Approach to Post-Neoadjuvant Breast Cancer Specimens

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Park City Anatomic Pathology Update
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Learning Objectives

- Understand the clinical advantages for using neoadjuvant chemotherapy in certain breast cancer cases
- Know the relative rates of pCR among the different receptor subtypes of breast cancer following neoadjuvant treatment
- Understand appropriate sampling technique for post-neoadjuvant breast cancer cases
- Appreciate the different reporting systems for post-neoadjuvant breast cancer cases and know how to apply them to individual cases

Outline

- Whats/Whys/Whos of Neoadjuvant Chemotherapy
- Approach to Evaluating Neoadjuvant Treated Breast Cancer Cases:
  - 1) Gather Data
  - 2) Gross Evaluation/ Adequate Sampling
  - 3) Microscopic Evaluation
  - 4) Reporting

Outline

- **Whats/Whys/Whos of Neoadjuvant Chemotherapy**
- Approach to Evaluating Neoadjuvant Treated Breast Cancer Cases:
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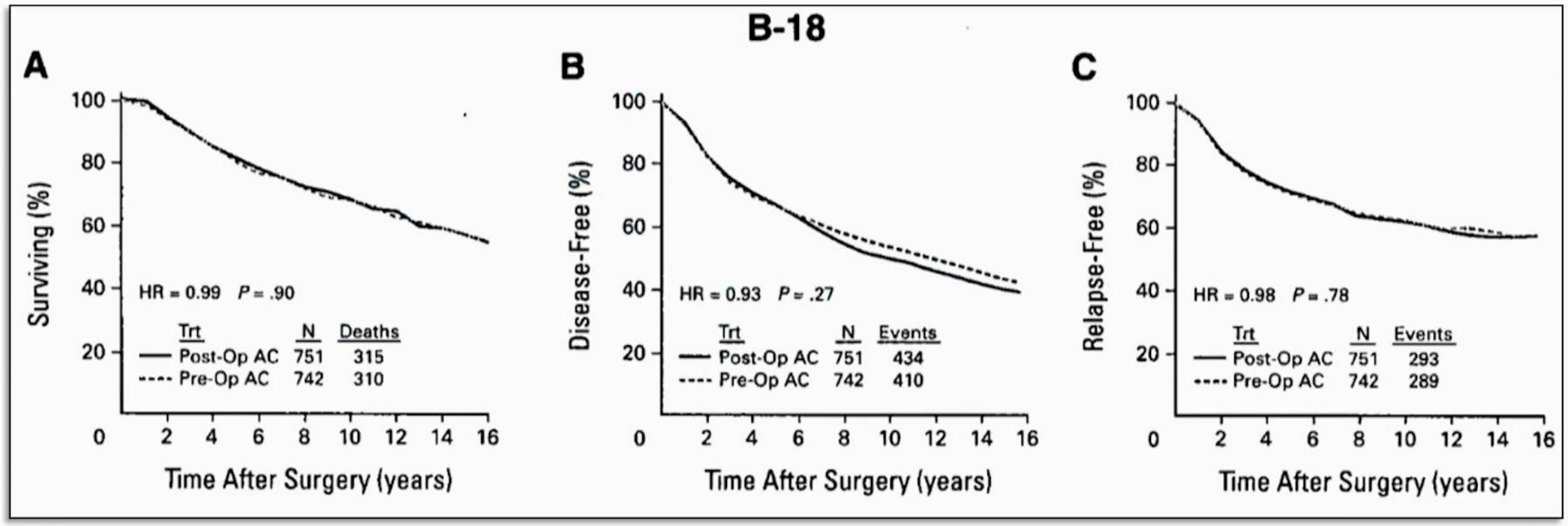
What is neoadjuvant chemotherapy (NAC)?

- Neoadjuvant Chemotherapy refers to systemic cytotoxic chemotherapy that is administered prior to definitive cancer surgery.

- Can also sometimes refer to preoperative endocrine therapy.

Neoadjuvant chemotherapy is equivalent to adjuvant (post-operative) chemotherapy with respect to OS, DFS, and RFI



Rastogi P et al., J Clin Oncol 2008; 26(5):778-85

So why give NAC?

- **“Downstage” tumors.**
  - May help shrink non-operable tumors to help get the patients to definitive surgery.
  - May facilitate breast conservation.
  - May allow for less aggressive axillary surgery (SLNB vs Axillary dissection)
- Treatment response provides important prognostic information
- In patients with residual disease, allows for escalation/ selection of appropriate adjuvant treatment

2023 NCCN Guidelines for Breast cancer

Among patients ineligible for Breast Conservation Surgery (BCS) due to large tumor size, conversion to BCS-eligibility was high following NAC

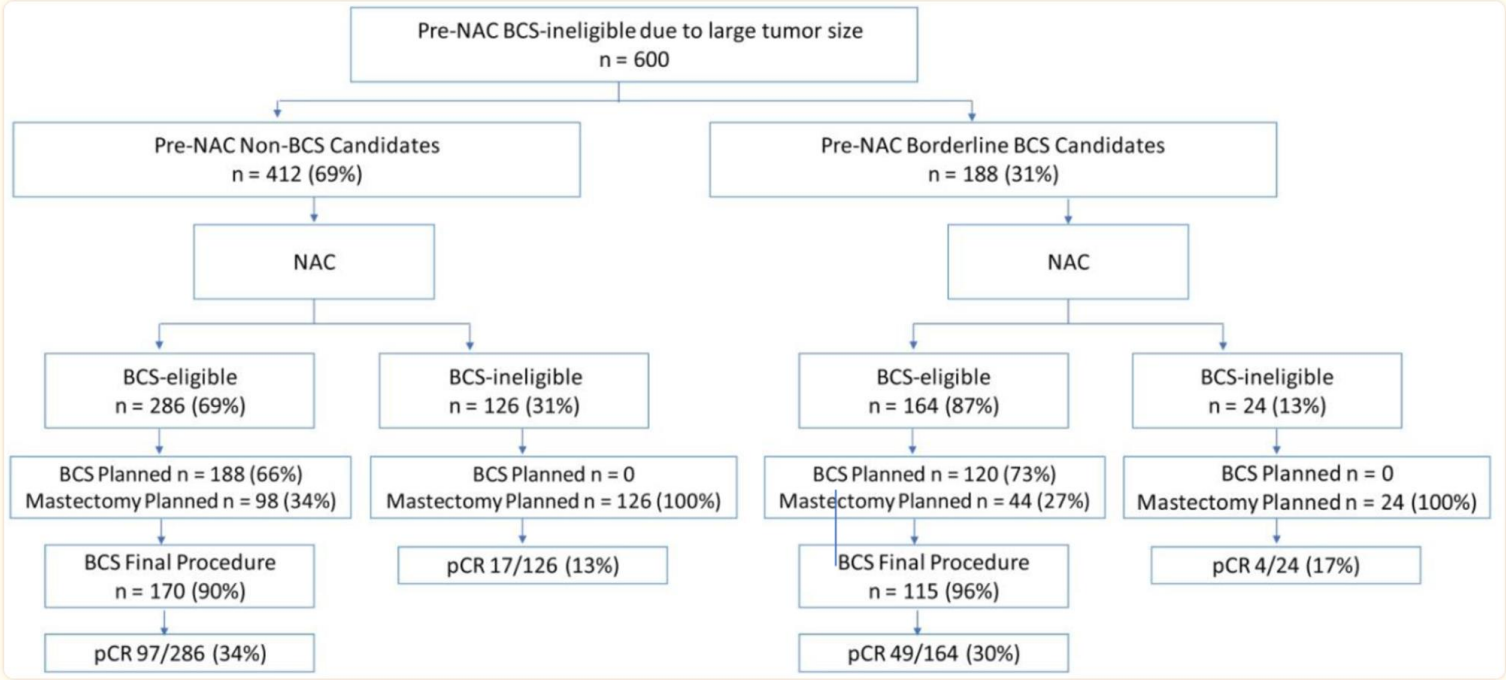


Fig. 2.

Conversion to BCS-eligibility post-NAC stratified by borderline vs. non-BCS candidates.

NAC neoadjuvant chemotherapy, *BCS* breast-conserving surgery, *pCR* pathologic complete response

Features associated with conversion to BCS eligibility:

- Lower cT stage
- cN0 status,
- Absence of calcifications
- HER2+/triple negative receptor status
- Poor differentiation
- Ductal histology
- Breast pCR

Petruolo O et al., Ann Surg Oncol 2021; 28(10):287-94

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2023 NCCN Guidelines for Breast cancer

Pathological complete response (pCR) following NAC is associated with improved EFS and OS

Pooled analysis of 12 trials with 11,955 patients

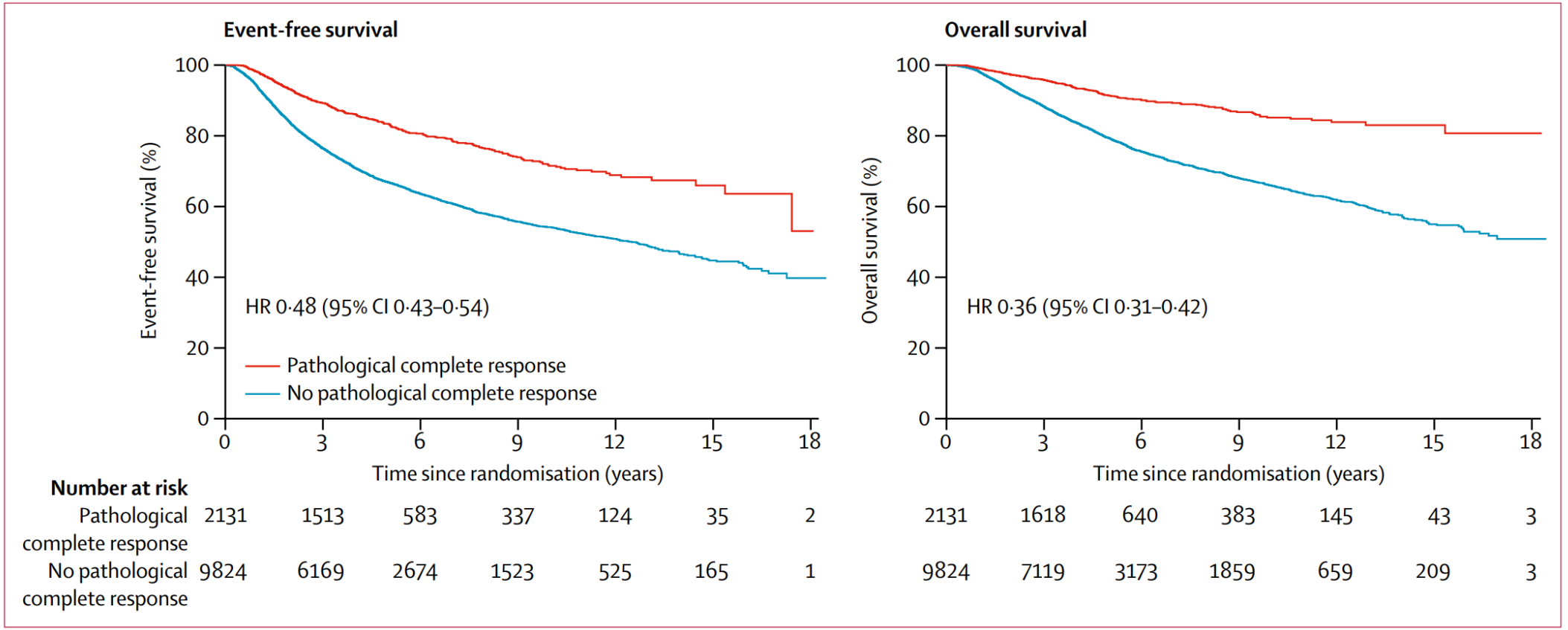

Figure 2: **Associations between pathological complete response and event-free survival and overall survival**
ypT0/is ypN0 definition of pathological complete response (ie, absence of invasive cancer in the breast and axillary nodes, irrespective of ductal carcinoma in situ). HR=hazard ratio.

Cortazar P et al., Lancet 2014; 384(9938):164-72

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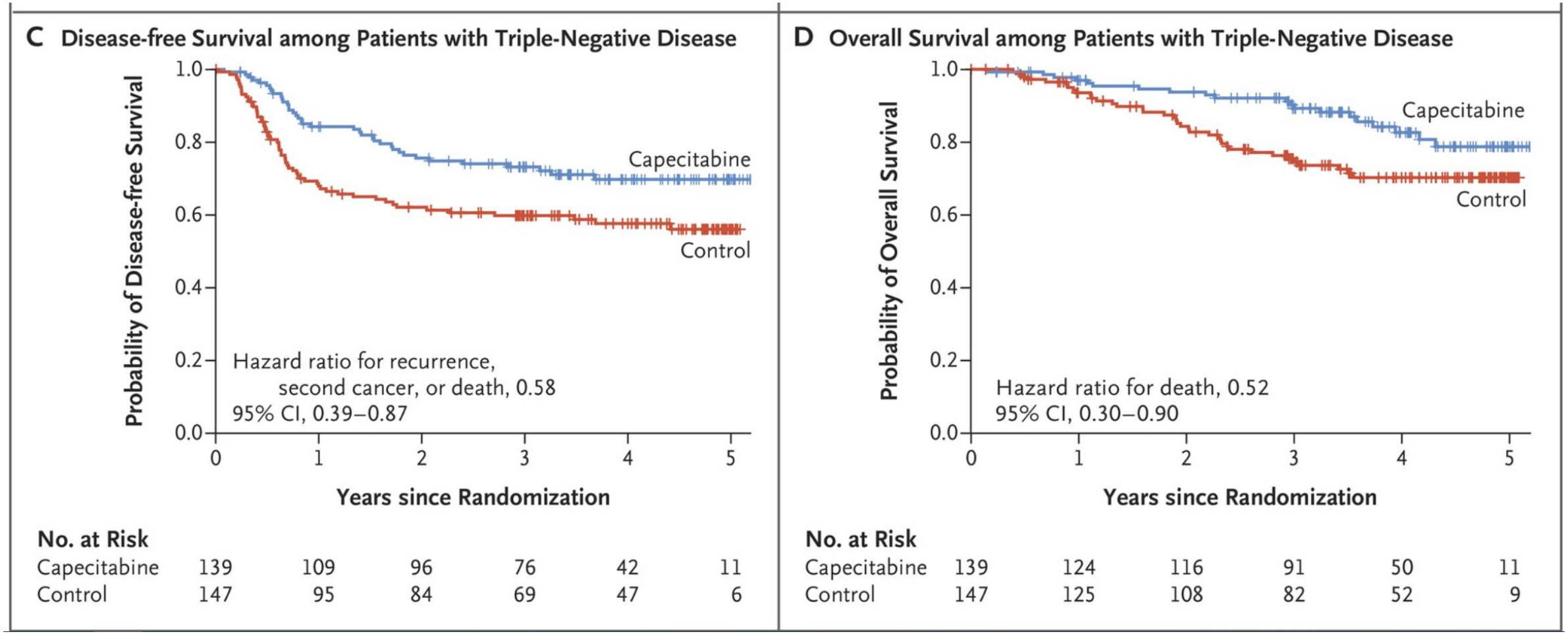
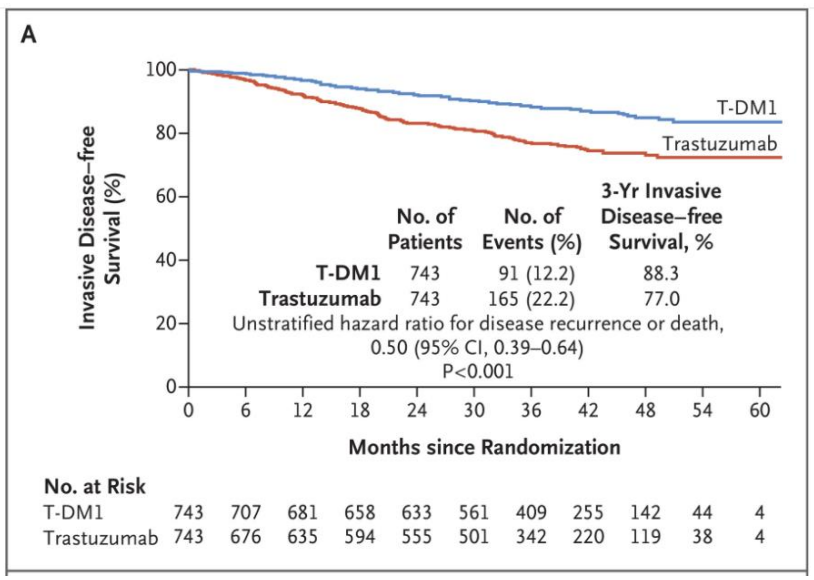
2023 NCCN Guidelines for Breast cancer

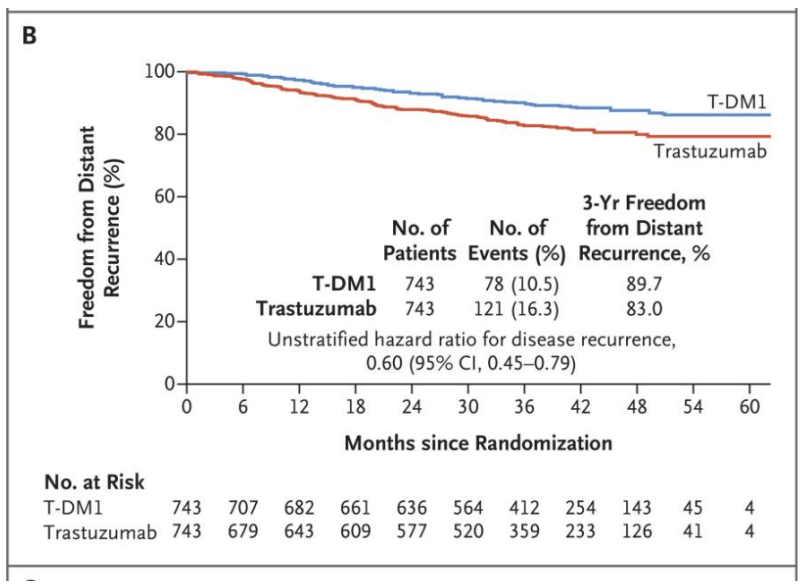
Patients with residual TNBC following NAC show increased DFS and OS when treated with adjuvant Capecitabine (CREATE-X Trial)

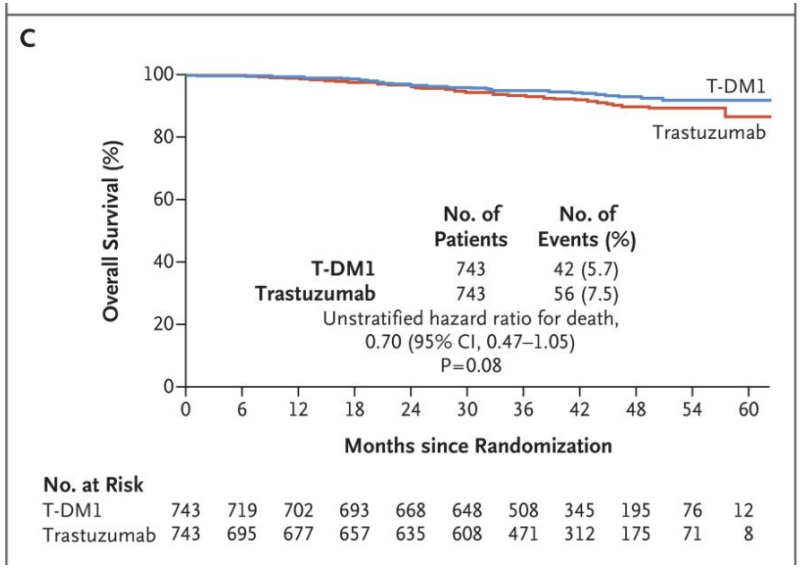


Masuda N et al. NEJM 2017; 276:2147-59

Patients with residual HER2-positive breast cancer following NAC show improved IDFS and FFDR when treated with adjuvant TDM-1 (KATHERINE Trial)







Von Minckwitz G et al., NEJM 2019; 380:617-28

Update at 2023 SABCS: after 8.4 years follow up, patients treated with TDM-1 show sustained improvement in IDFS over trastuzumab (80.8% vs 67.1%) and show significantly improved OS (89.1% vs 84.4%)

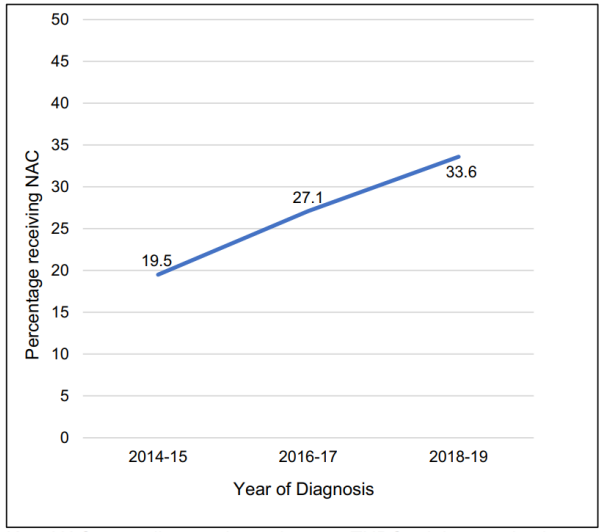
Loibl S. et al., Abstract GS03-12, 2023 SABCS

Who gets NAC?

- Patients with inoperable breast cancer:
  - Inflammatory breast cancer
  - Bulky or matted cN2 axillary nodes or cN3 disease
  - cT4 tumors
- Select patients with operable breast cancer:
  - HER2-positive or TNBC if ≥cT2 or ≥cN1
  - Large tumor relative to breast size in patient who desires breast conservation
  - Patients with cN+ disease, with an effort to downstage the axilla
  - Can be considered in patients with cT1c cN0 HER2-positive or TNBC

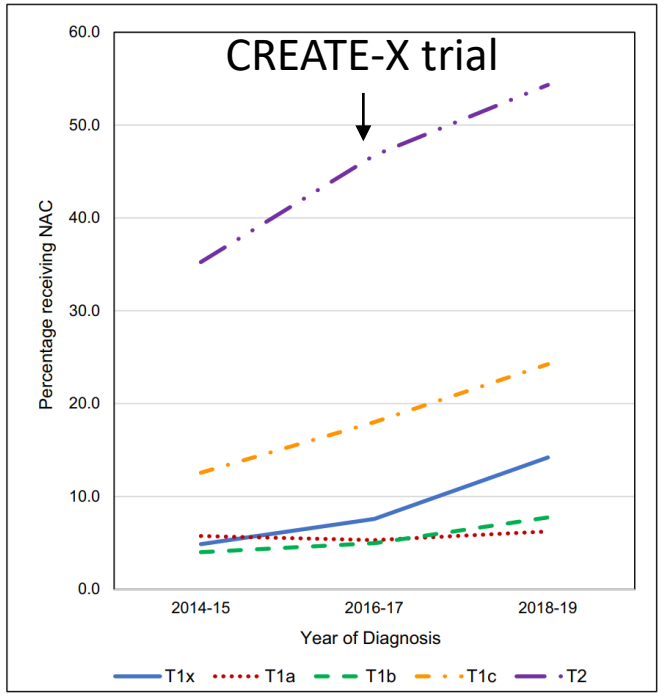
2023 NCCN Guidelines for Breast cancer

National trends show use of NAC is steadily increasing, especially for TNBC and HER2-positive BC



Key: NAC=neoadjuvant chemotherapy; TNBC=triple negative breast cancer.

Fig. 2 Rates of women receiving neoadjuvant chemotherapy in surgically managed cT1-2N0M0 TNBC, by year of clinical diagnosis from the NCDB

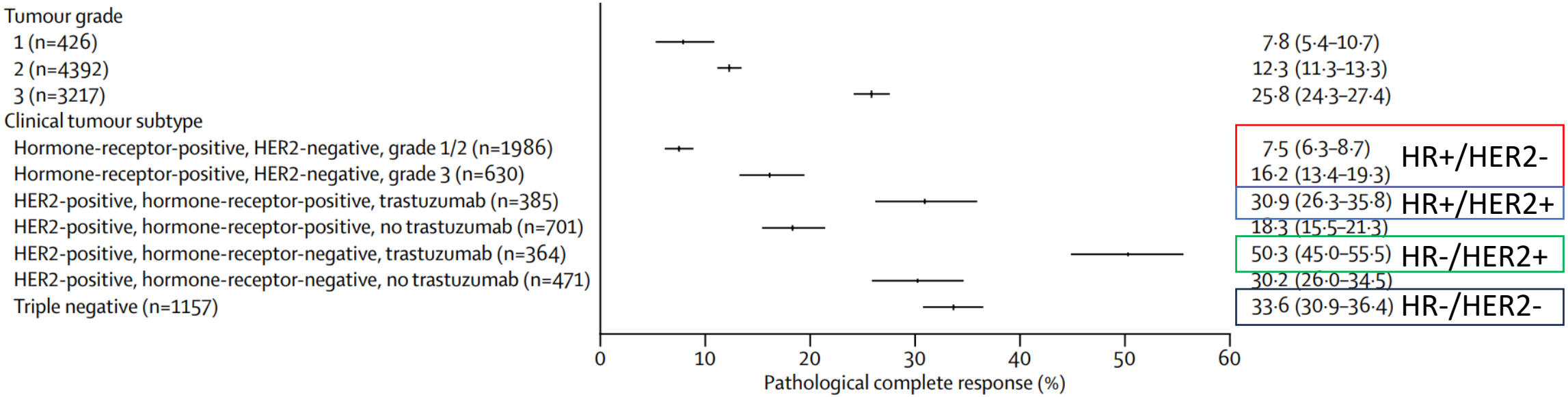


Key: NAC=neoadjuvant chemotherapy; TNBC=triple negative breast cancer.

Fig. 3 Rates of women receiving neoadjuvant chemotherapy in surgically managed cT1-2N0M0 TNBC, by year of clinical diagnosis and specific clinical T stage from the NCDB. Key: *NAC* neoadjuvant chemotherapy, *TNBC* triple-negative breast cancer

Rogers C et al., Breast Cancer Res Treat 2024; 203(2): 317-28

Response rates to NAC vary according to tumor subtype.



