Melanoma: An Overview

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Melanoma is a malignant tumor originating from a special cell called a melanocyte, which has the ability to synthesize melanin, the only pigment found in man. Melanin, produced within melanocytes, is derived from the amino acid L-tyrosine by way of a sophisticated intracellular enzyme system. The chemical reaction involving the ultimate role of L-tyrosine in melanin production is complex, and although much of this process is known, it is still not completely understood. It is believed, however, that the basic reaction in melanin biosynthesis is initiated by the conversion of L-tyrosine to 3,4-dihydroxyphenylalanine (DOPA), a compound that is converted to melanin under the influence of the enzyme dopa-oxidase.

Zimmerman and Becker1 demonstrated pigmented granules within pre-melanocytes (melanoblasts) in the dermis of black fetuses as early as the 10th week of development. By the 12th week of fetal growth, melanocytes had developed and numbered up to 800 to 1,000 per square millimeter. These developing cells are located in the vicinity of the epidermal-dermal junction, where they develop long dendritic processes that intermingle with other cells in the epidermis. These dendrites become filled with numerous melanin granules that ultimately are released and absorbed by neighboring nonpigmented cells, thereby creating a pigment blanket composed of melanin-producing cells as well as non-melanin-producing but pigment-filled cells. Thus there can be heavy local pigmentation on the body, such as in the nipple and areola, or the entire skin surface may be pigmented, as in blacks.

Nevus

A nevus, more commonly called a mole, is an aggregation of melanocytes that are present at birth. These clusters of pigment-filled cells may not become apparent until puberty, suggesting that the pigmentation process is initiated by steroid hormones at this time. All humans except albinos have nevi on their bodies, which Pack2 has reported to average 15 per individual.

The clinical importance of nevi is that most melanomas originate from these apparently harmless lesions. It is this close relationship between nevi and melanoma that makes it necessary for a clinician to appreciate the clinical classification of the various neval forms.
Classification of Nevi

Junctional Nevus

These nevi are usually flat, well circumscribed, and vary in size from a few millimeters to one to two cm. Their color is frequently dark, but the degree depends on the amount of pigmentation present. Hairs can be present, but are not seen as often as in other neval types.

Melanocytes of a junctional nevus are located in the basal layer of the epidermis, with cell aggregation occurring in the rete processes. As melanocyte multiplication occurs in this area, melanin-containing cells may move toward the superficial layers of the skin and can eventually reach the cutaneous surface. Clusters of melanocytes along the basal layer of the epidermis occasionally hang down into the dermal layer of the skin and have the potential for breaking loose from this junctional area and dropping into the dermis, thus forming a compound nevus.

It is the junctional nevus that is most likely to develop into a melanoma, but this very rarely happens before puberty.

Compound Nevus

Compound nevi are most common in adolescents and comprise the majority of pigmented lesions in children. Only rarely does this type of lesion develop into a melanoma.

Usually less than one cm in size, a compound nevus ranges in color from brown to black. The surface is often elevated and finely nodular or smooth in texture. Hairs may be present. Occasionally, a whitish, depigmented ring develops around a compound nevus, resulting in a so-called halo nevus.

Microscopically, a compound nevus has melanocytes both at the epidermal-dermal interface and within the depths of the dermal layer. Clusters of melanocytes residing in the junctional layer in the child can disappear with age, simultaneously with melanocyte proliferation in the dermis, the result being an intradermal nevus.

Intradermal Nevus

This type has only a slight likelihood of developing into a melanoma. As mentioned, it originates from a compound nevus when neval cells in the junctional zone cease to be active and eventually disappear, leaving neval cells mainly or entirely within the dermal layer.

An intradermal nevus is small, usually under one cm, with regular edges and a surface texture that ranges from smooth to papillary. Bristle-like hairs are often, but not invariably, present. The color ranges from skin tone to light brown; only occasionally do these nevi become heavily pigmented.

An uncommon entity that has the histologic pattern of either an intradermal or a compound nevus is the giant progressive nevus, or bathing trunk nevus, a pigmented lesion that can be very extensive. Most importantly, these lesions can undergo malignant transformation in as high as 10 percent of cases. A patient with this condition must be carefully followed throughout his or her life. Since a very extensive pigmented region does not lend itself to total excision, any area within the lesion that shows even the most subtle changes requires biopsy.

Spitz Nevus (Benign Juvenile Melanoma)

Spitz,3 in 1948, first described this rare form. The great majority develop in prepubertal children, though Allen4 reported a 15 percent incidence arising in adolescents and adults in a series of 262 cases. The diagnosis of a Spitz nevus is therefore not dependent on the age of the patient but on strict histologic criteria.

These nevi are usually one to two cm in size and exhibit a spectrum of colors ranging from light pink-red to brown-black. Their shapes vary considerably but generally they have regular borders. They can be found any place on the body and are most often hairless.

Histologically, the Spitz nevus is a variant of a compound nevus, with specific microscopic changes that define it, including:

VOL. 29, NO. 4 JULY/AUGUST 1979 195
- An abrupt change from cutaneous normality to increased cellular activity in the junctional area;
- Giant cells with single or multiple nuclei;
- Ectasia of superficial, thin-walled venules, arterioles and lymphatics;
- Circumscribed nests of neval cells in the upper dermis.

The major histologic characteristic of this lesion is that it resembles a melanoma by demonstrating great cellular activity; clinically, however, its behavior is benign. While there have been rare cases in which benign juvenile melanoma has become malignant, the overwhelming majority remain benign.

