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Malignant melanoma: Treatments emerging, but early detection is still key

■ ABSTRACT

Although we are beginning to develop treatment options for malignant melanoma, earlier recognition of potential primary melanomas remains the most effective way to increase survival in this highly malignant disease. This article reviews prominent risk factors for melanoma, key physical findings in at-risk patients, new melanoma staging guidelines, and recent and emerging therapy options.

■ KEY POINTS

Although sun exposure remains a strong risk factor for melanoma, people with multiple atypical moles are at the highest risk of developing melanoma.

Although epidemiologic data are inconclusive about whether using a tanning bed or sunlamp increases the risk for melanoma, it is probably prudent to counsel patients to minimize such exposure.

Thickness of the primary lesion is the best predictor of prognosis.

Interferon alfa-2b significantly increases disease-free survival as well as overall survival of patients at high risk of recurrent melanoma.

Vaccines show promise but are still experimental.

WE NOW HAVE A DRUG—interferon alfa-2b—that can increase disease-free survival rates in malignant melanoma. Nevertheless, primary care physicians can have far more of an impact on this disease by detecting it earlier in its course and by counseling patients at risk on how to recognize and possibly avoid it.

An aggressive and deadly cancer, melanoma affects relatively young patients: about 60% of deaths due to melanoma occur in patients younger than 60 years, and 20% occur in patients younger than 40 years.^{1,2}

This review clarifies:

- The prominent risk factors for melanoma
- Physical findings in people at higher-than-average risk for developing malignant melanoma—signs that may be discovered on brief examination
- New staging guidelines for melanoma
- Surgical treatment for the primary lesion
- Adjuvant medical treatment for patients at high risk for recurrent melanoma and for patients with metastatic disease.

■ INCIDENCE IS INCREASING: A DIRECT RESULT OF SUN EXPOSURE

The incidence of melanoma is rapidly increasing, almost tripling in men and doubling in women in the 25-year interval from 1973 to 1998.³ In absolute numbers, 41,600 cases of melanoma and 7,300 deaths due to melanoma were reported in 1998, and the American Cancer Society estimates that in 2002 more than 53,000 new cases will be diagnosed and about 7,400 people will die of it.¹ Yet, malig-



nant melanoma accounts for only approximately 3% to 4% of all skin cancers.

Epidemiologic studies suggest that the increase is not an epiphenomenon of increased surveillance for the disease. Rather, it is thought to be a direct result of increased sun exposure.⁴

■ RISK FACTORS

Prominent risk factors for melanoma include dysplastic nevi, genetic factors, and sun exposure.

Dysplastic nevi indicate greater risk

From 18% to 35% of cutaneous primary melanomas arise from a preexisting nevus. In fact, the number of both common (benign or congenital) and dysplastic nevi is one of the strongest risk factors for melanoma, and the more pigmented nevi that are present and the larger they are, the greater the risk.⁵⁻⁷

Dysplastic nevi, present in 2% to 5% of Caucasian adults, raise the risk much further than large or numerous benign nevi.^{8,9} However, dysplasia is a pathologic diagnosis. The term *atypical nevus* is more clinically useful in raising the suspicion of nevi likely to be harboring underlying dysplasia from benign congenital or acquired nevi.

How to recognize possibly dysplastic nevi. In a recent large case-control study,¹⁰ a nevus was recognized as possibly dysplastic if it met both of the following criteria:

- At least 5 mm in diameter with flatness of texture (either entirely flat or some portion flat)
- Two of the following: variable pigmentation, an irregular asymmetric outline, or indistinct borders.

Using these criteria, and after controlling for other risk factors (eg, sun exposure), the investigators estimated that having one dysplastic nevus doubled a person's lifetime risk of melanoma, and having two or more dysplastic nevi increased the risk sevenfold (TABLE 1).

Management of dysplastic nevi. Not all dysplastic nevi evolve into melanomas; rather, they should be thought of as markers of risk. Although there are no firm guidelines for their management, it is reasonable to refer any patient with an atypical-appearing nevus to a

TABLE 1

Relative risks of melanoma by nevus type and number

TYPE	NUMBER	RELATIVE RISK
Nevi > 2 mm and < 5 mm	0-24	1.0
	25-49	1.8
Nondysplastic nevi > 5 mm	2-4	1.3
	5-9	1.7
Dysplastic nevi	1	2.3
	2-4	7.3

ADAPTED FROM TUCKER MA, HALPERN A, HOLLY EA, ET AL. CLINICALLY RECOGNIZED DYSPLASTIC NEVI: A CENTRAL RISK FACTOR FOR CUTANEOUS MELANOMA. JAMA 1997; 277:1439-1444.

dermatologist for evaluation and possible biopsy.

Patient education is equally important. Patients with atypical nevi need to know about their increased risk of melanoma, should be counseled to limit unprotected sun exposure, and should be clearly told to seek immediate attention for any newly appearing nevus or any nevus that changes in appearance.