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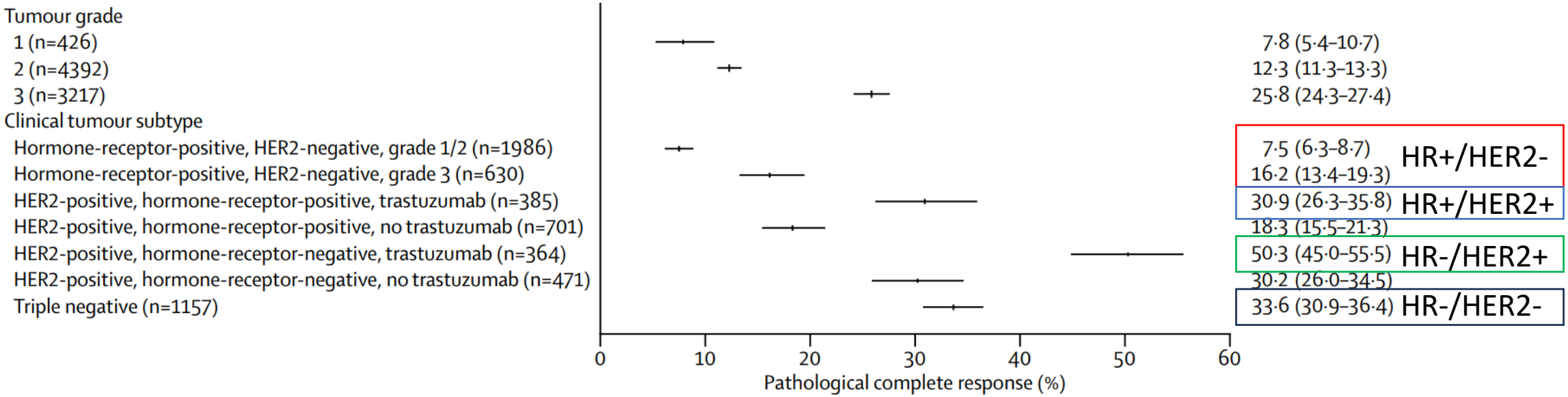

Cortazar P et al., Lancet 2014; 384(9938):164-72

Tumor receptor subtype (n value)	% pCR (n value)
All cases (n=5161)	32.5% (n=1676)
HR- HER2 + (n=488)	68.9% (n=336)
HR- /HER2 – (n=1774)	43.4% (n=770)
HR+/ HER2 + (n=756)	38.4 % (n=290)
HR+/ HER2 – (n=1957)	11.1% (n=217)

Yau C et al., Lancet Oncol 2022; 23(1): 149-160

Approach to Evaluating Neoadjuvant Treated Breast Cancer Cases

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Gather Data

- Did the patient receive NAC?
- What did the pre-treatment imaging show?
  - Size/ Number/ Location of lesion(s)?
  - How many clips are present?
  - Were there lesions that were unbiopsied?
  - Were any abnormal nodes identified in the axilla? Were they biopsied?
- What did the pathology from the biopsy show? What was the receptor profile?
- What was the clinical response to NAC?
- Was there any post-treatment imaging? What did it show?

Gather Data: Minimum required information

- **Did the patient receive NAC?**
- **What did the pre-treatment imaging show?**
  - **Size/ Number/ Location of lesion(s)?**
  - **How many clips are present?**
  - **Were there lesions that were unsampled?**
  - **Were any abnormal nodes identified in the axilla? Were they biopsied?**
- **What did the pathology from the biopsy show? What was the receptor profile?**
- What was the clinical response to NAC?
- Was there any post-treatment imaging? What did it show?

Example requisition form

[Appropriate identification]

NEOADJUVANT SPECIMEN REQUISITION FORM (to be completed by surgeon)

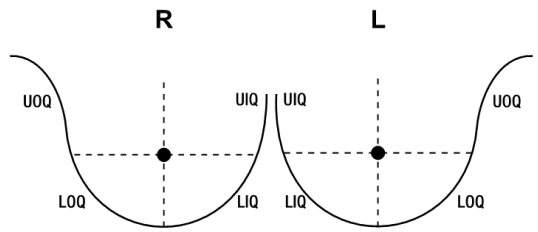
Fill in blank or circle appropriate

CLINICAL TRIAL: _____ / Not applicable

Note to pathologist: If a trial, please verify if trial requires a particular grading system.

PRE-TREATMENT:

Indicate location of lesion(s) on figure:



Lesion 1: Location: _____o'clock, _____cm from nipple
Size: _____ Depth: Superficial Mid-depth Deep
Calcifications Clip Ink Marked with suture

Lesion 2: Location: _____o'clock, _____cm from nipple
Size: _____ Depth: Superficial Mid-depth Deep
Calcifications Clip Ink Marked with suture

Lesion 3: Location: _____o'clock, _____cm from nipple
Size: _____ Depth: Superficial Mid-depth Deep
Calcifications Clip Ink Marked with suture

Primary tumor biopsy: Lab ref. number: _____ At this / Different institution

If at different institution, please complete this box:
Slides requested for review : Yes No
Diagnosis: Invasive ductal carcinoma Other type: _____ Grade: 1 2 3
ER: pos/ neg PR: pos/ neg HER2 (IHC): 0 1+ 2+ 3+ HER2 (FISH/ CISH): Not amplified Ratio:___ / Copy number: ___

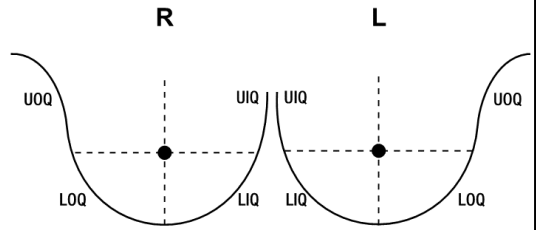
Pretreatment lymph node biopsy/ sampling performed: No Yes
If "Yes": Lab ref. number: _____ At this / Different institution
Clip(s) placed in biopsied lymph node(s)? Yes No

If at different institution, please complete this box:
Slides requested for review: Yes No
Biopsy procedure: SLN FNA Core Number of lymph nodes: Examined:__ Positive:__ (Size of largest metastasis:_____)

POST-TREATMENT:

Clinical residual disease in breast: No Yes If "Yes" please indicate on diagram.
Post-treatment imaging of breast: Mammography US MRI PET Cycle # at imaging: ___
Post-treatment imaging of axilla?: No Yes (If "Yes": US Mammography MRI PET Cycle #: ____)
Clinically positive nodes in axilla present post-treatment?: No Yes If "Yes": number of positive nodes: ____

Indicate location of lesion(s) on figure:



Lesion 1: Location: _____o'clock, _____cm from nipple
Size: _____ Depth: Superficial Mid-depth Deep
Describe response: concentric/ scattered/ _____

Lesion 2: Location: _____o'clock, _____cm from nipple
Size: _____ Depth: Superficial Mid-depth Deep
Describe response: concentric/ scattered/ _____

Lesion 3: Location: _____o'clock, _____cm from nipple
Size: _____ Depth: Superficial Mid-depth Deep
Describe response: concentric/ scattered/ _____

Intraoperative findings: Close margin(s): No Yes If "Yes": Describe:_____

Provenzano E et al., Modern Pathol 2015; 28:1185-1201

Private Information

Approach to Evaluating Neoadjuvant Treated Breast Cancer Cases

- 1) Gather Data
- **2) Gross Evaluation/ Adequate Sampling**
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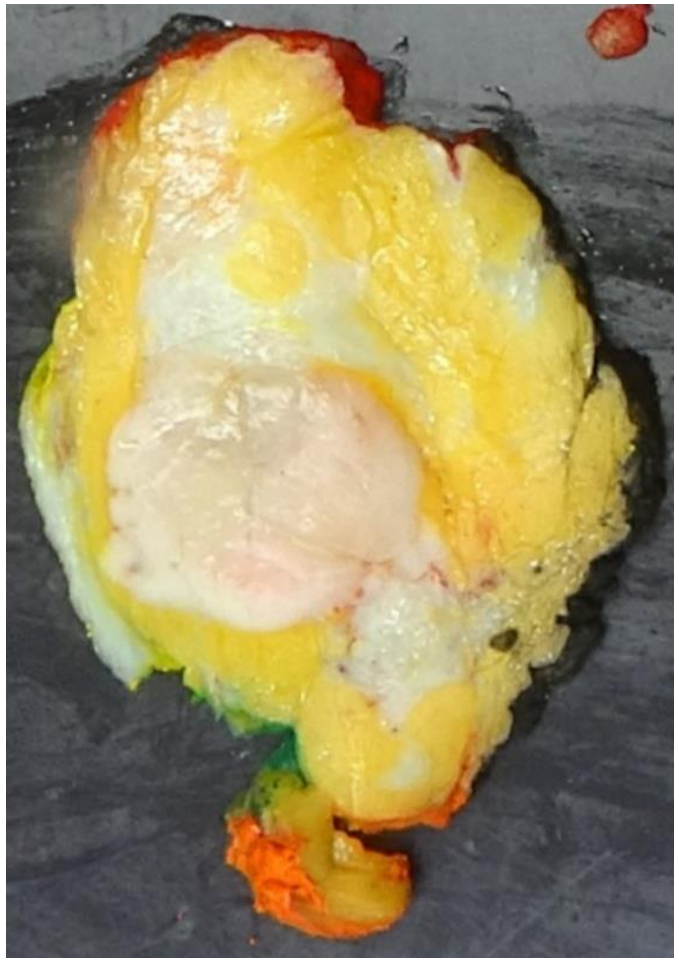
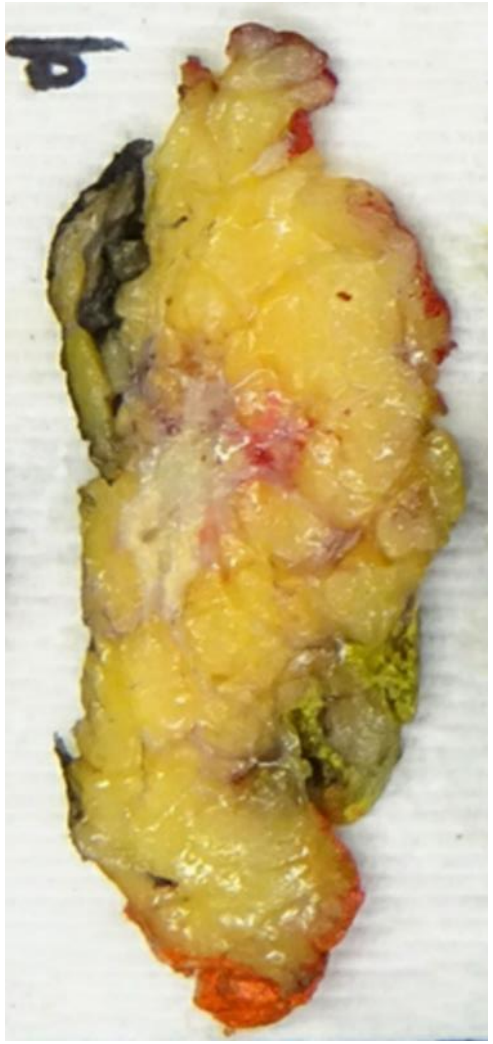
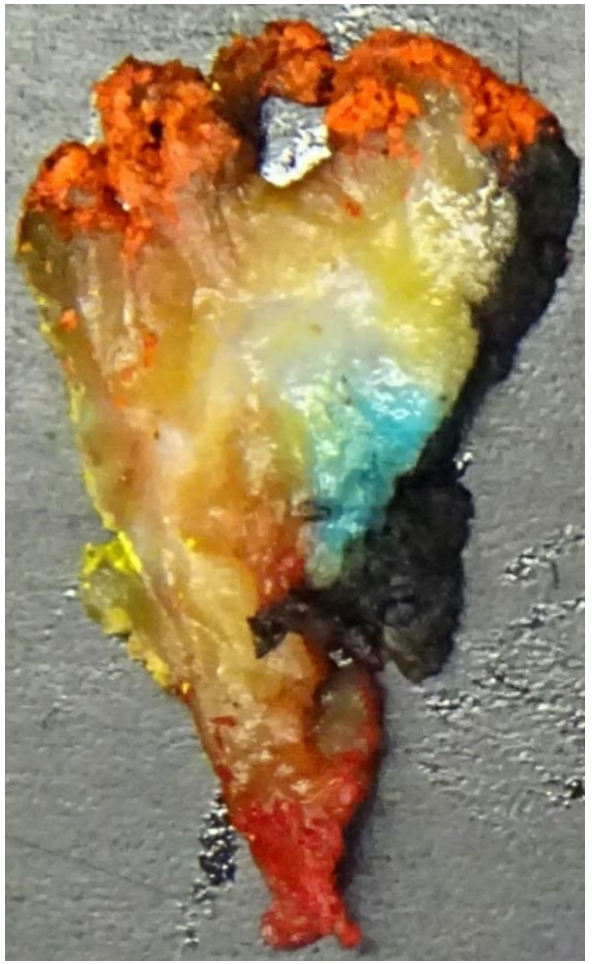
Gross appearance can vary widely following NAC. Residual tumor usually softer than untreated tumor and less well-defined, making gross evaluation more difficult.







Careful mapping and more extensive sampling is often required in order to get an accurate representation of residual disease

- Correlation with clinical and imaging findings is required to ensure that the correct area(s) are sampled.
- Sampling should include any grossly apparent residual tumor and fibrotic tumor bed and/or location of biopsy clips and adjacent tissue to encompass the *pre-treatment* area of tumor involvement.
- Highly recommended to create a map of sections taken

Provenzano E et al., Modern Pathol 2015;28:1185-1201
Sahoo S et al., Arch Pathol Lab Med 2023; 147:591-603

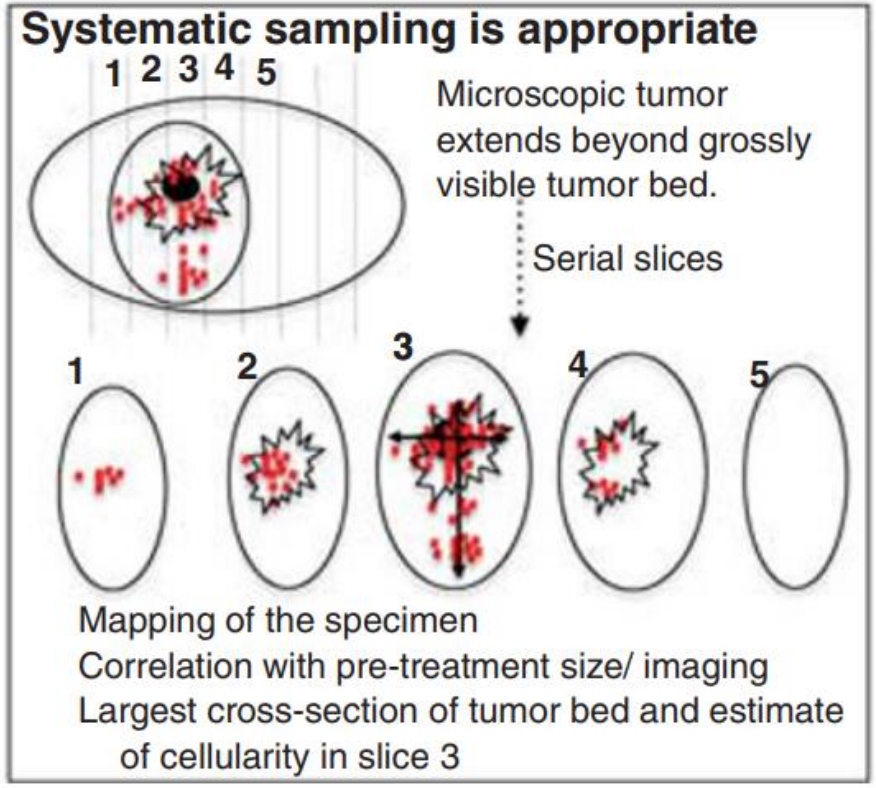
Gross Evaluation/ Adequate Sampling: Small Lumpectomy Specimens

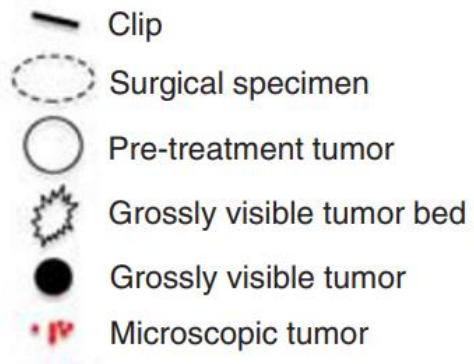
- For lumpectomies <5 cm in greatest dimension (Yale University's SOP) or < 30 g (Dutch national guideline)
  - Thinly slice and sequentially submit the specimen in its entirety.

Provenzano E et al., Modern Pathol 2015;28:1185-1201

Gross Evaluation/Adequate Sampling: Large Lumpectomy/ Mastectomy Specimens

- Specimen sliced to reveal the largest cross-section of pretreatment area involvement
- Map a complete cross section of the tumor bed along its longest axis
- At least one section per centimeter of the pretreatment carcinoma size





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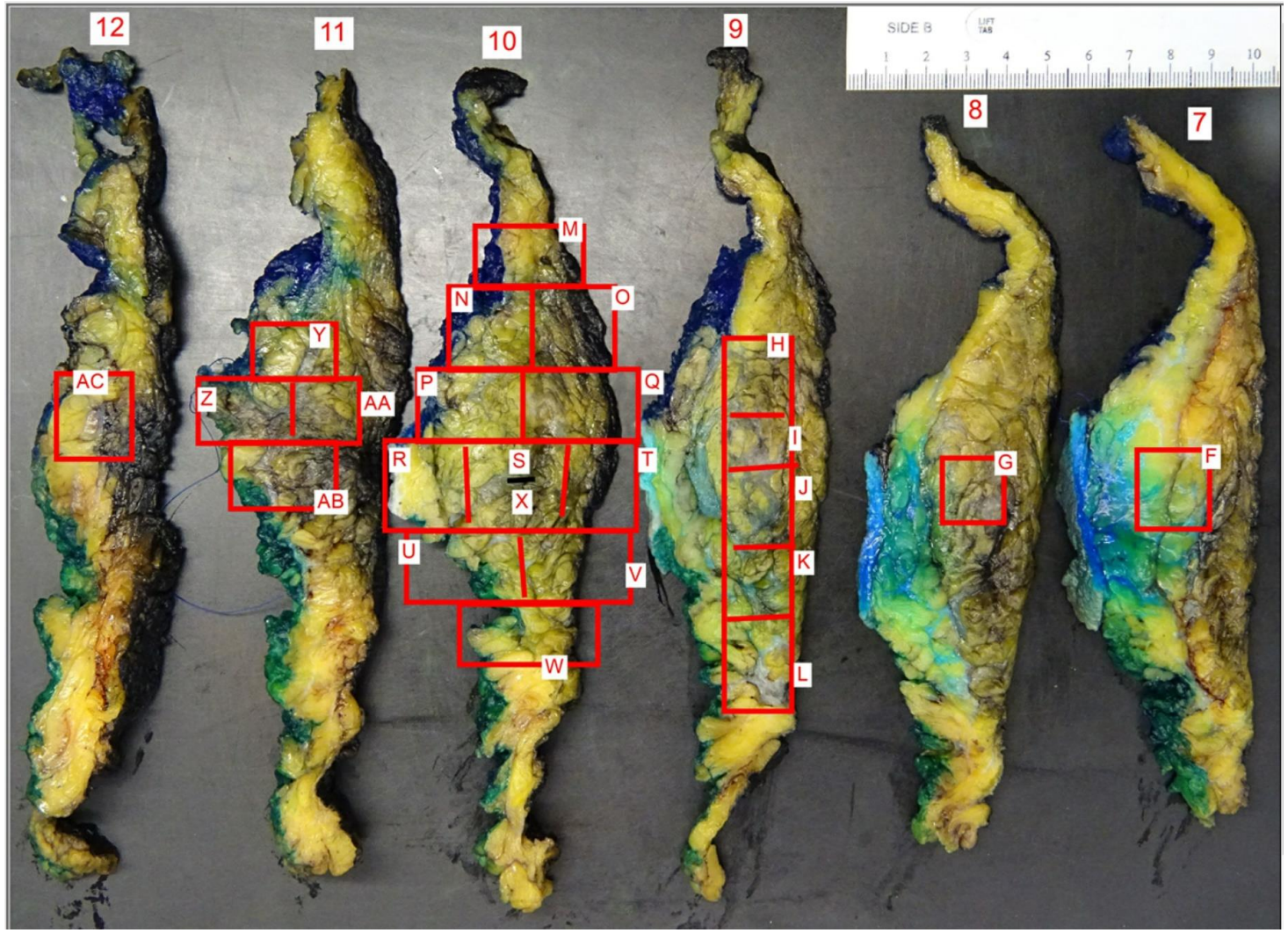
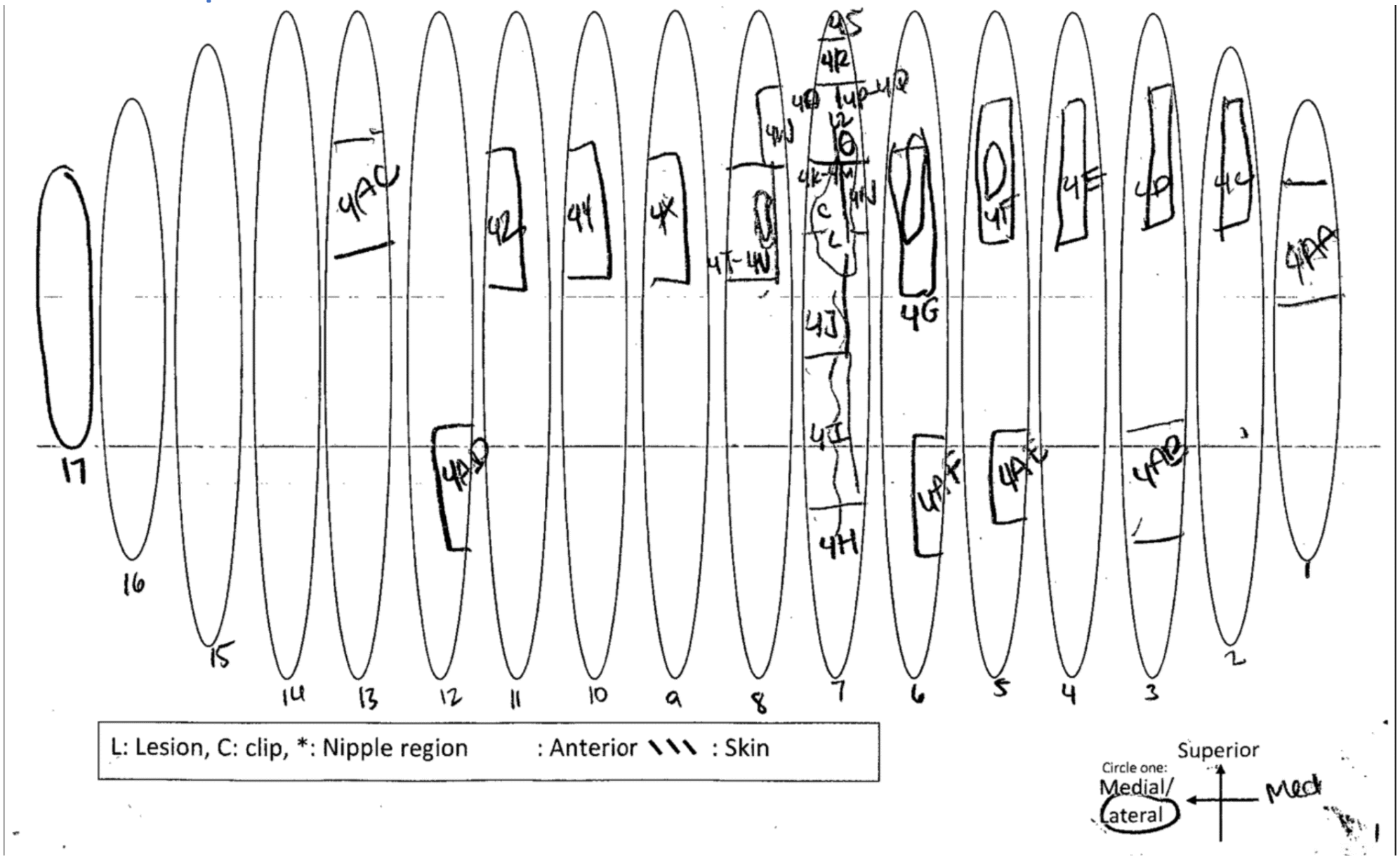
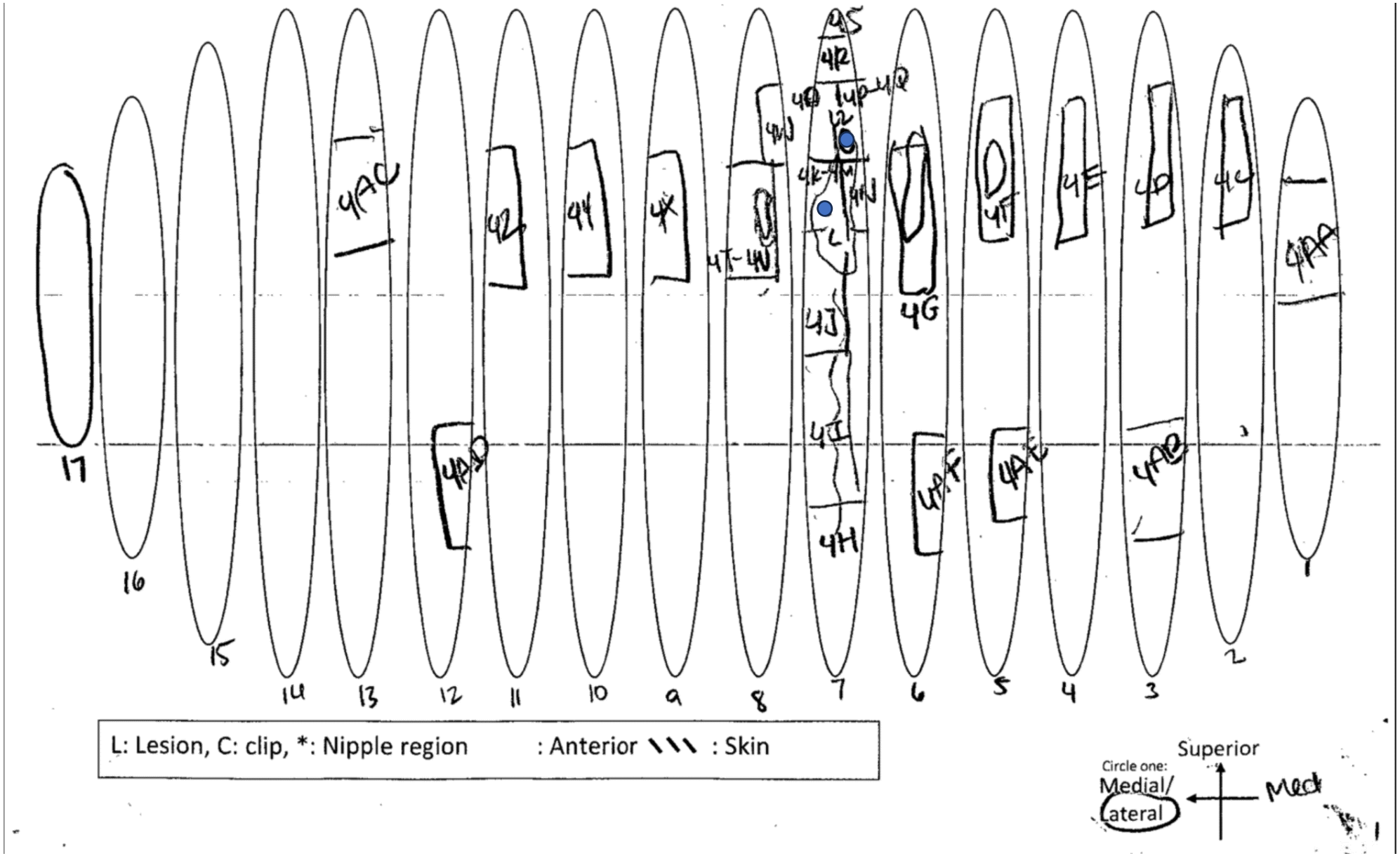
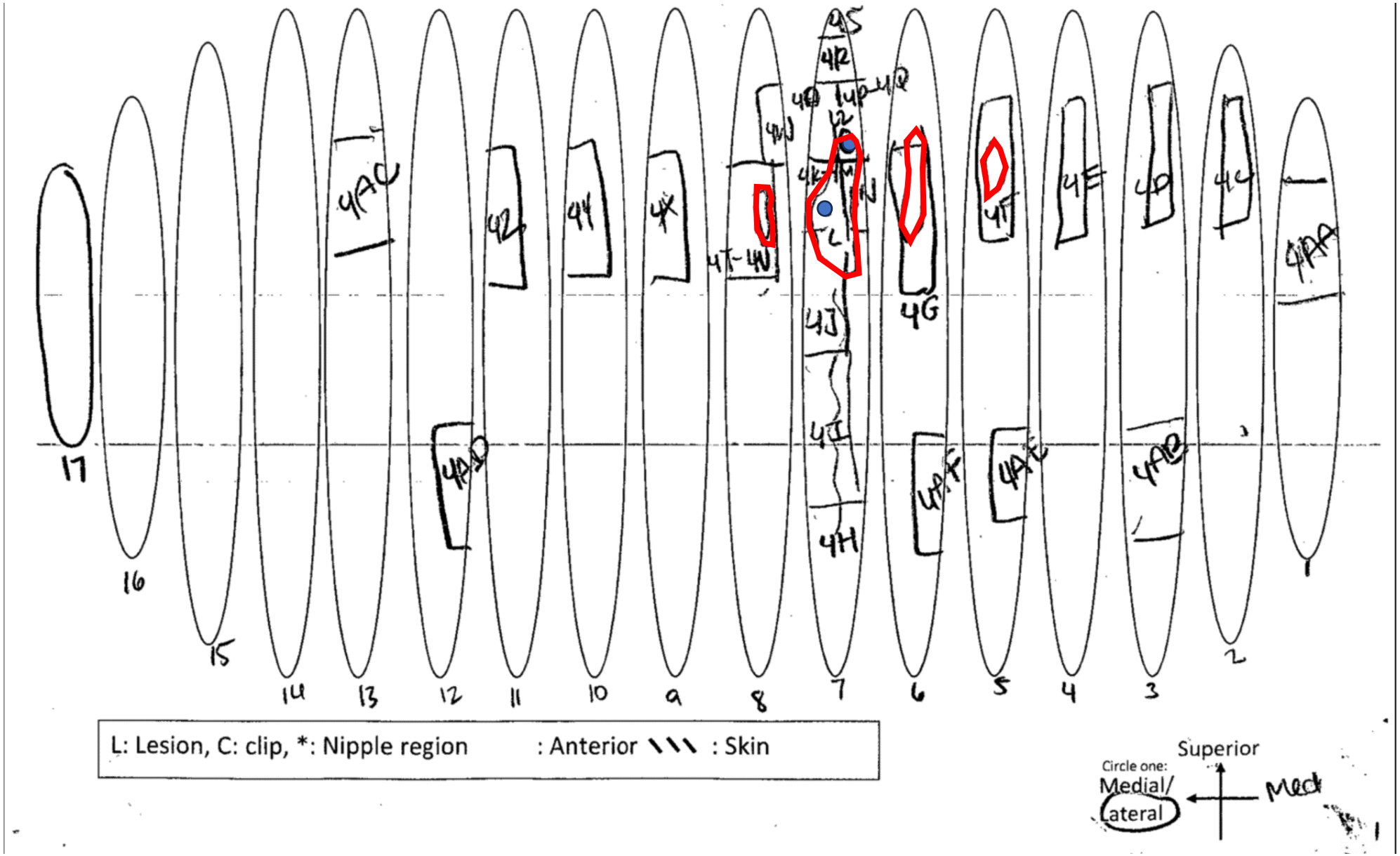
Creating a map of the sections taken is highly recommended