**Blue (Jadassohn) Nevus**

These nevi are characteristically blue because of the refraction of light from the collagen fibers that are located superficial to the melanin in the underlying pigment cells.
Clinically, they are usually one cm or less in size, smooth in outline, and hairless, with color ranging from royal to gun-metal blue. They can occur any place on the body and are almost always benign, though there have been a few reports of metastasizing blue nevi.

Treatment of Nevi

Most nevi never become clinically suspicious, which is fortunate, since the removal of large numbers of them is impractical if not impossible. What is extremely important, however, is the removal and histologic examination of all suspicious pigmented lesions, since it is estimated that approximately two-thirds of all melanomas arise from preexisting nevi. Being aggressive in removing even a minimally suspicious nevus is the correct clinical approach. Also, nevi that are constantly irritated, such as those occurring at the beltline or under a bra strap, should be removed.

Since the majority of nevi that undergo malignant transformation are the junctional type, one might make a case for their routine removal. But this is more theoretical than realistic; one cannot be certain of the pathology of any nevus without its surgical removal and histologic examination. Furthermore, there is no convincing evidence that areas of the body with a high incidence of junctional nevi (such as the skin overlying the genitalia and the palms of the hands) have a high incidence of melanoma.

When a nevus is very large, an incisional biopsy may provide adequate tissue for diagnosis. However, an excisional biopsy of the entire nevus should be performed whenever possible. The biopsy should include only a very small margin of skin surrounding the nevus, because of the possibility that it is benign. Also, the depth of the biopsy should not include the underlying fascia; firstly, if the nevus is benign, excision of the fascia is not necessary and secondly, in case the lesion proves to be melanoma, an intact fascia provides a natural barrier to vertical penetration of malignant cells prior to surgical removal. Clark has shown that the potential for melanoma to metastasize to lymph nodes depends largely on the vertical penetration of the primary melanoma through the dermis.

The vast majority of nevi are removed under local anesthesia. Though some experienced pathologists will make a definitive diagnosis on frozen section, most pathologists agree that the safest thing to do for a suspicious nevus is to remove it and wait for the pathology report.

Melanoma

Melanoma is the result of malignant degeneration of melanocytes. Most arise from an existing nevus that has been present since birth, but a small number arise de novo. McNeer and Das Gupta, reporting on 557 patients with melanoma, claimed that in 27 percent the melanoma arose in a nevus that the patient considered to have been present since birth, and in another 39 percent, in a nevus of at least five years' duration. The remaining 34 percent of patients felt that their melanomas developed in a nevus that had appeared within five years or less of discovery; this latter group probably represents the de novo instances.

Classification of Melanoma

Primary cutaneous melanomas fall into three categories that can be recognized clinically and microscopically.

Lentigo Maligna Melanoma (LMN)

This growth pattern is the rarest of the three forms and accounts for about 10 percent of all cases. LMN develops at a median age close to 70 years and is two to three times more common in females than in males. These large, variably pigmented, freckle-like lesions are often located on the cheek or temple but can occur on any exposed body surface.
LMN develops on a benign structure called a Hutchinson's freckle, which is an extensively pigmented lesion having grossly irregular borders, indicating regression and/or migration of pigment cells. A Hutchinson's freckle usually has a very smooth surface, and when LMN occurs it generally becomes apparent by the development of a very noticeable thickened and elevated nodule within the freckle. The malignant transformation can take years. McGovern7 reported 33 cases of LMN that took from 15 months to 40 years to develop, with an average developmental period of nine years. The prognosis of LMN is excellent because the tumor is very slow to invade deeply.

Superficial Spreading Melanoma (SSM)

These lesions, which are equally divided in incidence between males and females, are the most common type of melanoma, comprising approximately 75 percent of all cases. This variety usually occurs at an earlier age (40 to 50 years) than does LMN.

The major clinical feature of an SSM is the kaleidoscopic variety of colors, ranging from tan-black, brown, blue-grey, to violaceous pink. These lesions can occur in any area of the body and are characteristically flat to slightly elevated, with pigmentation ranging from 0.5 to 3.0 cm in diameter.

There is no uniformity of opinion among pathologists as to whether the melanocytes in SSM are more or less bizarre than melanocytes seen in LMN. The major histologic characteristic of SSM is the lateral junctional spread of the extending pigmented process (Fig. 1a). Clark5 has stated that for a melanoma to be classified as an SSM, the melanocytes must be present within the surrounding epithelium for a distance of three rete pegs or more from the area of dermal invasion.

Nodular Melanoma (NM)

This malignant pattern comprises 10 to 15 percent of all melanomas, occurs twice as frequently in males as in females, can occur in any location, and usually develops in patients who are around 50 years of age.

The color of a nodular melanoma is characteristically a shade of blue, e.g., blue-black, blue-grey or reddish blue. An unpigmented (amelanotic) form of NM can be extremely difficult to diagnose by color, but occasionally there are small, dark specks at the base of the lesion.

Nodular melanoma can develop in either a preexisting nevus or de novo. Regardless of its origin, what characterizes NM is the absence of lateral spread of pigmentation with an immediate vertical invasion of the dermis by the malignant nodule (Fig. 1b), which may grow so rapidly that it can lead to early surface ulceration (Fig. 2). For a histologic diagnosis of nodular melanoma, there must be invasion of the underlying dermis with lateral junctional spread being restricted to less than three rete pegs.