Genetic factors

Melanoma seems to have a genetic component, although it is not yet clearly defined.

Familial syndromes. Approximately 8% to 10% of melanomas arise in people with a family history of the disease, and a number of kindreds have been reported whose members are at very high risk.^{11,12} These people likely have a heterogeneous group of syndromes, all characterized by multiple cutaneous melanomas with multiple atypical nevi; various names for these syndromes include the B-K mole syndrome, dysplastic nevus syndrome, atypical mole syndrome, and familial multiple mole-melanoma syndrome.

CDKN2A deletion. The CDKN2A gene, residing at the 9p21 locus, is often deleted in people with familial melanoma. Linkage analysis studies show that this gene's absence plays an important role in melanoma and other malignancies.^{13,14}

CDKN2A encodes for two products, p16 and p14ARF, both of which appear to help suppress cell growth and proliferation. p16

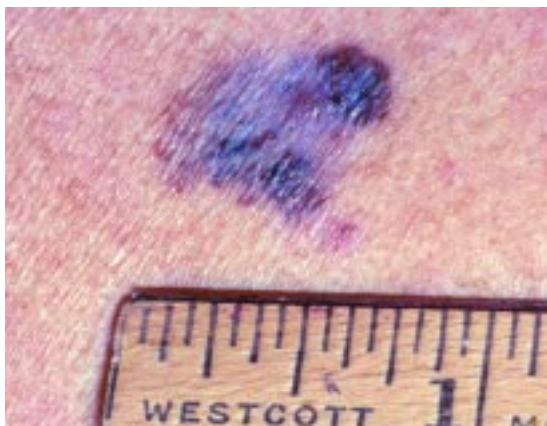
Melanoma has doubled to tripled in incidence in the past 25 years

The ABCs of malignant melanoma:

Asymmetry



Border irregularity



Color variegation



FIGURE 1. The ABCD mnemonic for the appearance of malignant melanoma. Top, **A**symmetry. Highly regressed primary melanoma demonstrating prominent asymmetry. Middle, **B**order irregularity. Primary melanoma with indistinct borders, color variation, and diameter of about 15 mm. Bottom, **C**olor variegation. Deeply pigmented melanoma with irregular borders and slight color variation. (“**D**” in this scheme stands for diameter > 6 mm.)

PHOTOS COURTESY OF PHILIP BAILIN, MD

inhibits cyclin-dependent kinase 4 (CDK4), an enzyme that promotes cellular proliferation. p14ARF inhibits an enzyme that degrades p53, a protein that helps maintain genomic integrity and cellular homeostasis.¹⁵

CDK4 overexpression. A second mutation has been linked to a locus at 12q14, which encodes for CDK4 itself. In this mutation, CDK4 is constitutively overexpressed and is active in phosphorylating the retinoblastoma protein that drives cell proliferation.¹⁵

Unidentified mechanisms likely. A study of the genetics of melanoma found that only 30% of the persons with dysplastic nevi had abnormalities of CDKN2A.¹⁵ Therefore, unidentified genetic mechanisms are likely involved in the development of dysplastic nevi and subsequent melanoma.

Sun exposure and tanning beds

Sun exposure is a well-recognized risk factor for melanoma,^{4,16} with case-control studies, geographic studies, and migrant studies showing a higher risk for melanoma in people living in sunny vs less sunny climates.¹⁷ Because excessive sun exposure has been implicated in the increasing incidence of this disease, it has received considerable attention in the lay press and in public education programs from the American Cancer Society and the American Academy of Dermatology.

Individual characteristics such as light complexion, blond, fair, or red hair, and blue eyes confer a greater risk, as does a propensity to easily sunburn, inability to tan, and ease of freckling.¹⁸

Is continuous exposure safer? Epidemiologic data gathered since the 1970s suggest that intense, intermittent sun exposure and repeated sunburns in childhood are associated with a higher risk of melanoma than continuous exposure throughout life.¹⁸ Supporting this hypothesis: melanomas tend to occur on body areas sporadically exposed to the sun, such as the back in men and the legs in women.⁴ A review of 10 epidemiologic studies concluded there is “reasonably consistent evidence for a positive association with intermittent sun exposure.”¹⁷

However, the studies were largely based on subjects’ ability to recall past sun exposure.

