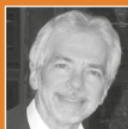


APRIL 11 & 12, 2024 - INSTITUT CURIE  
AMPHITHEATER CONSTANT BURG, FRANCE



## THE PATHOLOGY OF MELANOMA: AN INTERNATIONAL COURSE

### DIRECTED BY:



**Director of Course**  
**Pr Raymond Barnhill**,  
Paris, France



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San Francisco, USA



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New York, USA



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Sydney, Australia

### OBJECTIVE

Following the success of our Courses in 2017, 2018, 2020, and 2022 the objective of the Fifth International Melanoma Course in 2024 will continue to stress due diligence and practical diagnosis of melanocytic lesions. We will emphasize the theme of "Acknowledging uncertainty and avoiding over diagnosis of melanoma", as well as updates of all cutting-edge knowledge on difficult melanocytes lesions relevant to practicing pathologists and clinicians.

This 2024 venue will again include expertise from the SIRIC (Integrated Cancer Research Site at Institut Curie), the WHO 5th Edition Classification of Melanocytic Tumours, the revised MPATH-Dx Classification schema (2023), the MPATH Group, and the International Melanoma Pathology Study Group.

### THE REVISED MPATH-DX CLASSIFICATION

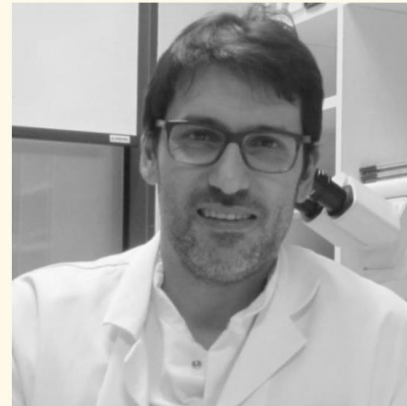
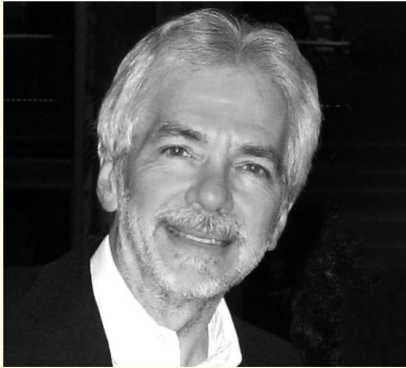
- Online access in advance and review of digitized images from extensively-characterized cases constituting the MPath study set. This unique study set has been reviewed by the MPath Pathology Panel (Prs. Barnhill, Elder, and Piepkorn), and a large diverse group of pathologists.
- The Course will be practical and based on the extensive experience of the international faculty participating in the Course. The Course will consist of didactic lectures and interactive sessions during the two-day program.

### THE COURSE PROGRAMME AND CONTENT

- The Course will consist of didactic lectures and interactive sessions during the two-day program.
- An approach of practical diagnosis is based on the extensive experience of the international faculty in the Course.
- The latest advances in ancillary diagnostic techniques including immunohistochemistry and molecular genetics will be emphasized.
- Particular attention will be given to predictive biomarkers for targeted, immune and checkpoint inhibitors therapies.



LANGUAGE  
CONGRESS:  
ENGLISH





**AUSTRALIAN** STORY

# 'PATIENT ZERO'

**NEWS**



# Criteria for Melanocytic Lesions: An Introduction

Raymond Barnhill

Institut Curie

Paris, France



PARIS 2024



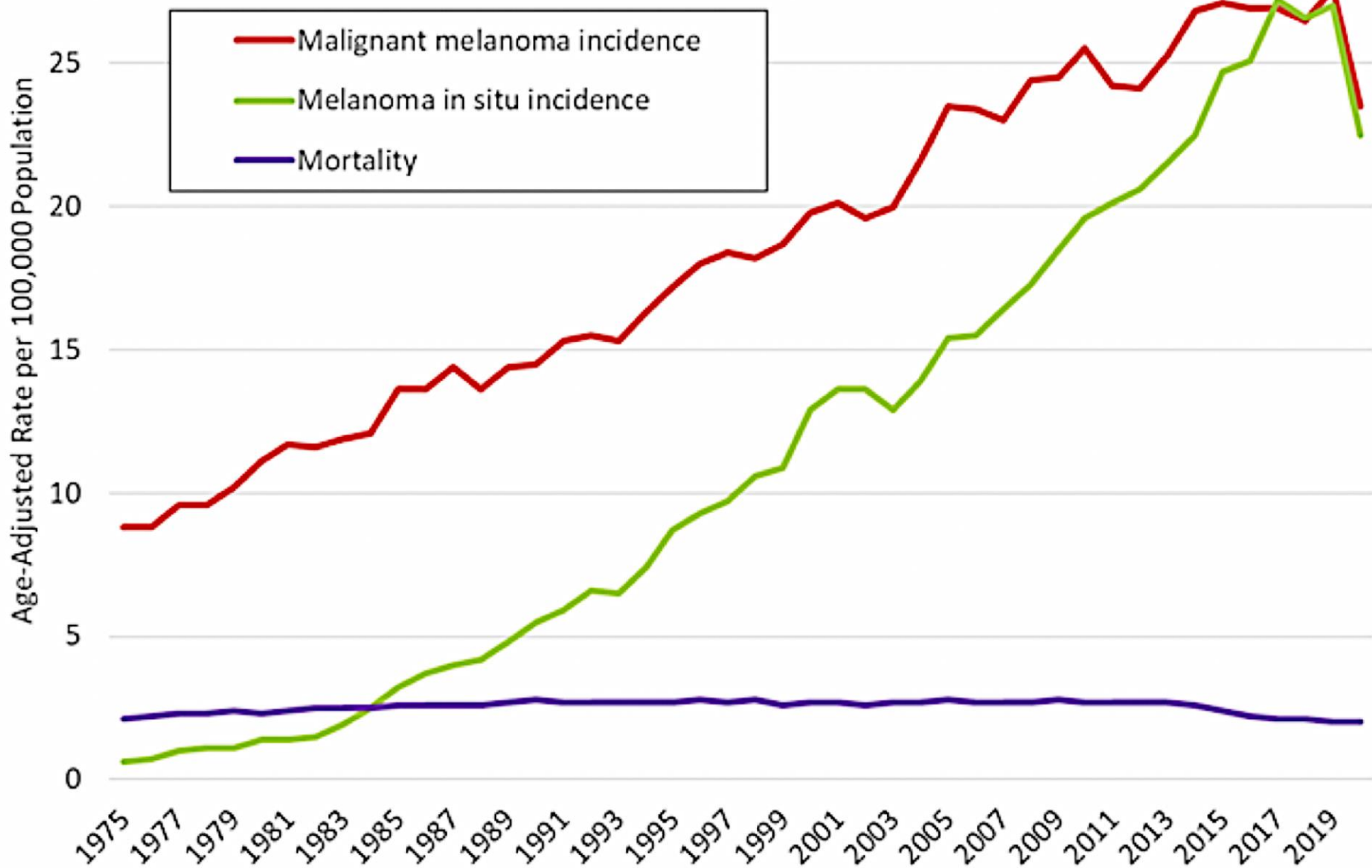
# Themes of the Course:

## Balancing Diagnosis for Optimal Patient Care

- Avoid overdiagnosis and underdiagnosis of melanoma
- Communicate uncertainty!
- All diagnostic techniques have limitations
- The gold standard is biological outcome
- Due diligence



# Overdiagnosis of Melanoma?



# Due Diligence

Standardized, Methodical, and  
Comprehensive Approach to  
Difficult Melanocytic Lesions

**Clinical Criteria\***

**Dermoscopy**

**Histopathological  
Criteria\***

**Ancillary Techniques**

**Artificial Intelligence**

# Guidelines for Criteria

- Obtain as much information as possible
- Always use several/multiple criteria
- No single criterion is diagnostic
- There are exceptions to every criterion... often leading to uncertainty!

# I. Clinical Criteria

Obtain as much information as possible, especially complete clinical information before finalizing a diagnosis

- ✓ Age
- ✓ Gender (sex)
- ✓ Anatomic site
- ✓ Diameter
- ✓ Clinical features of the lesion
- ✓ Clinical history

# Clinical Criteria

| Criterion                                     | Benign   | Melanoma  |
|---|--|---|
| Age   | Young age, especially<br>< 10-12 years   | Increasing age<br>Increasing prevalence   |
| Gender  | Hormonal effects in<br>women   | Older men - increased<br>risk   |
| Anatomic site                                 | Extremities favor Spitz,<br>special sites: acral, vulvar                         | Scalp, neck, back, trunk,<br>lower legs women   |
| Gross morphological<br>features<br>Dermoscopy | < 5 mm, well<br>circumscribed,<br>symmetrical, regular<br>borders, uniform color | > 6 mm >10mm, poorly<br>circumscribed<br>asymmetrical, irregular<br>color, black, ulceration,<br>amelanotic |
| Clinical history                              | Stable, long-standing<br>lesion, history of trauma                               | Changing lesion, new<br>lesion, itching, pain,<br>bleeding  |

# Clinical Criteria

## Age Matters!

| Criterion  | Benign                  | Melanoma                                      |
|------------|-------------------------|---|
| <b>Age</b> | Young age<br>< 10 years | Increasing<br>age<br>Increasing<br>prevalence |

# Clinical Criteria

| Criterion            | Benign   | Melanoma   |
|----------------------|--|--|
| <b>Anatomic site</b> | Extremities<br>favor Spitz<br><br>Special sites:<br>acral, vulvar<br><br><i>Can mimic melanoma</i> | Scalp, neck,<br>back, trunk,<br>lower legs in<br>women |

# Anatomic Site - Scalp

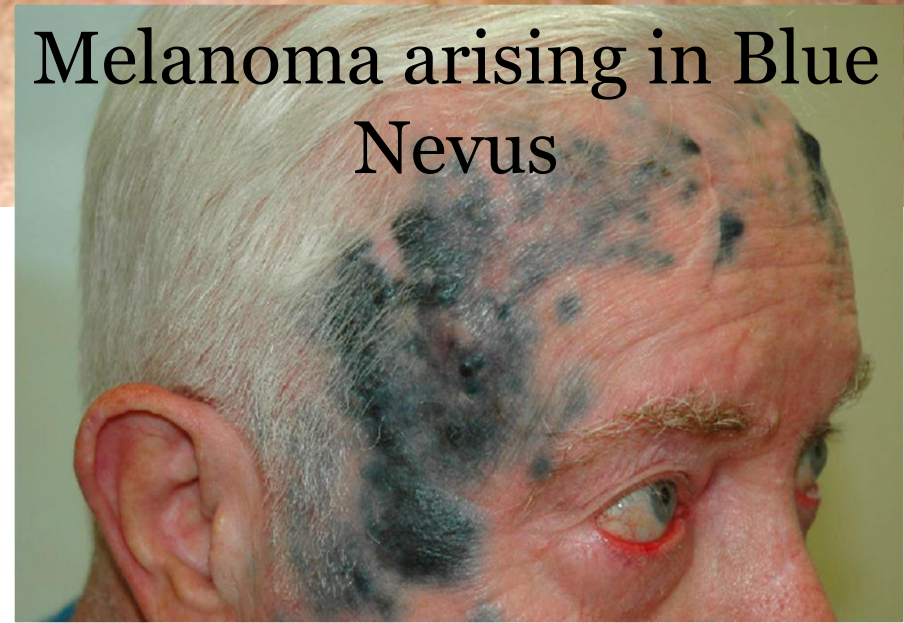
Desmoplastic Melanoma



Congenital/Pediatric  
Melanoma

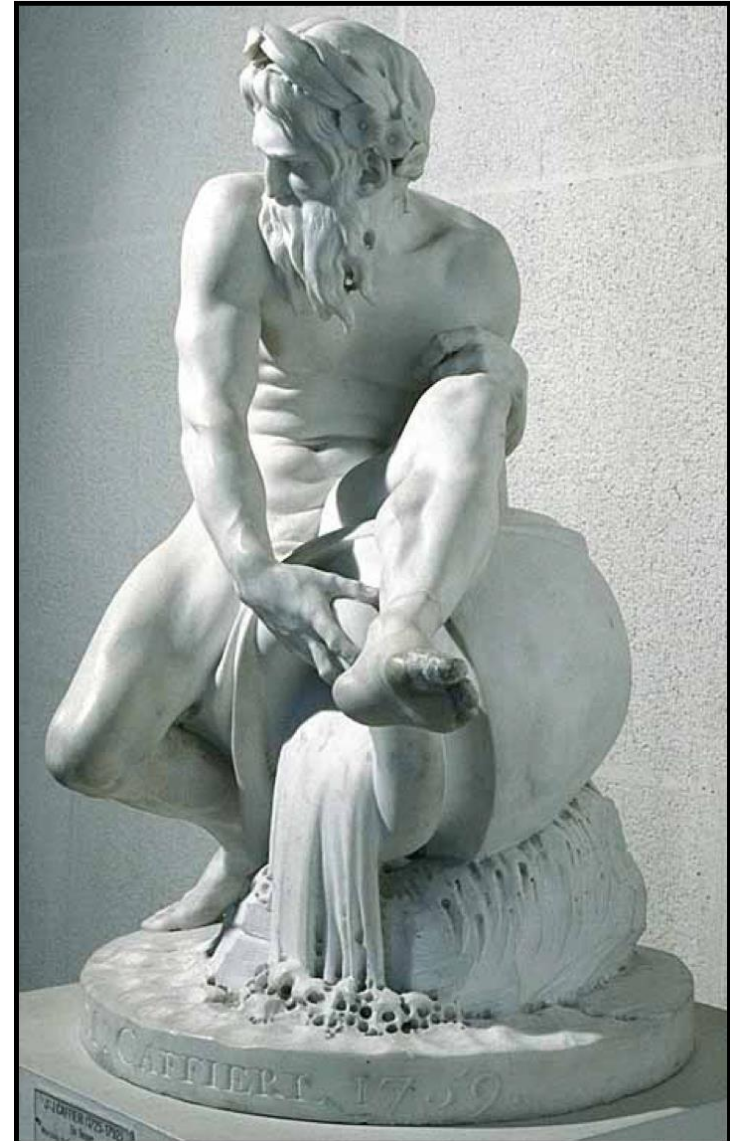


Melanoma arising in Blue  
Nevus



# Anatomic “Special” Sites

- Anatomic site influences the histopathology of nevi/lesions
  - the skin is structurally different
  - degree of sun exposure, exposure to trauma, hormonal



# Anatomic Site

- Chronically sun-damaged sites:
  - High CSD (lentigo maligna) melanoma
  - Desmoplastic melanoma
- Intermittently sun-exposed skin:
  - Common acquired nevi
  - Low CSD melanoma
- Acral skin

# Clinical Criteria [“ABCDEs”]

Clinical Diagnosis is 80 to 90%

| Gross Morphological Features  | Benign Nevus   | Melanoma   |
|---|--|--|
| <ul style="list-style-type: none"><li>• <b><u>D</u>iameter (size)</b></li><li>• <b><u>A</u>symmetry</b></li><li>• <b><u>B</u>orders</b></li><li>• <b><u>C</u>olor</b></li></ul> | <ul style="list-style-type: none"><li>• &lt; 5 mm</li><li>• Symmetry</li><li>• Regular borders</li><li>• Uniform color</li></ul> | <ul style="list-style-type: none"><li>• &gt; 6 mm, &gt; 10 mm</li><li>• Asymmetry</li><li>• Irregular borders</li><li>• Non uniform color</li><li>• Black</li><li>• Amelanotic</li></ul> |

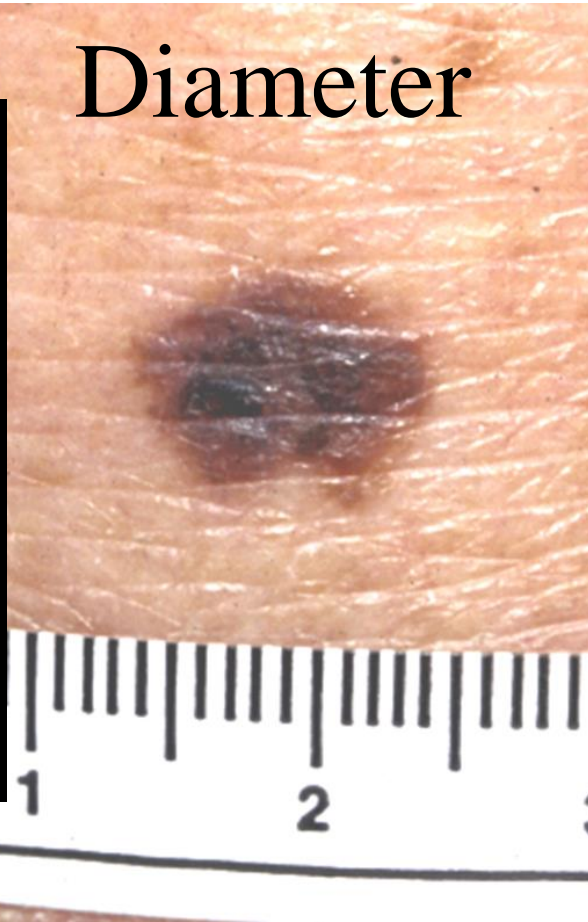
# Clinical Features

Size Matters!

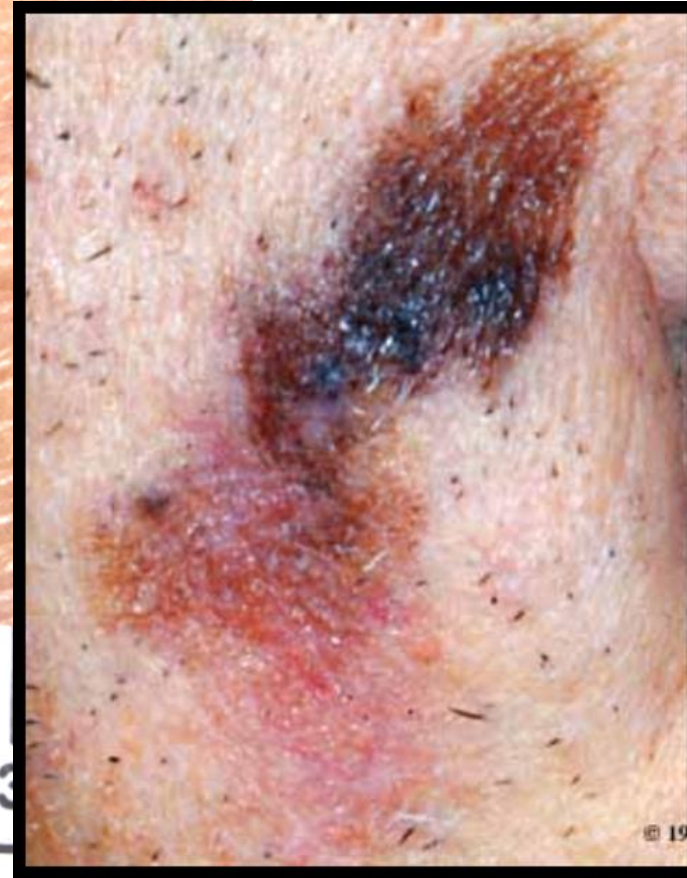
Diameter



$< 5 \text{ mm}$



$5 - 12 \text{ mm}$



$\geq 6 \text{ mm}, > 10 \text{ mm}$

# Clinical Criteria

| Criterion  | Benign  | Melanoma  |
|--|---|---|
| <b>Clinical History<br/>[Evolution, enlargement]</b> | <ul style="list-style-type: none"><li>• Stable</li><li>• Long-standing lesion</li><li>• History of trauma</li></ul> | <ul style="list-style-type: none"><li>• Changing</li><li>• New lesion</li><li>• Itching, pain, bleeding</li></ul> |

# Clinical History

## Enlarging and Changing Lesion



Congenital Melanoma

## II. Histopathological Criteria

# WHO 5<sup>th</sup> Edition Histopathology is the Gold Standard



# How Does Histopathology Really Function?

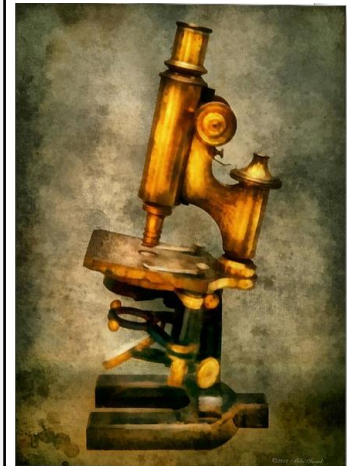
Benign  
Nevus



- Intermediate zone:  
suboptimal gold  
standard



Clear-cut  
Melanoma



# What is an Intermediate Melanocytic Lesion?

Benign  
Nevus

- Atypical nevus
- Dysplastic nevus
- Atypical Spitz tumor
- Melanocytoma
- Melanoma in situ
- Uncertain lesions



Clear-cut  
Melanoma

# What is an Uncertain Melanocytic Lesion?

- A lesion difficult to interpret (usually as benign or malignant)
- A lesion with uncertain potential for:
  - Persistence, recurrence, progression, or metastasis

# Why Does Histopathology Function So Poorly in This Intermediate Zone?

- The lack of correlation between histopathological criteria and precise molecular data with neoplastic progression (metastases, death)

# This is the Gold Standard!

- Biological outcome
  - metastases
  - death

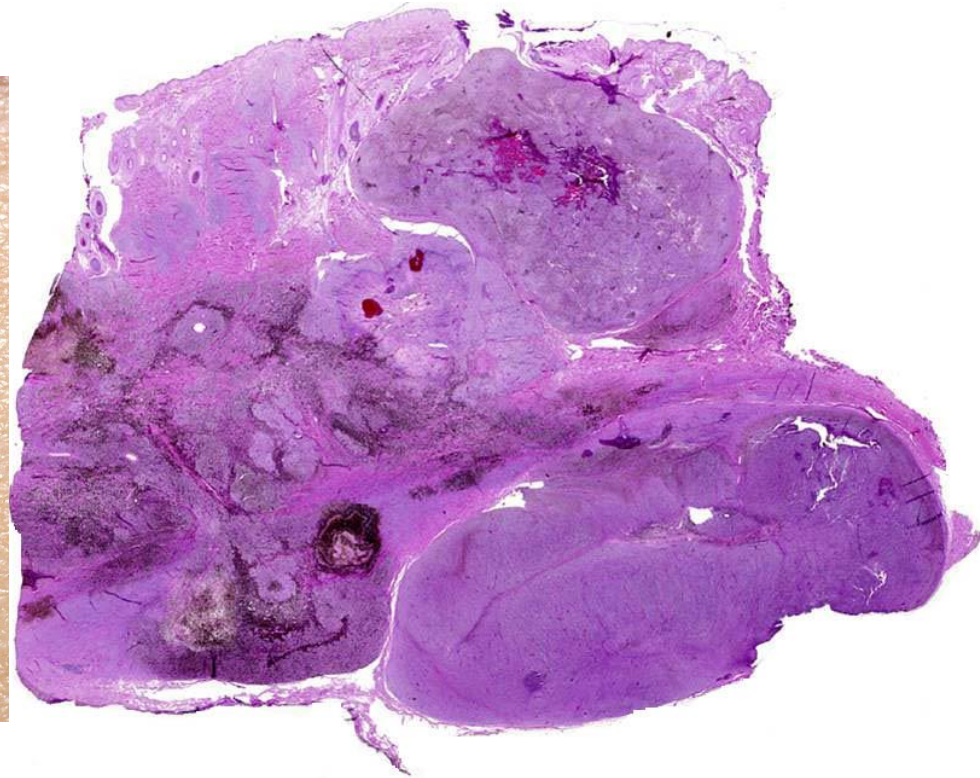
# Criteria for Diagnosis

What are the most important histopathological criteria?

- Objective or quantifiable criteria
  - ❖ Size: diameter, thickness
  - ❖ Architecture
  - ❖ Ulceration
  - ❖ Mitotic rate
  - ❖ Cytology, grade of atypia
  - ❖ Regression %

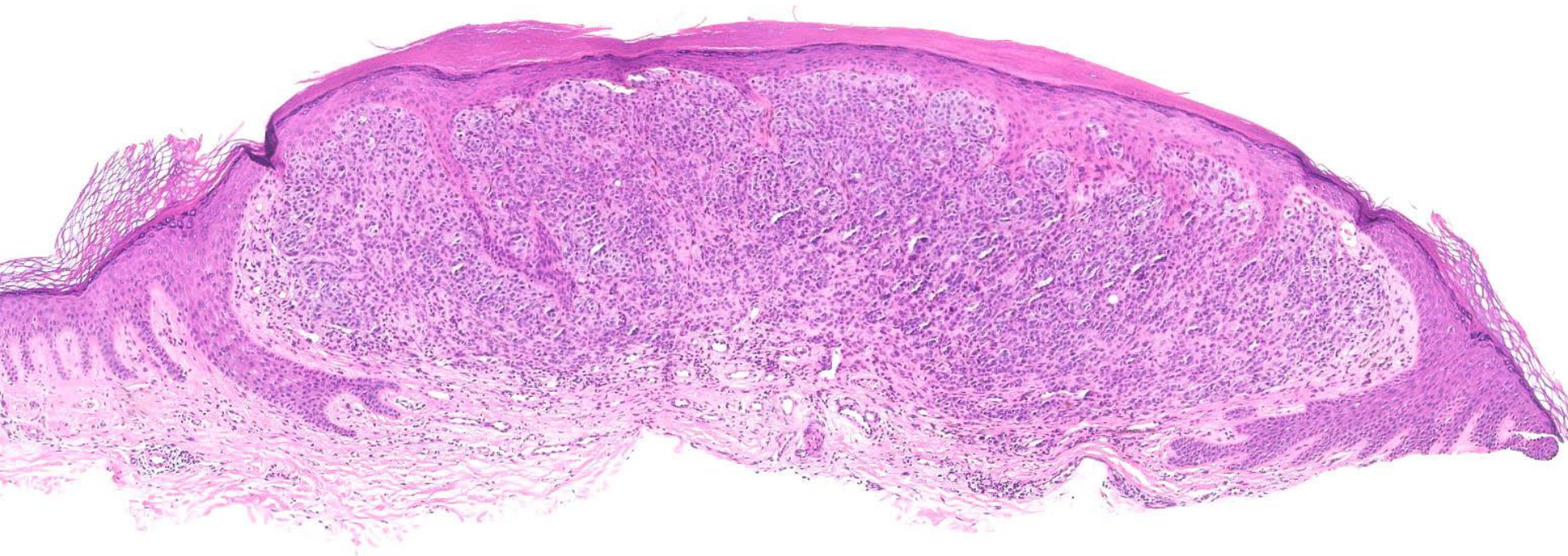
# The Certain Lesion

Diagnosis by Gestalt



# The Uncertain Lesion

## Comprehensive Criteria



# Due Diligence

Standardized, Methodical, and  
Comprehensive Approach  
to Difficult/Intermediate  
Uncertain Melanocytic Lesions

# Histopathological Criteria Linked to Biological Outcome

## HISTOLOGIC CRITERIA FOR THE DIAGNOSIS OF SUPERFICIAL SPREADING MALIGNANT MELANOMA: FORMULATED ON THE BASIS OF PROVEN METASTATIC LESIONS

NORMAN M. PRICE, MB, CHB,\* ARKADI M. RYWLIN, MD,<sup>†</sup>  
AND A. BERNARD ACKERMAN, MD<sup>‡</sup>

Histologic material was studied from 30 patients with metastasizing cutaneous superficial spreading malignant melanoma in an attempt to establish reproducible criteria for the accurate diagnosis of the disease. This paper details the criteria for the histologic diagnosis of primary superficial spreading malignant melanoma of the skin.

*Cancer* 38:2434-2441, 1976.

# Histopathological Criteria

Poor circumscription

Pagetoid spread of solitary melanocytes and nests

Variation in the size and shape of melanocytic nests

Confluence of melanocytic nests

Absence of maturation

Cytological atypia

Mitoses

Necrosis

# Histopathological Criteria

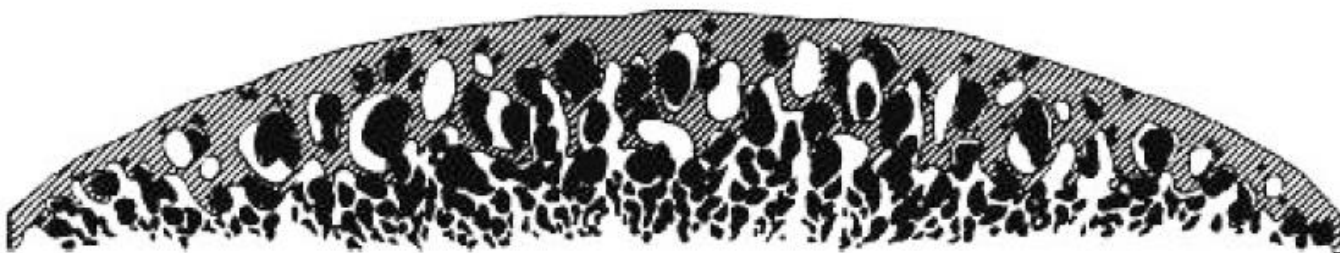
| Criterion   | Benign         | Intermediate                    | Melanoma          |
|---|----------------|---------------------------------|-------------------|
| Diameter (size)                                   | < 4 mm         | 4 – 12 mm                       | > 5 mm >10mm      |
| Symmetry  | Symmetry       | ± Symmetry                      | Asymmetry         |
| Circumscription                                   | Sharp          | Sharp to poor                   | Poor              |
| Pagetoid spread                                   | Usually none   | ± , focal                       | Often present     |
| Architecture of nesting<br>Confluence melanocytes | Regular nests  | Often irregular<br>± Confluence | Irregular nesting |
| Maturation  | Present        | ±                               | Absent            |
| Mitoses   | Usually absent | ±                               | Often present     |
| Cytological atypia                                | Usually none   | Variable                        | Moderate - severe |
| Host response/regression                          | Usually absent | Increasing                      | Prominent         |

# Microscopic Examination

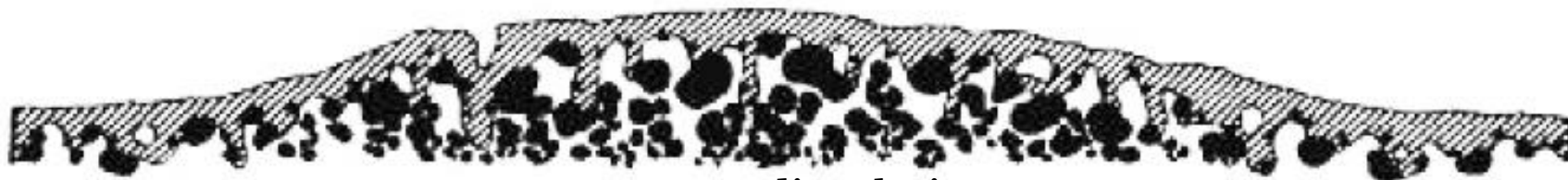
## Histopathological Criteria

1. Low/scanning magnification:  
Architecture
2. High magnification:  
Cytology, other

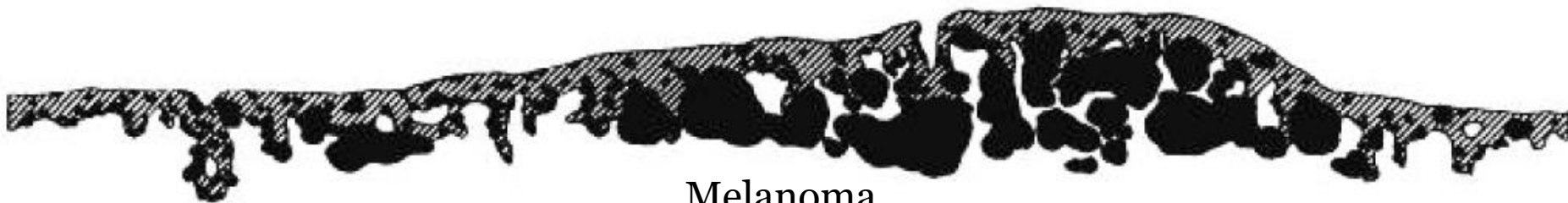
# Evaluation of Microscopic Architecture by Silhouette



Benign nevus



Intermediate lesion



Melanoma

# Histopathological Criteria

## Size Matters!

| Criterion       | Benign      | Intermediate | Melanoma    |
|-----------------|-------------|--------------|-------------|
| <b>Diameter</b> | $\leq 4$ mm | 4 – 12 mm    | $\geq 6$ mm |
|                 | Common      | Dysplastic   | $>10$ mm    |
|                 | nevi        | nevi         |             |

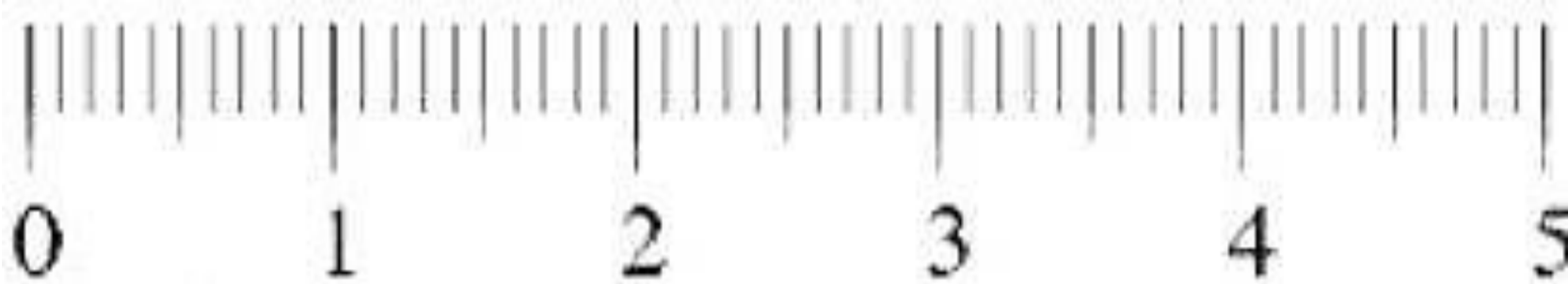
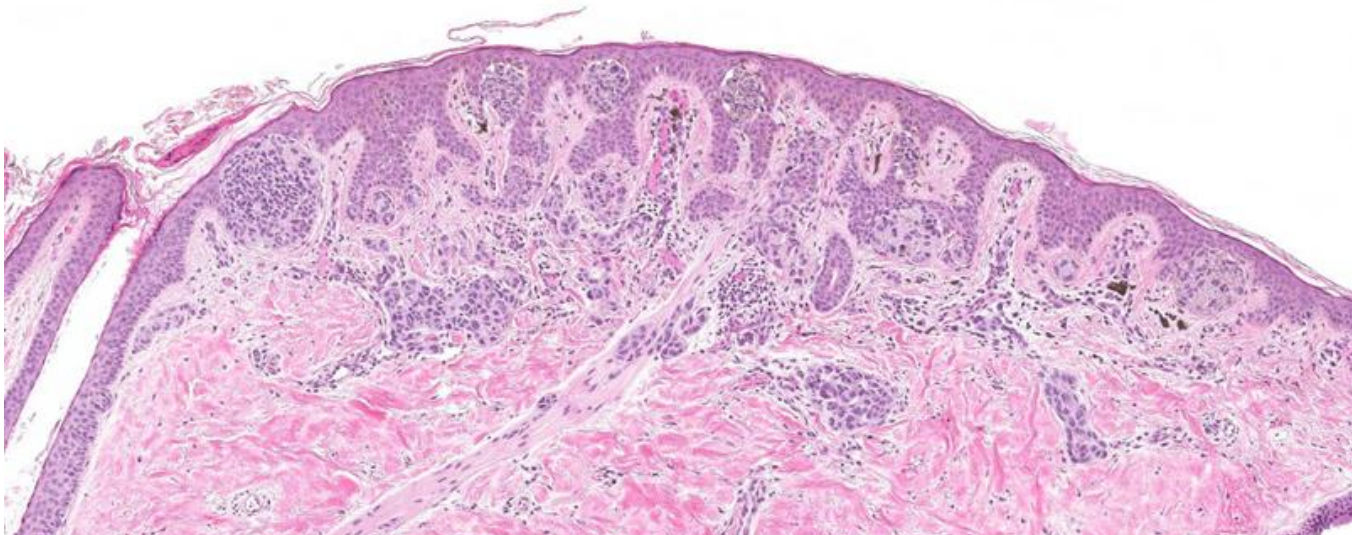
Diameter of Dysplastic Nevus Is a More Robust Biomarker of Increased Melanoma Risk Than Degree of Histologic Dysplasia: A Case-Control Study

Xiong MY, Rabkin MS, Piepkorn MW, Barnhill RL, Argenyi Z, Erickson L, Guitart J, Lowe L, Shea CR, Trotter MJ, Lew RA, Weinstock MA. J Am Acad Dermatol. 2014 Dec;71(6):1257-1258.e4.



