



Sentinel lymph nodes and other prognostic factors in cutaneous melanoma

Lyn McDivitt Duncan, MD

Professor of Pathology, Harvard Medical School

Massachusetts General Dermatopathology Service

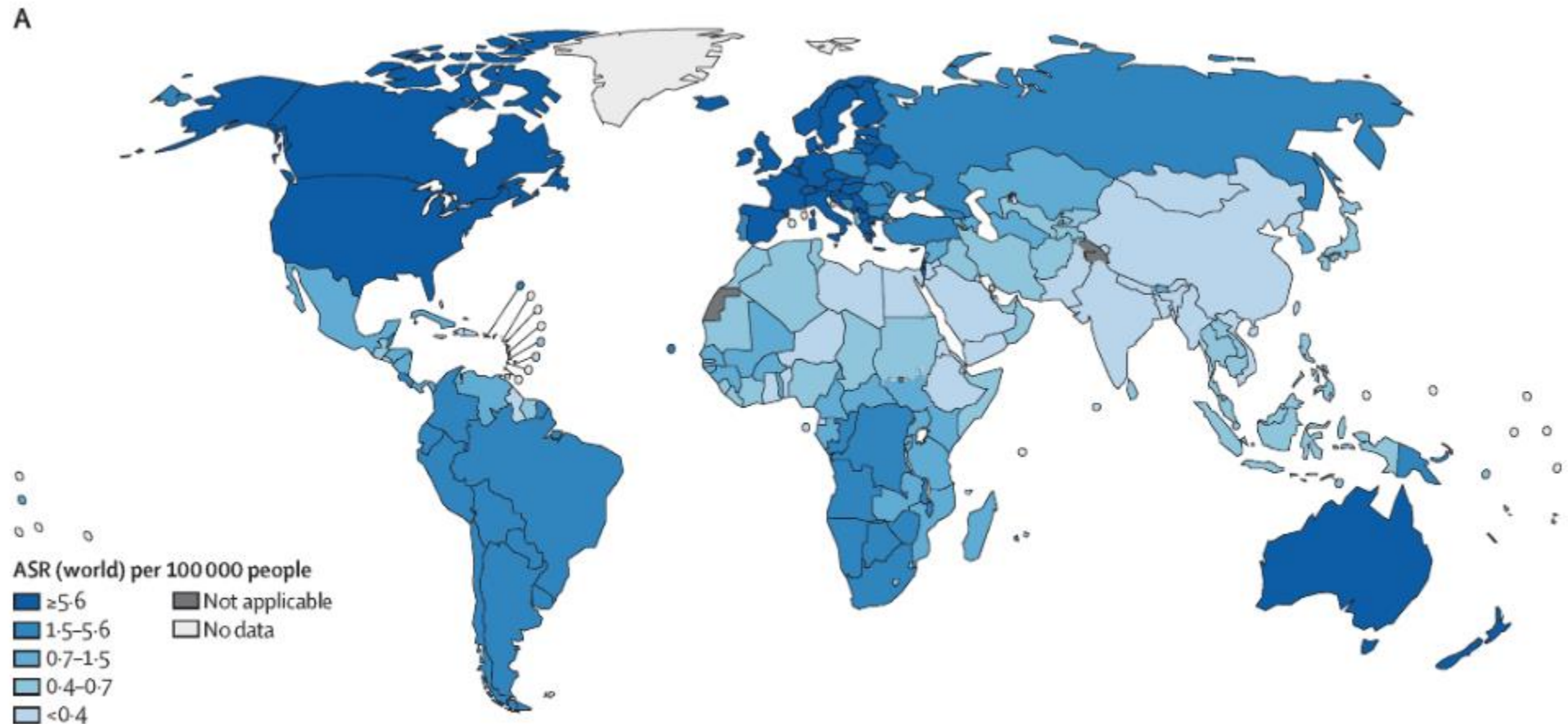
Boston, MA, USA



Global Incidence of Melanoma

Over 325 000 new melanoma cases worldwide in 2020

Over 57,000 melanoma related deaths worldwide in 2020



Primary Melanoma Tumor Factors

Histopathological factors in Melanoma

Primary Tumor

Tumor Thickness

Ulceration

Microscopic satellites

Mitoses

Lymphovascular invasion

Tumor infiltrating lymphocytes

Regression

Neural invasion

Margins

Sentinel Lymph Nodes

Presence of metastasis

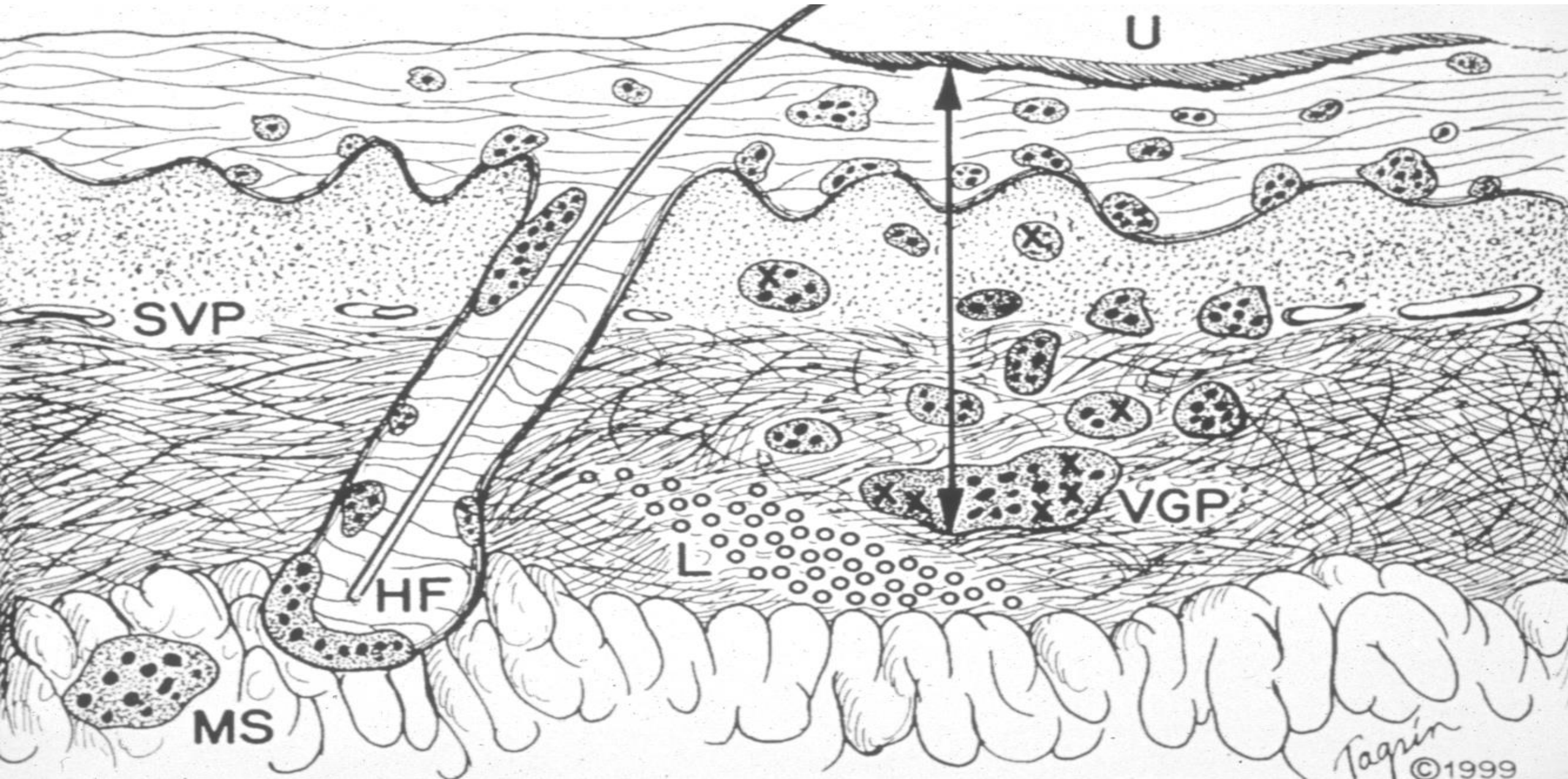
Number of positive lymph nodes

Size of metastasis

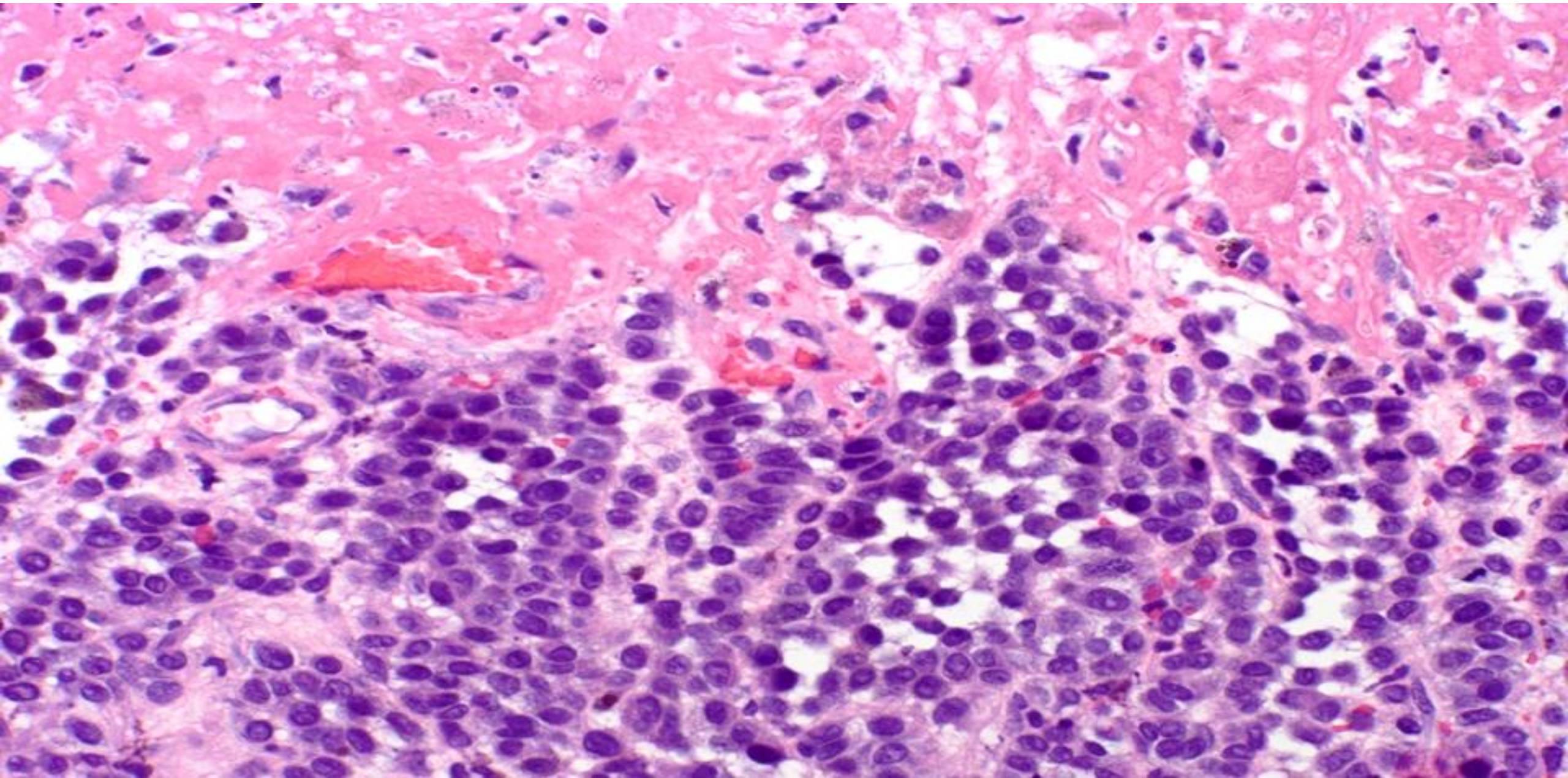