TABLE 2

New staging system for cutaneous malignant melanoma

T*	THICKNESS OF PRIMARY TUMOR		
Tis	In situ		
T1	≤ 1.0 mm		
T2	1.01–2.0 mm		
T3	2.01–4.0 mm		
T4	> 4.0 mm		
N†	NO. OF POSITIVE LYMPH NODES		
N0	0		
N1	1		
N2	2 or 3		
N3	≥ 4 (or combinations of in-transit metastases, satellite lesions, or an ulcerated primary lesion with any number of nodes)		
M	METASTASES		
M0	0		
M1	Distant subcutaneous or lymph node metastases		
M2	Lung metastases		
M3	All other visceral or any distant metastases or an elevated lactate dehydrogenase level not attributable to another cause		

CLINICAL STAGE	T	N	M
0	T0	N0	M0
IA	T1a	N0	M0
IB	T1b	N0	M0
	T2a	N0	M0
IIA	T2b	N0	M0
	T3a	N0	M0
IIB	T3b	N0	M0
	T4a	N0	M0
IIC	T4b	N0	M0
	T1–T4a	N1b	M0
IIIA	T1–T4a	N1b	M0
IIIB	T1–T4a	N2b	M0
IIIC	Any	N2c	M0
	Any	N3	M0
IV	Any	Any	≥ M1

*a, without ulceration; b, with ulceration

†a, micrometastasis; b, macrometastases; c, in-transit metastases with metastatic lymph nodes

ADAPTED FROM BALCH CM, BUZAID A, ATKINS MB, ET AL. A NEW AMERICAN JOINT COMMITTEE ON CANCER STAGING SYSTEM FOR CUTANEOUS MELANOMA. CANCER 2000; 88:1484–1491.

shortcomings when counseling patients, since patients may misinterpret the findings and believe that continuous or consistent, unprotected sun exposure is in some way safer than intense intermittent exposure.

Are tanning beds safer? Many people in the United States use tanning beds. Most tanning lamps emit nearly 100% ultraviolet A (UVA) radiation, whereas natural sunlight contains both UVA and UVB.³ UVB causes sunburn and is thus implicated in increasing the risk of melanoma.

However, a recent review found evidence that UVA causes DNA damage in cell cultures and human skin and induces melanoma in animals.⁴ Although epidemiologic data are inconclusive about whether using a tanning bed or sunlamp increases the risk for melanoma, it is probably prudent to counsel patients to minimize such exposure.

■ DIAGNOSIS

To aid physicians in diagnosing malignant melanoma earlier and to improve patient awareness of the disease, the National Institutes of Health (NIH) developed a consensus statement with the popular “ABCD” system for identifying potentially malignant moles and lesions.¹⁹ Clinical features of a new or changing pigmented lesion suggestive of melanoma include:

- Asymmetry
- Border irregularity
- Color variegation
- Diameter greater than 6 mm (FIGURE 1).

Since one survey demonstrated that 70% of melanomas are discovered by the patient or a family member,²⁰ this mnemonic device may be helpful to increase patient suspicion. However, any mole undergoing change should be considered highly suspect.

The initial evaluation of patients with a suspicious lesion should consist of a complete history with careful attention to family history. The entire skin surface should be thoroughly examined, and the regional lymph nodes palpated. The NIH recommends a biopsy with a narrow margin of normal-appearing skin for any suspicious lesion. Histologic evaluation determines the prognosis and plan for treatment.

There was no standard among questionnaires to ensure uniformity or to counteract recall bias.¹⁷ Physicians must be aware of these



■ STAGING AND PROGNOSIS

Like other types of cancer, melanoma has its own “TNM” staging system (TABLE 2), in which information about the primary tumor, lymph nodes, and metastases is used to derive the stage, from 0 (best prognosis) to IV (worst prognosis).

T: Primary tumor

Thickness. In the past, the pathologic classification system devised by Clark was used to determine the deepest level of anatomic invasion into the dermal sublayers and subcutaneous tissue; this was the principal variable for prognosis.²¹

Subsequently, Breslow²² devised a more reproducible method: measuring the thickness of the primary melanoma in millimeters. Multiple analyses subsequently proved that the thickest dimension of the primary tumor, regardless of depth of invasion, is the most important prognostic factor.²³ The current American Joint Committee on Cancer staging system has been revised to reflect this important change.²⁴

Kaplan-Meier survival curves (FIGURE 2) underscore that tumor thickness is an independent predictor of prognosis,^{23,25} and they suggest that physicians can improve survival by detecting tumors sooner, when they are thinner.

Ulceration is defined as absence of an intact epidermis over a portion of the primary tumor when viewed histologically (FIGURE 3).²³ Multivariate analyses have demonstrated that ulceration is the second most important factor in predicting prognosis and risk of metastasis.²³

Hence, the new staging system incorporates ulceration in the T category by assigning each T number an “a” (no ulceration) or “b” (ulceration). Since ulceration worsens prognosis, its presence requires that the primary lesion be upstaged to the next higher level.

Additional but secondary features that may affect prognosis are gender (males worse than females), anatomic site of the primary lesion (the extremities are better than the trunk), age (patients younger than 60 years tend to do better), presence of infiltrating lymphocytes, and the mitotic index.

