MALIGNANT MELANOMA
(Prof. A. Riccardi)
EPIDEMIOLOGY
MELANOMA
EPIDEMIOLOGY. I.

* cutaneous melanoma (M, often lethal) must be distinguished from other pigmented skin lesions (frequent and usually benign);
  * from melanocytes (pigment cells, in epidermis and sometimes in dermis);
  * about 44,300 pts / yr in USA (with 7,300 deaths);
  * with the present, dramatically increased incidence (700% in the past 40 yrs) the lifetime risk of M will exceed 1%
MELANOMA
EPIDEMIOLOGY. II.

* in adults of all ages, even teenagers;
* usually, on the skin surface (= it is visible), with distinct clinical features (= detectable at a time of possible cure by surgical excision)
ETIOLOGY AND RISK FACTORS
* the overall increase in M incidence is mainly linked to recreational sun exposure, especially early in life;

- individuals of similar ethnic background who immigrate after childhood to areas of high sun exposure (e.g., Israel and Australia) have lower melanoma rates than individuals of similar age who were either born in those countries or immigrated before age 10
Figura 2. Le proprietà fisiche dei vari tipi di radiazione ultravioletta servono a spiegare i loro differenti effetti biologici. Nonostante le lunghezze d'onda della radiazione UVC siano quelle più facilmente assorbite dal DNA (grafico in basso), questa radiazione è filtrata dall’ozono atmosferico e non raggiunge la superficie terrestre.

La radiazione UVB penetra nella pelle fino alla zona di transizione dermo-epidermica, dove sono situati i melanociti. Questa è la radiazione ultravioletta solare maggiormente responsabile dello sviluppo dei melanomi. La radiazione UVA, responsabile delle alterazioni cutanee correlate con l’età, penetra nella pelle finó al livello del collagene dermico.
Row 1) high- or low-dose UV radiation on epidermis interact with DNA (open red circles) of keratinocytes (K) and melanocytes (M) next few days: K with extensive DNA damage undergo apoptosis (X = eliminated), while other K repair minimal DNA damage (open circle disappeared) or give rise to a mutation in the next DNA replication (solid red circle); the greater resistance of M to UV–induced apoptosis leads to survival of virtually all M (often mutated) regardless the UV dose;
Row 2) later: the skin mounts an SOS response to UV injury, with increased melanin content (tanning) and repair DNA capacity = apoptosis of severely damaged K results in survival of similar numbers of mutated K after either high- or low-dose UV radiation; by contrast mutated M undergo clonal expansion during the next cycles of M division (high-dose UV radiation results in many more mutated M than does low-dose);
Row 4 and 5) second low-dose UV: increased melanin content and DNA capacity to repair DNA results in nearly complete DNA repair in K, while already mutated M continues clonal expansion
Figure 1. Structure and Function of the CDKN2A Tumor-Suppressor Locus.

The four exons (E1α, E1β, E2, and E3) of the locus are shown (not to scale). The p16INK4a mRNA (mRNA) is derived from exons E1α, E2, and E3. The p16INK4a protein blocks phosphorylation (P) of the retinoblastoma protein (RB) by binding and inhibiting the cyclin D–cdk4 and cyclin D–cdk6 kinases. RB phosphorylation results in the release of bound E2F proteins, allowing them to bind and activate E2F target genes. The p19ARF mRNA is derived from exons E1β, E2, and E3. Splicing of E1β to E2 generates mRNA that uses a different reading frame than that used in the p73G1a transcript. The p19ARF protein appears to be an upstream regulator of the p53 pathway.
MELANOMA
ETIOLOGY AND RISK FACTORS. II.

* especially, in individuals with fair complexions, red or blond hair, blue eyes and freckles, poor tanners and easy subburners;

* family history of M (1/10 of M pts have an affected family member);

* presence of a clinically atypical mole (dysplastic nevus), a giant congenital melanocytic nevus, or a small to medium-sized congenital melanocytic nevus (30% of M arise in a nevus)
MELANOMA
ETIOLOGY AND RISK FACTORS. III.

