Breast Cancer Treatment

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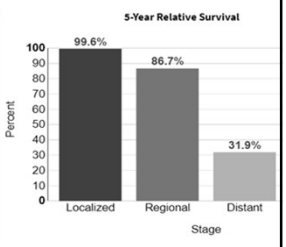
Topics of Discussion

- ❑ Epidemiology & Risk Factors
- ~~❑ Screening~~
- ~~❑ Non-invasive Breast Cancer~~
- ~~❑ Invasive Breast Cancer~~
- ❑ Treatment
- ❑ Sequencing of Therapy
- ❑ Systemic therapies:
  - ❑ Chemotherapy
  - ❑ Endocrine therapy
  - ❑ Targeted therapy
  - ❑ Immunotherapy
- ❑ Conclusion

Epidemiology & Risk

Epidemiology

	Common Types of Cancer	Estimated New Cases 2024	Estimated Deaths 2024
1.	**Breast Cancer (Female)**	**310,720**	**42,250**
2.	Prostate Cancer	299,010	35,250
3.	Lung and Bronchus Cancer	234,580	125,070
4.	Colorectal Cancer	152,810	53,010
5.	Melanoma of the Skin	100,640	8,290
6.	Bladder Cancer	83,190	16,840
7.	Kidney and Renal Pelvis Cancer	81,610	14,390
8.	Non-Hodgkin Lymphoma	80,620	20,140
9.	Uterine Cancer	67,880	13,250
10.	Pancreatic Cancer	66,440	51,750



SEER Cancer Stat Facts: Female Breast Cancer. National Cancer Institute. Bethesda, MD. 2024. https://seer.cancer.gov/statfacts/html/breast.html

Risk Factors

- Non-modifiable risk factors:
  - Female sex, older age, race, ethnicity, early menarche, late menopause, genetic mutations, dense breast tissue.
- Modifiable risk factors:
  - Hormone replacement therapy, nulliparity, no breast feeding, obesity, alcohol use, diet, lack of physical activity.

Label 1 – Cancer Warning

Label 2 – Canada's National Drinking Guidelines

Label 3 – Standard Drink Information (example for wine)

Zhao J et al, Journal of Studies on Alcohol and Drugs, 2020.
https://commons.wikimedia.org/wiki/File:Intervention_alcohol_warning_labels_-_Jsad.2020.81.2626g1.jpg

Familial breast cancer risk

- High penetrance genes:
  - TP53 (Li-Fraumeni syndrome)
  - STK11 (Peutz-Jeghers syndrome)
  - PTEN (PTEN hamartoma tumor syndrome)
  - CDH1 (Hereditary diffuse gastric cancer syndrome)
  - MSH1/MLH1/MSH6/PMS2/EPCAM (Lynch syndrome)
  - PALB2
  - BRCA1
  - BRCA2
- Moderate penetrance genes:
  - CHEK2 (HR+)
  - ATM (HR+)
  - BARD1 (HR-)
  - RAD51 paralogs (HR-)
  - NF1 (both)
  - BRIP1 (breast & ovarian).
- Least significant genes:
  - MUTYH
  - NBN

Table 1-4 **Selected Hereditary Neoplastic Syndromes for Which Clinical Tests are Available**

Syndrome	Site(s) of Most Common Cancer	Associated Gene
Breast, ovarian, and prostate cancers	Breast, ovary, prostate	*BRCA1, BRCA2*
Cowden	Breast, thyroid	*PTEN*
Li-Fraumeni	Brain, breast, adrenal cortex, leukemia, sarcoma	*TP53*
Familial adenomatous polyposis	Large bowel, small bowel, brain (Turcot), skin, bone (Gardner)	*APC*
Hereditary nonpolyposis colorectal cancer (Lynch syndrome)	Colorectal and endometrium; also ovary, pancreas, stomach, small bowel	*MSH2, MLH1, PMS1, PMS2, MSH6*
Multiple endocrine neoplasia 1	Pancreatic islet cell, pituitary adenoma, parathyroid adenoma	*MEN1*
Multiple endocrine neoplasia 2	Medullary thyroid, pheochromocytoma	*RET*
Neurofibromatosis type 1	Neurofibrosarcoma, pheochromocytoma	*NF1*
von Hippel-Lindau	Hemangioblastoma, nervous system, renal cell	*VHL*
Retinoblastoma	Eye, bone	*RB1*
Melanoma, hereditary	Skin	*CDKN2/p16, CDK4*
Basal cell	Skin	*PTCH*
Hereditary diffuse gastric cancer	Stomach, lobular breast	*CDH1*

