



2022 MCGILL FAMILY MEDICINE REFRESHER COURSE

Workshop: Breast Cancer Pathology and Treatment

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No disclosures.

- BIRADS 4 & 5 lesions and the need for a biopsy
- Discussing biopsy results & key pathologic features
- Staging breast cancer: the 2018 AJCC 8th edition
- Types of treatment: local vs systemic
- Sequencing of treatment: neoadjuvant vs. upfront surgery

How do I know my patient needs a biopsy?

A 50 year-old female patient undergoes her first ever screening mammography demonstrating a focal asymmetry in the right breast, BIRADS 3. You explain that:

- a) A biopsy is required for definitive tissue sampling
- b) This is a benign finding and she can repeat her mammogram in 1 year.
- c) This is a benign finding and she can repeat her mammogram in 1 year.
- d) This is a probably benign finding that requires short interval follow up in 6, 12 and 24 months.

A 46 year-old female patient with a family history of breast cancer in her mother undergoes routine annual screening mammography demonstrating a BIRADS 4A left upper outer quadrant breast nodule with a sonographic correlate. You explain that:

- a) Short interval follow up is necessary at 6, 12 and 24 months
- b) A biopsy is required for tissue sampling, but reassure her that this has a less than 10% risk of being malignant
- c) A biopsy is required for tissue sampling, and there is a 10-50% likelihood of malignancy
- d) A biopsy is required as this is a most likely breast cancer (>95%)

The BI-RADS (Breast Imaging Reporting and Data System) designation is used to describe and classify findings by degree of suspicion

Patients with a BIRADS 4 or 5 lesion require tissue sampling with a biopsy...

BIRADS	Suspicion of malignancy	Recommended Action
3	<2%	Short interval FU at 6, 12, 24 mos
4a	3-9%	Biopsy (US guided if sonographically
4b	10-49%	visible, stereotactic if visible on
4c	50-94%	mammogram only, MRI guided if
5	>95%	visible on MRI only)

...BIRADS 5 lesions need urgent evaluation & biopsy for breast cancer NYD by tissue sampling

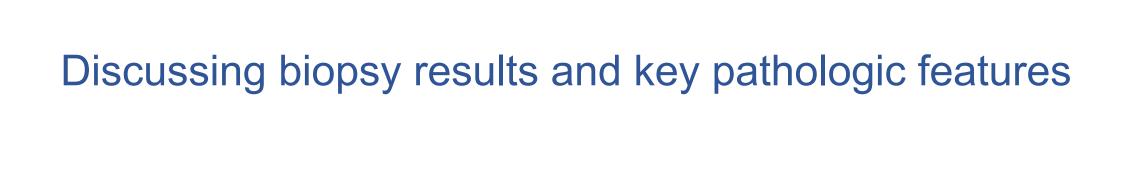
BIRADS	Suspicion of malignancy	Recommended Action
3	<3%	Short interval FU at 6, 12, 24 mos
4a	3-9%	Biopsy (US guided if sonographically
4b	10-49%	visible, stereotactic if visible on
4c	50-94%	mammogram only, MRI guided if
5	>95%	visible on MRI only)

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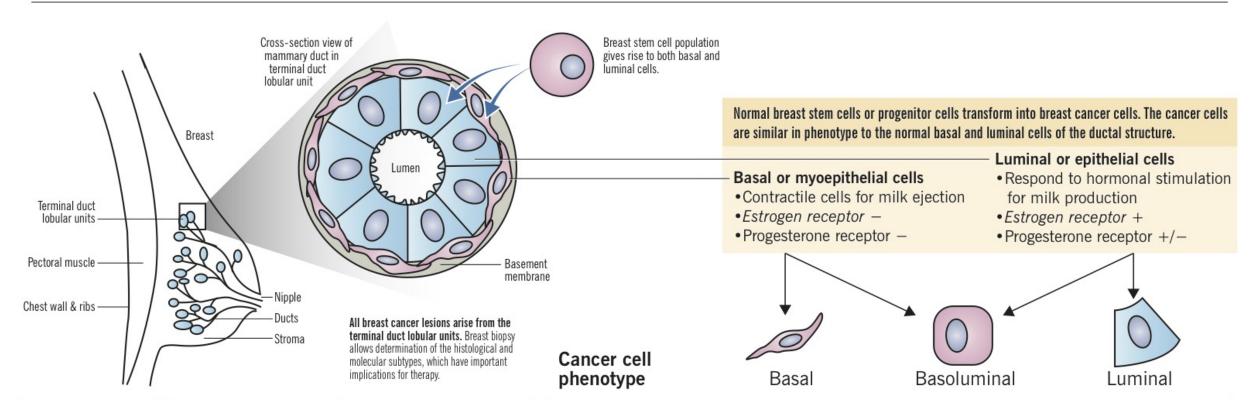
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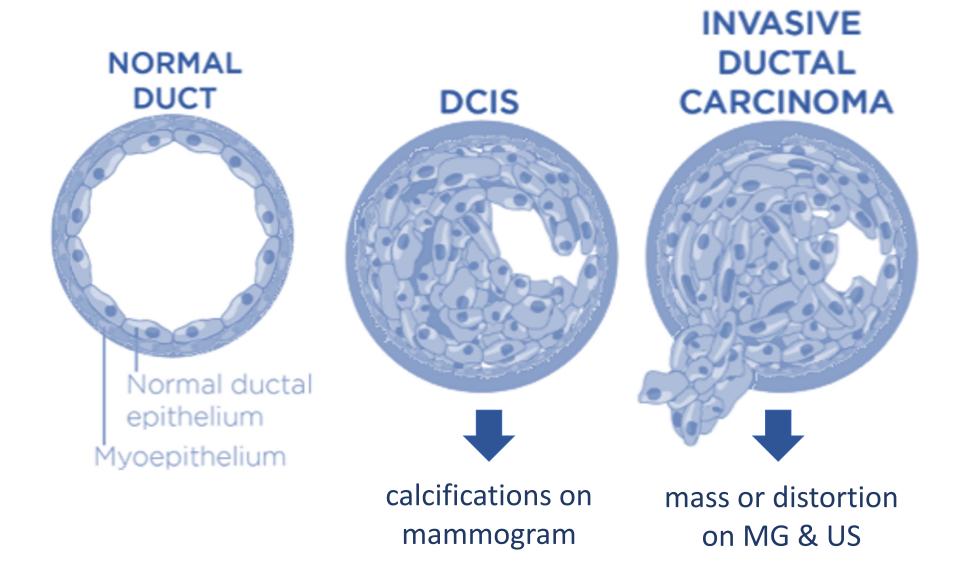


