

Diagnosing Melanocytic Lesions: Integrating
Morphologic, Immunohistochemical and
Molecular Features
Session number:1023

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Segment 3

Pathology report of the morphologic
parameters:

- impact staging
- fulfill laboratory accreditation

(Dr. Curry)

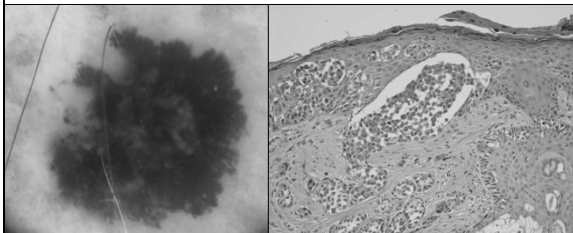
Speaker Disclosure

In the past 12 months, I have not had a significant financial interest or other relationship with the manufacturer(s) of the product(s) or provider(s) of the service(s) that will be discussed in my presentation.

Overview of Presentation

1. Cancer protocol template
2. Major histologic types of melanoma
3. Parameters that impact staging
 - a) Breslow thickness
 - b) Mitotic rate
 - c) Ulceration
4. Other histologic parameters
5. Lymph node status and satellitosis
6. Distant metastasis

Invasive Cutaneous Melanoma



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Pathology Report

- Improved scientific knowledge of the biology and pathogenesis tumors
- Pathology reports have become more comprehensive
 - Diagnosis
 - Prognostic factors
 - Mutation information
- Impact clinical decisions and treatment modalities
- CAP cancer protocol templates

Cancer Templates

- Required for accreditation:
 - College of American Pathologists
 - Laboratory
 - American College of Surgeons' Commission on Cancer
 - Cancer center
 - National Cancer Institute
 - Cancer center
- Reimbursement

Synoptic Reports

- To avoid omission of critical information
- Cancer protocol templates have commenced
- Attempt to better standardize pathology

Histopathologic Parameters of Melanoma

DIAGNOSIS

Five outside slides [redacted] right extensor forearm, skin punch:

MELANOMA, INVASIVE, UNCLASSIFIED TYPE
 CLARK LEVEL IV
 BRESLOW THICKNESS, 0.95 MM
 RADIAL (NON-TUMORIGENIC) GROWTH PHASE, NOT EVALUABLE
 VERTICAL (TUMORIGENIC) GROWTH PHASE, PRESENT
 MITOTIC FIGURES/MM², 3 (IN THE RECUIT SECTIONS EXAMINED)
 ULCERATION, NOT IDENTIFIED
 REGRESSION, NOT IDENTIFIED
 VASCULAR INVASION, NOT IDENTIFIED
 PERINEURAL INVASION, NOT IDENTIFIED
 MICROSCOPIC SATELLITOSIS, NOT IDENTIFIED
 TUMOR-INFILTRATING LYMPHOCYTES, NON-BRISK
 ASSOCIATED MELANOCYTTIC NEVUS, NOT IDENTIFIED
 PREDOMINANT CYTOLOGY, EPITHELIOID
 SURGICAL MARGINS: MELANOMA PRESENT AT PERIPHERAL TISSUE EDGES

Cancer Protocol Template

MD Anderson
 Cancer Center
 1515 HOLCOMB BOULEVARD
 HOUSTON, TX 77030-4009
 Tel: 713.745.3000 Fax: 713.745.4000

Department of Pathology, Box 95
 Tel: 713.745.3000 Fax: 713.745.4000

Collected: _____
 Received: _____

Surgical Pathology Report

CAP PROTOCOL ON PATHOLOGY MATERIAL REVIEWED IN THIS ACCESSION
 The CAP and PIM information provided in this report is a combination of both the current specimen and the prior HEDCC B.

Procedure, specimen identifier: Skin biopsy, lymphadenectomy, Right
 Tumor site: _____
 General description: n/a
 Microscopic specific identifier: Not identified
 Histologic type: Superficial spreading type
 Maximum tumor thickness (Breslow): 0.95 mm
 Anatomic level (Clark): IV
 Ulceration: Not identified
 Mitotic rate: n/a
 Mitotic rate (mm²): _____
 Microsatellite: Not identified
 Lymphovascular invasion: Not identified
 Margins: _____

Perineural invasion: Unidentified
 Tumor site: _____
 Radial growth phase: Present
 Vertical growth phase: Present
 Pagetoid: Not identified
 Growth: n/a
 Perineural invasion: Not identified
 Tumor site: n/a
 Tumor infiltrating lymphocytes, non-brisk: _____
 Associated nevus: Not identified
 Type of associated nevus: n/a
 Perineural lymphitis: Unidentified and focal nevus
 Lymph nodes: _____

Number of satellite nodules examined: 3
 Total number of nodules examined: _____
 Number of lymph nodes with metastases: 1
 Location of lymph node metastases: Subcapsular
 Largest tumor deposit: 2.5 x 0.5 mm
 Extracapsular extension: Not identified

Pathologic staging (pT): _____
 Regional lymph nodes (pN): _____
 Number of lymph nodes identified: 3
 Number of lymph nodes with metastases: 1
 Metastatic: Not identified
 Sentinel node: Not identified
 Distant metastases (pM): n/a
 Metastases to skin, subcutaneous or distant lymph nodes: Unknown
 Metastases to lung: Unknown
 Metastases to all other visceral sites or distant metastases by any site combined with an elevated serum LDH: Unknown

(A) RIGHT AXILLARY SENTINEL LYMPH NODE #1, HOT AND BLUE, EX VIVO IIL, LYMPHADENECTOMY
 MELANOMA, METASTATIC TO ONE OF ONE LYMPH NODES (1/1)
 Largest tumor deposit size: 2.3 x 0.5 mm (Five cells, measured on H&E0 scan)
 Location: Subcapsular
 Extracapsular extension: Not identified
 (See comment)

(B) RIGHT AXILLARY SENTINEL LYMPH NODE #1, HOT AND BLUE, EX VIVO ISE, LYMPHADENECTOMY
 One lymph node(s), negative for malignancy (0/1) (See comment)

(C) RIGHT AXILLARY SENTINEL LYMPH NODE #1, HOT AND BLUE, EX VIVO ISE, LYMPHADENECTOMY
 One lymph node(s), negative for malignancy (0/1) (See comment)

(D) RIGHT FOREARM SKIN BIOPSY
 SKIN AND SUBCUTIS WITH HEALING SURGICAL WOUND AND MELANOMA, INVASIVE
 SUPERFICIAL SPREADING TYPE
 CLARK LEVEL, EARLY IV
 BRESLOW THICKNESS, 0.95 MM
 RADIAL (NON-TUMORIGENIC) GROWTH PHASE, PRESENT
 PREDOMINANT CYTOLOGY (EPITHELIOID AND FOCAL NEVUS)
 SURGICAL MARGINS, FREE OF TUMOR

Histopathologic Parameters of Melanoma

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* CAP required elements

Histopathologic Parameters of Melanoma

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* CAP required elements
→ Elements for AJCC

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Histologic Types of Melanoma

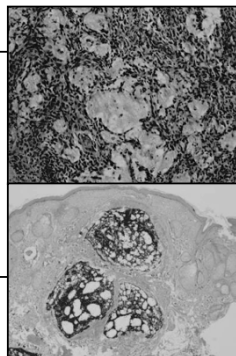
- 4 major histologic types
 - Superficial spreading melanoma
 - Lentigo maligna melanoma
 - Nodular melanoma
 - Acral lentiginous/mucosal melanoma
- Many morphologic variants

Melanoma Variants

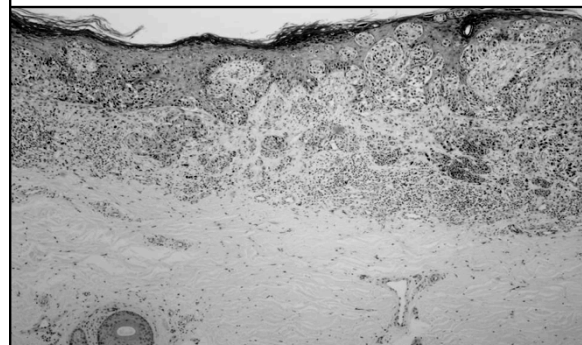
Table 32.5 Variants of malignant melanoma