Clinical Diagnosis

The diagnosis of melanoma is usually based on the clinical appearance of a pigmented or unpigmented (amelanotic) lesion in addition to a history of recent change, the latter being the most important clue. The change can occur over a period of weeks or months. The following clinical criteria suggest the possibility of melanoma:

- A change in the surface area of a nevus.
- A change in elevation of a lesion, with a flat mole becoming raised, palpable, nodular, or thickened.
- A change in color, especially when brownish pigmentation becomes black. However, one should not rely completely on the type and degree of pigmentation observed in any lesion, since highly malignant, but unpigmented, melanomas can occur.
- A change in surface characteristics whereby a previously smooth cutaneous surface may become brown and scaly, with or without the occurrence of serous discharge or bleeding after minor trauma.
A change in sensation, e.g., the development of itching or tingling in an area of pigmentation. Regardless of these considerations, it is not until the specimen has been removed and examined histologically that a definitive diagnosis of melanoma can be made.

Clinical and Histologic Staging

Even though various clinical features of melanoma have yielded important retrospective information about survival, it remained for Clark to elucidate and refine what appears to be the most important characteristic in the staging of melanoma: the vertical depth of melanotic penetration through the skin.

Prior to Clark's work, staging was done solely on a clinical basis. Stage I melanoma is local disease only, with the primary melanoma present, previously excised, or locally recurrent. Stage II consists of the primary lesion and palpable regional lymph nodes, and stage III melanoma indicates widespread disease.

While stage III melanoma is easily determined, the major difficulty when using a clinical classification is in distinguishing stage I from stage II disease; here, the differential diagnosis is dependent on palpability of regional lymph nodes, and such a clinical judgment is vulnerable to error. Approximately 25 percent of patients who have a regional lymph node dissection on an elective (prophylactic) basis are found to have histologic evidence of melanoma in the
Clark's microstaging classification (Figs. 2-4) has become widely adopted as the method for classifying melanoma. Based on the level of penetration of the nonpalpable excised lymph nodes. This explains why a staging system based solely on clinical evaluation is unreliable in predicting long-range survival.

| Clinical Staging                                                                 | Clark's Five Levels of Cutaneous Invasion |
|----------------------------------------------------------------------------------|------------------------------------------|
| **Stage I**                                                                      | Level I                                  |
| Localized melanoma without metastasis to distant or regional lymph nodes         | Melanoma located above the basement      |
| 1. Primary melanoma untreated or removed by excisional biopsy                    | membrane (basal lamina) of the epidermis |
| 2. Locally recurrent melanoma within 4 cm of primary site                        | (Fig 4). These lesions are essentially   |
| 3. Multiple primary melanomas                                                    | in situ, are extremely rare, and present |
| **Stage II**                                                                     | no danger                                |
| Metastasis limited to regional lymph nodes                                       | Level II                                 |
| 1. Primary melanoma present or removed with simultaneous metastasis             | Melanoma invades through the basement    |
| 2. Primary melanoma controlled with subsequent metastasis                       | membrane down to the papillary dermis.   |
| 3. Locally recurrent melanoma with metastasis                                   | Level III                                |
| 4. In-transit metastasis beyond 4 cm from primary site                          | Melanoma at this level is characterized   |
| 5. Unknown primary melanoma with metastasis                                     | by filling and widening by melanoma      |
| **Stage III**                                                                    | cells of the papillary dermis at its     |
| Disseminated melanoma                                                            | interface with the reticular dermis.     |
| 1. Visceral and/or multiple lymphatic metastases                                 | Characteristically, there is no invasion |
| 2. Multiple cutaneous and/or subcutaneous metastases                             | of the underlying reticular layer (Figs 5 |
|                                                                               | and 6).                                  |
|                                                                               | Level IV                                 |
|                                                                               | These lesions show melanoma penetration  |
|                                                                               | into the reticular dermis.               |
|                                                                               | Level V                                  |
|                                                                               | Melanoma at this level is evident by its  |
|                                                                               | presence in the subcutaneous tissue.     |
Clark's five levels of cutaneous invasion and clinical staging are shown in Table 1. Breslow further refined Clark's classification, relating the prognosis of melanoma to the actual measured depth (thickness) of invasion as determined by a hand optical micrometer. It is generally accepted that a melanoma that has extended to a depth of 0.65 mm in Breslow's classification is comparable to Clark's level II and that a melanotic lesion that is 1.5 mm or thicker is comparable to Clark's levels IV and V, respectively. Clark's level III falls roughly between 0.65 mm and 1.5 mm in thickness (Fig. 5).

**Treatment**

**Excision of Primary Melanoma**

The most important element in the treatment of melanoma is the manner in which the primary lesion is removed. Adequate treatment requires a wide three-dimensional excision of the cutaneous tumor with the removal of a cuff of skin surrounding the lesion that should ideally be four to five cm in all directions. A critically located melanoma, such as one on the face, is not suitable for an excision of this magnitude, so that in such situations, anatomic limitations and clinical experience must dictate the extent of the excision.

Removal of a primary melanoma must be planned with precision. When the lesion is on an extremity (the location in 75 percent of all cases), the incision should be made in an elliptic manner, being started proximally and continued distally. This technique of initial interruption of proximal lymphatic channels connecting the melanoma to the regional lymph nodes theoretically minimizes the opportunity for tumor cells within the lymphatics to be milked toward regional lymph nodes during the surgical procedure (Fig. 6).

The excision should include removal of the underlying deep fascia. Some surgeons believe that leaving the deep fascia intact at the time of melanoma removal improves survival statistics. This is based on the concept that there is an effective valve system in the lymphatic vessels which, as they pass through the deep...
fascia, acts as a barrier to continued lymphatic spread deep to the overlying melanoma. However, this has never been confirmed, and most surgeons continue to remove the deep fascia, mainly to ensure that the excision has been carried below this deep natural tissue barrier.

