Evaluation of Breast Cancer After Neoadjuvant Therapy

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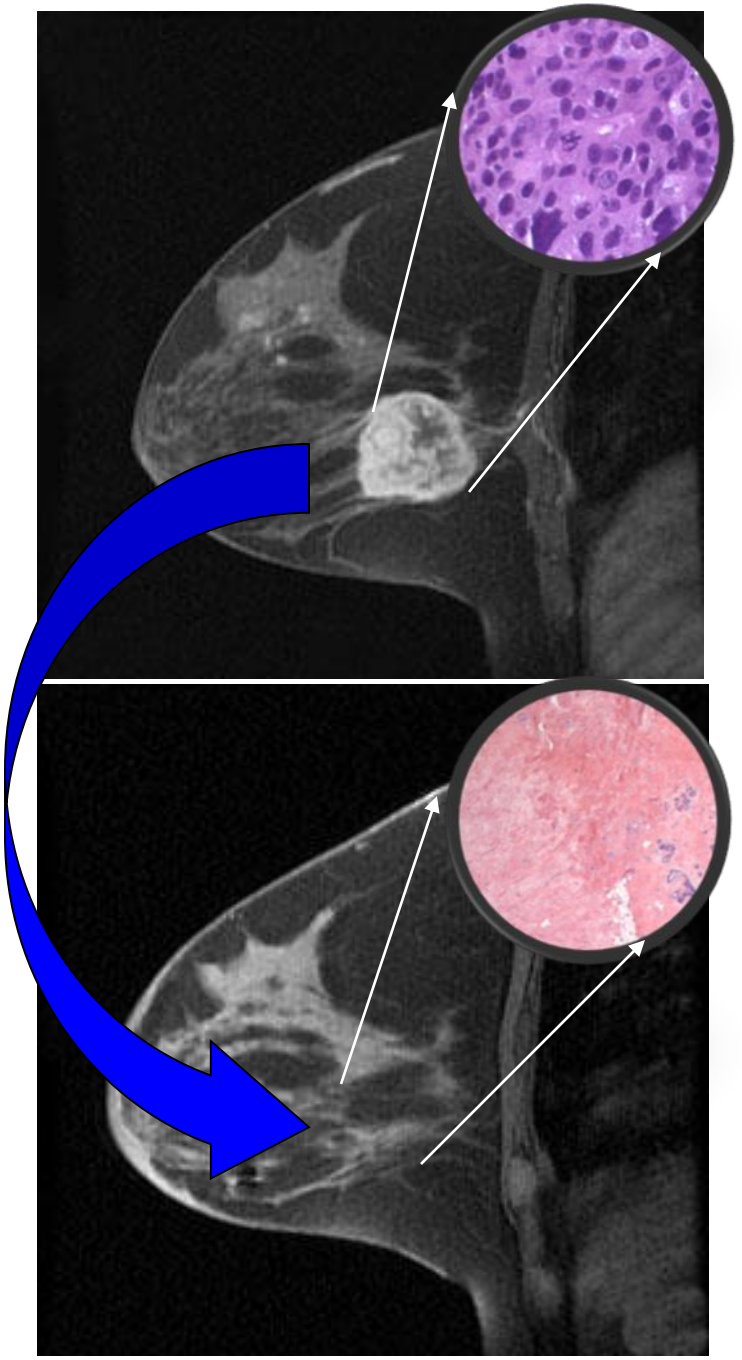


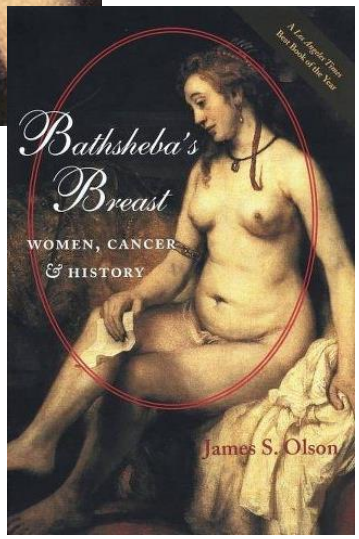
Hendrickje Stoffels 1626-1663

She was the longtime partner of Rembrandt and appears in several of his paintings.

It has been suggested that she had breast cancer due to the skin retraction of her lateral breast and axillary fullness.

She will be our example of a locally advanced breast cancer in a 28 year old woman.

Bathsheba at her bath
Rembrandt, 1654
Louvre, Paris



Braithwaite PA, Shugg D. Rembrandt's Bathsheba: the dark shadow of the left breast. Annals Royal College Surgeons England. 65:337-338, 1983.

Heijblom M, et al, Monte Carlo simulations shed light on Bathsheba's suspect breast, J Biophotonics 7:323-331, 2014.

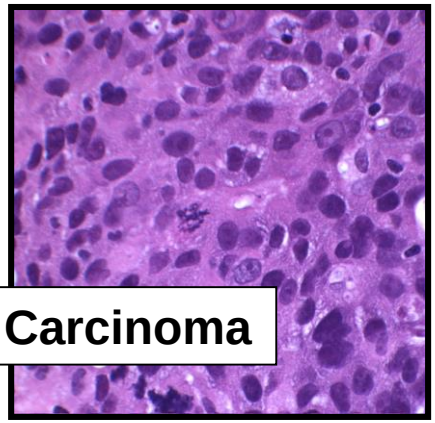
Patient H.S.

HS presents with a 3 cm palpable carcinoma with skin retraction but no skin ulceration.

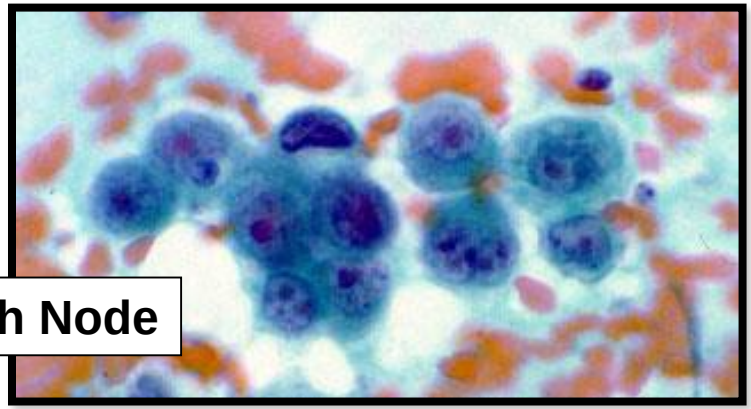
A core needle biopsy shows a poorly differentiated carcinoma negative for ER, PR, and HER2 (triple negative breast cancer=TNBC).

Multiple palpable nodes are present (>3). A fine needle aspiration confirms metastatic carcinoma.

AJCC Stage: T2 N2 = IIIA.



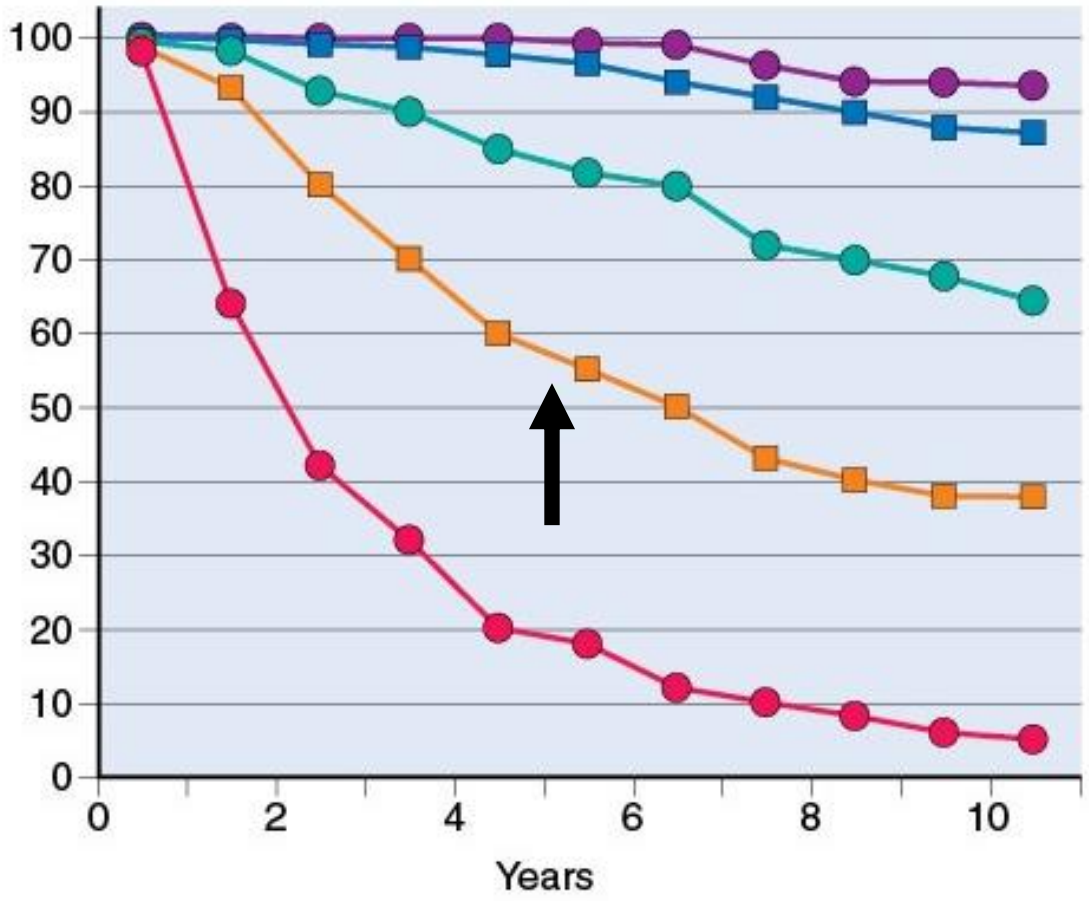
Primary Carcinoma



Lymph Node

AJCC: Breast Anatomic Stage and Survival

% of women surviving



Stage 0: Carcinoma in situ

Stage I: small, lymph node (-)

Stage II: large and/or node (+)

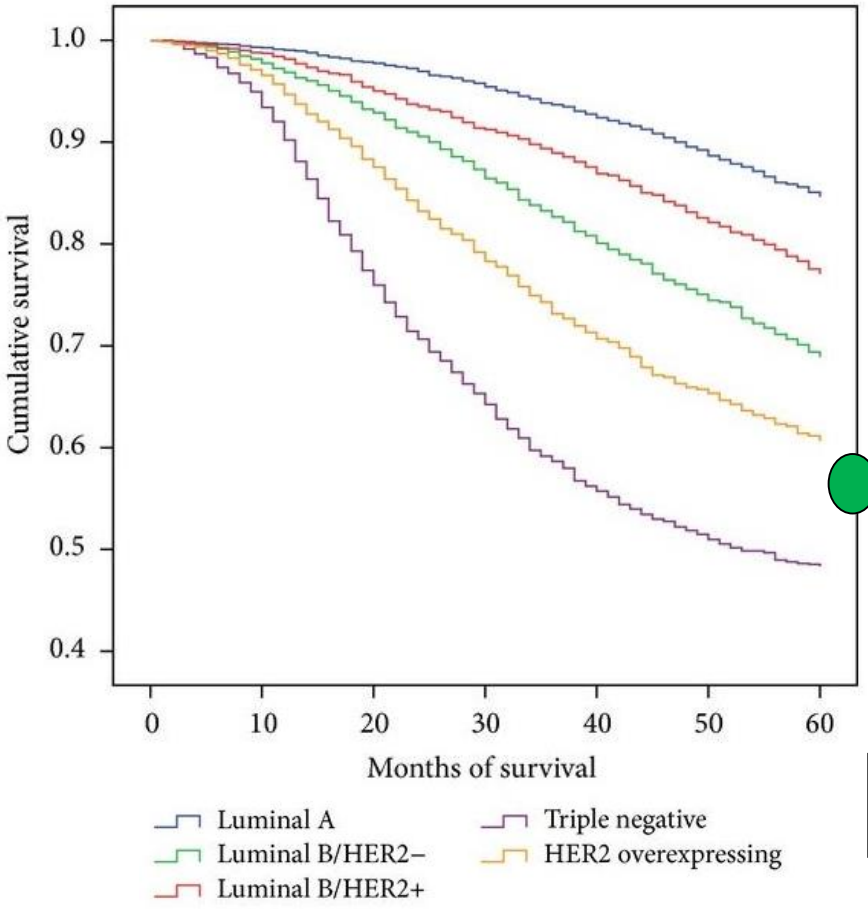
Stage III: locally advanced

Stage IV: distant metastases

H.S. = ~55% survival at 5 years

Survival According to Anatomic Stage and Biologic Type

Stage 3 – 5 year survival



Within each anatomic stage, survival varies according to biologic type.

Luminal (ER positive/HER2 negative) – grades 1 and 2: 86% survival

All cancers – ~55% survival

TNBC: 48% survival

H.S. = 48% survival at 5 years

Parise, CA, Caggiano, V. Breast cancer survival defined by the ER/PR/HER2 subtypes and a surrogate classification according to tumor grade and immunohistochemical biomarkers. J Cancer Epidem 2014.

What if H.S. receives neoadjuvant chemotherapy?

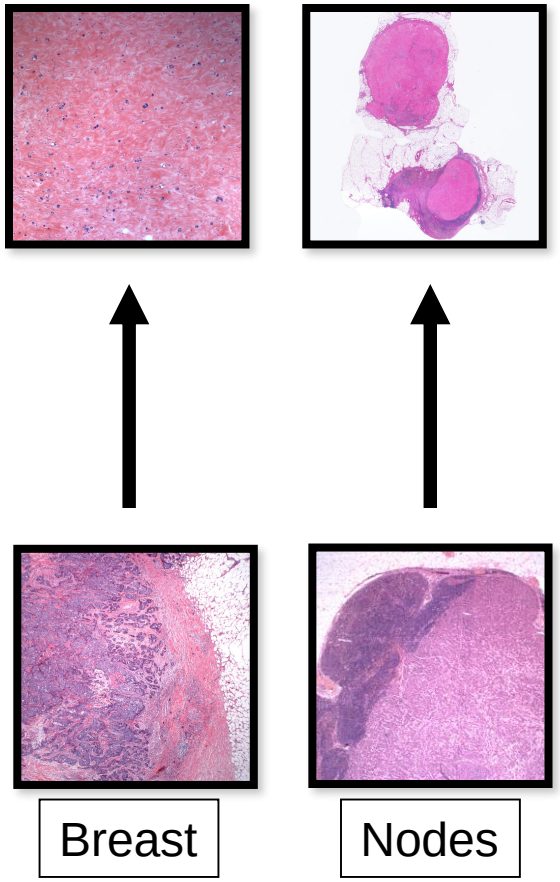
Four major outcomes:

1) No residual cancer in the breast or nodes
(pathological complete response (pCR).

2) Almost complete response.

3) Some response but incomplete.

4) No response or progression during treatment.

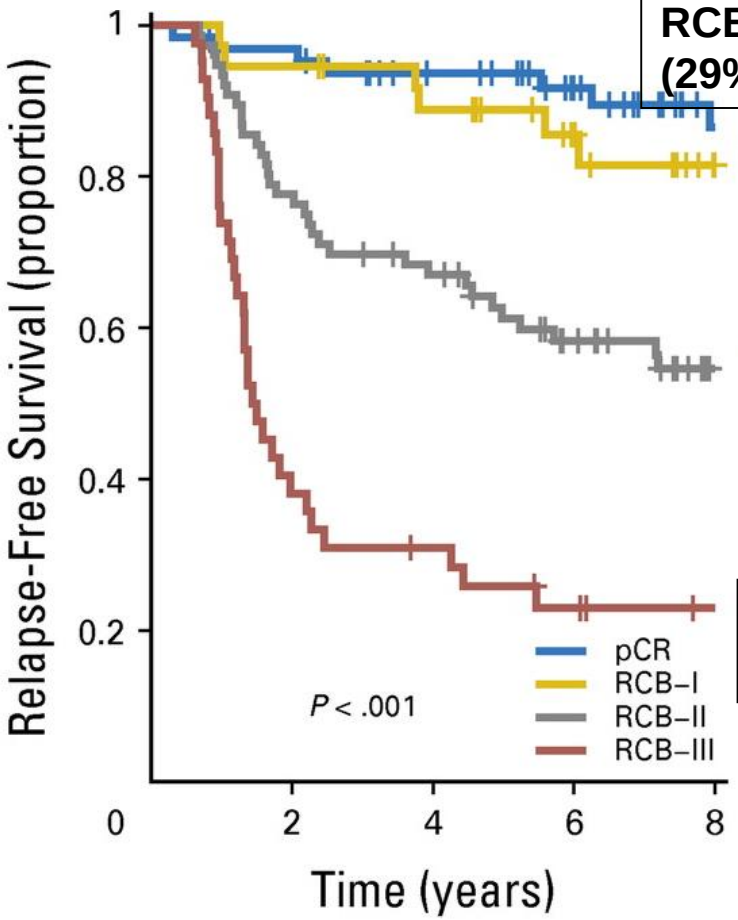


Important note: *The ultimate outcome (survival or death due to breast cancer) is the same whether chemotherapy is given before or after surgery.*

Neoadjuvant Therapy – Triple Negative Breast Cancer (TNBC)

Short term endpoint
RCB

Long term outcome
Recurrence



RCB-0 pCR (29% of patients)

RCB-I (17% of patients)

RCB-II (35% of patients)

RCB-III (14% of patients)

Survival remains uncertain in 1/3.

For TNBC's, response to treatment identifies ~50% of patients with good prognosis and ~15% with very poor prognosis.

Symmans, WF, et al, Long-term prognostic risk after neoadjuvant chemotherapy associated with residual cancer burden and breast cancer subtype, JCO 35:1049, 2017.

Tumor Response – Value of Information

Individual patients – strong prognostic factor for many cancers

May benefit from additional and/or different treatment
Prophylactic surgery is of greater value for patients with a good prognosis

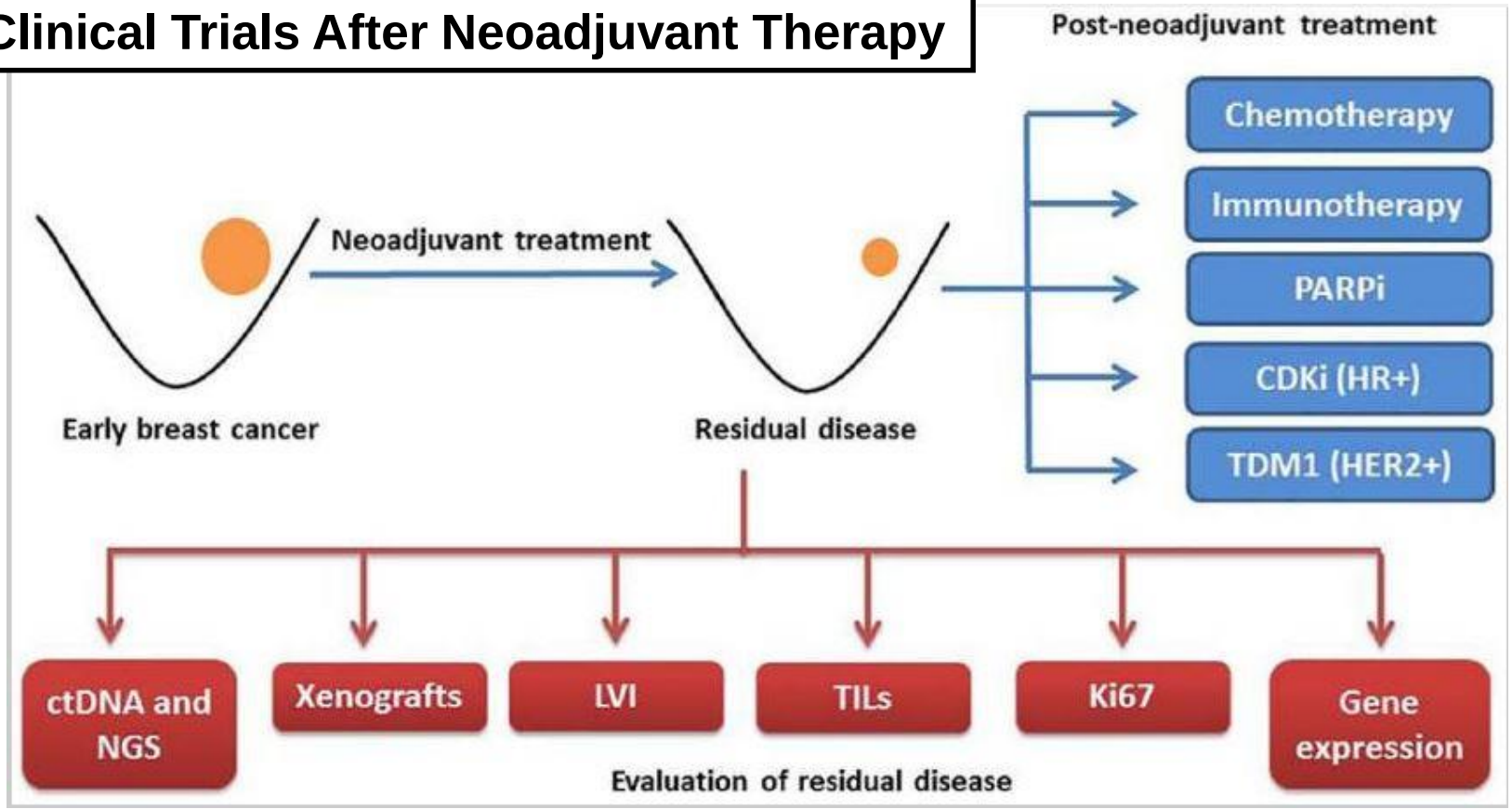
Clinical trials

Treatments can be compared using smaller numbers of patients over a shorter time span

Research

Rapid evaluation of new treatments
Investigation of resistance to therapy
Identification of new targets . . .

