Objectives

1. Examine the clinical considerations that distinguish oncologic clinic practice.
2. Discuss the survivorship continuum and the epidemiological and clinical ramifications of this population.
4. Examine common physical and functional impairments in this population, including anemia and low blood counts, bone metastases, sexual health, cancer-related fatigue and pelvic floor dysfunction, and explore considerations for intervention.
5. Delineate treatment approaches and modifications specific to the above impairments with review of relevant patient cases and literature.
6. Highlight informational resources and recent publications to promote further exploration into oncologic rehabilitation and the skilled prescription of exercise in cancer survivors.

Survivorship Continuum

Estimated New Cancer Cases* in the US in 2019

The Lifetime Probability of Developing Cancer for Males, 2012-2014

The Lifetime Probability of Developing Cancer for Females, 2012-2014
Impairments

Physical
- Cheville et al, 2008
  - Community-Dwelling Patients with Metastatic Breast Cancer
  - 92% had at least one physical impairment
  - Of those, 88% required physical and/or occupational therapy
  - Only 21% of those requiring PT and/or OT received treatment
- Nayak et al, 2016
  - Gynecological Cancer Survivors 1 year after diagnosis
  - 38% reported functional impairments, fewer than 55% meet physical activity guidelines

Physical
- Kenzik et al, 2016
  - 5991 Cancer Survivors, age 65 and older
  - Prostate, Breast, Lung, Colorectal, Bladder, Kidney, HNC, Gun, NHL
  - Chronic condition cluster prevalence, pre- and post-cancer diagnosis
  - All Cancer Types: p<0.001 for Metabolic, CVD, MDDr, GI, Pulm
  - Breast: Metabolic, >2 clusters
  - All Cancer Types: p<0.05 MSK, Metabolic, CVD, MDDr, GI, Pulm

Cognitive
- Tanimukai et al, 2018
  - Breast Cancer Survivors following Adjuvant Chemotherapy
  - Concentration, processing speed, attention, memory, confusion, getting lost
  - Hospital Anxiety and Depression Scale (HADS)
  - Prevalence of perceived cognitive impairment (PCI): 79%; >3 PCI: 43%
  - 43% were determined to be ‘clinically depressed’ per HADS scoring
- Blackwood, 2019
  - 573 Older Cancer Survivors: Falls versus No Falls Group
  - Impaired immediate and delayed word recall (WR)
  - Executive function, WR, and orientation significantly associated with gait speed
  - “For every SD decline in executive function (SD = 6.28) as measured with the verbal fluency task, falls in the older cancer survivor increase by 2.”

Red Flags and Screening

General, Non-Specific
- Previous History of Cancer
- Fever / Chills / Drenching Night Sweats
- Unexplained Weight Loss (>10lbs)
- Night Pain
- Unexplained, Persistent Pain
- Unexplained Bleeding
- Appetite Loss
- Fatigue

Treatment Risk Factors:
- Chronic Use of Steroids or Immunosuppressors

Neurological:
- New-Onset Back Pain
- New-Onset Numbness or Tingling
- Bowel and/or Bladder Changes
- New-Onset Balance Impairments
- Frequent Falls
- Cognitive Changes or Confusion
Lab Values and Blood Counts

Blood Basics Review
- **Red Blood Cells** (erythrocytes)
  - 40-45% blood volume; O₂ and CO₂ carrying
- **Platelets** (thrombocytes)
  - Fragments of cells; coagulation
- **Leukocytes** (eg. granulocytes, lymphocytes)
  - Immunity and infection protection
  - Production and distribution of antibodies
- Develop from hematopoietic stem cells in the bone marrow
  - "Stem cells": bone marrow, circulating in the blood, umbilical cord

Reference Values
- **Hemoglobin**: Males: 14-17.4 g/dL
  - Female: 12-16 g/dL
  - Values slightly decreased in the elderly
- **White Blood Cells**: 5.0-10.0 \(10^9\)/L
- **Platelets**: 140-400 k/uL

Anemia
- **Anemia**: Hemoglobin < 11g/dL
- **Severe Anemia**: Hemoglobin < 8 g/dL
  - Based on symptoms and protocol, transfusion likely to occur at 7 g/dL.
- **Symptoms**:
  - Easy fatigue
  - Decreased energy, malaise
  - Dyspnea or shortness of breath
  - Lightheadedness
  - Headache
  - Pallor
  - Tachycardia
Leukopenia
Leukopenia: <4000/μl
Neutropenia: <1.5 10⁹/L

