

Melanoma of the Skin

Protocol applies to melanoma of cutaneous surfaces only.

*Protocol revision date: January 2004
Based on AJCC/UICC TNM, 6th edition*

Procedures

- **Biopsy** (No Accompanying Checklist)
- **Excision**
- **Re-excision**

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Surgical Pathology Cancer Case Summary

Protocol revision date: January 2004
Applies to invasive melanoma only
Based on AJCC/UICC TNM, 6th edition

MELANOMA OF THE SKIN: Excision; Re-Excision

Patient name:

Surgical pathology number:

Note: Check 1 response unless otherwise indicated.

MACROSCOPIC

Specimen Type

- Excision, ellipse
- Excision, wide
- Excision, other (specify): _____
- Re-excision, ellipse
- Re-excision, wide
- Re-excision, other (specify): _____
- Lymphadenectomy, sentinel node(s)
- Lymphadenectomy, regional nodes (specify): _____
- Other (specify): _____
- Not specified

Macroscopic Tumor

- Present
- Absent
- Indeterminate

Tumor Site

- Specify (if known): _____
- Not specified

Lesion Size

- Greatest dimension: ____ cm
- *Additional dimensions: ____ x ____ cm
- Cannot be determined (see Comment)

Satellite Nodule(s)

- Absent
 Present (specify): _____
 Cannot be determined

***Pigmentation**

- * Absent
 * Present, diffuse
 * Present, patchy/focal
 * Indeterminate
 * Cannot be determined

MICROSCOPIC**Histologic Type**

- Superficial spreading melanoma
 Lentigo maligna melanoma
 Nodular melanoma
 Acral lentiginous melanoma
 Mucosal-lentiginous melanoma
 Desmoplastic (spindle desmoplastic; neuroid) melanoma
 Neurotropic melanoma
 Malignant blue nevus
 Melanoma in congenital melanocytic nevi
 Minimal deviation (nevroid) melanoma
 Other (specify): _____
 Melanoma, type cannot be determined

Ulceration

- Present
 Absent

Depth of Invasion

- Specify: ___ mm
 Cannot be determined (see Comment)

* Data elements **with asterisks** are **not required** for accreditation purposes for the Commission on Cancer. These elements may be clinically important, but are not yet validated or regularly used in patient management. Alternatively, the necessary data may not be available to the pathologist at the time of pathologic assessment of this specimen.

Pathologic Staging (pTNM)Primary Tumor (pT)

- pTX: Primary tumor cannot be assessed (see Comment)
 pT0: No evidence of primary tumor
 pTis: Melanoma in situ (ie, not an invasive tumor: level I)
 pT1: Melanoma 1.0 mm or less in thickness, with or without ulceration
 pT1a: Melanoma 1.0 mm or less in thickness and level II or III, no ulceration
 pT1b: Melanoma 1.0 mm or less in thickness and level IV or V or with ulceration
 pT2: Melanoma 1.01 to 2mm in thickness, with or without ulceration
 pT2a: Melanoma 1.01 to 2.0 mm in thickness, no ulceration
 pT2b: Melanoma 1.01 to 2.0 mm in thickness, with ulceration
 pT3: Melanoma 2.01 to 4.0 mm in thickness, with or without ulceration
 pT3a: Melanoma 2.01 to 4.0 mm in thickness, no ulceration
 pT3b: Melanoma 2.01 to 4.0 mm in thickness, with ulceration
 pT4: Melanoma greater than 4.0 mm in thickness, with or without ulceration
 pT4a Melanoma greater than 4.0 mm in thickness, no ulceration
 pT4b Melanoma greater than 4.0 mm in thickness, with ulceration

Regional Lymph Nodes (pN)

- pNX: Regional lymph nodes cannot be assessed
 pN0: No regional lymph node metastasis
 pN1: Metastasis in 1 regional lymph node
 pN1a Clinically occult (microscopic) metastasis
 pN1b Clinically apparent (macroscopic) metastasis
 pN2: Metastasis in 2 to 3 regional nodes or intra-lymphatic regional metastasis without nodal metastasis
 pN2a: Clinically occult (microscopic) metastasis
 pN2b: Clinically apparent (macroscopic) metastasis
 pN2c: Satellite or in-transit metastasis without nodal metastasis
 pN3: Metastasis in 4 or more regional lymph nodes, or matted metastatic nodes, or in-transit metastasis or satellites(s) with metastasis in regional node(s)

Number identified: _____

Number containing metastases identified macroscopically: _____

Number containing metastases identified microscopically: _____

Matted nodes:

 Present AbsentDistant Metastasis (pM)

- pMX: Presence of distant metastasis cannot be assessed
 pM1: Distant metastasis (documented in this specimen)
 * pM1a: Metastasis in skin, subcutaneous tissues, or distant lymph nodes
 * pM1b: Metastasis to lung
 * pM1c: Metastasis to all other visceral sites or distant metastasis at any site associated with an elevated serum lactic dehydrogenase (LDH)
 *(Other site, specify: _____)

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Margins (check all that apply)Lateral Margins

- Cannot be assessed
- Uninvolved by invasive melanoma
Distance of invasive melanoma from closest lateral margin: ____ mm
Specify location(s), if possible: _____
- Involved by invasive melanoma
Specify location(s), if possible: _____
- Uninvolved by melanoma in situ
Distance of melanoma in situ from closest margin: ____ mm
Specify location(s), if possible: _____
- Involved by melanoma in situ
Specify location(s), if possible: _____