Clinical Trials After Neoadjuvant Therapy



A burgeoning area of research is the development of second-tier treatment to improve the survival of patients who do not achieve a pCR.

Caparica R, et al, Post-neoadjuvant treatment and the management of residual disease in breast cancer: state of the art and perspectives. Therapeutic Advances Med Oncol 11:1-23, 2019.

Neoadjuvant Therapy – The Role of the Pathologist

Pathologists play a key role in the successful implementation of neoadjuvant therapy.

Learning objectives for this talk:

1) Evaluation of the pre-treatment breast core needle biopsy.

2) Evaluation of the lymph nodes pre-treatment.

3) Gross evaluation of the post-treatment specimen.

4) Determining and reporting response to treatment.

The BIG-NABCG (Breast International Group-North American Breast Cancer Group; comprised of pathologists, radiologists, surgeons, medical and radiation oncologists, and gynecologists) has made recommendations for reporting breast cancers after neoadjuvant therapy.

The recommendations are for patients on clinical trials, but may also be considered for the evaluation of specimens from all patients.

Bossuyt, V, et al, Recommendations for standardized pathological characterization of residual disease for neoadjuvant clinical trials of breast cancer by the BIG-NABCG collaboration, Ann Oncol 26:1280-1291, 2015.

Provenzano E, et al, Standardization of pathologic evaluation and reporting of postneoadjuvant specimens in clinical trials of breast cancer: recommendations from an international working group, Mod Pathol 28:1185-1201, 2015.

Bossuyt V, Symmans WF, Standardizing of pathology in patients receiving neoadjuvant chemotherapy, Ann Surg Oncol 23:3153-3161, 2016.

Bossuyt V, Processing and reporting of breast specimens in the neoadjuvant setting, Surg Pathol 11:213-230, 2018.

Pre-Treatment Core Needle Biopsy

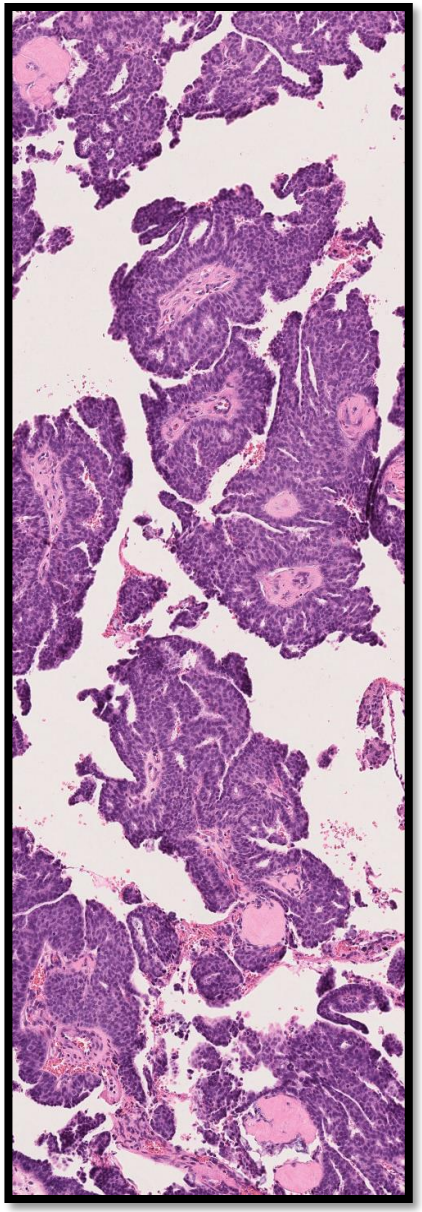
There must be a definite diagnosis of invasive carcinoma.

Definitive results of ER, PR, and HER2 testing must be available. If amount or quality of tissue is inadequate for optimal studies, repeat biopsy is indicated.

Grade, necrosis, and a dense lymphocytic infiltrate are important predictors of response to therapy.

A clip should always be placed to mark the site of the cancer. It may not be possible to determine the location of a cancer with certainty by palpation or imaging after treatment.

Neoadjuvant Therapy Gone Awry

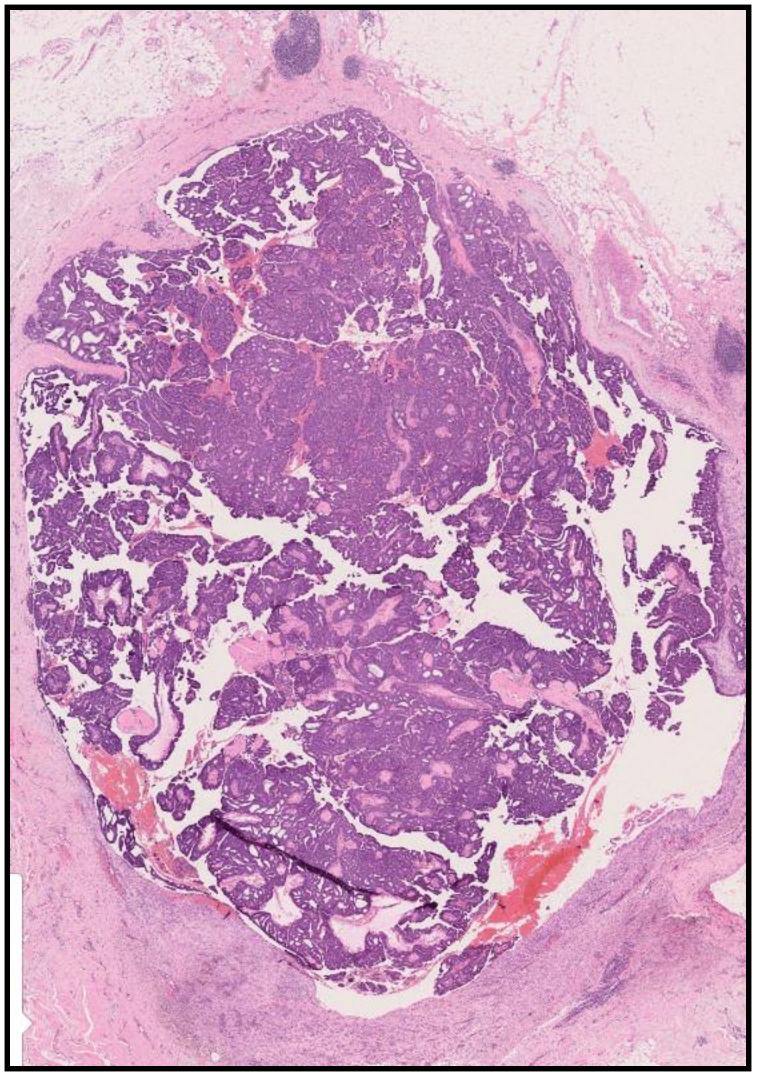


A woman was found to have a breast mass.

A core needle biopsy was diagnosed as “papillary carcinoma”. The carcinoma was positive for hormone receptors and negative for HER2.

She underwent neoadjuvant therapy.

Neoadjuvant Therapy Gone Awry



The residual cancer was encapsulated papillary carcinoma (EPC) – which is classified as Tis.

Did she have an invasive carcinoma that responded to systemic treatment?

Did she only have EPC and did not require systemic therapy?

In this case, poor communication led to neoadjuvant therapy resulting in less – rather than more – information for this woman.

Neoadjuvant Therapy – The Role of the Pathologist

Pathologists play a critical role in the successful use of neoadjuvant therapy.

Objectives for this talk:

1) Evaluation of the pre-treatment core needle biopsy.

2) Evaluation of the lymph nodes pre-treatment.

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Pre-Treatment Lymph Node Evaluation

To obtain the greatest amount of information, palpable or enlarged nodes by ultrasound should be sampled with core needle biopsy or fine needle aspiration (FNA). A clip may (or may not) be placed.

This leaves the metastasis in place and allows for response in nodes to be evaluated. This is more predictive of survival than response in the breast cancer.

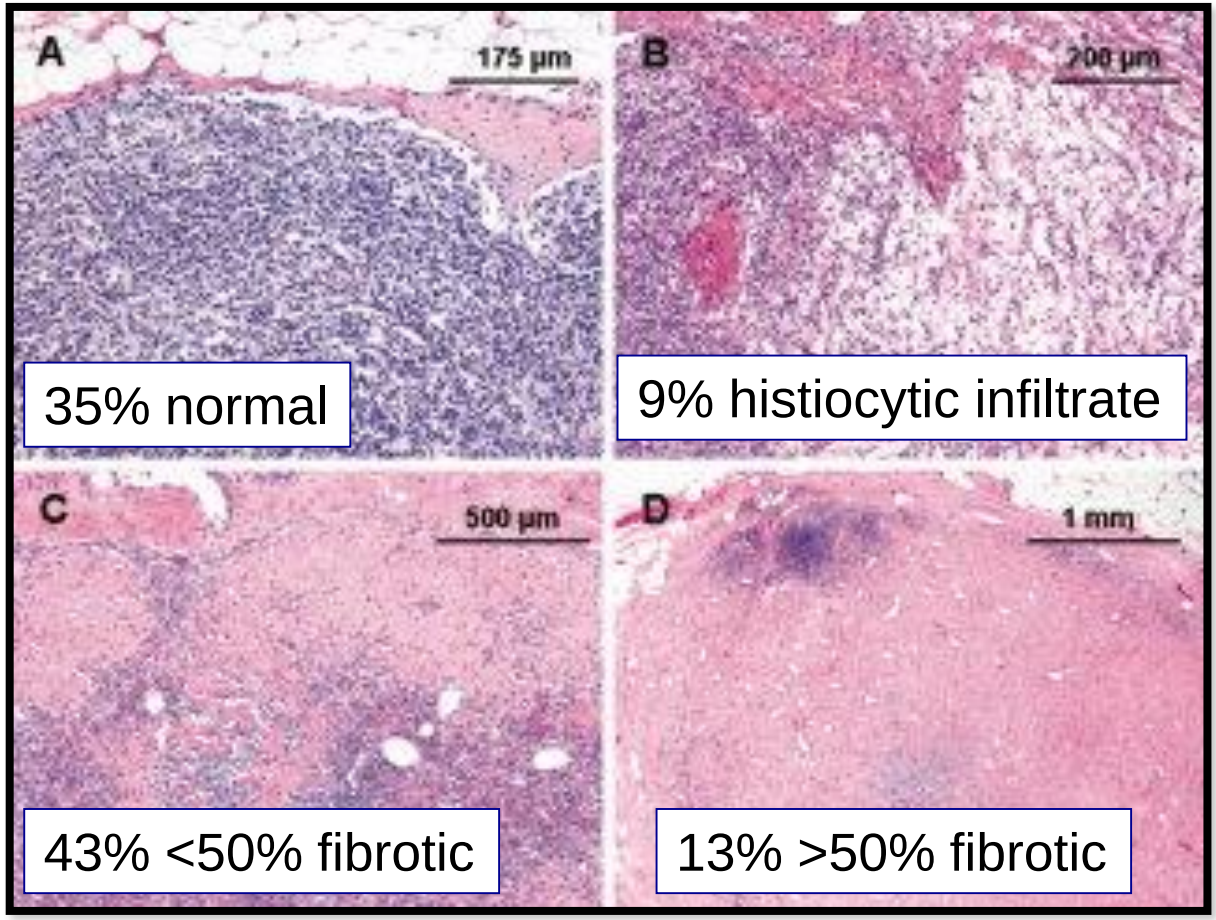
Sentinel node biopsy may be performed if there are no enlarged nodes or the needle biopsy is negative.

If negative, no nodal sampling after treatment is necessary.

If a positive node is completely removed by excision, response cannot be evaluated. RCB cannot be calculated.

Donker M, et al, Marking axillary lymph nodes with radioactive iodine seeds for axillary staging after neoadjuvant systemic treatment in breast cancer patients, Ann Surg 261:378-382, 2015.

Post-Treatment Lymph Node Evaluation



Nodes need to be evaluated prior to treatment to know the node status (positive or negative) with certainty.

Metastases resolve without evidence of prior involvement (e.g. fibrosis) in ~1/3 of cases.

Brown, AS, Histologic changes associated with false-negative sentinel lymph nodes after preoperative chemotherapy in patients with confirmed lymph node-positive breast cancer before treatment, Cancer 116:2878-2883, 2010.

Neoadjuvant Therapy – Clinical and Radiologic Response

It is helpful to know what changed during treatment in order to correlate these changes with the post-treatment pathology:

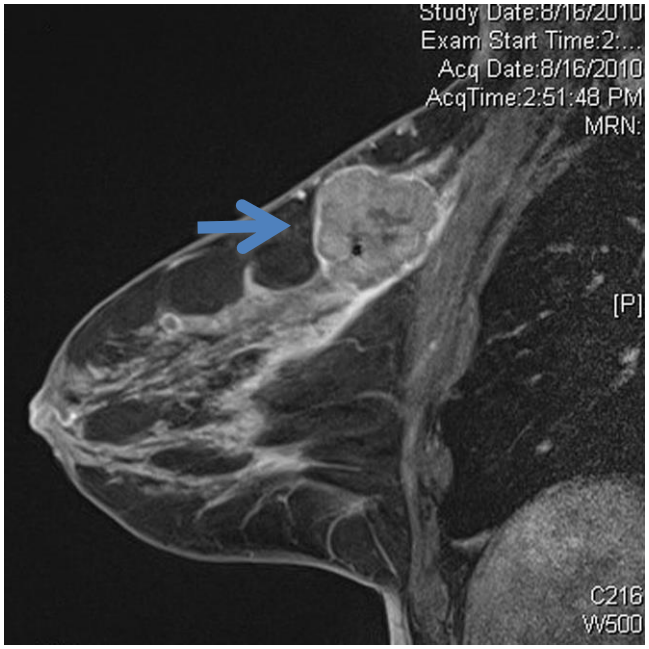
Did a palpable cancer or lymph node metastasis remain palpable or resolve?

Did the cancer change in size by imaging?

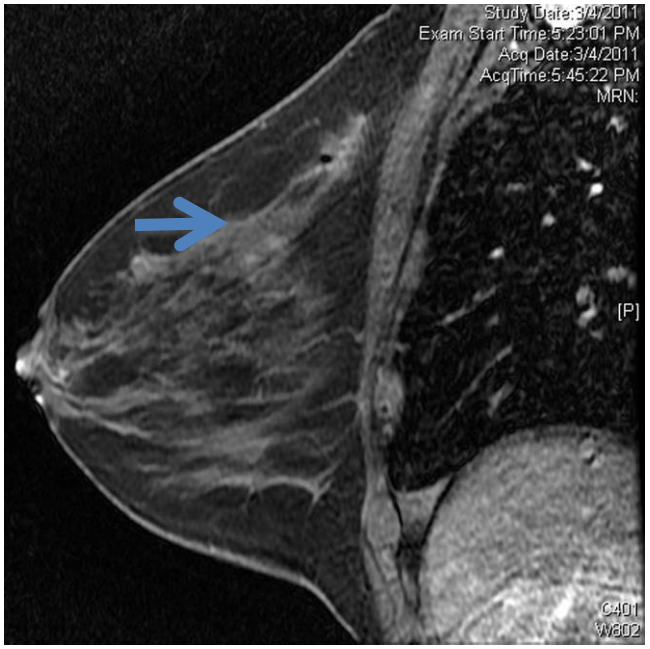
Did skin changes (e.g. erythema or retraction) resolve?

Did fixation to the chest wall resolve?

Pre-Treatment MRI



Post-Treatment MRI



In this case, a large palpable invasive carcinoma cannot be palpated or seen by MRI after treatment.

It will be essential to identify the clip in the specimen in order to identify the tumor bed.

Residual invasive cancer was present in the tumor bed.

Neoadjuvant Therapy – The Role of the Pathologist

Pathologists play a critical role in the successful use of neoadjuvant therapy.

Objectives for this talk:

1) Evaluation of the pre-treatment core needle biopsy.

2) Evaluation of the lymph nodes pre-treatment.

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Post-Treatment Breast Evaluation

Information about the pre-treatment carcinoma is necessary for optimal processing of the specimen –

Number, size, and location of carcinomas

Presence or absence of clips marking the cancers and/or nodes

Presence or absence of tumor related calcifications

Prior involvement of skin by invasion or due to “inflammatory” skin changes (dermal lymphovascular invasion)

Prior involvement of the chest wall (muscle invasion)

Ideally, the specimen is radiographed intact to identify clips marking the carcinoma and/or lymph nodes.

Failure to find tumor bed ≠ **pCR**

It is critically important to identify the clip or clips marking the pre-treatment tumor site before classification as pCR.

Neoadjuvant Treatment Gone Awry

A 45 year old woman presented with a 3 cm palpable mass.

MRI showed the mass and 5 cm of adjacent non mass enhancement.

A core needle biopsy of the mass showed a poorly differentiated triple negative breast cancer (TNBC). A clip was placed.

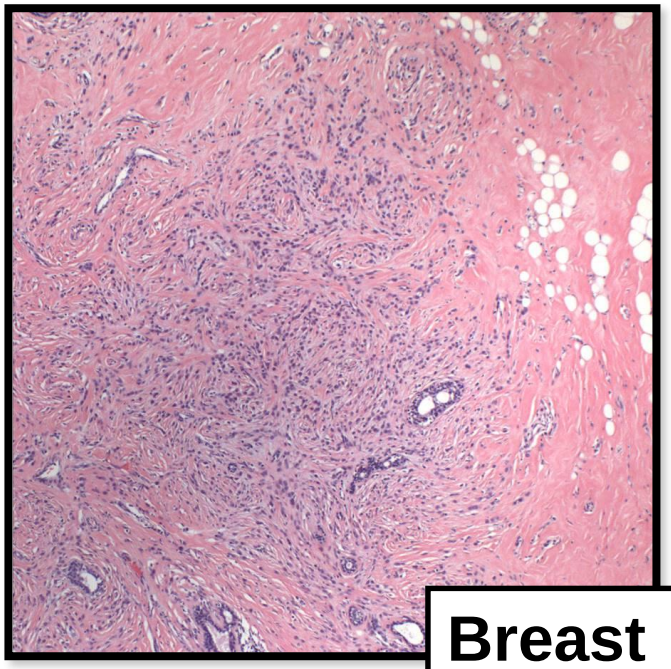
A fine needle aspiration of a single enlarged lymph node was positive for metastatic carcinoma.

The patient underwent neoadjuvant therapy followed by mastectomy.

Neoadjuvant Treatment Gone Awry

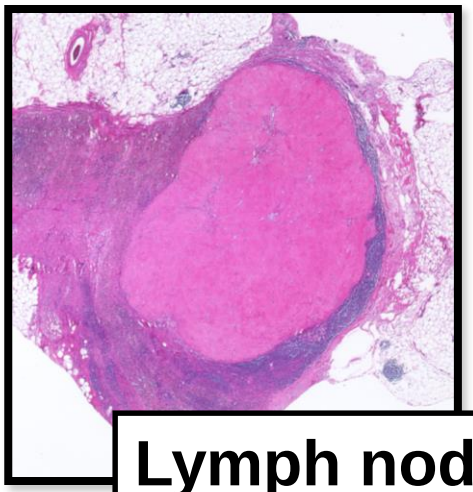
The mastectomy was not radiographed and the clip was not identified grossly.

Sampling of dense tissue revealed a 5 cm moderately differentiated invasive carcinoma with lobular morphology and no evident response to treatment. No additional studies were performed.



Breast

One node showed fibrosis consistent with prior tumor involvement, but no residual cancer.



Lymph node

Neoadjuvant Treatment Gone Awry

The patient was referred to the Dana Farber Cancer Institute.