Daly M et al, NCCN guidelines, 2024.

Familial breast cancer risk

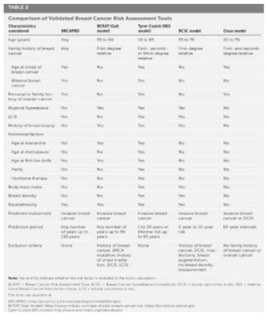


TABLE 2
Comparison of Validated Breast Cancer Risk Assessment Tools

Characteristics considered	BRCAPRO	BCRAT (Gail model)	Tyrer-Cuzick (IBIS model)	BCSC model	Claus model
Age (years)	Any	35 to 90	18 to 85	35 to 74	20 to 79
Family history of breast cancer	Any	First-degree relative	First-, second-, or third-degree relative	First-degree relative	First- and second-degree relative
Age at onset of breast cancer	Yes	No	Yes	No	Yes
Bilateral breast cancer	Yes	No	Yes	No	No
Personal or family history of ovarian cancer	Yes	No	Yes	No	Yes
Atypical hyperplasia	No	Yes	Yes	Yes	No
LCIS	No	Yes	Yes	Yes	No
History of breast biopsy	No	Yes	Yes	Yes	No
Hormonal factors					
Age at menarche	No	Yes	Yes	No	No
Age at menopause	No	No	Yes	No	No
Age at first live birth	No	Yes	Yes	No	No
Parity	No	No	Yes	No	No
Hormone therapy	No	No	Yes	No	No
Body mass index	No	No	Yes	No	No
Breast density	No	No	Yes	Yes	No
Race/ethnicity	Yes	No	Yes	Yes	No
Predicted outcome(s)	Invasive breast cancer	Invasive breast cancer	Invasive breast cancer	Invasive breast cancer	Invasive breast cancer or DCIS
Prediction period	Any number of years; up to 100 years	Any number of years; up to 90 years	1 to 29 years or lifetime risk up to 90 years	5 year or 10 year risk	65 year intervals
Exclusion criteria	None	History of breast cancer, BRCA mutation, history of chest irradiation, DCIS, LCIS	None	History of breast cancer, DCIS, male breast cancer, augmentation, no breast density measurement	No family history of breast cancer or ovarian cancer

Note: Yes and No indicate whether or not risk factor is included in the tool's calculation.
BCRAT = Breast Cancer Risk Assessment Tool; BCSC = Breast Cancer Surveillance Consortium; DCIS = ductal carcinoma in situ; IBIS = International Breast Cancer Intervention Study; LCIS = lobular carcinoma in situ.
The tools are available at:
BRCAPRO: https://bcrisktool.cancer.gov/calculator.html
BCRAT (Gail model): https://bcrisktool.cancer.gov/gail-model.html
Tyrer-Cuzick (IBIS model): http://www.ems-trials.org/riskevaluator/

- Risk models: Gail, Claus, Tyrer–Cuzick, BCSC, BRCAPRO, Mirai
- Gail model for chemoprevention = 5 year risk >1.7%
- Tyrer-Cuzick & Claus models for MRI screening = lifetime risk >20%
- Chemoprevention: ALH, ADH, DCIS, LCIS

- Genetic testing is recommended if there is a family history of:
  - -Breast cancer diagnosed before age 50
  - -Male breast cancer in the family
  - -Member with recurrent disease or bilateral cancers
  - -Multiple cases of breast cancer in the family, particularly if one-sided.
  - -Known genetic mutations in family relevant to breast cancer
  - -Ashkenazi Jewish ethnicity
  - -Family members with ovarian, uterine, colorectal, or aggressive prostate cancer, particularly if one-sided.
  - -Triple negative, inflammatory, or metaplastic subtypes of any age if affected family member was noted tested.