Angiomatoid melanoma	Melanoma with rosettes
Angiolipid melanoma	Melanoma with sebocytes
Amelanotic melanoma (pigmented epithelioid melanocytoma)	Myxoid melanoma
Bullous melanoma	Neuroendocrine melanoma
Bullous melanoma	Nevoid melanoma
Chondroid melanoma	Osteogenic melanoma
Clear cell sarcoma (melanoma of soft parts)	Plasmacytoid melanoma
Cystic (retinoid cystic) melanoma	Psuedopigmented melanoma
Dermal melanoma	Pseudopigmented melanoma
Follicular melanoma	Rubroid melanoma
Gonadotropin-releasing hormone melanoma	Sarcomatoid melanoma
Lentiginous melanoma	Schwannian melanoma
Melanosarcoma	Signifying cell melanoma
Melanoma mimicking Merkel cell carcinoma	Small cell melanoma
Melanoma resembling Merkel	Small-diameter melanoma
Melanoma with moose-like cells	Spitzoid melanoma
Melanoma with psammoma bodies	Verru-like melanoma

Weedon

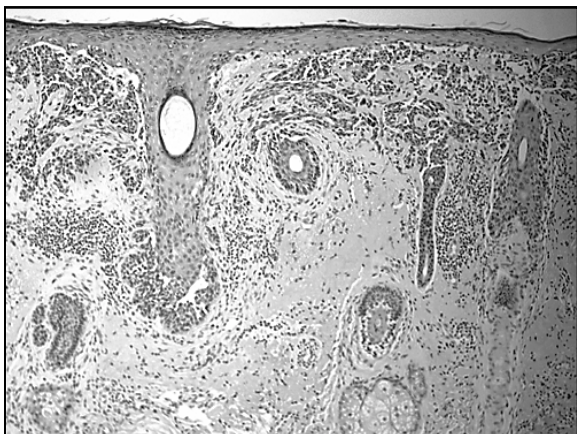
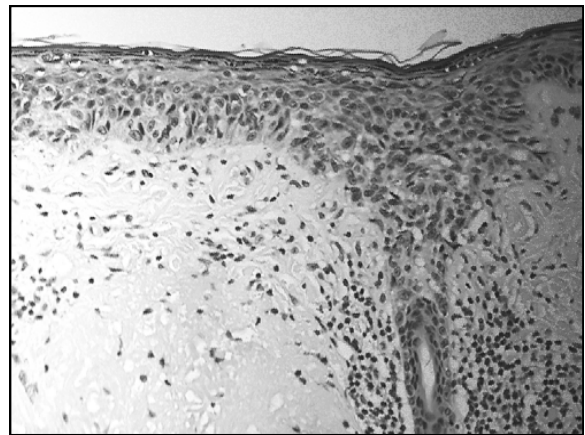
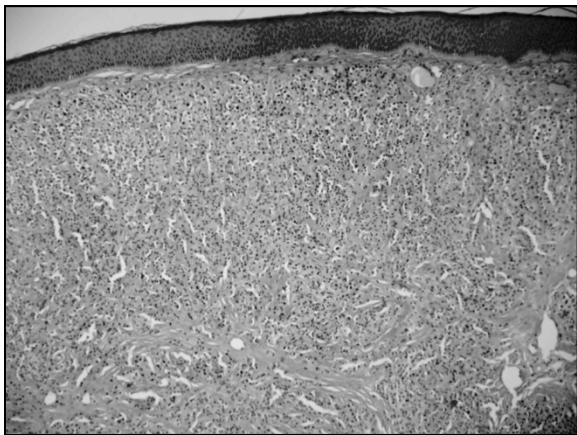
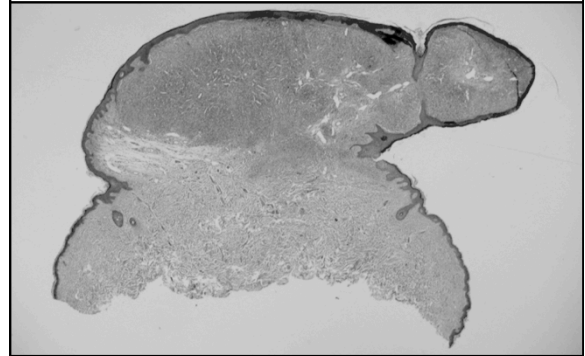


Superficial Spreading Type

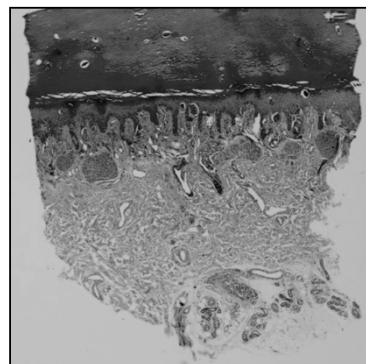


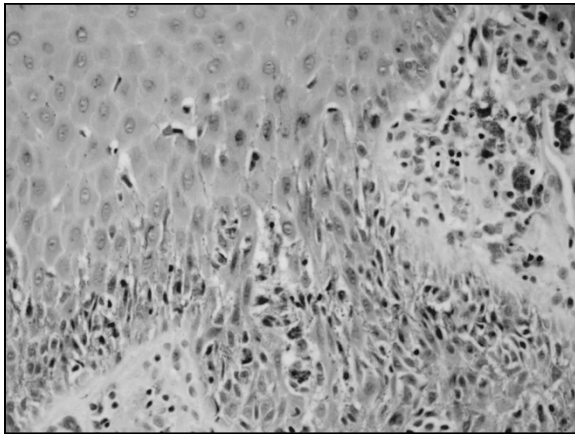


Nodular Type



Acral Lentiginous Melanoma





Desmoplastic Melanoma

- Morphologic feature-seen with any of the major histologic type of melanoma

Desmoplastic Melanoma

Not DMM-Cellular and spindle

DMM=Hypocellular

Pure Desmoplastic Melanoma

- Defined as >90 % of tumor with uniform desmoplastic stroma and hypocellular proliferation of spindle cells
- 1/46 (2.2%) pure DM with positive SLN
- 3/19 (15.8%) mixed DM with positive SLN
- 312/1785 (17.5%) patients with non-DM with positive SLN

SLN Status	Histologic subtype			P value ^a
	Non-DM	Mixed DM	Pure DM	
n =	1785	19	46	
Positive, %	17.5	15.8	2.2	< 0.01

^a P values refer to comparisons between pure DM melanoma versus other melanomas (i.e., non-DM and mixed DM).
SLN, sentinel lymph node; DM, desmoplastic melanoma.

Pawlik, Ross, Prieto, et al. Cancer, 2005

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- Other histologic parameters
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- Distant metastasis

Melanoma Staging and Classification

- American Joint Committee on Cancer (AJCC) and International Union Against Cancer (UICC)
- TNM staging system
 - T = Primary tumor (Stage I and II)
 - N = Regional metastasis (Stage III)
 - M = Distant metastasis (Stage IV)
- Determine prognosis, treatment, and enrollment in clinical trials

Final Version of 2009 AJCC Melanoma Staging and Classification

Charles M. Balch, Jeffrey E. Gershenwald, Seog-jaw Soong, John F. Thompson, Michael B. Atkins, David R. Byrd, Antonio C. Buzaid, Alistair J. Cochran, Daniel G. Covic, Shouhuan Ding, Alexander M. Eggermont, Keith T. Flaherty, Phyllis A. Gimotty, John M. Kirkwood, Kelly M. McMasters, Martin C. Milam Jr, Donald L. Morton, Merrick I. Ross, Arthur J. Sober, and Vernon K. Sondak

- Revision of the 2001 AJCC, 6th Edition
- Data through 2008
 - Increased sample size
 - ~ 31 K vs. ~ 18 K
 - ~ 8 K stage IV
- Addressed:
 - Significance of mitotic rate T1 lesions
 - Role of micrometastasis (specifically, isolated cells detected only by IHC)
 - Incorporation of serum LDH levels in defining stage IV disease

TNM

- **T = Primary tumor (Stage I and II)**
 - Breslow (Tumor) thickness
 - Mitotic rate
 - Ulceration
- **N = Regional metastasis (Stage III)**
 - Lymph node
 - Microscopic
 - Macroscopic
 - Skin/subcutaneous tissue (Intransit metastasis/satellites)
- **M = Distant metastasis (Stage IV)**
 - Lymph node
 - Skin/subcutaneous tissue
 - Visceral metastasis
 - Pulmonary
 - Non-pulmonary
 - Serum LDH

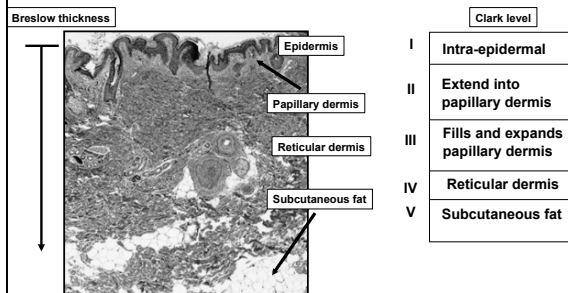
Impact T Stage

- T = Primary tumor (Stage I and II)
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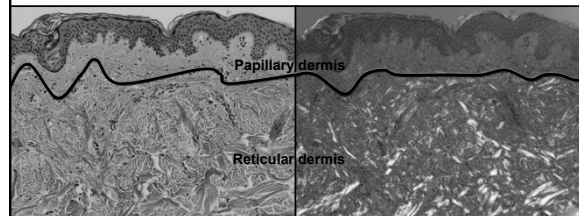
Breslow (Tumor) Thickness (T)