According to the oncologist's reading of the original pathology report, the patient had a residual 5 cm invasive carcinoma (presumably her original TNBC) that had not responded to treatment.

Second tier therapy for TNBC was under consideration.

This included additional chemotherapy and immune therapy.

However . . .

Neoadjuvant Therapy Gone Awry

The clip marking the site of the TNBC was not identified.

A marked discordance in response in breast (none) and in node (complete) is unusual.

Change in type and grade of a cancer after treatment is unusual.

Likely scenario:

Patient had two cancers – TNBC (mass) and ER+ lobular cancer (NME).

TNBC underwent pCR or near pCR in breast and pCR in lymph node.

ER+ lobular cancer did not respond to chemotherapy.

Subsequent studies showed the lobular cancer was strongly positive hormone receptors.

Neoadjuvant Treatment Gone Awry

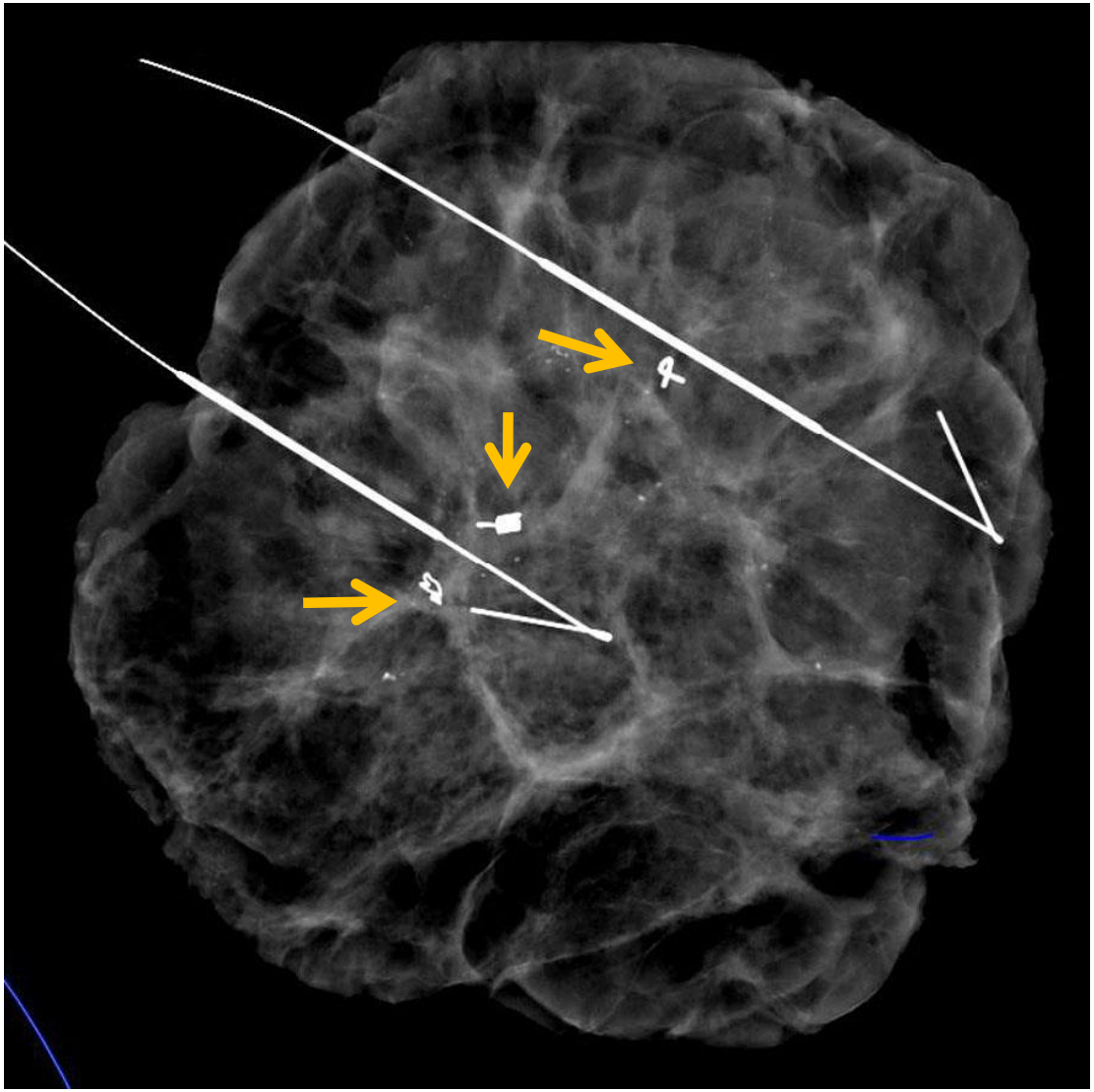
The patient could have received additional chemotherapy with possibly no benefit as only an ER(+) cancer was left.

The patient could have been denied effective endocrine therapy as the oncologists did not know she had an ER(+) cancer.

It is critical for the pathologist to identify the tumor bed in order to evaluate response.

It is also important to correlate the post-treatment findings with the pre-treatment findings in order to recognize discordant results.

Breast Conserving Surgery

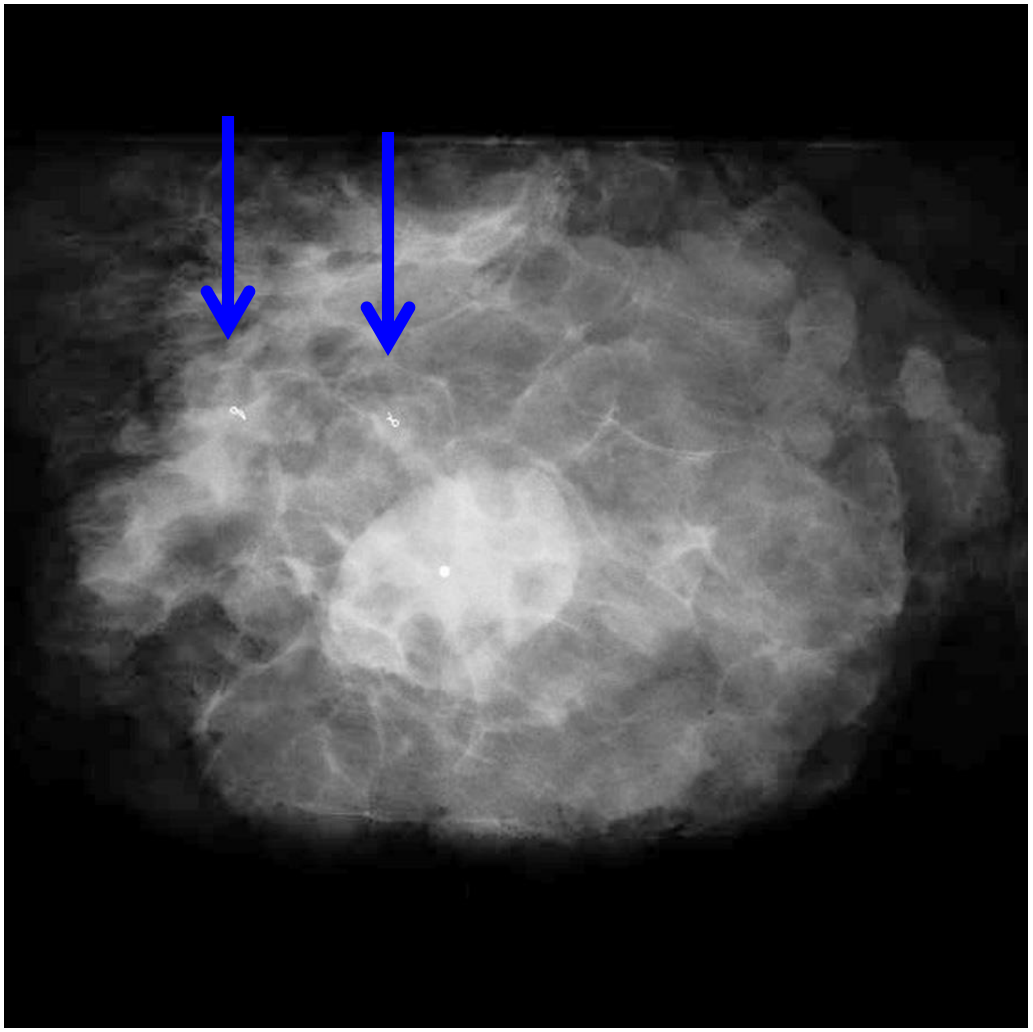


For patients undergoing breast conserving therapy, clips are necessary to identify the site for the surgeon.

The clips and specimen radiograph are used by the pathologist to identify the tumor bed.

In this case, two wires bracket 3 clips and calcifications at the site of the cancer.

Mastectomies



Clips are essential to identify the site of the cancer or cancers in mastectomies.

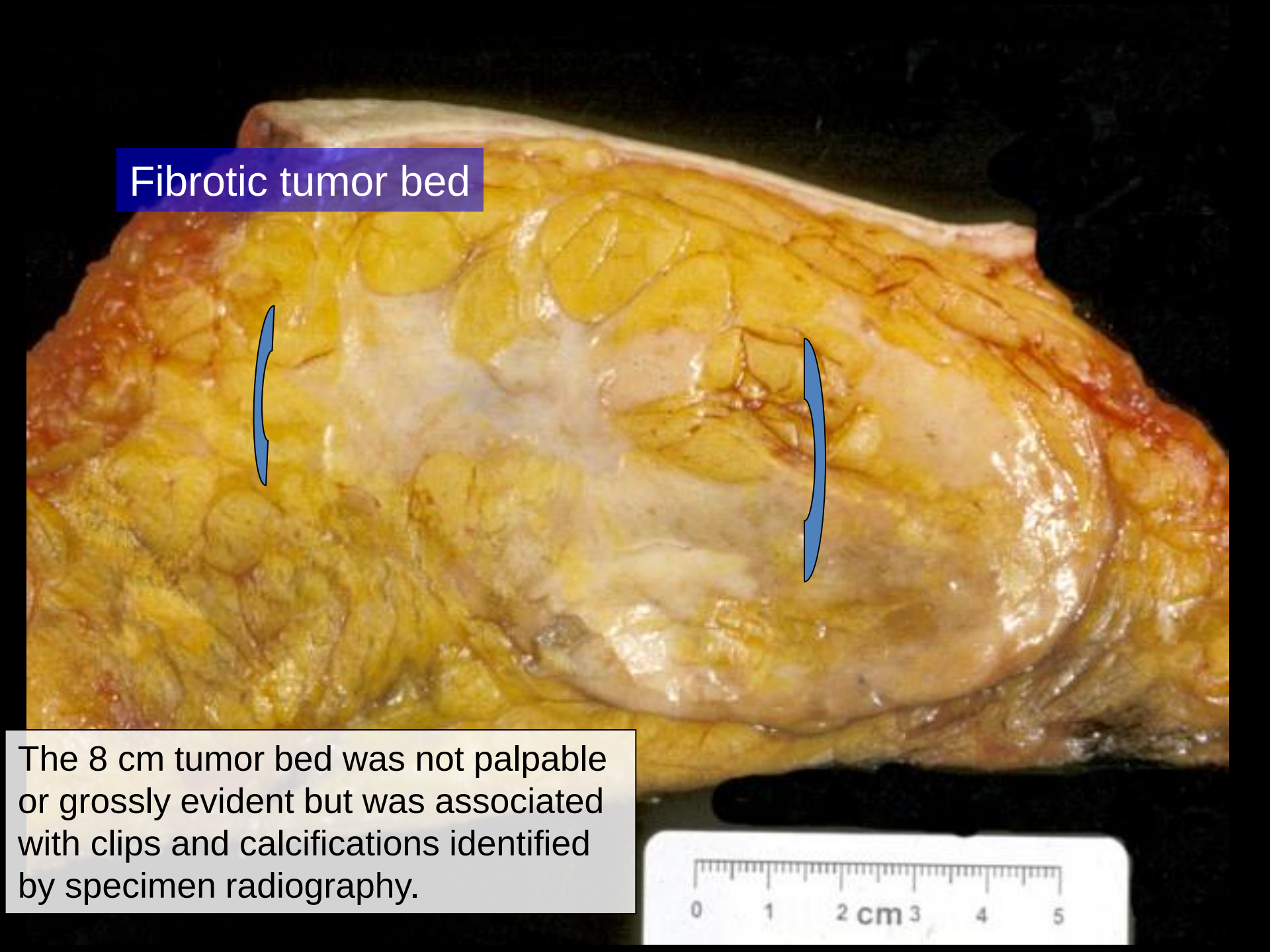
If there has been a marked response, it may be impossible to identify the site of the cancer without a clip.

If possible, radiographing the mastectomy specimen before sectioning is preferable as clips can be lost or dislodged during processing.

The two clips mark two cancers that could not be seen by imaging or by gross inspection after neoadjuvant treatment.

Cancers typically become softer and ill-defined after treatment.

Where was the 8 cm pre-treatment cancer located in this mastectomy?



The 8 cm tumor bed was not palpable or grossly evident but was associated with clips and calcifications identified by specimen radiography.

Sampling the Tumor Bed

If grossly evident invasive carcinoma is present, extensive sampling is not necessary.

If no grossly evident cancer is present, it is helpful to sample the entire tumor bed when possible to document a pCR.

Recommendations by the international working group:

> Blocks representing the full face of the tumor bed should be taken for every 1 cm slice up to 5 blocks per slice (total maximum ~25 blocks).

If initial sampling is does not show cancer, submitting additional blocks of tumor bed could be considered to document a pCR.

Provenzano, E, Standardization of pathologic evaluation and reporting of postneoadjuvant specimens in clinical trials of breast cancer, Mod Pathol 28:1185-1201, 2015.

Sampling Lymph Nodes

If a clip was placed in a node undergoing biopsy prior to treatment, it is important to radiograph the nodes to identify the clip.

Nodes may be smaller and more difficult to identify after treatment.

It is important to identify as many nodes as possible.

Nodes should be thinly sliced and completely sampled.

If slices from more than one node are placed in the same cassette, ink each node a different color.

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Neoadjuvant Therapy – The Role of the Pathologist

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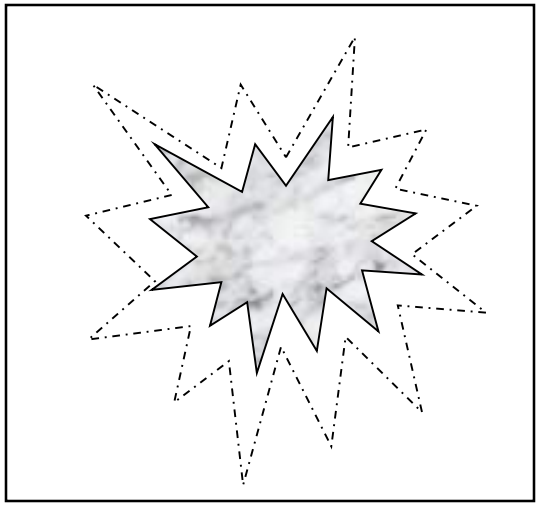
Response Patterns

Pre-Treatment Invasive Carcinoma

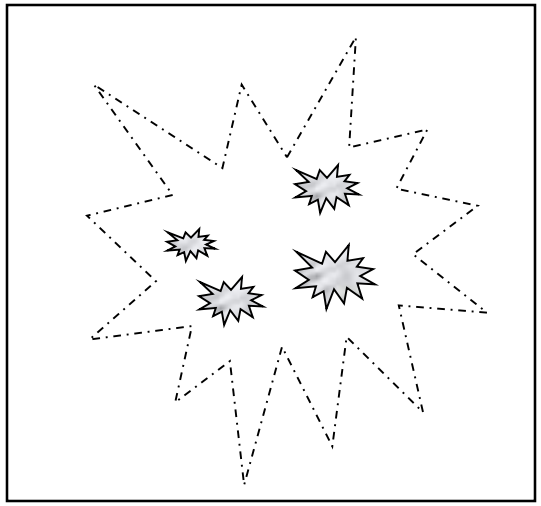
Invasive carcinoma =

Tumor bed =

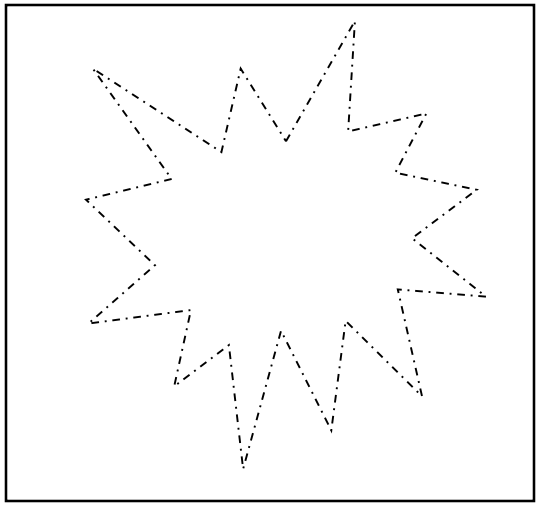
Neoadjuvant Treatment



Minimal response - single focus of invasion, slightly smaller after treatment



Moderate/marked response – Multiple foci of invasive carcinoma in the tumor bed



Complete response - No residual invasive carcinoma

Evaluation of Response

The international working group recommends reporting –

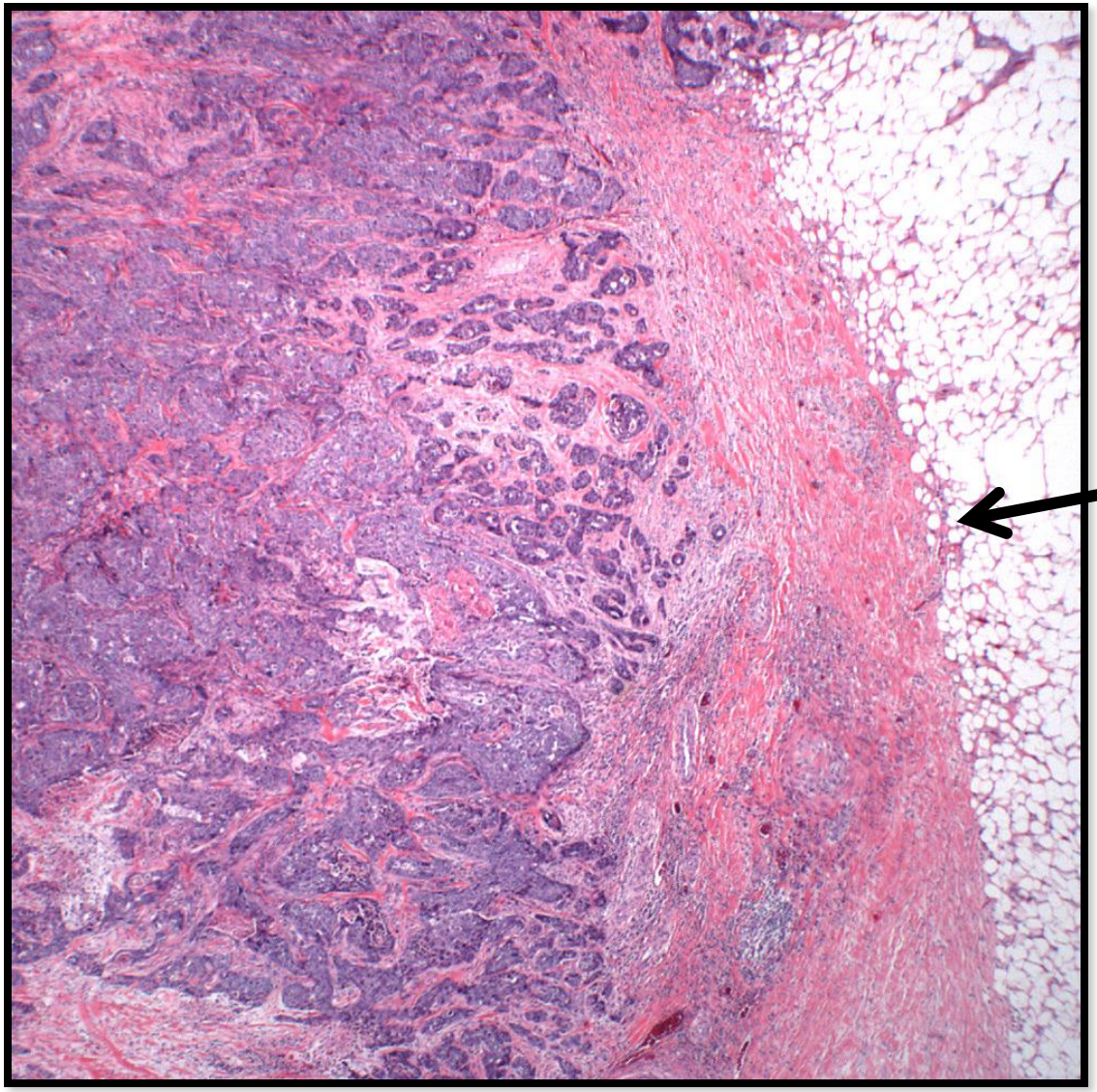
AJCC “y”

Residual Cancer Burden (RCB)

Provenzano, E, et al, Standardization of pathologic evaluation and reporting of postneoadjuvant specimens in clinical trials of breast cancer, Mod Pathol 28:1185-1201, 2015.

