Breast Cancer Introductory Lecture

General Info: Breast Cancer

General Information:

Avg age diagnosis 62
Lifetime risk 1/8 (~13%)

Standard Screening:

Age 40-45

Annual mammography

MRI/MMG Q6M if high risk

Clinical Risk Factors:

Clinical Characteristics
- Age
- Obesity
- Tall height
- Dense breasts

Estrogen Exposure
- Early menarche/late menopause
- Nullparity/Late Pregnancy
- No breastfeeding
- OCP, IVF, HRT

Other Exposures
- ETOH, RT

Genetic Risk Factors:

Family History
- Ashkenazi Jewish

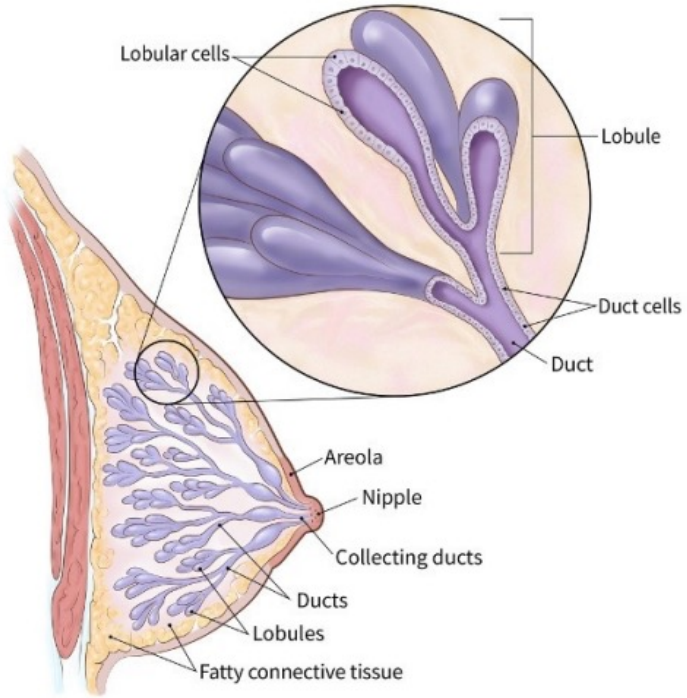
High Penetrance
- BRCA1/2
- PALB2
- TP53 (Li Fraumeni)
- PTEN (Cowden's)
- STK11 (Peutz-Jegher)
- CDH1 (Hereditary Gastric)

Moderate Penetrance
- CHEK2
- ATM
- NF1
- RAD51C/D
- BARD1

Breast Cancer Pathology

Breast Cancer Pathology

Normal breast tissue is composed of **lobules** where milk is made and breast **ducts** where milk is channeled to the nipple



American Cancer Society

Ductal Carcinoma

~80% of cancers
Positive for e-cadherin = cellular adhesive
Cells are cohesive, often in clusters
More easily identified on imaging or exam

Lobular Carcinoma

~10% of cancers
Defined as absence of e-cadherin = cellular adhesive
Cells are dis-cohesive, can appear single file
Less easily identified on imaging or exam

Breast Cancer Histology

Breast cells develop into malignant cells along a spectrum

Atypical Ductal/Lobular Hyperplasia (ADH/ALH)