* the presence of a higher than average number of ordinary melanocytic nevi (> 50 moles > 2 mm have a 64-fold increased risk), and;
  - immunosuppression
Risk Factors for Cutaneous Melanoma

High risk (> 50-fold increase in risk)
* Persistently changing mole
* Clinically atypical moles in patient with two family members with melanoma
* Adulthood (vs. childhood)
* > 50 nevi > 2 mm in diameter

Intermediate risk (> 10-fold increase in risk)
* Family history of melanoma
* Sporadic clinically atypical moles
  * Congenital nevi (?)
* White ethnicity (vs. black or East Asian ethnicity)
  * Personal history of prior melanoma

Low risk (2 - 4-fold increase in risk)
* Immunosuppression
* Sun sensitivity or excess exposure to sun
* relatively rare in heavily pigmented peoples;
  - rates 10 - 20 times lower in dark-skinned populations (such as from India and Puerto Rico, blacks, and East Asians) than in lighter-skinned whites;
  - in keeping with the role of sun exposure, the incidence is inversely correlated with the latitude of residence (with, at any latitude, darker-skinned persons having a lower incidence)
Figura 3. La sintesi della melanina da parte dei melanociti ed il successivo trasporto del pigmento alle cellule epidermiche adiacenti sono effettuati da un apparato specializzato. In risposta ad una varietà di stimuli, compreso quello prodotto dall'ormone melanocitosstimolante (MSH), il reticolo endoplasmico (RER) e l'apparato di Golgi dei melanociti producono le vescicole richieste per la formazione dei melanosomi. Le vescicole derivanti dall'apparato di Golgi contengono la tirosinasi necessaria per la produzione della melanina dalla tirosina. I melanosomi maturi provvedono al trasporto del pigmento neoformato ai cheratinociti intercalati con i dendriti dei melanociti. Nei cheratinociti il pigmento si dispone in modo da proteggere il nucleo dalla radiazione solare. Ai cheratinociti degli individui di pelle scura giungono grossi melanosomi contenenti una melanina più scura, denominata eumelanina. Ai cheratinociti delle persone di pelle chiara giungono gruppi di piccoli melanosomi, contenenti una melanina meno scura, denominata feomelanina.
MELANOMA
CLINICAL FEATURES. I.

* there are four types of cutaneous melanoma:

- superficial spreading melanoma;
- lentigo maligna;
- acral lentiginous melanoma, and
- nodular melanoma
MELANOMA
CLINICAL FEATURES. II.

* 3 types (superficial spreading M, lentigo maligna, and acral lentiginous M) have a period of superficial (radial) growth (= increase in size without deep penetration);

  - during the radial growth period M is curable by surgical excision
MELANOMA
CLINICAL FEATURES. III.

* M with a radial growth phase have irregular and sometimes notched borders, with variation in pigment pattern and color;

- increase in size or change in color in 70% of pts;
- late signs: bleeding, ulceration, and pain
MELANOMA
CLINICAL FEATURES. IV.
LENTIGO MALIGNA MELANOMA

* on chronically sun-damaged sites (face, neck, back of hands) in older individuals, (such as non-M skin cancers: basal cell and squamous cell carcinomas)
LENTIGO MALIGNA MELANOMA
LENTIGO MALIGNA MELANOMA
MELANOMA

CLINICAL FEATURES. V.

ACRAL LENTIGINOUS MELANOMA

* on palms, soles, nail beds, and mucous membranes (frequent in blacks and Orientals)
ACRAL LENTIGINOUS MELANOMA
MELANOMA
CLINICAL FEATURES. VI.
SUPERFICIAL SPREADING MELANOMA

* frequent in whites, sometimes deeply invasive (M arising in dysplastic nevi are usually of this type):

  - most common site: back in men and lower leg (from knee to ankle) in women
SUPERFICIAL SPREADING MELANOMA
SUPERFICIAL SPREADING MELANOMA
MELANOMA
CLINICAL FEATURES. VII.
NODULAR MELANOMA

* deeply invasive (dark brown-black to blue-black nodules), fully capable of early metastasis;
  - penetrates deeply into the skin in the vertical growth phase, without recognizable radial growth phase;
* occasionally amelanotic (in this case, the diagnosis of a new or changing skin nodule as M is histological)
NODULAR MELANOMA
AMELANOTIC MELANOMA
SUPERFICIAL SPREADING MELANOMA WITH A NODULAR PHASE
A) superficial spreading melanoma of the trunk:
B) lentigo maligna melanoma of the cheek, most frequently on sun-exposed areas in elderly patients;
C) nodular melanoma of the helix;
D) subungual melanoma of the thumb (a subtype of acral-lentiginous melanoma);
E) amelanotic melanoma on the arm
## CLINICAL FEATURES OF MALIGNANT MELANOMA

