilating.

Radiation therapy has also been found to offer effective palliation for selected melanoma patients with distant metastases. Hilaris and associates (1963) reported 73 patients who received 139 courses of external radiation therapy for distant metastases. In their series, measurable response were obtained in 57% of patients with osseous, cerebral, and visceral metastases. Equally favorable results were noted in patients with skin and lung metastases. A number of investigators have explored irradiation therapy in combination with hyperbaric oxygen, hyperthermia, chemotherapy, immunotherapy, or neutron-beam irradiation. The results have been encouraging but must be considered preliminary. Many of these experimental combined-treatment regimens are not widely available currently and thus are not as promising for study as simple alteration of the fractionation regimen.

Adjuvant immunotherapy

Immunology of melanomas

The immunologic aspects of melanomas have fascinated clinicians and basic scientists for decades. A number of observations have suggested that the immune system plays a role in the outcome of this disease. Spontaneous regressions of both primary and metastatic lesions have been well documented and imply that immunologic mechanisms are responsible (Everson, 1964; Sumner, 1980). In addition, the long disease-free intervals that frequently characterize the natural history of melanoma suggest that host mechanisms may be operative in suppressing tumor growth. Melanoma also appears to be one of the more highly antigenic human malignancies, since host immune responses to tumor cells or extracts can be readily detected in vivo and in vitro. Evidence for this is based on demonstrations of complement-fixing antibodies to human melanoma antigens (Gupta and Morton, 1975), autologous serum cytotoxicity (Lewis et al, 1969), autologous antibodies to cultured melanoma cells (Carey et al, 1976), delayed hypersensitive skin reactivity to tumor extracts (Bluming et al, 1972; Hollinshead et al, 1974) and in vitro lymphocyte reactivity to melanoma extracts (Cochran et al, 1972; Mavligit et al, 1974). Taken together, these data indicate that tumor-associated melanoma antigen exist and that a patient's immune system can frequently recognize and respond to them.

In most studies decline in immune reactivity was noted with tumor dissemination. Other studies suggested that parameters of immunity correlated with clinical outcome after treatment (Bernengo et al, 1983; Eilber and Morton, (1970; Lee et al, 1982); however, such correlations have not been consistently demonstrated. The majority of evidence suggests that immune competence is relatively intact in early melanomas, and that depression in immune response is only regularly detected in advanced or disseminated disease. Although the cellular mechanisms responsible for tumor rejection or for the escape of tumor cells from immune recognition are not clearly understood, existing data on the immune response have prompted early optimism that non-specific stimulation of the immune system may be of survival benefit in melanoma, particularly in those patients in whom immune competence can be demonstrated.

The recent discovery of regulating cytokines belonging to the class of interleukins has accelerated interest in the immunobiology of cell-mediated tumor immunity. In particular, interleukin-2 has been shown to stimulate the proliferation of cytotoxic lymphocytes termed lymphokine activated kill cells (LAK) and natural kill cells (NK cells). These cells are felt to be critical in cell-mediated tumor cytotoxicity. With the use of recombinant human interleukin-2, autologous LAK cells can be grown in large numbers in vitro and can be administered to patients. These discoveries have opened a new and exciting frontier of adoptive immunotherapy for patients with melanoma.

Adjuvant immunotherapy trials

For perhaps no other solid malignancy have the concepts of immunotherapy held such strong theoretic appeal as they have for melanomas. Early animal-model evidence of the efficacy of immunotherapeutic approaches for highly antigenic tumors, together with demonstrations of host immune reactivity to tumor-associated antigens in patients with

melanoma, led to widespread clinical experimentation of immunotherapeutic and chemoimmunotherapeutic strategies. The rationale for these approaches was further supported by correlations of immune response with prognosis, which suggested that therapeutic benefit might be derived by immune stimulation in patients with localized disease who were at high risk of relapse from occult microscopic disease. Unfortunately, the interpretation and comparison of data from extensive clinical experiences with immunotherapy have been difficult because many trials were not adequately controlled or consisted of small numbers of patients treated with a variety of immunotherapeutic agents and schedules.

The largest experience with nonspecific immunotherapy in melanoma has been with the bacterial immunostimulant bacillus Calmette-Guerin (BCG). Of significant importance were early observations that the injection of BCG into intradermal melanoma nodules could cause regression not only of the injected nodules, but of distant noninjected cutaneous lesions (Morton et al, 1970, 1974). However, injection of visceral or subcutaneous tumors was not equally effective. A large number of trials of systemic and regional BCG were subsequently undertaken. Benefit from BCG as a postsurgical adjuvant was suggested in regional node-positive patients with head and neck melanomas (Eilber et al, 1976) and when used in combination with dacarbazine in disseminated disease (Gutterman et al, 1974). However, the design of these trials suffered from the use of historical or nonrandomized controls in which comparability of tumor extent and other prognostic factors could not be ensured. The results of randomized trials of BCG immunotherapy for sites including the head and neck have uniformly shown no significant improvement in relapse rates or survival among treatment arms (Constanzi, 1978; Cunnnigham et al, 1978; Morton et al, 1978; Pinsky et al, 1978; Strechi et al, 1985).

