Malignant Melanoma: Prevention, Early Detection, and Treatment in the 21st Century

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Abstract

Malignant melanoma continues to present a significant public health problem as its incidence is rising faster than that of any other cancer in the US. At current rates, 1 in 74 Americans will develop melanoma during his or her lifetime.

Management of melanoma is a complex issue requiring a multidisciplinary approach. The most effective method of protection against the development of melanoma is minimization of ultraviolet exposure from sunlight. Early detection and treatment are critical and result in improved patient survival rates. Surgical excision remains the mainstay of treatment but many new promising therapies are being investigated.

It is hoped that increased public and professional awareness and education in all areas relating to the prevention, detection, and treatment of malignant melanoma will contribute to decreasing trends in the incidence and mortality from this cancer in the future. (CA Cancer J Clin 2000;50:215-236.)

Introduction

Malignant melanoma represents a significant and growing public health burden in the US and worldwide. This year, it is estimated that 47,700 cases of invasive malignant melanoma and 20,000 to 40,000 cases of melanoma in-situ will be newly diagnosed in the US.

Melanoma is also one of the few remaining cancers with an increasing incidence rate. In the 1930s, the lifetime risk of an American developing invasive malignant melanoma was 1 in 1,500. Currently, that risk is 1 in 74 (Fig. 1). Deaths from malignant melanoma are also increasing. The mortality rate from malignant melanoma has risen about 2% annually since 1960 (Fig. 2). This year, it is estimated that 7,700 persons will die from malignant melanoma in the US.

Survival of patients with malignant melanoma is directly related to early detection. Melanoma that is confined to the epidermis (in-situ) carries no risk of death and a thin melanoma lesion carries very little risk of metastatic spread. Although multiple factors influence survival, thickness of the tumor has been shown to be the most important factor across multiple studies. The five-year survival rate for patients with early melanoma, defined as thinner than 1 mm, is 94% versus less than 50% for those with melanomas greater than 3 mm in thickness (Fig. 3).

Fortunately, despite rising incidence, there has been a marked concomitant increase in the five-year survival rate, from approximately 40% in the 1940s to almost 90% now. As the effectiveness of the principal treatment modality for primary malignant melanoma (i.e., surgical excision) has not changed substantially over the past several decades, the improved five-year survival rate can be attributed to...
earlier detection. Despite improved survival rates, the death rate from malignant melanoma continues to climb as a result of exponential increases in incidence.6

Malignant melanoma is a potentially lethal melanocytic neoplasm with a propensity for distant metastasis. Lesions may arise de novo, or within dysplastic, congenital, or banal nevi.7-10 Early detection and definitive therapy are necessary to minimize the risk of metastatic disease.

Melanoma may be virtually preventable with simple behavioral changes. Even with new strategies being developed to treat advanced disease, therefore, emphasis on prevention in professional and public education, as well as on early detection and treatment of this tumor is becoming increasingly important in this new century.

**Prevention of Melanoma**

**IDENTIFICATION OF INDIVIDUALS AT HIGH RISK**

The identification of individuals at high risk for malignant melanoma is important for the development of focused and efficient prevention efforts. Acute sun exposure resulting in sunburn remains a significant risk factor for the development of melanoma,11 but numerous other potential risk factors have been cited.12 Included among these are atypical mole syndrome/dysplastic nevus syndrome (Fig. 4),10,13-15 blistering sunburns,16 immunosuppression,17,18 prior therapy with psoralen with ultraviolet (UV) A light,19,20 UV exposure at tanning salons,21 elevated socioeconomic status,22 and history of melanoma in a first-degree relative.23-26

Certain phenotypic factors—including blue/green eyes, blond or red hair, light complexion, freckles, sun sensitivity, and an inability to tan—have been consistently associated with increased risk for the development of malignant melanoma. Other significant risk factors include a family history of melanoma,28 a personal history of nonmelanoma skin cancer or precancer, increased numbers of melanocytic nevi,27 increased num-
Both incidence and mortality rates from melanoma are increasing in the US. From Rigel et al, NYU Melanoma Cooperative Group, 2000.