After the completion of a wide three-dimensional excision, primary skin closure is usually impossible, regardless of the extent of skin undermining. In fact, primary skin closure usually indicates failure to have removed sufficient skin surrounding the primary tumor; a split-thickness skin graft is usually required to cover the area of excision. The skin graft should be obtained prior to excision of the melanoma and should be taken from a donor site far distant from the melanoma. Occasionally, rotation or advancement flaps can be mobilized to cover the skin defect at the site of an excision of a trunk melanoma.10

Regional Lymph Node Dissection

There is little disagreement among clinicians as to the need for therapeutic lymph node dissection for melanoma when regional lymph nodes are palpable. Certain melanomas also deserve consideration for a prophylactic (elective) regional lymph node dissection, including large lesions (over two cm), nodular melanomas, ulcerated and rapidly growing tumors, and previously treated or locally recurrent melanomas.

There is still controversy as to whether nonpalpable regional lymph nodes should be routinely excised in addition to removing the primary melanoma. For many years it was thought that the best way to treat the disease when the lymph nodes draining the primary melanoma were nonpalpable was to perform a wide excision of the primary tumor and a simultaneous regional lymph node dissection, carried out if possible in an incontinuity fashion. The rationale for prophylactic lymph node dissection was based on retrospective analysis of a large number of patients. Those who had prophylactic lymph node dissection showed a 10 percent difference in overall survival as compared with patients who had not had the dissection, a figure considered to be statistically significant.11 Another reason for recommending an elective lymph
node dissection is the knowledge that approximately 25 percent of patients with melanoma have metastases to regional lymph nodes in spite of nonpalpability of these nodes.

Some Australian clinicians have strongly argued against the routine excision of regional lymph nodes, a reasonable suggestion since only five percent of their patients have been found to have histologic evidence of melanoma in clinically uninvolved nodes, a very low figure compared with rates elsewhere in the world.

Since Clark’s system has now become almost standard, one can neither advocate nor refute elective lymph node dissection on the basis of retrospective information from patients who were evaluated as a group rather than on an individual microstaging basis. Clark’s and Breslow’s microstaging classifications have yielded correlative information regarding lymph node metastases and cutaneous depth of the primary tumor; prophylactic lymph node dissection can now be recommended on the histology of the individual primary melanoma.

Data indicate that a Clark level I melanoma is an in situ lesion requiring no lymph node dissection. A Clark level II melanoma indicates deeper cutaneous penetration with a potential incidence of lymph node metastases of approximately two to five percent, not mending an elective lymph node dissection for these deeply penetrating melanomas seems reasonable (Fig. 7).

The question that has not been resolved is whether a lymph node dissection should be recommended for patients with a Clark level III melanoma. These lesions are known to metastasize to regional lymph nodes in up to 20 percent of cases. Is one justified in carrying out an elective lymph node dissection when only one of five patients might be benefitted by the procedure? To many clinicians, including the author, this also seems reasonable.

Breslow’s system, based on the direct measurement of the primary melanoma, asserts the absence of lymph node metastases from any primary melanoma less than five mm in diameter, less than 6.01 sq mm in maximum cross sectional diameter, and most importantly, less than 0.76 mm in thickness. Since a melanoma thicker than 1.5 mm is in the Clark levels IV and V categories, which have a high incidence of lymph node metastases, and since anything thinner than 0.76 mm is in the Clark levels I and II categories, which have a very small rate of lymph node metastasis, it would seem that the thickness of any melanoma between these measurements becomes a matter of clinical judgment, for purposes of recommending a prophylactic lymph node dissection. Factors that might influence this decision include the closeness of regional lymph nodes to the primary tumor and/or the presence of a nodular melanoma which, because of its immediate vertical infiltration, demands a more aggressive surgical approach. Wanebo and his associates have suggested that any melanoma thicker than 1.0 mm, rather than 1.5 mm, warrants a prophylactic lymph node dissection.

An incontinuity dissection should always be done if anatomically possible, since the procedure removes the primary melanoma, the regional lymph nodes, and the lymphatics connecting these two areas. If an incontinuity dissection is not possible, anatomically or technically, e.g., when the primary tumor is on the sole

“...approximately 25 percent of patients with melanoma have metastases to regional lymph nodes in spite of nonpalpability of these nodes.”

justifying a routine elective lymph node dissection. At the other end of the pathologic spectrum are melanomas of Clark levels IV and V, which metastasize to regional lymph nodes in the range of 40 and 70 percent, respectively. Recom
Fig. 7 Effect of elective lymph node dissection for melanoma of the extremity. N.E.D. signifies no evidence of disease. Samples of patients with Clark level V lesions were too few for evaluation.\(^{13}\)

of the foot, the alternative is to perform a discontinuous dissection, whereby the regional lymph nodes are removed separately from the excision of the primary melanoma. Survival statistics that have included both techniques of lymph node dissection have shown comparable survival rates.\(^ {14} \)

An incontinuity dissection, by definition, removes the primary lesion and regional lymph nodes simultaneously. However, a discontinuous procedure is less defined in this regard. Varying periods have been postulated as the time required for melanoma cells to travel from the primary site to the regional lymph nodes, and for this reason, varying periods have been suggested as being necessary between excision of the primary melanoma and lymph node dissection. However, the speed with which melanoma cells travel within the lymphatic system remains unknown. While vital dyes injected into the skin spread extensively throughout the lymphatic system within a matter of minutes, many years may pass before melanoma appears in a lymph node following removal of the primary tumor. Since there are no definitively proved advantages in doing a staged procedure, it seems reasonable, from a clinical standpoint, to do simultaneous node dissection with excision of the primary melanoma. Also, knowing that he or she has only one surgical procedure to undergo is of great psychological benefit to the patient.