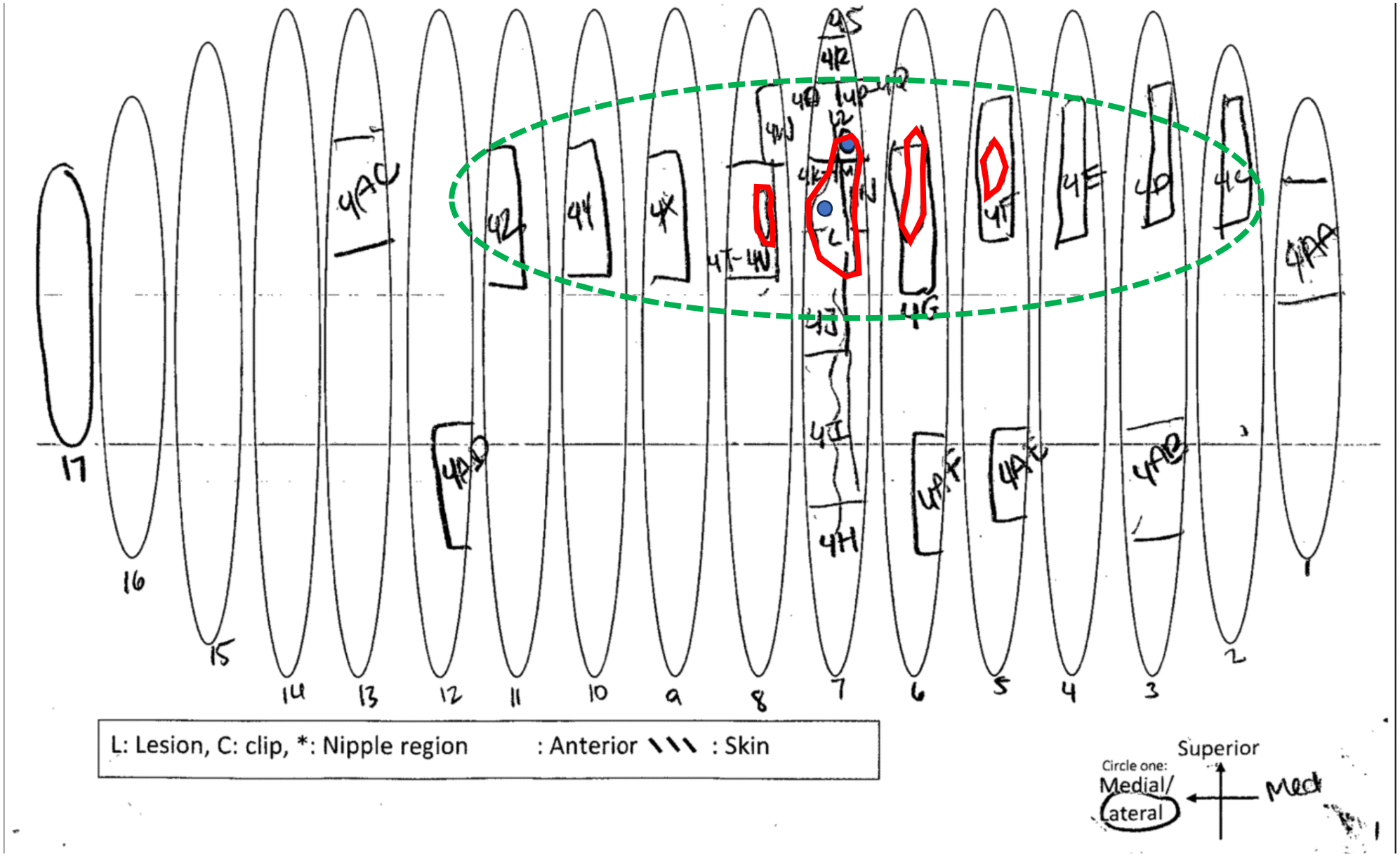


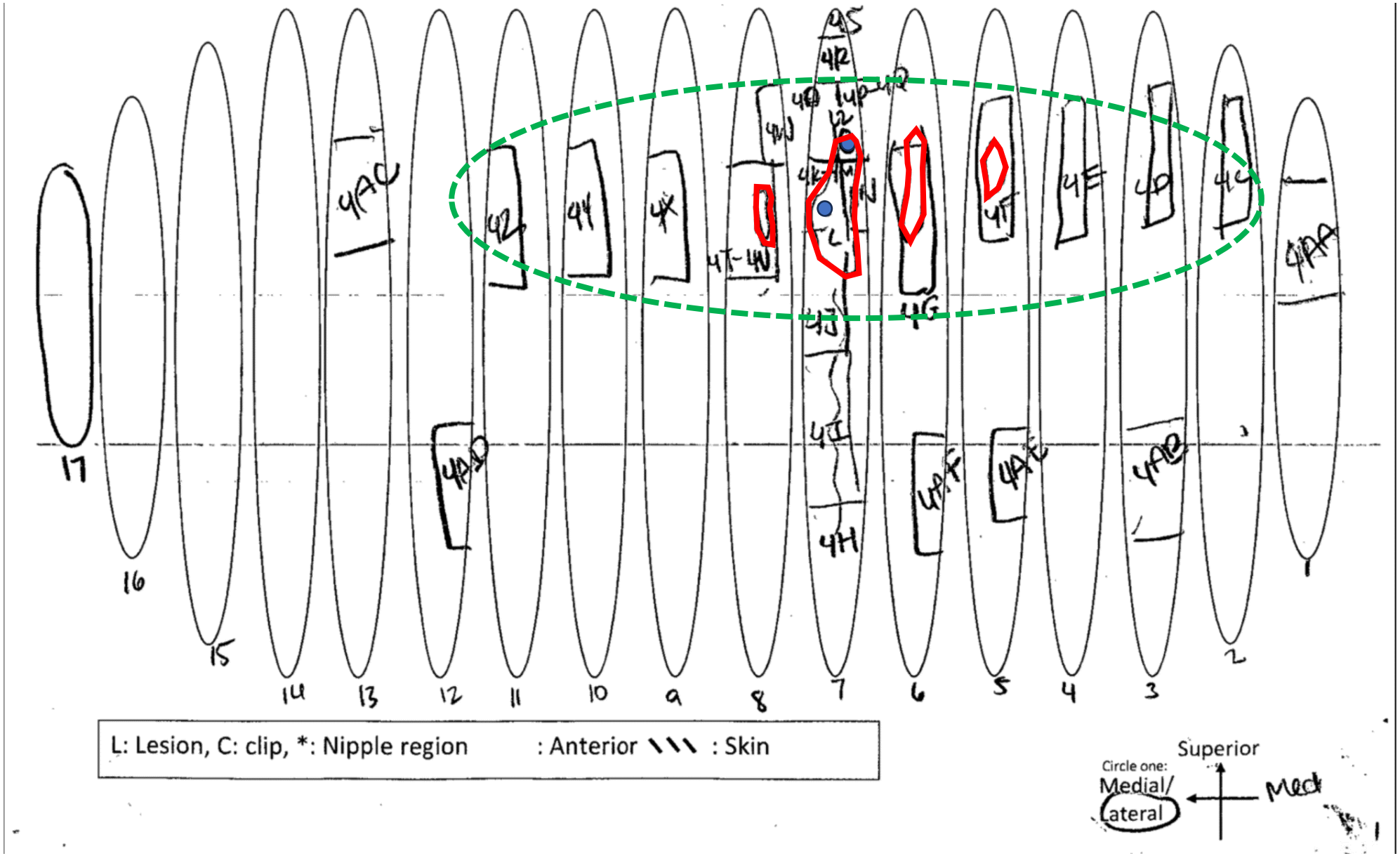
Another example…











**If no residual tumor is identified on initial sections, may be necessary to go back and submit more tissue!

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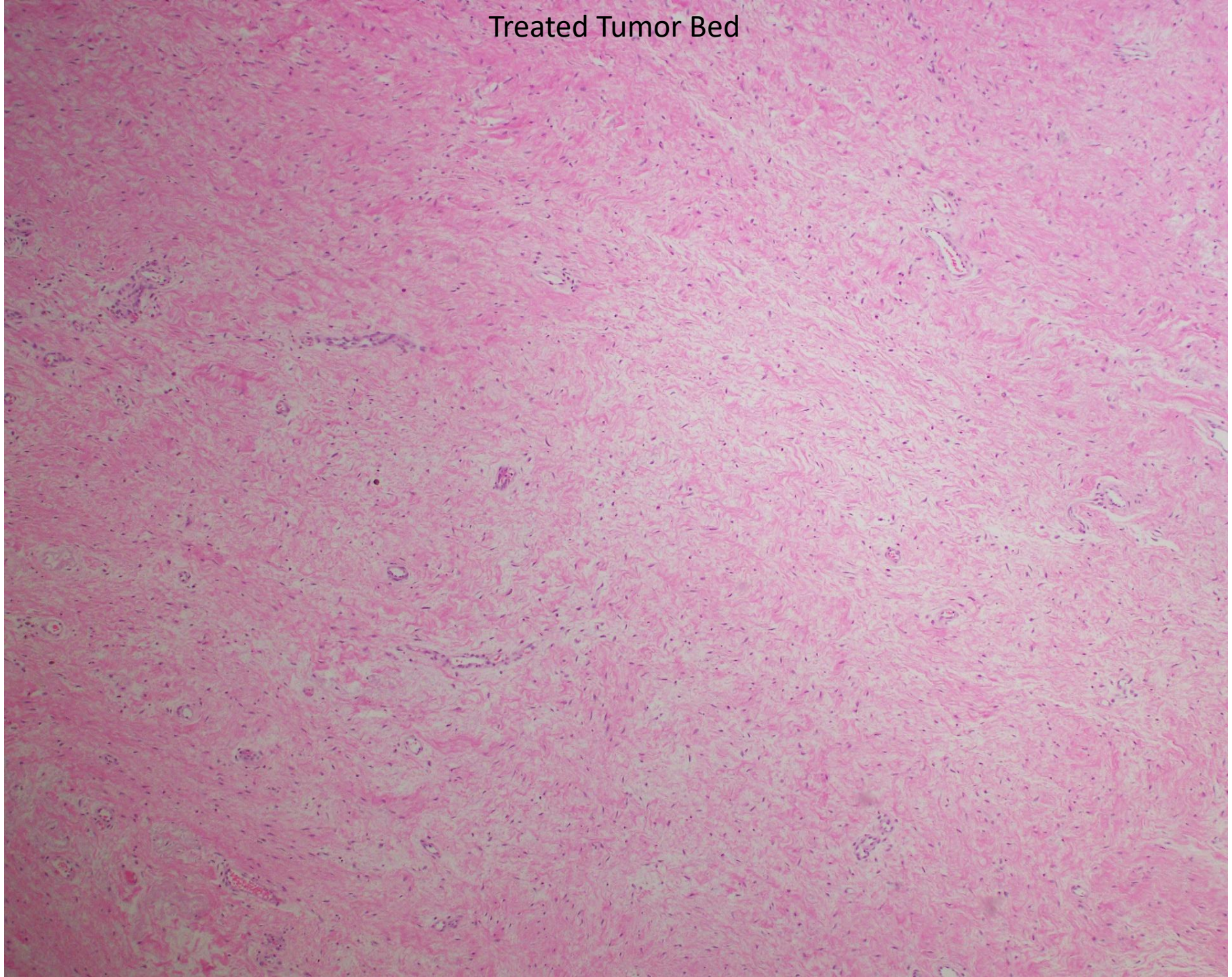
Microscopic Evaluation

- Histologic evidence of treated tumor bed, biopsy site
- Treatment related changes in tumor cells
- Treatment related changes in lymph nodes
- Patterns of residual disease

Treated Tumor Bed



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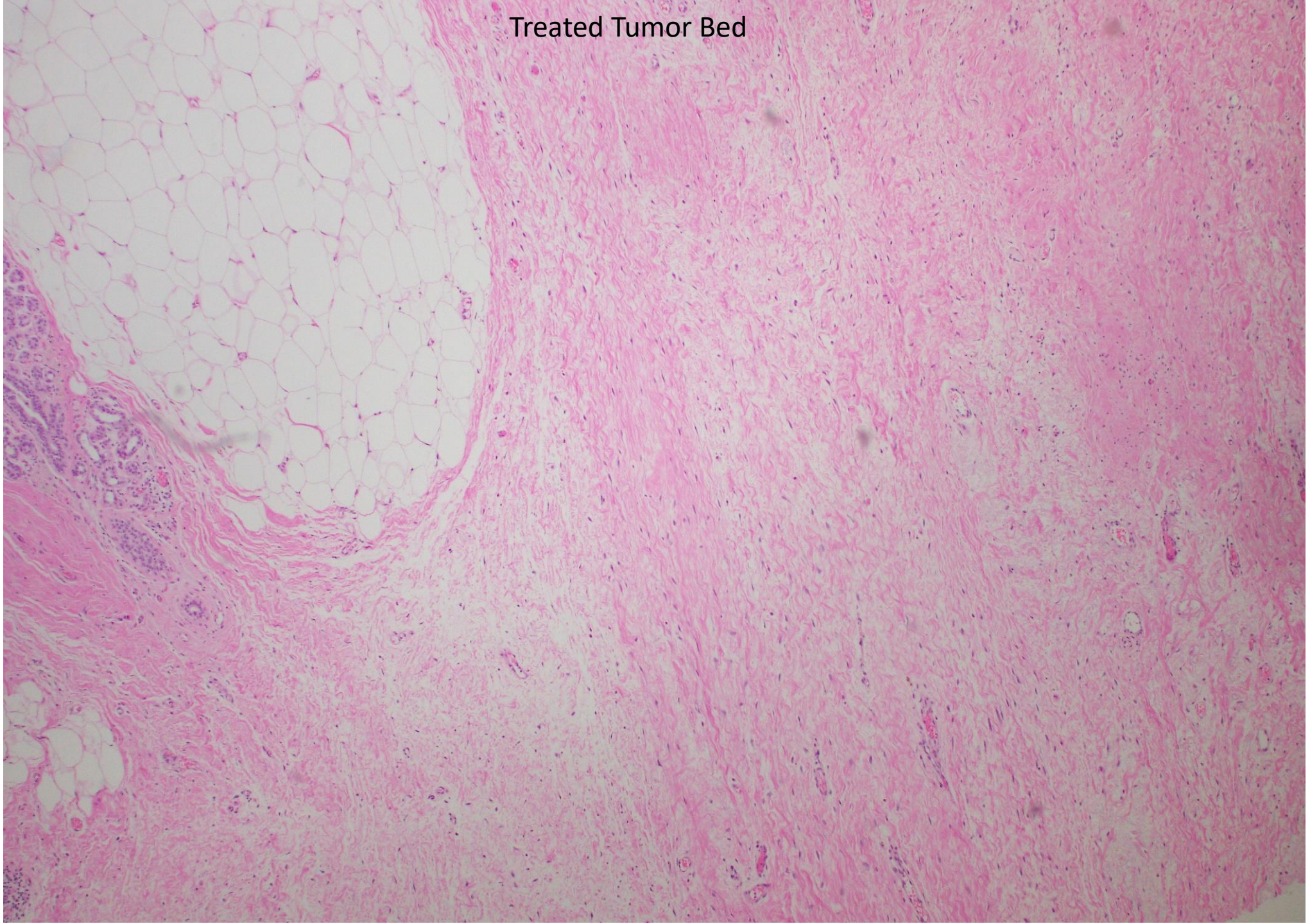

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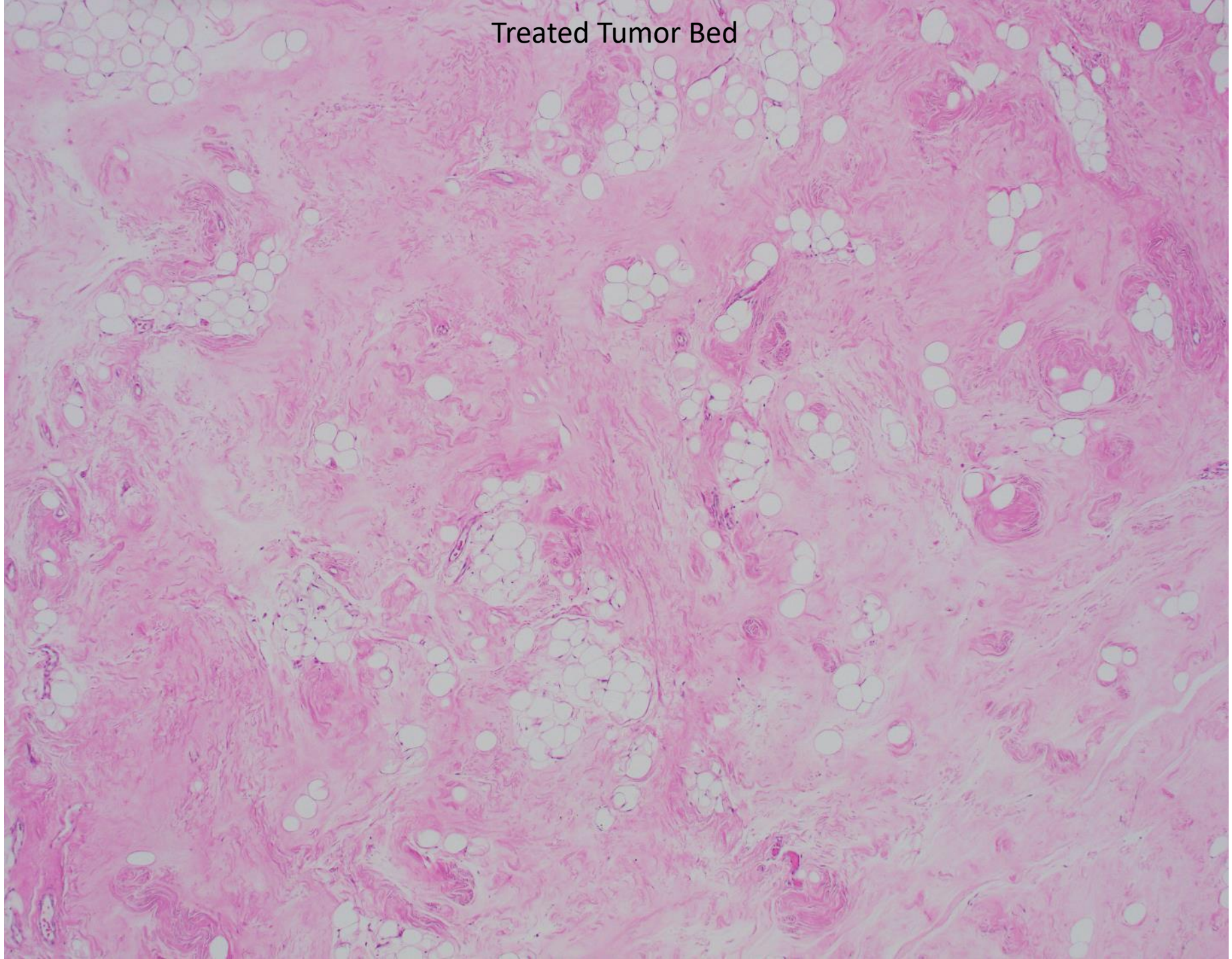

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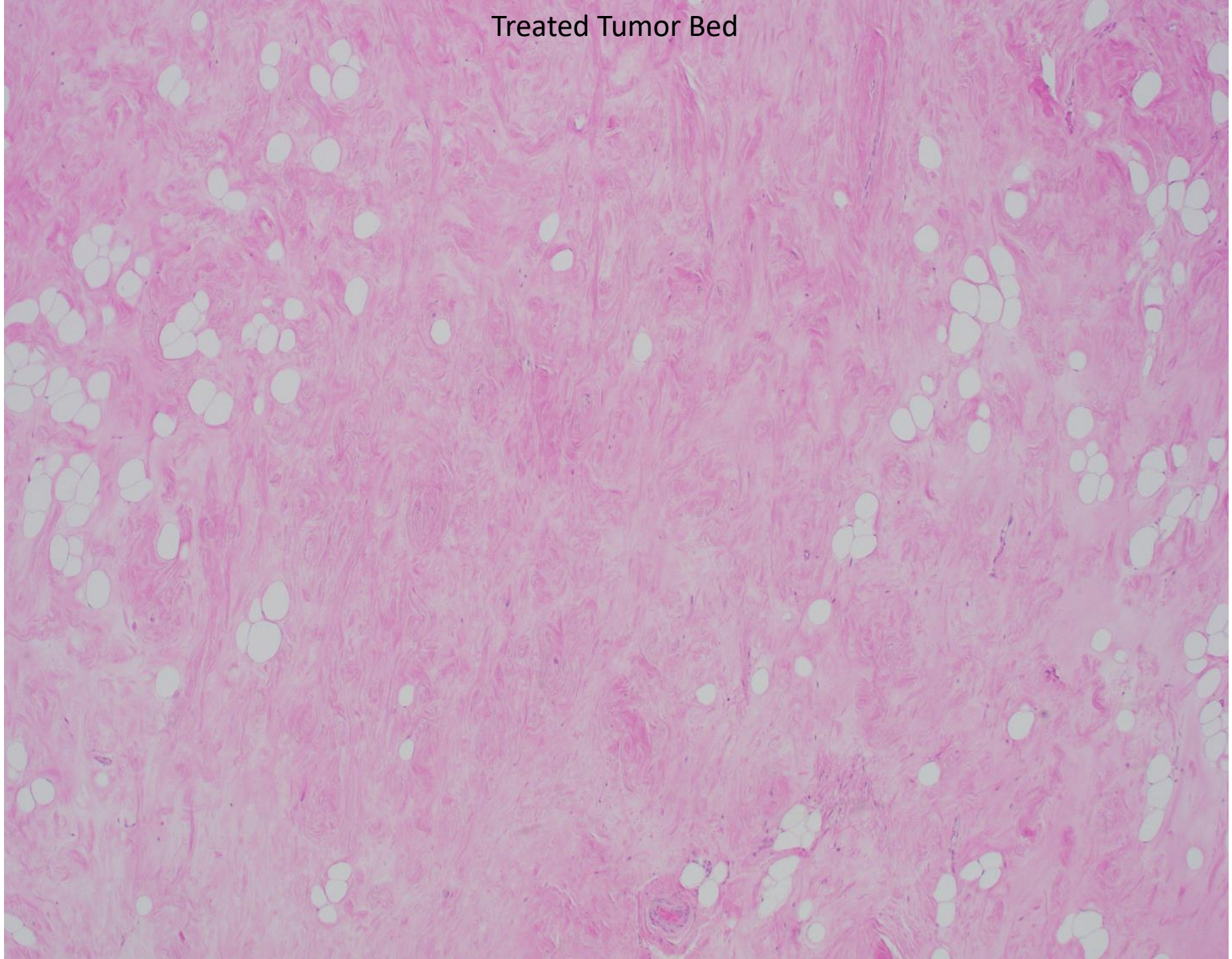