<table>
<thead>
<tr>
<th>Type</th>
<th>Site</th>
<th>Average Age at Diagnosis, Yrs</th>
<th>Duration of Known Existence, Years</th>
<th>Color</th>
</tr>
</thead>
<tbody>
<tr>
<td>lentigo maligna</td>
<td>Sun-exposed surfaces, particularly malar region of cheek and temple</td>
<td>70</td>
<td>5-20&lt;sup&gt;a&lt;/sup&gt; or longer</td>
<td>In flat portions, shades of brown and tan predominant, but whitish gray occasionally present; in nodules, shades of reddish brown, bluish gray, bluish black</td>
</tr>
<tr>
<td>melanoma</td>
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<td></td>
</tr>
<tr>
<td>superficial spreading</td>
<td>Any site (more common on upper back and, in women, on lower legs)</td>
<td>40-50</td>
<td>1-7</td>
<td>Shades of brown mixed with bluish red (violaceous), bluish black, reddish brown, and often whitish pink, and the border of lesion is at least in part visibly and/or palpably elevated</td>
</tr>
<tr>
<td>melanoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nodular</td>
<td>Any site</td>
<td>40-50</td>
<td>Months to less than 5 years</td>
<td>Reddish blue (purple) or bluish black; either uniform in color or mixed with brown or black</td>
</tr>
<tr>
<td>melanoma</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>acral lentiginous</td>
<td>Palm, sole, nail bed, mucous membrane</td>
<td>60</td>
<td>1-10</td>
<td>In flat portions, dark brown predominantly; in raised lesions (plaques) brown-black or blue-black predominantly</td>
</tr>
<tr>
<td>melanoma</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

<sup>a</sup> During much of this time, the precursor stage, lentigo maligna, is confined to the epidermis
PROGNOSTIC FACTORS
MELANOMA
PROGNOSTIC FACTORS. I. Stage

* main prognostic factor is clinical stage at time of presentation:

- **stage I** = primary tumor with no clinical evidence of disease elsewhere (5-yr surv = 85%);

- **stage II** = clinically palpable regional nodes containin tumor (5-yr surv = 15-50%, also depending of no. of nodes involved);

- **stage III** = disseminated disease (5-yr surv < 5%)
MELANOMA

PROGNOSTIC FACTORS. II. Breslow’s thickness

* most M are diagnosed in stage I - II and prognosis is based on their thickness = the likelihood of metastasis correlates with thickness (= the best indicator of M volume):

- < 1,0 mm thick (about 40%): usually cured by surgical removal (5-yr surv = > 95%);
- > 4,0 mm thick: lethal metastatic disease in 60% of cases (M almost always raised above the plane of skin);
- 2 other intermediate categories of thickness
MELANOMA
PROGNOSTIC FACTORS. III. Clark’s levels

* based on the anatomic level of invasion in the skin for clinical stages I and II M:
  - level I = intraepidermal (in situ);
  - level II = penetrates the papillary dermis;
  - level III = spans the papillary dermis;
  - level IV = penetrates the reticular dermis;
  - level V = penetrates the subcutaneous fat;

* 5-year survival are 100, 95, 82, 71, and 49%, respectively
Figure 21. The thickness of melanoma is measured as the distance between the granular layer and the deepest invasive melanoma cell (arrow at level III). **Level I**: melanoma cells confined to the epidermis; **level II**: melanoma cells within the papillary dermis; **level III**: melanoma cells filling and widening the papillary dermis; **level IV**: melanoma cells extensively dispersed in the reticular dermis; **level V**: melanoma cells invading subcutaneous tissue.
MELANOMA
Clark’s levels and Breslow’s thickness
MELANOMA
PROGNOSTIC FACTORS. IV.

* in low-risk pts who develop metastases, primary M exhibit either microscopic anaplasia or a vertical growth phase;
* in high risk pts, M is almost always raised above the plane of the skin;
* the time to recurrence varies inversely with tumor thickness (about 10-15% of first time recurrences develop after 5 yrs, but, as breast cancer, M may recur after many yrs)
MELANOMA
PROGNOSTIC FACTORS. V.