Deep Margin

- Cannot be assessed
- Uninvolved by invasive melanoma
Distance of invasive melanoma from margin: ____ mm
Specify location(s), if possible: _____
- Involved by invasive melanoma
Specify location(s), if possible: _____

***Venous (Large Vessel) Invasion (V)**

- * Absent
- * Present
- * Indeterminate

***Perineural Invasion**

- * Absent
- * Present
- * Indeterminate

***Tumor-Infiltrating Lymphocytes**

- * Absent
- * Nonbrisk
- * Brisk

***Tumor Regression**

- * Absent
- * Present involving less than 75%
- * Present involving 75% or more of lesion

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***Mitotic Index**

* Less than 1 mitotic figure per mm²

* 1 or more mitotic figure per mm²

***Additional Pathologic Findings (check all that apply)**

* Nevus remnant

* Actinic keratosis

* Other (specify): _____

***Comment(s)**

Background Documentation

Protocol revision date: January 2004

I. Biopsy (Note A)

A. Clinical Information

1. Patient identification
 - a. Name
 - b. Identification number
 - c. Age (birth date) (Note B)
 - d. Sex (Note B)
2. Responsible physician(s)
3. Date of procedure
4. Other clinical information
 - a. Relevant history
 - (1) duration of lesion
 - (2) previous similar lesions
 - (3) family history of similar lesions
 - b. Relevant physical findings
 - (1) anatomic site (Note C)
 - (2) ulceration (Note D)
 - (3) contour of advancing borders of lesion
 - (4) pigmentation, if any
 - (5) fixation to deeper tissues on palpation
 - c. Relevant clinical findings (eg, serum lactate dehydrogenase) (Note E)
 - d. Clinical diagnosis
 - e. Procedure (eg, punch biopsy, incisional biopsy, excisional biopsy)

B. Macroscopic Examination

1. Specimen
 - a. Tissues received (specify nature and site)
 - b. Unfixed/fixed (specify fixative)
 - c. Number of pieces of tissue
 - d. Dimensions
 - e. Results of intraoperative consultation, if performed (Note F)
2. Tumor, if discernible
 - a. Location
 - b. Configuration
 - c. Pigmentation (color and intensity)
 - d. Dimensions (3)
 - e. Ulceration (Note D)
 - f. Other descriptive characteristics (eg, consistency, hemorrhage)
3. Tissue submitted for microscopic examination
 - a. Submit all
 - b. Frozen section tissue fragment(s) (Note F)
4. Special studies (specify) (eg, histochemical stains, immunohistochemistry, electron microscopy, flow cytometry, cytogenetics)

C. Microscopic Evaluation

1. Tumor
 - a. Histologic type (Note G)
 - b. Thickness in millimeters (Note H)
 - c. Level of invasion (Note H)

- d. Growth pattern (Note **G**)
- e. Ulceration (Notes **D** and **H**)
- f. Perineural invasion (with extent) (Note **I**)
- g. Venous/lymphatic vessel invasion (with extent) (Notes **H** and **J**)
- h. Tumor-infiltrating lymphocytes (absent, nonbrisk, brisk) (Note **K**)
- i. Presence and percentage extent of regression, if present (Note **L**)
- j. Mitotic index (number of mitosis per square millimeter) (Note **M**)
- 2. Additional pathologic findings, if present
 - a. Nevus remnant (absent or present; if present, specific type)
 - b. Actinic keratosis
- 3. Results of special studies (specify)
- 4. Comments
 - a. Correlation with intraoperative consultations, if any (Note **F**)
 - b. Correlation with prior specimens, if any
 - c. Correlation with clinical findings, as appropriate
 - d. Margin status, if clinically relevant

II. Excision; Re-excision (Note **A**)

A. Clinical Information

- 1. Patient identification
 - a. Name
 - b. Identification number
 - c. Age (Note **B**)
 - d. Sex (Note **B**)
- 2. Responsible physician(s)
- 3. Date of procedure
- 4. Other clinical information
 - a. Relevant history
 - (1) duration of lesion
 - (2) previous similar lesions
 - (3) family history of similar lesions
 - b. Relevant physical findings
 - (1) anatomic site (Note **C**)
 - (2) ulceration (Note **D**)
 - (3) contour of advancing borders of lesion
 - (4) pigmentation, if any
 - (5) fixation to deeper tissues on palpation
 - c. Relevant clinical findings (eg, serum lactate dehydrogenase) (Note **E**)
 - d. Clinical diagnosis
 - e. Procedure (eg, punch biopsy, ellipse, wide excision)

B. Macroscopic Examination

- 1. Specimen
 - a. Tissues received (specify nature and site)
 - b. Unfixed/fixed (specify fixative)
 - c. Orientation of specimen, if indicated by surgeon
 - d. Number of pieces of tissue
 - e. Dimensions
 - f. Results of intraoperative consultation, if any (Note **F**)
- 2. Tumor
 - a. Location
 - b. Configuration

- c. Pigmentation (color and intensity)
- d. Dimensions
- e. Ulceration (Note **D**)
- f. Other descriptive characteristics (eg, consistency, fixation to other tissues, necrosis, hemorrhage)
- g. Estimated depth of invasion from skin surface (specify compartment, eg, deep dermis, subcutis)
3. Previous biopsy site, if re-excision
 - a. Location
 - b. Tumor, if present (describe as above)
4. Margins (specify distance from the closest margin)
5. Regional lymph nodes, if any
 - a. Location (as specific as possible)
 - b. Number identified
 - c. Number with macroscopic metastasis
 - d. Matted lymph nodes, if present
6. Additional pathologic findings, if present
 - a. Actinic keratoses
 - b. Melanocytic nevi
 - c. Other
7. Tissue submitted for microscopic examination
 - a. Specify location in specimen of each sample
 - b. Margins submitted as radial, not en face, sections
8. Special studies (specify) (eg, histochemical stains, immunohistochemistry, electron microscopy, flow cytometry, cytogenetics)