- Powerful predictor of survival
- T category for thickness
 - Defined in even integers: 1.0, 2.0, and 4.0 mm
- 10 year survival
 - T1: 92%
 - T2: 80%
 - T3: 63%
 - T4: 50%

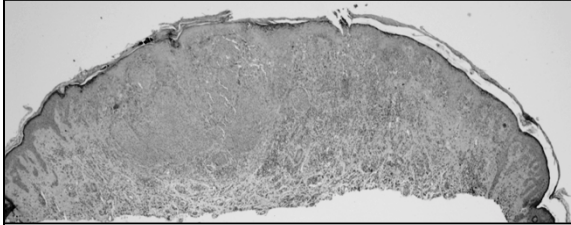
Breslow Thickness



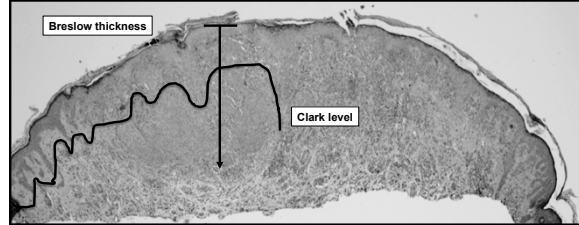
Microanatomic Compartment



Breslow Thickness and Clark level

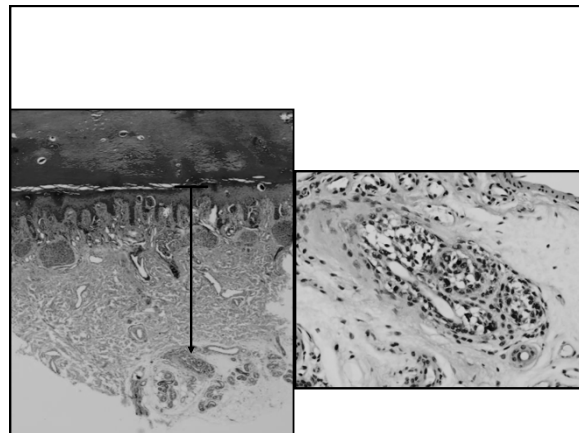


Breslow Thickness and Clark level

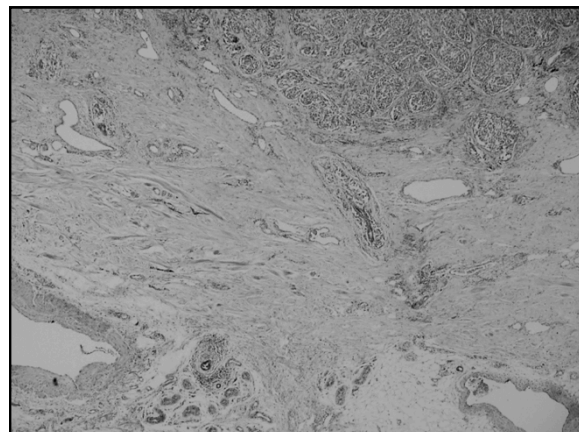
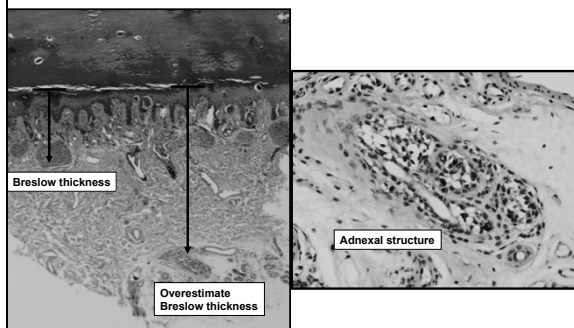


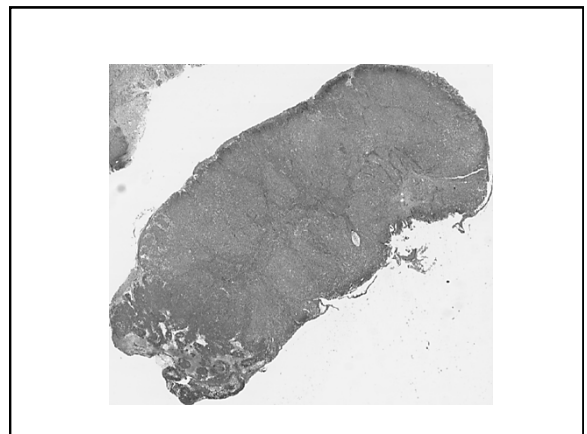
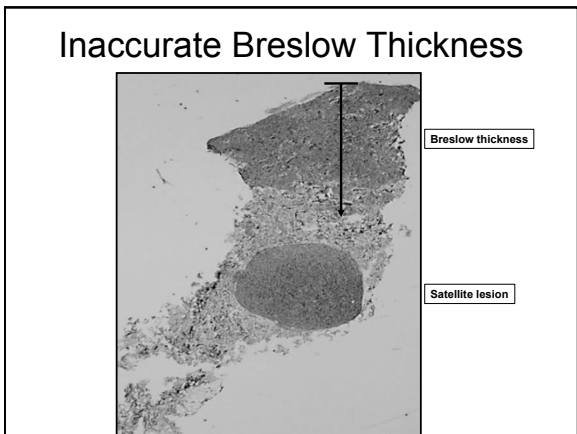
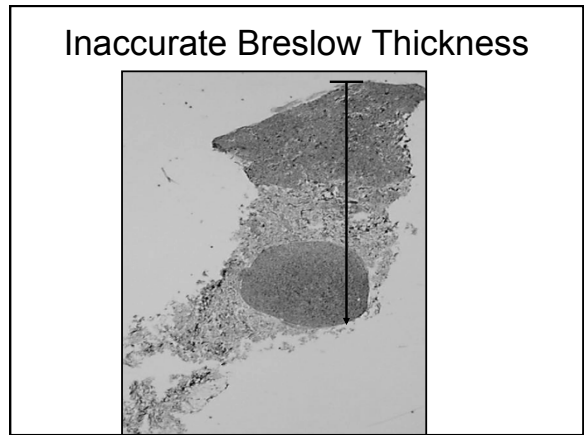
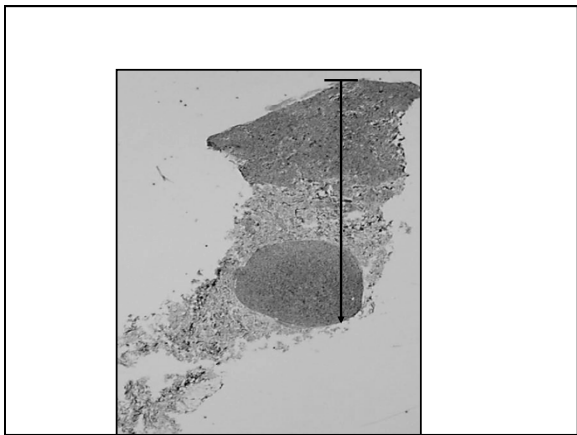
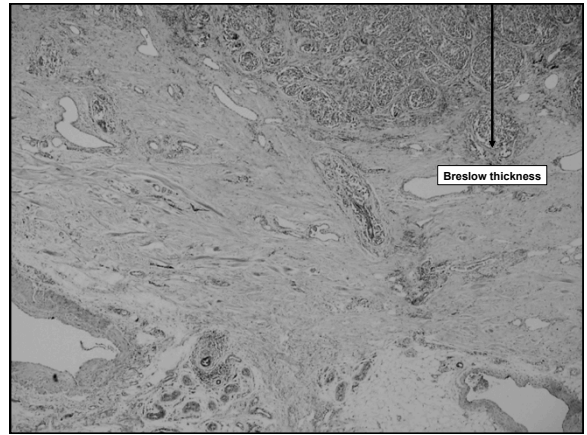
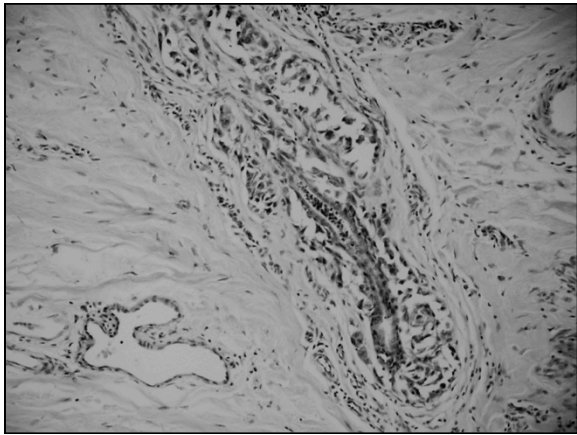
Inaccurate Measurement of Breslow Thickness

