Surgical treatment of breast cancer

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Screening and Diagnosis

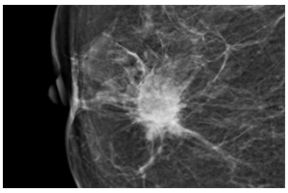
Patient presentations

- Asymptomatic
  - Abnormal mammogram
- Symptomatic
  - Palpable mass
  - Changes in the skin of the breast/nipple
  - Nipple discharge
  - Axillary mass

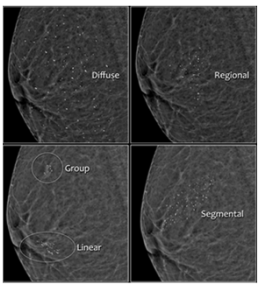
Screening Guidelines, general population

- Clinical encounter about every three years for women in their 20s-30s, and annually for women ≥ 40
- Annual screening mammogram beginning at age 40 (tomosynthesis)
- Breast awareness

NCCN Guidelines, version 2.2016



Spiculated mass



Suspicious microcalcifications

Symptomatic patients

- Evaluate with complete history and physical examination
- Diagnostic imaging
  - Bilateral mammogram, even if unilateral symptoms
  - May use other imaging modalities
    - Ultrasound
    - MRI

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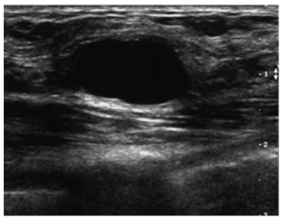
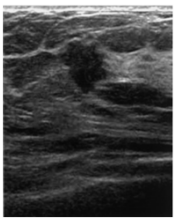
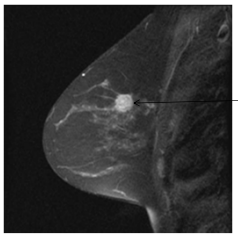


Cystic lesion, requires no further therapy



Solid mass with features suspicious for malignancy

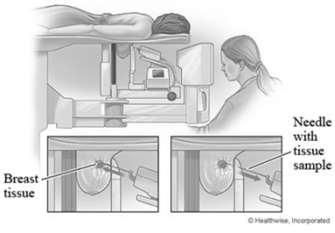
MRI



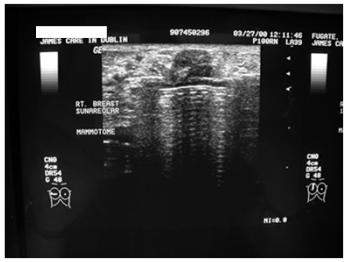
Methods of Diagnosis

- Palpable lesion
  - fine needle aspiration (FNA)
  - Core/Tru-cut biopsy
  - excisional biopsy
- Nonpalpable lesion
  - stereotactic biopsy
  - ultrasound-guided core needle biopsy
  - imaging localized excisional biopsy
- Abnormal skin—punch biopsy

Stereotactic Breast Biopsy



Ultrasound-Guided Core or Mammotome Biopsy



Non-invasive breast cancer

DCIS

- Usually presents as an abnormal mammogram with clustered calcifications
- Nodal metastases are rare (1%), likely associated with unrecognized microinvasion
- Up to ½ of recurrences are invasive

Management

- Treatment → lumpectomy with radiation therapy (negative margins) or total mastectomy
- Evaluation of the axillary lymph nodes is generally **not** necessary (unless mastectomy)

Invasive cancers

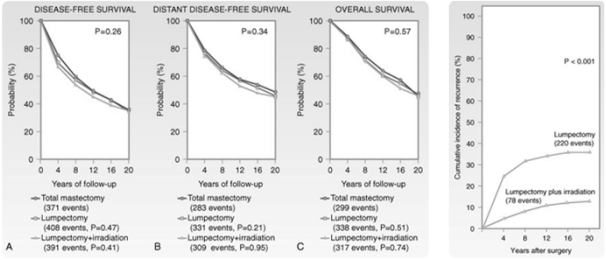
Invasive breast cancer

- Most common type is infiltrating ductal (75%)
- Less common variants of ductal
  - Medullary (6%)-better prognosis
  - Tubular (2%)-excellent prognosis
  - Colloid (1-2%)-better prognosis
- Invasive lobular (10%)
  - Indistinct margins, extensive infiltration
  - Harder to detect mammographically
  - Significant incidence of multicentricity

