2014 Annual Breast Cancer Rehabilitation Healthcare Provider Event

A Manual Therapy and Exercise Approach to Breast Cancer Rehabilitation Course

November 7th and 8th, 2014
Mercer University, Atlanta, GA

Sponsored By:
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A Manual Therapy and Exercise Approach to Breast Cancer Rehabilitation Course

Long-Term Effects of Surgery and Radiation on Biomechanics of the Upper Quarter Post-Breast Cancer

Pamela K. Levangie, PT, DSc, DPT, FAPTA
Professor and Chair
MGH Institute of Health Professions
Agenda: Consideration of

- Surgery and Axillary Lymph Nodes
- Radiation Therapy\(^1\):
  - Overview, definitions, late effects
  - Shoulder Impairment Evidence
- Pathokinesiologic Implications
  - Normal kinesiology review
  - Pathokinesiology and potential management issues

\(^1\)With thanks to Dr. Craig Tyree, Radiation Oncologist
Breast Cancer Treatments:

- **Surgical Options:**
  - Lumpectomy (WLE or BCT) - the MOST common
  - Mastectomy (± reconstruction)
- **Sentinel node biopsy (SNB) ± Axillary lymph node dissection (ALND)**
- **Chemotherapy**
  - Pre- or Post-surgery; highly variable options
- **Radiation**
  - Standard of care post-lumpectomy
  - ±Post-mastectomy (~if lymph node positive)
- **Hormone therapy**
Breast Cancer Treatments:

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  - Adjuvant (2°) Therapies: enhance tumor suppression
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- **Radiation**
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  - ±Post-mastectomy (~if lymph node positive)

- **Hormone therapy**
Axillary Lymph Nodes:

- Sequential filtration System (distal to proximal)
Lymph Node Status:

- May contain cancer cells from the primary site (local metastasis)
  - Increased risk of distant metastasis
- Full axillary lymph node dissection (ALND) or “sampling”
- Sentinel lymph node biopsy
  - May STILL lead to ALND
- Has implications for selection and extent of treatments (chemotherapy and radiation)
Axillary Dissection:

- Incision into or removal of axillary fascia
  - Removal/sampling of imbedded lymph nodes
  - Scarring/tissue change
- Increased morbidity with ALND
Radiation Therapy (XRT):

- Who gets it?
  - Lumpectomy (standard of care)
  - Mastectomy with node involvement
    - Node negative: no radiation
    - $\geq 1$ node $\pm$ radiation (uncertain standard)
    - $\geq 4$ nodes = radiation (fields dependent on staging)
  - Reconstruction (+flaps, -implants): variable issues around timing of radiation
Radiation Therapy Definitions:

- Dose – amount of energy delivered per unit mass (cGy = rad)
  - Typical dose is 5500-6500 cGy (55-64 Gy)
- Fractionation – how many treatments are given for a given TOTAL dose
  - 3000cGy/10fx = 300 cGy per fraction
  - Std fx size is 180-200 cGy (1.8-2.0 Gy).
Types of Radiation Beams:

- **Photons (x-rays)** – delivered by linear accelerator, skin sparing, good depth dose
- **Gamma rays** – electromagnetic wave, delivered by Co-60, moderate skin sparing, good depth
- **Electrons** – particulate radiation, delivered by linear accelerator, no skin sparing, limited depth penetration (EBRT)
- **Brachytherapy**
Electron Beam Radiation Therapy (EBRT):

- Rapidly proliferating tissues (↑oxygenation) = ↑radiosensitivity
  - Tumor, skin, mucosa, bone marrow
- Non-proliferating (slowly proliferating) tissues respond later to XRT.
  - Connective tissue
  - CNS, PNS, bone
Electron Beam Radiation Therapy (EBRT):

1. **Tangential opposed fields** – used to treat breast or chest wall, and a portion of axilla (Level I, II).
   
   ✓ Any radiation for breast cancer includes tangential opposed fields
   
   ✓ Minimize exposure of heart and lungs
Electron Beam Radiation Therapy (EBRT):

1. **Tangential opposed fields**
2. **Boost** – usually given with electrons to treat scar & tumor bed.
3. **Posterior axillary boost** – boosts dose to level III nodes in axilla.
4. **Supraclavicular field** – treat nodes level IV nodes in SC.
Radiation Therapy

- Immediate effects (esp. skin) well-documented.

