

MALIGNANT MELANOMA

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Once an uncommon cancer, cutaneous melanoma is rapidly increasing in incidence throughout the world. Melanoma now accounts for approximately 3% of all cancers diagnosed in the United States.¹ The reasons for this rapidly increasing incidence remain unclear but may be related to the reduction in the ozone layer.² The prognosis for patients with melanoma is directly related to the depth of invasion of the primary lesion and to initial treatment. When diagnosed early in the biologic course of the disease, melanoma is readily cured by simple wide surgical excision. However, once melanoma metastasizes, no treatment currently available reliably affects the course of disease. For this reason, physicians must be cognizant of the classic clinical signs associated with melanoma (change in color, recent enlargement, nodularity, pruritus, ulceration or bleeding) and recognize the more subtle clinical characteristics, such as irregular or angular borders or variations in color. These characteristics often signal minimally invasive, early, and curable melanomas.

HISTORY OF MELANOMA

Cancer has plagued mankind since antiquity. In Peru, paleopathologists examining mummies from the 4th century BC found diffuse metastases in the bones of the skull and extremities as well as rounded melanotic masses in the skin.³ The first accredited description of malignant melanoma appeared in the writings of Hippocrates (460–375 BC), followed by that of the Greek physician Rufus of Ephesus (60–120 AD). Over the centuries, many other physicians have described pigmented malignant lesions of the skin that presented with distant metastases. It was not, however, until the 1800s that significant gains were made in the description and treatment of human malignant melanoma.

In an unpublished paper presented to the Faculté de Médecine in Paris in 1806, Laennec discussed “la melanose,” describing its color as “melanotic.”⁴ The first description of the genetic basis of melanoma was offered by Norris in 1820.⁵ Carswell⁶ used the medical term “melanoma” in 1838 to describe pigmented malignant lesions of the

skin. In 1858, Pemberton⁷ advocated and performed wide and deep radical excision for melanoma. This concept, which developed a full century before becoming the accepted surgical technique, also encouraged the removal of all implicated lymph nodes by groin dissection. In 1907, Handley⁸ again advocated en bloc excision of melanoma with wide margins, following the principle of dissection in continuity.

EPIDEMIOLOGY AND ETIOLOGY

During the past decade in the United States and Canada, the incidence of melanoma has increased at a rate exceeding all other malignant neoplasms except lung cancer in women. At present, the incidence increases by 5 to 7% yearly, doubling the population risk every 10 to 15 years. The age-adjusted annual incidence in the U.S. is approximately 10 per 100,000, although some geographic areas have a greater incidence. Australia has the highest incidence of melanoma in the world: approximately 17 per 100,000 per year.

According to the American Cancer Society, 47,700 new cases of melanoma will be diagnosed in the United States in 2000, and there will be approximately 7,700 deaths from the disease.¹ Current projections indicate that 1 in 75 individuals will develop cutaneous melanoma (lifetime risk). Melanoma is now more common than Hodgkin's lymphoma and primary tumors of the brain.

Although the etiology of melanoma is unknown, case-control studies have identified a number of characteristics present in populations at high risk for developing melanoma.^{9,10} These studies have shown that melanoma is largely a disease of individuals with fair complexions. Individuals with red or blond hair and fair skin, who historically do not tan well, burn easily even after minimal exposure, or have a history of severe sunburn are at substantially higher risk of developing melanoma than more darkly pigmented, age-matched controls. Individuals with an increased number of nevi or a tendency to develop freckles are also at increased risk for developing melanoma.¹⁰

Several observations suggest that ultraviolet light may be a critical factor leading to the development of cutaneous melanoma.^{11,12} There is an increasing incidence of melanoma in fair-complected populations and a correlation with increasing distance from the poles. Adults who migrate to sunny climates are at less risk of developing melanoma than similar individuals who were born there, suggesting that duration of exposure to ultraviolet (UV) radiation is important in the development of melanoma. Freckles and nevi are induced by solar irradiation and are risk factors for the development of melanoma. These epidemi-

ologic observations suggest that sunlight, particularly UV light, has an important role in the induction of cutaneous melanoma. The depletion of the ozone in the stratosphere and the resulting increased intensity of UV light may be responsible in part for the increasing incidence of cutaneous melanoma. Recent studies have suggested that the ozone layer may have decreased by 3 to 7% since 1969.

Despite the strong association between sun exposure and development of melanoma, the details of this relationship remain unclear. A number of observations suggest that factors other than UV light contribute to the development of melanoma. Melanoma can occur in relatively unexposed areas of skin, such as the palms and soles. In contrast to squamous and basal cell carcinoma, melanoma does not have a direct relationship to cumulative sun exposure. Melanoma is more common among white-collar workers than individuals whose occupation is largely outdoors. These observations suggest that the relationship between sun exposure and the risk of developing melanoma is complex and related not only to the cumulative level of sun exposure but also to acute, intense, and intermittent exposure associated with blistering sunburn.⁹

The increased incidence of melanoma may be related to two observed patterns. First, younger people appear to have a proportionally greater incidence of melanoma than do people over 65 years old. Second, there has been an increase in the appearance of melanoma at certain sites: the incidence of melanoma around the head and face has increased slightly, and there has been a marked increase in the incidence of melanoma on the legs in females and the trunk in males.¹³ This trend reflects changes in clothing styles and materials, as well as in recreational habits. Melanoma rarely occurs on the double-covered areas on which brassieres and underpants are worn.

FAMILIAL MELANOMA UV-mediated induction of melanoma is believed to result from damage to the DNA of melanocytes. This is suggested by the fact that metastatic melanoma cells are usually highly aneuploid, whereas normal melanocytes are diploid. Further evidence for the genetic etiology of melanoma comes from the recognition that chromosomal alterations involving the short arm of chromosome 1 and both arms of chromosomes 6 and 7 have been identified in melanomas and cell lines derived from either primary melanomas or metastases.¹⁴⁻¹⁷ Evidence suggests a 9p21 deletion in familial melanoma,¹⁸ and consistent lesions of 9p have become apparent.¹⁹ Common losses also occur on chromosomes 10 and 8p, along with gains in copy number for chromosomes 7, 8, 6p, 19, 20, 17, and 2.²⁰

In 1820, Norris⁵ documented the heritable form of malignant melanoma. Over 130 years passed before the appearance of other reports on familial human melanoma.²¹ Members of certain families are more susceptible to the development of the genetic abnormalities associated with melanoma. As a result, these family members have an exceedingly high risk of developing melanoma. Approximately 8 to 12% of all cases of cutaneous melanoma occur in persons with familial predisposition to the development of melanoma.

Familial human melanoma is characterized by an increased risk of developing primary melanoma, a higher incidence of multiple primary melanomas, and an earlier age at onset.^{22,23} These characteristics are common to many other heritable malignant and premalignant conditions such as retinoblastoma, Gardner's syndrome, xeroderma pigmentosum, and nevoid-basal cell carcinoma.²⁴ In individuals with familial melanoma, the locus for cutaneous malignant melanoma-dysplastic nevus resides on the distal portion of the short arm of chromosome 1. Bale and colleagues¹⁴ suggest that the assignment of the locus for cutaneous melanoma to a region of the human genome frequently involved in karyotypic abnormalities in melanoma cells demonstrates that chromosomal deletion may represent the second event in a recessive model of tumorigenesis. Two genetic lesions relating to p16 and the cell cycle regulating cyclin (CDK4) have been identified in familial melanoma; in these patients, the predisposition to melanoma appears to be associated with an increased risk of developing pancreatic cancer and perhaps other cancers.²⁵ The p53 tumor suppressor gene, although overexpressed in melanoma, may only be a sign of genetic disruption and is not an initiating event.²⁶ All patients and

their families should undergo complete skin surveys as part of their routine medical care.²⁷

PRECURSOR LESIONS

DYSPLASTIC NEVUS SYNDROME This familial form of malignant melanoma is distinguished by multiple, large (greater than 5 mm in diameter) macular moles with irregular borders and often variable shades of brown, black, and red. Dysplastic nevi have both macular and papular components and may appear anywhere on the body, but especially on the trunk. The frequent appearance of dysplastic nevi on areas of the body that are normally covered, such as the buttocks, scalp, and breasts, is distinctive of this form of malignant melanoma. Microscopically, these lesions are active junctional or compound nevi with well-described patterns of melanocytic atypia, dermal fibrosis, telangiectasia, and lymphocytic infiltration. The patient with dysplastic nevus syndrome (DNS) may present with 10 to 20 dysplastic nevi.²⁸

Histologic confirmation is desirable for initial diagnosis of dysplastic nevi. According to the National Institutes of Health Consensus Conference on Precursors to Malignant Melanoma,²⁹ these histologic features are superimposed on those of a junctional or compound nevus and include melanocytic hyperplasia with elongation of rete ridges; enlarged, hyperchromatic melanocytic nuclei; bridging of aggregated melanocytes at rete ridges; lamellar and concentric dermal fibroplasia; and lymphocytic infiltrates.³⁰

Melanoma may arise from dysplastic nevi or from apparently normal skin remote from nevi in patients with DNS. This is one reason to avoid the common inclination to resect all atypical nevi for melanoma prevention. Melanomas found in association with dysplastic nevi are of the superficial spreading type and are often relatively thin. It has been reported that dysplastic nevi are contiguous with melanoma in 20 to 50% of all melanomas.^{30,31} It has been difficult to prove conclusively the direct link between dysplastic nevi and tumorigenesis, and it is presently believed that dysplastic nevi are nonobligate precursors and markers of malignant potential.

The molecular genetic mechanism by which melanoma develops in DNS is not known. DNS was first attributed to an autosomal dominant single gene with incomplete penetrance.^{32,33} Other data suggest that transmission is polygenic from an undetermined number of alleles at separate loci, perhaps influenced by a cytoplasmic component.³⁴

CONGENITAL NEVI Congenital melanocytic nevi, present at birth, are usually classified as small or giant congenital nevi. Congenital nevi are collections of nevus cells present in almost 1% of newborn infants.³⁵ These hamartomas originate in the neural crest. Clinical features of congenital nevi are readily recognizable to the experienced physician. These features include grossly irregular surface, increased pigmentation in varying shades of brown, and hypertrichosis. Although melanoma may arise de novo, it arises in association with congenital nevi at increased frequency, and all congenital nevi should be viewed with suspicion.

Large congenital nevi are regarded as formal precursors for human malignant melanoma.³⁶ It is not yet clear whether small congenital nevi should be considered precursors to melanoma. The lifetime risk of melanoma in patients with congenital nevi approaches 20%.^{29,35} Small congenital nevi should be monitored by an experienced dermatologist. Larger nevi should be followed very closely and excised or biopsied if any change is noted.

MELANOCYTES AS ANTECEDENT LESIONS Melanocytes arise from the neural crest and migrate to their final destinations in the skin, uveal tract, meninges, and ectodermal mucosa. Most melanocytes are found at the epidermal-dermal junction of the skin, and the vast majority of melanomas arise from cutaneous sites. However, melanoma has also been reported in the meninges, in the mucosa of the gastrointestinal and respiratory tract, and in the vagina. Clinical and histologic observations indicate that melanoma may arise in association with a pre-existing lesion or from apparently normal skin.³⁷ Some of the antecedent lesions of melanoma are atypical melanocytic proliferations that represent the radial growth phase of malignant melanoma.

BIOLOGIC GROWTH PHASES Most melanomas have two distinctive biologic growth phases, radial and vertical.²⁴ During the period of radial growth, neoplastic cells grow in a radial fashion, either above or

just below the basal lamina. The radial growth phase is not associated with the ability to metastasize. Radial growth may last many years for superficial spreading melanoma and lentigo maligna melanoma but is generally brief or undetected for nodular melanoma. Eventually, the melanoma evolves into the vertical growth phase, the malignant cell population invades the dermis, and the potential for cells to metastasize commences.

CLINICAL CHARACTERISTICS

If the diagnosis of melanoma is made early in the course of its natural history, cure is usually achieved by simple wide surgical excision. Cutaneous melanoma can occur anywhere on the body but most commonly occurs on the lower extremities in women and on the trunk in men. The classic clinical signs of cutaneous melanoma are alterations in a pigmented lesion's color, size, or surface, with nodularity, ulceration, bleeding, and pruritus. However, these classic clinical manifestations of melanoma are most often associated with advanced, deeply invasive lesions. More subtle signs such as irregular borders and variegated color are more common in early melanomas. About 1% of melanomas lack pigment and are termed "amelanotic." Common to all melanomas is change in size, configuration, character, or color. For this reason, pigmented lesions exhibiting any change, particularly in patients with high-risk characteristics, should be biopsied and examined histologically.

CLASSIFICATION The American Joint Committee on Cancer (AJCC) identifies five different forms of extraocular melanoma: lentigo maligna melanoma, superficial spreading melanoma, nodular melanoma, acral-lentiginous melanoma, and mucosal lentiginous melanoma. Eighty to 85% of melanomas are lentigo maligna melanoma, superficial spreading melanoma, or nodular melanoma. These different forms of melanoma represent distinct pathologic entities that have different clinical and biologic characteristics. The differential clinical features of these common types of melanoma are summarized in Table 120.1.

Superficial Spreading Melanoma (SSM). SSM is the most common form of cutaneous melanoma, accounting for approximately 70% of all melanomas. SSM generally arises in a preexisting lesion and is the lesion most commonly associated with pigmented DNS. SSM may have a relatively long natural history. Typically, diagnosis follows an increased rate of change in a precursor lesion that had exhibited minor change over several years. Early in their evolution, SSMs usually appear flat, with irregular borders. Notching of the border is particularly characteristic. The lesions are usually multicolored with shades of tan, brown, black, red, and white (Plate 37, Fig. 120.1). Amelanotic areas often represent areas of regression. As the lesion grows, it may develop an irregular surface. SSMs tend to occur throughout adulthood, with a peak incidence in the fifth decade of life. Most commonly, they occur on the head, neck, and trunk in males and on the extremities in females.

Lentigo Maligna Melanoma (LMM). LMM, which constitutes approximately 10% of all melanomas, arises from lentigo maligna (melanotic freckle of Hutchinson or precancerous melanosis of Dubreuilh). LMM is found most commonly on sun-exposed skin in elderly individuals (median age, 70 years). Clinically, the lesions are generally large (3–4 cm in diameter) and flat with irregular borders, in variable shades of tan to dark brown (Plate 37, Fig. 120.2). Hypopigmented areas in the lesion represent areas of regression. The precursor lesion, lentigo maligna, usually has been present for long periods (5–15 years) prior to the development of invasive melanoma.