C. Microscopic Evaluation

1. Tumor
 - a. Histologic type (Note **G**)
 - b. Thickness in millimeters (Note **H**)
 - c. Level of invasion (Note **H**)
 - d. Growth pattern (Note **G**)
 - e. Ulceration (Notes **D** and **H**)
 - f. Perineural invasion (with extent) (Note **I**)
 - g. Venous/lymphatic vessel invasion (with extent) (Notes **J** and **H**)
 - h. Tumor-infiltrating lymphocytes (absent, nonbrisk, brisk) (Note **K**)
 - i. Presence and percentage extent of regression, if present (Note **L**)
 - j. Mitotic index (number of mitosis per square millimeter) (Note **M**)
2. Margins (Note **N**)
 - a. Closest approximation to margin (in millimeters)
3. Additional pathologic findings, if present
 - a. Nevus remnant (absent or present)
 - b. Actinic keratosis
4. Regional lymph nodes (pN) (Notes **H** and **O**)
 - a. Number identified
 - b. Number containing metastases identified macroscopically
 - c. Number containing metastases identified microscopically
 - d. Matted nodes, if present
5. Metastases to other organs (pM) (Note **H**)
 - a. Location, if known
 - (1) distant skin, subcutis, or extra-regional lymph nodes
 - (2) lung, other

6. Results of special studies (specify)
7. Comments
 - a. Correlation with intraoperative consultations, if any (Note F)
 - b. Correlation with prior specimens, if any
 - c. Correlation with clinical findings, as appropriate
 - d. Comments on prognostic findings, as appropriate

Explanatory Notes

A. Procedure

Optimal evaluation of melanocytic lesions requires complete excision that incorporates the full thickness of the involved lesion removed intact. "Shave" procedures should be avoided.

B. Patient Age and Sex

Older patient age and male sex have been shown to be adverse prognostic factors in some studies, but the effect of these factors, independent of other strong adverse prognostic factors with which they correlate, is unclear.

Data from selected treatment centers indicate that the average patient age at diagnosis ranges from about 48 to 59 years.¹⁻⁵ A correlation between advanced age (ie, age greater than the median at diagnosis) and decreased survival has been suggested by several studies.^{3,4,6-8} However, some multivariate analyses have failed to support an independent effect of age.⁹⁻¹² In other studies, correlative trends have been noted between advanced age and increased melanoma thickness at diagnosis, which is a very strong adverse prognostic factor, suggesting that this interrelationship may account for the apparent prognostic effect of age.⁹ In more recent multivariate analyses of data from melanoma centers worldwide, a strong independent relationship between age and outcome was demonstrated.¹

Male sex also has proven to be an adverse prognostic factor in many studies, many using multivariate analysis of results.^{1-3,6,7,9,11,13,14} However, anatomic site of origin, tumor ulceration, and tumor stage (see Notes C, D, and H) are very strong prognostic factors in cutaneous melanoma, and all of these factors correlate with sex. That is, males are more likely than females to develop melanomas in unfavorable sites, to have ulcerated tumors, and to have a higher stage of disease presentation.¹

C. Anatomic Site

For cutaneous melanoma, location on the extremities is associated with a better survival compared with location on the trunk or head and neck.¹ Sublocation analyses have indicated that location on the upper extremities is associated with a slightly better survival than location on the lower extremities. In the head and neck region, location on the face or neck is associated with a survival advantage compared to location on the scalp.²

D. Ulceration

Ulceration is a dominant prognostic factor in cutaneous melanoma without metastasis. It is defined as the absence of an intact epidermis over any part of the primary tumor based on microscopic observation of histologic sections.^{15,16} The presence or absence of ulceration must be confirmed on microscopic examination. Ulcerated melanomas

typically show invasion through the epidermis, whereas nonulcerated melanomas tend to lift the overlying epidermis. Thus, ulceration is widely regarded as an indication of biological aggressiveness in cutaneous melanoma, and clinical data strongly support this interpretation.

Ulceration has been shown repeatedly to be among the most powerful adverse prognostic factors in stage I and II melanomas (see Note **H** below for stage definitions), and in several studies, it has proven to be the single most important feature predicting outcome.^{1,2} Overall, for patients with stage I and II melanomas, the 10-year survival rate is 50% if the tumor is ulcerated and 78% if the tumor is not ulcerated.² In almost every Cox regression analysis of prognostic factors in cutaneous melanoma that includes ulceration, a significantly worse prognosis and a higher risk of metastatic disease have been demonstrated for ulcerated versus nonulcerated tumors of equivalent thickness.^{1,15,16}

There is a positive correlation between ulceration and thickness. For ulcerated tumors, the median thickness has been shown to be about 3 mm; for nonulcerated tumors, it is about 1.3 mm. Nevertheless, the adverse prognostic significance of melanoma ulceration has been shown to be independent of tumor thickness. For thin melanomas (1.0 mm or less in thickness), level of invasion is more predictive of survival outcome than ulceration. For all melanomas greater than 1.0 mm, ulceration is clearly more predictive than thickness.¹

E. Pretreatment Serum Lactate Dehydrogenase (LDH) and Serum Albumin

Data from numerous studies have suggested that an elevated serum level of LDH is a stage-independent prognostic factor for decreased survival in melanoma. In these studies, pretreatment LDH elevation has been variably defined as serum levels greater than 200 to 225 U/L or levels elevated above the normal levels of the reference laboratory.^{1,2,11} It is recommended that any elevation above normal should be checked by repeat LDH testing after at least 24 hours. For stage IV melanoma, a decreased serum albumin level (less than or equal to 3.5 to 4.0 g/dL) has also been shown to be an independent adverse prognostic factor.^{1,2,11}

F. Frozen Sections

The use of frozen sections in biopsies or excisions of pigmented lesions is discouraged. Optimal histologic evaluation of cutaneous melanoma requires formalin fixation.