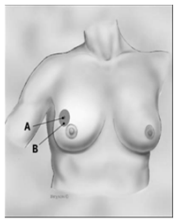
Surgical Management of Invasive Breast Cancer

- Breast (removal of primary tumor)
  - total mastectomy
  - lumpectomy (breast conservation) plus radiation therapy
- Axillary lymph nodes (staging evaluation)
  - axillary node dissection
  - sentinel lymph node mapping and biopsy

NSABP B-06



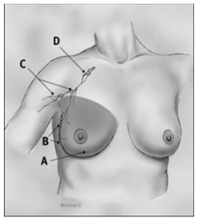
Partial mastectomy/ lumpectomy



Contraindications to Breast Conservation

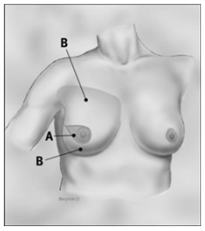
- Large tumors or large tumor : breast ratio
  - Oncoplastic lumpectomy
- Multicentric disease
- Extensive DCIS
- Indeterminant mammographic findings elsewhere in breast
- Previous breast radiation
- Autoimmume disorders affecting skin: scleroderma (contraindication to RT)

Total (simple) mastectomy



A. Tissue in pink is removed. This represents all breast tissue
- No effort is made to remove axillary lymph nodes
- Can be used for treatment or prophylaxis

Skin-sparing mastectomy



- "Keyhole" incision (skin preserved)
- Tissue removed at mastectomy
- Allows for more natural reconstruction by preserving breast envelope

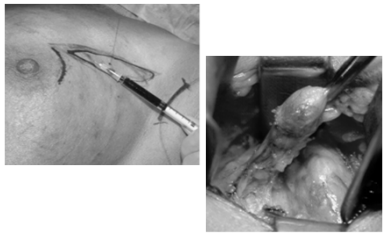
NSM/ASM

- Combines skin sparing mastectomy with preservation of nipple and/or areola
- Appropriate when nipple is not involved with cancer or atypical cells.
- Usually involves incision in inframammary fold with preservation of entire skin envelope.
- Most appropriate in breasts without ptosis as nipple can not be repositioned.

Nodal assessment

- Sentinel lymph node biopsy current standard
- Axillary node dissection if sln pos or can't be identified
  - Higher risk of lymphedema (25% vs 5%)
  - Higher likelihood of nerve injury
  - More mobility issues

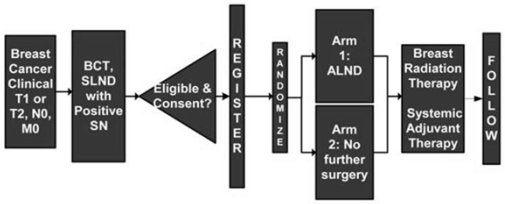
Sentinel Lymph Node Biopsy



Management of Positive SLN

- Previously, completion node dissection in all cases
- Currently, completion node dissection still standard for patients treated with mastectomy (Amaros)
- Certain patients treated with BCT may be able to avoid completion node dissection

ACOSOG Z11



Clinical Implications

In clinically node-negative patients undergoing BCT with macrometastases in the SN:

- Systemic Rx decision made
- ALND not necessary for local control
- ALND does not contribute to survival

Reconstruction Options/Issues Following Mastectomy

- Skin-sparing procedures
- Saline tissue expanders / saline implants
- Tissue transfer procedures
  - DIEP flap
  - TRAM or other rotational flaps
- Immediate versus delayed reconstruction