**Drainage Patterns of Lymphatics**

It is important for surgeons to be aware of the lymph drainage patterns of the

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\(^{13}\) Clark's Levels

\(^{14}\) Drainage Patterns of Lymphatics
Fig. 8 The relationship between the lymphatic system and the spread of melanoma cells to regional lymph nodes may be of extreme importance in treatment planning.

Body (Fig. 8). Melanoma on the leg initially drains to the superficial inguinal lymph nodes before draining into the deep inguinal groin nodes. Popliteal lymph nodes only rarely become involved with lymphatic spread of melanoma from the lower leg, and when involvement does occur, it usually indicates tumor blockage of the inguinal lymph nodes and retrograde flow of melanoma cells down to the popliteal lymph node area.

A melanoma on the arm drains mainly to ipsilateral axillary lymph nodes but can also drain to cervical lymph nodes, especially when the location of the melanoma on the upper arm is close to the shoulder. Das Gupta reported that 57 percent of patients have cervical lymph node involvement when melanoma is located high on the anterior shoulder. A melanoma on the hand and forearm rarely metastasizes to the epitrochlear lymph nodes, but when this does occur, it usually indicates axillary lymph node blockage, which causes retrograde spread of melanoma cells down to the epitrochlear area, a situation comparable to that seen in popliteal node involvement of the leg.

A melanoma of the trunk has a poorer prognosis than does a melanoma on an extremity (Fig. 9). These poor survival statistics reflect the fact that 40 percent of trunk melanomas have lymph node metastases at the time of their initial treatment, as opposed to a 25 to 30 percent incidence of lymph node involvement for a melanoma located on an extremity. The opportunity for a trunk melanoma to drain to more than one lymph node area makes awareness of the variations in lymphatic spread important in making the decision as to which lymph node areas should be removed when nodes are nonpalpable. The basis for this decision rests on the anatomic position of the lesion. A melanoma located above the umbilicus anteriorly, the eighth rib laterally, or the first lumbar vertebra posteriorly makes the ipsilateral axillary node region the area most likely to receive metastatic cells. If the melanoma lies between the umbilicus and pubis, in the lumbosacral region, or below the first lumbar vertebra, the ipsilateral inguinal nodes should be removed since this is the most common metastatic lymph node basin.

A midline melanoma on the upper back, especially in a young person, justifies a bilateral axillary dissection if the lesion is located at a deep Clark level (level III or higher) and/or is a thick lesion by the Breslow classification (greater than 1.0 to 1.5 mm). When a melanoma develops close to the umbilicus, there is no alternative but to observe the patient very carefully for subsequent evidence of metastatic spread to any of the possible inguinal or axillary nodal areas.

Lymphadenectomy of the neck, axilla, or inguinal areas is performed by standard surgical techniques. Over the years,
there has been a trend to modify the standard radical groin dissection by removing deep inguinal nodes only when the femoral-superficial inguinal nodes are either visually suspicious at the time of surgery or are reported by frozen section to be positive for melanoma. The rationale for avoiding the removal of deep inguinal nodes is the likelihood of deep nodal involvement in the absence of melanoma metastases in the femoral-superficial inguinal lymph nodes. If at operation the surgeon feels that the superficial inguinal lymph nodes are not involved but the final histologic report shows melanoma to be present, a subsequent deep inguinal lymph node dissection can be performed through a separate abdominal incision. The author has continued to perform a standard radical groin dissection. Work by Das Gupta showed three five-year survivors in seven patients with lymph node metastases from melanoma on the leg that had traveled only to the deep pelvic lymph nodes. This appears to justify a standard radical groin dissection despite its increased morbidity over the modified radical groin dissection.

Strong arguments continue to be made against the use of elective lymph node dissection for melanoma in the presence of nonpalpable lymph nodes. However, the potential for lymph node involvement in advanced Clark levels and in melanomas that are thicker than 1.5 mm is such that an elective lymph node dissection based on these microstaging characteristics appears to far outweigh the possible disadvantages of the operation.

Amputation

When amputation is necessary to control a melanoma on an extremity, the prognosis is poor. The decision to perform such a major procedure must be based on the particular clinical situation since it is very difficult to establish firm rules concerning the indications for a major amputation for melanoma.

One instance in which an amputation appears logical is when a melanoma recurs at the site of the primary excision, in association with development of clinically palpable regional lymph nodes. Another situation that may warrant amputation is extensive recurrence of melanoma between the site of a previous regional lymph node dissection and the primary excision site.

Melanoma on the arm with extensive axillary lymph node involvement justifies an interscapulothoracic (forequarter) amputation, since the operation removes not only the involved extremity but also the entire axilla. While a forequarter amputation can be justified with an upper extremity lesion, the same cannot be said for a hemipelvectomy (hindquarter amputation) when melanoma is present above the inguinal ligament, since the chance of cure in this clinical setting is extremely small. A mid-thigh amputation performed simultaneously with a radical groin dissection is suitable for managing a local recurring melanoma below the knee joint. A hip disarticulation with radical groin dissection is appropriate when the recurrence is above the knee.

An inviolate rule associated with any amputation for melanoma is to always explore the abdominal cavity before amputating, to rule out the possibility of either intra-abdominal or retroperitoneal metastasis. There is nothing more distressing than to discover metastases during the early period following an amputation. Careful evaluation of the lungs, using tomography, is also required.

