



# Sentinel Lymph Node in Breast Cancer 2020

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UNIVERSITY OF MIAMI  
MILLER SCHOOL  
of MEDICINE

**Pathology & Laboratory Medicine**

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- SLN for axillary lymph node staging
- Significance of occult metastases in SLN
- Protocol for histopathologic evaluation of SLN
- Intraoperative evaluation of SLN
- Management of axilla with positive SLN
- Neoadjuvant therapy and SLN



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# Validated Prognostic/Predictive Factors in 2020

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Tumor Size  
Histologic Grade  
Histologic Type  
Nodal Status  
Steroid Receptor Status  
HER2-*neu*  
Oncotype DX



# Validated Prognostic/Predictive Factors in 2020

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Tumor Size

Histologic Grade

Histologic Type

**Nodal Status**

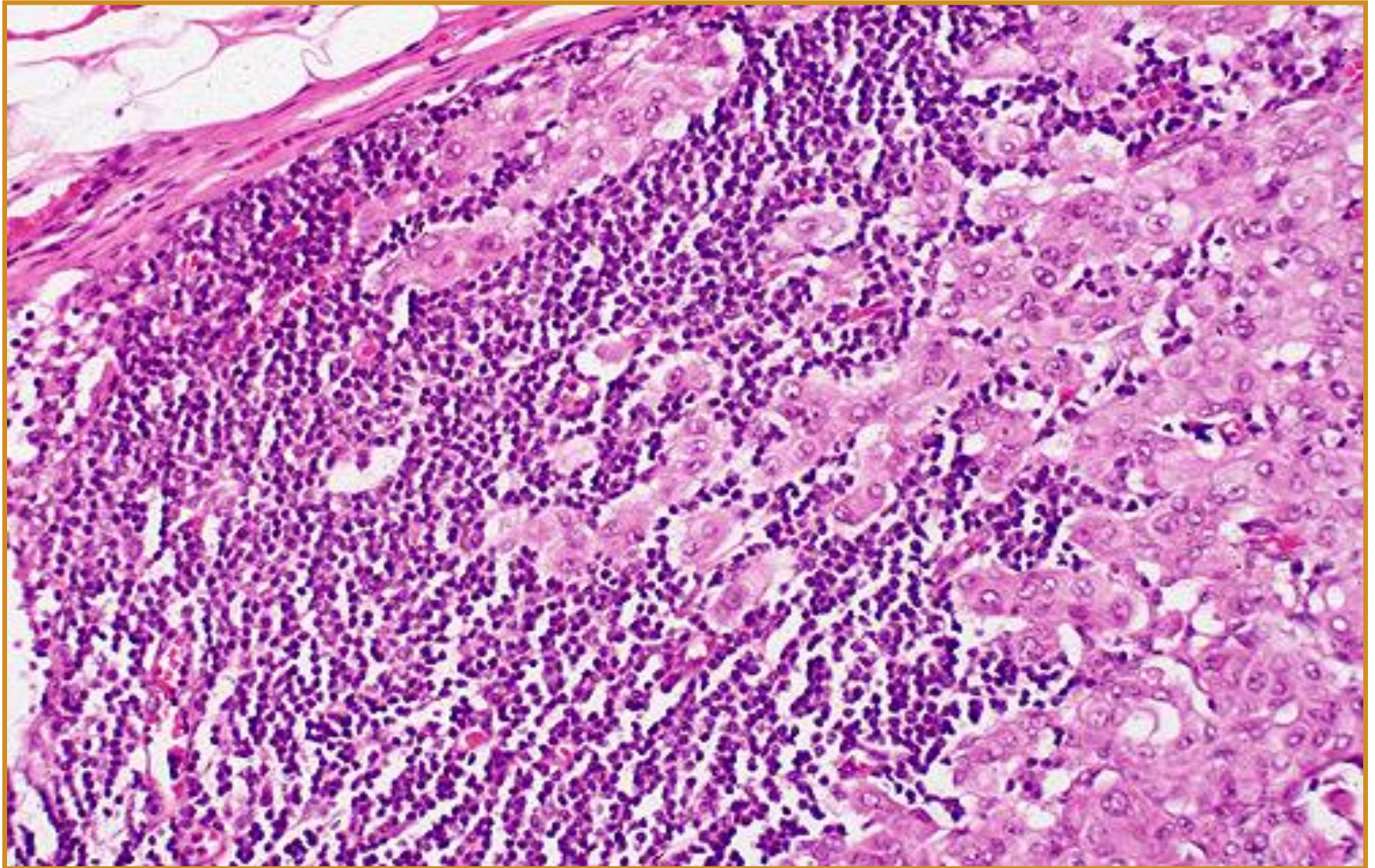
Steroid Receptor Status

HER2-*neu*

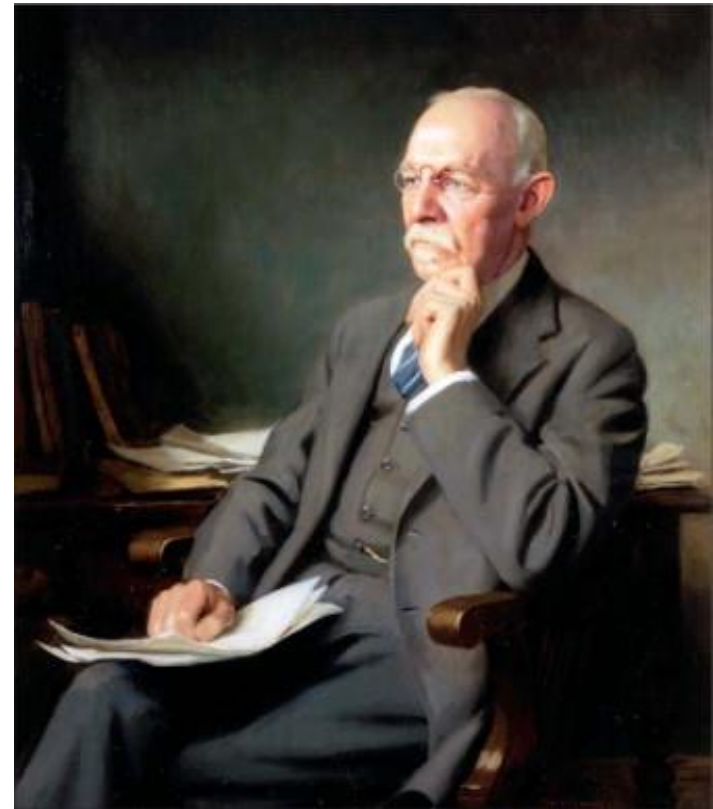
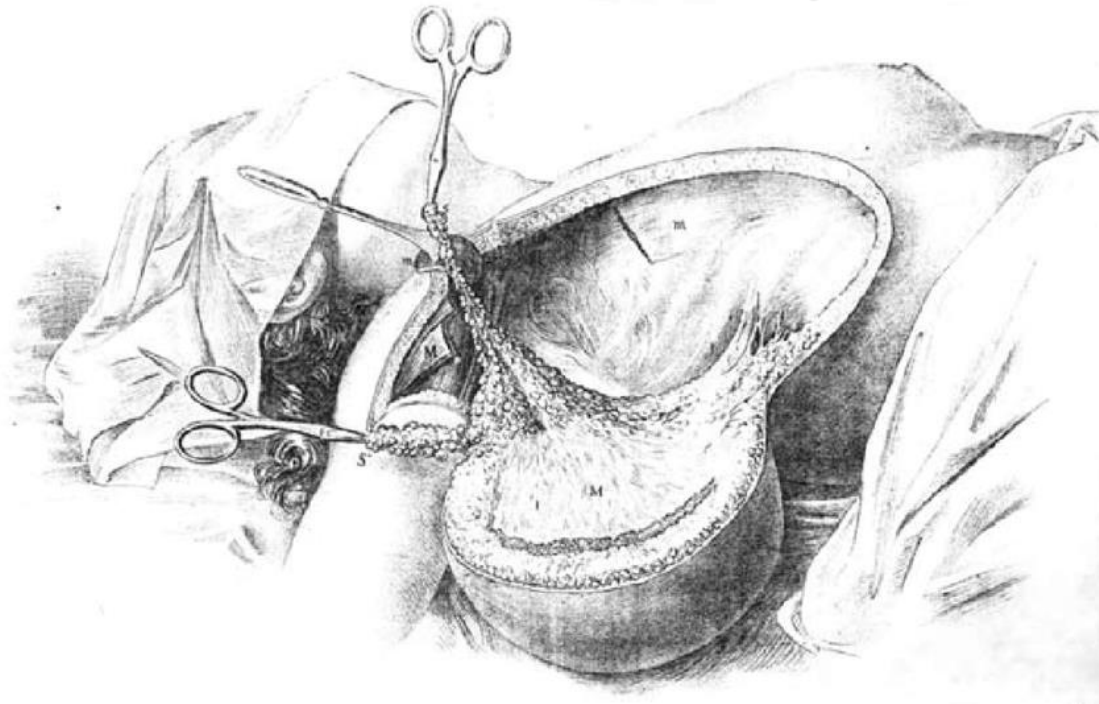
Oncotype DX



Nodal Status: T N M



# Halsted Radical Mastectomy, 1882



William S. Halsted, MD

## Halstedian Principles

Breast cancer arose in one location and spread to nearby lymph nodes and then throughout the body.

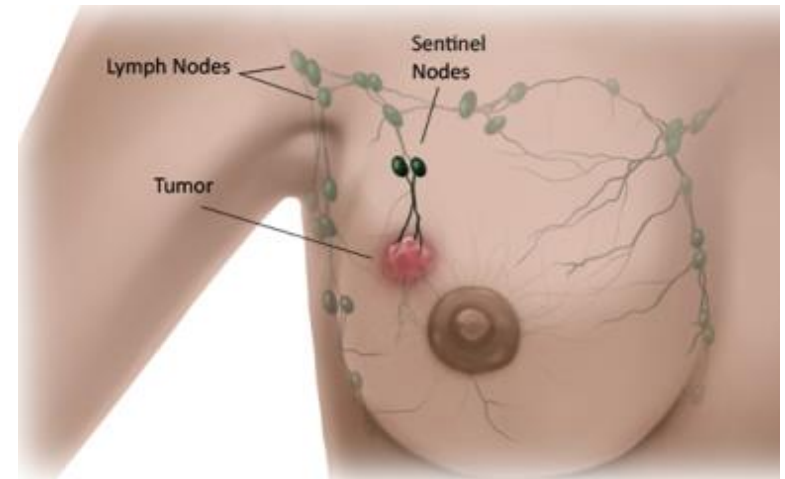
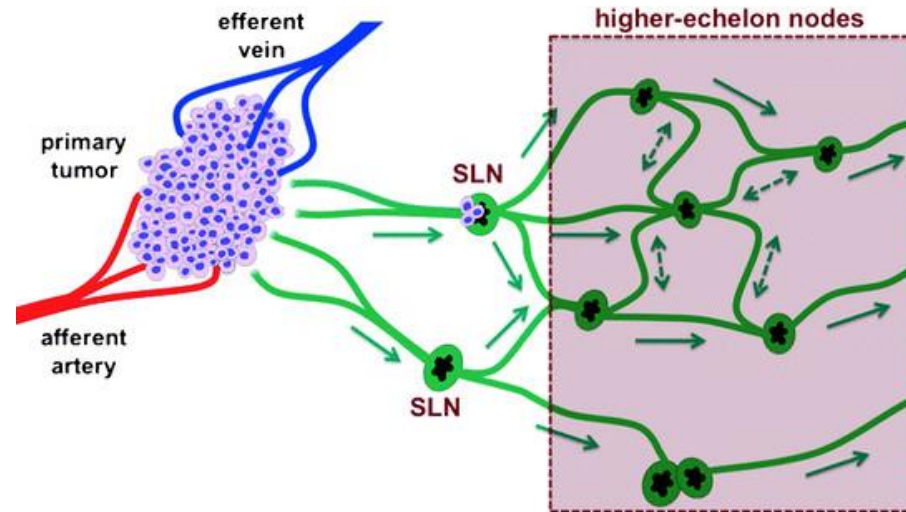
So, removal of **breast, chest wall muscles, and lymph nodes** was the logical treatment.



Lymphedema, pain, numbness, impaired range of motion

# Sentinel lymph node (SLN)

The first lymph node(s) draining the tumor bed

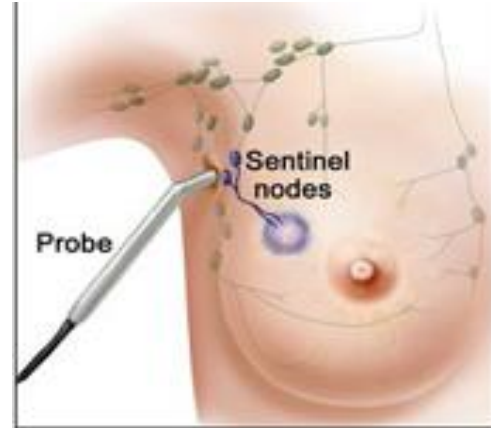
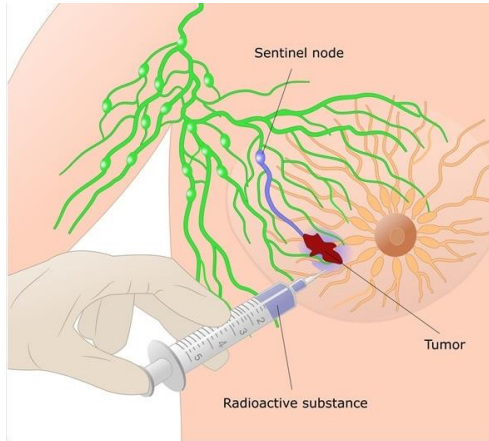


The first lymph node(s) to which tumor will metastasize

If the SLN is negative, then the rest of the nodes should be negative

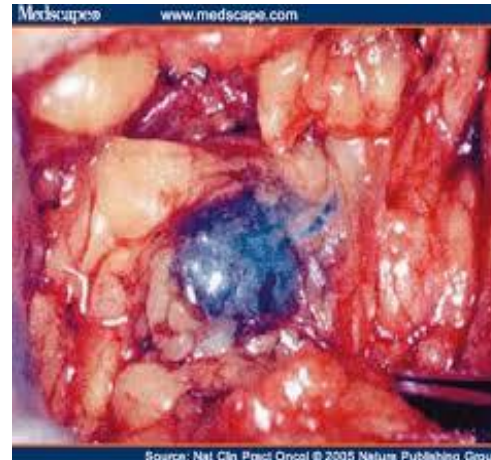
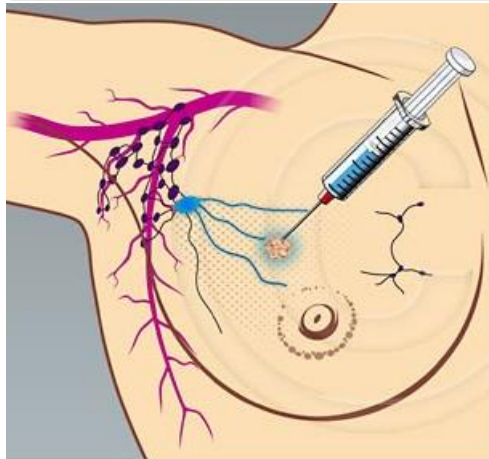
# SLN for Axillary Node Staging

Radioactive tracer and probe



“Hot” radioactive count

Blue dye injection



Blue-colored lymph node



# SLN for Axillary Node Staging

- Milan, NSABP-32 and ALMANAC trials:
  - Prospective studies looking at SLN biopsy to replace ALN dissection for axillary staging
  - Compared SLN biopsy + ALN dissection to SLN biopsy alone for survival outcomes in cN0 patients
  - Demonstrated a 90% identification rate (IR) and a 5-10% false negative rate (FNR) for the SLN biopsy procedure
  - Equivalent disease free (DFS) and overall survival (OS)
  - Less than 1% regional recurrence when SLN is negative
  - Established the SLN biopsy as a safe, reliable, and effective standard procedure for pathologic staging cN0 patients.



