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# Protocol for the Examination of Specimens From Patients With Melanoma of the Skin

**Protocol applies to melanoma of cutaneous surfaces only.**

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**Based on AJCC/UICC TNM, 7th edition**

Protocol web posting date: October 2013

## Procedures

- Biopsy
- Excision
- Sentinel node examination
- Regional node examination

## Authors

David P. Frishberg, MD, FCAP\*

Department of Pathology and Laboratory Medicine, Cedars-Sinai Medical Center, Los Angeles, California

Charles Balch, MD

Departments of Surgery, Oncology, and Dermatology, Johns Hopkins University, Baltimore, Maryland

Bonnie L. Balzer, MD, PhD, FCAP

Department of Pathology and Laboratory Medicine, Cedars-Sinai Medical Center, Los Angeles, California

A. Neil Crowson, MD, FCAP

Regional Medical Laboratory, Departments of Dermatology, Pathology and Surgery, University of Oklahoma, Tulsa, Oklahoma

Mukund Didolkar, MD, FACS

Division of Surgical Oncology, Sinai Hospital of Baltimore, Department of Surgery, Johns Hopkins University, Baltimore, Maryland

Alexander Lazar, MD, PhD, FCAP

Department of Pathology and Dermatology, The University of Texas MD Anderson Cancer Center, Houston, Texas

Jennifer M. McNiff, MD, FASCP

Departments of Dermatology and Pathology, Yale University School of Medicine

Roger R Perry, MD, FACS

Department of Surgery, Eastern Virginia Medical School, Norfolk, Virginia

Victor G. Prieto, MD, PhD, FCAP

Departments of Pathology and Dermatology, The University of Texas MD Anderson Cancer Center, Houston, Texas

Priya Rao, MD, FCAP

Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, Texas

M. Timothy Smith, MD

Department of Pathology and Laboratory Medicine, Medical University of South Carolina, Charleston, South Carolina

Bruce Robert Smoller, MD, FCAP

Department of Pathology, University of Arkansas for Medical Sciences, Little Rock, Arkansas

Mark R. Wick, MD, FCAP

Department of Pathology, University of Virginia Health System, Charlottesville, Virginia

For the Members of the Cancer Committee, College of American Pathologists

\* Denotes primary author. All other contributing authors are listed alphabetically.

**Previous lead contributors:** Charles Balch, MD; Raymond Barnhill, MD; Carolyn Compton, MD, PhD; Mark Wick, MD

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## CAP Melanoma Protocol Revision History

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### Version Code

The definition of the version code can be found at [www.cap.org/cancerprotocols](http://www.cap.org/cancerprotocols).

**Version:** Melanoma 3.3.0.0

### Summary of Changes

The following changes have been made since the June 2012 release.

### Biopsy, Excision, Re-excision

#### Margins

##### Deep Margin

Deleted "Specify location(s), if possible."

#### Microsatellitosis

"Not applicable" was added.

#### Pathologic Staging (pTNM)

##### Regional Lymph Nodes (pN0)

Deleted the designations of "(microscopic)" and "(macroscopic)" and added "(micrometastasis)" and "(macrometastasis)"; and changed "Number containing metastases identified macroscopically/microscopically" to "Number containing metastases" as follows:

#### 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 metastasis (micrometastasis)

\_\_\_ pN1b: Clinically apparent metastasis (macrometastasis)

pN2: Metastasis in 2 to 3 regional nodes or intralymphatic regional metastasis without nodal metastasis

\_\_\_ pN2a: Clinically occult metastasis (micrometastasis)

\_\_\_ pN2b: Clinically apparent metastasis (macrometastasis)

\_\_\_ 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)

\_\_\_ No nodes submitted or found

Number of lymph nodes identified: \_\_\_\_

Number containing metastases: \_\_\_\_

### Explanatory Notes

#### O. TNM and Stage Groupings

Corrected a typographic error in subheading: changed "R Category Considerations" to "N Category Considerations."

Edited paragraph: "Isolated Tumor Cells, Micrometastasis, and Sentinel Lymph Nodes."

Added paragraph: "Micrometastasis versus Macrometastasis."