- Measure melanoma cells associated with follicle/adnexal structures
- Measurement that includes a satellite lesion
- Measure tangential sections
- Combine measurements from two separate biopsies
- Include nevus cells in measurement
- Measurement includes artifact spaces or tears in tissue
- We do include Breslow thickness measurement to area of perineural invasion

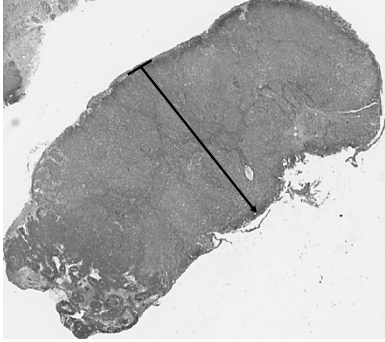


Inaccurate Breslow Thickness

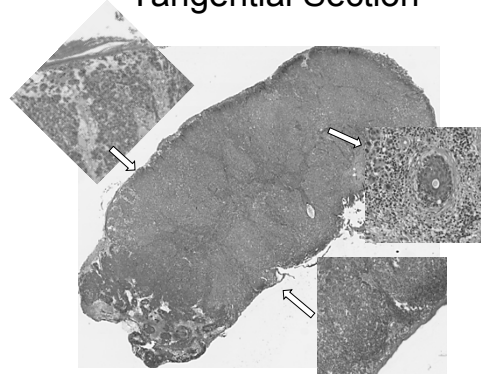




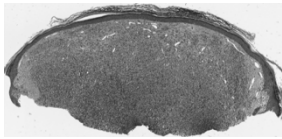
Inaccurate Breslow Thickness



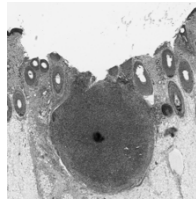
Tangential Section



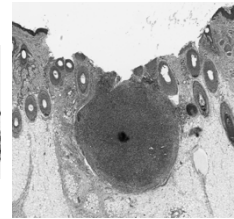
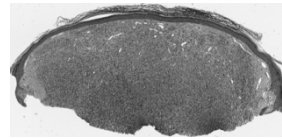
Specimen 1



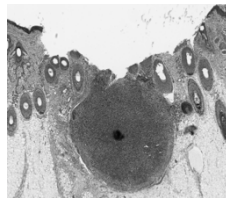
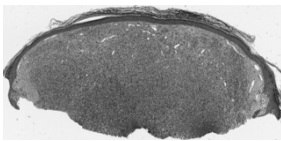
Specimen 2



Do Not Add Together Section

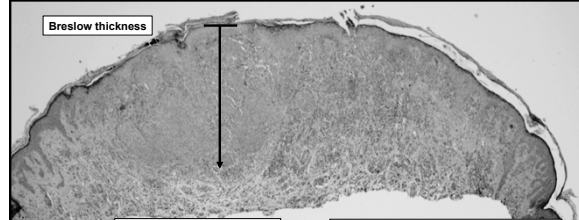


Breslow Thickness Are Not Additive



$$BT1 + BT2 \neq BT3$$

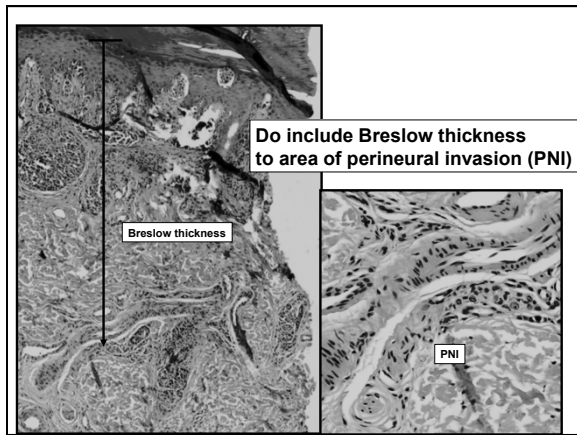
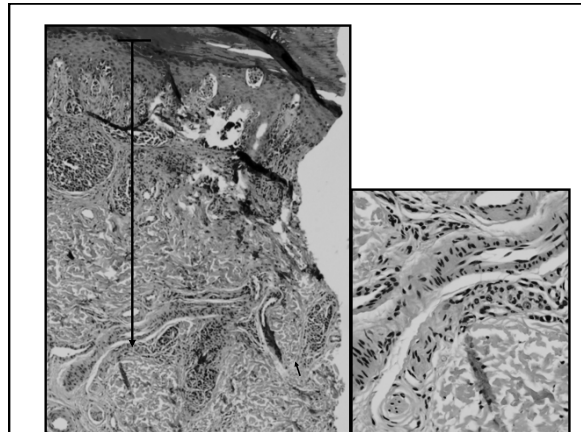
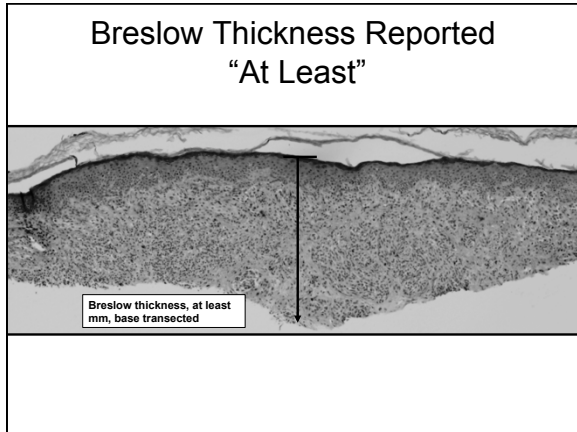
Breslow Thickness in Melanoma with Associated Nevus



Breslow thickness

Do not include nevus cells in Breslow thickness

Do not report Breslow thickness at least, since nevus cells at the base of shave



Perineural Invasion

- Seen more frequently in melanomas with desmoplastic features and acral lentiginous melanoma
- Presence of PNI may be indicator for further adjuvant therapy with XRT

Impact T Stage

- T = Primary tumor (Stage I and II)
- Breslow (Tumor) thickness
- Mitotic rate
- Ulceration

T= Primary Tumor

Mitotic rate (MR)

Table 1. Melanoma TNM Classification			Table 1. TNM Staging Categories for Cutaneous Melanoma		
T classification	Thickness	Ulceration Status	Classification	Thickness (mm)	Ulceration Status/Mitoses
T1	≤ 1.0 mm	a: without ulceration and level II/III b: with ulceration or level IV/V	Tis	NA	NA
T2	1.01-2.0 mm	a: without ulceration b: with ulceration	T1	≤ 1.00	a: Without ulceration and mitoses < 1/mm ² b: With ulceration or mitoses ≥ 1/mm ²
T3	2.01-4.0 mm	a: without ulceration b: with ulceration	T2	1.01-2.00	a: Without ulceration b: With ulceration
T4	> 4.0 mm	a: without ulceration b: with ulceration	T3	2.01-4.00	a: Without ulceration b: With ulceration
			T4	> 4.00	a: Without ulceration b: With ulceration

2001

2010

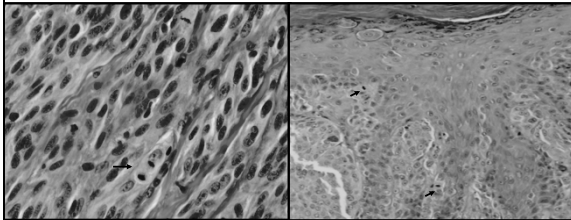
Mitotic Rate

- Second most powerful predictor of survival
- Determined by identifying mitotic active area or “hot spot”
- Extend mitotic count to adjacent fields until one mm² of tumor examined
 - 4.5 HPF = mm²
 - Report in whole numbers
 - Less than 1 (equivalent to zero)

Mitotic Rate

- 5 year survival rate non-ulcerated T1 melanoma
 - Mitosis: < 1=98%; 1-2=95%; 3-5=87%; 6-10=78%; 11-19 =70%; >20=59%
- T1 > 0.76 mm with at least 1 mitosis
 - 10% risk of occult metastasis
- 78% of ulcerated T1 melanomas associated with mitotic rate of at least 1/ mm²