Bossuyt, V, et al, Recommendations for standardized pathological characterization of residual disease for neoadjuvant clinical trials of breast cancer by the BIG-NABCG collaboration, Ann Oncol 26:1280-1291, 2015.

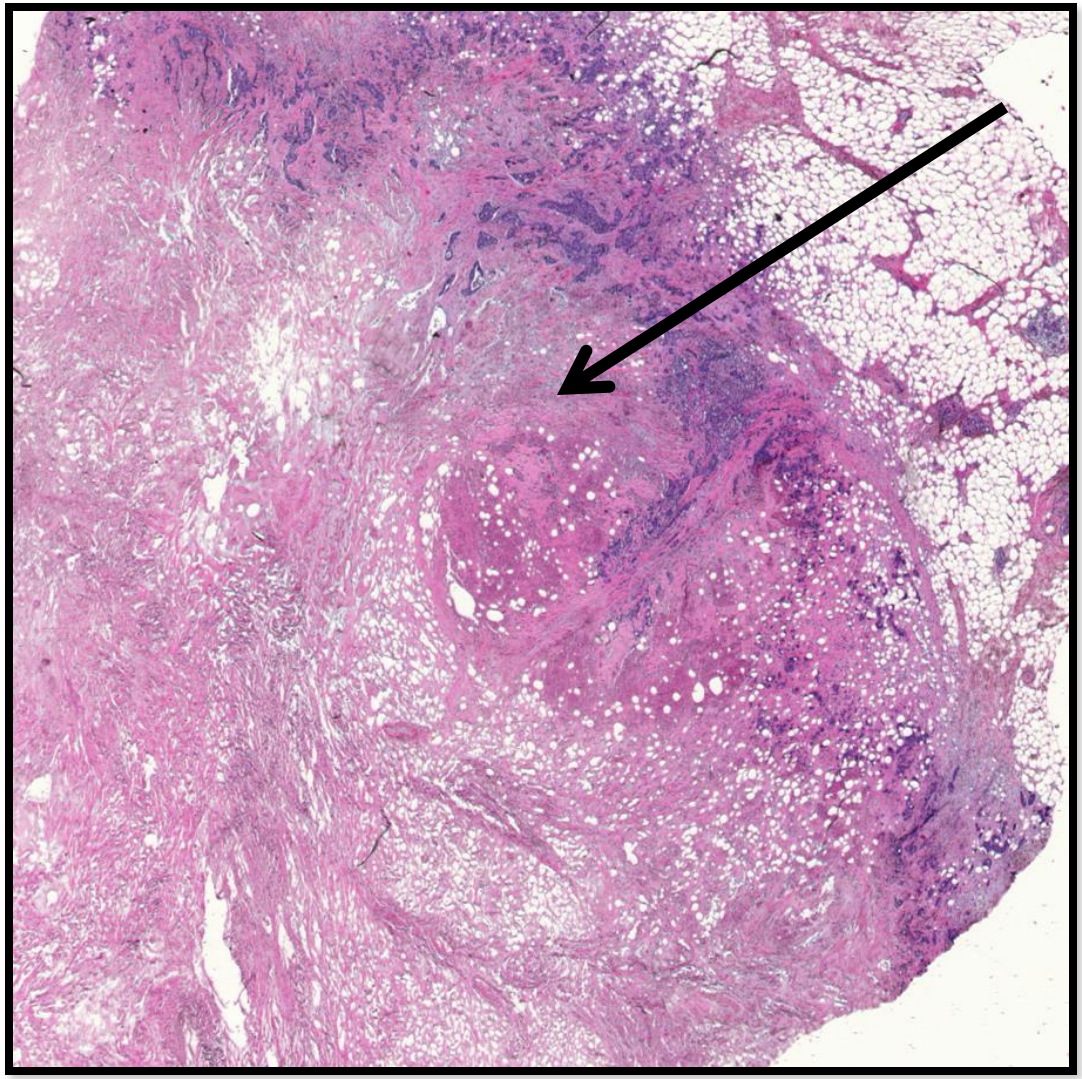
Minimal Response – Concentric Tumor Shrinkage



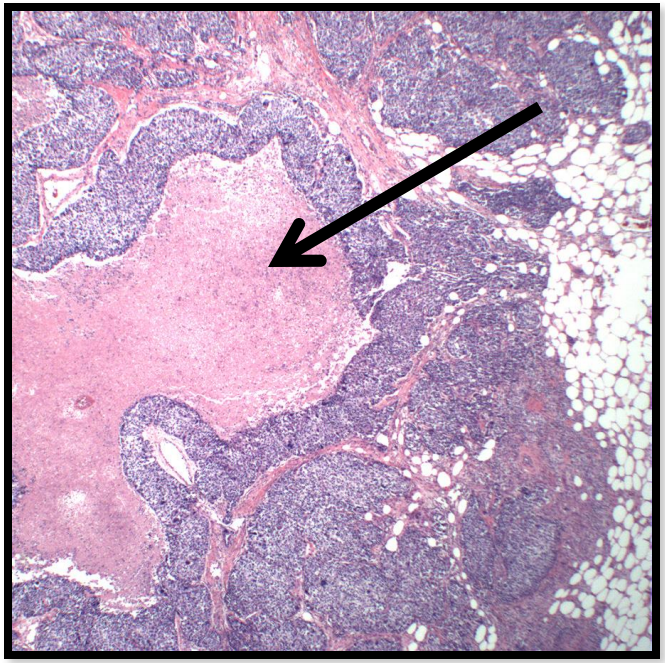
A cancer with a minimal response has a ~2-5 cm rim of fibrosis at the periphery.

The tumor cells at the periphery show the highest proliferative rate and are the most susceptible to chemotherapy.

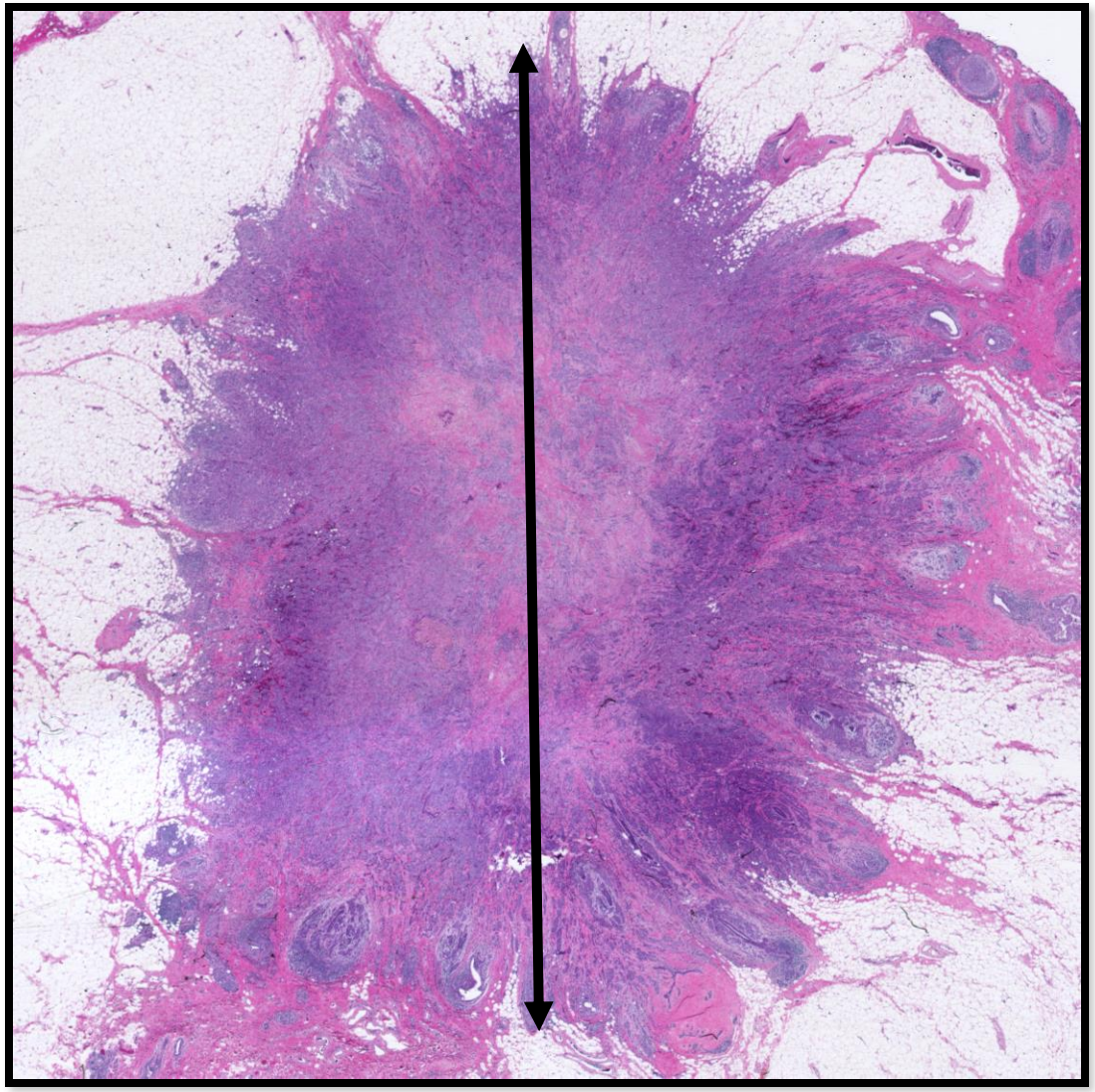
Central Necrosis and Fibrosis – Not a Response Pattern



Central fibrosis and necrosis are seen in untreated cancers. This is due torapid growth and ischemia and is not a response to treatment.

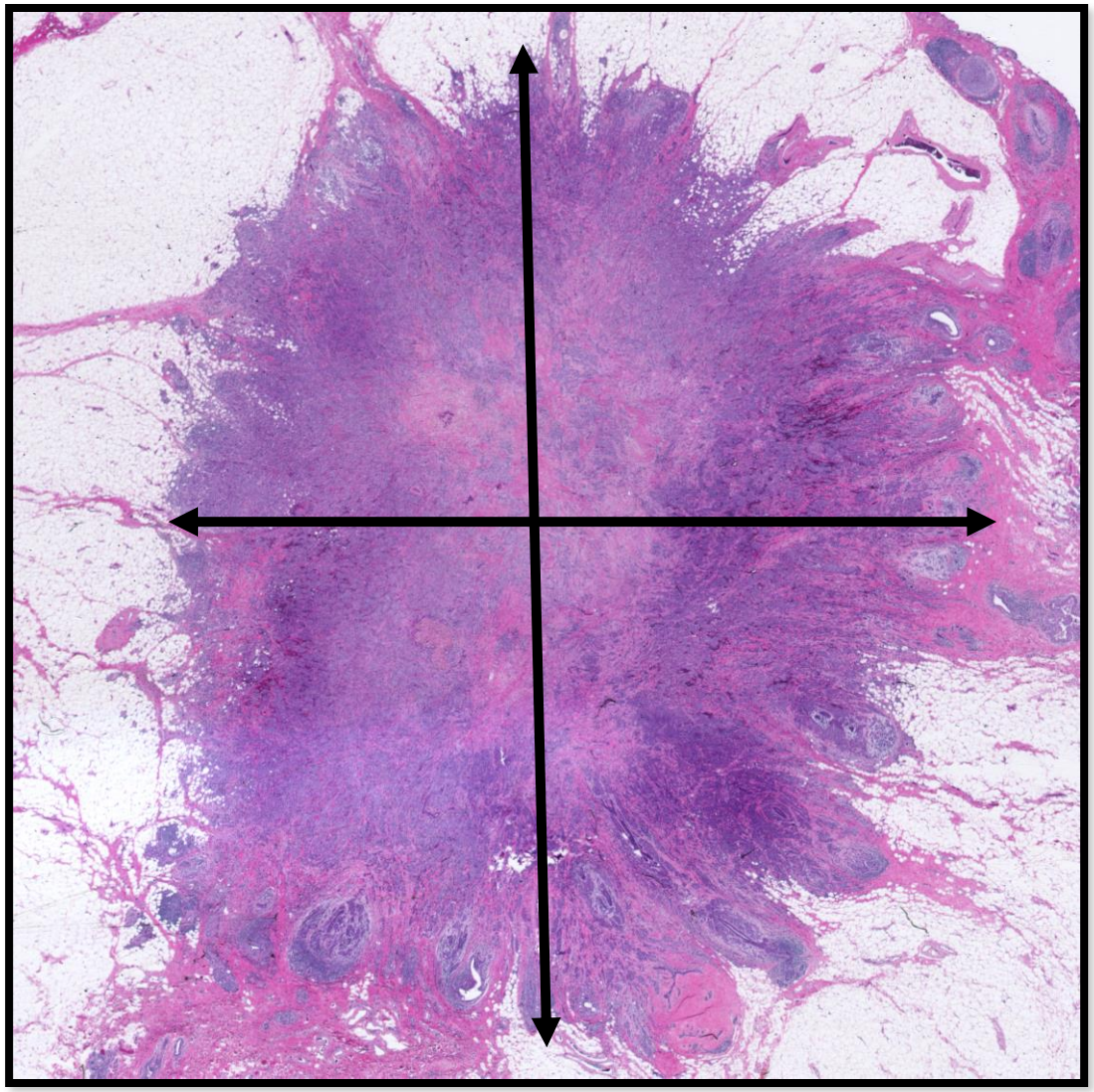


AJCC T classification



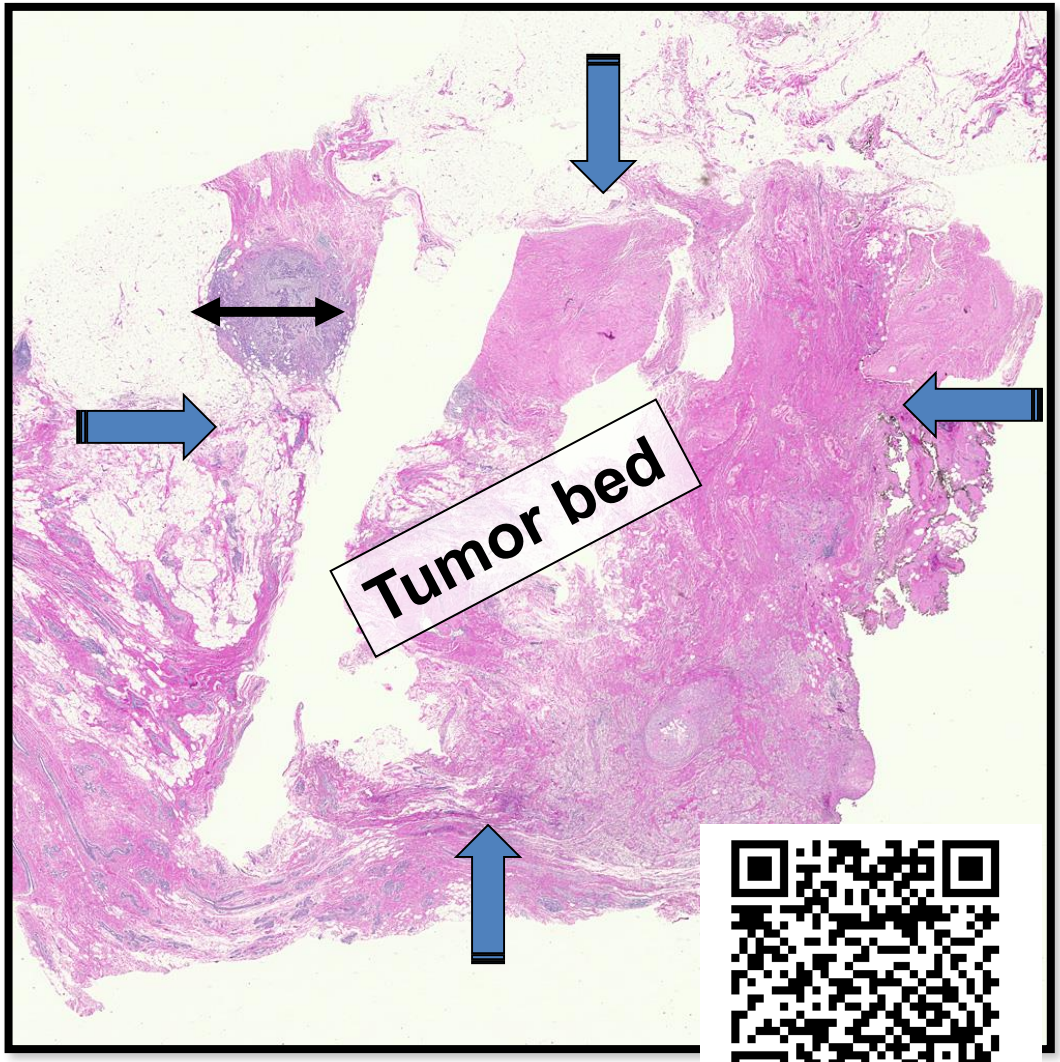
For AJCC T classification, the size of the largest contiguous focus of invasive carcinoma is used.

RCB classification



For RCB, the area of the cancer in 2 dimensions (in mm’s) and the % cellularity is used.

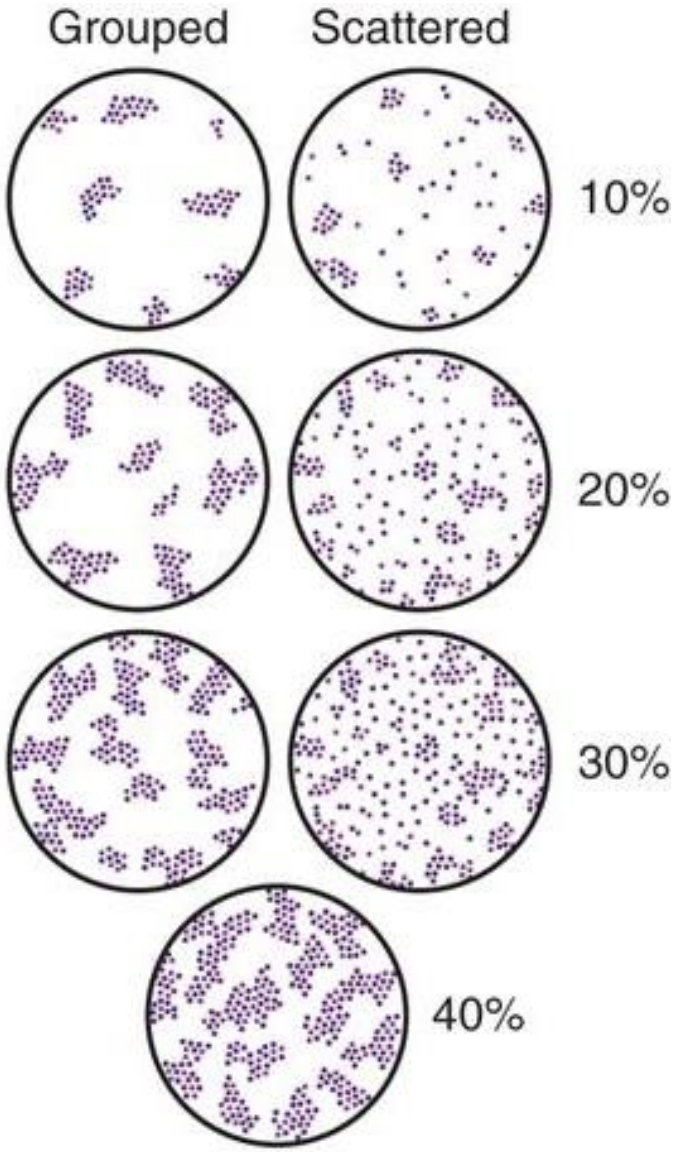
AJCC T classification: Moderate/marked response – multiple tumor foci



The size of the largest contiguous focus of invasive carcinoma is used for T classification.

“m” is used to indicate the presence of additional foci of invasion which may not be grossly evident.

(In the absence of neoadjuvant therapy, “m” is only used to indicate multiple invasive cancers identified clinically or macroscopically.)



Largest contiguous focus?

Determining the largest contiguous focus can be difficult when there are are scattered foci over the tumor bed.

Pathologists need to use their best judgment (or an educated guess!).