**Surgical Pathology Cancer Case Summary**

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Protocol web posting date: October 2013

**MELANOMA OF THE SKIN: Biopsy, Excision, Re-Excision****Select a single response unless otherwise indicated.****Procedure (select all that apply) (Note A)**

- Biopsy, shave  
 Biopsy, punch  
 Biopsy, incisional  
 Excision  
 Re-excision  
 Lymphadenectomy, sentinel node(s)  
 Lymphadenectomy, regional nodes (specify): \_\_\_\_\_  
 Other (specify): \_\_\_\_\_  
 Not specified

**Specimen Laterality**

- Right  
 Left  
 Midline  
 Not specified

**Tumor Site (Note B)**

- Specify (if known): \_\_\_\_\_  
 Not specified

**Tumor Size (required only if tumor is grossly present)**

- Greatest dimension: \_\_ cm  
 + Additional dimensions: \_\_ x \_\_ cm  
 Indeterminate (see "Comment")

**Macroscopic Satellite Nodule(s) (required for excision specimens only)**

- Not identified  
 Present  
 Indeterminate

**+ Macroscopic Pigmentation**

- +  Not identified  
 +  Present, diffuse  
 +  Present, patchy/focal  
 +  Indeterminate

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

**Histologic Type (Note C)**

Malignant melanoma

- Melanoma, not otherwise classified
- Superficial spreading melanoma
- Nodular melanoma
- Lentigo maligna melanoma
- Acral-lentiginous melanoma
- Desmoplastic and/or desmoplastic neurotropic melanoma
- Melanoma arising from blue nevus
- Melanoma arising in a giant congenital nevus
- Melanoma of childhood
- Nevoid melanoma
- Persistent melanoma
- Other (specify): \_\_\_\_\_

**Maximum Tumor Thickness (Note D)**

Specify: \_\_\_ mm

At least \_\_\_ mm (see "Comment")

Indeterminate (see "Comment")

**+ Anatomic Level (Note D)**

- +  I (Melanoma in situ)
- +  II (Melanoma present in but does not fill and expand papillary dermis)
- +  III (Melanoma fills and expands papillary dermis)
- +  IV (Melanoma invades reticular dermis)
- +  V (Melanoma invades subcutis)

**Ulceration (Note E)**

- Present
- Not identified
- Indeterminate

**Margins (select all that apply) (Note F)**

Peripheral Margins

- Cannot be assessed
- Uninvolved by invasive melanoma
  - Distance of invasive melanoma from closest peripheral margin: \_\_\_ mm (required for excisions only)
  - 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 (required for excisions only)
  - Specify location(s), if possible: \_\_\_\_\_
- Involved by melanoma in situ
  - Specify location(s), if possible: \_\_\_\_\_

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Deep Margin

- Cannot be assessed  
 Uninvolved by invasive melanoma  
     Distance of invasive melanoma from margin: \_\_\_\_ mm (required for excisions only)  
 Involved by invasive melanoma

**Mitotic Rate (Note G)**

- None identified  
  $\geq 1/\text{mm}^2$  (specify number: \_\_\_\_\_)

**Microsatellitosis (Note H)**

- Not identified  
 Present  
 Indeterminate  
 Not applicable

**Lymph-Vascular Invasion (Note I)**

- Not identified  
 Present  
 Indeterminate

**+ Perineural Invasion (Note J)**

- +  Not identified  
 +  Present  
 +  Indeterminate

**+ Tumor-Infiltrating Lymphocytes (Note K)**

- +  Not identified  
 +  Present, nonbrisk  
 +  Present, brisk

**+ Tumor Regression (Note L)**

- +  Not identified  
 +  Present, involving less than 75% of lesion  
 +  Present, involving 75% or more of lesion  
 +  Indeterminate

**+ Growth Phase (select all that apply) (Note M)**

- +  Radial  
 +  Vertical  
 +  Indeterminate

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

**Lymph Nodes (required only if lymph nodes are present in the specimen) (select all that apply) (Note N)**

Number of sentinel nodes examined: \_\_\_\_

Total number of nodes examined (sentinel and nonsentinel): \_\_\_\_

Number of lymph nodes with metastases: \_\_\_\_

+ Extranodal tumor extension:

+ \_\_\_\_ Present

+ \_\_\_\_ Not identified

+ \_\_\_\_ Indeterminate

+ Size of largest metastatic focus: \_\_\_\_ (mm) (for sentinel node)

+ Location of metastatic tumor (for sentinel node)