From Rigel et al, NYU Melanoma Cooperative Group, 2000.
bers of melanocytic nevi in childhood, and xeroderma pigmentosum. Nevertheless, malignant melanoma can develop in any individual. The incidence of plantar surface melanoma in blacks is the same as in Caucasians.

Using multivariate analysis, it was determined that the following six risk factors independently influenced the risk of developing malignant melanoma:

- Family history of malignant melanoma
- Presence of blond or red hair
- Presence of marked freckling on the upper back
- History of three or more blistering sunburns prior to age 20
- History of three or more years of an outdoor summer job as a teenager
- Presence of actinic keratosis

Persons with one or two of these risk factors had a 3.5-fold increased risk for developing malignant melanoma compared with the general population. Those having three or more of the factors had an approximately 20-fold increased risk.

Environmental factors that increase the risk for malignant melanoma include living near the equator, working outdoors, and having primarily outdoor recreational habits.

Furthermore, people who have had one malignant melanoma are at an increased risk of developing another. Their risk ranges from 4% to 30% compared with the approximately 1% lifetime risk of malignant melanoma in all Americans.

Previous studies have demonstrated an association between germline mutations in tumor suppressor p16 and development of melanoma in melanoma kindreds, and recent studies have noted somatic p16 mutations in sporadic melanoma, as well. Potentially, a better understanding of these mutations and characterization of other molecular risk factors may enable us to identify highest risk individuals at the molecular level for more effective targeting of prevention and early detection efforts.

Prevention and Photoprotection

Since virtually all of the known risks for melanoma are related to susceptibility to, and the magnitude of, UV radiation exposure, protection from the sun’s rays plays a critical role in prevention. The most appropriate endpoint for determining the effectiveness of public policies regarding sun protection is the melanoma incidence rate.

Almost $500 million is spent on sunscreen annually in the US, and recent retrospective studies have shown the protective effect of sunscreens on malignant melanoma.
In Australia, where 74% of the population regularly uses sunscreen, melanoma incidence and mortality rates are beginning to fall. As sunscreen is the most commonly used method of sun protection in Australia, it is clear that these products have played a major role in this turnabout. Melanoma rates are also falling among Hawaiian Caucasians, a group that has among the highest per capita use of sunscreen in the US. Until we have prospective data to show the effect of sunscreens on melanoma risk more directly, these findings represent some of the best evidence of the protective effect of sunscreen use on melanoma incidence in large populations of individuals.

The conclusion that currently can best be drawn from all existing data is that a combination regimen of sun protection that includes protective clothing, avoiding midday sun, and regular use of broad-spectrum high sun protection factor (SPF) sunscreen (such as practiced in Australia), may be beginning to reduce melanoma incidence rates in some populations. This is the current recommendation of the American Academy of Dermatology and the American Cancer Society.

Enhancing Early Diagnosis

The goal of effective clinical recognition of early melanoma remains foremost for the successful management of this cancer. Early melanoma can be recognized using the following ABCD guideline (Fig. 5):

- **Asymmetry**—Most early lesions grow at an uneven rate resulting in an asymmetric pattern.
- **Border Irregularity**—The uneven growth rate also results in an irregular border.
- **Color Variegation**—Irregular growth also causes new shades of black, and light and dark brown.
- **Diameter**—Lesions with ABC features and diameters of greater than 6 mm should be considered suspicious for melanoma.

Advanced melanomas are more readily apparent and may be typically nodular or ulcerated (Fig. 6).

In addition to the classic appearing melanoma, a non-pigmented variant, amelanotic malignant melanoma, may mimic a pyogenic granuloma or a basal...
cell carcinoma clinically (Fig. 7). Also, melanoma may simulate benign lesions, including seborrheic keratoses, melanocytic nevi, lentigines, and ephilides (Fig. 8).