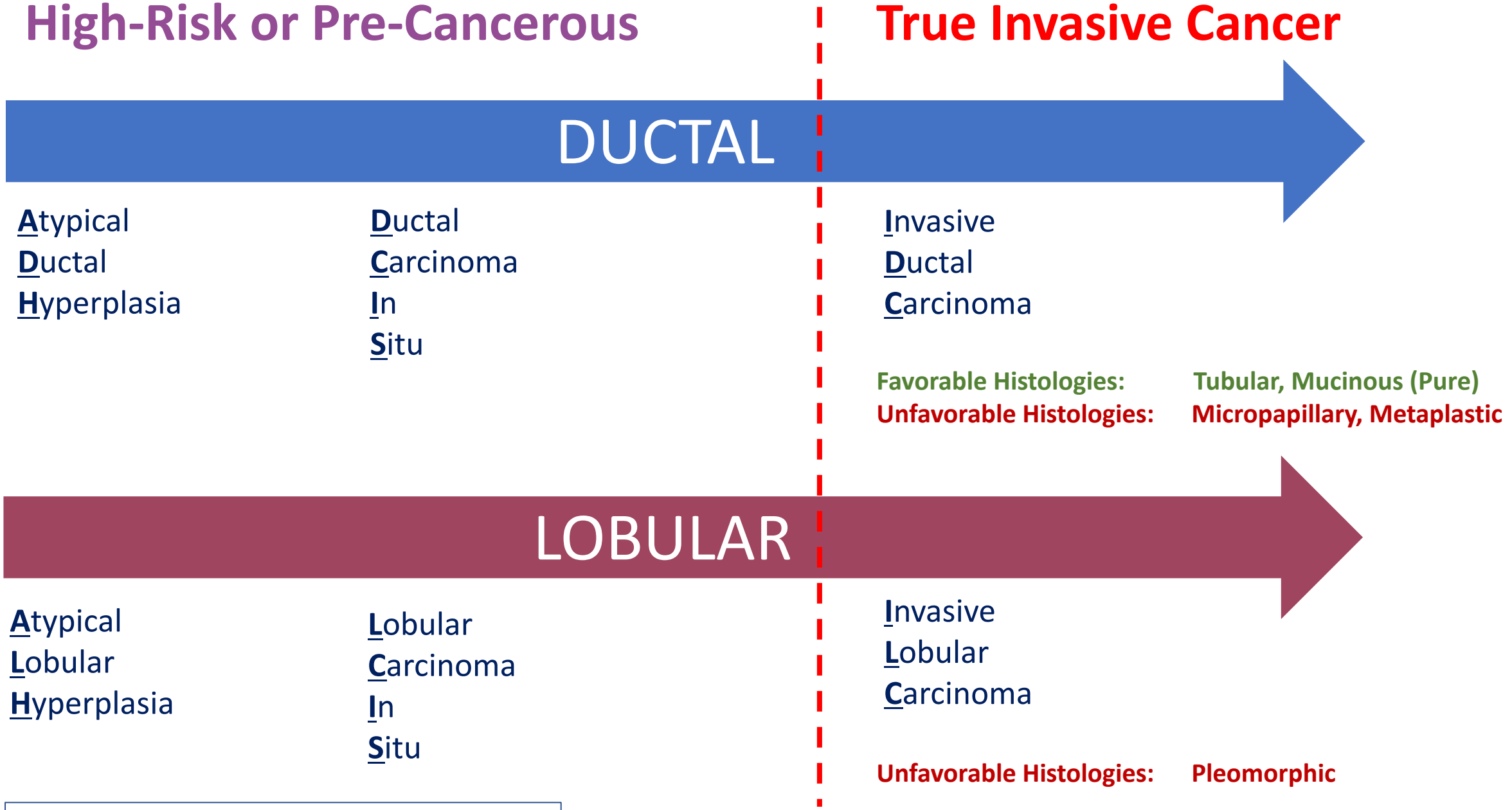
Abnormal High-Risk Cells
Portend higher risk of future cancer

Ductal/Lobular Carcinoma in Situ (DCIS/LCIS)

High-Risk (LCIS) or Pre-Cancerous Cells (DCIS) Stage 0
"in situ" = stuck "in place"
Do not have the ability to invade outside the breast

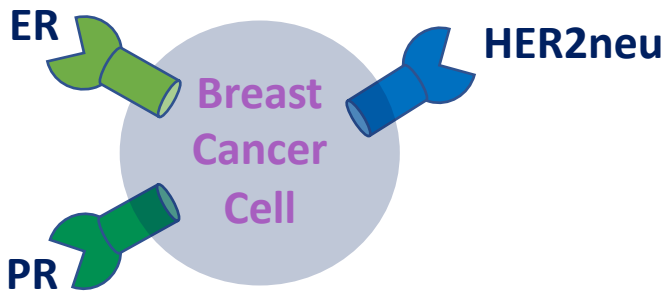
Invasive Ductal/Lobular Carcinoma (IDC/ILC)

Invasive Cancer (Stage I-IV)
Has the potential to invade outside the breast


High-Risk or Pre-Cancerous
True Invasive Cancer
DUCTAL
Atypical Ductal Hyperplasia
Ductal Carcinoma In Situ
Invasive Ductal Carcinoma
Favorable Histologies: Tubular, Mucinous (Pure)
Unfavorable Histologies: Micropapillary, Metaplastic
LOBULAR
Atypical Lobular Hyperplasia
Lobular Carcinoma In Situ
Invasive Lobular Carcinoma
Unfavorable Histologies: Pleomorphic
* Can have a mixed Ductal/Lobular phenotype

Breast Cancer Subtypes

Hormone receptors (estrogen and progesterone) & HER2 receptors
= expressed on some breast cancer cells