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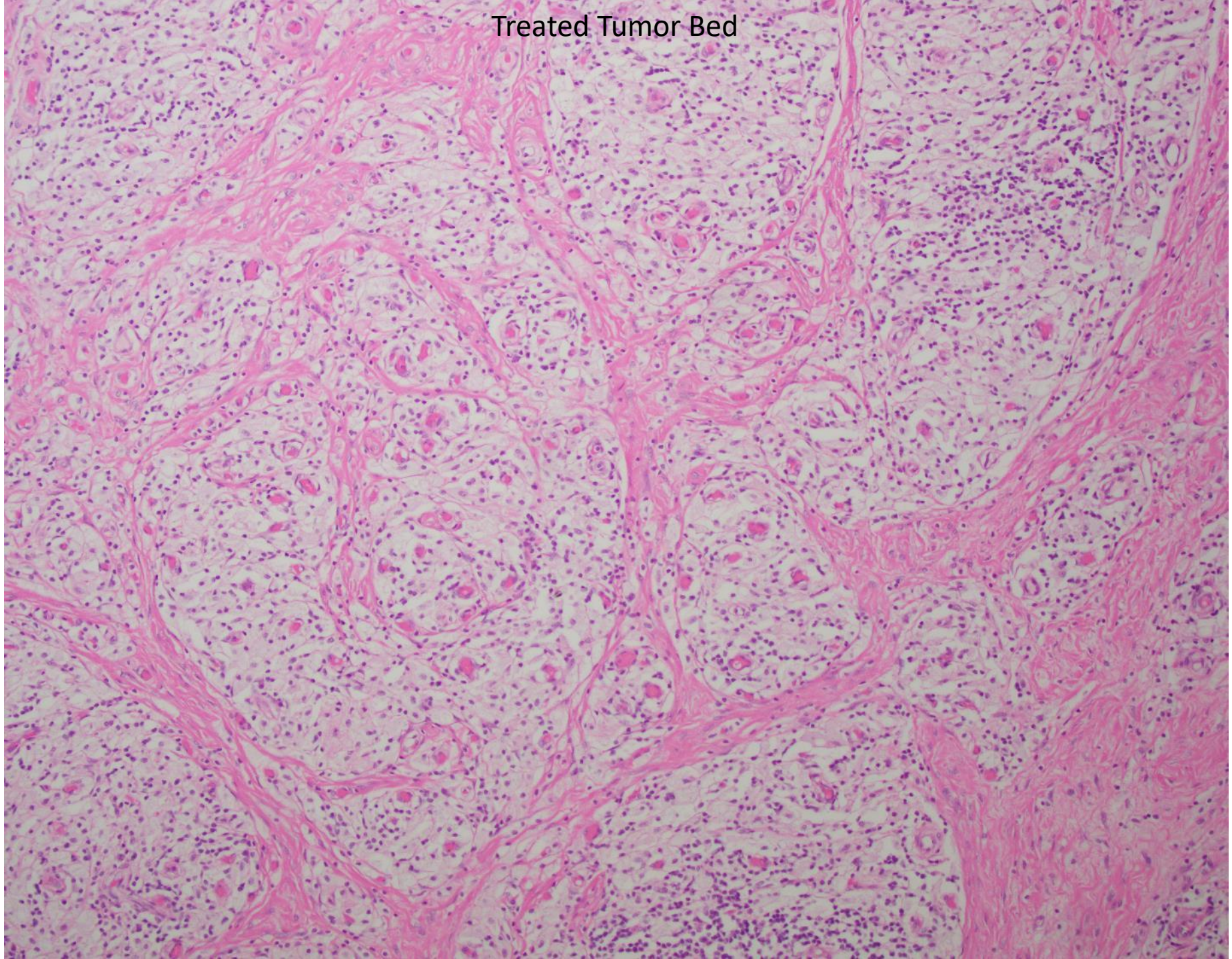

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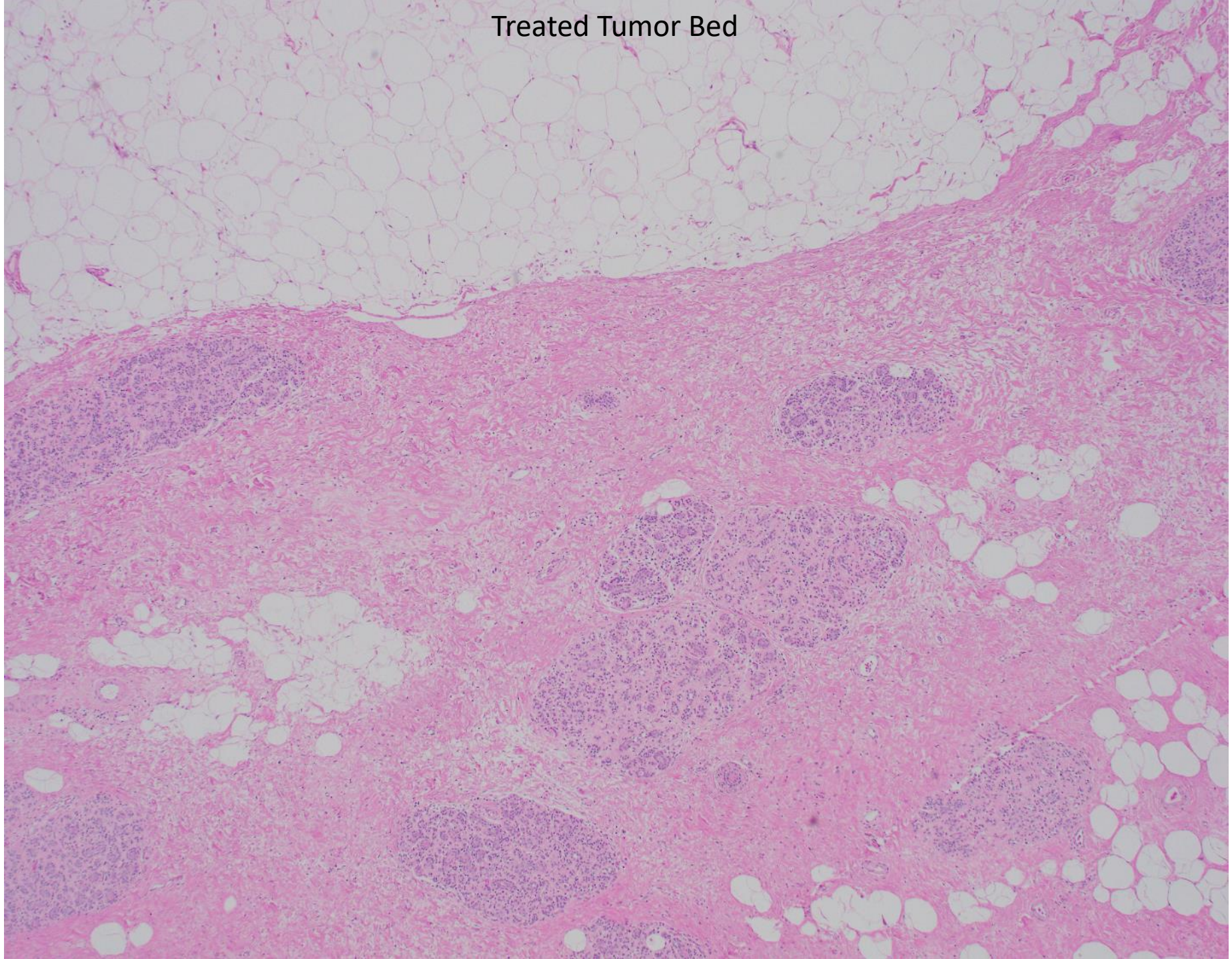
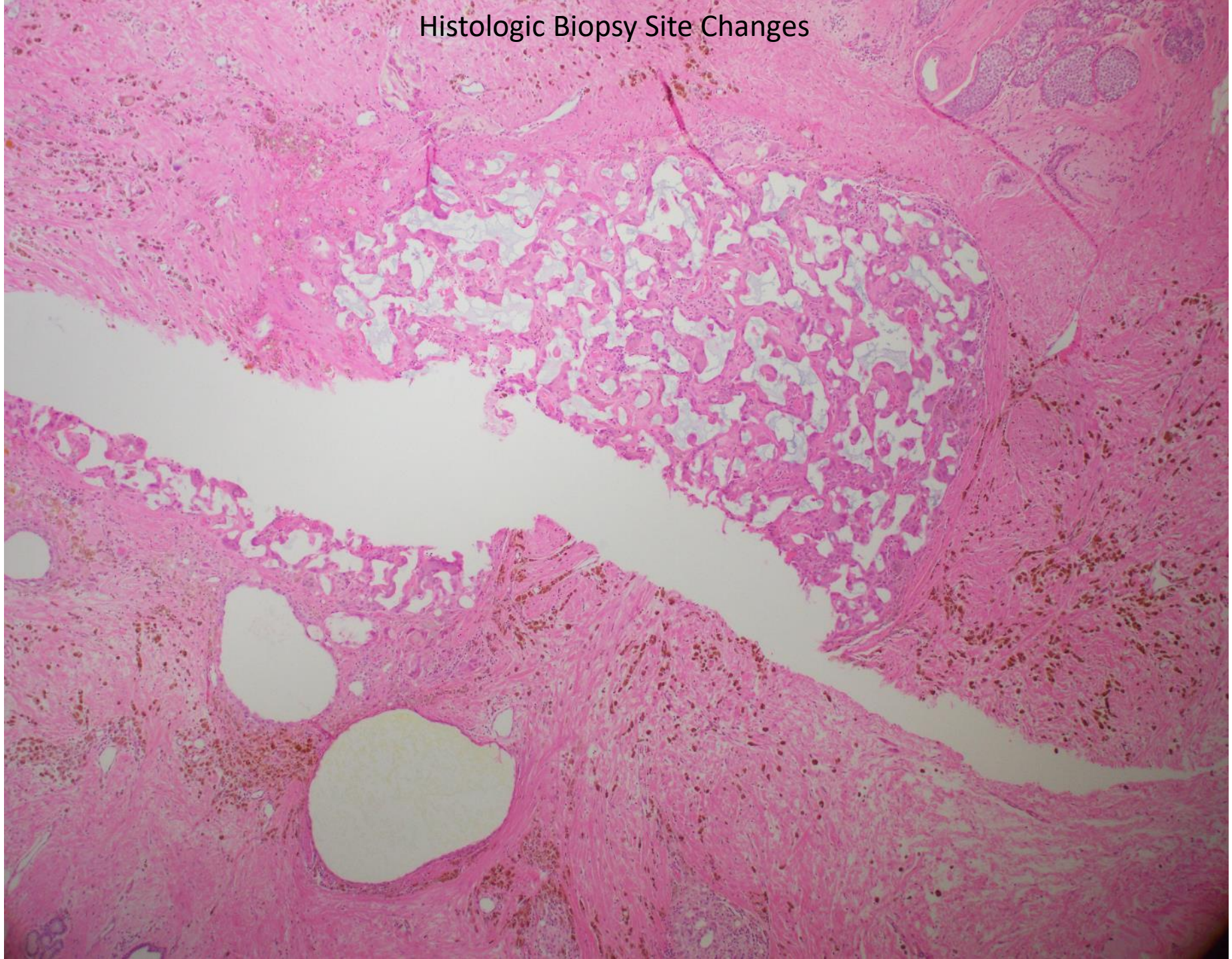


Histologic Biopsy Site Changes



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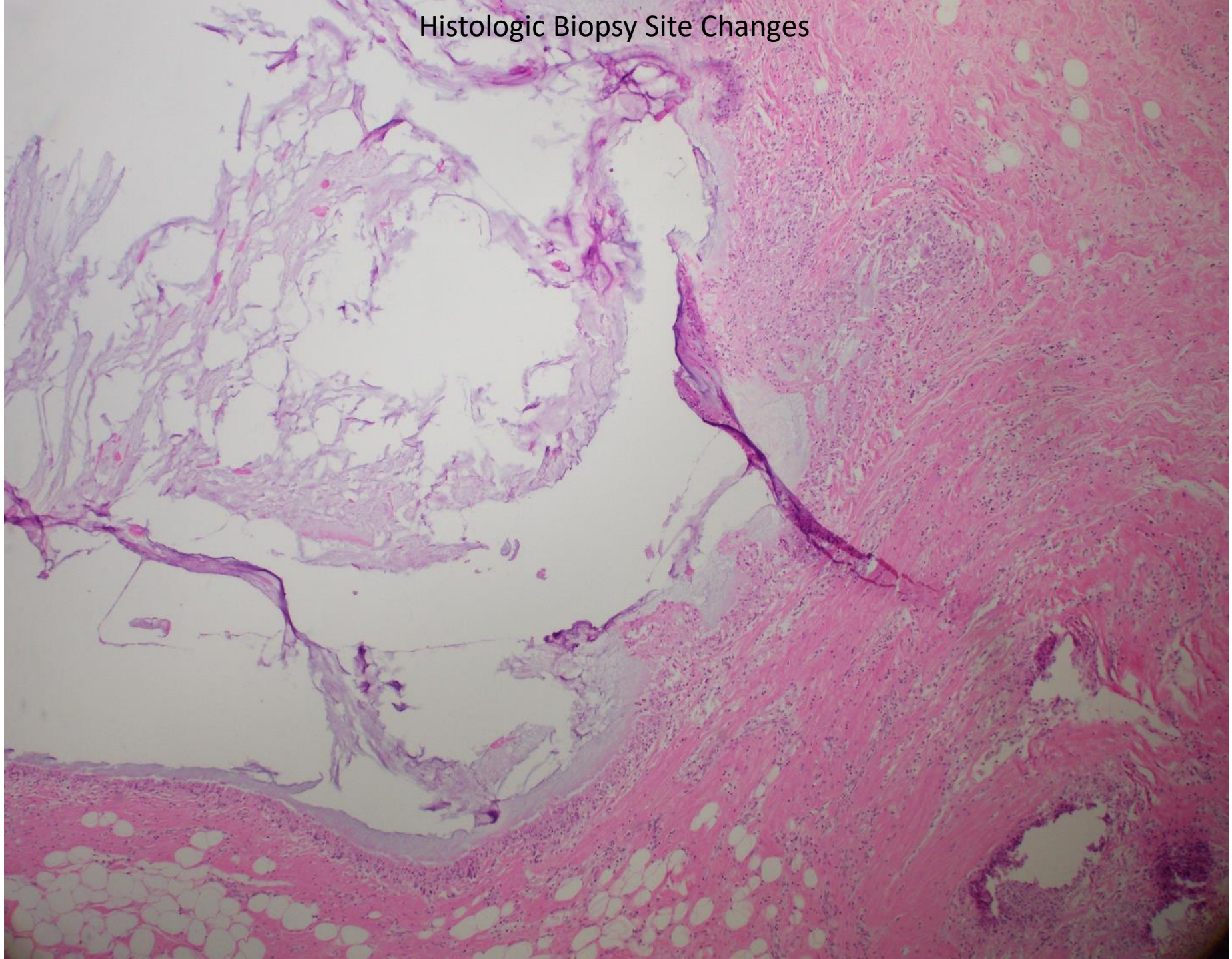
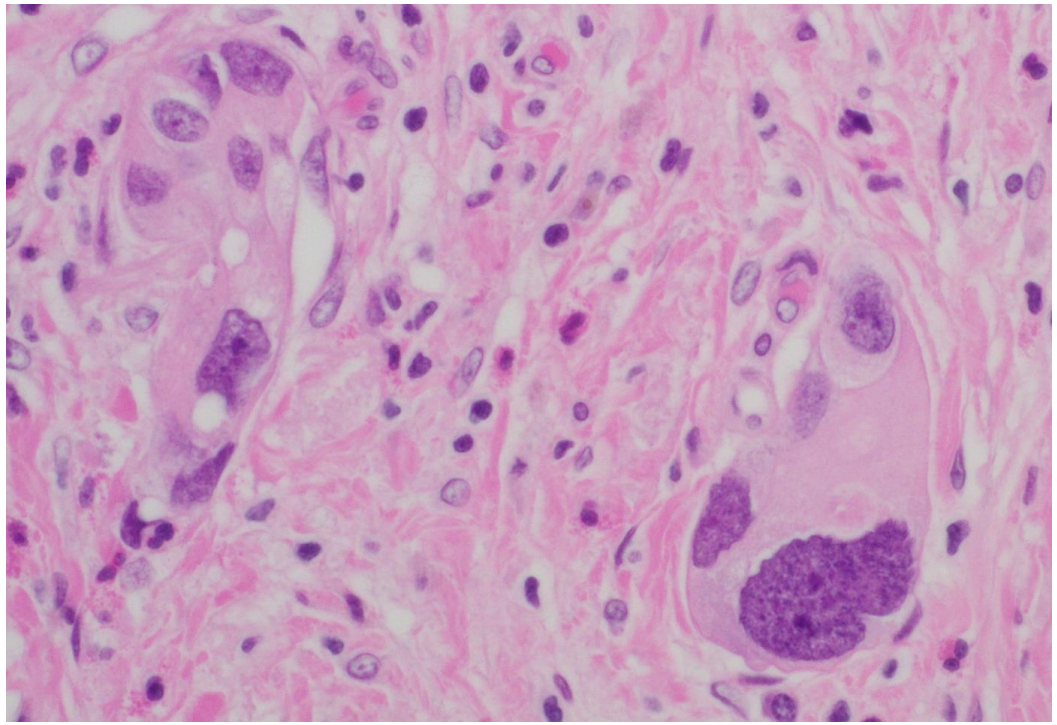
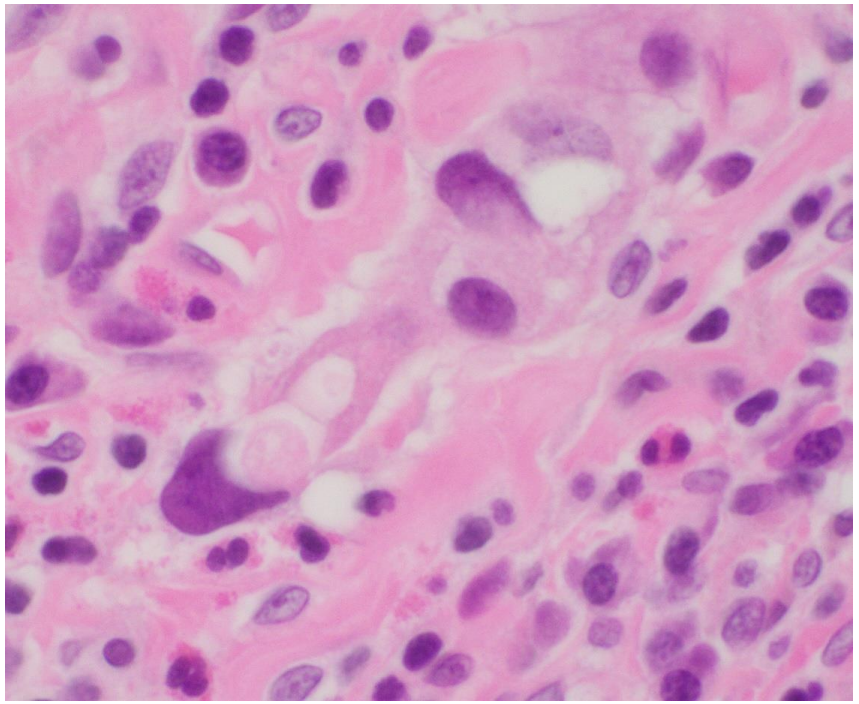
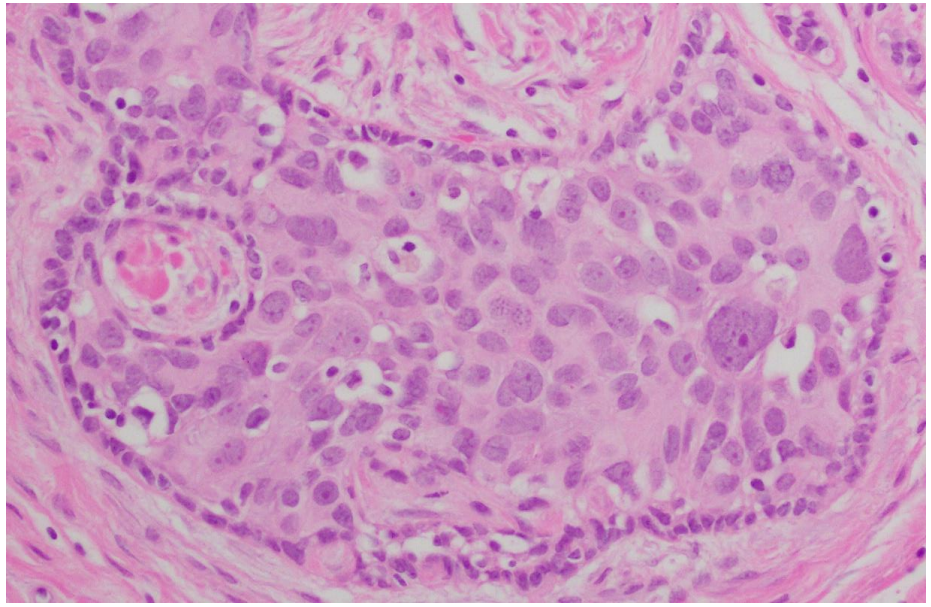


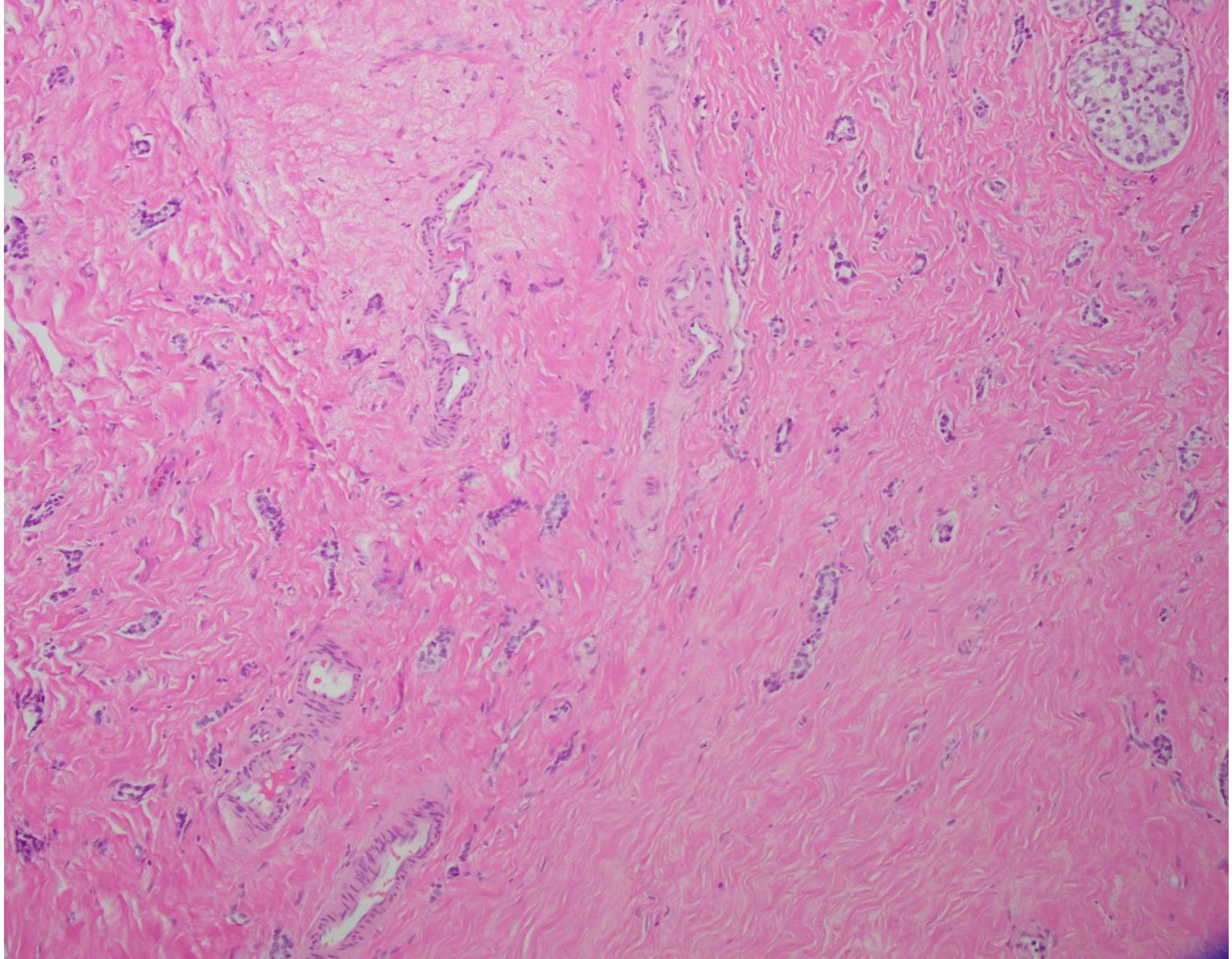
A note about Savi Scouts and biopsy sites

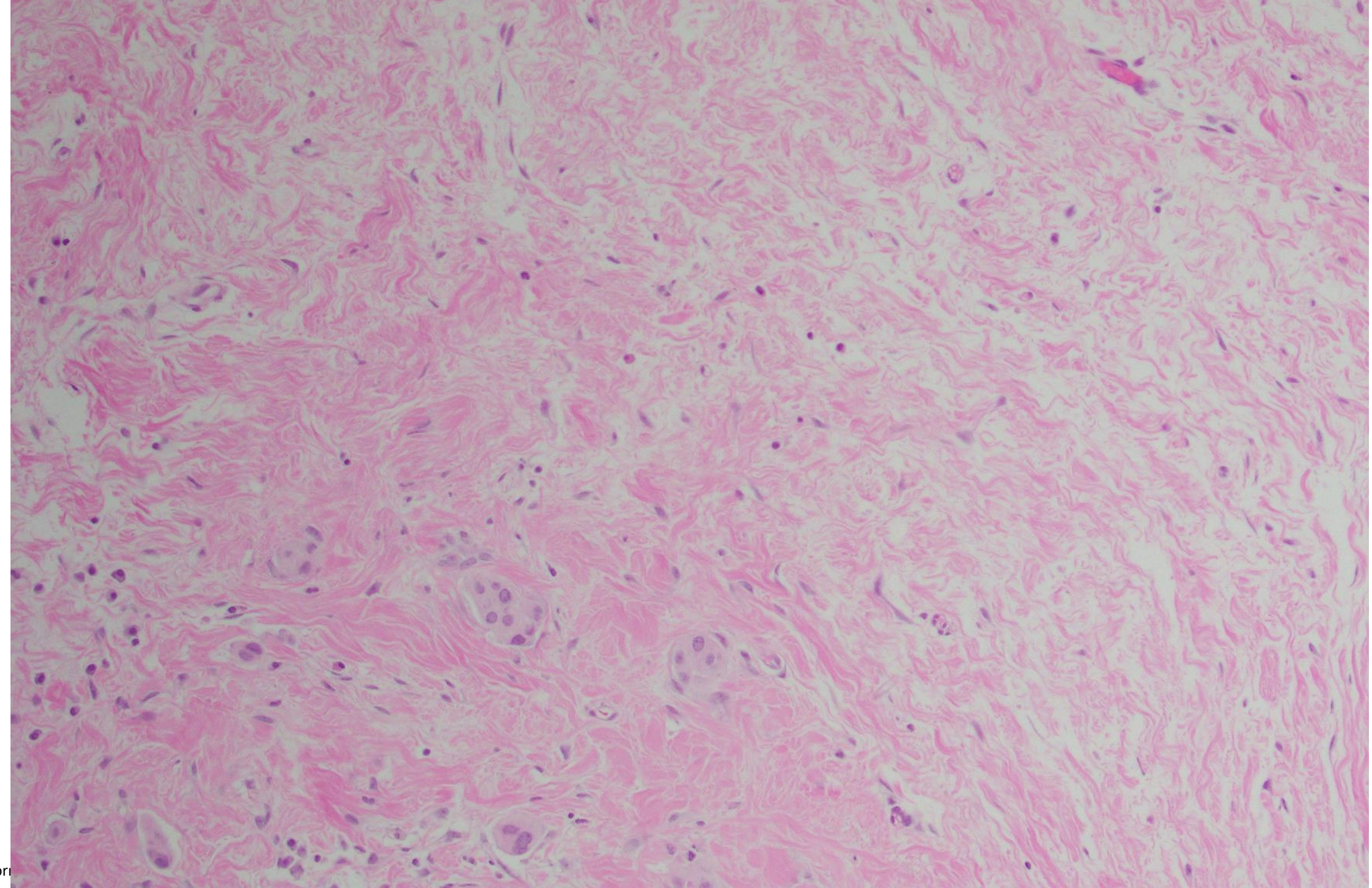
Wazir U et al., Cancers 2021: 13(10)2409