Nodular Malignant Melanoma (NM). NM is the second most common growth pattern, comprising 10 to 15% of all cutaneous melanomas. NM may develop on any body surface area but most commonly is diagnosed on the trunk of men. NM is thought to be biologically more aggressive than SSM. Clinically, the lesion is dark and most often uniform in color. Histologically, NM is notable for the complete absence of melanocytic abnormalities in the adjacent epidermis (Plate 37, Fig. 120.3). Approximately 5% of NM are amelanotic. Amelanotic NM may have a symmetric appearance but occasionally becomes polypoid or cauliflower in appearance. NM does not have a radial growth phase and is associated with rapid evolution to vertical growth and invasion of the dermis. For this reason, nodular melanomas tend to be thicker, more high-risk lesions.

Acral-Lentiginous Melanoma (ALM). ALM occurs on the palms, soles, and subungual regions. It represents approximately 3 to 5% of all cutaneous melanomas. ALM constitutes a substantially higher proportion of melanomas in dark-skinned individuals such as African Americans, Asians, and Hispanics. The majority of ALM lesions are large (3 cm in diameter) with irregular borders and occur in older individuals (median age, 59 years). Subungual melanoma most commonly occurs on the great toe or thumb. ALM often appears as a tan to dark brown macule with an irregular border, but in advanced lesions it may be ulcerating or may present as a fungating mass. Although similar in clinical appearance to LMM, ALM is a biologically much more aggressive lesion, with a relatively short evolution to the vertical growth phase.

Mucosal Lentiginous Melanoma (MLM). Similar in appearance to acral-lentiginous melanoma, this lesion occurs in a variety of mucosal sites, including the oral cavity, esophagus, anus, vagina, and conjunctiva. **STAGING** Since 1953, when Allen and Spitz³⁸ first attempted to predict the biologic behavior of melanoma by histologic microstaging of the primary lesion, a number of systems have been devised to microstage melanoma. The methods of Clark and colleagues³⁹ and Breslow⁴⁰ have successively dominated the microstaging of primary melanoma. Clark's method of microstaging defines five levels of penetration through the dermis to the subcutaneous fat (Fig. 120.4). Level

Table 120.1. Differential Clinical Features of the Common Types of Melanoma

Type of Melanoma	Common Locations	Median Age (yr)	Sex Predilection	Duration	Identifying Features of Radial Growth Phase*
Lentigo maligna	Sun-exposed surfaces (head and neck most common)	70	None	5–15 yr	Flat. Shades of tan to black Frequent areas of hypopigmentation
Superficial spreading	All body surfaces	56	Males: head, neck, trunk Females: lower legs	1–5 yr	Flat to slightly raised Irregular margins. Shades of brown, black, pink. Areas of hypopigmentation
Nodular	All body surfaces	49	None overall Males: head, neck, trunk	1 mo–2 yr	None
Acral-lentiginous	Volar and subungual areas	59	Slight female predominance	2 mo–10 yr	Tan to dark-brown macule
Mucosal lentiginous	Oral, ocular, and genital mucosa	56	Slight male preponderance but varies from area to area	4–20 yr	Tan to dark-brown macular area

*The invasive tumors in each melanoma subtype are basically similar, varying from low convex to polypoid in shape and from dark blue-black to light tan or even (amelanotic) reddish pink in color. They are usually hairless and may be ulcerated.

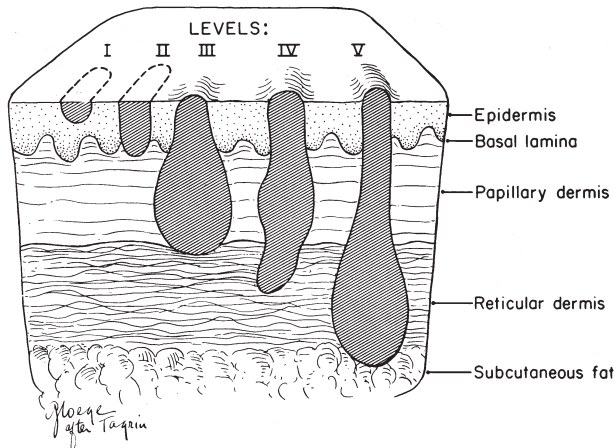


Figure 120.4. Clark's levels of invasion. Reprinted with permission from Eilber FR, Holmes EC, Morton DL. Malignant melanoma. In: Grabb WC, Smith JW, editors. *Plastic Surgery: a Concise Guide to Clinical Practice*. Boston, MA: Little, Brown; 1968. p. 511.

I melanoma lies in the epidermis above an intact basal lamina. When the melanoma has penetrated the basal lamina into the papillary dermis, it is classified as level II. When the melanoma involves the papillary dermis and may extend to the papillary-reticular dermis interface, it is classified as level III; as it extends into the reticular dermis, it becomes level IV; and as it extends into the subcutaneous fat, it becomes level V. The success of Clark's method of microstaging is directly related to the experience of the examining dermatopathologist and the ability to recognize the microscopic anatomy of the skin accurately.⁴¹ Clark's original observation suggested that the deeper the level of penetration, the poorer the prognosis, an observation that has been repeatedly confirmed when primary lesions are microstaged by experienced dermatopathologists.

Breslow's microstaging method, which is simpler and more reproducible than Clark's method, uses an ocular micrometer to measure the vertical thickness of the primary tumor from the granular layer of the epidermis, or the base of an ulcer, to the deepest identifiable contiguous melanoma cell. The technique has now found wide acceptance and has been clearly demonstrated to be a more accurate prognostic parameter than Clark's level of invasion. The thicker the melanoma, the greater the risk for developing metastatic disease.

The first clinical staging system for melanoma was a macrostaging system of three stages: I, localized melanoma; II, regional metastatic melanoma; and III, disseminated melanoma. This original three-stage system offered the advantage of simplicity but failed to account for important prognostic factors derived from microstaging of the primary lesion. It also did not differentiate the metastatic risk of the majority of patients with melanoma, since approximately 85% of patients present with clinically localized, stage I melanoma.

Because of the demonstrated prognostic value of Clark's level and tumor thickness, AJCC has adopted a primary tumor nodes metastases (pTNM) staging system for melanoma, which incorporates the histologic characteristics of the primary tumor.⁴² This staging system more accurately assesses the metastatic potential of the majority of melanoma patients who present with clinically localized disease and provides a more practical, although more complex, classification for clinicians (Table 120.2).

PROGNOSTIC FEATURES OF CLINICALLY LOCALIZED DISEASE

One of the most notable clinical characteristics of melanoma is its capricious clinical course. It is usually not difficult to determine prognosis for patients with distant metastatic disease, but outcome is far less clearly defined in the majority of patients with clinically localized

melanoma. A number of variables have prognostic value, including the patient's age and sex, and the primary tumor's anatomic location, size, Clark's level, Breslow's thickness,⁴³ and histopathologic type, as well as the status and number of subclinically involved regional lymph nodes.

ULCERATION Ulceration of the primary melanoma is associated with a biologically more aggressive lesion and a poorer prognosis.⁴⁴ Balch and colleagues⁴⁵ reported that 5-year survival rate dropped from 80% for nonulcerated melanomas to 55% for ulcerated melanomas. It is not known why ulcerated primaries have a more aggressive biologic nature. It is not likely due to underestimation of the thickness due to the ulcer crater. Ulcerated lesions tend to be thicker and have a nodular growth pattern, but the increased thickness does not account for the poorer prognosis. However, the width of surface ulceration has been significantly correlated with survival.⁴⁵

OTHER HISTOLOGIC PROGNOSTICATORS The mitotic rate per square millimeter⁴⁴ and the presence or absence of lymphatic or blood vessel invasion are relevant to prognosis. The histologic growth pattern also has prognostic value; LMM may have a more favorable prognosis than SSM or NM.⁴⁶ Most of these differences may, however, merely reflect a tendency for NM to be thicker and more invasive from inception, whereas LMM tends to be thinner and exhibit a prolonged radial growth phase.

A faint white halo surrounding a cutaneous melanoma may represent regression of the lesion. Microscopically, partial (> 50%) regression is seen as subtotal loss of the melanocyte nest and replacement with lymphocytes. Although regression is generally associated with thin primaries, these lesions have a less favorable outcome than would be expected on the basis of their thickness alone.⁴⁷⁻⁴⁹ The development of new molecular biology techniques may soon allow genetic characteristics to replace histologic features as the most important prognostic indicators.^{26,50,51}

SEX A number of studies have demonstrated that women with melanoma fare substantially better than men.⁵²⁻⁵⁴ The survival advantage enjoyed by women may be primarily due to the location of the lesion, which is more commonly on the extremity, and the less frequent presence of ulceration.

ANATOMIC SITE The significance of anatomic site for prognosis remains unclear. Several studies using multifactorial analysis suggest that the anatomic site of the primary lesion is an important prognostic factor.^{52,53,55} Both male and female patients with melanomas of the extremities have a better survival rate than patients with melanomas of the head and neck; patients with melanomas of the trunk appear to have the worst prognosis.⁵⁶

Day and colleagues⁵⁷ identified a group of patients with thin melanomas, apparently at low risk for developing recurrent disease, who nonetheless had unanticipated higher mortality. These patients

Table 120.2. The AJCC Staging System for Melanoma⁴²

Stage	TNM	Criteria
I	pT1, N0, M0	Primary melanoma < 0.75 mm thick and/or Clark's level II No nodal or systemic metastasis
	pT2, N0, M0	Primary melanoma 0.76–1.50 mm thick and/or Clark's level III No nodal or systemic metastasis
II	pT3, N0, M0	Primary melanoma > 1.51–4.00 mm thick and/or Clark's level IV No nodal or systemic metastasis
III	pT4, N0, M0	Primary melanoma > 4.0 mm thick and/or Clark's level V and/or satellite(s) within 2 cm of the primary tumor No nodal or systemic metastasis
	Any pT, N1, M0	Regional nodal metastasis ≤ 3 cm in greatest dimension No systemic metastasis
	Any pT, N2, M0	Regional nodal metastasis > 3 cm in greatest dimension or in-transit metastasis No systemic metastasis
IV	Any pT, Any N, M1	Systemic metastasis

Table 120.3. Long-Term Survival of 1,134 Patients with Melanoma Metastases to the Lymph Nodes Treated at the JWCI

Years of Follow-up	Survival Rate (%)	Cumulative Number of Deaths	Total Number of Patients
1	84	175	902
2	66	362	647
3	55	461	496
5	46	537	357
10	41	573	197
15	38	582	87

Standard deviations for survival estimates vary between ± 1.1 and 1.8%. Modified from Morton et al.⁶⁵

had primary lesions on the skin of the upper back, posterior arm, neck, and scalp. The acronym BANS (back, arm, neck, scalp) was introduced to suggest that these particular anatomic sites had prognostic value. Others have suggested that melanoma arising on the trunk and the head and neck is associated with a poor prognosis.⁵⁸ The John Wayne Cancer Institute (JWCI) found that patients with primary lesions arising in the BANS region appeared to have a slightly worse outcome than those with lesions in non-BANS regions, particularly in the presence of nodal metastases.⁵⁹ These results support the hypothesis that lesions arising in these anatomic sites may be more aggressive. Cascinelli and colleagues⁶⁰ however, have questioned the validity of the BANS concept.

PREGNANCY The question of whether pregnancy impacts melanoma remains unanswered. It has been widely held that pregnancy exerts an adverse effect on patients with melanoma and that melanoma arising during pregnancy is associated with a particularly aggressive clinical course and an extremely grave prognosis. However, a study from JWCI found that women whose melanoma arose during pregnancy were not significantly different from their nonpregnant cohorts in characteristics recognized as being prognostic in melanoma.⁶¹ The 5-year survival of female patients of child-bearing age with localized melanoma was 87%, nearly identical to the 86% 5-year survival of their pregnant counterparts. Similar results have been reported by others,⁶² and a study from the World Health Organization (WHO) found that female melanoma patients presenting during pregnancy had slightly deeper melanomas but not a different prognosis.⁶³ Anecdotal reports of rapid progression of melanoma when associated with pregnancy⁶⁴ may represent valid observations but should not guide recommendations for therapy.

PROGNOSTIC FEATURES OF REGIONAL LYMPH NODE METASTASES

Lymph node metastases (AJCC stage III melanoma) may be discovered when a patient presents with palpable lymph nodes or when pathologic examination of nodes removed during elective lymph node

Table 120.4. Univariate and Multivariate Analyses of Prognostic Factors for Survival of Patients with AJCC Stage III Melanoma (any pT, N1, or N2)

Factor	p Value	
	Univariate	Multivariate*
Number of tumor-positive lymph nodes	.0001	.0001
Breslow thickness of primary lesion	.0487	.0334
Gender	.0103	.0627
Age	.0670	
Location of primary lesion		
Extremity	.0104	.0059
Unknown	.0876	
Head and neck	.1845	
Trunk	.1168	
Nonpalpable vs. palpable lymph nodes		
0.76 – 4.00 mm	.0016	.0942
> 4.00 mm	.2960	
Synchronous vs. metachronous nodal disease	.0170	
Clark's level of primary lesion	.3685	
Postoperative adjuvant immunotherapy	.4118	

*Data shown only for factors with p < .10. Modified from Morton et al.⁶⁵

dissection reveals clinically occult tumor deposits. According to Morton and colleagues,⁶⁵ the overall survival rate in patients with tumor-positive nodes is 46% at 5 years, 41% at 10 years, and 38% at 15 years (Table 120.3). Similar observations have been reported by other investigators.^{66,67}

A number of clinical and pathologic variables have been examined for their prognostic value in patients with AJCC stage III melanoma. Morton and colleagues⁶⁵ studied the significance of age, sex, parity, site of primary lesions, presence of satellitosis, clinical status of lymph nodes, and number of histologically positive nodes. Their analysis by both univariate and multivariate methods failed to demonstrate any significant survival impact for age, nodal status, biopsy type, growth pattern of the primary lesion, or Clark's level of invasion in patients with nodal metastases (Table 120.4). By univariate analysis, only the number of positive lymph nodes, Breslow's thickness, sex, location of the primary lesion, and clinical status of nodes, and synchronous versus metachronous metastases significantly affected survival. By multivariate analysis, only the number of tumor-containing lymph nodes, thickness, and primary site were significant; the number of nodes was the strongest predictor of survival.

