1

Objectives

- Appreciate the role of the pathologist in the evaluation of response to neoadjuvant chemotherapy
- Define the pathologic appearance of the residual tumor after neoadjuvant chemotherapy
- Identify possible pathologic predictors of residual disease after neoadjuvant chemotherapy
- Evaluate the pathologic parameters required in the post-neoadjuvant chemotherapy pathology report, and
- Discuss possible de-escalation of surgery after neoadjuvant chemotherapy.

2

Neoadjuvant Chemotherapy: Goals

- Downstaging
  - Initially: locally advanced cancers in order to convert inoperable tumors to operable
  - In earlier stage disease to avoid mastectomy for pts with large tumors and allow breast conserving therapy instead
  - Avoid axillary dissection and convert pts to sentinel lymph node biopsy instead
- In vivo real-time assessment of tumor response to treatment
- Evaluation of extend of response is a prognostic factor
  - FDA uses response to NAC as a short term endpoint in clinical trials to expedite drug approvals

3

pCR per Breast Tumor Molecular Subtype

- Higher for TNBC and HER2+ tumors
- Lower for ER+ tumors
- Lower for ILC

	HR- / HER-	HR- / HER2+	HR+ / HER2+	HR+ / HER2-
pCR rates	30-40%	35-50%	15-30%	<10%
LN conversion	50%	45-65%	35%	10-20%

Ref: Breast specimen handling and reporting in the post neoadjuvant setting: challenges and advantages; M. Mrkonjic et al, J Clin Pathol, 2019

4

Role of the Pathologist in the Evaluation of Response to NAC

- Identify pts who had a pCR
- Accurately assess pCR in the breast and the LNs by careful gross and microscopic evaluation
- Evaluate residual tumor and biologic characteristics if pPR
- NEED clinical history: s/p NAC

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Possible response of a tumor to NAC

- Complete pathologic response: pCR
- Partial pathologic response: pPR
- No response (stable disease)
- Progression

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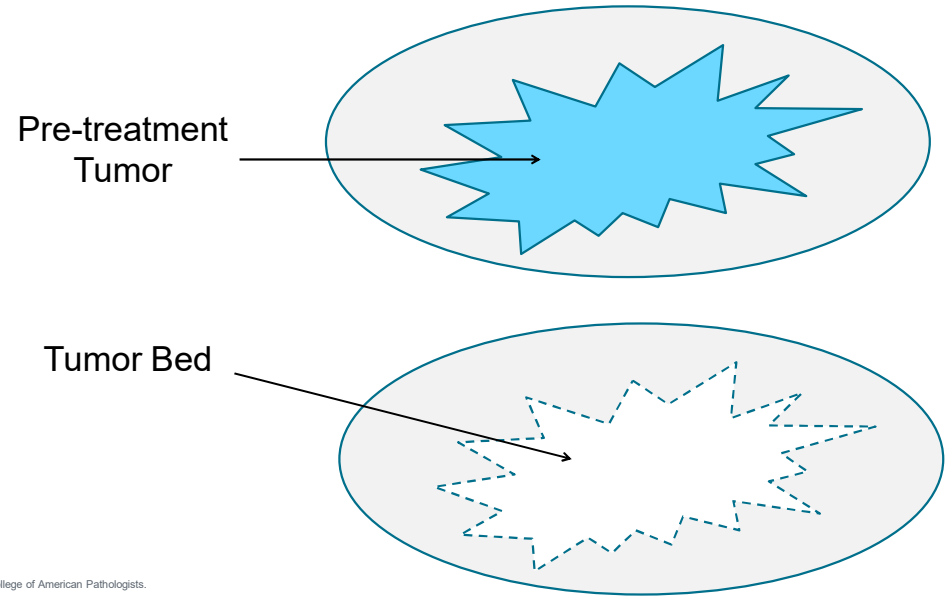
Effect of NAC: pCR