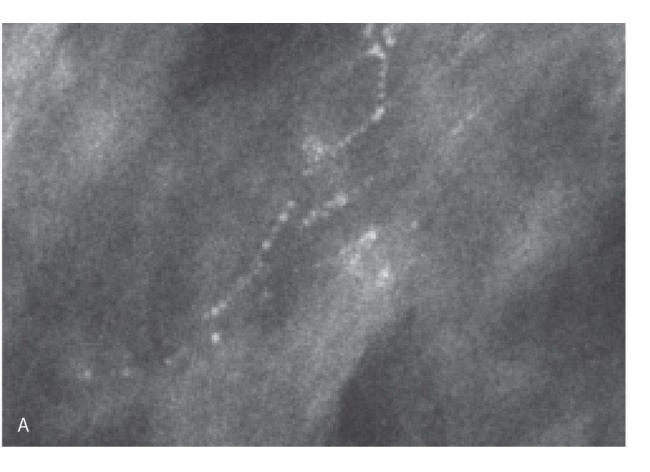
- 1. in situ vs. Invasive
- 2. Histologic subtype
- 3. Histologic grade
- 4. Biologic subtype

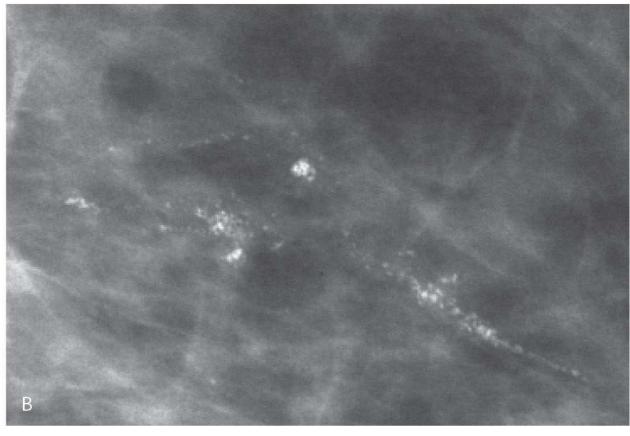
Breast cancer pathogenesis and histologic vs. molecular subtypes

Eric Wong and Jenna Rebelo









- 1. in situ vs. invasive
 - in situ carcinoma: cancerous cells remain within the duct
- 2. Histologic subtype
- 3. Histologic grade
- 4. Biologic subtype

TREATMENT IMPLICATIONS

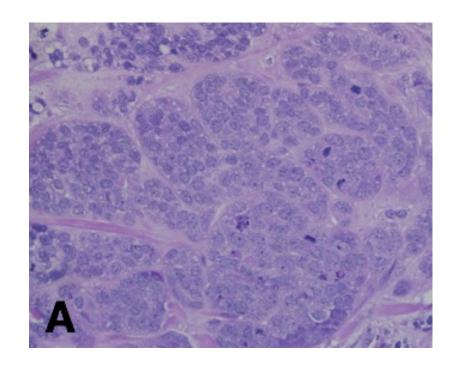
Biopsy Result	Implications	Standard treatment		
Ductal carcinoma in situ DCIS aka "stage 0" aka "precancer"	Theoretically cannot spread to nodes or metastasize = No need for nodal evaluation = No chemotherapy	(1) Surgery (always)(2) Possible radiation (prevention of recurrence)(3) If ER+, possible endocrine therapy (prevention of recurrence)		
Invasive carcinoma (stage I-III)	Could spread to other areas of the body = Check axillary lymph nodes = Need to use multimodality treatment to prevent it from coming back in the locally (breast lymph nodes) as well as other areas of the body	(1)Surgery (always)(2)Usually radiation(3)If ER+, endocrine therapy(4)Possible Chemotherapy/targeted therapy		
Metastatic invasive carcinoma (stage IV)		(1)Chemotherapy/targeted therapy (2)If ER+, endocrine therapy (3)Palliative radiation for symptoms		

Ductal carcinoma *in situ* (DCIS) is precancer or "stage 0" cancer that is contained within the duct, and theoretically cannot spread. For DCIS, chemotherapy is never indicated.