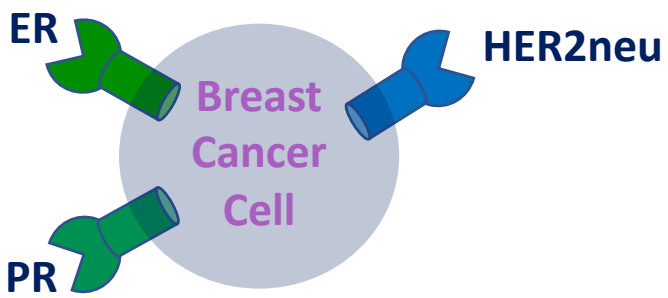


Receptors always written in order:

ER → PR → HER2
ER+/PR+/HER2- or +/+/-

Types of Breast Cancer		Incidence
HR+/HER2-	HR positive	70%
HR-/HER2+ HR+/HER2+	HER2 positive Triple positive	20%
HR-/HER2-	Triple negative	10%

Breast Cancer Receptors



Definition of HR+ (ER+ or PR+)

Hormone Receptor positive = HR+

Estrogen Receptor (ER)
Progesterone Receptor (PR)

HR "Low"
1-10% ER or PR = HR "low" but still positive
> 10% ER or PR = positive

either ER or PR > 1% = HR+

Definition of HER2+

HER2+ IHC is graded 1+ to 3+ (1+ = weak; 3+ = strong)

HER2 IHC 1+ = negative
HER2 IHC 2+ = equivocal, requires confirmatory FISH
HER2 IHC 3+ = positive

FISH Tests: HER2/CEP17 and HER2 CN

HER2/CEP17 > 2 = Positive
HER2/CEP17 = HER2 gene/chromosome 17 centromere expression

HER2 CN > 4-6 = Positive
HER2 CN = HER2 copy number

Breast Cancer Staging

Receptors:
Staging includes HR and HER2 receptor status, grade, as well as TNM

Notable T Sizes:
T1a: < 0.5 cm
T1b: 0.5 – 1 cm
T1c: 1-2 cm
T2: 2-5 cm
T3: > 5 cm
T4: chest wall or skin

Notable lymph Nodes:
N1 = 1-3 axillary LN
N2 = 4-9 axillary LN or internal mammary LN
N3 = 10+ axillary LN or supraclavicular LN
axillary LN with IM or supraclavicular LNs

M1 = mediastinal or cervical LN

Work Up:

CT torso with either PET or Bone Scan
if advanced disease or symptoms of metastatic disease

Consider staging in more aggressive N+ cancers
Ex: HER2+ or TNBC N+ cancers
Some stage II
Most/all stage III

Breast Cancer Prognosis

Prognosis varies significantly based on: staging (early vs late) and receptor status

Early Stage Breast Cancer:

Stage I-III BC 5Y OS around 75-95%

HR+	5Y OS 95%
HER2+	5Y OS 85%
TNBC	5Y OS 75%

Metastatic Breast Cancer:

Stage IV HR+	5Y OS around 30%
Stage IV HER2+	5Y OS around 20%
Stage IV TNBC	5Y OS around 10%

Stage IV HR+	median OS 57 months
Stage IV HR-	median OS 31 months

Early Stage Breast Cancer Treatment

Early Breast Cancer Treatment Paradigm

Local Control

Goal = remove cancer locally

Surgery

+/- **Radiation Therapy**

Systemic Therapy

Goal = reduce risk of local & distant recurrence

(1) Destroy any microscopic cells not removed in local resection
(2) Modify hormonal environment to reduce risk of recurrence

+/- **Chemotherapy**

+/- **Endocrine Therapy** if HR+

+/- **Antibody Therapy** if HER2+

+/- **Immunotherapy** if TNBC+

Early Breast Cancer Treatment Paradigm

Chemotherapy	Cellular poison. Kills rapidly dividing cells.
Endocrine Therapy	Anti-estrogen hormone therapy. Reduces the estrogen in the body that stimulates the estrogen receptor or blocks the estrogen receptor. Removes the “food source” for HR+ cancer
Antibody Therapy	Antibody therapy directed at targets such as the HER2+ receptor. Prevents the HER2 receptor from stimulating downstream signaling pathways.
Other Therapies	Additional therapies such as immunotherapy, conjugated antibodies, CDK4/6 inhibitors, PARP inhibitors, etc

Local Therapy: Breast Surgery

Lumpectomy +/- RT

Partial breast removal
for **smaller** tumors

- Often requires adjuvant RT

Mastectomy +/- RT

Total breast removal
for **larger** tumors or if **contraindication to RT**

- Often negates need for adjuvant RT
  Post-mastectomy RT if T3 (> 5 cm) or N2 (> 4 LN)

