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Contemporary Issues in Cancer Rehabilitation

A Focused Review of Safety Considerations in Cancer Rehabilitation

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Abstract

Cancer and its treatments introduce various adverse effects that may affect survivors' physical, cognitive and psychological functioning. Frequently both tolerance to activity and exercise are affected as well. Rehabilitation providers should have substantive knowledge about the effect of cancer progression and common side effects associated with antineoplastic treatment to safely integrate rehabilitation interventions. Rehabilitation may mitigate loss of function and disability; however, these patients are among the most medically complex that providers treat. This report provides a focused review that synthesizes the current evidence regarding disease progression and oncology-directed treatment side effects within the context of safety considerations for rehabilitation interventions throughout the continuum of cancer care. Descriptive information regarding the evidence for precautions and contraindications is provided so that rehabilitation providers can promote a safe plan of rehabilitation care. It is incumbent upon but also challenging for rehabilitation providers to stay up to date on the many advances in cancer treatment, and there are many gaps in the literature regarding safety issues. Although further research is needed to inform care, this review provides clinicians with a framework to assess patients with the goal of safely initiating rehabilitation interventions.

Introduction

Cancer- and oncology-directed treatments introduce a variety of side effects that can adversely affect multiple body systems during and after disease treatment [1]. Each disease treatment modality (eg, surgery, chemotherapy, radiation) may individually or collectively introduce risk for a host of potential safety issues. In addition, a complex array of biopsychosocial factors such as an individual's pre-existing comorbidities, polypharmacy, and other lifestyle factors also affect and amplify risk for adverse side effects during treatment.

It is incumbent upon rehabilitation providers to be knowledgeable about safety issues related to the disease or progression of the cancer as well as side effects and serious adverse events associated with antineoplastic therapies that may have an impact on care. Early identification and management of emerging adverse events may affect morbidity and survival [2]. The purpose of this report is to provide a focused narrative review of the current literature regarding safety with rehabilitation interventions for individuals with cancer with consideration for the disease process, side effects of disease treatment, and associated precautions and contraindications.

Pretreatment Risk Assessment

Pretreatment risk assessment helps to identify potential safety problems and to establish a patient's baseline physical and functional status. Understanding the disease and treatment trajectory provides an opportunity to assess the potential risk for problems that may affect rehabilitation interventions. Before initiating antineoplastic therapies, an extensive medical workup is undertaken to diagnose, stage, and determine a treatment plan for the disease. Baseline imaging, laboratory, and other testing provides insight into various markers and system functions. In addition to a comprehensive medical history to identify existing comorbidities and medication regimens, assessing functional measures is important in predicting mortality and disease-free

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survival and prognosticating functional decline. An ideal construct for rehabilitation professionals is to obtain a comprehensive functional assessment before the initiation of any cancer-directed intervention, as this may optimize performance outcomes during and after treatment [3] and will help identify early functional status decline [4].

Various models of pretreatment assessment and planning have been investigated and typically involve an interdisciplinary team-based approach. These include the prospective surveillance model, multimodal prehabilitation, and enhanced perioperative surgical recovery programs [5].

Safety Considerations With Antineoplastic Treatment Adverse Effects

During active oncology-directed treatment, various modalities are sequentially and sometimes concurrently delivered. Rehabilitation providers must be aware of postsurgical precautions and contraindications regarding movement and activity restrictions so that a plan of care can be developed that facilitates tissue healing, prevents restrictions in function, and optimizes functional status. These precautions, however, should be balanced with evidence-based mobilization and postoperative activity recommendations, and should be informed by surgical precautions and guidance. Mobility and exercise participation in the acute postoperative stage of treatment may reduce the risk of adverse events [6,7], affect overall length of stay [8], and reduce readmissions and complications in various cancer populations [6,9].

Chemotherapeutic interventions typically include multidrug therapies administered cyclically over a standardized period of time. Chemotherapy side effects contribute to multisystem dysfunction and have considerable influence on the safe administration of a rehabilitation plan of care. Table 1 identifies common chemotherapy, immunotherapy, and hormonal drugs and side effects (www.cancer.gov) that may be particularly relevant to rehabilitation specialists.