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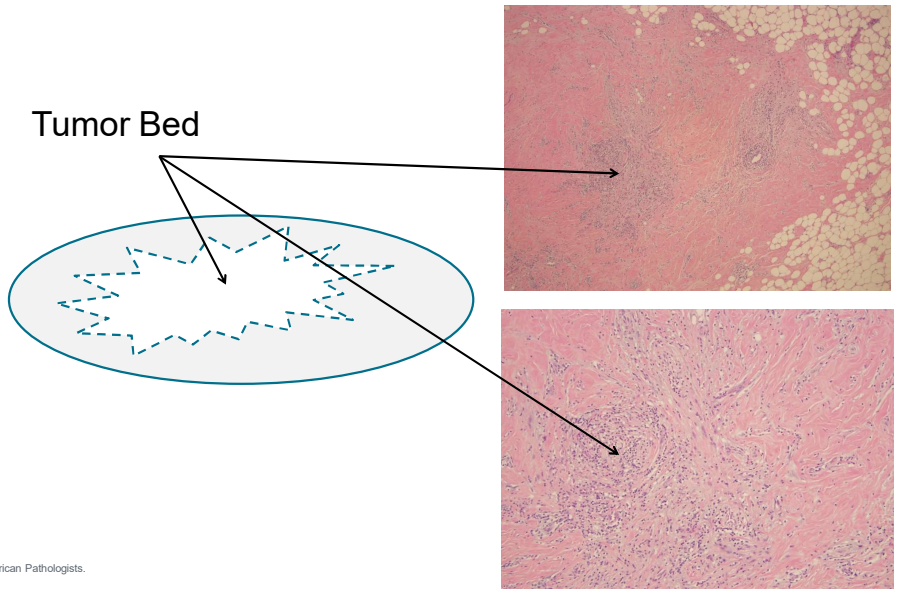
Effect of NAC: pCR



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Pathologic Appearance of Tumor Bed after NAC

- Fibrosis and edema
- Chronic inflammation
- Foamy histiocytes
- Hemosiderin deposition
- Increased vascularity
- Microcalcifications

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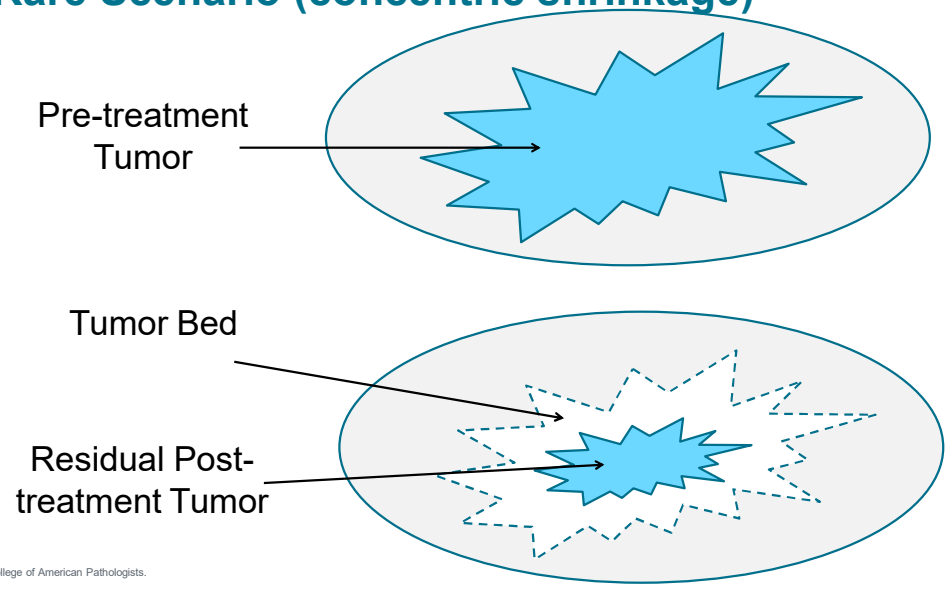
Effect of NAC: pPR
Rare Scenario (concentric shrinkage)



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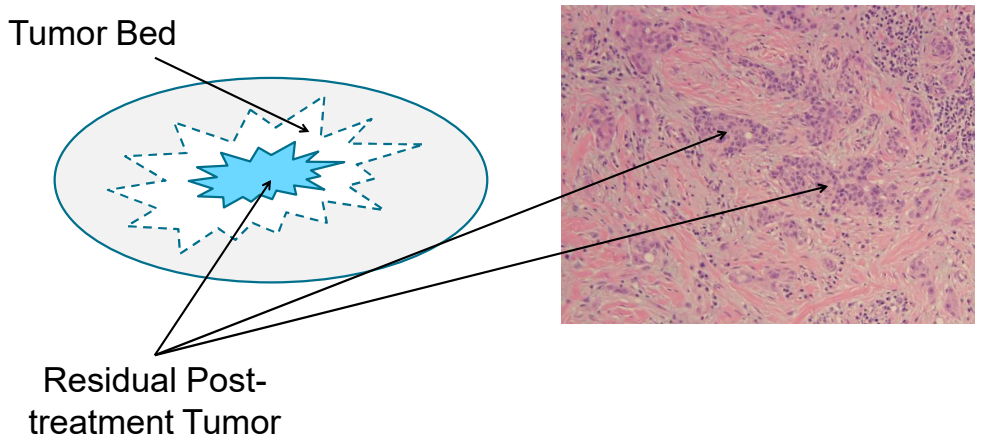
Effect of NAC: pPR
Rare Scenario (concentric shrinkage)