With careful patient selection, major amputation can result in a 33 percent five-year survival rate. However, amputation for melanoma has never been popular, and now, with improving survival statistics associated with other treatment innovations, it is likely that amputation for melanoma will become even less frequent.

Regional Perfusion

Creech and his associates, in 1958, first introduced the concept of using isolation
perfusion of an extremity for treatment of melanoma, the rationale being that if large amounts of chemotherapeutic agents could be introduced and maintained in a closed system, high doses of the drug (eight to 10 times greater than the tolerated systemic dose) could be introduced into the limb with little risk of generalized systemic toxicity.

Since the initial report of Creech, several investigators have used this treatment, using phenylalanine mustard as the perfusate. Initially, the perfusate was given at room temperature, but in 1967 Cavaliere and his associates in Rome reported improved survival statistics associated with hyperthermic perfusion. They felt that this was the result of the tumoricidal effect of heat on cancer cells.

Regional perfusion has been used alone or in combination with excisional surgery to the degree that major amputations for melanoma are decreasing in frequency. However, in a patient with stage I melanoma (Clark level III or greater), the relative efficacy of excision of the primary melanoma plus elective lymph node dissection as compared to excision of the melanoma in addition to prophylactic isolation perfusion has not been determined.

McBride and his associates at the M.D. Anderson Hospital presented data on 202 patients with stage I melanoma who were subjected to hyperthermic isolation perfusion with L-phenylalanine mustard between the years 1960 and 1970, with a five- and 10-year determinant survival rate of 86 percent and 83 percent, respectively. Krementz, in reporting his survival statistics of 608 patients using isolation perfusion with hyperthermia, had a five- to 15-year survival of 82 percent for patients with stage I melanoma. The interesting aspect of these figures is that Krementz, whose patients...
had almost identical statistics as those of McBride, did an elective lymph node dissection plus isolation perfusion in 183 of 197 determinant cases, whereas McBride used only isolation perfusion. This suggests that an elective lymph node dissection may not be necessary when isolation perfusion is performed.

At present there are many institutions, without facilities for isolation procedures, treating patients with melanoma. If future clinical studies continue to show that the prophylactic use of isolation perfusion increases the survival statistics of melanoma, especially if it eliminates the need for elective lymph node excision in patients with stage I melanoma, it will become necessary for those institutions without facilities to either develop capabilities for treating these patients or arrange to transfer them to appropriate treatment centers.

**Chemotherapy**

Radiation therapy has little to offer patients with melanoma. Surgery also can do little for a patient with disseminated melanoma, except to remove bulky disease when there is danger of ulceration of the tumor, and to eliminate a large amount of tumor antigen in the hope of possibly increasing any effectiveness of chemotherapy and/or immunotherapy. The inadequacy of radiation therapy and surgery in treating patients with advanced

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"Unfortunately, there is no drug available that gives prolonged clinical response to most patients with extensive melanoma."

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Fig. 10  Relationship between clinical staging of melanoma and survival.11
melanoma has spurred a continuing search for some drug that might be effective. Unfortunately, there is no drug available that gives prolonged clinical response to most patients with extensive melanoma.

The agent that has been most intensively studied in patients with widespread melanoma is dimethyltriazenoimidazole carboxamide (DTIC), which has been reported to have produced tumor regression greater than 50 percent in 166 of 758 patients, a response rate of 22 percent.\(^2\) Even though this rate is somewhat encouraging, the duration of remission lasted only 16 to 20 weeks, which tempts one's enthusiasm for this form of chemotherapy.

Five-year survival of patients with stage I melanoma is excellent—70 to 80 percent. Unfortunately, there is a progressive drop-off in survival with each five-year interval, so that by 10 years the survival rate has fallen to 60 percent and by 15 years, to 50 percent\(^{11}\) (Fig. 10). This continued drop-off is due to the subsequent development of metastatic melanoma, and suggests that melanotic micrometastases were present at the time of initial treatment but that these cells lay dormant until something happened to host resistance that allowed the micrometastases to become active once again. This might prove to be an excellent situation in which to use adjunctive chemotherapy, such as DTIC, which might destroy micrometastases at the time of initial treatment of patients with clinical stages I and II melanoma, and might increase the five-year survival rate in these patients.

Immunotherapy

Over the past decade there has been increasing interest in attempting to stimulate a patient's immune system to more effectively control the inhibition of recurrence following removal of a primary melanoma. That some type of immunologic control might prove effective is strongly suggested by a variety of clinical features of melanoma, including:

- Well documented cases of spontaneous regression of the primary melanoma.
- Late recurrence after many years following removal of the primary melanoma.
- An extended period of time in which a melanoma remained localized before dissemination occurred.
- Spontaneous disappearance of the primary melanoma with presence of malignant cells in the regional lymph nodes.
- Spontaneous regression of metastatic lesions while new lesions appeared spontaneously.

Bacillus Calmette-Guerin (BCG) is the most common agent being used to stimulate an immunologic response of the host against melanoma. Its antitumor effect is attributed to its stimulation of the immune system in the tumor-bearing host by way of a microbacterial antigen. Although the initial response of BCG may not be specific, there is evidence indicating that the material activates macrophages and histocytes, which in turn react with tumor-associated antigens that ultimately produce specific immunity in the host. However, the precise role of BCG in treating melanoma is still uncertain.

Special Considerations

Melanoma of Special Sites

Certain areas in which a melanoma can develop deserve special mention in terms of treatment.