Malignant melanoma: The thicker the lesion, the worse the prognosis

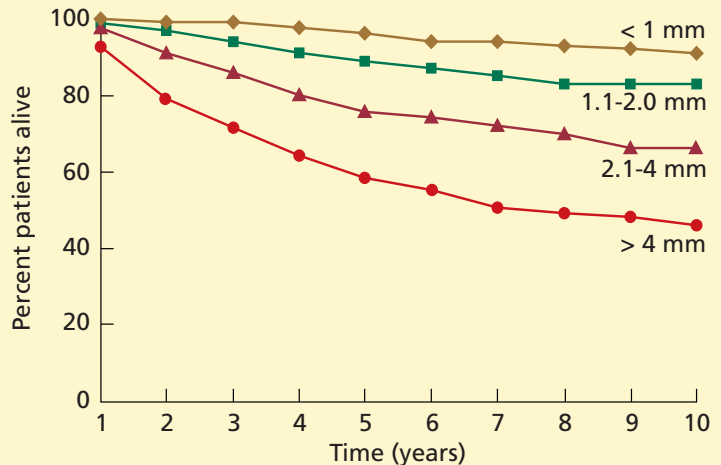


FIGURE 2. Kaplan-Meier survival curves according to thickness of primary lesion; combined data from 9,256 patients.

DATA ADAPTED FROM BUZAI A, ROSS M, BALCH CM, ET AL. CRITICAL ANALYSIS OF THE CURRENT AMERICAN JOINT COMMITTEE ON CANCER STAGING SYSTEM FOR CUTANEOUS MELANOMA AND PROPOSAL OF A NEW STAGING SYSTEM. *J CLIN ONCOL* 1997; 15:1039-1051; AND GARBE C, BUTTNER P, BERTZ J, ET AL. PRIMARY CUTANEOUS MELANOMA: IDENTIFICATION OF PROGNOSTIC GROUPS AND ESTIMATION OF INDIVIDUAL PROGNOSIS FOR 5093 PATIENTS. *CANCER* 1995; 75:2484-2491.

N: Regional nodal status

Nodal status in malignant melanoma is based on the number of positive lymph nodes: 0; 1; 2 or 3; or 4 or more. The staging system is based on recent reviews and meta-analyses that demonstrated that the absolute number of nodes involved carries the best prognostic information for survival^{23,24} and on a “best fit” model for prognosis.²⁴

Is elective lymph node dissection warranted? Approximately 90% of patients with newly diagnosed melanoma have no clinical evidence of regional nodal involvement on initial physical examination.²⁶ In the past, many of them might have undergone elective lymph node dissection.

However, three large randomized controlled trials tested the need for this procedure,²⁷⁻²⁹ and none of them found it consistently beneficial. For example, in one trial,²⁹ 553 patients with no clinically detectable lymph node involvement underwent either

Malignant melanoma: Nonulcerated and ulcerated

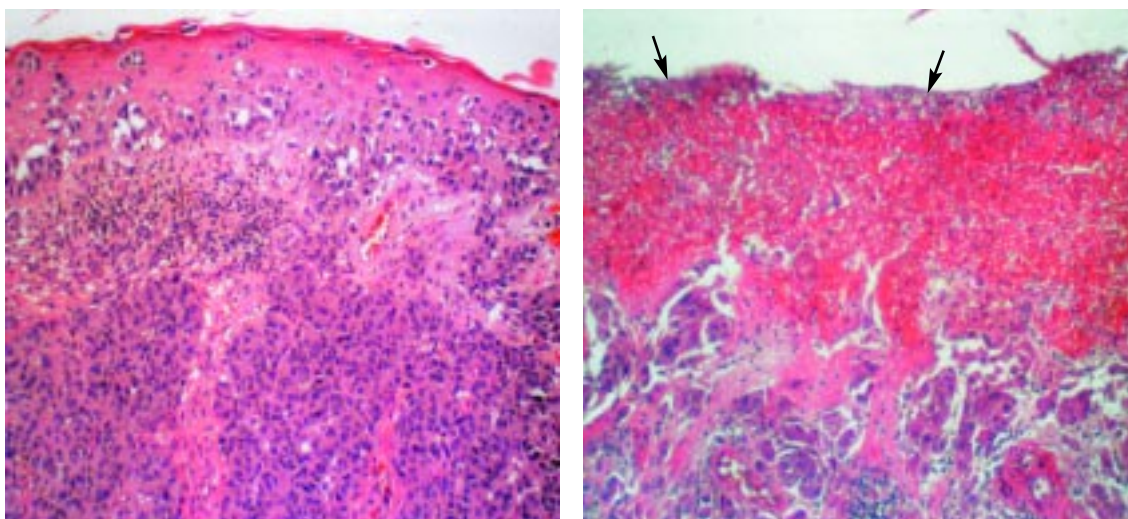


FIGURE 3. Left, nonulcerated melanoma; right, primary melanoma with ulcerated epithelium (arrows) (hematoxylin and eosin stain, $\times 200$).