Detection Technique

Location of metastasis

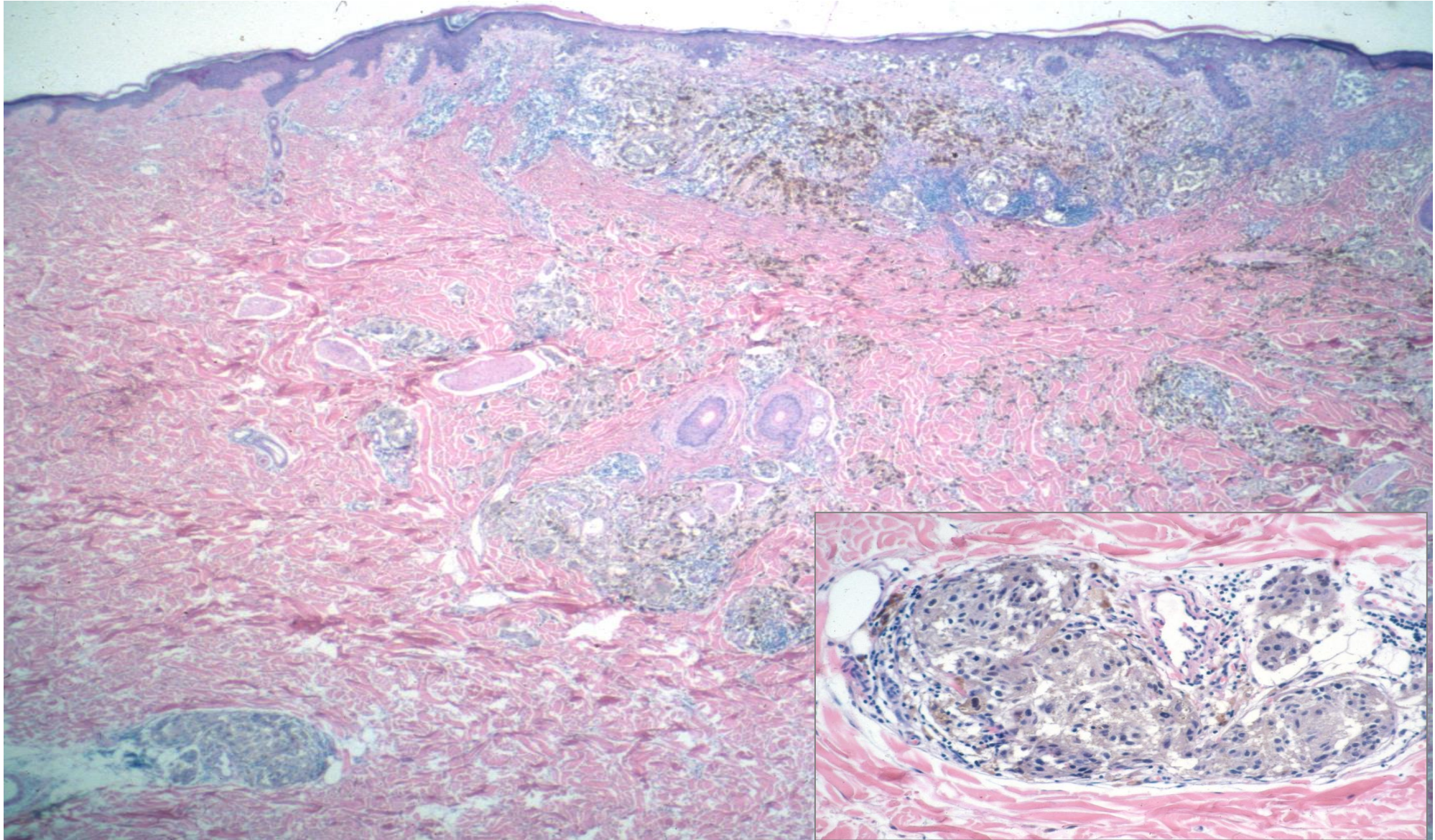
Primary Melanoma Thickness (Breslow 1970)



Ulceration



Microscopic Satellite Metastasis



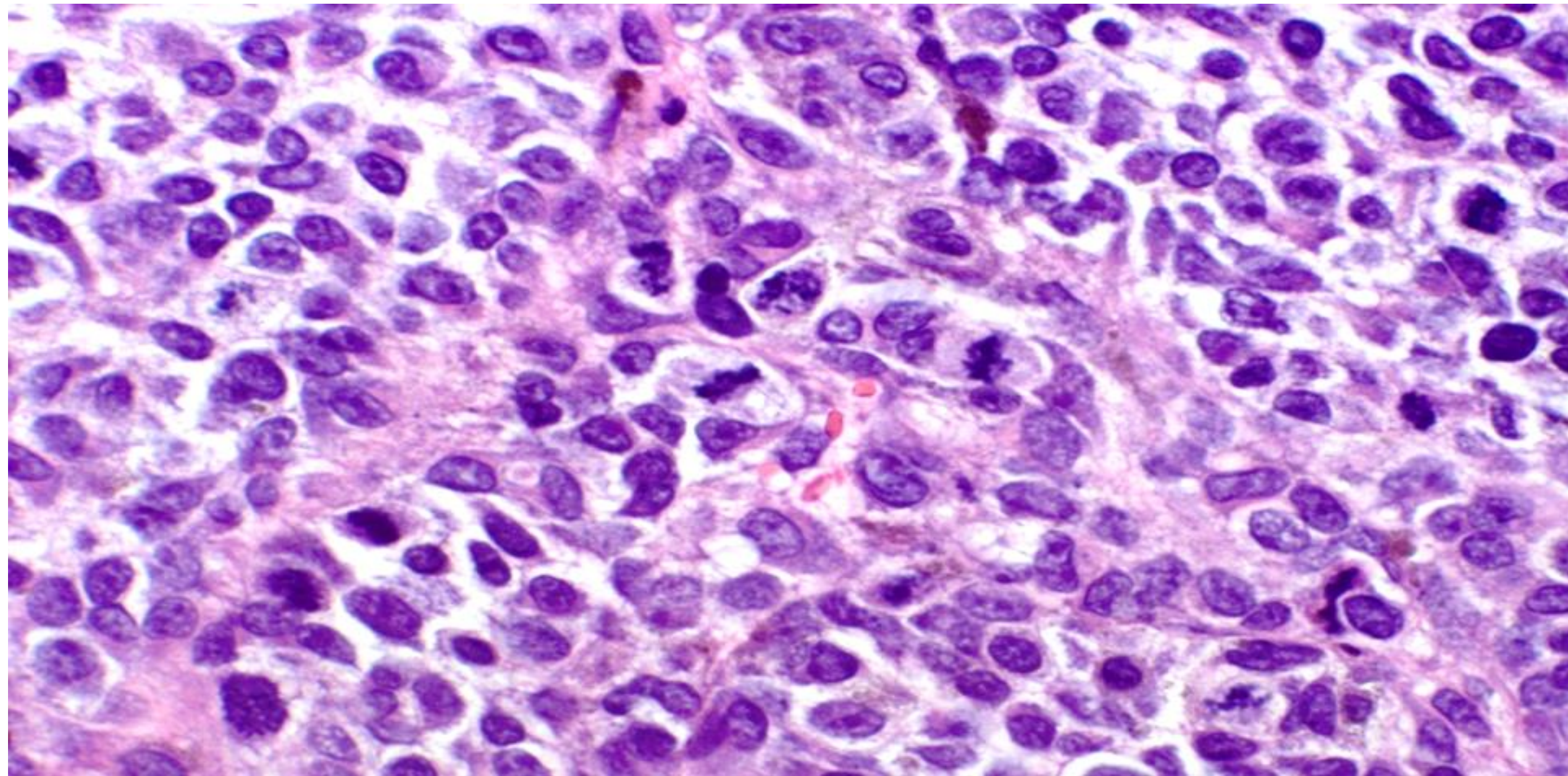
Microscopic Satellite Metastasis

- nest of malignant melanocytes
- >0.05 mm in diameter
- present in reticular dermis, panniculus or in vessels beneath the tumor
- separated from the tumor by normal tissue
- in the section in which the Breslow measurement is made
- upstage to IIIB or IIIC

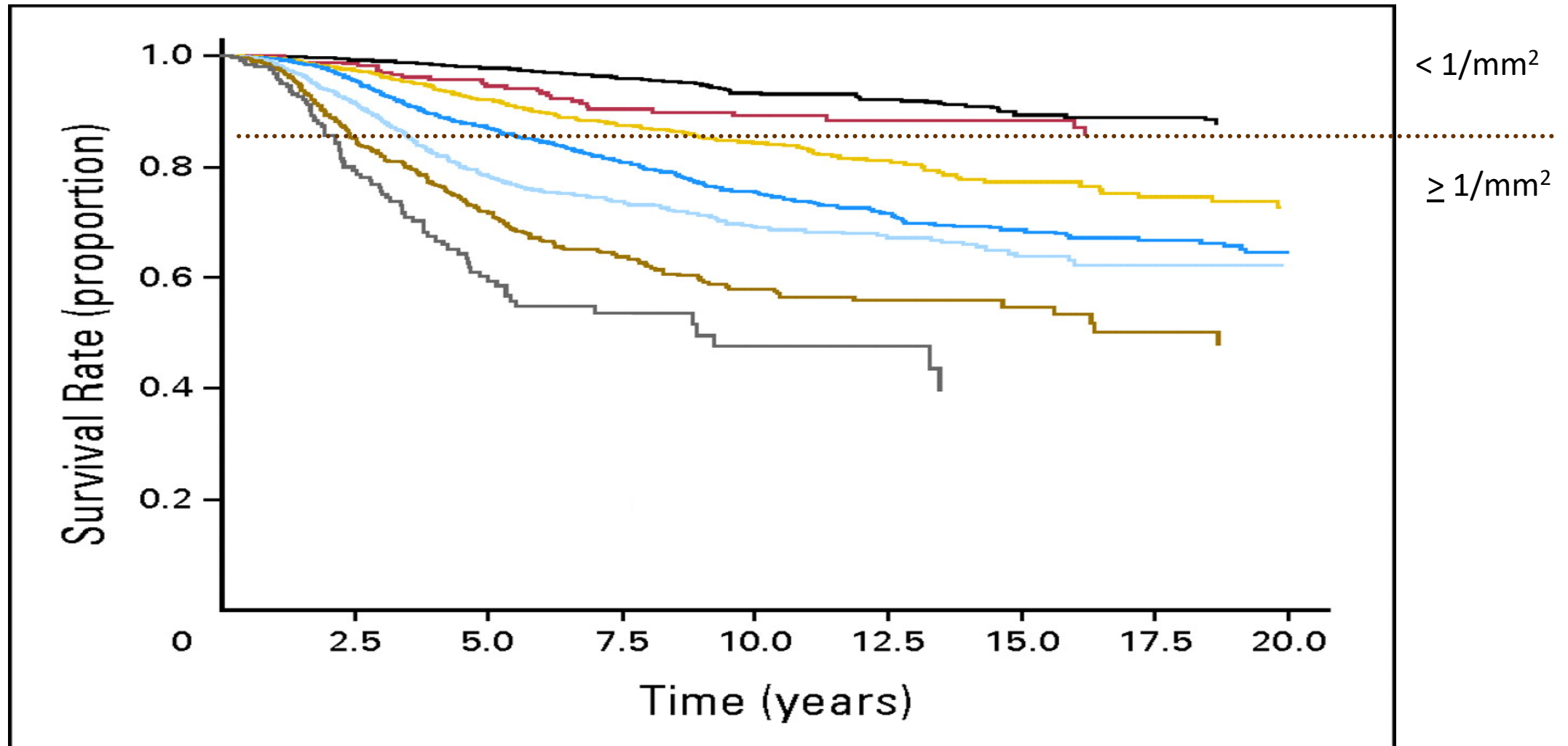
Five-year survival	With satellite	36%
	Without satellite	89%
Ten-year survival	With satellite	37%
	Without satellite	65%

Harrist TJ et al. Cancer 1988
Leon P, et al. Arch Surg 1991

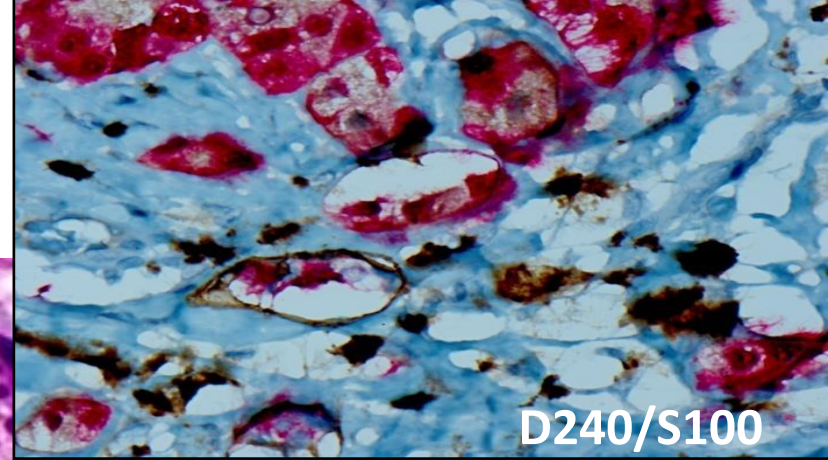
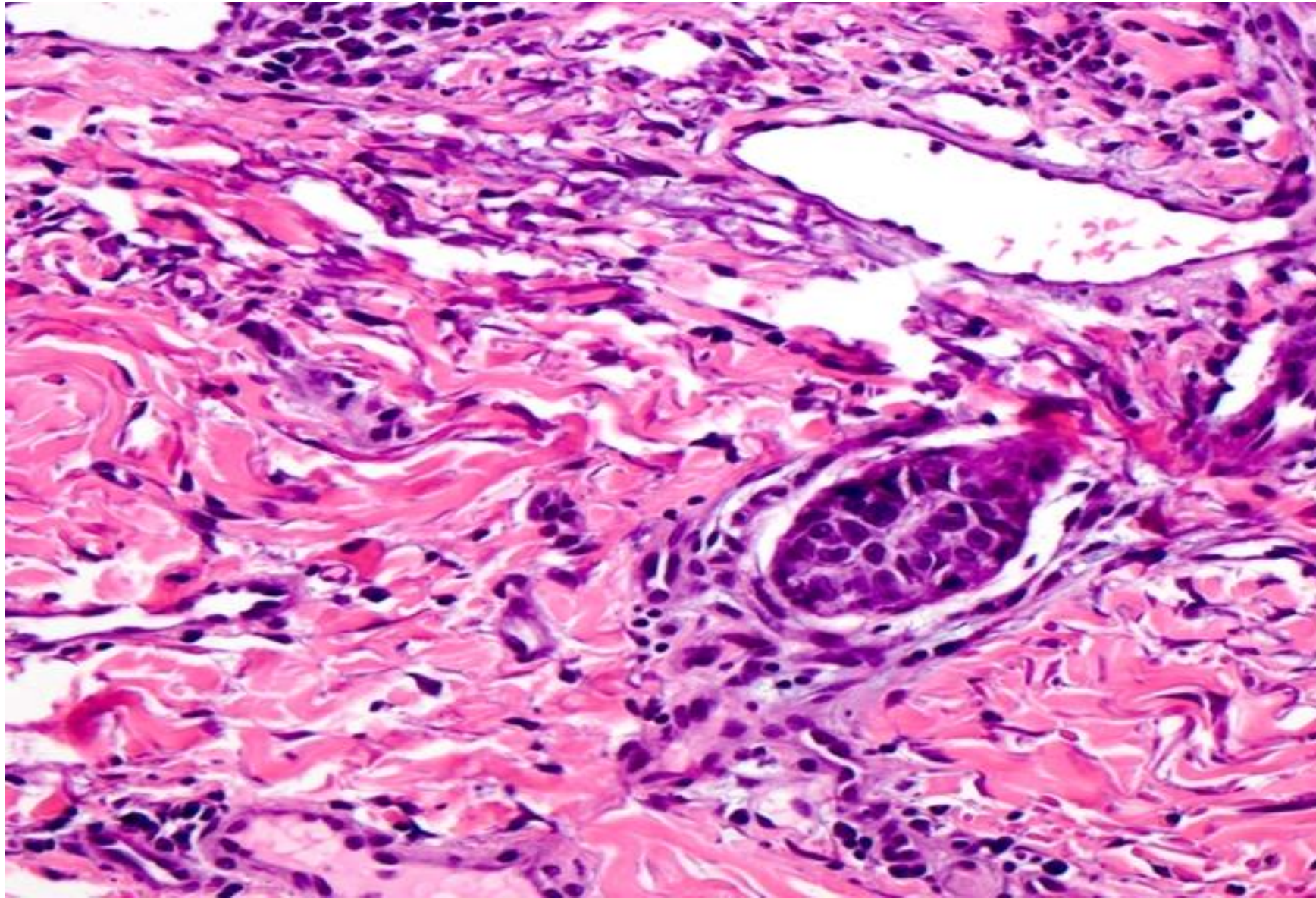
Mitotic Activity