Sole of the Foot

A melanoma on the sole of the foot requires a three-dimensional excision with coverage by a slightly thick split-thickness skin graft (15/1,000 inch). Use of a split-thickness graft raises questions about the patient's ability to bear weight at the excision site; it has been found that these grafts can fulfill this function. In addition, the author has been impressed over the years with the degree of wound contracture that occurs around and beneath the graft, which gives added support to the skin graft and stability to the foot.
Occasionally, a wide excision on the sole of the foot leaves the recipient site for a skin graft unsuitable for immediate acceptance of the graft because of the inability to gain complete hemostasis at the time of surgery. Rather than place the graft on an area that is still bleeding, it is best to put bandage pressure on the bleeding site and refrigerate the skin graft wrapped in penicillin-impregnated gauze. Twenty-four hours later, the skin graft can be applied with an excellent chance for a successful take. This technique can even be done with the patient in bed, using only sedation and small amounts of local anesthesia.

**Subungual Melanoma**

A subungual melanoma is a lesion that develops beneath a nail. Because of the protection of the overlying nail and the usual hesitation to surgically remove an entire nail, there may be a long diagnostic delay. Even though a subungual melanoma can resemble a pyogenic granuloma, fungal infection, and other benign lesions, it must be remembered that any persistent lesion beneath a nail bed, with or without pigmentation, always raises the possibility that a malignant process is present. The treatment of a subungual melanoma is complete removal of the involved digit, including the corresponding metacarpal or metatarsal bone (a ray amputation). Since it has been shown that approximately 25 percent of subungual melanomas have metastasized to the ipsilateral regional lymph nodes (in spite of their nonpalpability), an elective lymph node dissection seems warranted. The five-year survival rate for subungual melanoma is approximately 50 percent with negative lymph nodes, but it is much lower if the nodes are positive, especially if they are fixed in the regional lymph node area.24

**Anal Canal**

A melanoma in the anal region is fortunately extremely rare, since the prognosis is very poor. Anal lesions are often overlooked because of the infrequency with which the area is carefully inspected by a clinician as well as the patient's inability to observe the area. Because pigmented lesions around the anus are so rare, they should be biopsied when encountered.

If a melanoma is diagnosed in the anal region, clinical judgment and experience must dictate which treatment approach is best for the patient. Knowledge of lymph drainage patterns is extremely important because the rectum, anal canal, and anus drain by different pathways despite their close anatomic proximity. Lymphatics of the anal canal accompany the middle and inferior hemorrhoidal arteries and drain into the hypogastric lymph nodes. Anal lymphatics accompany lymphatics of the perineal skin and drain primarily into the superficial inguinal lymph nodes.

An abdominal-perineal resection with an associated bilateral pelvic and groin dissection can be justified in the young patient in spite of a five-year survival rate of only five percent to 10 percent,25 mainly because of the age and the usual physical well being of the patient. However, in an older patient, this very aggressive treatment is inappropriate and a lesser procedure is warranted for these highly malignant tumors.

**Vulva**

This is another very rare lesion and most often presents with vaginal bleeding and pruritis as the initial complaint. A bluish-black lesion in the area of the genitalia is usually melanoma, but other benign lesions, such as hemangioma or a nevus, may be responsible. It is therefore important to biopsy the lesion, and if it is a melanoma, radical vulvectomy with bilateral groin dissection is the treatment of choice. Fortunately, the postoperative sequelae of this procedure are far less severe than those associated with the treatment of melanoma of the anal canal. The five-year survival rate of melanoma of the vulva—about 30 percent—is also better.26
Melanoma and Pregnancy

Melanoma in a pregnant woman raises the dilemma of whether or not to terminate the pregnancy. A consideration of greatest importance is whether the birth of a child is desirable in the face of a strong statistical probability that the mother will not be alive during the child's early years and adolescence. Obviously, this is an exquisitely sensitive decision that can be made only by the parents.

The basis for the pessimism associated with melanoma in a pregnant female is the belief that the gestational process accelerates malignant activity. While it is well known that hormonal changes in pregnancy have a profound effect on melanoblast activity, no evidence has been reported to incriminate pregnancy in the exacerbation of the disease, especially in the absence of lymph node involvement. A pregnant woman with melanoma who decides against an abortion can be comforted by the knowledge that five- and 10-year reports of survival for pregnant women with stage I melanoma are comparable to those of nonpregnant women with stage I melanoma, and further work is necessary to clarify whether survival rates are comparable in stage II disease. Shiu and associates, in a small series, suggested that the survival statistics of pregnant women with melanoma metastases to regional lymph nodes are significantly lower than those of their nonpregnant counterparts. There have also been case reports in the literature in which documented melanoma has regressed spontaneously following pregnancy.

Melanoma in Blacks

There have been several reports in the world literature showing that the black race has a predisposition to develop melanoma on unpigmented areas of the body, i.e., the soles of the feet, and to a lesser extent, the palms of the hands. Lewis has postulated that melanoma on the sole of the foot is due to an increased number of melanocytes in this nonpigmented area, which he considers to be potentially unstable collections of melanocytes that are genetically determined.

When a pigmented lesion is discovered on the sole of the foot of a black patient, it is most important to perform an excisional biopsy. Unfortunately, as evidenced by more advanced disease at the time of diagnosis, most lesions in this area either go unnoticed for long periods of time, or the tumors are more aggressive in their biologic behavior than are comparable melanomas in white patients. Blacks with a localized melanoma (stage I disease) have a five-year survival rate of 78 percent, a figure comparable to that of whites. But since most black patients unfortunately are not seen in this early clinical stage, the overall five-year survival rate for black patients with melanoma is approximately 20 percent.