TREATMENT IMPLICATIONS

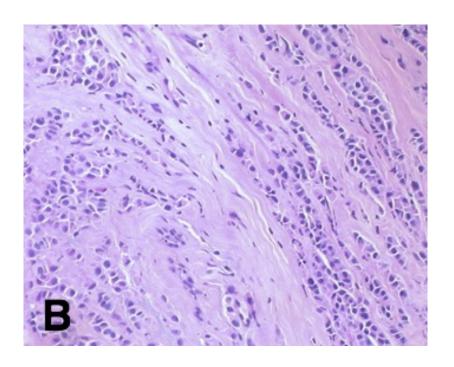
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Invasive carcinoma (stage I-II/early stage/ operable or stage III/locally advanced)	Could spread to other areas of the body = Check axillary lymph nodes = Need to use multimodality treatment to prevent it from coming back in the breast, lymph nodes and other areas of the body	(1) Surgery (always)(2) Usually radiation(3) If ER+, endocrine therapy(4) Possible Chemotherapy/targeted therapy		
Metastatic invasive carcinoma (stage IV/advanced breast cancer)		(1) Chemotherapy/targeted therapy(2) If ER+, endocrine therapy(3) Palliative radiation for symptoms		

- 1. in situ vs. invasive
- 2. Histologic subtype
 - Tells us about what the cancer looks like under the microscope and how it grows
- 3. Histologic grade
- 4. Biologic subtype



Ductal (80-85%)

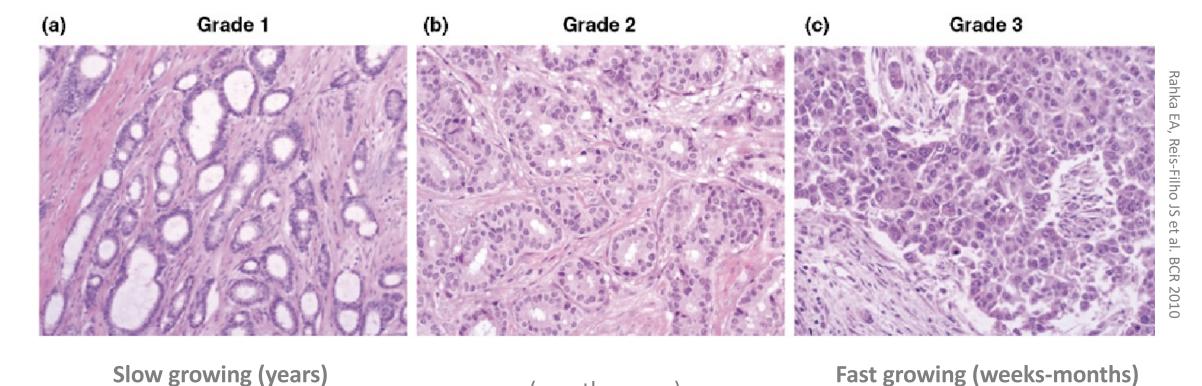
Cells grow into ducts - Produce
a firm, irregular mass that is
often palpable; can be any
biologic subtype



Lobular (10-15%)

Cells grow single file - Diffuse infiltrative growth pattern; more likely to be clinically & radiologically occult; almost always ER+HER2-

- 1. in situ vs. invasive
- 2. Histologic subtype
- 3. Histologic grade
 - Tells us about how abnormal the cells are and how quickly they are dividing
- 4. Biologic subtype



Well differentiated, cells uniform and nuclei similar to normal breast cells

(months-years)

Most common; moderate variability in size and shape, cells larger than normal, visible nucleoli

Fast growing (weeks-months)

Aggressive; Cells variable in size and shape, prominent nucleoli

- 1. in situ vs. invasive
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- 4. Biologic subtype

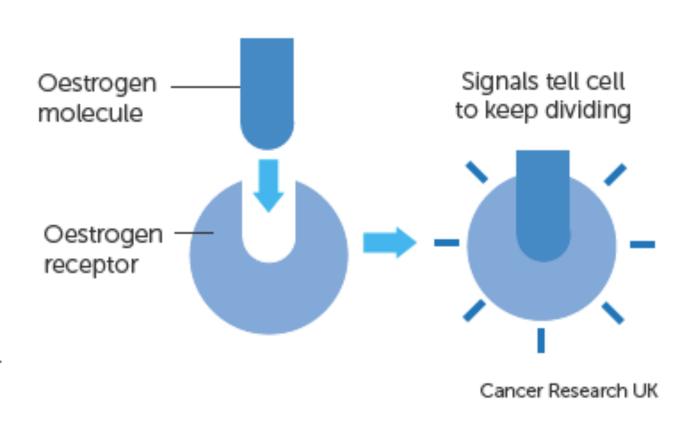
ER+ HER2-

"Hormone-positive" or "Luminal" (60-65%)

Tend to be low-intermediate grade with good prognosis

Only treat with chemotherapy if high risk for recurrence (high OncotypeDx RS or N2)

Always receive endocrine therapy for a minimum of 5 years



Biopsy Result	Implications	Surgery	Radiation*	Chemo	Endocrine
ER+HER2-	"Tumor uses estrogen like food or like fuel"; good prognosis	YES	+/-	+/-	YES

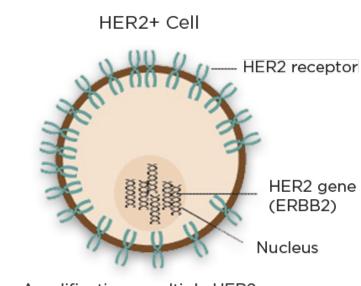
*Decision for radiation depends on surgery and pathologic factors; if breast conserving surgery or lumpectomy performed, radiation is almost always recommended

HER2+

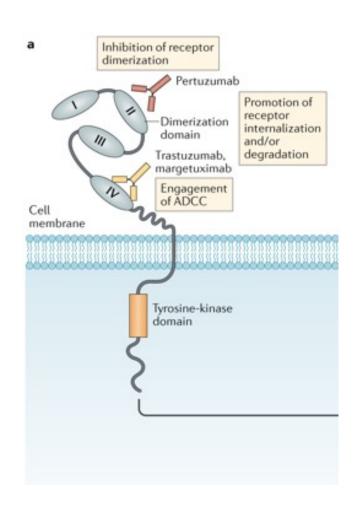
"HER2-enriched" or "Triple positive" (15-20%)