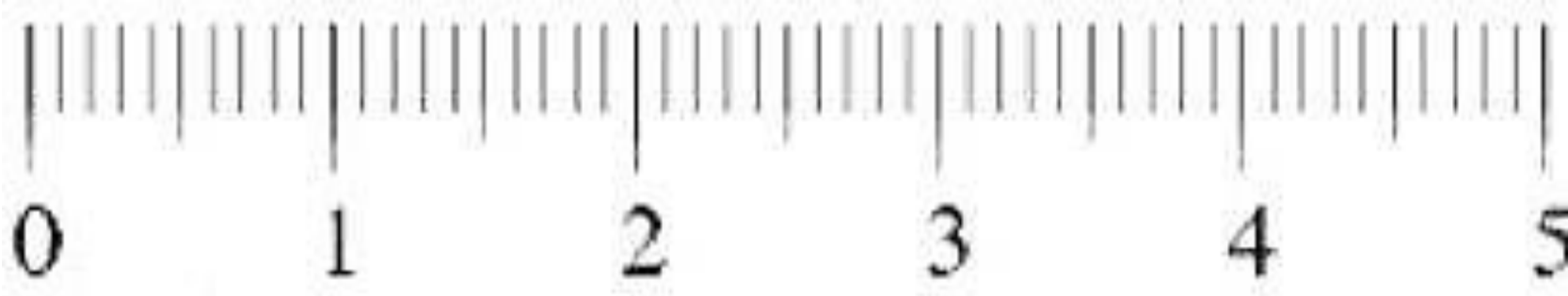
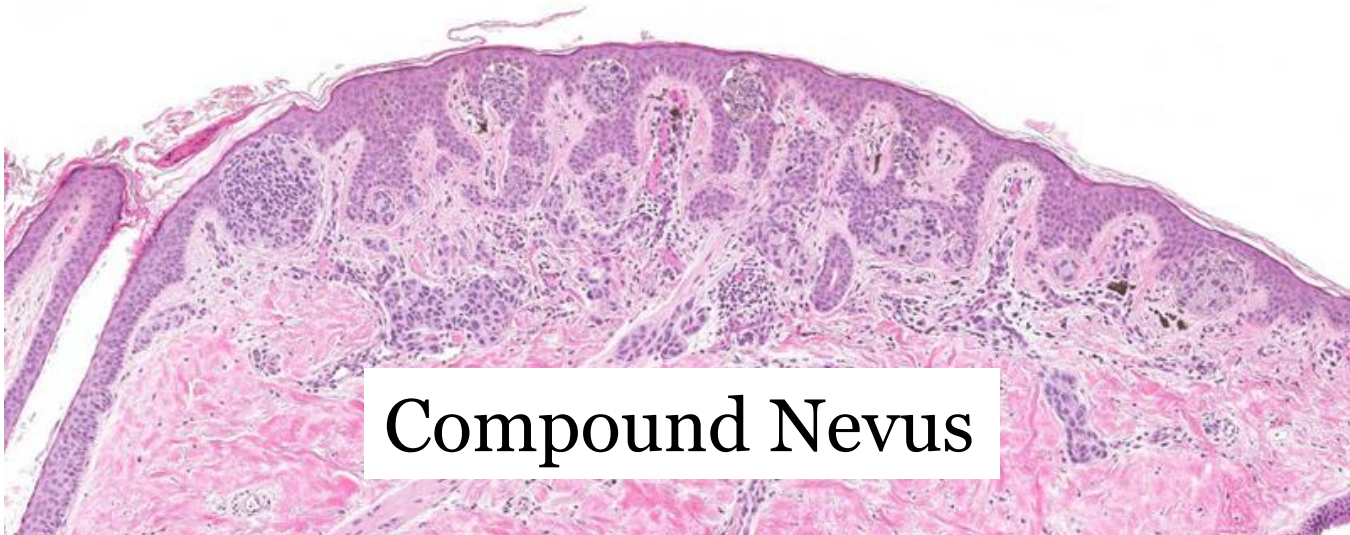
# Diameter

Diameter - 3 mm



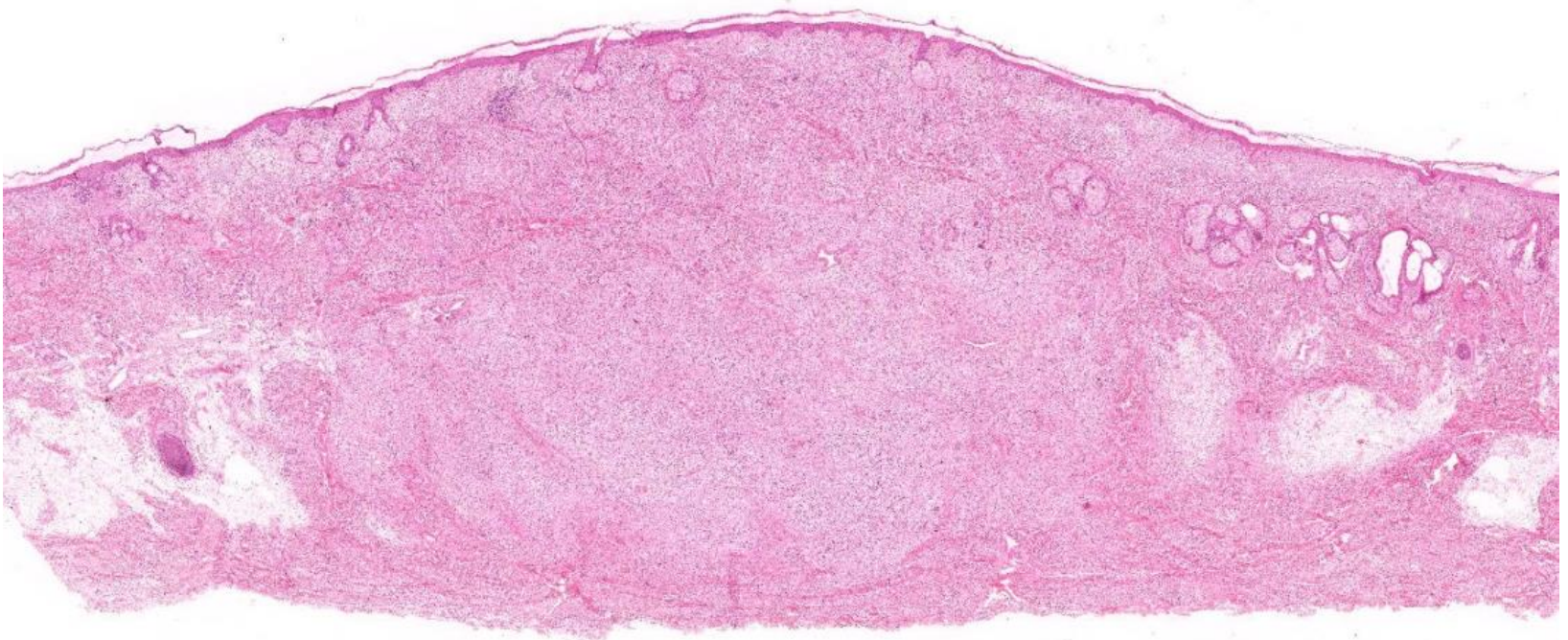
# Diameter

Diameter - 3 mm



# Diameter

Diameter - 20 mm



# Diameter

Diameter - 2 cm

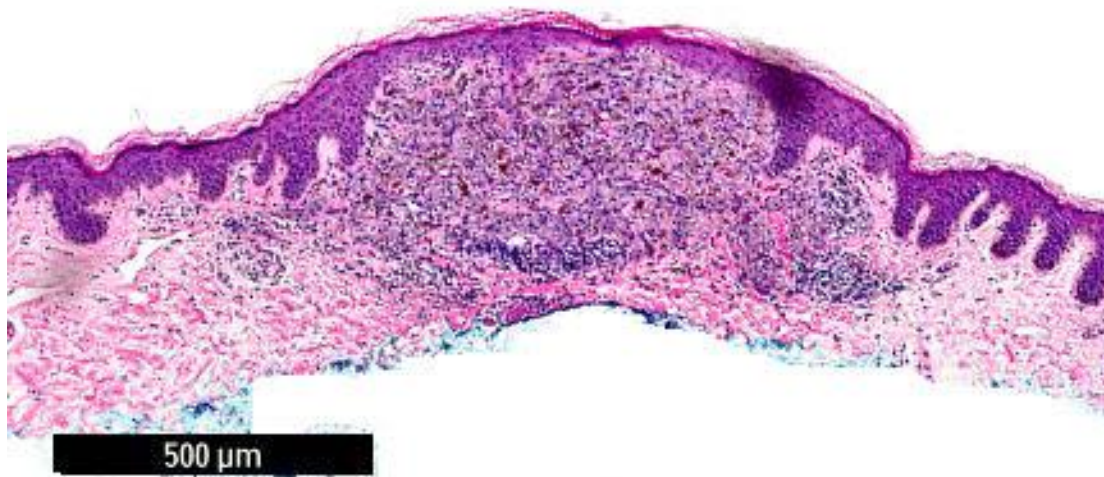


Desmoplastic Melanoma



# Diameter

Diameter < 3 mm



# Diameter

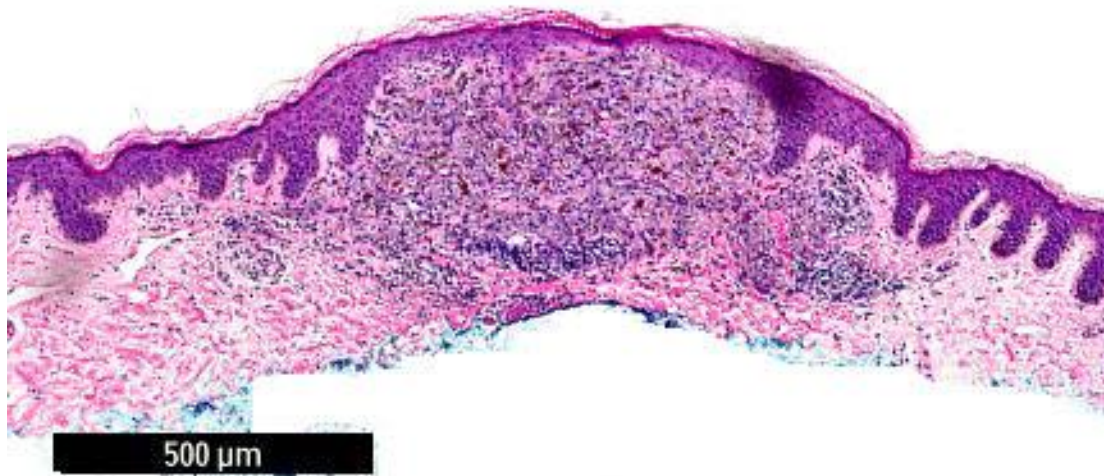
Exceptions



# Diameter

## Metastatic Melanoma !

Diameter < 3 mm



Clinical History!

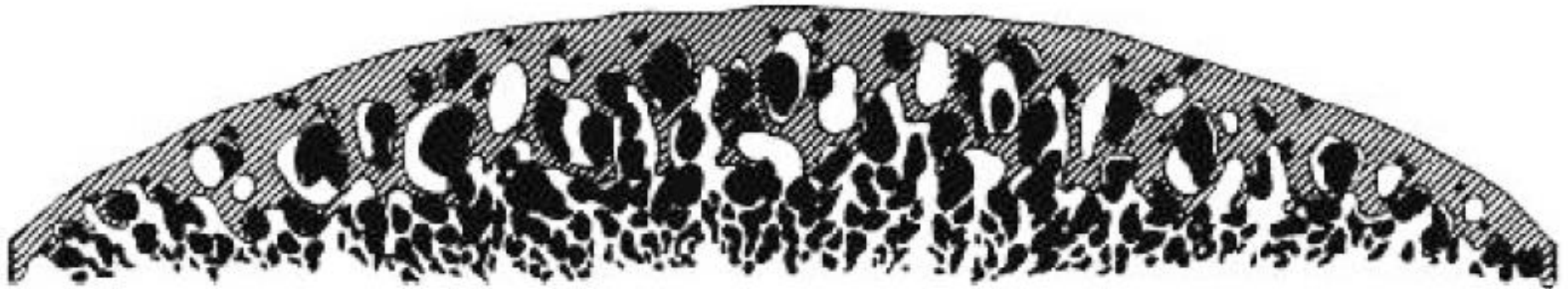
# Histopathological Criteria\*

| Criterion   | Benign   | Intermediate                | Melanoma  |
|---|----------|-----------------------------|-----------|
| <b>Symmetry</b><br>➤ Silhouette <ul style="list-style-type: none"><li>• Epidermal contour</li><li>• Melanocytes</li><li>• Melanin</li><li>• Host response</li></ul> | Symmetry | Symmetry<br>or<br>asymmetry | Asymmetry |

# Mirror Image Symmetry

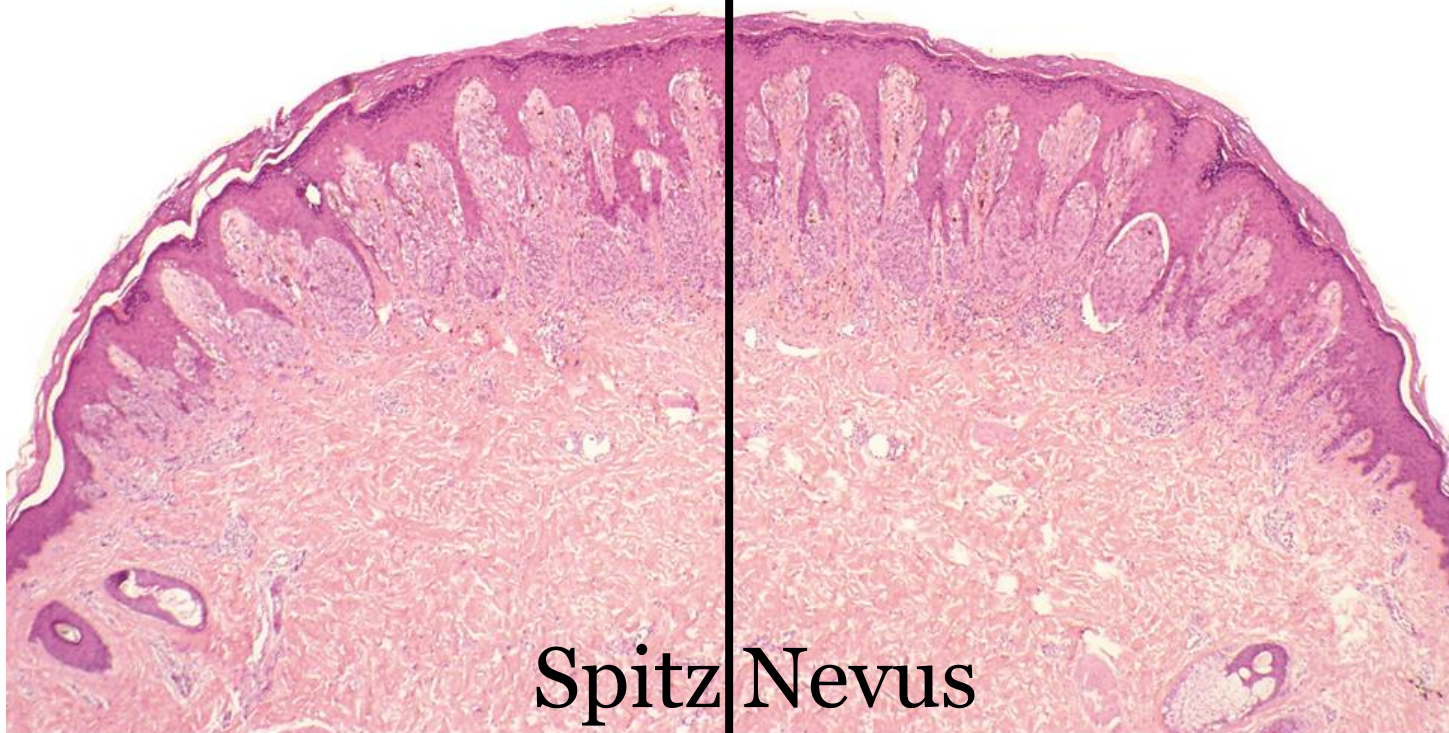
- Overall silhouette
- ? Biphase silhouette
- Comparison of individual elements
  - ✓ Melanocytes
  - ✓ Melanin
  - ✓ Host response
  - ✓ Epidermal contour

# Symmetry



Spitz Nevus

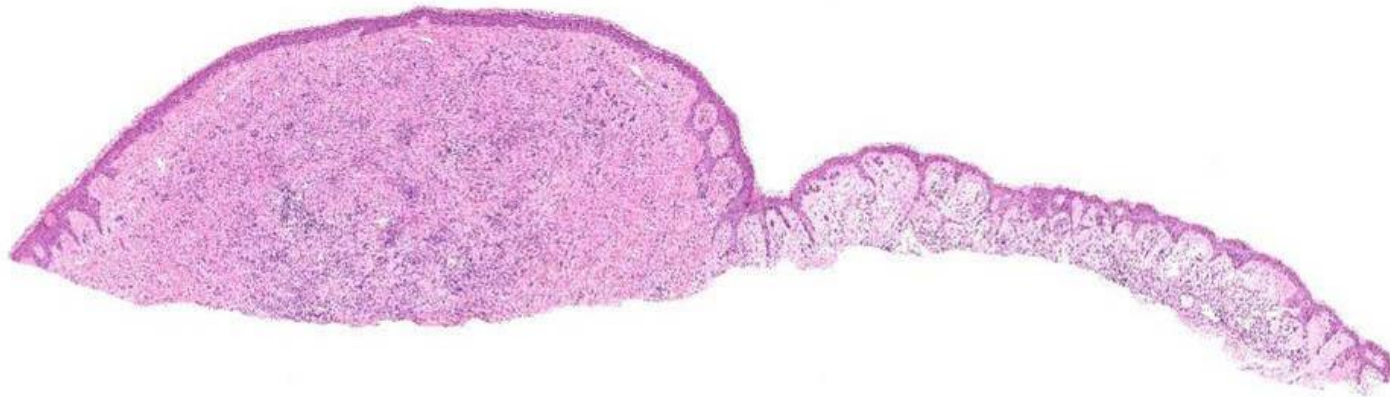
# Mirror Image Symmetry



# Asymmetry

## The Biphasic Lesion

Two distinct components



# Asymmetry

## The Biphasic Lesion

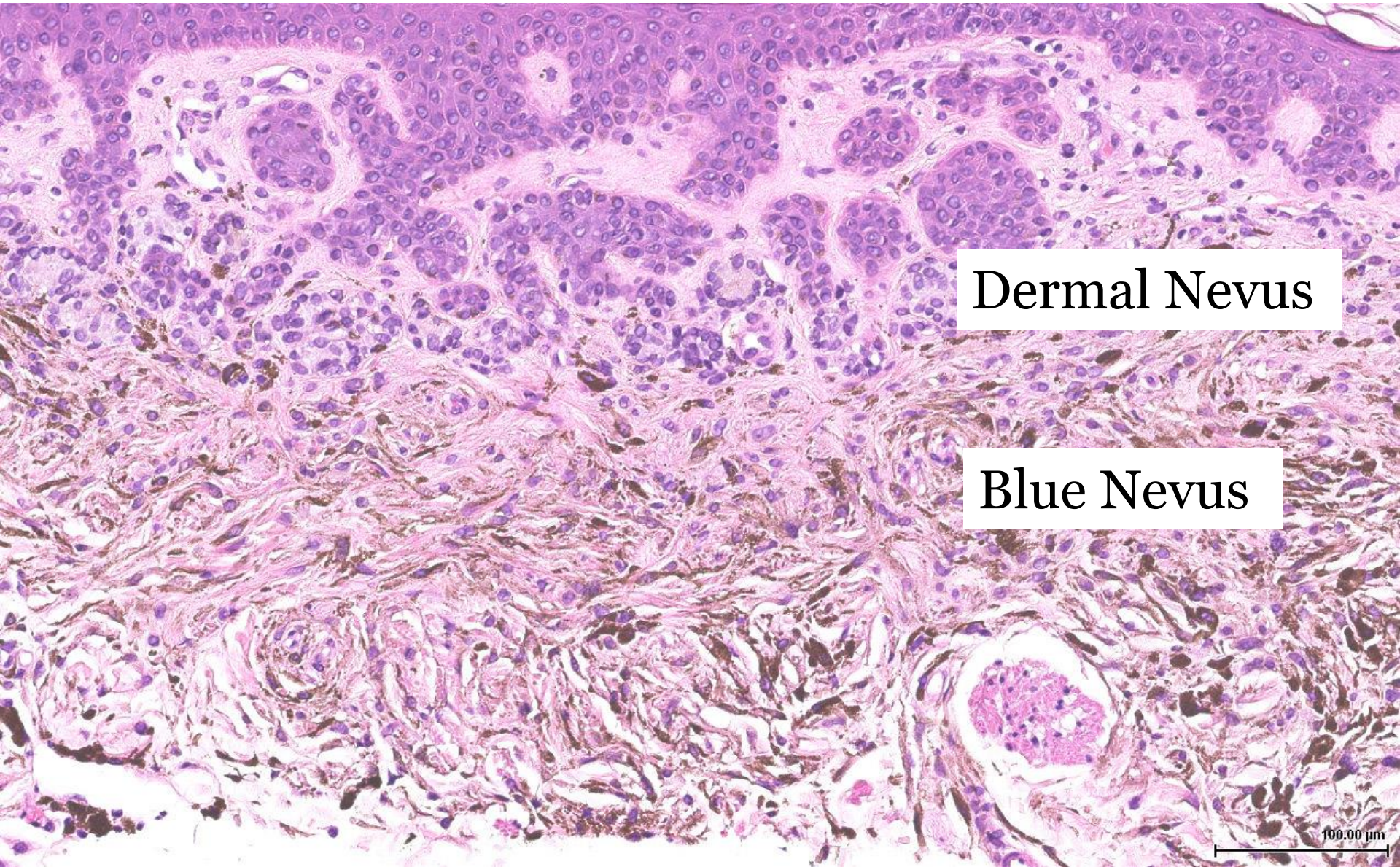
Marker of Neoplastic Progression

Melanoma

Nevus



# Benign Biphasic Lesion: Combined Nevus

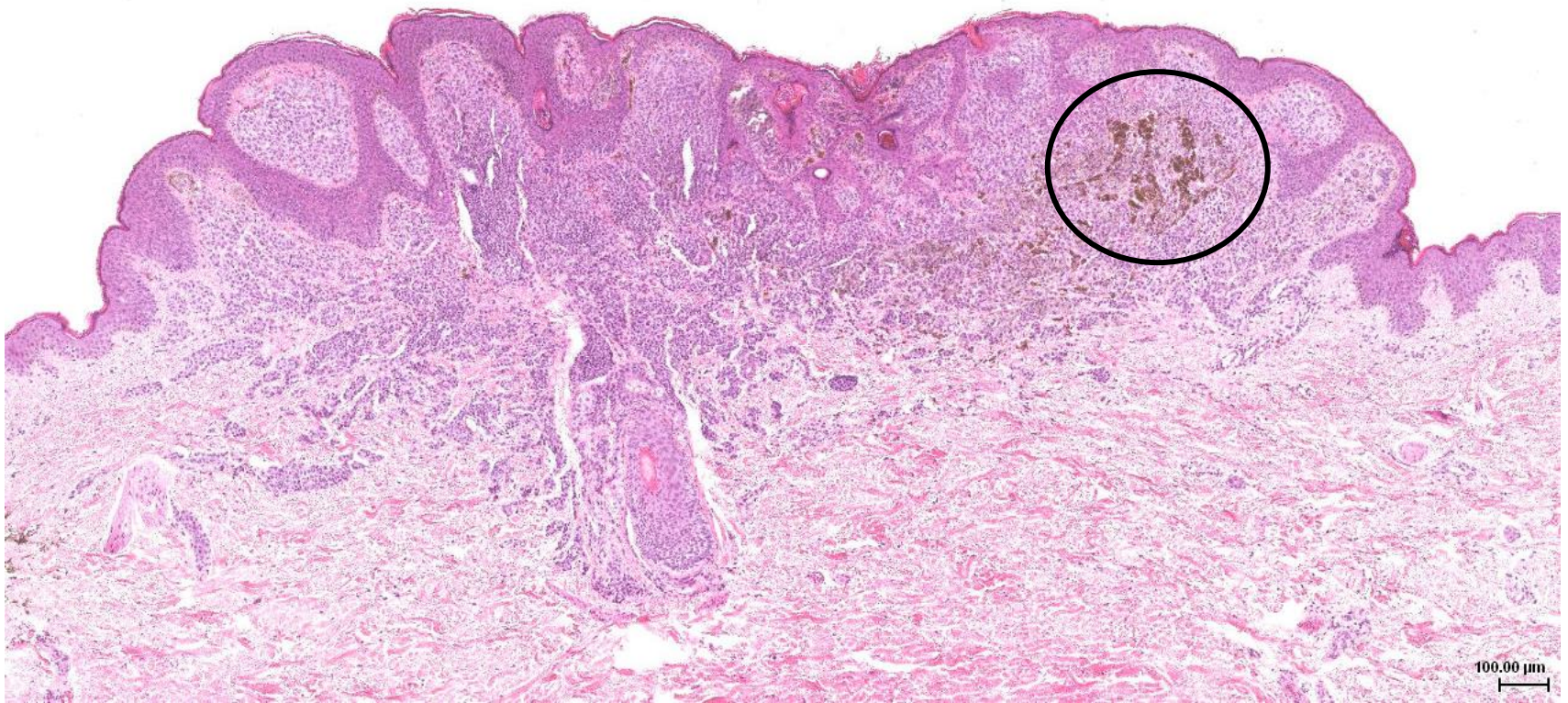


Dermal Nevus

Blue Nevus

100.00 µm

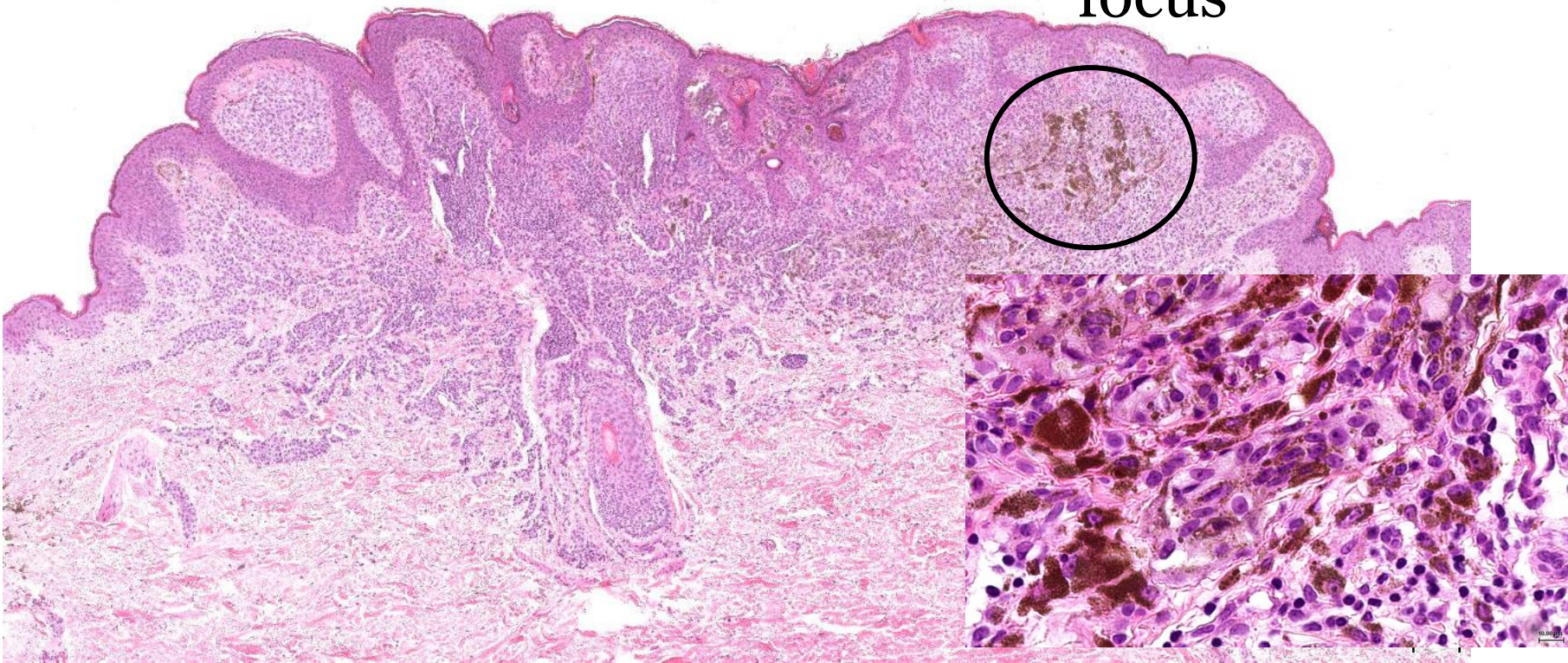
# Atypical Biphasic Lesion: Nevus with neoplastic progression?



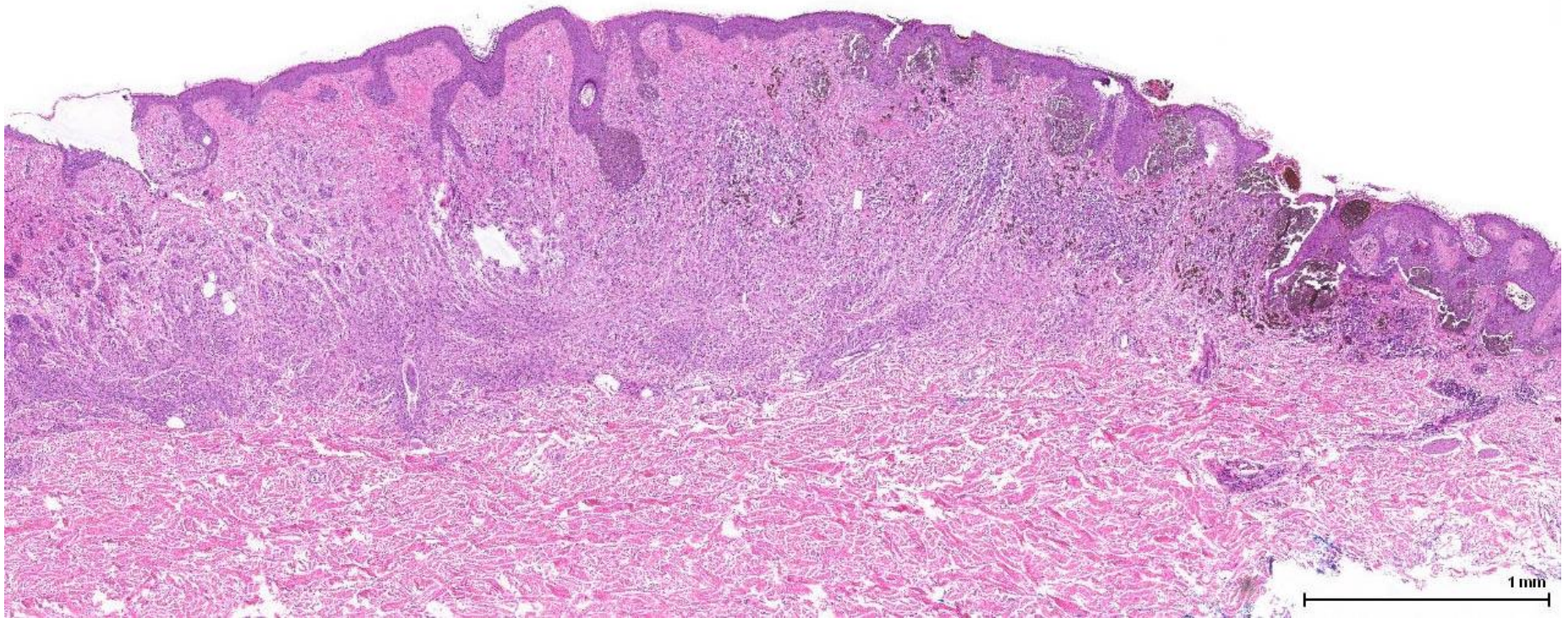
# Atypical Biphasic Lesion: Combined Nevus Neoplastic Progression?