PHOTOMICROGRAPH COURTESY OF RALPH J. TUTHILL, MD

immediate node dissection at the time of primary lesion excision, or node dissection only if positive nodes were clinically detected. No statistically significant difference was found in overall survival between the two groups.

If the sentinel node is negative, the rest are likely negative. Both preclinical and clinical research suggested that primary melanomas metastasize to regional node basins in an orderly fashion.^{30,31} The hypothesis was proposed that if the first node to which the lymphatic afferent vessels drain (ie, the sentinel node) is free of microscopic metastasis, then the remaining nodes in the region will be negative as well.

Initial data supporting this hypothesis came from a study of 223 patients with clinical stage I disease who underwent sentinel node identification (using isosulfan blue dye) and excision along with en bloc excision of the remaining regional node group. A total of 237 lymphadenectomies were performed (some patients with primary tumors on the trunk had more than one draining node region). The investigators identified 194 sentinel nodes. Forty of the lymphadenectomy samples contained malignant cells in at least one node: 38 in the sentinel node and 2 in nonsentinel nodes. This translated to a false-negative rate of less than 1%.³¹

Lymphoscintigraphic sentinel node identification continues to evolve as a procedure for diagnostic and prognostic purposes. Identifying a negative node can spare the patient a subsequent lymph node dissection, with its potential related morbidity.

In this procedure, approximately 1 to 4 hours before wide local excision, radiolabelled colloid solution is injected into the skin immediately surrounding the melanoma. Then isosulfan blue dye is injected into the same area by the surgeon in the operating room. Intraoperatively, the regional draining nodes are identified by scintigraphic counts, and the sentinel node is confirmed visually to contain the isosulfan dye.

It is recommended that patients with a positive sentinel node undergo complete regional nodal dissection. However, it is unknown if this will impart a better prognosis, especially if the remaining nodes are negative. Trials to address this issue are underway.

Many oncologists advocate the sentinel node procedure in patients who have no clinical evidence of node-positive disease but have a primary melanoma 1.0 mm or thicker.³² If the node is microscopically positive, then complete lymphadenectomy is recommended.

Ultraviolet A light, used in tanning beds, may not be as safe as thought



M: Metastases

In studies of patients with distant metastases,²⁴ the factors most predictive of a poor prognosis were:

- The site of metastasis. Patients with metastases to distant skin, subcutaneous tissue, or lymph nodes fared better than those with metastasis to the lung. Both of these groups had a somewhat better prognosis than patients with metastases to any other visceral organs (TABLE 2).
- The number of metastatic sites
- Elevated levels of serum lactate dehydrogenase (LDH), if not attributed to a cause other than melanoma.

■ EXCISION OF THE PRIMARY LESION

Until about 20 years ago, the standard of care for a primary melanoma lesion was to excise it along with a margin of 4 to 5 cm. This wide margin often led to significant morbidity (eg, bleeding, infection) and frequently necessitated the use of split-thickness skin grafts.

Large trials in the last 20 years have obviated the need for such aggressive local treatment.

In the first study to address this issue,³³ 612 patients with primary cutaneous lesions of 2 mm or less in thickness were randomly assigned to have either a 1-cm margin of excision or a 3-cm margin. Actuarial survival rates for both groups were similar at 4 years (96.8% in the 1-cm group vs 96.0% in the 3-cm group; $P = .58$).

A similar trial³⁴ included 486 patients with lesions 1 to 4 mm thick, who were randomized to have either a 2-cm or a 4-cm surgical margin. The 5-year survival rate was 79.5% in the 2-cm group and 83.7% in the 4-cm group (P NS).³⁴ Patients with primary melanomas thicker than 4 mm seem to gain no benefit from margins greater than 2 cm (TABLE 3).³⁵

■ ADJUVANT THERAPY

Patients with stage IIB or III malignant melanoma face a high risk that the melanoma will recur after the lesion is removed. For example, if the primary lesion is thicker than 4 mm with no pathologic evidence of nodal

TABLE 3

Recommended margins of excision for primary melanomas

THICKNESS OF PRIMARY LESION	MARGIN
Melanoma in situ	0.5 cm
< 1 mm	1 cm
≥ 1 mm (including lesions > 4 mm)	2 cm

involvement (stage IIB), the chance of recurrence is approximately 60%. If one or more lymph nodes are positive (stage III), the chance is 75% after resection of the primary lesion along with the regional nodes.

Until the recent Food and Drug Administration approval of interferon (IFN) alfa-2b, no adjuvant treatment was available to reduce the risk of recurrent disease in these high-risk patients.

Efficacy of interferon alfa-2b

IFN alfa-2b in high doses has been proven in three multi-institutional trials^{36–38} to improve prognosis after resection of the primary melanoma lesion.