- Contraindication to RT
  Ex: Pregnancy, prior RT, certain connect tissue disorders

** Can be nipple-sparing*
** Top surgery for transgender or gender diverse patients is not equivalent to a mastectomy. Natal breast tissue is not entirely removed*

Local Therapy: Lymph Node Dissections

SLNB

Sentinal Lymph Node Biopsy

Removal of a few targeted lymph nodes identified via a tracer injected near the cancer
ex: blue dye, radioactive isotope

If cT1N0 low risk sometimes can avoid SLND

Risk of lymphedema ~10%

ALND

Axillary Lymph Node Dissection (ALND)

Removal of many axillary lymph nodes, regardless of tracer uptake

If cT1-T2N0 with 0-2+ SLN or PCR after neoadjuvant treatment sometimes can avoid ALND

Risk of lymphedema ~40%

Breast Cancer Treatment Paradigm

Atypical Ductal/Lobular Hyperplasia (ADH/ALH)

+/- Surgery evaluate upstaging

+/- ET prevention

Ductal/Lobular Carcinoma in Situ (DCIS/LCIS)

Surgery +/- RT eval upstaging + treatment

+/- ET prevention

Invasive Ductal/Lobular Carcinoma (IDC/ILC)

Surgery +/- RT

+/- Chemo

+/- ET

+/- HER2 AB

+/- Immunotherapy

Chemotherapy, HER2 ABs, Immunotherapy are ONLY used for invasive disease

Early Breast Cancer Treatment Paradigm

Neoadjuvant Therapy
systemic therapy **BEFORE** surgery

Adjuvant Therapy
systemic therapy **AFTER** surgery

Adjuvant vs. Neoadjuvant Therapy

SURGICAL INDICATIONS FOR NEOADJUVANT TX

(1) Down-Sizing of Surgery

ex: can allow for lumpectomy instead of mastectomy or spare an axillary LN dissection

(2) Rendering Inoperable Tumors Operable

ex: Inflammatory breast cancer (T4)

Early Breast Cancer: Adjuvant vs. Neoadjuvant Therapy

MEDICAL INDICATIONS FOR NEOADJUVANT TX

(3) Pathologic Assessment of Response to Therapy
Change of Adjuvant Therapy in HER2+ and TNBC

HER2+ w/ pathologic complete response (PCR) → adjuvant **HP (Herceptin/Perjeta)**
HER2+ w/ residual disease (RD) → adjuvant **TDM1 (Kadcyla)**

TNBC w/ pathologic complete response (PCR) → no adjuvant chemo
TNBC w/ residual disease (RD) → adjuvant **capecitabine (Xeloda)**

Early Breast Cancer: Systemic Treatment Schema

Breast Cancer treatment is Receptor Based

+/- Chemotherapy

✚

HR positive

Endocrine Therapy

HER2 positive

Antibody Therapy

HR+/HER2+

Endocrine Therapy

Antibody Therapy

Common Chemotherapy Regimens

HER2- Chemotherapy Regimens:

ACT: (A) Adriamycin
(C) Cyclophosphamide
(T) Paclitaxel

TC: (T) Docetaxel
(C) Cyclophosphamide

CMF: (C) Cyclophosphamide
(M) Methotrexate
(F) 5FU
* *older regimen, less frequently used*

HER2+ Chemotherapy-Antibody Regimens:

TC-HP: (T) Docetaxel (H) Trastuzumab/Herceptin
(C) Carboplatin (P) Pertuzumab/Perjeta

T-H: (T) Paclitaxel (H) Trastuzumab/Herceptin

ACT-H/P: (A) Adriamycin
(C) Cyclophosphamide
(T) Paclitaxel
* *older regimen, less frequently used*

Important Side Effects:

Adriamycin → cardiotoxicity (monitor with TTE)
Paclitaxel/Docetaxel → neuropathy, transaminitis
A, C, T, M, F → myelosuppression, hair loss, infertility

Common Chemotherapy Regimens

TNBC Regimens:

ACT: (A) Adriamycin
(C) Cyclophosphamide
(T) Paclitaxel

TC-AC-Pembro: ”Keynote 522”

(T) Paclitaxel
(C) Carboplatin

(A) Adriamycin
(C) Cyclophosphamide

Pembrolizumab (*Keytruda*)

Important Side Effects:

Adriamycin → cardiotoxicity (monitor with TTE)
Paclitaxel → neuropathy, transaminitis
Carboplatin → neuropathy, nephropathy, ototoxicity
A, C, T, M, F → myelosuppression, hair loss, infertility