Locally advanced breast cancers

- Large tumor (>5cm) or skin changes (edema, ulceration, chest wall fixation) or fixed axillary lymph nodes
- Account for 10-15% of breast cancer in US, higher in developing countries
- Best results with neoadj chemo, followed by surgery with adjuvant RT as needed

Inflammatory breast cancers

- Account for <3% of breast cancers
- Characterized by brawny induration, erythema, and edema of the skin (peau d'orange)
- Dermal lymphatic involvement seen on skin biopsy
- May be mistaken for bacterial infection

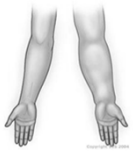
Inflammatory breast cancer

- Distant metastasis is present in about 25% at presentation
- Neoadjuvant chemo may affect dramatic regression
- After chemo, MRM is performed
- Adjuvant chemo is often given
- RT to chest wall, supraclav, IM and axillary nodal basins is also given
- 5-yr survival rates approach 30%

Complications of local therapy

Angiosarcoma

Lymphedema



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Systemic Therapy for Breast Cancer

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Learning Objectives

- ❑To Review Breast Cancer Basics
- ❑To Review Systemic Therapy of Breast Cancer
- ❑To Review Approved Indications for Immunotherapy in Breast Cancer

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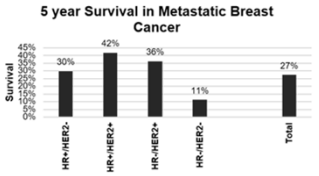
Breast Cancer Basics

Breast Cancer Basics: Stats

- **Incidence:** In 2022, there will be an estimated 290,560 new cases of breast cancer with 43,780 deaths
  - 2nd most common cause of death in women
- **De novo Metastatic:** 5% of cases are metastatic at diagnosis

	Women	Men
New Cases	287,850	2,710
Deaths	43,250	530
Lifetime Risk	1 in 8 women	1 in 833 men



Siegel et al. Ca Cancer j Clin. 2022.
Malmgren et al. Breast Cancer Res Treat. 2018.
Howlander et al. CEBP. 2018.

It's All About the Receptors

- Breast Cancers are typically tested for 3 main receptors
  - Estrogen Receptor (ER)
  - Progesterone Receptor (PR)
  - Human Epidermal Growth Factor Receptor 2 (HER2)
- The presence (or absence) of these receptors determines:
  - Clinical Outcomes
  - Systemic Treatment
    - Timing of treatment
    - Type of treatment
    - Duration of treatment

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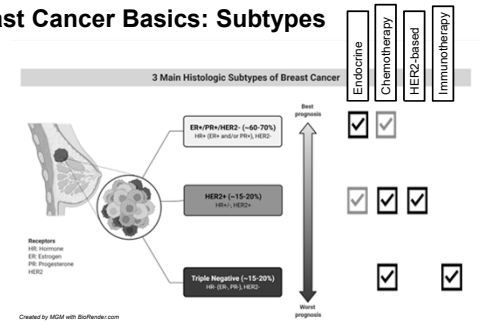
Breast Cancer Basics: Subtypes



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The Pillars of Early Breast Cancer Treatment

Local Therapy

- Breast Surgery and Nodal Evaluation
  - Mastectomy vs lumpectomy
  - Sentinel node vs axillary node dissection
- Radiation

Systemic Therapy

- Neoadjuvant or Adjuvant
  - Chemotherapy
  - HER2-Base Therapy
  - Immunotherapy
  - Endocrine therapy

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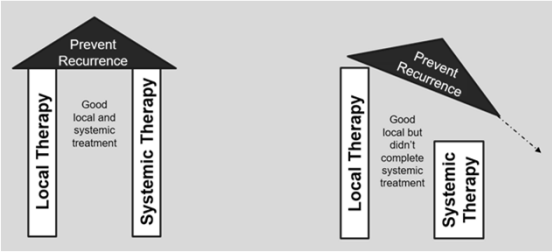
The Pillars of Breast Cancer Treatment



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Systemic Therapy

Neoadjuvant (before surgery) Breast Cancer Treatment

Biopsy | Chemo | Surgery | Radiation | Endocrine +/- PARPi, +/- Abemaciclib or Capecitabine