G. Histologic Subtypes and Growth Patterns

The classification of variants of malignant melanocytic neoplasms¹⁷ of the skin includes the following:

- Superficial spreading melanoma
- Nodular melanoma
- Lentigo maligna melanoma
- Acral lentiginous melanoma
- Mucosal-lentiginous melanoma
- Desmoplastic (spindle desmoplastic; neuroid) melanoma
- Neurotropic melanoma
- Malignant blue nevus
- Melanoma in congenital melanocytic nevi
- Minimal deviation (nevus) melanoma

Other terms for variants not included in the above-cited classification¹⁸ include:

- Micronodular melanoma
- Pleomorphic (sarcomatoid) melanoma
- Rhabdoid melanoma
- Myxoid melanoma
- Pseudopapillary (adenoid) melanoma
- Small cell melanoma
- Balloon cell melanoma
- Hemangiopericytoid melanoma
- Signet ring-cell melanoma
- Additional forms not otherwise specified

The prognostic significance of histologic type is less significant than the growth patterns and depth of infiltration displayed by those histologic types. For example, superficial spreading melanomas, by definition, demonstrate prominent radial growth and have a better prognosis than nodular melanomas, which predominantly demonstrate vertical growth.⁹

Radial growth phase: tumor demonstrates a uniform cytological appearance and is generally wider than it is deep. The presence or absence of a radial growth phase should be noted because the information may be used clinically to plan the extent of the re-excision.

Vertical growth phase: tumor exhibits at least 2 cytologically distinct clones of tumor cells microscopically and shows an inconstant relationship between width and depth. Nodular melanomas are by definition vertical growth phase tumors. The presence or absence of a vertical growth phase should be noted. If a vertical growth phase is present, the character of the cells may also be noted as follows: epithelioid, spindled, or small. Vertical growth phase is an adverse prognostic factor for cutaneous melanoma.

H. TNM and Stage Groupings

The TNM Staging System of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) recommended by this protocol is shown below.^{19,20} In the sixth editions of the AJCC and the UICC staging manuals, the staging system for melanoma of the skin has been completely changed, using different criteria for T, N, and M. Thus, the current staging system cannot be directly compared with previous TNM classifications.

Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy. Pathologic stage 0 or stage 1A patients are exceptions; they do not require pathologic evaluation of their lymph nodes.¹⁹

In virtually all studies of cutaneous melanoma, tumor thickness has been shown to be a dominant prognostic factor^{15,16} and forms the basis for the stratification of pT. Clark levels are also commonly used to indicate depth of invasion of the primary tumor.¹⁹⁻²²

By AJCC/UICC convention, the designation “T” refers to a primary tumor that has not been previously treated. The symbol “p” refers to the pathologic classification of the TNM, as opposed to the clinical classification, and is based on gross and microscopic examination. pT entails a resection of the primary tumor or biopsy adequate to evaluate

the highest pT category, pN entails removal of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant lesions. Clinical classification (cTNM) is usually carried out by the referring physician before treatment during initial evaluation of the patient or when pathologic classification is not possible.

Pathologic staging is usually performed after surgical resection of the primary tumor. Pathologic staging depends on pathologic documentation of the anatomic extent of disease, regardless of whether the primary tumor has been completely removed. If a biopsied tumor is not resected for any reason (eg, when technically unfeasible) and if the highest T and N categories or the M1 category of the tumor can be confirmed microscopically, the criteria for pathologic classification and staging have been satisfied without total removal of the primary cancer.

Primary Tumor (T)[#]

TX	Primary tumor cannot be assessed (eg, shave biopsy or regressed melanoma)
T0	No evidence of primary tumor
Tis	Melanoma in situ (ie, not an invasive tumor: level I) ^{##}
T1	Melanoma 1.0 mm or less in thickness, with or without ulceration
T1a	Melanoma 1.0 mm or less in thickness and level II or III, no ulceration ^{##}
T1b	Melanoma 1.0 mm or less in thickness and level IV or V or with ulceration ^{##}
T2	Melanoma 1.01 to 2.0 mm in thickness, with or without ulceration
T2a	Melanoma 1.01 to 2.0 mm in thickness, no ulceration
T2b	Melanoma 1.01 to 2.0 mm in thickness, with ulceration
T3	Melanoma 2.01 to 4.0 mm in thickness, with or without ulceration
T3a	Melanoma 2.01 to 4.0 mm in thickness, no ulceration
T3b	Melanoma 2.01 to 4.0 mm in thickness, with ulceration
T4	Melanoma greater than 4.0 mm in thickness, with or without ulceration
T4a	Melanoma greater than 4.0 mm in thickness, no ulceration
T4b	Melanoma greater than 4.0 mm in thickness, with ulceration

[#] Clinical T classification (cT) is usually not possible for melanoma, and pathologic (microscopic) assessment of the primary tumor is required for proper staging. Therefore, excision of the primary tumor, rather than punch or other incisional biopsy, is always advised. The T classification of melanoma is based on the thickness of the primary tumor, its anatomic level of invasion, and the presence or absence of ulceration. Maximal thickness is measured with an ocular micrometer at a right angle to the adjacent normal skin. The upper point of reference is the granular layer of the epidermis of the overlying skin or, if the lesion is ulcerated, the base of the lesion (ulcer). The lower reference point is the deepest point of tumor invasion (ie, the leading edge of a single mass or an isolated group of cells deep to the main mass). Ulceration is a strong adverse prognostic factor^{1,16} (see Note **D**).