Tend to be intermediate-high grade

Aggressive & recurs early to liver, lung and brain if HER2-directed therapy (Herceptin +/-Pertuzumab) not administered



Amplification - multiple HER2 genes Overexpression - many HER2 receptors



Biopsy Result	Implications	Surgery	Radiation*	Chemo	Endocrine
ER+HER2-	"Tumor uses estrogen like food or like fuel"	YES	+/-	+/-	YES
HER2+	"Tumor is aggressive and requires HER2-targeted treatment which includes chemotherapy"	YES	+/-	YES	If ER+HER2+

*Decision for radiation depends on surgery and pathologic factors; if breast conserving surgery or lumpectomy performed, radiation is almost always recommended

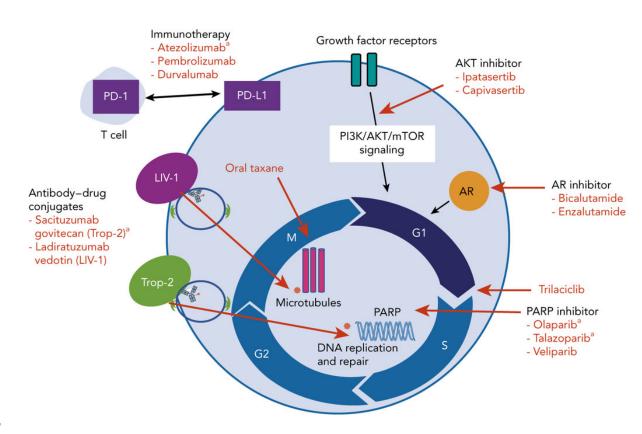
Triple Negative

(15-20%)

Tend to be high grade; Young women, *BRCA1* carriers (need genetics!)

Aggressive but chemo-sensitive; often recur early (within 3 years) almost always treated with chemotherapy as there are no good targeted therapies*;

*Immune checkpoint inhibitors and antibodydrug conjugates the new paradigm; PARPi for *BRCA-associated* TNBC



BIOLOGIC SUBTYPES

Biopsy Result	Implications	Surgery	Radiation*	Chemo	Endocrine
ER+HER2-	"Tumor uses estrogen like food or like fuel"	YES	+/-	+/-	YES
HER2+	"Tumor is aggressive and requires HER2-targeted treatment which includes chemotherapy"	YES	+/-	YES	If ER+HER2+
TNBC	"Tumor is aggressive and requires chemotherapy/immunotherapy"	YES	+/-	YES	NO

*Decision for radiation depends on surgery and pathologic factors; if breast conserving surgery or lumpectomy performed, radiation is almost always recommended

A 62 year-old female patient undergoes biennial screening mammography which reveals a new cluster of microcalcifications in the UOQ of the right breast. Ultrasound shows no underlying mass, and stereotactic biopsy reveals intermediate grade DCIS. What are the recommendations for treatment?

- a) Surgery with endocrine therapy alone
- b) Surgery with adjuvant radiation alone
- c) Surgery, adjuvant radiation and adjuvant endocrine therapy if ER+ DCIS
- d) Observation alone is the new standard of care for low-risk DCIS

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A 41 year old presents with a right 3 cm palpable breast mass. She has a family history of breast cancer in her sister. You order diagnostic investigations which reveal a node negative high-grade triple negative invasive ductal carcinoma. You organize referral to a surgical oncologist, and review her biopsy results explaining that:

- a) She will likely need staging to rule out metastatic disease
- b) She will likely need chemotherapy in addition to local therapy
- c) She is unlikely to need systemic treatment
- d) She will likely need genetic testing and chemotherapy, in addition to local therapy

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A 53 year old presents with a left 3.5 cm screen detected breast mass. Additional investigations including a left breast US and US-guided biopsy reveal a hypoechoic irregular mass at 1 oclock with normal appearing lymph nodes. Biopsy results show high grade ER-PR-HER2+ breast cancer. You organize referral to a surgical oncologist, and she asks you if she will need chemotherapy. You tell her that:

- a) She will not likely need chemotherapy but will need HER2-directed treatment (ie. Herceptin), as well as local therapy
- b) She will likely need chemotherapy that includes HER2-directed treatment (ie. Herceptin), as well as local therapy

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- 1. in situ vs. Invasive
- 2. Histologic subtype
- 3. Histologic grade
- 4. Biologic subtype
- 5. ...+/- tumor size, nodal status (imaging reports)

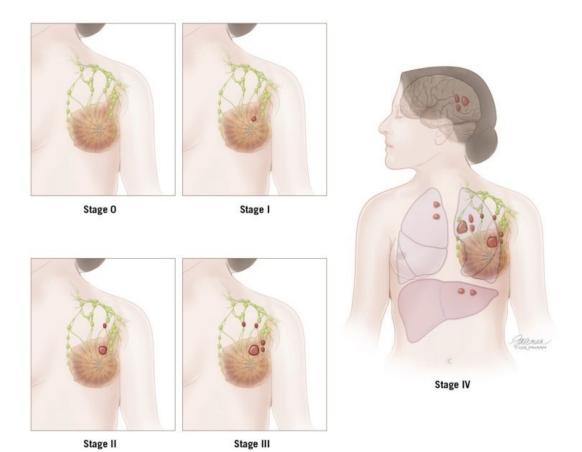
Since 2018, the AJCC 8th Edition Staging System has incorporated all of the following for clinical prognostic staging, EXCEPT:

- a) Histologic grade
- b) Histologic subtype
- c) Tumor size
- d) Biologic subtype
- e) Nodal status

