

Breast-cancer related arm and breast lymphedema: update

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Breast cancer-related arm and breast lymphedema



- Lymphedema of the arm and breast are common in breast cancer patients and long-term breast cancer survivors
- Screening and identification of breast cancer-related lymphedema is everyone's responsibility

Arm edema is common in breast cancer patients: but may not be lymphedema

- **Swelling** in breast cancer patients has many potential causes:
 - Arm or subclavian blood clot (DVT especially port side)
 - Stricture of subclavian vein (from surgery, port or radiation)
 - Cancer recurrence
 - Joint problems/arthritis
 - Medications: taxanes, amlodipine, steroids, PI3K/mTOR/CDK4/6 inhibitors (for metastatic breast cancer)
 - **Swelling of *all* causes: may respond to traditional “lymphedema” therapy (decongestive PT) but that does not = diagnosis**

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Lymphedema: lymphatic insufficiency

Definition: An abnormal accumulation of protein-rich fluid in the interstitium which leads to chronic inflammation and reactive fibrosis

Caused by lymphatic system injury or dysfunction



Complexity of cancer-related lymphedema

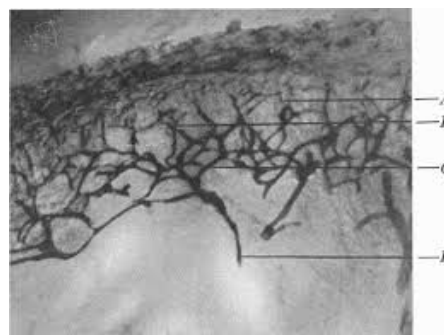
- Lymphedema is a soft tissue, immune system and vascular disorder- not just a fluid disorder
- Genetic predisposition to cancer-related arm lymphedema (Newman, Leung)
- Surgical lymph stasis leads to rise in CD4+ T cell and T-Helper 2 cell differentiation that causes fibrosis and lymphangion pump failure (Angeli, Liao)
- Inflammation from lymphedema leads to subcutaneous adipose deposition (Brorson)
- Taxane based chemo is associated with higher risk of lymphedema (Tokumoto 2022, Armer 2019, Akezaki 2019, Johnson 2019)
- Tumor biology may play a role
 - increased arm lymphedema in patients on anti Her2 therapy (Invernizzi 2019)
 - Increased radiation induced breast lymphedema in Her2 positive patients (Ganju 2019)
- Race/ethnicity (Black women 3x risk-Barrio-2021-SABC)



Initial Lymphatics are in Linings: “Garbage Collectors” to keep the blood circulation free of harmful substances

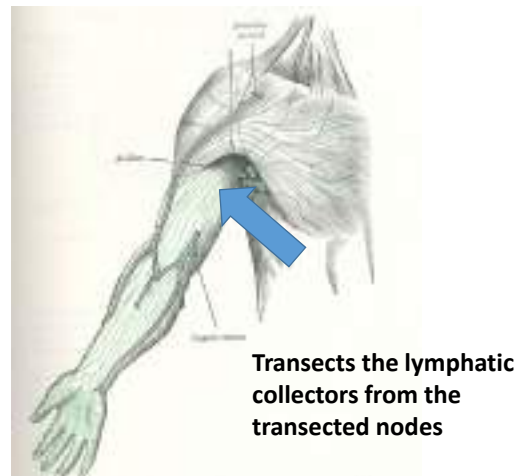
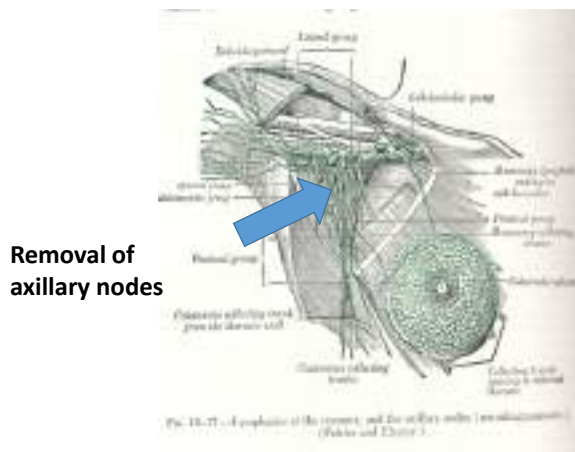
Initial lymphatic capillaries in *skin* move fluid to subfascial lymphatic collectors that go to lymph nodes