^{##} Clark levels are defined as follows:

I	Intraepidermal tumor only
II	Tumor invades into papillary dermis
III	Tumor invades into papillary dermis and expands it
IV	Tumor invades into reticular dermis
V	Tumor invades subcutis

Regional Lymph Nodes (N)[#]

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis ^{##}
N1	Metastasis in 1 lymph node ^{###}
N1a	Clinically occult (microscopic) metastasis
N1b	Clinically apparent (macroscopic) metastasis
N2	Metastasis in 2 to 3 regional nodes or intralymphatic regional metastasis without nodal metastasis
N2a	Clinically occult (microscopic) metastasis
N2b	Clinically apparent (macroscopic) metastasis
N2c	Satellite or in-transit metastasis without nodal metastasis [^]
N3	Metastasis in 4 or more regional lymph nodes, or matted metastatic nodes, or in-transit metastasis or satellites(s) with metastasis in regional node(s) ^{^^}

[#] The regional lymph nodes are the most common sites of metastasis. The widespread use of cutaneous lymphoscintigraphy, lymphatic mapping, and sentinel lymph node biopsies has greatly enhanced the ability to identify the presence of lymph node metastasis.¹⁹ By convention, the term “regional lymph nodal metastasis” refers to disease confined to 1 nodal basin or 2 contiguous nodal basins, as in patients with nodal disease in combinations of femoral/iliac, axillary/supraclavicular, cervical/supraclavicular, axillary/femoral, or bilateral axillary or femoral metastases.

^{##} Isolated Tumor Cells, Micrometastasis, and Sentinel Lymph Nodes^{20,21,23}

Use of published guidelines for definitions of nodal metastasis is recommended.^{20,21,23} Accordingly, any histologically identified focus of tumor (ie, seen on routine hematoxylin-eosin [H&E] stain), greater than 0.2 mm in size is classified as nodal involvement. However, tumor measuring 0.2 mm or less identified only by immunohistochemistry or nonhistologic methods should be classified as pN0, as described in the following list, with a comment on the finding in the pathology report.

The biologic significance of minute amounts of tumor (isolated tumor cells [ITCs]) in regional lymph nodes or distant metastatic sites is unproven at present. Isolated tumor cells are defined as single cells or small clusters of cells not more than 0.2 mm in greatest dimension.^{20,21} They are always clinically occult, but when seen on routine histologic examination, are classified as pN0. Lymph nodes or distant sites that are histologically negative but contain ITCs found by either special morphologic (immunohistochemistry) or nonmorphologic techniques (eg, flow cytometry, DNA analysis, polymerase chain reaction [PCR] amplification of a specific tumor marker) should be classified as N0 or M0, respectively. Specific denotation of the assigned N category is suggested as follows for cases in which ITCs are the only evidence of possible metastatic disease.

pN0	No regional lymph node metastasis histologically, no examination for isolated tumor cells (ITCs)
pN0(i-)	No regional lymph node metastasis histologically, negative morphologic (any morphologic technique, including hematoxylin-eosin and immunohistochemistry) findings for ITCs
pN0(i+)	No regional lymph node metastasis histologically, positive morphologic (any morphologic technique, including hematoxylin-eosin and immunohistochemistry) findings for ITCs

pN0(mol-)	No regional lymph node metastasis histologically, negative nonmorphological (molecular) findings for ITCs
pN0(mol+)	No regional lymph node metastasis histologically, positive nonmorphological (molecular) findings for ITCs

Sentinel lymph node identification and evaluation may be included in the surgical approach to cutaneous melanoma. A sentinel lymph node is defined as the first node to receive lymphatic drainage from a primary tumor. There may be more than 1 sentinel node for some tumors. The clinical rationale for sentinel lymph node identification and separate evaluation is based on the assumption that metastatic involvement of a sentinel node increases the likelihood that other more distant nodes may also contain metastatic disease. Conversely, if sentinel nodes are negative, other regional nodes would be less likely to contain metastasis. Like other regional lymph nodes, sentinel lymph nodes that contain histologically identified tumor that is greater than 0.2 mm are classified as pN1. Sentinel lymph nodes that are histologically negative for true metastasis but have been examined for ITCs by any approach are denoted as follows.

pN0(i-)(sn)	No sentinel lymph node metastasis histologically, negative morphologic findings for ITCs (i = "isolated")
pN0(i+)(sn)	No sentinel lymph node metastasis histologically, positive morphologic findings for ITCs (i = "isolated")
pN0(mol-)(sn)	No sentinel lymph node metastasis histologically, negative nonmorphologic findings for ITCs
pN0(mol+)(sn)	No sentinel lymph node metastasis histologically, positive nonmorphologic findings for ITCs

In almost all studies using Cox regression analysis, either the number of regional lymph nodes containing metastases or the percentage of regional nodes containing metastases more strongly predicted outcome than the size of metastasis.^{1,4,15,16} Patients with 1 involved lymph node have longer survivals compared to patients with any combination of 2 or more involved nodes, regardless of the size of the metastasis. In their review of reported studies, the AJCC Melanoma Staging Committee found no compelling evidence that the gross dimension of lymph nodes metastases was an independent predictor of outcome.²²

^ The presence of in-transit metastasis between the primary tumor and the regional lymph nodes portends a poor prognosis. In-transit metastasis is defined arbitrarily as intralymphatic tumor in skin or subcutaneous tissue more than 2 cm from the primary tumor but not beyond the nearest regional lymph node basin.

