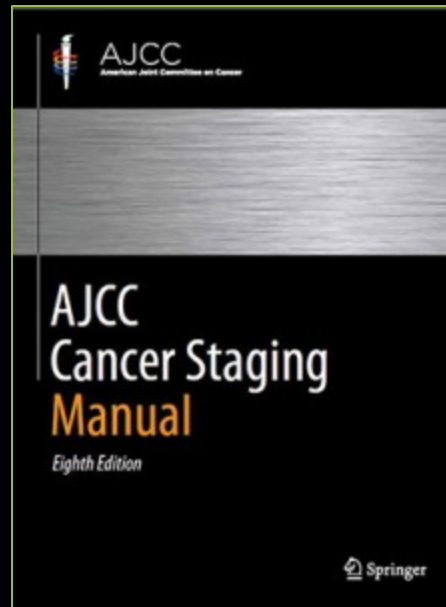# New changes in breast cancer AJCC 8th Edition

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Background in making AJCC 8th ed

- 3 yrs in making
- 434 individuals
- 6 continents
- 23 countries
- 188 institutions
- 63 CAP protocols + 14 biomarker templates
- 12 entirely new staging systems

Breast cancer AJCC 8th ed:

New AJCC edition : start using the 8th edition on 1/1/2018

- Anatomic Stage Group: T N M categories
- Clinical Prognostic Stage:
  - Anatomic stage group TNM stage
  - Tumor grade: G1, G2, G3
  - Biomarkers status for ER, PR, Her-2/neu
- Prognostic Stage Groups: used in US (includes biomarker status and Genomic Profile)
  - Inclusion of Genomic profile in HR+, Her-2/neu-, T1-T2, node-

    (Oncotype Dx, Mammaprint, Endopredict, PAM50 (Prosigna), Breast Cancer Index)

Pathologic Prognostic Staging Groupings

When TNM is...	And Grade is...	And HER2 Status is...	And ER Status is	And PR Status is	The Clinical Prognostic Stage Group is...
Tis N0 M0	Any	Any	Any	Any	0
T1* N0 M0	1	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
T0 N1mi M0	2	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB
T1* N1mi M0	3	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB

*Includes T1mi

Pathologic Prognostic Staging Groupings - 2

When TNM is...	And Grade is...	And HER2 Status is...	And ER Status is	And PR Status is	The Clinical Prognostic Stage Group is...
T0 N1** M0 T1 N1** M0 T2 N0 M0	1	Positive	Positive	Positive	IA
				Negative	IB
			Negative	Positive	IB
				Negative	IIA
		Negative	Positive	Positive	IA
				Negative	IB
			Negative	Positive	IB
				Negative	IIA
	2	Positive	Positive	Positive	IA
				Negative	IB
			Negative	Positive	IB
				Negative	IIA
		Negative	Positive	Positive	IA
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
	3	Positive	Positive	Positive	IA
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
		Negative	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA

**Does not include N1mi

Pathologic Prognostic Staging Groupings - 3

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is	And PR Status is	The Clinical Prognostic Stage Group is…
T2 N1 MO T3 N0 M0	1	Positive	Positive	Positive	IA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
		Negative	Positive	Positive	IA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
	2	Positive	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
		Negative	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
	3	Positive	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIIA

Pathologic Prognostic Staging Groupings - 4

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is	And PR Status is	The Clinical Prognostic Stage Group is…
T0 N2 M0 T1 N2 M0 T2 N2 M0 T3 N1 M0 T3 N2 M0	1	Positive	Positive	Positive	IB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
	2	Positive	Positive	Positive	IB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIB
	3	Positive	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IIB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIC

Pathologic Prognostic Staging Groupings - 5

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is	And PR Status is	The Clinical Prognostic Stage Group is…
T4 N0 M0 T4 N1 M0 T4 N2 M0 Any T N3 M0	1	Positive	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
	2	Positive	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIC
	3	Positive	Positive	Positive	IIIB
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIB
				Negative	IIIC
			Negative	Positive	IIIC
				Negative	IIIC
Any T Any N M1	Any	Any	Any	Any	IV

Clinical Implications of the New Staging System

TNM Groups	Anatomic Staging Groups	Pathologic Prognostic Staging Groups
T1 N0 M0	IA	IA IB
T1 N1 M0	IIA	IA IB 2A
T3 N0 M0	IIB	IA IB IIA IIB IIIA
T3 N2 M0	IIIA	IA IB IIA IIB IIIA

When T is...	And N is...	And M is...	And G is...	And HER2 Status* is...	And ER Status is...	And PR Status is...	Then the Prognostic Stage Group is...
MultiGene Panel** – Oncotype Dx® Recurrence Score Less Than 11							
T1-2	N0	M0	1-3	Negative	Positive	Any	IA
T1	N0	M0	1	Negative	Positive	Negative	IB
T1	N0	M0	1	Negative	Negative	Positive	IB
T1	N0	M0	2	Positive	Positive	Negative	IB
T1	N0	M0	2	Positive	Negative	Any	IB
T1	N0	M0	2	Negative	Negative	Positive	IB
T1	N0	M0	3	Positive	Negative	Any	IB
T1	N0	M0	3	Negative	Positive	Positive	IB
T0-1	N1mi	M0	1	Negative	Positive	Negative	IB
T0-1	N1mi	M0	1	Negative	Negative	Positive	IB
T0-1	N1mi	M0	2	Positive	Positive	Negative	IB
T0-1	N1mi	M0	2	Positive	Negative	Any	IB
T0-1	N1mi	M0	2	Negative	Negative	Positive	IB
T0-1	N1mi	M0	3	Positive	Negative	Any	IB
T0-1	N1mi	M0	3	Negative	Positive	Positive	IB
T2	N0	M0	1-3	Positive	Positive	Positive	IB
T2	N0	M0	1,2	Negative	Positive	Positive	IB
T1	N1	M0	1-3	Positive	Positive	Positive	IB
T1	N1	M0	1-2	Negative	Positive	Positive	IB
T2	N1	M0	1	Negative	Positive	Positive	IB***
T2	N1	M0	2	Positive	Positive	Positive	IB***
T0-2	N2	M0	1-2	Positive	Positive	Positive	IB***

Who should do what?

Anatomic stage	TNM	Pathologist
Prognostic stage group	Tumor grade	Pathologist
	Biomarkers	Pathologist
	Genomic profile	Oncologist/Pathologist
Clinical prognostic stage group		Oncologist

Changes in T category

	T-stage
1.	LCIS is removed from Tis
2.	No rounding to the nearest mm in microinvasive carcinoma T1mi
3.	Do not add the tumor size from Multiple synchronous tumors
4.	Do not add the small microscopic satellite foci of tumors
5.	T4b satellite nodules in the skin criteria
6.	T4a invasion into skeletal muscle clarification
7.	Histologic grade is required element
8.	Post Neoadjuvant therapy tumor size (ypT)
9.	What defines complete pathologic response (cPR)

T-stage change #1: Deletion of Tis (LCIS)

AJCC 2010	AJCC 2017
pTis (LCIS)	Removed. LCIS is a benign entity and is removed from TNM staging