# Results Reporting of SLN Metastases

AJCC 6<sup>th</sup> ed. 2002

Current staging systems classify nodal stage based on *size*

Macrometastases (>2.0mm) pN1

Micrometastases (0.2-2.0mm) pN1(mi)

“Isolated Tumor Cells” (<0.2mm) pN0(i+)



# Results Reporting of SLN Metastases

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Current staging systems classify nodal stage based on *size*

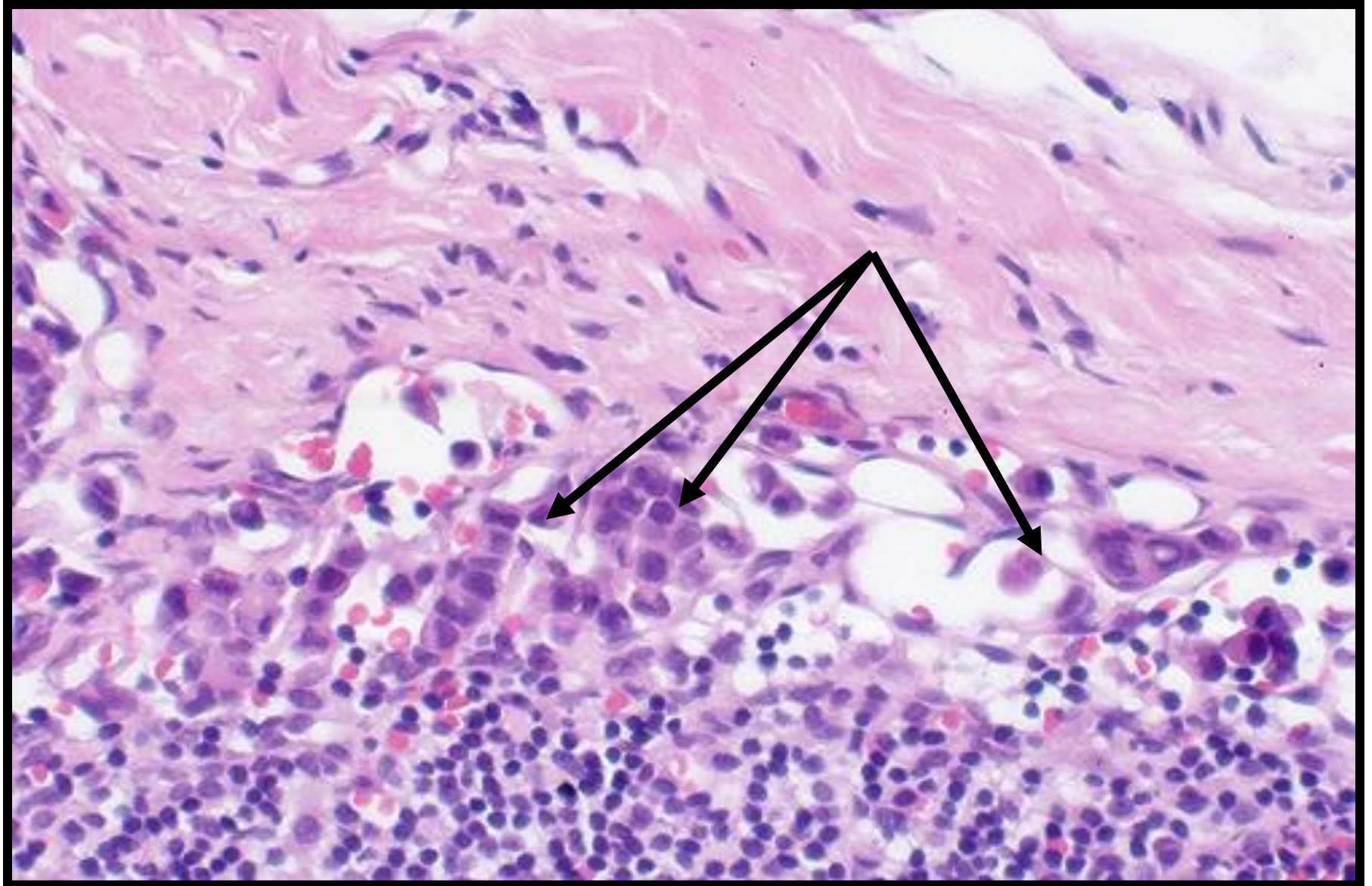
Macrometastases (>2.0mm) pN1

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“Isolated Tumor Cells” (<0.2mm) pN0(i+)



# “Micrometastasis”



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# Significance of occult metastases

- “Occult” metastasis is any metastasis not identified on initial examination using a “standard” evaluation protocol.
- With SLN biopsy, the number of lymph nodes received by pathology ↓ but the intensity of the pathological examination and the rate of axillary node positivity ↑
- “Enhanced” pathology protocols for SLN includes step-sections and cytokeratin immunohistochemistry for improved detection
- The era of SLN has resulted in increased detection of occult metastases



# Significance of occult metastases

## The NSABP-B32 trial

- Prospective, randomized, controlled phase III trial
- Designed to compare SLN biopsy to ALN biopsy.
- 5611 cN0 women with 95.6 mo follow-up
- 3,986 SLN-negative by “routine” histopathologic testing, defined as routine (H&E) stained slides at 2mm intervals
- Presented an opportunity to investigate the biological and clinical significance of occult metastasis in “negative” SLN
- SLN are 4.3 times as likely to contain overt metastases and 12.3 times as likely to contain occult metastases compared to non-sentinel nodes.





5611

Patients with clinically negative axillary lymph nodes cN0

2807	2804
SLN biopsy + ALN dissection	SLN biopsy only
1978	2011
SLN-Negative	SLN-Negative
1924	1960
Blocks and follow-up data	Blocks and follow-up data
316	300
Positive for occult metastases	Positive for occult metastases

616 positive for occult metastases **15.9%**

430 had isolated tumor cells 11.1%

172 had micrometastases 4.4%

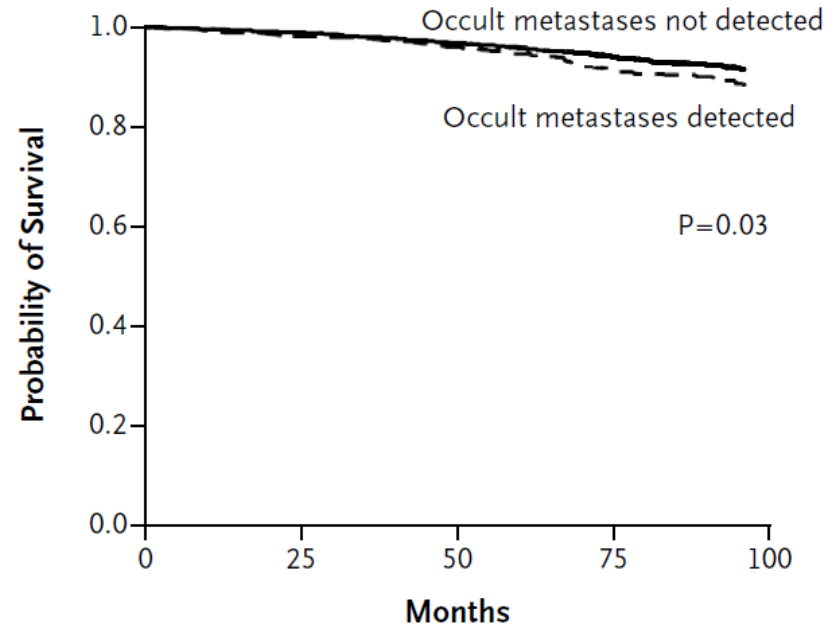
14 had macrometastases 0.4%

# Significance of occult metastases

## The NSABP-B32 trial:

The difference of 1.2 percentage points in overall survival (95.8% v. 94.6%) was **statistically significant (p=0.03), but clinically irrelevant.**

A Overall Survival



No. at Risk

Occult metastases not detected	3197	3085	2295	575
Occult metastases detected	598	581	416	108



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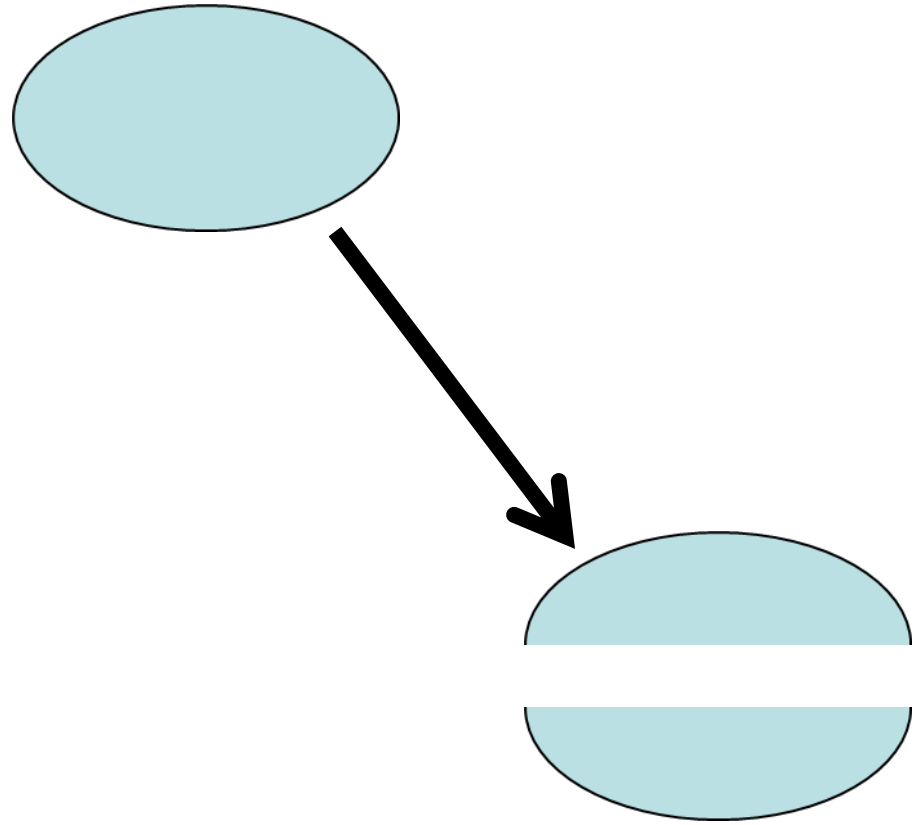
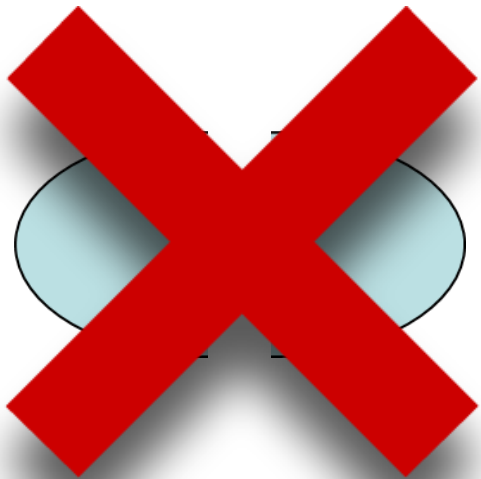


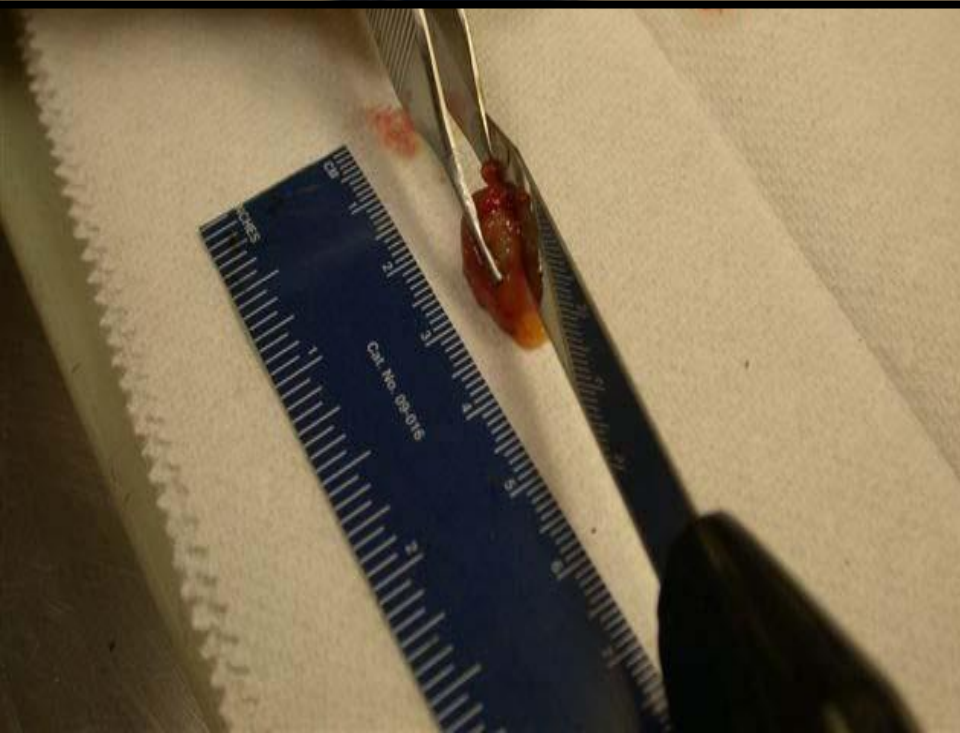
# Protocol for Histopathologic Evaluation of SLN