+ \_\_\_\_ Subcapsular

+ \_\_\_\_ Intramedullary

+ \_\_\_\_ Subcapsular and intramedullary

**Pathologic Staging (pTNM) (Note O and Note P)**TNM Descriptors (required only if applicable) (select all that apply)

\_\_\_\_ m (multiple)

\_\_\_\_ r (recurrent)

\_\_\_\_ y (posttreatment)

**Primary Tumor (pT)**

\_\_\_\_ pTX: Primary tumor cannot be assessed (eg, shave biopsy or regressed melanoma) (see "Comment")

\_\_\_\_ pT0: No evidence of primary tumor

\_\_\_\_ pTis: Melanoma in situ (ie, not an invasive tumor: anatomic level I)

pT1: Melanoma 1.0 mm or less in thickness, with or without ulceration (see Note D)

\_\_\_\_ pT1a: Melanoma 1.0 mm or less in thickness, no ulceration, <1 mitoses/mm<sup>2</sup>\_\_\_\_ pT1b: Melanoma 1.0 mm or less in thickness with ulceration and/or 1 or more mitoses/mm<sup>2</sup>

pT2: Melanoma 1.01 to 2 mm 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

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

**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 metastasis (micrometastasis)
  - pN1b: Clinically apparent metastasis (macrometastasis)
- pN2: Metastasis in 2 to 3 regional nodes or intralymphatic regional metastasis without nodal metastasis
  - pN2a: Clinically occult metastasis (micrometastasis)
  - pN2b: Clinically apparent metastasis (macrometastasis)
  - 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)
  
- No nodes submitted or found

Number of lymph nodes identified: \_\_\_\_

Number containing metastases: \_\_\_\_

Matted nodes:

- Present
- Not identified

**Distant Metastasis (pM)**

- Not applicable
- 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)
    - + Specify site, if known: \_\_\_\_\_

**+ Additional Pathologic Findings (select all that apply)**

- +  Nevus remnant
- +  Other (specify): \_\_\_\_\_

**+ Comment(s)**

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.



## Explanatory Notes

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### A. Procedure

Optimal evaluation of melanocytic lesions requires complete excision that incorporates the full thickness of the involved lesion removed intact.<sup>1</sup> "Shave" procedures that do not include the intact base of the lesion should be avoided. Similarly, "punch" procedures may not include intact lateral borders for assessment of symmetry and lateral circumscription, which can be essential for distinction of melanoma from melanocytic nevus.<sup>2,3</sup>

The use of frozen sections in biopsies or excisions of melanocytic lesions is strongly discouraged.<sup>4</sup> Optimal histologic evaluation of cutaneous melanoma requires well-cut, well-stained hematoxylin-and-eosin (H&E) sections prepared from formalin-fixed paraffin-embedded tissue. Frozen sections of sentinel lymph nodes are similarly discouraged, because the manipulation required for intraoperative handling may decrease the sensitivity of the procedure.<sup>5</sup>

### B. Anatomic Site

For cutaneous melanoma, prognosis may be affected by primary anatomic site.<sup>6,7</sup>

### C. Histologic Subtypes

The (modified) World Health Organization (WHO) classification<sup>7</sup> of variants of malignant melanocytic neoplasms of the skin includes the following:

- Superficial spreading melanoma
- Nodular melanoma
- Lentigo maligna melanoma
- Acral lentiginous melanoma
- Mucosal-lentiginous melanoma
- Desmoplastic/neurotropic melanoma
- Melanoma arising from blue nevus
- Melanoma arising from a giant congenital nevus
- Melanoma in childhood
- Nevoid melanoma
- Persistent melanoma
- Melanoma, not otherwise classified

The WHO list is not exhaustive; this protocol does not preclude use of other diagnostic terms, for example, mucosal lentiginous melanoma, a form commonly observed in the vulva.

There is ongoing research to correlate molecular abnormalities in malignant melanoma, particularly *BRAF* mutations, with histologic parameters. Given the wide variety of reported mutations in melanoma<sup>8</sup> and the lack of predictably effective targeted molecular therapy,<sup>9</sup> practical application of such morphologic correlates remains an issue for future protocols.

### D. Primary Tumor Thickness (Breslow Thickness) and Anatomic (Clark) Levels<sup>7</sup>

Maximum tumor thickness is measured with a calibrated 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 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).

If the tumor is transected by the deep margin of the specimen, the depth may be indicated as "at least \_\_ mm" with a comment explaining the limitation of thickness assessment.