Internal lymphatics are in the *epithelium and peritoneum* and carry lymph to collectors that go to lymph nodes



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Lymphadenectomy reduces fluid removal capacity



Fewer lymphatic collectors means residual collectors have to handle more fluid than designed for

Lymphangions are the segments of lymphatic collector vessels

- Each segment is bounded by a valve
- Filling causes contraction to move lymph fluid
- Damage caused by excess pressure, overfilling, fibrosis

Lymphedema is the result of lymphangion pump failure



Lymph stasis in the dermis and subcutaneous tissues leads to

- Soft tissue immune dysfunction
- Recurrent cellulitis
- Fibrosis
- Pain
- Disability

The resulting non-liquid fibro-fatty deposition will not respond to compression or CDT (lymphedema therapy) and limits joint mobility



Distress of Breast Cancer Lymphedema



Lymphedema has a major negative impact on daily living, work, social interactions, anxiety, depression, finances and overall quality of life. (Armer 2004, 2006. Yen 2009. Fu 2006, 2008, Lam 2006. Quality of life decreases at limb volume change of just 5-10% (Cormier)



Psychologic, Social, Financial Impact of Breast Cancer Lymphedema

- Lymphedema self management takes up to 2 hours each day
- Putting on and taking off garments is difficult
- Management is expensive
- Garments are necessary but can cost up to \$1000 and have to be replaced every 6 months
- Insurance coverage is often inadequate for optimal management
- Catching at an earlier stage means self care is less burdensome and reduces total cost of care to the health system



Prospective Surveillance Model

2012 *Cancer Journal Supplement: Prospective Surveillance Model* created framework for identifying and treating BrCa upper body morbidity, including lymphedema, in a holistic context

Original Article

Upper-Body Morbidity After Breast Cancer*
Incidence and Evidence for Evaluation, Prevention, and Management
Within a Prospective Surveillance Model of Care

Sandra C. Hayes, PhD¹, Karen Johansson, PT, PhD², Nicole L. Stout, MPH, CLU, LANA³, Robert Pericelli, MD, MPH⁴, Jane M. Armer, RN, PhD⁵, Sheryl Graham, MD, MBA⁶, and Kathryn M. Schwetz, PhD⁷

The purpose of this paper is to review the incidence of upper-body morbidity (arm and breast symptoms, impairments, and functional status) and methods for diagnosis, prevention, and treatment strategies. It was also the purpose to highlight the evidence base for integration of prospective surveillance for upper-body morbidity within standard clinical care of women with breast cancer. Between 50% and 60% of women report upper-body symptoms between 6 months and 3 years after breast cancer, and approximately 20% develop lymphedema. Lymphedema, however, remains a long-term occurrence, and although lymphedema may be transient for some, those who present with mild lymphedema are at increased risk of developing moderate to severe lymphedema. The etiology of morbidity seems to be multifactorial, with the most consistent risk factors being those associated with extent of treatment. However, breast cancer risk factors remain relatively distinct between those who will and will not develop upper-body morbidity. Upper-body morbidity may be treatable with exercise therapy. There is also evidence in support of integrating exercise surveillance for upper-body morbidity into the routine care provided for women with breast cancer, with early diagnosis potentially contributing to more effective management and prevention of progression of these conditions. *Cancer* 2012;119(10):2237-46. © 2012 American Cancer Society.

KEYWORDS: breast cancer, upper-body morbidity, lymphedema, incidence, prevention, treatment.