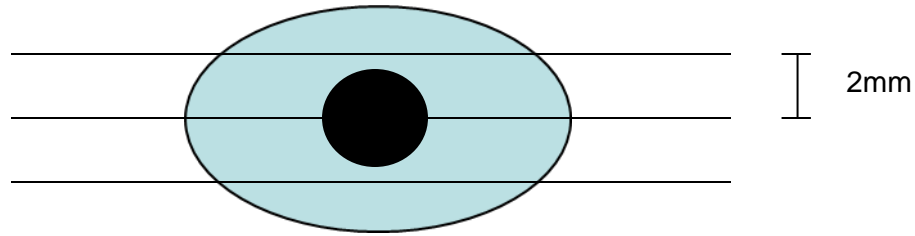
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- The main goal of SLN examination is to detect all macrometastases ( $\geq 2\text{mm}$ )
- Lymph nodes should be thinly sliced at 2mm intervals, parallel to its longest axis
- Embed slices in a manner that eliminates more than 2mm of unexamined tissue.
- One H&E stained section per 2mm slice +/- use of cytokeratin immunohistochemistry (CAP and ASCO guidelines, informed by NSABP-B32 results)









Lymph node slices should be placed in cassette to avoid missing more than 2mm of unexamined tissue

Correct



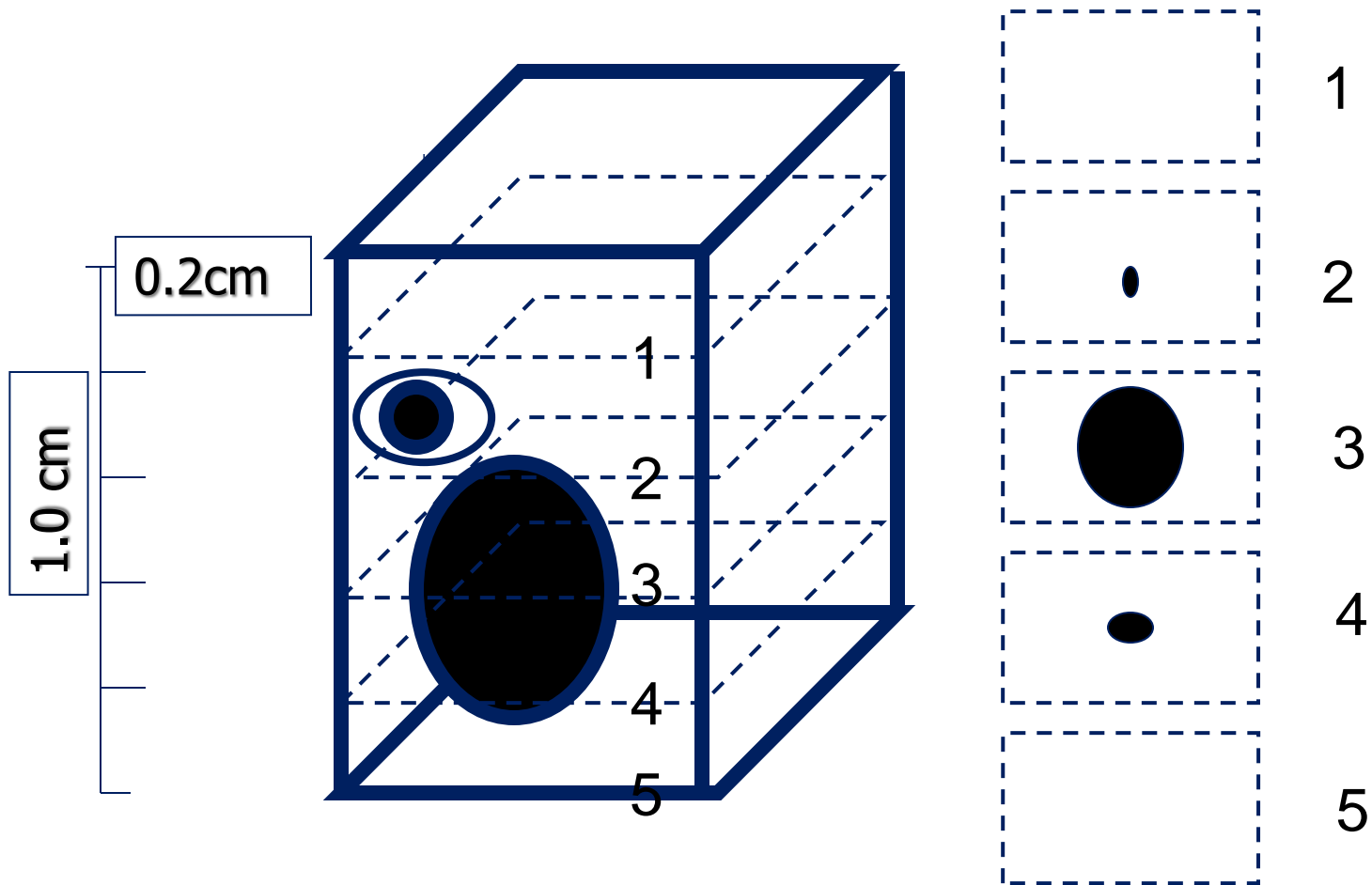
Incorrect



Dashed lines represent surface placed down in cassette



# Sectioning of sentinel lymph nodes

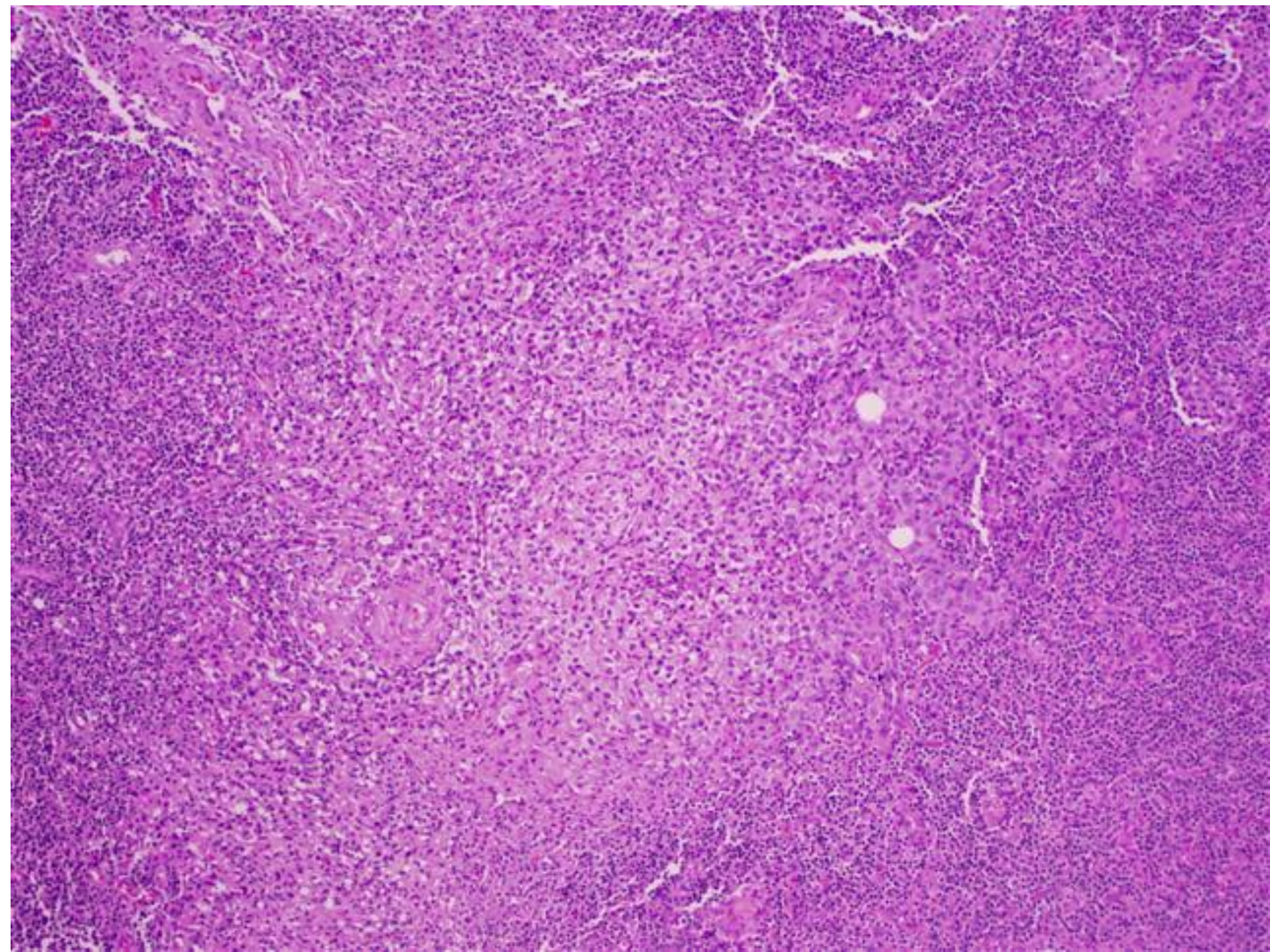


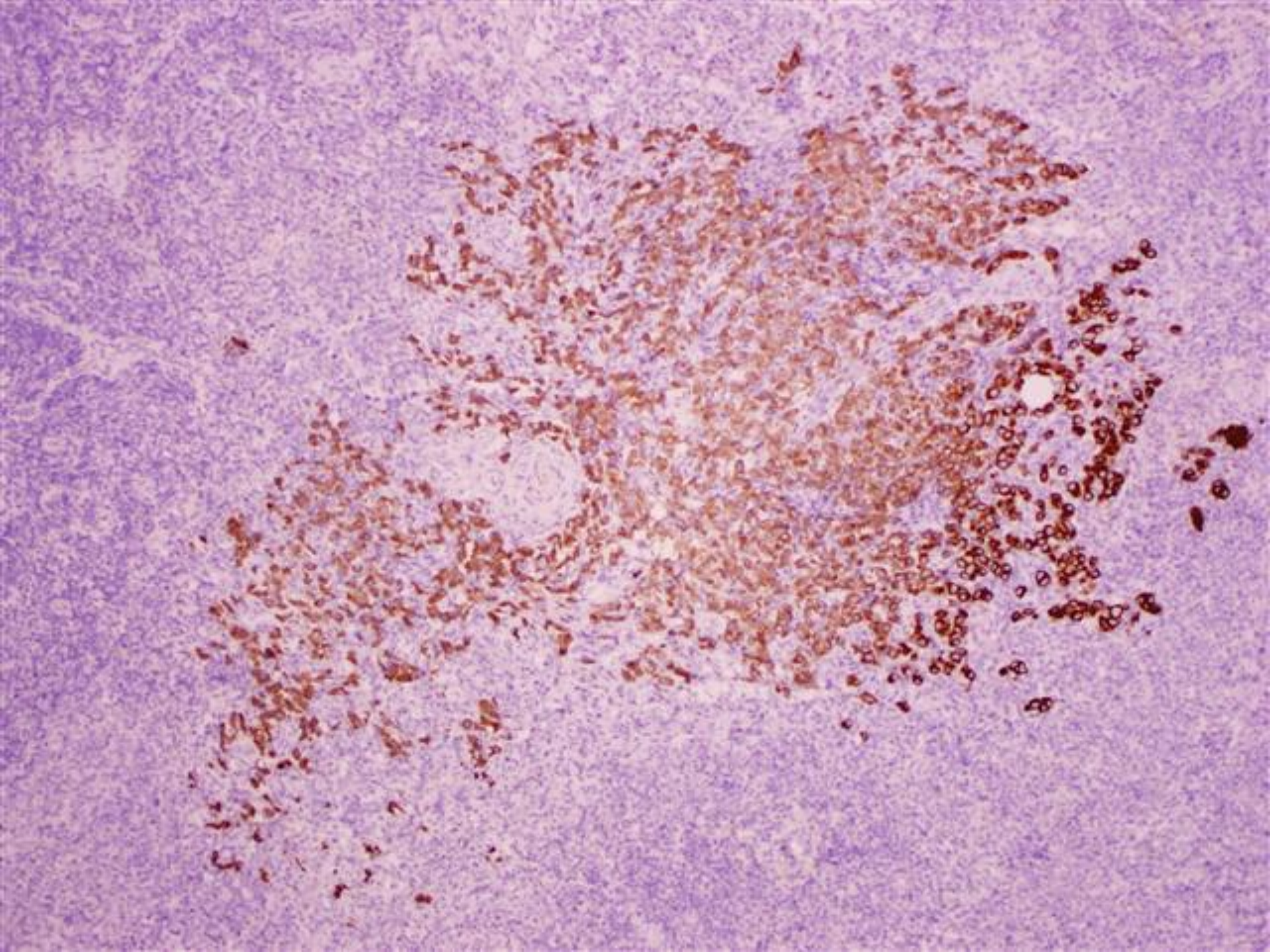
# What about Immunohistochemistry?