Problem:
High grade LCIS and pleomorphic LCIS also is not included in the Tis classification (AJCC 2017; p604)
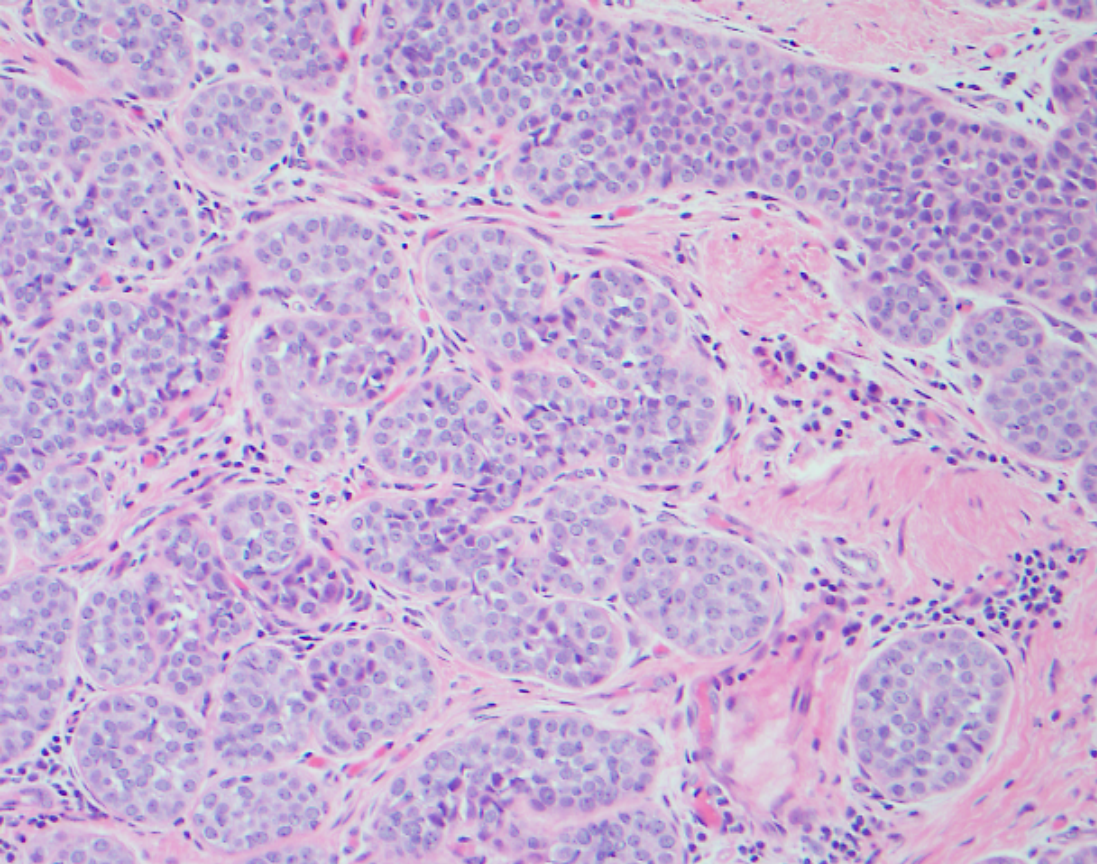
Classic LCIS
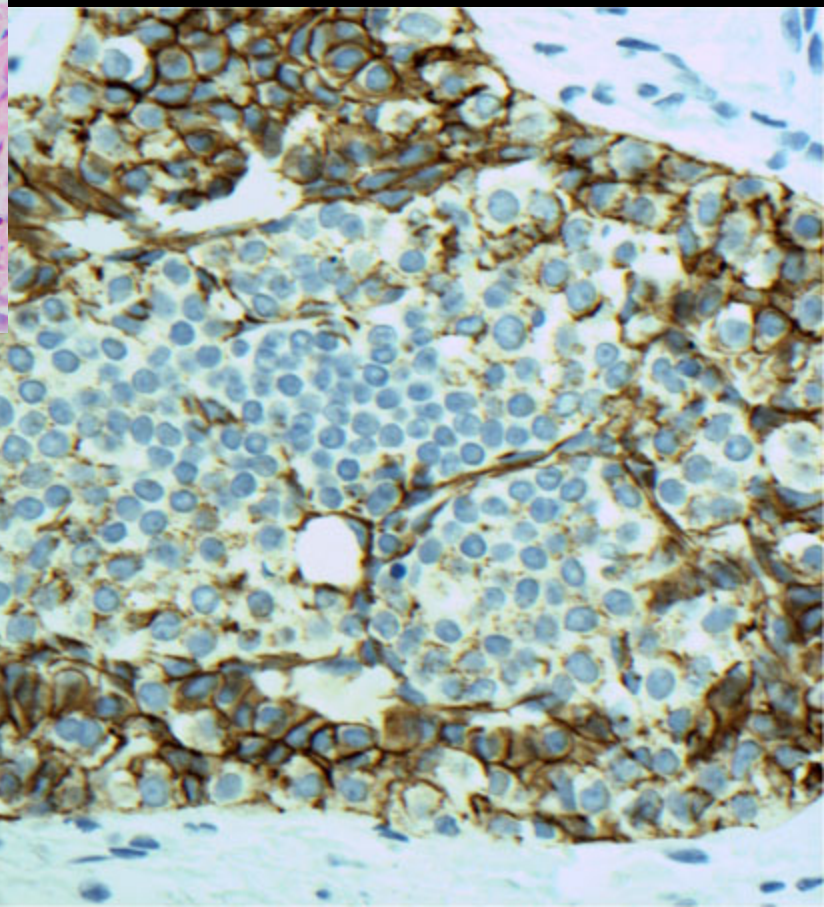
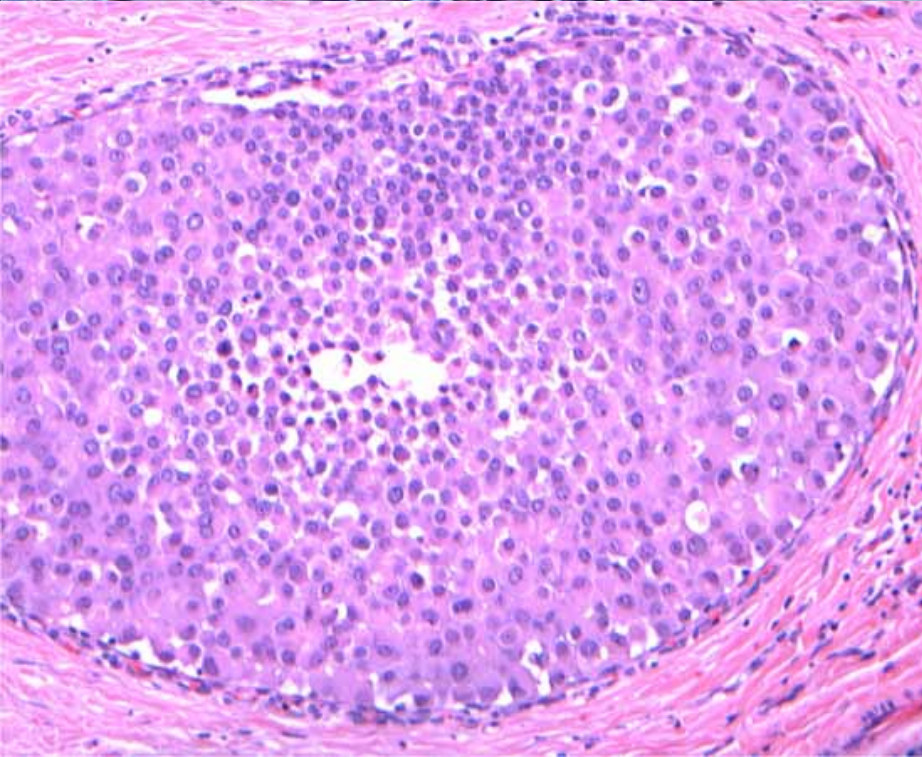E-cadherin: negative
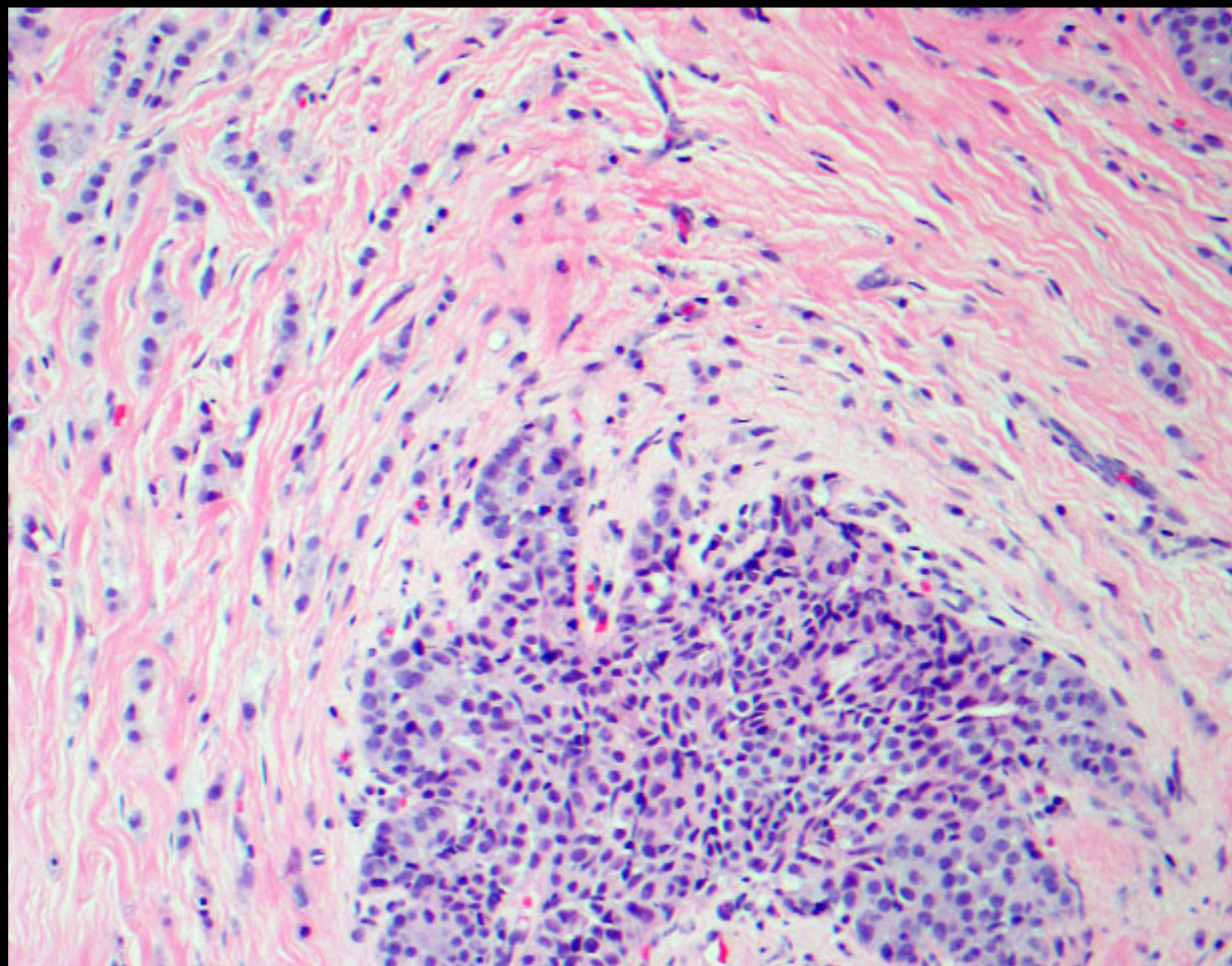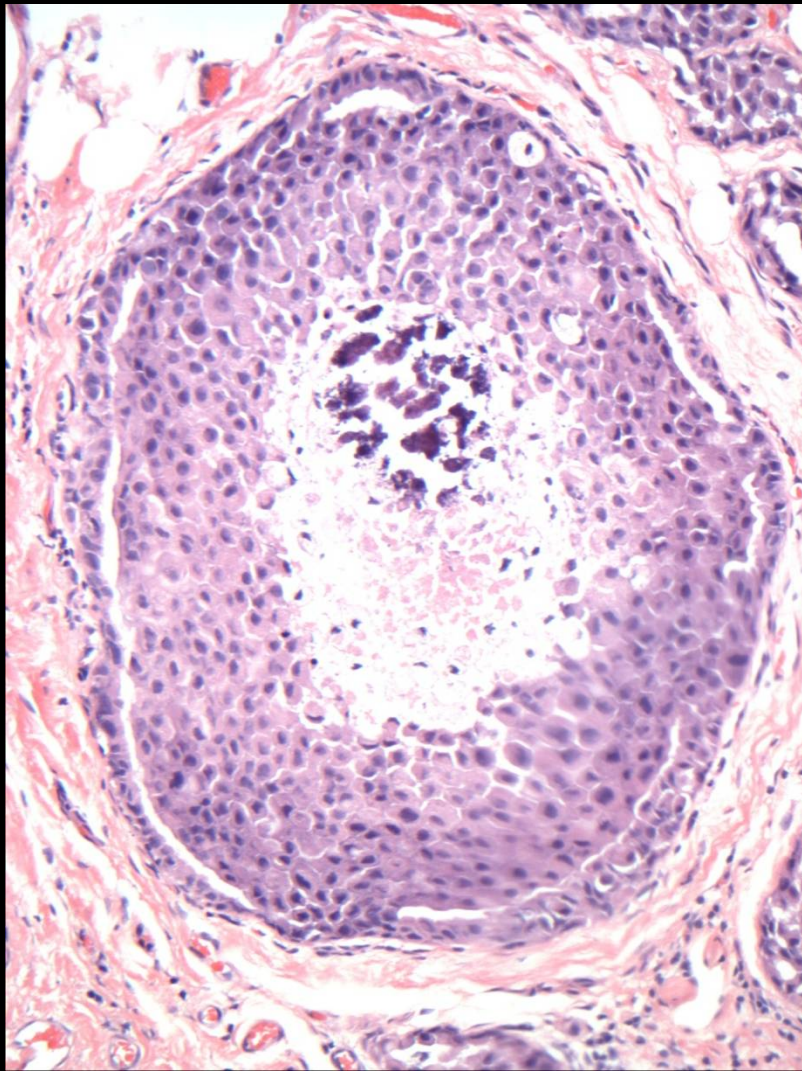
Distended LCIS with central necrosis
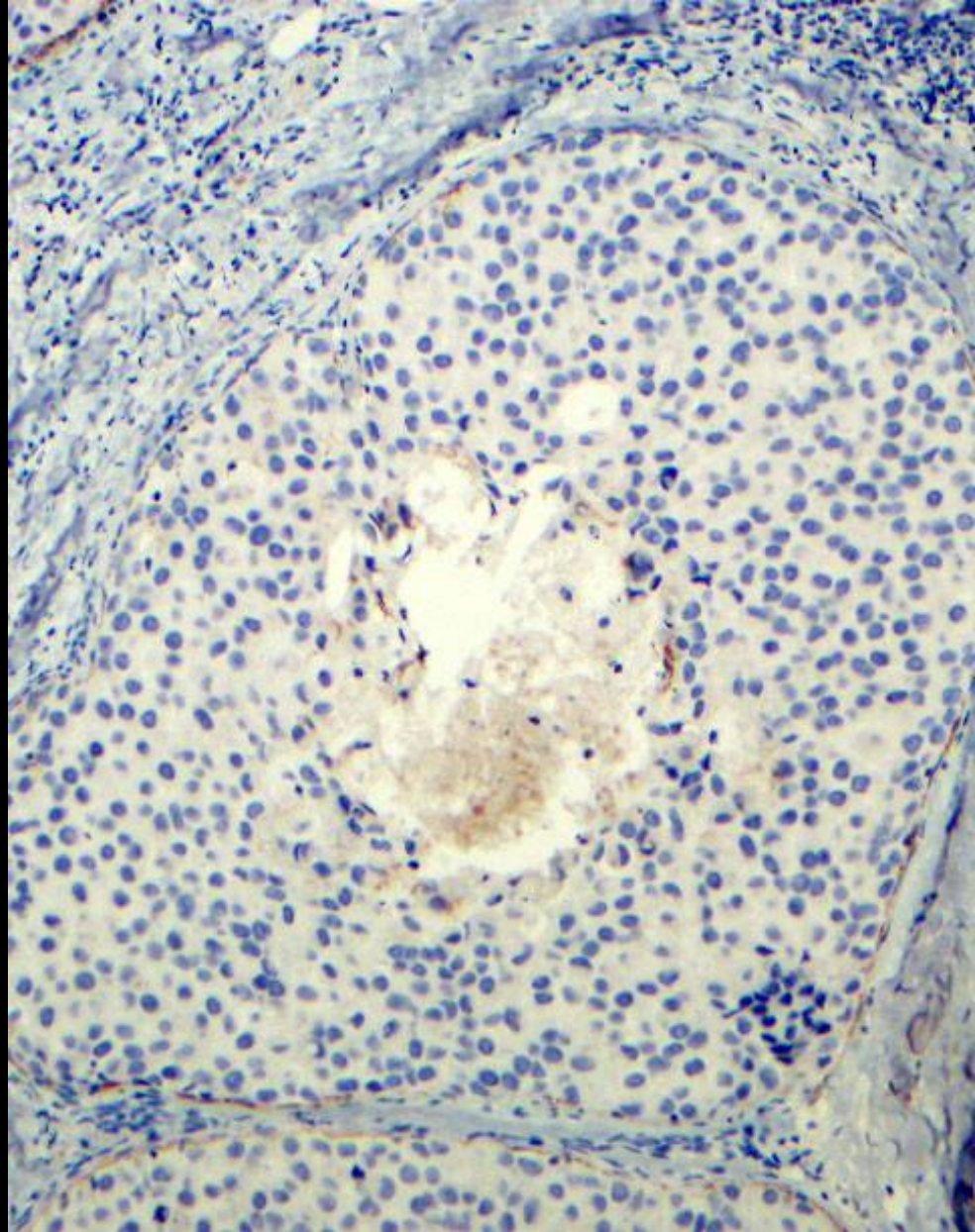
E-cadherin: negative
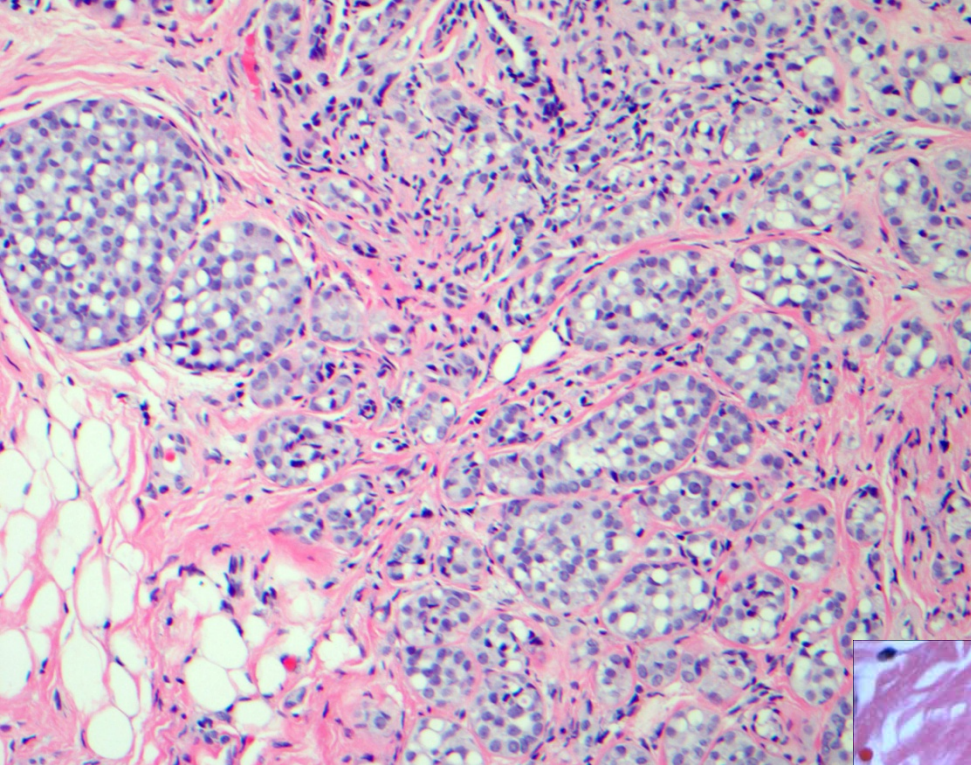
Invasive lobular ca-signet ring cells