Nevus

Pigmented  
spindle/epithelioid cell  
focus



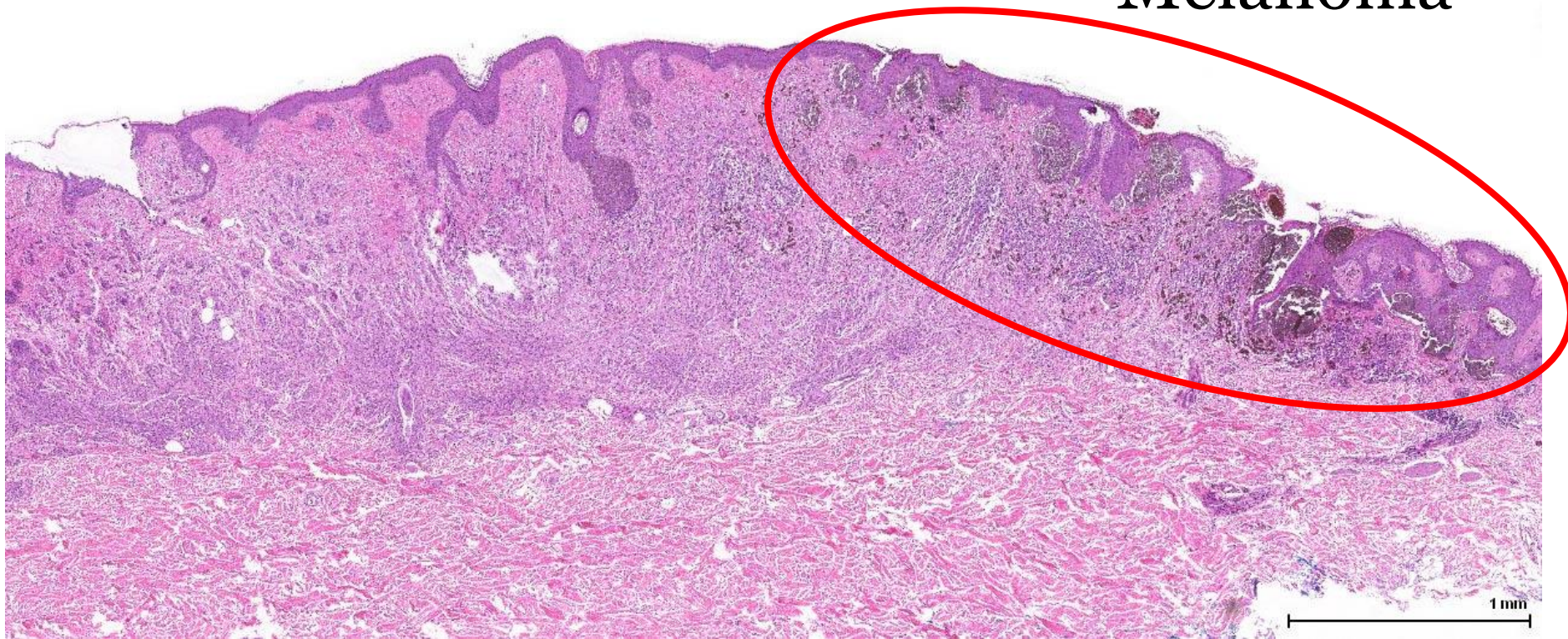
# Atypical Biphasic Lesion: Nevus and Melanoma?



# Atypical Biphasic Lesion: Nevus and Melanoma

Nevus

Melanoma



# Atypical Biphasic Lesions: Melanocytomas

- Conventional nevus (BRAF mutation) + second component:
- Plexiform/deep-penetrating nevus/tumor
- Pigmented epithelioid melanocytoma
- BAP1-inactivated tumor
- Others

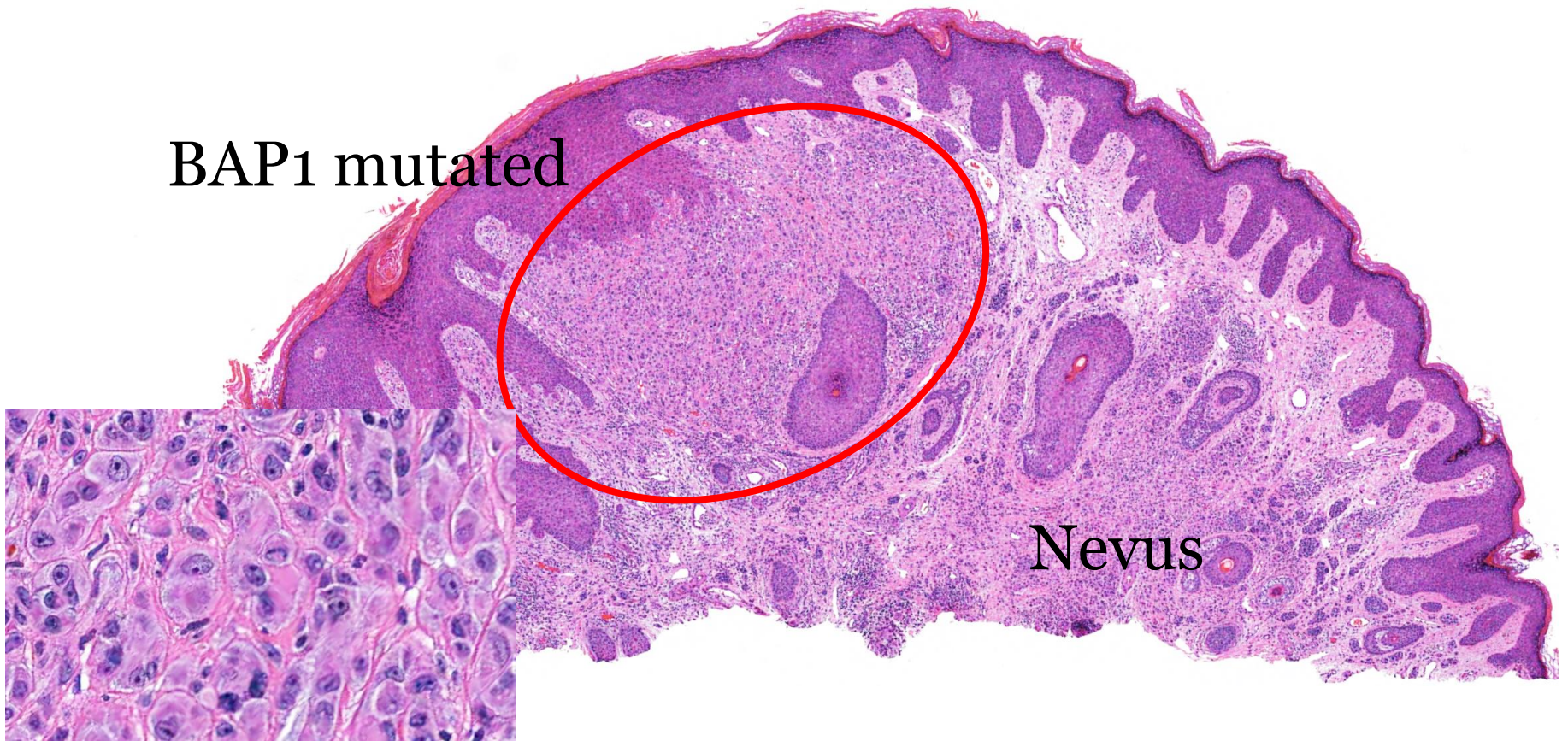
# Atypical Biphasic Tumors

## BAP1-inactivated tumor/melanocytoma

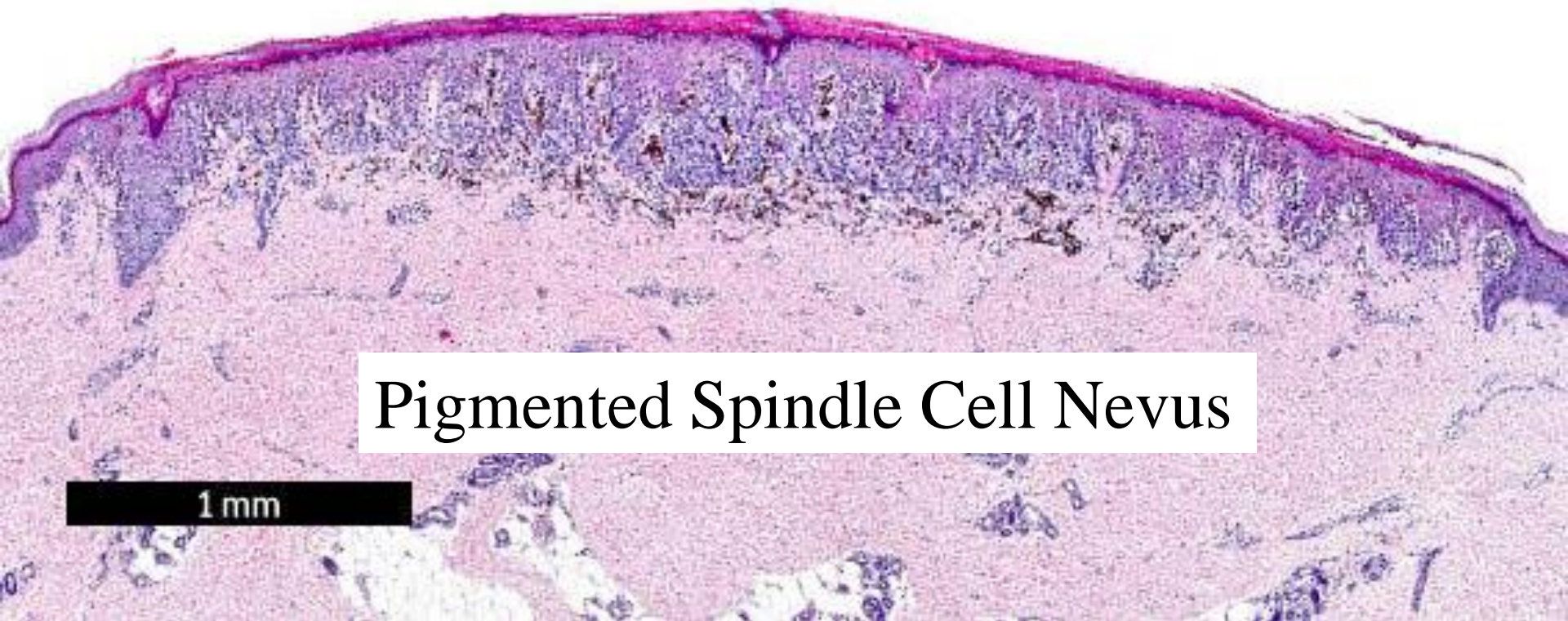
- Conventional nevus (BRAF mutation) + BAP1-mutated second component:

BAP1 mutated

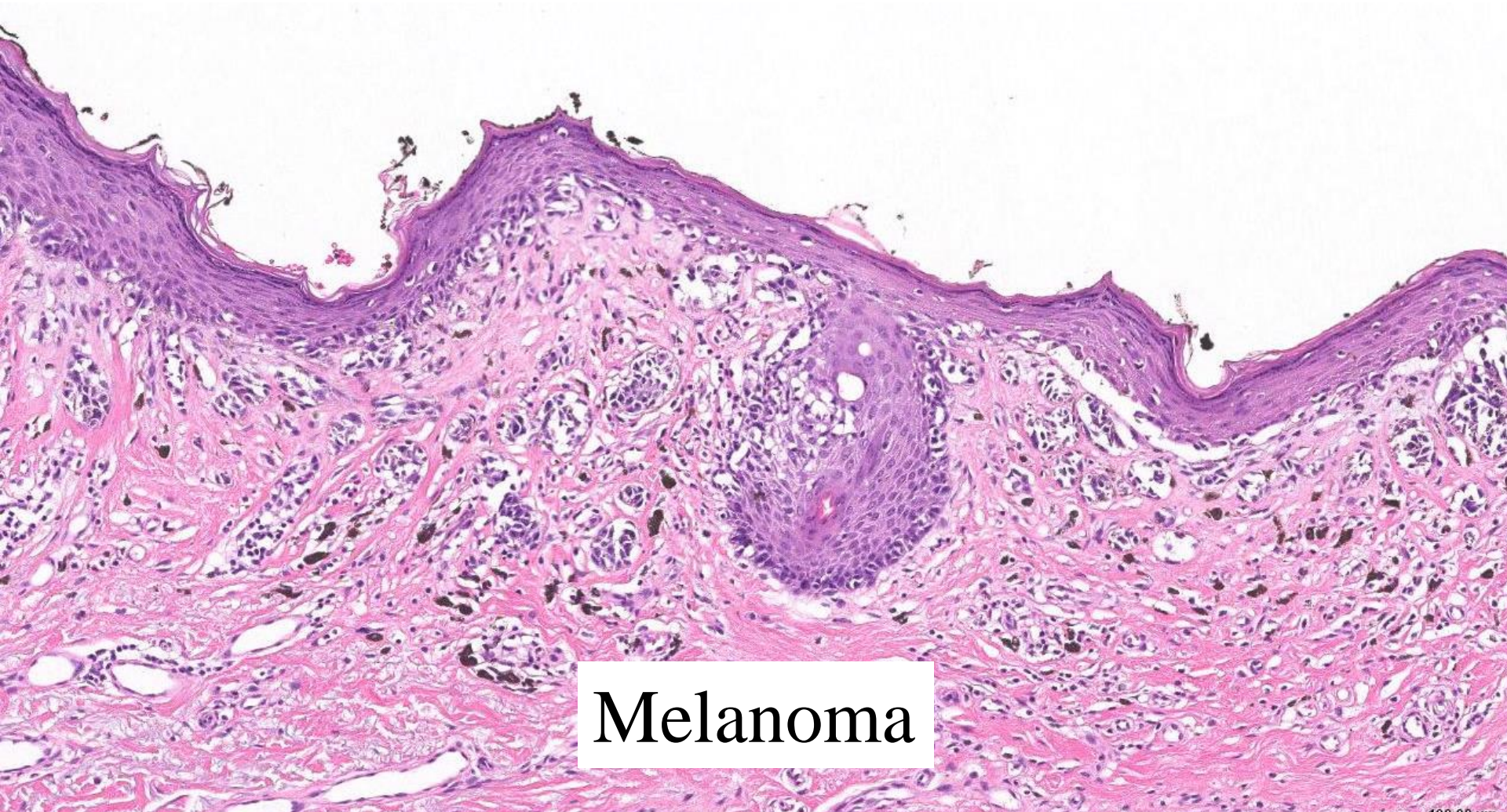
Nevus



# Epidermal Contour Uniform



# Epidermal Contour Effacement



Melanoma

# Symmetry

## Exceptions



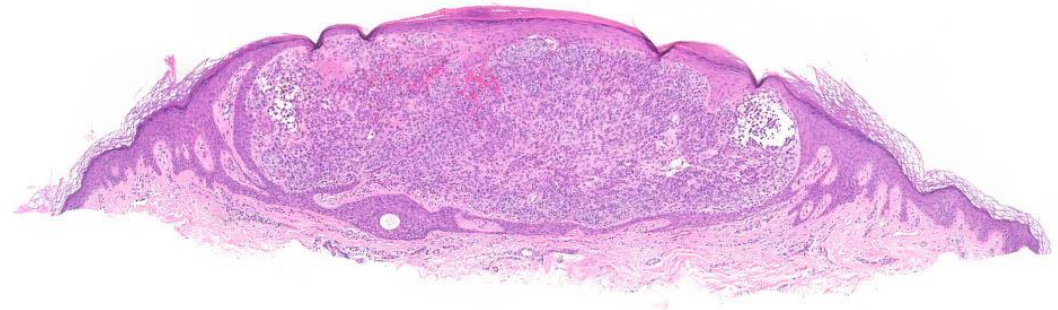
# Symmetry

Nevoid Melanoma

Nodular Melanoma

Metastatic Melanoma!

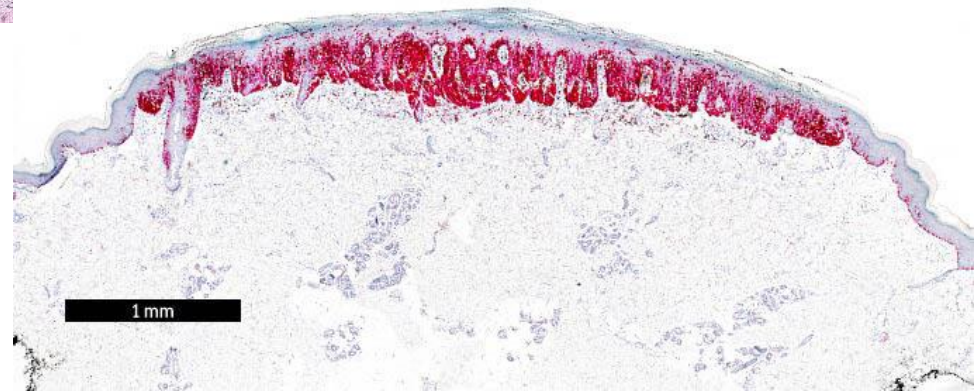
- Size < 4 mm
- Well-circumscribed
- Symmetrical
- No pagetoid scatter
- Nevoid



# Histopathological Criteria

| Criterion              | Benign                              | Intermediate                     | Melanoma             |
|------------------------|-------------------------------------|----------------------------------|----------------------|
| <b>Circumscription</b> | Sharp borders<br>Nests at periphery | Sharp to poor<br>Dysplastic nevi | Poor<br>Single cells |

# Sharp Circumscription



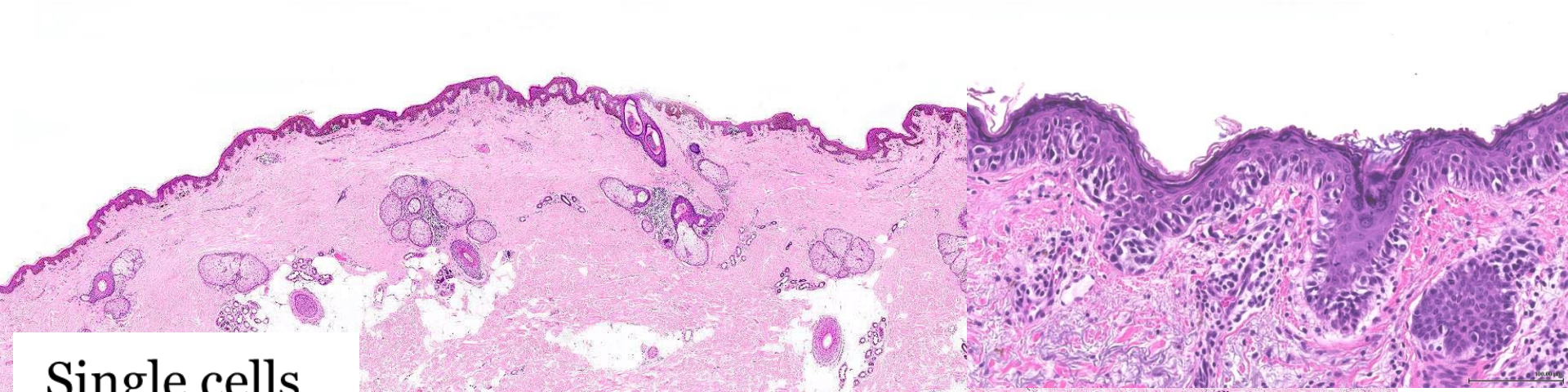
# Poor Circumscription



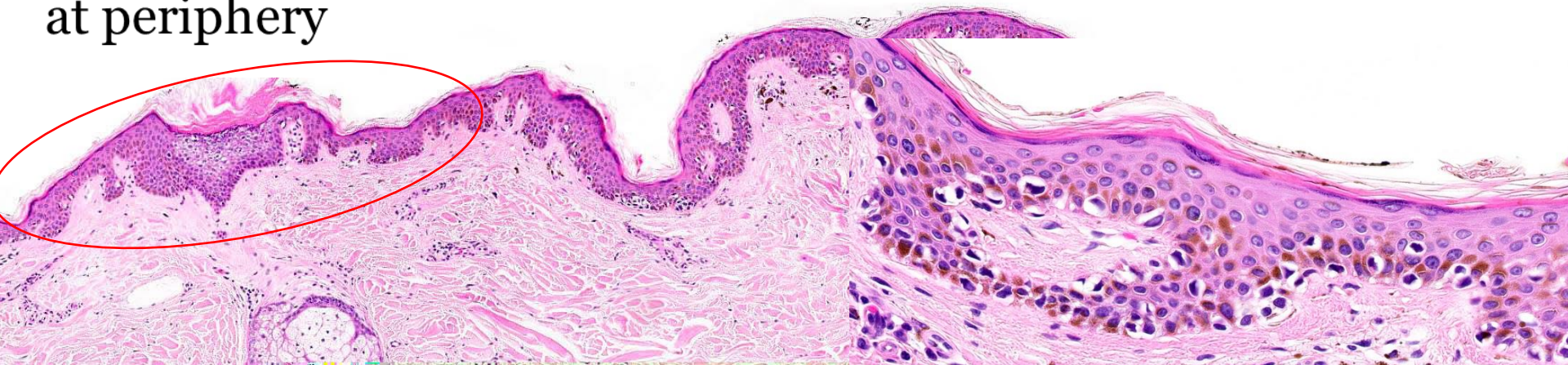
Melanoma

# Poor Circumscription

## Lentiginous Melanoma



Single cells  
at periphery



# Circumscription

Exceptions

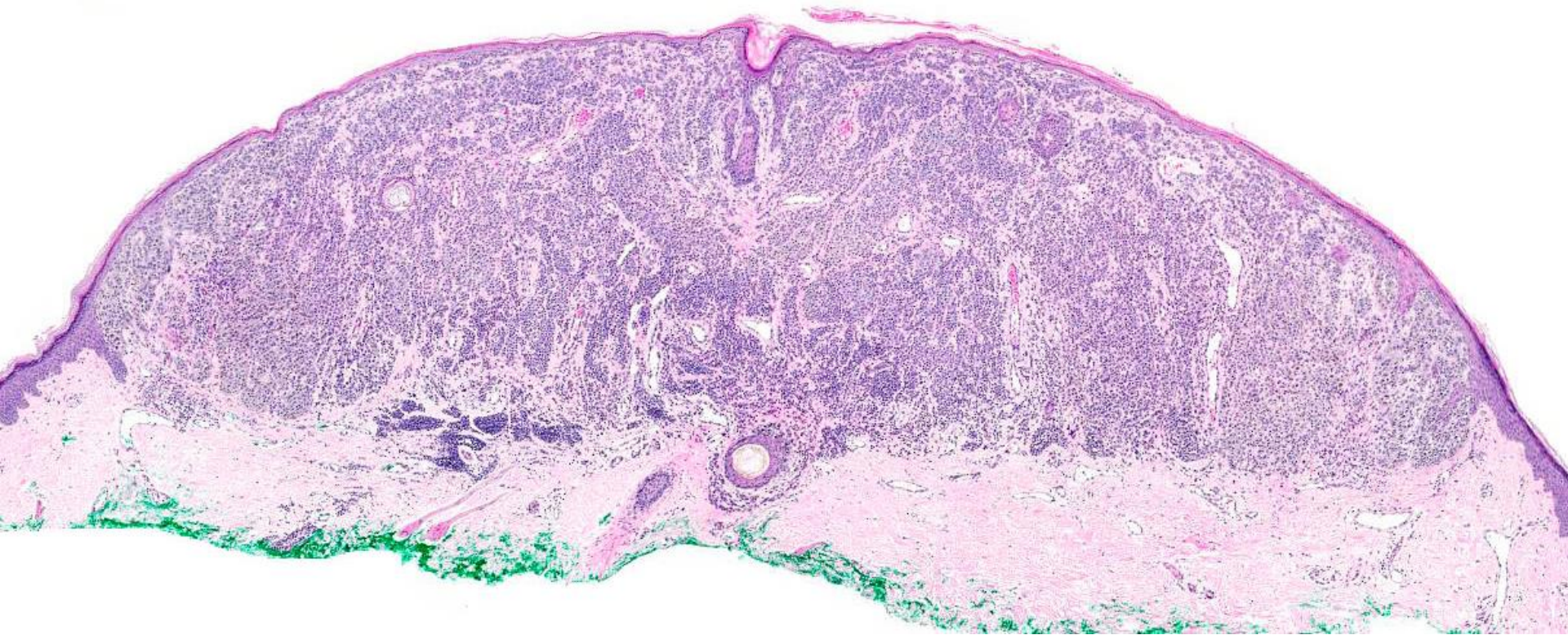


# Sharp Circumscription

Nevoid Melanoma

Nodular Melanoma

Melanoma Metastasis





# Architecture of the Junctional/Intraepidermal Component

- Junctional nesting
- Lentiginous (single cell) melanocytic proliferation
- Pagetoid spread

# Histopathological Criteria Architecture

| Criterion                         | Benign           | Intermediate                          | Melanoma  |
|-----------------------------------|------------------|---------------------------------------|---|
| Disordered junctional nests       | No disorder      | Disordered nesting                    | Highly disordered                                     |
| Lentiginous melanocytic prolifer. | Absent or slight | Often present, increased in frequency | Contiguous, often extending between rete              |
| Pagetoid spread                   | Absent           | Absent, focal, not full thickness     | Full thickness to granular layer<br>High grade atypia |

# Histopathological Criteria

## Intra-epidermal Melanoma

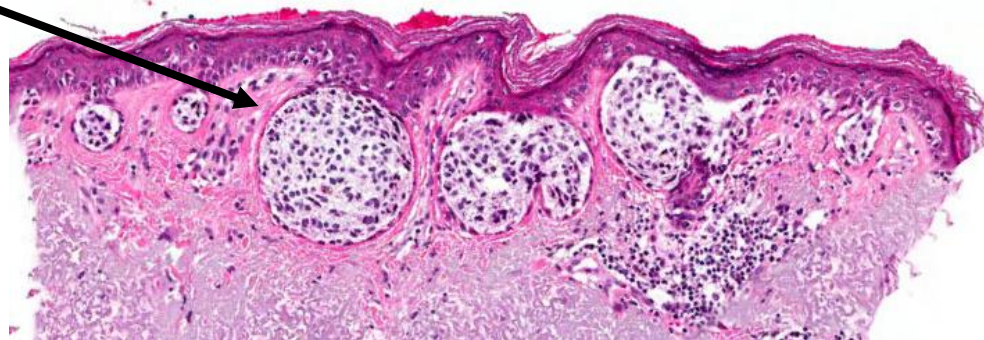
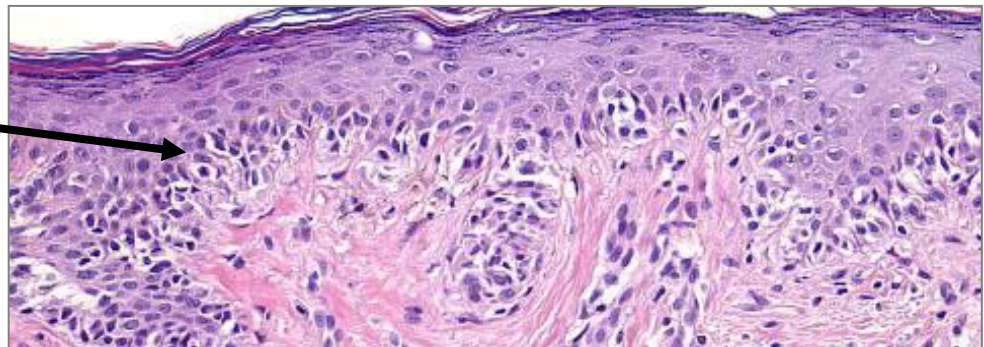
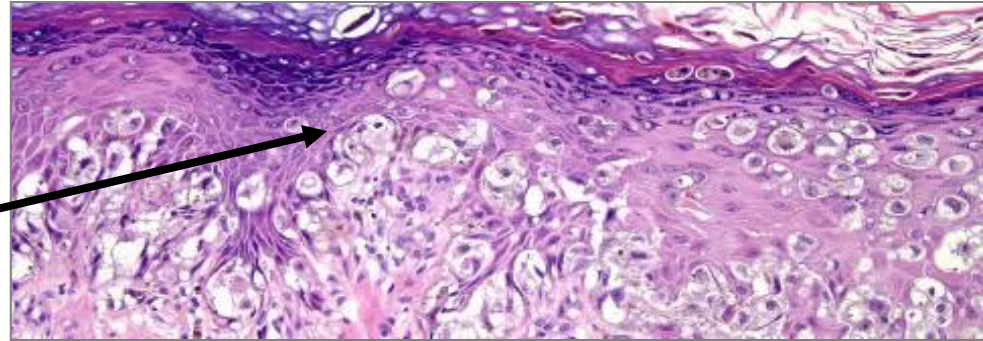
- Architecture

1. Pagetoid

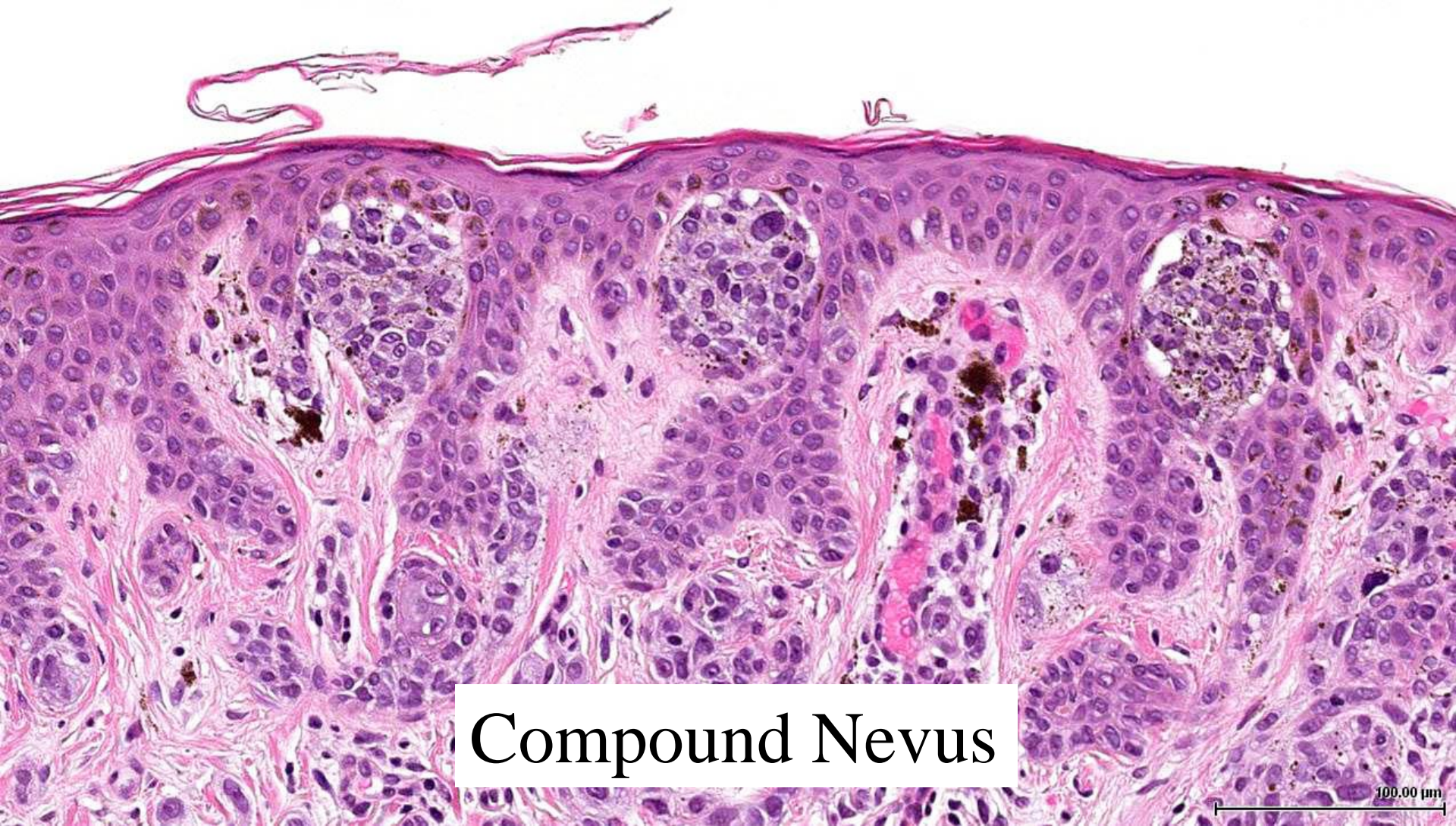
2. Lentiginous

3. Nested

- Moderately to severely atypical melanocytes (high grade)