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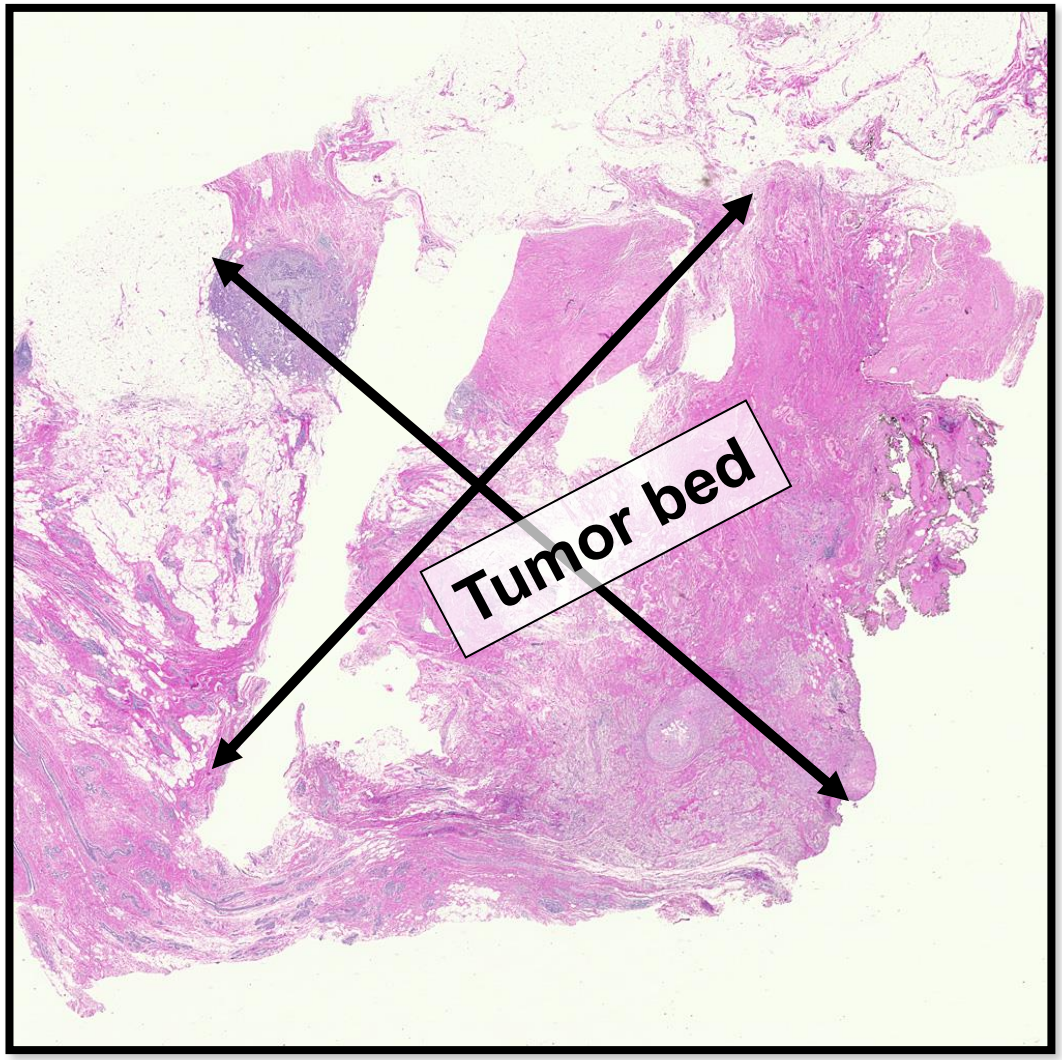
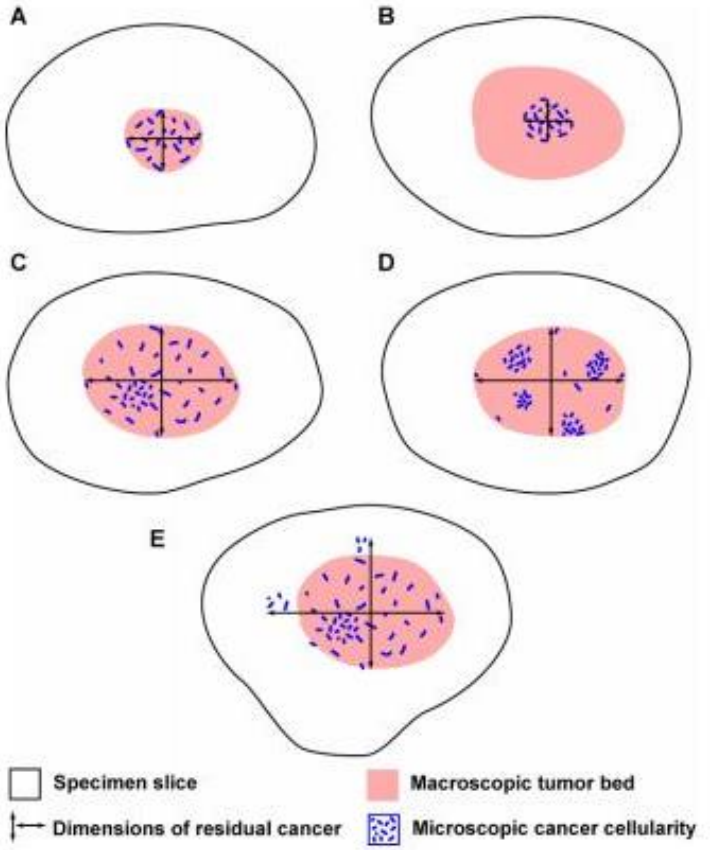
RCB classification: Moderate/marked response – multiple tumor foci



RCB evaluates residual cancer by using:

The size of the tumor bed in 2 dimensions.

Overall cellularity of invasive carcinoma.



The tumor bed size for RCB calculation is defined by the area involved by residual foci of invasive cancer.

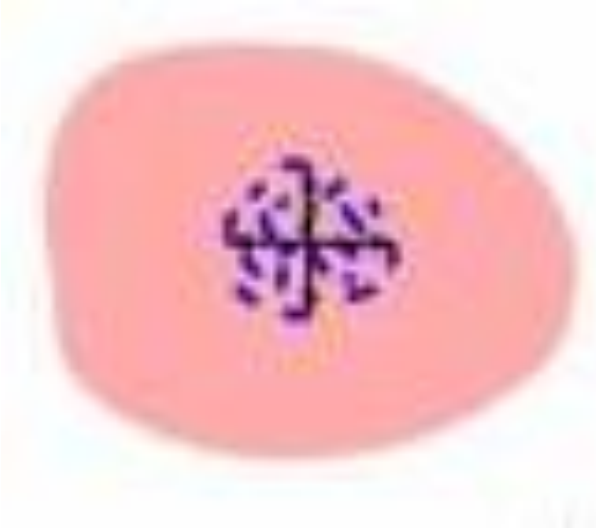
The tumor bed size can be difficult to determine on single slides.

It is unusual for the macroscopic tumor bed to be markedly different in size from the tumor bed as defined by the extent of residual cancer.

For practical purposes, the tumor bed size is typically close to the size of the pre-treatment cancer.

From https://www.mdanderson.org Guide for Measuring Cancer Cellularity

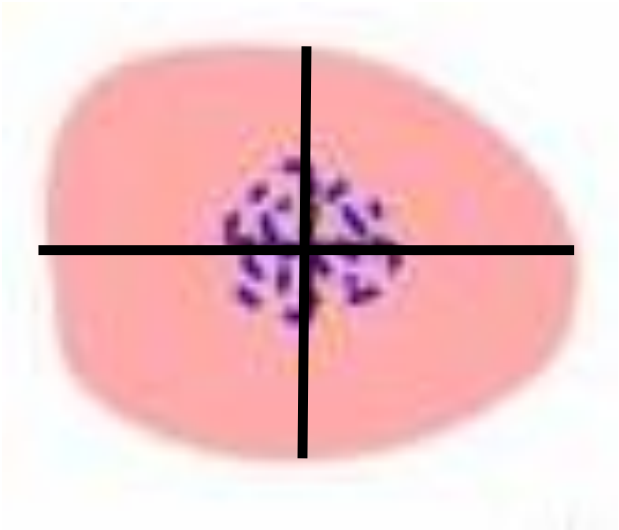
Tumor bed size/Cellularity



In this unusual case, the gross macroscopic tumor bed is much larger than the area of residual invasive carcinoma.

The ”correct” RCB calculation would use (for example) a 20 mm x 20 mm tumor bed and ~30% cellularity.

RCB=1.899



However, if the macroscopic tumor bed (or the pre-treatment tumor size) is used, this would result in a 60 mm x 45 mm tumor bed and ~10% cellularity.

RCB=1.853

Cellularity

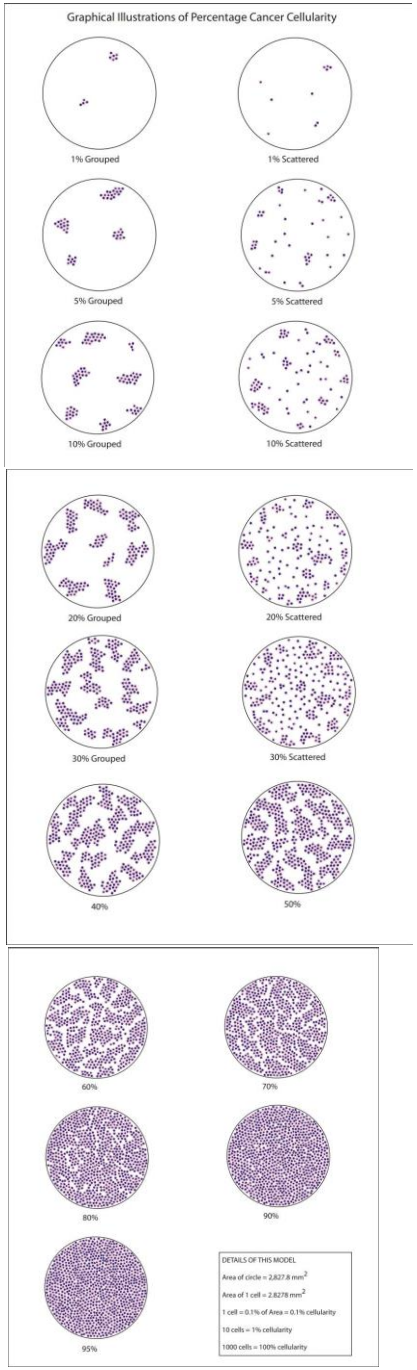
Diagrams are available to aid in the visual estimation of cellularity in BIG-NABCG publications and on the M.D. Anderson website.

Cellularity is estimated over the tumor bed (% area, not % of cells).

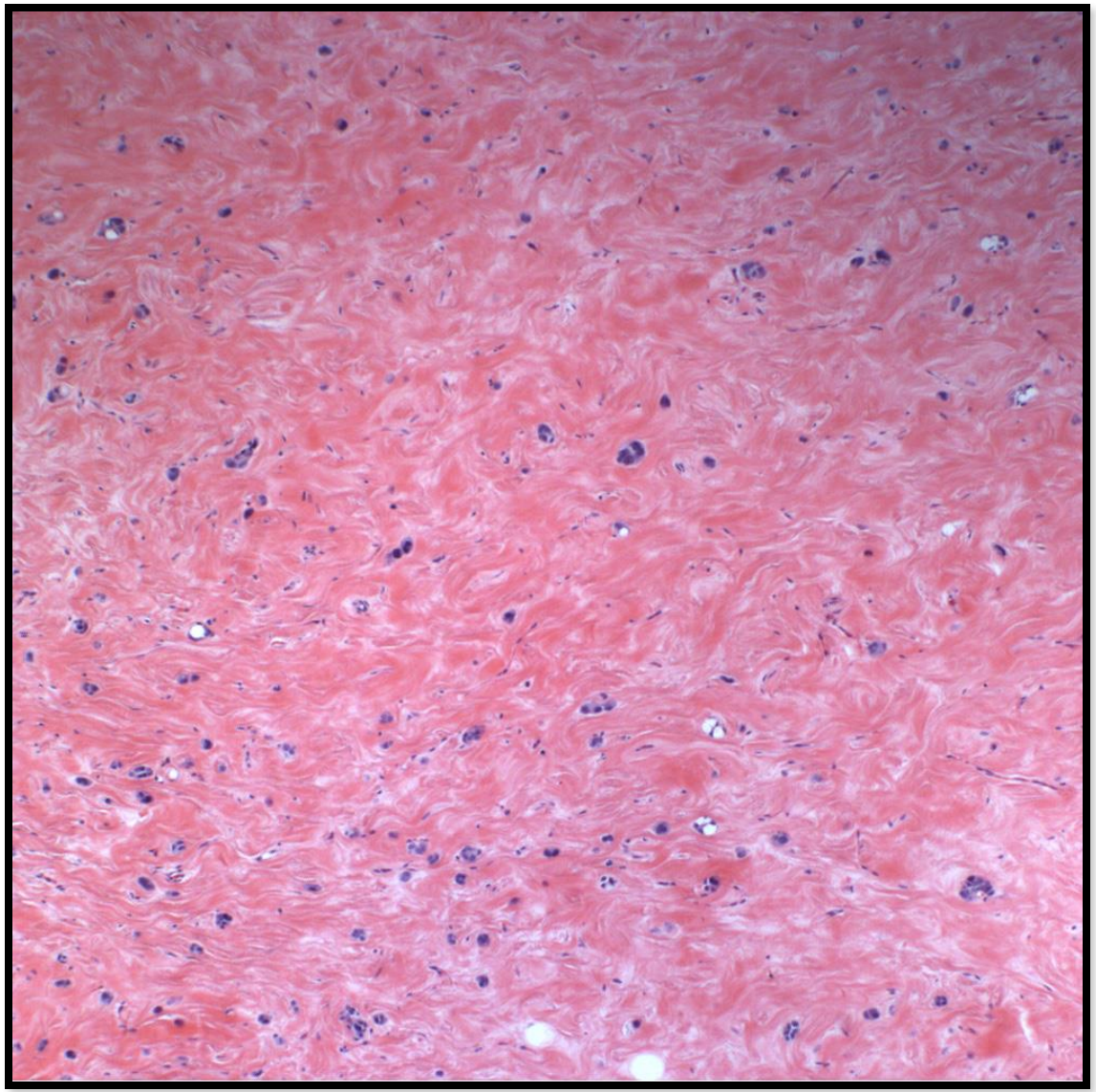
Cellularity due to lymphovascular invasion is included.

Cellularity due to DCIS is also included, but only the invasive cancer cellularity is used for the calculation of RCB. DCIS is subtracted from the total.

From https://www.mdanderson.org Guide for Measuring Cancer Cellularity

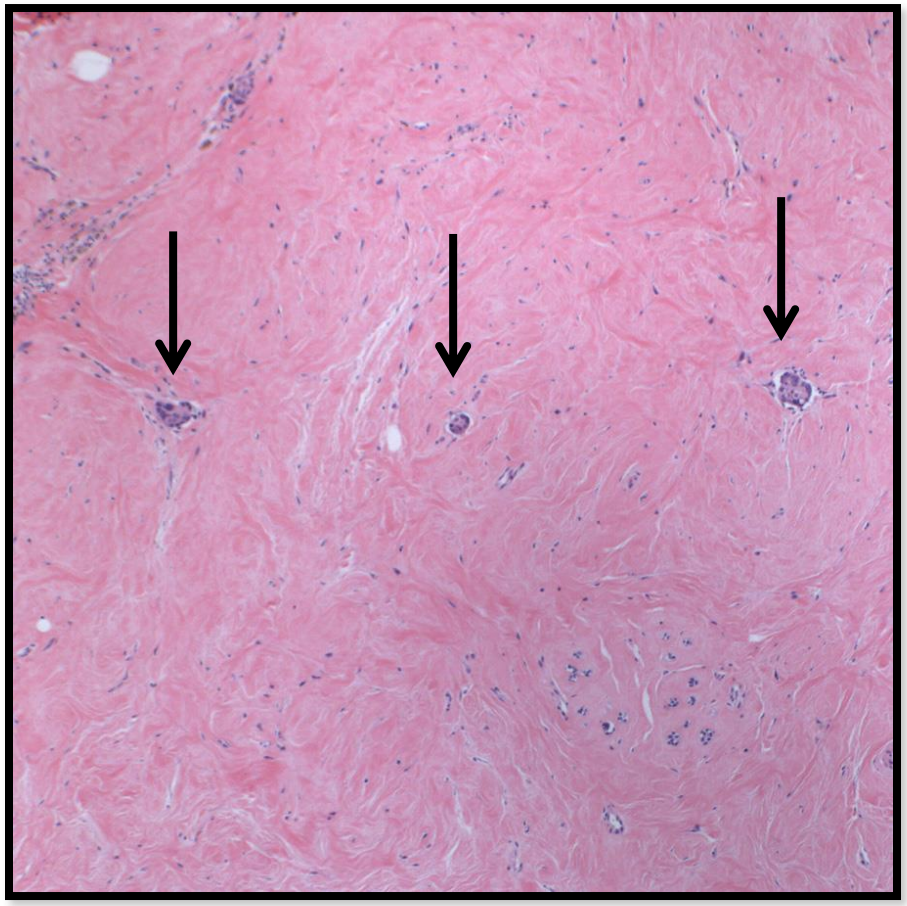


Residual Carcinoma – Sparse Cellularity



In cases with very sparse residual tumor, IHC for keratin may be necessary to ensure the cells are tumor cells.

Residual Carcinoma – Only Lymphovascular Invasion



In <5% of cases, the only residual carcinoma is in lymphatic spaces in the absence of stromal invasion.

LVI is included in estimating overall cellularity for RCB.

There is no AJCC category for this finding.

Classify as TX and describe residual LVI in a note.

Rabban, JT, et al, Pure and predominantly pure intralymphatic breast carcinoma after neoadjuvant chemotherapy, Am J Surg Pathol 33:256-263, 2009.

Cheng E, et al, Residual Pure Intralymphatic Breast Carcinoma Following Neoadjuvant Chemotherapy is Indicative of Poor Clinical Outcome, Even in Node-Negative Patients. Am J Surg Pathol 41:1275-1282, 2017.

Guilbert, MC, et al, Pure intralymphatic invasion in the absence of stromal invasion after neoadjuvant therapy: a rare pattern of residual breast carcinoma of uncertain significance. Am J Surg Pathol 42:679-686, 2018.