Signet ring cell LCIS
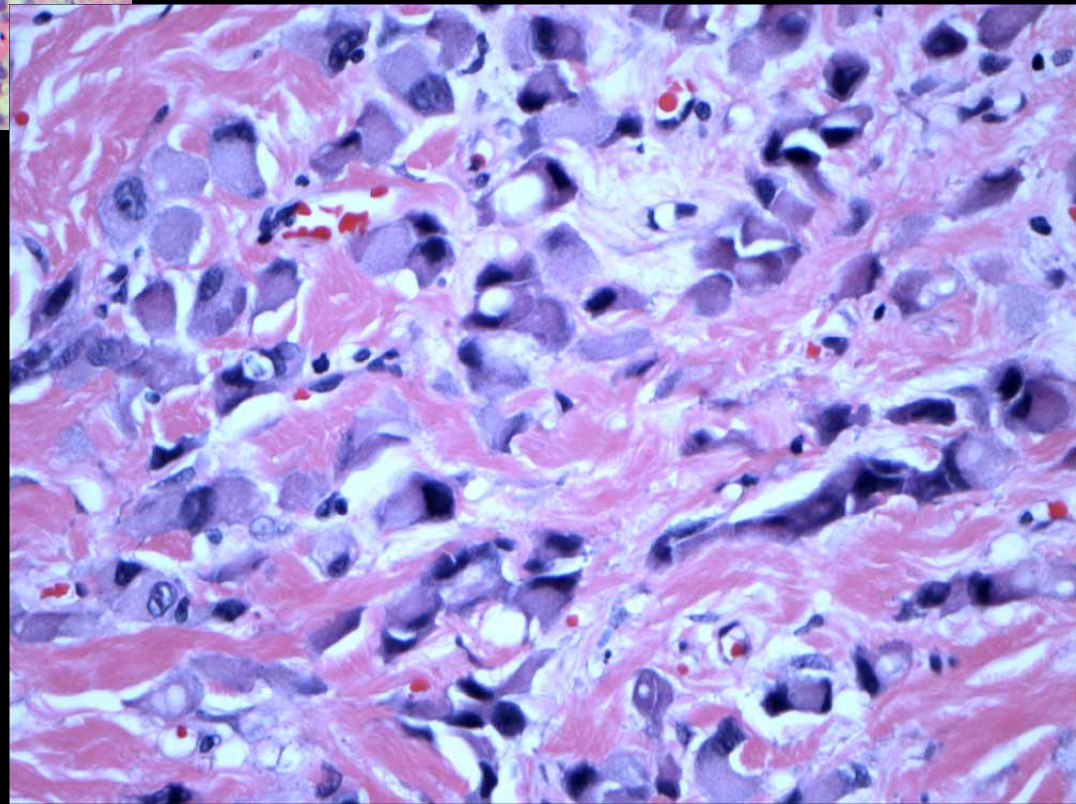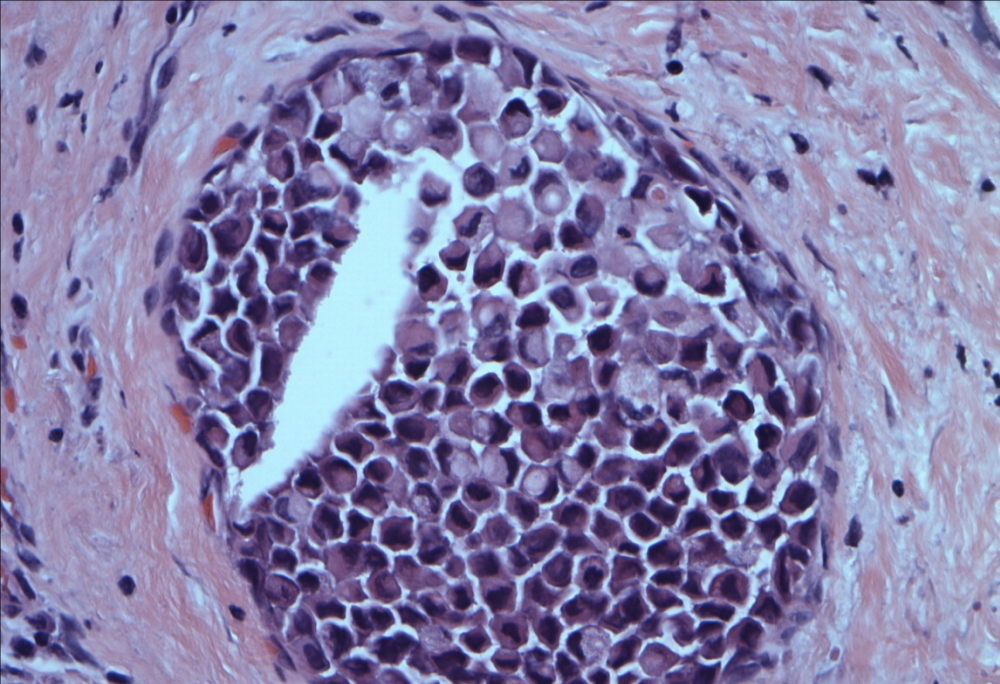
Pleomorphic LCIS
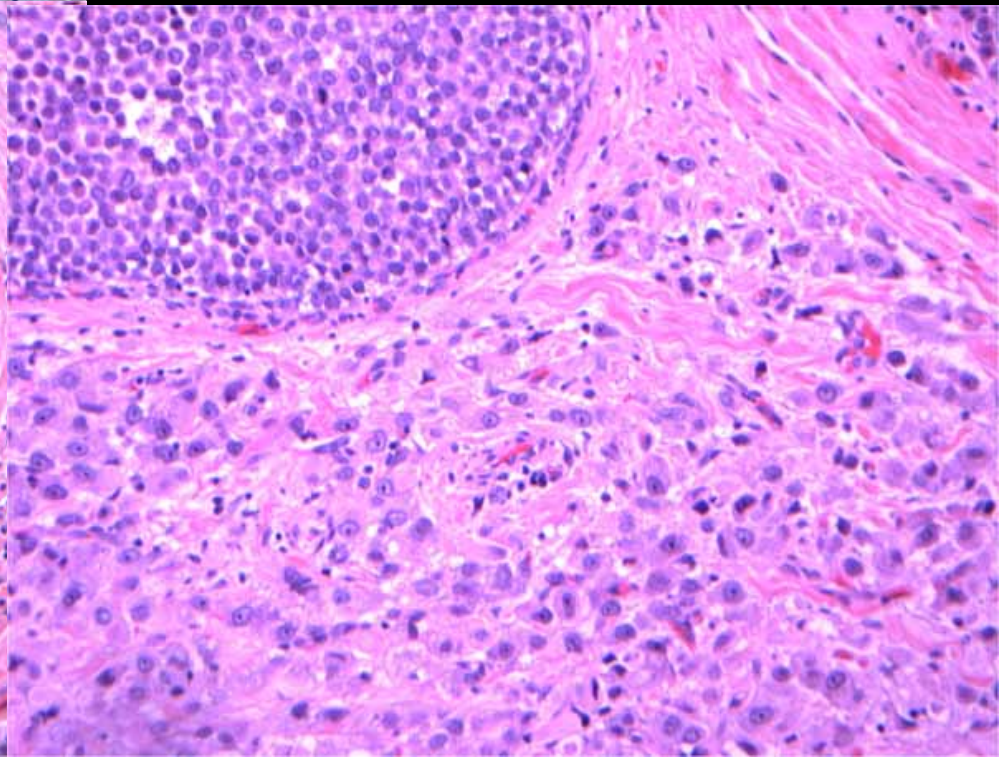
T-stage change #2: Rounding tumor size

- Tumor measuring between 1.0 mm - 1.5 mm:

    Do not round up to the nearest millimeter.