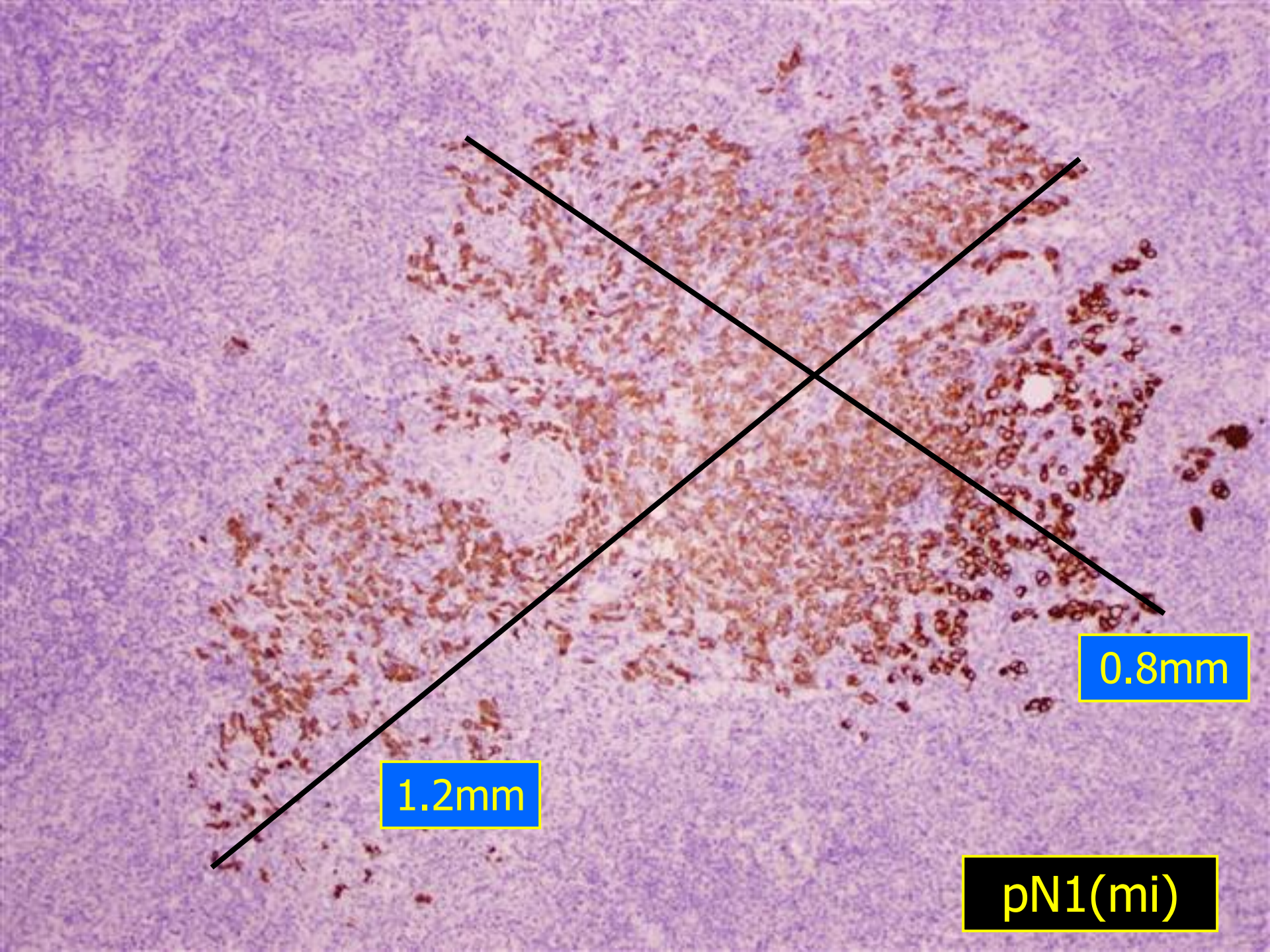
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- IHC for anticytokeratin (CK) increases the sensitivity of H&E
- Combination ↑ the detection of metastases between 5% - 23%
- IHC should be compared against adjacent H&E stained section
- Diagnostic pitfalls include CK-positive interstitial reticulum cells, macrophages, plasma cells, and benign epithelial inclusions
- Mostly detects micrometastases and isolated tumor cells
- May lead to overtreatment without survival impact. (NSABP-B32)
- Can be most helpful in cases of invasive lobular carcinoma





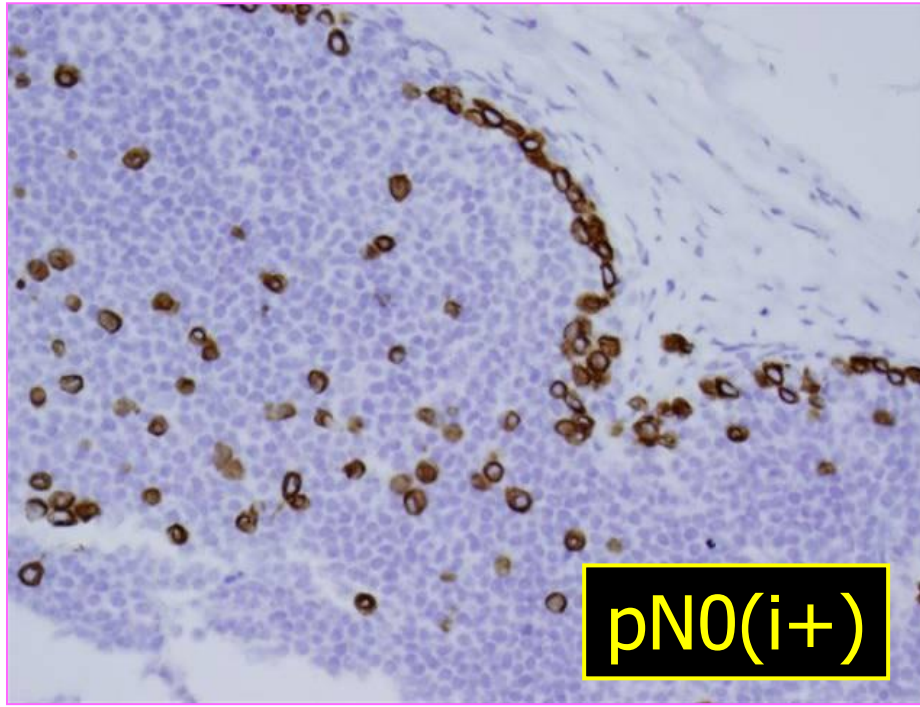
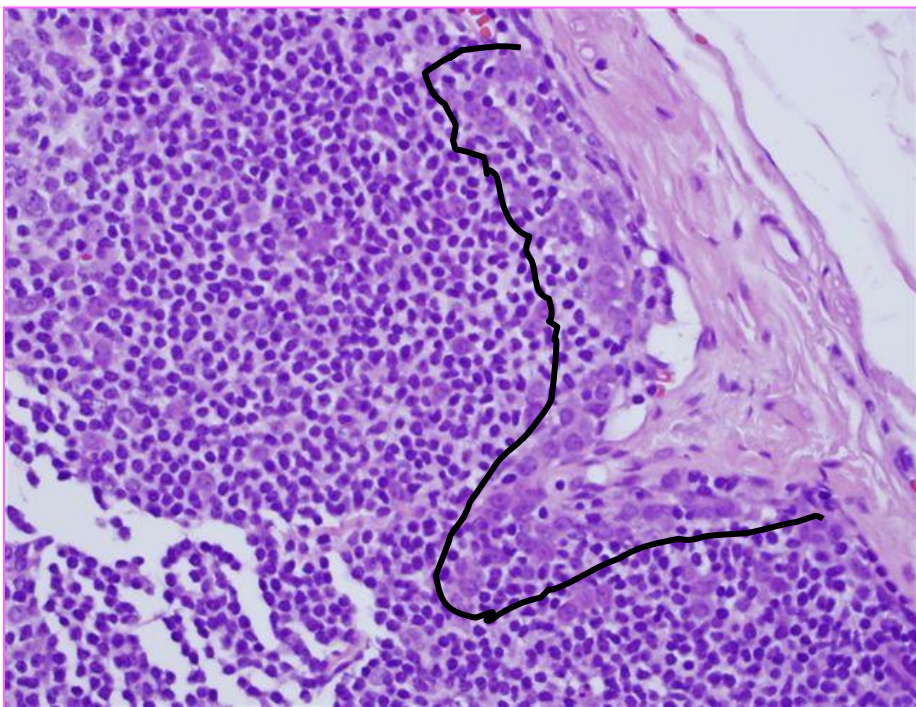
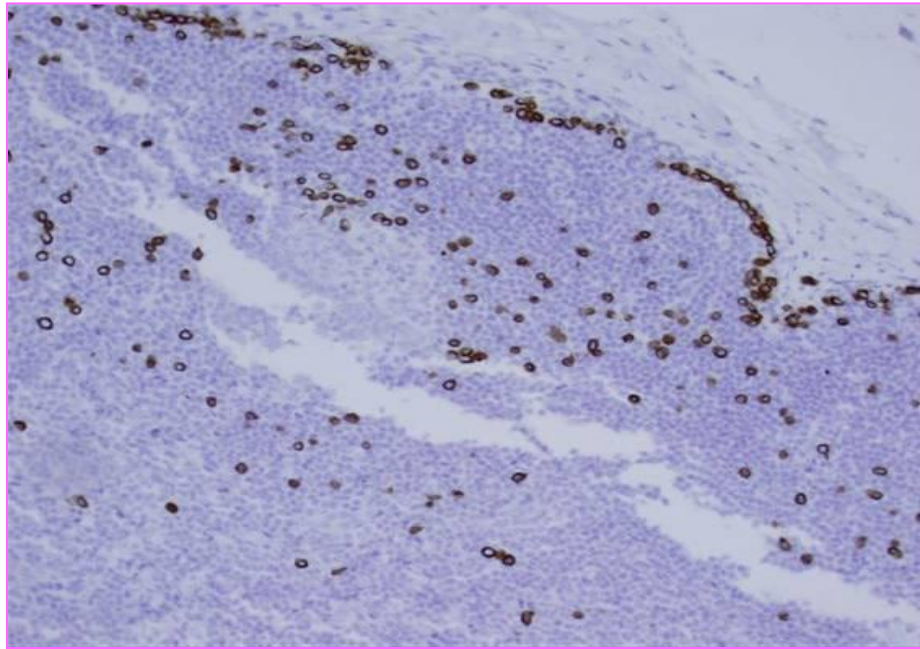
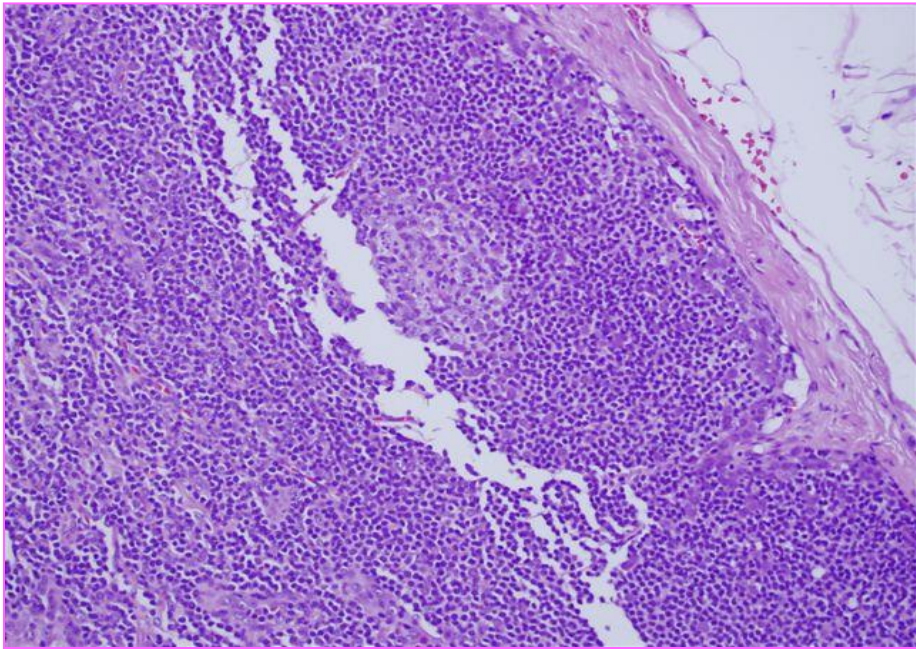




1.2mm

0.8mm

pN1(mi)



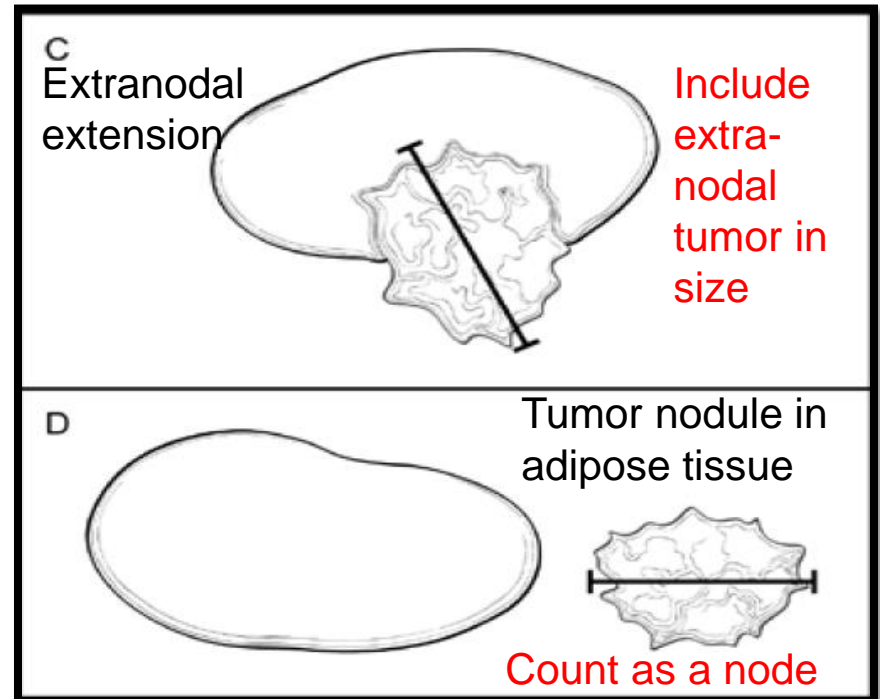
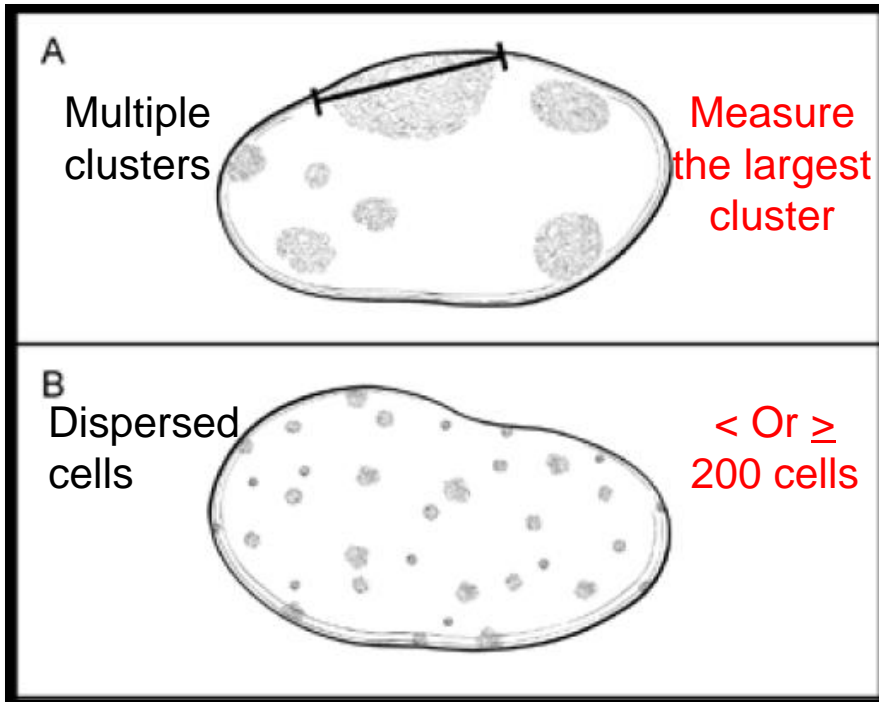