The evolving health care environment has placed an increasing emphasis on the diagnosis of melanoma by primary care physicians. Yet a recent study showed that non-dermatologists may be three times as likely to misdiagnose melanoma compared with dermatologists. It is especially important, therefore, for primary care providers to raise their index of suspicion regarding pigmented lesions and to sharpen their diagnostic skills with respect to melanoma.

HISTOLOGIC CHARACTERISTICS
Melanoma is histologically characterized by proliferation of atypical melanocytes with single cells predominating. Also characteristic is the presence of mitotic figures. Special stains, such as S100, HMB45, and most recently Mel45 in lentigo malignant melanoma, may be useful in the histologic diagnosis of melanoma. These stains are particularly useful in distinguishing the spindle cell variant of melanoma from other spindle cell neoplasms, including the spindle cell variant of squamous cell carcinoma and atypical fibroxanthoma, as well as in the diagnosis of melanomas initially presenting as metastatic malignancy of unknown primary site. In the future, these and other special stains may be useful in determining tumor-free margins on frozen section, thus allowing utilization of tissue conservation in melanoma surgery.

Figure 7. Amelanotic melanoma. Note red color and lack of melanin pigmentation.

Figure 6a-d. Progression of melanoma. a) Macular pigmented lesion on sole of foot with features of early melanoma; b) Progression of this lesion two years later with typical features of thicker melanoma; c) Melanoma on the foot of a black patient; d) More advanced melanoma with ulceration.
Diagnosis

Diagnosis of melanoma depends on clinical identification with histopathologic confirmation. To rule out melanoma in a clinically suspicious lesion, adequate biopsy must be performed and the specimen should be evaluated by a dermatopathologist or a pathologist experienced in the evaluation of pigmented lesions. In some patients, particularly those with atypical mole syndrome, biopsy of each suspicious lesion may be impossible. Full body or lesional photography may assist in the identification of recently changed lesions in these patients.

Recently, epiluminescence microscopy has been used in the evaluation of pigmented lesions. With this technique, pigmented lesions are examined in situ, under immersion oil, using a dermatoscope (a specially designed 10x lens mounted in an ophthalmoscope-like configuration). Use of dermatoscopy has led to the definition of a new set of subsurface features that may be helpful for in vivo diagnosis and holds exciting potential for improved diagnosis in the future (Fig. 9).

Another area of active research involves computer-assisted analysis of digitized dermatoscopic images. In the future, digitized clinical and dermatoscopic images compared with a sizeable database might offer increased sensitivity and/or specificity in the diagnosis of potentially malignant pigmented lesions. Telemedicine may also play an increasing role. Nevertheless, the bottomline in the diagnosis of melanoma is likely to continue to depend on the clini-
causal acumen of the clinician and the histologic expertise of the pathologist.

Maximizing Early Detection: Routine Examination of the Skin

As Neville Davis said, unlike other cancers, which are generally hidden from view, “Malignant melanoma writes its message in the skin with its own ink and it is there for all of us to see. Some see but do not comprehend.”47 As survival rates of patients with thinner malignant melanomas are much higher than those for patients with thicker ones, it is incumbent upon health care professionals to “comprehend” and “act” as early as possible.

Early detection of breast cancer is facilitated by both regular clinical and frequent self-examinations.63 Similarly, if malignant melanomas are to be identified while they are still curable, complete cutaneous examinations by physicians and other health care providers should be made, coupled with periodic self-examination of the skin by the individual.

Clinical Examination of the Skin

The equipment needed for complete examination of the skin is simple: An examination table, a source of bright light, and, occasionally, a magnifying lens. To facilitate examination of the scalp, an ordinary inexpensive blow dryer can be used.

The entire cutaneous surface should be examined. All pigmented lesions should be examined and carefully evaluated. Since a skin biopsy is usually such a simple procedure, any lesion even remotely suggestive of malignant melanoma should be given special attention and considered for histologic evaluation.