^ The presence of clinical or microscopic satellite lesions around a primary melanoma and in-transit metastases both portend a poor prognosis, and an analysis of the available data by the AJCC Melanoma Staging Committee revealed no significant difference in survival for these 2 entities.^{15,16} They both are associated with a prognosis equivalent to multiple lymph node metastases.^{15,16}

Distant Metastasis (M)

MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis in skin, subcutaneous tissues, or distant lymph nodes
M1b	Metastasis to lung
M1c	Metastasis to all other visceral sites or distant metastasis at any site associated with an elevated serum lactic dehydrogenase (LDH)

Pathologic Stage Groupings

Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T3a	N0	M0
Stage IIB	T3b	N0	M0
	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage IIIA	T1-4a	N1a	M0
	T1-4a	N2a	M0
Stage IIIB	T1-4b	N1a	M0
	T1-4b	N2a	M0
	T1-4a	N1b	M0
	T1-4a	N2b	M0
	T1-4a/b	N2c	M0
Stage IIIC	T1-4b	N1b	M0
	T1-4b	N2b	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

Note that for cutaneous melanoma, clinical and pathologic stage groupings differ for stage III. The complete clinical stage groupings are shown below for comparison.

Clinical Stage Groupings

Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T3a	N0	M0
Stage IIB	T3b	N0	M0
	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage III	Any T	N1	M0
	Any T	N2	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

TNM Descriptors^{19,20}

For identification of special cases of TNM or pTNM classifications, the “m” suffix and “y,” “r,” and “a” prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

The “m” suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

The “y” prefix indicates those cases in which classification is performed during or following initial multimodality therapy (ie, neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy). The cTNM or pTNM category is identified by a “y” prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The “y” categorization is not an estimate of tumor prior to multimodality therapy (ie, before initiation of neoadjuvant therapy).

The “r” prefix indicates a recurrent tumor when staged after a documented disease-free interval, and is identified by the “r” prefix: rTNM.

The “a” prefix designates the stage determined at autopsy: aTNM.

Additional Descriptors^{19,20}Residual Tumor (R)

Tumor remaining in a patient after therapy with curative intent (eg, surgical resection for cure) is categorized by a system known as R classification, as follows.

RX	Presence of residual tumor cannot be assessed
R0	No residual tumor
R1	Microscopic residual tumor
R2	Macroscopic residual tumor

For the surgeon, the R classification may be useful to indicate the known or assumed status of the completeness of a surgical excision. For the pathologist, the R classification is relevant to the status of the margins of a surgical resection specimen. That is, tumor involving the resection margin on pathologic examination may be assumed to correspond to residual tumor in the patient and may be classified as macroscopic or microscopic according to the findings at the specimen margin(s).

Vessel Invasion

By AJCC/UICC convention, vessel invasion (lymphatic or venous) does not affect the T category indicating local extent of tumor unless specifically included in the definition of a T category. In all other cases, lymphatic and venous invasion by tumor are coded separately as follows.

Lymphatic Vessel Invasion (L)

LX	Lymphatic vessel invasion cannot be assessed
L0	No lymphatic vessel invasion
L1	Lymphatic vessel invasion

Venous Invasion (V)

VX	Venous invasion cannot be assessed
V0	No venous invasion
V1	Microscopic venous invasion
V2	Macroscopic venous invasion

I. Perineural Invasion

Perineural invasion may be seen in melanomas, particularly desmoplastic-neuroid subtypes.²⁴ Although still debated, this feature may correlate with an increased risk for local recurrence. It is suggested that the presence of perineural infiltration be noted in surgical pathology reports on melanomas.

J. Venous Vessel Invasion

At least 1 study²⁵ has suggested that vascular invasion by melanomas correlates independently with worsened overall survival. It is suggested that this parameter be recorded if it is present.

K. Tumor-Infiltrating Lymphocytes (TILs)

A paucity of TILs is an adverse prognostic factor for cutaneous melanoma.²⁶ Although a precise numerical characterization of that finding has not been made, a recent study²⁷ has shown good to excellent overall interobserver agreement in the classification of TILs as brisk, nonbrisk, or absent according to Clark,²⁸ using the guidelines that follow.²⁷ To qualify as TILs, lymphocytes needed to surround and disrupt tumor cells of the vertical growth phase.

TILs absent: no lymphocytes present, or lymphocytes present but do not infiltrate tumor at all.

TILs nonbrisk: lymphocytes infiltrate melanoma only focally or not along the entire base of the vertical growth phase.

TILs brisk: lymphocytes diffusely infiltrate the entire invasive component of the melanoma or the entire base of the vertical growth phase.