# Regular Nesting



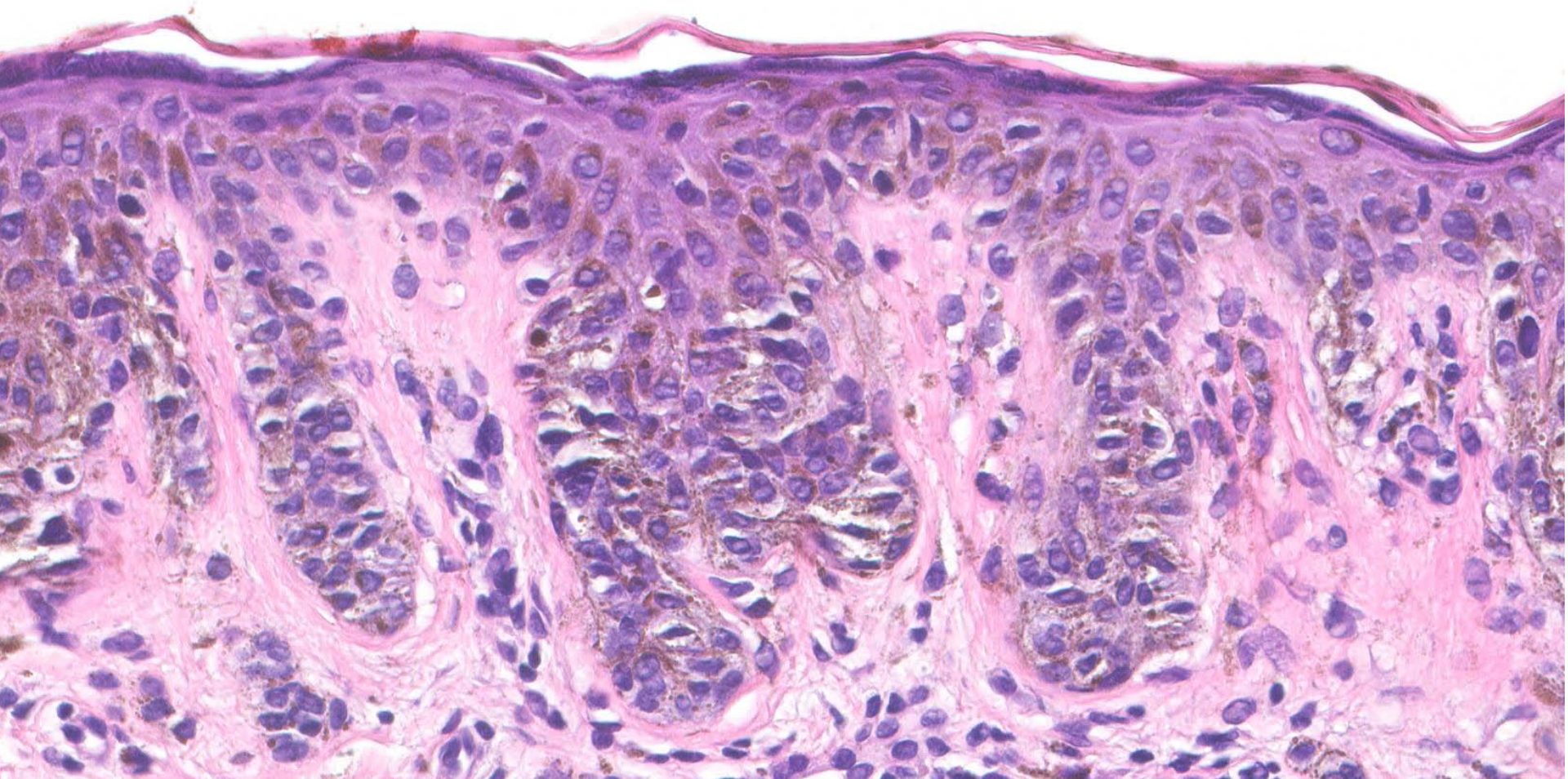
Compound Nevus

# Irregular and Confluent Nesting

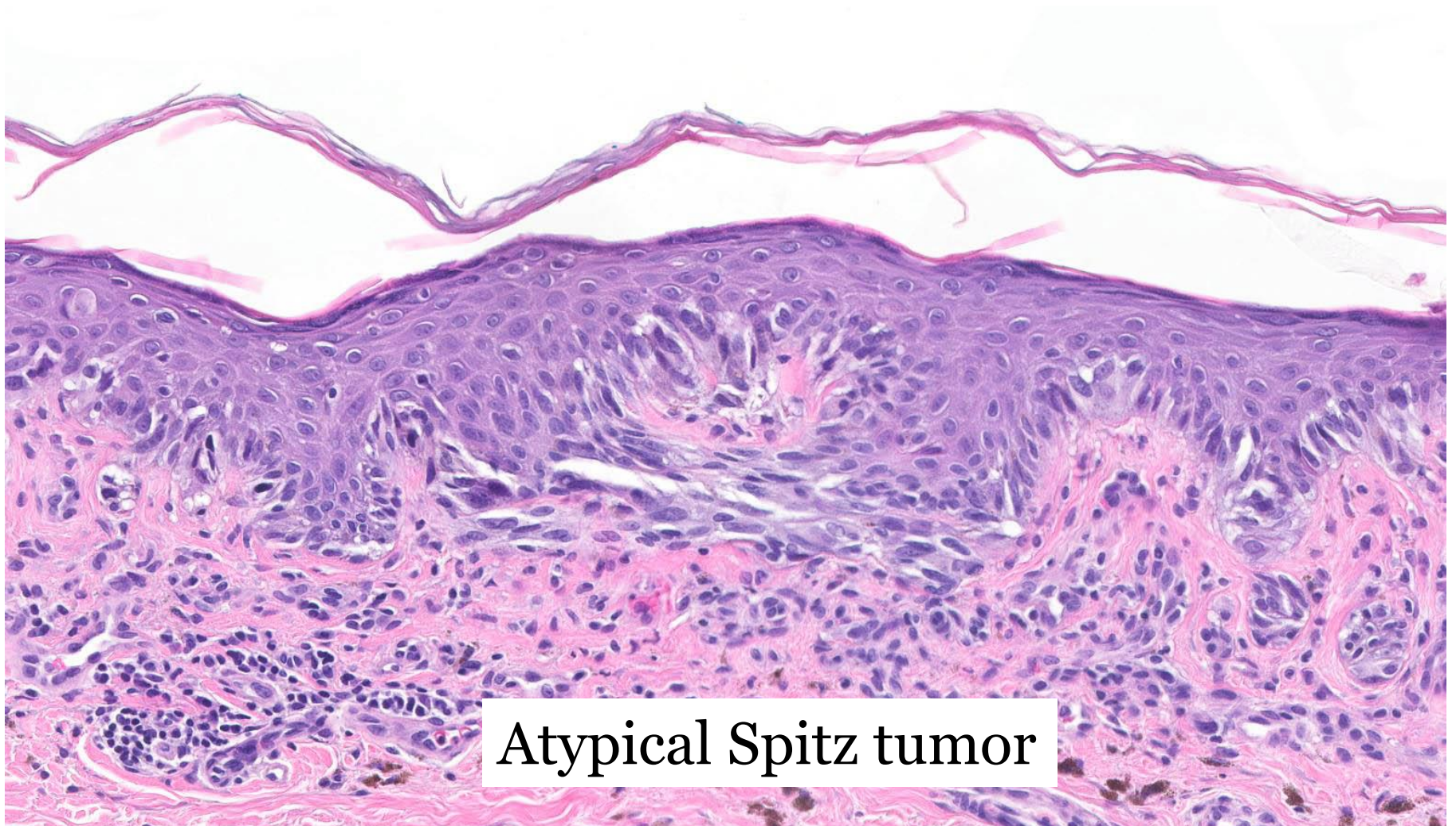


Dysplastic and  
Intermediate Nevi

# Irregular Junctional Nesting



# Irregular and Confluent Nesting



Atypical Spitz tumor

# Irregular and Confluent Nesting



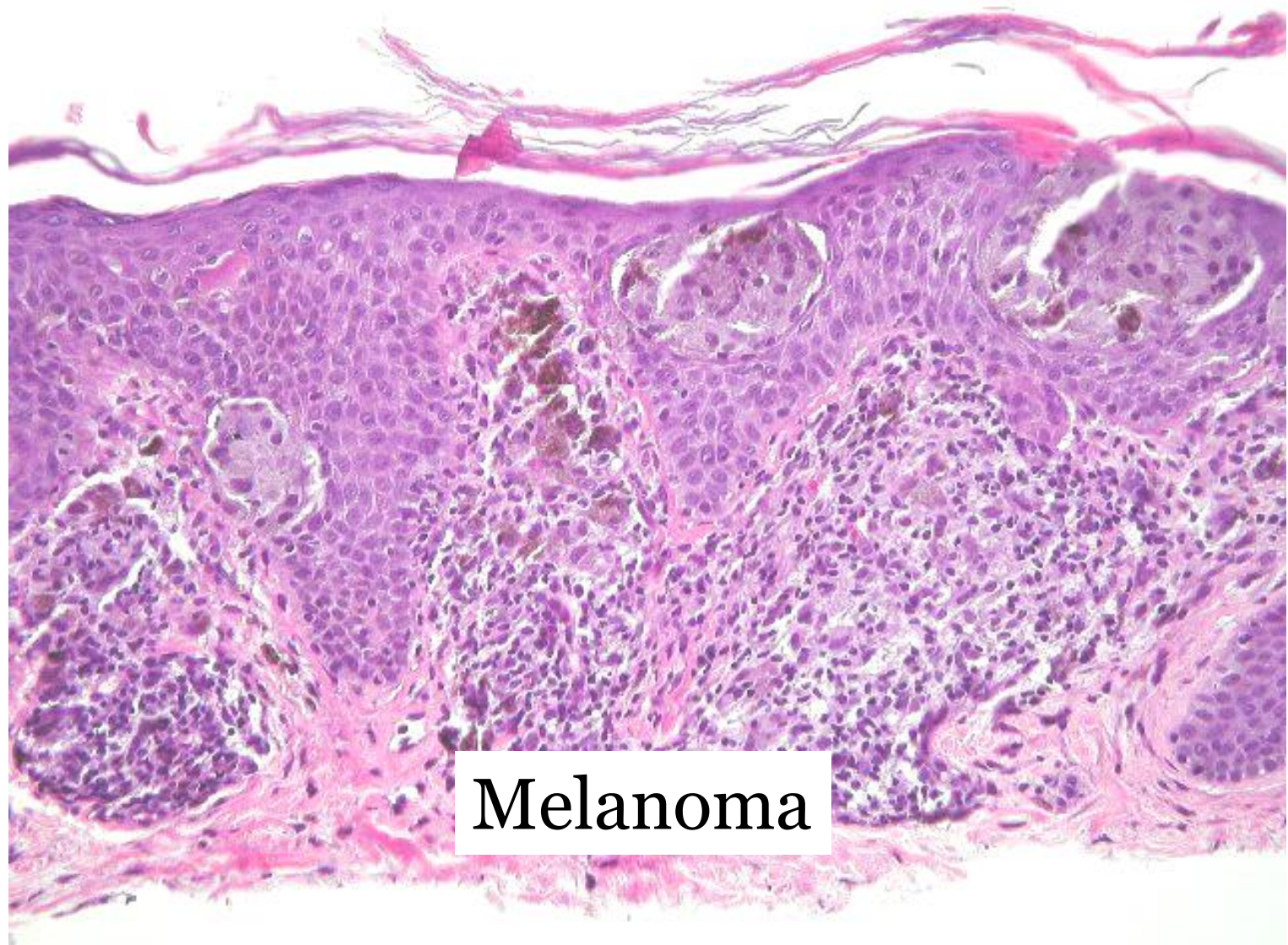
Atypical acral nevus

# Irregular and Confluent Nesting



Melanoma

# Irregular and Confluent Nesting



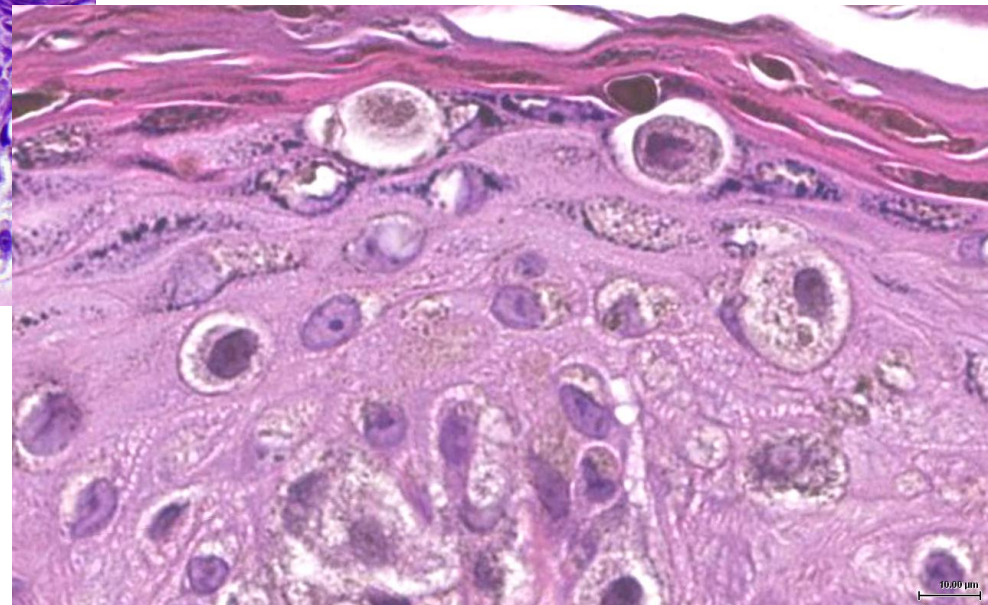
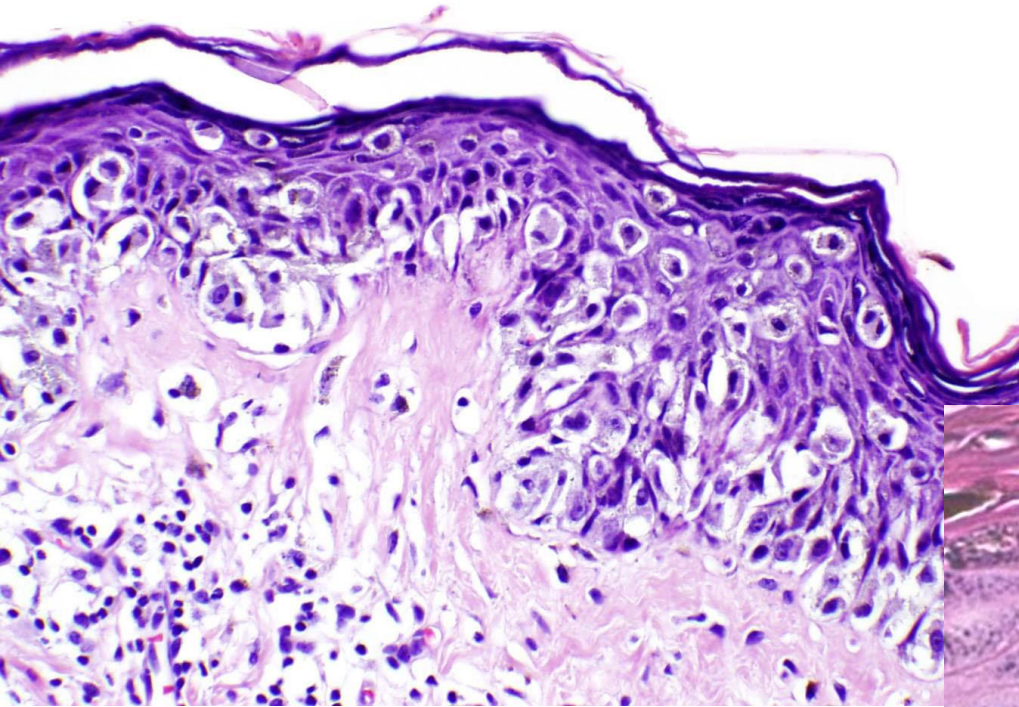
Melanoma

# Histopathological Criteria

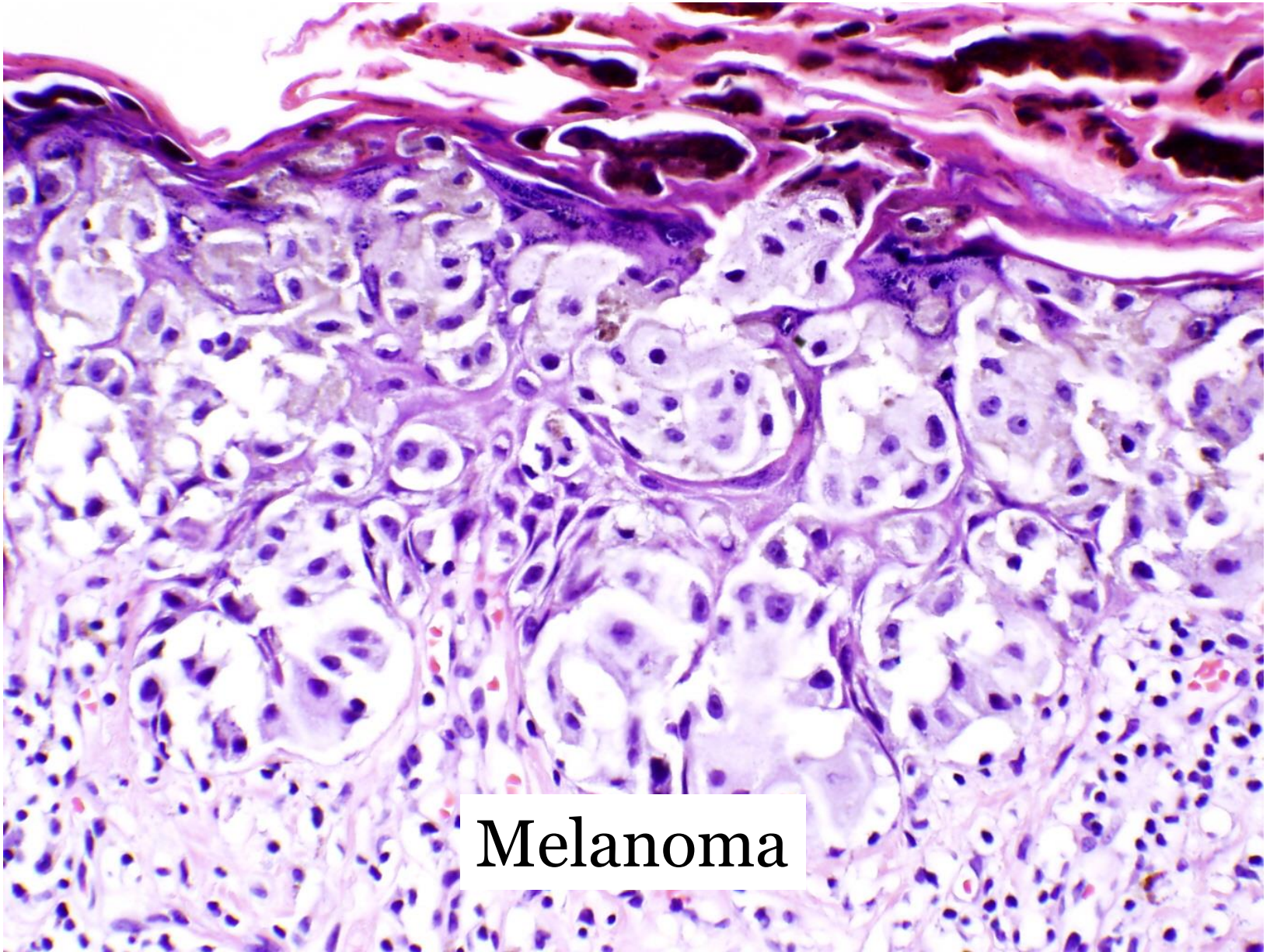
| Criterion              | Benign         | Intermediate    | Melanoma        |
|------------------------|----------------|-----------------|-----------------|
| <b>Pagetoid spread</b> | Usually absent | Absent<br>Focal | Usually present |

# Pagetoid Spread

Melanoma

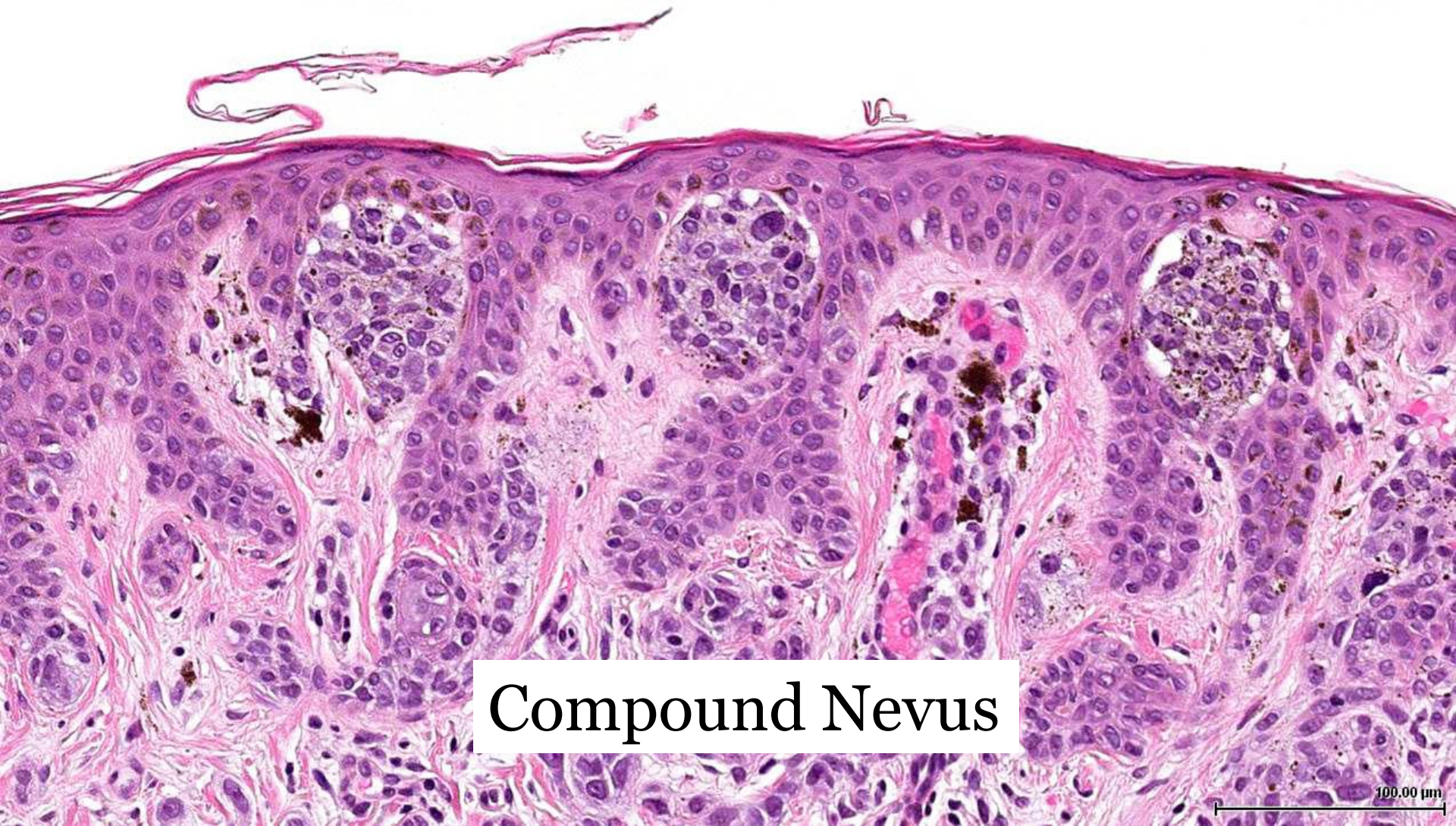


# Pagetoid Spread



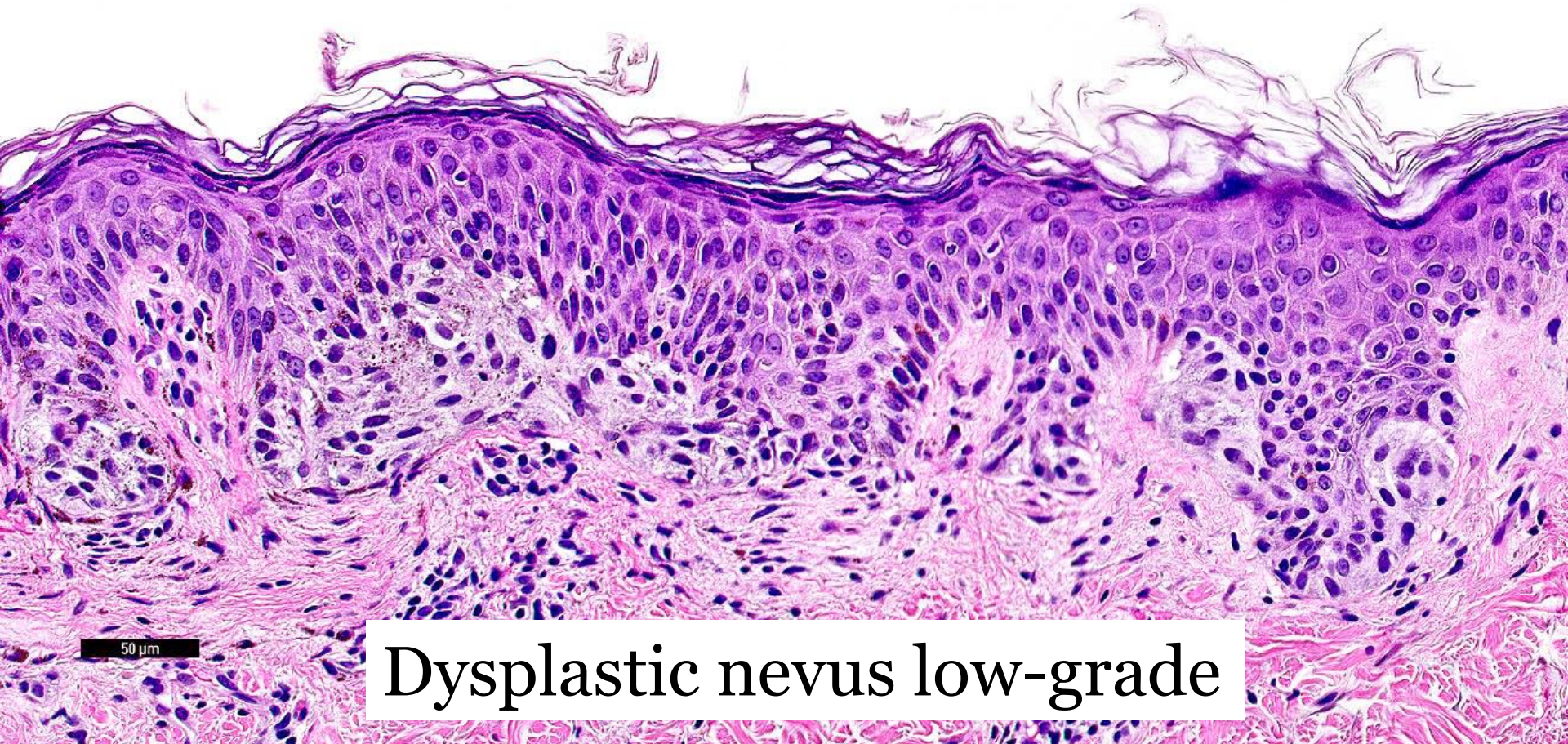
Melanoma

# No Pagetoid Spread



Compound Nevus

# No Pagetoid Spread



Dysplastic nevus low-grade

# Pagetoid Spread

Intermediate Lesions

# Pagetoid Spread

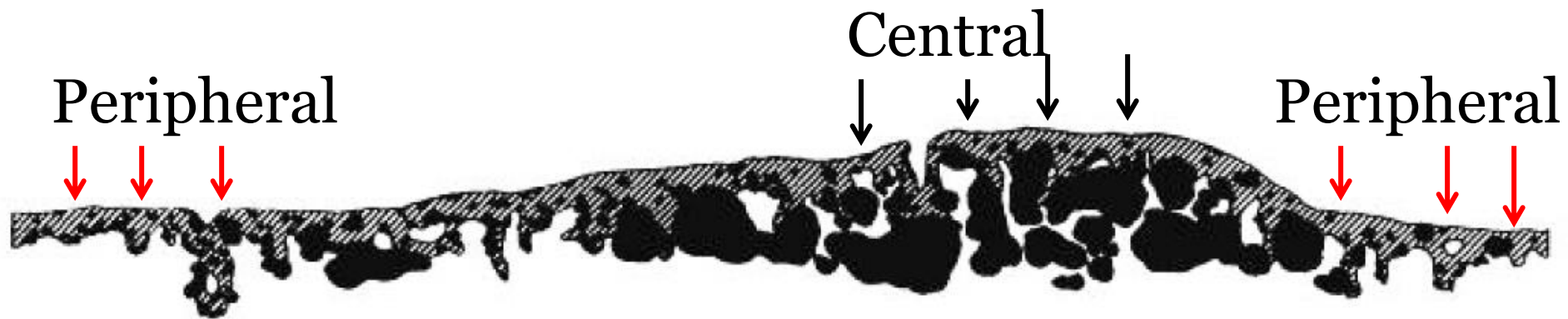
- Congenital nevi
- Spitz tumors
  - Pagetoid Spitz nevi
- Pigmented spindle cell nevi
- Acral nevi
- Other special site nevi: vulva
- Nevi with trauma, UV exposure
- Recurrent nevi



# Pagetoid Spread

| Criterion             | Nevi                            | Melanoma                   |
|-----------------------|---------------------------------|----------------------------|
| Distribution          | Focal                           | Diffuse                    |
| Central vs peripheral | Central                         | Central, <u>peripheral</u> |
| Density               | Sparse                          | Dense                      |
| Level                 | Suprabasal to mid epidermis     | Full thickness             |
| Atypia                | Absent, low-grade or high-grade | High-grade                 |