The first trial³⁶ included 287 patients with thick primary lesions (> 4 mm), with or without clinical or pathologic regional node involvement, or who had regional nodal recurrence after resection of the primary lesion. Patients were randomly assigned to undergo either observation or 1 year of treatment with IFN alfa-2b in high doses. Median follow-up was 6.9 years (range 0.6–9.6 years).

The median disease-free survival for patients receiving IFN alfa-2b was 1.72 years, compared with 0.98 years in the observation group, a 43% difference ($P < .01$). The estimated 5-year survival for patients receiving IFN alfa-2b was 46%, compared with 37% for those in the observation group. Twelve-year follow-up of these results confirms the preliminary analysis (JM Kirkwood, personal communication, 2001).

The two more recent trials gave similar results: IFN alfa-2b had an impact on disease-free survival in both clinical trials and a significant improvement in overall survival

It is reasonable to refer any patient with an atypical-appearing nevus to a dermatologist

when compared to a ganglioside-based vaccine.^{37,38}

Side effects of IFN alfa-2b

Patients receiving adjuvant IFN alfa-2b therapy may have concerns about the treatment and its potential side effects. Although they will be under the care of an oncologist, the yearlong treatment makes it likely that some of these concerns will be brought to the attention of the primary care physician.

The most common toxicities of high-dose IFN alfa-2b are constitutional, hematologic, and neurologic.

Constitutional symptoms of fever, chills, and myalgias generally become more tolerated as treatment continues, but fatigue and anorexia tend to persist and can become quite troublesome, requiring dosage adjustment.

Hematologic effects. Leukopenia and thrombocytopenia are common and may respond well to a decrease in dose.

Neurologic effects. Many patients receiving high-dose IFN alfa-2b therapy experience depression, with anhedonia, flattened affect, and overall depressed mood. Whether this is a primary effect of IFN or a secondary reaction to the constitutional side effects is not known. Regardless, this depressed mood seems to respond well to serotonin reuptake inhibitor antidepressants in low doses. Indeed, some medical oncologists start one of these medications at the time the patient begins high-dose IFN alfa-2b treatment.

Despite such toxicities, 74% of the patients randomized to treatment with IFN alfa-2b in clinical trials were able to continue treatment for 1 year or until disease recurrence, with close observation and dosage adjustment when necessary.³⁶

Vaccines: Promising but experimental

Many patients ask about vaccines for treating melanoma. The lay press and media occasionally highlight important preclinical and clinical advances in this large area of research, as does the Internet.

Examples of melanoma vaccines include whole tumor-cell vaccines prepared from both autologous and allogeneic tumors, which are harvested from patients and inactivated with radiation. In addition, several antigenic

melanoma cell peptides are being used to stimulate cytotoxic T lymphocytes *in vivo*. Similarly, investigators are assessing ways of enhancing dendritic cell activity to enhance antigen presentation and improve T-cell response to tumor inactivation.³⁹

Patients should understand that although vaccines are a promising and evolving area of research, they are investigational and their role is yet to be established. Indeed, one recent trial was terminated early when more people died who were treated with vaccine than with high-dose IFN alfa-2b.⁴⁰

■ DISTANT METASTATIC DISEASE

Patients with distant metastatic melanoma have a median survival of a little more than 6 months, with a 95% risk of death.⁴¹ As reflected in the staging criteria, site of metastasis affects prognosis.

Dacarbazine (DTIC) and interleukin 2 (IL-2) are currently the only FDA-approved drugs for use in metastatic melanoma. Both have objective response rates of about 15% to 20%, as does IFN alfa-2b. Patients who achieve objective responses, particularly when complete, have improvement in survival.

Multi-institutional phase 3 clinical trials are underway to determine if combinations of chemotherapeutic agents or biologic agents can offer a survival advantage. Other treatments such as palliative surgery and radiation to improve quality of life are also used on an individual basis, and are best coordinated by the medical oncologist.

■ SURVEILLANCE AND FOLLOW-UP MUST BE VIGILANT

Regardless of the initial thickness of the primary lesion, all patients with a history of malignant melanoma need careful follow-up, as their risk of developing a second cutaneous melanoma is approximately fivefold higher than in the general population.⁴²

The risk of local or distant recurrence depends on the thickness of the primary lesion (FIGURE 2) and is most likely to occur within the first 3 years of diagnosis.⁴¹ Although there are no unanimously accepted guidelines for follow-up, practical recommendations can be made.


Any mole that changes is highly suspect

In general, patients should receive a complete skin examination every 6 months by a dermatologist, along with education about the increased risk of a second melanoma. In this way, new lesions can be discovered early, when they are thinner.⁴²

Patients with a history of primary melanoma less than 1 mm thick should be seen every 6 months during the first 3 years and annually thereafter. A history and physical examination should be performed, with particular attention to the site of the previously excised melanoma and regional lymph nodes. There are no data to support the routine use of laboratory or radiographic studies in these patients. However, some clinicians advocate periodic chest radiographs, since the lungs are the most common site of distant recurrence.