L. Tumor Regression

Regression of 75% or more of the lesion (defined by replacement of tumor cells by lymphocytic inflammation, with or without dermal melanophages and fibrosis) carries adverse prognostic importance in invasive melanomas.²⁹

M. Mitotic Index

A mitotic rate of 1 or more mitotic figure per square millimeter is an adverse prognostic factor for cutaneous melanoma.³⁰ For a X25 objective with a field diameter of 0.59 mm, the field area is 0.274 mm². For a X40 objective with a field diameter of 0.44 mm, the field area is 0.152 mm².

N. Margins

Microscopically measured distances between tumor and labeled lateral or deep margins are appropriately recorded for melanoma because these neoplasms may demonstrate clinical "satellitosis," as discussed in Note H. A comment on margins is necessary only for excisional biopsies or formal resections. If a lateral margin is involved by tumor, it should be stated whether the tumor is in situ or invasive.

O. Lymph Nodes

Pathologic examination of lymph nodes has become increasingly important in cutaneous melanoma.^{19,31} Therefore, a comment may be needed that documents the clinical nodal status (cN substage) versus pathologic (pN substage) status in assigning the stage grouping for the tumor. It is strongly recommended that patients with clinically negative nodes undergo pathologic staging using the sentinel lymph node technique or complete regional lymph node dissection. This is especially important for patients being considered for clinical trials.

Removal of sentinel lymph nodes may be performed for patients with primary localized vertical growth phase cutaneous melanomas with a thickness of 1 mm or greater, and recent data indicates that it also may be justified for lesions less than 1 mm thick (incidence of sentinel lymph node metastasis is about 6% in so-called “thin melanomas” versus about 15% for melanomas greater than or equal to 1 mm thick).³² Frozen section analysis of sentinel lymph nodes is not advised. Review of H&E-stained slides from multiple (6 to 10) levels through sentinel lymph nodes increases the sensitivity of detecting microscopic melanoma metastasis; routine analysis (H&E-stained sections of the cut surfaces of a simply bisected lymph node) may lead to a false-negative rate of 10% to 15%. The use of immunohistochemical stains (eg, for tyrosinase or MART-1) also increases the sensitivity of detection of microscopic melanoma metastases and may also be considered in the examination of sentinel lymph nodes. However, immunohistochemical staining should not be used in place of standard histologic examination.

For histologic examination, whether for sentinel node analysis or routine regional lymph node evaluation (see Note **H**), the entire node should be submitted. Large lymph nodes may be bisected or sliced at 2-mm intervals, whereas smaller nodes (less than 5 mm) may be submitted whole. On histologic examination, metastatic tumor measuring greater than 0.2 mm is classified as pN1.

References

1. Balch CM, Soong SJ, Gershenwald JE, et al. Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system. *J Clin Oncol.* 2001;19:3635-3648.
2. Balch CM. Cutaneous melanoma: prognosis and treatment results worldwide. *Semin Surg Oncol.* 1992;8:400-414.
3. Thorn M, Ponten F, Bergstrom R, Sparen P, Adami HO. Clinical and histopathologic predictors of survival in patients with malignant melanoma: a population-based study in Sweden. *J Natl Cancer Inst.* 1994;86:761-769.
4. Buzaid AC, Tinoco LA, Jendiroba D, et al. Prognostic value of size of node metastasis in patients with cutaneous melanoma. *J Clin Oncol.* 1995;13:2361-2368.
5. Kuehnl-Petzoldt C, Wiebelt H, Berger H. Prognostic groups of patients with stage I melanoma. *Arch Dermatol.* 1983;119:816-819.
6. Masback A, Westerdahl J, Ingvar C, Olsson H, Jonsson N. Cutaneous malignant melanoma in southern Sweden 1965, 1975, and 1985: prognostic factors and histologic correlations. *Cancer.* 1997;79:275-283.
7. Averbook BJ, Russo LJ, Mansour EG. A long-term analysis of 620 patients with malignant melanoma at a major referral center. *Surgery.* 1998;124:746-756.
8. Roses DF, Provet JA, Harris MN, Gumpport SL, Dubin N. Prognosis of patients with pathologic stage II cutaneous malignant melanoma. *Ann Surg.* 1985;201:103-107.