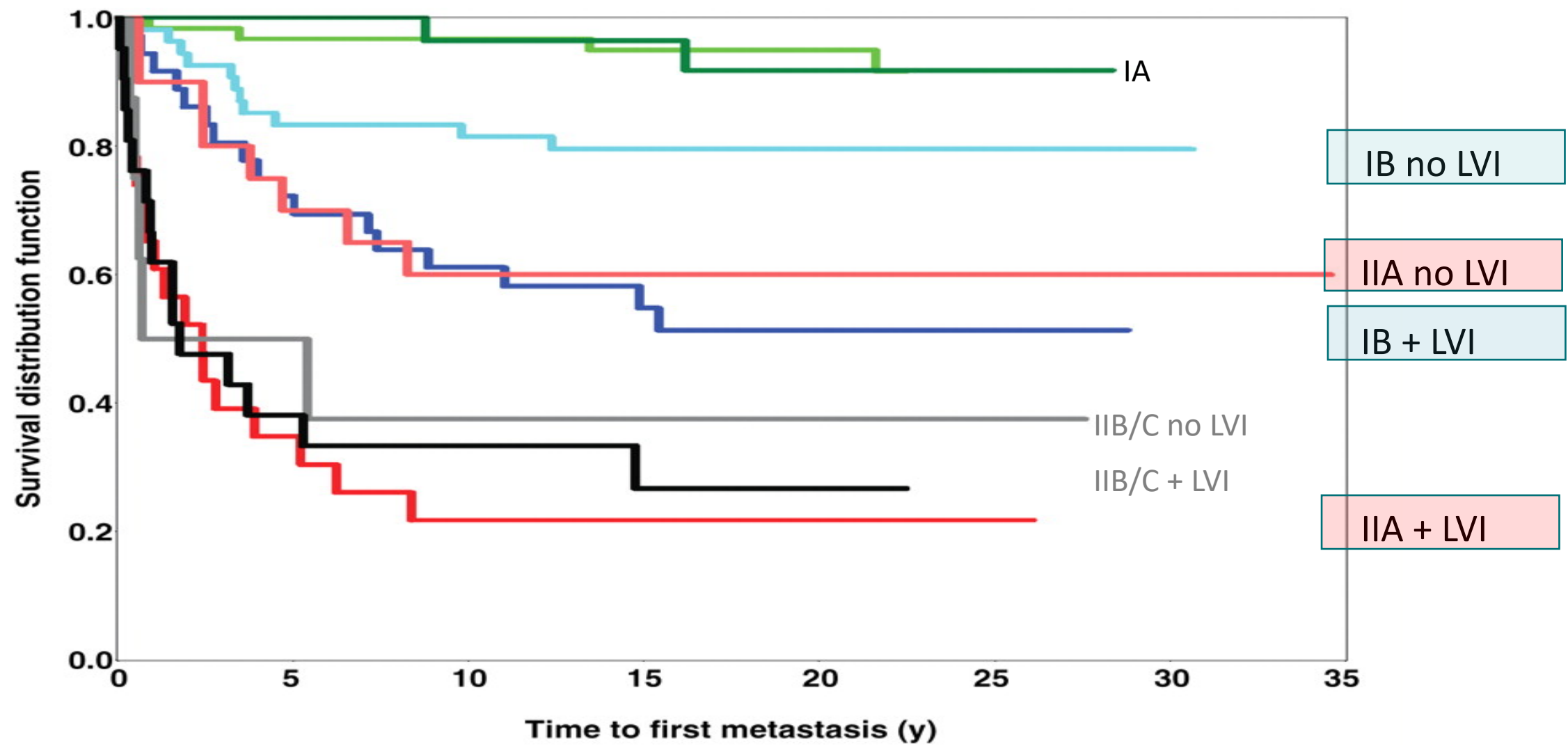
Survival curves by number of mitoses per mm²



Lymphovascular Invasion



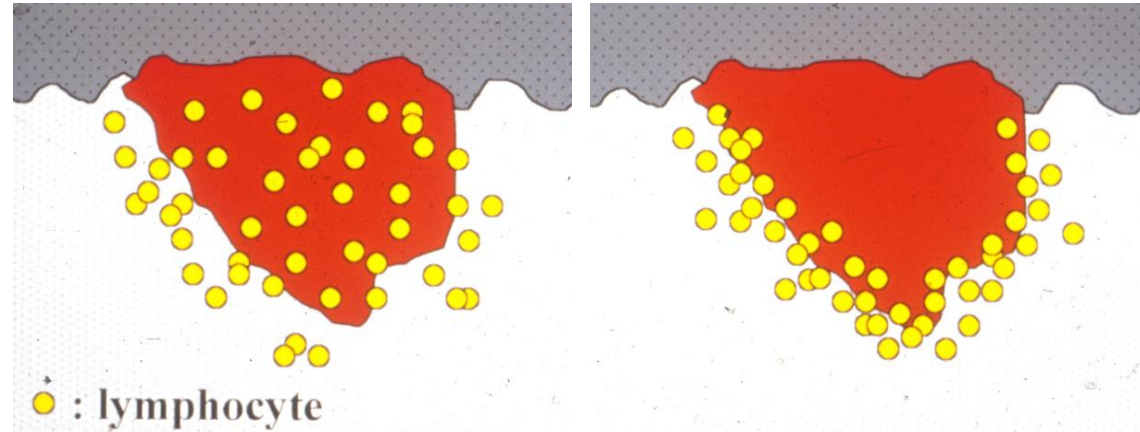
Lymphovascular invasion, AJCC stage & time to first metastasis



Tumor infiltrating lymphocytes (TILs)

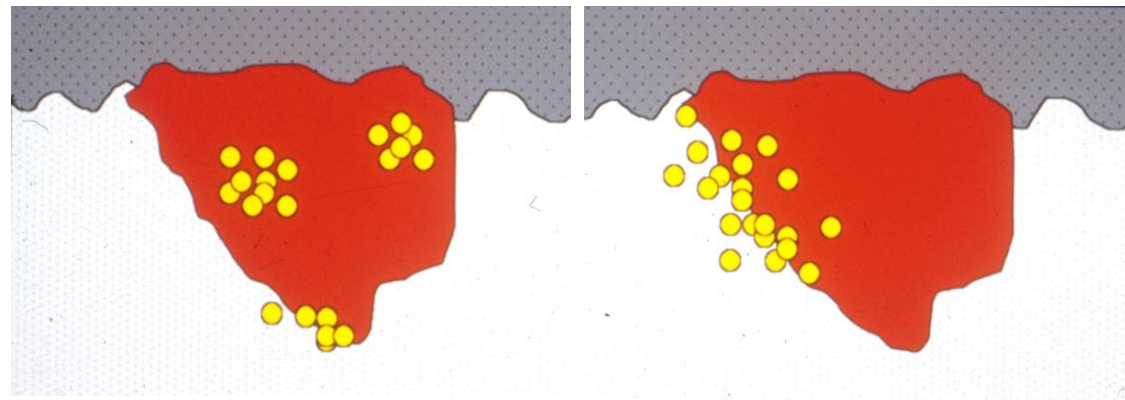
Brisk

“TILs are present throughout the substance of the vertical growth phase or present infiltrating across the entire base of the vertical growth phase.”

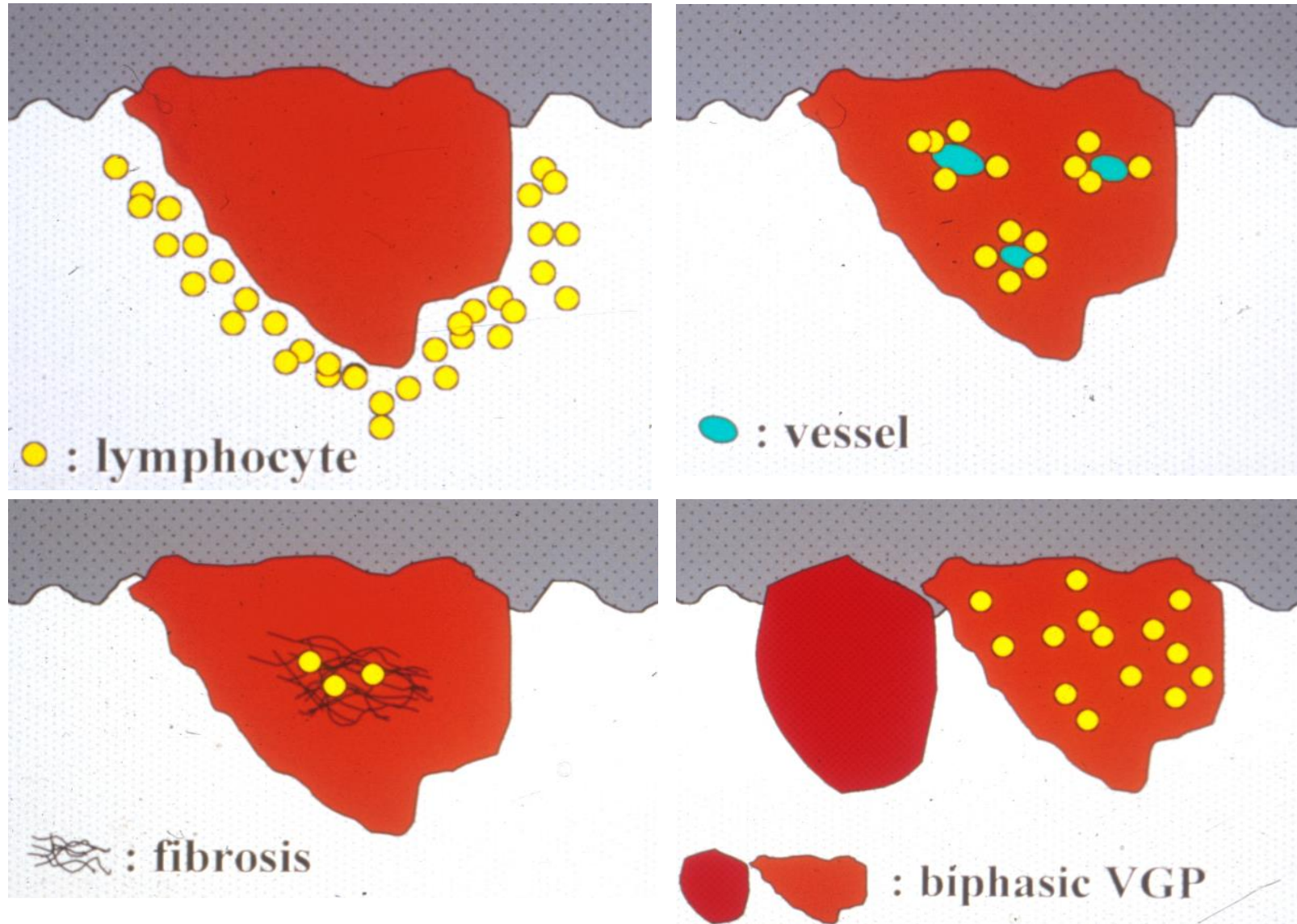


Non-brisk

“TILs are present in one or more foci of the vertical growth phase”



TILs – “absent”