* anatomic sites:
  - favorable: forearm and leg (excluding feet);
  - unfavorable: scalp, hands, feet, and mucous membranes;

* women better than men (more likely early self-recognition of M, often on the lower leg);

* age (poor prognosis for older pts: delayed diagnosis, thicker tumors, often palmar-plantar M)
RETROAURICOLAR MELANOMA
* other bad prognostic factors for stage I:
  - an ulcer in the primary tumor;
  - high mitotic rate and poor differentiation, and
  - microscopic tumor satellites (> 0.05 mm) in the dermis or subcutaneous fat (predictive of microscopic metastases to the regional nodes)
MELANOMA CON LINFONODI ASCELLARI E NODULI SATELLITE
# SOME RISK FACTORS

<table>
<thead>
<tr>
<th>Characteristics of primary tumor</th>
<th>Risk Ratio</th>
<th>10 year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumor thickness:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.0-2.0</td>
<td>1.0</td>
<td>83</td>
</tr>
<tr>
<td>2.1-3.0</td>
<td>1.8</td>
<td>67</td>
</tr>
<tr>
<td>3.1-4.0</td>
<td>2.6</td>
<td>50</td>
</tr>
<tr>
<td><strong>Ulceration</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>1.0</td>
<td>81</td>
</tr>
<tr>
<td>Present</td>
<td>2.0</td>
<td>59</td>
</tr>
<tr>
<td><strong>Anatomical site</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extremity</td>
<td>1.0</td>
<td>81</td>
</tr>
<tr>
<td>H&amp;N</td>
<td>1.6</td>
<td>70</td>
</tr>
<tr>
<td>Trunk</td>
<td>1.7</td>
<td>69</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>1.0</td>
<td>77</td>
</tr>
<tr>
<td>≥60</td>
<td>1.5</td>
<td>68</td>
</tr>
</tbody>
</table>
MELANOMA
NATURAL HISTORY

* stage I M usually spreads by the lymphatics or the bloodstream:
- earliest metastases to regional lymph nodes (drainage pathways is predicted by anatomic charts, or on lymphoscintigraphy = Tc99m is injected around the primary tumor);
  - lymphadenectomy usually controls regional disease;
* liver, lung, bone, and brain are common sites of hematogenous spread;
  - with metastatic disease, the likelihood of cure is negligible (most deaths are from brain metastases).
CUTANEOUS METASTASES FROM MELANOMA
CLINICAL MANAGEMENT AND PRECURSOR LESIONS
MELANOMA
CLINICAL MANAGEMENT. I.

* protection from the sun (sunblock of SFP > 15, protective clothing, avoiding intense midday ultraviolet exposure);
- education in the clinical features of M;
- self-examination at 6-8 week intervals (new growth or change in a pigmented lesion)
MELANOMA
CLINICAL MANAGEMENT. II.

* history (for relevant risk factors);

- routine follow-up visits for clinically atypical moles (dysplastic nevi), with examination of the entire cutaneous surface, including scalp and mucous membranes (with bright room illumination and a 10x hand lens);

- biopsy of any suspicious lesions (or photography for follow-up);

- examen of lymph nodes and abdominal viscera
MELANOMA PRECURSORS LESIONS. I.

* dysplastic nevus (DN);
* giant congenital melanocytic nevus;
* small congenital melanocytic nevus;

* DN present at birth or in the neonatal period (tardive forms);
  - the giant and the small congenital melanocytic nevi are less frequent < DN
MELANOMA
PRECURSORS LESIONS. II. Dysplastic nevus

* DN vary from one to hundreds and usually look different one compared to another;
  - hazy and indistinct borders;
  - variable pigment pattern (> than in benign acquired nevi);
* however, the diagnosis of DN is by histology
NEVUS
DYSPLASTIC NEVUS
MELANOMA
MELANOMA
A) piccolo nevo comune; B) grosso nevo non displastico (margini simmetrici e ben definiti e pigmentazione uniforme); C) nevo displastico (bordi irregolari, margini mal definiti e colore non uniforme); D) nevo congenito (dimensioni importanti, margini definiti e chiazzato)
### CLINICAL FEATURES
DISTINGUISHING ATYPICAL MOLES FROM BENIGN ACQUIRED NEVI