## Protocol for the Examination of Specimens From Patients With Invasive Carcinoma of the Breast

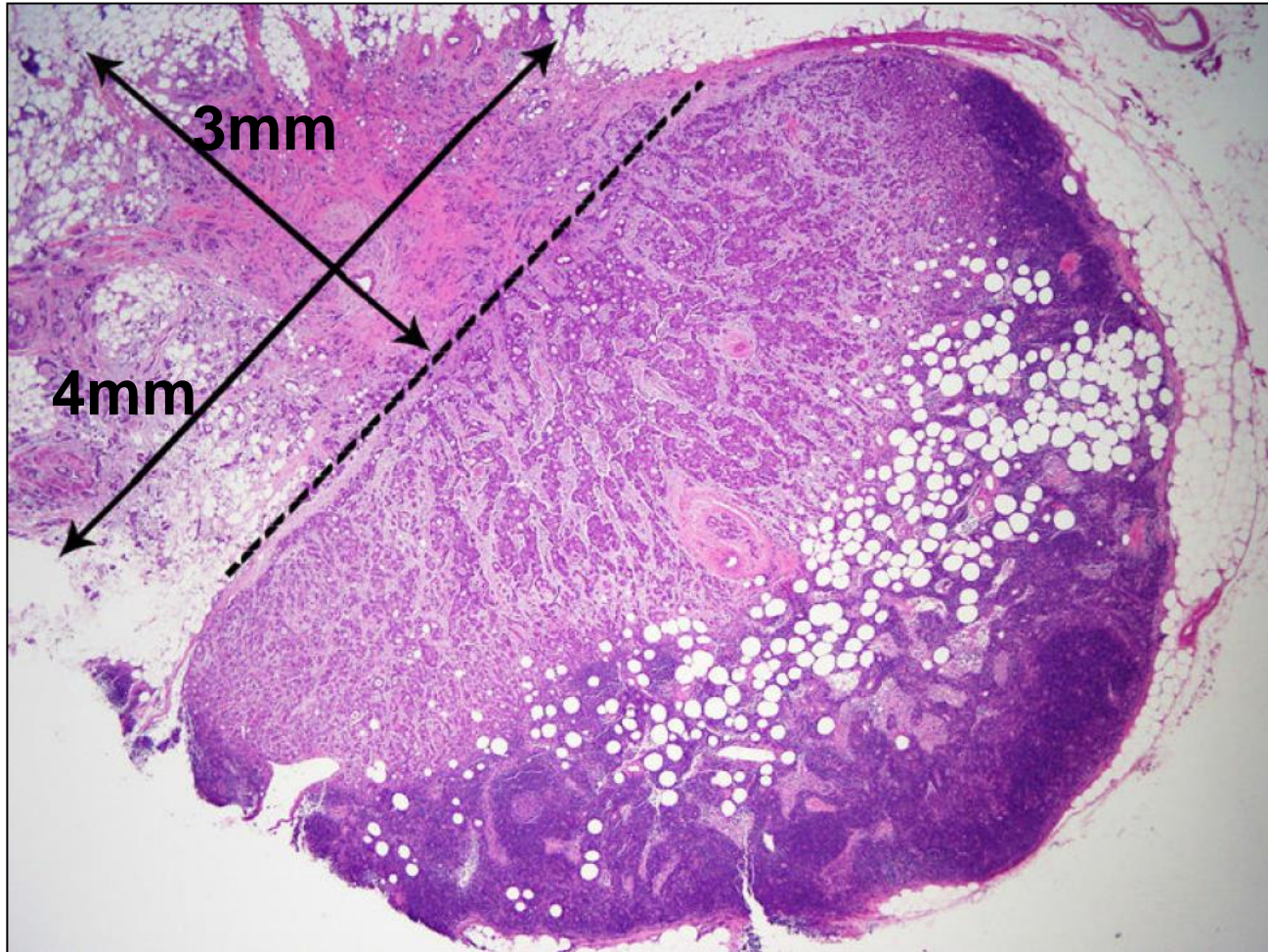
Version: InvasiveBreast 4.0.0.0

Protocol Posting Date: June 2017

Includes pTNM requirements from the 8<sup>th</sup> Edition, AJCC Staging Manual



# Assessment of Extracapsular Extension



# Histopathologic Report of SLN

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- Total number of SLN examined
- Total number of SLN with metastatic carcinoma
- Size of largest met. focus in the SLN (CAP guidelines)
- Presence/absence of extracapsular extension (ECE)
- Size of largest span of tumor outside the lymph node
- Result of cytokeratin immunohistochemistry (if used)



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# Frozen Section Evaluation of SLN

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Positive result enables completion of comprehensive dissection

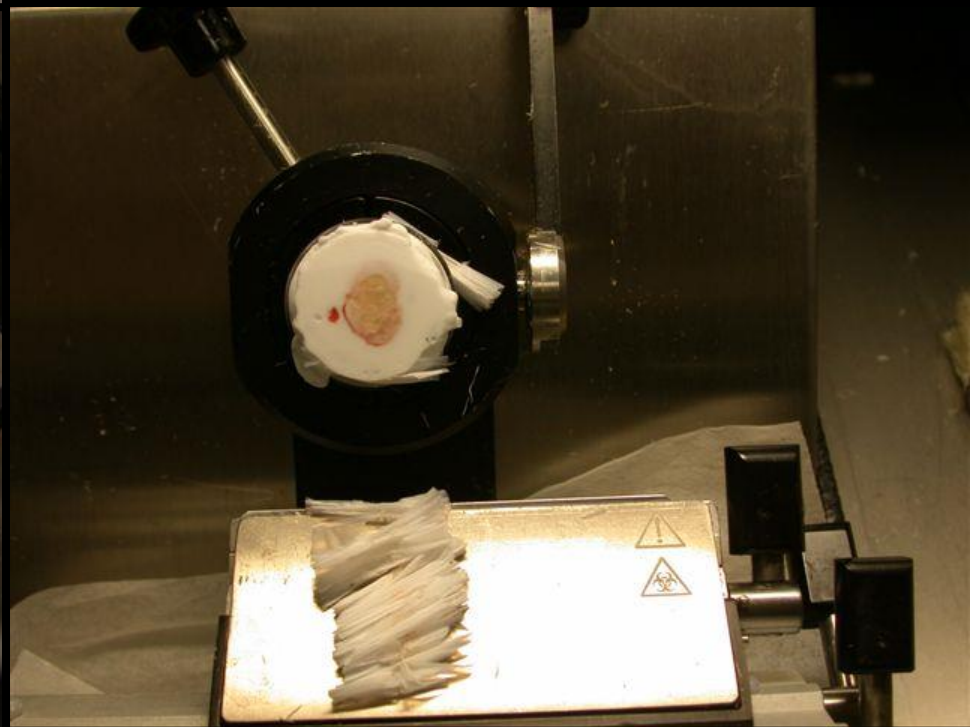
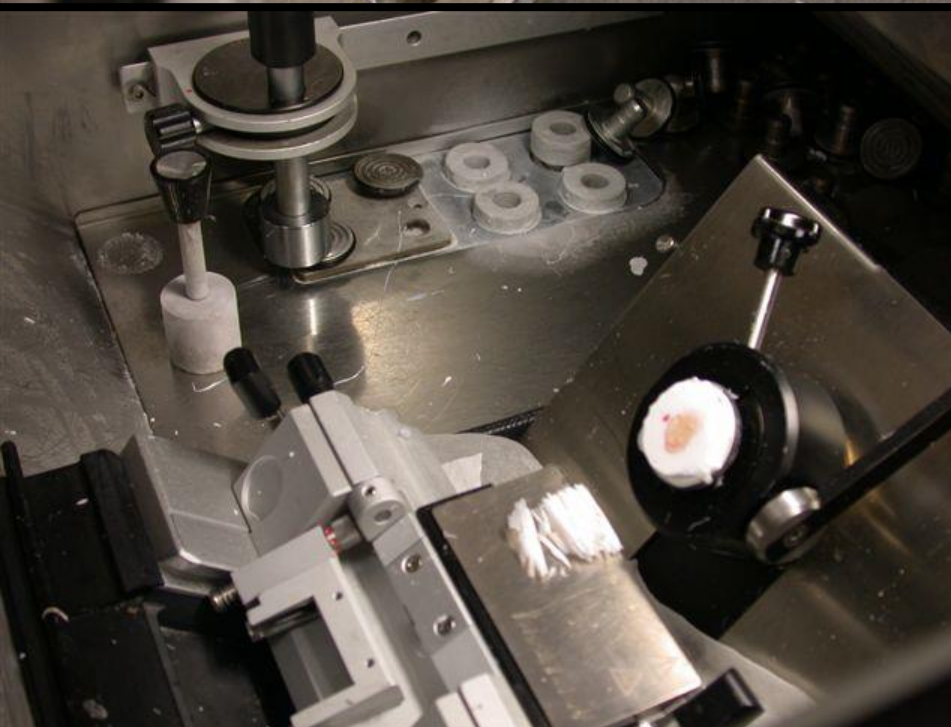
Sensitivity as low as 55%; false negative rate as high as 45%

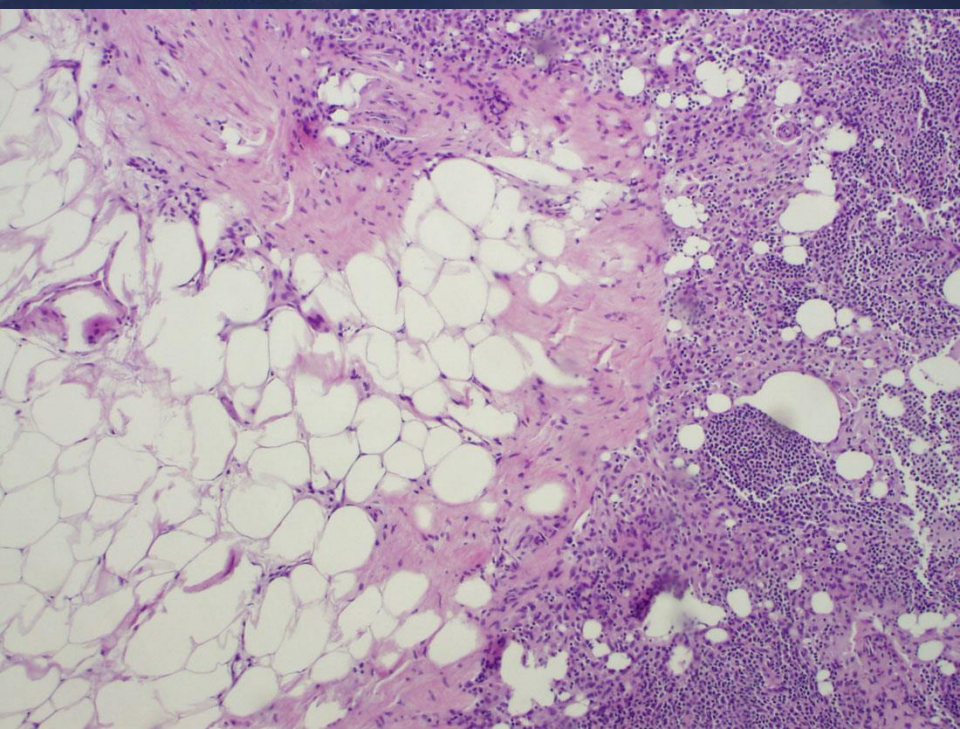
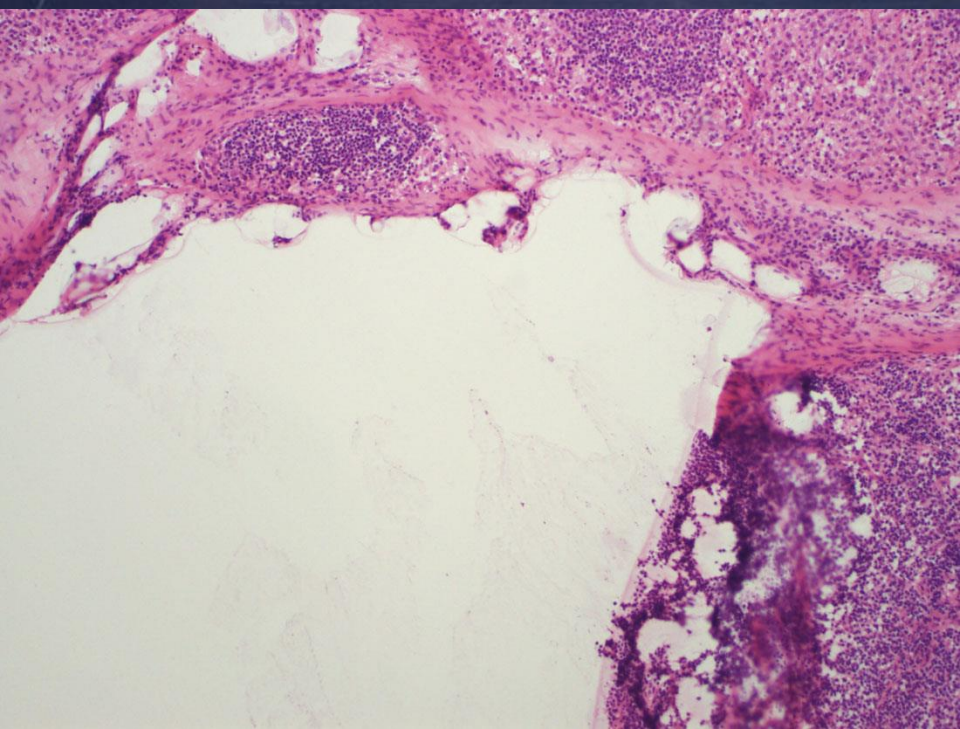
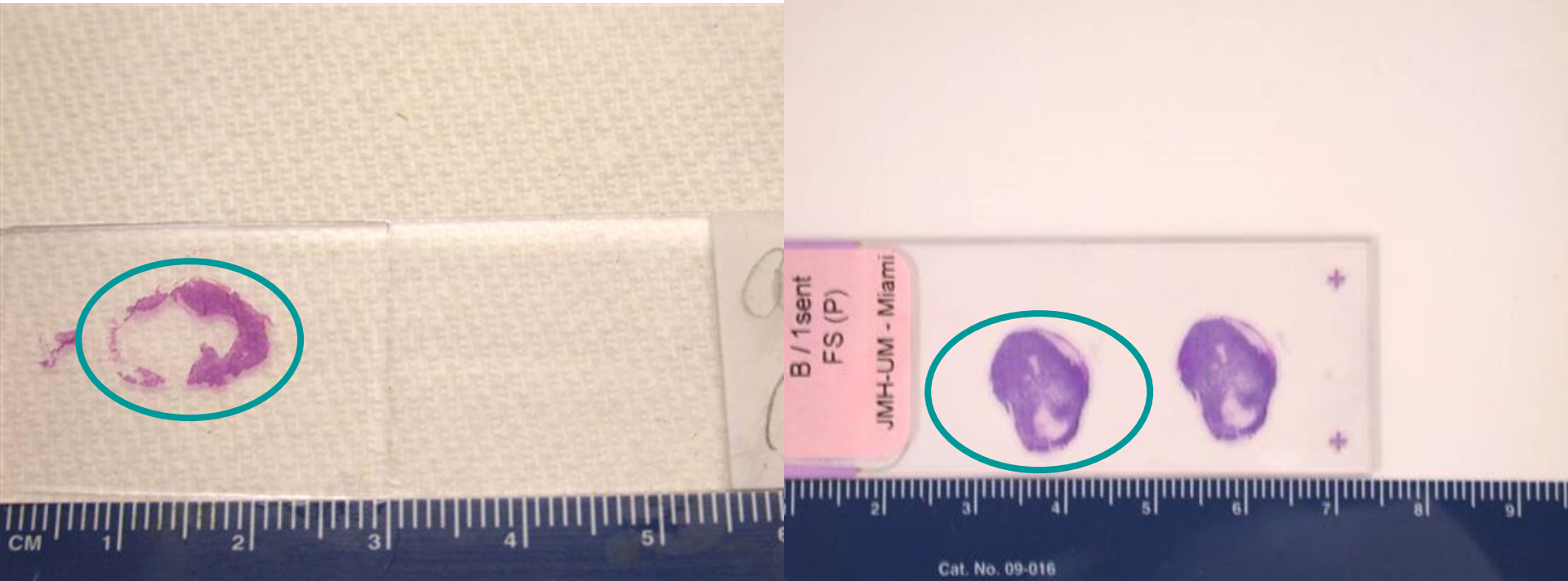
Sensitivity may be increased to 93% with fine-sectioned analysis