Because the number of tumor-positive lymph nodes is the single most important prognostic factor in AJCC stage III melanoma (Table 120.5), accurate assessment of these nodes is of paramount impor-

Table 120.5. Five-Year Survival Rates for JWCI Patients According to Prognostic Factors

	Extremity or unknown site of primary melanoma			
	Males		Females	
	< 1.5 mm	≥ 1.5 mm	< 1.5 mm	≥ 1.5 mm
Breslow thickness of primary:				
1 node	50% ± 8 (49)	45% ± 10 (29)	66% ± 7 (53)	79% ± 9 (24)
2–4 nodes	57% ± 7 (52)	48% ± 14 (20)	67% ± 8 (31)	54% ± 11 (25)
≥ 5 nodes	46% ± 9 (32)	14% ± 13 (13)	63% ± 12 (17)	57% ± 15 (16)
	Nonextremity site of primary melanoma			
	Males		Females	
	< 1.5 mm	≥ 1.5 mm	< 1.5 mm	≥ 1.5 mm
Breslow thickness of primary:				
1 node	73% ± 8 (45)	49% ± 7 (75)	76% ± 12 (14)	45% ± 13 (23)
2–4 nodes	47% ± 10 (33)	32% ± 6 (77)	49% ± 16 (11)	35% ± 12 (22)
≥ 5 nodes	21% ± 9 (26)	34% ± 9 (32)	44% ± 17 (10)	14% ± 13 (8)

(N) = number of patients in each category. Modified from Morton et al.⁶⁵

tance. Immunohistochemistry permits more detailed microstaging of lymph nodes than conventional histologic techniques using hematoxylin and eosin (H&E) staining, which may underestimate the number of lymph nodes containing tumor. Immunohistochemical assessment of nodal status using antibodies to S-100 protein and other melanoma-associated antigens improves prognostic accuracy and provides a more homogeneous population for trial stratification (Plate 38, Fig. 120.5). Molecular assays using reverse transcriptase-polymerase chain reaction (RT-PCR) with specific melanoma-associated markers are even more sensitive than immunohistochemical techniques.^{68,69}

Patients with clinically occult lymph node involvement are generally considered to have a better prognosis than those with palpable lymph nodes (Table 120.6). Data from JWCI indicate that the long-term survival of patients with subclinical regional node metastases is 16% better than that of patients with clinically positive nodes.⁶⁵

LYMPH NODE METASTASES FROM UNKNOWN PRIMARY SITE Melanoma sometimes presents as lymph node involvement in the absence of an identifiable cutaneous primary site. At JWCI, 14% of melanoma patients with lymph node metastases have an unknown primary site.⁶⁵ Their median survival is 37 months; 5- and 10-year survival rates are 46 and 41%, respectively.⁷⁰ When stratified by the number of tumor-containing lymph nodes, there is no significant survival difference between patients with an unknown primary melanoma and patients with clinically involved lymph node metastases from a known primary site. However, patients with lymph node metastases from an unknown primary site consistently enjoy a slight survival advantage, particularly beyond 5 years. This prognosis is similar to that for thin melanomas of the extremity (see Table 120.5). Therefore, these patients should undergo therapeutic lymphadenectomy with expectations of prolonged survival in a significant proportion of patients, similar to those with known primary sites.

PROGNOSTIC FEATURES OF DISTANT METASTASES

Once melanoma metastasizes to distant sites, the prognosis is grave, with a median survival of only 4 to 8 months in most series.^{71,72} At JWCI, a recent review of 1,521 melanoma patients with AJCC stage IV disease revealed a median survival of 7.5 months and an estimated 5-year survival rate of 5.5%, with no improvement over the past 22 years (Fig. 120.6).⁷² Melanoma has the relatively unusual ability to spread to almost any organ site and does so in a variety of clinical patterns. For this reason, we consider melanoma to be the “syphilis” of oncology. Therefore, any symptom in a patient with a history of melanoma must be considered to be secondary to metastatic disease until proven otherwise.

Table 120.6. Long-Term Survival Rates of Patients with Clinical versus Nonclinical Evidence of Regional Node Metastasis*

Source	Nonpalpable/ Nonsuspicious Lymph Nodes (%)	Palpable/ Suspicious Lymph Nodes (%)	Difference (%)
McNeer and Das Gupta (Surgery 1964;56:512)	52	19	33
Cohen et al. (Ann Surg 1977;186:635)	55	38	17
Das Gupta (Ann Surg 1977;186:201)	69	20†	49
Balch et al. (Ann Surg 1981;193:77)	48	24	24
Callery et al. (Ann Surg 1982;196:69)	48	36	12
Roses et al. (Ann Surg 1985;201:103)	44	20	24
Morton et al. (Ann Surg 1991;214:491)	59	43	16

*All data are 5-year survival rates except Cohen et al., which are 10-year results.

† Patients with Clark’s level III and IV.

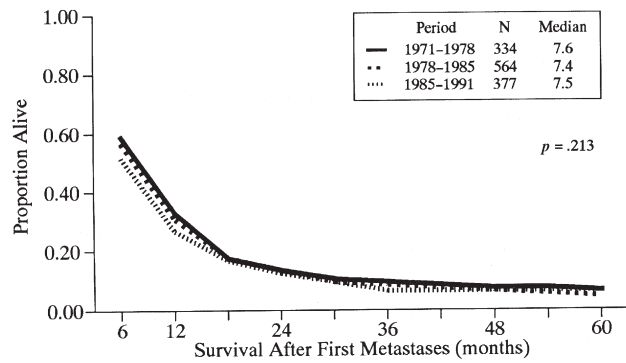


Figure 120.6. JWCI’s melanoma database of AJCC stage IV patients (distant metastatic disease) shows the survival of 1521 patients treated between 1971 and 1993. Reprinted with permission from Barth et al.⁷²

Clinical variables such as age, sex, and primary site and histologic variables such as Clark’s level, Breslow’s thickness, and ulceration have no bearing on the outcome of metastatic disease. At JWCI, the initial site of distant metastasis, the disease-free interval before distant metastases, and stage of disease preceding distant metastases are the three independent clinical variables predicting survival (Table 120.7).⁷² AJCC stage IV melanoma patients can be divided into three distinct prognostic groups based on their initial site of metastases: (1) cutaneous, nodal, or gastrointestinal metastases (median survival, 12.5 months; estimated 5-year survival rate, 13.5%); (2) lung metastases (median survival, 8.3 months; estimated 5-year survival rate, 3.6%); and (3) liver, brain, or bone metastases (median survival, 4.4 months; estimated 5-year survival rate, 2.5%).

The number of metastatic sites has been reported to be an important prognostic variable. Patients with a single metastatic site may do better than patients with multiple metastatic sites. The median survival is 7 to 12 months for patients with one metastatic site but only 2 to 8 months for patients with multiple metastatic sites.⁷¹

DISEASE-FREE INTERVAL A multifactorial analysis from the University of Alabama demonstrated significantly improved outcomes among patients whose disease-free interval exceeded 12 months.⁷³ Review of the JWCI database showed a 5-year survival rate of 6% when the disease-free interval between AJCC stage III and IV disease was at least 18 months, compared with 3% when this interval was shorter (see Table 120.7).⁷²

MANAGEMENT OF PRIMARY MELANOMA

SURGICAL RESECTION AND BIOPSY At present, surgical resection is the major curative therapy for melanoma. The first surgical considera-

Table 120.7. Univariate and Multivariate Analyses of Prognostic Factors for Survival of 1,521 Patients with AJCC Stage IV Melanoma

Factor	p Value	
	Univariate	Multivariate*
Gender	.0120	
Age (yr)	.3907	
Site (extremity vs. nonextremity)	.3376	
Breslow depth	.0264	
Clark level	.0273	
Year of diagnosis	.1431	
Initial site of metastases	< .0001	< .0001
Number of initial metastatic sites (1 vs. 2 vs. ≥ 3)	.0001	
Preceding AJCC stage (I/II vs. III)	.0001	.0001
Disease-free interval (> 18 vs. ≤ 18 months)	.0004	.0001

*Data shown only for factors with p < .10 by multivariate analysis.

Adapted from Barth et al.⁷²

tion is confirmation of the diagnosis. An algorithm for the management of primary melanoma is given in Fig. 120.7. Histologic verification of the diagnosis is essential before embarking upon any treatment plan, since the surgical recommendations may vary depending on the microstaging of the lesion. There is no evidence that an interval of 1 to 2 weeks between excisional biopsy and wide excision adversely affects outcome. To microstage the lesion accurately, all layers of the skin must be included in the sample. For this reason, shave biopsy or curetting is contraindicated. For most lesions less than 2 cm in diameter, where sufficient skin is present to allow a primary closure, an excisional biopsy is appropriate (Fig. 120.8). For large lesions or those located where sufficient skin might not be available for primary closure, such as on the face, hands, or feet, incisional biopsy of the most nodular or irregular area is appropriate to establish the diagnosis (Fig. 120.9).

Margins of Excision. Failure to perform re-excision following biopsy of a primary melanoma is associated with a local recurrence rate as high as 40%. However, although the necessity of re-excision requires little discussion, the margins of excision are the subject of considerable recent evaluation. Since 1907, when Handley⁸ originally recommended a 5-cm margin around the primary site as the treatment of choice for melanoma, wide excision has been the standard treatment for primary melanoma. Although the width of excision was originally empiric, Cochran⁷⁴ noted increased numbers of melanocytes in the clinically normal skin surrounding many melanomas, supporting the need for a wide margin of excision. In 1962, Peterson and colleagues⁷⁵

recommended margins up to 15 cm for some patients with melanoma after they identified a group of patients who had developed recurrences within that distance of the primary.

In contrast to these findings, others have indicated that the width of excision does not influence the pattern of recurrence or survival.⁷⁶ Elias and colleagues⁷⁷ found no correlation between the initial surgical approach and survival, whereas Olsen⁷⁸ reported nearly identical rates of local recurrence for patients with surgical margins less than 1 cm and those with surgical margins of 5 cm or more. Observations such as these have led some to question Handley's original recommendation for extensive surgical resection of skin and subcutaneous tissue.⁷⁹

However, many of these early studies failed to account for the effect of tumor thickness on survival. Breslow and Macht⁸⁰ suggested that a surgical margin less than 5 cm did not influence prognosis or local control of thin or intermediate-thickness melanomas. Balch and colleagues⁸¹ reported a minimal risk of local recurrence for thin melanomas (< 0.76 mm). It appears that wide local excision as originally described by Handley is not necessary for very thin melanomas; however, increasing level and thickness increase the risk of local recurrence because of occult permeation of adjacent tissues and probably justify a more extensive resection.

In 1988, WHO published the results of a randomized trial comparing narrow excision (1 cm) and wide surgical excision (3 cm or more)

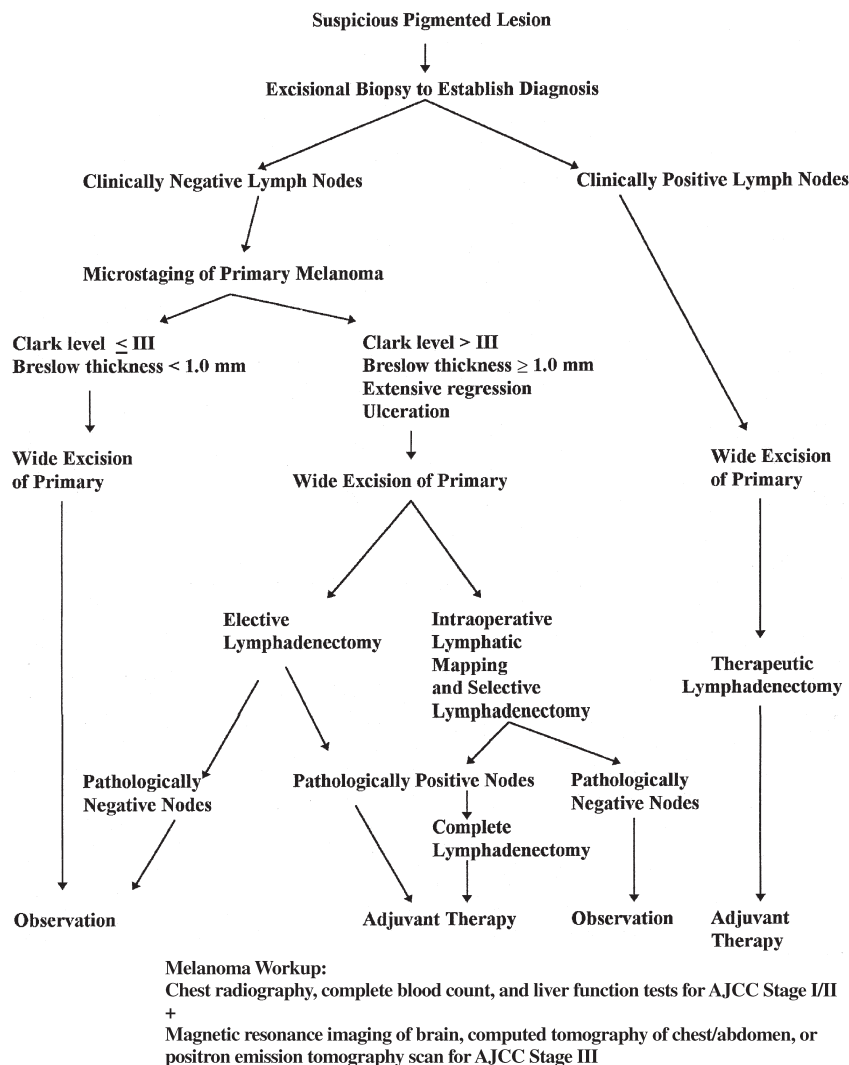


Figure 120.7. Algorithm for the management of primary melanoma.

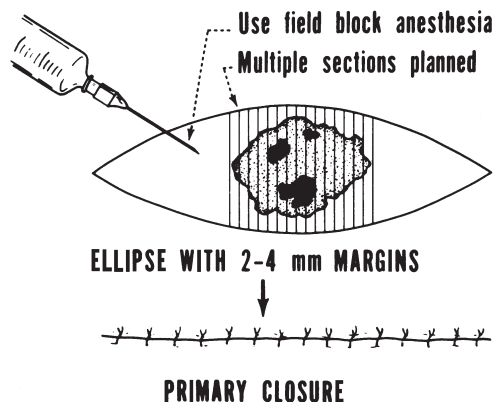


Figure 120.8. Excisional biopsy is considered preferable because the entire lesion is available for step-section pathologic analysis, providing evidence of the maximum depth of penetration. Reprinted with permission from Sugarbaker EV, Roseman JM, Weingard DN. Malignant melanoma. In: Copeland EM, editor. Surgical oncology. New York, NY: Wiley; 1983. p. 17.

for melanomas less than 2 mm in thickness.⁸² Although three patients in the group treated by narrow excision developed local recurrence, all had melanomas thicker than 1 mm, suggesting that narrow excision for lesions less than 1 mm in thickness is a safe and effective surgical treatment. Other studies stratifying patients according to thickness of the primary tumor have demonstrated that the surgical margin has no effect on survival, although a trend toward increasing incidence of local recurrence with narrow margins has been observed.⁸³ A prospective, multi-institutional randomized trial headed by Balch and colleagues⁸⁴ found that surgical margins could be safely reduced to 2 cm if the primary melanoma was intermediate in thickness (1.0–4.0 mm).