Self-Examination of the Skin

By routine self-examination of the skin, the patient assumes some of the responsibility for identifying early malignant melanoma at a time when such lesions are thin and curable.64

A thorough self-examination of the skin requires the individual to undress completely and to have a full-length mirror, a hand-held blow dryer, two chairs, and a well-lit room.

During the first self-examination, the patient should spend a good deal of time carefully inspecting the entire surface of the skin. With experience, self-examination should take but a few minutes. To look at parts of the skin surface that may be hard to see—e.g., some areas of the back, scalp, and buttocks—the patient may find it helpful to enlist the help of a spouse, relative, or friend.

Self-examination of the skin should be carried out step-by-step as shown in Figure 10. These pages can be photocopied and given to patients to encourage learning and practice of this important technique. Educational pamphlets for the public are also available through the American Cancer Society, the American Academy of Dermatology, and the Skin Cancer Foundation.

The patient should see a physician if he or she discovers a new pigmented lesion or any significant change in a preexisting pigmented lesion. Most early malignant melanomas are macular and grow in diameter for some time before they become elevated. Macular lesions are almost always curable, whereas lesions that develop plaques, papules, or nodules have a greater risk for metastases. The goal is to recognize early
Step 1: Make sure you have good lighting. You will need a full-length mirror, a hand-held mirror, a hand-held blow dryer, and two chairs or stools. Undress completely.

Step 2: Hold your hands out in front of you with your palms facing up, as shown. Look at your palms, fingers, the spaces between your fingers, and your forearms. Now turn your hands over and examine the backs of your hands, fingers, the spaces between fingers, your fingernails, and your forearms.

Step 3: Now stand in front of the full-length mirror. Holding your arms up and bent at the elbows, with palms facing you (as shown), examine the backs of your forearms and elbows in the mirror.
Step 4: Now observe the entire front of your body in the full-length mirror. Examine the front of your face and both sides. Look at your eyes, lips, hairline. Turn your palms toward the mirror and look at your upper arms; your chest; your abdomen; pubic area; thighs; and lower legs.

Step 5: Lift your arms over your head with the palms facing each other. Turn so that you can see your right side in the full-length mirror and look at the entire side of your body—your hands and arms, underarms, sides of your trunk, thighs, and lower legs. Turn and repeat the process, looking at your left side.
Step 6: Turn around and, with your back toward the full-length mirror, look at your buttocks and the backs of your thighs and lower legs.

Step 7: Now, using the hand-held mirror angled to help you see in the full-length mirror (as shown), examine the back of your neck, your back, and buttocks. You may also be able to examine the backs of your arms this way. Some areas are hard to see. You may find it helpful to ask your spouse or a friend to assist you.
Step 8: Continue using the hand-held mirror to look at your ears and scalp. The scalp is difficult to examine, especially if you have thick hair. You may use the hand-held blow dryer to lift the hair from the scalp. While some people are able to hold the mirror in one hand, the dryer in the other, and look in the full-length mirror, many cannot. It may be particularly useful to ask a spouse or friend to assist you with this part of the examination.

Step 9: Sit down and prop one leg up in front of you on a chair or stool, as shown. Using the hand-held mirror, look at the inside of the propped-up leg, beginning at the groin area and moving the mirror down the leg to your foot. Repeat this procedure with your other leg.

Step 10: Still sitting, cross one leg over the other. Use the hand-held mirror to examine the top of your foot, the toes, toenails, and spaces between the toes. Then look at the sole or bottom of your foot. Repeat the procedure for the other foot.
(thin) malignant melanomas when they are flat and curable.

Maximizing Early Detection: Screening

Since 1985, the American Academy of Dermatology has sponsored free annual National Melanoma/Skin Cancer Prevention Campaigns. By this year, over 1,000,000 persons have been screened and thousands of melanomas have been detected, most in their earliest stages. Local divisions of the American Cancer Society have also greatly aided in these programs, along with many volunteer dermatologists and other interested health care professionals.

Clearly, if every American were completely examined yearly for malignant melanoma, death from this disease would be a rare event. The cost-benefit ratio of skin-cancer screening, as well as the feasibility of screening 280 million Americans for skin cancer, however, need to be resolved.