<table>
<thead>
<tr>
<th>feature</th>
<th>clinically atypical moles</th>
<th>benign acquired nevi</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Color</strong></td>
<td>Variable mixtures of tan, brown, black, or red/pink within a single nevus; nevi may look very different from each other</td>
<td>Uniformly tan or brown</td>
</tr>
<tr>
<td><strong>Shape</strong></td>
<td>Irregular borders; pigment may fade off into surrounding skin; macular portion at the edge of the nevus</td>
<td>Round; sharp, clear-cut borders between the nevus and the surrounding skin; may be flat or elevated</td>
</tr>
<tr>
<td><strong>Size</strong></td>
<td>Usually more than 6 mm in diameter; may be more than 10 mm; occasionally &lt; 6 mm</td>
<td>Usually less than 6 mm in diameter</td>
</tr>
<tr>
<td><strong>Number</strong></td>
<td>Often very many (more than 100), but occasionally may be only one</td>
<td>In a typical adult, 10 to 40 are scattered over the body; perhaps 15% of patients have no nevi</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>Sun-exposed areas; the back is the most common site, but dysplastic nevi may also be seen on the scalp, breasts, and buttocks</td>
<td>Generally on the sun-exposed surfaces of the skin above the waist; the scalp, breasts, and buttocks are rarely involved</td>
</tr>
</tbody>
</table>

MELANOMA
PRECURSORS LESIONS. III. Dysplastic nevus

* in some families, M occurs nearly exclusively in individuals with DN ( = precancerous lesion, transmitted as an autosomal dominant trait involving chr 9p16), while in others DN may be or may be not present;

- M may arise within the DN (= a precursor) or in normal skin (DN is simply a marker of increased risk)
MELANOMA
PRECURSORS LESIONS. IV. Dysplastic nevus

* clinically DN in the 40% of 90% of pts with apparently sporadic M (i.e., without a family history of M) (5 - 10% in the general population);

* individuals with DN and two family members with M have a > 50% lifetime risk for developing M;

= DN is the most important precursor for M (= importance of recognition)
MELANOMA
PRECURSOR LESIONS. V. Giant melanocytic nevus

* rare malformation (1 / 100,000 people):
  - usually > 20 cm in diameter (may cover > half of the body surface);
  - sharp borders (sometimes with hair);
  - usually dark brown (dark and light may coexist);
  - smooth to rugose to cerebriform surface;
* lifetime risk of M about 6% (usually < age 10);
* difficult detection of M (deep dermal or subcutaneous origin of M, large and varied surface);
* prophylactic excision + skin grafts (or of cultured keratinocytes)
GIANT MELANOCYTIC NEVUS
MELANOMA
PRECURSOR LESIONS. V.
Small melanocytic nevus

* it affects about 1% of people:
  - raised dark to medium brown lesion, with sharp border;
  - sometimes hyper- and hypo-pigmentation (salt-and-pepper configuration), with thick coarse hairs;
* the risk of developing M is unknown, but:
  - coincidence of M and these lesions is > than by chance;
  - histologic remnants of this lesion are found observed in 2-6% of M;
* prophylactic removal in the early 10 yrs
SMALL MELANOCYTIC NEVUS
DIFFERENTIAL DIAGNOSIS
MELANOMA
DIFFERENTIAL DIAGNOSIS

* to distinguish benign pigmented lesions from M and its precursors (biopsy appropriate if M is suspected);

* early detection of M facilitated by applying the "ABCD rules":

  A = asymmetry (benign lesions are usually symmetric); B = border irregularity (most nevi have clear-cut borders); C = color variegation (benign lesions usually have uniform light or dark pigment); D = diameter > 6 mm (the size of a pencil eraser)
LOOK FOR DANGER SIGNS IN PIGMENTED LESIONS OF THE SKIN

Consult your dermatologist immediately if any of your moles or pigmented spots exhibits:

A Asymmetry—one half unlike the other half.

B Border irregular—scalloped or poorly circumscribed border.

C Color varied from one area to another: shades of tan and brown; black; sometimes white, red or blue.

D Diameter larger than 6mm as a rule [diameter of pencil eraser].
PIGMENTED LESIONS THAT MUST BE DISTINGUISHED FROM CUTANEOUS MELANOMA AND ITS PRECURSORS. I