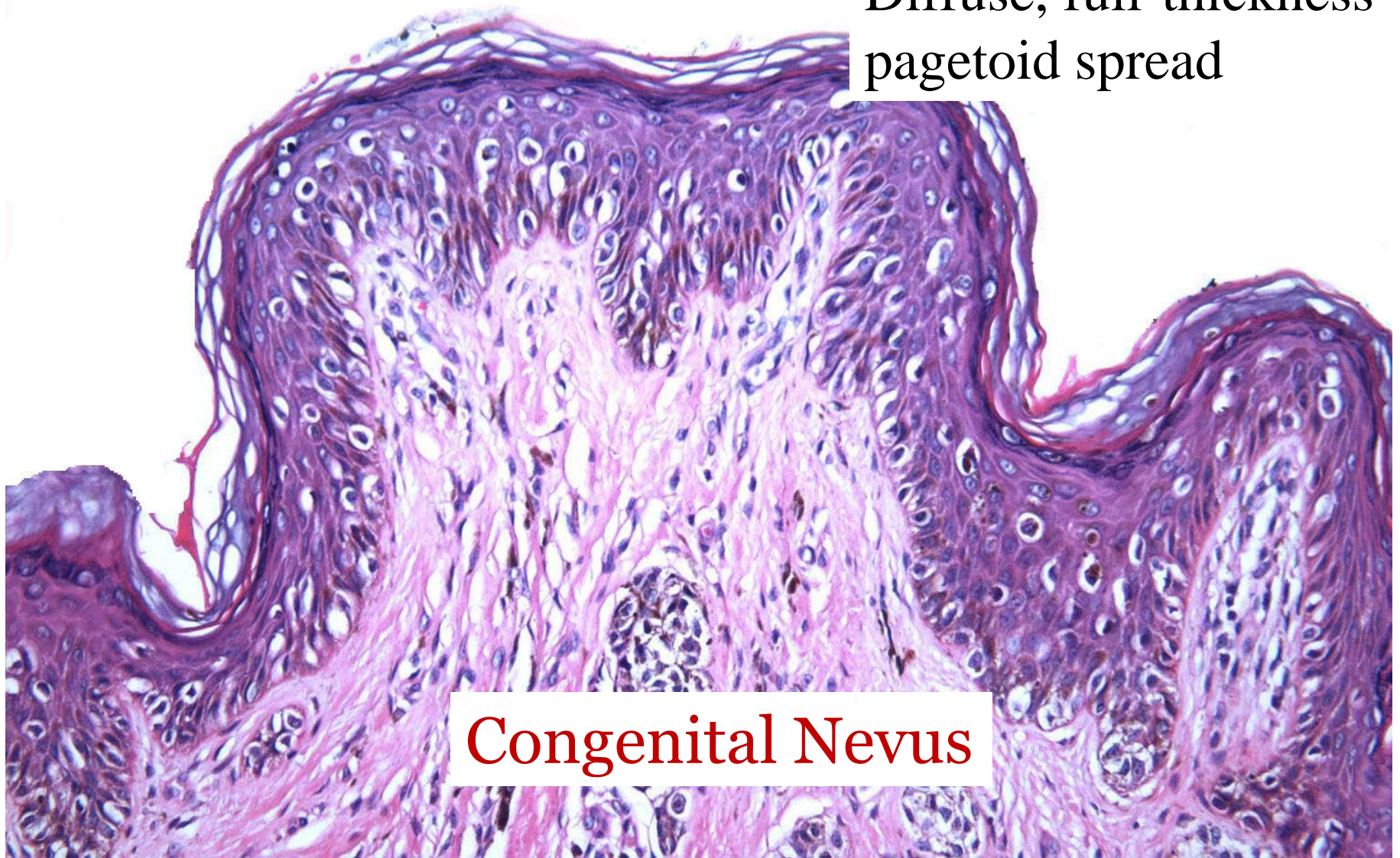
# Pagetoid Spread



Melanoma

# Pagetoid Spread

Diffuse, full-thickness  
pagetoid spread



**Congenital Nevus**

# Pagetoid Spread

Central, sparsely  
cellular, lower epidermis

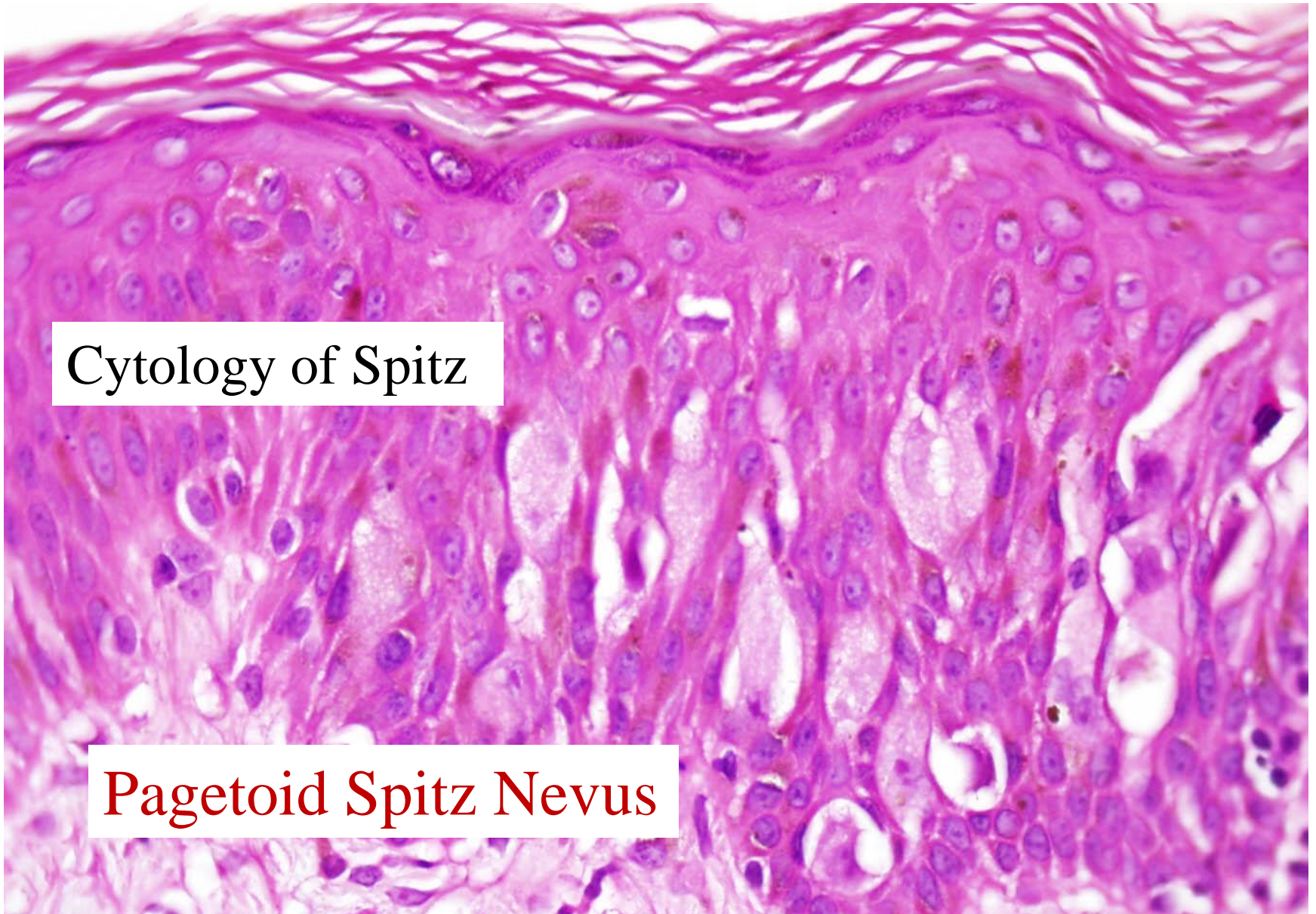


Pagetoid Spitz Nevus

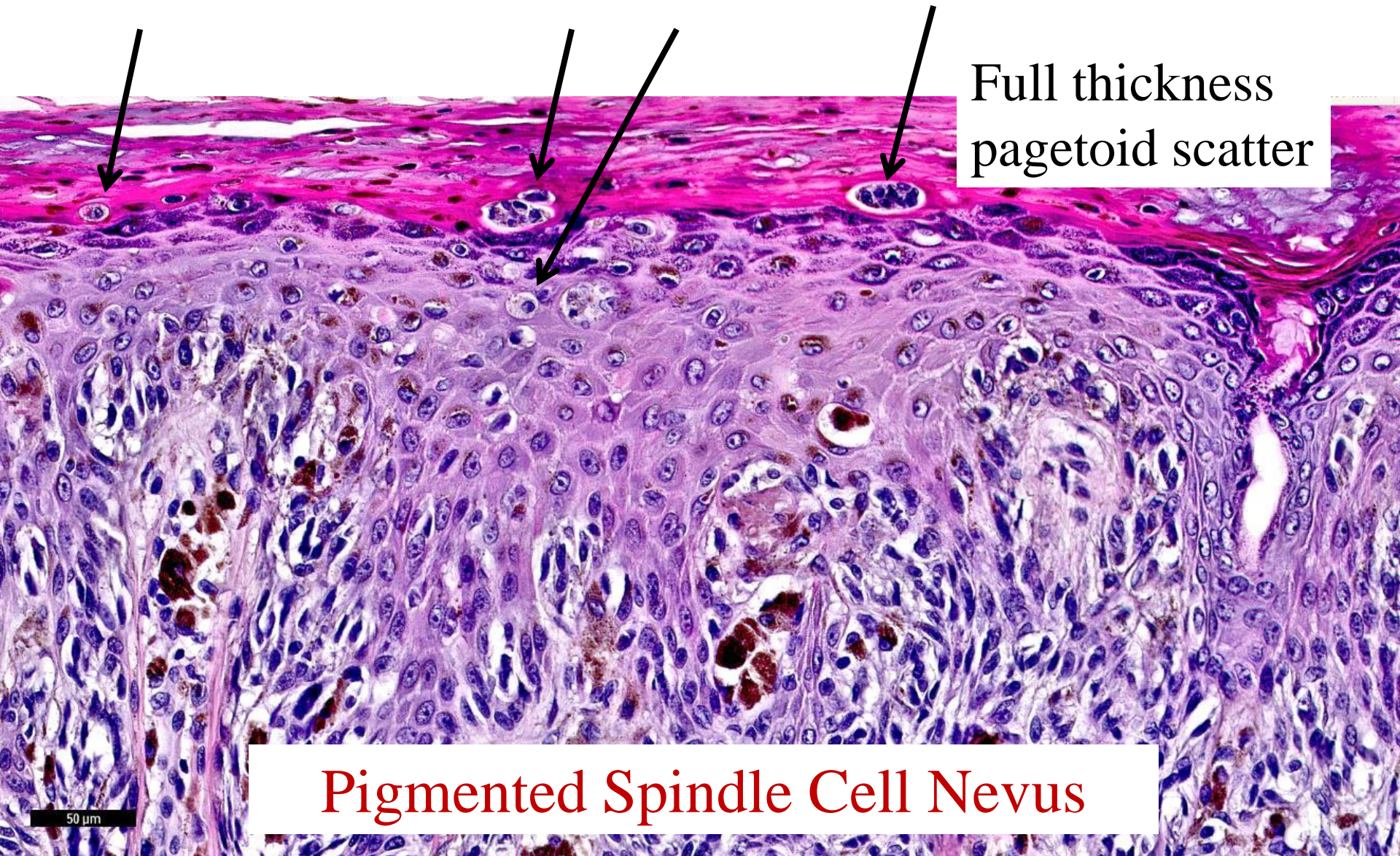
# Pagetoid Spread

Cytology of Spitz

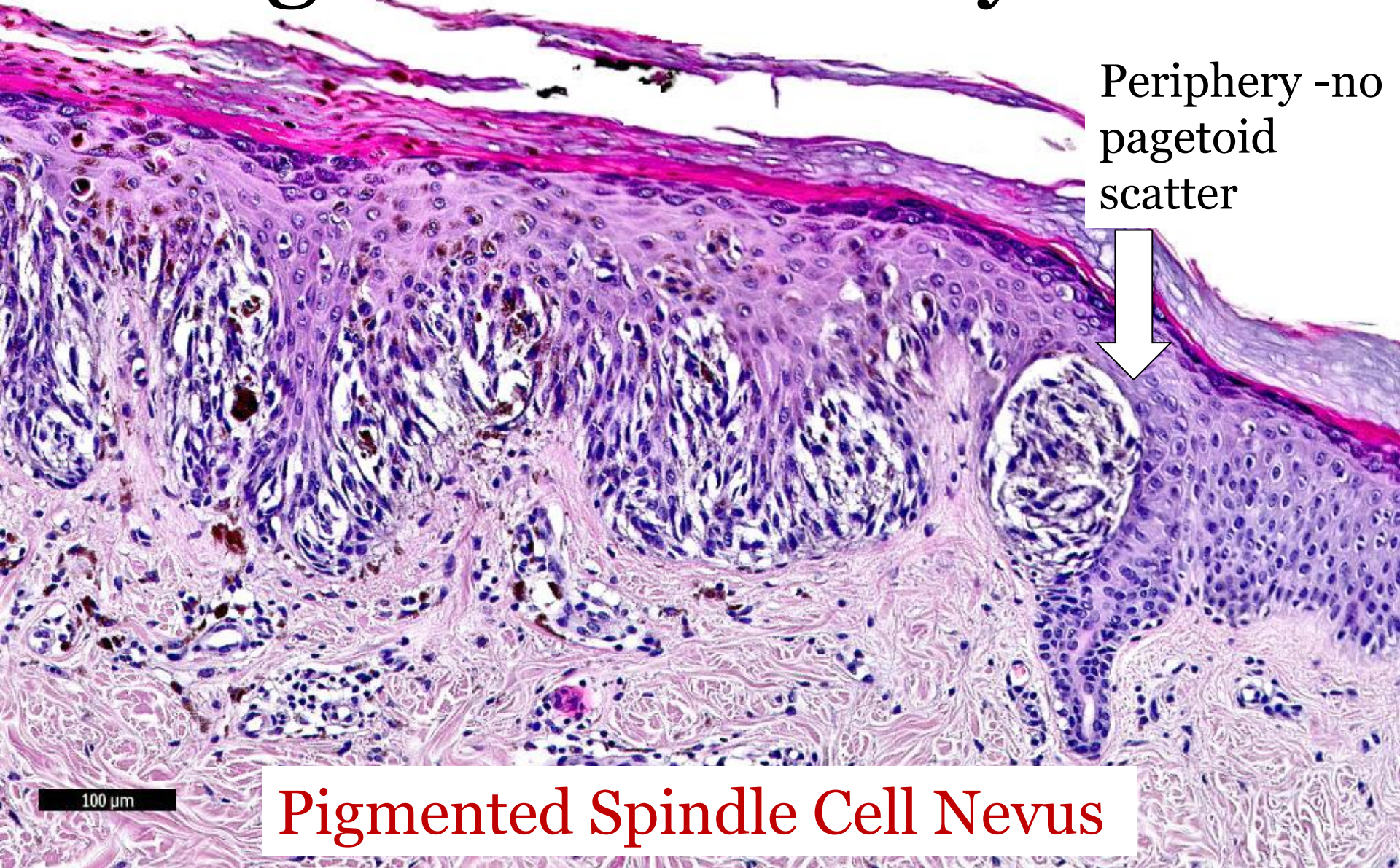
Pagetoid Spitz Nevus



# Pagetoid Spread

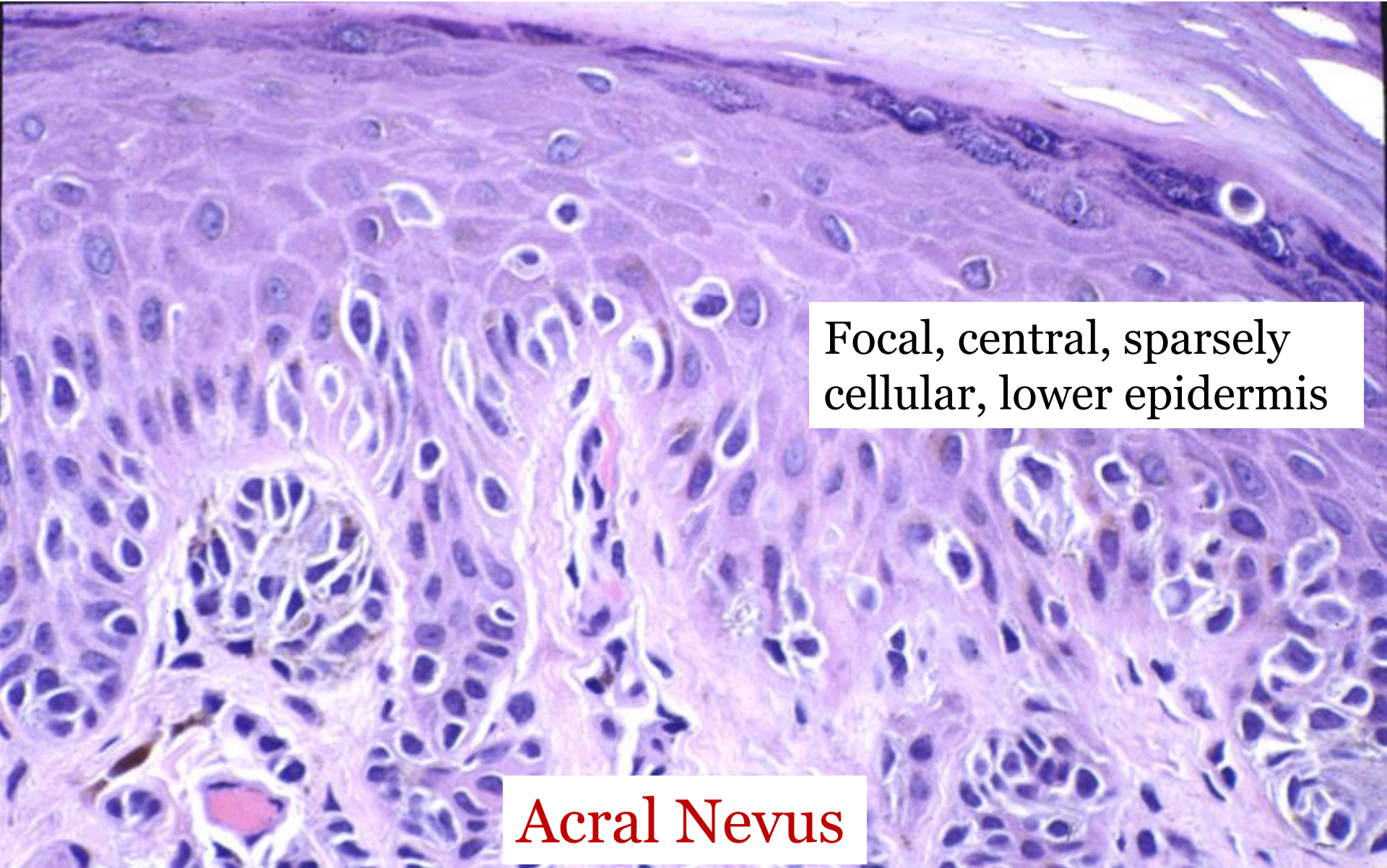


# Pagetoid Melanocytosis



Pigmented Spindle Cell Nevus

# Pagetoid Melanocytosis



Focal, central, sparsely  
cellular, lower epidermis

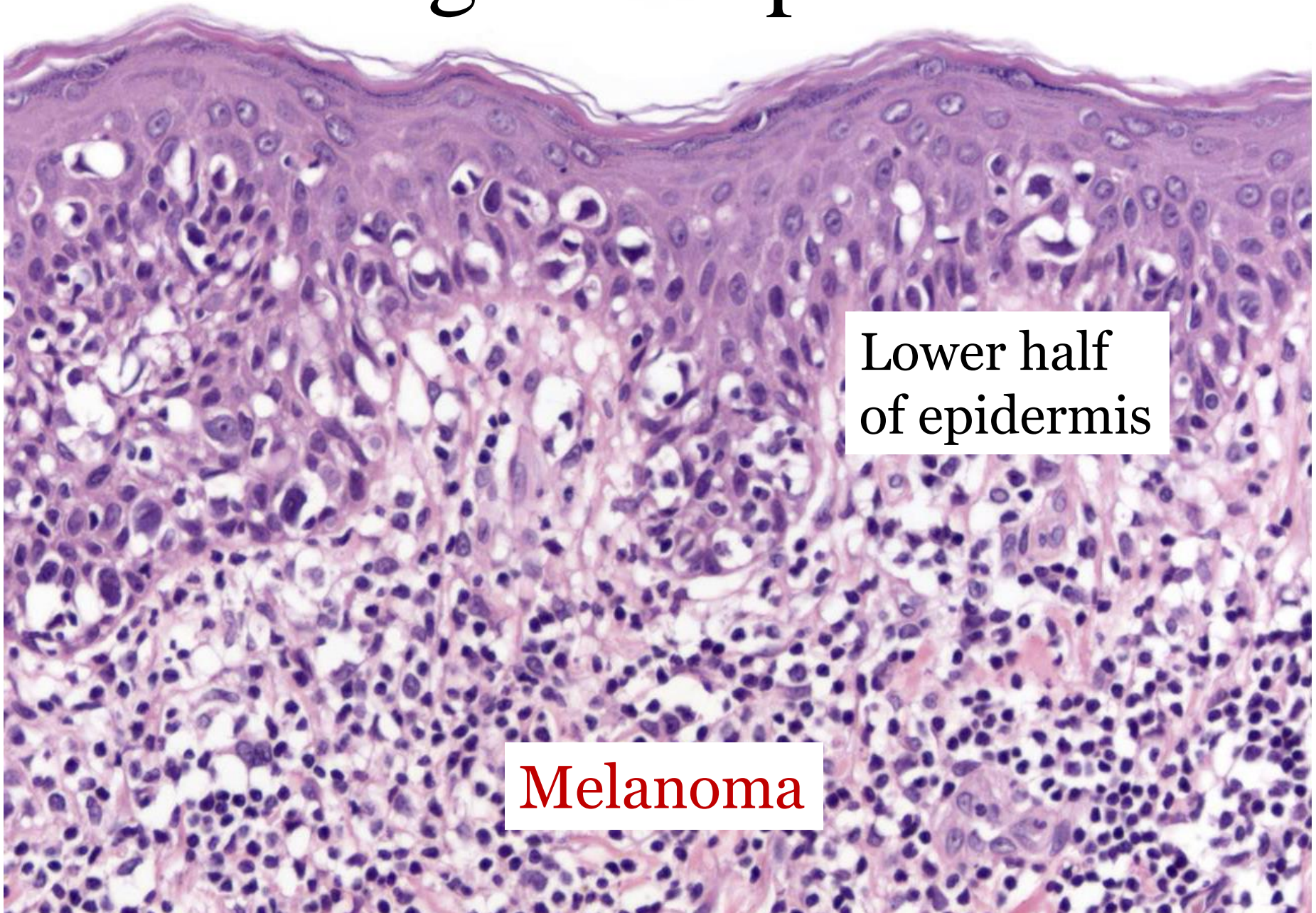
**Acral Nevus**

# Pagetoid Spread

Exceptions  
Melanoma!



# Pagetoid Spread

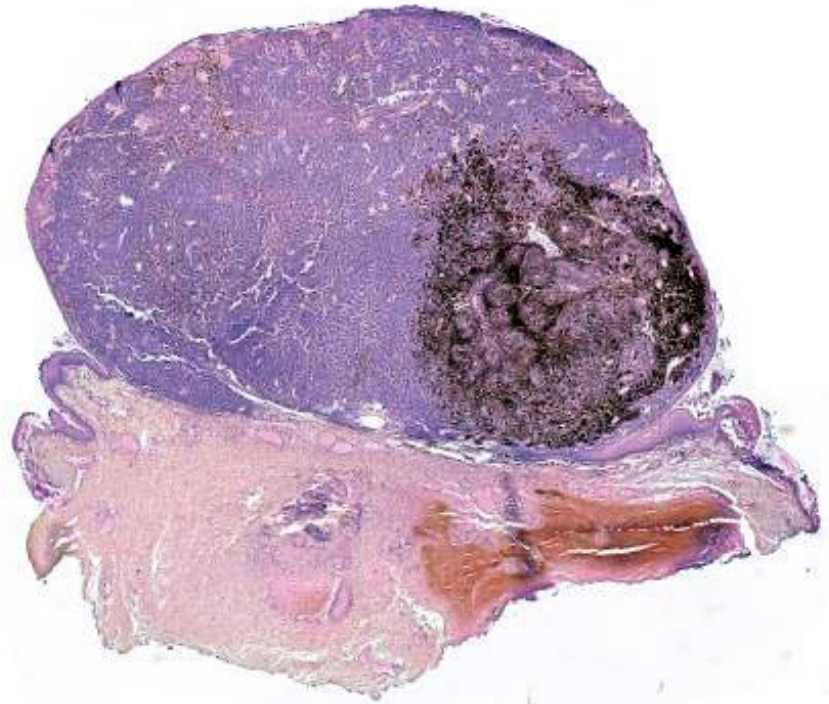


Lower half  
of epidermis

Melanoma

# Evaluation of the Dermal Component

- Diameter
- Breslow thickness
- Symmetry
- Circumscription
- Architecture
  - Nodule
- Maturation
- Mitotic rate
- Regression



# Histopathological Criteria

| Criterion                | Benign         | Intermediate               | Melanoma          |
|--------------------------|----------------|----------------------------|-------------------|
| <b>Breslow thickness</b> | Not applicable | Useful for dermal neoplasm | Prognostic factor |

# Histopathological Criteria

| Criterion         | Benign | Intermediate                  | Melanoma          |
|-------------------|--------|-------------------------------|-------------------|
| <b>Ulceration</b> | Absent | May be present<br>Risk marker | Prognostic factor |

# Ulceration



Melanoma

# Histopathological Criteria

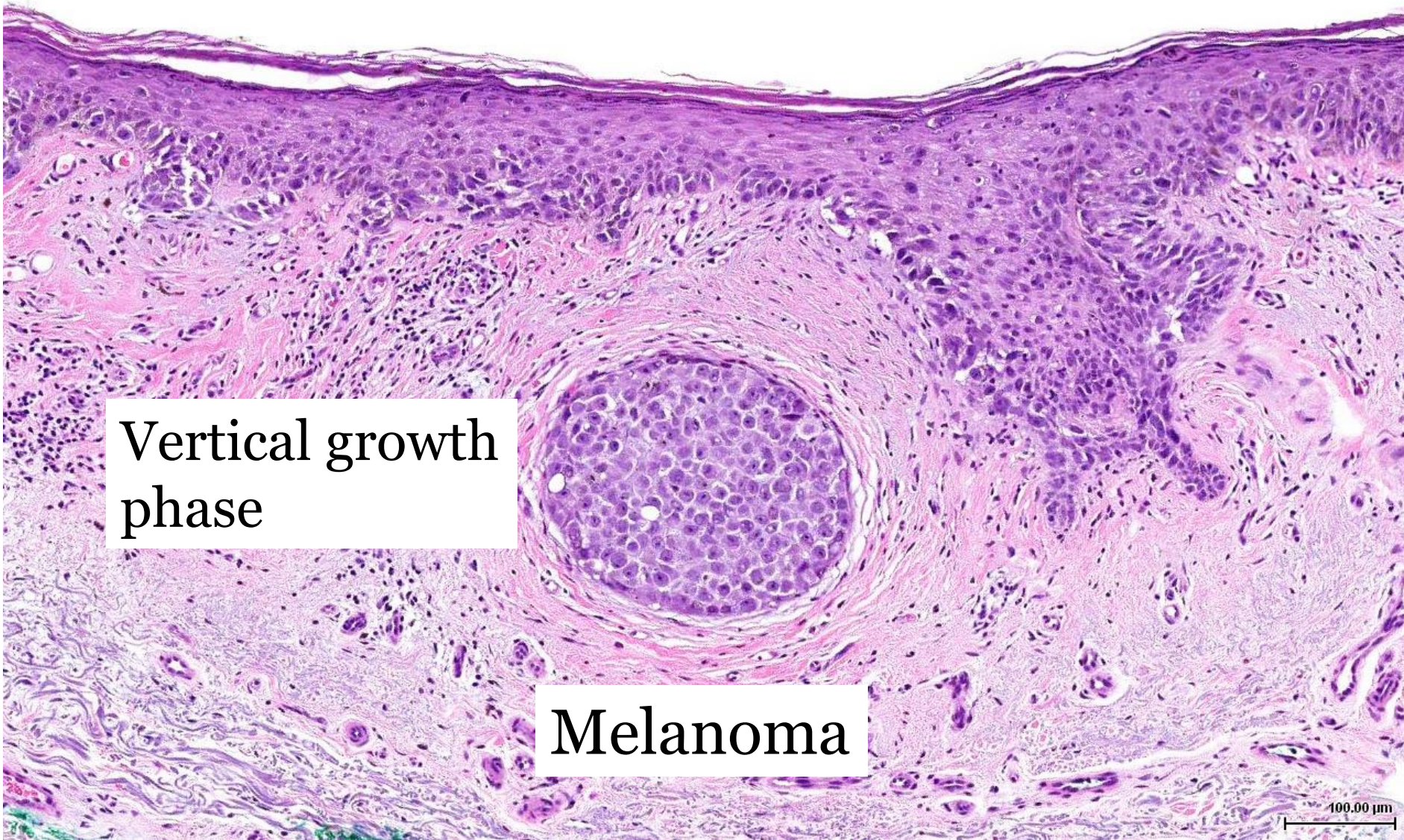
| Criterion  | Benign | Intermediate                  | Melanoma             |
|--|--------|-------------------------------|----------------------|
| <b>Dermal<br/>expansile nodule<br/>(Vertical growth<br/>phase)</b> | Absent | May be present<br>Risk marker | Prognostic<br>factor |

# Expansile Nodule

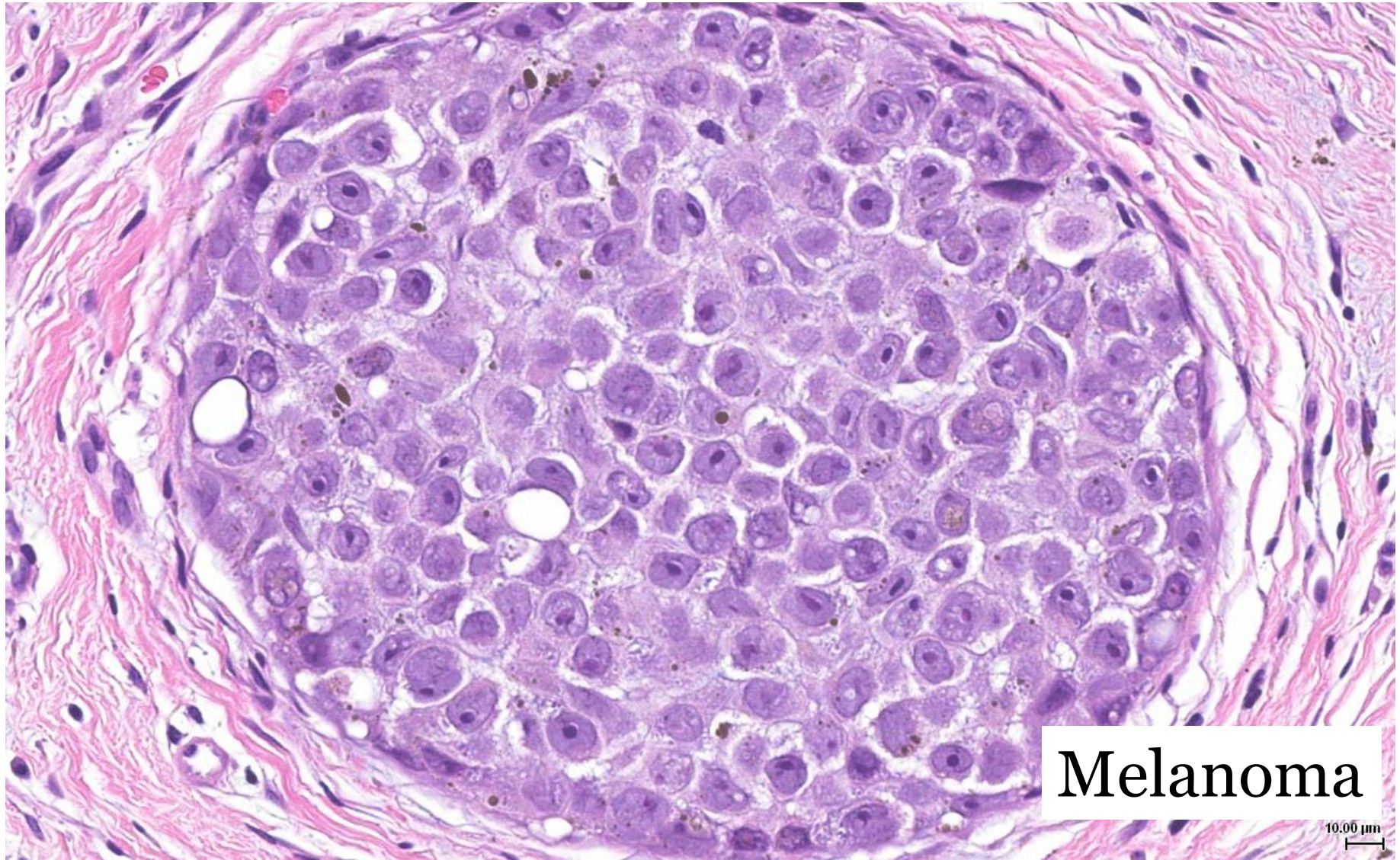
Vertical growth  
phase

Melanoma

100.00 µm



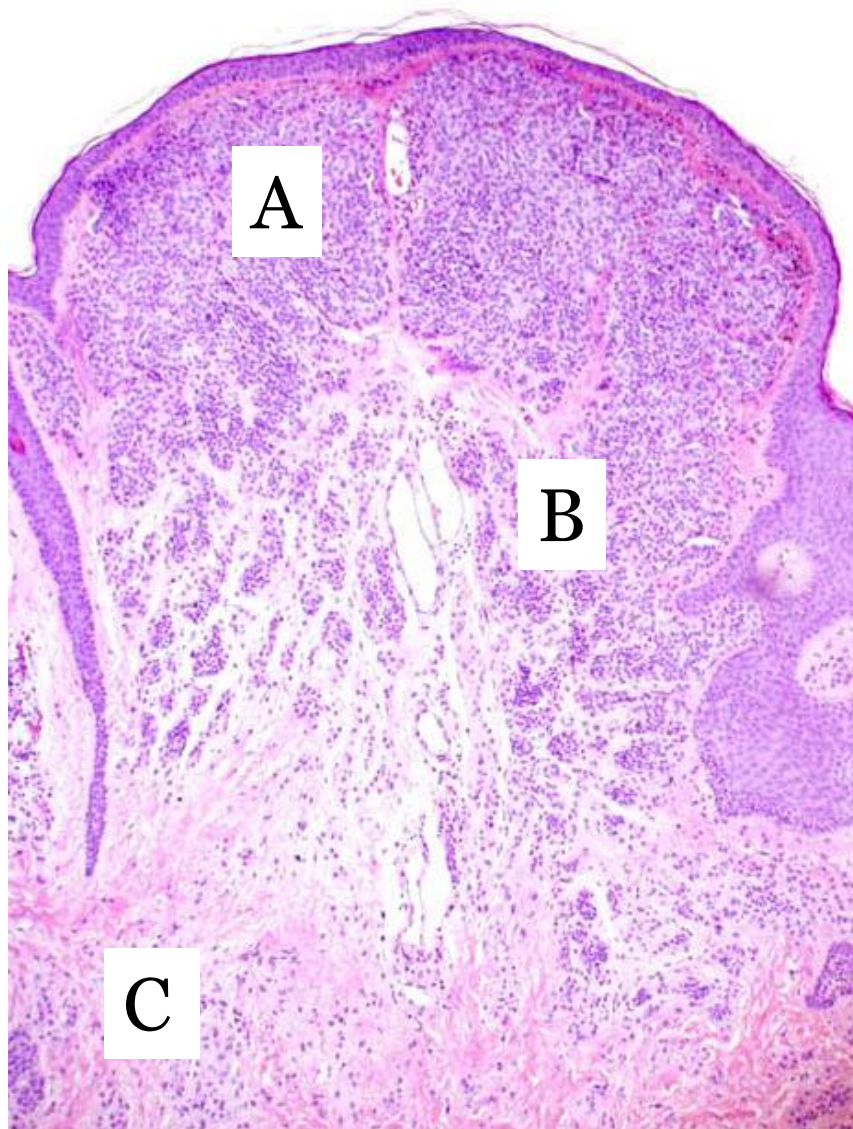
# Confluent Nesting in Dermis



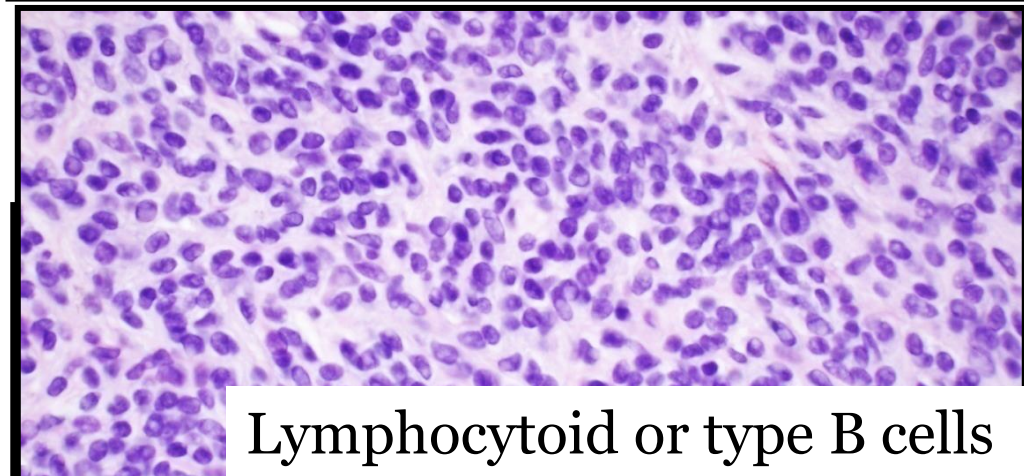
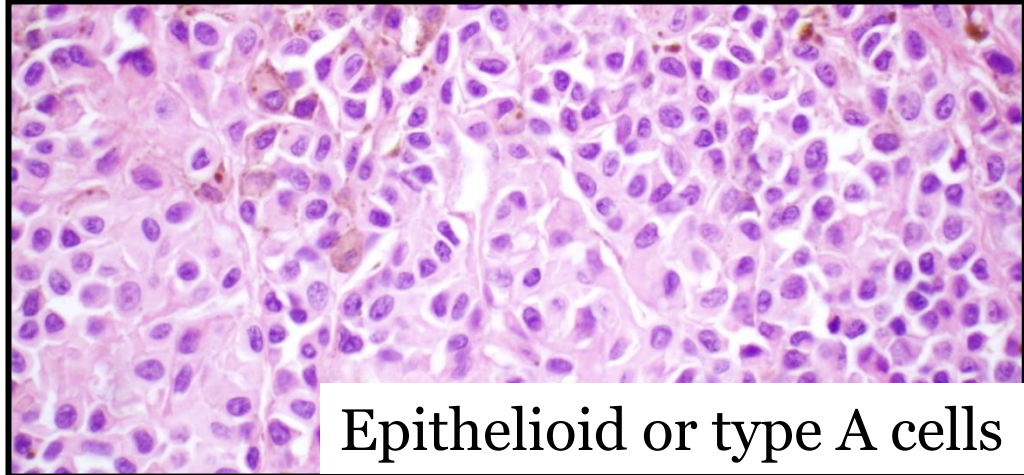
# Histopathological Criteria

| Criterion         | Benign  | Intermediate          | Melanoma |
|-------------------|---------|-----------------------|----------|
| <b>Maturation</b> | Present | Present or diminished | Absent   |