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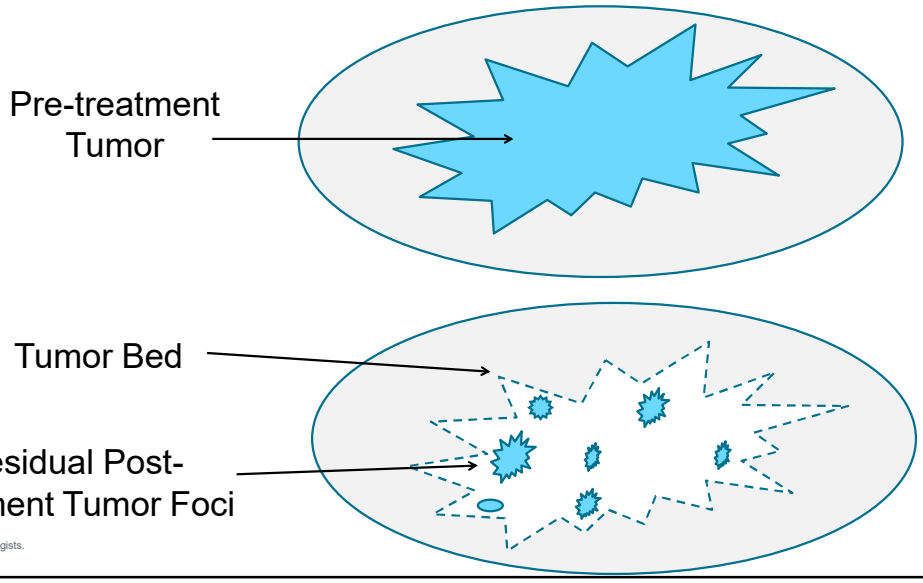
Effect of NAC: pPR
Most Common Scenario (scattered foci)



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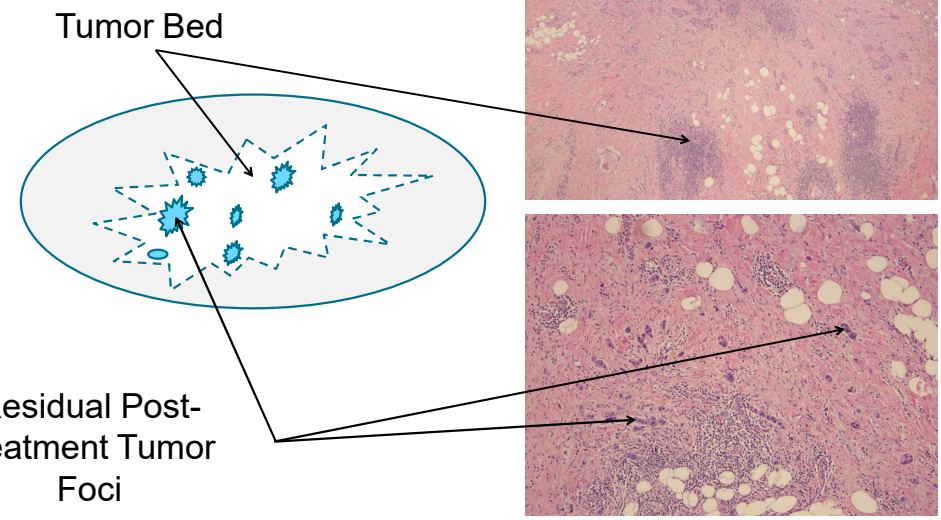
Effect of NAC: pPR Most Common (scattered foci)



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Pathologic Appearance of Residual Invasive Tumor after NAC

- No difference in histologic appearance
- Reduction in overall cellularity with the tumor breaking up in small nests or individual cells
- Larger cell size, abundant cytoplasm
- Larger nuclei, multinucleation, pleomorphism
- Chronic inflammation, histiocytic reaction
- Stromal retraction around residual tumor cells/nests