Daly M et al, NCCN guidelines, 2024.

Screening

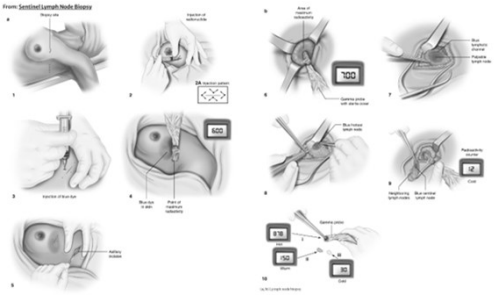
Treatment

Surgical therapies

Removal of breast mass
- ➔ Partial mastectomy (aka “lumpectomy”)
- ➔ Simple mastectomy
- ➔ ~~Radical mastectomy~~

Lymph node staging
- ➔ Sentinel lymph node biopsy
- ➔ Axillary lymph node dissection

Sentinel lymph node biopsy



Rosenthal R et al. Mental Conditioning to Perform Common Operations in General Surgery Training. Springer Nature, 2020. https://scholar.google.com/scholar?hl=en&as_sdt=0%2C36&q=Mental+Conditioning+to+Perform+Common+Operations+in+General+Surgery+Train ing&btnG=

Surgical complications

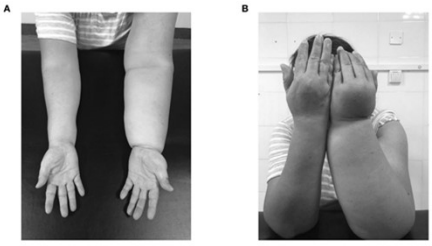


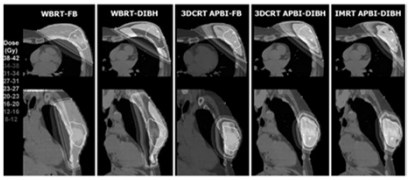
FIGURE 1
Left Upper Limb Lymphedema. (**A**: Palmar Side of Forearm, **B**: Dorsal Side of Forearm).

Sui YF et al. Front Oncol, 2023.
https://pubmed.ncbi.nlm.nih.gov/37287367/

Radiation therapies

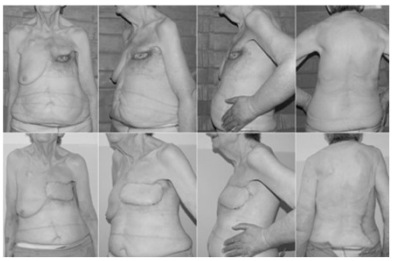
Radiation to breast
- ➔ Whole breast radiation therapy (WBRT)
- ➔ Accelerated partial breast irradiation (APBI)
- ➔ Chest wall radiation

Radiation to lymph nodes
- ➔ Axillary nodes, intramammary nodes, supraclavicular nodes.
- ➔ Boost/No Boost



Moran J et al, Int J Radiat Oncol Biol Phys, 2009.
https://pubmed.ncbi.nlm.nih.gov/19540076/

Radiation therapy complications

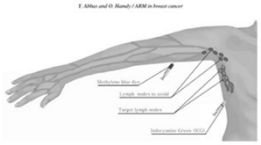


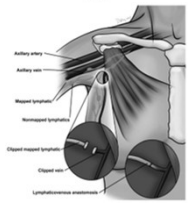
Vairinho A et al, Ann Chir Plast Esthet, 2018.
https://pubmed.ncbi.nlm.nih.gov/29402546/