Pembrolizumab → autoimmune inflammation in *any* organ
commonly thyroid, skin, colon, liver

Endocrine Therapy (ET)

Hormone Therapy: 5-10 years adjuvant

Selective Estrogen Receptor Modulator
SERM = PRE-MENOPAUSAL drug
inhibits estrogen receptor

Tamoxifen

* SERMs CAN be used for post-menopausal women

Aromatase Inhibitors
AI = POST-MENOPAUSAL drug
Inhibits peripheral conversion of androgens to estrogen

Anastrozole (Arimidex)
Letrozole (Femara)
Exemestane (Aromasin)

* AIs CANNOT be used for pre-menopausal women unless given with OFS

Important Side Effects:

SERM → DVT (1-2%), endometrial cancer (1%, mostly in post-men women), teratogenic, dysmenorrhea
hot flashes, night sweats, vaginal secretion changes, mood, weight, cognition changes, cataracts

AI → arthritis (10-30%), osteoporosis, cholesterol changes
hot flashes, night sweats, vaginal dryness, mood, weight, cognition changes, cataracts

HER2+ Antibodies, Conjugated ABs, TKIs

HER2 Antibodies: 1 year total

Trastuzumab (Herceptin): HER2 AB
Commonly part of neo/adjuvant treatment

Pertuzumab (Perjeta): HER2 AB
** Only used with trastuzumab for >T2 or N+ tumors*

TDM1 (Kadcyla): HER2 Conjugated AB
** Only used if residual disease after neoadjuvant trastuzumab*

Neratinib: HER2 Tyrosine Kinase Inhibitor
** Can give after 1 year adjuvant HER2 AB if high-risk, often TPBC*

Important Side Effects:

Trastuzumab/TDM1 → cardiotoxicity (Q3 month TTE during treatment)
Pertuzumab → diarrhea
TDM1 → thrombocytopenia, transaminitis/hepatopathy, neuropathy

HR+ Early Breast Cancer Treatment Overview

Small

T1-T2, N0-N1

Surgery

Low Oncotype

ET: SERM (Tamoxifen)$^{PRE\text{-}MEN}$ or AI (Anastrozole)$^{POST\text{-}MEN}$
For 5-10Y

RT: Radiation Therapy

High Oncotype

TC [ddACT if high risk]
(T) Docetaxel
(C) Cyclophosphamide

ET (for 5-10Y)

RT

Large

T3-T4, N2-N3

ddACT: AC Q2W → T
(A) Anthracycline
(C) Cyclophosphamide
(T) Paclitaxel

Surgery

ET (for 5-10Y)

RT

HER2+ Early Breast Cancer Treatment Overview

Small

T1N0

Surgery → **T-H**
(T) Paclitaxel
(H) Herceptin
→ **Radiation**
H (Herceptin)
To complete 1Y HER2 AB

Large

T2 or N+

TC-HP
(T) Docetaxel
(C) Carboplatin
(H) Herceptin
(P) Perjeta
→ **Surgery +/- RT**

→ **PCR**
pathologic complete response
→ **HP +/- ET**
To complete 1Y HER2 AB
For 5-10Y

→ **RD**
ANY residual invasive disease
*does not have to be HER2+
→ **TDM1 +/- ET**
To complete 1Y HER2 AB
For 5-10Y

TNBC Early Breast Cancer Treatment Overview

Small

T1N0

Surgery → **ddACT**
(A) Doxorubicin
(C) Cyclophosphamide
(T) Taxol
→ **Radiation**

Large

T2 or N+

TC-AC-Pembrolizumab
(T) Taxol
(C) Carboplatin
(A) Doxorubicin
(C) Cyclophosphamide
(P) Pembrolizumab
→ **Surgery +/- RT**

→ **PCR**
pathologic complete response
→ **Pembrolizumab**

→ **RD**
residual disease
→ **Capecitabine + Pembrolizumab**

* Consider Olaparib (PARP inhibitor) in place of capecitabine if RD and gBRCA+

Metastatic Breast Cancer Treatment

Metastatic Breast Cancer: Front Line Therapy Overview

HR+ Breast Cancer:

Hormone Therapy: SERM or AI

with

CDK4/6 Inhibitor: palbociclib, ribociclib, abemaciclib

HER2+ Breast Cancer:

HER2+ Therapy: trastuzumab + pertuzumab

with

Chemotherapy: docetaxel or paclitaxel

HR-/HER2-: Triple Negative Breast Cancer

CPS+ (>10%): pembrolizumab + chemotherapy

or

Chemotherapy: single-agent chemotherapy

HR+/HER2+: Triple Positive Breast Cancer

HER2+ Therapy: trastuzumab + pertuzumab

with

Chemotherapy: docetaxel or paclitaxel
** or with ET in place of chemotherapy for select patients*