Although this debate concerning the appropriate width of primary excision continues, it seems likely that optimal therapeutic effects will be achieved by excisions of at least 1 cm for melanomas thinner than 1 mm and at least 2 cm for melanomas thicker than 1 mm. Furthermore, because the time to recurrence is inversely proportional to the thickness of the primary lesion, thin lesions may take longer to recur locally than thick lesions. Long-term follow-up (8–10 years) is required to determine the actual local recurrence rate. In sites with sufficient surrounding skin, a wide excision would appear to be the conservative approach, especially for thicker melanomas or those with satellites. There is little cosmetic difference between narrow and wide excision as long as primary closure uses flap rotation and advancement techniques. Skin grafts are rarely necessary except on the scalp and distal to the elbows or knees.

At JWCI, the surgical approach to primary melanoma has been guided by the depth of the primary melanoma.⁸⁵ Until the optimum width of excision of a primary melanoma can be determined by longer follow-up of current trials, we have adopted the following guidelines

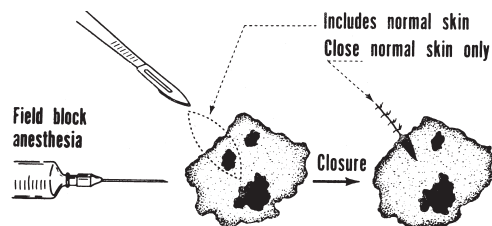


Figure 120.9. Incisional biopsy. Full-thickness excision of a nodular portion of the lesion ensures maximum depth of penetration. This procedure does not worsen the patient's prognosis. Reprinted with permission from Sugarbaker EV, Roseman JM, Weingard DN. Malignant melanoma. In: Copeland EM, editor. Surgical oncology. New York, NY: Wiley; 1983. p. 17.

based on the observation that the risk of local recurrence is directly proportional to the depth of the primary melanoma.

1. For Clark's level II melanoma or thin level III lesions that measure less than 1.00 mm in thickness, excise with 1-cm radial margins.
2. For Clark's level III melanoma, lesions that are 1.0 to 4.0 mm in thickness, and all Clark's level IV melanomas, excise with 2- to 3-cm radial margins.
3. For Clark's level V melanoma and all melanomas thicker than 4 mm, excise widely with > 3-cm radial margins around the primary site, including the underlying fascia, because these lesions are more likely to have microsatellites surrounding the primary lesion and involvement of the subdermal lymphatics close to the primary lesion.

Site-Specific Considerations. General recommendations regarding the extent of surgical resection are applicable to most areas of the body. However, certain anatomic sites are not amenable to rigid surgical criteria. The appropriate treatment for melanoma occurring in the subungual areas is amputation, usually at the level of the distal interphalangeal joint, although with an extensive lesion, amputation of the whole digit may be necessary. For lesions of the helix of the ear, wedge excision of the lesion with careful plastic reconstruction can achieve excellent cosmetic results without compromising the incidence of local recurrence. Rarely should total amputation of the ear be necessary. Because of the obvious cosmetic defect associated with wide excision on the face, as well as the close proximity of vital structures, lesions on the face generally are excised with margins of 1.0 to 2.5 cm, depending on the location of the lesion and the microstaging of the primary. Fortunately, the majority of lesions on the face are relatively thin. Moh's micrographic surgery has been used for treating some low-risk melanomas on the face, but there is no support in the literature for use of this technique.⁸⁶

RADIATION THERAPY Historically, melanoma has been considered a radioresistant tumor. The basis for this was early laboratory work that suggested that melanoma cells in vitro required higher doses for equivalent cell kill when compared to squamous cell or adenocarcinoma cell lines.^{87,88} In addition, there were scattered clinical reports of poor responses of patients with melanoma treated with early x-rays or radium.⁸⁹ Correspondingly, radiation was reserved as a treatment of last resort in melanoma and was poorly studied.

In the era of megavoltage radiotherapy, more and more reports have challenged the concept of melanoma's radiation insensitivity. Patients with recurrent or metastatic melanoma involving the brain or bones formed the bulk of those initially treated. Numerous reports showed very high rates of response and/or palliation of symptoms (50–70%).⁹⁰ Accumulated evidence now shows that the determinants of melanoma's radioresponsiveness are no different than those of other tumors: volume of disease, site of disease, and dose that can be safely administered.⁹¹

Encouraging reports have suggested the role of radiation following surgical resection in the axillary, vaginal, and head and neck regions. In these sites, where microscopic disease is often present following surgical resection, radiation may enhance local control and/or disease-free survival.^{92–94} Another area where radiation has proven useful is the treatment of brain metastases with stereotactic/gamma-knife radiosurgery.⁹⁵ In fact, it is now clear that some melanomas may be cured solely by radiation. Intermediate-stage choroidal melanomas are usually managed with brachytherapy or with particle irradiation,^{96–98} with local control rates of 85 to 97%. On the other hand, radiation is no longer believed to be of benefit in the preoperative treatment of larger choroidal melanomas. The Zimmerman hypothesis, formulated from anecdotal and retrospective studies, held that enucleation leads to increased distant metastases in this rare disease. The Collaborative Ocular Melanoma Study randomized 1,003 patients with choroidal melanomas to surgery versus surgery plus pre-enucleation radiation therapy (20 Gy in 5 fractions). Patients were accrued from 1986 to 1994 at 43 centers in the United States and Canada. Results at 5 and 8 years have demonstrated no benefit to the preoperative radiation arm.^{99,100}

ADJUVANT TREATMENT BY LIMB PERFUSION The role of isolated limb perfusion in the adjuvant treatment of primary cutaneous melanoma of the extremity has generated considerable debate. In 1958, Creech and colleagues¹⁰¹ first reported the use of regional isolated limb

perfusion with L-phenylalanine mustard (L-PAM) for patients who had developed regional cutaneous melanoma. Since their original description, single institutional studies have suggested that hyperthermic, isolated limb perfusion with L-PAM substantially reduces the rate of recurrence and improves survival of patients with localized melanoma or melanoma with regional node metastases when compared to those treated with conventional surgical therapy alone.^{102,103}

Ghussen and colleagues¹⁰⁴ prospectively randomized patients to wide excision and regional node dissection with or without isolated limb perfusion of L-PAM at a temperature of 42°C. A reportedly significant improvement in disease-free status was achieved in the isolated limb perfusion treatment group, which led to early closure of the study. This study cannot be accepted without further confirmation, however, because the control arm relapse rate was substantially worse than the experience obtained at institutions practicing similar management of primary melanoma without isolated limb perfusion. Recent studies suggest that biologic response modifiers such as tumor necrosis factor and interferon (IFN)-gamma may increase the effectiveness of chemotherapy. It remains to be determined by well-designed, prospective randomized trials what role, if any, adjuvant isolated limb perfusion has in the treatment of primary melanoma.

MANAGEMENT OF REGIONAL LYMPH NODES

ELECTIVE VERSUS THERAPEUTIC LYMPHADENECTOMY When melanoma metastasizes, it most commonly spreads initially to the regional lymph nodes. Surgical excision of the involved lymph nodes is currently the only effective treatment for melanoma metastatic to lymph nodes. Lymphadenectomy for individual lymphatic stations has been described in detail.¹⁰⁵ When performed for clinically identifiable disease in the lymph node station, surgical excision is referred to as therapeutic; when performed without palpable metastases but because there is sufficient risk of metastases, it is referred to as immediate or elective. There is little argument about the utility of therapeutic lymphadenectomy because surgical excision is the only effective modality for both local control and potential cure. The long-term survival of such patients depends on the number of involved nodes but approaches 25 to 40% at 10 years (see Table 120.6).

Considerable controversy remains concerning the efficacy of elective lymphadenectomy in the management of clinically uninvolved lymph nodes. If melanomas metastasize sequentially to regional lymph nodes and subsequently to distant sites, patients treated earlier in the natural history of the disease, prior to the dissemination of tumor cells to distant sites, should have a survival advantage compared with patients treated for clinically palpable disease. This premise is supported by multiple reports that the 5- and 10-year survival is approximately 25% higher for patients with clinically negative/histopathologically positive lymph nodes than for patients with clinically positive/histopathologically positive nodes (see Table 120.6).

The disadvantage of elective lymph node dissection is that approximately 80% of patients have tumor-free lymph nodes. These patients are subjected to an operation with little or no likely therapeutic benefit and placed at risk for the immediate and long-term complications of these radical procedures.

Prospective and Retrospective Studies of Routine Elective Lymphadenectomy. Most large, long-term, retrospective studies from single institutions have demonstrated a small but consistent therapeutic benefit for patients with intermediate to thick melanomas treated with immediate lymph node dissection. Results of nonrandomized prospective studies from the Sydney Melanoma Unit demonstrated improved survival in patients with intermediate to thick lesions (0.76–4.0 mm) who underwent immediate lymph node dissection.^{105,106} Similar results have been achieved at the University of Alabama,¹⁰⁷ Duke University,¹⁰⁸ Memorial Sloan-Kettering,¹⁰⁹ JWCI,⁶⁵ and in a recent European trial.¹¹⁰

Three prospective randomized trials have examined whether early lymph node dissection in patients with clinically negative lymph node involvement offers any therapeutic advantage over later dissection after the patient has developed obvious nodal metastases. Veronesi and colleagues⁸² reported a prospective randomized study of 553 patients who had melanoma confined to the distal two-thirds of the extremity

with clinically uninvolved lymph nodes. Two hundred sixty-seven patients underwent wide excision followed by immediate node dissection, and 286 had wide excision followed by node dissection when clinically positive nodes were detected. No statistically significant survival difference was observed. Although no subset of patients appeared to derive large benefit from immediate node dissection, patients with lesions that were Clark's level IV and intermediate in thickness and who were treated by wide excision and elective regional node dissection had a 10% better survival rate at 5 years (20% at 10 years) than similar patients who underwent a therapeutic node dissection later. This survival advantage did not achieve statistical significance, however, because of the small number of patients in this subset of the trial. The results of this trial have been questioned because of the large number of patients for whom lesion thickness was not obtained.

Similar results were reported in a Mayo Clinic study of 171 patients with clinically uninvolved lymph nodes who were prospectively randomized into three subgroups: no lymphadenectomy, delayed lymphadenectomy, and immediate excision of the regional lymph nodes.¹¹¹ No significant difference in total survival or metastasis-free survival was found among the three treatment arms.

The results of the Mayo Clinic study appear to support the WHO study, but most of the primary lesions in this study were low-risk thin lesions that were unlikely to recur regardless of therapy (the study was initiated before the importance of tumor thickness was recognized). The WHO study has certain limitations that could lead to differences in interpretation of the results. These include the restriction of melanomas to the extremities, the predominance of females, and the limited number of patients in certain subgroups. Such limitations might have obscured any benefit achieved by immediate lymph node dissection. Despite these objections, the studies suggest that any value achieved by immediate lymphadenectomy may, at best, be confined to a subgroup of patients with lesions of intermediate thickness. The most recent randomized prospective studies conducted by Balch and colleagues¹¹² examined elective node dissection in patients who had primaries 1 to 4 mm thick at any cutaneous site. Seven hundred forty patients were randomized: 379 to elective lymph node dissection (ELND) and 361 to observation. Patients were allowed to cross over to the alternative treatment, which allowed these investigators to examine survival of the "randomized intent" and the "actual treatment" groups. Although there was no survival difference overall ($p = .25$), specific subsets of patients appeared to achieve a survival benefit from ELND — a finding that fuels the controversy. Cascinelli and colleagues¹¹³ recently completed a randomized trial for patients with truncal primaries > 1.5 mm thick. Two hundred fifty-two patients were randomized to one of the two treatments. Overall, these investigators found no difference ($p = .09$) in survival. This study has been criticized because lymphoscintigraphy was not routine for patients undergoing ELND.

Complications of Lymphadenectomy. The most common complications associated with lymph node dissection are those related to the wound itself and may lead to prolongation of hospitalization. However, the severity and type of the complication vary with the site of node dissection. For example, morbidity associated with axillary and neck dissections generally is minimal. Wound seroma and infection are relatively infrequent in axillary node dissection, whereas significant arm edema occurs in approximately 1% of patients. Similarly, long-term complications associated with neck dissection are infrequent and usually do not involve functional deficits. On the other hand, radical inguinal node dissection may be associated with significant edema, particularly if the iliac and obturator nodes are removed with the superficial inguinal nodes and those of the femoral triangle.^{114,115} In approximately 2 to 10% of patients, this can be a particularly debilitating complication. Regardless of the site of node dissection, the rate of edema formation can usually be minimized by prophylactic measures following inguinal node dissection, such as elevating the leg while recumbent and wearing elastic compression stockings.

MICROSTAGE OF PRIMARY MELANOMA AND RISK OF NODAL METASTASES Microstaging the primary lesion by Breslow's thickness and Clark's level of invasion can identify patients who have an increased

probability of harboring microscopic metastatic disease.⁴⁴ Patients with thin melanomas (Clark's level II, Breslow's thickness < 0.76 mm) without evidence of regression rarely have nodal metastases, whereas patients with increasingly thick melanomas (Clark's level III or IV, Breslow's thickness 0.76–4.0 mm) have an increased risk of harboring occult metastatic disease. Microstaging, along with other prognostic variables such as anatomic site, ulceration, and gender, can identify patients at substantial risk for harboring microscopic metastatic disease. These are the patients most likely to benefit from immediate lymph node dissection.

Cutaneous Lymphoscintigraphy. Ambiguous lymphatic drainage has been advanced as one argument against immediate lymph node dissection for truncal melanomas. Sappey¹¹⁶ defined a 2-cm-wide line that encircles the trunk at the level above and below the umbilicus; lesions above this line were predicted to drain to the axillae and those below to the inguinal nodes. However, certain midline lesions, particularly those of the umbilical area or midline of the back, can drain to all four areas.