Mitotic Rate



Dermal mitosis

Junctional mitosis

Mitotic Rate

- Do
 - Try to find highest mitosis per mm²
 - Examine all sections and levels for mitosis or “hot spot”
 - Search for mitosis in invasive melanoma
 - Look for mitosis by morphology
- Do not
 - Average mitotic count in more than one mm² area (1/2mm² = 0.5/mm²)
 - Cut additional sections only to evaluate for mitosis
 - Junctional mitosis
 - Report Ki-67 positive cells as mitotic rate

Inaccurate Identification of Mitotic Figure

- Report mitotic rate in inflammatory cell or endothelial cell as positive
- Resolve with IHC studies

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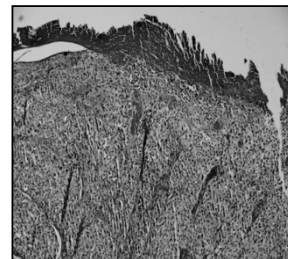
T= Primary Tumor

Ulceration

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T1	≤ 1.0 mm	a: without ulceration and level II/III b: with ulceration or level IV/V	Tis	NA	NA
T2	1.01-2.0 mm	a: without ulceration b: with ulceration	T1	≤ 1.00	a: Without ulceration and mitoses < 1/mm ² b: With ulceration or mitoses ≥ 1/mm ²
T3	2.01-4.0 mm	a: without ulceration b: with ulceration	T2	1.01-2.00	a: Without ulceration b: With ulceration
T4	> 4.0 mm	a: without ulceration b: with ulceration	T3	2.01-4.00	a: Without ulceration b: With ulceration
			T4	> 4.00	a: Without ulceration b: With ulceration
					2010

Ulceration

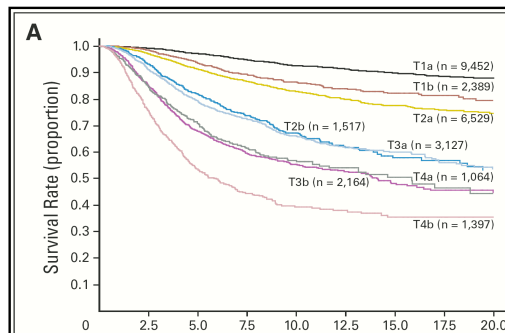
- Defined as absence of intact epidermis overlying primary invasive melanoma
- Based on microscopic examination
- Distinguish from artifactual or traumatic disruption of epidermis



Ulceration

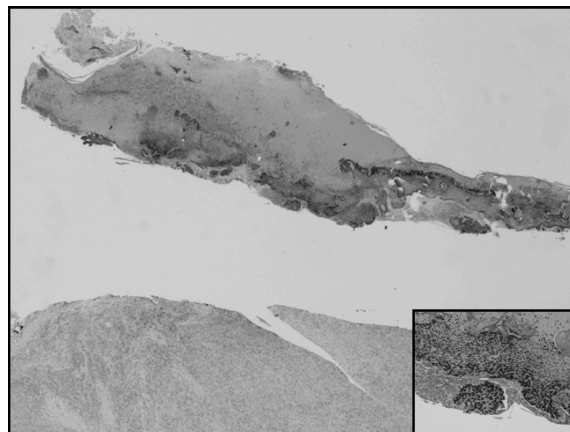
- Staging category for ulceration unchanged from 2001
- Survival rates are lower than non-ulcerated melanoma with equivalent thickness
 - a) non-ulcerated
 - b) ulcerated
- Tumor with ulceration similar survival rates as next T category with no ulcer

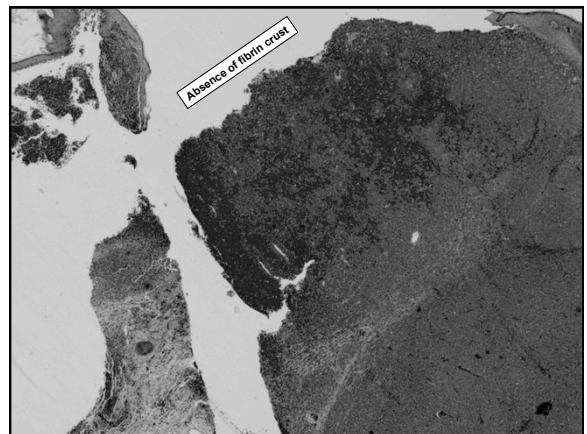
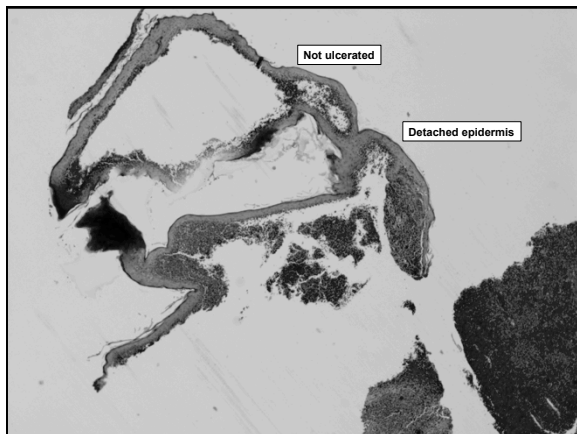
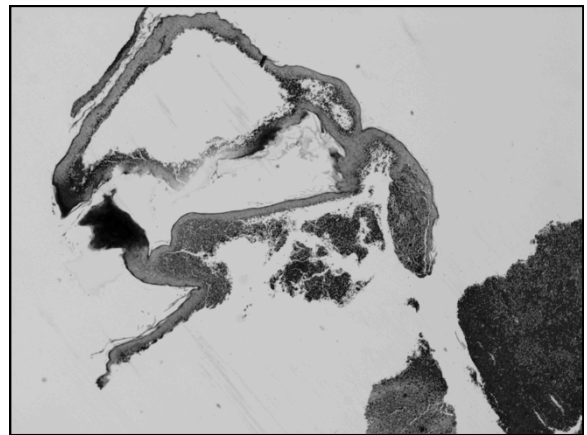
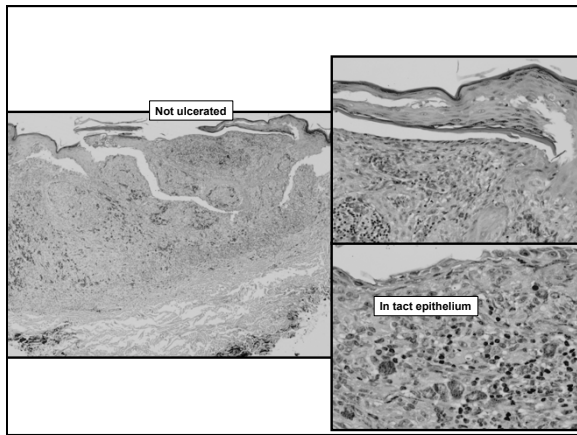
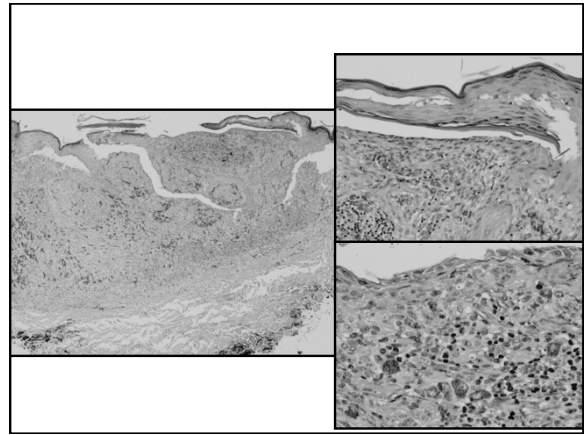
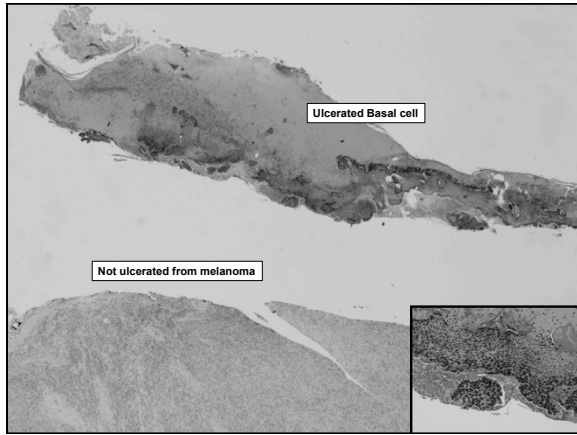
Ulceration