**Question:** What is the potential for long-term effects?
Late Effects of Radiotherapy:

- Radiation-induced fibrosis
- Lymphedema (± fibrosis)
- Brachial plexopathy
Late Effects of Radiotherapy:

- Radiation-induced fibrosis
- Lymphedema (± fibrosis)
- Brachial plexopathy
Radiation-Induced Fibrosis (RIF)

- Large inter-patient variation in susceptibility (genetic?) for long-term changes;
- Not predictable;
- May affect both cutaneous and subcutaneous tissues;
- May be related to initial inflammatory response to XRT.
Radiation-induced Fibrosis:

- Replacement of normal tissue with mesenchymal cells (fibroblasts) and overproduction of extracellular matrix.

Let’s examine normal connective tissue composition
Connective Tissue Structures

Cells (eg. fibroblasts) are imbedded within an ‘extracellular matrix’ including:

- Proteins (aggrecan, hyaluronan)
- Collagen
- Interstitial fluid: relates to protein composition

Adapted from Nordin & Frankel
One Proposed RIF Mechanism:

- TGF-β (Transforming Growth Factor β)
  - Deposits extracellular matrix
  - Stimulates fibroblast formation
  - Increased cross-linked collagen (type I);

Adapted from Nordin & Frankel
Effects of RIF:

Collagen Matrix

At Rest

What if this IS at rest?

30% Tension

Now add 30% tension...

From: Nordin & Frankel
TGF- β:

- Highly variable levels among normal individuals;
- Increased concentration w/ radiation
  - An immediate response to XRT;
  - May persist for extended periods of time;
- Fibroblast behavior in response to ↑ TGF- β may a genetic variant.
TGF- $\beta$:  

- The correlation between fibroblast behavior and TGF- $\beta$ levels is not usefully predictive of RIF.
- $\uparrow$ TGF- $\beta$ is typically also accompanied by $\uparrow$ degradation ($\uparrow$ turn-over);
  - $\uparrow$ Turn-over: typical of aging tissue
  - RIF may be an acceleration of normal aged-related tissue changes.
Pulmonary fibrosis
Huang et al: Radiat Oncol. 2000; 57:91-96

- Associated with convex thorax or deep tangential fields → excessive lung vol.
- Max. of Grade I (asymptomatic/mild) fibrosis in MRM pts. over 3-14 months:
  - 43% BMI <23.8; 6% BMI ≥23.8;
  - Increased risk with Tamoxifen;
  - Non-sig. increased risk w/ chemotherapy
Pulmonary fibrosis

• Early Phase:
  • Begins within a few weeks;
  • Peaks ~6 mos., partially resolves thereafter;
  • Stabilizes around 1 year (83.6% of pts).

• Late Phase:
  • Density changes progressed for 4-5 years in 7.7% of patients.
RIF [and TGF-\(\beta\)]:

- May increase fibroblasts and extra-cellular matrix - leading to:
  - Proliferation of vascular endothelium;
  - Decreased sweat gland production;
  - Constriction of lymphatic vessels.

**EFFECTs ON:** Cut/Subcut flexibility, tissue repair, sensation, vulnerability to infection, edema control
Late Effects of Radiotherapy:

- Radiation-induced fibrosis
- Lymphedema (± fibrosis)
- Brachial plexopathy
Lymphedema & Radiation:

- Lymph vessels insensitive to radiation
- Lymphatic constriction secondary to surrounding fibrosis
- Radiation does delay the normal growth of lymphatics into tissues undergoing repair after surgery
Lymphedema & Radiation:

- Lymph nodes are radiosensitive
- Lymphocyte depletion followed by fatty replacement then fibrosis
- Radiation also decreases the filtering function of lymph nodes & alters their immune function (through RIF?)