Trastuzumab/Pertuzumab (or adjuvant T-DM1) for 1 year

Pembrolizumab for 1 year

- **Who gets neoadjuvant chemotherapy?**
  - Triple Negative Breast Cancer ≥ 1cm or + lymph nodes
  - HER2+ Breast Cancer ≥ 2cm or + lymph nodes
  - Some ER+ Breast Cancer
- Can be followed by adjuvant therapy after surgery
  - Some agents will span both neoadjuvant and adjuvant settings

Adjuvant (after surgery) Breast Cancer Treatment

Biopsy | Surgery | Chemo | Radiation | Endocrine +/- PARPi +/- Abemaciclib

Trastuzumab +/- Pertuzumab for 1 year

- **Who gets adjuvant chemotherapy?**
  - Triple Negative Breast Cancer, < 1cm and no lymph nodes
  - HER2+ Breast Cancer, < 2cm and no lymph nodes
  - Some ER+ breast cancer, Oncotype ≥ 26*
- **Who can be spared chemotherapy?**
  - Most ER+ patients
  - Some small (<5mm), node negative triple negative or HER2+ breast cancers

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Multigene Assays Help with Risk Recurrence Estimates

	Oncotype (preferred)	MammaPrint
No. Genes	21 genes	70 genes
Predictive	YES	Unknown
Prognostic	YES	YES
Result Range	0 to 100 [0 to 11 = Stage 1A] [0 to 25*, no chemo] [26+, chemo]	Low [no chemo] High [chemo]

**Premenopausal patients with oncotype score 18 to 25, consider ovarian suppression and/or chemotherapy*

ALL patients with ER+ breast cancer will receive 5 to 10 years of endocrine therapy *(Tamoxifen or an aromatase inhibitor like anastrazole, letrozole, or exemestane)*

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Metastatic (advanced) Breast Cancer Treatment

Biopsy → Systemic Therapy Based on Receptors

RT

- Receptors determine if a patient will receive oral or IV chemotherapy for advanced disease
- There is a very limited role for surgery in metastatic breast cancer
- Radiation can help with pain associated with metastatic tumors

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Metastatic ER+/PR+ Breast Cancer

- **First and second line treatment is generally oral chemotherapy**

1st Line:
Aromatase Inhibitor
+ CDK 4/6 inhibitor

CDK 4/6 Inhibitors
Palbociclib
Ribociclib
Abemaciclib

2nd Line:
Fulvestrant +
Alpelisib (Pi3K) or
Everolimus (mTOR) or
CDK 4/6 inhibitor

3rd Line:
Chemotherapy

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Metastatic HER2+ Treatment Algorithm

- **Chemotherapy + HER2-Directed Antibody**

1st Line
Docetaxel + Trastuzumab + Pertuzumab

2nd Line *(or if recurrence < 6 months)*
T-DM1 (Kadcyla) or **Trastuzumab Deruxtecan**

3rd Line *(optimal sequence is unknown)*
- Trastuzumab Deruxtecan (T-DXd)
- Trastuzumab + Capecitabine + Tucatinib
- Margetuximab + (Gemcitabine, Capecitabine, Navelbine, or Eribulin)
- Neratinib + Capecitabine
- Lapatinib + Capecitabine
- Trastuzumab + Chemotherapy

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Immunotherapy

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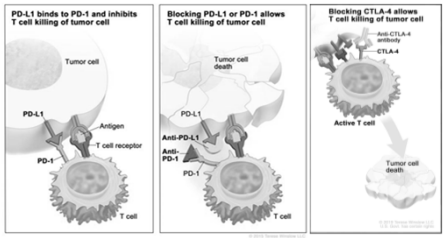
Immune Checkpoint Inhibitors (ICIs)



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Accessed 4/24/18: https://visualsonline.cancer.gov/details.cfm?imageid=10396
Accessed 10/10/21: https://nci-media.cancer.gov/pdq/media/images/776560.jpg