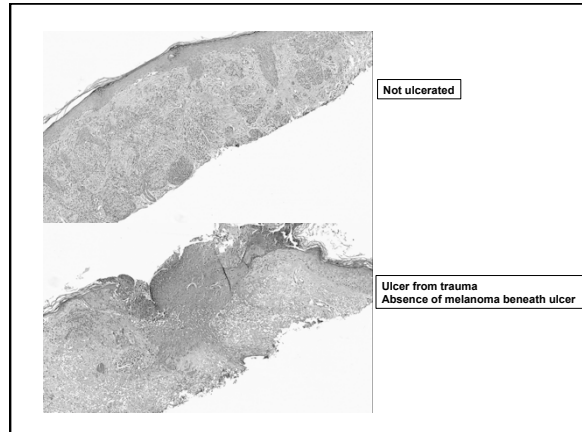
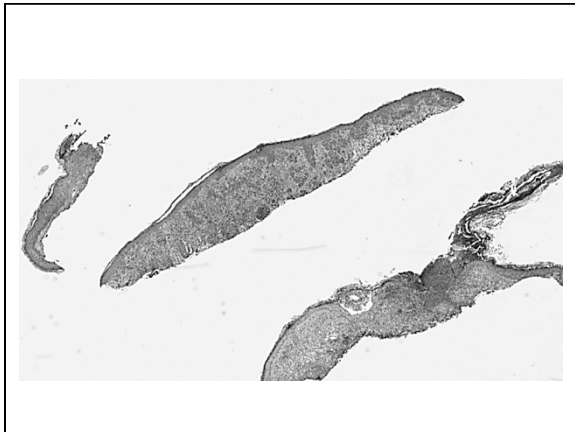


Inaccurate Assessment of Ulceration

- Transepidermal elimination of tumor
- Incomplete sections
- Prior trauma or biopsy site
- Detached epidermis







Mimics of Ulceration

Histologic Mimics of Ulceration in Melanoma		
Consumption of the epidermis		
Scale crust over intact epidermis		
Incomplete sections		
Detached epidermis		
Iatrogenic		
External trauma		

AJCC Recommendation for T Classification

- Mitotic rate replace Clark level of invasion in T1 lesions
- Include Clark level of invasion when mitotic rate can not be accurately determined
- Ulceration for T categories remain unchanged

Overview of Presentation

1. Cancer protocol template
2. Major histologic types of melanoma
3. Parameters that impact staging
 - a) Breslow thickness
 - b) Mitotic rate
 - c) Ulceration
4. Other histologic parameters
5. Lymph node status and satellitosis
6. Distant metastasis

Histopathologic Parameters of Melanoma

MD Anderson Cancer Center
1515 HOLCOMBE BOULEVARD
HOUSTON, TX 77030-6056

Department of Pathology, Box 05
Tel: 713-792-3200 Fax: 713-794-4650

Re: 12-29
cc: Merrick, Ross, MD

Mail to: St Joseph Dermopath
8909 Greenbrier St
Houston TX 77030

MATERIALS RECEIVED

Collected	Received	Slides	Blocks	Unst	Slides
06/29/2010	07/14/2010	1	0	0	0

DIAGNOSIS
One section slide * right mid chest, skin shave:

- * MELANOMA, INVASIVE, SUPERFICIAL-SPREADING TYPE
- CLARK LEVEL, II
- BRESLOW THICKNESS, 0.97 MM
- RADIAL (NON-TUMORIGENIC) GROWTH PHASE, PRESENT
- VERTICAL (TUMORIGENIC) GROWTH PHASE, NOT IDENTIFIED
- * MITOTIC FIGURES/MM², <1
- ULCERATION, NOT IDENTIFIED
- REGRESSION, NOT IDENTIFIED
- * VASCULAR INVASION, NOT IDENTIFIED
- PERINEURAL INVASION, NOT IDENTIFIED
- * MICROSCOPIC SATELLITISIS, NOT IDENTIFIED
- TUMOR-INFLTRATING LYMPHOCYTES, NON-BRISK ASSOCIATED MELANOCYTIC NEVUS, NOT RULED OUT
- PREDOMINANT CYTOLOGY, EPITHELIOID AND NEVOID
- * SURGICAL MARGINS: TUMOR PRESENT AT PERIPHERAL TISSUE EDGE

* CAP required elements

Detection of Vascular Invasion in Melanoma with D2-40

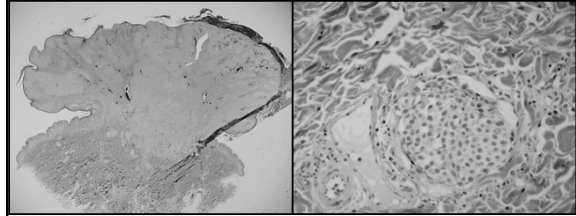
- LVI with D2-40 in primary melanoma
 - 67% cases with positive SLN
- Absence of LVI with D2-40 in primary melanoma
 - 19% cases with positive SLN
- Patients with LVI
 - Decreased disease specific survival

Journal of Cutaneous Pathology

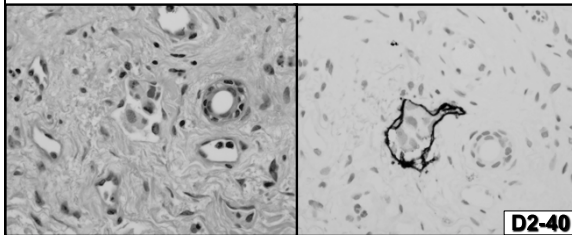
Immunohistochemical detection of lymphovascular invasion with D2-40 in melanoma correlates with sentinel lymph node status, metastasis and survival

Petersson et. al. J Cutan Pathol. 2009

Vascular Invasion



Detection of Vascular Invasion



Histopathologic Parameters of Melanoma

DIAGNOSIS

Five outside slides [redacted] right extensor forearm, skin punch;

- * MELANOMA, INVASIVE, UNCLASSIFIED TYPE
 - [CLAR LEVEL, IV]
- * Breslow thickness: 0.66 mm
- [RADIAL (NON-TUMORIGENIC) GROWTH PHASE, PRESENT]
- [VERTICAL (TUMORIGENIC) GROWTH PHASE, PRESENT]
- * MITOTIC FIGURES/MM²: 3 (IN THE RECURT SECTIONS EXAMINED)
- * ULCERATION, NOT IDENTIFIED
- [REGRESSION, NOT IDENTIFIED]
- * VASCULAR INVASION, NOT IDENTIFIED
- [PERINEURAL INVASION, NOT IDENTIFIED]
- * MICROSCOPIC SATELLITOSIS, NOT IDENTIFIED
- [TUMOR-INFILTRATING LYMPHOCYTES, NON-BRISK]
- [ASSOCIATED MELANOCYTIC NEVUS, NOT IDENTIFIED]
- [PREDOMINANT CYTOLOGY, EPITHELIOD]
- * SURGICAL MARGINS: MELANOMA PRESENT AT PERIPHERAL TISSUE EDGES

* CAP required elements

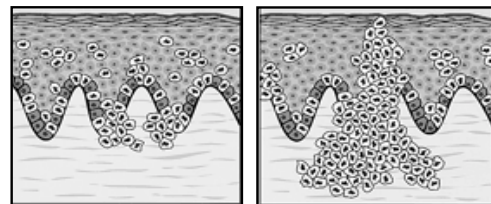
→ Elements for AJCC

not required elements in cancer checklist

Radial and Vertical Growth Phase

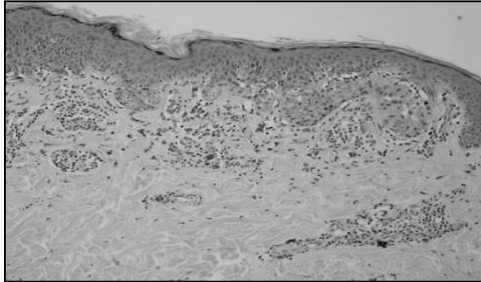
- Radial growth phase (RGP)
 - Expansion of tumor parallel to the epidermis
 - invasive tumor cells are not proliferative
 - in situ and/or invasive components
- Vertical growth phase (VGP)
 - Expansion of tumor perpendicular to the epidermis
 - invasive tumor cells are proliferative
 - mitogenic-presence of dermal mitosis
 - tumorigenic-dermal nest larger than junctional nests

Radial and Vertical Growth Phase

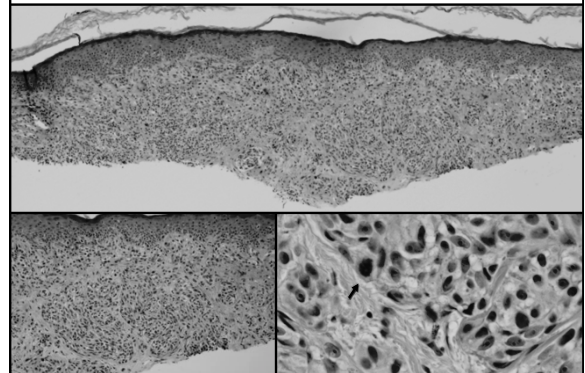


Chin et. al

Radial Growth Phase (RGP)