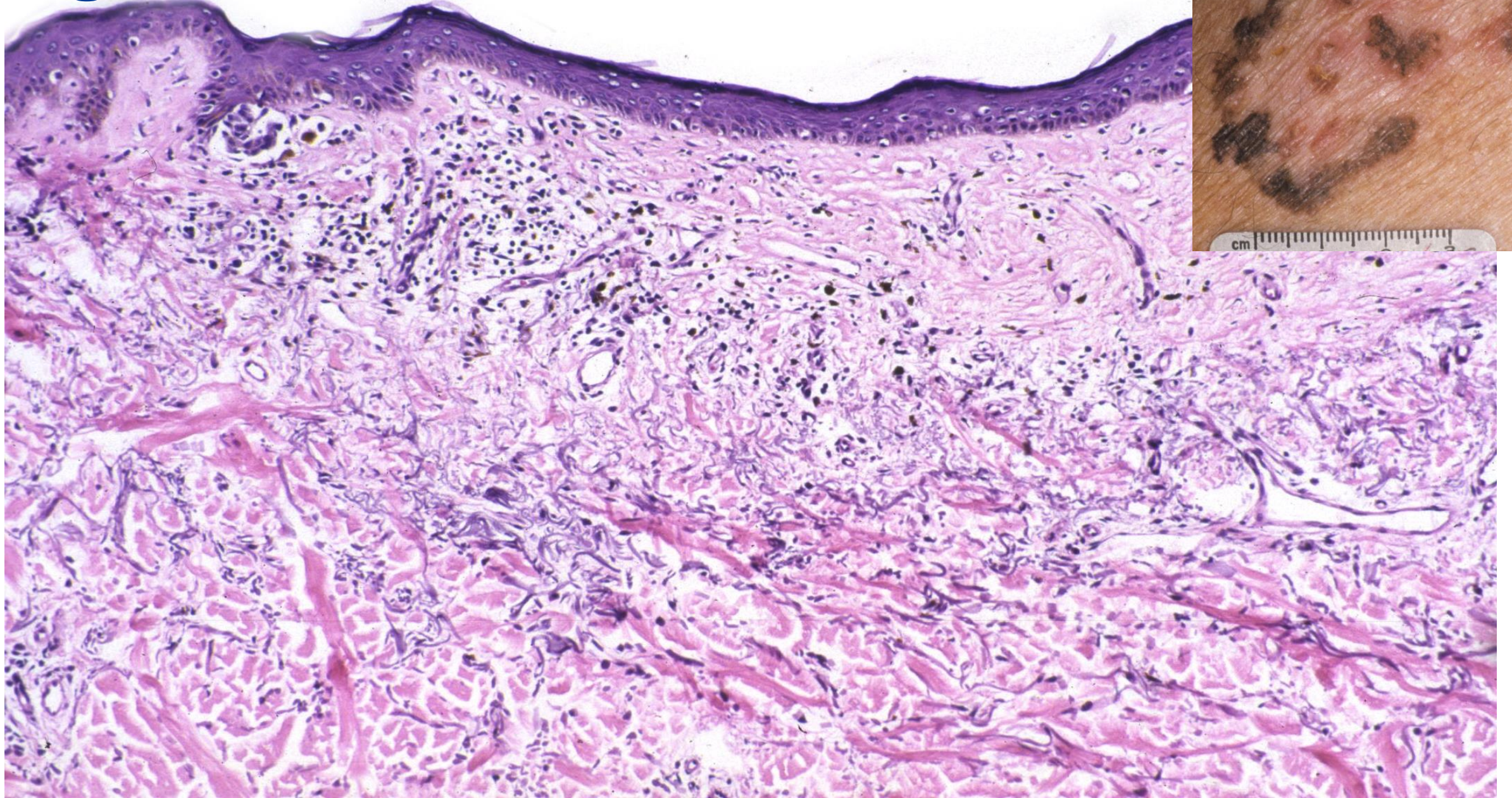
Tumor Infiltrating Lymphocytes

Overall survival for patients with localized (Stage I and II) melanoma

TILs	10 year Survival	5 year Survival
Brisk	55%	77%
Non-brisk	43%	53%
Absent	27%	37%

Clemente CG, Mihm MC,Jr, Bufalino R, et al. Cancer 1996
Clark WH, Jr., Elder DE, Guerry DI, et al. JNCI 1989

Regression



Histopathological factors in Melanoma

Primary Tumor

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Sentinel Lymph Nodes

Presence of metastasis

Number of positive lymph nodes

Size of metastasis

Detection Technique

Location of metastasis



Sentinel lymph node analysis:

a shifting landscape

Detection of one melanoma cell in a sentinel lymph node (SLN) upstages to AJCC III

Management of Stage III melanoma is shifting, nevertheless the presence of even one melanoma cell indicates metastatic potential of the primary tumor

Technical aspects impact sensitivity of melanoma detection:

Surgical technique

- is a sentinel node only one node? hottest vs. not-hottest

Histopathological technique

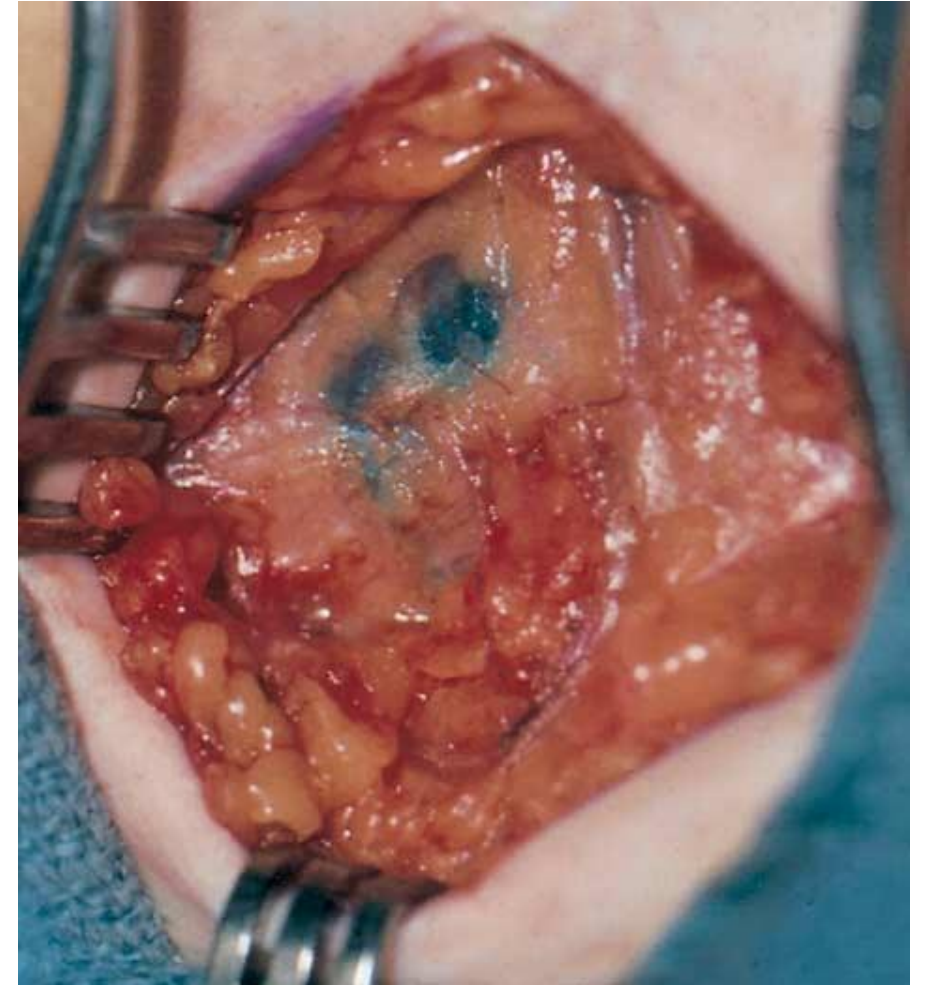
- levels vs. not
- immunohistochemical stains

Histopathological interpretation

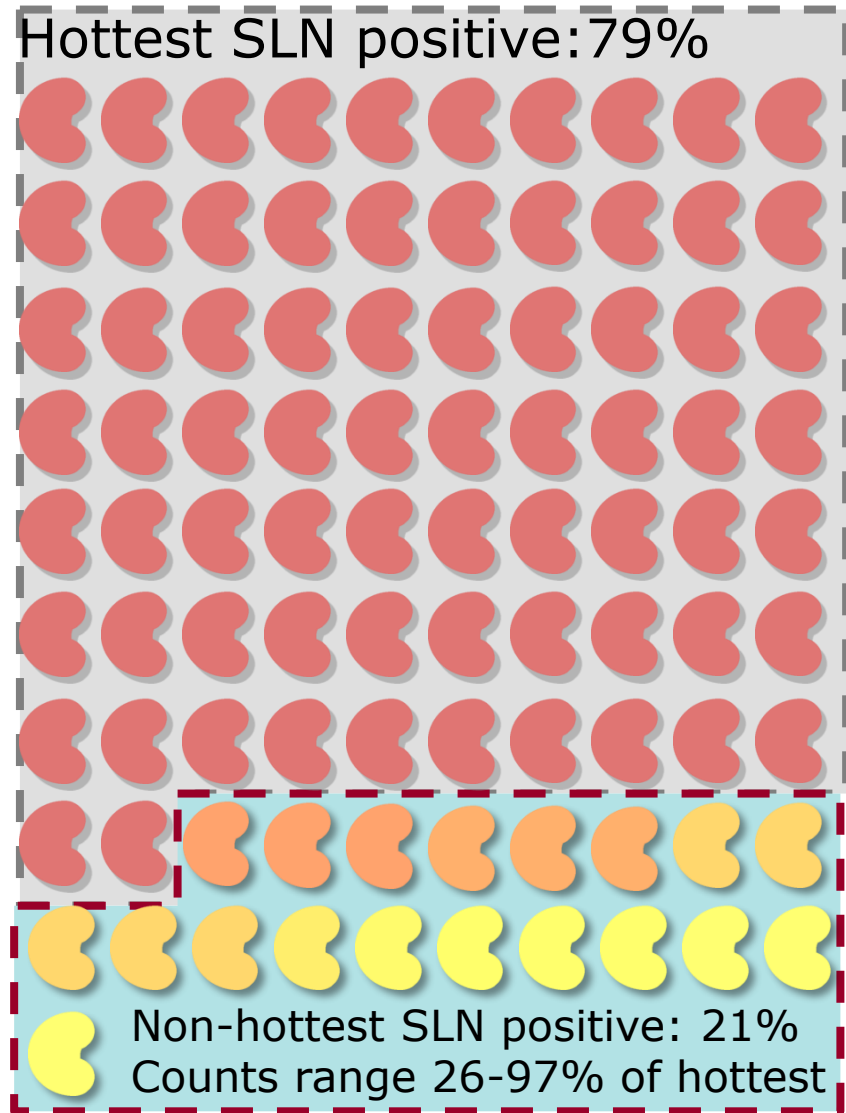
- nevus vs. melanoma

Intraoperative Lymphatic Mapping

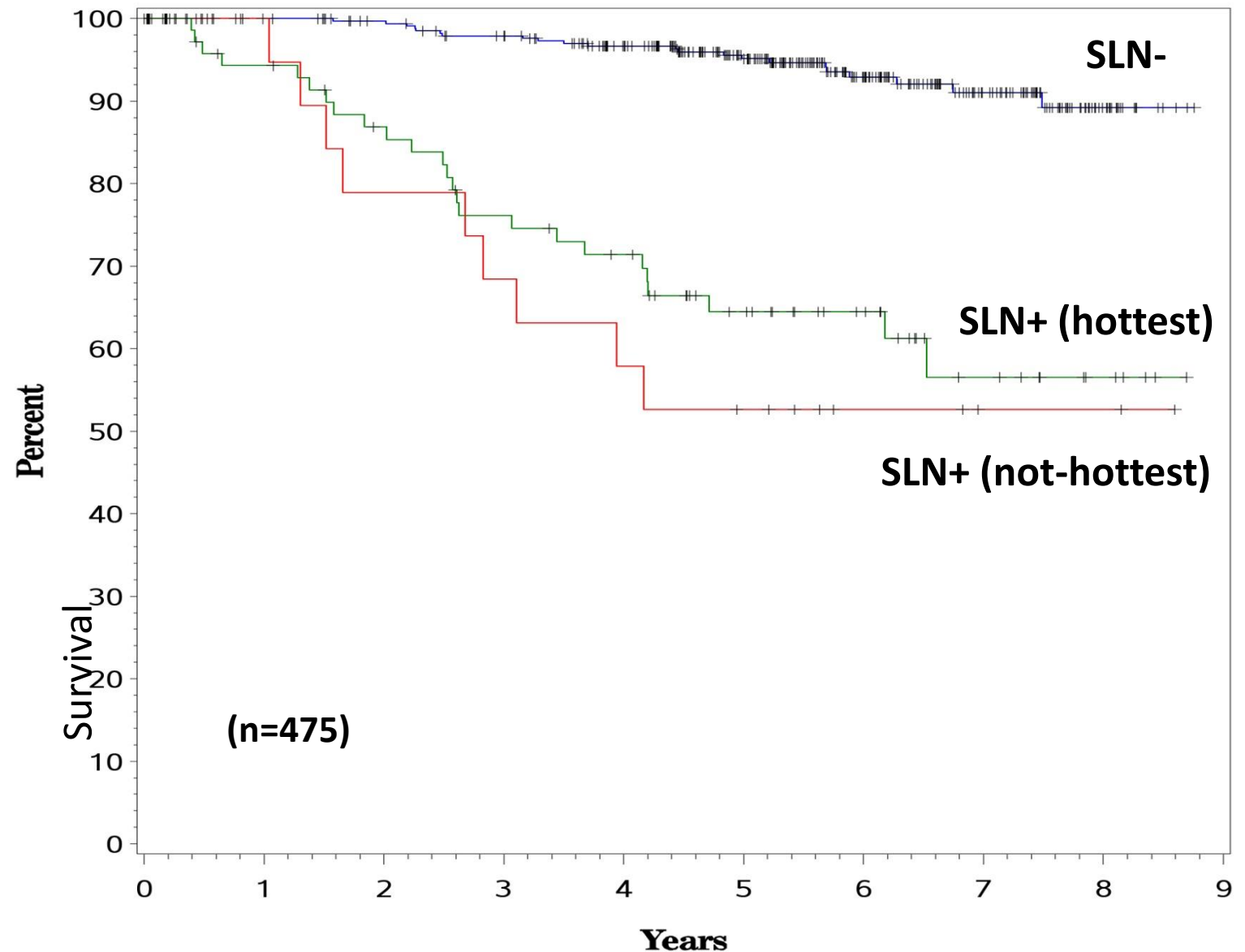
- Isosulfan blue & Tc99m sulfur colloid
- Blue staining of node and lymphatic
- Hand held gamma counter
- Removal of hot nodes (to 10% of #1)
- Wide excision of cutaneous lesion