Perhaps a more realistic goal is to target screening for melanoma to those at highest risk. Indeed, in a 1987 screening in Massachusetts, 86% of the people screened had at least one risk factor for malignant melanoma and 78% had at least two.

Enhancing Treatment Effectiveness

Melanoma is a tumor with aggressive metastatic potential, particularly to lymph nodes, lung, and brain. Reports of metastases to other organs including bone, pancreas, adrenals, and small intestine have been described.

Treatment options and follow-up intervals for patients with melanoma vary with the depth of the primary lesion and stage. The primary therapeutic approach for melanoma is surgical excision, which is almost 100% effective when treating an early tumor. Chemotherapy and adjuvant therapy, including the use of biologic response modifiers and vaccines, provide supplemental treatment for more advanced tumors. Combination regimens are often used, depending on tumor stage (Table 1a and b).

Surgery

Surgical excision is the mainstay of therapy for malignant melanoma. Recent studies support more conservative margins than were suggested previously. A margin of 0.5 cm is currently suggested for in-situ melanoma, whereas a margin of 1 cm is considered adequate for lesions less than 1 mm deep. For lesions between 1 and 2 mm in depth, a 2-cm margin is suggested, while most studies support margins of 2 to 3 cm for lesions greater than 2 mm in depth. Depth of excision should be to the level of fascia, as no added benefit has been shown for excisions of greater depth.

Wide and deep excision of malignant melanoma may be difficult to impossible to perform, depending on anatomic site. Thus, some dermatologic surgeons are attempting to perform tissue-conserving procedures, particularly for melanomas occurring on the face. The role of Mohs micrographic surgery in the treatment of lentigo malignant melanoma is the subject of ongoing debate. Proponents cite the added benefit of histologic margin control and tissue conservation in this highly recurrent tumor. Others cite the difficulties inherent in distinguishing atypical melanocytes in frozen sections. Increased sensitivity may be gained through the use of special stains. Zitelli et al report a success rate of 99.5% at five years in the treatment of malignant melanoma with the Mohs technique.

Lymph Node Biopsy

Elective Lymph Node Dissection: The appropriate role of elective lymph node dissection (ELND) for patients with clinical stage I, intermediate thickness melanoma has been the subject of debate and has been reviewed extensively.
Patients most likely to benefit from ELND are those with a high probability of harboring occult nodal disease and low probability of distant spread. Patients with intermediate thickness melanomas (1.0 to 4.0 mm) may have occult disease in 40% of cases but distant spread in only 10% of cases. In contrast, patients with lesions greater than 4 mm in thickness not only have a higher likelihood of occult disease (60%), but also an increased likelihood of distant spread (70%) and thus

| Table 1a | Management of Melanoma Patients |
|----------|---------------------------------|
| Tumor thickness | In-situ | <1 mm | 1-4 mm | 4 mm+ |
| Surgical Margins | 5 mm | 1 cm | 2-3 cm | 2-3 cm |
| Node Dissection | No | No | Sentinel node biopsy, then regional dissection if positive | If clinically positive |
| Adjuvant Therapy | No | Only if high-risk | Consider | Consider |

| Table 1b | Follow-up Schedule for Melanoma Patients |
|----------|------------------------------------------|
| Months Between Visits | 1 | 2 | 3 | 4 | 5 | 6+ |
| In-situ | 12 | 12 | 12 | 12 | 12 | 12 |
| <0.75 mm | 6 | 6 | 12 | 12 | 12 | 12 |
| 0.76-3.99 mm | 4 | 4 | 4 | 6 | 6 | 12 |
| >4.0 mm | 3 | 3 | 3 | 4 | 6 | 12 |
| Stage III & IV | 3 | 3 | 3 | 4 | 4 | 6-12 |

Adapted from data in Romero, et al.69
would be less likely to benefit from lymph node dissection.