    Do not classify as microinvasive

    e.g., 1.2 mm tumor = T1a (not T1mi)

- Tumors > 1mm and <2mm should be reported rounding to 2 mm

    -1.4 mm = T1a

    -1.6 mm = rounding to 2mm = T1a
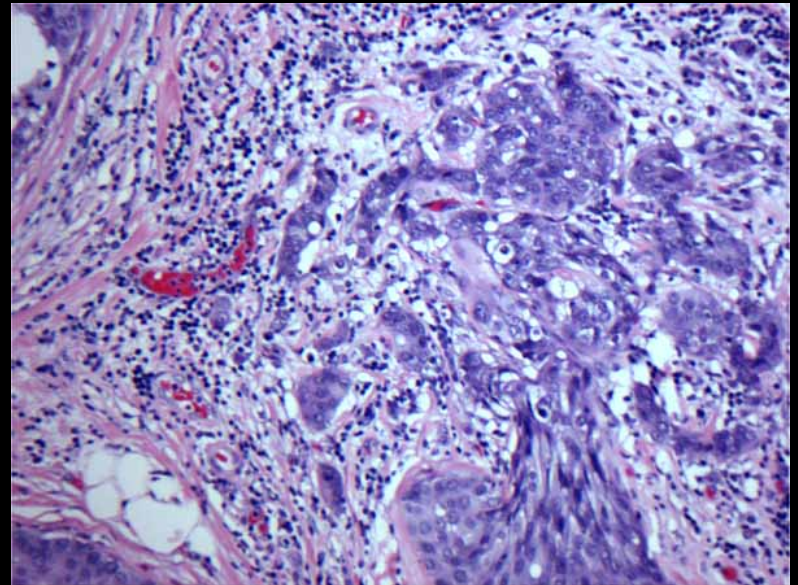
T-stage change #3-4: multiple tumors

- Use m modifier
- The size of the largest carcinoma is used for T-stage. The sizes of multiple invasive carcinoma should not be added.
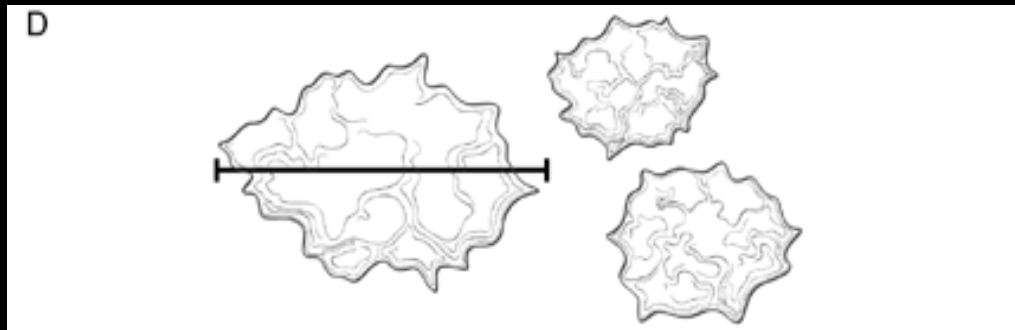
T-stage change #5: T4b satellite tumor nodules

- Clarification: Satellite tumor nodules in the skin must be separated from the primary tumor and macroscopically identified to categorized as T4b.

- Skin and dermal tumor satellite nodules identified only on microscopic examination and in the absence of epidermal ulceration or skin edema (clinical peau d'orange) do not qualify as T4b.
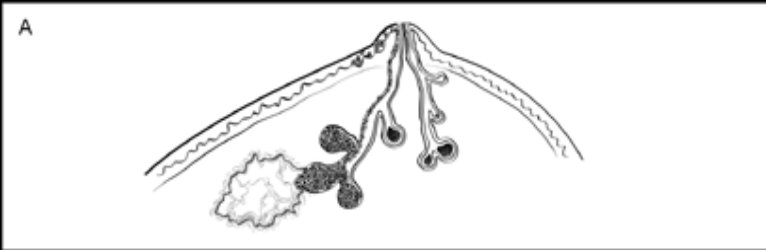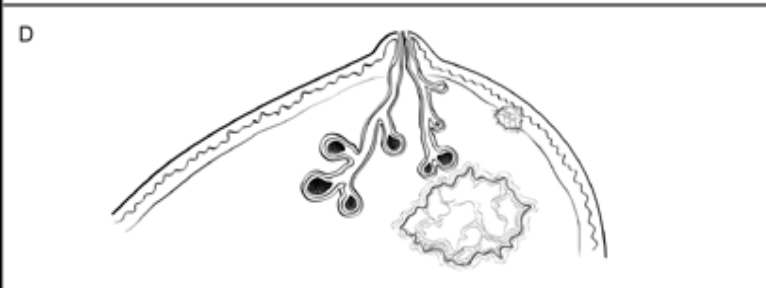
A — DCIS + Paget's disease in nipple and Invasive Carcinoma (IC): T stage is from the size of IC.
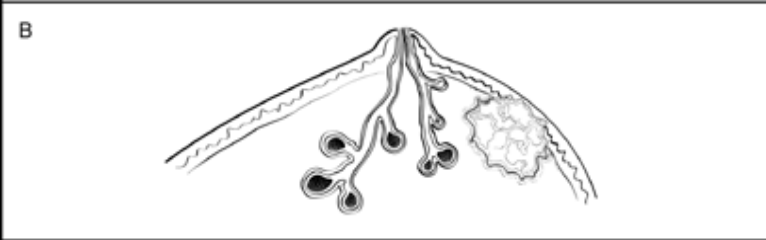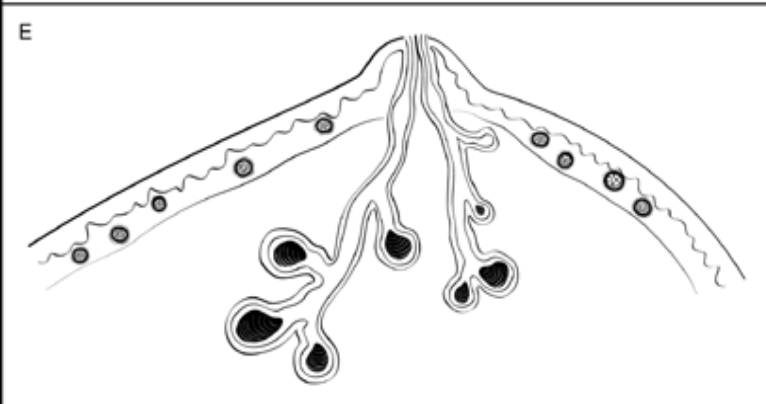
B — IC involving dermis or epidermis without ulceration: T stage is from the size of IC.
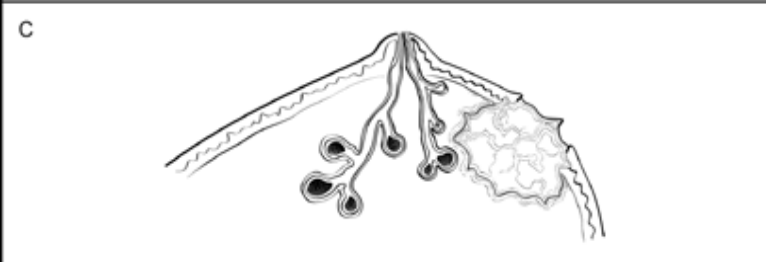
C — IC involving dermis or epidermis with ulceration: T4b

D — Ipsilateral macroscopic satellite skin nodules: T4b
Ipsilateral microscopic satellite skin nodules:
T stage is from the size of IC

E — Dermal LVI with the clinical features of inflammatory Carcinoma (diffuse erythema and edema involving ≥1/3 of the breast): T4d

T-stage change #6: T4a clarification

- Invasion into skeletal muscle is not included as T4a.
- Invasion must extend through the muscle into the chest wall (intercostal muscles or deeper)

  -Imaging/clinical finding

  -Radical mastectomy + Rib cage removal

Inflammatory carcinoma
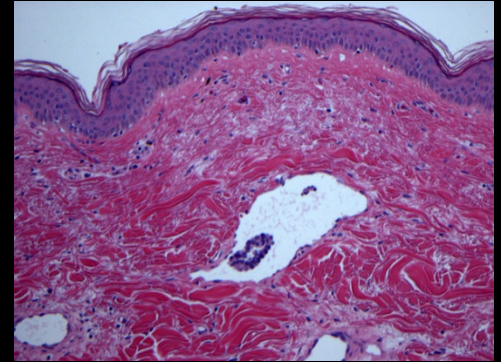
- cT4d: clinical findings
  - Dermal lymphatic invasion of skin is **not** T4d
  - Tumor emboli in dermal lymphatics without clinical skin changes is classified as T1, T2, T3 based on tumor size
  - pT4c (Both T4a and T4b) without clinical changes is not T4d
  - Dimpling of the skin, nipple retraction or any other skin changes may occur in T1, T2, T3

T-stage change #7: Histologic grade

Scarf, Bloom and Richardson score standardized by the Nottingham group is now required element for invasive carcinoma and DCIS

Modified Bloom and Richardson score   of 9
Tubule formation:
Nuclear pleomorphism:
Mitosis:

Grade	mBR scores
Grade 1	Scores from 3-5
Grade 2	Scores from 6-7
Grade 3	Scores 8-9

T-stage change #8: post neoadjuvant therapy tumor size

- Tumor size is based on the largest continous focus of residual invasive carcinoma

- Treatment related fibrosis or between foci of residual cancer is not included in the ypT size