Symptoms:
• Likely, none.
• Symptoms of infection
• Fever, chills, sweating
• Anemia
• Fatigue
• Weakness

Thrombocytopenia
Thrombocytopenia: <150k/μl

Symptoms:
• Easy or excessive bleeding
• Petechiae
• Ecchymoses
• Bleeding from gums or nose
• Blood in urine or stool
• Fatigue
• Unusually heavy menstrual flows

Causes of Altered Blood Counts
• Cancer
  – Leukemia (ALL, AML, CLL, CML, MDS)
  – Multiple Myeloma
  – Lymphoma
• Myelosuppression from Treatment
  – Chemotherapy
  – Radiation Therapy
  – Surgery

Cancer-Related Anemia (CRA)
Most commonly viewed as toxicity to antineoplastic chemotherapy
• >30% of patients present with CRA at diagnosis before starting chemo
• >67% with CRA after treatment is initiated

Influenced by:
• Stage of disease (advanced disease and advanced age)
• Cancer type (lung cancer, gynecologic or genitourinary, and gastrointestinal tumors)
• Hb inversely correlated with the levels of inflammatory markers

Pathogenesis of CRA
• Shortened erythrocyte survival w/ increased erythrocyte destruction
• Suppressed erythropoiesis in bone marrow
• Effects of inflammation on erythropoietin production
• Alterations in iron metabolism → iron-restricted erythropoiesis induced by hepcidin increase (i.e. inflammatory marker)

Cancer-Related Thrombosis

<table>
<thead>
<tr>
<th>Table 5.8: Risk Factors for Cancer-Associated Thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient-related</td>
</tr>
<tr>
<td>Malignancy-related</td>
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<tr>
<td>Therapy-related</td>
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<tr>
<td>Laboratory</td>
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</tbody>
</table>

Hb = hemoglobin, ESA = erythropoietic stimulating agent.
Contraindications and Precautions

Historical Contraindications:
- Hemoglobin: <8 g/dL; light exercise 8-10 g/dL
- Platelets: <20,000/mL
- White blood cells: <5,000/mm³ accompanied by a fever

Thrombocytopenic Guidelines:
- >150k: Normal activity, no restrictions
- >50k: PREs, low-mod intensity aerobic; monitor for bleeding
- >30k: AROM, low intensity aerobic, light walking, aquatic
- >20k: AROM only, light exercise with physician approval
- <20k: Restricted to light ADLs, light walking with physician approval
- <5k: only AAROM, no Valsalva; Risk for spontaneous bleeding is present

Symptom-Based Rehabilitation

Oncologic Specific Guidelines

Tips, tricks, “trombopenia”

Table 2: Target adaptations to clinical parameters and symptoms related to thrombocytopenia

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Target Adaptation</th>
<th>Physical Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia (low red blood cells)</td>
<td>- Safely appropriate hygiene (e.g., frequent hand washing) and ensuring that exercise equipment is cleaned before and after use.</td>
<td>AROM, AAROM, ADLs</td>
</tr>
<tr>
<td>Leukopenia (low white blood cells)</td>
<td>- Monitor vitals and subjective symptoms.</td>
<td>AROM, AAROM, ADLs</td>
</tr>
<tr>
<td>Thrombocytopenia (low platelet count)</td>
<td>- Avoid positions that compromise circulation.</td>
<td>AROM, AAROM, ADLs</td>
</tr>
</tbody>
</table>

Oncologic Specific Guidelines

Anemia:
- Symptom-based approach
- Monitor vitals and subjective symptoms

Leukopenia:
- Symptom-based approach
- Review chart, check vitals as indicated
- Precautions (mask; hand hygiene; equipment isolation)

Thrombocytopenia:
- <150k cells/ul, symptom-based approach
- Monitor for bruising or bleeding
- Assess equipment / environment
- Educate!
- <20k: Functional mobility exercises
What is Lymphedema?