The various observations of tumor regression after intralesional BCG offer an additional form of therapy that is often overlooked for patients with recurrent metastatic disease. Best candidates for such treatment are those patients with intradermal metastases. Long-term remissions have been reported (Bauer et al, 1990). More recently, additional interest has been shown in intralesional alpha-interferon. A response rate of 45% for injected metastases and a rate of 21% for noninjected skin metastases has been reported in patients with advanced disease (Von Wussaw et al, 1988). Although patients occasionally achieve complete regressions of tumor, only a minority of patients benefit, and the results are temporary. Similar regression rates have also been achieved with the systemic administration of alpha-interferon (Creagan et al, 1986). Thus although responses are few, these forms of therapy show activity, occasionally result in prolonged remissions, and could be considered in selected patients.

Despite the negative results of most trials, great interest in the immunotherapy of melanoma persists. A variety of adjuvant immunotherapy strategies have been studied including use of levamisole, chemoimmunotherapy, and active specific immunotherapy. None have yet shown definite benefit in the adjuvant setting, although studies continue to test melanoma vaccines as adjuvant therapy (Bystryn, 1988; Wallack et al, 1989). Levamisole has been reported to be beneficial as an adjuvant, however, study results have been controversial. Quirt et al (1991) reported decreased death and recurrence rates with levamisole in a large 4-arm trial comparing levamisole to BCG, BCG and levamisole, or observation. In contrast, Spitler (1991) has shown no differences in survival or recurrence in a randomized blinded adjuvant study of levamisole versus placebo. Negative results with levamisole have also been

reported in another small randomized study (Loutfi et al, 1987).

Specific immune stimulation with melanoma antigens using either neuraminidase-treated tumor cells or partially purified antigens has not been thoroughly explored. Preliminary encouraging results have been reported, but need to be confirmed in prospective randomized studies (Hollinshead et al, 1982; Sielger et al, 1979). Some studies have reported tumor remissions with treatments using autologous, irradiated tumor cell vaccines (Berd et al, 1990). However, adjuvant treatment with viral oncolysates of human melanoma cell lines has failed to show significant disease-free survival benefit (Plager et al, 1990). In some investigations, cyclophosphamide has been added to try and increase the induction of the immune response by elimination of suppressor lymphocytes. This has resulted in enhanced development of delayed hypersensitivity skin test responses to autologous melanoma cells (Berd and Mastrangelo, 1988). Other studies have reported some remissions with the use of monoclonal antibodies directed against melanoma-associated cell surface glycoproteins (p97) or ganglioside antigens such as GD2, GD3, or GM2 (Mitchell et al, 1990; Morton et al, 1991; Vadhan-Raj et al, 1988). In all cases, these approaches are highly experimental and must be limited to well-designed research studies.

Equally promising is the development of specific in vivo imaging of melanomas using monoclonal antibodies. Such imaging has been successfully performed in both animal models and human subjects using radiolabeled monoclonal antibodies (Carrasquillo et al, 1984; Mann et al, 1984). Highly selective binding of monoclonal antibodies to disseminated melanoma nodules has also been demonstrated in phase I clinical trials, as assessed after immunohistologic examination of biopsy specimens (Oldham et al, 1983). These preliminary observations offer encouraging evidence that such techniques may be useful not only for diagnostic imaging but for treatment approaches using antibodies labeled with therapeutic isotopes or cytotoxic agents conjugated to monoclonal antibodies. Further, improved diagnostic and prognostic information may be derived through immunohistologic studies of tumor sections using highly specific antisera or monoclonal antibodies (Atkinson et al, 1984; Nakajima et al, 1982).