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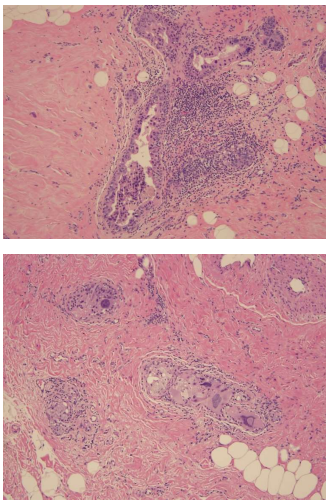
Pathologic Appearance of DCIS after NAC

- DCIS foci may show changes similar to the invasive component such as:
  - Larger cell size, abundant cytoplasm
  - Larger nuclei, multinucleation, pleomorphism
  - Chronic inflammation, histiocytic reaction



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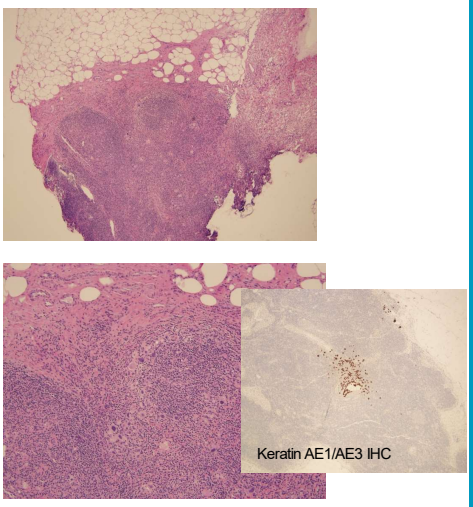
Pathologic Appearance of Lymph Nodes after NAC

- Lymphocytic depletion
- Stromal fibrosis/hyalinization without any residual tumor
- Residual tumor with changes similar to that seen in the breast
- Note # of LNs involved and # of LNs evaluated
- Note presence and extent of extranodal extension
- Pre-NAC clip placement helps the pathologist identify the originally targeted LN
- As per AJCC if ITCs are present post NAC, the node is staged as ypN0(i+) but that precludes pCR classification



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Pathologic Evaluation of Margins after NAC

- Not clear how to best evaluate margins
- Tumor bed extending to margins should be documented
- Full resection of original tumor bed is not necessary
- “No ink on tumor cells” standard approach is favored
- If multifocal disease or scatted foci, some authors favor “more generous margins”
- Other factors such as tumor biologic subtype, LVI, additional therapy may play a role

Recommendations for standardized pathological characterization of residual disease for neoadjuvant clinical trials of breast cancer by the BIG-NABCG collaboration; V. Bossuyt et al, Annals Oncol, 2015

De-escalating and escalating treatments for early stage breast cancer: the St. Gallen International Expert Consensus Conference on the primary therapy of early breast cancer 2017; G.Curigliano et al, Annals Oncol 2017

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Evaluation of Tumor Markers post-NAC

- Most tumors retain their pretreatment tumor marker profile
- Discordant results are seen for ER (up to 15%), PR (up to 30%) and HER2 (up to 10%) (Jabbour et al, BCRT, 2012, Zhang et al, Cancer Invest, 2011)
- Tumor heterogeneity, technical issues, changes resulting from treatment eliminating dominant clones allowing subclones to manifest themselves
- Repeat evaluation of tumor markers post-NAC (Northwestern)
- Policies vary; no uniform guidelines

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Pathologic Predictors of Residual Disease post-NAC

- 665 pts (278 lumpectomy, 387 mastectomy) post-NAC
- pCR was seen in 177 pts (26.6%)
  - 7.9% of HR+/HER2-, 37% of HER+, 37.7% of TNBC (p<0.001)
- 389 pts (143 lumpectomy, 246 mastectomy) with residual disease post-NAC
  - 102 (26.2%): concentric shrinkage, 287 (73.8%): scattered foci
  - Associated with scattered foci of residual disease:
    - Larger tumor size
    - Positive LNs
    - Lower tumor grades (1 and 2: 90.8% vs. 3: 62.6 %)
    - Breast cancer subtype (HR-pos: 86.1% vs. HR-neg: 47%)

Ref: RG Pastorello et al, Modern Pathology, published online 20 November 2020.

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Pathologic Predictors of Residual Disease post-NAC; Effect of Tumor Subtype

	Concentric shrinkage	Scattered foci
HR+/HER-	10.6%	89.4%
HER2+	29.0%	71.0%
TNBC	54.8%	45.2%

p<0.001

Ref: RG Pastorello et al, Modern Pathology, published online 20 November 2020.