Fibrosis may be the common denominator
= Increased risk over time?
Late Effects of Radiotherapy:

- Radiation-induced fibrosis
- Lymphedema (± fibrosis)
- Brachial plexopathy
Brachial Plexopathy

- Xsectional study of 81 women (median follow-up = 10 years) ; MRM (57%), BCT (43%)

- Axillary dissection & XRT (tangents, SC, PAB)

  - 20% had plexopathy confirmed by neurological exam (mild to severe)
  - Assumed to be radiation-induced (RIBP) w/ no other overt explanations
Shoulder Impairment Evidence: Effects of XRT
Long-term Impact: Functional Limitations


- 105 women at least 5 years post-dx vs. age- and work-matched control group

- Cases
  - Avg. 7 years post-diagnosis
  - Early stage (> 80% surgery, most with chemo and/or radiation)

- Compared current to Pre-dx status among cases
Those with BCa are more likely to be newly impaired at time of survey than matched controls. [OR = 2.5 (1.2, 5.0)]

“Work-related outcomes tended to be uniformly poorer for the newly impaired group than for the rest of the sample”.

“BCa group more likely to experience .. adverse economic outcomes..”,

Therefore: “economic benefits of interventions that minimize or prevent these problems are potentially very high.”
XRT to No XRT (Blomqvist et al):

- Prospective study
- 75 women with MRM (mean: 15 mos. post)
  - Comparison: 30 XRT vs 45 no-XRT
- Goniometric active ROM:
  - Side-to-side differences
- Self-report impairment of ADL:
  \[ \text{OR} = 1.47 \ (0.56-3.87)(p=0.46) \]
Blomqvist et al (con’t)

<table>
<thead>
<tr>
<th>ROM</th>
<th>XRT patients: std ES (mean diff: side-to-side)</th>
<th>Non-XRT patients std ES (mean diff: side-to-side)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extension</td>
<td>2.3 (2.3°) (p&lt;.05)</td>
<td>1.8 (1.5°) (NS)</td>
</tr>
<tr>
<td>Flexion</td>
<td>8.94 (17°) (p&lt;.001)</td>
<td>1.8 (3.0°) (p&lt;.05)</td>
</tr>
<tr>
<td>Abduction</td>
<td>11.78 (33°) (p&lt;.001)</td>
<td>3.2 (6.9°) (p&lt;.05)</td>
</tr>
<tr>
<td>ER</td>
<td>2.9 (10.8°) (p&lt;.01)</td>
<td>0 (NS)</td>
</tr>
<tr>
<td>IR</td>
<td>2.33 (4.2°) (p&lt;.01)</td>
<td>0 (NS)</td>
</tr>
</tbody>
</table>

Self-report impairment of ADL (XRT vs. None): [OR = 1.47 (.56-3.87)(p=.46)]
XRT to No XRT (Hørjis et al)


- MRM patients, 6-13 yrs post-treatment
- 42 w/ XRT and chemo; 42 w/ chemo alone
- Subjective reports of any dysfunction
- Measured ROM (< 170°)
- Comparison: XRT to no XRT
Hørjís et al: (con’t)

- Loss of any mobility: OR=12.18 (2.55-58.03)
- Sx loss of mobility: OR=8.75 (1.02, 74.83)
- Interference w/ function: OR=7.66 (1.57-37.30)
- Detectable weakness: OR=2.78 (1.06-7.29)
- Flex or Abd <170°: OR=5.66 (1.95-16.46)
- Detectable wkness (obj): OR=6.66 (0.78, 58.06)
- Impaired mobility\(^1\): OR=7.0 (2.2-22.0)

\(^1\)Effect of XRT after controlling for other variables
Shoulder Impairment Evidence: Effects of ALND
ALND vs. SLNB (Rietman et al):


- Prospective study of 181 patients: Stage I and II breast cancer (’99-’01)
- Seen pre-operatively (t0) and 2 years later (t1)
- 57 ALND (axillary lymph node dissection);
- 125 SLNB (sentinel lymph node biopsy)
Rietman et al (2006)(con’t)

<table>
<thead>
<tr>
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<th>SLNB (t1-t0)</th>
<th>ALND (t1-t0)</th>
<th>p-value¹</th>
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<tr>
<td>Flexion (°)</td>
<td>Not reported</td>
<td></td>
<td></td>
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<tr>
<td>Abduction (°)</td>
<td>-5.5 (21.0)</td>
<td>-21.0 (33.5)*</td>
<td>&lt;.001</td>
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<tr>
<td>Abduction/ER (°)</td>
<td>-3.5 (8.0)*</td>
<td>-7.2 (13.7)*</td>
<td>.025</td>
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<td>Grip Strength (Nm)</td>
<td>-17.2 (48.2)*</td>
<td>-41.3 (51.7)*</td>
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¹Difference between groups