Approved Indications for ICIs in Solid Tumors

- Most indications are for advanced/metastatic cancer, but some are in earlier settings*
- Indications are for ICI +/- other agents (chemotherapy, small molecules, etc)

Lung Cancers
- Non-Small Cell* □□□□□□
- Small Cell □□
- Pleural Mesothelioma □

Genitourinary Cancers
- Kidney (Renal Cell) Cancer □□□□
- Bladder Cancer* □□□

Skin Cancers
- Melanoma* □□□□
- Merkel Cell Carcinoma □□
- Squamous Cell Carcinoma □□
- Basal Cell Carcinoma □

Women's Cancers
- Cervical Carcinoma □
- **Triple Negative Breast Cancer*** □☒
- Endometrial Cancer □□

Gastrointestinal Cancers
- Colorectal Cancer, MSI-H □□□
- Hepatocellular Carcinoma □□
- Gastric/GE Junction/Esophageal □□□□
- Head and Neck, Squamous □□

Not Tumor Specific
- MSI-High □□□
- TMB-High □

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https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm. Accessed Sept 29, 2021

Survival and ICI

- Patient outcomes are improved with ICI when compared to chemotherapy
  - Among responders, we see longer periods of disease control and better overall survival
- Ipilimumab (Nov 2011 FDA approved for metastatic melanoma)
  - Overall Cancer Death Rate significantly decreased in future years
    - Cancer Statistics 2020: ↓ by *29% from 1991 to 2017, with a **2.2% decline from 2016 to 2017***
      - *Progress in **treatment for melanoma** drove the **most rapid death rate decline** seen, as the overall melanoma death rate dropped by 7% per year during 2013-2017.*
    - Cancer Statistics 2021: ↓ *by 31% from 1991 to 2018, with a **2.4% decline from 2017 to 2018***

Siegel et al. Ca Cancer J Clin. 2020. Seigel et al. Can Cancer J Clin. 2021.
Sun et al. Scientific Reports. 2020.
Accessed 10/13/20: https://www.cancerresearch.org/immunotherapy/timeline-of-progress

Approved FDA Indications of ICIs in Breast Cancer

Not Breast Cancer Specific

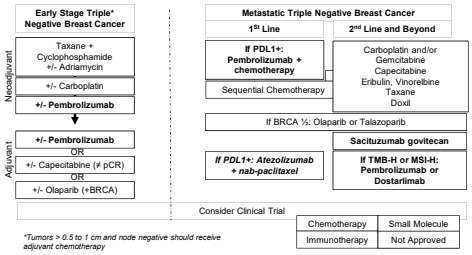
- **Pembrolizumab*** in MSI-High or mismatch repair deficient tumors
- **Pembrolizumab*** in TMB-High (≥ 10 mutations/megabase)
- **Dostarlimab*** in mismatch repair deficient tumors

Breast Cancer Specific

- ~~***Atezolizumab*** + Nab-Paclitaxel in 1st line, metastatic TNBC~~
- **Pembrolizumab** + Chemotherapy (nab-paclitaxel, paclitaxel or gemcitabine/carboplatin) in 1st line, metastatic TNBC
- **Pembrolizumab*** + neoadjuvant chemotherapy in early stage, high risk TNBC

*Accelerated approvals based on PFS, response rate/durability. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Triple Negative Breast Cancer Treatment



*Tumors > 0.5 to 1 cm and node negative should receive adjuvant chemotherapy

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Learning Objectives

- ✓To Review Breast Cancer Basics
  - ✓Stats and Subtypes
  - ✓Sequencing of Local and Systemic Therapies
- ✓To Review Systemic Therapy of Breast Cancer
  - ✓Neoadjuvant Breast Cancer Treatment
  - ✓Adjuvant Breast Cancer Treatment
  - ✓Metastatic Breast Cancer Treatment for ER+ and HER2+
- ✓To Review Approved Indications for Immunotherapy in Breast Cancer
  - ✓Early and Adjuvant Triple Negative Breast Cancer

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