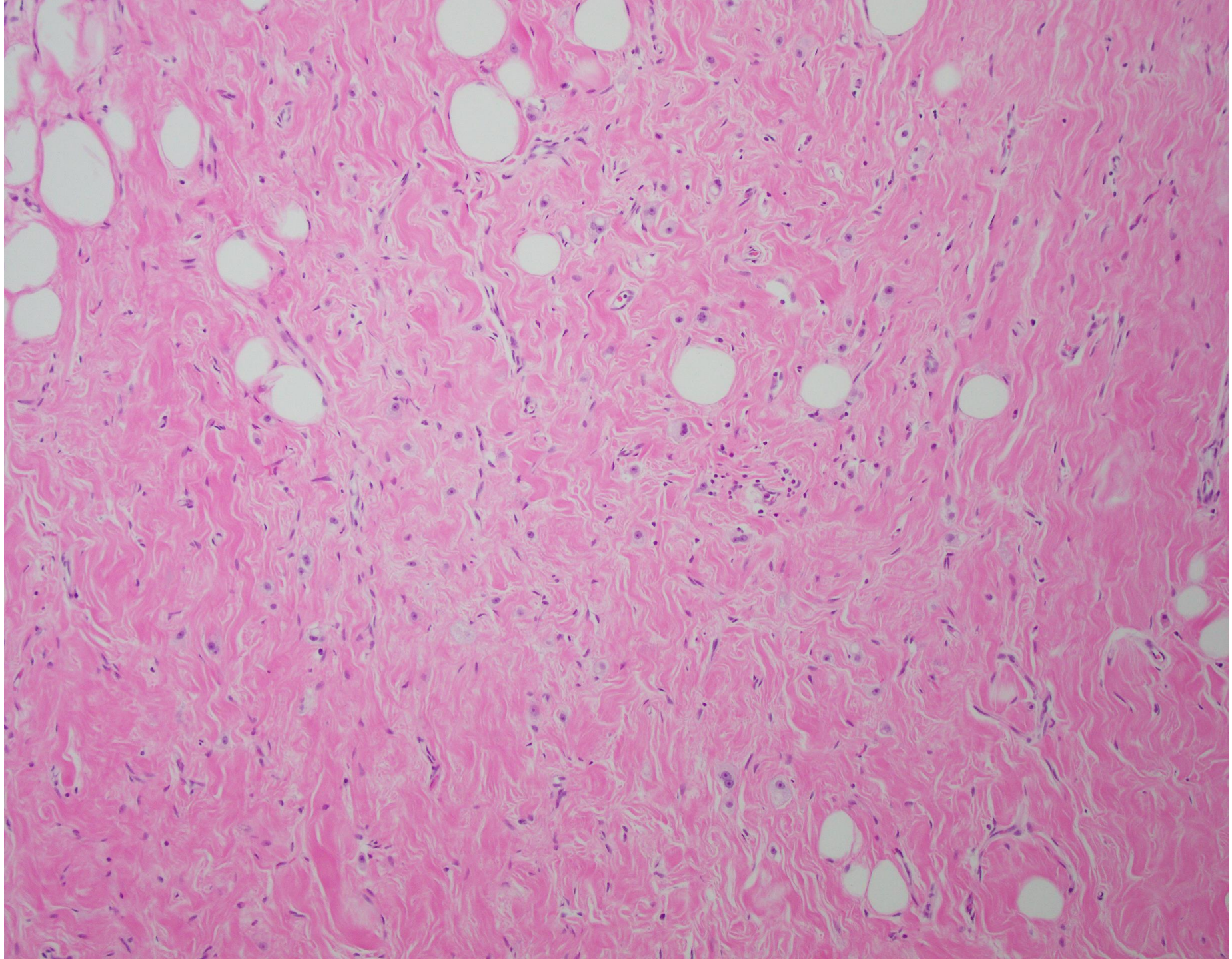




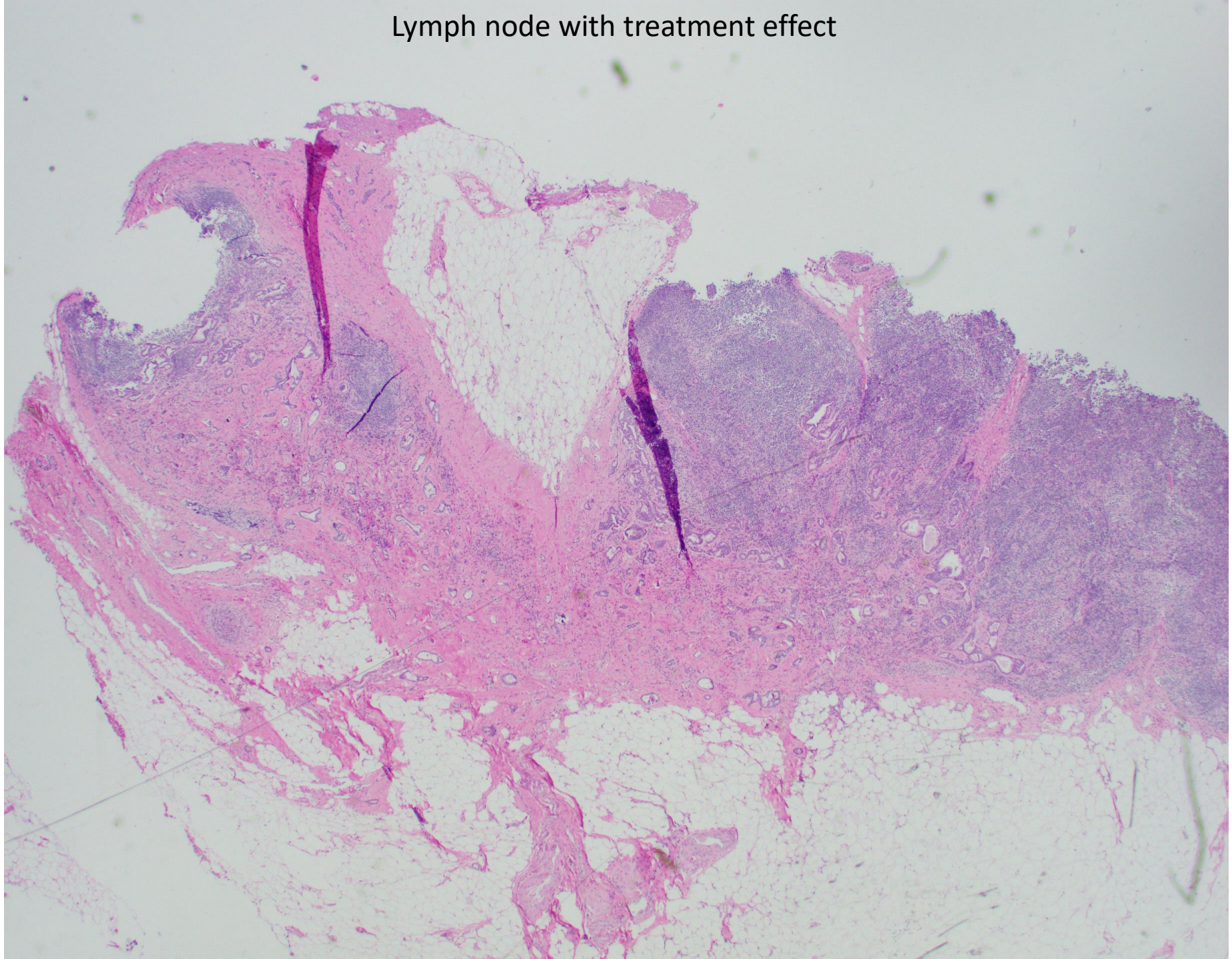




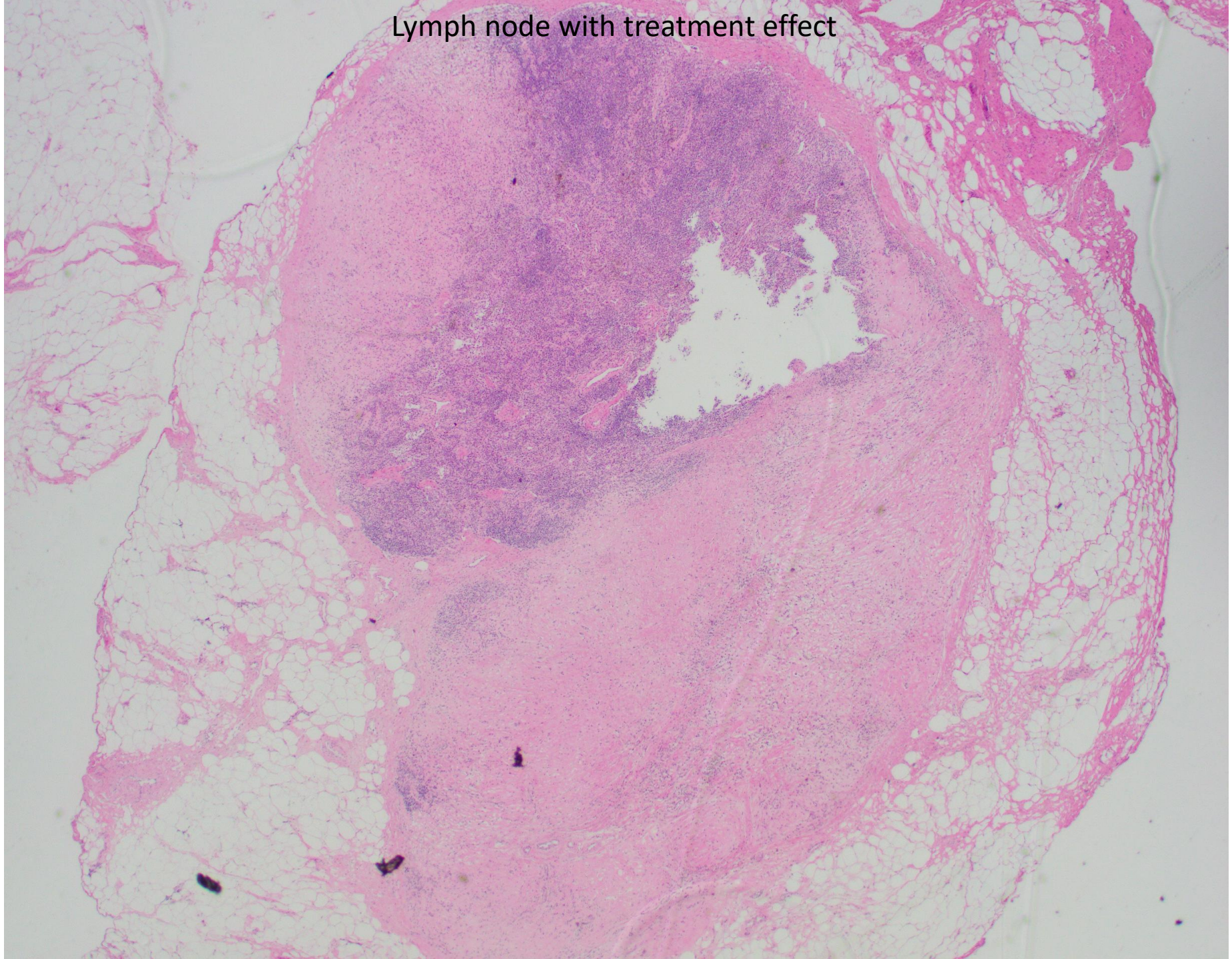




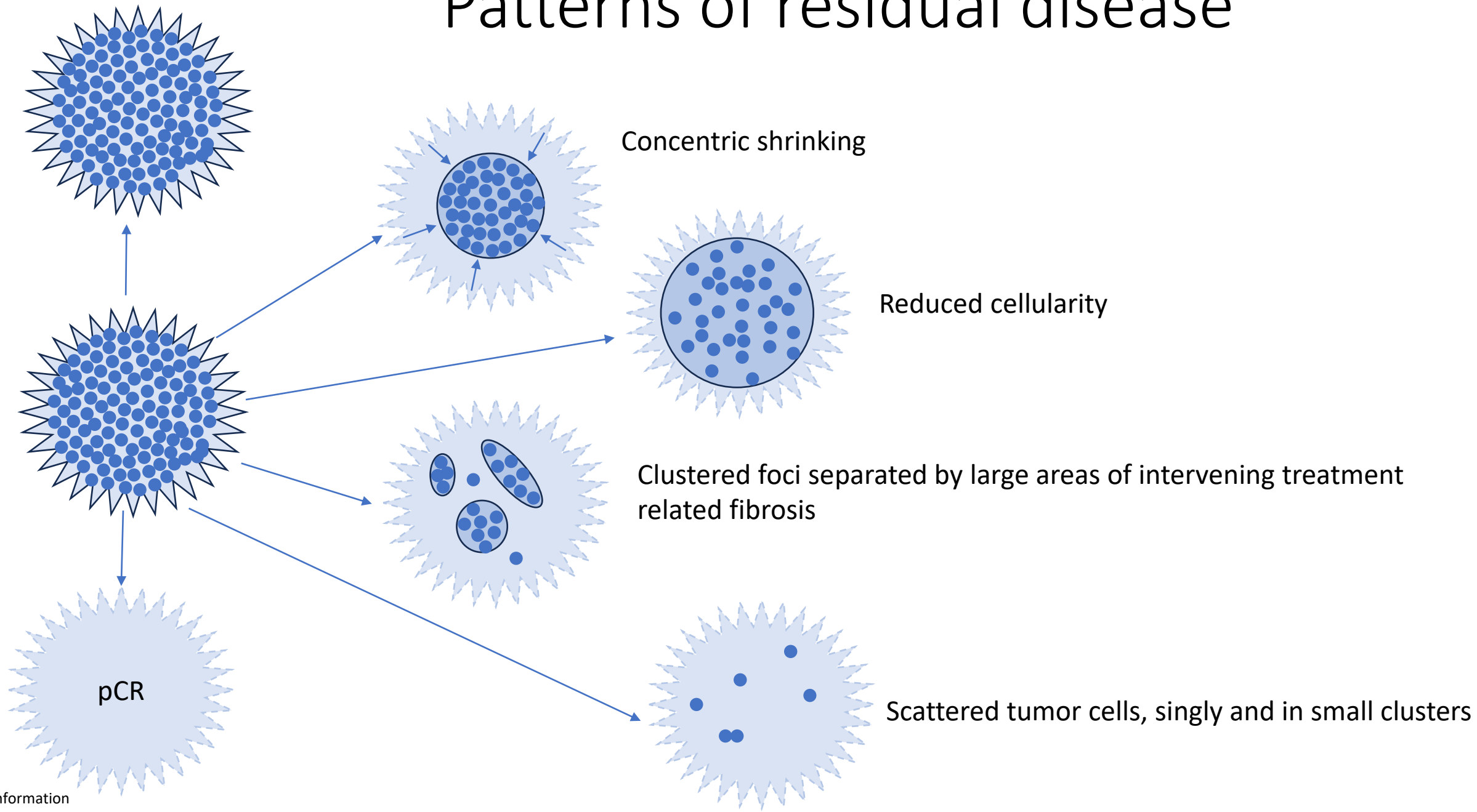
Lymph node with treatment effect



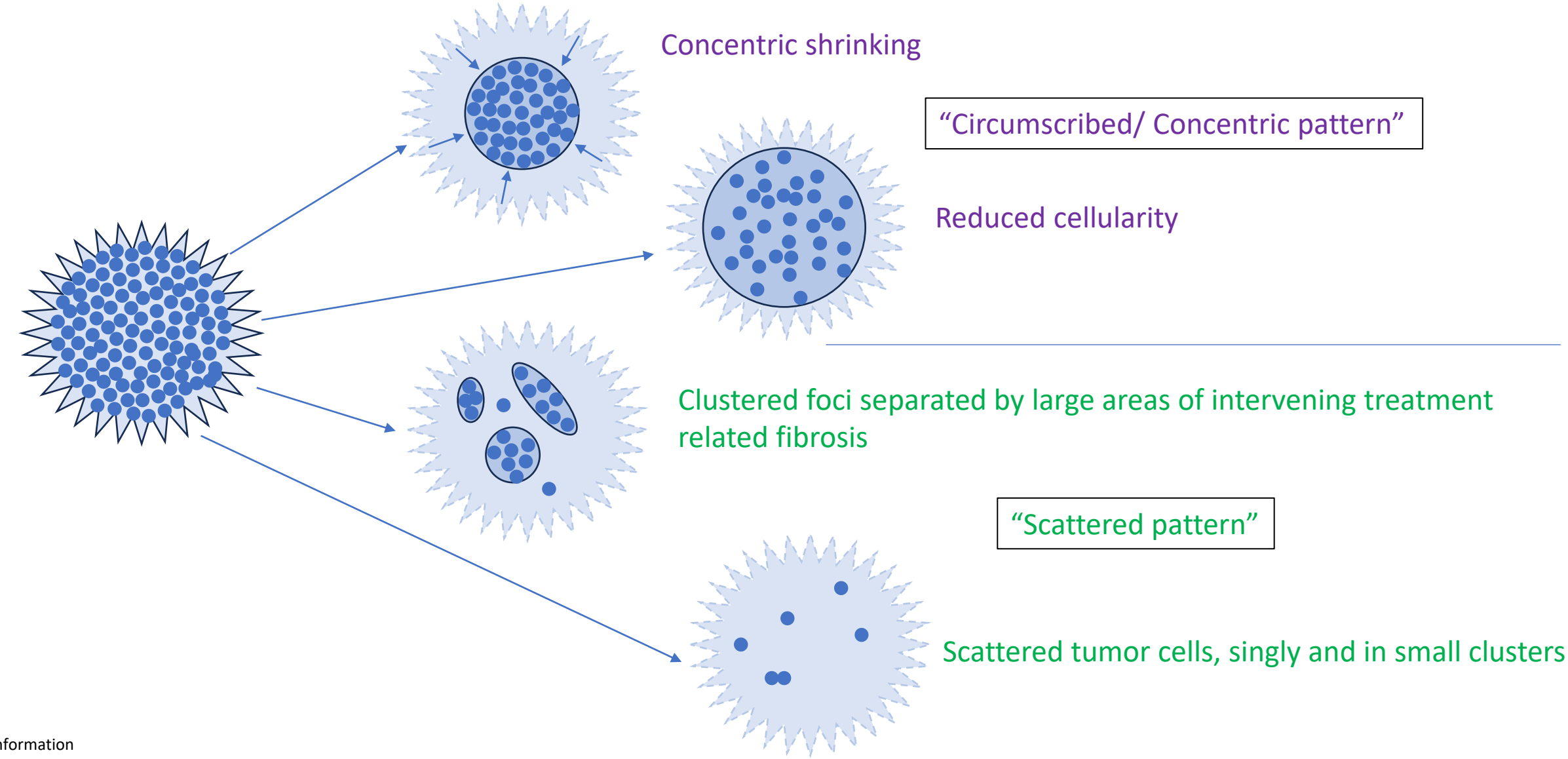
Lymph node with treatment effect



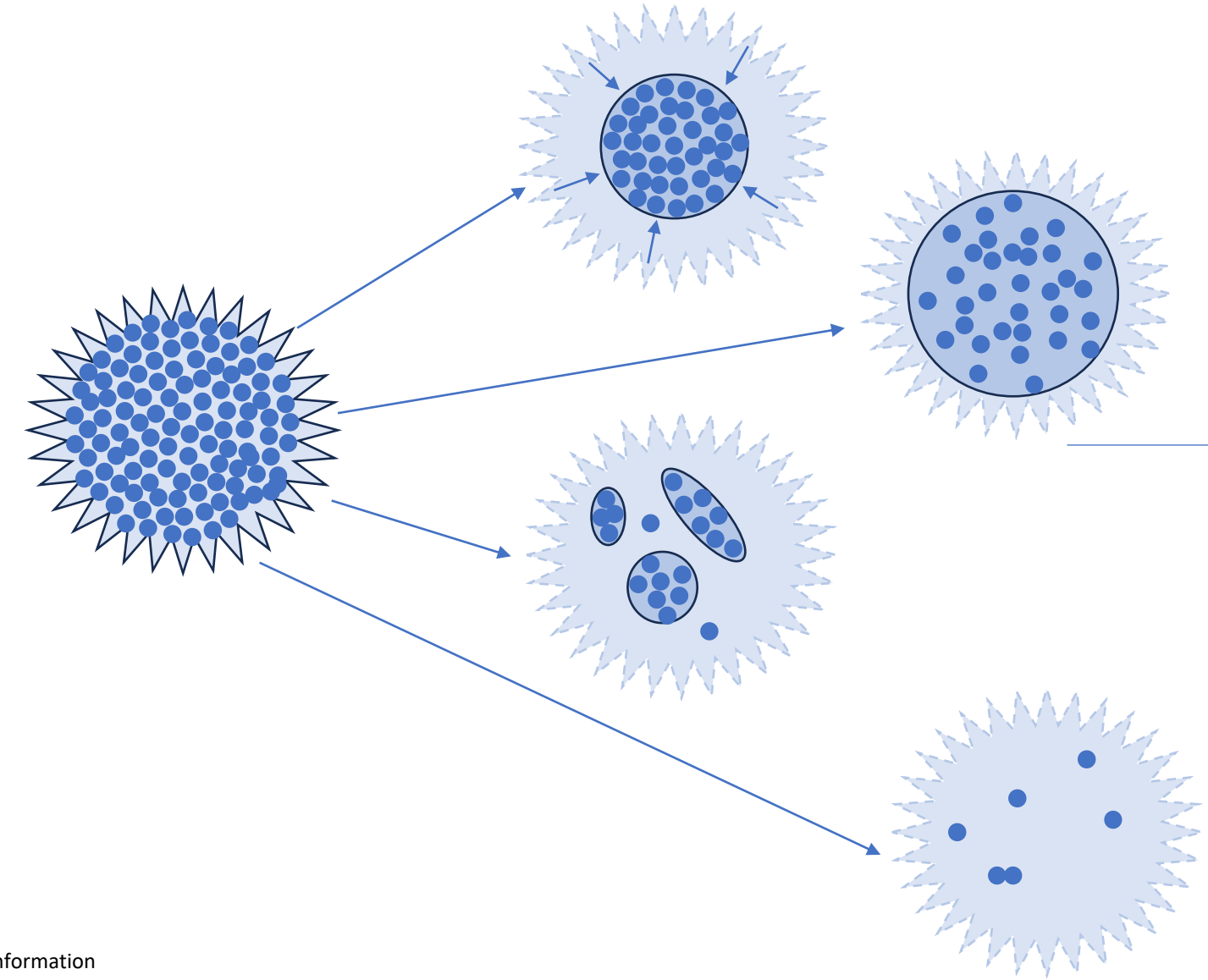
Patterns of residual disease



Patterns of residual disease



Patterns of residual disease



"Circumscribed pattern"

26% of overall cases

TNBC: 55%
HER2+: 29%
HR+/HER2-: 11%

"Scattered pattern"

74% of overall cases

TNBC: 45%
HER2+: 71%
HR+/HER2-: 89%

Pastorello RG et. al., Modern Pathology (2021)

Compared with the concentric pattern, the scatter pattern of residual disease was associated with inferior RFS and OS, especially among TNBC

TABLE 4 Unadjusted and adjusted estimates for the effect of each pattern of residual in-breast invasive tumor on RFS and OS

	RFS				OS			
	Unadjusted analysis		Adjusted* analysis		Unadjusted analysis		Adjusted* analysis	
	Hazard ratio [95% CI]	*p* value	Hazard ratio [95% CI]	*p*-value	Hazard ratio [95% CI]	*p* value	Hazard ratio [95% CI]	*p* value
Scattered (versus concentric)	1.9 [1.1–3.1]	0.014	2.0 [1.1–3.5]	0.015	1.6 [0.8–3.1]	0.119	2.2 [1.1–4.3]	0.026
No/minimal response (versus concentric)	2.2 [1.2–4.2]	0.016	2.2 [1.1–4.2]	0.021	2.3 [1.1–5.1]	0.031	2.5 [1.1–5.5]	0.023
No residual disease (versus concentric)	0.4 [0.2–0.8]	0.008	1.0 [0.4–2.4]	0.968	0.3 [0.1–0.8]	0.012	1.1 [0.4–3.1]	0.910

RFS recurrence-free survival, *OS* overall survival, *CI* confidence interval

*Adjusted for biologic subtype, pathologic nodal stage (ypN) and pathologic complete response (pCR) for all patients; additionally adjusted for endocrine therapy use among hormone receptor (HR)-positive subgroup

TABLE 5 Unadjusted and adjusted estimates for the effect of each pattern of residual in-breast invasive tumor on RFS, stratified by biologic subtype

	Unadjusted analysis		Adjusted* analysis	
	Hazard ratio [95% CI]	*p* value	Hazard ratio [95% CI]	*p* value
Scattered (versus concentric)				
HR^+ $HER2^-$	1.6 [0.6–4.4]	0.372	1.4 [0.5–4.0]	0.520
HR^+ $HER2^+$	1.9 [0.4–8.5]	0.389	1.4 [0.3–6.6]	0.642
HR^- $HER2^-$	3.0 [1.4–6.5]	0.005	2.8 [1.3–6.2]	0.010
HR^- $HER2^+$	1.2 [0.2–7.3]	0.834	0.8 [0.1–6.5]	0.829
No/minimal response (versus concentric)				
HR^+ $HER2^-$	0.7 [0.2–3.0]	0.603	0.7 [0.1–3.0]	0.602
HR^+ $HER2^+$	4.2 [0.7–25.4]	0.114	2.7 [0.4–17.4]	0.297
HR^- $HER2^-$	3.6 [1.6–8.4]	0.003	3.5 [1.4–8.3]	0.006
HR^- $HER2^+$	1.3 [0.1–14.1]	0.856	0.8 [0.0–12.8]	0.846
No residual disease (versus concentric)				
HR^+ $HER2^-$	0.4 [0.1–2.0]	0.285	0.8 [0.1–4.6]	0.799
HR^+ $HER2^+$	0.4 [0.1–2.7]	0.338	0.6 [0.1–6.8]	0.683
HR^- $HER2^-$	0.4 [0.1–1.0]	0.044	1.6 [0.5–5.1]	0.460
HR^- $HER2^+$	0.6 [0.1–3.4]	0.573	0.8 [0.1–5.8]	0.833

RFS recurrence-free survival, *CI* confidence interval, *HER2* human epidermal growth factor receptor 2

*Adjusted for pathologic nodal stage (ypN) and pathologic complete response (pCR) for all patients; additionally adjusted for endocrine therapy use among hormone receptor (HR)-positive subgroups

Patients treated with NAC and surgery for stage I-III breast cancer from 2004 to 2014 (975 patients, 666 with central pathology review)

Patients in this cohort not offered adjuvant capecitabine, TDM-1, or immunotherapy, which may influence results

Laws A et al., Ann Surg Oncol (2022) 29:7726-36

Approach to Evaluating Neoadjuvant Treated Breast Cancer Cases

- 1) Gather Data
- 2) Gross Evaluation/ Adequate Sampling
- 3) Microscopic Evaluation
- **4) Reporting**

There are multiple systems for reporting in post-neoadjuvant specimens

AJCC →

RCB →

Table 1. Classification Systems That Included Both Breast and Lymph Nodes to Categorize Treatment Responses

Classification System, y	Primary Tumor (T) Assessment	Lymph Node (N) Assessment	Overall Response Categorization
AJCC 8th edition,[75] 2016	Presence or absence of residual invasive carcinoma with or without histologic evidence of response Size of largest contiguous tumor focus of residual tumor	No metastatic disease and no evidence of changes No metastatic disease but evidence of response Metastatic disease and evidence of response Metastatic disease and no evidence of response	pCR: no residual invasive carcinoma in breast, lymphatics, or lymph nodes, with or without DCIS pPR: residual invasive carcinoma with decrease in either the T or N category or both compared with the clinical (pretreatment assignment), and with no increase in either T or N pNR: presence of residual invasive carcinoma without change or with an increase in the T or N category compared with clinical (pretreatment) assignment
Sataloff et al,[32] 1995	Presence of residual invasive carcinoma and degree of therapeutic effect as percentage: T-A: total or near-total therapeutic effect T-B: >50% but less than near-total effect T-C: <50% effect T-D: No effect	N-A: No metastatic disease but evidence of therapeutic effect N-B: No metastatic disease or therapeutic response N-C: Metastatic disease with evidence of response N-D: Metastatic disease and no evidence of response	4 primary tumor categories: T (A–D) 4 lymph node categories: N (A–D)
Penault-Llorca et al,[27] 2008	Chevallier categories (Ch1 through Ch4) Sataloff categories (T-A through T-D)	Sataloff categories (N-A through N-D)	Class I: Ch 1+2 and TANA–NB: complete or almost complete response in breast and absence of node involvement Class II: Ch3, TANC–ND and TB or C and N: partial response, any N/complete or almost complete response and node involvement Class III: Ch4 and TD any N: nonresponders
Pinder et al,[29] 2007	Presence or absence of residual carcinoma as percentage of tumor remaining	No metastatic disease or evidence of response No metastatic disease but evidence of response Metastatic disease with evidence of response Metastatic disease and no evidence of response	3 categories: pCR (complete response): no residual carcinoma pPR (partial response): near total response (<10% remaining), 10%–50% tumor remaining, >50% tumor remaining pNR (no response): No evidence of response to therapy
Smith et al,[33] 2002	Grade 1: no reduction in overall numbers of malignant cells compared with pretreatment biopsy Grade 2: mild loss of invasive tumor cells but cellularity still high Grade 3: considerable reduction in cellularity (up to 90% loss) Grade 4: marked disappearance of cells; only widely dispersed clusters Grade 5: no residual invasive carcinoma with or without DCIS	A: no malignant cells or treatment effect B: malignant cells present without treatment effect C: malignant cells present with evidence of partial response D: no malignant cells present with treatment effect (previously positive node)	5 primary tumor categories: grades 1–5 4 lymph node categories: A–D
Residual Disease in Breast and Nodes,[34] 2008	Size of residual invasive tumor Tumor SBR grade	Index of number of involved lymph nodes 0: no positive node 1: 1–4 nodes 2: 5–7 nodes 3: ≥8 nodes	4 risk levels: Level 1: pCR (no invasive carcinoma in breast or lymph nodes, with or without DCIS) Levels 2–3: residual disease in increasing amount calculated by 0.2 (residual breast tumor size in cm) + index of involved nodes (0–3) + SBR grade (1, 2, 3)
Residual Cancer Burden,[30] 2007	Span of residual invasive tumor in 2 dimensions (including intervening fibrosis) Cellularity of invasive carcinoma as a percentage of residual tumor bed area (mm)	Number of positive lymph nodes Span of largest metastatic deposit (including intervening fibrosis)	Continuous score and 4 index categories: 0: pCR (complete response, no invasive carcinoma in breast or lymph nodes, with or without DCIS) I–III: residual disease in increasing amount calculated by formula

Abbreviations: DCIS, ductal carcinoma in situ; pCR, pathologic complete response; pNR, no pathologic response; pPR, pathologic partial response; SBR, Scarff-Bloom-Richardson.