MBC: Targetable Mutations

ADDITIONAL STUDIES:

NGS: Look for actionable mutations (targeted agents used 2nd line)

Tumor Testing (more sensitive)

Liquid Testing (ctDNA = circulating tumor DNA)

ESR1 → Resistance to AIs (use SERDs) in HR+ MBC

PIK3CA → Responds to PI3K inhibitors (ex: alpelisib, capivasertib)

BRCA → Responds to PARP inhibitors (ex: olaparib, talazoparib)

CPS → Sensitive to Immunotherapy (ex: pembrolizumab) in TNBC

MBC HR+: Treatment Schema

* There is no SOC 2nd line onward therapy for HR+ MBC. Below is one proposed schema

Tx Line	Regimen	 Genetic Testing: ESR1, PIK3CA, BRCA, etc 
1st	AI Sensitive:	AI + CDK4/6 Inhibitor (ribociclib, abemaciclib, palbociclib)
	AI Resistant:	Fulvestrant + CDK4/6 Inhibitor
2nd	ET Sensitive:	1. Elacestrant ESR1 > WT 2. Fulvestrant Combination: + Capivasertib PIK3CA/PTEN/AKT, Aleplisib PIK3CA, Everolimus, alt. CDK4/6 3. Fulvestrant Monotherapy
	ET Resistant:	BRCA WT = ADC or single agent chemo (see below) BRCA Δ = PARP inhibitor (olaparib, talazoparib)
3rd	HER2 Low =	1. TDxd (*Enhertu*) 2. Sacituzumab after ET + 2 systemic txs 3. Single agent chemo (ex: anthracycline, taxane)
	HER2 Neg =	1. Sacituzumab (*Trodelvy*) after ET + 2 systemic txs 2. Single agent chemo (ex: anthracycline, taxane)
★	Clinical Trial	

MBC HER2+: Treatment Schema

* There is no SOC 2nd line onward therapy for HER2+ MBC. Below is one proposed schema

Tx Line	Regimen
1st	Taxane + Trastuzumab + Pertuzumab
2nd	**Trastuzumab Deruxtecan = TDXd (*Enhertu*)** * consider earlier if brain mets
3rd – 4th	**Tucatinib + Trastuzumab + Capecitabine** * consider earlier if brain mets
3rd - 4th	**Trastuzumab Emtansine = TDM1 (*Kadcyla*)**
5th	**Margetuximab + Chemo** **Neratinib + Capecitabine**

★	**Clinical Trial**

MBC TNBC: Treatment Schema

* There is no SOC second+ line therapy for TN MBC. Below is one proposed schema

Tx Line	Regimen
1st	PDL1 >10% = pembrolizumab + chemo
	PDL1 <10% = single agent chemo (ex: anthracycline, taxane)
2nd	gBRCA = PARP inhibitor (Olaparib, Talazoparib) * consider in other HRD
3rd	1. ADC Sacituzumab (*Trodelvy*) after 2 systemic lines of therapy, at least 1 for MBC Trastuzumab Deruxtecan TDXd (*Enhertu*) HER2 Low 2. Single agent chemotherapy

★	Clinical Trial

Breast Cancer Reference Handout

Breast Cancer Dx

Atypical Ductal/Lobular Hyperplasia (ADH/ALH)

Abnormal "high-risk" lesions
+/- Surgery (to evaluate up-staging)
+/- ET (for prevention, not typically stained for HR)

Ductal/Lobular Carcinoma in Situ (DCIS/LCIS)

High-risk lesion (LCIS)
Non-invasive cancer, Stage 0, "Pre-Cancer" (DCIS)
Surgery (to evaluate up-staging, treatment for DCIS)
+/- ET if HR+ (for prevention)

Invasive Ductal/Lobular Carcinoma (IDC/ILC)

Invasive cancerous lesions
Stage I-IV
Surgical resection +/- RT if stage I-III
Receptor-based neoadjuvant or adjuvant therapy (I-III)

Definition of HR+

ER or PR > 1% IHC
(1-10% = low)

Definition of HER2+

1. HER2 2+ IHC
   AND + FISH
   Ratio >2, CN >4-6
2. HER2 3+ IHC

Types of Breast Cancer	Incidence
HR+/HER2-	70%
HR-/HER2+ HR+/HER2+	20%
HR-/HER2-	10%