Clark levels are defined as follows:

- I Intraepidermal tumor only
- II Tumor present in but does not fill and expand papillary dermis
- III Tumor fills and expands papillary dermis
- IV Tumor invades into reticular dermis
- V Tumor invades subcutis

Clark levels were previously a primary requirement for subclassifying pT1 lesions according to the American Joint Committee on Cancer (AJCC) 6<sup>th</sup> edition TNM classification system and are commonly reported. Anatomic level has been replaced by mitotic rate in the AJCC 7<sup>th</sup> edition tables for subclassifying pT1 lesions as T1a or T1b, but in the text and in a table comment of the AJCC chapter,<sup>10</sup> Clark level IV or V is referred to as a tertiary criterion for T1b in cases with no ulceration and “if mitotic rate cannot be determined.” Clark level should therefore be reported whenever it would form the basis for upstaging T1 lesions.

The distinction of T1a versus T1b is of significant clinical importance, as the AJCC recommends that sentinel node examination be considered for melanomas stage T1b and above.

#### **E. Ulceration**

Ulceration is a dominant prognostic factor in cutaneous melanoma without metastasis,<sup>6</sup> and if present, changes the pT stage from T1a to T1b. The presence or absence of ulceration must be confirmed on microscopic examination.<sup>11</sup> Melanoma ulceration is defined as the combination of the following features: full-thickness epidermal defect (including absence of stratum corneum and basement membrane); evidence of reactive changes (ie, fibrin deposition, neutrophils); and thinning, effacement, or reactive hyperplasia of the surrounding epidermis in the absence of trauma or a recent surgical procedure. Ulcerated melanomas typically show invasion through the epidermis, whereas nonulcerated melanomas tend to lift the overlying epidermis. 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.<sup>12</sup> In Cox regression analyses of prognostic factors in cutaneous melanoma that include ulceration, a significantly worse prognosis and a higher risk of metastatic disease have been demonstrated for ulcerated versus non-ulcerated tumors of equivalent thickness.<sup>6,11</sup>

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 melanomas greater than 1.0 mm, ulceration is more predictive than thickness.<sup>6</sup> Recent studies suggest that ulceration may lose its independent prognostic significance when mitotic rate is taken into account.<sup>13</sup>

#### **F. Margins**

Microscopically measured distances between tumor and labeled lateral or deep margins are appropriately recorded for melanoma excision specimens because these neoplasms may demonstrate clinical “satellitosis.” Nevertheless, a “safe minimum” margin has not been established in the literature. If a lateral margin is involved by tumor, it should be stated whether the tumor is in situ or invasive.

#### **G. Mitotic Rate**

A mitotic rate of 1 or more mitotic figure per square millimeter is a powerful adverse prognostic factor for cutaneous melanoma<sup>13</sup> and will upstage pT1 lesions from pT1a to pT1b in the 7<sup>th</sup> edition of the AJCC staging manual. The AJCC recommended method<sup>10</sup> is provided below:

“The recommended approach to enumerating mitoses is to first find the areas in the dermis containing the most mitotic figures, the so called hot spot. After counting the mitoses in the hot spot, the count is extended to adjacent fields until an area corresponding to 1 mm<sup>2</sup> is assessed. If no hot spot can be found and mitoses are sparse and randomly scattered throughout the lesion, then a representative mitosis is chosen and beginning with that field the count is then extended to adjacent fields until an area corresponding to 1 mm<sup>2</sup> is assessed. The count then is expressed as the number of mitoses/mm<sup>2</sup> (ie, an area corresponding to approximately four high power fields at 400x in most microscopes). To obtain accurate measurement, calibration of individual microscopes is recommended. For classifying thin ( $\leq 1$  mm) melanomas, the threshold for a nonulcerated melanoma to be defined as T1b is  $\geq 1$  mitoses/mm<sup>2</sup>.

When the invasive component of tumor is  $< 1$  mm<sup>2</sup> (in area), the number of mitoses present in 1mm<sup>2</sup> of dermal tissue that includes the tumor should be enumerated and recorded as a number per millimeter squared. Alternatively, in tumors where the invasive component is  $< 1$  mm<sup>2</sup> in area, the simple presence or absence of a mitosis can be designated as *at least 1/mm<sup>2</sup>* (ie, "mitogenic") or *0/mm<sup>2</sup>* (ie, "nonmitogenic"), respectively. At some institutions when mitotic figures are not found after numerous fields are examined, the mitotic count has been described as " $< 1/\text{mm}^2$ ". For most tumor registries the designation " $< 1/\text{mm}^2$ " equals 0 as has been customarily used in the past. This practice may be continued for historical data. For the future, we urge pathologists to list 0 or 1 or more, and this practice should also be demanded by clinicians.