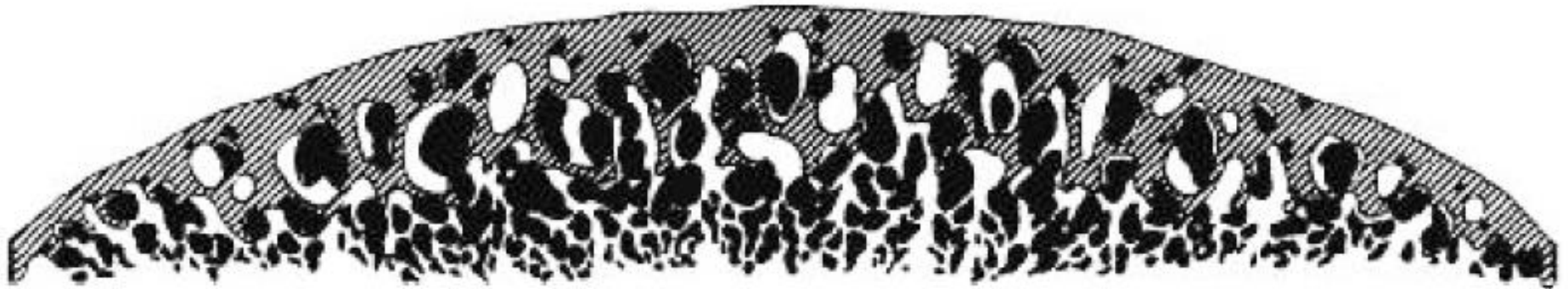
# Maturation



Dermal Nevus

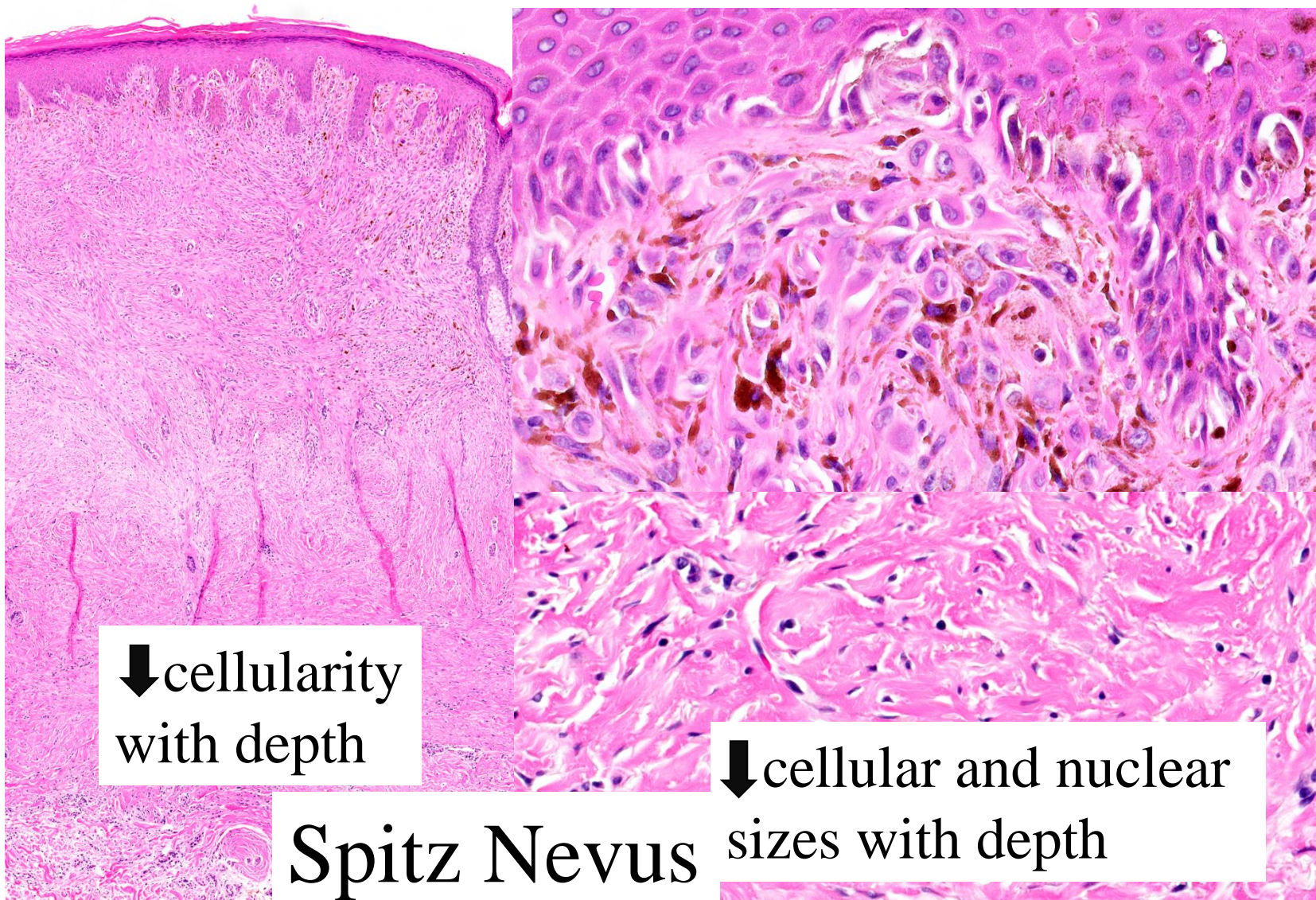


# Maturation



Spitz Nevus

# Maturation



↓cellularity  
with depth

↓cellular and nuclear  
sizes with depth

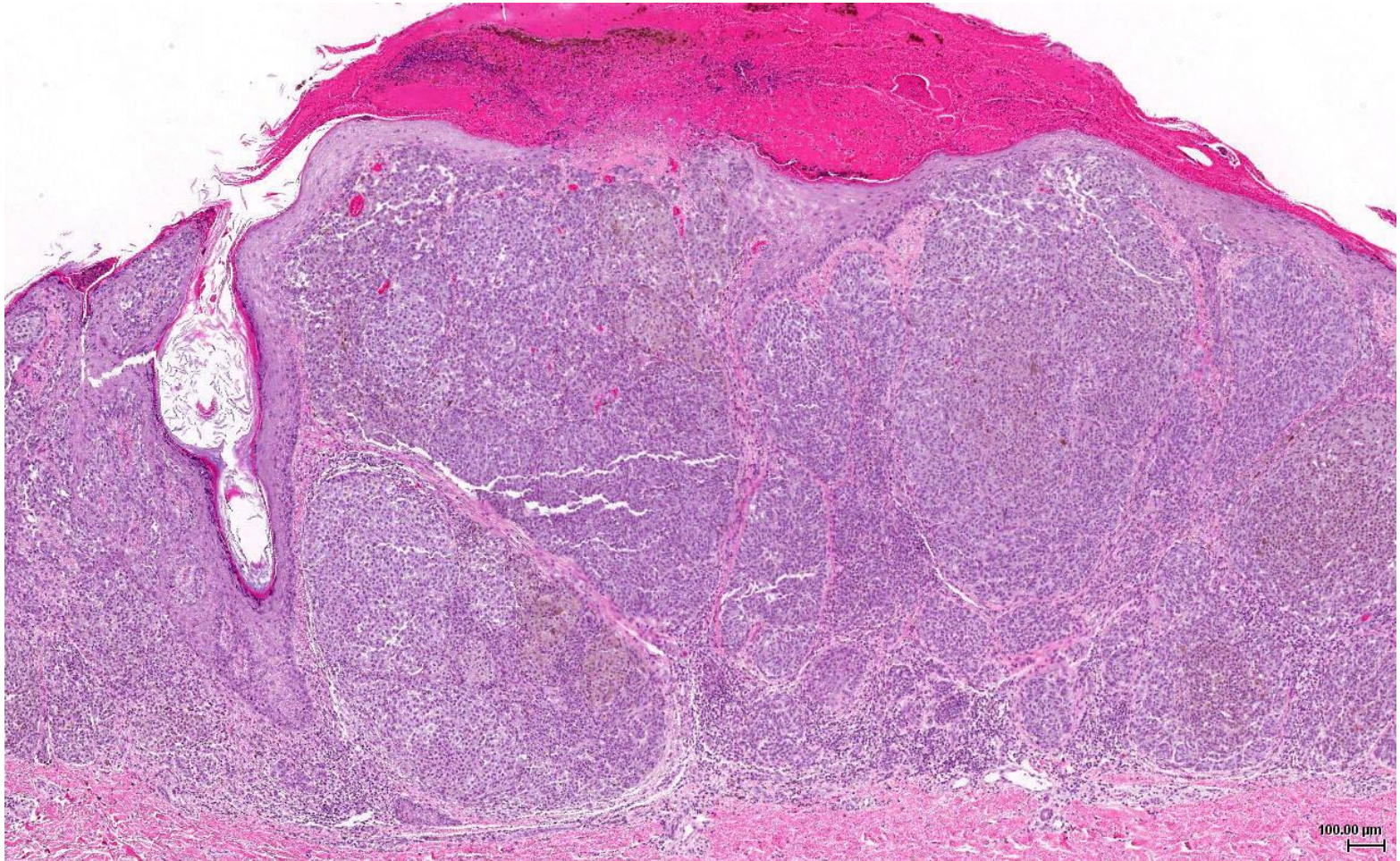
Spitz Nevus

# No Maturation



Melanoma

# No Maturation



Melanoma

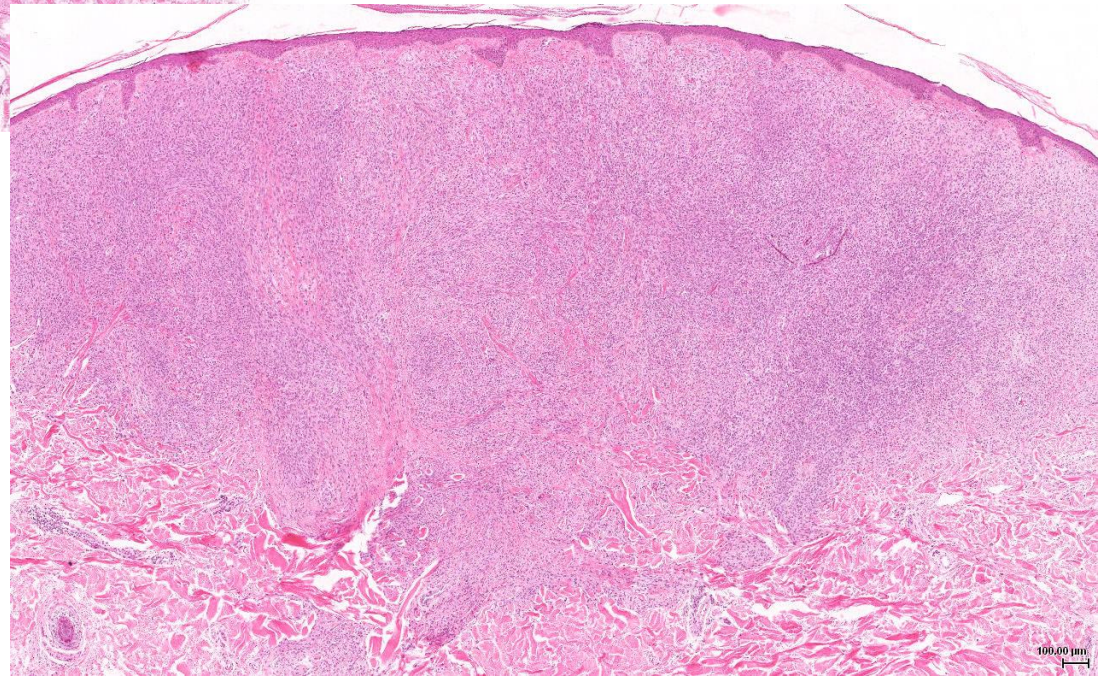
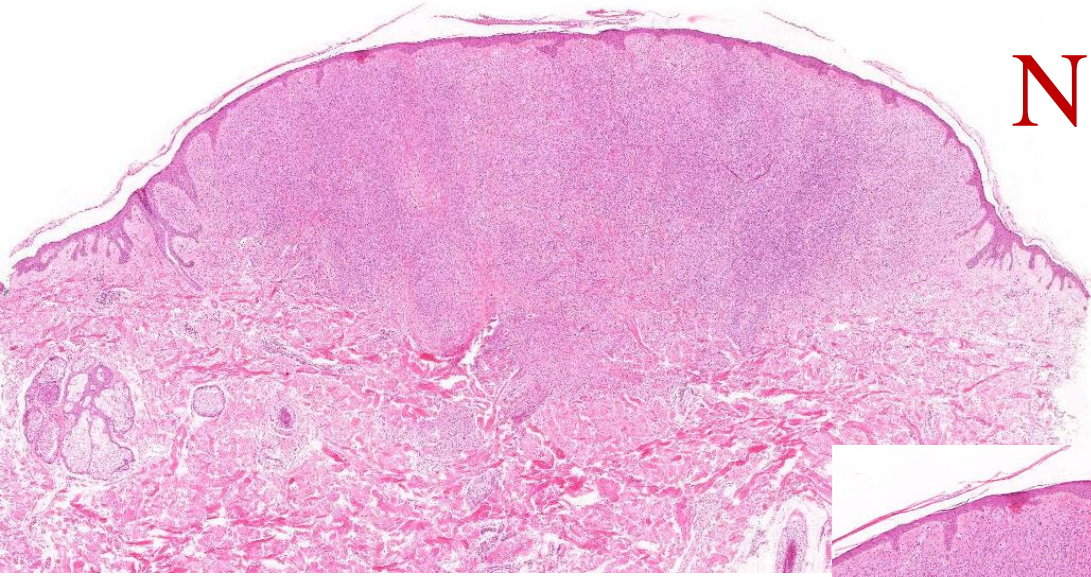
# Maturation

Exceptions



# Partial Maturation

**Nevoid Melanoma!**



# Histopathological Criteria

| Criterion         | Benign          | Intermediate   | Melanoma   |
|-------------------|-----------------|----------------|--|
| <b>Regression</b> | Halo-associated | May be present | Partial regression common, Extensive regression rare |

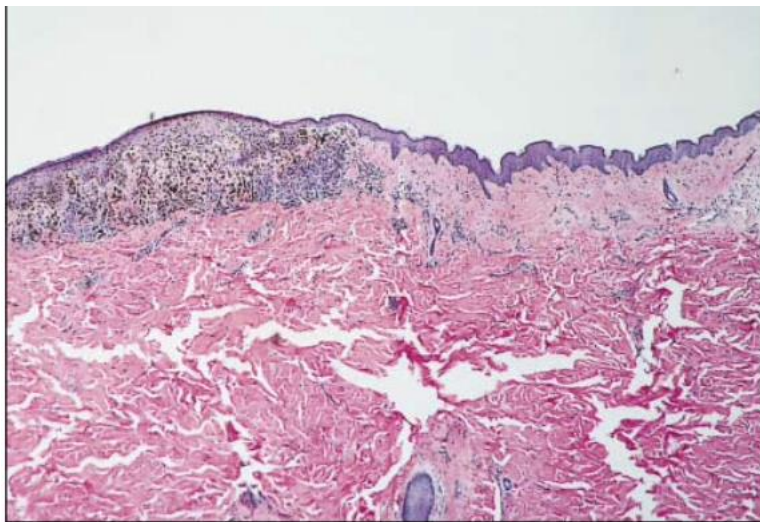
# Histological Characteristics of Metastasizing Thin Melanomas

## *A Case-Control Study of 43 Cases*

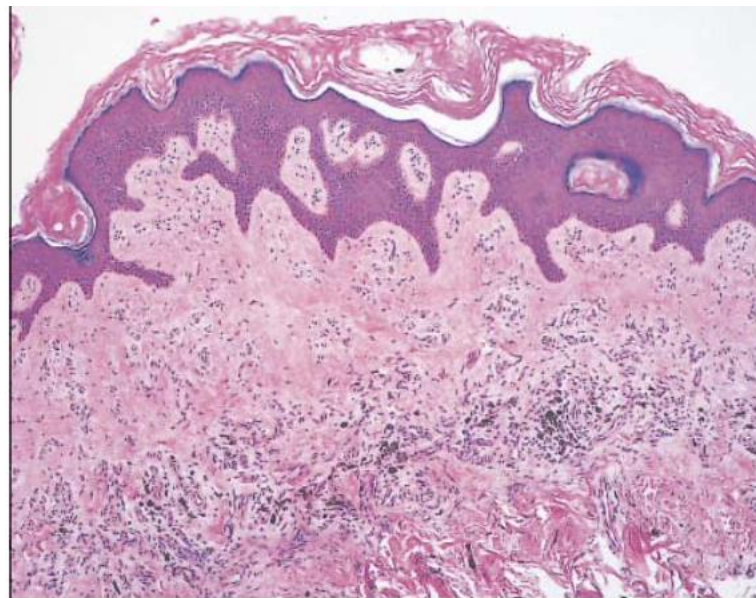
Joan Guitart, MD; Lori Lowe, MD; Michael Piepkorn, MD, PhD; Victor G. Prieto, MD, PhD; Michael S. Rabkin, MD, PhD; Salve G. Ronan, MD†; Christopher R. Shea, MD; Victor A. Tron, MD; Wain White, MD; Raymond L. Barnhill, MD

Arch Dermatol 2002

## Extensive Regression ( $\geq 50\%$ of Tumor)



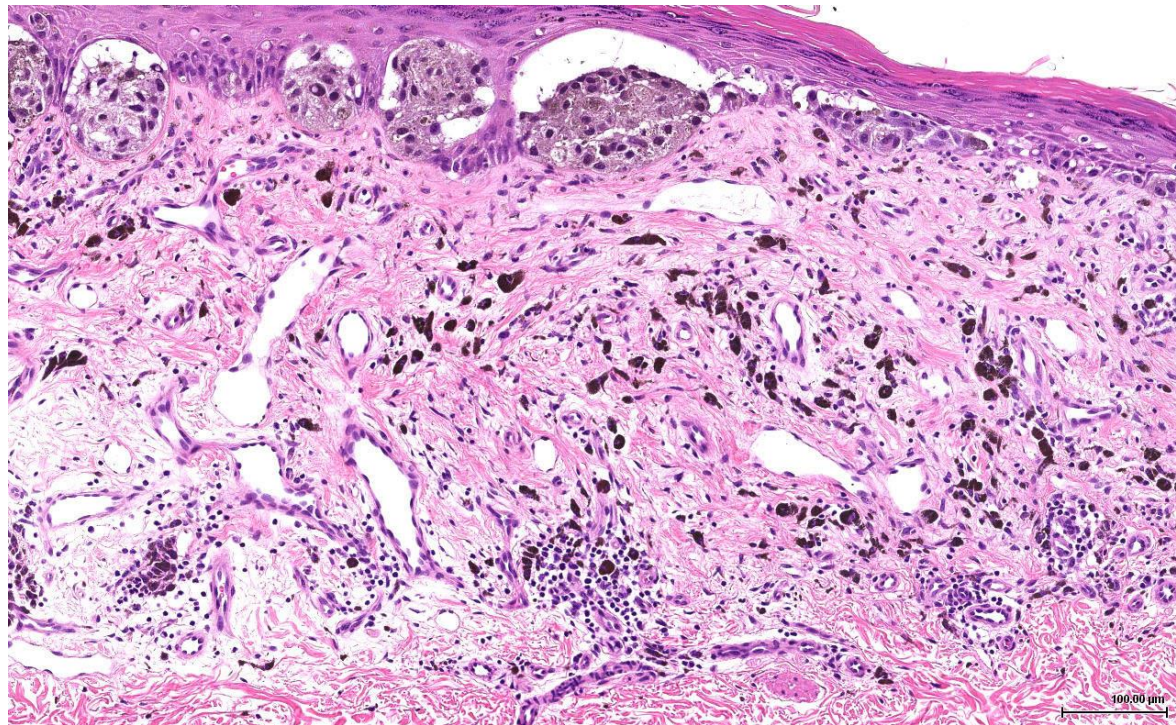
**Figure 3.** Low-power view of a metastasizing thin melanoma showing extensive areas of regression and melanoderma (hematoxylin-eosin, original magnification  $\times 50$ ).



**Figure 5.** Expansion of the papillary dermis in an area of extensive regression and fibrosis with scattered lymphocytes and melanophages (hematoxylin-eosin, original magnification  $\times 50$ ).

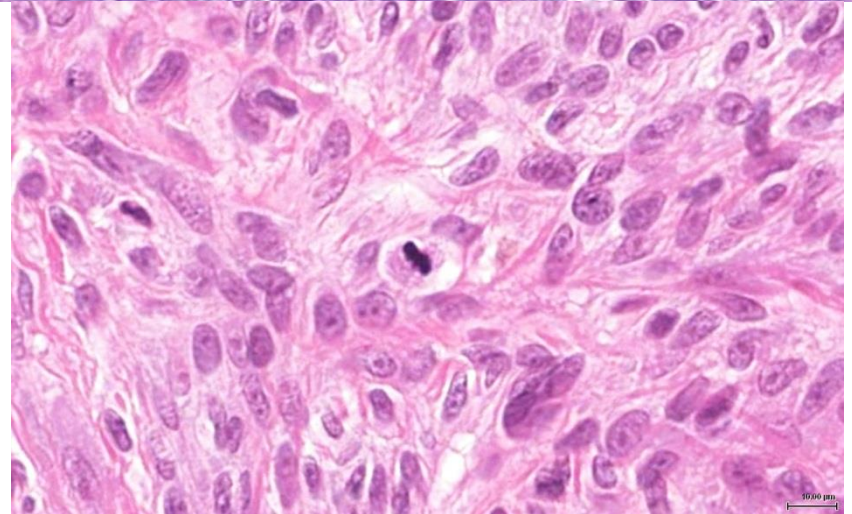
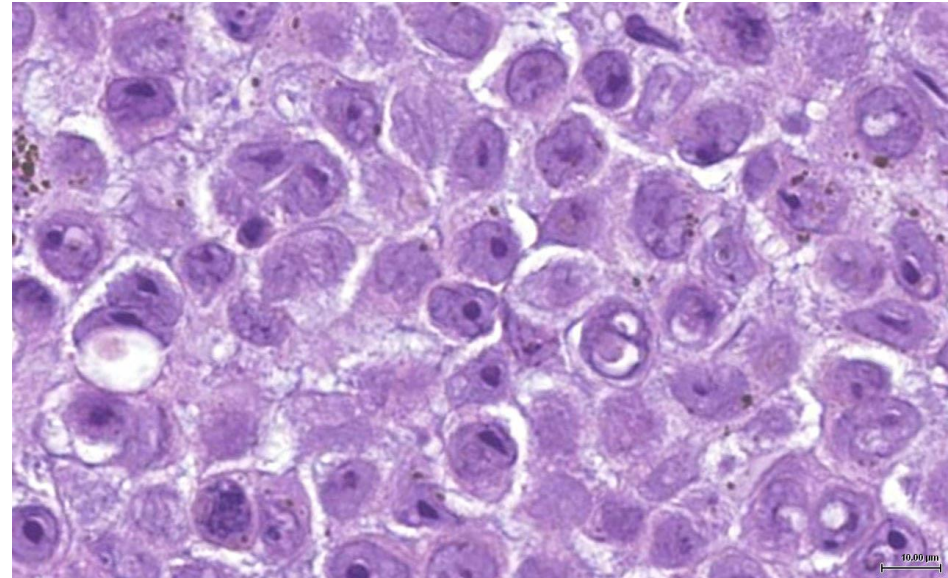
# Histopathological Criteria

- pT1a melanoma
- Breslow 0.4 mm
- Extensive regression  
> 50% of tumor
- No ulceration
- No mitoses
- No vertical growth  
phase



# Microscopic Examination at High Magnification

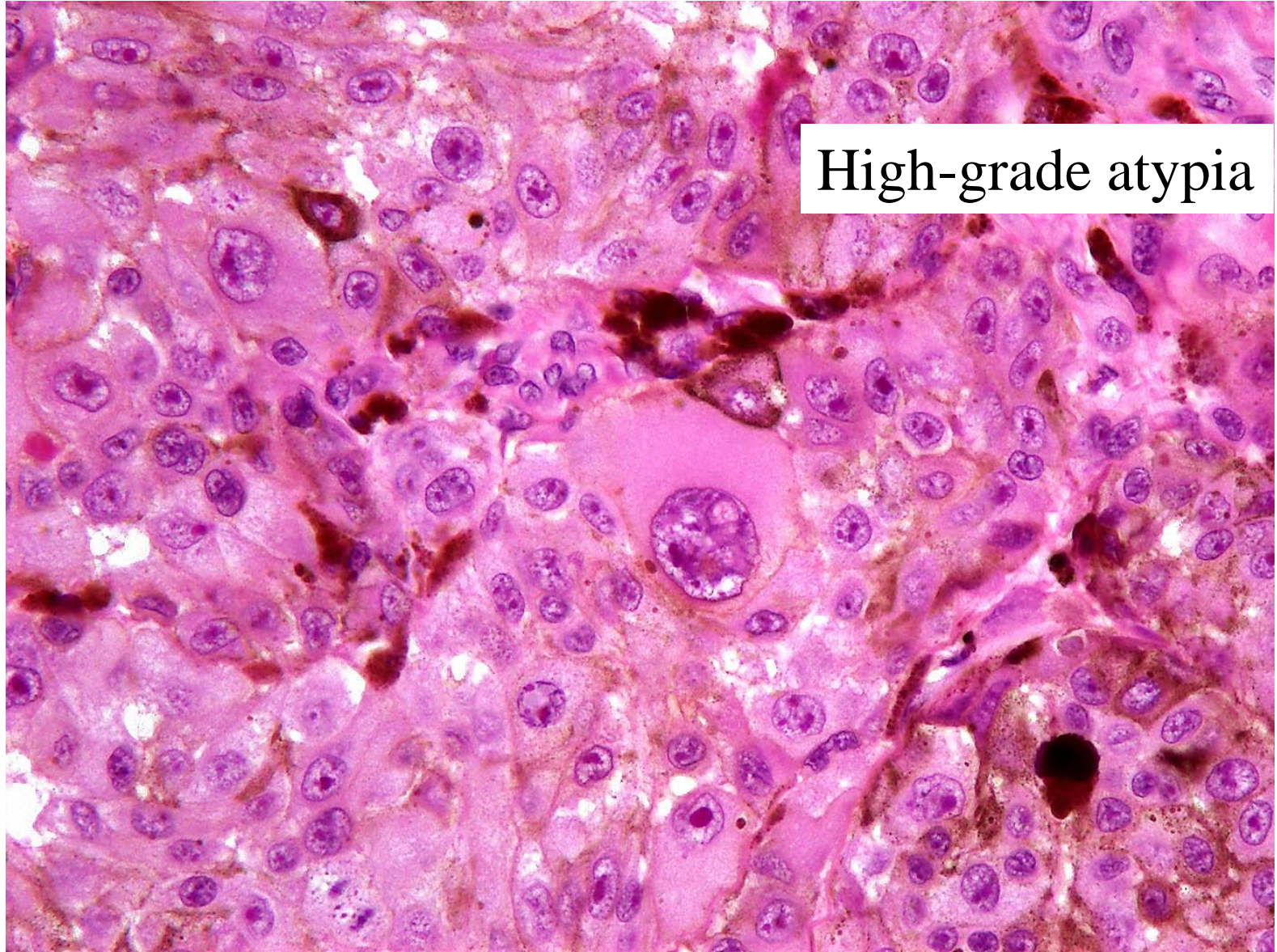
- Cytological characteristics
- Cytological atypia
- Mitotic activity



# Histopathological Criteria

| Criterion   | Benign            | Intermediate                                       | Melanoma   |
|---|-------------------|--|------------|
| <b>Cytological atypia</b><br><br>Nuclear enlargement<br>Pleomorphism<br>Hyperchromatism<br>Irregular nuclear contours<br>Uneven/thickened nuclear membranes<br>Chromatin coarse<br>Prominent nucleoli<br>Increased nuclear to cytoplasmic ratio | None to low-grade | Low- to high-grade<br><br>(Mild, moderate, severe) | High-grade |

# Cytological Atypia



High-grade atypia

# Histopathological Criteria

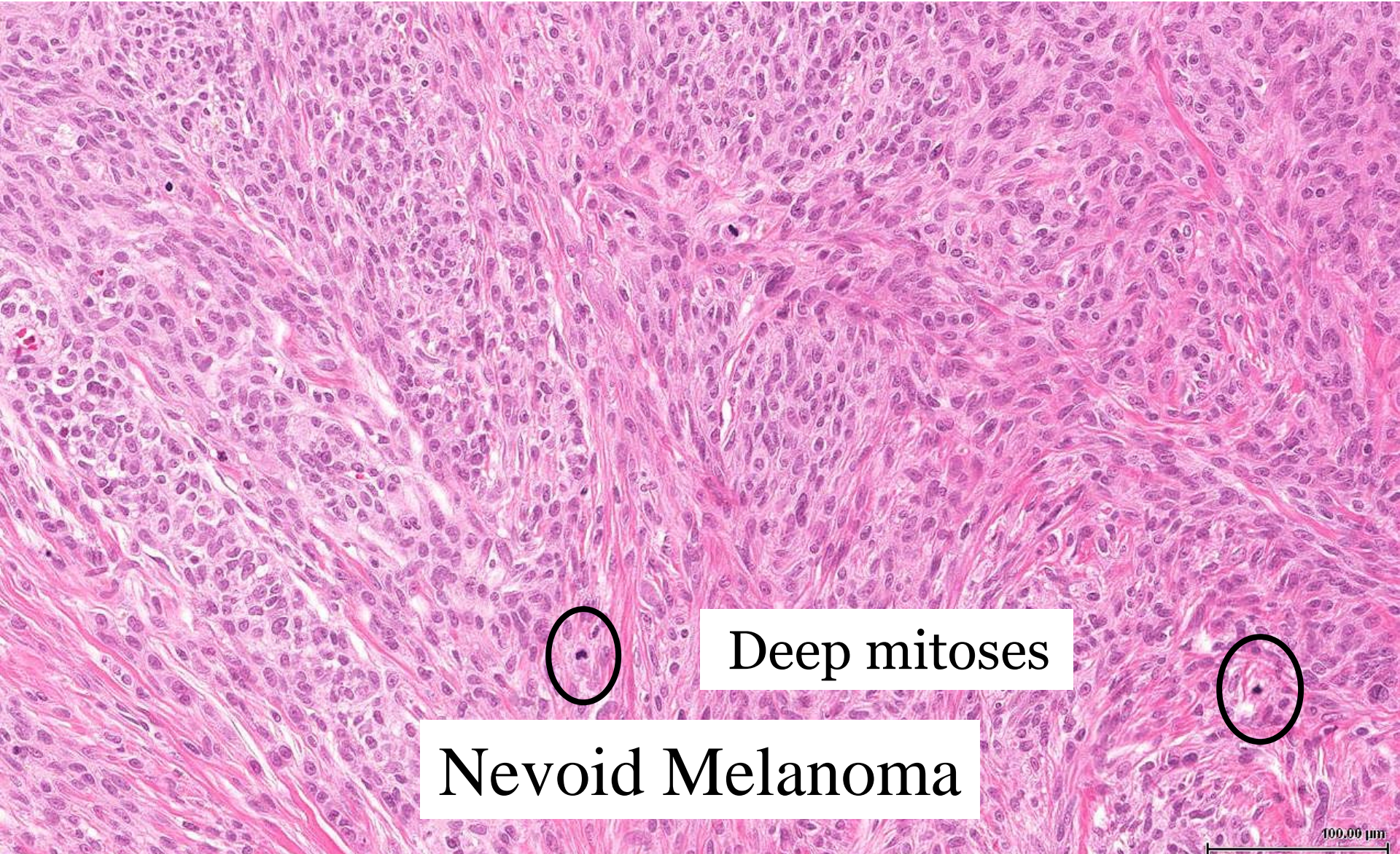
| Criterion                                | Benign   | Intermediate  | Melanoma  |
|--|--|---|---|
| <b>Mitoses</b><br>Junctional<br>Dermal** | <ul style="list-style-type: none"><li>• Usually absent</li><li>• Superficial</li></ul> | Increased<br>Mitotic rate<br>1 to 2/mm <sup>2</sup> | <ul style="list-style-type: none"><li>• Increasing frequency</li><li>• Hot spots</li><li>• Deep</li></ul> |

# Mitoses

Mitotic rate:  
6 per mm<sup>2</sup>

Nevoid Melanoma

# Mitoses



Deep mitoses

Nevoid Melanoma

# Histopathological Criteria

How many sensitive and specific criteria?

- for pT1, esp. pT1a, almost all sensitive criteria are needed for distinction from atypical nevi and to diminish overdiagnosis
- increasing numbers of specific criteria assure true biologic melanoma
- presence of only a few sensitive criteria may promote overdiagnosis of dysplastic nevi as melanoma

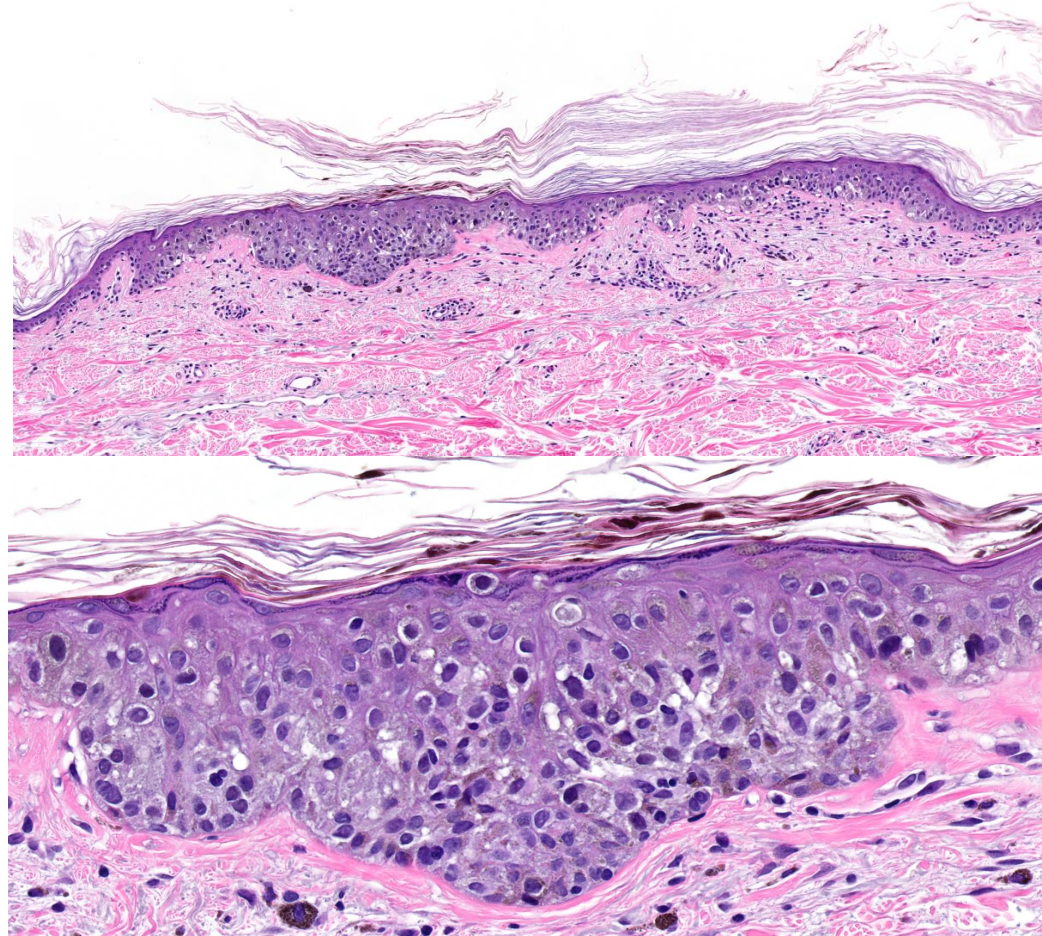
# Histopathological Criteria

How many are needed?

| Sensitive Criteria                    | Specific Criteria  |
|---------------------------------------|--|
| Diameter 4 to 10 mm                   | Diameter $\geq$ 10 mm                                    |
| Poor circumscription                  | Ulceration   |
| Pagetoid spread                       |  |
| Marked variation in melanocytic nests | Thickness $>$ 0.8 mm, esp., subcutaneous fat involvement |
| Confluence of nests                   | Expansile nodule in dermis (VGP)                         |
| Absence of maturation                 | Regression $\geq$ 50% of tumor                           |
| Cytological atypia                    | High-grade cytological atypia                            |
| Mitoses, 1 to 2 per mm <sup>2</sup>   | Mitotic rate $\geq$ 5 to 6 per mm <sup>2</sup>           |
| Necrosis                              |  |

# In situ or pT1a Melanoma?

- Sensitive criteria
- Disorder, pagetoid spread
- High-grade atypia
- Specific criteria:
- No, diameter 2 mm
- No, thickness 0.1 mm
- No expansile nodule
- No ulceration
- No dermal mitoses
- No regression



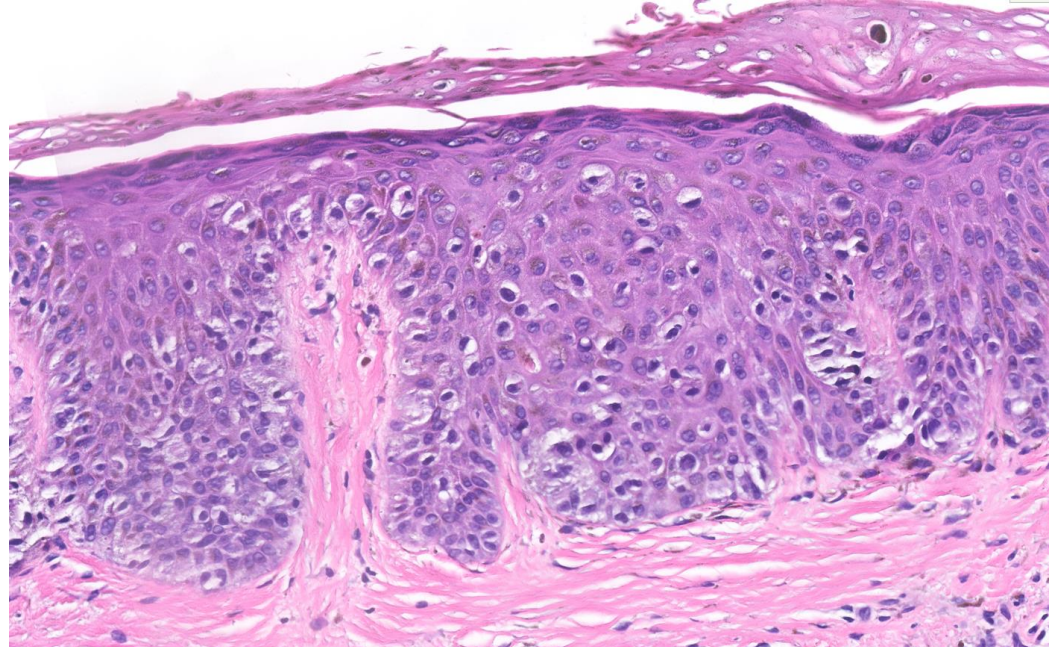
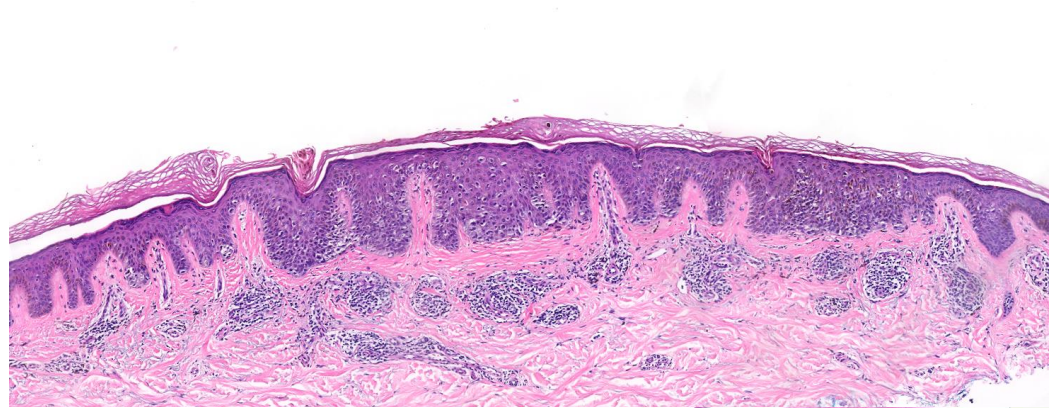
# In situ or pT1a Melanoma ?