Cutaneous lymphoscintigraphy was introduced in 1977 to determine the route of lymphatic drainage from a primary melanoma.^{114,117} This procedure is particularly useful for melanomas arising from an axial location on the trunk or the head and neck because these skin sites may drain to one or more lymphatic areas. Morton's group has replaced colloidal gold with technetium (Tc 99m)-labeled dextran and more recently with Tc 99m-labeled human serum albumin or sulfur colloid; Tc 99m is injected into the site of the primary melanoma to identify lymph node stations draining that site.^{118,119}

Cutaneous lymphoscintigraphy is used to select lymph node stations for immediate lymphadenectomy. It can identify regional lymph node stations at risk for harboring occult microscopic metastatic disease, but it cannot identify nodal metastases.

Intraoperative Lymphatic Mapping and Sentinel Lymphadenectomy. Because of the controversy surrounding immediate lymph node dissection, Morton and colleagues devised a minimally invasive technique to identify occult metastases in the regional lymph nodes of patients with primary cutaneous melanoma. Intraoperative lymphatic mapping is based on the hypothesis that lymph from a primary melanoma drains initially to one or more "sentinel" lymph nodes, which therefore should be the first nodes at risk for harboring occult metastatic disease.^{118–120} Briefly, mapping involves the intradermal injection of a tracer such as vital blue dye or radiocolloid. This tracer readily enters the subdermal lymphatics and passes through the lymphatic channels to the regional nodal basin/station draining that particular skin site. This permits identification of the sentinel lymph node(s) (Plate 38, Fig. 120.10), which is selectively excised and examined by conventional H&E staining and highly sensitive immunohistochemical techniques. If metastatic melanoma is identified, a complete lymphadenectomy is performed; if not, the procedure is terminated (see Fig. 120.7).

Using intraoperative lymphatic mapping and selective lymphadenectomy, Morton and colleagues¹²⁰ have found that only 20% of patients with clinically localized melanoma have occult regional node metastases. These patients can be treated by standard lymphadenectomy, whereas the other 80% of patients without nodal metastases can avoid the complications of radical lymphadenectomy. A large number of investigators have validated the accuracy of the sentinel node technique and demonstrated its strength as a lymph node staging procedure.^{121–123} Intraoperative lymphatic mapping has been performed using blue dye alone or in combination with a radiopharmaceutical that is tracked by a hand-held gamma probe. At this time, the blue dye remains the gold standard for identifying the sentinel nodes, based on the original work of Morton and colleagues¹²⁰ and the gamma probe serves as a useful adjuvant. The various definitions of a radioactive ("hot") sentinel node make radiopharmaceuticals impractical as the sole mapping agent.¹¹⁹ JWCI investigators have compared the therapeutic value of sentinel lymph node dissection and standard elective lymph node dissection.¹²⁴ The data suggest that these procedures are equal but sentinel lymphadenectomy is better for staging the regional lymph nodes. With respect to treatment of the primary melanoma, the

efficacy of sentinel lymphadenectomy is being compared with excision alone as part of a multicenter randomized phase III trial.¹²⁵

ADJUVANT THERAPY Because there is a high rate of recurrence (60–70%) in patients with nodal metastases, multiple trials of adjuvant therapy have been carried out in this group. Unfortunately, none has yielded convincing evidence to justify routine adjuvant therapy outside a clinical trial setting, until the recent trials with IFN- α -2b as a post-surgical adjuvant in AJCC stage III melanoma.

Immunotherapy. Adjuvant immunotherapy continues to generate interest because it is associated with minimal toxicity. Unfortunately, the value of adjuvant immunotherapy in the treatment of high-risk melanoma remains to be demonstrated.

Melanoma Vaccines. Trials at JWCI have demonstrated that certain patients receiving a polyvalent allogeneic whole-cell melanoma vaccine generate immune responses that are correlated with prolonged survival.^{126,127} The Southeastern Cancer Study Group used a viral melanoma oncolysate in an attempt to decrease recurrence of melanoma.¹²⁸ The results of the phase I/II trial, which suggested a benefit for patients treated by this approach, were not validated in a phase III trial.¹²⁹ In a phase II trial, Hersey¹³⁰ demonstrated improved survival of patients receiving a viral melanoma oncolysate; however, results of a subsequent phase III trial were indeterminate. The Southwestern Oncology Group (SWOG) has completed a study of melanoma cell line-derived vaccine (Melacine), which will be unblinded in the year 2000. The Eastern Cooperative Oncology Group (ECOG) is also awaiting follow-up on a completed trial of the ganglioside GM₂ for adjuvant vaccine immunotherapy. The JWCI phase III trial of a polyvalent allogeneic whole-cell melanoma vaccine as postsurgical adjuvant therapy for patients with AJCC stage III melanoma should be completed late in the year 2000.

Interferons. Given the evidence for antitumor activity of IFN α -2a/b in advanced melanoma treated with maximally tolerated dosages of IFN, ECOG and North Central Cancer Treatment Group (NCCTG) launched adjuvant trials of IFN α -2 in 1983–1984. Patients with either lymph node metastasis or deep primary (T4) lesions received a 1-year (ECOG) or 3-month (NCCTG) course of therapy and were compared with patients who underwent observation.

ECOG trial EST 1684 tested IFN α -2b given intravenously at 20 MU/m²/day, 5 days a week for the first 4 weeks (induction), followed by alternate-day treatment using 10 MU/m²/day 3 days a week subcutaneously for the subsequent 11 months (maintenance).¹³¹ These were projected to be the maximally tolerated dosages on the basis of phase I-II trial experience in metastatic melanoma.¹³² The NCCTG has tested a 3-month regimen using IFN α -2a at maximally tolerated dosages given intramuscularly at 20 MU/m²/day on an alternate-day schedule, based upon a series of phase II trials at the Mayo Clinic.¹³³ These two trials reached accrual goals and were closed in 1990. At a median follow-up of 7 years, the ECOG trial showed almost a 1-year increase in median disease-free and overall survival for patients treated with IFN α -2b. The NCCTG study failed to demonstrate a survival benefit for a shorter course of high-dose interferon.

The results of IFN α -2 in several other cancers suggest that protracted periods of treatment may achieve the most beneficial results. Clinical experience has shown that the maximally tolerated dosages employed in the ECOG trial are not feasible for longer than approximately 1 year. No other regimen has been demonstrated to achieve a durable impact on the recurrence and survival rates of melanoma patients. The potential role of chronic or longer-term therapy with low-dose IFN α -2 therefore has been of interest.

Building on the prior trial of high-dose therapy for 1 year, ECOG conducted a three-arm adjuvant trial for patients with deep primary melanomas (pT4) or regional lymph node metastasis (N1). The three arms were (1) IFN α -2b at high dosages (administered as in the foregoing EST 1684 for 1 year); (2) IFN α -2b at low dosages of 3 MU on alternate days (3 times a week) for 2 years; and (3) standard follow-up. The ECOG intergroup trial E1690 accrued 642 patients and its preliminary findings, reported in 1999,¹³⁴ confirmed the effect of high-dose IFN α -2b given for 1 year on continuous disease-free survival (median follow-up 4.3 years). However, disappointingly, there was no effect on overall survival.

The rationale for protracted treatment at lower dosages includes observations that natural killer (NK) cell activation is maximal after single doses of 3 MU,¹³⁵ and that the antiproliferative antitumor activity depends upon continued exposure to the agent. Despite many studies seeking laboratory correlates of IFN alfa therapy, and the observation of effective prolongation of relapse-free and overall survival by high-dose IFN alfa-2b, the mechanism of prophylaxis of high-risk melanoma has not been established.^{136,137} WHO completed a trial of postoperative adjuvant low-dose IFN alfa-2a versus standard observation for patients with lymph node metastases; in this trial, 3.0 MU of IFN alfa-2a was given on alternate days for 3 years. Preliminary reports (median follow-up 3 years) do not suggest a significant impact on disease-free survival when this regimen is compared with the high-dose IFN alfa-2 regimen used in the earlier ECOG trial.¹³⁸ However, longer follow-up is necessary for more definitive conclusions with respect to survival.

Chemotherapy. Dacarbazine (DTIC) is the only agent approved for chemotherapy of disseminated melanoma by the United States Food and Drug Administration (FDA). However, adjuvant trials with DTIC, either alone or in combination with immunotherapy or other chemotherapeutic agents, have demonstrated no better survival than that associated with surgery alone.¹³⁹⁻¹⁴¹

Radiation Therapy. The role of radiation therapy in the adjuvant setting remains controversial. The majority of reports are small retrospective comparisons of patients treated to a variety of sites, with varying doses and doses per fraction, usually following surgical resections of varying degrees of completeness.⁹¹ Not surprisingly, it is quite difficult to draw conclusions from these data. Johanson and colleagues¹⁴² reported 54 patients treated to a variety of sites with the Princess Margaret hospital's 0-7-21 protocol (8 Gy in three fractions on days 0, 7, and 21). Of these patients, 22 were treated for microscopic residual disease following surgery to 7 different sites. Local control was maintained in 18 of 22 (82%) at 12 to 44 months following irradiation. Creagan and colleagues¹⁴³ reported the only randomized prospective study of adjuvant radiation for lymph node-positive melanoma. Fifty-six patients with positive regional lymph nodes following surgical resection (from a variety of sites) were randomized to no further therapy or to irradiation of the involved nodal basin. Radiation was a split-course of 25 Gy in 1.78-Gy fractions followed by a 3- to 4-week break, then a further 25 Gy in 1.78-Gy fractions. Only one field was treated daily. Despite these suboptimal techniques and inadequate numbers of patients, radiation therapy conferred a small advantage in disease-free survival (20 vs. 9 months) and median overall survival (33 vs. 22 months). These differences did not reach statistical significance. In what has become the most influential study of adjuvant radiation for melanoma, Ang and colleagues¹⁴⁴ from M.D. Anderson treated 174 patients with cutaneous melanoma of the head and neck who were felt to be at high risk of relapse. There were three high-risk groups: (1) clinically node-negative with lesions > 1.5 mm or Clark's level higher than IV (n = 79); (2) clinically node-positive (n = 32); and (3) nodal relapse but no distant metastases (n = 63). Patients underwent surgical resection of the primary tumor in group 1 and surgical resection plus lymph node dissection in groups 2 and 3. Radiation consisted of 6 Gy per fraction twice weekly to a total dose of 30 Gy in 2.5 weeks. Ipsilateral electrons were the most commonly applied modality. Five-year local-regional control and survival was 88% and 47%, respectively. These results greatly exceeded historic control rates for similar patients at M.D. Anderson or reported in the literature.

To verify these results, the Radiation Therapy Oncology Group (RTOG) initiated a randomized trial of adjuvant radiation for high-risk head and neck melanoma patients. The trial was closed prematurely due to poor accrual, most likely because of the concurrently reported results with interferon (KK Ang, personal communication, 1999). Thus, the role of radiation in the adjuvant setting remains unclear.

MANAGEMENT OF LOCALLY RECURRENT AND IN-TRANSIT MELANOMAS Melanomas recurring within 5 cm of the primary site are referred to as locally recurrent, and melanomas metastasizing between the primary and the regional lymphatic station are referred to as "in transit." Locally recurrent melanomas suggest inadequate treat-

ment of the primary lesion, although at least 0.5% will recur regardless of the operative margins.⁸² In-transit metastases represent the trapping of melanoma cells in the lymphatics "in transit" to the regional lymphatic station, although the actual mechanism for this is unknown.

Patients with locally recurrent melanoma have a variable clinical course. The majority eventually develop systemic metastases, but about 20% are apparently cured following further surgical excision, suggesting that the initial surgical margins were inadequate. In contrast, with only rare exceptions, patients with in-transit metastases are most likely to develop systemic metastases within 6 to 12 months. The prognosis appears to be related to the number of in-transit lesions and the interval before development of recurrence.¹⁴⁵ The reported incidence of in-transit lesions is variable; at JWCI, patients with in-transit lesions represent approximately 1% of all melanoma patients.¹⁴⁵ Calabro and colleagues¹⁴⁶ from M.D. Anderson reviewed their experience with 1,001 consecutive patients who had nodal metastases. Ten percent subsequently developed in-transit metastases. Lower extremity primaries draining to the groin were associated with an increased risk (19%) of in-transit metastases, a finding noted by others.^{147,148} The patient's age and sex, the timing of nodal dissection (immediate or delayed), and the number of excised nodes did not affect the incidence of in-transit metastases. Although Calabro's group did not attempt to explain the higher incidence of in-transit metastases associated with primaries on the lower extremities, some investigators suspect that gravity and delayed lymphatic drainage may be responsible.

There is no standard treatment for patients who develop locally recurrent or in-transit melanoma. A number of therapeutic options are available. Because symptoms are rarely associated with in-transit melanoma, it seems reasonable to avoid the toxicities of systemic chemotherapy, which rarely provides long-term complete regression. Rather, these lesions should be treated with aggressive local therapy, which in some patients results in prolonged control,¹⁴⁵ or with active immunotherapy using a whole-cell vaccine.¹⁴⁹ Clinicians at JWCI use an algorithm for the management of in-transit melanoma (Fig. 120.11).

Surgery. Surgical excision of in-transit lesions can be considered in patients in whom the number of lesions is relatively limited and the rate of development is slow. Because of the eventual development of systemic disease in the majority of these patients, amputation is rarely indicated.

Intralesional Immunotherapy. At JWCI, intralesional immunotherapy, most commonly with bacillus Calmette-Guérin (BCG), has been reported as an alternate means to control the regional manifestations of recurrent inoperable melanoma (Plate 38, Fig. 120.12). BCG incites an inflammatory reaction that may control in-transit metastases in approximately 60% of patients.¹⁵⁰ Human monoclonal antibodies are another alternative for intralesional treatment of recurrent in-transit melanoma.^{151,152} These human monoclonal antibodies recognize the melanoma-associated ganglioside antigens GD₂ and GM₂. Intralesional therapy with human monoclonal antibodies directed against these ganglioside antigens has resulted in complete clinical and histologic regression of dermal metastases in approximately 90% of patients whose melanomas contain the target antigen (Plate 38, Fig. 120.13).