Overview of the Epidemiology of Upper-Body Morbidity
Upper-body morbidity after breast cancer is typically characterized by the presence of sensory or motor symptoms and impairments such as pain, weakness, tightness, poor range of motion, nerve paresthesia, altered movement patterns or muscle recruitment, numbness, or swelling in the shoulder, arm, and/or breast of the affected side. Upper-body morbidity is typically associated with alterations in the use and function of the upper body and adverse physical, psychosocial, and social ramifications that profoundly influence all aspects of daily life and hence quality of life (QOL).^{1,2} Although lymphedema (swelling) is regarded as the most feared and problematic,^{3,4} the purpose of this paper is to review upper-body morbidity incidence and risk factors, methods for diagnosis, and prevention and treatment strategies. The evidence base for integration of prospective surveillance of upper-body morbidity within standard clinical care of women with breast cancer will also be highlighted.

Incidence of Upper-Body Morbidity After Breast Cancer
Upper-body symptoms and impairments
Despite advances in breast cancer treatment methods that have led to less invasive surgical techniques, such as sentinel node biopsy,^{5,6} and more refined radiation techniques, such as intensity modulation,^{7,8} upper-body symptoms and

Arm BCRL is part of a spectrum of soft tissue and vascular morbidities that should be screened for and treated together

Screening vs staging: we use the same measurement tools for different reasons

- **Screening:** institutional protocol usually in surgeon clinics to identify lymphedema at the lowest detectible Stage (Stage 0 and I) and refer patient to rehab for intervention
 - Measures volume at determined intervals
 - Self Report: NCCN guideline to ask about lymphedema every breast clinic follow up, may use a PROM and then refer
 - Most accurate if first measurement is *pre treatment* (chemo, port or surgery)
 - Highest risk of developing BCRL is within the first 2 years post-operative (Armer, Bar-Ad) so this is recommended period for screening
 - Screening allows implementation of “early compression sleeve” instead of full decongestive therapy
- **Staging:** evaluation in lymphedema rehab clinics of clinically evident lymphedema (Stage I-III) to assess severity for treatment
 - Volume: uses same volume modalities as screening but must be able to follow intervention in the lymphedema therapy clinic to assess treatment change
 - Tissue Texture
 - Imaging when needed (usually lymphoscintigraphy) for accurate diagnosis

Clinical Staging of Extremity Lymphedema (ISL) Done by Certified Lymphedema Therapists or MD/NP Lymphologists

Tissue Stage	Characteristics
Stage 0	Latent or subclinical (at risk but no visible swelling)
Stage 1	Reversible swelling with mild or no pitting
Stage 2	Non-reversible swelling with pitting, fibrofatty accumulation in the dermis and subcutis, tissue architectural distortion and loss of landmarks
Stage 3	Progressive dermal overgrowth :papillomas, wart like dermal growths increasing fibrofatty tissues that become firm and non-pitting
Severity of size/volume	Percentage by interlimb difference or ipsilateral with a pre-op baseline
Minimal	5-10%
Mild	10-20%
Moderate	20-40%
Severe	>40%

Staging is not diagnosis (it is a severity index).
Diagnosis requires imaging (not needed for screening)
For early BCRL staging is presumed diagnosis, may need later confirmatory imaging

The Diagnosis and Treatment of Peripheral Lymphedema: 2016 Consensus Document of the International Society of Lymphology. *Lymphology*. 2016;49(4):170-184.

Limb volume measurement techniques (LVM)- used for screening/staging



Water Displacement



Sum of Limb Circumferences
by Tape Measure



Perometer-IR scanner



3D Optical Scanner

- Measurements can be done in various ways
- Volume measurements assist in following response to treatment as well as screening
- Tape measurement is accurate when done consistently (Chance-Hetzler, Blaney)

Soft tissue fluid composition techniques-screening



- **Tissue Dielectric Constant (TDC):** Reflected electromagnetic energy from an applied electromagnetic field. TDC value determined by tissue water content
- **Ultrasound, MRI, Dual energy X-ray absorptiometry (DEXA)**
- **Soft tissue and fluid composition techniques do not compare well to LVM**
 - Expensive
 - Do not move seamlessly from screening to staging to treatment (limitations BIS for staging-Ward 2021)
 - TDC and BIS can be used for screening and then referral for staging with standard LVM
 - MRI and DXA are sometimes used when assessing for lymphatic debulking surgery