Patients with a previously excised melanoma of 1 mm or larger should be seen more frequently. Most authors suggest physician visits every 3 months during the first 2 to 3 years, and then every 6 to 12 months indef-

initely. Again, there are no data to support other laboratory or radiographic studies in the routine follow-up. The National Comprehensive Cancer Network guidelines for melanoma say that chest radiographs and liver enzyme levels, including LDH, are optional every 6 to 12 months for these patients.⁴³

All patients with a past history of melanoma should be counseled on the use of sun-protective clothing as well as sunscreens. Physicians should be certain that patients can conduct a complete skin self-examination, with particular attention to the scar of a previously excised primary lesion. First-degree relatives of patients should undergo a complete skin examination as well, especially if they have evidence of multiple atypical moles. 

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REFERENCES

1. **American Cancer Society.** Melanoma Resource Center. www3.cancer.org/downloads/STT/CancerFacts&Figures2002TM.pdf. Accessed 6/10/02.
2. **Borden EC.** Melanoma: chemoimmunotherapy (biologic and cytotoxic therapies for disseminated disease). In: Brain MC, Carbone PP, editors. *Current Therapy in Hematology-Oncology*. St. Louis: Mosby-Year Book, Inc; 1995:506-510.
3. **Jamal A, Devesa SS, Hartge P, Tucker MA.** Recent trends in cutaneous melanoma incidence among whites in the United States. *J Natl Cancer Inst* 2001; 93:678-683.
4. **Gilchrist BA, Eller MS, Geller AC, Yaar M.** The pathogenesis of melanoma induced by ultraviolet radiation. *N Engl J Med* 1999; 340:1341-1348.
5. **Bruce AJ, Brodland DG.** Overview of skin cancer detection and prevention for the primary care physician. *Mayo Clin Proc* 2000; 75:491-500.
6. **Rhodes AR.** Common acquired nevocytic nevi and the fourth dimension [editorial]. *Arch Dermatol* 2000; 136:400-405.
7. **Newton JA, Bataille V, Griffiths K, et al.** How common is the atypical mole syndrome phenotype in apparently sporadic melanoma? *J Am Acad Dermatol* 1993; 29:989-996.
8. **Tucker MA.** Individuals at high risk for melanoma. In: Elwood JM, editor. *Pigment Cell, 9th ed. Melanoma and Naevi: Incidence, Interrelationships, and Implications*. Basel: Karger; 1988:95-109.
9. **Rhodes AR.** Dysplastic melanocytic nevi. In: Freeberg IM, Eisen AZ, Wolff K, et al, editors. *Fitzpatrick's Dermatology in General Medicine, 5th ed.* New York: McGraw-Hill Co.; 1999:1060-1079.
10. **Tucker MA, Halpern A, Holly EA, et al.** Clinically recognized dysplastic nevi. A central risk factor for cutaneous melanoma. *JAMA* 1997; 277:1439-1444.
11. **Goldstein AM, Tucker MA.** Genetic epidemiology of familial melanoma. *Dermatol Clin* 1995; 13:605-612.
12. **Haluska FG, Hodi FS.** Molecular genetics of familial cutaneous melanoma. *J Clin Oncol* 1998; 16:670-682.
13. **Kamb A, Gruis NA, Weaver-Feldhaus J, et al.** A cell cycle regulator potentially involved in genesis of many tumor types. *Science* 1994; 264:436-440.
14. **Nobori T, Miura K, Wu DJ, Lois A, Takabayashi K, Carson DA.** Deletions of the cyclin-dependent kinase-4 inhibitor gene in multiple human cancers. *Nature* 1994; 368:753-756.
15. **Tsao H.** Update on familial cancer syndromes and the skin. *J Am Acad Dermatol* 2000; 42:939-969.
16. **Finkel E.** Sorting the hype from the facts in melanoma. *Lancet* 1998; 351:1866-1869.
17. **Elwood JM.** Melanoma and sun exposure. *Semin Oncol* 1996; 23:650-666.
18. **Langley RG, Barnhill RL, Mihm MC Jr, Fitzpatrick TB, Sober AJ.** Melanoma. In: Freeberg IM, Eisen AZ, Wolff K, et al, editors. *Fitzpatrick's Dermatology in General Medicine, 5th ed.* New York: McGraw-Hill Co.; 1999:1080-1116.
19. **NCI CancerNet.** What you need to know about moles and dysplastic nevi. http://cancernet.nci.nih.gov/cancer_information. Accessed 6/10/02.
20. **Koh HK, Miller DR, Geller AC, Clapp RW, Mercer MB, Lew RA.** Who discovers melanoma? Patterns from a population-based survey. *J Am Acad Dermatol* 1992; 26:914-919.
21. **Clark W Jr, From L, Bernardino EA, Mihm MC.** The histogenesis and biologic behavior of primary human malignant melanomas of the skin. *Cancer Res* 1969; 29:705-726.
22. **Breslow A.** Thickness, cross-sectional areas and depth of invasion in the prognosis of cutaneous melanoma. *Ann Surg* 1970; 172:902-908.
23. **Buzaid A, Ross M, Balch CM, et al.** Critical analysis of the current American Joint Committee on Cancer staging system for cutaneous melanoma and proposal of a new staging system. *J Clin Oncol* 1997; 15:1039-1051.
24. **Balch CM, Buzaid A, Atkins MB, et al.** A new American Joint Committee on Cancer staging system for cutaneous melanoma. *Cancer* 2000; 88:1484-1491.
25. **Garbe C, Buttner P, Bertz J, et al.** Primary cutaneous