Active Immunotherapy with a Melanoma Vaccine. At JWCI, the best overall results in the management of regional skin and soft-tissue metastases (AJCC stage IIIA) have been obtained with active specific immunotherapy using a polyvalent allogeneic whole-cell melanoma vaccine.^{126,149} During the last 20 years, the median survival associated with local and regional metastatic melanoma has remained constant for patients treated by other modalities, such as intralesional immunotherapy and surgery, with an overall median survival of 28.7 months and a 5-year survival rate of 20%. A recent JWCI study of 54 patients receiving a whole-cell vaccine for treatment of in-transit melanoma reported a 17% rate of objective clinical responses (9 of 54 patients), with a 13% rate of complete remission (7 of 54 patients). The median duration of complete remission exceeded 22 months. Median survival was > 53 months for vaccine responders, 42 months for nonresponders, and 53 months overall (Fig. 120.14).¹⁴⁹

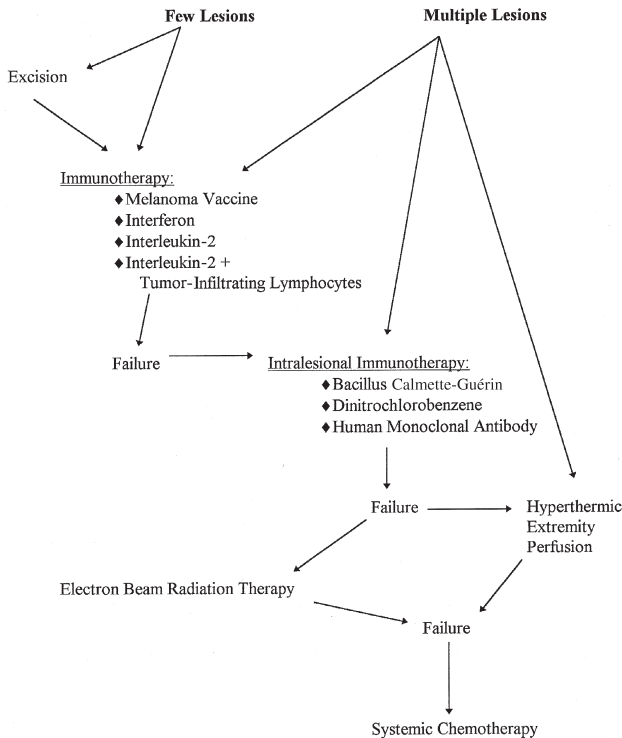


Figure 120.11. Algorithm for management of in-transit melanoma metastases (AJCC stage III).

Regional Chemotherapy. Chemotherapy administered by arterial infusion or by isolated perfusion of the extremities has been undertaken for more than 40 years for treatment of in-transit melanoma recurrence.¹⁰¹ More recently, hyperthermic isolation/perfusion has generally employed melphalan and has gained adherents as a means to expose tumor cells to dosages (and physical conditions) not systemically feasible in the host.^{104,153} Isolated limb perfusion has had substantial success in patients with in-transit melanoma. Dramatic results have been achieved by perfusing melphalan at 41.8°C.¹⁵⁴ Other drugs, such as DTIC and cisplatin, may have similar activity, although experience with these drug regimens has not been as successful as with melphalan. Although benefits from this therapy have been reported for patients with metastatic in-transit recurrence, the use of this technique as an adjuvant to curative surgery for lesser stages of disease has not been substantiated. Randomized multi-institutional studies of WHO, EORTC, and the North American Perfusion Group are in progress or have failed to determine the value of this therapy for resected high-risk melanoma.

Systemic Chemotherapy and Biotherapy. Local disease rarely undergoes complete regression for prolonged periods, although partial and temporary responses are frequent. Therefore, unless systemic disease becomes manifest, systemic chemotherapy is rarely indicated in the management of in-transit melanoma. The issue is more controversial with biologics like interleukin (IL)-2 and IFN alpha-2, for which durable complete responses may be possible. These and newer chemobiotherapy combinations are being investigated prospectively in cooperative group trials (ECOG/SWOG 3695).

Radiation Therapy. Radiation therapy for locally recurrent and in-transit melanoma has been inadequately investigated. Several reports in the literature have shown encouraging response rates. Johanson's report of the Princess Margaret's 0-7-21 protocol (vide supra) included 23 patients with locally recurrent or in-transit melanoma. Of these, 7 achieved a complete remission, 2 had a complete remission followed by in-field failure, 5 had a partial remission, 3 had disease stabilization, and the remainder (5 patients) had no response. Given

the poor survival in these clinical situations, it certainly appears reasonable to consider radiation for palliation in those patients who are not candidates for the therapies listed above.

MANAGEMENT OF DISTANT METASTASES

Autopsy and clinical studies confirm that when melanoma metastasizes, it usually does so to almost all of the major organ systems. At the time of autopsy, the lung, liver, brain, and lymph nodes are the most common sites of metastasis. However, essentially every visceral site, including the heart, adrenal gland, spleen, pancreas, gastrointestinal tract, bone, thyroid, pleura, diaphragm, ovaries, prostate, and genitourinary tract, may be involved. The median survival in this setting is usually only 4 to 6 months. The site of metastasis is an important prognostic variable. Patients with subcutaneous and lymph node metastases (median survival, 11 months) and pulmonary metastases (median survival, 8 to 10 months) have a better prognosis than those with central nervous system and hepatic metastases (median survival, 2-4 months).

Symptoms associated with disseminated melanoma vary with the site of involvement. In the absence of abnormal physical findings, abnormal serum chemistries or an abnormal chest x-ray, it is unlikely that extensive radiologic evaluations will identify unsuspected metastases. Although some patients have no symptoms associated with even extensive metastases, others experience seizures associated with intracranial metastases, gastrointestinal bleeding from small-bowel metastases, and/or pain from masses. Because of the variable presentation of patients with metastatic melanoma, the onset of new and persistent symptoms in individuals previously diagnosed with melanoma deserves special attention. Evaluation in this setting should involve standard radiologic studies, including computed tomography of chest and abdomen and magnetic resonance imaging of the brain. Contrast studies of the small bowel in patients with unexplained anemia or with evidence of blood loss from the gastrointestinal tract often reveal evidence of small-bowel metastases. Positron emission tomography (PET) scanning using fluorine-18 deoxyglucose can comprehensively evaluate the entire patient with one study, and whole-body PET may prove to be the most accurate and effective staging tool now available for patients with malignant melanoma.¹⁵⁵

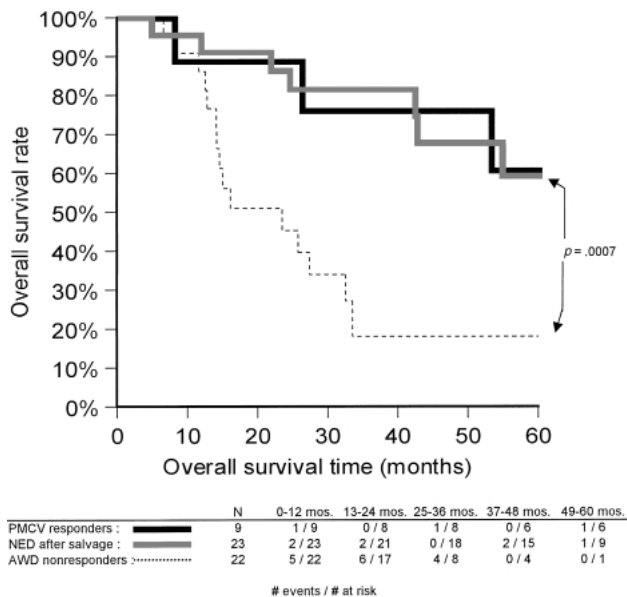


Figure 120.14. Overall survival curves for patients whose in-transit melanoma metastases were treated by a polyvalent melanoma cell vaccine (PMCV). Solid black line, PMCV clinical responders (9 patients); solid gray line, PMCV nonresponders rendered clinically free of disease (NED) by salvage therapy (23 patients); dashed line, PMCV nonresponders not rendered NED (22 patients). A partial response was defined as at least a 50% decrease in the products of the greatest tumor dimensions for at least 30 days. Reprinted with permission from Hsueh et al.¹⁴⁹

Currently, disseminated melanoma is not curable. The clinical course of patients with metastatic melanoma may, however, vary widely. Progression of disease may be extremely rapid, or existing metastases may remain stable for prolonged periods. For these reasons, careful clinical judgment is required for optimal palliation of distant metastatic melanoma. A number of modalities are available for the treatment of disseminated melanoma, including surgical excision, systemic chemotherapy, radiation therapy, immunotherapy with vaccines and biologic response modifiers, and other investigational treatment options. An algorithm for suggested management is given in Fig. 120.15.

SURGERY Despite the well-recognized tendency of melanoma to disseminate widely, surgical excision of metastases can provide excellent palliation and sometimes long-term survival in selected patients. The general principles of surgical resection of metastatic disease are applicable to patients with metastatic melanoma. In general, the excision of multiple metastases from multiple organ sites does not appear to improve outcome; however, complete surgical resection can confer a survival benefit in patients who have a limited number of lesions in a limited number of sites. A significant number of patients sequentially develop metastases at surgically accessible sites, however, and appear to derive some benefit from surgical excision of these metastatic sites. Furthermore, some patients with multiple metastases in the same organ, such as the lung, may enjoy long-term survival.

Brain Metastases. Brain metastases are clinically present in approximately 50% of patients with disseminated melanoma at some time during their clinical course. Symptoms may be due to mass effect and include headache, double vision, and seizures as well as symptoms associated with the location of the lesion in the brain. Although the symptoms may be improved substantially with the use of steroids, they usually progress in the absence of definitive treatment. Some brain metastases appear to be solitary. Surgical removal of solitary brain metastases may relieve associated symptoms and occasionally results in long-term survival.¹⁵⁶ Several retrospective analyses have suggested that excision of a solitary brain metastasis results in improved survival and an 87% rate of neurologic improvement.¹⁵⁷ Recent prospective randomized studies also indicate the value of surgical resection of solitary brain metastases.¹⁵⁸ Postoperative cranial radiotherapy is generally considered of value since other occult lesions may exist.

Subcutaneous and Lymph Node Metastases. Metastatic deposits in subcutaneous sites and lymph nodes are frequent in patients with disseminated melanoma and may represent the only manifestation of disease. Surgical excision of these clinically involved sites can be associated with prolonged disease-free periods and a median survival as long as 29 months.¹⁵⁹

Lung Metastases. The lungs represent one of the most frequent sites of metastatic involvement by melanoma. Occasionally, patients present with a solitary pulmonary nodule as the only manifestation of recurrent melanoma. The value of thoracotomy in this setting remains controversial. At JWCI, patients with isolated pulmonary metastases account for approximately 5% of patients with disseminated melanoma. Patients are initially evaluated according to the tumor doubling time and treated with a melanoma cell vaccine.¹⁶⁰ Patients with a tumor doubling time > 60 days are considered for thoracotomy.¹⁶¹ Although the best candidates for resection are patients with a solitary pulmonary lesion, no evidence of extrapulmonary intrathoracic metastases, and a tumor doubling time longer than 60 days, patients with multiple metastases and no extrapulmonary intrathoracic disease can still have a 5-year survival rate of 19% and therefore should be considered for resection.

Gastrointestinal Metastases. Gastrointestinal metastases from metastatic melanoma may produce highly symptomatic and immediately life-threatening clinical manifestations. Most commonly, gastrointestinal metastases present as the result of occult blood loss or as obstructing lesions at the lead point of an intussuscepting segment of small bowel. Indications for surgery are most frequently associated with acute bowel obstruction from intussuscepting small bowel or chronic gastrointestinal bleeding. At the time of exploration, most patients are found to have multiple sites of involvement. Operative intervention, whether for curative or palliative intent, can be performed with minimal morbidity and mortality. A JWCI study reported

a 5-year survival rate of 41% for 46 patients undergoing curative resection of gastrointestinal tract metastases.¹⁶²

IMMUNOTHERAPY The inverse correlation between prognosis and the degree of host lymphoid infiltration of the primary tumor suggests that host immunity plays a role in the natural history of melanoma.^{46,107} The prognosis associated with primary melanoma, otherwise defined by the depth of primary invasion and the presence or absence of regional lymph node and distant metastatic disease, may thus be governed by underlying immunologic response. The fact that the first effective adjuvant medical therapy for patients with resected high-risk melanoma has major effects on the tumor's major histocompatibility complex (MHC) expression and on the function of the host's T cells, NK cells, and dendritic cells has prompted exploration of newer immunomodulating agents.

The elements of the host response to melanoma may be separated into acute, subacute, and chronic components: the NK system and IFN systems along with the dendritic (antigen-presenting) cell system provide acute/subacute responses, whereas the antigen-specific T cell and B cell humoral responses are the more chronic/enduring mechanisms of response against malignant neoplastic disease, accompanied by the IFN systems, as they are for infectious disease.¹⁶³ The manner and degree to which host response mechanisms may determine the outcome of a melanoma patient have yet to be determined, but recombinant DNA technology has afforded oncologists the opportunity to test and dissect the therapeutic role of each component, separately and in combination, for melanoma.

Active Specific Immunotherapy Using Melanoma Vaccines. Based on the observation that antibodies in the sera of melanoma patients recognize surface antigens on melanoma cells, numerous attempts have been made to develop a vaccine to induce active immunity against melanoma to cause the regression of established tumors or, more frequently, to prevent recurrence. The majority of these vaccines are based on whole melanoma cells or extracts obtained from melanoma cells.^{164,165}

In 1992 Morton and colleagues¹²⁶ at JWCI reported a phase II trial of a polyvalent allogeneic whole-cell melanoma vaccine (MCV) administered to 75 patients with melanoma metastatic to distant sites (AJCC stage IV). Overall survival significantly ($p < .0001$) increased to a median of 23.1 months, compared with 7.3 months for AJCC stage IV patients in JWCI's 20-year historic database (Fig. 120.16). This

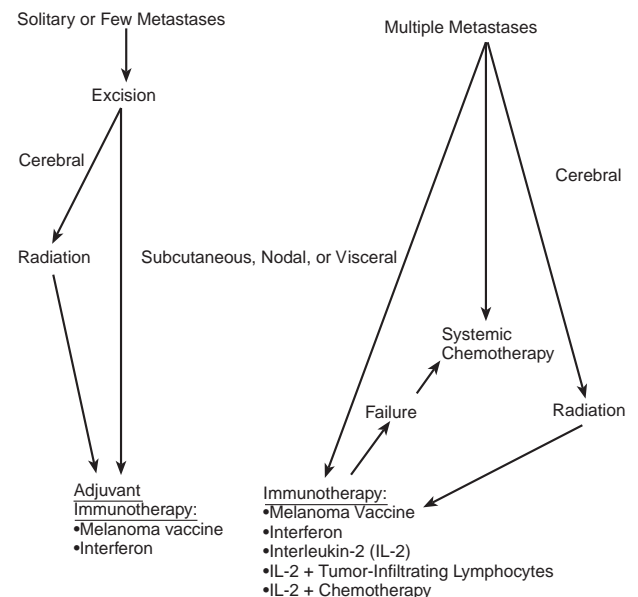


Figure 120.15. Algorithm for the management of melanoma metastatic to distant sites (AJCC stage IV).