- Localized form of tissue swelling resulting from excessive retention of lymphatic fluid in the interstitial spaces and caused by impaired lymphatic drainage
  - Lymphatic fluid = protein rich fluid
- Lymphedema occurs when the transport capacity (TC) falls below the normal lymphatic load (LL)

Causes of Lymphedema

<table>
<thead>
<tr>
<th>Causes of Lymphedema</th>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dysplasia (abnormal development) of the lymphatic system</td>
<td>Known insult to the lymphatic system</td>
</tr>
<tr>
<td></td>
<td>- Aplasia</td>
<td>- Filariasis</td>
</tr>
<tr>
<td></td>
<td>- Hypoplasia</td>
<td>- United States:</td>
</tr>
<tr>
<td></td>
<td>- Hyperplasia</td>
<td>- Cancer-related treatments</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Lymphadenectomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Radiotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Chemotherapy</td>
</tr>
</tbody>
</table>
Incidence of Lymphedema & BR Cx

- Incidence:
  - 2 years follow-up: 13.5%
  - 5 years follow-up: 30.2%
  - 10 years follow-up: 41.1%

- Increased Risk:
  - Underwent radiotherapy, obese, seroma formed after surgery, underwent chemotherapy infusion in the affected limb, advanced disease staging

Incidence of Lymphedema & GYN Cx

- Lower limb lymphedema (LLL) is one of the most frequent postoperative complications of retroperitoneal lymphadenectomy for Gyn Cx

  - LLL often impairs quality of life, ADLs, sleep, and sex

  - Incidence:
    - 45.2%

  - Increased Risk (Stage II):
    - Adjuvant concurrent radiochemotherapy
    - Age ≥ 55-years-old

Diagnosis of Lymphedema

- Disease without “gold standard” diagnostic criteria

- Current diagnostic criteria are based solely on physical exam findings

- Clinic Findings:
  - Subjective Symptoms:
    - Swelling, warmth, heaviness, tingling, tightness, skin changes
  - Physical Examination:
    - Decreased visibility of veins, smoothing of the contours of the medial elbow region, increased skin and subcutaneous thickness upon palpation, pitting edema
    - 2 cm Rule
    - Limb Volume Measurement

Treatment of Lymphedema

- Complete Decongestive Therapy (CDT)
  - Fourfold treatment including:
    - Manual Lymphatic Drainage (MLD)
    - Compression Therapy
    - Skin Care
    - Lymph-Reducing Exercises (LRE)
      - AROM vs. Resistance Exercise
    - Education on Risk-Reduction Practices
    - Limb Elevation
    - Sequential Intermittent Pneumatic Compression Device

CDT and Lymphedema

Manual lymphatic drainage for breast cancer-related lymphoedema

Y. SHAO, MD, medical oncologist, Department of Oncology, Tianjin Medical University General Hospital, Tianjin, & D.A. ZHONG, MD, professor of oncology, Department of Oncology, Tianjin Medical University General Hospital, Tianjin, China

“Contraindications” to MLD

- CHF
- Renal Failure
- Acute Infections
  - Cellulitis
- Acute DVT
- Cancer
Takeaways

- Lymphedema is a common side-effect of cancer treatments
- The diagnosis of Lymphedema is based solely on physical exam findings
- AROM and Resistance Training is safe!
Bone Metastases

“BLT with a kosher pickle...annnnnnd mustard and mayonnaise”

Cancers most likely to cause, or be associated, with bone metastases:
- Breast Cancer
- Lung Cancer
- Thyroid Cancer
- Kidney Cancer
- Prostate Cancer
- Multiple Myeloma

Bone Metastases and Lesions

Lytic
- Bone destruction, “moth-eaten” radiographic appearance
- Associated Diagnoses: Multiple Myeloma, Renal Cell Carcinoma, Thyroid

Blastic
- Poor quality bone growth, dense on radiograph
- Associated Diagnoses: Prostate, Lymphoma, SCLC

Mixed
- Combination of bone destruction and poor bone quality
- Associated Diagnoses: Breast (typically sclerotic), Lung (typically lytic), Testicular

Pain and Bone Metastases

- Bone pain: the earliest, most common symptom of bone metastases
- Experienced by 83% of those with metastatic bone disease
- Functional pain is associated with ↑↑↑ risk of pathologic fracture.