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blue nevus</td>
<td>Gunmetal or cerulean blue, blue-gray. Stable over time. One-half occur on dorsa of hands and feet. Lesions are usually single, small, 3 mm to &lt; 1 cm. Must be distinguished from nodular melanoma.</td>
</tr>
<tr>
<td>Compound nevus</td>
<td>Round or oval shape, well-demarcated, smooth-bordered. May be dome-shaped or papillomatous; colors range from flesh colored to very dark brown, with individual nevi being relatively homogeneous in color.</td>
</tr>
<tr>
<td>Hemangioma</td>
<td>Dome-shaped reddish, purple, blue nodule. Compression with a glass microscope slide may result in blanching. Must be distinguished from nodular melanoma.</td>
</tr>
<tr>
<td>Junctional nevus</td>
<td>Flat to barely raised brown lesion. Sharp border. Fine pigmentary stippling visible, especially upon magnification.</td>
</tr>
<tr>
<td>Lentigo</td>
<td>Flat, uniformly medium or dark brown lesion with sharp border. Solar lentigines are acquired lesions on sites of chronic solar exposure (face and backs of hands). Lesions are 2 mm to &lt; 1 cm. Solar lentigines have reticulate pigmentation upon magnification.</td>
</tr>
</tbody>
</table>
PIGMENTED LESIONS THAT MUST BE DISTINGUISHED FROM CUTANEOUS MELANOMA AND ITS PRECURSORS. II

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pigmented basal cell carcinoma</td>
<td>Papular border. May have central ulceration. Usually on a sun-exposed surface in an older patient. Patient usually has dark brown eyes and dark brown or black hair.</td>
</tr>
<tr>
<td>Pigmented dermatofibroma</td>
<td>Lesion is not well demarcated visually, is firm, and dimples downward when compressed laterally. Usually on extremities. Usually &gt; 6 mm.</td>
</tr>
<tr>
<td>Seborrheic keratosis</td>
<td>Rough, sharp-bordered lesions that feel waxy and &quot;stuck on&quot;; range in color from flesh to tan, to dark brown. Presence of keratin plugs in surface is helpful for discriminating especially dark lesions from melanoma.</td>
</tr>
<tr>
<td>Subungual hematomia</td>
<td>Maroon (red-brown) coloration. As lesion grows out from nail fold, a curving clear area is seen.</td>
</tr>
<tr>
<td>Tattoo (medical or traumatic)</td>
<td>In medical tattoo, lesions are small pigmented dots, often blue or green, which make a regular pattern (rectangle). Traumatic tattoos are irregular, and pigmentation may appear black.</td>
</tr>
</tbody>
</table>
MELANOMA
BIOPSY. I.

* for any suspected, pigmented lesion that has changed in size or shape:
  * excisional biopsy recommended:
    - facilitates pathologic assessment;
    - permits accurate measurement of thickness, and
    - is the treatment if the lesion is benign;
* no indicated shave biopsy or curettage
MELANOMA
BIOPSY. II.

* incisional biopsy through the most nodular or darkest area for lesions large or on particular anatomic sites (such as the face, hands, or feet) where excisional biopsy is not feasible, including (if present) the vertical growth phase of the tumor;
  - no suggestion that incisional biopsy facilitates the spread of M
* after histologic diagnosis, M is staged:
  - history (malaise, weight loss, headaches, visual difficulty, or bone pain suggest metastases);
  - physical examination (skin, regional lymph nodes, CNS, liver, and spleen);
  - chest x-ray and liver function tests and ultrasound;
* no other tests or scans routinely indicated (unless history or physical examination suggest metastases);
  - if signs of metastases exist, examination of favored sites (liver, lungs, bone, and brain)
MELANOMA STAGING. II.

* staging categories are:
- stage I (confined to the skin);
- stage II (disease spreads to regional lymph nodes), and
- stage III (distant metastases);

* stage may be clinical or pathologic (e.g., a patient without palpable adenopathy but with microscopic disease on biopsy is clinical stage I and pathologic stage II, with different prognosis from one that is stage I by both clinical and pathologic criteria)
### MELANOMA
### TNM NOMENCLATURE