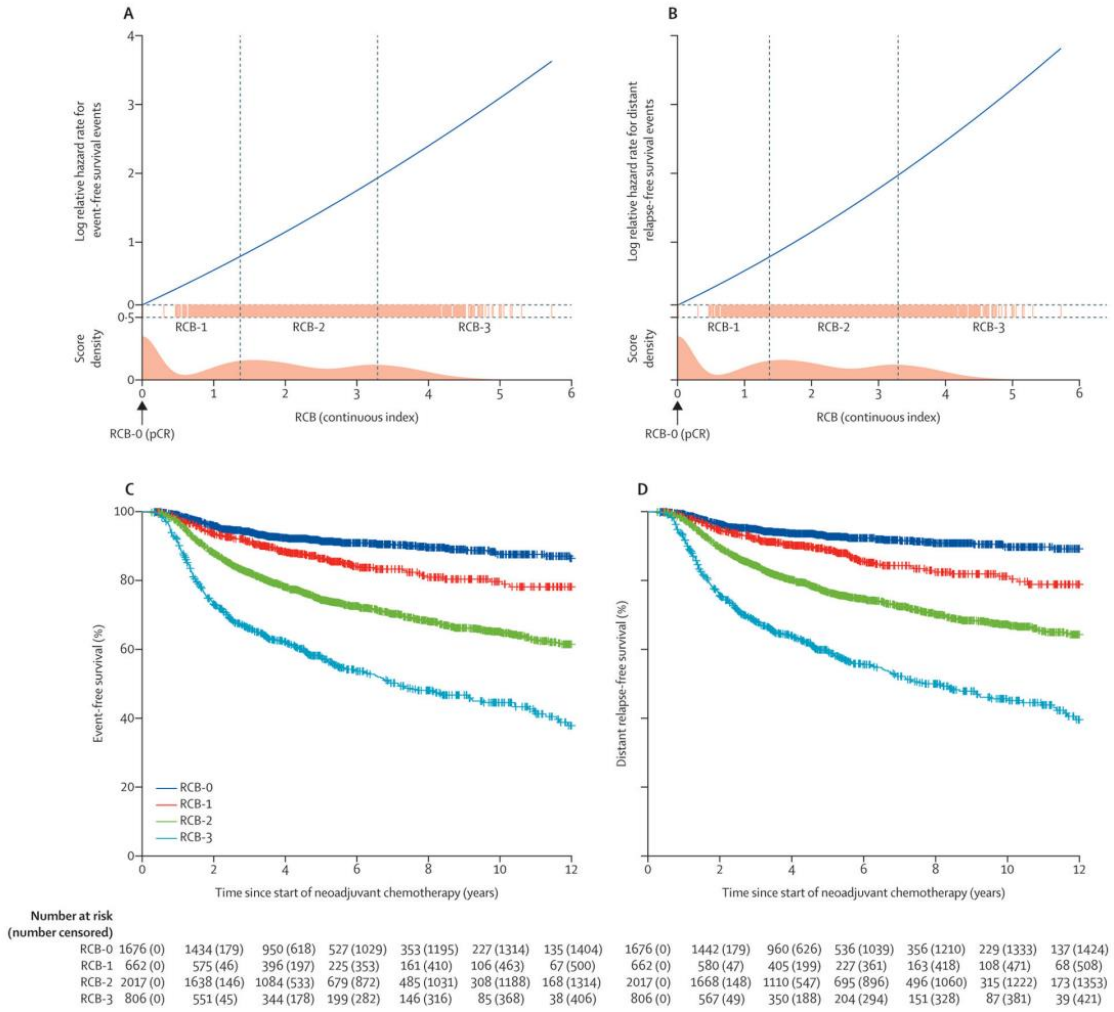
Sahoo S et al., Arch Pathol Lab Med 2023; 147:591-603

Residual Cancer Burden (RCB) system

- First described in 2007
- Provides a standard method for evaluating and quantifying extent of residual disease following NAC
- Specific criteria are entered into a formula which yields a continuous score (pCR= RCB-0)
- Empiric cutoffs separate the score into 4 classes (RCB-0 to RCB-III) representing increasing amounts of residual tumor burden
- RCB classes correlate with patient prognosis

Yau C et al., Lancet Oncol 2022; 23(1): 149-160
Symmans WF et al., JCO 2007; 25(28):4414-22

RCB score shows strong correlation with patient outcomes



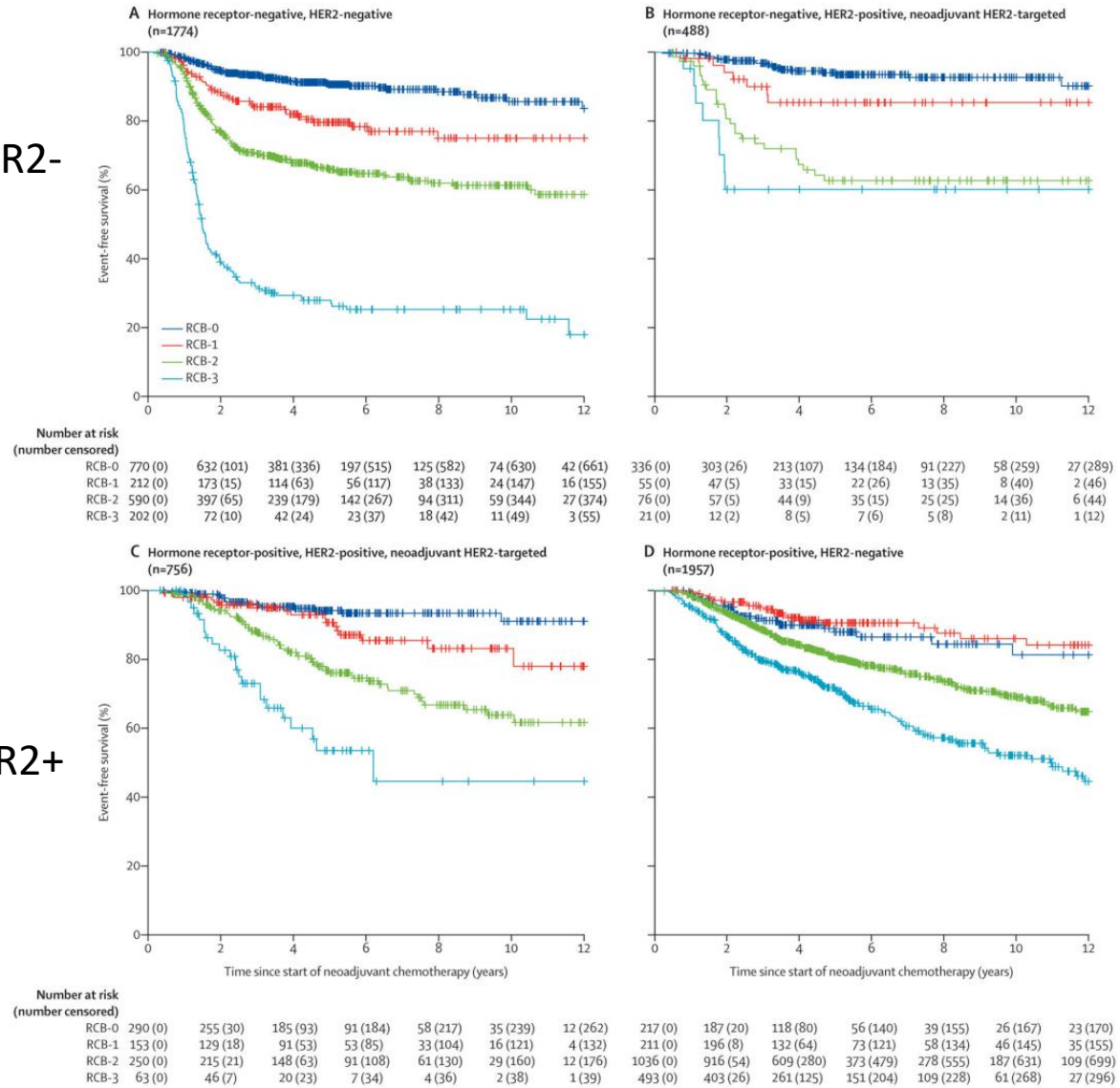
Pooled analysis of 5295 patients from 4 clinical trials and 8 clinical cohorts

Figure 2: Prognostic value of RCB score and RCB class in the overall pooled analysis cohort
Plots of log relative hazard rate for event-free survival events (A) and distant relapse-free survival events (B) as a function of RCB score. Splines approximation of RCB with two degrees of freedom was used to allow for non-linear effect. A log linear increase in relative hazard rate implies that the hazard ratio associated with change in RCB remains constant over the range of RCB. Thresholds for corresponding RCB classes (RCB-0 to RCB-3) are shown for reference (vertical dashed lines). Vertical bars represent all RCB scores recorded on a continuous scale. Kaplan-Meier plots of event-free survival (C) and distant relapse-free survival (D) stratified by RCB class. Crosses denote patients censored. RCB=residual cancer burden. pCR=pathological complete response.

Yau C et al., Lancet Oncol 2022; 23(1): 149-160

HER-/HER2-

HER-/HER2+



HER+/HER2+

HER+/HER2-

Figure 4: Prognostic value of RCB class for hormone receptor and HER2 subtypes
Kaplan-Meier plots of event-free survival by RCB classes among breast cancer subtypes. For the two HER2-positive subtypes, plots of the subset of patients who received neoadjuvant HER2-targeted therapy are shown (plots for all HER2-positive patients, with or without HER2-targeted therapy, are presented in the appendix p 13). Crosses denote patients censored. RCB=residual cancer burden.

Yau C et al., Lancet Oncol 2022; 23(1): 149-160

MD Anderson RCB calculator

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Google: MD Anderson RCB

Mdanderson.org/breastcancer_RCB

Residual Cancer Burden Calculator

*Values must be entered into all fields for the calculation results to be accurate.

(1) Primary Tumor Bed

Primary Tumor Bed Area: _____ (mm) X _____ (mm)

Overall Cancer Cellularity (as percentage of area): _____ (%)

Percentage of Cancer That Is *in situ* Disease: _____ (%)

(2) Lymph Nodes

Number of Positive Lymph Nodes: _____

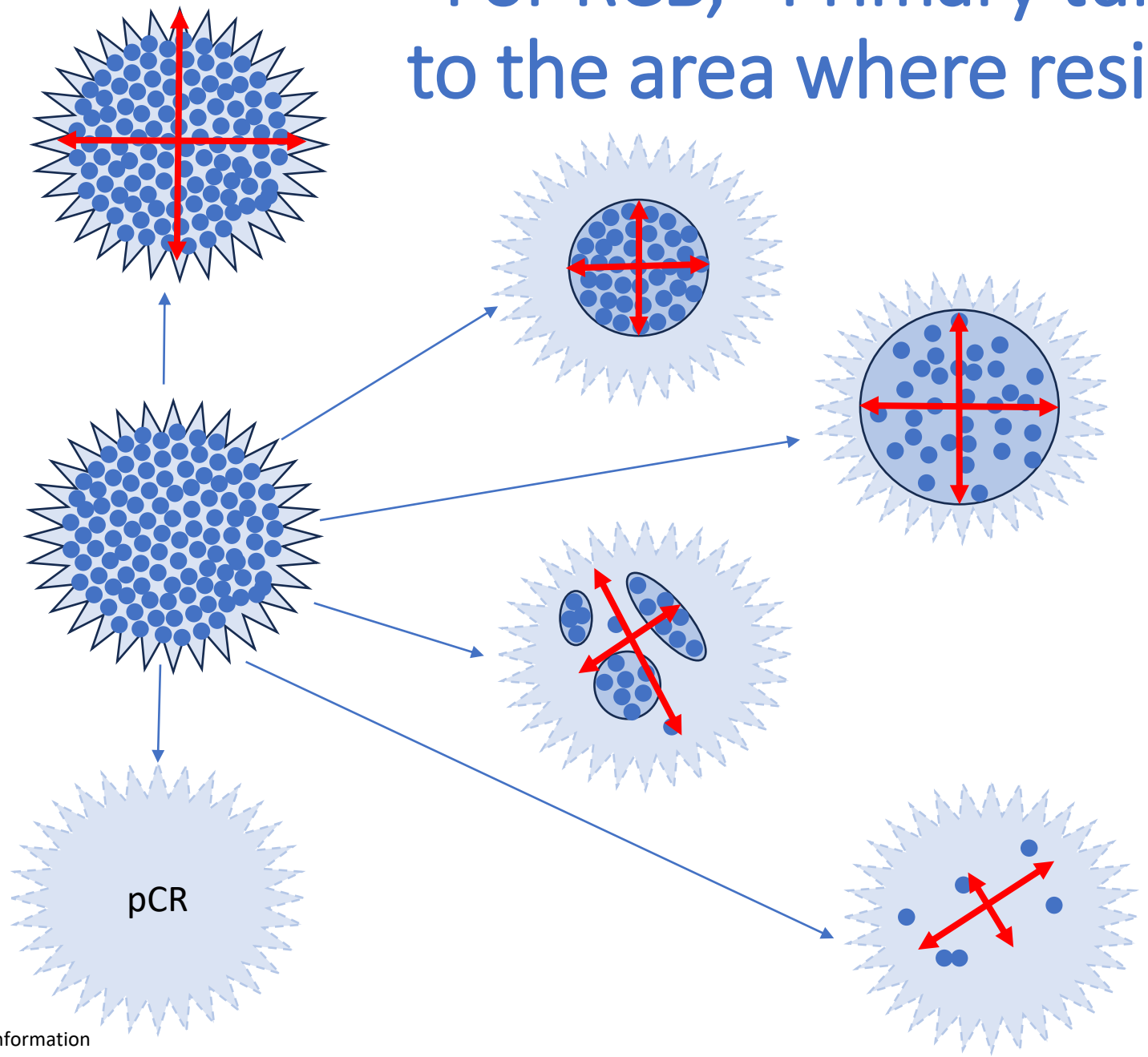
Diameter of Largest Metastasis: _____ (mm)

Reset Calculate

Residual Cancer Burden: _____

Residual Cancer Burden Class: _____

For RCB, “Primary tumor bed area” refers to the area where residual tumor is present



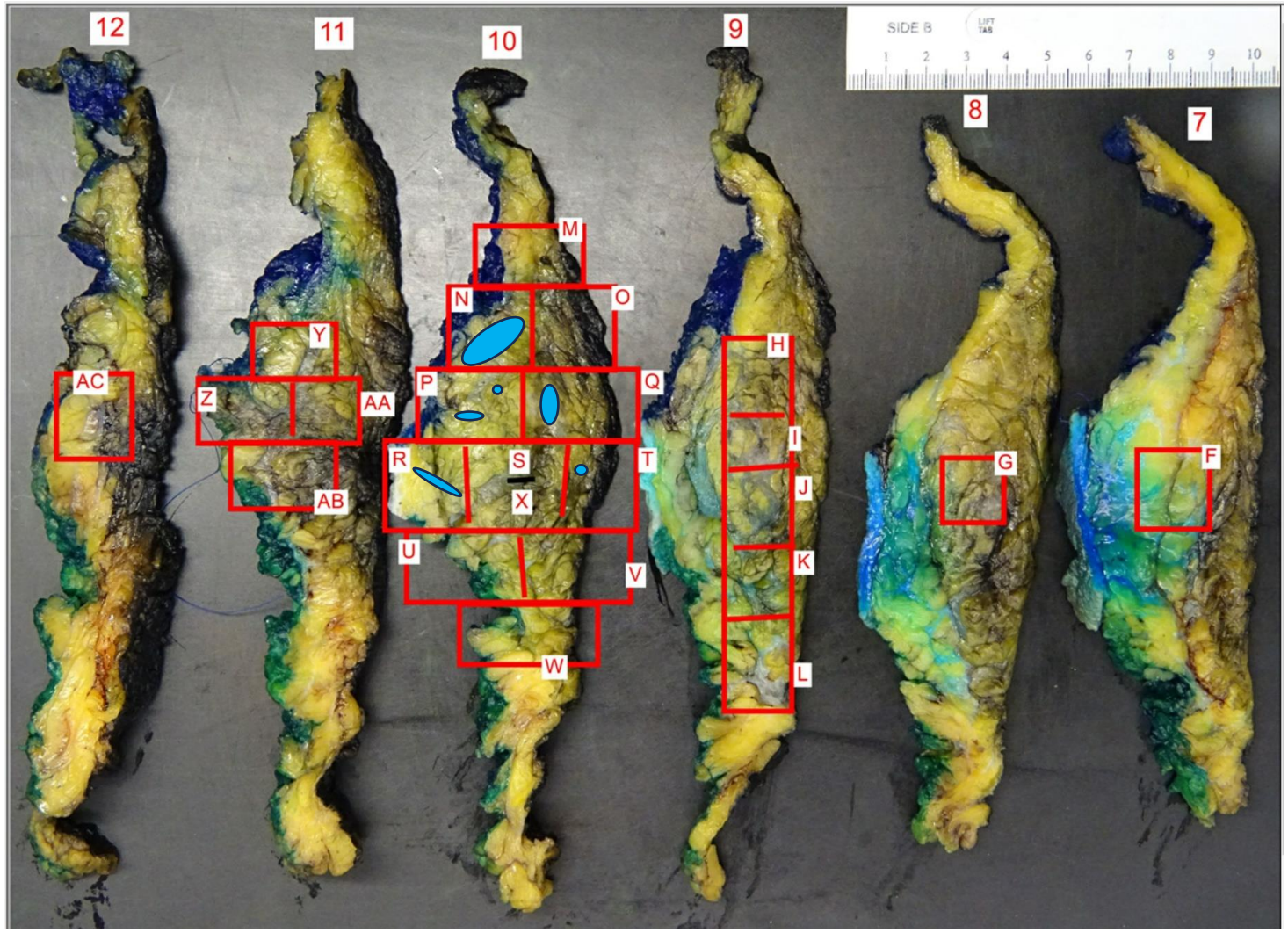
- Measure in 2 dimensions

- Includes intervening treatment related fibrosis between tumor nests

- Does not include any treatment related fibrosis outside the area where tumor is Present

- The “primary tumor bed area” for RCB calculation may or may not correlate with “pre-treatment tumor bed area” or the grossly identified tumor bed area

Creating a map of the sections taken is highly recommended



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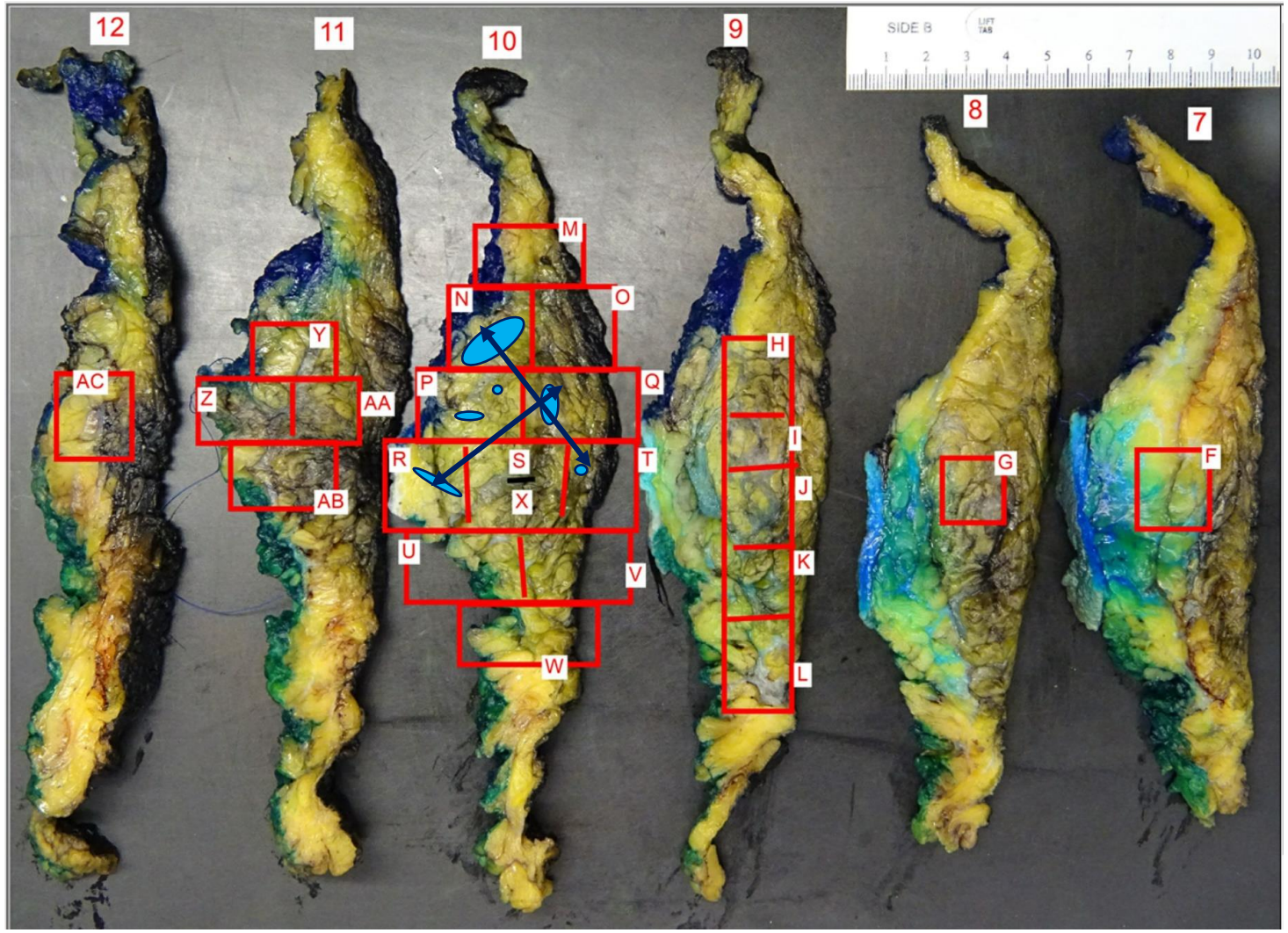

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Percentage of Cancer That Is *in situ* Disease: _____ (%)

(2) Lymph Nodes

Number of Positive Lymph Nodes: _____

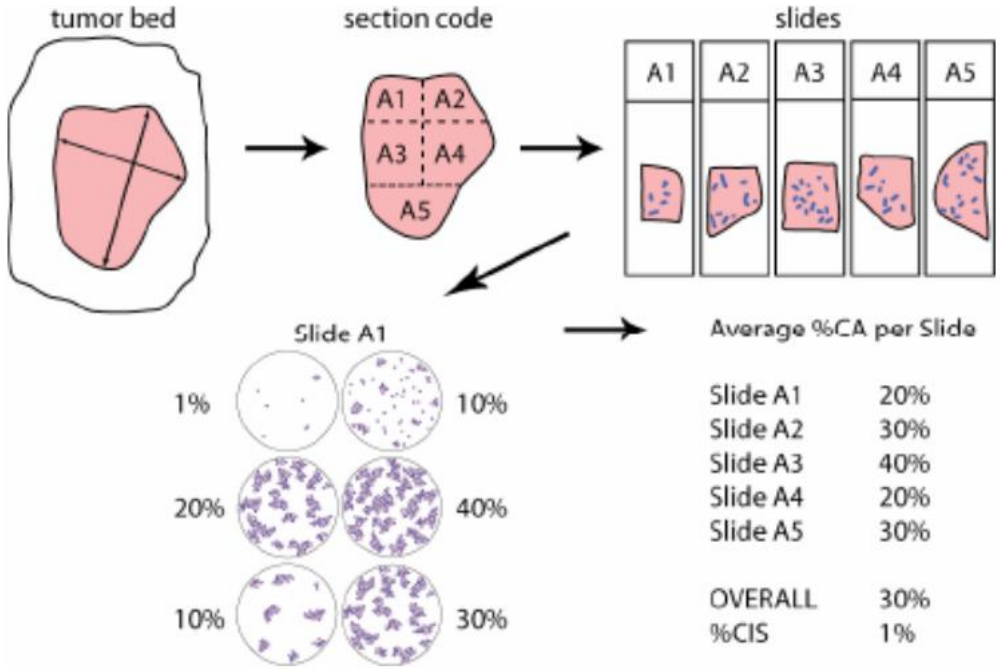
Diameter of Largest Metastasis: _____ (mm)

Reset Calculate

Residual Cancer Burden: _____

Residual Cancer Burden Class: _____

Estimate residual tumor cellularity over tumor bed area



A practical way to estimate %CA in a slide is to encircle with ink dots the tumor bed on each slide from the grossly defined residual tumor bed (e.g., slides A1-A5 in the example above). Then use the microscope to estimate the cellularity in each microscopic field across the area of tumor bed. In each microscopic field, %CA can be estimated by comparing the proportion of residual tumor bed area containing cancer (invasive or *in situ*). Estimate an average of the readings for %CA in the cross-sectional area. The same can be done for *in situ* component (%CIS). Estimates are to the nearest 10%, but include 0%, 1%, and 5% for areas with low cellularity. The average cellularity within the tumor bed from each slide across the tumor bed can then be estimated (illustrated above). The website contains computer-generated diagrams of % cellularity per area to assist pathologists to estimate accurately the cellularity of a microscopic field. Those diagrams are appended at the end of this document.