Skeletal Pain: Neurobiology Review

Innervated by A-delta and unmyelinated C fibers
- Fibers arranged in a “fishnet-like” pattern
- Detects mechanical injury or distortion of underlying cortical bone
- Cortical bone and marrow: same population, less dense

Innervated by sympathetic nerve fibers
- Associated with regulation of bone destruction and formation, vasodilation and -constriction, macrophage infiltration and bone progenitor cell function

Bone Metastasis Considerations
Bone Metastases and Standard Guidelines

<table>
<thead>
<tr>
<th>Table 4</th>
<th>General safety measures with bone metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>No manual muscle testing in affected limb</td>
<td></td>
</tr>
<tr>
<td>No progressive resistive exercises in affected limb</td>
<td></td>
</tr>
<tr>
<td>Offloading weight bearing through the affected limb with an assistive device</td>
<td></td>
</tr>
<tr>
<td>Avoid excessive spinal flexion, extension, and rotation; clarify need for bracing</td>
<td></td>
</tr>
<tr>
<td>Monitor for increasing functional pain</td>
<td></td>
</tr>
</tbody>
</table>

Bone Metastases Considerations

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Guide for prescribing exercise for patients with bone metastases (112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise Modality</td>
<td>Resistance</td>
</tr>
<tr>
<td>Push-ups</td>
<td>✓</td>
</tr>
<tr>
<td>Squats</td>
<td>✓</td>
</tr>
<tr>
<td>Hip abduction</td>
<td>✓</td>
</tr>
<tr>
<td>Abdominal crunches</td>
<td>✓</td>
</tr>
<tr>
<td>Multimodal Exercise Program (Galvao et al, 2018)</td>
<td></td>
</tr>
<tr>
<td>– Prostate Cancer Survivors</td>
<td></td>
</tr>
</tbody>
</table>

Rehabilitation and Bone Metastases

- Impact + Resistance Training (Winters-Stone et al, 2014)
- PRE Program (Cormie et al, 2014)
  - Breast and Prostate Cancer Survivors
- Multimodal Exercise Program (Galvao et al, 2018)
  - Prostate Cancer Survivors

Findings:
There are multiple areas of abnormally increased tracer activity identified that are compatible with diffuse osseous metastatic disease, including the sternum, multiple anterior and posterior bilateral ribs, proximal right humerus, thoracic and lumbar spine, bilateral iliac bones, superior right acetabulum, bilateral proximal femurs and the distal right femur.
Sexual Health

“Sexual health is the state of physical, emotional, mental, and social well-being in relation to sexuality”

Prevalence of Sexual Dysfunction
- Sexual Dysfunction among general U.S. population: ~ 40%
- Sexual Dysfunction among cancer survivors: 40-100%

Surgery & SH Side Effects
- Urinary Incontinence
- Erectile Dysfunction
- Menopausal Symptoms
- Lymphedema
- Changes in Body Image

Chemotherapy & SH Side Effects
- Nausea
- Vomiting
- Diarrhea
- Fatigue
- Weakness
- Joint Pain
- Sleep Disturbances
- Decreased Libido
- Ovarian Failure
Radiotherapy & SH Side Effects

- Skin Changes
  - Thickening, Fibrosis, Contractures, Changes in texture/color, Pain
- Erectile Dysfunction
- Vaginal Fibrosis
- Stiffening and hardening of a shortened vaginal vault
- Bladder Pain
- Urinary Incontinence

Endocrine Therapy & SH Side Effects

- Impotence
- Vaginal Dryness
- Dyspareunia
- Osteopenia → Osteoporosis

Provider Communication

- Provider communication regarding how cancer diagnosis and cancer treatments impact sexual health is LIMITED
- Potential Reasons:
  - Provider lack of knowledge
  - Concern for inadequate resources once issue is identified
  - Time constraints

Patient Preference

Sexual health communication between cancer survivors and providers: how frequently does it occur and which providers are preferred?

Stubblefield, 2018

Effective patient-provider communication about sexual concerns in breast cancer: a qualitative study

Stubblefield, 2018

Screening Questions

- Normalize Symptoms
- Do you experience …
  - Urinary incontinence
  - Pain during pelvic examinations or intercourse
  - Sexual arousal difficulties
  - Lack of sexual desire
- If yes → Refer to Medical Oncologist or Pelvic Floor Physical Therapist

Vaginal Dryness Treatment

Vaginal Moisturizers
- Used daily
- Examples:
  - Coconut Oil
  - Replens
  - Hyalo-Gyn

Vaginal Lubricants
- Used as needed, during sexual activity
- Examples:
  - Coconut Oil
  - Water-based
  - Silicone-based
  - Oil-based
Dyspareunia Treatment
- Relaxation Strategies
  - Diaphragmatic Breathing
  - Overflow Stretches
- EMG/Biofeedback
- Manual Therapy
  - External/Internal
- Dilator Training