- When multiple foci of residual tumors are seen, then use m modifier: ympT
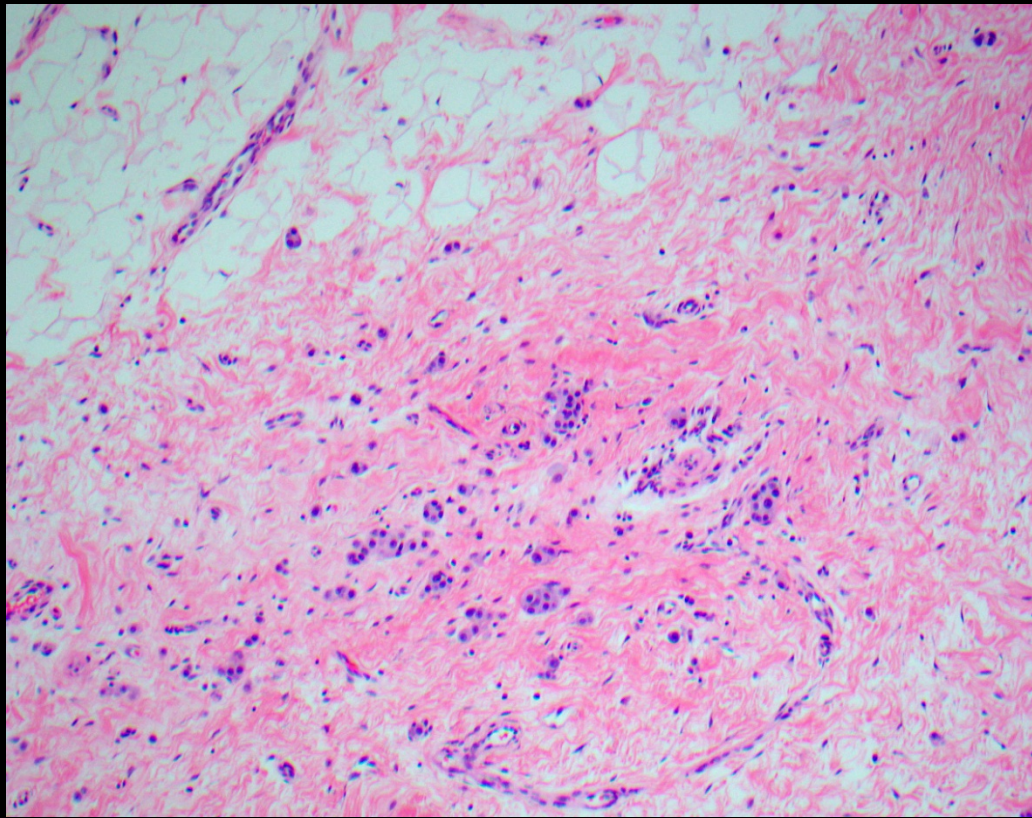
Maximum linear dimension tumor size: 2 mm
Primary tumor bed: 5.3 cm x 2.0 cm
Estimated overall cancer cellularity: 5%
Percentage DCIS: 0%
Lymph node # positive: 1
Diameter of largest metastasis: 5 mm
Residual cancer burden: calculation

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

(1) Primary Tumor Bed

Primary Tumor Bed Area: 53 (mm) X 20 (mm)

Overall Cancer Cellularity (as percentage of area): 5 (%)

Percentage of Cancer That Is *in situ* Disease: 0 (%)

(2) Lymph Nodes

Number of Positive Lymph Nodes: 1
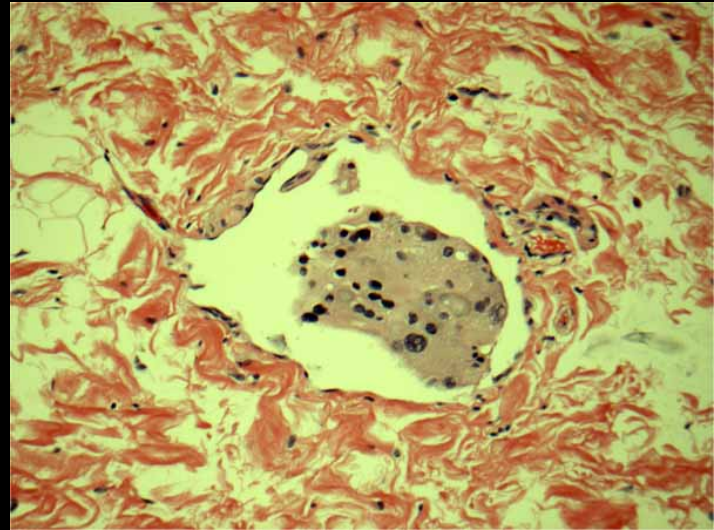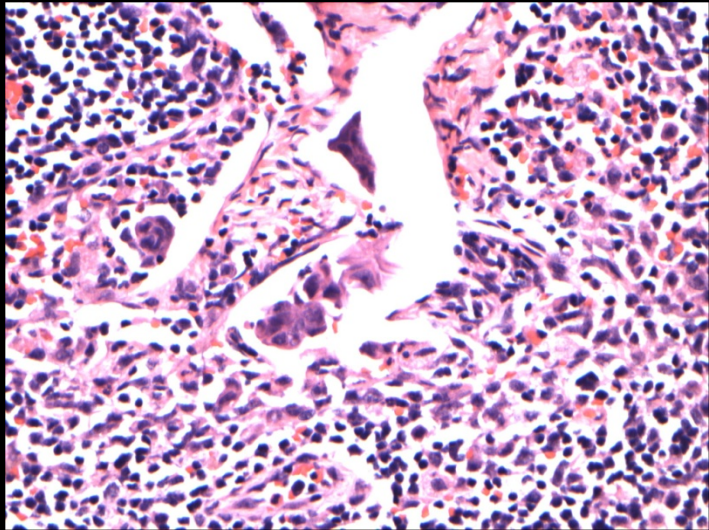
Diameter of Largest Metastasis: 5 (mm)

Calculate

Residual Cancer Burden: 2.836

Residual Cancer Burden Class: RCB-II

T-stage change #9: complete pathologic response (cPR) definition

- Any residual invasive carcinoma in the breast including tumor within blood/lymphatic vessels or lymph nodes precludes classification as a cPR.

AJCC 2010

m (multiple foci of invasive carcinoma)
r (recurrent)
y (posttreatment)

Primary Tumor (Invasive Carcinoma) (pT)
pTX: Primary tumor cannot be assessed
pT0:   No evidence of primary tumor
pTis (DCIS):   Ductal carcinoma in situ
pTis (LCIS):   Lobular carcinoma in situ
pTis (Paget):   Paget disease of the nipple *not* associated with   invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma

pT1: Tumor ≤20 mm in greatest dimension
    pT1mi: Tumor ≤1 mm in greatest dimension (microinvasion)
    pT1a: Tumor >1 mm but ≤5 mm in greatest dimension
    pT1b: Tumor >5 mm but ≤10 mm in greatest dimension
    pT1c: Tumor >10 mm but ≤20 mm in greatest dimension

pT2: Tumor >20 mm but ≤50 mm in greatest dimension

pT3: Tumor >50 mm in greatest dimension

pT4: Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules). *Note:* Invasion of the dermis alone does not qualify as pT4.
    pT4a: Extension to chest wall, not including only pectoralis muscle adherence/invasion
    pT4b: Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin which do not meet the criteria for inflammatory carcinoma
    pT4c: Both T4a and T4b
    pT4d: Inflammatory carcinoma

AJCC 2017

m (multiple foci of invasive carcinoma)
r (recurrent)
y (posttreatment)

Primary Tumor (Invasive Carcinoma) (pT)
pTX: Primary tumor cannot be assessed
pT0:   No evidence of primary tumor
pTis (DCIS):   Ductal carcinoma in situ
pTis (Paget):   Paget disease of the nipple *not* associated with invasive carcinoma and/or carcinoma in situ (DCIS) in the underlying breast parenchyma

pT1: Tumor ≤20 mm in greatest dimension
    pT1mi: Tumor ≤1 mm in greatest dimension (microinvasion) Do not round up
    pT1a: Tumor >1 mm but ≤5 mm in greatest dimension
    pT1b: Tumor >5 mm but ≤10 mm in greatest dimension
    pT1c: Tumor >10 mm but ≤20 mm in greatest dimension

pT2: Tumor >20 mm but ≤50 mm in greatest dimension

pT3: Tumor >50 mm in greatest dimension

pT4: Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or macroscopic nodules). *Note:* Invasion of the dermis alone does not qualify as pT4.
    pT4a: Extension to chest wall; invasion or adherence to pectoralis muscle in the absence of invasion of chest wall structures does not apply as T4
    pT4b: Ulceration and/or ipsilateral macroscopic satellite nodules and/or edema (including peau d'orange) of the skin that do not meet the criteria for inflammatory carcinoma
    pT4c: Both T4a and T4b
    pT4d: Inflammatory carcinoma

Questions regarding T-stage

- Scenario #1:
- Lumpectomy T size = 5.1 x 2.5 x 1.5 cm

  IDC mixed with DCIS (DCIS 50%), margin positive with IDC
- Mastectomy T size = 2.0 x 1.0 x 1.0 cm
- Clinician's conclusion: 5.1 cm (50%) = 2.5 cm + 2.0 cm in mastectomy; final tumor size = 4.5 cm; T-stage: T2
- This is incorrect. The correct T-stage= T3
- Do not add the size of tumors in two procedures

Questions regarding T-stage

- Scenario #2:
- Post neoadjuvant chemotx, Lumpectomy tumor bed = 5.1 x 2.5 x 1.5 cm with multifocal IDC with max contiguous linear dimension of 0.3 cm
- T-stage: T3 or mT1b?

- Scenario #3:
- Prior clinical findings: cT4d
- Post neoadjuvant chemotx, ypT1a, ypN0, cM0
- Document the pretreatment cT category: cT4d, ypT1a, ypN0, cM0