- **BioImpedance Spectroscopy (BIS):** Application of a sinusoidal wave current measures electrical impedance at multiple frequencies. Excess fluid causes reduced impedance. **The most studied and most accurate for screening**

Lymphedema Stage 1



Early Lymphedema: 5-10% volume. Reduces with elevation. No fibrosis. Pitting evident



Lymphedema Stage 2

- Accumulation of protein-rich edema fluid
- Pitting becomes progressively more difficult
- Connective tissue proliferation (fibrosis)
- More susceptibility to infections
- >10% volume



Lymphedema Stage 3

- Accumulation of protein-rich edema fluid
- No pitting
- Fibrosis , severe dense tissues
- Skin changes: papillomas hyperkeratosis (previously called elephantiasis)
- Usually associated with volume >20%



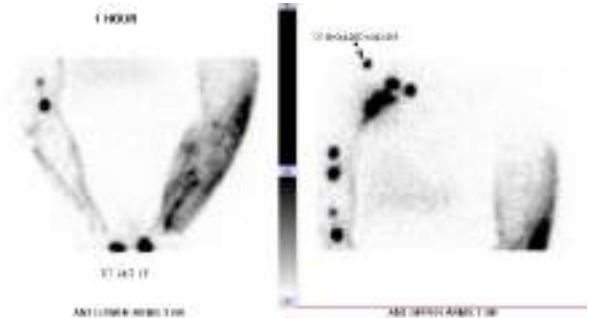
Arm swelling indications for lymphatic imaging (lymphoscintigraphy) in breast cancer patients

- Lymphedema onset in affected side arm > 1 year post treatment
 - CT or MRI including axilla to rule out cancer recurrence
 - Doppler US or CT venogram to evaluate for DVT
 - Xray to rule out soft tissue or bone abnormality
 - Lymphoscintigraphy to determine lymphatic failure, ie is swelling etiology lymphatic
- Swelling (even early) when lymphedema is unexpected
 - Arm swelling after sentinel lymph node biopsy, especially if no radiation
 - When suspicion of soft tissue, joint or bone abnormality
 - If port or pacemaker on the affected side

Lymphoscintigraphy-
gold standard for diagnosis of lymphedema

- Technetium [99mTc] sulfur colloid (not Tilmanocept or Dextran)
 - Immediate image and delayed images 60-90 minutes
- Functional assessment of lymphatic system
- Guides treatment and determines prognosis
- Insurance covers according to radiology benefit (may need prior auth)

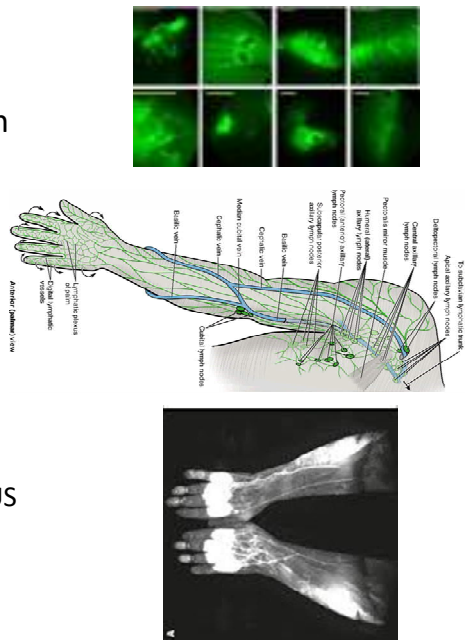
1 hour images of severe lymphedema left arm
Split image-Left: lower arms, Right: upper arms



- Evidence of lymphatic failure;
1. Non visualization deep collectors
 2. No uptake in remaining lymph nodes
 3. Dermal backflow