Potential loss of tissue with trimming of section

Useful for intraoperative evaluation of grossly suspicious nodes







# Intraoperative Imprint Cytology for SLN

Positive result enables completion of comprehensive dissection

No significant loss or damage to lymph node tissue

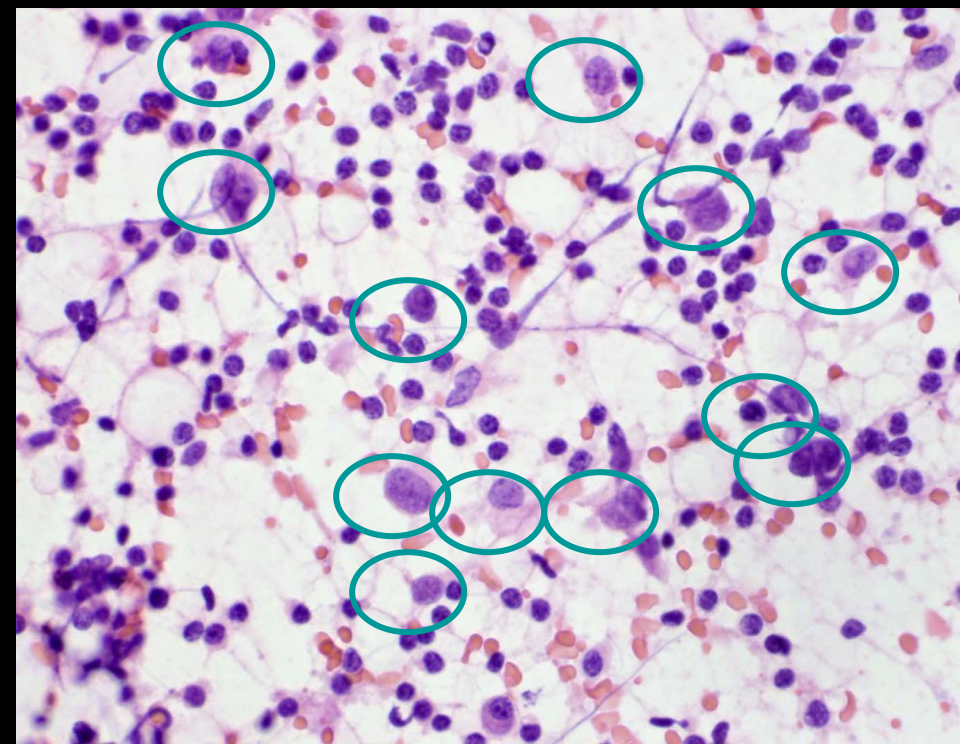
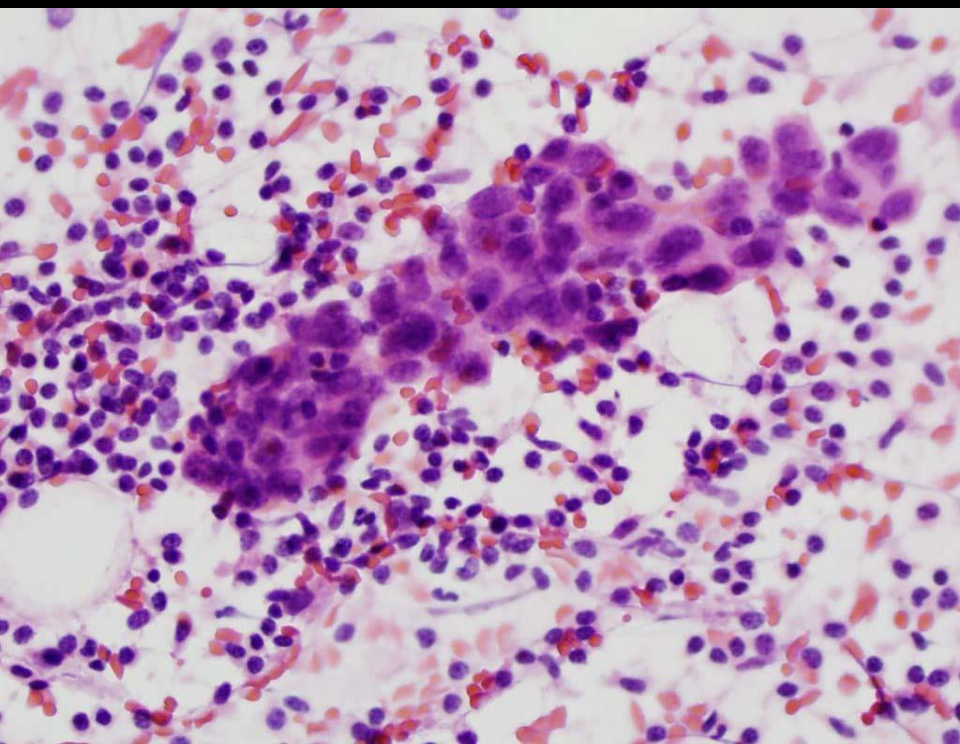
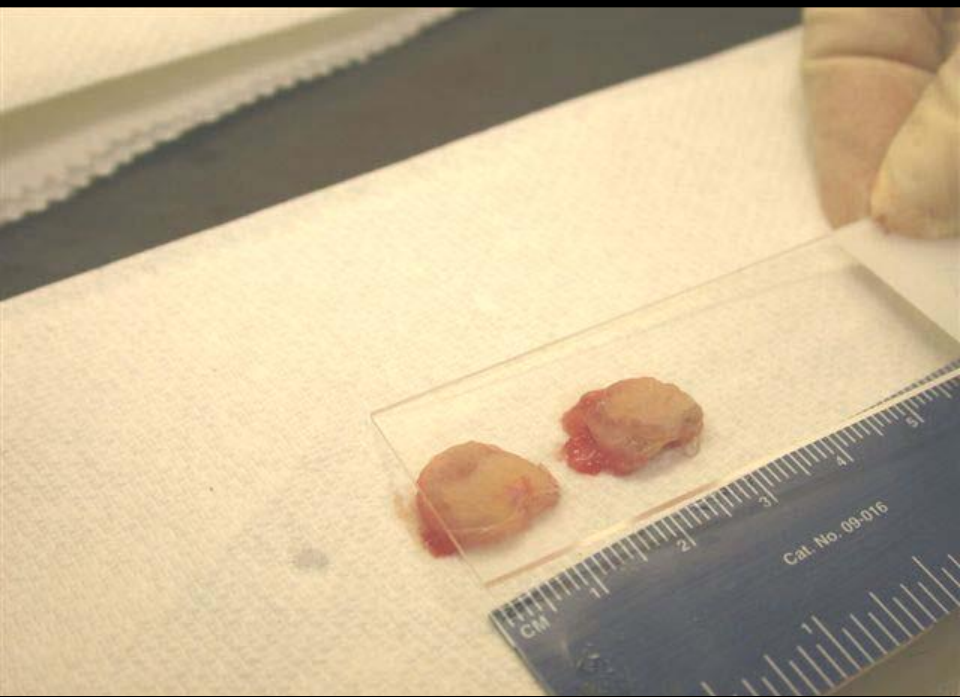
Requires some expertise for interpretation of cytologic material

Sensitivity as low as 46%; false negative rate as high as 70%

Sensitivity may be increased with fine-sectioned analysis

Useful for intraoperative evaluation of grossly suspicious nodes





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# Management of Positive SLN

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- The initial value of SLN was to predict the status of the axilla.
- The standard management of a positive SLN was an ALN dissection
- The SLN biopsy procedure is associated with a high identification rate (96%) and low false negative rate (<10%)
- The majority (approximately 66%) of patients with a positive SLN have no residual disease in the axilla
- ACOSOG Z0011 and AMAROS are prospective, randomized multicenter trials that provided **level one evidence** for the omission of ALN dissection for select patients with positive SLN



# Management of Positive SLN

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*Completion axillary lymph node dissection may be omitted in patients with early stage breast cancer and < 3 positive SLN, who are treated with breast conservation therapy, whole breast irradiation and adjuvant systemic therapy, without compromising locoregional control or survival.*

American College of Surgeons Oncology Group  
American Society of Clinical Oncology  
St. Gallen International Expert Consensus  
NCCN Guidelines



# ? Intraoperative Evaluation of SLN

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- Post-Z0011: Use of FS for evaluation of SLN has decreased
- MD Anderson: FS for SLN has decreased from 69% to 26%
- MSKCC: FS for SLN has decreased from 100% to 62% (2012)
- Currently, FS for SLN of clinically “Z0011 eligible” patients (cT1-T2, N0) is not routinely performed at many centers.



# Post-ACOSOG Z0011

*The Breast Journal*

ORIGINAL ARTICLE

## Healthcare Costs Reduced After Incorporating the Results of the American College of Surgeons Oncology Group Z0011 Trial into Clinical Practice

Michelle M. Fillion, MD, MS,<sup>\*,†,‡</sup> Katherine E. Glass, MPH, MS,<sup>†</sup> Joe Hayek, BS,<sup>§</sup> Allison Wehr, MS,<sup>¶</sup> Gary Phillips, MAS,<sup>¶</sup> Alicia Terando, MD,<sup>\*,†</sup> and Doreen M. Agnese, MD<sup>\*,†</sup>

The Ohio State University

2007-2013: ALN dissection decreased 79% to 21% and intraoperative FS for SLN decreased from 95% to 66%.

*Overall mean cost savings of \$571,653 between 2011-2013*



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# Neoadjuvant Therapy and SLN

- Neoadjuvant chemotherapy (NAC) can be used to reduce the size of the primary tumor for breast conservation therapy and to assess response to systemic therapy.
- Downstaging of axillary lymph nodes occurs in 30%-40% of patients.
- Triple negative and HER2 positive breast cancers can achieve pCR in the breast and the axilla with NAC.
- The possibility of a negative axilla after NAC has prompted consideration for the use of SLN biopsy



# Neoadjuvant Therapy and SLN

cN0 patients:

-Several studies have demonstrated that SLN biopsy post-NAC is associated with identification rates of 90%-94% and false negative rates of 7%-12%.

cN+ patients:

-SENTINA, ACOSOG Z1071 (ALLIANCE), and SN FNAC are 3 prospective, multi-institutional trials assessing the accuracy of SLN biopsy post-NAC for cN+ patients.

-The 3 studies demonstrate identification rates (80%-93%) and false negative rates <10% with the use of dual tracers and excision of  $\geq 3$  SLN



# Neoadjuvant Therapy and SLN

- Patients with pCR in the breast and axilla have significantly improved survival outcomes (OS and DFS)
- Patients with complete response in the axilla have an excellent prognosis, even with residual breast disease
- NAC may be used to avoid an ALN dissection in cN+ patients who achieve a pCR in the axilla
- SLN biopsy represents a viable predictor of the post-NAC axilla
- Intraoperative FS of SLN may be used to assess the need for ALN dissection in post-NAC patients.