91 patients with positive SLN



SLN melanoma metastases and Survival



Sentinel lymph node (SLN) number of basins mapped and overall outcomes

Recurrence in mapped SLN basin

4.3% sentinel lymph node positive (SLNP)

3.4% sentinel lymph node negative (SLNN)

Progression beyond the SLN basin

43% sentinel lymph node positive (SLNP)

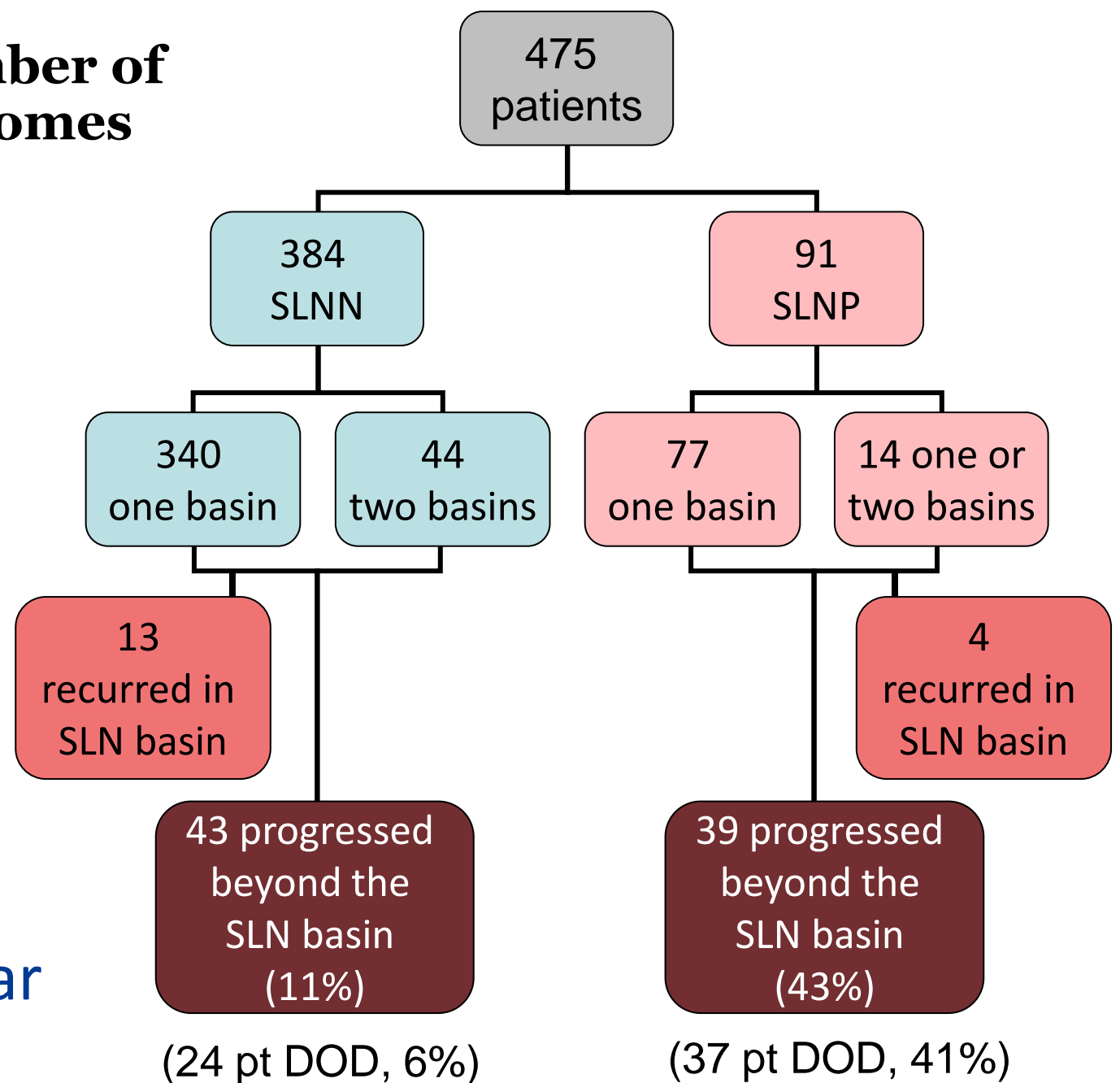
11% sentinel lymph node negative (SLNN)

Deaths from melanoma related disease

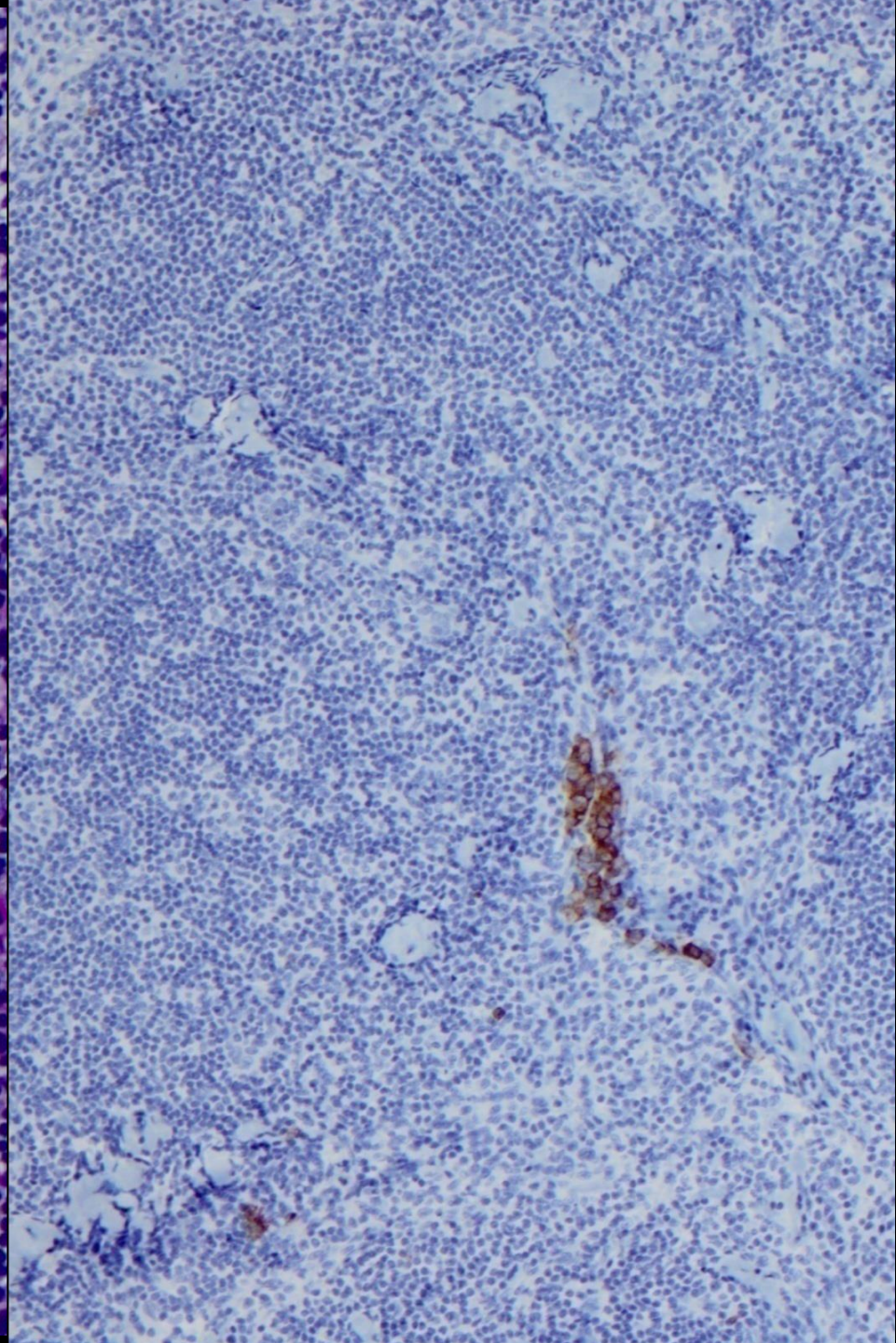
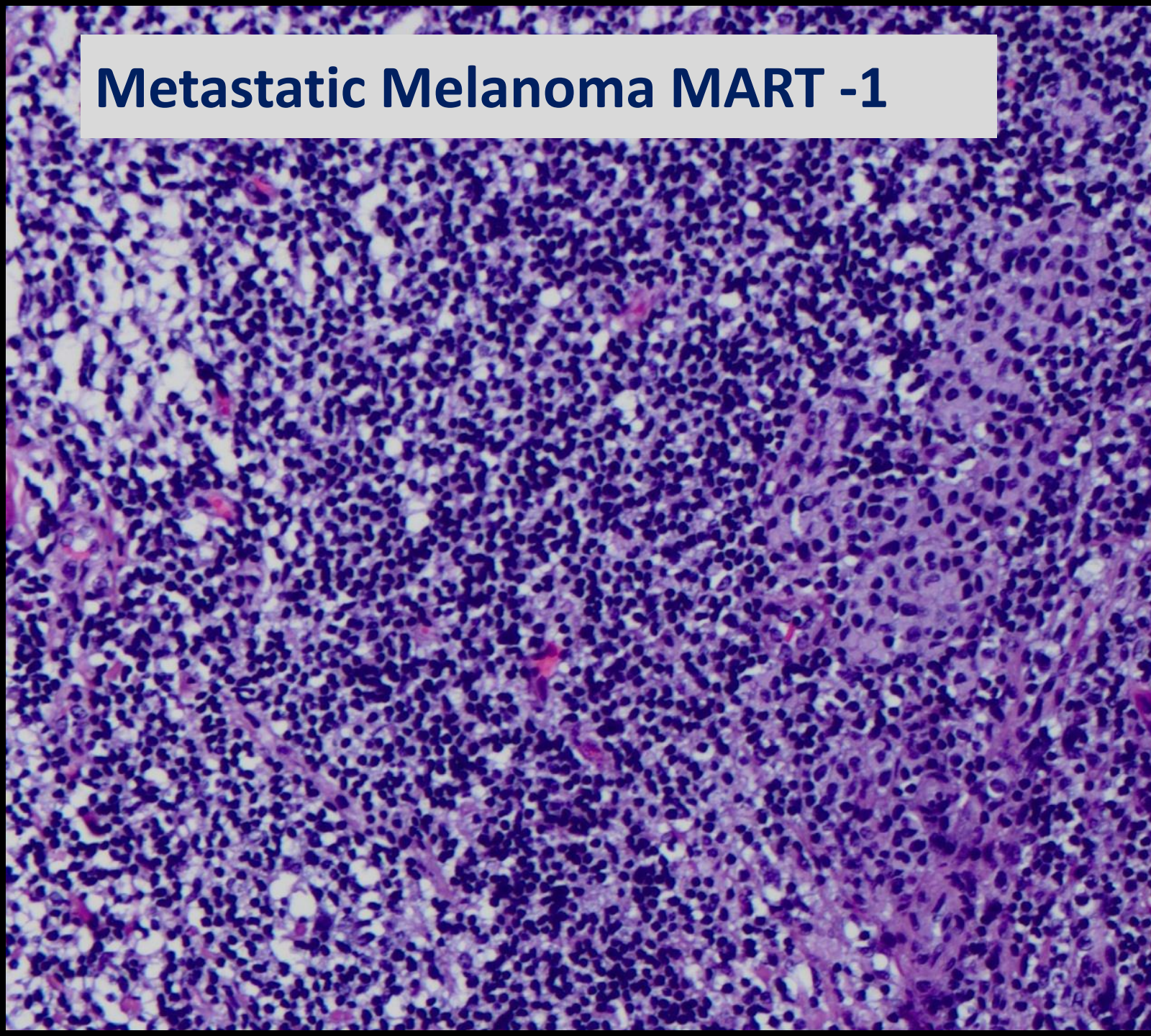
41% sentinel lymph node positive (SLNP)

6% sentinel lymph node negative (SLNN)