The question regarding potential benefit of lymph node dissection in malignant melanoma has been evaluated in several studies. Results of the WHO trial No. 1 study suggested that ELND confers no significant benefit in malignant melanoma, although no subgroup analysis was performed. The WHO trial No. 14 demonstrated improved survival in patients with nodal metastases.

The MAYO Clinic Surgical Trial, which included patients with malignant melanoma of all thicknesses, showed no survival benefit with ELND. The Inter-group Melanoma Surgical Trial, on the other hand, showed improvement in survival in patients younger than 60 years old with intermediate thickness lesions (1.0 to 4.0 mm) on any anatomic site.

However, any possible benefit of ELND needs to be weighed against the known significant morbidity of resultant lymphedema. Thus, the question remains as how to best identify those patients with occult disease in whom distant spread has not yet developed and where nodal dissection may be helpful.

**Sentinel Lymph Node Dissection:** Sentinel lymph node (SLN) dissection may prove to be an answer to this question. The SLN is defined as the first node in the lymphatic basin to which the primary melanoma drains. Theoretically, the histology of the SLN should reflect the histology of the basin in that a negative SLN should rule out nodal disease. SLN can be accurately identified with 96% sensitivity using a combination of blue dye mapping and radiolymphoscintigraphy. The specificity of these techniques, however, needs to be carefully examined.

Currently, it appears that detection of melanoma in the sentinel node identifies those patients at higher risk of metastasis and therefore those who may benefit from complete lymph node dissection or adjuvant therapy. In the future, the combination of SLN dissection with molecular diagnostic techniques may provide increased sensitivity in identifying patients at high risk for metastasis.

**Polymerase Chain Reaction (PCR):** PCR may play an increasingly important role in identifying melanoma-positive lymph nodes in the future. In one study, recurrence rates and disease-free survival were significantly different in node-negative PCR-positive patients compared with node-negative PCR-negative patients.

The results suggested that use of the PCR assay for detection of submicroscopic melanoma metastases in SLN improved the prediction of disease recurrence and overall survival over routine pathological examination. However, the clinical significance of PCR positive-histologically negative nodes is yet to be determined. Longer longitudinal follow-up for these patients is needed.

**Adjuvant Therapeutic Approaches**

Nonsurgical modalities used in the treatment of advanced disease include chemotherapy and adjunctive therapy in the form of biologic response modifiers and melanoma vaccines (Table 2).

**Chemotherapy**

Chemotherapeutic approaches to treating melanoma have been uniformly disappointing. Dacarbazine (DTIC) remains the only chemotherapeutic agent

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**Table 2**

| Promising Modalities for Treatment of Advanced Melanoma |
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| • Biological Response Modifiers |
| • Novel Chemotherapeutic Agents |
| • Biochemotherapy |
| • Immunotherapy |
| • Gene Therapy |

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approved by the FDA for the treatment of metastatic melanoma. No single chemotherapeutic agent currently offers response rates greater than 25%. Side effects of DTIC may include myelosuppression, nausea, and emesis.

Various combination regimens including BOLD (bleomycin, vincristine, CCNU, DTIC), CVD (cisplatin, vinblastine, DTIC), and CBDT (cisplatin, BCNU, DTIC, tamoxifen) have been studied in numerous trials and have been associated with response rates ranging from 9% to 55%. An imidazotetrazine oral agent, temozolamide, was recently shown to be as effective as DTIC in the treatment of metastatic melanoma. Advantages potentially include convenient dosing and relatively fewer side effects. The challenge for the oncologist in the future will be to identify which combination of chemotherapeutic agents, if any, will offer consistent improvement over DTIC alone.

Exciting advances have been made and continue to be made in the area of biological response modifiers.

**Interferon alpha 2b (IFNα2b)**

IFNα2b is currently FDA approved for the treatment of stage IIB and stage III melanoma. In the Eastern Cooperative Oncology Group (ECOG) trial 1684, high-dose IFNα2b treatment for one year resulted in prolongation of survival from 2.8 to 3.8 years and prolongation of the relapse-free interval from 1.0 to 1.7 years. A subsequent trial showed significantly increased disease-free survival but no increase in overall survival. It must be emphasized, however, that treatment with INFα 2b is associated with significant toxicity.