In addition, it has been shown that black patients who survive melanoma for periods of five to 10 years still run a great risk of eventually succumbing to their disease.

Amelanotic Melanoma

Some melanomas have no pigmentation; these amelanotic melanomas are composed of melanoblasts, which completely lack melanin, and the lack of melanin in the primary tumor is also observed in the cells that have metastasized.

Patients with stage I amelanotic melanoma have a five-year survival rate of approximately 70 percent, which is comparable to that seen in patients with pigmented melanomas. However, patients with stage II amelanotic melanoma have only a 15 percent five-year survival rate, in contrast to approximately 40 percent for patients with a pigmented stage II melanoma (Fig. 11).

If a cutaneous lesion proves histologically to be an amelanotic melanoma, a wide surgical excision of the primary site, with a skin graft for coverage, should be performed. It seems reasonable to suggest to these patients that an elective lymph node dissection be performed regardless of nonpalpability of regional
lymph nodes, since in a series of 28 patients from the Memorial Sloan-Kettering Cancer Center, the average survival time from date of diagnosis of amelanotic melanoma until death was only 22 months, and 75 percent of the patients died within one year.

The poor survival associated with amelanotic melanoma gives the clinical impression that its biologic behavior is more aggressive than that of its melanotic counterpart. The extreme degree of cell undifferentiation, as evidenced by the inability of these melanin-producing cells to make pigment, lends weight to this speculation. On the other hand, any growing, indurated, nonpigmented cutaneous lesion can easily be misdiagnosed, at first, as a benign condition, and its subsequent biologic aggressiveness may simply represent diagnostic delay, allowing these tumors to advance significantly prior to biopsy and treatment (Fig. 12).

Unknown Primary Melanoma

In any large series of patients who have melanoma, there are a certain number who present without any manifestation of the primary tumor, but have metastatic melanoma, usually in a lymph node. The previous existence of a primary tumor can often be determined by careful retrieval of information from a patient who recalls having had a pigmented lesion that was removed or cauterized and completely forgotten. A thorough physical examination may reveal an occult primary lesion in an area previously overlooked, and demands studies that include complete head and neck, ocular, proctoscopic and gynecologic examinations. Such procedures may locate the primary; treatment usually requires removal of the primary melanoma and the regional lymph nodes in the area in which the metastatic melanoma was discovered.

When a patient is found to have disseminated melanoma from an unknown primary site, there is little reason to subject him or her to extensive studies, since there is little that can be offered in terms of treatment. This is not the case, however, when the melanoma is located only in a lymph node, but without the cutaneous origin of the tumor being apparent. In these cases, aggressive diagnostic workup and treatment are indicated. Das Gupta and his associates reviewed 992 melanoma patients in whom 37 had an occult primary lesion. Of these 37 patients, 13 had disseminated melanoma (stage III) and were considered incurable. The remaining 24 patients had excision of the regional lymph node area in which the metastatic melanoma was found. Ten of these patients survived five or more years, giving a 42 percent five-year survival rate, which is as good as, and in fact even slightly better than, survival figures of patients with stage II primary melanoma. This statistic raises the question as to why patients with an unknown primary melanoma should do so well; it is the author's opinion that the primary melanoma undergoes spontaneous regression at the primary site simultaneous with metastasis to regional lymph nodes. By the time the primary melanoma has been eliminated by this autodestructive process, the regional lymph nodes may harbor the only remaining manifestation of melanotic disease. The fact that a patient has the ability to mount such an excellent immunologic response at the site of the primary tumor gives added confidence to the surgeon to be aggressive in removing the metastatic melanoma despite unawareness of the primary site.

Prognosis

Until the past few years, most statistics on melanoma were based on large numbers of patients and were usually gathered retrospectively. While clinicians await accumulating data from the new Clark-Breslow microstaging systems, which will yield more specific survival statistics for individual primary melanomas, there exists a large body of survival information based on physical characteristics of melanomas.38
Fig. 11 Overall survival rates for pigmented and amelanotic melanomas. Groups include all clinical stages and histologic types.36

Fig. 12 Distribution of pigmented and amelanotic melanomas by clinical stage of disease.36

Fig. 13 Relationship of age at onset of melanoma to survival.38
Most melanomas develop during the middle years of life, with the best survival rates seen in the very young and the poorest in the very old (Fig. 13). Females with melanoma consistently demonstrate a better survival rate than do males (Fig. 14). One of the most important prognostic features of melanoma is the size of the lesion at the time of its removal. This is likely due to a direct relationship between the increased surface area of a melanoma and its greater opportunity for contact with subcutaneous lymphatics, through which melanoma cells enter and travel toward regional lymph nodes.

Unfortunately, the five-year survival rate of patients with stage III (disseminated) melanoma has remained at one to two percent, with no form of treatment currently available that might result in improvement in these figures.

But for patients with localized disease, the picture is more hopeful, and one cannot help but be impressed with the tremendous improvement in survival statistics associated with melanoma over the past 50 years. Between 1917 and 1935 at the Memorial Sloan-Kettering Cancer Center, the five-year survival rate for all patients with melanoma was 12 percent, but by 1952, patients with stages I and II melanoma had a five-year survival rate of 40 percent and 14 percent, respectively. Another study, made in 1970 at the same institution, showed that the survival rate of patients with stages I and II had risen to 80 percent and 39 percent, respectively. These improved statistics do not reflect any change in the natural history of melanoma, but rather in earlier diagnosis and treatment, since the public is now better informed regarding the potential danger of any pigmented skin lesion.

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