Absolute numbers of progressed and died are similar between SLNP and SLNN



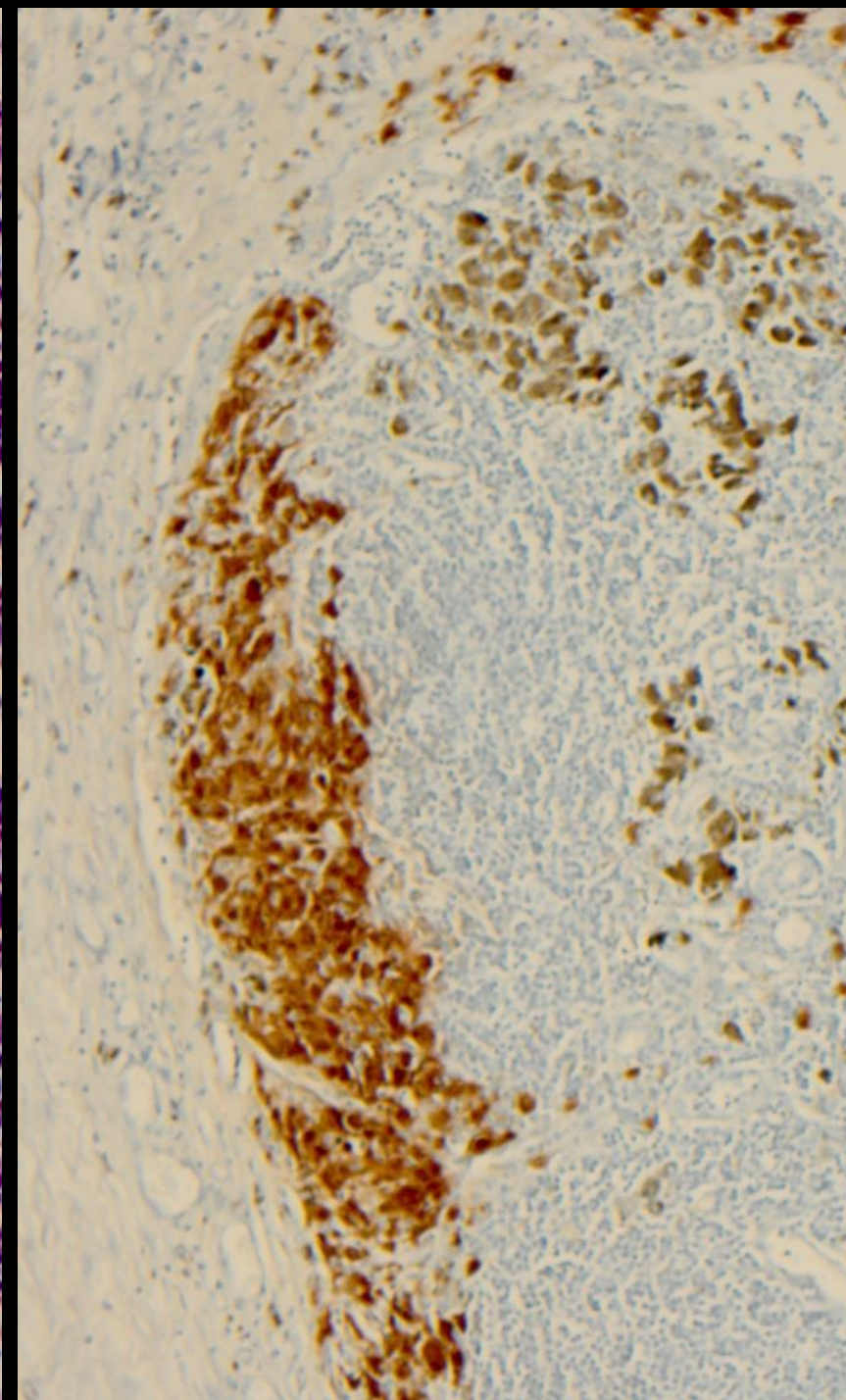
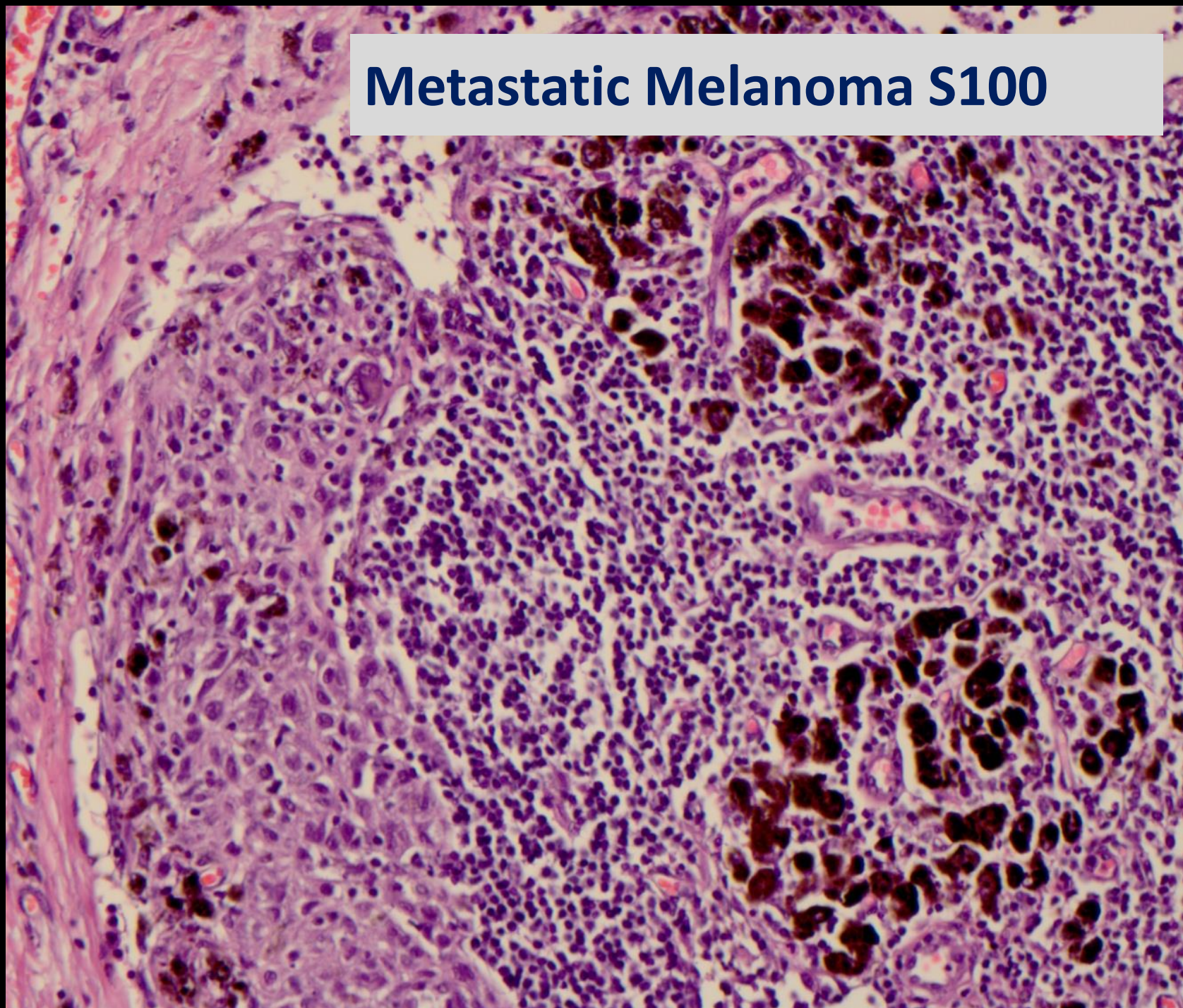
Metastatic Melanoma MART -1



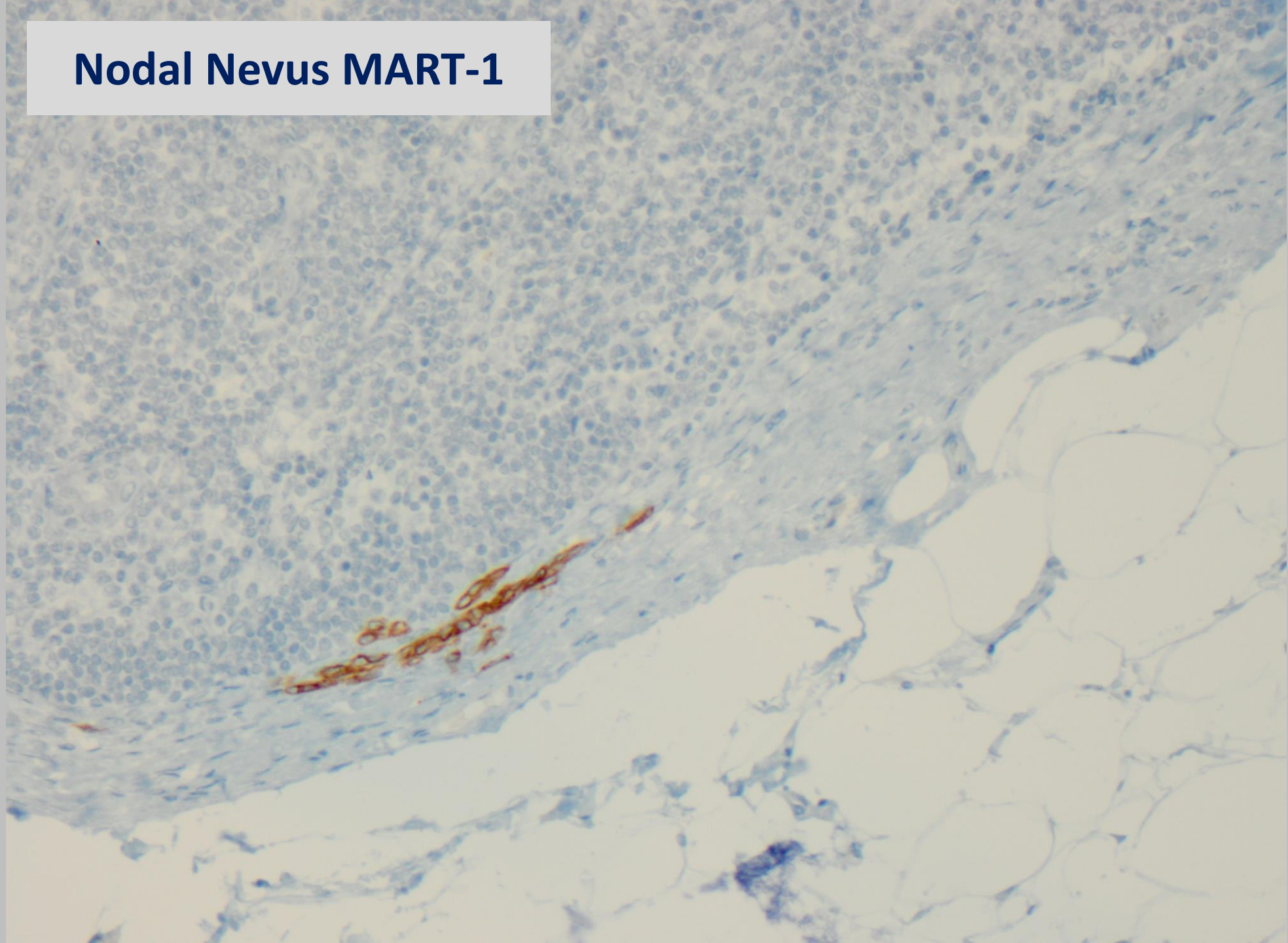
Diagnostic criteria for metastatic melanoma

- individual cells or nests of epithelioid or spindle cells foreign to the lymph node
- cytological atypia defined as large cells with nuclear pleomorphism, prominent nucleoli, or dusty cytoplasmic melanin granules
- positive staining for one or more melanocytic marker (S-100, MART-1)
- identification of the cells on H&E (not required)