It is a common and appropriate practice with small, thin melanomas to have the technician place multiple sections cut from the block on a single slide. As a guide, we suggest that no more than two slides with such multiple sections be evaluated so that exhaustive evaluation of the lesion is not performed."

Several points deserve emphasis:

The enumerated mitoses must be melanocytic and *dermal*.

Implied by the "hot spot" method, as applied in the first paragraph above, is that *the identification of even a single mitosis in the dermal component, regardless of the size of that component, is sufficient to report the mitotic rate as greater than or equal to 1 per square millimeter and upstage a thin melanoma to pT1b*. This concept has been more explicitly elaborated upon in a recent paper.<sup>14</sup>

The apparent limit on "exhaustive evaluation" is interpreted as indicating that skin specimens containing melanoma should not be processed in a special manner to increase detection of mitoses, but rather should be processed in the same manner as other specimens in that laboratory.

Although the AJCC recommends reporting "0" rather than "none identified" or "less than 1," for the purposes of cancer registry reporting all of these terms should be considered equivalent and equally acceptable.

#### **H. Microsatellitosis**

Microsatellitosis is defined as the presence of tumor nests greater than 0.05 mm in diameter, in the reticular dermis, panniculus, or vessels beneath the principal invasive tumor but separated from it by at least 0.3 mm of normal tissue on the section in which the Breslow measurement was taken.<sup>15</sup>

See also Note O.

**I. Vascular Invasion**

At least one study<sup>16</sup> has suggested that vascular invasion by melanoma correlates independently with worsened overall survival.

**J. Perineural Invasion**

Perineural invasion may be seen in melanoma, particularly desmoplastic-neuroid subtypes.<sup>7</sup> 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.

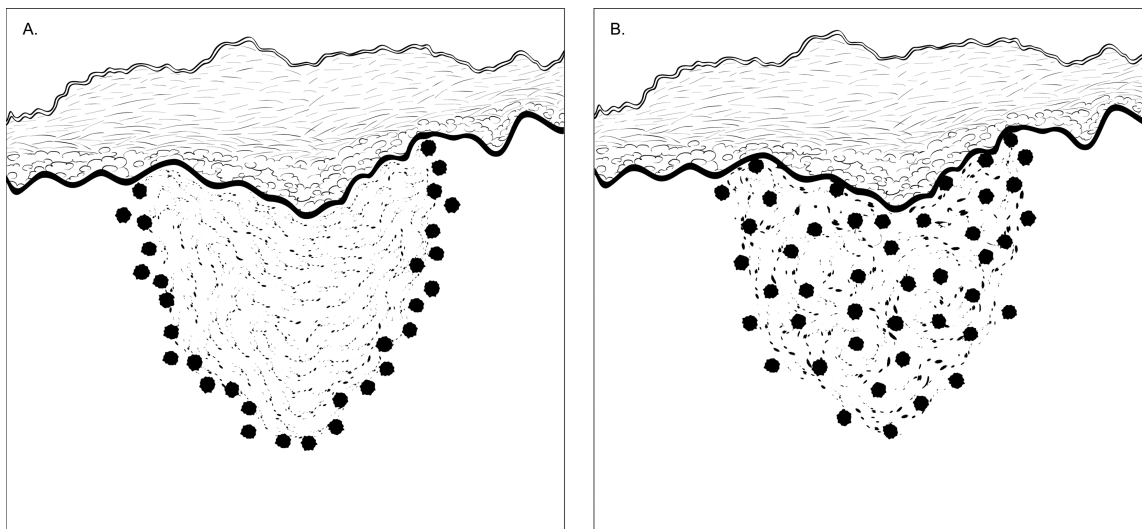
**K. Tumor-Infiltrating Lymphocytes**

A paucity of tumor-infiltrating lymphocytes (TILs) is an adverse prognostic factor for cutaneous melanoma.<sup>17</sup> Tumor-infiltrating lymphocytes may be assessed in a semiquantitative way, as defined below. To qualify as TILs, lymphocytes need to surround and disrupt tumor cells of the vertical growth phase.