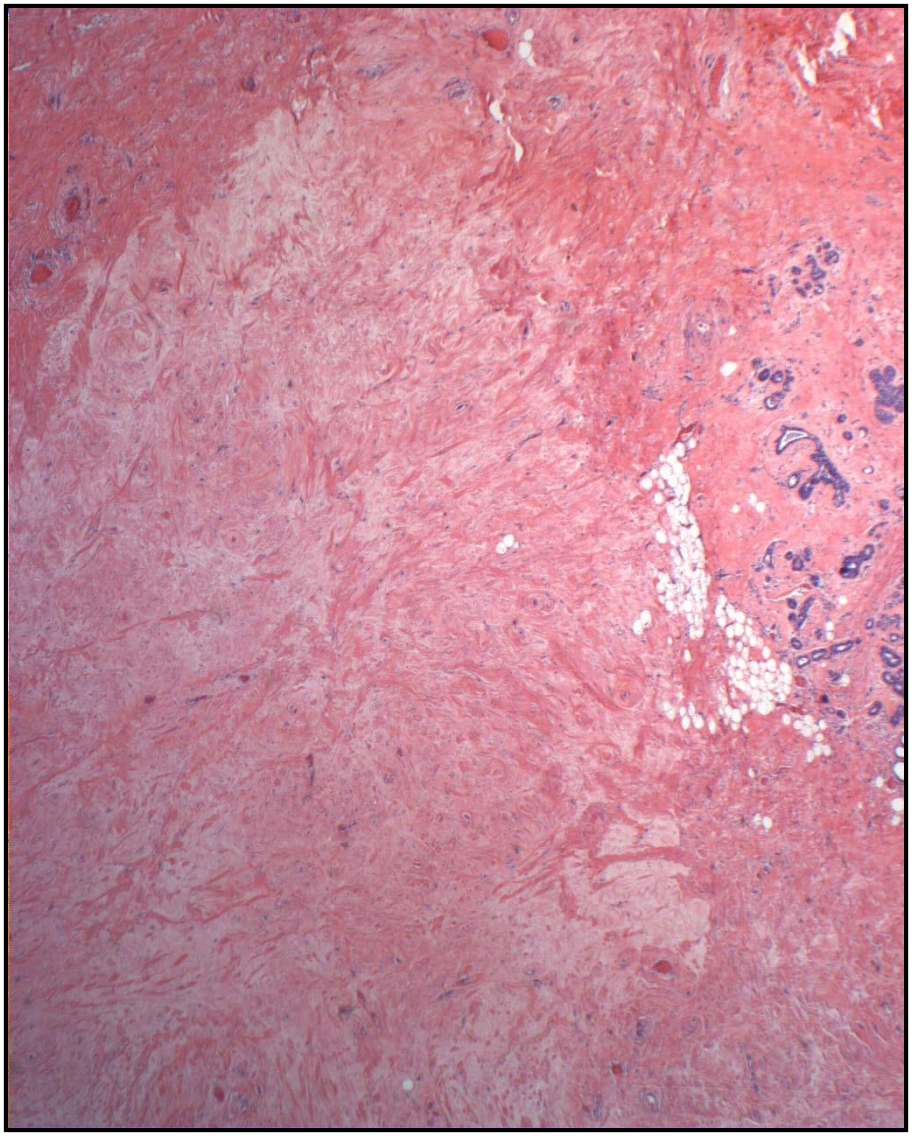
Pathologic Complete Response in Breast

Tumor bed microscopic appearance –

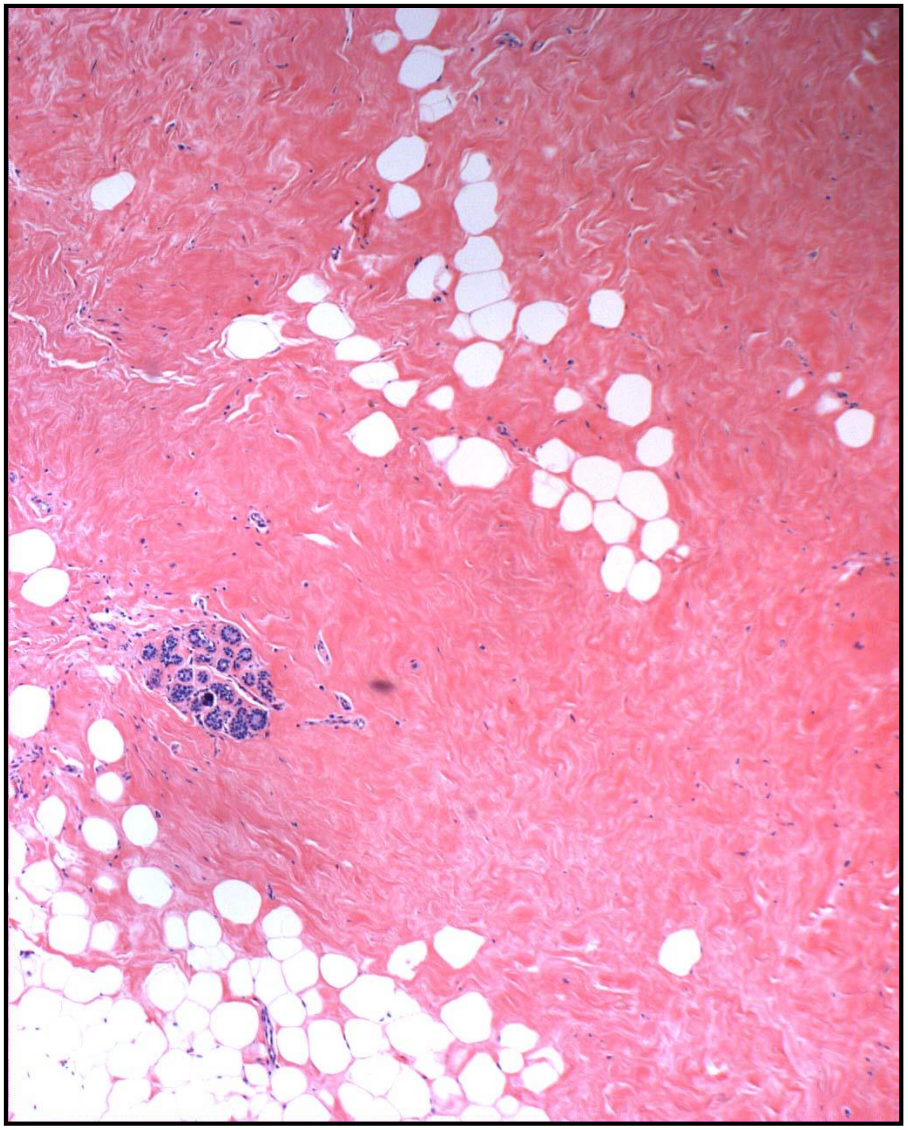
- Dense fibrous stroma - absence of normal epithelium
- Foamy histiocytes, lymphocytes, giant cells
- Calcifications
- Hemosiderin
- Residual DCIS may be present

The tumor bed does not look like normal breast tissue!

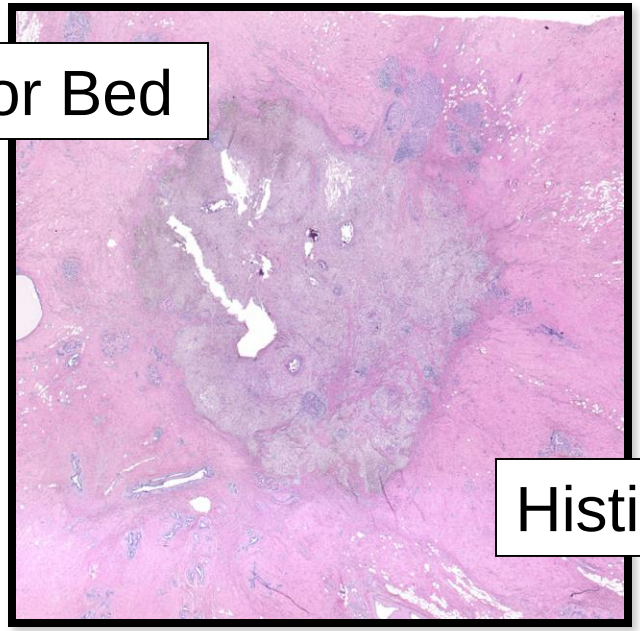
Tumor Bed

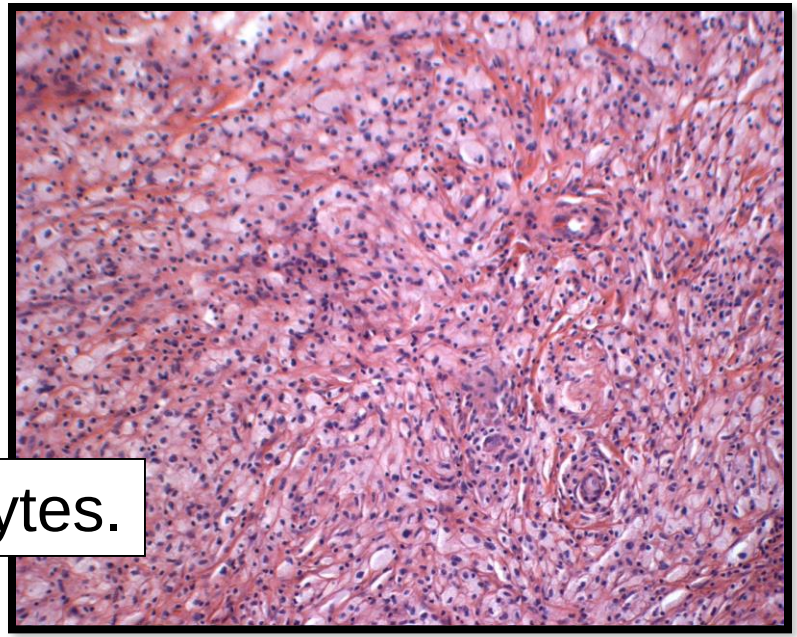


Normal breast stroma

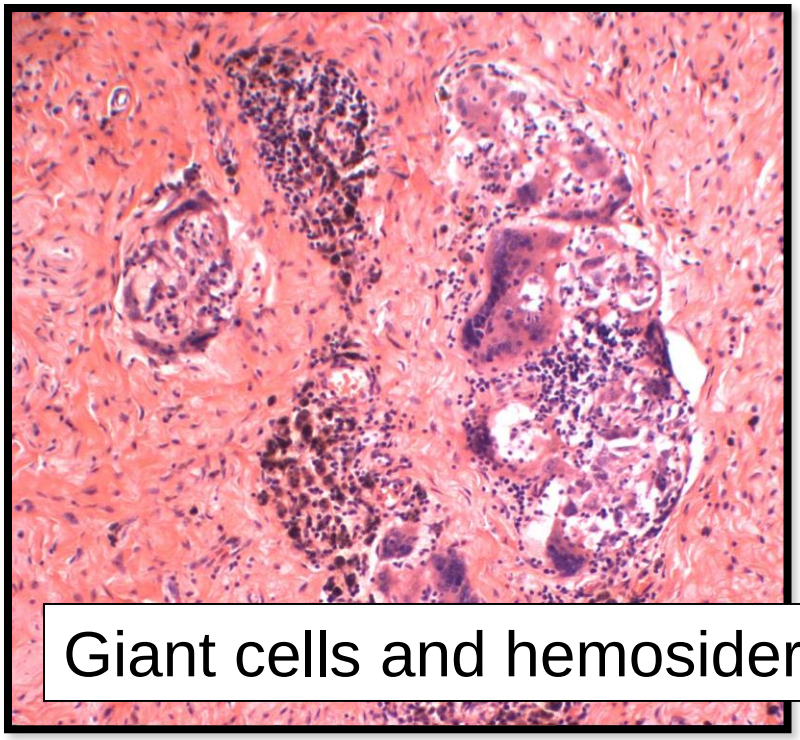


Tumor Bed

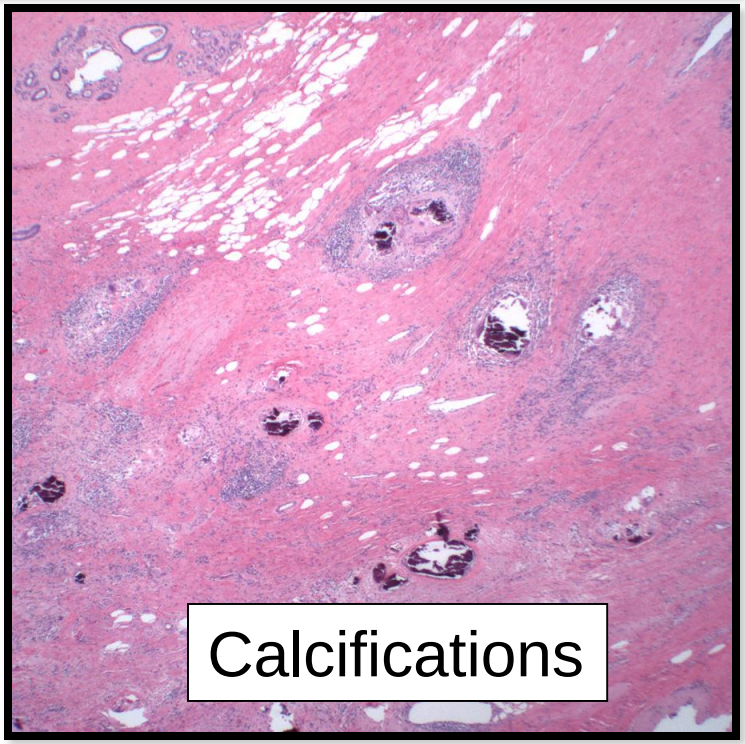




Histiocytes.

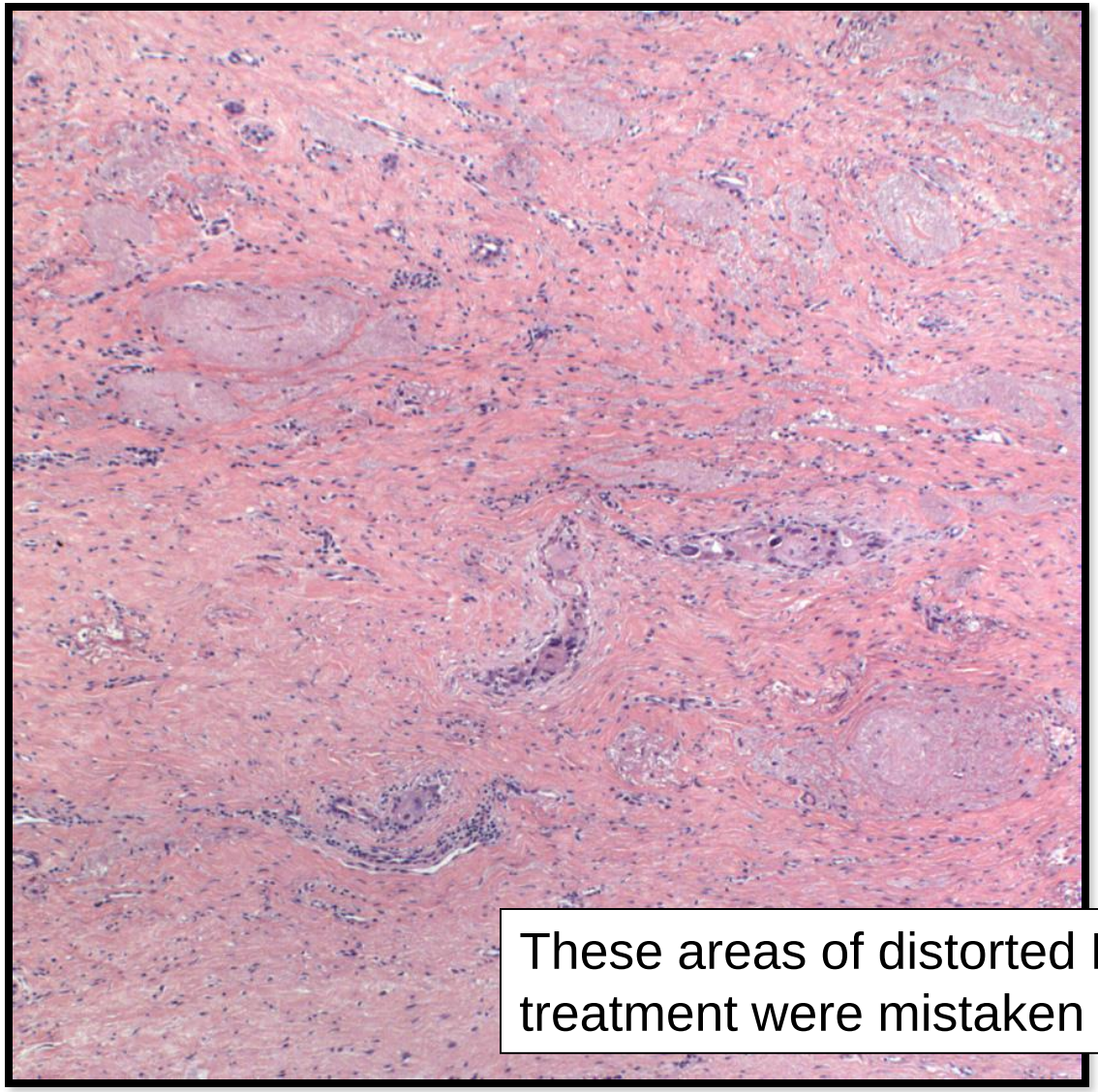


Giant cells and hemosiderin.



Calcifications

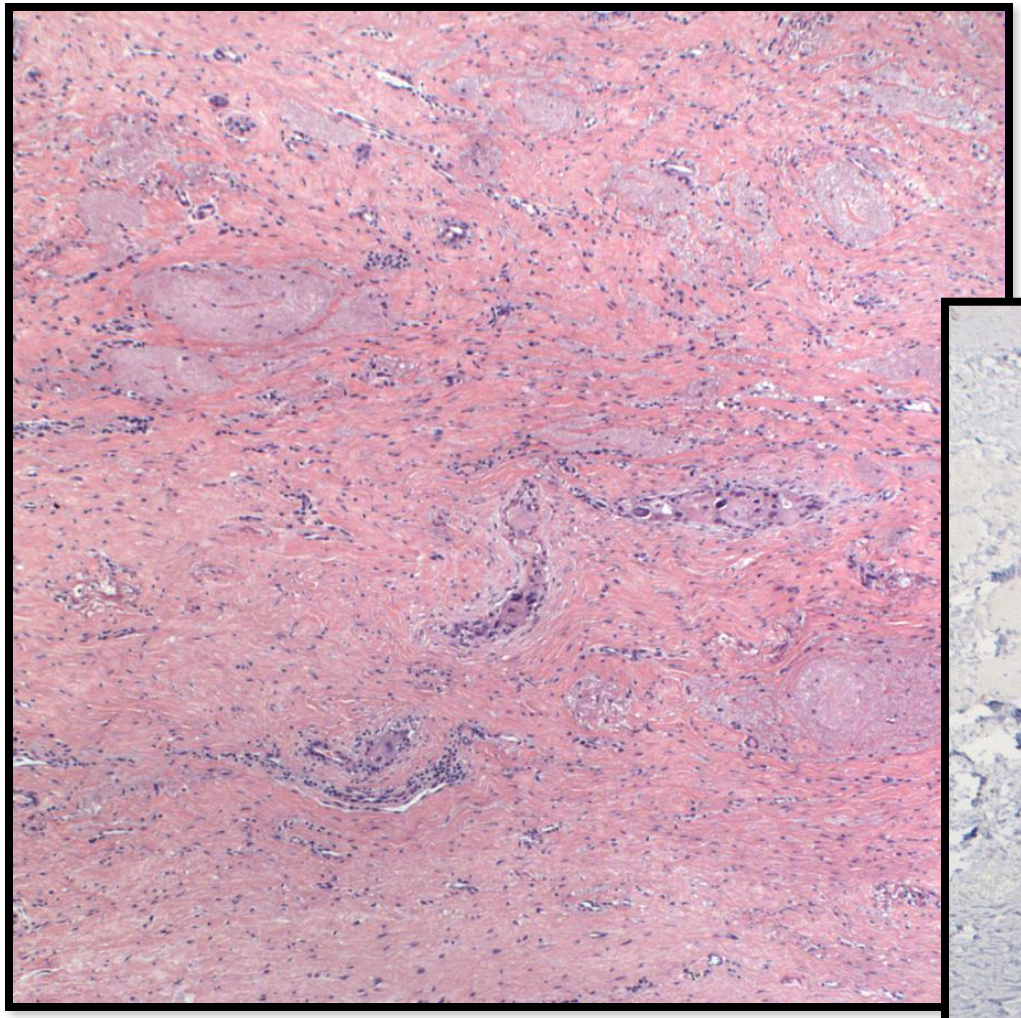
Residual Carcinoma – DCIS vs Invasive Carcinoma



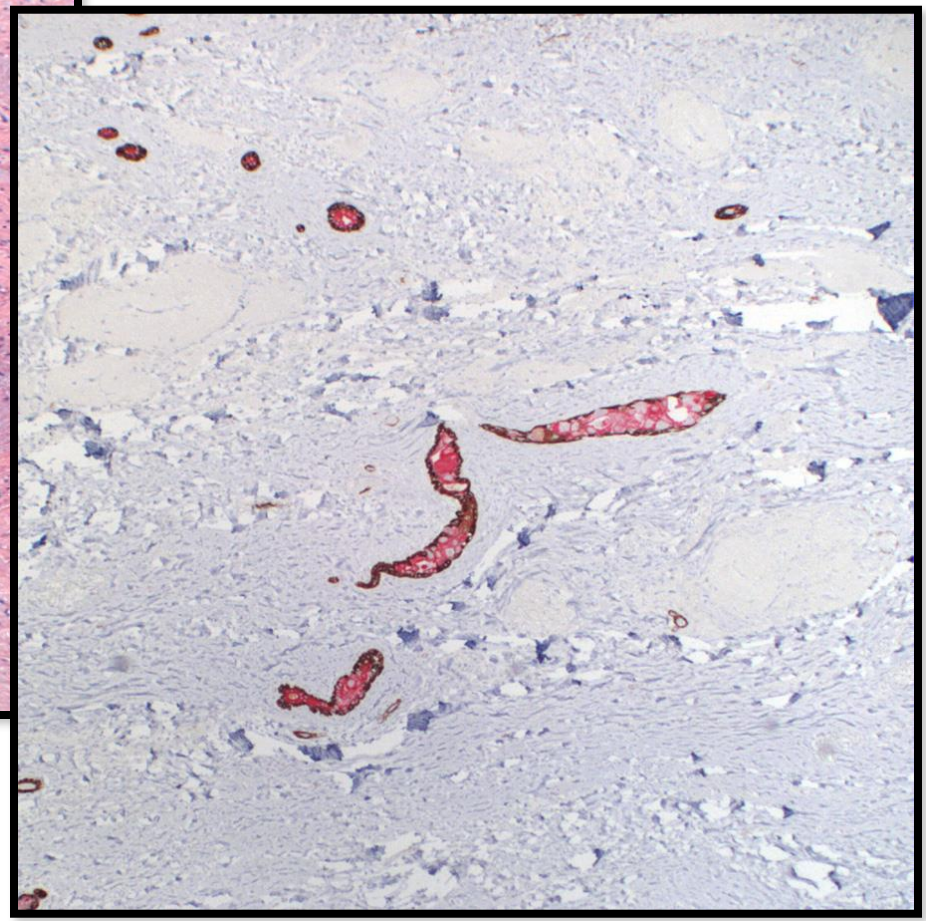
These areas of distorted DCIS in a tumor bed after treatment were mistaken for invasive carcinoma.