Metastatic Melanoma S100



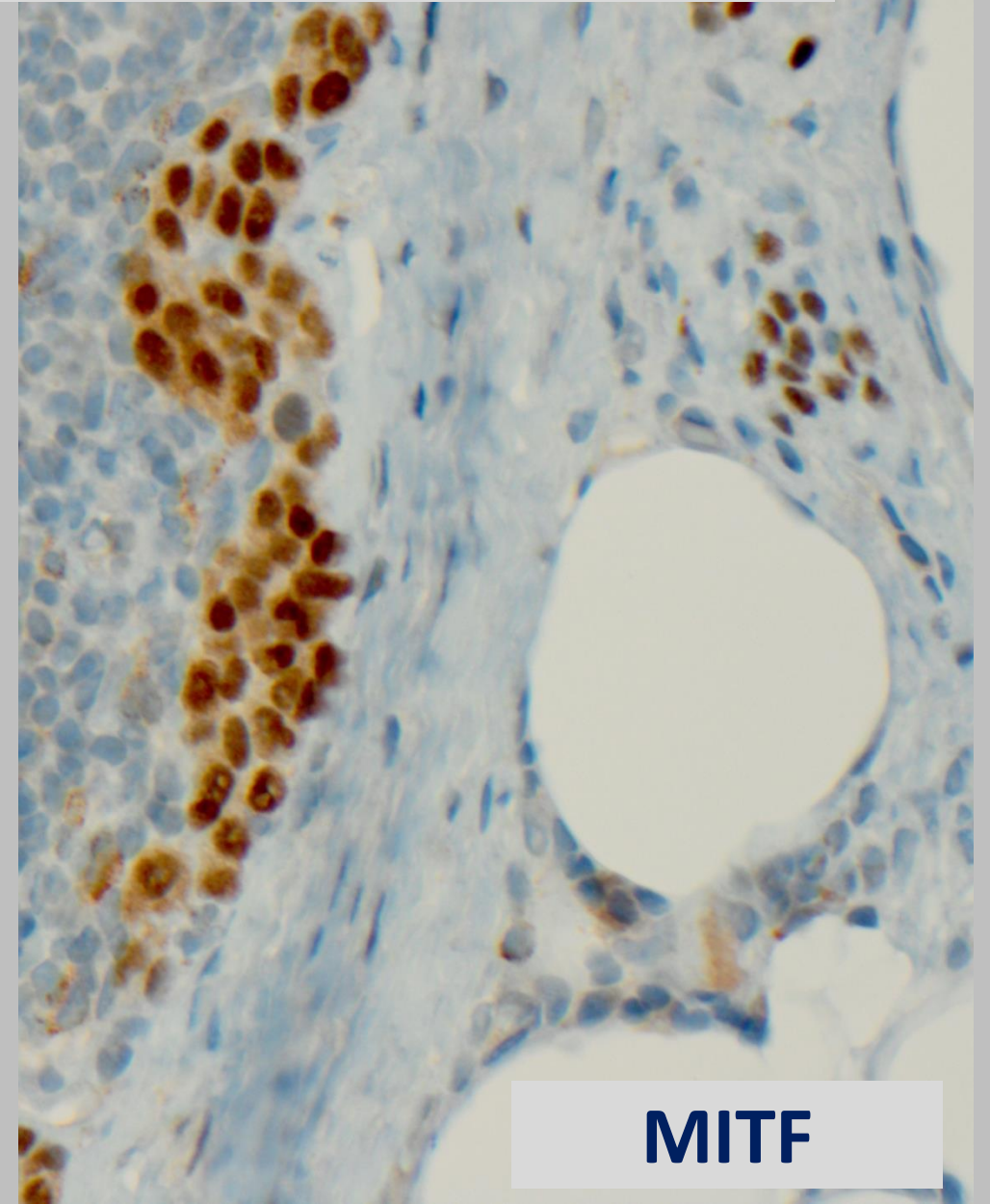
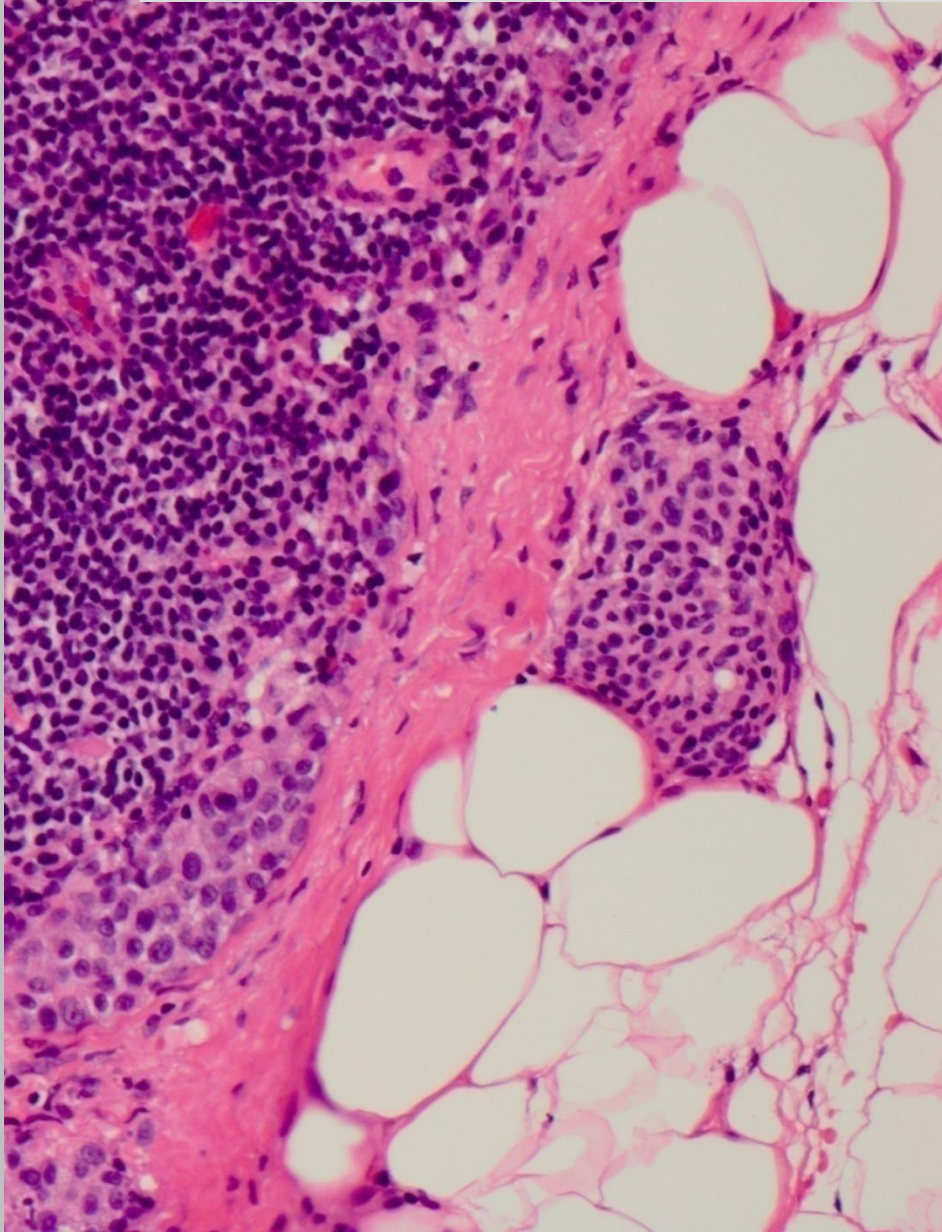
Nodal Nevus MART-1



Criteria for melanocytic nevus in lymph node

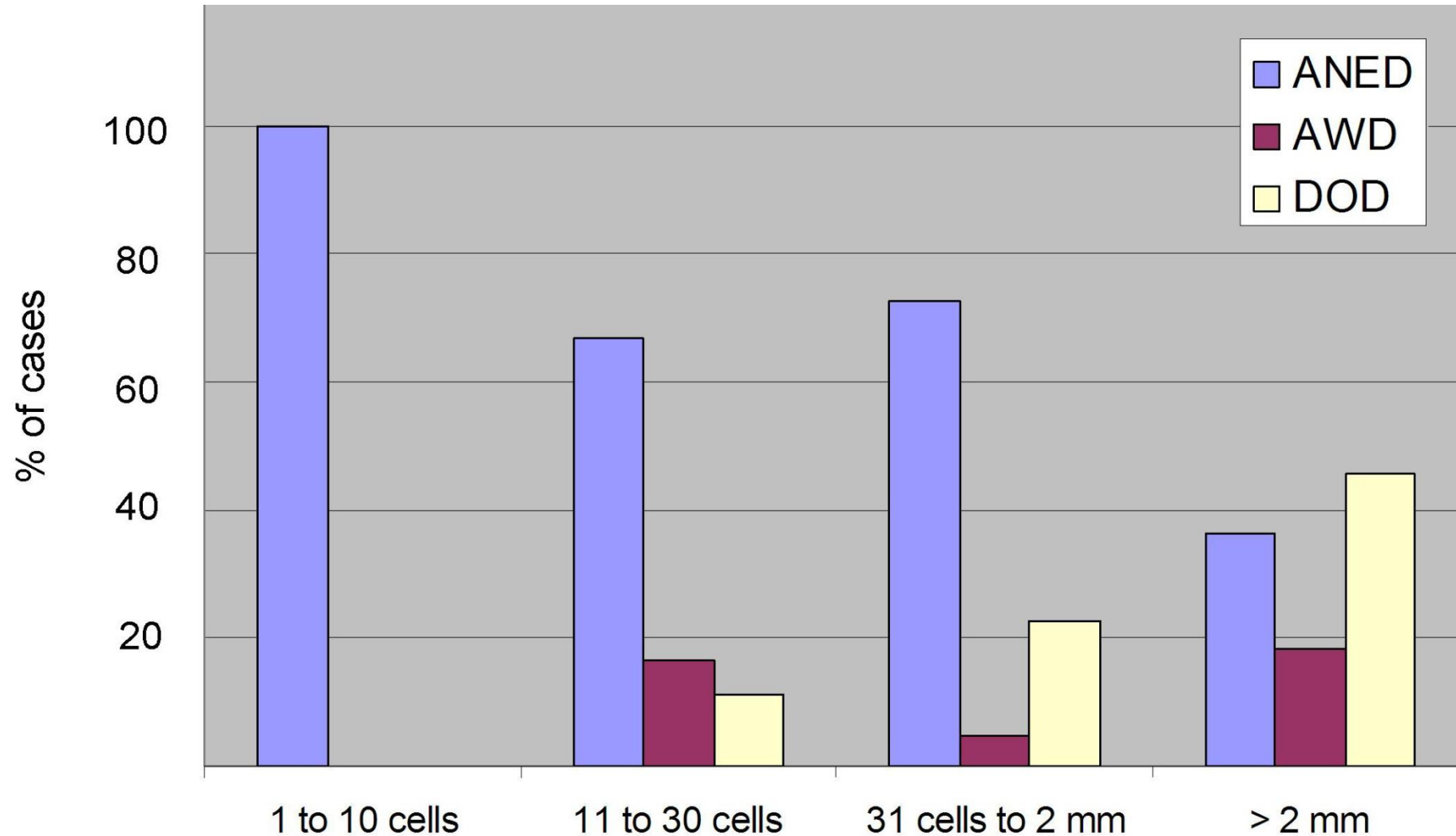
- individual cells in a linear array or nests of epithelioid or spindled cells foreign to the lymph node
- no cytological atypia
- positive staining for one or more melanocytic marker (S-100, MART-1, MelanA, MITF)
- identification of the cells on H&E
- cells are usually present in the fibrous capsule or trabeculae

Metastatic Melanoma and Nodal Nevus



MITF

Size of SLN metastasis correlates with outcome



SLN Analysis Take Home Points

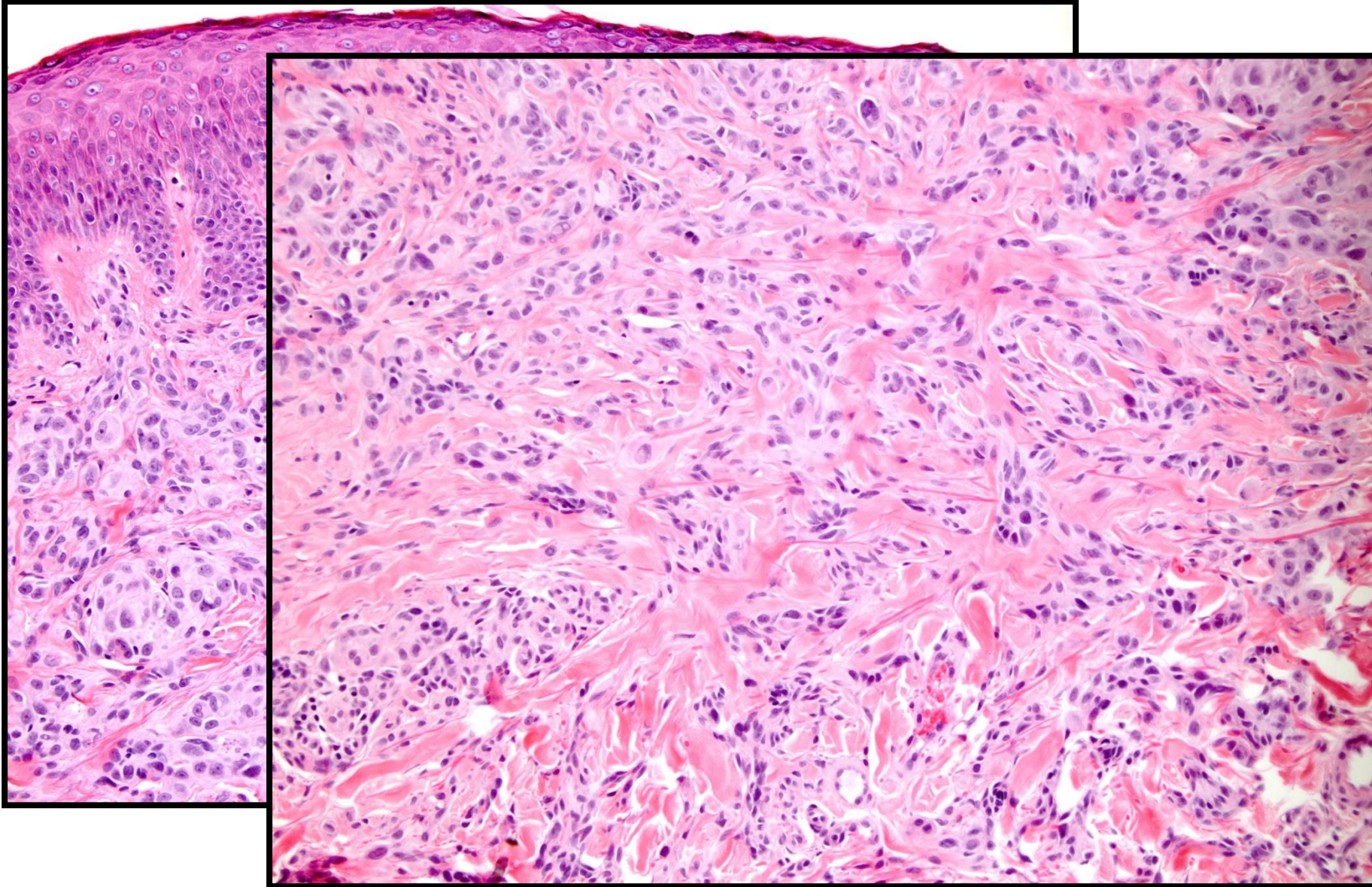
- The presence of one metastatic tumor cell upstages patient to stage III
- Failure to examine deeper levels leads to a 12-15% false negative rate
- Immunohistochemical stains help to identify microscopic melanoma