Post-neoadjuvant
Chemotherapy
H&E slide
ER stain
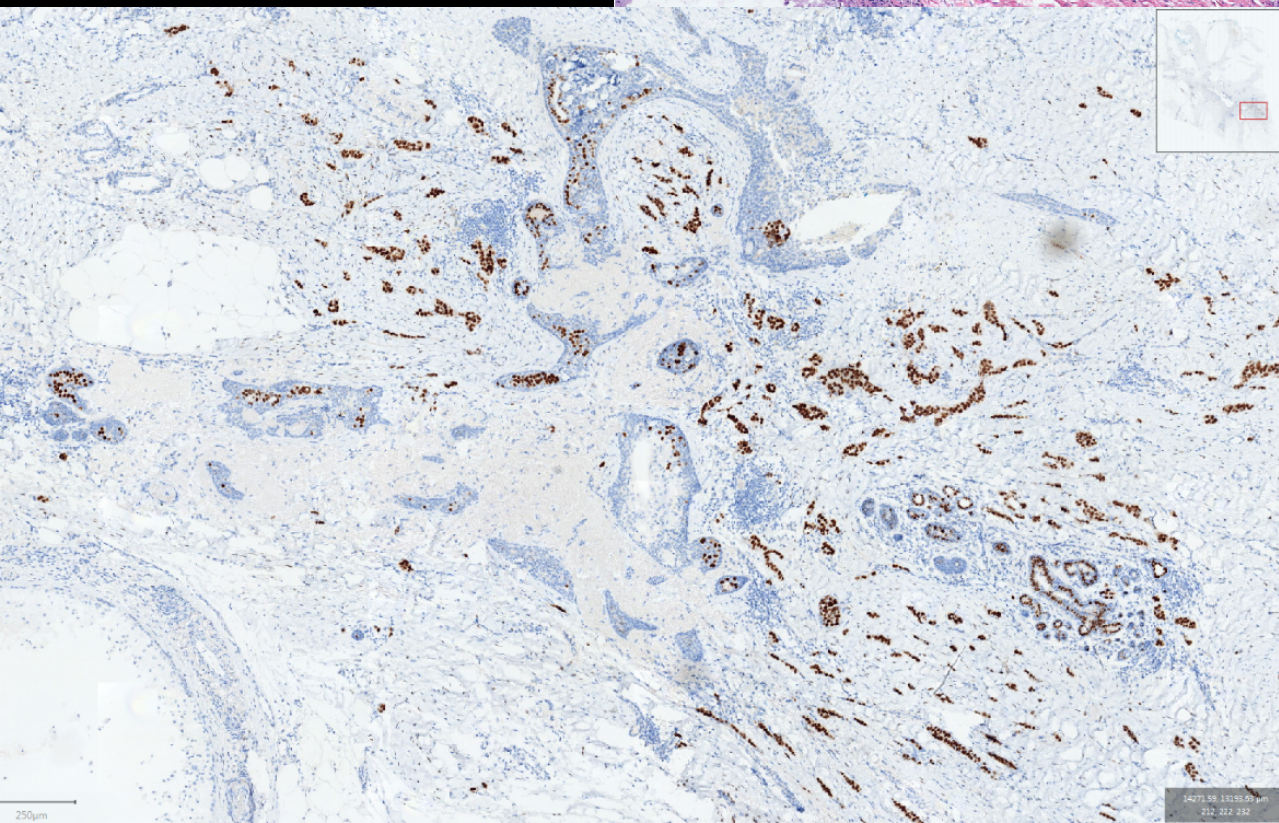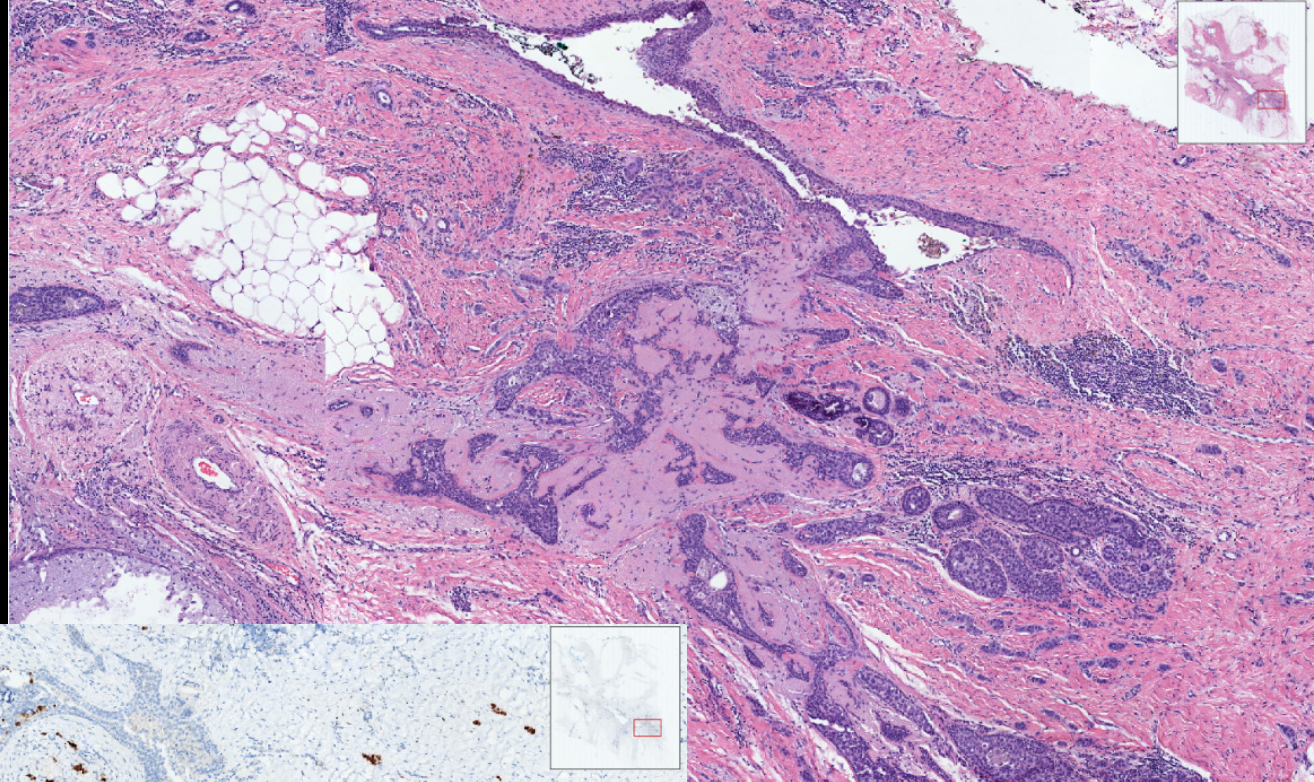
What is the T-stage?
-multiple slides, scattered
areas of invasive tumor
-Tumor bed 5.1 cm
-largest contiguous size
of 0.3 cm. T1a? or T4?

Changes in N category

	N-stage
1.	cN0 assignment
2.	cNx is valid only if nodal basin removed
3.	Criteria for microscopic measurement of nodal metastasis
4.	Criteria for nodal metastasis post neoadjuvant chemotherapy (ypN)
5.	Intramammary lymph node count as ALN
6.	N(f) modifier
7.	cN1 (f) modifier
8.	cN3c: Supraclavicular LN
9	Internal mammary LN
10.	LN outside the supraclavicular fossa triangle area is M1 not N-stage

N-stage change #1: cN0 assignment

- Evaluation of nodes is possible
- Physical exam or imaging is negative for nodal involvement

N-stage change #2: cNx assignment

- valid only if nodal basin is removed
- Cannot be examined by imaging or physical exam

N-stage change #3: Criteria for microscopic measurement of nodal metastasis

- Largest contiguous tumor deposit for pN

- Do not add adjacent satellite metastatic tumor deposits

- Size of metastasis includes the tumor cells and surrounding desmoplastic stroma response within the LN (tumor cells need not be touching)

N-stage change #4: Criteria for nodal metastasis post neoadjuvant chemotherapy (ypN)

- Do not include treatment-related fibrosis
- Only the largest contiguous focus of residual tumor as ypN stage

N-stage change #5: Intramammary LN

- Count as axillary lymph node for N-stage

N-stage change #6: N(f) modifier

- Nodal mets confirmed by FNA or CNB
- Nodal metastases confirmed by FNA or core needle biopsy are classified as macrometastases (cN1, not pN1) regardless of the size of the tumor

N-stage change #7: cN1 (f) modifier

- For FNA pre-treatment: add cN1 (f), Stage IIA

N-stage change #8: cN3c

- Supraclavicular LNs are included for LN staging; automatic cN3c

pN3c	Ipsilateral supraclavicular lymph node +	Stage IIIc	T1-T4

N-stage change #9: Internal mammary nodes

	Internal mammary lymph node	axillary lymph node	Clinical or imaging (excluding lymphoscintigraphy)
pN1b	+	-	-
pN1c	+	1-3 +	-
pN3b	+	4-9+	-
pN2b	+	-	+
pN3b	+	+	+

# N-stage change #10: supraclavicular nodes

- M1 (and not included for LN staging):

  - LN outside the supraclavicular fossa triangle are considered as lower cervical LN

  - cervical LN

  - contralateral internal mammary LN

  - contralateral axillary LN
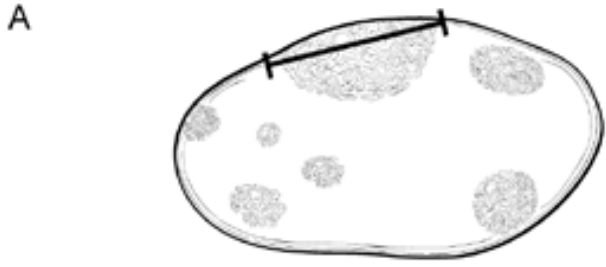
A — Multiple clusters of tumor cells: Report the largest
Size of mets: the distance between clusters not be
Included in the size. 7 clusters of mets, largest
Contiguous mets measuring ___mm.
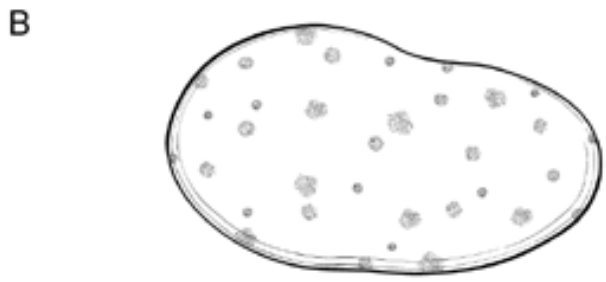
B — Dispersed pattern of LN mets as in ILC:200 cells
Cut off between ITC and micromets.
No cut off in # of cells for micro and macromets
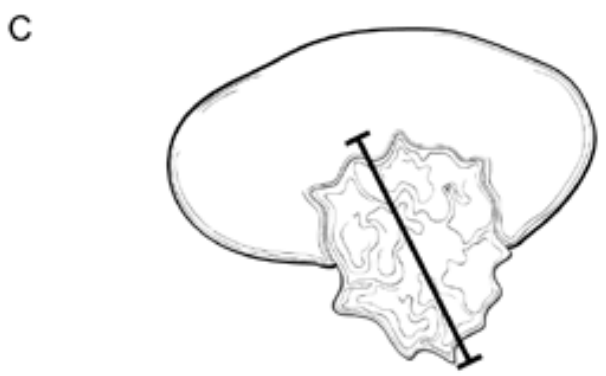
C — Extranodal/extracapsular tumor extension: the size
Should include in the overall size of mets.

D — Cancerous nodules in axillary fat without residual
Nodal tissue: count as a positive LN.
Cancerous nodules in axillary fat with DCIS/breast
Tissue: include as T-stage and not N-stage.

Additional N stage changes

- Intramammary LN: count as ALN for N-stage.
- The size of mets includes the tumor cells and the surrounding desmoplastic response within LN (tumor cells need not be touching)
- After neoadjuvant chemotx: Do not include treatment-associated fibrosis. Only the largest contiguous focus of residual tumor as ypN stage
- N (f) modifier: Nodal mets confirmed by FNA or CNB

  Nodal metastases confirmed by FNA or core needle biopsy are classified as Macrometastases (cN1, not pN1) regardless of the size of the tumor
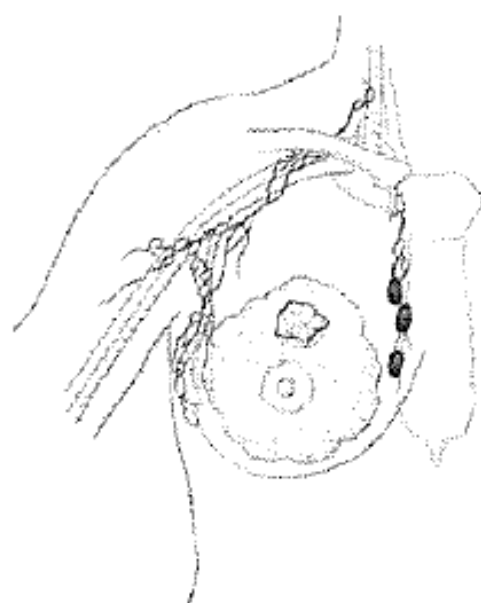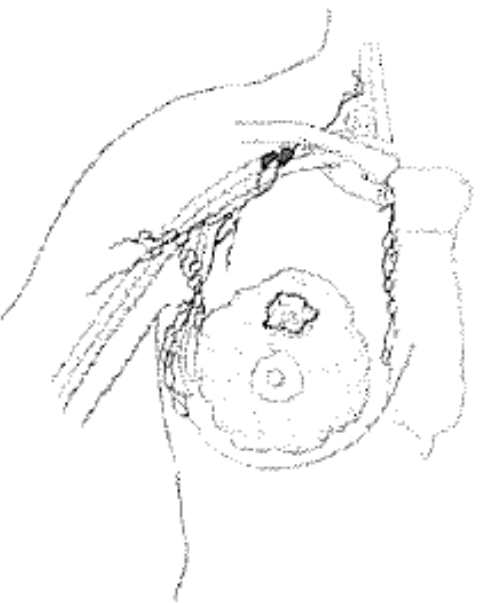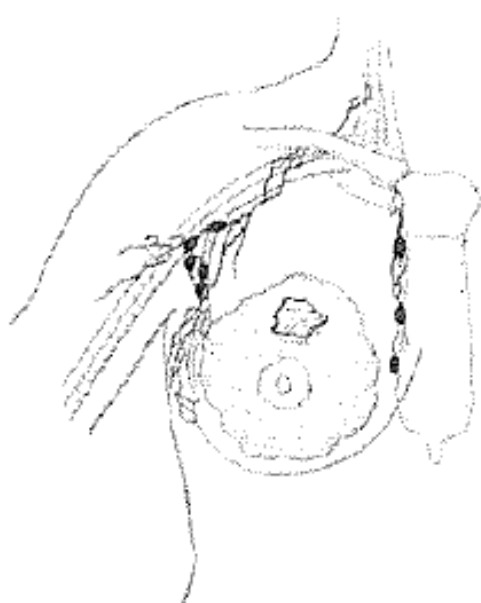- For FNA pre-treatment: add cN1 (f), Stage IIA