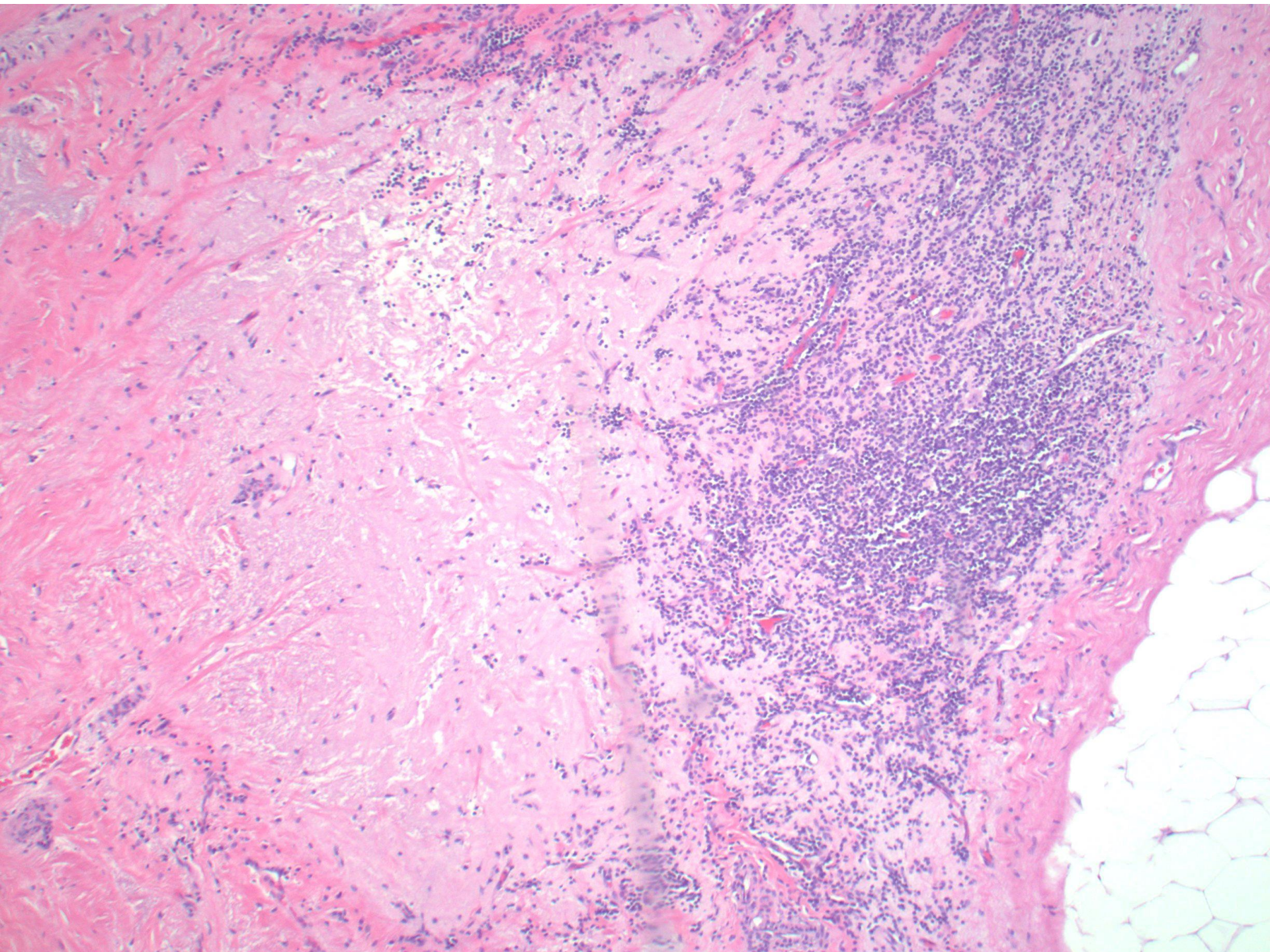


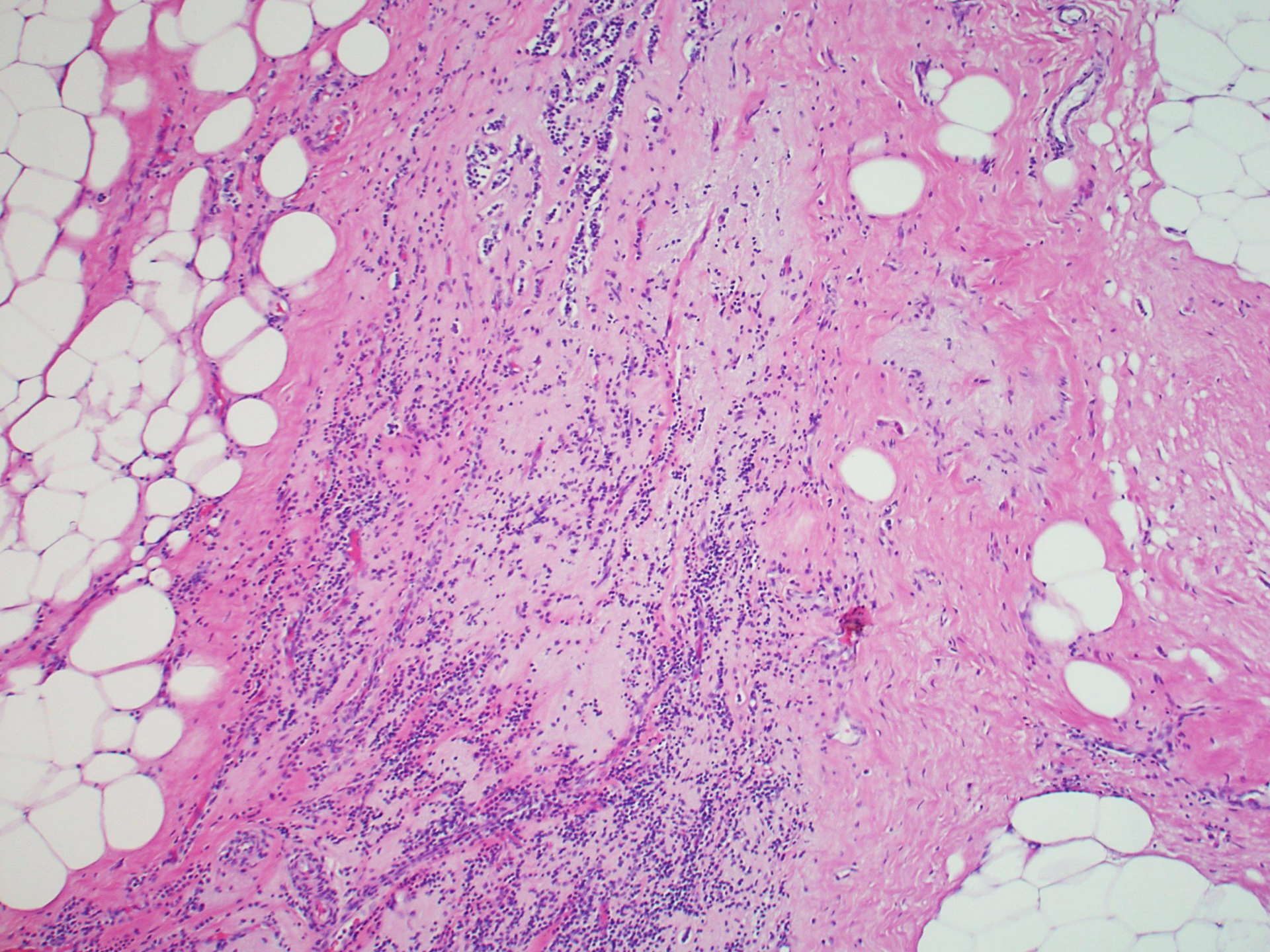
# Histopathologic Assessment of SLN after NAC

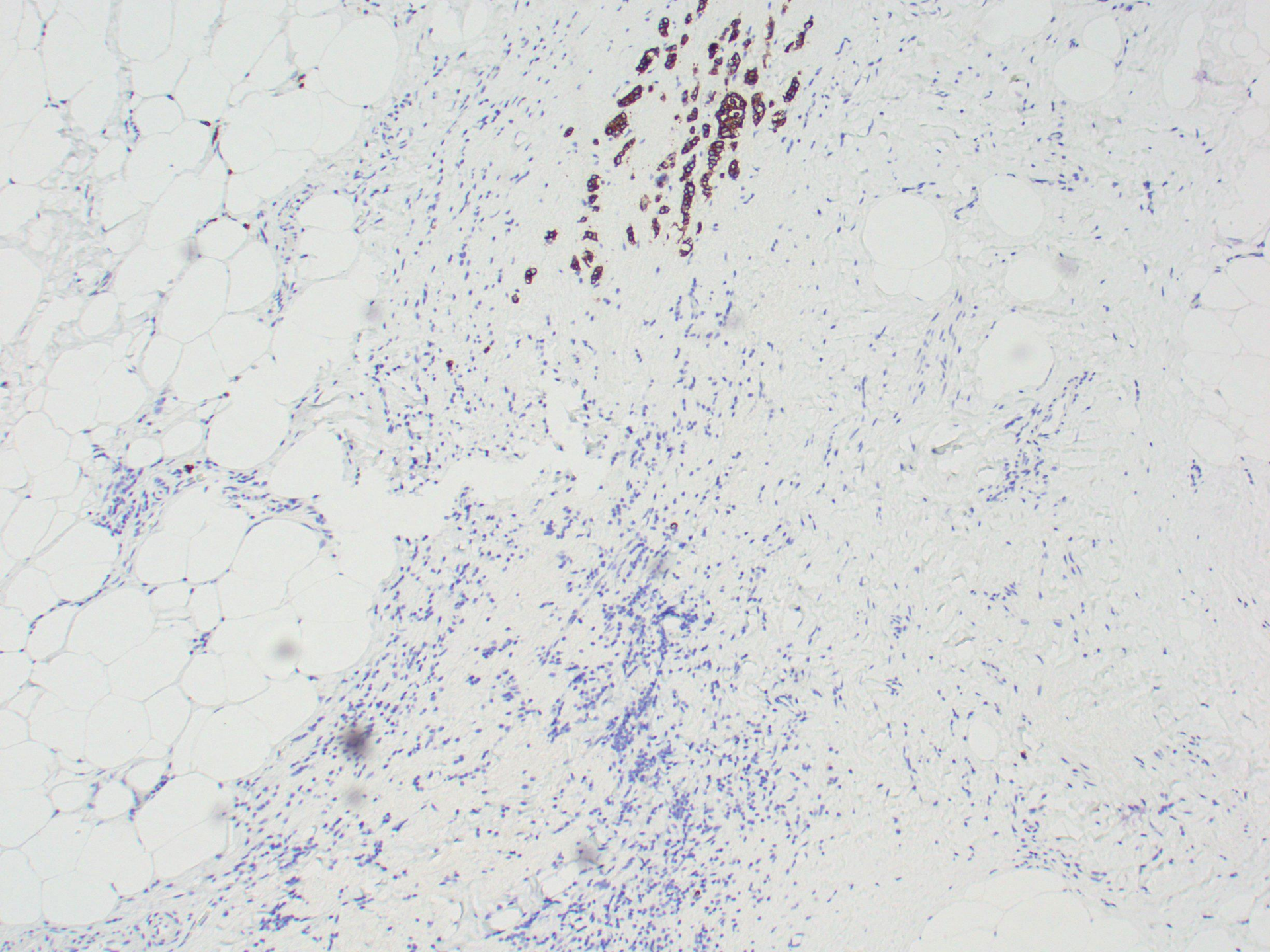
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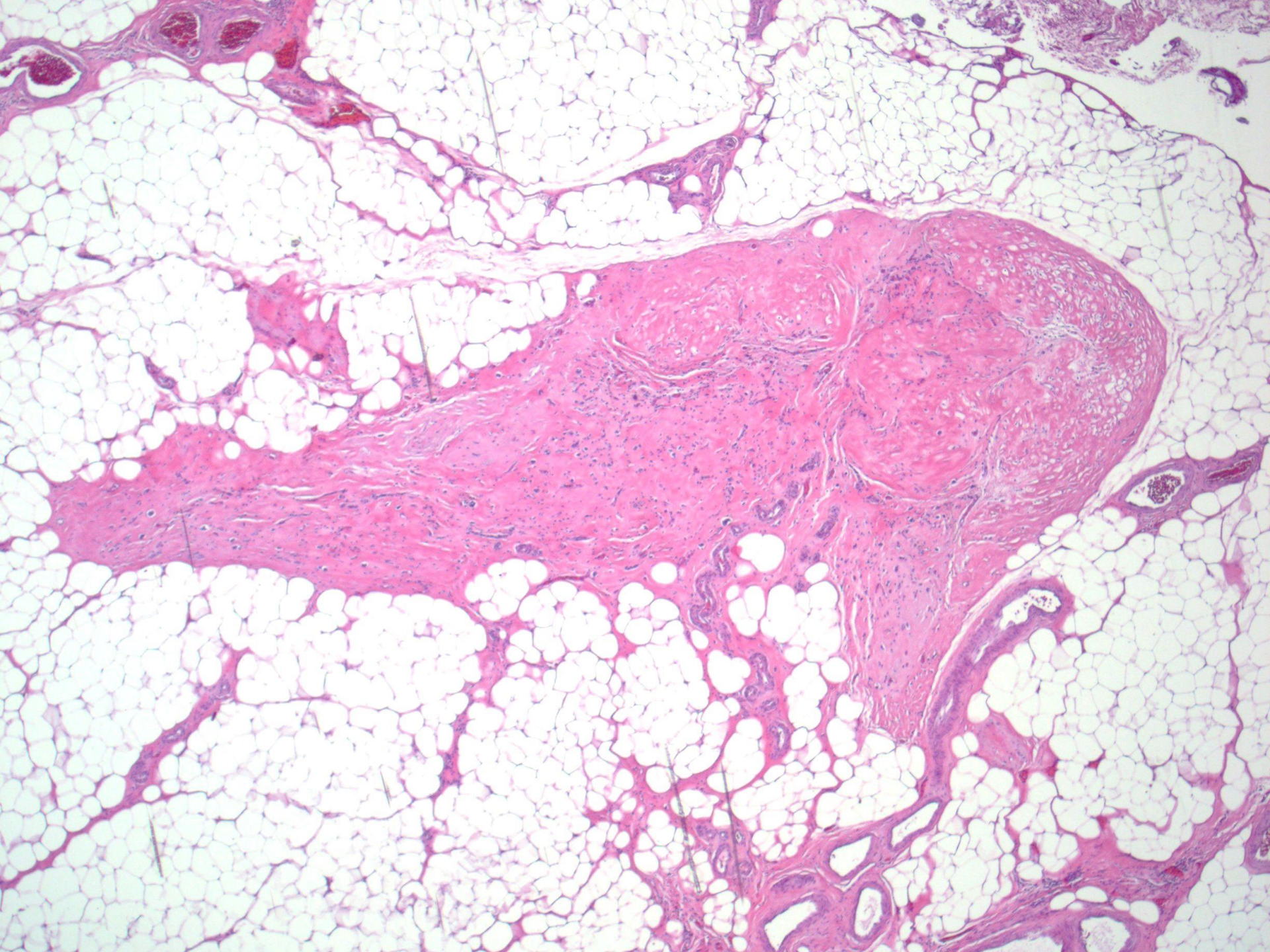
- Post-NAC SLN are smaller and lymphocyte depleted.
- Therapy response is evident with fibrosis and macrophages
- Residual metastatic cells may be scattered in fibrous tissue and may require cytokeratin immunohistochemistry.
- Use caution with frozen section to avoid false positive interpretations
- A positive SLN on FS requires completion ALN dissection