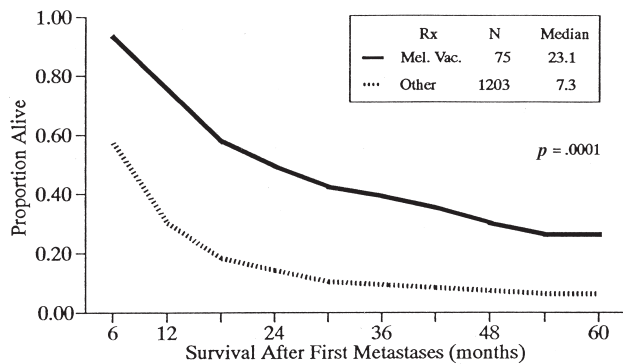


Figure 120.16. JWCI's melanoma database of patients with distant metastatic melanoma (AJCC stage IV) shows that the survival of 75 patients who received active immunotherapy with melanoma vaccine was better than that of 1,275 historic controls who received other types of therapy. Five-year survival was 26 vs. 6%. Reprinted with permission from Morton et al.¹²⁶

improvement was evident for all metastatic sites. In addition, the proportion of MCV patients alive 5 years following appearance of distant metastases was 26%, compared with 6% historically. Morton's group¹⁶⁶ recently proposed a management paradigm based on cytoreductive surgery plus adjuvant immunotherapy, and two phase III multicenter trials are examining postoperative MCV therapy in patients with stage III or stage IV melanoma.

Interferon Therapy. IFNs have served as prototypes of biologic response modifiers. The pleiotropy of the IFNs and other biologic agents

represents an alternative to conventional chemotherapy for combating tumor growth; direct, indirect, and composite effects on tumor cell surface markers have been documented (Fig. 120.17). The biologic effects of IFN differ from the chemotherapeutic effects of cytotoxic drugs. Optimal biologic response modification by IFN may not necessarily be obtained at its maximal tolerable dosage, where the maximal antitumor effects of a cytotoxic agent would be anticipated.

IFN Alfa-2. Considerable experience has been gained in the treatment of metastatic melanoma with native IFN alfa of leukocyte and lymphoblastoid cell origin and with several recombinant subspecies (IFN alfa-2a [Roferon, Hoffmann-La Roche, Inc.], IFN alfa-2b [Intron, Schering-Plough], IFN alfa-2c [Boehringer]). A response to IFN alfa was observed in 8 of 112 subjects treated with the earliest available native IFN alfa (Le or N1) (Table 120.8). The low dosages ($0.5-10 \times 10^6$ U/dose, daily or alternate-daily) and limited periods of treatment (less than 2 months, generally 4-6 weeks) may have compromised the assessment of antitumor effect. As IFN produced by recombinant DNA became available for clinical trials, the maximal tolerable dosages of IFN alfa-2a, -b, and -c were defined in the range of 10 to 50×10^6 U/dose administered daily subcutaneously, intramuscularly, or intravenously; trials employing dosages verging on the maximal tolerable dose were carried out. In these phase II studies,^{132,167-170} 25 of 174 (14.4%) evaluable subjects treated with one recombinant species (IFN alfa-2a) and 24 of 106 (22.6%) evaluable subjects receiving another IFN alfa subspecies (IFN alfa-2b) had clinical responses to therapy administered by a variety of dosages and routes, in daily or alternate-daily schedules (see Table 120.8).

Regimens employing intermittent therapy interrupted by one or more weeks of nontreatment have produced inferior response rates.^{171,172} The results of treatment with the two subspecies of recombinant IFN alfa are otherwise comparable in 11 published studies, achieving an objective clinical response rate of 17.5% overall. Multiple studies have observed that smaller tumor masses respond more fre-

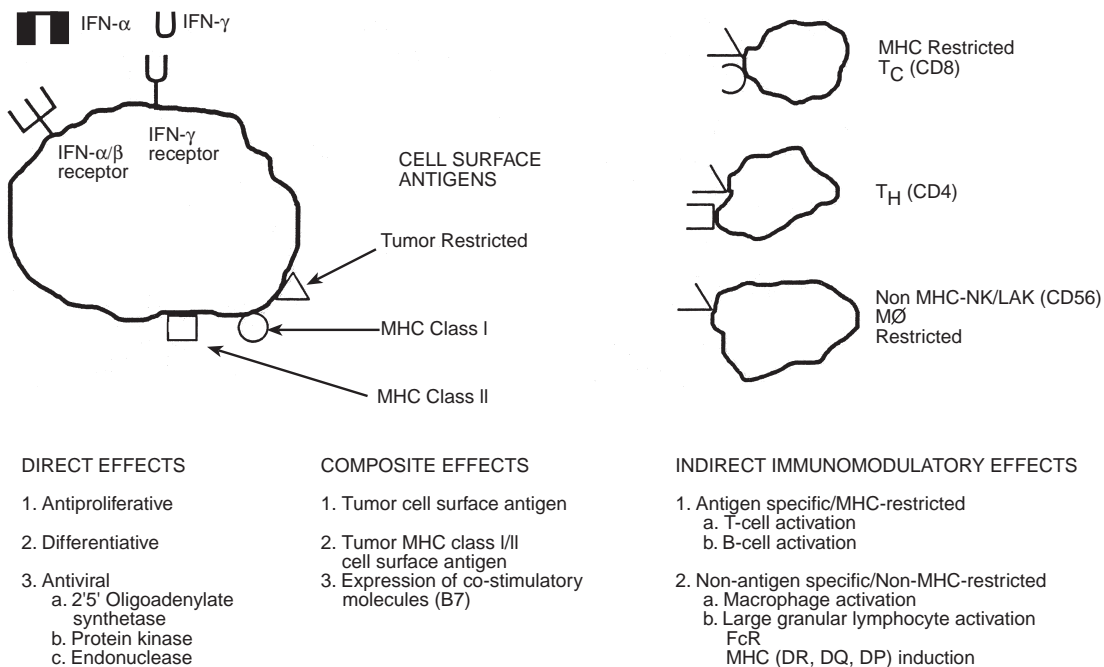


Figure 120.17. Each effect of interferon (IFN) provides a basis for therapeutic trials in melanoma. A number of functions, including enzyme induction, effector cell activation, and tumor cell antigen modulation, may be more relevant than antiviral activity, which is currently used for IFN quantification. The practice of reporting IFN quantities in terms of mass is increasingly common for recombinant IFN gamma. As the central mechanisms of antitumor activity are identified for each of the biologicals in clinical application, functional standardization should take precedence. IFNs inhibit proliferation and induce melanization in melanoma. Through these direct effects, or through modulation of the expression of tumor cell surface antigens, IFNs may permit more effective host recognition and response to tumor in vivo. Composite antitumor effects depend on both a direct antigenic alteration and the appropriate host effector cell response to the antigenically marked tumor cell. The induction of increased expression of class I as well as class II major histocompatibility antigens and tumor antigens may benefit IFN-mediated therapy; the induction of adhesion molecules, which have been correlated with the metastatic and invasive potential of melanoma, may counterbalance these effects.

Table 120.8. Interferons in Treatment of Metastatic Melanoma

Dose/Schedule	No. of Evaluable Patients	No. of PR	No. of CR	OR rate* (%)
Nonrecombinant interferon- α 0.5–60 MU/m ² daily 15–50 MU/m ² three times a week	112	6	2	7 (3–14)
Recombinant interferon- α -2a 3–50 MU/m ² three times a week	174	16	9	14 (9–20)
Recombinant interferon- α -2a 10–100 MU/m ² daily	106	15	9	23 (15–31)

PR = partial responses; CR = complete responses; OR = objective response.
*95% confidence interval.

quently to IFN α than do larger masses, and that the response to IFN follows a time course that may be more characteristic of endocrine hormonal therapy than of chemotherapy: some responses have been observed after protracted periods of treatment. The optimal dosage for therapy, however, has not been rigorously determined, nor have in vitro correlates of response been defined among the multiple mechanisms known to be influenced by IFN α and its subspecies.

IFN Gamma. The SWOG has tested the adjuvant activity of IFN gamma administered at the putative optimal immunomodulatory dosage derived from the Biological Response Modifiers Program (BRMP) studies cited above. Patients with intermediate or deep primary tumor invasion (T2–T4, > 0.76 mm) or positive regional nodes (N1–2) were eligible. SWOG terminated this study following an interim analysis in early 1990.¹⁷³ At the time of study closure, death or relapse was observed among 34 of 58 subjects treated with IFN gamma and among 25 of 66 subjects in the control arm; analysis suggested that it would be impossible to demonstrate a 50% improvement in disease-free survival. An ongoing EORTC study of IFN gamma versus IFN α or control has been completed in 350 subjects; neither adverse nor beneficial effects were observed (JM Kirkwood, personal communication).

A number of immunologic investigations have been carried out in conjunction with clinical trials of recombinant IFN gamma in melanoma (Table 120.9). Two studies are of particular note. One phase I-II trial from the Pittsburgh Melanoma Center evaluated the immunomodulatory effect of IFN gamma (Biogen, Inc.) administered in five different dosages (3, 30, 300, 1000, and 3000 mg/m²/d) to groups of six patients. Continuous intravenous infusion and 2-hour daily infusions were comparable.^{174,175} ECOG has formally assessed immunobiologic correlates of IFN gamma in an extended phase II(B) trial (ECOG EST 4687/EST 4987) that evaluated doses of IFN gamma over a three log₁₀ range in 98 patients treated for at least 3 months, three

Table 120.9. Summary of Clinical Trials in Melanoma: Interferon Gamma Alone and in Combinations

Drug (Dose)	No. of Evaluable Patients	No. of PR	No. of CR	OR Rate* (%)
IFN- δ (.01–4.5 mg/m ²)	69	4	1	7 (2–16)
IFN- δ and IFN- β IFN- δ (2 mg) IFN- β (30 MU/m ²)	15	0	0	0 (0–22)
IFN- δ and IFN α -2a IFN- δ (.01–.05 mg/m ²) IFN α -2a (2–10 MU/m ²)	20	0	1	5 (0–25)
IFN- δ and IFN α -2c IFN- δ (.05–.2 mg/m ²) IFN α -2c (2 MU/m ²)	15	0	0	0 (0–22)

PR = partial responses; CR = complete responses; OR = objective response.
*95% confidence interval.

times a week. This study failed to detect antitumor effects of IFN gamma at any dose. Although profound immunomodulatory effects were observed, the absence of antitumor activity has halted further single-agent studies of IFN gamma for metastatic melanoma.

In the future, the use of IFN in a rational combined-modality regimen may improve results. IFN administered in conjunction with vaccines or antibodies may augment antigenic modulation, dendritic cell activity, and angiogenesis, thereby improving immunization or tumor localization.¹⁷⁶ Ernstoff and colleagues¹⁷⁷ reported that the sequential application of IFN gamma and IFN α for renal cell carcinoma enhanced the response rate, which correlated with (CD8) T cell depression on treatment. Whether similar therapy may lend itself to melanoma has yet to be tested. In summary, the role of IFNs as adjuncts to chemotherapy and biologic therapy of melanoma is being studied intensively (Table 120.10). There are encouraging data to suggest that IFNs may act through vascular mechanisms that reduce tumor tissue pressure and other physiologic barriers to antitumor therapies and imaging agents.¹⁷⁸

Interleukin-2 and Adoptive Immunotherapy. IL-2 has been intensively explored for therapy of melanoma since this central immunoregulatory cytokine (T cell growth factor) was obtained from lectin-stimulated lymphoid cell lines over a decade ago.

IL-2 and Lymphokine-Activated Killer Cells. In 1982, Grimm and colleagues¹⁷⁹ reported that natural IL-2 and recombinant DNA-produced IL-2 could activate large granular lymphocytes to kill a variety of human tumor cells, suggesting that tumor cells might be susceptible to IL-2 with or without lymphokine-activated killer (LAK) cells. The modality of adoptive effector cell transfer and of IL-2 on which it depends, was developed preclinically and rapidly translated to large-scale clinical studies through recombinant DNA technology.^{180,181} Based on experimental studies demonstrating that the greatest antitumor activity is obtained at the maximally tolerated dosages of IL-2 and that IL-2 with LAK cells has greater antitumor effects than IL-2 alone in mice,¹⁸² the National Cancer Institute (NCI)'s surgery branch conducted a series of mural and extramural clinical studies of IL-2 with LAK cells.¹⁸¹ In six extramural clinical research centers assembled as the IL-2 Extramural Working Group, high-dose IL-2 with the adoptive transfer of effector cells was intensively pursued to confirm the antitumor activity in melanoma, renal cell carcinoma, and colorectal carcinoma.

Table 120.10. Summary of Clinical Trials in Melanoma Chemotherapy and Biologic Therapy Combinations

Drug(s)/Dose(s)	No. of Evaluable Patients	No. of PR	No. of CR	OR Rate* (%)
rIL-2 and DTIC rIL-2 (2–18 x 10 ⁶ IU/m ²) DTIC (850–1000 mg/m ²)	86	12	5	20 (12–30)
Interferon and chemotherapy DMFO (6 g/m ²) Interferon (6 x 10 ⁶ U/m ²)	17	2	1	18 (4–43)
IFN α -2a and DFMO IFN α -2a (36 x 10 ⁶ U/m ²) DFMO (2.25 g/m ²)	16	0	0	0 (0–21)
IFN α -2b and cyclophosphamide IFN α -2b (10 x 10 ⁶ IU/m ²) Cyclophosphamide (25 mg)	17	1	0	6 (0–29)
IFN α -2a and dacarbazine IFN α -2a (3–9 MU/m ² daily) Dacarbazine (200 mg/m ²)	43	7	6	20 (17–46)
IFN α -2b and dacarbazine IFN α -2b (10 MU/m ²) Dacarbazine (200 mg/m ² daily)	21	4	0	19 (5–42)
IFN- β and chemotherapy IFN- β (30 MU/m ² daily) Dacarbazine (10 mg/m ²) Cimetidine (300 mg)	12	0	0	0 (0–27)

PR = partial responses; CR = complete responses; OR = objective response.
*95% confidence interval.