Reconstructive therapies

Breast reconstruction
- ➔ Tissue expanders
- ➔ Permanent implants
- ➔ Autologous fat grafts: DIEP, SIEA, TRAM,

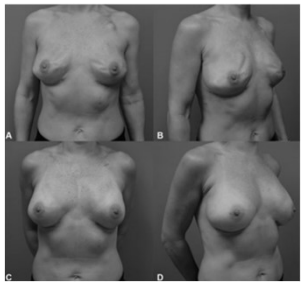
Lymphedema prophylaxis
- ➔ Lymphovascular bypass (LVB)
- ➔ Axillary Reverse Mapping (ARM)
- ➔ Vascularized lymph node transfer (VLNT)





Weber W et al, Am Soc Clin Oncol Educ Book, 2024.
https://pubmed.ncbi.nlm.nih.gov/38815195/
Abbas Y et al, Breast Disease, 2023
https://pubmed.ncbi.nlm.nih.gov/37154174/

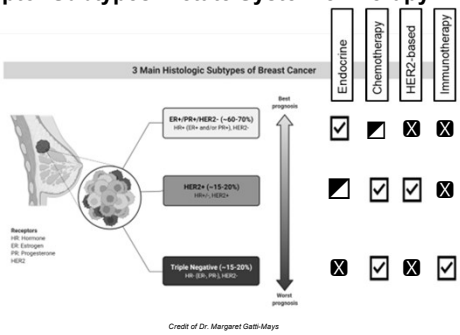
Complications of reconstructive surgery



Turner A et al, Semin Plast Surg, 2020. https://pubmed.ncbi.nlm.nih.gov/32071575/
Singh M et al, Plast Reconstr Surg Glob Open, 2015.
https://pubmed.ncbi.nlm.nih.gov/26495224/

Treatment sequencing

Receptor Subtypes Dictate Systemic Therapy Choices



Credit of Dr. Margaret Gatti-Mays

Timing of systemic therapy

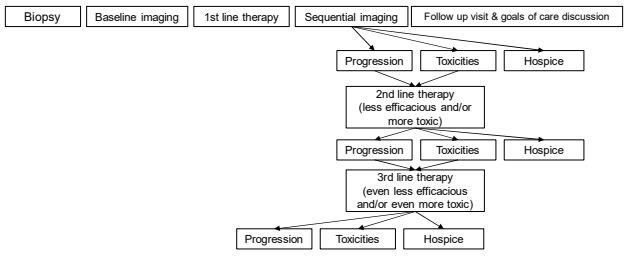
HR+BC
TNBC
HER2+BC

Neoadjuvant therapy:
- TNBC:
  - ≥1cm (≥T1c)
  - N+ (N1-3)
- HER2+BC:
  - ≥2cm (T2-4)
  - N+ (N1-3)
- HR+BC:
  - Bulky nodes (N2-3)
  - Bulky tumor (T4)

Adjuvant therapy:
- TNBC:
  - <1cm (<T1c)
  - N0
- HER2+BC:
  - <2cm (T2-4)
  - N0
- HR+BC:
  - T1-3
  - N0-1

Biopsy	+/- Chemo	Surgery	+/- Chemo	+/- Radiation	Endocrine therapy +/- targeted therapy
Biopsy	+/- Chemo +/- Immunotherapy	Surgery	+/- Chemo	+/- Radiation	+/- Targeted therapy
Biopsy	+/- Chemo +/- HER2 therapy	Surgery	+/- Chemo +/- HER2 therapy	+/- Radiation	+/- Endocrine therapy +/- targeted therapy