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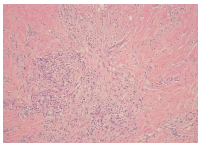
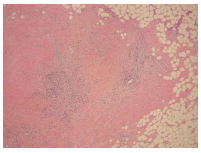
Tumor Bed Features post-NAC; Effect of Tumor Subtype

	Foamy Macrophages	Hemosiderin deposition
HR+/HER-	16.1%	54.5%
HER2+	27.8%	49.1%
TNBC	32.4% (p<0.001)	70.5% (p<0.001)





	Stromal Elastosis	Myxoid change
HR+/HER-	38.8%	19%
HER2+	31%	13.4%
TNBC	24.6% (p=0.005)	8.2% (p=0.004)

Ref: RG Pastorello et al, Modern Pathology, published online 20 November 2020.

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Classification Systems for Evaluation of Pathologic Response to NAC

	Definition of pCR	Is DCIS only OK for pCR?	Requirement for pre/post comparison
Sinn et al, 1994	Breast and LNs	No	Yes
Sataloff et al, 1995	Breast and LNs	Yes	Yes
Chevallier et al,1995	Breast and LNs	No	No
NSABP B-18, 2001	Breast Only	Yes	No
Miller-Payne, 2003	Breast Only	Yes	Yes
Pinder et al, 2007	Breast and LNs	Yes	Yes
Residual Cancer Burden (RCB), 2007	Breast and LNs	Yes	No
RDBN, 2008	Breast and LNs	Yes	No
AJCC ypTNM, 2017	Breast and LNs	Yes	No

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Classification Systems for Evaluation of Pathologic Response to NAC

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AJCC ypTNM, 2017	Breast and LNs	Yes	No

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Pathologic Parameters required to calculate Residual Cancer Burden post-NAC

- Tumor bed dimensions
- Overall residual tumor cellularity as a percentage of the area
- Percentage of residual tumor that is DCIS
- Number of positive LNs
- Diameter of largest metastatic focus in the LNs

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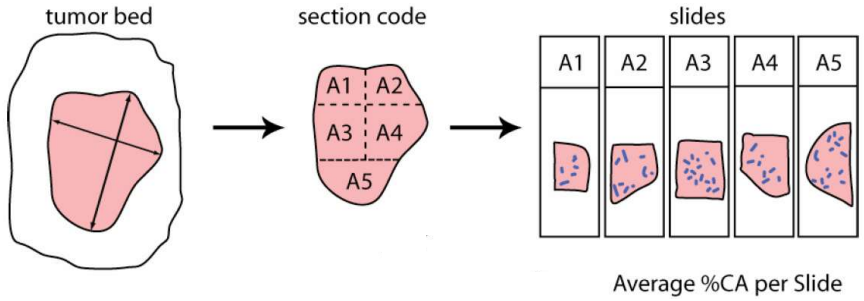
Residual Cancer Burden: Submission of Tumor Bed



- Identify the largest cross-section of the tumor bed
- Submit sections of the entire area; indicate how they are submitted
- Assess % cellularity of invasive Ca and DCIS; calculate the average

Source: http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3

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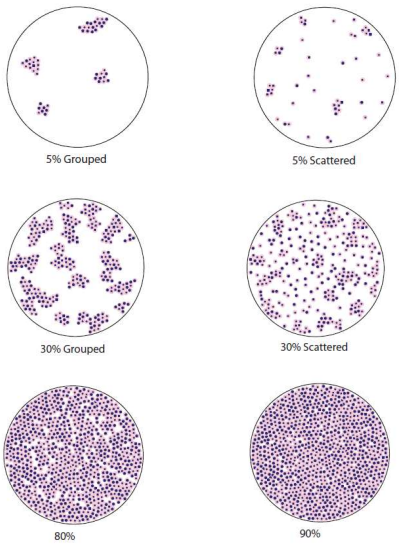
Recurrence Cancer Burden – Assessing Cellularity



- Use **average** tumor cellularity across the entire tumor bed (invasive and in situ)
- Use cellular estimates to nearest 10% (and 1% and 5% for low cellularity)

Source:http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3

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THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

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:

Source: http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3

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Residual Cancer Burden (RCB)

- The RCB score and the RCB class (0, I, II, III) correlate with outcomes in all molecular subgroups