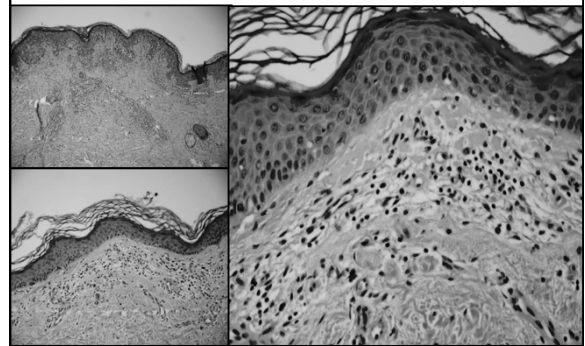
Vertical Growth Phase (VGP)



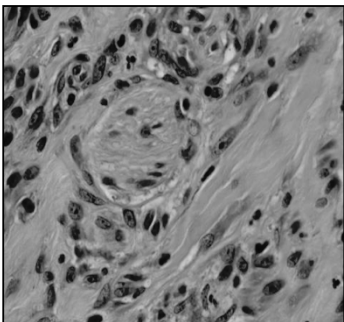
Regression

- Defined as replacement of melanoma cells in the dermis with fibrosis, vascular proliferation, lymphocytic infiltrate, and melanophages
- Changes of epidermis with loss of rete ridges
- Regression reported as focal or extensive (>50% or >75% as stated in CAP guidelines)

Regression

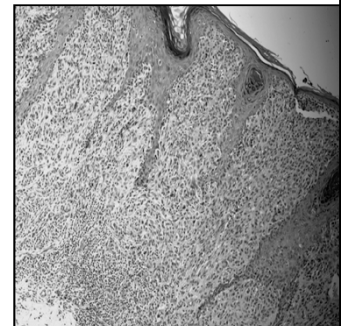


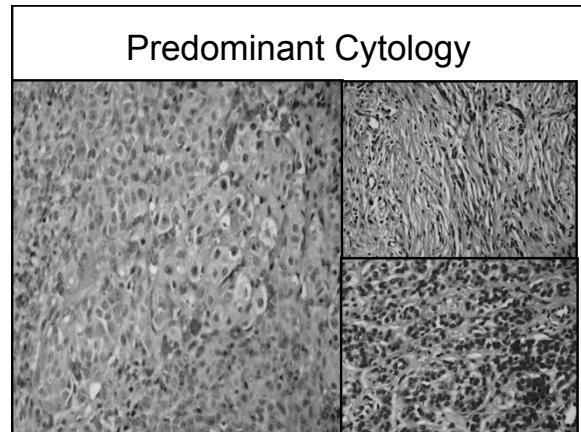
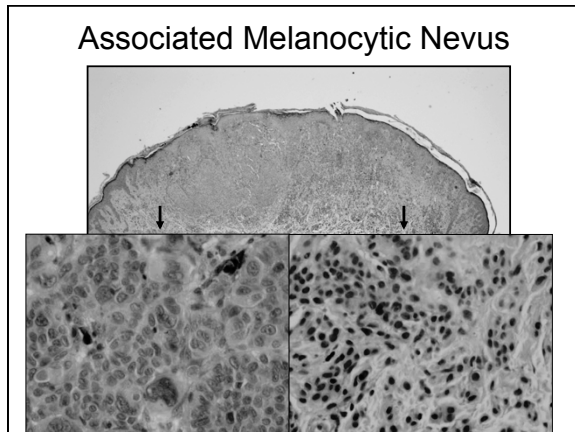
Perineural Invasion



Tumor-infiltrating Lymphocytes (TIL)

- Brisk: lymphocytes infiltrate entire base of invasive melanoma
- Non-brisk: lymphocytes infiltrate focally
- Absent: lymphocytes not associated with tumor





- ### Primary Tumor Parameters
- Initial histologic evaluation is critical in diagnosis and staging
 - Breslow thickness
 - Mitotic rate
 - Ulceration
 - Clinically suspected melanoma
 - Excise entire lesion with 1 or 2 mm margins
 - Deep saucerization or punch biopsy of large lesions are acceptable
 - Superficial shave biopsy should be avoided

- ### Overview of Presentation
1. Cancer protocol template
 2. Major histologic types of melanoma
 3. Parameters that impact staging
 - a) Breslow thickness
 - b) Mitotic rate
 - c) Ulceration
 4. Other histologic parameters
 5. Lymph node status and satellitosis
 6. Distant metastasis

- ### TNM
- T = Primary tumor (Stage I and II)
 - Breslow (Tumor) thickness
 - Mitotic rate
 - Ulceration
 - N = Regional metastasis (Stage III)
 - Lymph node
 - Microscopic
 - Macroscopic
 - Skin/subcutaneous tissue (Intransit metastasis/satellites)
 - M = Distant metastasis (Stage IV)
 - Lymph node
 - Skin/subcutaneous tissue
 - Visceral metastasis
 - Pulmonary
 - Non-pulmonary
 - Serum LDH

- ### Regional Metastatic Melanoma
- Stage III
 - Number of positive nodes
 - any size, including isolated tumor cells detected by IHC
 - Category: N0=0; N1=1; N2=2-3; N3=>4
 - Tumor burden
 - (a) microscopic diagnosed at SLN
 - (b) macroscopic clinically/radiographically detectable metastasis confirmed by pathology
 - (c) Intransit metastasis/satellite

Sentinel Lymph Node

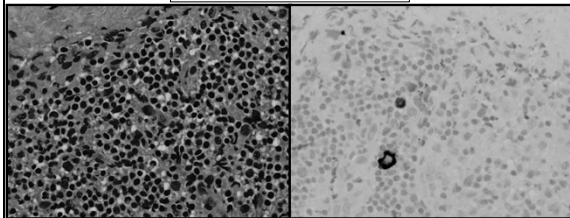
- Sentinel lymph nodes in melanoma
 - Positive in ~20% of patients
 - 15% > 1.0 mm
 - 5% < 1.0 mm
 - 16% detected on initial H&E
 - 4% detected with additional sections/ IHC
 - <5% with extracapsular extension

SLN Isolated Melanoma Cell

- Acceptable to classify nodal metastasis on IHC alone
 - H&E confirmation no longer required
 - Tumor size limit
- Positive for one melanocytic marker (HMB45, Melan-A/Mart-1)
- Cells have malignant morphology

Detection of Micrometastasis

Metastatic melanoma

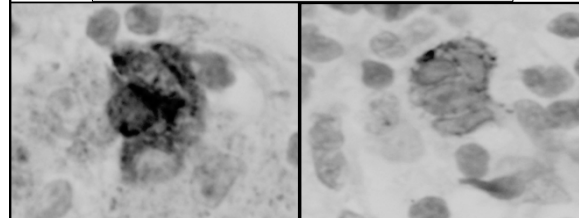


H&E

Panmelanocytic cocktail
(HMB-45, tyrosinase, Mart-1)

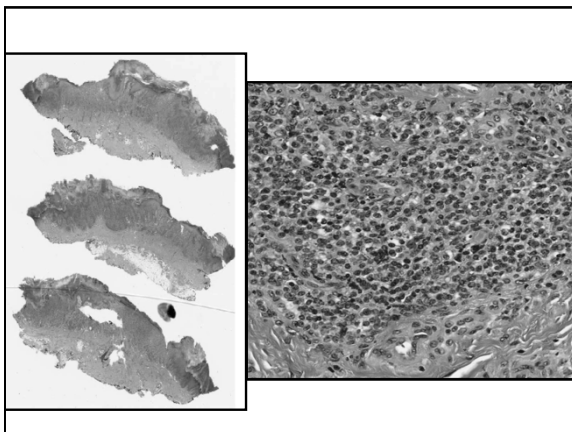
SLN with Micrometastasis (Na)

Metastatic melanoma (micrometastasis)



Panmelanocytic cocktail

HMB-45

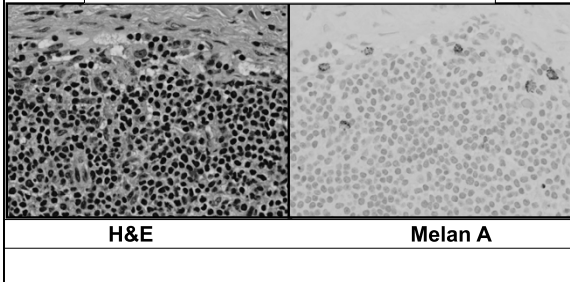


SLN with Micrometastasis

- Overall 5 year survival
 - 67% micrometastasis (vs. 43% macrometastasis)
 - Heterogeneity of survival in micrometastasis group
 - 23% (high risk group) to 87% (low risk group)
- Parameters of primary melanoma correlated with survival in micrometastasis and not with macrometastasis