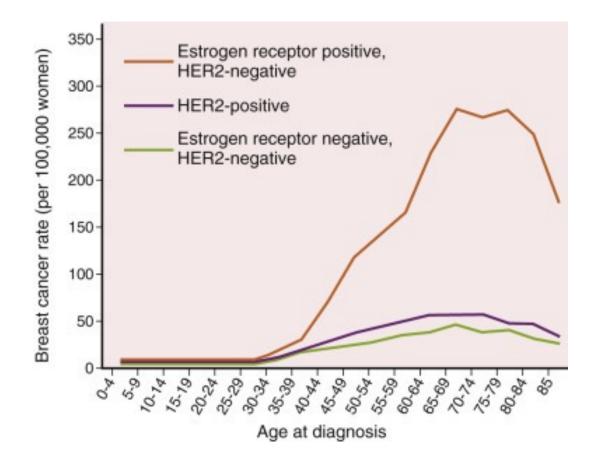
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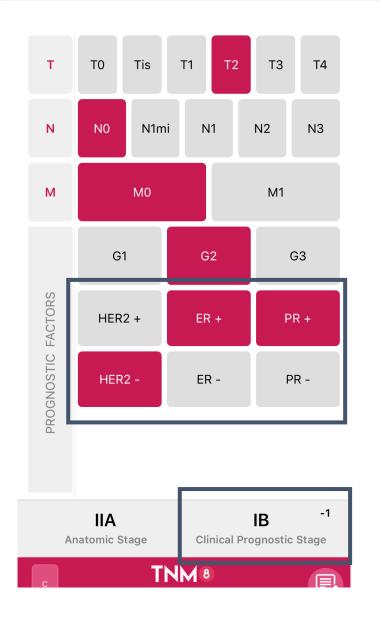
6-7th Edition: ANATOMIC (TNM)

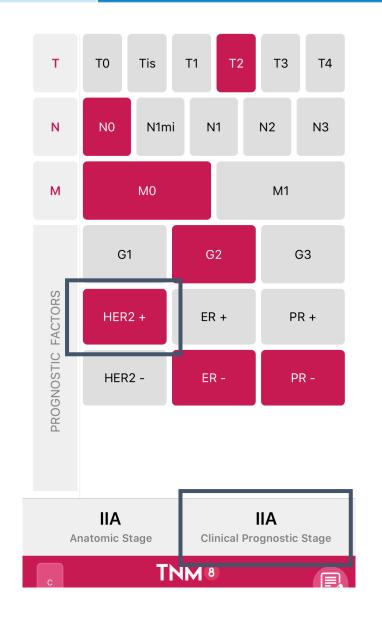


8th Edition: ANATOMIC + BIOLOGIC (GRADE + SUBTYPE)



Tumor biologic factors (biologic subtype) have become increasingly important for determining both treatment and prognosis.





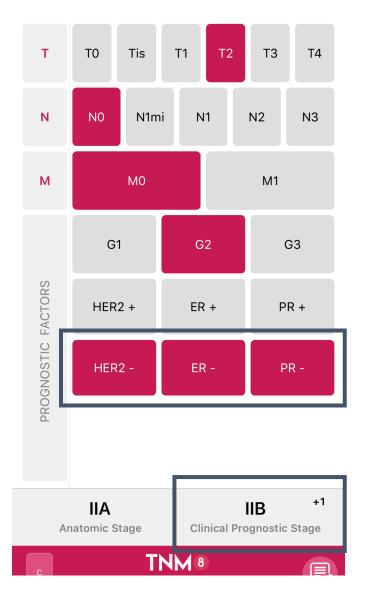
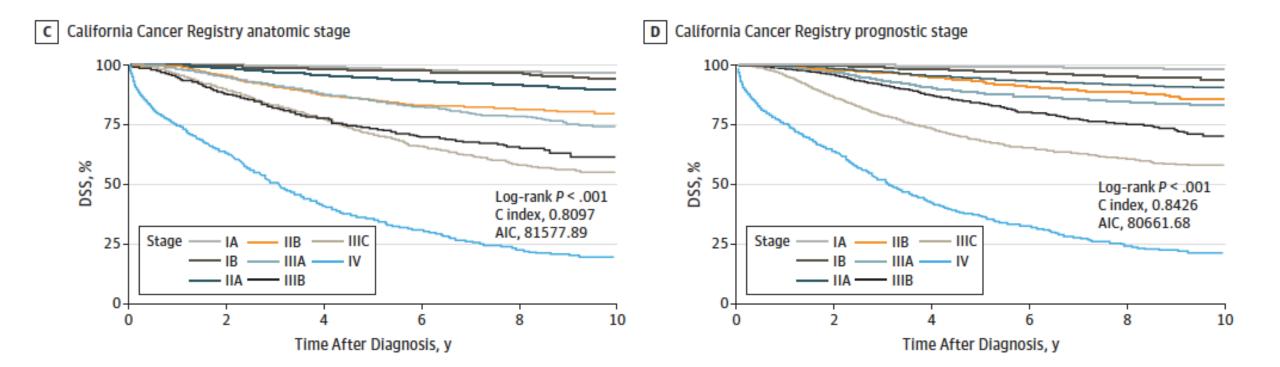


Table 1. Five-Year Disease-Specific Survival (DSS)