*Change from t0
Rietman et al (2006)(con’t)

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¹Difference between groups
*Change from t0
Shoulder Dysfunction (Kwan et al):
J Clin Oncol 2002; 20(20): 4242-8

- Random sample of 750 patients treated ’93-’97 (w/o recurrence)
- 467 responded to questionnaire asking about presence or problems w/ shoulder, arm or hand (including lymphedema).
- Analyzed by patient and treatment characteristics

Effects of ALND and Axillary XRT
Kwan et al (con’t): Self-reported problems

- **ALND: No ALND** (no axillary XRT)
  - Effect of ALND alone
  - OR = 2.42 (1.4-4.1)

- **ALND w/ axillary XRT: ALND w/o axillary XRT**
  - Effect of axillary XRT *in addition to* ALND
  - OR = 2.6 (1.7-4.1)
Radiation and Shoulder Function:
Bentzen, et al. IJROBP, 1989;17:531-537

- Shoulder impairment from radiation directly related to fraction size.
- Time to expression of 90% of affected shoulder mobility is 3.9 yrs.

Continued change → 10 yrs (Spitalier)
Factors in Long-Term Effects on Shoulder:

- Radiation: # and extent of fields [+Fractionation]
- Type of surgery: MRM vs. BCT (~)
- Degree of axillary resection (ALND vs SLNB)
- Prior injury or limitation
- BMI
- +/- Age
- +/- Chemo
- +/- reconstructive surgery
- Infection
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- +/- Chemo
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Considerations in Shoulder Dysfunction

- How do the surgical and radiation-induced changes lead to dysfunction?

Requires review of normal kinesiology
Normal Shoulder Kinematics

Shoulder Elevation: 150°-180°

Components:

- Glenohumeral (GH) Joint
  - 90°-120° (abd/flex)
- Scapulothoracic (ST) Joint
  - 60°
Glenohumeral Contribution (90°-120°):

- Adequate Suprathoracal Space to avoid impingement from:
  - Inadequate downward sliding of humeral head
  - Abnormal acromial (scapular) position
  - Inflammation of rotator cuff (supraspinatus, subacromial bursa)
  - Acromial variants

- Lateral rotation of humerus (abd/scaption)
  - Impact of tubercle on acromion (≤60°)
ST Contribution (60°):

- Clavicular elevation and clavicular rotation

- The scapula will also posteriorly tip during clavicular rotation

- Need both SC and AC mobility
Scapulothoracic Kinetics:

- **Upward Rotation**
  - Trapezius
  - Serratus Anterior
- **Protraction (flexion*)**
  - Serratus Anterior
- **Retraction (abduction*)**
  - Trapezius
Elevation of the Arm (150-180°)

- **GH Contribution**
  - Downward slide
  - Suprhumeral space
  - GH lateral rot (abd.)
  - No capsular restrictions

- **ST Contribution**
  - Clavicular elev/rot
  - Scapular post. tipping
  - Ms. extensibility

- Intact Prime Movers

Implications of Treatment for Breast Cancer for Pathokinesiology of the Shoulder Girdle
Axillary Dissection:

- Incision into or removal of axillary fascia
  - Removal/sampling of imbedded lymph nodes
  - Scarring/tissue change

- Implications for elevation ± brachial plexus (long thoracic nerve)
  - Short-term impairment
  - Improvement over time
Radiation-Induced Tissue Changes:

- Muscular and fascial fibrosis

- Highly variable among individuals
  - Decreased active and passive extensibility
  - Limitation to GH and ST joint ROM
  - Decreased ms. shortening capacity ⇒ active ROM lag (?)
Shoulder Impairments with XRT:

<table>
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<tr>
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<th>Non-irradiated patients</th>
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<tr>
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<td>Operated side</td>
<td>Opposite side</td>
<td>Operated side</td>
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<td>Extension</td>
<td>57.5 (1.2)</td>
<td>59.8 (1.0)</td>
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<tr>
<td>Flexion</td>
<td>155.8 (3.2)</td>
<td>172.8 (1.9)</td>
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<td>139.5 (6.6)</td>
<td>172.5 (2.8)</td>
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<td>71.0 (3.8)</td>
<td>81.8 (2.2)</td>
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<td>57.8 (2.6)</td>
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Comparison of shoulder ROM between operated and non-operated side in irradiated and non-irradiated patients (Wilcoxon signed rank test)

Shoulder Impairment with XRT

**Fig 1.** Comparison of shoulder range of motion (degrees) in groups of irradiated (n = 30) and non-irradiated patients (n = 45). *** = p < 0.001.