Mdanderson.org/breastcancer_RCB
Detailed Pathology Methods for Using Residual Cancer Burden

Mdanderson.org/breastcancer_RCB

Graphical Illustrations of Percentage Cancer Cellularity

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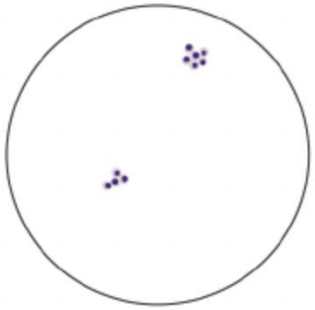
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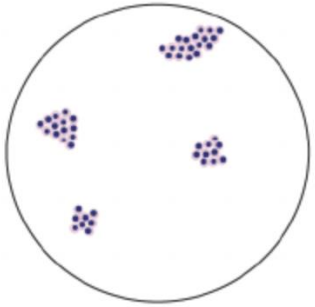
1% Scattered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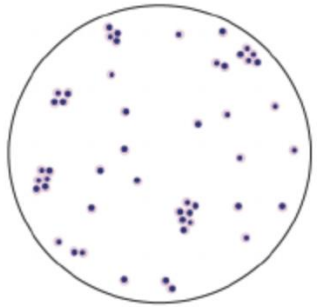
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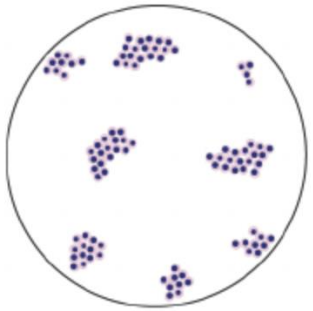
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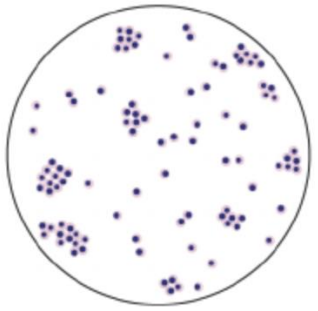
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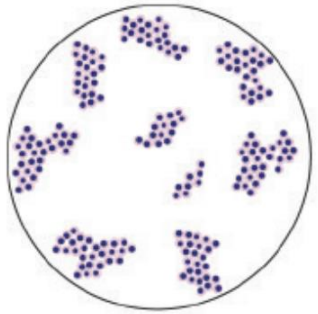
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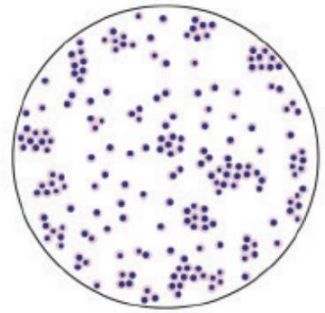
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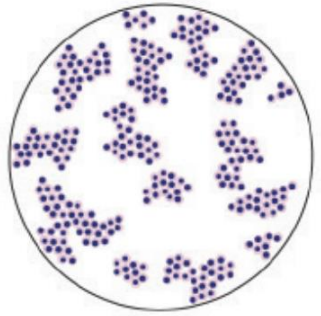
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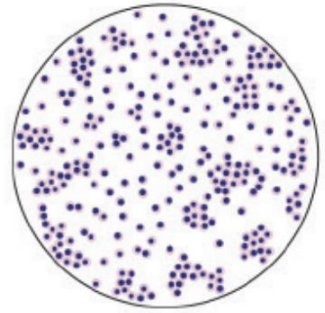
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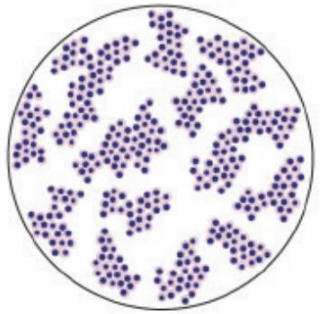
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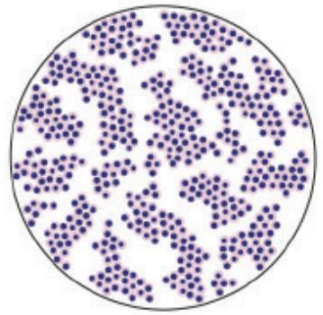
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Residual Cancer Burden Calculator

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(1) Primary Tumor Bed

Primary Tumor Bed Area:	(mm) X (mm)
Overall Cancer Cellularity (as percentage of area):	(%)
Percentage of Cancer That Is *in situ* Disease:	(%)

(2) Lymph Nodes

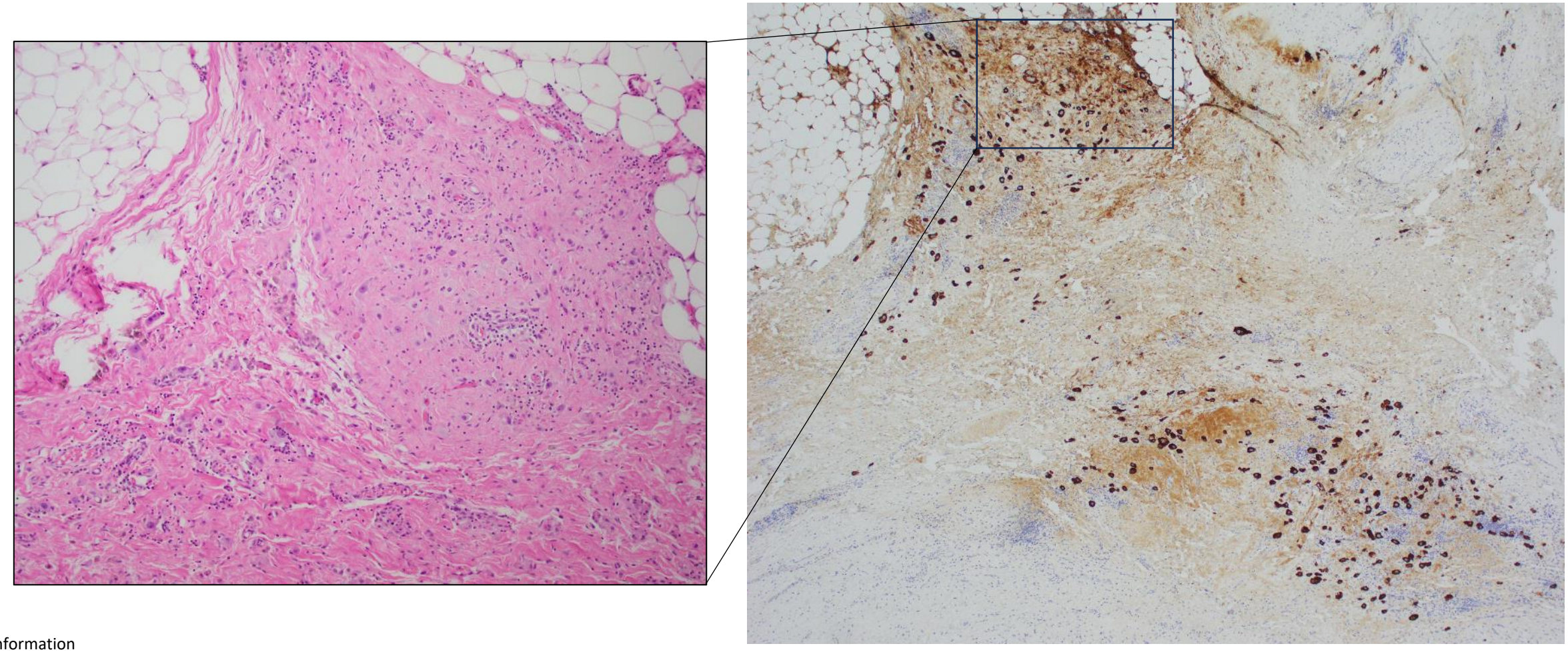
Number of Positive Lymph Nodes:	
Diameter of Largest Metastasis:	(mm)

Reset Calculate

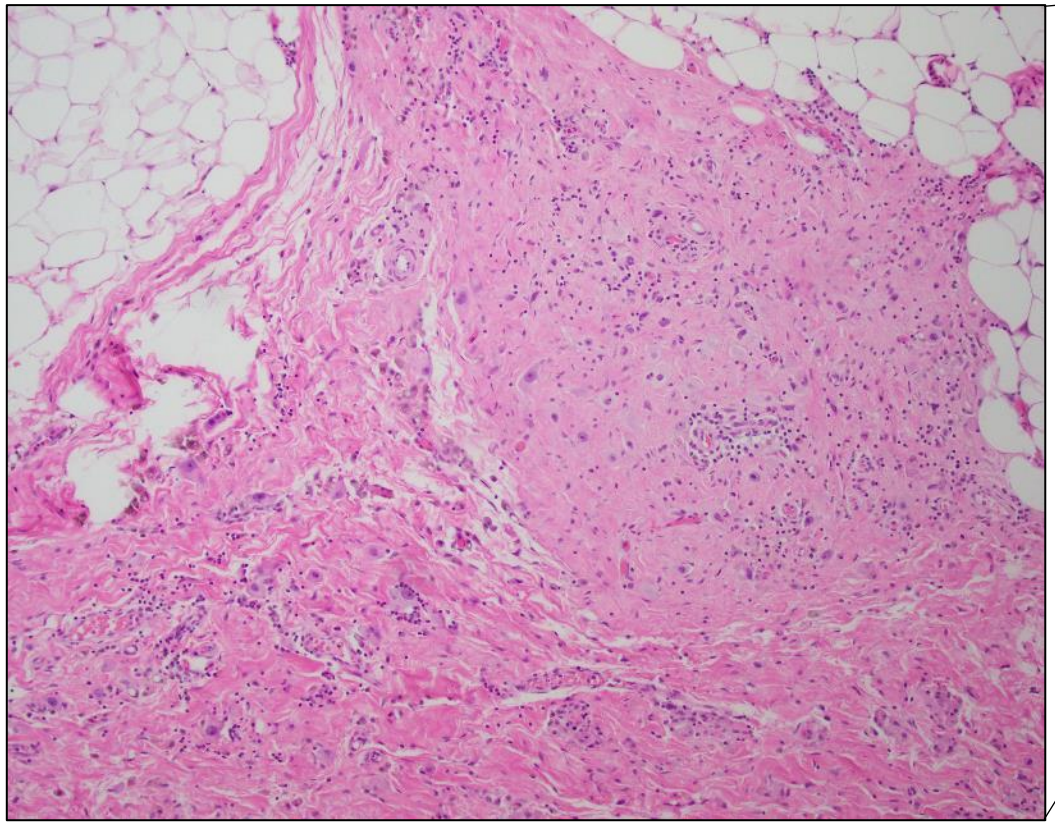
Residual Cancer Burden:	
Residual Cancer Burden Class:	

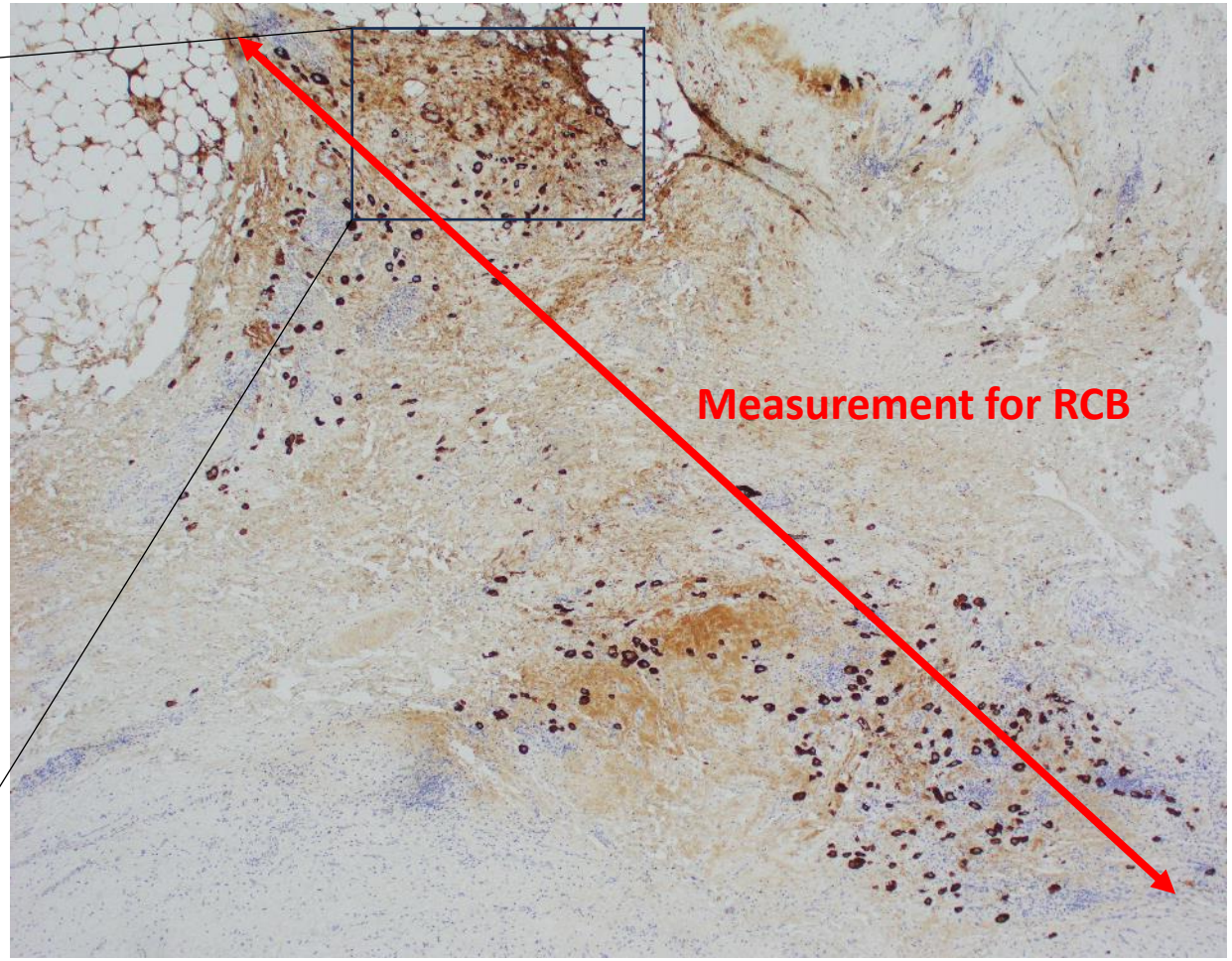
Private Information

For RCB, the measurement of diameter of the largest lymph node metastasis is inclusive of any intervening treatment-related fibrosis

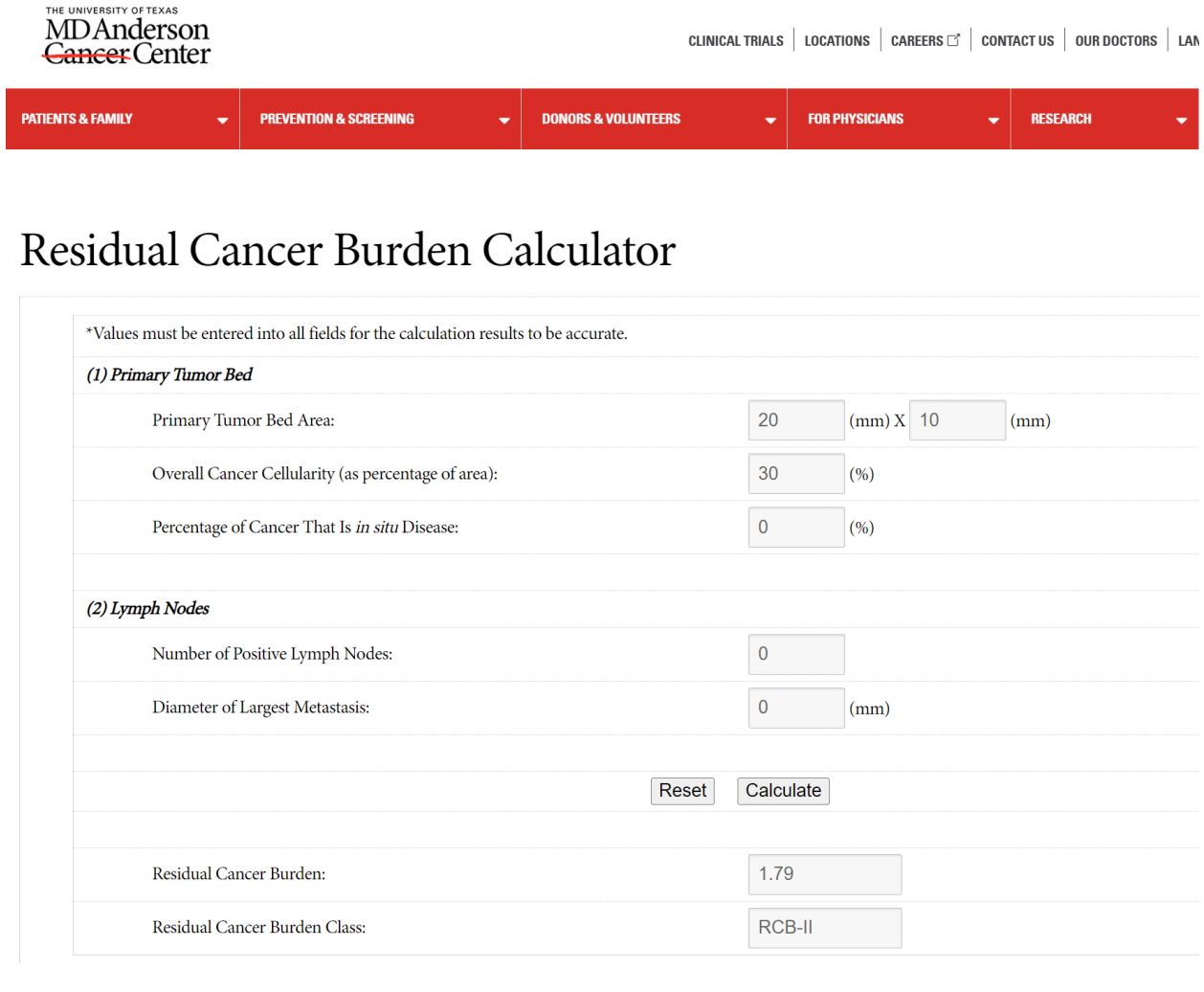


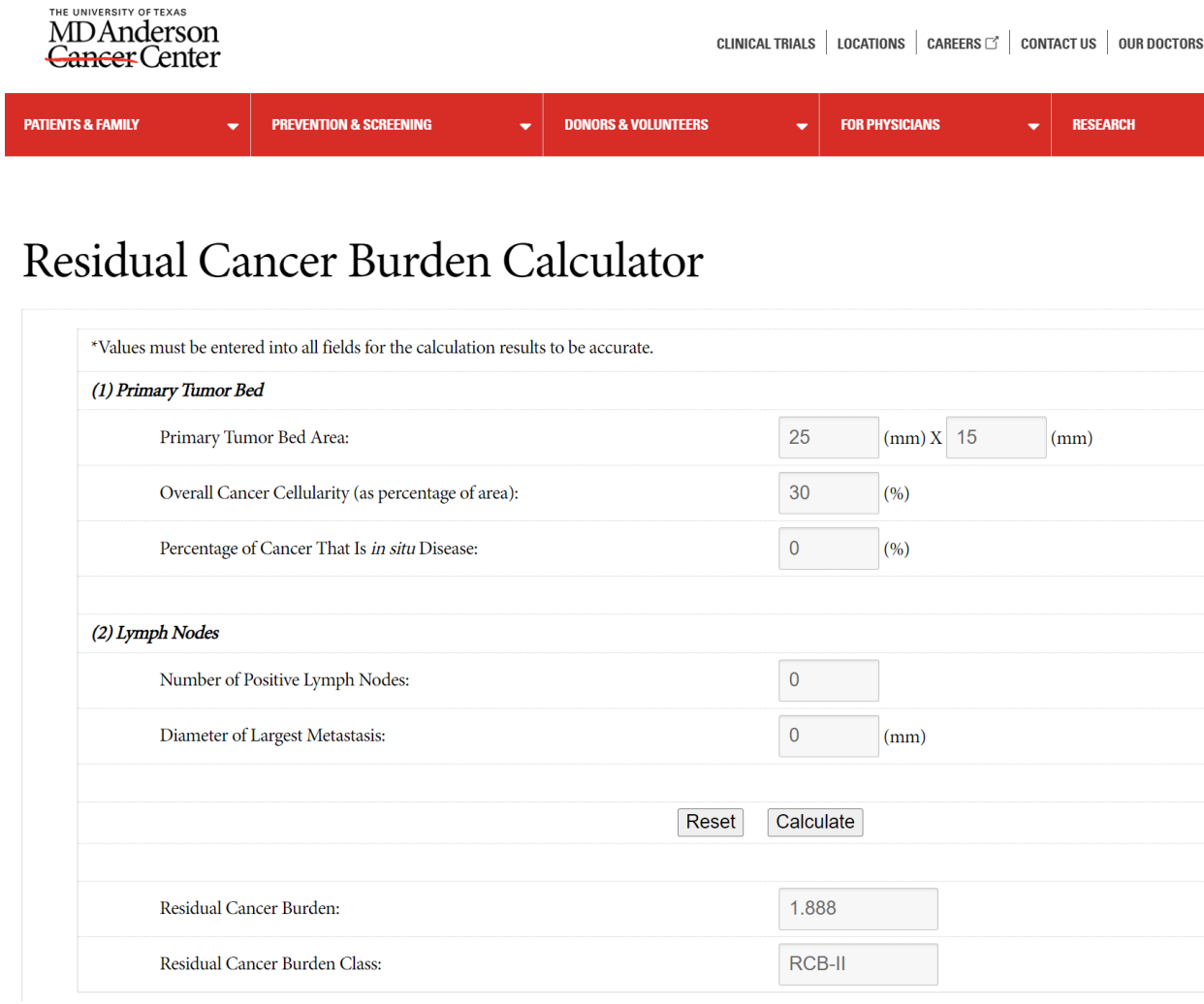
For RCB, the measurement of diameter of the largest lymph node metastasis is inclusive of any intervening treatment-related fibrosis