If only DCIS is present, the findings are classified as a pCR – DCIS does not diminish overall survival (but does reduce disease free survival due to local recurrence).

Residual Carcinoma – DCIS vs Invasive Carcinoma

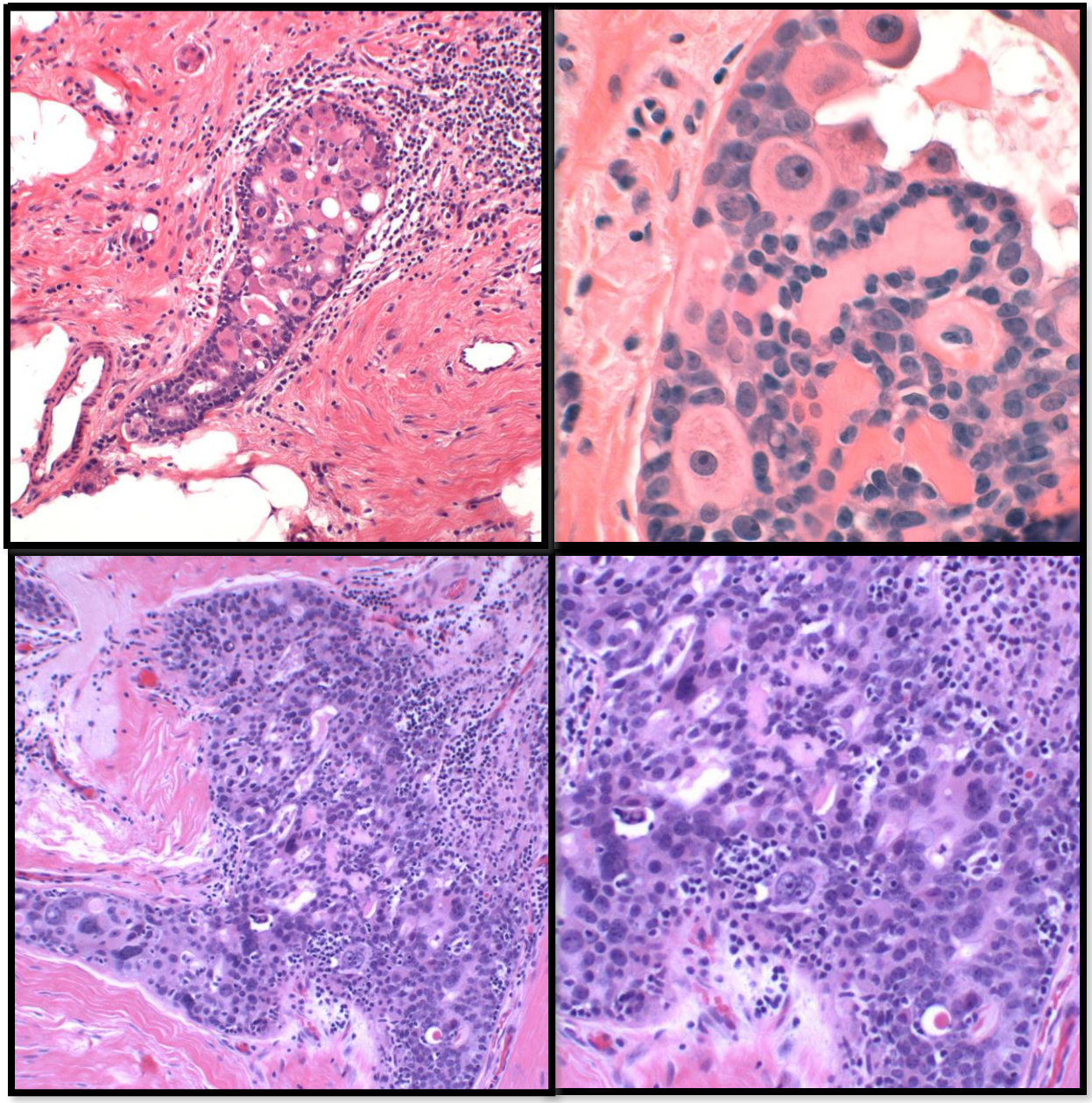


An immunoperoxidase study for myosin and cytokeratin confirmed that all the residual carcinoma was DCIS.



Therefore, this would be classified as a pCR.

Residual Carcinoma – DCIS



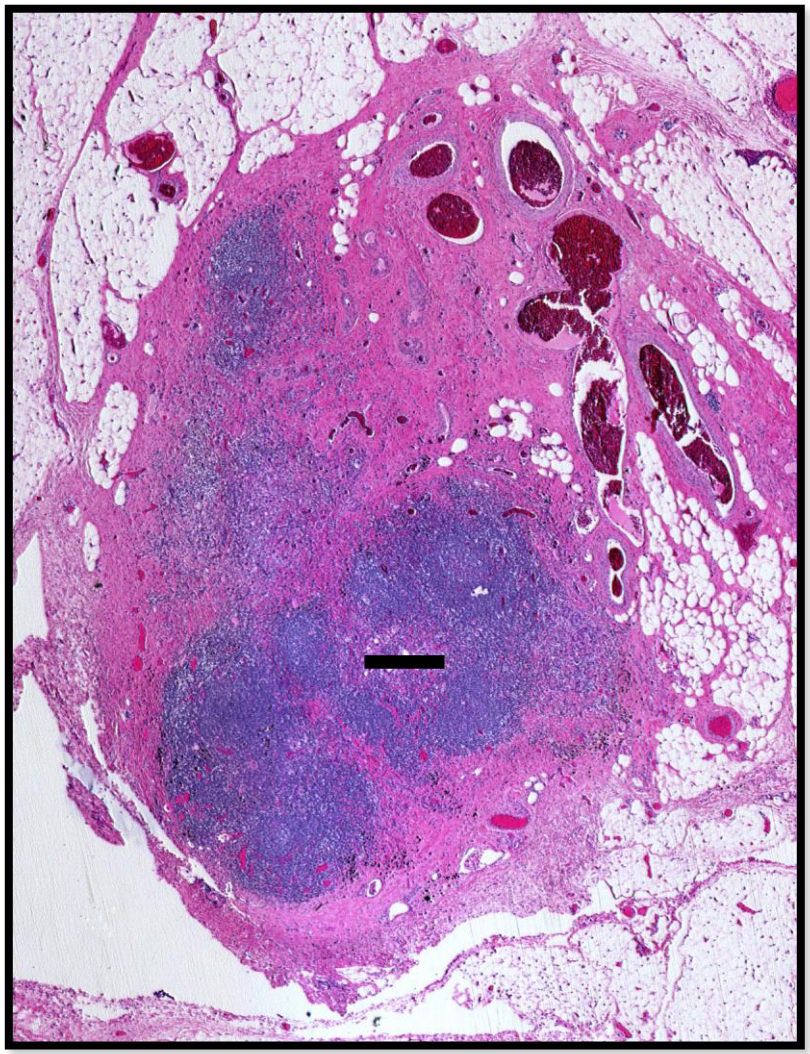
Residual DCIS may have unusual histologic appearances and involve sclerotic ducts – making it difficult to recognize.

Lymph Node Evaluation

Both AJCC and RCB use the size of the largest lymph node metastasis and the number of positive nodes for classification.

However, the method of measuring size is different for each system.

AJCC N classification: Lymph Nodes

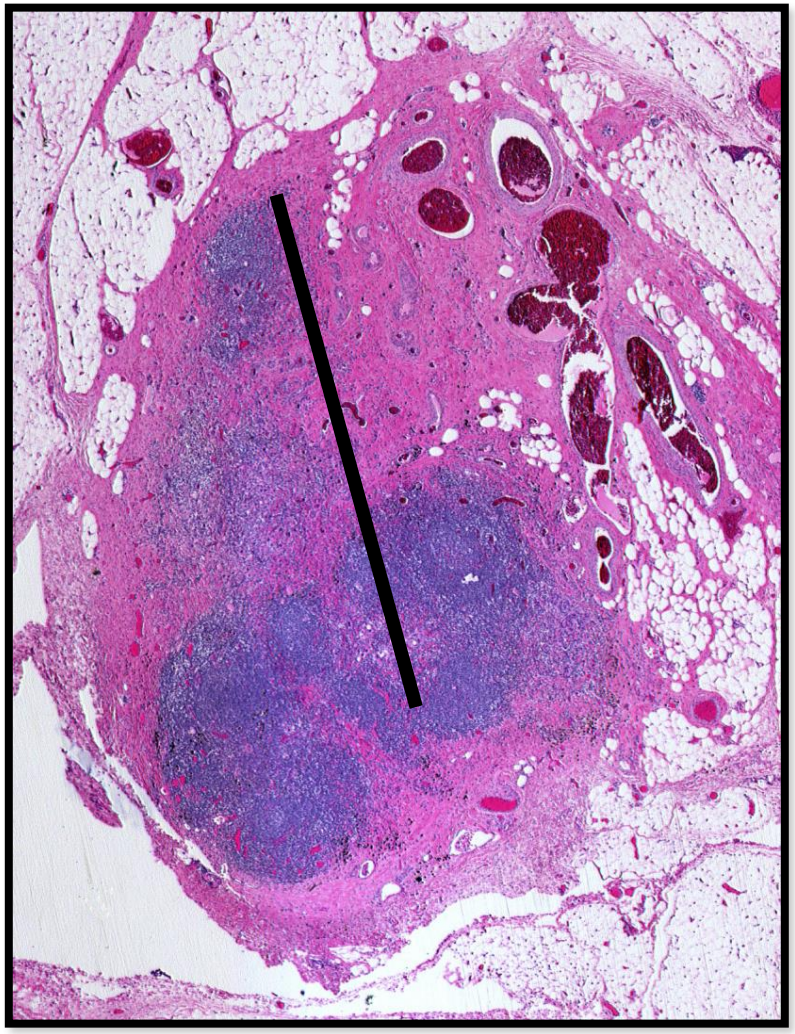


The largest contiguous focus of metastatic carcinoma is used to determine the size of the metastasis. Fibrosis (tumor bed) is not included.

In this case, there are multiple small clusters and single cells throughout a tumor bed. The largest contiguous focus is 0.1 cm.

The classification would be a micrometastasis.

RCB: Lymph Nodes



Fibrosis (tumor bed) is included in the size of the metastasis.

In this case, the size would include the entire area of fibrosis demonstrating the tumor cell nests farthest apart.

This would be classified as a macrometastasis.

BIG-NABCG Recommendations: Lymph Nodes

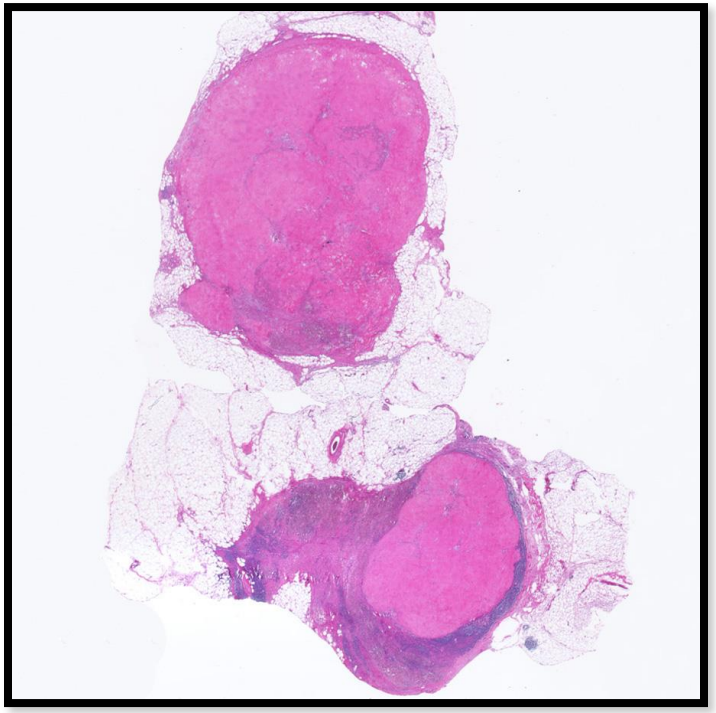
Number of nodes with metastases

Isolated tumor cells are reported as N0 (i+), but are not included as a pCR.

Size of largest metastasis

Presence of treatment effect in metastases

Number of nodes without metastatic disease but with fibrosis suggestive of prior involvement.



Provenzano, E, et al, Standardization of pathologic evaluation and reporting of postneoadjuvant specimens in clinical trials of breast cancer, Mod Pathol 28:1185-1201, 2015.

Bossuyt, V, et al, Recommendations for standardized pathological characterization of residual disease for neoadjuvant clinical trials of breast cancer by the BIG-NABCG collaboration, Ann Oncol 26:1280-1291, 2015.

Neoadjuvant Therapy – Reporting

All information important in the absence of pre-surgical treatment is important after treatment, including . . .

Grade, ER/PR/HER2

In addition –

Evidence of tumor bed when no residual carcinoma is present.

Evidence of involvement of nodes when no residual carcinoma is present (i.e. large scars).

AJCC stage ”y”

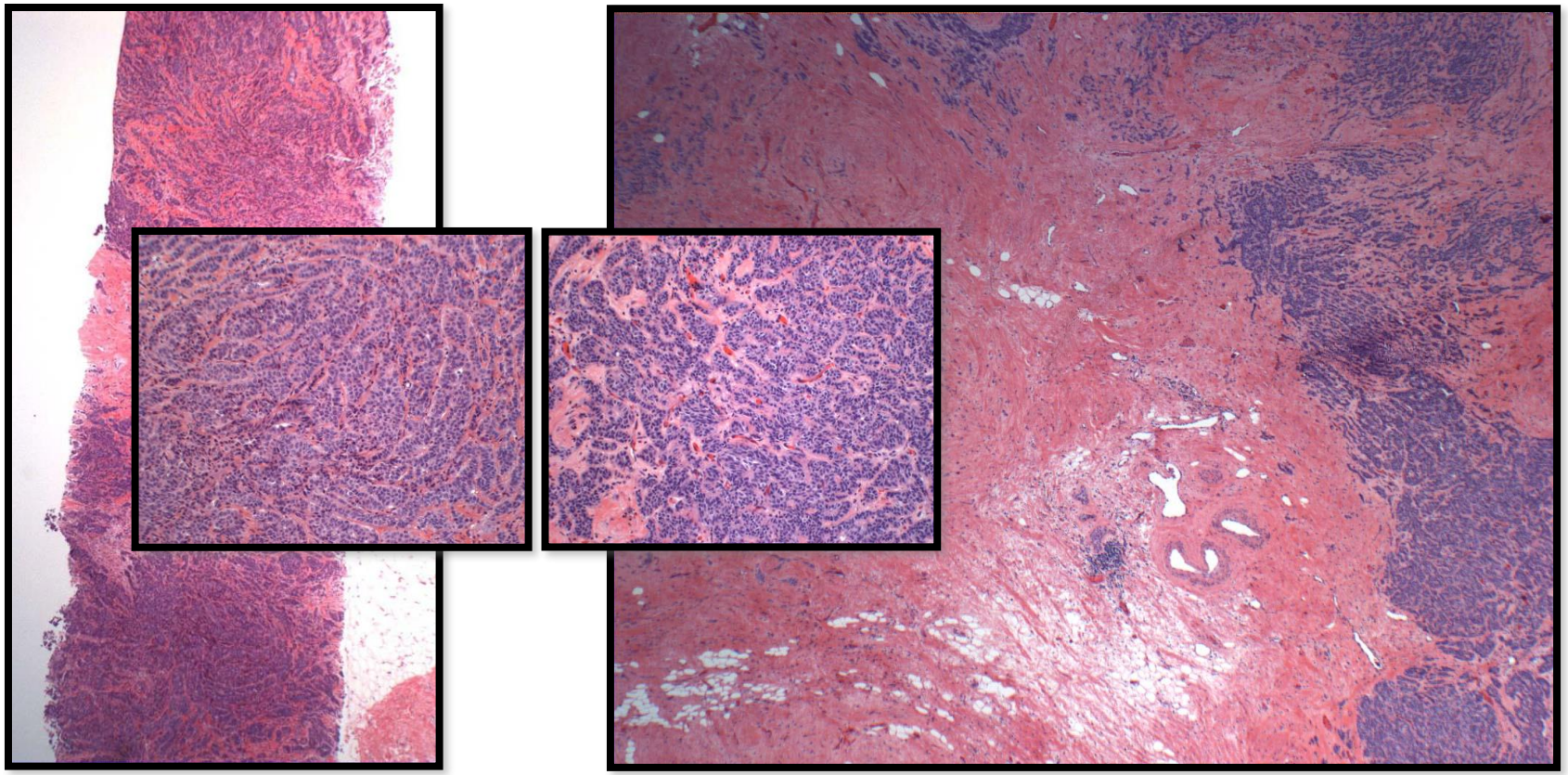
Residual Cancer Burden

Grade after Neoadjuvant Chemotherapy

In the majority of cases, cancers look similar to the pre-treatment cancer, but are less cellular.

Pre-Treatment Core needle biopsy

Post-Treatment Excision

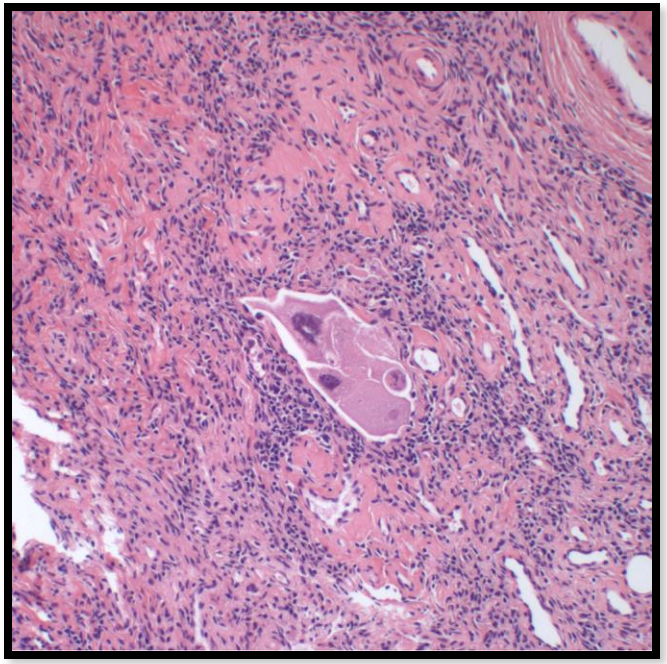


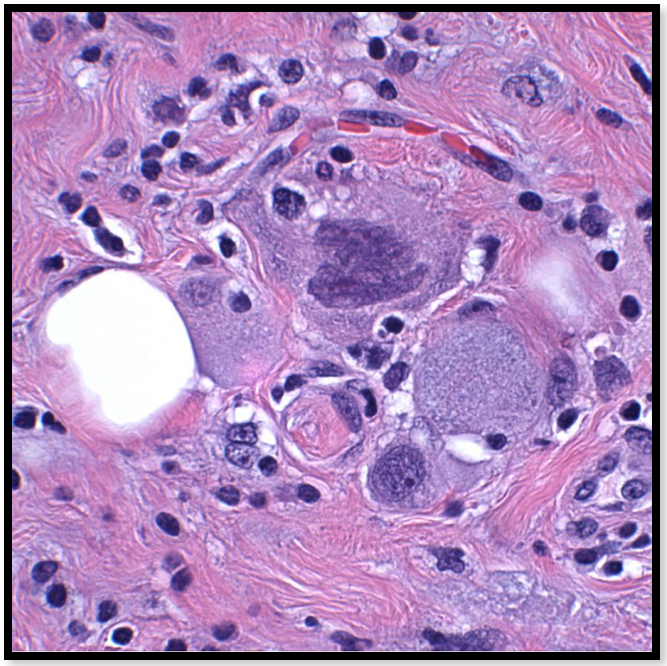
Grade Too High?

In unusual cases, tumor cells after treatment have markedly enlarged abnormal nuclei and abundant foamy cytoplasm.

This is usually in the setting of sparse residual cancer.