Potential Pitfall in Interpretation

Melan-A positive macrophages in SLN

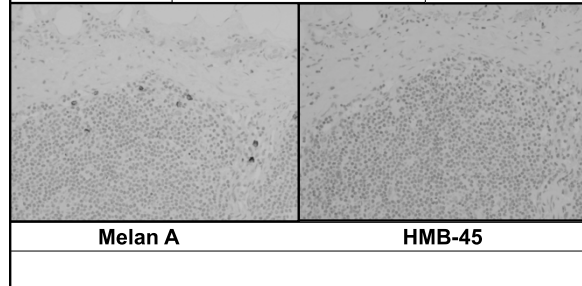


H&E

Melan A

Potential Pitfall in Interpretation

Sentinel lymph node

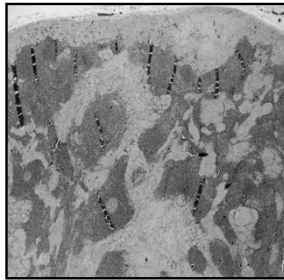


Melan A

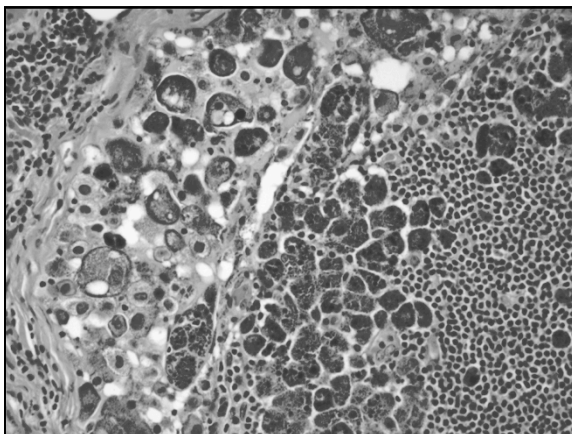
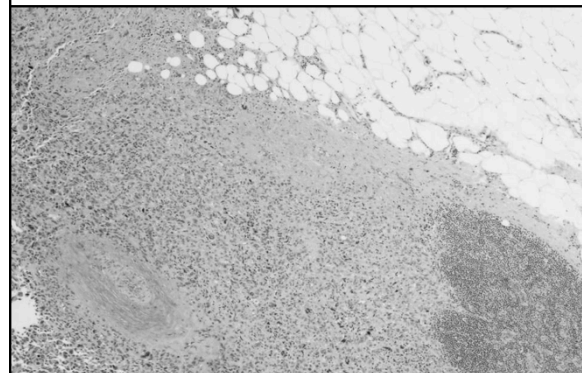
HMB-45

CAP Protocol Template for Lymph Nodes

- Number of lymph nodes (SLN and non-SLN)
- Number containing metastasis
- Tumor location
 - Subcapsular
 - Intraparenchymal
- Tumor size
 - Reported in mm
 - Measured gross exam or slide
- Extracapsular extension
- Matted lymph node



Extracapsular Extension

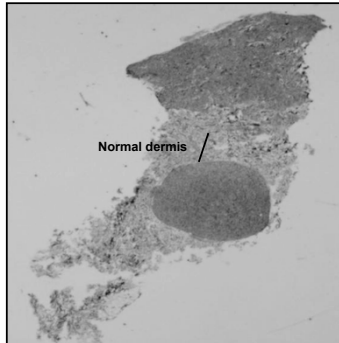


In-transit metastasis/satellites (Nc)

- 2.0 cm distance
- Metastatic cells >0.05 mm
- At least 0.3 mm from primary component
- Separated by normal tissue
- N2c regardless of number of in transit metastasis/satellites

N	No. of Metastatic Nodes	Nodal Metastatic Burden
N0	0	NA
N1	1	a: Micrometastasis*
		b: Macrometastasis†
N2	2-3	a: Micrometastasis*
		b: Macrometastasis†
N3	4+ metastatic nodes, or matted nodes, or in transit metastases/satellites with metastatic nodes	c: In transit metastases/satellites without metastatic nodes

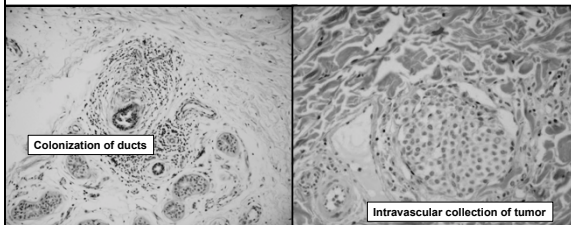
Microscopic Satellitosis



Inaccurate Assessment of Microscopic Satellitosis

- Colonization of adnexal structures
- Intravascular deposit
- Lesion contiguous on deeper sections
- Incidental nevus

Mimics of Satellitosis



Melanoma: AJCC-N Stage

Regional Lymph Nodes (N)		
NX	Patients in whom the regional nodes cannot be assessed (e.g., previously removed for another reason)	
N0	No regional metastases detected	
N1-3	Regional metastases based upon the number of metastatic nodes and presence or absence of intralymphatic metastases (in transit or satellite metastases)	
Note: N1-3 and a-c subcategories assigned as shown below.		
N Classification	No. of Metastatic Nodes	Node Metastatic Mode
N1	1 node	a: micrometastasis* (Figure 31.15) b: macrometastasis** (Figure 31.16)
N2	2-3 nodes	a: micrometastasis* (Figure 31.17) b: macrometastasis** (Figure 31.18) c: in transit met(s)/satellite(s) without metastatic nodes (Figure 31.19)
N3	4 or more metastatic nodes, or matted nodes, or in transit met(s)/satellite(s) with metastatic node(s) (Figure 31.20)	

*Micrometastases are diagnosed after sentinel lymph node biopsy and completion lymphadenectomy (if performed).
**Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension.

AJCC Recommendation for N Classification

- Isolated cells on IHC accepted
 - Positive for melanocytic marker (HMB45, Melan-A/Mart-) and not S100
 - H&E confirmation no longer required
 - Cells have malignant morphology
- Stage III
 - No known primary with localized skin or lymph node metastasis

Overview of Presentation

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2. Major histologic types of melanoma
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 - a) Breslow thickness
 - b) Mitotic rate
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5. Lymph node status and satellitosis
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TNM

- **T = Primary tumor (Stage I and II)**
 - Breslow (Tumor) thickness
 - Mitotic rate
 - Ulceration
- **N = Regional metastasis (Stage III)**
 - Lymph node
 - Microscopic
 - Macroscopic
 - Skin/subcutaneous tissue (Intransit metastasis/satellites)
- **M = Distant metastasis (Stage IV)**
 - Lymph node
 - Skin/subcutaneous tissue
 - Visceral metastasis
 - Pulmonary
 - Non-pulmonary
 - Serum LDH

Distant Melanoma Metastasis (M)

- Stage IV
- Site of visceral metastasis and normal LDH levels
 - pulmonary
 - non pulmonary
- LDH levels
 - Elevated LDH independent predictor of survival

Distant Melanoma Metastasis (M)

M	Site	Serum LDH
M0	No distant metastases	NA
M1a	Distant skin, subcutaneous, or nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

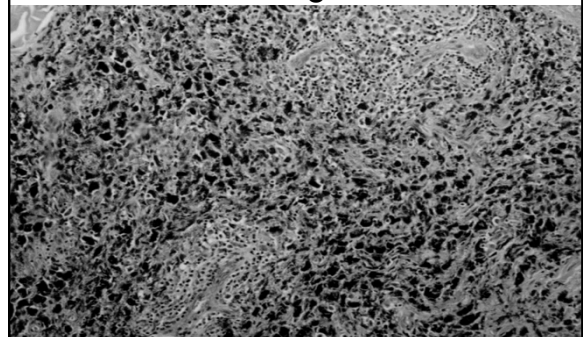
Protocol Template for Distant Metastasis

- pMX-removed from AJCC-TNM system
- pM0 stage defined clinically
- Pathologists should not report pMx or pM0
- pM1 reported only when metastases documented by pathology examine



Provided by Dr. Kim

Targeted Therapy Related Tumor Regression



TNM Descriptors

- Post-therapy state (y or c) pTNM
- Retreatment classification (r) pTNM
 - Recurrent tumor
 - Not change original stage
- Autopsy classification (a) pTNM
 - Disease only recognized post mortem
- R classification (residual tumor)
 - RX, R0, R1, R2

Summary of Melanoma Parameters

- Elements for CAP cancer protocol template
- AJCC-TNM staging system
- Inaccurate measurement of Breslow thickness
- Include PNI in Breslow thickness
- Mimics of ulceration and satellitosis
- Recommend to report other histologic parameters
- May be used for further clinical management decisions and evaluation of SLN

Thank you