Other lymphatic imaging

- Near Infrared Fluorescence with Indocyanine Green (NIRF-ICG)
 - Optical imaging device visualizes small cutaneous lymph vessels, not collectors or lymph nodes
 - Multiple injections of ICG in the extremity
 - Available to lymphatic surgeons for planning lymphatic reconstructive surgeries or research institutions
 - Not covered by insurance
- MR Lymphography
 - Intradermal injection of gadolinium followed by MRI for detailed imaging of the lymphatic collector vessels
 - Gadolinium is not approved for dermal injection in the US
 - Europe and research institutions



“Early Sleeve” protocol is effective

- 2008 Stout et al showed benefit of 30 day sleeve intervention for early low volume lymphedema
- 2013 Dayes et al showed that sleeve alone managed low volume early lymphedema as well as CDT
- 2014 Soran showed that sleeve intervention for subclinical lymphedema significantly reduced progression to clinical lymphedema at 21 months
- **Studies with volume measures indicate that it is reasonable to consider early BCRL threshold at approximately 5% limb volume increase (Stout, Specht, Cormier) to implement sleeve protocol and follow in lymphedema clinic for regression/progression**
- Your institution must set up a sleeve intervention protocol
 - ordering “lymphedema therapy” may lead to full CDT and confuse patients about whether they have lymphedema vs “pre-lymphedema”
- A just published paper (Pramanandam) suggests that it is more effective to issue prophylactic sleeves-this is a reversal of past 10 years of practice-stay tuned!



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Complete Decongestive Therapy: For Stage II-III

- on average 50% reduction maintained 9-12 months if compliant with sleeve

Before and after
CDT



If it is Lymphedema Stage II: Complete Decongestive Therapy (CDT) is indicated

- CDT is gold standard for treatment Stage II lymphedema-outpatient
- Therapist must be Certified Lymphedema Therapist (CLT). Best if LANA certified.
- **Phase I: Reductive:** Daily for average 15 days
 - manual lymphatic drainage (a targeted skin stretch lymph flow technique using the hands)
 - **inelastic** bandaging
 - Lymphatic exercise (promotes lymph flow sequentially)
 - skin care (reduces portal of entry for bacteria)



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Phase II: CDT Home Management including maintenance compression garment

- Standard Compression Garments
 - Sleeves and gloves
 - Determine flat (inelastic) versus circular (elastic)
 - For lymphedema: Inelastic is default
- Padded or velcro night garments
 - Paired with daytime sleeve/glove when needed
- Other home management
 - Skin care
 - Exercises
 - Self lymphatic drainage



Pneumatic compression aka “pumps”



- Pneumatic compression is not a substitute for correct garments
- Pneumatic compression should be added when patients are not controlled with **correctly prescribed** day/night compression
- Pneumatic compression is not a first line treatment for edema/lymphedema
- Insurance companies require a high degree of documentation of failure of standard treatment

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Incidence BCRL (Arm)-many inaccuracies

- BCRL Incidence statistics are averages: BCRL 5%-60%
 - Variability in timing of measurement relative to the natural latency and progression of swelling
 - Variability in measurement techniques
 - Lack of stratification for differences in treatment
 - No standard threshold of severity determined to indicate a pathologic state
 - No studies using actual imaging of lymphatics to determine true incidence

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Incidence of Breast Cancer Related Lymphedema – An Accurate Study Protocol

- Naoum G et al. Quantifying the impact of axillary surgery and nodal irradiation on breast cancer-related lymphedema and local tumor control: Long term results from a prospective screening trial. J Clin Oncol. 2020. 38:3430-3438
 - 5 year cumulative incidence rates: SLNB 8.0%, SLNB+RLNR 10.7% (versus 6% in AMAROS), ALND 24.9% (versus 13% in AMAROS), ALND+RLNR 30.1%.
 - This study (as opposed to AMAROS) used a valid measure for lymphedema, the perometer, and used pre and post op measurements
 - **BCRL SLNB 8-11%, BCRL ALND 25-30%**