In the future, IFNα may have a role as an adjunct to vaccine therapy. Trials are currently underway to determine, for example, whether anti-GM2 antibody responses are diminished or enhanced when IFNα2b is administered with or following initiation of vaccination with GMK. A commercial vaccine preparation from cultured tumor cell lines given with Detox (monophosphoryl lipid-A) has been shown to induce antitumor responses among patients with metastatic melanoma. Limited data from a pilot study suggest improved responses among patients who have also received IFNα 2b.

**Interferon gamma (IFNγ)**

IFNγ was not effective in phase I or phase II trials of metastatic melanoma but remains potentially attractive due to immunomodulatory effects on natural killer cell-mediated cytotoxicity, macrophage activation, and HLA class II antigen expression.

**Interleukin-2 (IL-2)**

IL-2 has been used to treat melanoma. Early studies showed that high-dose IL-2, either alone or in combination with lymphokine-activated killer (LAK) cells, produced responses in 15% to 20% of patients, with complete responses observed in 4% to 6%. Median response duration was reported to be 6.5 months, with 60% of complete responders free of disease progression at five years. High-dose administration of IL-2 appears to be superior to low doses, although high doses are associated with significant toxicity. Adverse effects of high-dose IL-2 include hypotension, cardiac arrhythmia, pulmonary edema, fever, increased capillary permeability, sepsis, and death. Further studies will be required to assess the potential role of IL-2 in the management of advanced melanoma.

**Biochemotherapy**

Therapies based on biological response modifiers remain attractive due to the potential durability of complete responses rather than to the magnitude of the overall response rate. Initial studies indicate that 5% to 10% of complete responses may be durable. Biochemotherapy holds promise as a therapeutic option for
Histologic partial regression of malignant melanoma has been documented in up to 20% of cases and, in rare cases, even complete spontaneous regression has been observed.
kinase suicide genes. In a phase I/II study, retrovirus vector producing M11 cells were injected into cutaneous malignant melanoma nodules, rendering the transfected cells susceptible to ganciclovir. Patients were then treated with ganciclovir following a seven-day transduction period. Tumor size was moderately affected and tumor necrosis was noted histologically.

In another study, autologous tumor cells transfected with IL-2 genes were injected back into patients with the hope of generating an immune response. Anti-tumor delayed-type hypersensitivity and cytotoxic T-lymphocytes were generated in some patients. Yet another approach involved injection of vaccinia/GM-CSF constructs directly into subcutaneous metastases. Immune responses were generated and a partial response was noted in one of seven patients.

**Summary**

Despite potentially exciting developments in the treatment of advanced malignant melanoma, prevention and early detection remain the primary goals in the war against this cancer as we enter the new century. With improved professional education, public awareness, patient education, and research advances, we may be able to decrease the incidence and mortality of malignant melanoma. As incidence continues to rise, however, our best weapon against this potentially deadly neoplasm is a multidisciplinary approach using the best skills of all involved.

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Call for Volunteers

Volunteers Sought for Osteosarcoma Study

The National Cancer Institute is looking for volunteers diagnosed with osteosarcoma to participate in a research study. Newly diagnosed patients, those with recurrent and/or progressive disease, and those who have not responded to standard treatments or surgery will be considered. For more information, call the NCI’s Clinical Studies Support Center at 1-888-624-1937.

Volunteers Sought for Lymphoma Vaccine Study

The National Cancer Institute is seeking previously untreated adults with low-grade stage III or IV follicular lymphoma to participate in a multi-center phase III vaccine clinical study. Results of the earlier phase of the study showed an anti-tumor effect in a small group of patients who were vaccinated over the course of five years, according to NCI researchers. For more information, call the NCI’s Clinical Studies Support Center at 1-888-624-1937.