Local vs Systemic Tx

Local Control:
Lumpectomy +/- RT or Mastectomy +/- RT

Receptor-Based Systemic Therapy:
Chemotherapy, Antibody Therapy, Endocrine Therapy

Receptor Based Tx

Chemo/Immunotherapy Regimens

HR+ Chemo	HER2+ Chemo	TNBC Chemo
ddACT	TC-HP	ddACT
TC	TH	TC-AC-Pembro "Keynote 522"

* All EBC requires chemo EXCEPT low-risk HR+

HR+ — **Endocrine Therapy [5-10 years]**
Pre-menopausal = SERM (tamoxifen)
Post-menopausal = AI (anastrozole, letrozole, exemestane)

HER2+ — **HER2+ Antibody Therapy [1 year]**
Trastuzumab (Herceptin) +/- Pertuzumab (Perjeta)

Important Side Effects:

Adriamycin → cardiotoxicity
Paclitaxel, Docetaxel → neuropathy, transaminitis
Trastuzumab → cardiotoxicity
A, C, T, M, F → myelosuppression, hair loss, neuropathy, infertility
SERM → DVT, endometrial cancer, hot flashes/sweats, vaginal dryness
AI → hot flashes/sweats, vaginal dryness, arthritis, osteoporosis

Early Stage Breast Cancer Tx

Simplified Front-Line Approach
for tumors >T1a

HR+ BC:

Adjuvant Therapy
Low Risk Oncotype (≤ 25): ET (+/- OFS if Pre-men)
High Risk Oncotype (≥ 26): TC (N-) or ACT (N+) + ET
* Pre-men oncotypes more complex
* If T3-T4 or N2-N3 = chemo (often ACT)

HER2+ BC:

Neoadjuvant Therapy: TC-HP if T2 or N+
Adjuvant Therapy RD: TDM1
Adjuvant Therapy PCR: HP (dual antibodies)
* Adjuvant TH if <2 cm, N0

HR+/HER2+ BC: Triple Positive

Neoadjuvant Therapy: TC-HP if T2 or N+
Adjuvant Therapy RD: TDM1 + ET
Adjuvant Therapy PCR: HP (dual antibodies) + ET
* Adjuvant TH if <2 cm, N0

HR-/HER2- BC: Triple Negative

Neoadjuvant Therapy: ACTC + Pembro if T2 or N+
Adjuvant Therapy RD: Capecitabine + Pembro
Adjuvant Therapy PCR: Observation + Pembro
* Neo/Adjuvant ddACT if <2 cm, N0 (no IO)

HR+ Early Breast Cancer Risk

Oncotype
21 gene recurrence score sent on tumor to determine risk of recurrence and need for chemotherapy

When to send Oncotype:
- T1b-T3, N0-N1

When not to send Oncotype:
- Too small (T1a < 5mm)
- Too large (consider in T3 > 5 cm, N2 ≥ 4 LN)
- Good prognosis histology (mucinous, tubular)

Oncotype

Menopausal Status	Node Negative	Node Positive (N1 = 1-3+ LN)
POST	≤ 25: ET	≤ 25: ET
	≥ 26: Chemo + ET	≥ 26: Chemo + ET
PRE	< 16: ET	≤ 25: Chemo + ET
	16-25: +/- Chemo + ET * Consider AI/OFS in place of chemo	
	≥ 26: Chemo + ET	≥ 26: Chemo + ET

Menopause Definition
1. Age >60
2. Age <60 and no menses >1Y OFF ET
3. BSO

ET

For 5-10Y

Pre-Menopausal
1. **Tamoxifen (SERM)**

Post-Menopausal
1. **Aromatase Inhibitors (AI)** *preferred*
   anastrozole, letrozole, exemestane
2. **Tamoxifen (SERM)**

Important Side Effects:

AI + SERM → hot flashes/sweats, vaginal secretion changes, mood/weight changes
SERM → 1% DVT, 1% endometrial cancer, teratogenic
AI → 10-30% arthritis, osteoporosis

Chemo

Node Negative or N1 Chemo	N2+ or High Risk N1 Chemo
TC (TC, Q3 week) (T) Docetaxel (C) Cyclophosphamide	**ddACT (AC Q2W→ T)** (A) Doxorubicin (C) Cyclophosphamide (T) Taxol

Uncommonly consider neoadjuvant chemotherapy
- Give if unresectable tumor
- Controversial for downstaging tumors as HR+ BCs respond less robustly to chemo (consider if high oncotype)