Adoptive immunotherapy

In 1976, Morgan, Rusetti, and Gallo (Farrar et al, 1982) reported the isolation of a T cell growth factor that was found to be important in the induction and proliferation of a subset of nonspecific "killer" lymphocytes. This lymphokine, later termed interleukin-2 (IL-2), is now known to be a member of a large family (interleukins) of related cytokines that modulate and regulate a variety of hematopoietic and immunologic cell functions. IL-2 has been extensively characterized and is now produced in large, highly purified quantities through recombinant DNA technology. Seminal in vitro and animal model studies using IL-2 by Rosenberg and associates (1985) and others (Lafreniere and Rosenberg, 1985; Mule et al, 1986) demonstrated in vitro proliferation of lymphokine activated "killer cells" (LAK cells) that when adoptively transformed to tumor bearing animals, resulted in regression of established tumors and experimental metastases. In subsequent human trials in patients with advanced metastatic melanoma, therapy with in vitro cultivated autologous LAK cells combined with recombinant IL-2 or recombinant IL-2 alone resulted in significant tumor regression in 20% to 35% of patients (Rosenberg et al, 1987, 1989; Sondel et al, 1988). This treatment was associated with substantial toxicity and was generally reserved for younger

patients without evidence of brain metastases. Durable complete responses have been seen occasionally and have prompted investigations of combinations of other cytokines (Rosenberg et al, 1989) and trials of cultured autologous tumor infiltrating lymphocytes (TIL) that have been shown in vitro to be 50 to 100 times more potent than LAK cells (Rosenberg et al, 1988). With TIL cells, response rates as high as 60% have been reported in metastatic melanoma (Rosenberg et al, 1988). Recently, these efforts have been combined with gene therapy through the introduction of the gene coding for tumor necrosis factor into TIL (Kasid et al, 1990; Rosenberg et al, 1990). Tumor necrosis factor secretion by these transduced TIL is increased 100-fold and should result in enhanced effectiveness of these cells.

Toxic side effects associated with high dose IL-2 therapy include fever, hypotension, malaise, nausea, vomiting, fluid retention, confusion, and liver/renal dysfunction. Despite these toxicities, biologic approaches to the treatment of advanced melanoma represent attractive alternatives to conventional palliative therapy. However, their usefulness is limited by the necessity for extensive immunologic research facilities and complex techniques for expanding and maintaining large numbers of cultured lymphocytes.

Cytogenetics

One of the most exciting frontiers of knowledge in melanoma is the exploration and discovery of those basic genetic changes that lead to malignant melanocyte behavior. Although some cytogenic changes in cancer may be conserved across tumor types, many changes appear to be both tissue specific and extremely variable. Our basic knowledge of the process of malignant transformation in melanoma has expanded to include ultraviolet light-induced changes that result in expansion of suppressor T cells, inactivation of Langerhans' cells, keratinocyte damage with release of cytokines that stimulate melanocytic growth and oncogene function, direct DNA damage, phenotypic changes in melanocytes and ultimately clonal genetic changes. These concepts have led to an appreciation that malignant change is a continually evolving process of accumulated genetic damage. Studies of chromosomal alterations in melanoma are of considerable importance because alterations found consistently may represent locations of growth regulating genes and could have important diagnostic and prognostic implication. Recent cytogenetic analysis of premalignant and primary melanomas have implicated specific regions on chromosomes 9 and 10 (9p, 10q) as possibly associated with early malignant change (Cowan et al, 1988; Parmiter et al, 1988). However, every little other information exists about cytogenetic changes in common nevi, dysplastic nevi, or other atypical moles. More work has been directed at studies of metastatic melanoma where selected cytogenetic changes have been associated with prognosis (Trent et al, 1990a). Patients with melanomas showing abnormalities of chromosome 7 or 11 had significantly shorter survival compared with patients without these structural chromosome abnormalities. Numerous other chromosomal abnormalities were detected in over 95% of tumors studied (particularly on chromosomes 1, 6, 9, and 21), however, these other karyotypic changes did not correlate with survival. The biologic relevance of these various specific chromosomal abnormalities is unclear, however, certain consistently identified changes may correlate with regions known to affect cellular growth. A frequent finding in melanoma was the loss of the long arm of chromosome 6 (Trent et al, 1990b). Studies to determine if a tumor suppressor gene might map to this region were performed by directly inserting a normal chromosome 6 into melanoma cell lines. This resulted in a dramatic change of in vitro morphology and suppressed tumorigenicity compared with parental lines. Although cytogenetic studies in

melanoma are in their infancy, further evaluation of the basic genetics of melanoma should enhance our understanding of the progression of this cancer and will be useful in determining prognosis and therapy.

Prevention

The contrasting survival rates between patients with metastatic and those with nonmetastatic melanoma and the nearly universal cure of patients with noninvasive (Clark's level I) or thin melanoma, underscore the importance of prevention and early detection in this malignancy. Because predisposing environmental factors, and in some cases genetic factors, have been clearly implicated, high-risk populations and individuals can be identified. Routine, noninvasive screening and increased public awareness should be promoted widely. Whether such interventions can affect survival rates is currently under study (Koh et al, 1990b; Miller et al, 1990; Rigel et al, 1986). For screening to be effective, physicians need to be able to recognize the varied clinical presentations of melanoma. Prevention rather than early recognition is also an attractive goal. Avoidance of excessive sun exposure and routine surveillance skin examinations for patients with dysplastic nevi and early excision of atypical pigmented lesions is warranted. With increasing knowledge of cell biology, it may be possible in the not too distant future to regulate on the genetic level those tumor initiators or promoters that are involved in melanoma carcinogenesis. As evidenced by tumor regression after adoptive immunotherapy, indirect approaches through manipulation of the immune system may also hold promise for prevention strategies.