N1

N2a

Fixed/matted
nodal mass
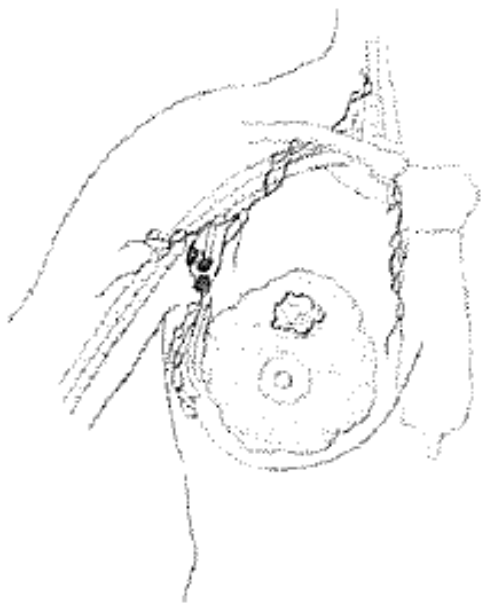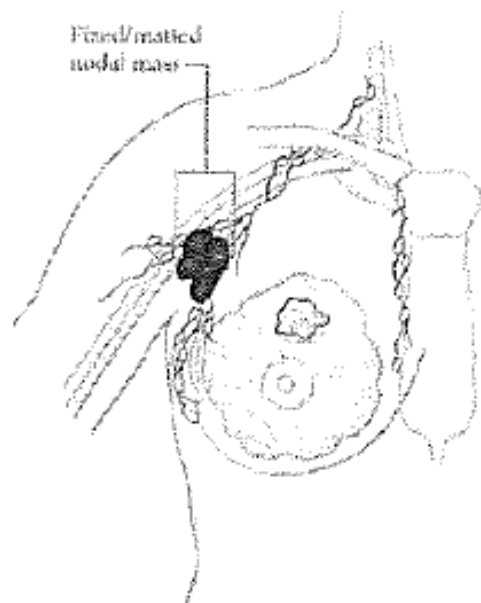
N2b

N3a

N3b

N3c

AJCC 2010

pNX: Regional lymph nodes cannot be assessed (eg, previously removed, or not removed for pathologic study)

pN0: No regional lymph node metastasis identified histologically

    pN0 (i-): No regional lymph node metastases histologically, negative IHC

    pN0 (i+): Malignant cells in regional lymph node(s) no greater than 0.2 mm and no more than 200 cells (detected by H&E or IHC including ITC)

    pN0 (mol-): No regional lymph node metastases histologically, negative molecular findings (reverse transcriptase polymerase chain reaction [RT-PCR])

    pN0 (mol+): Positive molecular findings (RT-PCR), but no regional lymph node metastases detected by histology or IHC

pN1: Metastases in 1-3 axillary lymph nodes

    pN1mi: Micrometastases (greater than 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm).

    pN1a: Metastases in 1 to 3 axillary lymph nodes, at least 1 metastasis greater than 2.0 mm

pN2a: Metastases in 4 to 9 axillary lymph nodes (at least 1 tumor deposit greater than 2.0 mm)

pN3a: Metastases in 10 or more axillary lymph nodes (at least 1 tumor deposit greater than 2.0 mm)
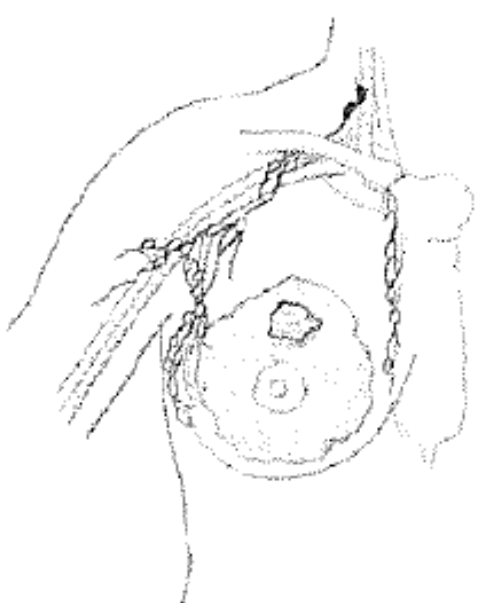
AJCC 2017

pNX: Regional lymph nodes cannot be assessed (eg, previously removed, or not removed for pathologic study)

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    pN0 (mol+): Positive molecular findings (RT-PCR), but no regional lymph node metastases detected by histology or IHC

pN1: Clinically negative internal mammary lymph node

    pN1mi: Micrometastases (greater than 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm).

    pN1a: Metastases in 1 to 3 axillary lymph nodes, at least 1 metastasis greater than 2.0 mm

    pN1b: Metastases in ipsilateral internal mammary sentinel nodes, excluding ITC

    pN1c: pN1a and pN1b combined

pN2: Positive ipsilateral internal mammary lymph nodes by imaging

    pN2a: Metastases in 4 to 9 axillary lymph nodes (at least 1 tumor deposit greater than 2.0 mm)

    pN2b: Metastases in clinically detected internal mammary lymph nodes with or without microscopic confirmation: with pathologically negative axillary lymph nodes

pN3: Infraclavicular (Level III ALN), supraclavicular LN

    pN3a: Metastases in 10 or more axillary lymph nodes (at least 1 tumor deposit greater than 2.0 mm) or metastasis to the infraclavicular (Level III axillary) lymph nodes

    pN3b: pN1a or pN2a in the presence of cN2b (positive internal mammary lymph nodes by imaging) or pN2a in the presence of pN1b

    pN3c: Metastases in ipsilateral supraclavicular nodes

Questions regarding N-stage

- Pericapsular LVI: N-stage or just LVI
- How to accurately measure multiple mets?
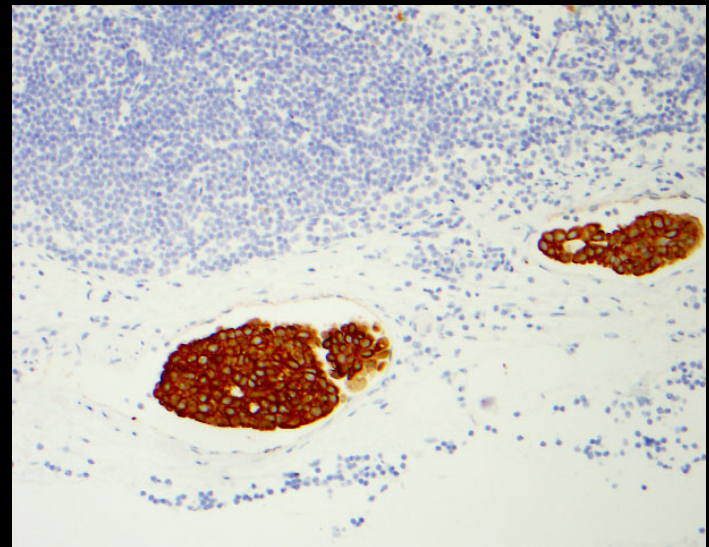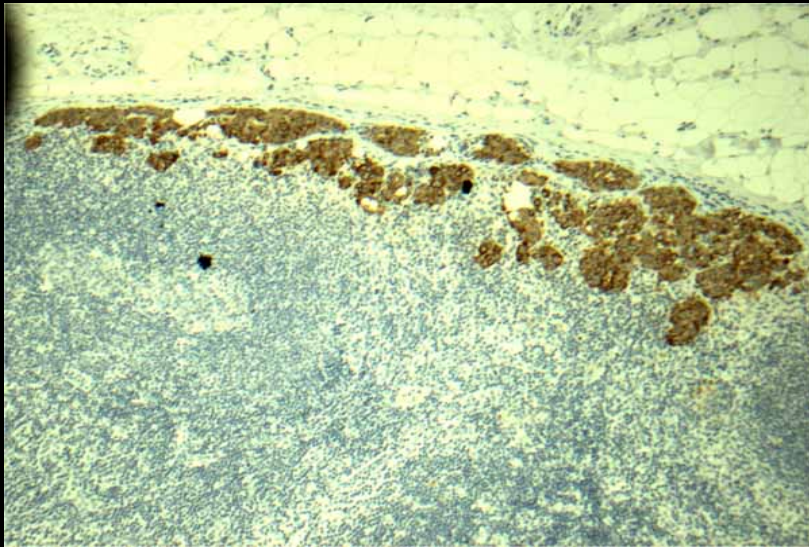
Questions regarding N-stage: post neoadjuvant chemotherapy
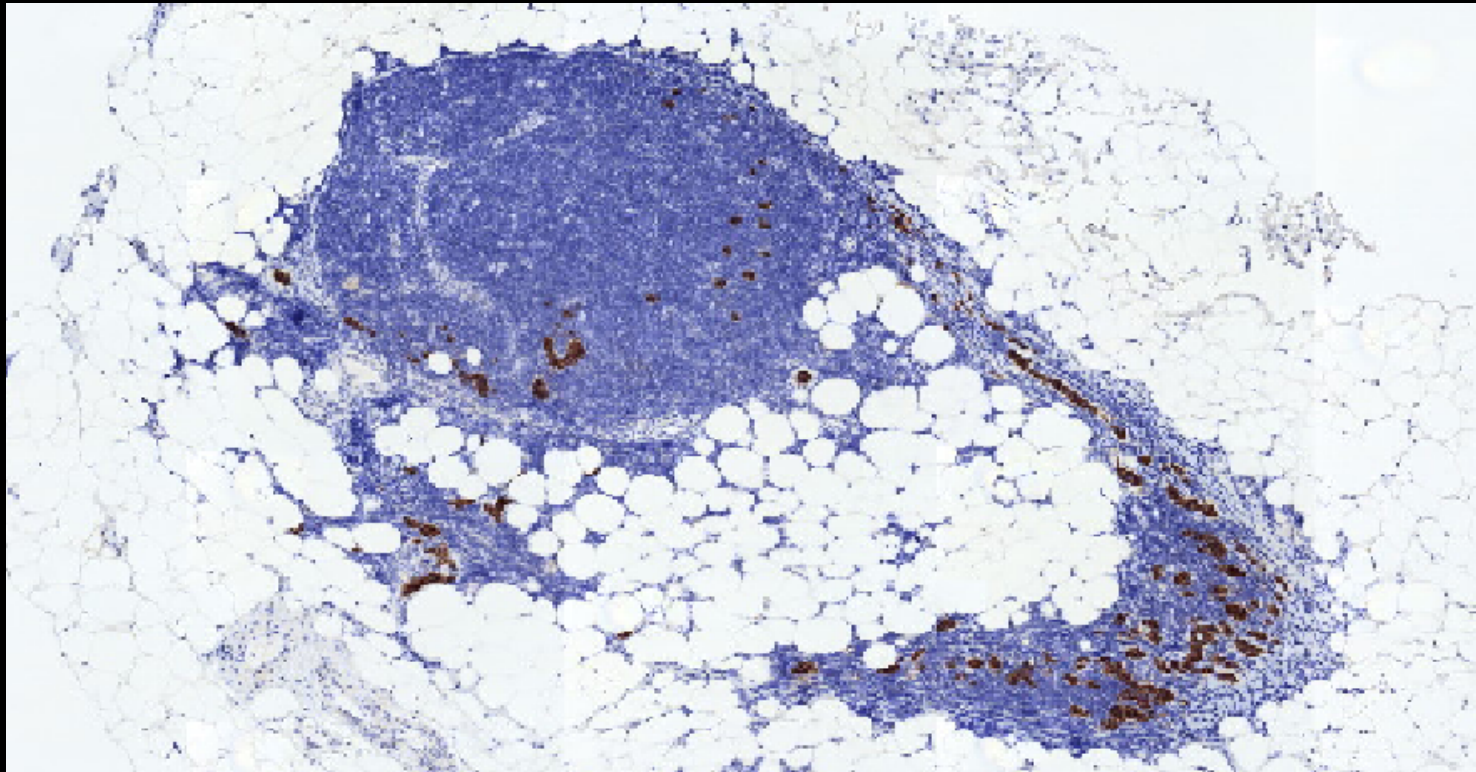
Maximum linear dimension: 0.4 mm pNmi
Does this capture all the volume of metastatic tumor size?