TILs Not Identified: 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 base of the vertical growth phase (Figure 1, A) or the entire invasive component of the melanoma (Figure 1, B).



**Figure 1.** Brisk tumor-infiltrating lymphocytes. A, Lymphocytes diffusely infiltrate the entire base of the vertical growth phase. B, Lymphocytes infiltrate the entire invasive component of the melanoma.

**L. Tumor Regression**

Characteristic features of regression include replacement of tumor cells by lymphocytic inflammation (definitional), as well as attenuation of the epidermis and nonlaminated dermal fibrosis with inflammatory cells, melanophagocytosis, and telangiectasia.

Complete regression carries adverse prognostic importance in invasive melanomas, as does regression involving more than 75% of the lesion.<sup>17</sup>

**M. Growth Patterns and Phases**

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.<sup>18</sup>

Radial Growth Phase: Tumor demonstrates a uniform cytological appearance and is generally wider than it is deep. One commonly applied criterion is presence of melanoma in situ 3 or more rete ridges beyond the invasive component.

Vertical Growth Phase: Vertical growth phase is an adverse prognostic factor for cutaneous melanoma. Nodular melanomas are by definition vertical growth phase tumors. Vertical growth pattern in superficial spreading melanoma is defined as the presence of 1 or more dermal clusters larger than the largest epidermal cluster and/or the presence of any mitotic activity in the dermis.<sup>19</sup>

**N. Lymph Nodes**

Removal of sentinel lymph nodes may be performed for patients with primary localized 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 4% to 6% in so-called thin melanomas versus about 15% for melanomas  $\geq 1$  mm thick).<sup>20</sup> Frozen section analysis of sentinel lymph nodes is not advised.<sup>5</sup> Review of the H&E-stained slides from multiple levels through serially sectioned 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 HMB-45 or MART-1) further increases the sensitivity of detection of microscopic melanoma metastases and should also be considered in the examination of sentinel lymph nodes. Although immunohistochemical staining should be used in conjunction with and not in place of standard histologic examination, immunohistochemically identified micrometastases are accepted as representing greater than N0 disease by the 7<sup>th</sup> edition of the AJCC staging system.<sup>10</sup>

For histologic examination, whether for sentinel node analysis or for routine regional lymph node evaluation, the entire node, except tissue collected for consented research protocols, should be submitted. For routine evaluation, large lymph nodes may be bisected or sliced at 2-mm intervals, whereas smaller nodes (<5 mm) may be submitted whole.

A number of studies<sup>21-23</sup> have suggested the sentinel lymph node tumor burden or the pattern of metastasis in the sentinel node (such as the S Classification)<sup>24</sup> may be useful in predicting patients who have additional disease in nonsentinel nodes and thus would help select patients who might benefit from complete lymph node dissection. Investigators have suggested that the amount or pattern of the disease in the sentinel node may also serve as a prognostic factor. If such results are validated and found to be reproducible, then they may be an issue for future protocols.

Although not required for AJCC staging, current National Comprehensive Cancer Network (NCCN) guidelines<sup>25</sup> recommend recording the size and location of tumor present in a positive sentinel node. These are included as optional elements in this protocol.

**O. TNM and Stage Groupings**

The TNM Staging System of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) is recommended by this protocol.<sup>10,26</sup>

Changes in the 7<sup>th</sup> edition AJCC *Cancer Staging Manual* of importance to practicing pathologists include:

- Assignment of pT1b status to lesions less than 1mm thick with 1 or more mitoses per mm<sup>2</sup>
- Relegation of Clark level IV or V to tertiary importance in assignment of pT1b status
- Classification of the presence of any nodal melanoma cells (including isolated tumor cells [ITCs]) as nodal involvement (>pN0)
- Allowing purely immunohistochemical detection of nodal metastasis

Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy.<sup>10</sup>

In virtually all studies of cutaneous melanoma, tumor thickness has been shown to be a dominant prognostic factor,<sup>7,10,16</sup> and it forms the basis for the stratification of pT. Clark levels are also commonly used to indicate depth of invasion of the primary tumor,<sup>7,10,17,26</sup> but are less predictive of clinical outcome than mitotic activity.<sup>20</sup>

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 of surgically removed tissues. 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 pathologic examination of distant lesions.