- Sensitive criteria:
- Disorder
- High-grade atypia
- Specific criteria:
- No, Diameter  $< 1$  cm
- No, thickness:  $< 0.8$  mm
- No expansile nodule
- No ulceration
- No dermal mitoses
- No regression



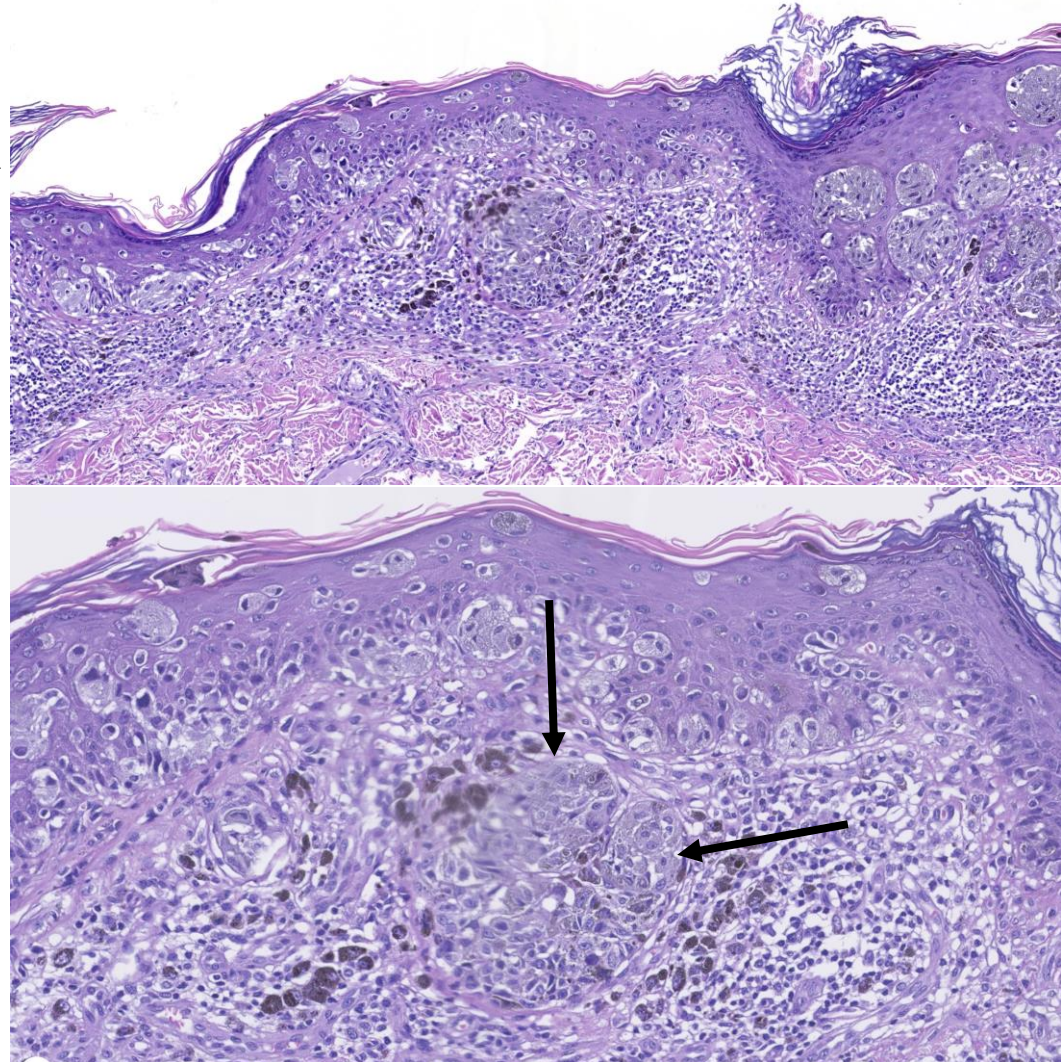
# In Situ or pT1a Melanoma?

- Sensitive criteria:
- Disorder, pagetoid spread
- High-grade atypia
- Specific criteria:
- No, Diameter 4 mm
- No, Thickness  $< 0.8$  mm
- No expansile nodule
- No ulceration
- No dermal mitoses
- No regression



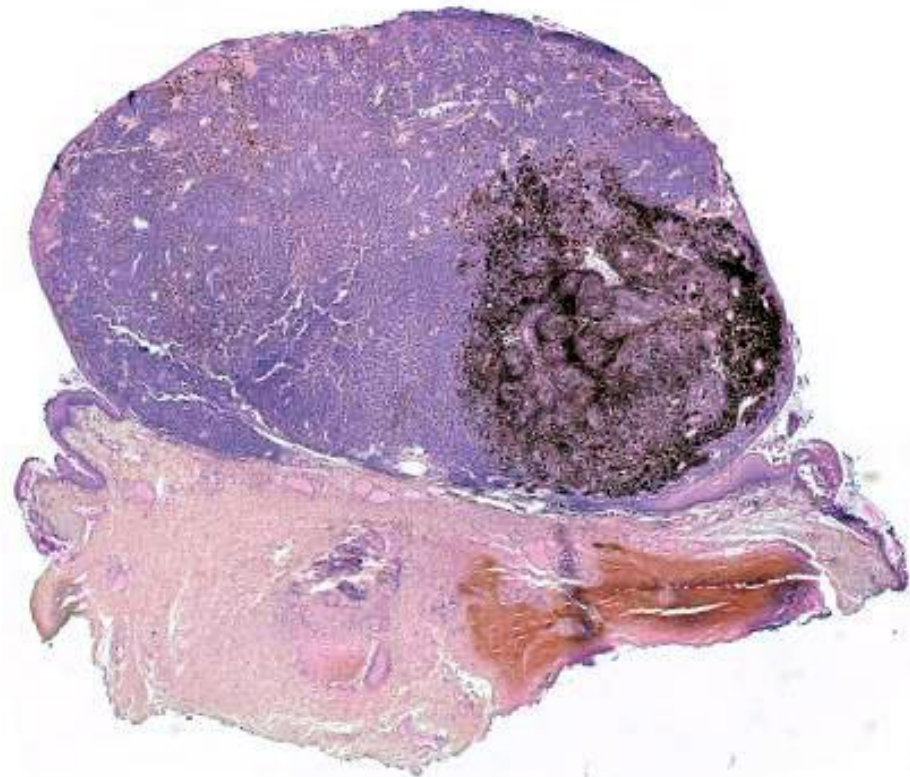
# pT1a Melanoma?

- Sensitive criteria
- Disorder, pagetoid spread
- High-grade atypia
- Specific criteria:
- Diameter  $> 1$  cm\*
- Thickness  $< 0.8$  mm
- Vertical growth phase\*
- No ulceration
- No dermal mitoses
- No regression



# Melanoma?

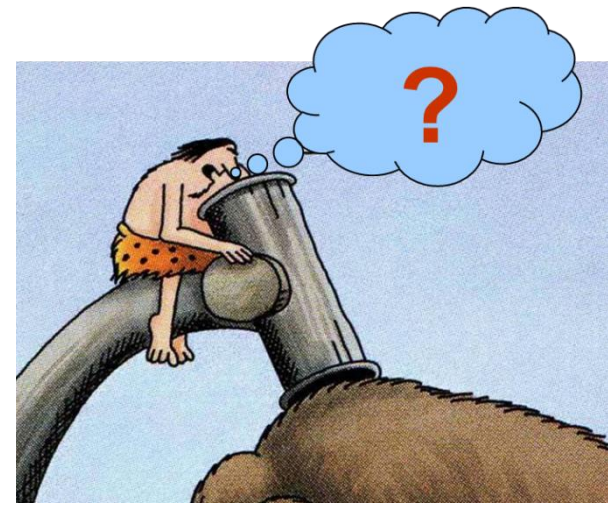
- Sensitive criteria
- Diameter: 10 mm\*
- Breslow thickness: 4 mm\*
- Absence of maturation
- Specific criteria
- Diameter: 10 mm\*
- Breslow thickness: 4 mm\*
- Ulceration\*
- Vertical growth phase \*
- Mitotic rate: 26 per mm<sup>2</sup>\*
- High-grade atypia\*



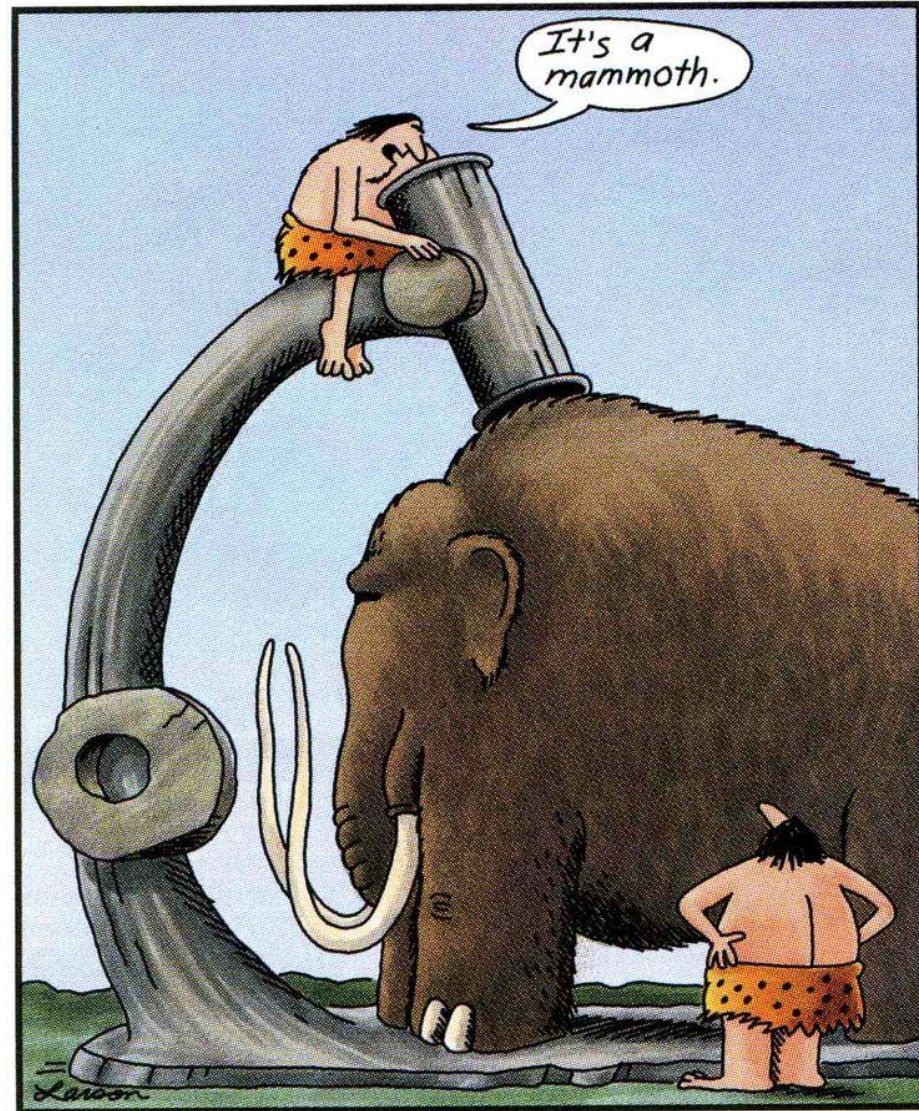
# Sampling of Melanocytic Lesions

# Sampling of Melanocytic Lesions

- Examine the entire lesion!
- Partial biopsies: cannot evaluate:
  - ✓ Diameter, thickness
  - ✓ Circumscription
  - ✓ Symmetry
  - ✓ Can miss the most important part of the lesion!
- May not be representative!



Examine the  
entire lesion  
before final  
diagnosis!



III.

# Ancillary Techniques

# The Two Most Under-Utilized Special Techniques

## 1. The human brain

- complex image analysis
- integration of all data
- permits judgement, acknowledges uncertainty, and the human touch
- better than AI!



## 2. The telephone

- direct communication to obtain information



# Take Home Messages



1. Balance to avoid over- and under-diagnosis of melanoma
2. Employ due diligence to obtain essential information for diagnosis
3. Invoke sufficient criteria and especially specific criteria to avoid overdiagnosis
4. Examine the entire lesion





# Mission of the Pathologist

## Re: Melanocytic Lesions

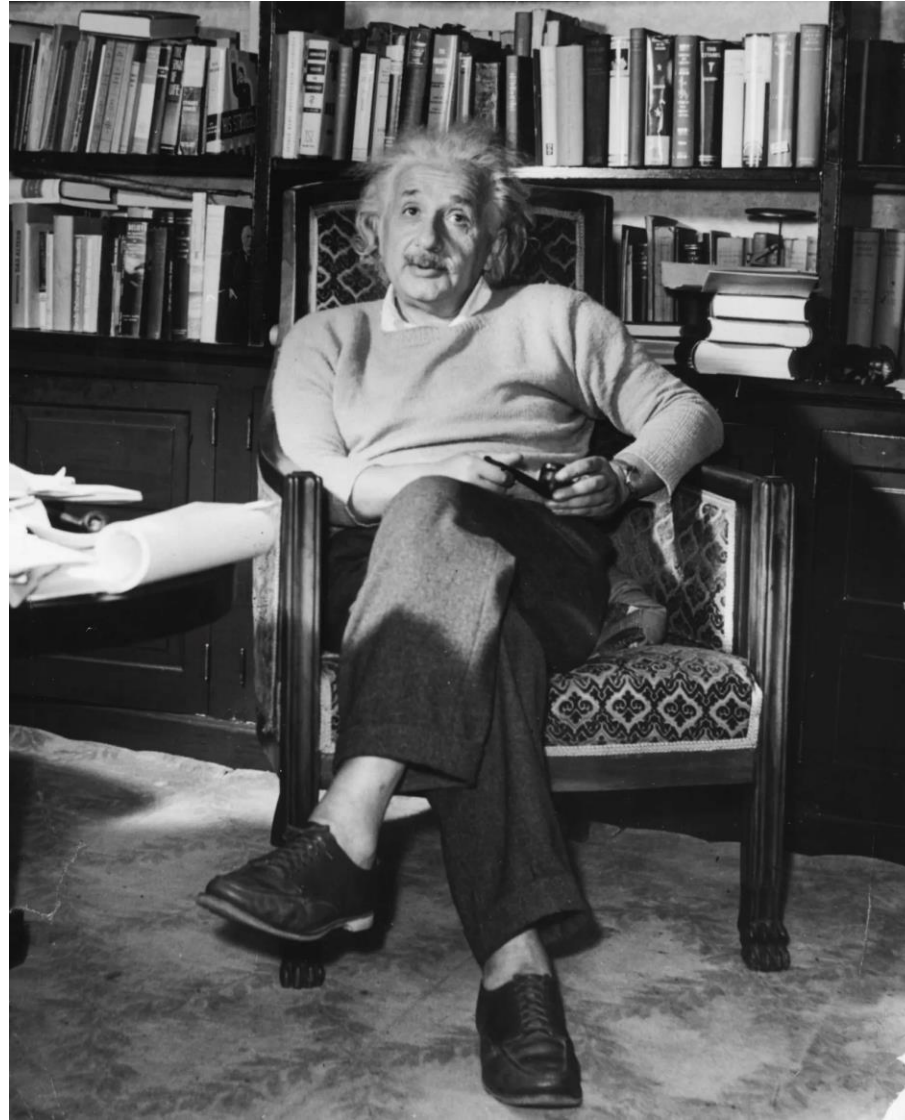
- Accurate and understandable diagnostic report for clinicians and patients
  - Prognosis and staging
  - Management, vis-à-vis, surgery and other therapies
- Exercise due diligence and do no harm:
  - Do not miss melanoma!
  - Do not over-diagnose melanoma!

# Classification: A Longstanding Dogma

- Benign  
or
- Malignant



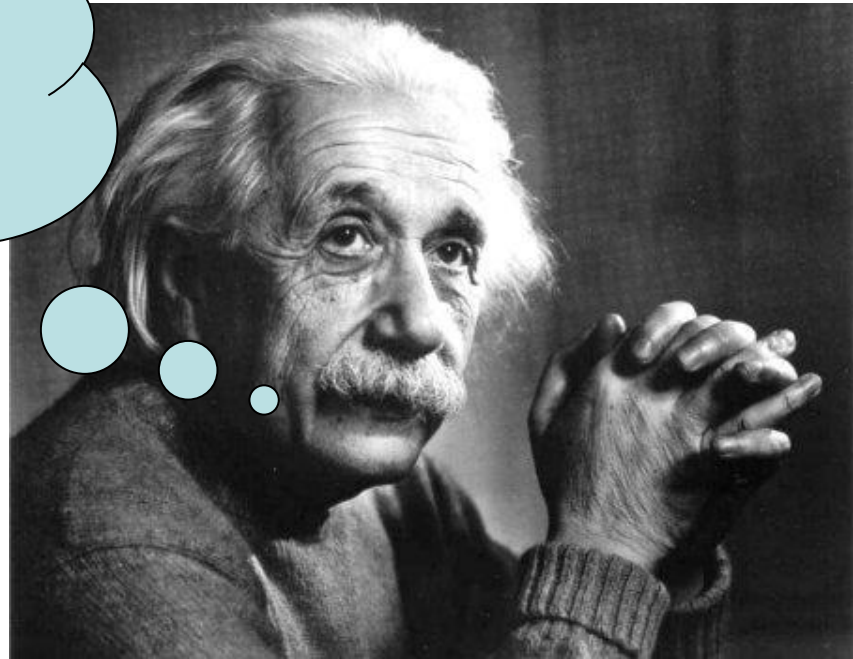
“One should try to make things simpler but not too simple...”



# Classification of Melanocytic Lesions

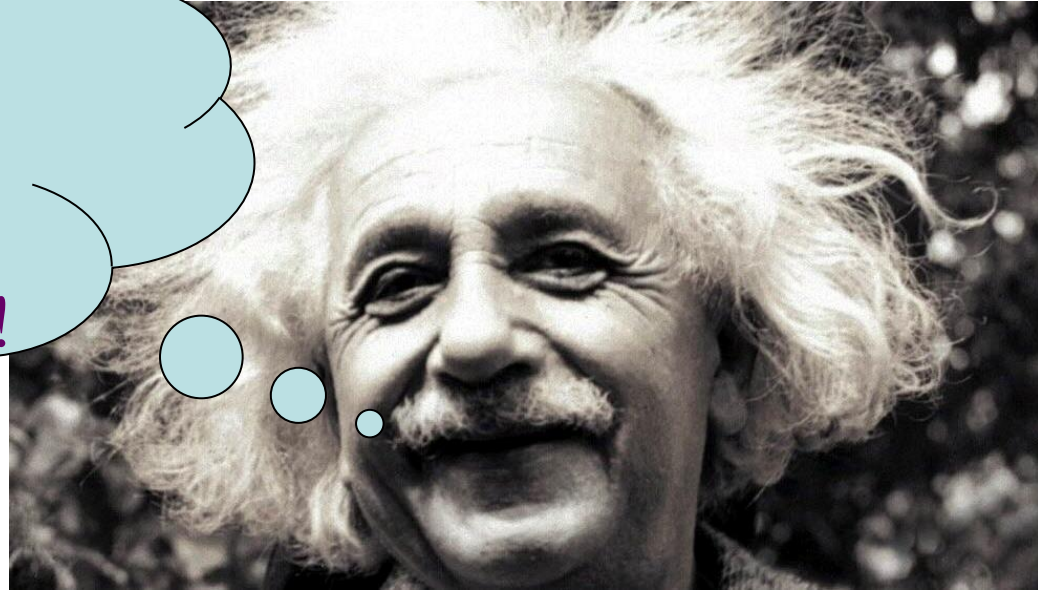
Too simple! This leads  
to over diagnosis and  
missed melanomas!  
And harm to patients.

- Benign
- Malignant



# MPATH and WHO 4<sup>th</sup> Edition Classifications

Much better! This  
acknowledges  
uncertain (and  
intermediate) lesions!



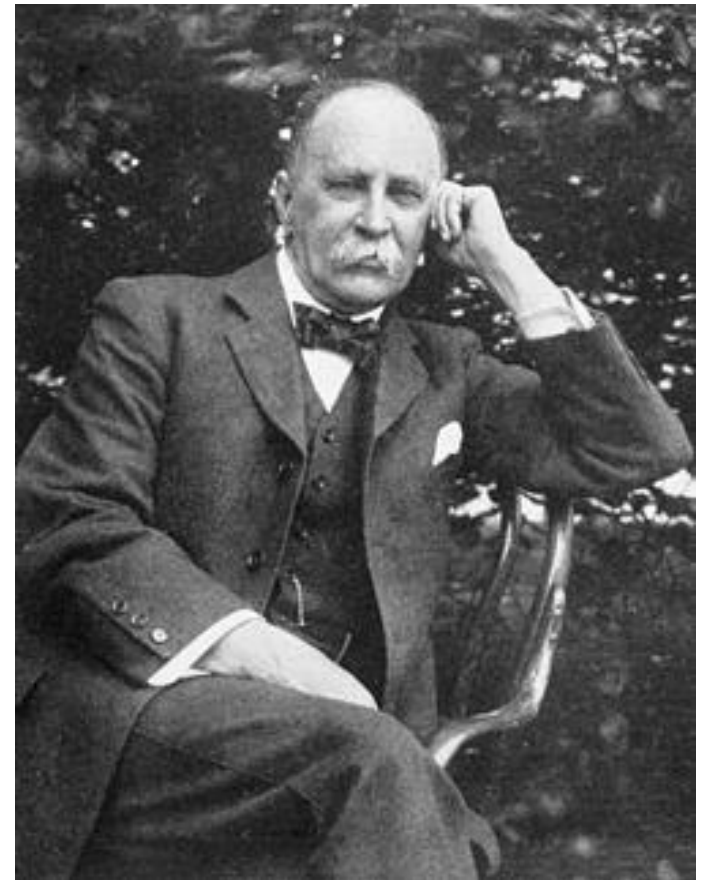
- Benign
- Uncertain
- Malignant

# What is an Uncertain Melanocytic Lesion?

- A lesion difficult to interpret as benign or malignant
- A lesion with uncertain potential for :
  - Recurrence, persistence, progression, or metastasis

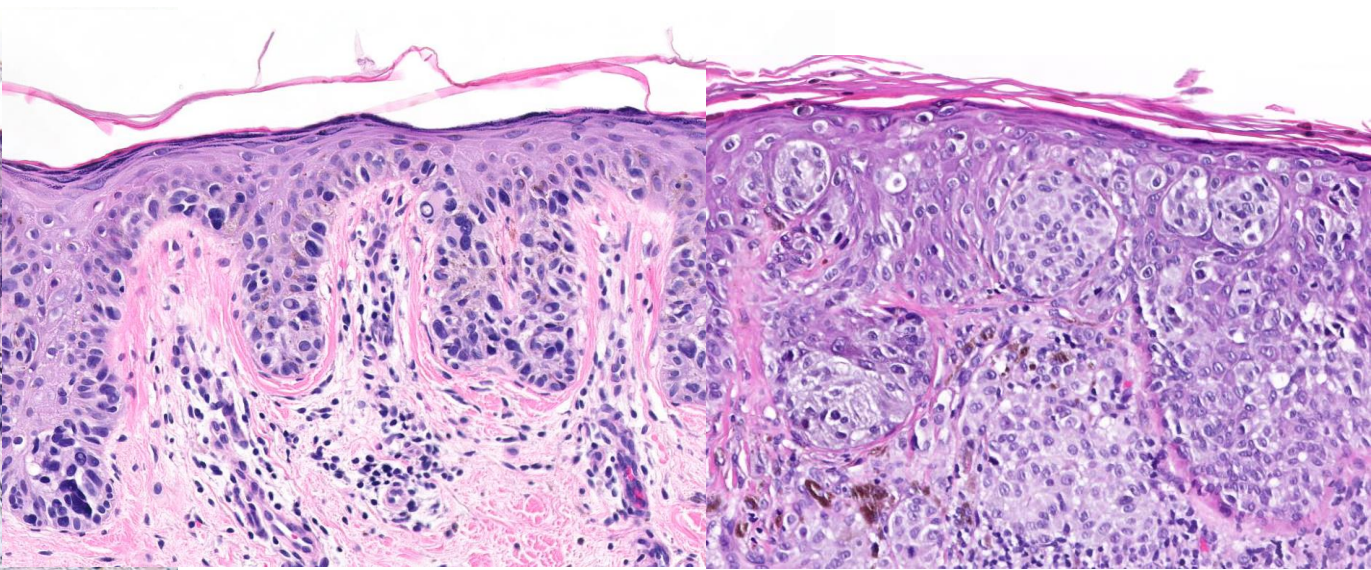
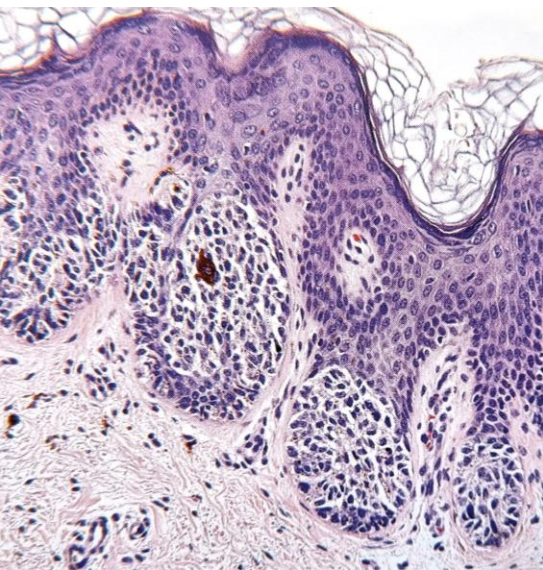
“Medicine is a science of uncertainty  
and an art of probability”

.....Sir William Osler

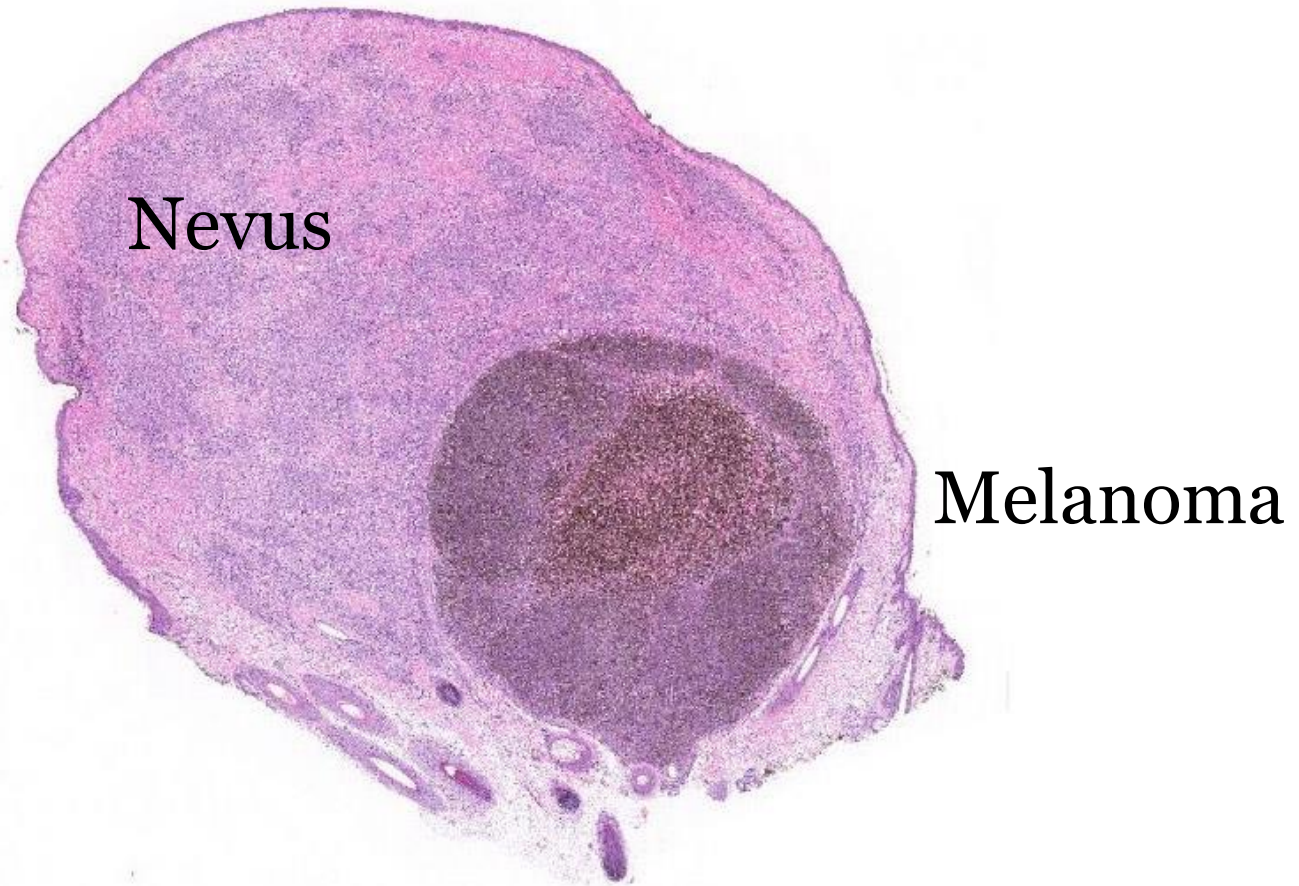


Uncertainty about  
melanocytic lesions exists  
and must be communicated  
for patient care