Metastatic breast cancer



Systemic therapies

Systemic therapies

A. Chemotherapy
   a. Doxorubicin, epirubicin, cyclophosphamide, carboplatin, docetaxel, paclitaxel, nab-paclitaxel, capecitabine, gemcitabine, vinorelbine, eribulin
B. Endocrine therapy
   a. Tamoxifen, anastrozole, letrozole, exemestane, fulvestrant, elacestrant
C. Targeted therapy
   a. Trastuzumab, pertuzumab, margetuximab, neratinib, lapatinib, tucatinib, abemaciclib, ribociclib, palbociclib, olaparib, talazoparib, alpelisib, capivasertib, everolimus
D. Immunotherapy
   a. Pembrolizumab
E. Combination
   a. Sacituzumab govitecan, trastuzumab deruxtecan, trastuzumab emtansine, datopotamab deruxtecan

Chemotherapies used for breast cancer

Anthracyclines: Doxorubicin, epirubicin

-Cardiotoxicity (CHF)

Taxanes: Docetaxel, paclitaxel, nab-paclitaxel

-Peripheral neuropathy

Platinum agents: Carboplatin, cisplatin

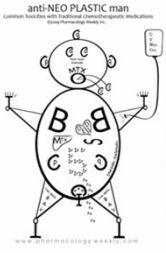
-Peripheral neuropathy, nephrotoxicity, ototoxicity

Antimetabolites: Capecitabine (prodrug), 5-fluorouracil (5-FU)

-Coronary vasospasms, hand-foot syndrome

Nitrogen mustards: Cyclophosphamide

-Hemorrhagic cystitis (rare with breast cancer dosing), cytotoxicity



Endocrine therapies for breast cancer

Aromatase inhibitors: Anastrozole, letrozole, exemestane

-Osteoporosis/osteopenia, hyperlipidemia, CAD/CVA risk

SERMs: Tamoxifen

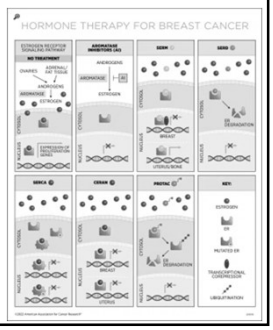
-DVT/VTE risk, uterine dysplasia/malignancy

SERDs: Elacestrant, fulvestrant

-Heightened menopause symptoms

GnRH agonists: goserelin, leuprolide

-Painful injection



Liccioli S et al, AACR, 2024.

Targeted therapies for breast cancer

Targeted alone

HER2: Trastuzumab, pertuzumab, margetuximab, lapatinib, neratinib, tucatinib

-Cardiotoxicity (CHF)

PI3K/PTEN/AKT/mTOR: Alpelisib, capivasertib, everolimus

-Hyperglycemia, rash, mouth sores, severe diarrhea

CDK4/6: abemaciclib, ribociclib, palbociclib

-Severe diarrhea, QTc prolongation

PARP: Olaparib, Talazoparib

-Secondary malignancy (leukemia)

Targeted treatment + chemotherapy payload

HER2: Trastuzumab deruxtecan, trastuzumab emtansine

-Cardiotoxicity (CHF), peripheral neuropathy, pneumonitis/interstitial lung disease (ILD)

TROP2: Sacituzumab deruxtecan

-Severe neutropenia, diarrhea

Immunotherapy for breast cancer

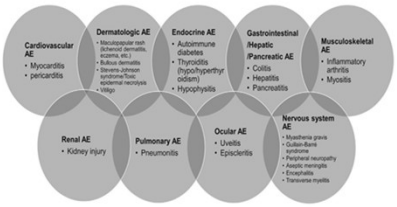
Immunotherapy

PD-1 inhibitor: Pembrolizumab,

-Adrenal insufficiency, hypo/hyper hypothyroidism, hypophysitis, type 1 diabetes, pneumonitis, myocarditis, transaminitis, colitis, rash

PD-L1 inhibitor: Atezolizumab (retracted)

-Similar findings



Okiyama N et al. Allergology International. 2021.