	MD Anderson				California	Cancer Registry		
Stage	Anatomic Stage		Prognostic Stage		Anatomic Stage		Prognostic Stage	
	No.	DSS (95% CI)	No.	DSS (95% CI)	No.	DSS (95% CI)	No.	DSS (95% CI)
IA	1437	99.1 (98.4-99.5)	1072	99.6 (98.8-99.8)	27 553	98.5 (98.4-98.7)	21 069	99.3 (99.2-99.4)
IB	82	100	844	99.3 (98.2-99.8)	1574	98.1 (97.2-98.6)	11944	97.5 (97.2-97.8)
IIA	999	98.0 (96.5-98.8)	387	97.9 (95.5-99.0)	12 663	94.6 (94.2-95.0)	5515	94.3 (93.6-94.9)
IIB	110	95.6 (92.3-97.5)	181	97.0 (90.0-99.0)	2175	85.2 (83.6-86.7)	2929	93.0 (92.0-93.9)
IIIA	183	95.4 (89.7-98.0)	207	95.0 (90.2-97.5)	3690	85.3 (84.1-86.4)	3501	88.0 (86.8-89.0)
IIIB	NA	NA	101	93.4 (84.6-97.3)	520	73.4 (69.2-77.2)	2181	83.6 (81.9-85.1)
IIIC	65	79.5 (65.6-88.2)	84	78.0 (66.4-86.0)	1592	70.8 (68.5-73.1)	2628	67.6 (65.7-69.4)
IV	NA	NA	NA	NA	1215	35.5 (32.7-38.3)	1215	35.5 (32.7-38.3)

Abbreviation: NA, not applicable.



STAGING: M0 vs. M1

Do I need to metastatic staging with CT scans, bone scans or PET scans to rule out cancer having spread to elsewhere in the body?

"Routine systemic staging is <u>not</u> indicated for patients with early-stage breast cancer in the absence of signs/symptoms of metastatic disease"

NCCN guidelines

(Consider staging with stage III/pN2 disease, inflammatory breast cancer, or recurrence)

TREATMENT IMPLICATIONS

Biopsy Result	Implications	Standard treatment		
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Metastatic invasive carcinoma (stage IV/advanced breast cancer)	Has spread to other areas of the body = focus on systemic therapies to treat metastatic disease	(1) Chemotherapy/targeted therapy(2) If ER+, endocrine therapy(3) Palliative radiation for symptoms		

Types of Treatment: Local vs. Systemic

Treatment of invasive breast cancer involves a multimodal approach including surgery, radiation therapy, chemotherapy, and endocrine therapy that work to remove the breast cancer and prevent it from coming back.

LOCAL vs. SYSTEMIC

SURGERY: LOCAL THERAPY

Breast conserving surgery (BCS)

Quadrantectomy

Partial mastectomy

Segmental mastectomy

Lumpectomy

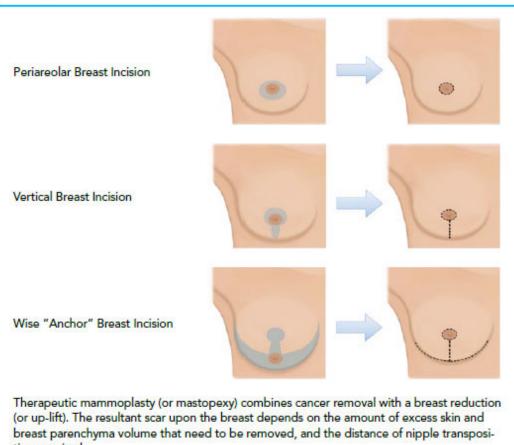
Mastectomy

Total mastectomy

Skin or nipple sparing with immediate or delayed reconstruction (implant based vs. autologous)

NEW Level I and II
Oncoplastic Approaches
for Breast Conserving Surgery

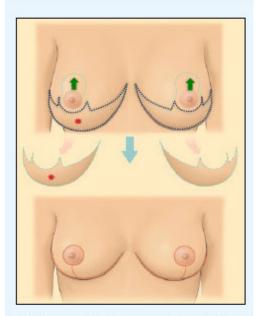
Figure 2a Therapeutic Mammoplasty / Therapeutic Mastopexy



tion required.

The most common scars usually leave the patient with a scar at the areolar edge (top), a 'lollipop' scar (middle), or one that is shaped like an 'anchor' (bottom). The horizontal limbs of the latter are typically well-hidden beneath the breast.

Figure 2b Therapeutic Mammoplasty / Therapeutic Mastopexy

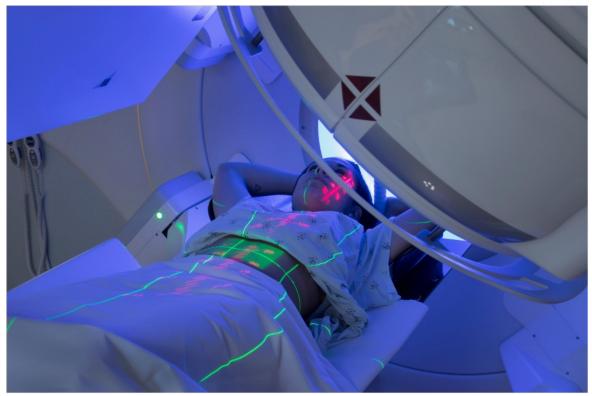


In this example, the cancer in the right breast is removed with additional breast tissue from the lower part of the breast. The nipple is repositioned higher, and the breast is reshaped to create an uplifted, smaller breast of normal shape.

The breast on the opposite side (left) undergoes a breast-lift surgery for better symmetry. Such surgery to the opposite breast is optional, and largely depends on the volume of tissue removed during the cancer resection.