The diagnostic pathology report should contain:

- Number of positive LN/ total number of LN
- Extracapsular extension present or absent
- Maximal diameter of the largest metastatic deposit
- Immunohistochemical stains performed and results

In ambiguous primary tumors, metastasis is not diagnostic of melanoma (AST)

37 year old woman Atypical Spitz Tumor (AST/Melanocytoma?)
upper arm with severe atypia and mitoses



Atypical Spitz Tumors (melanocytomas?)	Cases with +SLN/ total patients	Mean follow-up in months	Cases with mets beyond the SLN/ total	Deaths
Smith et al. 1989	6/32 (19%)	72	0/30	0/30
Lohmann et al. 2002	5/10 (50%)	33.7	0/10	0/10
Su et al. 2003	8/18 (44%)	9.8	0/18	0/18
Gamblin et al. 2006	3/10 (33%)	33.7	0/10	0/10
Urso et al. 2006	4/12 (33%)	26.3	0/12	0/12
Murali et al. 2008	6/21 (29%)	25.8	0/21	0/21
Ludgate et al. 2009	27/57 (47%)	43.8**	0/57	0/57
Busam et al. 2009	11 all + SLNB*	61.4	0/11	0/11
Cerroni et al. 2010	25/35 (71%)	83.5	8/35	1/35
Tom et al. 2011	2/4 (50%)	25.3	0/4	0/4
Raskin et al. 2011	8/15 (53%)	Not reported	0/15	0/15
Sepehr et al. 2011	1/6 (17%)***	64.6	0/76	0/76
Barnhill et al. 2011	4/5 *	10.5	0/5	0/5
Hung et al. 2013	6/23 (26%)	55.6	0/23	0/23
Totals	102/245 (42%)		8/327 (<3.0%)	1/327 <0.5%

Staging Parameters:

Primary tumor and Sentinel Lymph Nodes

AJCC staging 2018

- 80 percent of patients diagnosed with melanoma present with localized disease (AJCC clinical stage I & II)
- Prognosis for this group varies from 53-98%
- SLN is offered to those determined to be at highest risk for microscopic LN metastasis

AJCC Staging (8th Edition) Summary of Changes (T)

Thickness measured to nearest 0.1 mm (not 0.01 mm)

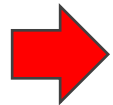
- 0.75 mm = 0.8 mm

Mitoses*: reported but not used in staging

Clark's level: reported but not used in staging

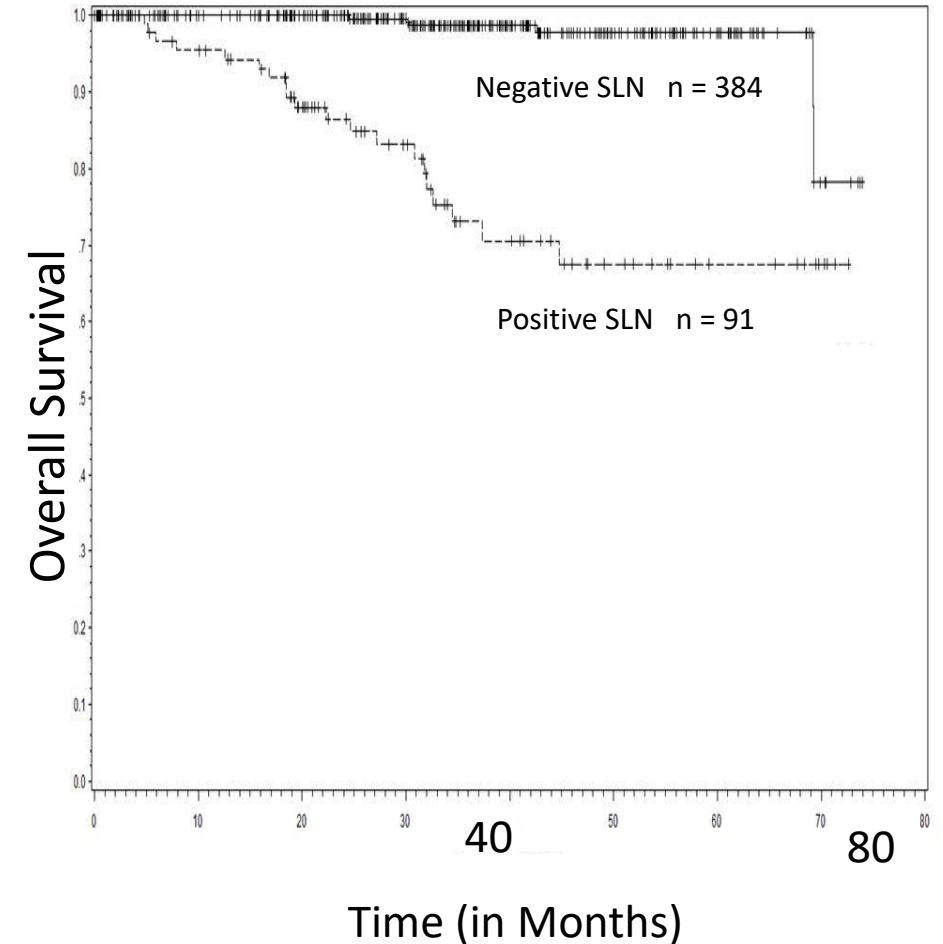
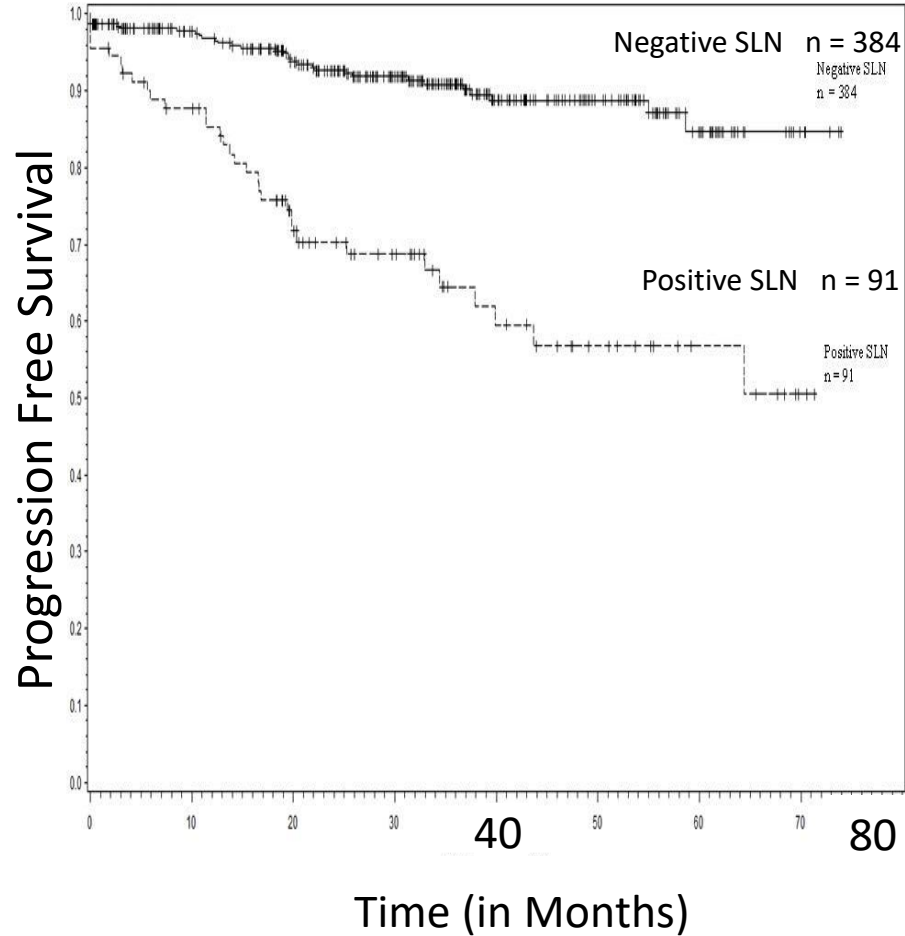
Difference between T1a and T1b now based on thickness*

- T1a: < 0.8 mm without ulceration
- T1b: < 0.8 mm with ulceration
0.8 – 1.0 mm with or without ulceration

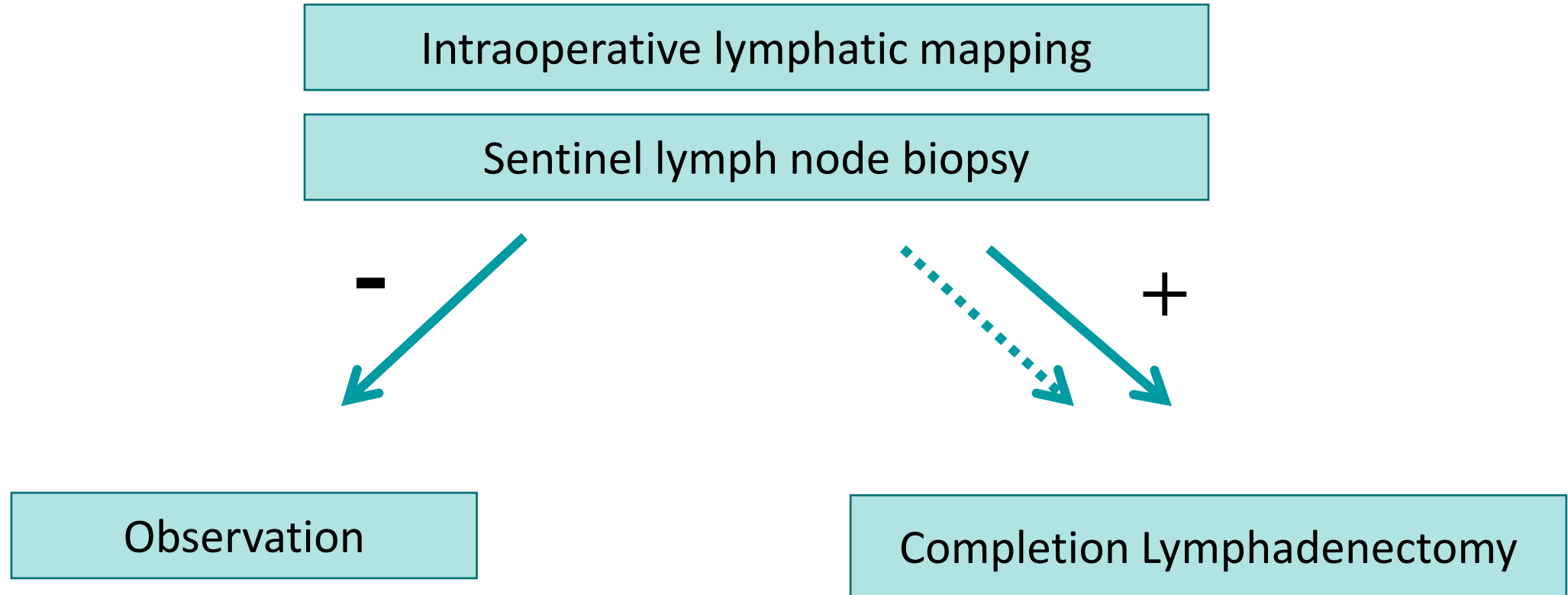


*Mitoses represent a significant prognostic factor across all tumor thicknesses

Progression free and overall survival in 475 MGH patients with sentinel lymph node biopsy



SLN and CLND a shifting landscape



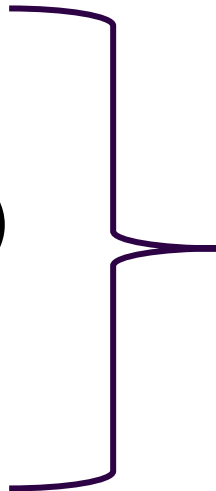
MSLTI vs. MLSTII

Now known and accepted and confirmed by MSLTI

- Pathological status of the SLN is the most important prognostic factor
- SLN removal led to fewer recurrences

MSLTII

international
multicenter (63 sites)
randomized
phase 3 trial



Evaluate the usefulness of
Completion Dissection
in melanoma patients
with positive SLN

MSLTII NEJM 2017: Conclusions

Completion Lymphadenectomy is associated with:

- increased rate of regional disease control
- prognostic information
- increased rate of lymphedema
- **no increase in melanoma specific survival**

There was no significant difference in melanoma specific survival between the CLND (86%) and Observation (86%) cohorts with a median follow up time of 43 months

SLN and CLND in Melanoma: a shifting landscape

SLN (Sentinel Lymph Node)

Until recently, SLN was offered for even very thin mitogenic or ulcerated primary cutaneous melanoma (0.3-0.7 mm)

Now only rare circumstances lead to SLN for tumors < 0.8 mm

CLND (Completion Lymphadenectomy)

Historically, CLND was offered to patients with SLN metastases of any size (including those with only one tumor cell detected)

Now CLND is rarely recommended (exceptions include requirement for clinical trial eligibility, or inability to comply with observation exams and imaging)

Approval of systemic therapy for patients with stage IIB/IIC disease...

... do we still need to do SLNB?

Continued utility of SNB in this patient subset

- SNB provides prognostic and staging information
- SLN biopsy in patients with positive SLN leads to fewer subsequent regional node metastases
- results inform clinician recommendations and allow for more informed choices regarding systemic therapy