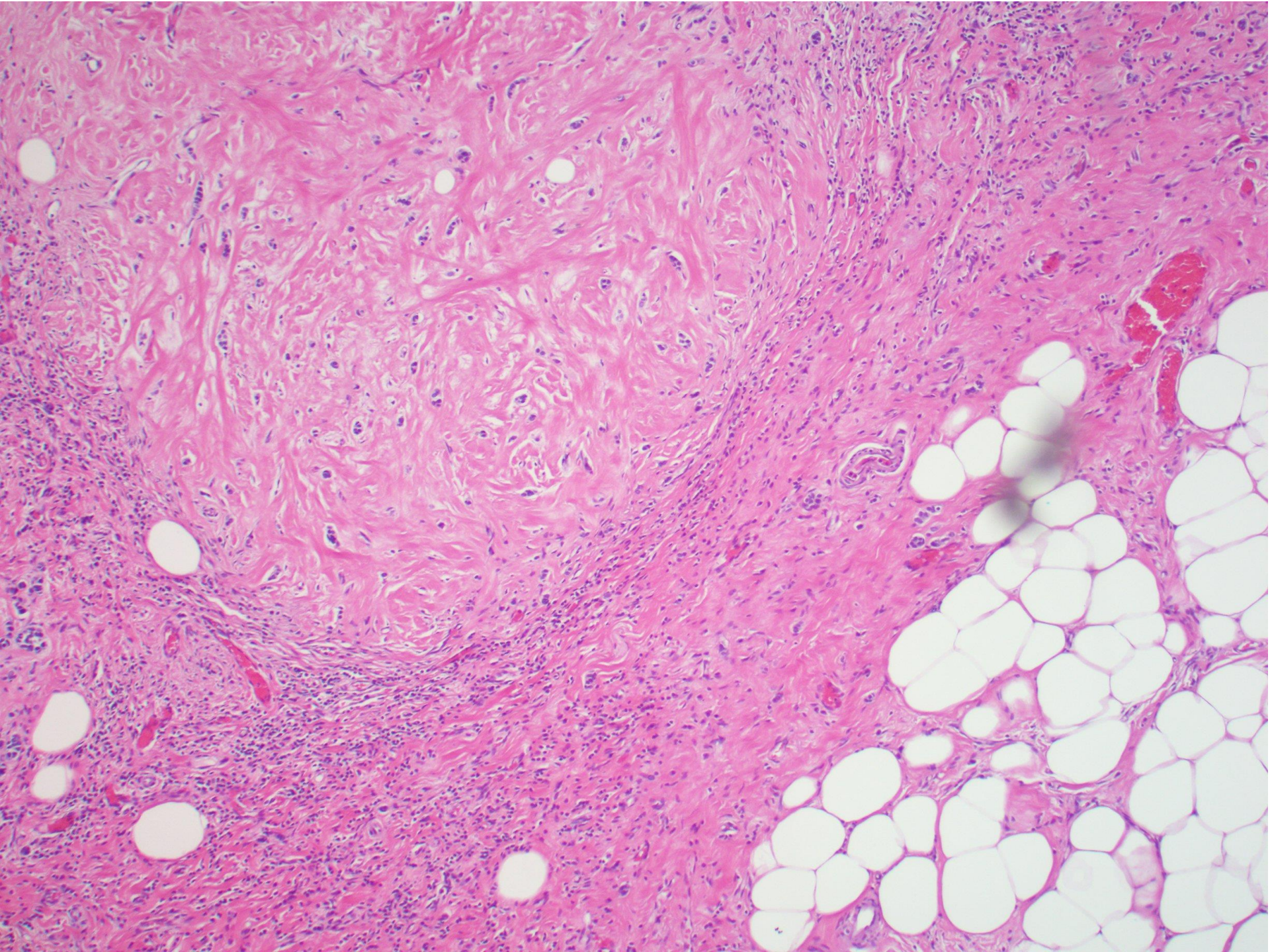


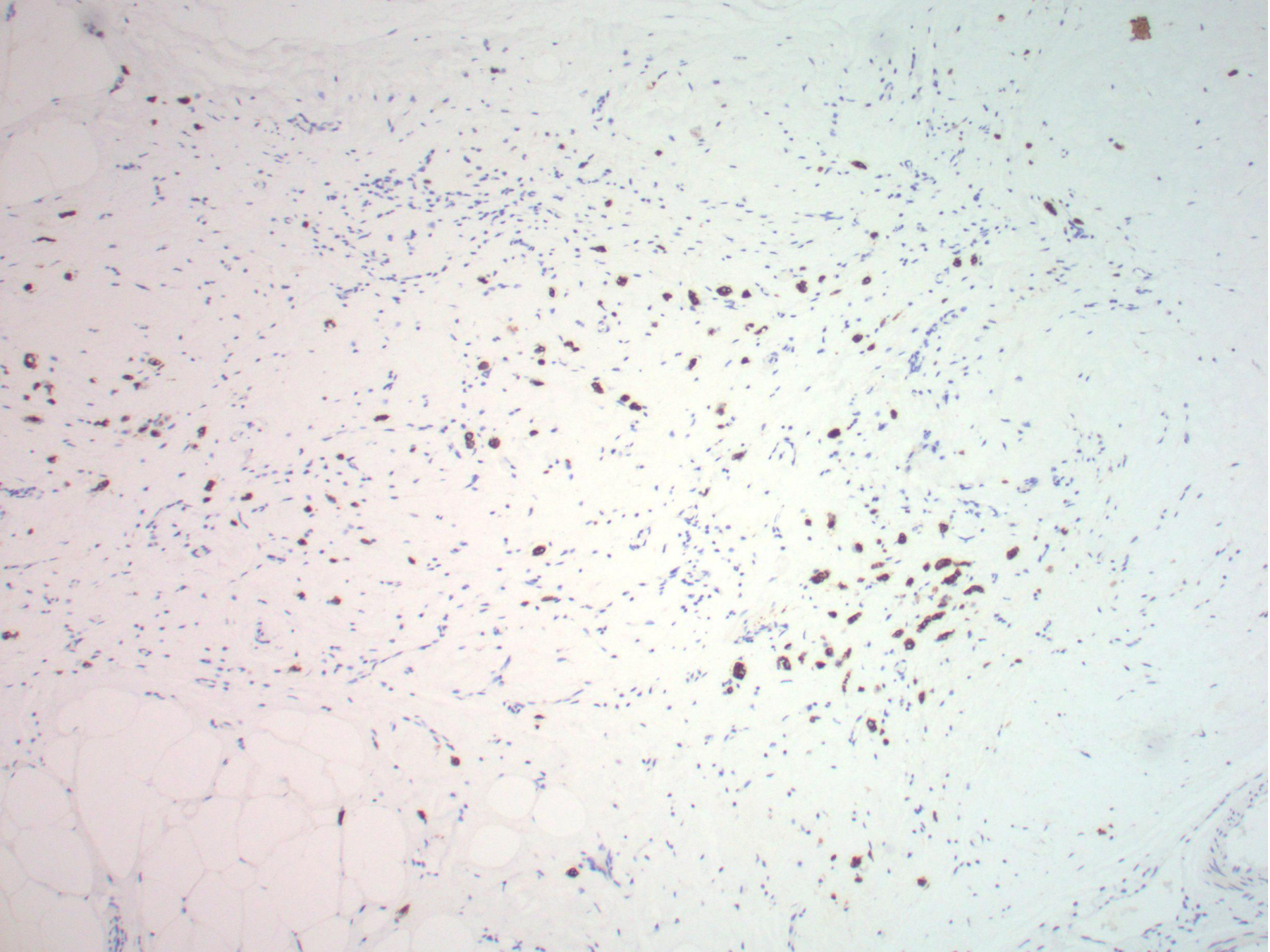




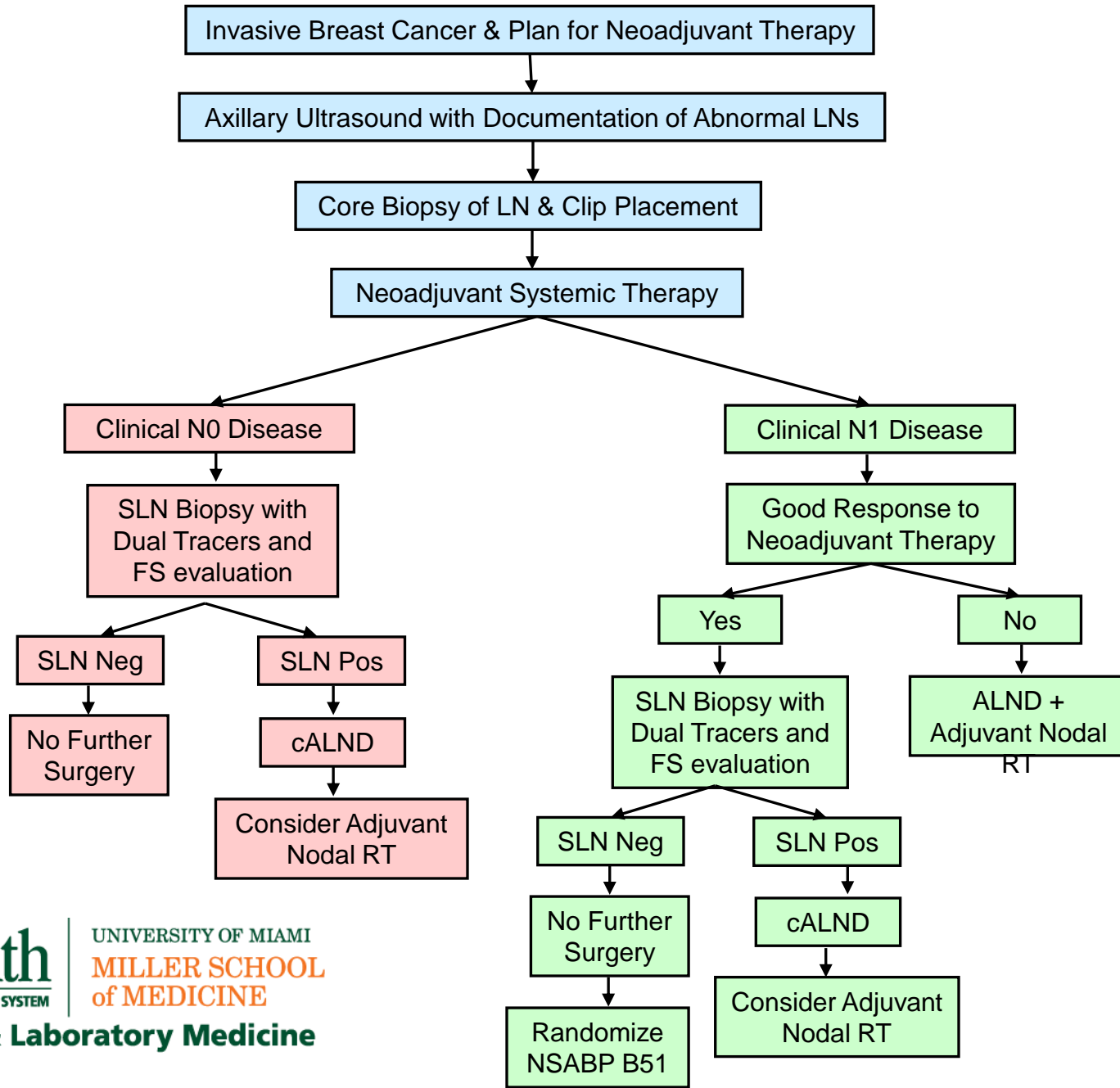








# Axillary Lymph Node Management in Breast Cancer Patients Receiving Neoadjuvant Therapy



# Histopathologic Reporting of SLN after NAC

- Number of SLN
- Number of total lymph nodes
- Number of lymph nodes with metastases
- Size of the largest metastasis\*
- Presence of extranodal extension
- Number of positive lymph nodes with treatment effect
- Number of negative lymph nodes with treatment effect
- Presence of clip whenever used

AJCC 8<sup>th</sup> edition classification: **yp**TNM

\* use of terms “isolated tumor cells” and “micrometastasis” may be misleading for post-NAC LN



# Sentinel Lymph Node (SLN) in Breast Cancer: 2020

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## Summary

- The SLN biopsy has replaced ALN dissection as the standard procedure for staging cN0 breast cancer.
- The detection of “occult” metastases does not impact survival outcomes.
- The main goal of SLN histologic examination is to detect all macrometastases ( $\geq 2\text{mm}$ ).
- Intraoperative evaluation (FS) of SLN can be challenging but has a role in determining the need for ALN dissection in select patients.



# Sentinel Lymph Node (SLN) in Breast Cancer: 2020

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- Patients with early stage breast cancer and  $< 3$  positive sentinel lymph nodes, who are treated with whole breast radiation and systemic therapy, may avoid completion axillary lymph node dissection. (utility of FS for SLN is low)
- SLN biopsy may be reliably performed in cN0 and select cN+ post-NAC patients to stage the axilla.
- ALN dissection may be omitted if the post-NAC SLN is negative, but is completed for any residual disease found in the SLN. (utility of FS for SLN is high)