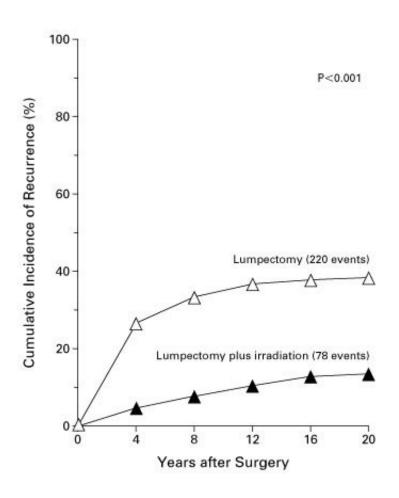
RADIATION: LOCAL THERAPY





Standard adjuvant whole breast RT typically Mon-Fri x 4-6 weeks

NEW ultra-hypofractionated options (UK FAST Forward) 1-2 weeks



When adjuvant WBRT is added to lumpectomy (termed "breast conserving therapy", LRR are reduced and survival is equivalent to mastectomy.

Cytotoxic Chemotherapy

- Can be given preoperatively (neoadjuvant chemotherapy) or postoperatively (adjuvant chemotherapy)
- When given in the adjuvant setting, always given before radiation
- Used in:
 - All locally advanced breast cancers/inflammatory breast cancers
 - All TNBC and HER2+ patients with T1c (> 5mm) or larger tumors
 - High risk ER+HER2- patients (premenopausal node positive, node negative with high Oncotype)

Recurrence Score® (RS) Result

32

Decision on individual treatment especially around the RS 25 cutoff may consider other clinical factors. Distant Recurrence Risk at 9 Years

With Al or TAM Alone

20%

95% CI (15%, 27%)

NSABP B-14

Al = Aromatase Inhibitor / TAM = Tamoxifen Cl = Confidence Intervals Group Average
Absolute
Chemotherapy (CT)
Benefit*

RS 26-100 All Ages

>15%

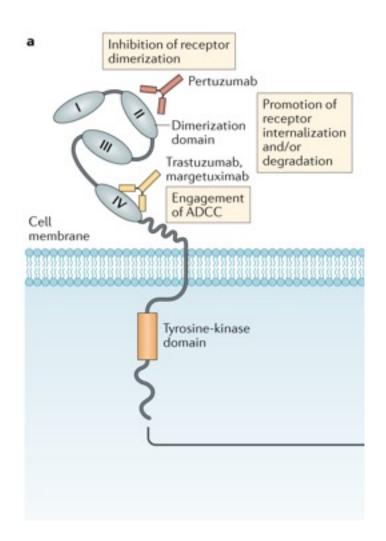
95% CI (9%, 37%)

NSABP B-20

*For estimated CT benefit for individual RS results, see page 2

Trastuzumab (Herceptin)

- Developed in the 90's, FDA approved in 1998
- Monoclonal Ab that binds to the extracellular domain of the human epidermal growth factor 2 receptor (HER2) = internalization + recycling of HER2
- Reduces signaling, arrests cells in G1 phase, halts proliferation
- "Targeted therapy" for HER2+ cancers but always given with chemotherapy

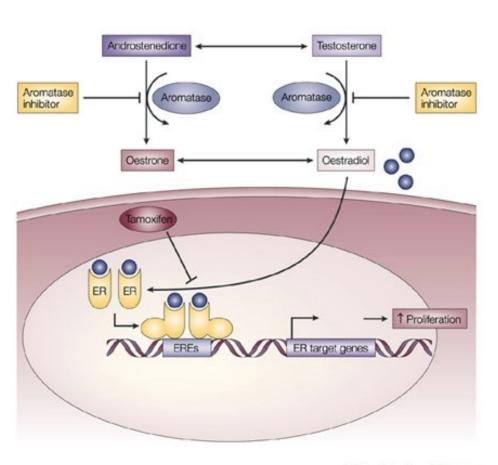


Pertuzumab (Perjeta)

- Discovered in 90's and first approved in 2012 following phase III trial CLEOPATRA (docetaxel-TP for metastatic HER2+)
- Monoclonal Ab that prevents dimerization of HER2 to prevent downstream signaling for growth and proliferation
- Now also used in neoadjuvant chemotherapy in HER2+ breast cancer

Tamoxifen (SERM)

- Use in premenopausal or postmenopausal women
- Antagonist in breast, agonist in bone and uterus
- Side effects: Hot flashes, night sweats, joint pain, cataracts, vaginal discharge, endometrial cancer (<1%), VTE (<1%)
- Take for 5 years; can also switch to Al after 5 years (extended endocrine tx)
- Also used for endocrine prevention in high-risk women



Nature Reviews | Cancer

Aromatase Inhibitors

- Include letrozole, anastrozole, exemestane
- Used in post menopausal women only (slightly better efficacy than Tamoxifen)
 - Can be given to premenopausal women on ovarian suppression
- Side effects: Joint pain, hot flashes, night sweats, vaginal dryness, osteoporosis
- Take for 5 years, with option to extend for 7-10 years in high-risk patients (extended endocrine therapy)

A 41-year-old premenopausal woman had a lumpectomy and sentinel lymph node biopsy for breast cancer. Pathological examination showed a high grade 4-cm estrogen-receptor positive invasive ductal carcinoma. Two sentinel lymph nodes were negative for malignancy. An Oncotype Dx test was sent and returned with a high Recurrence Score of 35 (high risk of distant recurrence at 10 years). What is the most appropriate management plan at this stage?

- a) Close follow-up with regular mammograms
- b) Radiation therapy
- c) Tamoxifen
- d) Radiation therapy followed by endocrine therapy
- e) Chemotherapy followed by radiation and endocrine therapy

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In a premenopausal 49 year old woman with a stage I ER+HER2- breast cancer (6 mm, with 2 negative sentinel lymph nodes), what is the standard recommendation following surgery and radiation?

- a) Endocrine therapy with tamoxifen (SERM)
- b) Endocrine therapy with an aromatase inhibitor (AI)
- c) Oophorectomy
- d) Endocrine therapy with Fulvestrant (SERD)
- e) Chemotherapy

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- d) Endocrine therapy with Fulvestrant (SERD)
- e) Chemotherapy

Which therapy is used exclusively in women with HER2-positive breast cancer?