- melanoma: identification of prognostic groups and estimation of individual prognosis for 5093 patients. *Cancer* 1995; 75:2484–2491.
26. **Morton DL, Wen DR, Wong JH, et al.** Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch Surg* 1992; 127:392–399.
 27. **Balch CM, Soong S-J, Bartolucci AA, et al.** Efficacy of an elective regional lymph node dissection of 1 to 4 mm thick melanomas for patients 60 years of age and younger. *Ann Surg* 1996; 224:255–266.
 28. **Veronesi U, Adamus J, Bandiera DC, et al.** Inefficacy of immediate node dissection in stage 1 melanoma of the limbs. *N Engl J Med* 1977; 297:627–630.
 29. **Veronesi U, Adamus J, Bandiera DC, et al.** Delayed regional lymph node dissection in stage I melanoma of the skin of the lower extremities. *Cancer* 1982; 49:2420–2430.
 30. **Wong JH, Cagle LA, Morton DL.** Lymphatic drainage of skin to a sentinel lymph node in a feline model. *Ann Surg* 1991; 214:637–641.
 31. **Morton DL, Wen DR, Wong JH, et al.** Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch Surg* 1992; 127:392–399.
 32. **Greshenwald JE, Thompson W, Mansfield PF, et al.** Multi-institutional melanoma lymphatic mapping experience: the prognostic value of sentinel lymph node status in 612 stage I or II melanoma patients. *J Clin Oncol* 1999; 17:976–983.
 33. **Veronesi U, Cascinelli N, Adamus J, et al.** Thin stage I primary cutaneous malignant melanoma: comparison of excision with margins of 1 or 3 cm. *N Engl J Med* 1988; 318:1159–1162.
 34. **Balch CM, Smith TJ, Jewell WR, Barnhill R.** Efficacy of 2-cm surgical margins for intermediate-thickness melanomas (1 to 4 mm): results of a multi-institutional randomized surgical trial. *Ann Surg* 1993; 218:262–269.
 35. **Heaton KM, Sussman JJ, Gershenwald JE, et al.** Surgical margins and prognostic factors in patients with thick (> 4 mm) primary melanoma. *Ann Surg Oncol* 1998; 4:322–328.
 36. **Kirkwood JM, Strawderman MH, Ernstoff MS, Smith TJ, Borden EC, Blum RH.** Interferon alfa-2b adjuvant therapy of high-risk resected cutaneous melanoma: The Eastern Cooperative Oncology Group Trial EST 1684. *J Clin Oncol* 1996; 14:10–17.
 37. **Kirkwood JM, Ibrahim JG, Sondak VK, et al.** High- and low-dose interferon alfa-2b in high-risk melanoma: first analysis of intergroup trial E1690/S9111/C9190. *J Clin Oncol* 2000; 18:2444–2458.
 38. **Jonasch E, Kumar UN, Linette GP, et al.** Adjuvant high-dose interferon alfa-2b in patients with high-risk melanoma. *Cancer J Sci Am* 2000; 6:139–145.
 39. **Thompson LW, Brinckerhoff L, Slingluff CL.** Vaccination for melanoma. *Curr Oncol Rep* 2000; 2:292–299.
 40. **Kirkwood JM, Ibrahim JG, Sosman JA, et al.** High-dose interferon alfa-2b significantly prolongs relapse-free and overall survival compared with the gm2-klh/qs-21 vaccine in patients with resected stage iib-iii melanoma: results of intergroup trial e1694/s9512/c509801. *J Clin Oncol* 2001; 19:2370–2380.
 41. **Ryan L, Kramer A, Borden EC.** Prognostic factors in metastatic melanoma. *Cancer* 1993; 71:2995–3005.
 42. **DiFronzo LA, Wanek LA, Morton DL.** Earlier diagnosis of second primary melanoma confirms the benefits of patient education and routine postoperative follow-up. *Cancer* 2001; 91:1520–1524.
 43. **Houghton A, Coit D, Bloomer W, et al.** NCCN melanoma practice guidelines. National Comprehensive Cancer Network. *Oncology* 1998; 12(7A):153–177.

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