Radiation Therapy for Breast Cancer

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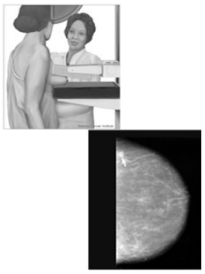
Agenda

- Background
  - Clinical Presentation
  - Anatomy of the breast
  - Staging & Patterns of metastasis
- Treatment
  - Surgical Management
  - Systemic Therapy
  - Radiation Therapy

Clinical Presentation of BC

- **Most common presentation is abnormal screening mammogram**
- Some symptoms related to bca include:
  - Slightly tender breast mass
  - Skin changes on the breast
  - Nipple discharge
  - Change in the size or shape of the breast
- Uncommon to present with palpable lymphadenopathy or even distant metastases
- Metastatic disease: weight loss, fatigue, new focal pain (bone metastases)

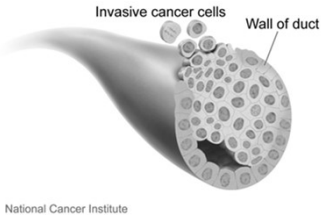


Breast Cancer Screening

- Clinical Breast Exam
- Mammography
- Ultrasound
- MRI (magnetic resonance imaging)
  - Young women (increased breast density)
  - BRCA1/2 carriers
  - Strong FH of bca

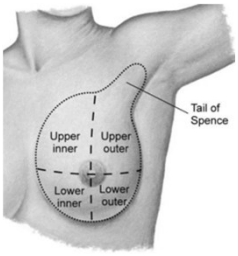
Invasive BC vs. DCIS

- **Ductal carcinoma *in situ*** is pre-invasive.
- Cancer cells located in the milk ducts that have not invaded the surrounding breast tissue
- Invasive breast cancer has broken out of the duct and invaded into breast tissue
- DCIS often detected on screening mammogram by calcifications (pts very rarely p/w breast mass)



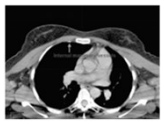
Breast Anatomy

- Breast lies on the anterior chest wall superficial to the pec major muscle
- Extends medially – laterally to mid axillary line, sup-inf from about 2nd rib to anterior 6th rib
- Upper outer quadrant extends into the low axilla and is referred to as the **axillary tail of Spence**
- There is more breast tissue in the UOQ and therefore, a greater percentage of breast cancers occurs in the UOQ



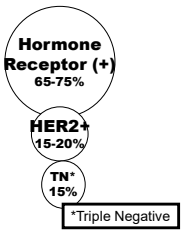
Breast Anatomy: Lymphatics

- About 20-30% of breast cancers have spread to lymph nodes at Dx
- Regardless tumor location in the breast, the axilla is the most common site of lymphatic involvement
- Other lymph node regions that drain the breast: Supraclavicular, axillary (Levels I-III), and internal mammary nodes just lateral to sternum



Not All Breast Cancer Is The Same

Both the ***type*** and ***stage*** of breast cancer influence what type of treatment a patient undergoes



BC Staging

- Utilizes TNM Categories
  - T: Tumor (1-4)
  - N: Lymph nodes (1-3)
  - M: Indicates metastatic disease (M0, M1)

5-year relative survival rates for breast cancer

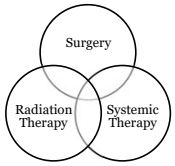
These numbers are based on women diagnosed with breast cancer between 2014 and 2020.

SEER Stage	5-year Relative Survival Rate
Localized*	>99%
Regional	87%
Distant	32%
All SEER stages combined	91%

BC TREATMENT

Treatment: Multi-modality

- Very few patients receive just one type of treatment, regardless of their stage at diagnosis
- The conventional paradigm has been surgery→ +/- chemo → radiation
- Some patients get up-front systemic therapy followed by surgery and then radiation



SURGICAL MANAGEMENT

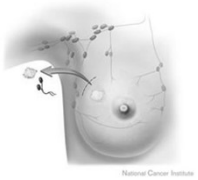
Surgical Management of BC

- Breast conservation
  - Lumpectomy, "Partial mastectomy"
  - +/- sentinel lymph nodes
- Mastectomy
  - Modified Radical Mastectomy
  - Total Mastectomy w/ sentinel lymph nodes
- In general, the move has been toward less invasive surgical management
  - Attempts to increase rates of breast conservation
  - Less complete axillary dissections and removal instead of only sentinel nodes (unless full axillary dissection is indicated)