	TNBC	HER2+	HR+/ HER2-
pCR (RCB 0)	86%	95%	83%
RCB I	81%	77%	97%
RCB II	55%	47%	74%
RCB III	23%	21%	52%

Ref: Long-term prognostic risk after neoadjuvant chemotherapy associated with RCB and breast cancer subtype; W. F. Symmans et al, J Clin Oncol, 2017

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AJCC 8th Edition Updates - Breast Specimens post-NAC

- pCR is defined either as ypT0N0 or ypTisN0
- The presence of any carcinoma in breast or LNs precludes pCR (including microinvasion and LVI in breast or ITCs in LNs)
- Only the largest continuous focus of residual tumor is used for the determination of ypT and ypN stage (in contrast to AJCC 7th edition)
- The “m” modifier should be used for multiple foci of residual carcinoma
- In the very uncommon scenario that only LVI is present, then ypTx with a description
- If a patient has been diagnosed with inflammatory carcinoma, the patient remains classified as T4 regardless of response to NAC
- If a patient has been diagnosed with distant metastases, the patient remains classified as M1 regardless of response to NAC

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Pathologic Parameters required in the post-NAC Pathology Report

- Tumor bed dimensions
- Residual tumor size
- Residual tumor cellularity
- Presence/absence of residual DCIS
- LVI
- LN status (# of positive LNs and diameter of largest metastatic focus)
- Treatment effect
- Margin status
- Re-evaluation of breast tumor marker

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Use of Image Guided Biopsies for the Evaluation of Neoadjuvant Response

Retrospective studies	Centers and "n"	Type of biopsy	False negative rate (FNR)
Heil et al	Multicentric, 164 pts	US guided VAB	49.0%
Rauch et al	Single institution 40 pts	Stereo or US guided VAB	5.0%
Tasoulis et al	Multicentric, 166 pts	Stereo or US guided VAB	18.7% (3.2% if: residual T<2 cm, VAB>6 cores)

1. Heil et al, Br J Cancer 2015; 113:1565
2. Rauch et al, Ann Surg Oncol, 2018; 25: 1953
3. Tasoulis et al, SABCS 2019

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Use of Image Guided Biopsies for the Evaluation of Neoadjuvant Response

Prospective studies	Centers and "n"	Imaging and Type of biopsy	False negative rate (FNR)
Heil et al, SABCS 2019	21 German sites N=398 pts	Mammogram and US US guided VAB (63% of cases 7-8G)	17.8% (6.2 % if: normal mammogram and US and VAB)
Basik et al, SABCS 2019	NRG-BR005 N=98 pts with clinical CR	Mammogram: mass <1cm US: mass <2.0cm Normal MRI VAB with 8-11G, removal of clip if possible	22.5%
Vrancken Peeters et al, SABCS 2019	Dutch MICRA study N=167 pts	MRI complete response or >30% reduction of T and Residual T <2 cm 8 US guided 14G cores of clip site	37.0% (45% in pts with radiologic CR)

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Summary

- NAC is used more and more often in clinical practice and is becoming the standard of care in subsets of breast cancer patients
- Detailed pathologic evaluation of the tumor response to NAC in surgical specimens: gold standard
- Evaluation of specimens after NAC poses unique challenges and is different than evaluation of specimens from patients not treated in such a manner; communication between the clinical team and the pathologist is essential for optimal patient care
- Accurate assessment of response after treatment and appropriate reporting of pathologic findings has major therapeutic management and prognostic implications

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Summary

- Underestimation of residual disease post-NAC leads to underdiagnosis and omission of possible beneficial additional adjuvant treatments
- Pathologic features of the tumor pre-treatment, such as tumor size, tumor grade and tumor subtype, are associated with the pattern of residual disease post-NAC when no pCR is achieved
- Pathologists play a critical role in standardizing classification systems post-NAC, and optimizing the knowledge gained by this approach to breast cancer therapy.

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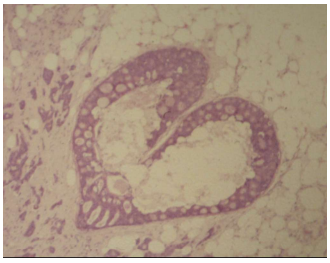
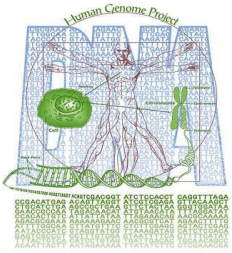
Thank you!





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Questions?

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