BCRL=breast cancer related lymphedema, SLNB=sentinel lymph node biopsy, RLNR=regional lymph node radiation, ALND=axillary lymph node dissection, LN=lymph node

AMAROS = Donker M et al. Radiotherapy or surgery of the axilla after a positive sentinel lymph node in breast cancer (EORTC 10981-22023 AMAROS): a randomized, multicenter, open-label, phase 3 non-inferiority trial. Lancet Oncol.2014 15(12):1303-13310

Talking to patients about their risk of developing arm lymphedema after breast cancer

- Explain
 - Higher risk or lower risk
 - Transient early lymphedema (usually reversible=common)
 - Long-term lymphedema (incompletely reversible-ie permanent=less common)
 - Lymphedema is a spectrum and not one entity
- Explain that studies on risk of developing long term lymphedema are very flawed
 - Studies use aggregate data that is not comparable
 - No standard threshold
 - No standard measurement technique
 - No standard length of follow up

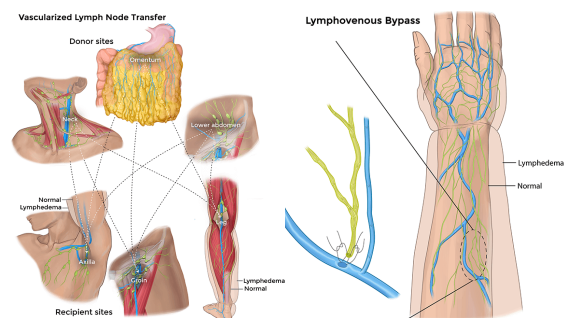
BCRL Arm Risk Reduction Practices

- BCRL Arm Risk Reduction Practices are published lists of Dos and Don'ts that are outdated
 - They are predicated on the erroneous belief that lifestyle factors and controllable physical factors play a role in triggering onset of secondary lymphedema
 - Do not risk stratify and do not determine an individual's unique risk
 - Studies have shown that patients who have had sentinel lymph node dissections can be reassured that they probably do not need to follow strict risk reduction protocols (McLaughlin).
 - From the NCCN Survivorship Lymphedema Guideline
 - "observational studies have demonstrated that air travel, venipuncture and blood pressure measurement (via arm cuff) are not associated with exacerbation or development of lymphedema, and **precautionary measures are likely unnecessary. In the absence of high-level data, however, the panel recommends that medical procedures such as venipuncture and blood pressure measurements be done on the non-at-risk arm/limb if possible**" NCCN Survivorship V3.2021
 - No evidence that exercise (cardio or strength) causes lymphedema to develop (Schmitz)
 - Early arm exercises reduce the risk of developing arm lymphedema (Zhang, Zimmerman, DeVogt)
 - Prophylactic sleeve may reduce risk of developing lymphedema-NEW (Paramanandam)

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Lymphatic Surgeries for Arm Lymphedema

- Removal of solid component lymphedema (debulking)
 - Suction-assisted lipectomy (lymphatic liposuction)
 - Tissue excision techniques
 - Long history and good outcomes (Brorson)
- Lymphatic Reconstructive Surgery
 - Vascularized lymph node transplant (VLNT)
 - Lymph-venous anastomosis (LVA)
- Comprehensive treatment is essential
 - Pre-surgical, surgical, comprehensive after care in a lymphedema clinic
- Improve function and cosmesis
 - Reduce cellulitis
 - Reduce pain
 - May still need garments, but can downstage lymphedema
 - Not routinely covered yet, but improving