**Fig 2.** Comparison of shoulder strength (arbitrary units) in groups of irradiated (n = 30) and non-irradiated patients (n = 45). ** = p < 0.01.

Comparison of shoulder ROM between operated and non-operated side in irradiated and non-irradiated patients (Wilcoxon signed rank test)

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### Active ROM Lag: *(Ryttov et al 1983 – OLD)*

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<th>Movement</th>
<th>XRT</th>
<th>No XRT</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>Active Flexion</td>
<td>69%</td>
<td>8.7%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Active Abduction</td>
<td>62%</td>
<td>4.3%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Passive Flexion</td>
<td>17.2%</td>
<td>4.3%</td>
<td>NS (&gt;0.05)</td>
</tr>
<tr>
<td>Passive Abduction</td>
<td>31%</td>
<td>4.3%</td>
<td>NS (&gt;0.05)</td>
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Percent Impairment compared to contralateral side
Radiation-Induced Tissue Changes:

- Implicated Structures for:
  1. Tangential Fields - 1° radiation fields
Tangential Fields: Implicated Structures

Adapted from Physiology of the Joints by Kapandji

- Intercostals
- Pectoralis Major
- Pectoralis Minor
- Serratus Anterior
Tangential Fields: Implicated Structures

- Pectoralis Major
- Pectoralis Minor
- Clavipectoral Fascia*
- +/- Serratus Anterior
- Intercostals (rib mobility)
Radiation-Induced Tissue Changes:

- Implicated Structures:
  1. Tangential Fields - 1° radiation field
  2. **Scar Boost**: Exaggerates effects of tangential fields?
Radiation-Induced Tissue Changes:

- **Implicated Structures:**
  1. Tangential Fields - $1^\circ$ radiation field
  2. Scar Boost: Exaggerates effects of tangential fields?
  3. **Plus Posterior Axillary Boost** ($2^\circ$ radiation field) *Hypothesis!*
Posterior Axillary Boost:

From Moore's Clinically Oriented Anatomy
Posterior Axillary Boost:

Muscle mass exposure increased at lower levels of thorax

Adapted from Physiology of the Joints: Kapandji
3 Field XRT: Implicated Structures

- **Tangential fields**
  - Pectoralis Major
  - Pectoralis Minor
  - Clavipectoral Fascia
  - Intercostals

- **Plus PAB (hypothesis)**
  - Serratus Anterior
  - Latissimus Dorsi
  - Teres Major
  - +/- Subscapularis
  - [Brachial Plexus]
Radiation-Induced Tissue Changes:

- Implicated Structures:
  1. Tangential Fields - 1° radiation field
  2. Scar Boost: Exaggerates effects of tangential fields?
  3. Plus Posterior Axillary Boost (2° radiation field)
  4. Plus Supraclavicular Field (2° radiation field)
Supraclavicular Field:

- Muscles and Fascia of the Neck

Affects on Cervical spine And scapula

From Goss' Gray's Anatomy

Levator scapula

Omohyoid

Trapezius
Pathokinesiology: Pectoralis Minor

[Variable Fibrotic Reaction]

- Limited elevation and rotation of clavicle
- Anteriorly tipped position
  - Limited posterior tipping for extension
- Limited retraction ± protracted position

Adapted from the Kinesiology Workbook: Perry, Rohe and Garcia (FA Davis, Publ).
Pathokinesiology: Pectoralis Minor (con’t)

Ant. Tipped scapular position:
- 😞⬇️ Suprahumeral space
- 😞⬆️ Likelihood of impingement
- 😞➡️ Upper trap tension ➞ lat. flexion of head

Limited scapular retraction
- 😞Ant. GH capsule tension in true frontal plane b/c humerus is behind the plane of the scapula
- 😞⬇️GH abduction
- 😞⬇️Extension of the humerus
Pathokinesiology: Serratus Anterior

- Additional limitation to retraction
- Scapula upwardly rotated? [Balance of Pec Minor and Serratus]
- ▼ Upward rotatory force in shortened range?