With high doses of IL-2 (100,000 U/kg, Cetus [Chiron] Corp.; or $1-6 \times 10^6$ U/m², Hoffmann-La Roche) administered daily for up to 5 days by intravenous bolus every 8 hours and repeated after 7 to 10 days,^{181,183,184} partial responses were obtained in 10 of 42 (24%) evaluable melanoma patients treated (60 total). By comparison, four complete and six partial responses were obtained among 48 (66 total) subjects treated with IL-2 and LAK (21%). There is no evidence that adoptive transfer of LAK cells has significantly improved the antitumor efficacy of IL-2 as a single agent for therapy of melanoma, either as tested at the NCI Surgery Branch or by the Extramural Working Group.^{185,186}

A major obstacle for the implementation of the high-dose bolus IL-2 regimen of the NCI Surgery Branch has been its toxicity. This toxicity is directly related to the dose of IL-2. Chills, pruritus, nausea, vomiting, and diarrhea are common. These may be associated with hypotension, somnolence, disorientation, and coma, as well as respiratory distress, shock, and even death. The major side effects of high-dose IL-2 are related to the induction of a capillary leak syndrome and to the secretion of other cytokines by cells of the immune system. Despite significant incidence of side effects, Rosenberg and colleagues¹⁸⁴ reported a treatment-related mortality rate of only 1.5% in all patients receiving high-dose IL-2 at the Surgery Branch of the NCI. West¹⁸⁷ has reported diminished toxicity and comparable antitumor activity from the use of continuous infusions of 3×10^6 U/m²/d (Cetus $5-18 \times 10^6$ IU/m²/d). A study of maximally tolerated doses of IL-2 delivered with LAK cell transfer suggests that the antitumor efficiency of continuous infusion may be less than that of bolus administration for melanoma.¹⁸⁸

High-dose IL-2 represents an evolving area of research in biologic therapy and forms the basis for the only FDA-approved systemic biologic therapy of disseminated melanoma.

IL-2 and Tumor-Infiltrating Lymphocytes. Experimental studies of effector cells derived from tumor-infiltrating lymphocytes (TIL) in mice suggest improved antitumor efficacy and the potential emergence of cytotoxic T cells from these TIL.¹⁸⁹ The first clinical translation of these studies suggests improved antitumor efficacy for melanoma.¹⁹⁰ An inherent problem with the therapeutic use of TIL has been the technical difficulty and low frequency of outgrowth of cells appropriate for adoptive transfer. The possibility of using tumor-specific T cells that are generated from TIL or induced by specific immunization of the host in vivo or in vitro is an evolving area of therapeutic research. To date, it has not been established that TIL add to the benefit of IL-2.

Combined-Modality Regimens. The use of IL-2 in a range of combined-modality regimens has been advanced, first with IFN alpha-2¹⁹¹⁻¹⁹³ and more recently with IFN gamma, TNF, low-dose cyclophosphamide, DTIC, and cisplatin and amifostine (WR2721).¹⁹⁴⁻¹⁹⁸ These combinations have not significantly elevated the response rate to IL-2. The experience to date with IL-2 and IFN alpha has been the largest, and whereas response rates are reported to be somewhat above those of IFN alpha and IL-2 taken individually at 17 to 20%, no evidence of synergism, or even of an additive benefit, can be adduced to balance the toxicity of this combination.

CHEMOTHERAPY Single-Agent Chemotherapy. Systemic medical management has failed to improve significantly the survival of patients with nonresectable melanoma. DTIC, the only agent that has reproducibly caused partial remissions of disease, in as many as 20% of subjects overall, is the only FDA-approved chemotherapy for melanoma.^{199,200} DTIC has undergone the most extensive clinical trials of any single agent, with an objective response rate of 11 to 28% in reported series of 100 or more patients. Although the overall response rate is cited as 20%, there is only a 4% rate of complete responses, primarily in patients with soft-tissue metastases,²⁰⁰ and responses are rare for visceral sites of metastasis.

Single agents with reported response rates of more than 15% include nitrosoureas, platinum-coordination compounds, *Vinca* alkaloids, dibromodulcitol (mitolactol), detorubicin, and paclitaxel (Taxol).²⁰¹⁻²¹⁷ None of these agents alone and, with few exceptions, none in combination have significantly exceeded the 20% efficacy of dacarbazine (Table 120.11). Phase II studies in patients without previ-

ous treatment are required to define the activity of new agents with greater precision. It appears, however, that available new chemotherapeutic agents have modest antitumor activity against melanoma.

Combination Chemotherapy. In multi-institutional cooperative group trials, combination chemotherapy regimens have had increased toxicity and until recently have not enhanced response rates significantly (> 20%) over DTIC (Table 120.12). An analysis of three phase III studies of DTIC given alone or in combination with other agents showed that 26 of 580 patients (4.5%) achieved complete remission. Of the 26 remissions, 17 were associated with soft-tissue metastases and 6 (1%) lasted over 30 to 60 months.²⁰⁰ By contrast, complete remissions were achieved in only 10 of 503 patients (2%) treated with a variety of investigative chemotherapeutic regimens, and only 3 of these survived disease-free for more than 60 months. This experience suggests that durable responses to chemotherapy are indeed rare and, conversely, argues that the benefits observed with DTIC or other biologic and chemotherapeutic agents should not be attributed to spontaneous remission.²¹⁸

Although two combinations employing cisplatin have been suggested to show significantly greater activity than DTIC alone, more recent studies indicate that these multiple agents may be no more effective.²¹⁹ The most recent advance in multi-agent chemotherapy for melanoma is the combination of chemotherapy with the biologic agents IL-2 and IFN alpha. Initial reports from single-institution trials have demonstrated response rates as high as 60% with short-term complete remission rates of 12 to 15%. Both sequential and concurrent biochemotherapy regimens have been employed. Their toxicity is primarily based on the high doses of IL-2, which limits their use in younger patients with high performance levels, a group that traditionally responds to DTIC alone. A combination of DTIC, carmustine (BCNU), cisplatin, and tamoxifen, first reported by Del Prete and colleagues,²⁰⁴ was extended by McClay and colleagues^{210,211,220} in two single-institution trials. A response rate of about 50% (11/20 objective responses) was reported. Phase III trials conducted by the University of Pittsburgh Cancer Institute²²¹ and by ECOG²²⁰ have not corroborated any benefit of tamoxifen in combination chemotherapy for melanoma.

A recent report from JWCI investigators showed that concurrent biochemotherapy using decrescendo dosing of IL-2, post-treatment G-CSF, and low-dose tamoxifen produced a 57% overall response rate in patients with poor-prognosis metastatic melanoma. This modified regimen was associated with significantly lower toxicity levels than those

Table 120.11. Clinical Trials of Single-Agent Chemotherapy Other Than Dacarbazine in Melanoma

Drug	Dose	Number of Evaluable Patients	No. of PR	No. of CR	Rate of OR* (%)
Alkylating agents and nitrosoureas					
Estramustine	12 mg/kg	26	3	0	12 (2-30)
Ifosfamide	1.2-3 g/m ²	48	3	1	8 (2-20)
Mitolactol (dibromodulcitol)	100-1800 mg/m ²	139	8	2	7 (4-14)
Lomustine (CCNU)	130 mg/m ²	41	4	1	12 (4-26)
Semustine (methyl-CCNU)	40-225 mg/m ²	47	10	1	23 (12-38)
PCNU	75-110 mg/m ²	66	6	2	12 (6-17)
Chlorozotocin	120-175 mg/m ²	161	12	4	10 (6-17)
Fotemustine	100 mg/m ²	69	17	2	26 (18-40)
Hormonal agents					
Tamoxifen	20 mg/day - 100 mg/m ²	172	7	5	7 (4-13)
Megestrol	500 mg/day	20	0	0	0
Plant-derived agents					
Paclitaxel (Taxol)	125-275 mg/m ²	63	10	2	19 (10-31)

PR = partial response; CR = complete response; OR = objective response.
*95% confidence interval.

of standard concurrent biochemotherapy.²²³ Several institutions are currently comparing the efficacy of these newer biochemotherapy regimens with that of DTIC-based combination therapy.²²⁴

HORMONAL THERAPY The natural history of malignant melanoma suggests at least a casual relationship between estrogen and the onset of malignant activity. Melanoma is infrequently seen before puberty, except in cases of familial melanoma, and the peak incidence of melanoma in females coincides with the late childbearing years and the beginning of menopause. In addition, cases have been reported of spontaneous regression following parturition, as well as periods of widespread dissemination during pregnancy.^{225,226} Furthermore, survival rates always favor the female population, especially postmenopausal women.

Estrogen receptors have been reported in benign nevi of melanoma patients and in tumor cells,²²⁷ but not in benign nevi from normal individuals. This supports the theory that malignant melanoma is estrogen-dependent and that the binding of estrogen to cell-specific receptors may result in a molecular alteration associated with the neoplastic transformation of normal, benign nevi. Other investigators have failed to support these findings.²²⁸ If human malignant melanoma is indeed estrogen-dependent, then a specific clinical application becomes feasible. Since estrogen, a steroid hormone, exerts its biologic effect through the mediation of cytoplasmic protein receptors, then the pres-

ence of an estrogen receptor on the cell surface might be a biologic marker in melanoma patients.

Tamoxifen alone at standard or high doses has little objective anti-tumor activity in metastatic melanoma.^{229,231} The mechanism of synergism between tamoxifen and the three agents employed by Del Prete and colleagues²⁰⁴ has been a matter of conjecture. The possibility of calcium channel activity²¹⁹ and interaction with cisplatin or BCNU has been raised. Cocconi and the Italian Cooperative Multicenter Oncology Group²³⁰ reported the results of a randomized study of DTIC with or without tamoxifen. A significant advantage was demonstrated for DTIC-tamoxifen, and the beneficial impact of tamoxifen seemed to occur chiefly among females. The benefits of adding tamoxifen to combination chemotherapy were not validated in a recently completed NCCTG and Mayo Clinic study.²³²

RADIATION THERAPY Radiation has been widely used, often with excellent results, in the palliation of symptoms from metastatic melanoma. Metastatic sites where radiation has been of great palliative benefit include the lung, lymph nodes, subcutaneous nodules, bone, brain, spinal cord, and abdomen. The response rates depend on the dose of radiation that can be safely delivered to the involved region, as well as the volume of disease and intrinsic radiosensitivity of the tumor cells. The most appropriate dose per fraction in the treatment of melanoma has been the subject of much controversy. Certain *in vitro* features of irradiated melanoma cell lines (a broad shoulder on many radiation cell-survival curves) suggested that a larger-than-standard dose per fraction would be more advantageous in cell kill. Because of the heterogeneity of the studies in the literature (with respect to doses employed, techniques of irradiation, sites of metastases, and performance status of patients), proof that high doses per fraction was beneficial remained elusive. Numerous studies supported the high dose per fraction model,²³³ whereas others refuted the concept.²³⁴ Because greater late toxicity is associated with larger doses per fraction, it was believed that a stronger scientific basis for its use was needed than uncontrolled, retrospective data. Thus, the RTOG initiated a prospective randomized trial in patients with measurable melanoma.²³⁵ This trial compared 4 fractions of 8 Gy (one fraction per week) to 20 fractions of 2.5 Gy (daily, 5 fractions per week). There was no difference in complete (24.2 and 23.4%, respectively) or in partial response (35.5 and 34.4%, respectively). It was concluded that the most appropriate fractionation should be determined by standard factors (location of lesion, life expectancy, convenience, and efficacy) rather than histology.

Brain Metastases. Conventional whole-brain radiation has been used for palliation of symptoms, typically with survival of only 4 to 6 weeks. Patchell and colleagues²³⁶ demonstrated a significant reduction in neurologic sequelae when surgical resection of solitary metastases from a variety of tumor types was followed by whole-brain radiation. More recent studies suggest that stereotactic radiosurgery may provide a safe and effective method for control of disease in patients who are not candidates for resection.²³⁷

FUTURE HORIZONS

Prevention of melanoma appears possible through education about the putative role of sunburn in fair-skinned individuals. Clothing, sun-blocking agents, and avoidance of exposure may impact high-risk behavior patterns. Intergovernmental action to eliminate the manufacture of chlorofluorohydrocarbons and other measures to preserve the ozone layer are fundamental to long-range cancer control measures.

Improvements in treatment for malignant melanoma, a cancer that is rapidly increasing in incidence, must be directed to both the early and late stages of the disease. Because thin, early-stage melanomas are highly curable by simple surgical excision, early diagnosis must be the foundation for more effective therapy. The most practical way to do this is by public education and skin screening projects, which have demonstrated effectiveness in establishing earlier diagnosis.^{238,239}

There is also an urgent need for improved therapy in the melanoma patient who has metastases. Perhaps the most promising approach to metastases in the regional nodes or distant sites is more aggressive surgery in combination with postsurgical adjuvant therapy. Phase II

Table 120.12. Clinical Trials of Combination Chemotherapy in Melanoma

Drug(s)/Dose(s)	No. of Evaluable Patients	No. of PR	No. of CR	OR Rate* (%)
Cisplatin-based agents with tamoxifen therapy	40	17	4	53 (36–68)
DTIC and CDDP combination	130	27	6	25 (18–34)
DTIC 200–750 mg/m ²				
CDDP 15–100 mg/m ²				
DTIC and CDDP combinations with vindesine	155	38	11	32 (24–39)
DTIC 250–450 mg/m ² /d				
CDDP 50–100 mg/m ² /d				
Vindesine 3 mg/m ² /d				
DTIC and CDDP combinations with vinblastine	157	30	5	22 (16–29)
DTIC 150–800 mg/m ²				
CDDP 20–50 mg/m ²				
Vinblastine 1.6–5 mg/m ²				
DTIC and CDDP combinations with carmustine	20	1	1	10 (1–25)
DTIC 220 mg/m ² qod				
CDDP 25 mg/m ² qod				
Carmustine 150 mg/m ² /6 wk				
Vinblastine/bleomycin/cisplatin combination	20	0	0	0 (0–17)
Vinblastine 6 mg/m ²				
Bleomycin 15 mg/m ²				
Cisplatin 50 mg/m ²				
Vinblastine/bleomycin/cisplatin combination with DTIC and DBD	42	10	1	26 (14–42)
Vinblastine 3–6 mg/m ²				
Bleomycin 15 mg/m ²				
Cisplatin 50 mg/m ²				
DTIC 800 mg/m ²				
DBD 125 mg/m ²				
BCNU/DBD combination	20	3	1	20 (6–44)
BCNU 180 mg/m ²				
DBD 100 mg/m ²				

PR = partial responses; CR = complete responses; OR = objective response;

DTIC = dacarbazine; CDDP = cisplatin; BCNU = carmustine; DBD = dibromodulcitol.

*95% confidence interval.

studies with melanoma vaccines have been promising, and the results of multi-center phase III trials should become available shortly.¹⁶⁵ The last 2 decades have seen no significant progress in extending the survival of patients with distant metastases, despite multiple trials of cytotoxic chemotherapy agents. Although some of the newer combination regimens appear to have improved the response rate when compared with DTIC alone, these responses are short-lived in patients with distant metastases. When combined with biologic response modifiers such as IFN and IL, immunotherapy based upon specific melanoma antigens, whether active or adoptive, probably holds the greatest promise for future progress.

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