Changes in M category

	M-stage
1.	pM0 deletion (not a valid category)
2.	pMx deletion (not a valid category)
3.	cM0: no signs or symptoms of distant metastasis
4.	cM1: signs and symptoms or imaging evidence of distant metastasis
5.	pM1: microscopic confirmation of distant metastasis (histologically proven metastases larger than 0.2 mm)
6.	cM0 (i+): incidentally detected cancer cells, clusters of cancer cells or foci $\leq$ 0.2 mm in bone marrow or other non-regional nodal tissue, or circulating tumor cells (CTCs) that are otherwise clinically and radiologically silent
7.	M1 prior to neoadjuvant chemotherapy, remains M1 following tx regardless of cPR
	Remember to repeat Biomarkers on metastatic disease

AJCC 2010

- Mx: Unknown metastasis
- Distant Metastasis (pM) (required only if confirmed pathologically in this case)

  pM1: Distant detectable metastasis as histologically proven larger than 0.2 mm

AJCC 2017

M0   No clinical or radiological evidence of distant metastases

cM0 (i+) No clinical or radiological evidence of distant metastases in the presence of tumor cells or deposits no larger than 0.2 mm detected microscopically or by molecular techniques in circulating blood, bone marrow, or other nonregional nodal tissue in a patient without symptoms or signs of metastases

M1   Distant metastases detected by clinical and radiographic means (cM) and/or histologically proven metastases larger than 0.2 mm (pM)

ER and PR

- ER & PR expression measured primarily by IHC

- $\geq$1% of cells stained considered positive for ER & PR

- Multiple results always use positive results
  - If biopsy and resection specimens are tested, and
  - One is positive, while the other is negative, then
  - Use the positive results to assign the stage group

HER2

- HER2 measurement by IHC or ISH

- 2013 ASCO/CAP Guidelines provide standards
  - Sequential performance of tests to determine HER2 status

- Summary of standards
  - IHC
    - Negative: 0 or 1+ staining
    - Equivocal: 2+ staining
    - Positive: 3+ staining

  - ISH, dual probe (Fluorescent – FISH or Chromogen – CISH)
    - Possible negative:
      - HER2/CEP17 ratio < 2.0 and HER2 copy number < 4
    - Possible equivocal:
      - HER2/CEP17 ratio < 2.0 andHER2 copy number ≥ 4 but < 6
    - Possible positive:
      - HER2/CEP17 ratio ≥ to 2.0 by ISH, or
      - HER2 copy number ≥ to 6 regardless of ratio by ISH

HER2 Equivocal

- HER2 determined to be "equivocal"

    – By ISH (FISH or CISH) testing

    – Under the 2013 ASCO/CAP HER2 testing guidelines

- Categorize HER2 "equivocal" by ISH as HER2 "negative"

    – For assigning stage in Prognostic Stage Group Table

Example case

- Tumor size = 3.5 cm
- SLN = negative
- No mets
- Biomarkers: ER+, PR-, Her-2/neu-
- Oncotype Dx: score <11

Anatomic stage	pT2 N0 M0
Clinical Prognostic stage	IIA
Pathologic prognostic stage	IIA
With Genomic modifier; Final Clinical Prognostic stage	IA

When T is...	And N is...	And M is...	And G is...	And HER2 Status* is...	And ER Status is...	And PR Status is...	Then the Prognostic Stage Group is...
MultiGene Panel** – Oncotype Dx® Recurrence Score Less Than 11							
T1-2	N0	M0	1-3	Negative	Positive	Any	IA
T1	N0	M0	1	Negative	Positive	Negative	IB
T1	N0	M0	1	Negative	Negative	Positive	IB
T1	N0	M0	2	Positive	Positive	Negative	IB
T1	N0	M0	2	Positive	Negative	Any	IB
T1	N0	M0	2	Negative	Negative	Positive	IB
T1	N0	M0	3	Positive	Negative	Any	IB
T1	N0	M0	3	Negative	Positive	Positive	IB
T0-1	N1mi	M0	1	Negative	Positive	Negative	IB
T0-1	N1mi	M0	1	Negative	Negative	Positive	IB
T0-1	N1mi	M0	2	Positive	Positive	Negative	IB
T0-1	N1mi	M0	2	Positive	Negative	Any	IB
T0-1	N1mi	M0	2	Negative	Negative	Positive	IB
T0-1	N1mi	M0	3	Positive	Negative	Any	IB
T0-1	N1mi	M0	3	Negative	Positive	Positive	IB
T2	N0	M0	1-3	Positive	Positive	Positive	IB
T2	N0	M0	1,2	Negative	Positive	Positive	IB
T1	N1	M0	1-3	Positive	Positive	Positive	IB
T1	N1	M0	1-2	Negative	Positive	Positive	IB
T2	N1	M0	1	Negative	Positive	Positive	IB***
T2	N1	M0	2	Positive	Positive	Positive	IB***
T0-2	N2	M0	1-2	Positive	Positive	Positive	IB***

I'm slowly
giving up.

Why tumor grade is added?

Multivariate Cox Regression Model (Model 3) (N=14,675)[1]

Covariate	Level	HzR	95% CI	p
Age at Diagnosis	< 40	1.55	1.39-1.72	<.0001
	40-69	REF		
	≥ 70	1.05	0.90-1.23	0.55
Pathologic Stage	I	REF		
	IIA	2.21	1.98-2.48	<.0001
	IIB	3.47	3.07-3.91	<.0001
	IIIAB	4.27	3.71-4.91	<.0001
	IIIC	6.55	5.49-7.81	<.0001
Biologic Subtype	TNBC	1.92	1.74-2.12	<.0001
	HR+/HER2+ (T)	0.68	0.53-0.87	0.002
	HR-/HER2+ (T)	1.07	0.85-1.34	0.58
	HR+/HER2-	REF		
Nuclear Grade	1	REF		
	2	1.63	1.26-2.11	0.0002
	3	3.19	2.47-4.13	<.0001

Abbreviations - HzR: hazard ratio, CI: confidence interval, Ref: reference group (1.00)
HzR refers to the hazard ratio of death with breast cancer.

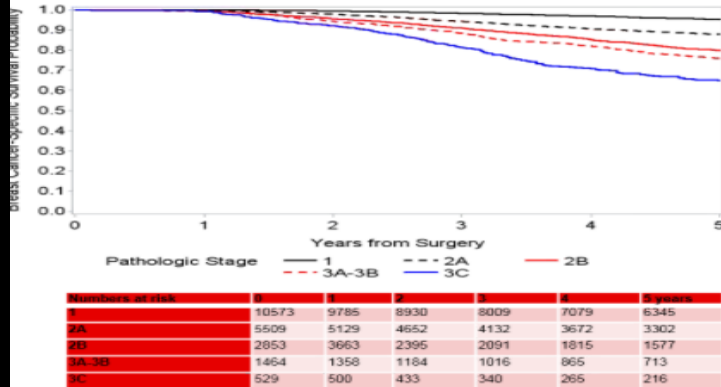[1] Patients with complete data including age, stage, HR status[2,3], HER2 status, and grade were included
[2] HR+: ER+ or PR+
[3] HR-: ER- and PR-

Why biomarker status was included?
6th and 7th ed. Not enough information to incorporate

Kaplan-Meier 5-year breast cancer specific survival estimates by pathologic stage

5-year breast cancer specific survival Kaplan-Meir estimates by pathologic stage

Stage	N N= 20,928	5Y BCSS K-M	5Y BCSS Cox
I	10573	95.3%	94.5%
IIA	5509	87.9%	87.6%
IIB	2853	79.8%	80.7%
IIIAB	1464	75.9%	78.5%
IIIC	529	64.8%	68.0%

Abbreviations ---n: number of patients; BCSS: breast cancer specific survival; 5Y: 5-year

Since 1990-follow up data:
1. ER negative survival rate is lower than ER positive (Cox regression 10-yr)
2. Her-2/neu positive survival rate is lower than Her-2/neu negative
   Her-2/neu positive with Her-2 targeted tx survival rate is similar to Her-2/neu neg
3. Triple negative breast cancer survival rate is worse

Data is incorporated in 8th ed.

Cox 5-year breast cancer specific survival estimates by pathologic stage, HR status, and HER2 status

Stage	TNBC		HR+/HER2+ (T)		HR-/HER2+ (T)		HR+/HER2-	
N=15,320	N	BCSS	N	BCS.	N	BCSS	N	BCSS
I	1033	89.0%	350	95.9%	188	93.5%	6326	95.8%
IIA	838	75.9%	183	90.5%	122	85.3%	2724	90.4%
IIB	423	63.2%	89	84.7%	57	76.8%	1374	84.6%
IIIAB	180	57.4%	71	81.7%	69	72.6%	815	81.6%
IIIC	83	42.3%	46	73.1%	46	60.9%	303	73.0%%

Multigene Panels

- Patients with
  - ER/PR-positive, HER2-negative, node-negative tumors
  - Size less than or equal to 5 cm

  - Combined with any of the following multigene panels
    - Oncotype Dx® recurrence score <11
    - Mammaprint® low-risk score
    - EndoPredict® low-risk score
    - PAM50® risk of recurrence score in low range
    - Breast Cancer Index in low-risk range

  - Stage IA: Are in same prognostic category as T1a-T1b N0 M0 with ER Positive, HER2 negative

Genomic Profile for Pathologic Prognostic Staging

- Level 1 evidence generated with the 21-gene assay suggests that:
- When the Recurrence Score is less than 11, and
- The Tumor is a T1-2 N0 M0
  - Any Grade
  - HER2-negative
  - ER-positive
  - Any PR
- Then the Pathologic Prognostic Stage is: IA

- It is likely that other Genomic Profiles (MammaPrint, ProSigna, Breast Cancer Index, EndoPredict, IHC4, etc.) provide similar prognostic information, although appropriately formatted data are unavailable.

40% moved one to another stage

Notes for Prognostic Stage Group Table

- Prognostic value of these Prognostic Stage Groups
  - Based on populations of patients with breast cancer that have been offered and mostly treated with appropriate endocrine and/or systemic chemotherapy

- Stage groups marked by asterisks ***
  - Changed by more than one stage group from 7th Edition
  - Due to use of grade and prognostic factors
  - Comparing 7th edition anatomic stage to 8th prognostic stage
  - Example of patient staged by 7th and 8th editions
    - Anatomic Stage Group IIB in 7th edition
    - Prognostic Stage Group IB in 8th edition