Erectile Dysfunction Treatment
- Physical Therapy
  - Pelvic Floor Exercises
  - Core Strengthening
- Medical
  - Oral Phosphodiesterase Type 5 (PDE-5)
  - Intracavernosus Injection Therapy
  - Transurethral Alprostadil
  - Vacuum Erection Devices

Cancer-Related Fatigue

Cancer-Related Fatigue (CRF)
“...distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer and/or cancer treatment that is not proportional to recent activity and interferes with usual functioning.”
CRF: Fast Facts

- **Prevalence**: 25-99% cancer survivors
- **Features**:
  - Known to vary day to day
  - Commonly occurs with other sx’s in symptom clusters
  - Pain, emotional distress, sleep disturbance, anemia
- **Anticipated Side Effect of Oncologic Treatments**
- **Prognosis**:
  - Improvements noted within the year following treatment completion
  - 25-30% experience persistent fatigue up to 10 years after cancer diagnosis
  - Associated with higher rates of disability and depression, lower levels of HR-QoL, difficulty returning to work, lack of motivation for exercise

CRF: Etiology

**Risk Factors**:
- Genetic Markers (IL6, TNFA, IL1B)
- Pretreatment Fatigue
- Depression
- Sleep disturbance
- Physical activity and deconditioning
- Coping and appraisal
- Childhood stress
- Marital Status

**Mechanisms**:
- Inflammation and Cytokine Signalling
- Cellular Immunity and Immune Regulation
- Neuroendocrine Alterations

**Predictors for Severe CRF**:
- Female Sex
- Chronic Pain
- Higher Disease Stage
- Receipt of Chemotherapy

CRF: Chemotherapeutic Agents

American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline

**Screening, Assessment, and Management of Fatigue in Adult Survivors of Cancer: An American Society of Clinical Oncology Clinical Practice Guideline Adaptation**
CRF: Assessment

- Fatigue is subjective\(^1\).  
- Fatigue is objective\(^2\).

- Comprehensive measurement requires both objective and self-report measures:
  - Use of patient-reported outcomes
    - Issues?
  - Ongoing development of objective assessment approaches
    - Hand grip\(^3\)
    - 30 Second Sit<>Stand\(^4\)
    - Smart Watch / Activity Monitors\(^5\)
  - Weak correlates → PRO’s remain the gold standard\(^6\)

Cancer-Related Fatigue

Screening and Assessment

1) Screen all survivors and assess risk.
   a) Quantitative:
      - "On a scale of 0 to 10..."
      - Threshold per NCCN: >4/10
   b) Qualitative: Focused history to identify specific causes\(^*\).
      - Chart review, Subjective (comorbidities, baseline activity level)
      - Treatment Plan of Care (anticipated regimen)

2) Establish baseline measures prior to treatment, if able

3) SLEEP.
   - Support - Listen - Educate - Enable - Provide

*In conjunction with patient’s primary oncologic provider to assess and treat causative factors

CRF Treatment

1) Provide education and counseling for all patients and their families.
   - Fatigue and its natural history
   - Normalization

1) Nonpharmacologic Interventions

2) Pharmacologic Interventions

Nonpharmacological Interventions

During Cancer Treatment

High Treatment Effect:
- Relaxation
- Moderate to Large Effect:
- Massage
- CBT combined with physical activity
- Combined aerobic and resistance training
- Resistance training
- Aerobic
- Yoga

After Cancer Treatment

Moderate to Large Effect:
- Yoga
- Small to Moderate Effect:
- Combined aerobic and resistance training
- Combined CBT
- Tai-Chi
- CBT
- Resistance training
- Aerobic
Different types of exercise programs are available for rehabilitation purposes... Overall resistance training or resistance training + CV endurance training provides the best results, especially on physical performance and perceived fatigue.

Blaney, 2010

“an exercise recommendation alone was not enough to change physical activity unless it was accompanied by resources for exercise (e.g., instructional DVDs, exercise logs, pedometers, and education)...”

Winters- Stone, 2018

Energy Conservation

- Modified Borg Scale
  - “On a scale of 0 to 10...”

- Pacing Strategies
  - DME (shower chair, BSC, AD)
  - Scheduling daily routine, appts
  - Options for HEP and corrective exercise

Energy Conservation: It’s a Process

Stubblefield, 2018