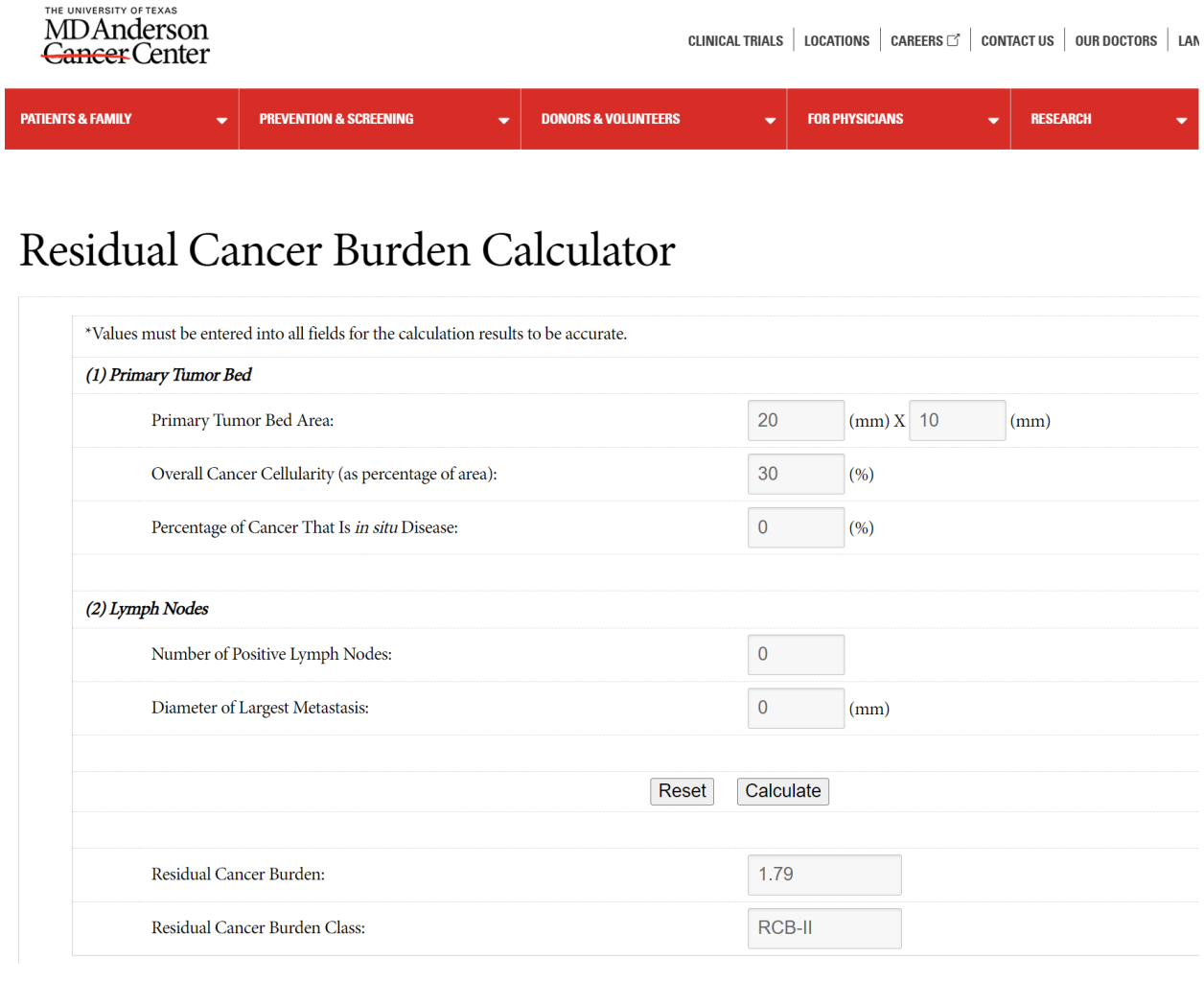


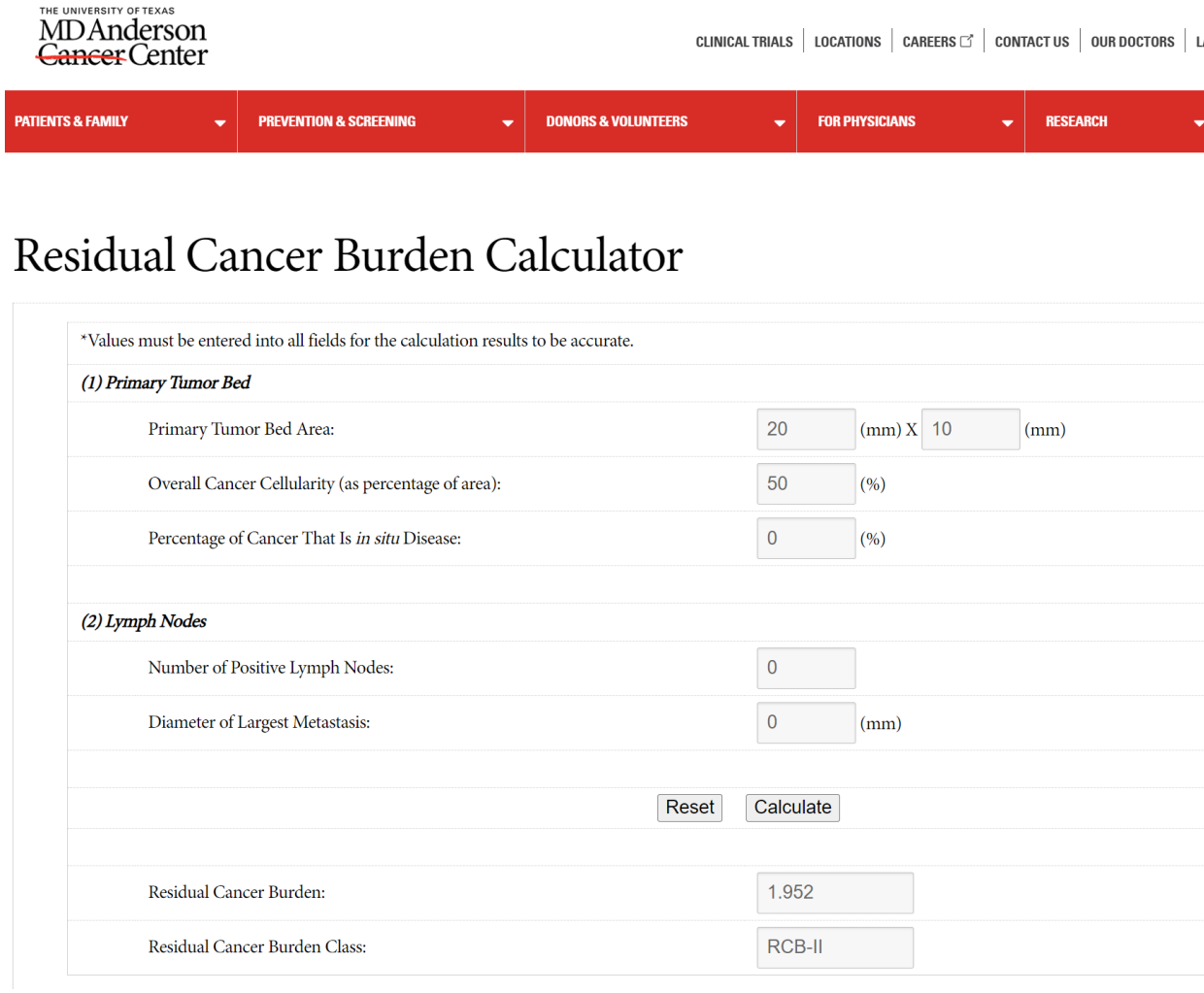
MD Anderson RCB calculator



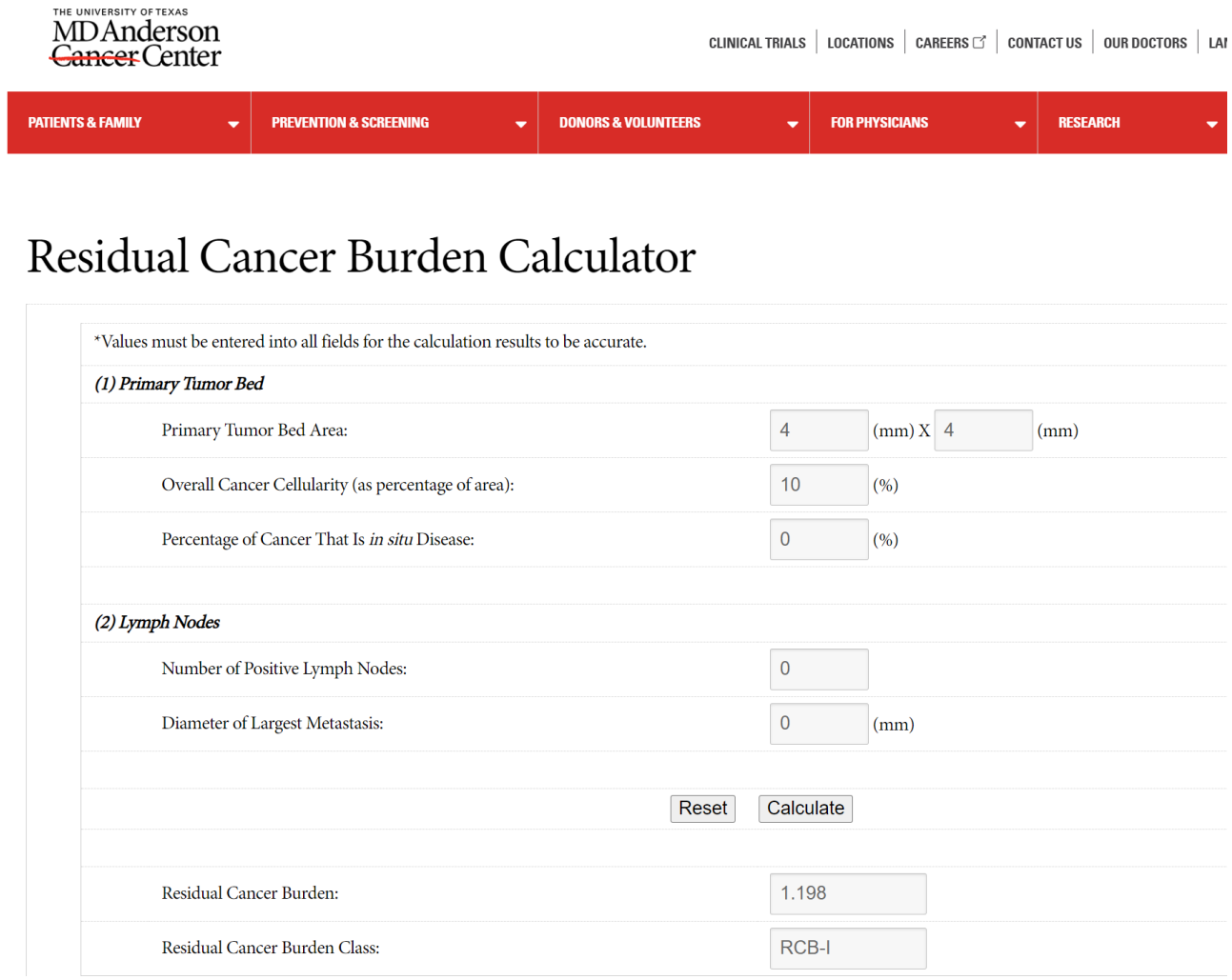


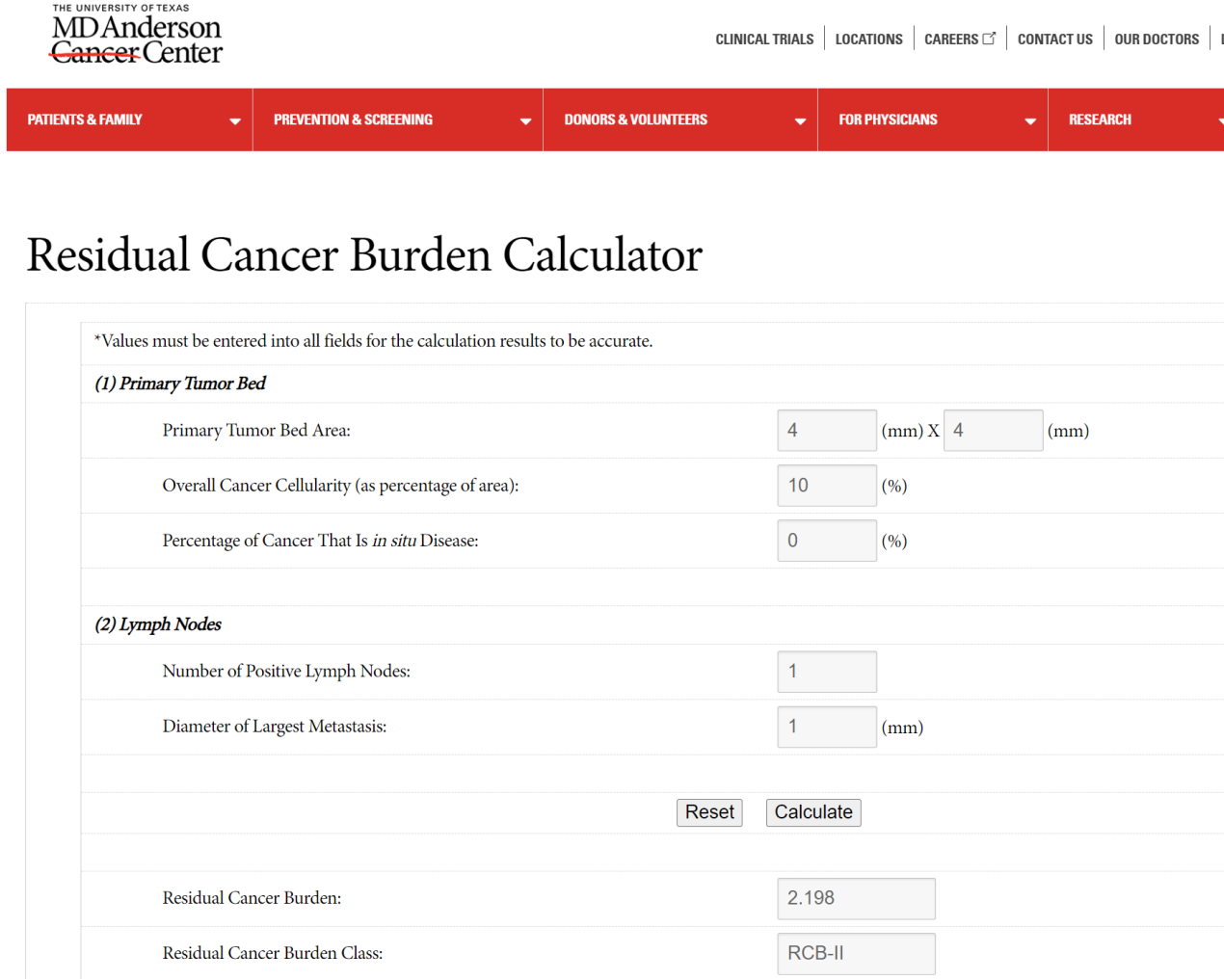
MD Anderson RCB calculator



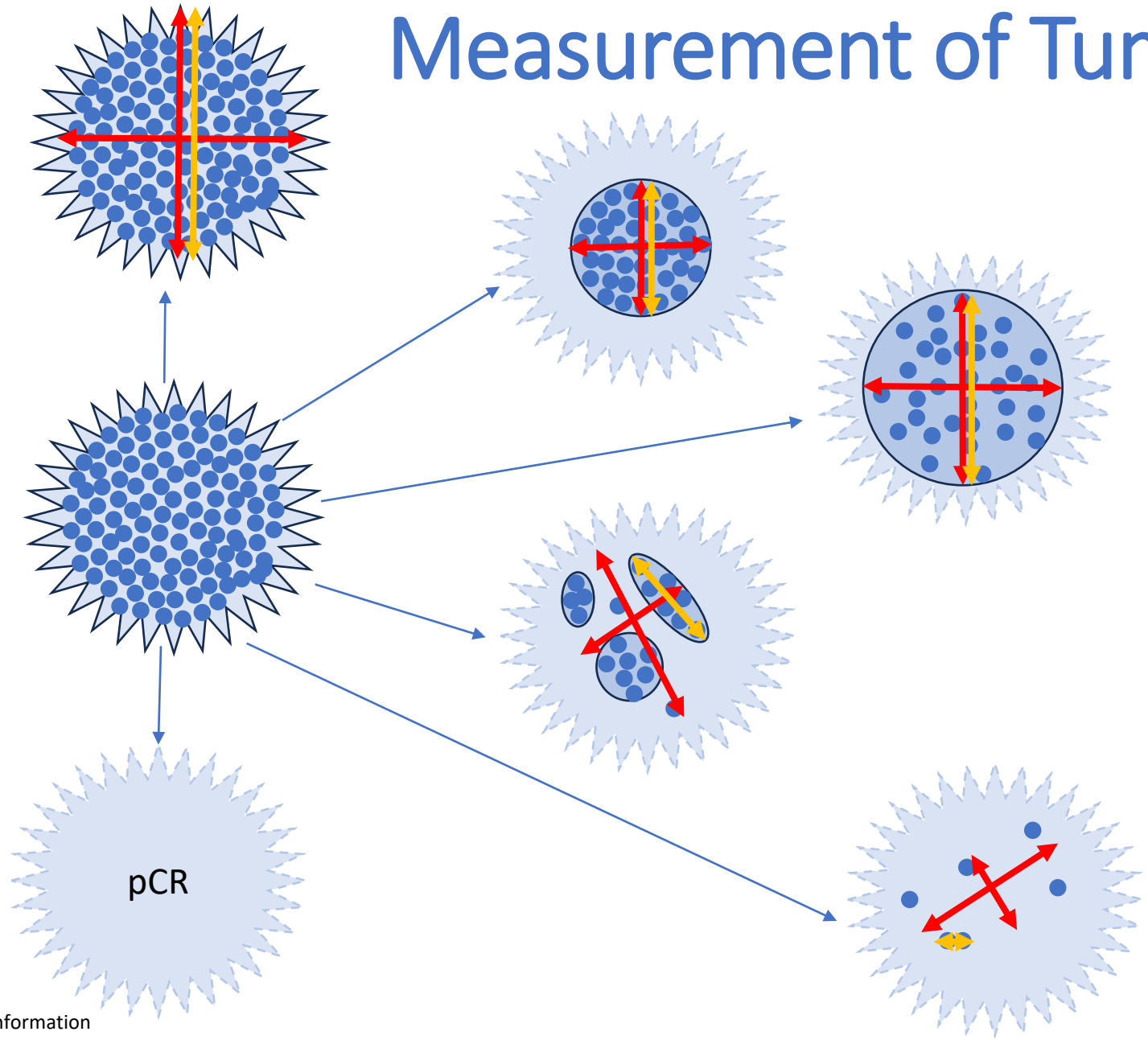


MD Anderson RCB calculator





Key differences between RCB and AJCC Systems: Measurement of Tumor Size

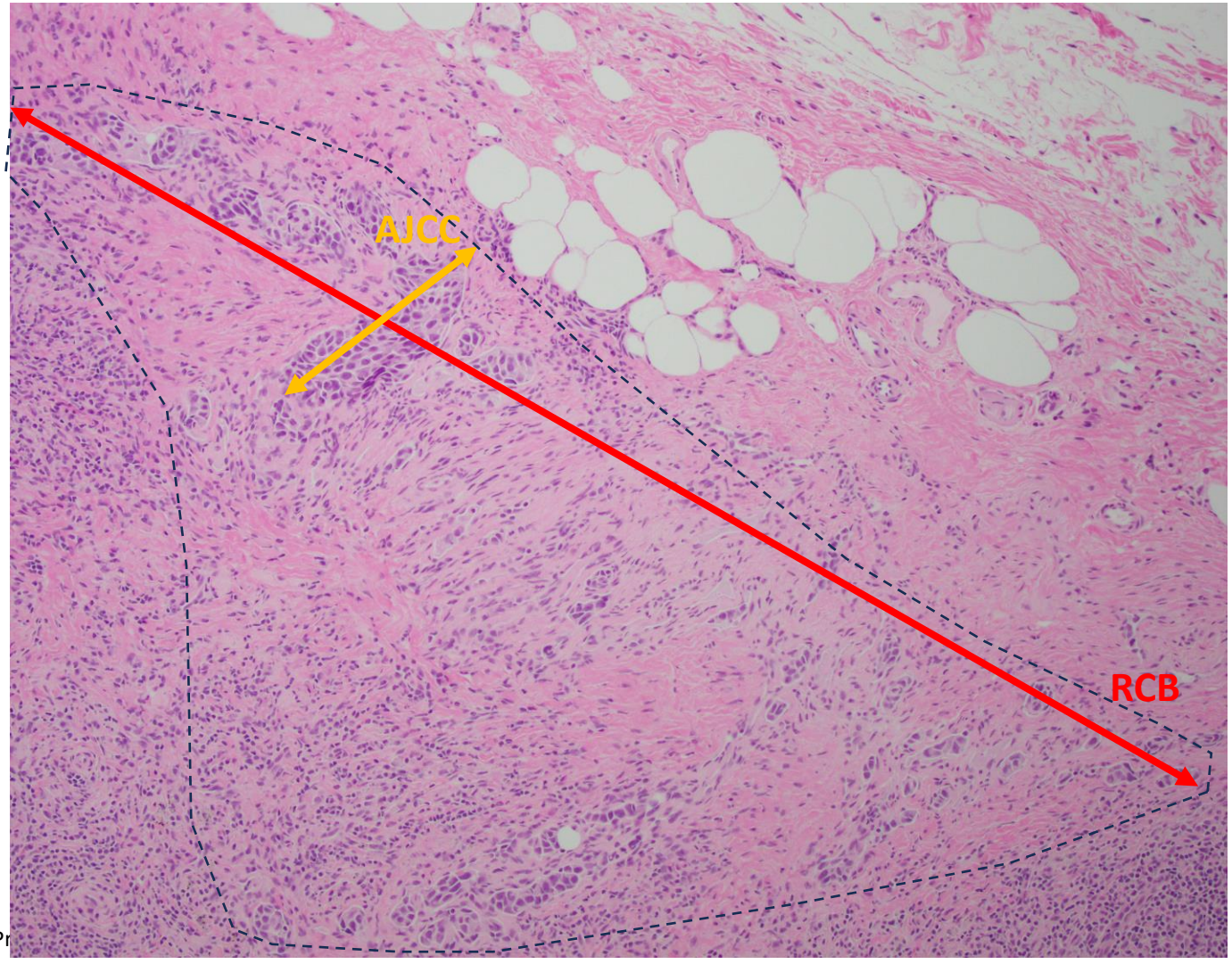


RCB: Area that encompasses all islands of residual invasive tumor cells and intervening stroma. (Does not include fibrosis/tumor bed beyond The area containing residual invasive tumor cells)

AJCC: Measurement of the largest contiguous focus of tumor exclusive of intervening treatment-related fibrosis/stroma; if multiple foci of tumor are present, an "m" designation is given

Sahoo S et al., Arch Pathol Lab Med 2023; 147:591-603

Key differences between RCB and AJCC Systems: Measurement of Largest Metastatic Deposit in Lymph Nodes

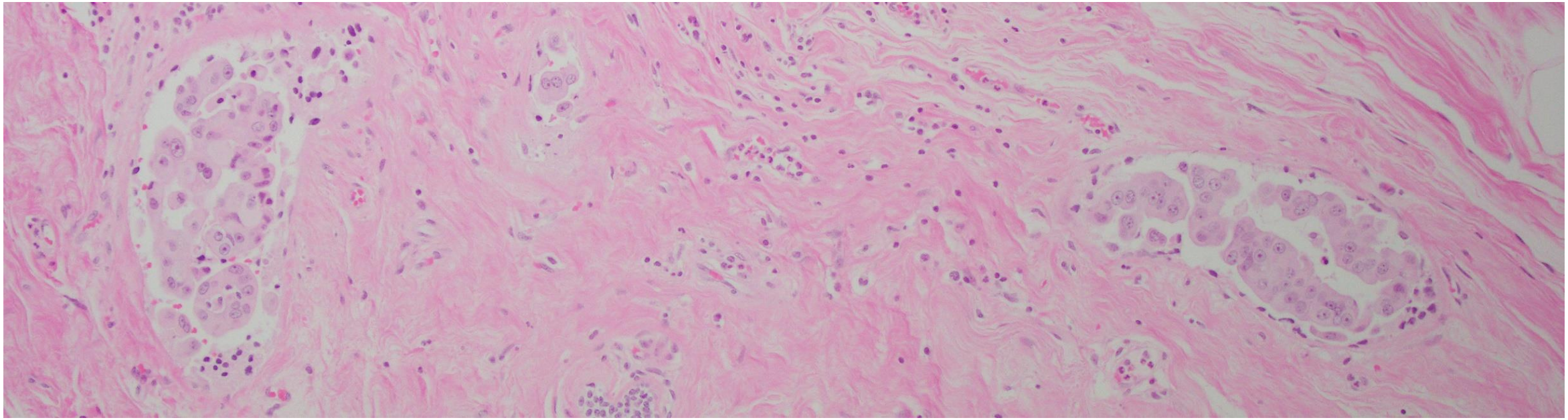


RCB: Measure the entire involved area, including intervening treatment-related fibrosis.
** nodes with ITCs only ARE counted toward the total number of positive nodes for RCB calculation
** ANY residual disease in lymph nodes (including ITCs and micrometastases) is NOT considered a pCR

AJCC: Measure the largest contiguous tumor deposit
** nodes with ITCs only ARE NOT counted toward the total number of positive nodes for AJCC staging

Sahoo S et al., Arch Pathol Lab Med 2023; 147:591-603

Other special circumstances:
Residual tumor is only present in lymphovascular spaces



RCB: NOT considered a pCR. LVI is included in residual tumor cellularity estimate
AJCC: currently staged as ypT0

Sahoo S et al., Arch Pathol Lab Med 2023; 147:591-603

Other special circumstances: Multifocal/multicentric disease prior to NAC

- If the tumors have similar morphologies/ receptor profiles, then the largest residual tumor should be used to calculate the RCB score.

- If the tumors have different morphologies/ receptor profiles, then treat the tumors separately and calculate an RCB score for each one

Sahoo S et al., Arch Pathol Lab Med 2023; 147:591-603

Other special circumstances: Neoadjuvant Endocrine Therapy

- RCB system was only validated for systemic cytotoxic chemotherapy
- Unknown whether the prognostic significance of the different RCB classes extends to neoadjuvant endocrine therapy
- In our practice, we provide the RCB information with a comment:

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A "y" descriptor is applied given the noted history of endocrine
therapy.  The values for RCB are included, however, the prognostic
significance outside the setting of systemic chemotherapy is
uncertain.
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Elements to be Included in Pathology Report of post-NAC Treated Breast Carcinomas

- Breast specimen
  - In cases with pCR, document confirmation of the microscopic tumor bed changes and/or histologic biopsy site changes
  - Histologic subtype and grade of residual invasive carcinoma
  - Size of residual invasive carcinoma (if reporting both RCB and AJCC, provide both size measurements)
  - Cellularity of residual invasive carcinoma (including LVI)
  - Presence of LVI
  - Presence and extent of DCIS
  - Margins with respect to invasive carcinoma and DCIS
  - Consider retesting tumor biomarkers
- Lymph nodes
  - Number of lymph nodes containing metastases
  - Size of largest metastases (if reporting both RCB and AJCC, provide both size measurements)
  - Presence of extranodal extension and extent
  - Number of lymph nodes with definite evidence of treatment effect
- Classification of response to treatment
  - RCB score
  - AJCC stage

Example report

1. LEFT SENTINEL LYMPH NODE #1, EXCISION:

- ONE LYMPH NODE, NEGATIVE FOR TUMOR (0/1).
- NO TREATMENT EFFECT IDENTIFIED.
- BIOPSY SITE CHANGES PRESENT.
- AE1/AE3 KERATIN STAIN EVALUATED.

2. LEFT BREAST, MASTECTOMY, POST NEOADJUVANT THERAPY:

- RESIDUAL INVASIVE DUCTAL CARCINOMA, MODERATELY DIFFERENTIATED (NOTTINGHAM GRADE 2 OF 3: TUBULE SCORE 3, NUCLEAR SCORE 3, MITOSIS SCORE 1), PRESENT AS MULTIPLE FOCI (AT LEAST 10 FOCI) RANGING FROM LESS THAN 0.1 CM TO 1.1 CM, SCATTERED THROUGHOUT TWO SEPARATE TUMOR BEDS SPANNING 4.5 CM AND 1.5 CM RESPECTIVELY; SEE COMMENT AND SYNOPTIC REPORT.

- NO LYMPHOVASCULAR INVASION IDENTIFIED.

- DUCTAL CARCINOMA IN SITU, HIGH NUCLEAR GRADE (SOLID PATTERN) WITHOUT NECROSIS OR CALCIFICATIONS, PRESENT IN 9 OF 43 BLOCKS.

- INVASIVE CARCINOMA AND DCIS ARE GREATER THAN 0.2 CM FROM THE DEEP AND ANTERIOR MARGINS.

- SKIN AND NIPPLE, NEGATIVE FOR TUMOR.

- LOOSE STROMAL FIBROSIS CONSISTENT WITH TREATED TUMOR BED CHANGES.

- BIOPSY SITE CHANGES X2.

- ANCILLARY STUDIES PERFORMED AT ARUP LABORATORIES WITH APPROPRIATELY REACTIVE CONTROLS DEMONSTRATE THE FOLLOWING STAINING PROFILE IN THE RESIDUAL INVASIVE CARCINOMA (BLOCK 2K):

ESTROGEN RECEPTOR: NEGATIVE (0%)
PROGESTERONE RECEPTOR: NEGATIVE (0%)
HER2 (IHC): NEGATIVE (0)

Example report continued

COMMENT:

The patient is a 45-year-old female who presented with two self-palpated left breast masses in the upper outer quadrant and axillary tail. Breast imaging revealed a mass in the upper outer quadrant which measured 3.1 cm by MRI with additional surrounding non-mass enhancement spanning 4.0 cm. A second mass was also identified in the axillary tail measuring 3.5 cm by MRI. The entire span of disease measured 7.5 cm. No abnormal axillary lymph nodes were identified. Breast biopsies of the two masses confirmed poorly differentiated invasive ductal carcinoma which was negative for estrogen receptor, progesterone receptor, and HER2. The patient received neoadjuvant chemotherapy with good clinical response. Post-treatment MRI showed residual non-mass enhancement in the upper outer quadrant measuring 2.0 cm. The mass in the axillary tail was also decreased, measuring 1.5 cm post-treatment.

Upon gross examination of the surgical specimen, an area of fibrosis consistent with tumor bed is identified in the upper outer quadrant spanning 4.5 x 4.0 cm. A second area of fibrosis is identified in the axillary tail spanning 1.5 x 1.5 cm. Histologic examination reveals multiple foci of residual invasive carcinoma ranging from less than 0.1 cm to 1.1 cm. The residual foci of invasive carcinoma are scattered throughout both grossly identified tumor beds. The tumor from both areas is histologically similar. The residual tumor cellularity is estimated as 10%. One axillary lymph node is negative for tumor and does not show evidence of treatment effect.

A Residual Cancer Burden score is calculated as: 1.79 (RCB-II).

AJCC Pathologic Classification (8th ed.): mypT1c ypN0(sn).

Thank you!