- a) Exemestane
- b) Anastrozole
- c) CDK4/6-inhibitors
- d) PARP-inhibitors
- e) Trastuzumab +/- Pertuzumab

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Sequencing treatments in early-stage disease: Neoadjuvant chemotherapy vs. surgery

A 61 year old female presents to the emergency room with a large fungating 8 cm left breast mass. Diagnostic investigations reveal an intermediate grade ER+HER2+ invasive ductal carcinoma with cN2 nodal metastases (locally advanced breast cancer, stage III). PET staging is negative for distant metastases. She is offered neoadjuvant chemotherapy to:

- a) Help avoid the need for surgery if she demonstrates exceptional response
- b) Shrink the tumor to render it amenable to a less extensive operation
- c) Evaluate in vivo response to treatment to help advise adjuvant therapy
- d) B & C
- e) A & C

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- d) B & C
- e) A & C

A young 38 year old patient develops a right breast mass. Diagnostic investigations reveal a high-grade triple negative invasive ductal carcinoma measuring 4 cm. Genetic testing is negative. What is the likely sequencing of her treatment?

- a) Neoadjuvant chemotherapy followed by surgery and radiation
- b) Surgery followed by chemotherapy, radiation therapy and endocrine therapy
- c) Surgery followed by radiation, chemotherapy and endocrine therapy

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ADJUVANT CHEMOTHERAPY (SYSTEMIC) 3-5 months

To treat any micrometastatic disease in order to prevent the breast cancer from coming back in the breast, lymph nodes (locoregional) or other sites in the body (distant recurrence)

ENDOCRINE THERAPY (SYSTEMIC) 5-10 years

To treat any estrogen-dependent micrometastatic cells in order to prevent locoregional and distant recurrences

SURGERY (LOCAL)

To remove the breast cancer
(BCS vs. mastectomy),
sample the axillary lymph nodes
and provide pathologic staging
information to help guide additional
local and systemic treatment
decisions

ADJUVANT RADIATION (LOCAL) 2-6 weeks

To treat the whole breast or chest wall +/involved lymph node basins (regional nodal
irradiation) to prevent a locoregional
recurrence

SURVIVORSHIP

Exercise and healthy diet to help prevent recurrences; monitor bone health and cardiac health; screening for new primary



To decrease the size of the tumor to facilitate less extensive surgery in the breast and axilla; to assess in vivo treatment response to obtain prognostic information

DE-ESCALATED OR ESCALATED ADJUVANT CHEMOTHERAPY

Depending on disease response (pCR = excellent response; residual invasive disease = possible chemoresistant micrometastases)

SURVIVORSHIP

Exercise and healthy diet to help prevent recurrences; monitor bone health and cardiac health; screening for new primary

SURGERY (LOCAL)

To remove the breast cancer
(BCS vs. mastectomy),
sample the axillary lymph nodes and provide
pathologic staging and response information
following neoadjuvant chemotherapy
(pCR vs. no pCR)

ADJUVANT RADIATION (LOCAL) 2-6 weeks

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irradiation) to prevent a locoregional
recurrence

NEOADJUVANT CHEMOTHERAPY (SYSTEMIC) 3-6 months

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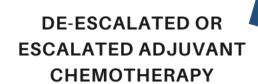
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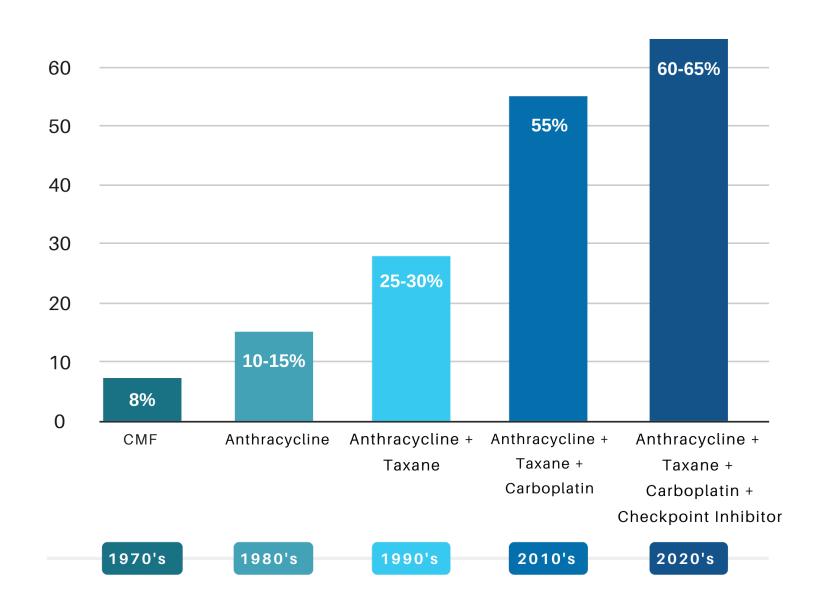
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- All BIRADS 4 & 5 lesions require biopsy for tissue sampling
- On biopsy pathology, biologic subtype is the most important variable for determining both treatment and prognosis
- Local treatments include surgery and radiation, and prevent the breast cancer from coming back in the affected breast and axillary lymph nodes

- Systemic therapies work to prevent breast cancer from recurring in the breast, lymph nodes, and elsewhere in the body (prevent distant metastases)
- For ER+HER2- breast cancer, the decision for chemotherapy depends on pathologic features and genomic assay results
- Neoadjuvant treatment is widely used in triple negative and HER2+ breast cancer to assess treatment response and tailor therapy