<table>
<thead>
<tr>
<th>T classification</th>
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<tbody>
<tr>
<td><strong>T1</strong></td>
<td>≤ 1.0 mm</td>
</tr>
<tr>
<td><strong>T1</strong></td>
<td></td>
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<tr>
<td><strong>T2</strong></td>
<td>1.01-2.0 mm</td>
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<tr>
<td><strong>T2</strong></td>
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</tr>
<tr>
<td><strong>T3</strong></td>
<td>2.01-4.0 mm</td>
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<tr>
<td><strong>T3</strong></td>
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<tr>
<td><strong>T4</strong></td>
<td>≥4.0 mm</td>
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<td><strong>T4</strong></td>
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<th>N classification</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N1</strong></td>
<td>One lymph node</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>N2</strong></td>
<td>2-3 lymph nodes</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>N3</strong></td>
<td>4 or more metastatic lymph nodes, matted lymph nodes, or combinations of in-transit met(s)/satellite(s), or ulcerated melanoma and metastatic lymph node(s)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M classification</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>M1</strong></td>
<td>Distant skin, sub-Q, or lymph node mets</td>
</tr>
<tr>
<td><strong>M2</strong></td>
<td>Lung mets</td>
</tr>
<tr>
<td><strong>M3</strong></td>
<td>All other visceral or any distant mets</td>
</tr>
<tr>
<td></td>
<td>Elevated LDH with any M</td>
</tr>
</tbody>
</table>
## PROGNOSIS OF MELANOMA
### BY THICKNESS (BRESLOW) AND AJCC STAGES
### 5-YEAR SURVIVAL RATES

<table>
<thead>
<tr>
<th>AJCC Stage</th>
<th>Thickness Range, mm</th>
<th>% Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA (localized)</td>
<td>&gt; 0.75</td>
<td>96</td>
</tr>
<tr>
<td>IB (localized)</td>
<td>0.76-1.49</td>
<td>87</td>
</tr>
<tr>
<td>IIA (localized)</td>
<td>1.5-2.49</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>2.50-3.99</td>
<td>66</td>
</tr>
<tr>
<td>IIB (localized)</td>
<td>&gt; 4.00</td>
<td>47</td>
</tr>
<tr>
<td>III (metastatic to regional nodes)</td>
<td>45 (one node)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 20 (two nodes)</td>
<td></td>
</tr>
<tr>
<td>IV (metastatic to distant sites)</td>
<td>8-10(^a)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) One-year survival.
TREATMENT
MELANOMA
TREATMENT. I. Stage I. I.

* wide surgical excision of the lesion
removes all malignant cells and minimizes
local recurrence;

* controversial the width of the normal skin
margins:
  - “5-cm rule” = the normal skin within 5 cm
from M is excised (often requires split-
thickness skin grafts, cosmetically disfiguring);
  - narrower margins = probable increase
local recurrences (with no effect on nodal or
distant metastases and on survival)
MELANOMA
TREATMENT. II. Stages I & II.

* possibly recommended:
  - in situ: 0.5 cm;
  - invasive < 1 mm thick: 1.0 cm;
  - 1 - 4 mm thick: 2.0 cm;
  - > 4 mm thick: > 2 cm;

* individual considerations about the constraints of surgery and minimization of morbidity for lesions on the face, hands, and feet;

* in all instances, inclusion of subcutaneous fat in the specimen
SURGICAL EXCISION OF A MELANOMA OF THE FACE
MELANOMA
TREATMENT. III.
Elective regional node dissection. I

* the hypothesis is that stage I M (= no palpable adenopathy) metastasizes in an orderly fashion (from skin to regional lymph nodes and finally to distant sites);

= surgical excision of nodal micrometastases could provide definitive treatment at a time of relatively low tumor burden
MELANOMA TREATMENT. IV.
Elective regional node dissection. II

* unproven survival efficacy in randomized studies (limb stage I M: no # between wide local excision + immediate regional node dissection vs wide local excision + delayed dissection, if nodes became palpable);

* associated morbidity
MELANOMA
TREATMENT. V.
Elective regional node dissection. III

* furthermore, many lesions (for example, on the trunk) have ambiguous nodal draining sites (lymphoscintigraphy is utilized to define the primary draining nodes = sentinel node)
SENTINEL NODE
MELANOMA
TREATMENT. VI.
Elective regional node dissection. IV.

* probably:
- pts with lesions < 1.0 mm have excellent prognosis and need no node dissection;
- at the other extreme, pts with lesions > 4.0 mm have a high risk for metastases = an elective node dissection is justified
<table>
<thead>
<tr>
<th>Tumor thickness (mm)</th>
<th>Number of patients</th>
<th>Positive SLN total</th>
<th>Positive SLN (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.5</td>
<td>230</td>
<td>11</td>
<td>4.8</td>
</tr>
<tr>
<td>1.51-4.0</td>
<td>271</td>
<td>52</td>
<td>19.2</td>
</tr>
<tr>
<td>≥4.1</td>
<td>64</td>
<td>22</td>
<td>34.4</td>
</tr>
</tbody>
</table>
MELANOMA TREATMENT. VII. Adjuvant therapy. I.