Lumpectomy

Removes primary tumor with negative margins and preserve natural breast cosmesis

May not be feasible with larger tumors, or patient may prefer breast removal



SYSTEMIC MANAGEMENT

Systemic Therapies for BC

- Endocrine Therapy/Anti-Hormone Therapy for ER+ disease
- Chemotherapy for all subtypes
- Biologic targeted therapy for HER2+
- Immunotherapy – TNBC, metastatic BC

RADIATION THERAPY

CT Simulator & TrueBeam Linear Accelerator

CT Simulator

Linear Accelerator

Indications for Radiotherapy for BC

- Ductal Carcinoma in Situ (DCIS)
  - Radiation therapy often indicated in post-lumpectomy setting
- Early-stage (Stage I/II) Invasive Breast Cancer
  - Radiation therapy indicated in post-lumpectomy setting
- Locally advanced (Stage III)
  - Indicated in post-lumpectomy setting (breast + regional nodes)
  - Indicated in many (most) instances post-mastectomy
- Inflammatory Breast Cancer
  - Radiation therapy **always** indicated after mastectomy
- Metastatic Disease
  - Radiation therapy reserved for palliation of symptoms
  - SBRT for select pts with oligometastatic disease

Radiation Following Lumpectomy

- Maintain intact, sensate breast
- Reduce risk of recurrence
  - DCIS: prevent first invasive bca
- Preserve cosmetic outcome
- Avoid mastectomy +/- reconstruction
- Lumpectomy and Radiotherapy (BCT) provide survival and control rates equivalent to Mastectomy

Locally Advanced Bca & Radiotherapy

- Improves overall survival following lumpectomy and mastectomy
- Prevents distant metastases
- Optimizes breast cancer-specific/overall survival

BCT vs. Mastectomy

Trial	Yrs F/U	% Overall Survival BCT	Mastectomy	p
Milan I	20	58	59	NS
Gustave Rousy	15	73	65	NS
NSABP B-06	20	46	47	NS
NCI	10	77	75	NS
EORTC 1081	15	65.8	66.1	NS
DBCG-82 Tm	6	79	82	NS

Breast Conservation Therapy is at least equivalent to mastectomy

Goals & New Areas

- Our goal in RO is to limit the dose of radiation to normal structures ("organs at risk") while treating the breast +/- lymphatics with effective, potentially curable dose
- Use shorter courses of radiation when possible
  - Accelerated partial and whole breast regimens: 5 treatments, delivered every other day
- We use several techniques to help us do that
  - Prone positioning
  - Deep Inspiratory Breath Hold (DIBH)
  - Intensity Modulated Radiation Therapy (IMRT)
  - Accelerated Partial Breast Radiotherapy (offered to women ≥40 years, low risk, early stage)
    - Treats lumpectomy cavity + margin

Prone breast treatment

- Position lets gravity work with us, allowing breast to hang below & pull away from chest wall
- Linac is then brought to sides & pt's breast treated from side/underneath
- Significantly reduces the dose of radiation to the lung
- Very often significantly reduces the dose to heart in left-side bca pts

De-escalation

- Better identify women in whom radiation can be safely omitted
  - Women who received Neoadjuvant Systemic therapy who clear disease in the lymph nodes (primarily Her-2+ and Triple negative breast cancers at this point)
    - Recently published data from RTOG 1304 clinical trial

Summary

- Radiation therapy is generally recommended in nearly all cases of breast conservation for DCIS and early-stage invasive disease
- Radiotherapy is recommended following mastectomy for most women with lymph-node positive disease.
  - Ommission in select cases in which disease in cleared in the lymph nodes following neoadjuvant systemic therapy