Survival

Much of the survival data regarding head and neck cutaneous melanomas have been presented in the preceding sections. It is clear that overall survival of patients with localized melanomas relates directly to tumor thickness and a number of other prognostic variables, such as the melanoma type (nodular versus others), ulceration site (scalp and posterior neck versus others), and other less important variables, such as age, sex, and lymphocytic infiltration. Differences in survival rates tend to equalize after controlling for thickness at time of presentation. Thus the belief that lentigo maligna type is inherently less ominous than other types has been questioned (Ackerman, 1980; Koh et al, 1984). The reported overall 5-year survival figures vary from 30% to 60%, depending on case mix. Emerging new concepts have included observations that 5-year survival figures may not be as reliable as 10-year figures when estimating the risk of failure in patients with localized melanoma and that the width of the resection margins is not as prognostically critical as was previously believed.

It has been consistently reported that the most important factor in survival is the presence of regional metastases. In localized melanomas tumor thickness is directly related to occult regional metastatic rates. The prognostic importance of tumor thickness is certainly related to the association of thickness with occult regional metastatic rates, but it may also be independently associated with local and distant relapse rates. Some disagreement remains as to whether the level of invasion and the tumor thickness remain prognostically important once regional metastases have occurred (Day et al, 1981; Storm and Eilber, 1981). Irrespective of this controversy, it is clear that once clinically evident regional metastases have occurred, distant dissemination exists in 70% to 97% of patients, and 5-year survival is reduced to between 10% and 20%. Five-year survival rates for patients with localized

melanoma are consistently reported as 70% to 80% when neck nodes are negative and 15% to 25% when neck nodes are positive (Ballantyne, 1970; Byers et al, 1980; Gussack et al, 1983; Sim et al, 1978; Storm and Eilber, 1981).

In most reports, the percentage of patients alive at 5 years who had occult, histologically positive nodes resected is slightly better (by 5% to 15%) than those with clinically and histologically positive nodes (Batsakis, 1979; O'Brien et al, 1990). Statistical proof of better survival in the former group is lacking, however, because of the small numbers of patients in most reports and other problems inherent in retrospective comparisons of groups that might differ in important prognostic variables. Because truly effective treatment for disseminated disease is lacking and clinically positive nodes portend distant dissemination, treating localized disease in an aggressive fashion appears justified when the risk of occult regional metastases is high. Finally, because of the documented prognostic information provided by accurate pathologic staging, it is of critical importance that trials of adjuvant treatment strategies in high-risk patients include histologic assessment of regional nodes to interpret survival end results reliably.

Conclusion

Melanomas are capricious malignancies with a reputation for aggressive growth and dissemination, which might be undeserved if the curability of early, thin lesions is considered. Advances in the treatment of melanomas have been derived primarily because of a better understanding of the natural history of the disease and the improved definition of prognostic factors. Because the incidence of melanomas appears to be increasing dramatically, it is crucial that lay and professional educational efforts be directed toward early recognition and diagnosis.

Accumulated data on the natural history of head and neck melanomas have provided reliable identification characteristics for nevi that may be dysplastic or frankly malignant. Advances in histologic staging have allowed improved prognostication of individual lesions, but continued interest and cooperation of surgeons and pathologists are required. Significantly less disfiguring and debilitating local resections for head and neck melanomas have been shown to be feasible in thin (less than 0.75 mm) lesions; however, controversy remains regarding the survival benefit of regional node dissections for intermediate-thickness localized melanomas. Nevertheless, prognostication is enhanced by histologic determination of the presence of regional metastases and may in the future define a population of patients that could benefit from effective adjuvant therapy.

The results of current chemotherapy and immunotherapy regimens for patients with melanomas have been more promising than in recent years. Further basic research into the biologic mechanisms of melanocyte differentiation and growth regulation should enhance the further development of chemoprevention strategies. The development of sophisticated immunologic probes that use monoclonal antibodies, tumor vaccines and new information regarding gene regulation offer the promise of new therapeutic approaches for melanomas in the future.

For individual patients the diagnosis of melanoma still connotes a dreaded prognosis that demands sensitive, knowledgeable counseling and skilled treatment by thoroughly informer surgical oncologist. It is hoped that the summary information contained in this chapter will contribute to the education of physicians interested in the management of head and neck melanoma.