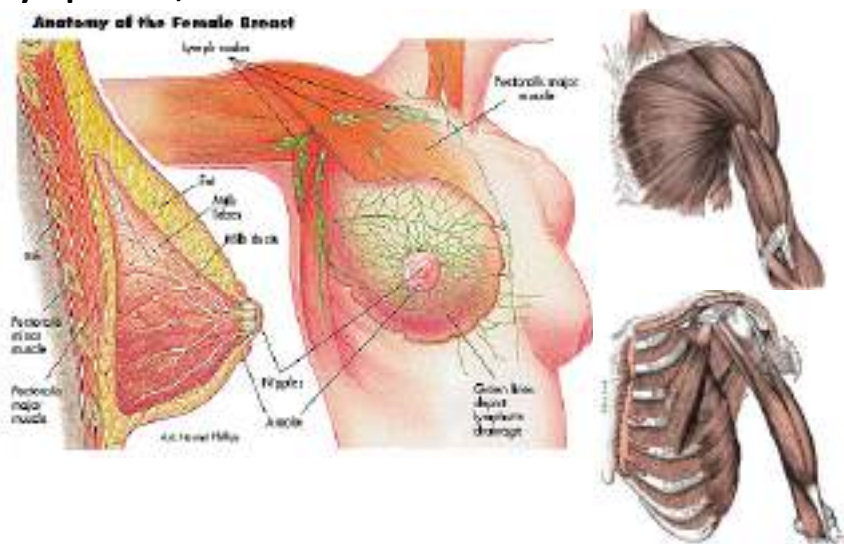
Breast Lymphedema

- Associated with skin changes
 - Pitting, peau d'orange, hyperpigmentation, thickening
- Edema most common in lower areas of breast
 - $\frac{1}{4}$ have in more than one quadrant
- Erythema without cellulitis or inflammatory cancer
 - $\frac{3}{4}$ patients with breast lymphedema
- Has a risk for breast cellulitis
- More common when lumpectomy in outer quadrants (collector bundle)
- Symptoms: breast heaviness, tenderness, soreness, **pain**
- May be more fibrotic than swollen
- Associated with distress
 - Poor cosmesis, asymmetry, distortion
 - Inability to choose flattering clothing
 - Impaired body image
 - Reduced quality of life
 - Impaired sexual function



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Radiation induced Fibrosis: nerves, muscles, skin, blood vessels, lymphatics, fascia



Breast lymphedema occurs in 50% of patients after lumpectomy

80% of breast lymphedema occurs after radiation (part of the spectrum of radiation induced fibrosis of soft tissues)

50% by 3 months, 40% by 6 months and 10% by 12 months

Radiation Induced Fibrosis leads to stiffness and pain in the chest wall and shoulder girdle along with breast lymphedema

Breast Lymphedema: Increased Risk Factors

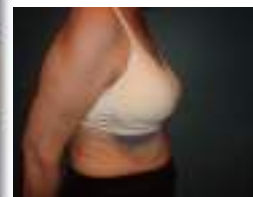
- Increased acute radiation toxicity
- Postoperative infection
- Larger breast/BMI
- Breast seroma
- Comorbid conditions, especially autoimmune and diabetes mellitis

Recent pilot study showed no difference hypofractionation vs traditional fractionation or association with total dose of radiation. Nelson 2021

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Breast Lymphedema Treatment

- Therapy by Certified Lymphedema Therapist:
 - Manual Lymphatic Drainage, compression wrap, swell spots and/or bra
 - 75% improve, 10% stabilize, 10% fluctuate, 5% progress
 - Treatment reduces overuse of antibiotics
- Do not rely on compression bras! Send to a Certified Lymphedema Therapist for treatment. MLD works better than compression
- Possibly anti-oxidants (Vit E + pentoxifylline - Kaidar-Person)



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Breast vs arm lymphedema:
can occur together but different mechanism

ARM LYMPHEDEMA	BREAST LYMPHEDEMA
Increase volume of affected part	Volume increase or decrease of affected part
Swelling is in non-radiated area	Swelling is in radiated area
Occurs in breast conserving surgery or mastectomy	Occurs after breast conserving surgery
Main factor is extent of axillary dissection	Main factor is radiation Extent of axillary surgery not as much a determining factor
Manual lymphatic drainage alone not enough. Compression is necessary and often need custom.	Manual Lymphatic Drainage and scar release most effective. Custom compression bra may not be necessary and supportive bra +/- swell spot can be enough

Thank you!

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Remaining slides are references

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