[Variable fibrotic reaction]
Pathokinesiology: Pectoralis Major

- More superficial than Pec Minor
- +/- Scar boost
- Limited GH lateral rotation
- Discomfort with muscle extensibility and/or contractility
- Axioscapular ms. (ribcage?)

Adapted from the Kinesiology Workbook: Perry, Rohe and Garcia (FA Davis, Publ).
Limited lateral rotation:

- ☹️ GH abduction (+/- scaption) and impingement c/o greater tubercle ⇒ arch;
- ☹️ 2° ant/inf capsular restrictions (.downcase lat. rot. and ~protracted scapular position);

Discomfort with many motions

- ☹️ Ms. is active or stretched in most shoulder motions
- ☹️ Ribcage and/or spinal mechanical effects
Pathokinesiology: Fascia

- **Supraclavicular field:**
  - Deep cervical fascia
- **Chest tangents:**
  - Costocoracoid membrane
  - Clavipectoral membrane
  - Suspensory ligament
  - Pectoral fascia

---

From Moore's Clinically Oriented Anatomy (3rd. 4)
Pathokinesiology: Fascia (con’t):

☑ Potential decreased extensibility of investing fascia
- ST and GH joint mobility
- Exaggerates effect on enclosed mss.

± Discomfort w/ depression/extension?
- Latissimus, teres major extensibility/contractility (PAB)

± Latissimus dorsi stiffness effect on thoracodorsal fascia?
Normal Kinesiology \(\Rightarrow\) Pathokinesiology:

- **GH Contribution**
  - ✔️ Downward slide
  - 🙁 Supr humeral space
  - 🙁 GH lateral rot (abd.)
  - 🙁 No capsular restrictions

- **ST Contribution**
  - 🙁 Clavicular elev/rot
  - 🙁 Scapular post. tipping
  - 🙁 Ms. extensibility

- **Intact Prime Movers**

Pathokinesiology:

- Biomechanical effects: Unpredictable in both incidence and magnitude
  - Shoulder $\Rightarrow$ Cervical spine $\Rightarrow$ Ribcage/spine
  - Subtle $\Rightarrow$ Overt
  - Tissue changes may progress over time
  - Interactive effect with normal use and aging issues
  - $\uparrow$ Likelihood of shoulder hypomobility +/- impingement

😊 See you in PT!
PT Examination $\Rightarrow$ PT Intervention:

- Impaired Joint Mobility, Muscle Performance and Range of Motion
- Additional Considerations:
  - Fibrosis c/o axillary surgery ± radiation
  - Impaired tissue integrity (superficial and deep) c/o radiation
PT Examination ⇄ PT Intervention:

- Additional Considerations (con’t):
  - Lymphedema risk c/o axillary dissection ± radiation
  - Impaired sensory integrity
  - Recurrence Issues?
  - Other implicated tissues/functions?
Research on Long-term Shoulder Effects

- Adverse effects are under-reported;
  - Adverse criteria Systems have evolved slowly (Andy Trotii, MD (H. Lee Moffitt Cancer Center, Tampa, FL));
  - Late effects are not widely accepted;
  - Lack of standardized screening pre-op or over time;
  - No standard for data analysis or reporting.
Implications for Clinical Research:

- Effectiveness of a prospective surveillance model \[\textit{Cancer: April 15, 2012; (8 suppl)}\]
- Use of standardized assessment tool(s)!!
- What tests and measurements are currently available? \(\text{BCa EDGE: Rehabilitation Oncology}\)
- Challenges to valid measures:
  - Responsiveness to small effects;
  - Assessing avoided behaviors?
  - Responsiveness to change;
Work to be done:

- Standardize and validate tests and measurements;
- Document the scope of the problems (short- and long-term);
- Evidence of “best” treatment(s);
- Evidence of “value” of a prospective surveillance model
Long-Term Effects of Surgery and Radiation on Biomechanics of the Upper Quarter Post-Breast Cancer

QUESTIONS?

Thank you

Pamela K. Levangie, PT, DSc, DPT, FAPTA
Pklevangie@mghihp.edu