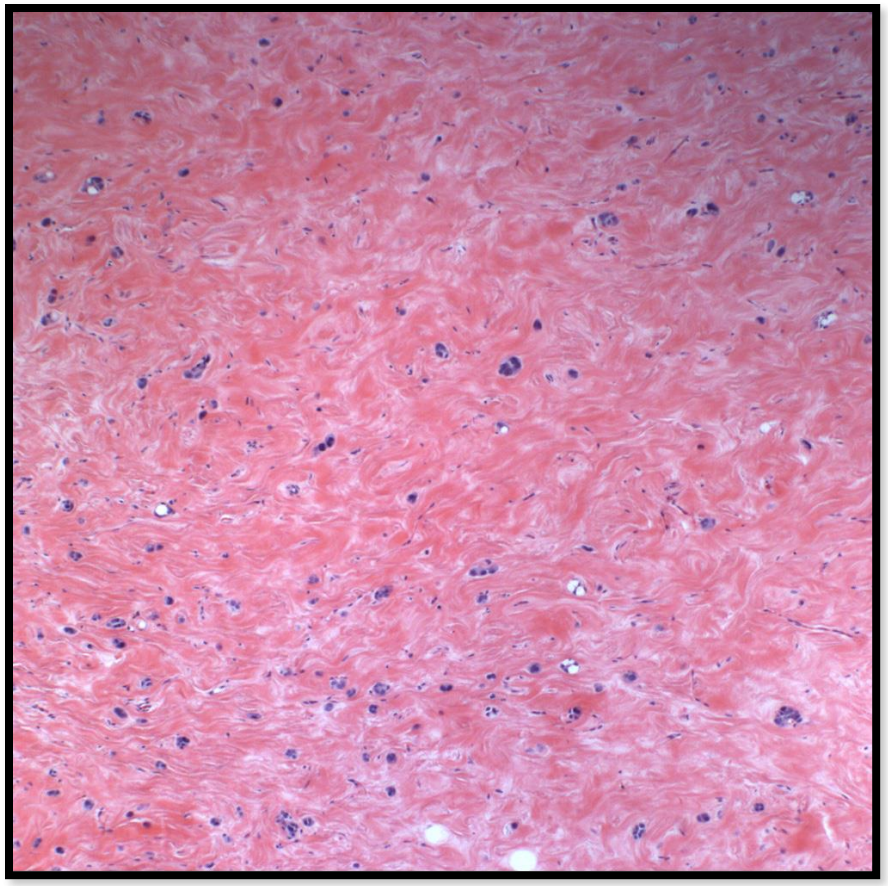
Mitoses are generally absent.





Grade Too Low?

Cancers after treatment are often less cellular, which will reduce the number of mitoses per HPF.



Grade – Pre and Post Treatment

Although pathologists may be concerned about reporting grade after treatment, two studies have shown that grade continues to have prognostic significance after treatment.

Pathologists should be alert to unusual changes in grade -

Grade 1 to Grade 3
Grade 3 to Grade 1

This could indicate the presence of multiple cancers. The residual cancer could express different tumor markers than the cancer undergoing biopsy prior to treatment.

Choi M, et al, Assessment of pathologic response and long-term outcome in locally advanced breast cancers after neoadjuvant chemotherapy: comparison of pathologic classification systems, Breast Cancer Res Treatment 160:475-489, 2016.

Sheri A, et al, Residual proliferative cancer burden to predict long-term outcome following neoadjuvant chemotherapy. Annals Oncol 26:75-80, 2015.

Evaluation of ER/PR/HER2 after Treatment

ER, PR, or HER2 results are different for the post-treatment carcinoma in 15-25% of patients.

Loss of expression:

Unclear if this finding should alter treatment.

Poor prognostic factor in some studies.

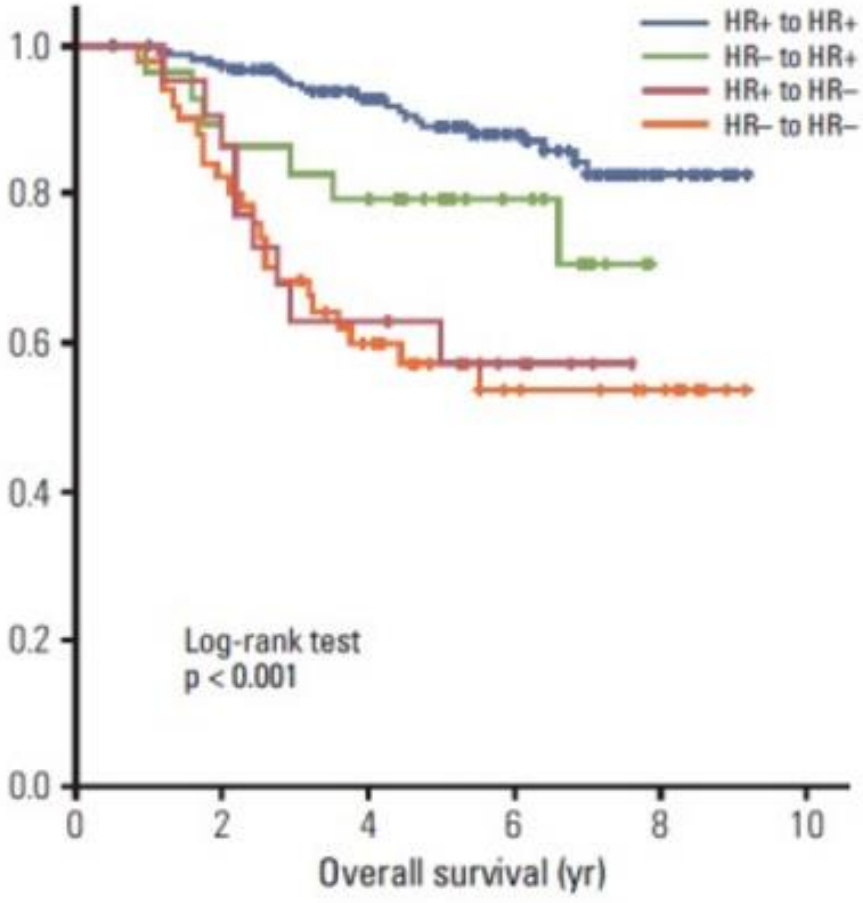
Gain of expression:

Favorable prognostic factor for ER (~10% of cases).

van de Ven, S, Discordances in ER, PR, and HER2 receptors after neoadjuvant chemotherapy in breast cancer, Cancer Treat Rev 37:422-430, 2011.

Dawood S, Gonzalez-Angulo AM, Biomarker discordance pre and post neoadjuvant chemotherapy in breast cancer, Cancer Biomarkers 12:241-250, 2012/2013.

Evaluation of ER/PR after Treatment



Patients with carcinomas that remained ER positive, or that were ER positive after treatment, had improved survival compared to carcinomas that were ER negative after treatment.

Repeating ER on residual cancer in cases in which the pre-treatment cancer was ER negative has the most clinical relevance.

Lim, SK et al, Impact of molecular subtype conversion of breast cancers after neoadjuvant chemotherapy on clinical outcome, Cancer Res Treat 48:133-141, 2016.

ER/PR/HER2 Working Group Recommendations

Routine reassessment of markers that were positive prior to treatment is not recommended – unless retesting is part of a clinical trial.

Reassessment should be considered if –

Results were negative prior to treatment

There was no response to treatment

There are multiple residual carcinomas with heterogeneous morphology

At BWH, tumor markers are repeated on residual carcinoma after neoadjuvant therapy.

Provenzano, E, et al, Standardization of pathologic evaluation and reporting of postneoadjuvant specimens in clinical trials of breast cancer, Mod Pathol 28:1185-1201, 2015.

Bossuyt, V, et al, Recommendations for standardized pathological characterization of residual disease for neoadjuvant clinical trials of breast cancer by the BIG-NABCG collaboration, Ann Oncol 26:1280-1291, 2015.

AJCC “y” Classification – 8th Edition

The AJCC “y” stage provides prognostic information in the neoadjuvant setting:

Pre-treatment stage

Post-treatment stage

Change in stage

The pathologist provides “T” and ”N”. If multiple foci of invasive cancer are present in the tumor bed, the “m” modifier is used.

Patients who have undergone neoadjuvant therapy are assigned a ”Clinical Prognostic Stage” as “Pathological Prognostic Stage” is only used for patients who have undergone definitive surgery in the absence of prior treatment.

Residual Cancer Burden (RCB)

RCB-0	No carcinoma in breast or lymph nodes (pCR)
RCB-I	Partial response (if RCB-III pre-treatment)
RCB-II	Partial response (if RCB-III pre-treatment)
RCB-III	No/little response

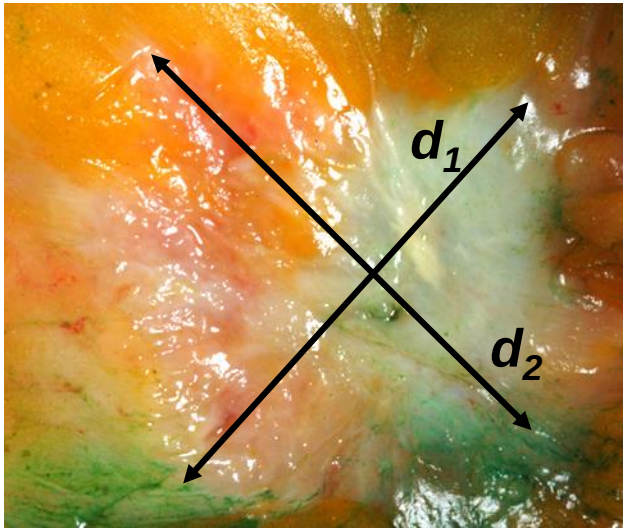
Uses cellularity of post-treatment residual invasive carcinoma over the tumor bed, the presence of lymph node metastasis, and the size of the largest lymph node metastasis.

RCB is a continuous variable with numerical cutpoints to define the four groups.

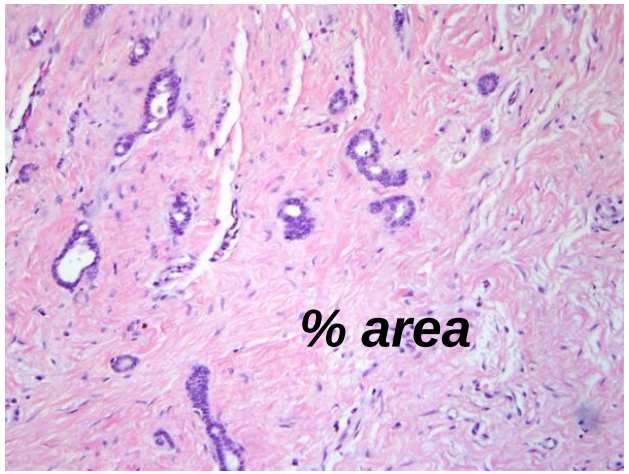
Symmans, WF, et al, Measurement of residual breast cancer burden to predict survival after neoadjuvant therapy, J Clin Oncol 25:4414-4422, 2007.

Residual Cancer Burden (RCB)

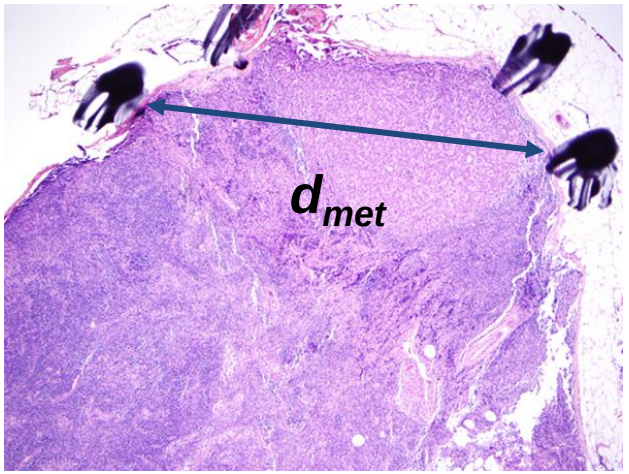
Primary Tumor Bed



Cellularity Invasive Cancer



LN = Number of Positive Nodes



Primary tumor variables

Lymph node (*LN*) metastases

$$RCB = 1.4\,(\text{cellularity} \times \text{diameters})^{0.17} + \left(\text{diameter of LN met} \times \frac{1-(1-\alpha)^{LN}}{\alpha}\right)^{0.17}$$

Adjustment and weighting factors

Adjustment and weighting factors

www.mdanderson.org/breastcancer_RCB

Breast Center

Residual Cancer Burden Calculator

(1) Primary Tumor Bed

Primary Tumor Bed Area:	10 (mm) X 8	(mm)
Overall Cancer Cellularity (as percentage of area):	10	(%)
Percentage of Cancer That Is *in situ* Disease:	0	(%)

(2) Lymph Nodes

Number of Positive Lymph Nodes:	0	
Diameter of Largest Metastasis:	0	(mm)

Reset Calculate

Residual Cancer Burden:	1.374
Residual Cancer Burden Class:	RCB-II

AJCC and Residual Cancer Burden (RCB)

Feature	AJCC "y"	Residual Cancer Burden (RCB)
Primary tumor	Size of largest contiguous focus of invasive cancer	Tumor bed in 2 dimensions and % cellularity of invasive cancer
Lymph nodes	Size of largest contiguous focus (ITC, micromet, macromet) – not including treatment related fibrosis Number (0, 1-3, 4-9, >10)	Largest size – including treatment related fibrosis Number (continuous variable)
Categories	Stage 0, I (A, B), II (A, B), III (A, B, C)	Continuous variable RCB 0, I, II, III
Significance for Biologic Types	OS & DDFS – ER negative	OS & DDFS – all types (most significant outcomes compared to 6 other systems tested)
Other settings	Clinical (pre-treatment) Change in stage (pre and post)	Only post-treatment

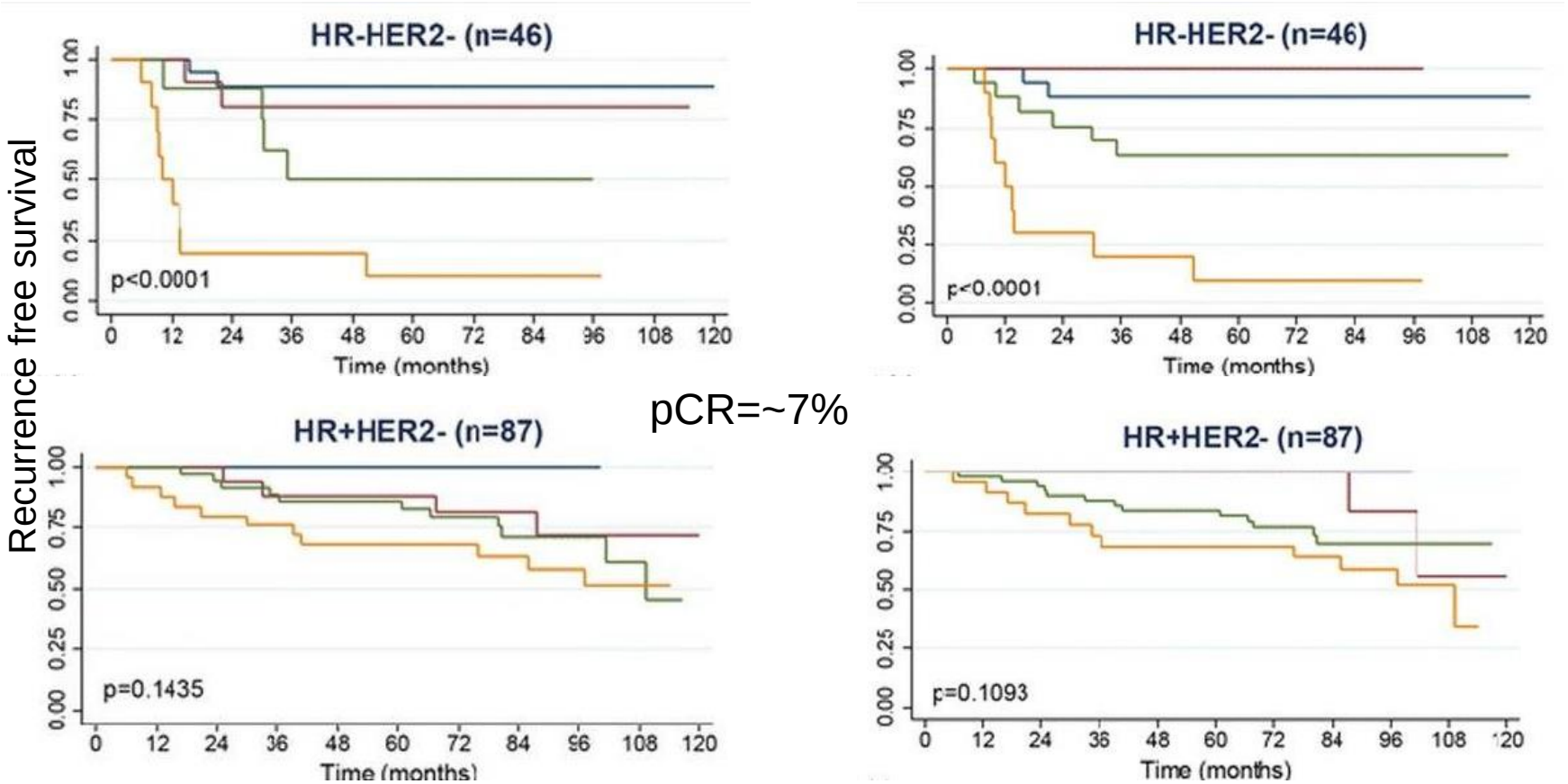
OS=overall survival; DDFS=distant disease free survival. Biologic types: ER+HER2- (luminal A); ER+HER2+ (luminal B); ER-HER2+(HER2); ER-HER2- (TNBC)

Choi M, et al, Assessment of pathologic response and long-term outcome in locally advanced breast cancers after neoadjuvant chemotherapy: comparison of pathologic classification systems, Breast Cancer Res Treatment 160:475-489, 2016.

AJCC "y"

pCR=~30%

RCB



Both provide prognostic information. The patterns of survival are different for each biologic type of breast cancer.

Campbell J I, et al, Comparison of RCB, AJCC staging and pCR in breast cancer after neoadjuvant chemotherapy: results from the I-SPY 1 TRIAL. Breast Cancer Res Treat 165:181-191, 2017.

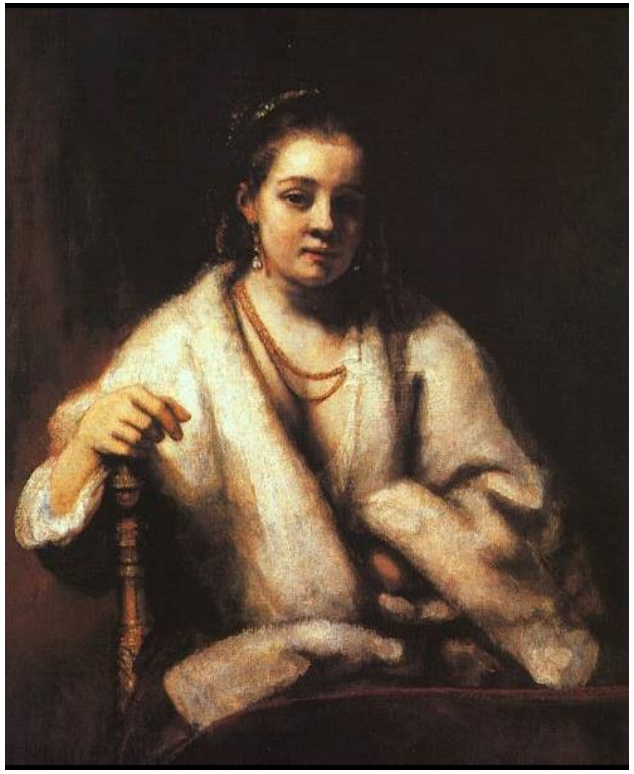
Neoadjuvant Therapy – Take Home Points

Pathologic evaluation of response to therapy is the gold standard (over clinical or radiologic response) and provides important information for individual patients, clinical trials, and research.

Attention to tumor location, lymph node status, and specimen evaluation optimizes the information obtained during a neoadjuvant trial.

New treatments create the possibility of pathologists seeing novel responses to treatment.

Pathologists are essential members of the neoadjuvant trial team – best practices to examine specimens and report results should be part of the design of all neoadjuvant trials.



Portrait of Hendrickje Stoffels
Rembrandt, 1654-6
National Gallery, London

Hendrickje Stoffels – Follow-up

Rembrandt and Hendrickje's daughter Cornelia was born in 1654 – the same year that "Bathsheba at Her Bath" was painted.

Hendrickje lived for 9 more years. She died at the age of 37 in 1663 – during an outbreak of the plague in Amsterdam.

Based on this history, she likely did not have breast cancer.

It has been suggested that the change in her breast may have been due to either a lactational, or non-lactational, abscess.

Hayakawa S, et al. Rembrandt's Bathsheba, possible lactation mastitis following unsuccessful pregnancy. Med Hypotheses. 66:1240-1242, 2006.


Thank you for your attention!
Newport, Rhode Island