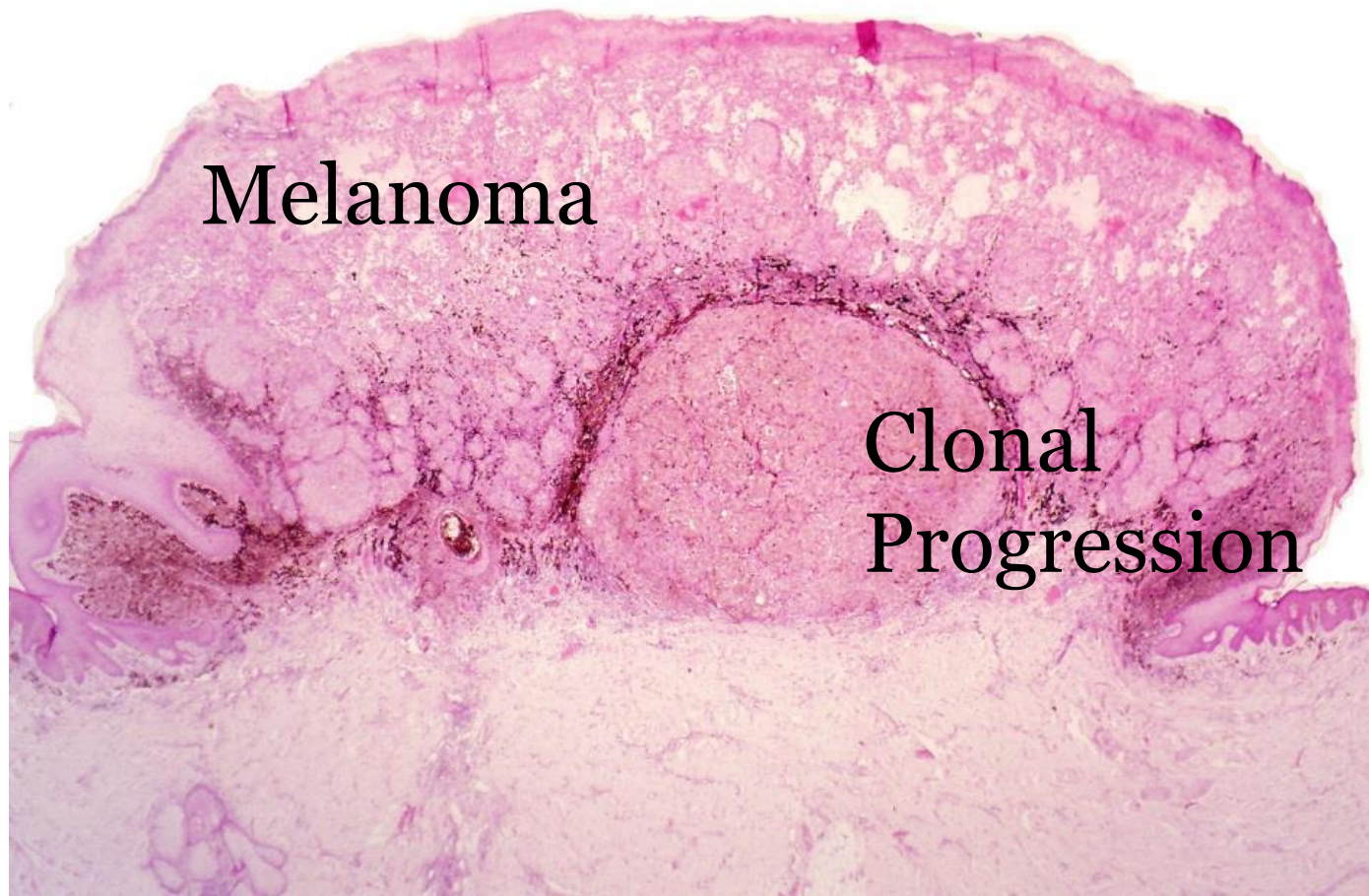




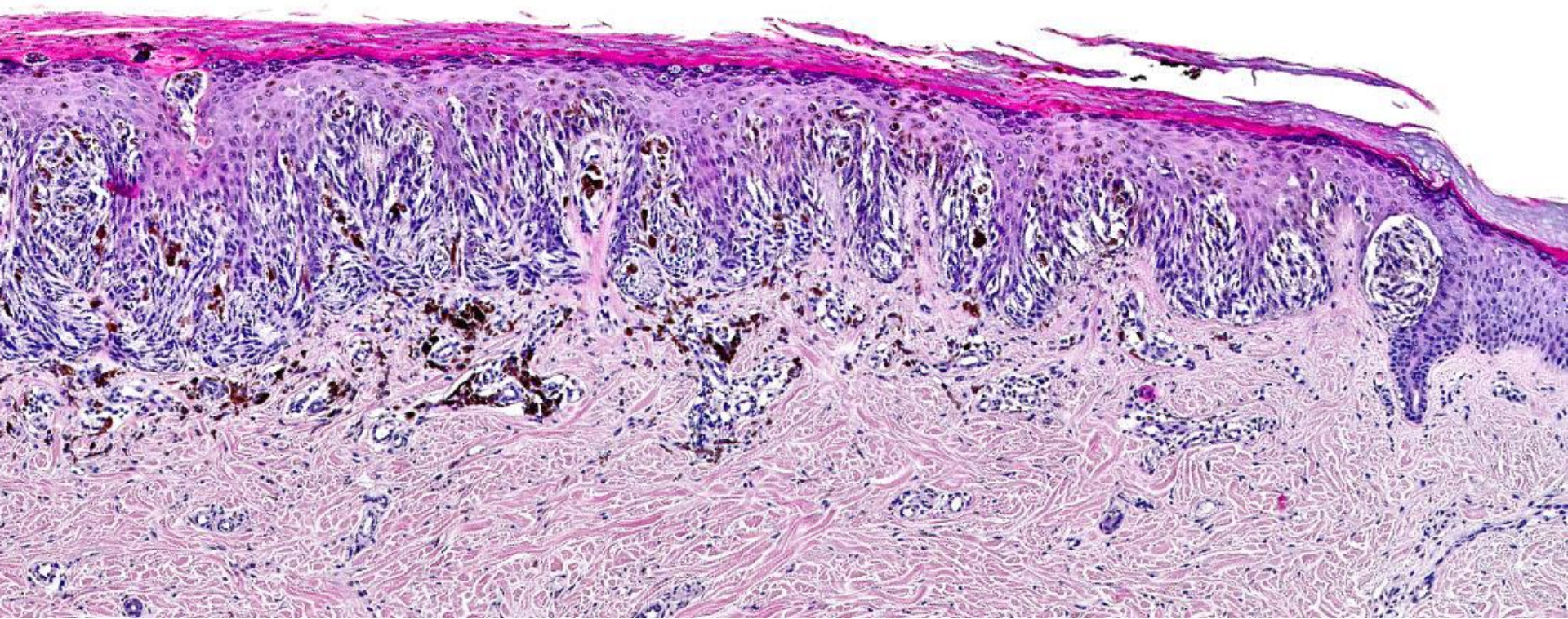
# Atypical Biphasic Lesion: Nevus and Melanoma



# Malignant Biphasic Lesion: Melanoma with Clonal Progression



# Pagetoid Melanocytosis



Pigmented Spindle Cell Nevus

# Overdiagnosis of Thin Melanoma pT1a

## Increased diagnosis of thin superficial spreading melanomas: A 20-year study

Jason E. Frangos, MD,<sup>a</sup> Lyn M. Duncan, MD,<sup>b</sup> Adriano Piris, MD,<sup>b</sup> Rosalynn M. Nazarian, MD,<sup>b</sup>  
Martin C. Mihm, Jr, MD,<sup>d</sup> Mai P. Hoang, MD,<sup>b</sup> Briana Gleason, MD,<sup>c</sup> Thomas J. Flotte, MD,<sup>f</sup>  
Hugh R. Byers, MD,<sup>g</sup> Raymond L. Barnhill, MD,<sup>h</sup> and Alexa B. Kimball, MD, MPH<sup>c</sup>

*Boston, Massachusetts; Sacramento, San Luis Obispo, and Los Angeles, California; and Rochester, Minnesota*

J Am Acad Dermatol 2012

Research

JAMA Dermatology | **Original Investigation**

JAMA Derm 2023

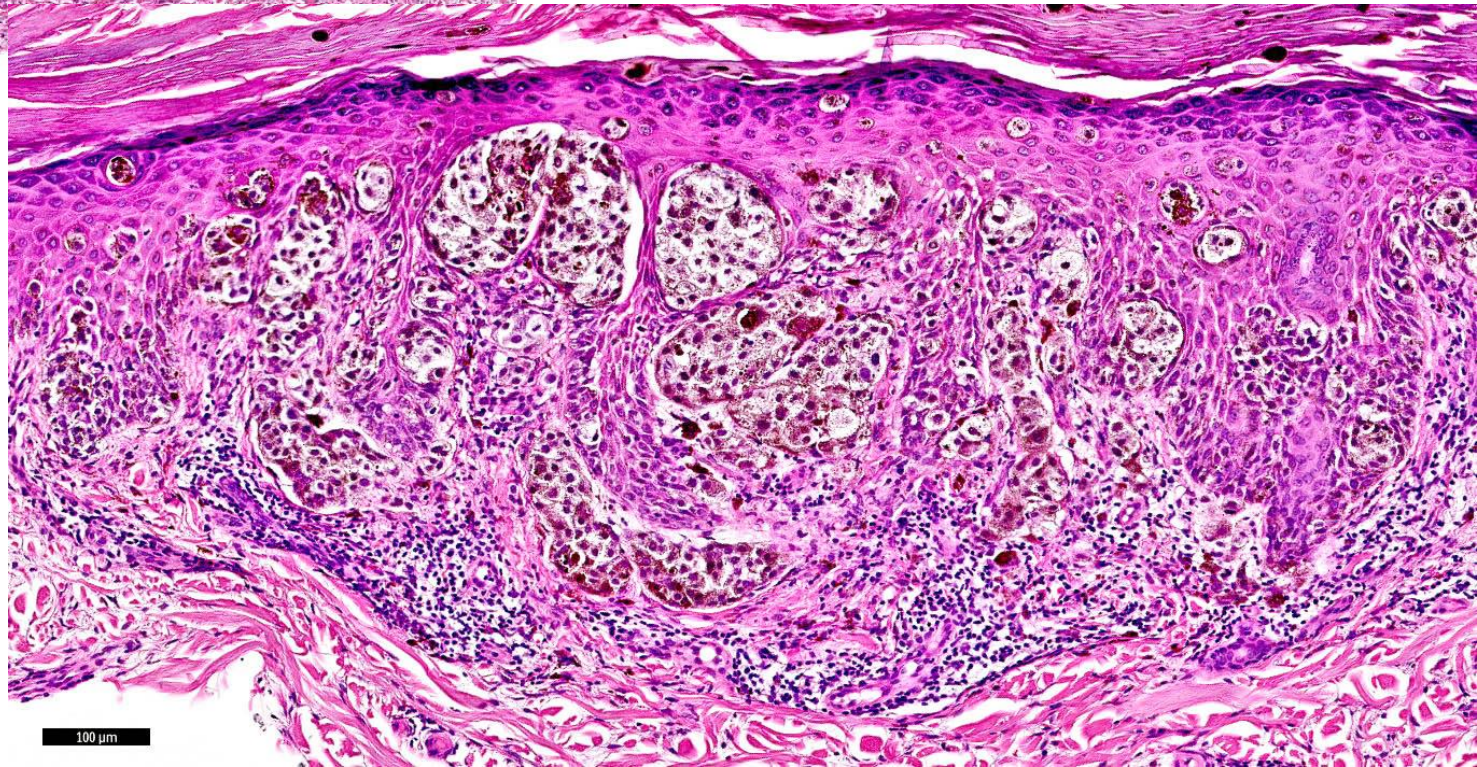
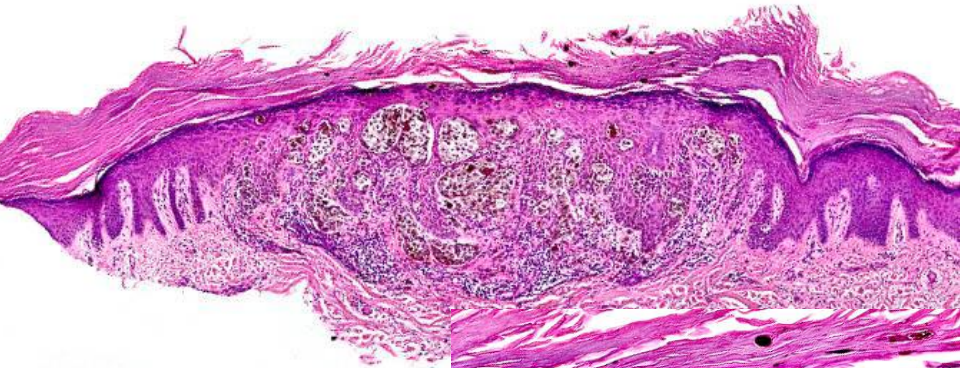
## Pathologist Characteristics Associated With Rendering Higher-Grade Diagnoses for Melanocytic Lesions

Kathleen F. Kerr, PhD; David E. Elder, MB, ChB; Michael W. Piepkorn, MD, PhD; Stevan R. Knezevich, MD, PhD;

Megan M. Eguchi, MPH; Hannah L. Shucard, MS; Lisa M. Reisch, PhD; Joann G. Elmore, MD, MPH; Raymond L. Barnhill, MD

# Diameter

- Diameter = 2 mm
- No ulceration
- No dermal mitoses
- No vertical growth phase
- Thickness < 0.8 mm

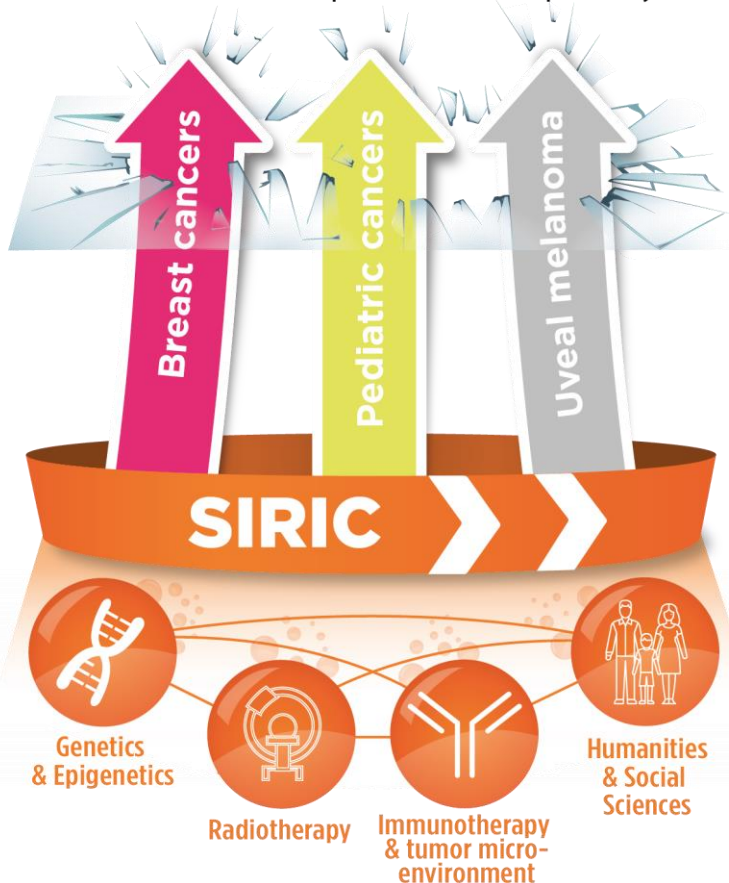


# SIRIC: French National Cancer Institute (INCa) label for Integrated Cancer Research Center

## ***SIRIC Curie***

### **BREAKING THE RESISTANCE**

Biomarkers • Therapeutics • Patient pathway



Sergio Roman Roman,  
Director



### **Uveal melanoma (UM) integrated research program**

**Innovative radiotherapy for UM**

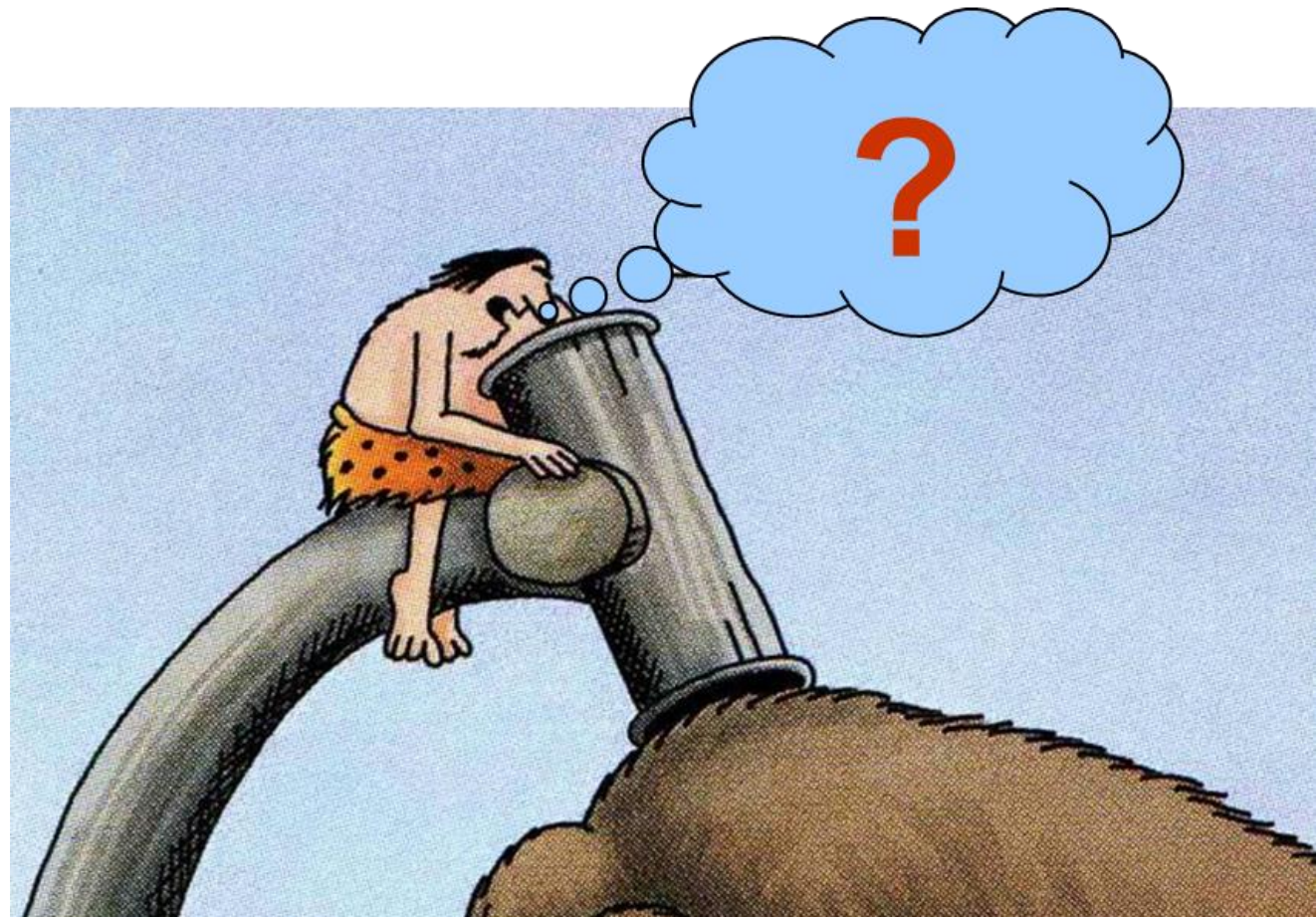
**Genetics and Epigenetics of UM**

**Immunotherapy opportunities in UM**

**Humanities and Social Sciences in UM**

<https://siric.institut-curie.org/page/uveal-melanoma>

First of all, is your specimen  
representative of  
the whole lesion?...



# Carte Touristique

- Mission of the pathologist
- Classification
- Uncertain lesions
- Intermediate lesions
- Criteria for diagnosis
  - Clinical criteria
  - Histopathological criteria



# Histopathological Criteria

## ➤ **Architecture/Silhouette**

- ✓ Diameter
- ✓ Ulceration
- ✓ Breslow thickness
- ✓ Circumscription
- ✓ Symmetry
- ✓ Pagetoid melanocytosis
- ✓ Architecture of nesting
- ✓ Confluence of melanocytes
- ✓ Cellularity
- ✓ Maturation

## ➤ **Cytological atypia**

## ➤ **Mitoses**

## ➤ **Solar elastosis**

# Cytological Atypia

Exceptions

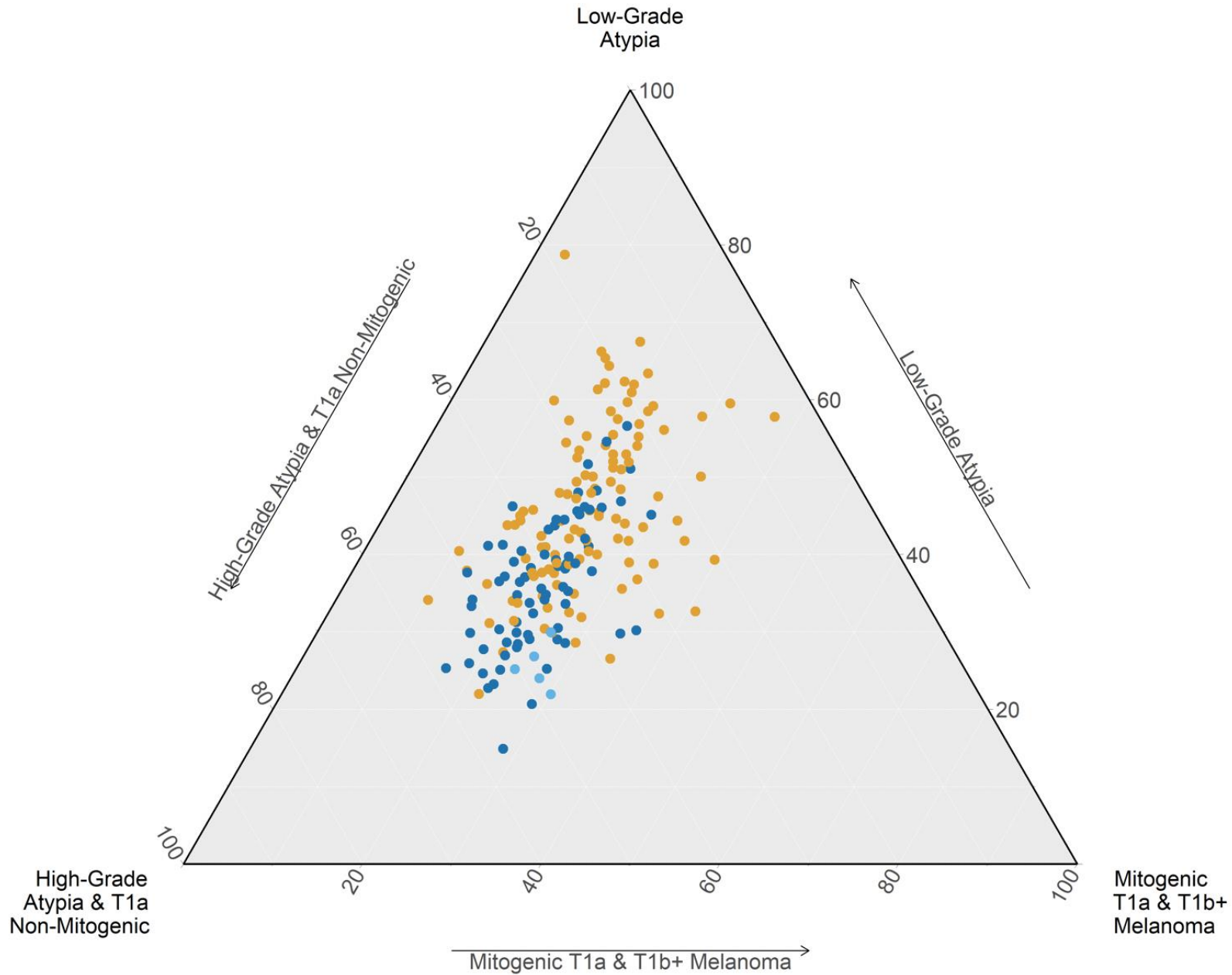
Lesions with Uncertainty



Age – 60 years

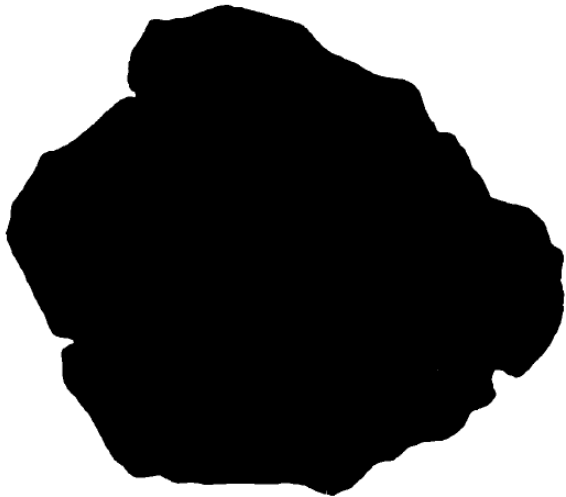


Lentigo Maligna Melanoma



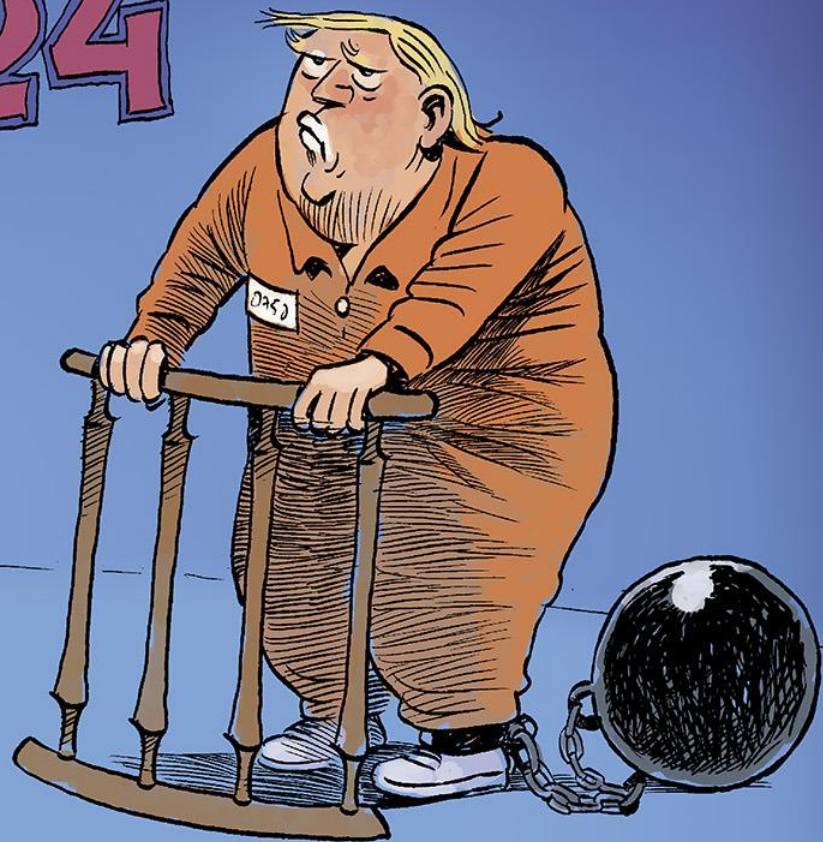
Gross Morphology and  
Microscopic Silhouette  
at Low/Scanning Magnification  
Are Complementary

Architecture/Silhouette





2024



CHAPPAPE

# Evaluation of Superficial Architecture by Silhouette

- Diameter (size)
- Breslow thickness
- Symmetry
- Circumscription
- Architecture of nesting
- Confluence of melanocytes
- Pagetoid spread
- Maturation



# Clinical Criteria:

## The Size Threshold for Melanoma

- ABCDE system - 6 mm
- Glasgow 7 point - 7 mm
- Acral lesions - 7 mm
- AB Ackerman - 3 mm

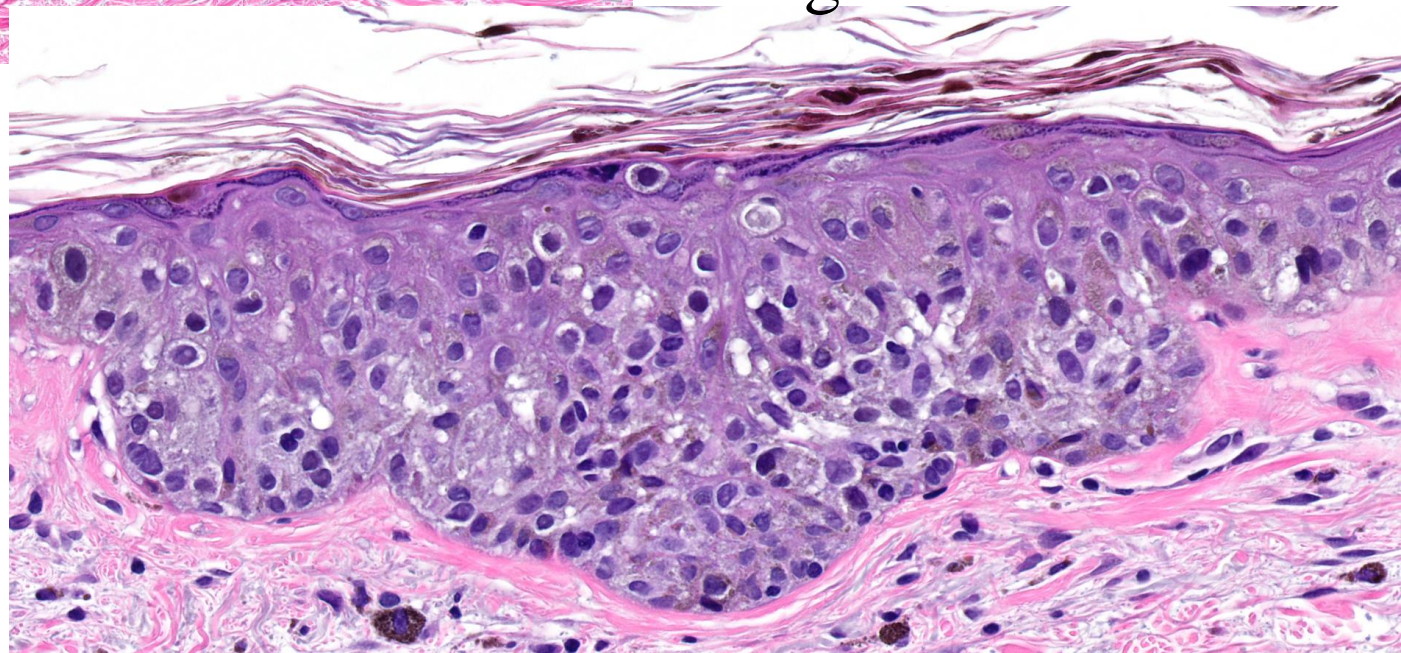
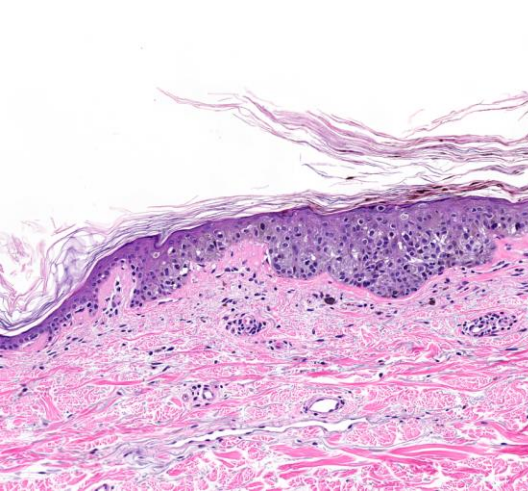
# Diameter

Avoid overdiagnosis  
of melanoma!



# Diameter

- Diameter = 2 mm
- No ulceration
- No dermal mitoses
- No vertical growth phase
- Thickness 0.2 mm
- No regression

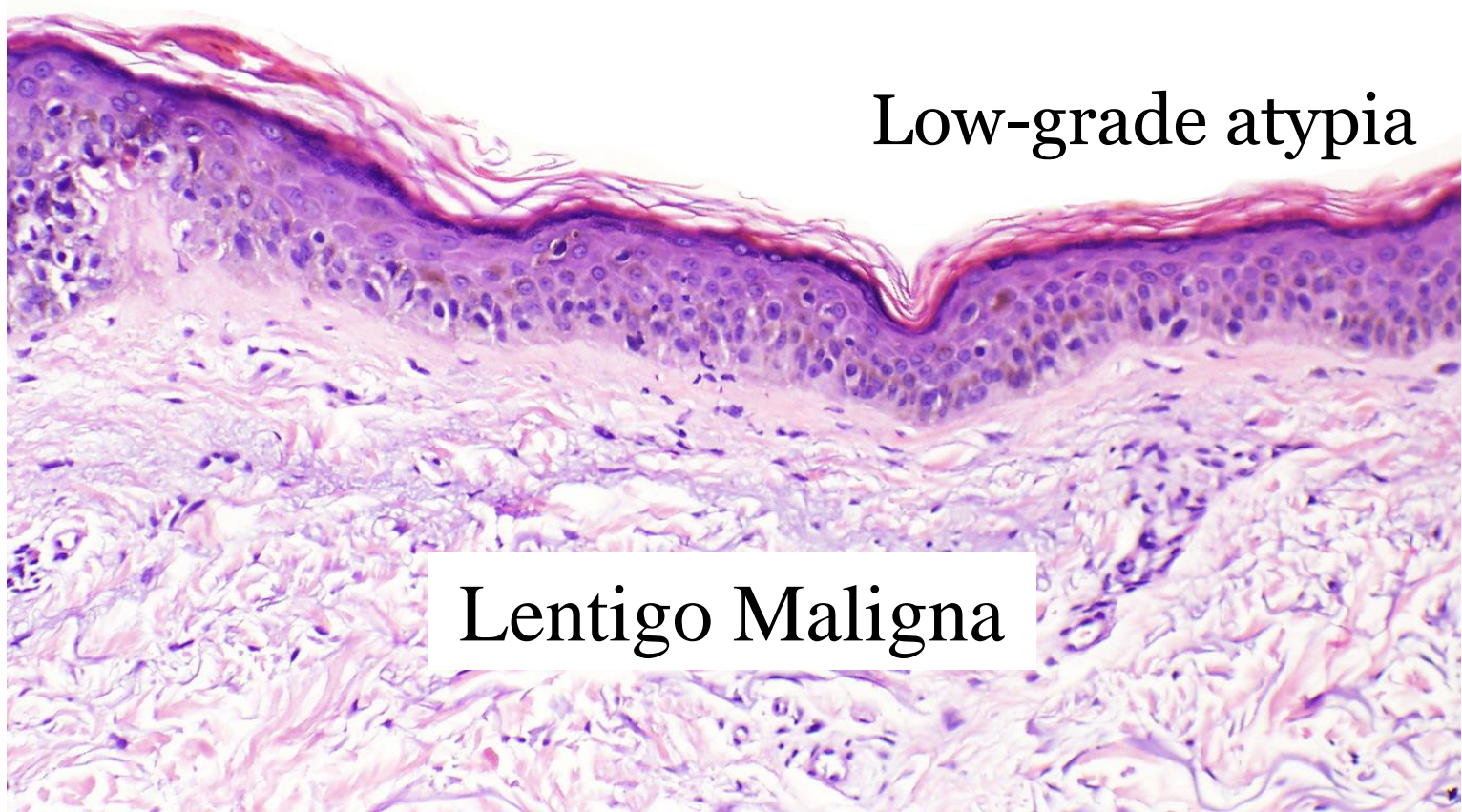


# Biphasic Melanocytic Lesions

Two distinct components

| Benign  | Intermediate<br>Melanocytoma  | Malignant  |
|---|---|--|
| <ul style="list-style-type: none"><li>• Combined nevus</li><li>• ? Malignant transformation</li></ul> | <ul style="list-style-type: none"><li>• Benign +<ul style="list-style-type: none"><li>✓ Atypical</li><li>✓ Uncertain</li><li>✓ Malignant transformation</li></ul></li></ul> | <ul style="list-style-type: none"><li>• Conventional radial +<ul style="list-style-type: none"><li>✓ vertical growth phases</li><li>✓ Clonal progression</li></ul></li></ul> |

# Cytological Atypia



# Confluent Nesting

Exception



# Histopathological Criteria

How many are needed?