9. Balch CM, Murad TM, Soong SJ, Ingalls AL, Halpern NB, Maddox WA. A multifactorial analysis of melanoma: prognostic histopathological features comparing Clark's and Breslow's staging methods. *Ann Surg*. 1978;188:732-742.
10. Balch CM, Soong SJ, Murad TM, Smith JW, Maddox WA, Durrant JR. A multifactorial analysis of melanoma, IV: prognostic factors in 200 melanoma patients with distant metastases (stage III). *J Clin Oncol*. 1983;1:126-134.
11. Eton O, Legha SS, Moon TE, et al. Prognostic factors for survival of patients treated systemically for disseminated melanoma. *J Clin Oncol*. 1998;16:1103-1111.
12. Coit DG, Rogatko A, Brennan MF. Prognostic factors in patients with melanoma metastatic to axillary or inguinal lymph nodes: a multivariate analysis. *Ann Surg*. 1991;214:627-636.
13. Cascinelli N, Marubini E, Morabito A, Bufalino R. Prognostic factors for stage I melanoma of the skin: a review. *Stat Med*. 1985;4:265-278.
14. Stidham KR, Johnson JL, Seigler HF. Survival superiority of females with malignant melanoma: a multivariate analysis of 6383 patients exploring the significance of gender in prognostic outcome. *Arch Surg*. 1994;129:1343-1344.
15. Balch CM, Buzaid AC, Atkins MB, et al. A new American Joint Committee on Cancer staging system for cutaneous melanoma. *Cancer*. 2000;88:1484-1491.
16. Balch CM, Buzaid AC, Soong SJ, et al. Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. *J Clin Oncol*. 2001;19:3635-3638.
17. Banerjee SS, Harris M. Morphological and immunophenotypic variations in malignant melanoma. *Histopathology*. 2000;36:387-402.
18. Nakhleh RE, Wick MR, Rocamora A, et al. Morphologic diversity in malignant melanomas. *Am J Clin Pathol*. 1990;93:731-740.
19. Greene FL, Page DL, Fleming ID, et al, eds. *AJCC Cancer Staging Manual*. 6th ed. New York: Springer; 2002.
20. Sobin LH, Wittekind C, eds. *UICC TNM Classification of Malignant Tumours*. 6th ed. New York: Wiley-Liss; 2002.
21. Hermanek P, Hutter RVP, Sobin LH, Wittekind C. Classification of isolated tumor cells and metastasis. *Cancer*. 1999;86:2668-2673.
22. Schuchter LM. Review of the 2001 AJCC staging system for cutaneous malignant melanoma. *Curr Oncol Rep*. 2001;3:332-337.
23. Singletary SE, Greene FL, Sobin LH. Classification of isolated tumor cells: clarification of the 6th edition of the American Joint Committee on Cancer Staging Manual. *Cancer*. 2003;90(12):2740-2741.
24. Anstey A, McKee P, Jones EW. Desmoplastic malignant melanoma: a clinicopathological study of 25 cases. *Br J Dermatol*. 1993;129:359-371.
25. Straume O, Akslen LA. Independent prognostic importance of vascular invasion in nodular melanomas. *Cancer*. 1996;78:1211-1219.
26. Clemente CG, Mihm MC Jr, Bufalino R, Zurrada S, Collini P, Cascinelli N. Prognostic value of tumor infiltrating lymphocytes in the vertical growth phase of primary cutaneous melanoma. *Cancer*. 1996;77:1303-1310.
27. Busam KJ, Antonescu CR, Marghoob AA, et al. Histologic classification of tumor-infiltrating lymphocytes in primary cutaneous malignant melanoma: a study of interobserver agreement. *Am J Clin Pathol*. 2001;115:856-860.
28. Clark WH Jr, Elder DE, Guerry DG 4th, et al. A model predicting survival in stage I melanoma based on tumor progression. *J Natl Cancer Inst*. 1989;81:1893-1904.
29. Ronan SG, Eng AM, Briele I-IA, et al. Thin malignant melanomas with regression and metastases. *Arch Dermatol*. 1987;123:1326-1330.

30. Barnhill RL, Fine JA, Roush GC, Berwick M. Predicting five-year outcome for patients with cutaneous melanoma in a population-based study. *Cancer*. 1996;78:427-432.
31. McMasters KM, Reintgen DS, Ross MI, et al. Sentinel lymph node biopsy for melanoma: controversy despite widespread agreement. *J Clin Oncol*. 2001;19:2851-2855.
32. Bedrosian I, Faries M, Guerry D 4th, et al. Incidence of sentinel node metastasis in patients with thin primary melanoma (< or = 1 mm) with vertical growth phase. *Ann Surg Oncol*. 2000;7:262-267.

Bibliography

- Aitchison TC, Sirel JM, Watt DC, MacKie RM. Prognostic trees to aid prognosis in patients with cutaneous malignant melanoma. Scottish Melanoma Group. *Br Med J*. 1995;311:1536-1541.
- Balch CM, Soong SJ, Murad TM, Ingalls AL, Maddox WA. A multifactorial analysis of melanoma, II: prognostic factors in patients with stage I (localized) melanoma. *Surgery*. 1979;86:343-351.
- Balch CM, Soong SJ, Murad TM, Ingalls AL, Maddox WA. A multifactorial analysis of melanoma, III: prognostic factors in melanoma patients with lymph node metastases (stage II). *Ann Surg*. 1981;193:377-388.
- Buzaid AC, Ross MI, Balch CM, et al. Critical analysis of the current American Joint Committee on Cancer staging system for cutaneous melanoma and proposal of a new staging system. *J Clin Oncol*. 1997;15:1039-1051.
- Clark WH Jr, Ainsworth AM, Bernardino EA, et al. Histogenesis and biologic behavior of primary human malignant melanoma of the skin. *Cancer Res*. 1969;29:705-727.
- Clark WH Jr, Elder DE, Guerry D IV. Dysplastic nevi and malignant melanoma. In: Farmer ER, Hood AF, eds. *Pathology of the Skin*. Norwalk, Conn: Appleton & Lange; 1990:684-756.
- Drzewiecki KI, Andersson A. Local melanoma recurrences in the scar after limited surgery for primary tumor. *World J Surg*. 1995;19:346-349.
- Elder DE, Guerry D 4th, Epstein MN, et al. Invasive malignant melanomas lacking competence for metastasis. *Am J Dermatopathol*. 1983;6(suppl):55-61.
- Reed RJ. The histologic variance of malignant melanoma: the interrelationship of histological subtype, neoplastic progression, and biological behavior. *Pathology*. 1985;17:301-312.
- Sirott MN, Bajorin DF, Wong, et al. Prognostic factors in patients with metastatic malignant melanoma: a multivariate analysis. *Cancer*. 1993;72:3091-3098.
- Whooley BP, Wallack MK. Surgical management of melanoma. *Surg Oncol*. 1995;4:187-195.