Additional Tx

1. Extended ET
7-10Y ET (high risk, ex: stage II-III)

2. CDK4/6
2Y Abemaciclib if N2
or N1 + (T3 or G3)

3. OFS
If premenopausal + high risk
(young, N+, high grade, got chemo)

4. PARP
If BRCA+ and high risk

HR+ Early Breast Cancer Tx

Small
T1-T2, N0-N1

Surgery →

Low Oncotype →
ET: SERM (Tamoxifen)$^{PRE-MEN}$ or AI (Anastrozole)$^{POST-MEN}$
(5-10Y)
+/- RT: Radiation Therapy

High Oncotype →
TC [ACT if high risk]
(T) Docetaxel
(C) Cyclophosphamide
→ **ET** (5-10Y)
+/- RT

Large or Unresectable
T3-T4, N2-N3

ddACT: AC Q2W→ T
(A) Anthracycline
(C) Cyclophosphamide
(T) Paclitaxel
→ Surgery → **ET** (5-10Y)
RT

HER2+ Early Breast Cancer Tx

Small
T1N0

Surgery → **T-H**
(T) Paclitaxel
(H) Herceptin
→ **H** (1Y HER2AB)
+/- RT
+/- ET (5-10Y)

Large
T2 or N+ (consider neo TCH+/- P in T1cN0)

TC-HP
(T) Docetaxel
(C) Carboplatin
(H) Herceptin
(P) Perjeta
→ Surgery →
PCR → **HP** to complete 1Y HER2 AB
+/- ET For 5-10Y
RD → **TDM1 t**o complete 1Y HER2 AB
+/- ET for 5-10Y
+/-RT

TN Early Breast Cancer Tx

Small
T1N0

Surgery → **ddACT**
(A) Doxorubicin
(C) Cyclophosphamide
(T) Taxol
→ **+/-RT**

Large
T2 or N+ (consider neo ddACT in T1cN0)

TC-AC-Pembrolizumab
(T) Taxol
(C) Carboplatin
(A) Doxorubicin
(C) Cyclophosphamide
(P) Pembrolizumab
→ Surgery →
PCR → **Pembrolizumab**
RD → **Capecitabine + Pembrolizumab**
* if RD and gBRCA+ consider Olaparib in place of cape
+/-RT

Metastatic Breast Cancer Tx

Front Line Therapy

HR+ Breast Cancer:

Hormone Therapy: Tamoxifen or AI
WITH
CDK4/6 Inhibitor: Palbociclib, Ribociclib, Abemaciclib

HER2+ Breast Cancer:

HER2+ Therapy: Trastuzumab +/- Pertuzumab
WITH
Chemotherapy: Docetaxel or Paclitaxel

HR+/HER2+: Triple Positive Breast Cancer

HER2+ Therapy: Trastuzumab +/- Pertuzumab
WITH
Chemotherapy: Docetaxel or Paclitaxel
* Consider ET in place of chemo in select pts

HR-/HER2-: Triple Negative Breast Cancer

CPS+ (>10%): Pembrolizumab + chemotherapy
OR
PDL1-: Chemotherapy: anthracyclines, taxanes, anti-metabolites, anti-tubulins, platins, etc

Metastatic Breast Cancer Tx

Additional Lines of Therapy: No SOC 2nd line onward therapy. Consider clinical trial

Tx Line	HR+ Breast Cancer
1st	1. AI + CDK4/6 Inhibitor (palbociclib, ribociclib, abemaciclib) AI Sensitive 2. Fulvestrant + CDK4/6 AI Resistant
2nd + ET Sensitive	1. Elacestrant ESR1 > WT 2. Fulvestrant +/- Capivasertib PIK3CA/AKT/PTEN Alpelisib PIK3CA Everolimus WT CKD4/6 Alter.
2nd + ET Resistant	BRCA - = Chemo or ADC: TDXd HER2 Low , Sacituzumab 2 prior LOT BRCA + = PARP inhibitor (olaparib, talazoparib)

Tx Line	HER2+ Breast Cancer
1st	Taxane + Trastuzumab + Pertuzumab
2nd	Trastuzumab Deruxtecan = TDXd (*Enhertu*)
3rd -4th	Trastuzumab Emtansine = TDM1 (*Kadcyla*)
3rd- 4th	Tucatinib + Trastuzumab + Capecitabine * consider 2nd line if brain mets

Tx Line	Triple Negative Breast Cancer
1st	PDL1 >10% = pembrolizumab + chemo PDL1 <10% = single agent chemo (ex: anthracycline, taxane)
2nd – 3rd	BRCA + = PARP inhibitor (consider in other HRD)
2nd – 3rd	ADC: TDXd HER2 Low , Sacituzumab 2 prior LOT, 1 for MBC Single agent chemotherapy