### T Category Considerations

Pathologic (microscopic) assessment of the primary tumor is required for proper staging. Therefore, excision of the primary tumor, rather than incisional biopsy, is advised. The T classification of melanoma is based on the thickness of the primary tumor, presence or absence of ulceration, mitotic rate, and in some cases its anatomic level of invasion (see also Notes D, E, and G).

### N Category Considerations (see also Note N)

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.<sup>10</sup> By convention, the term regional lymph nodal metastasis refers to disease confined to 1 draining nodal basin or 2 contiguous draining 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. Metastasis to nondraining nodal basin(s) is considered M1 disease.

### Isolated Tumor Cells, Micrometastasis, and Sentinel Lymph Nodes<sup>27,28</sup>

The previous edition of this protocol employed the use of ITC terminology analogous to that published for breast cancer. The 7<sup>th</sup> edition staging system defines nodal involvement by the presence of any tumor cells regardless of quantity, size, or mode of detection (ie, >pN0).

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.

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.<sup>6,11,29</sup> 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.<sup>30</sup>

#### Micrometastasis versus Macrometastasis<sup>10</sup>

The AJCC 7<sup>th</sup> edition staging system defines *micrometastasis* as nodal metastasis diagnosed after pathologic examination of sentinel lymph node biopsy or completion lymphadenectomy (if performed), in patients without clinical or radiologic evidence of metastasis, ie, "clinically occult." *Macrometastases* are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension. Because complete clinical staging information may not always be available to the pathologist, it may be advisable in cases with bulky nodal disease to add a comment to the report to the effect that if nodal disease was clinically apparent, that upstaging to pN1b or pN2b would be appropriate and that clinical correlation is needed. Centers receiving nodal dissections routinely may wish to make submission of presence or absence of clinical adenopathy part of their standard requisition data.

In-transit metastasis/satellitosis is used in the 7<sup>th</sup> edition AJCC staging system for definition of N2c disease. Satellitosis by definition occurs within 2 cm of the primary tumor. In-transit metastasis is defined 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 in-transit metastasis between the primary tumor and the regional lymph nodes portends a poor prognosis.

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 between the two, both of which are associated with a prognosis equivalent to multiple lymph node metastases.<sup>10</sup>

#### **M Category Considerations**

The category "MX" has been eliminated from the AJCC/UICC TMN system.<sup>10</sup> Unless there is clinical or pathologic evidence of distant metastasis the stage is classified as clinical M0 (ie, no distant metastasis). pM should *only* be reported when metastases have been documented by pathologic examination, that is, pM1 disease. pMX and pM0 should *not* be reported by the pathologist.

#### **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	N2c	M0

Stage III C	T1-4b	N1b	M0
	T1-4b	N2b	M0
	T1-4b	N2c	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
Stage IV	Any T	Any N	M1

### TNM Descriptors<sup>10,26</sup>

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

Post-therapy stage (yTNM) documents the extent of the disease for patients whose first course of therapy includes systemic or radiation treatment prior to surgical resection or when systemic therapy or radiation is primary treatment with no surgical resection. The extent of disease is classified using the same T, N, and M definitions and identified as post-treatment with a “yc” or “yp” prefix (ycT, ycN, ycTNM; ypT, ypN, ypTNM).

Retreatment classification (rTNM) is used because information gleaned from therapeutic procedures and from extent of disease defined clinically may be prognostic for patients with recurrent cancer after a disease-free interval. It is important to understand that the rTNM classification does not change the original clinical or pathologic staging of the case.

Autopsy classification (aTNM) is used to stage cases of cancer not recognized during life and only recognized postmortem.

### Additional Descriptors<sup>10,26</sup>

#### 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).

#### Lymph-Vascular Invasion

Lymph-vascular invasion (LVI) indicates whether microscopic lymph-vascular invasion is identified and includes lymphatic invasion, vascular invasion, or lymph-vascular invasion. By AJCC/UICC convention, LVI does not affect the T category indicating local extent of tumor unless specifically included in the definition of a T category.

#### **P. Pretreatment Serum Lactate Dehydrogenase 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 as levels elevated above the reference range of the reference laboratory.<sup>6,12,31</sup> It is recommended that any elevation above reference range should be checked by repeat LDH testing after at least 24 hours. For stage IV melanoma, a decreased serum albumin level ( $\leq 3.5$  to 4.0 g/dL) has also been shown to be an independent adverse prognostic factor.<sup>6,12,31</sup>

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