* the hypothesis is that adjuvant therapy destroys occult micrometastases, prolongs disease-free survival, and improves cure rates;

- however, no consistent evidence of effectiveness of chemotherapy, non-specific immunotherapy (such as immunization with bacillus Calmette-Guerin, BCG), chemo-immunotherapy, and radiation therapy
MELANOMA TREATMENT. VIII. Adjuvant therapy. II.

* high dose adjuvant interferon-α may improve disease-free and overall survival in pts with nodal metastases (stage III disease):
  - 20,000,000 U / sqm iv for 5 days / wk for 4 wks followed by 10,000,000 U / sqm sc 3 times / wk for 11 mos effective in some, but not all, studies;
  - severe, reversible toxicity in 50% of pts (including flulike illness, decline in performance status)

* probably, IFN-α benefits only a small fraction of treated pts
MELANOMA
TREATMENT. IX. Adjuvant therapy. III.

* new trials on specific active immunotherapy using viral antigens to induce tumor lysis (hypothesis: the juxtaposition of strong viral antigens and putative weak tumor-associated or tumor-specific antigens heightens a host immune response against micrometastases)
MELANOMA
TREATMENT OF METASTATIC DISEASE. I.

* with metastases, the disease is generally incurable (survival < 1 yr), and treatment is palliative (to improve the quality of life);

* pts with soft-tissue and node metastases fare better than those with liver and brain metastases;

* survival advantage from therapeutic lymph node dissection (for metastases limited to regional nodes = stage II disease) and surgical excision of a single metastasis (to the lung or brain)
MELANOMA
TREATMENT OF METASTATIC DISEASE. II.

* more often pts have multiple brain metastases that require radiation and glucocorticoids;

* radiation therapy (local palliation for recurrent tumors or metastatic sites);

- advanced regional disease isolated to a limb often benefit from hyperthermic limb perfusion (which concentrates the agents and minimizes systemic leakage) with melphalan and TNF
MELANOMA
TREATMENT OF METASTATIC DISEASE. III.

* chemotherapy disappointing = response rate of 20-25% with the best single agent [imidazole carboximide (dacarbazine) alone or in combination], with rare complete responses;

* IFN and IL-2 = similar response rate with greater toxicity
Adoptive immunotherapy

* the immune system has a critical role in the control of metastases from M:
  - lymphocytes from M pts are exposed to interleukin 2 (IL-2), to generate lymphokine-activated killer cells (LAK cells);
  - LAK cells are then reinfused together with IL-2;
* however, response is about 20% (usually partial and short, in pts with skin or lung metastases);
* high toxicity (especially due to increased capillary permeability);
* attempts at enhancing the results with the use of the more potent tumor-infiltrating lymphocytes (TIL)
* M often express cell-surface M-associated Ags recognized by host immune cells allowing attempts at vaccination strategies;
- M Ags (*MAGEs*)-1, -2, and -3 (endogenous proteins controlled by up to 12 genes on the chr X);
- tyrosinase (an enzyme of melanin synthesis);
- an M Ag (*MART*) recognized among class II MHC antigens
MELANOMA
TREATMENT OF METASTATIC DISEASE. VI.
Vaccination strategies. II.

* these Ags are processed into peptides and presented to T cells via HLA-A Ags on the tumor (particularly the HLA-A1 and -A2 alleles, expressed in 85% of M pts)
MELANOMA
TREATMENT OF METASTATIC DISEASE. VI.
Vaccination strategies. II.

* use of purified Ag-proteins as immunogens and of genetically altered tumor cells to elicit a T cell response;

* experimental, in vitro expanding tumor-specific T cells (obtained either from the tumor as tumor-infiltrating lymphocytes or harvested from the peripheral blood after vaccination) and transfer them into pts in large numbers;

* MoAbs to M Ags (early indication of efficacy in 15% of pts)
* tumor cells (TC) modified with genes for cytokines or B7;
  - (A) TC modified with B7 provide signals to trigger T cells;
  - (B) TC modified to secrete cytokines (IL-2) promoting T-cell activation and growth;
  - (C) TC modified with the gene for γ-IFN to secrete γ-IFN and up-regulate antigen presentation by HLA class I and II
MELANOMA
TREATMENT OF METASTATIC DISEASE. VI.

* all of these experimental approaches will need considerable further development;
* the absence of curative therapy for pts with metastatic M underscores the importance of prevention and early detection of the disease