Hematological Compromise

Myelosuppression is a common side effect associated with nearly all chemotherapy and immunosuppressive agents, particularly corticosteroids, and thus presents significant implications for rehabilitation interventions. Hematologic compromise can result in cytopenias that increase risk of infection, compromise metabolic function, and alter physiological responses to exercise in severe circumstances. Table 2 provides an overview of laboratory values and safety thresholds for consideration by the rehabilitation provider.

The cancer population, as a cohort, has a higher rate of transfer to acute care hospital during inpatient rehabilitation, and it is important to identify the risk factors for transfer [10]. In a study by Guo et al of 98 individuals with cancer undergoing inpatient rehabilitation, hemoglobin levels and absolute neutrophil and platelet counts at the time of admission were not associated with acute care transfers [11]. In another study by Fu et al, 143 lymphoma patients undergoing inpatient rehabilitation, male gender, creatinine >1.3, and hematopoietic stem cell transplantation were associated with a higher rate of transfer to acute service hospitals [12].

Anemia is a frequent complication of cancer and cancer treatment including chemotherapy and radiation [13]. Worsening anemia reduces exercise tolerance and endurance, leading to symptoms of fatigue, dizziness, and hemodynamic instability [14]. Although aerobic capacity is improved with higher hemoglobin levels, it is unclear whether there is a level of hemoglobin below which functional outcomes are compromised [14]. Caution should be used in prescribing progressive resistive and moderate- to high-intensity aerobic exercise in individuals with severe anemia (hemoglobin ≤ 8 g/dL) [15,16]. Low-intensity exercise may be beneficial to promoting improvements in blood counts. Rehabilitation professionals should monitor hemodynamic, functional, and exertional status as well as patient symptoms such as chest pain, lightheadedness, and inappropriate dyspnea [17].

Thrombocytopenia occurs with myelosuppression therapies and affects red blood cell counts. Individuals with platelet counts of $<10{,}000$ cells/μL are at significant risk for spontaneous hemorrhage and, as per current guidelines, will receive prophylactic transfusions [18]. Those with counts of $<20{,}000$ cells/μL are at increased risk, and special consideration for rehabilitation intervention should be considered; generally, activity is restricted to walking and activities of daily living [19]. Individuals with counts of $>20{,}000$ cells/μL can complete light exercise with close symptom monitoring. In general, this includes maintaining blood pressures below 170/100 mm Hg and screening the patient for symptoms of bleeding, including bruising and bleeding around the gums [20]. Those with counts of $>30{,}000$ cells/μL can engage in moderate exercise and light resistive exercise within tolerance [19].

Chemotherapy-induced neutropenia (absolute neutrophil count <500 mm^3/L) typically occurs 3-7 days after administration of chemotherapy. Neutropenia predisposes patients to infection. Typical signs and symptoms of infection are often absent in neutropenia, and fever remains the earliest sign of occult infection. Primary sites of infection are the gastrointestinal tract, sinuses, lungs, and skin [21]. Clinicians should practice hand hygiene with antimicrobial products during every patient encounter. The use of barrier precautions such as gowns, gloves, and masks are usually unnecessary, as patients are more likely to get infected with their own

Table 1
Common chemotherapy agents and side effects

Drug Category	Common Generic Drugs (Brand Name)	Side Effects*
Alkylating agents	Cyclophosphamide	Congestive heart failure
	Ifosfamide	Pericardial effusion
	Melphalan	Shortness of breath
	Busulfan	Dyspnea on exertion
	Thiotepa	Pulmonary fibrosis
	Carmustine	Dizziness, confusion agitation
	Dacarbazine	Joint pain
		Anemia
		Renal failure
Anthracyclines	Danorubicin	Cardiotoxicity
	Doxorubicin (Adriamycin)	Left ventricular dysfunction
	Epirubicin	Congestive heart failure
	Bleomycin	Cardiomyopathy
		Pulmonary fibrosis
Antiandrogens	Flutamide (Eulexin)	Muscle wasting
	Nilutamide	Osteoporosis
		Erectile dysfunction
Antimetabolites	5-Fluorouracil	Anemia
	Capecitabine (Xeloda)	Shortness of breath
	Gemcitabine	Skin rash/dermatitis
	Fludarabine	
	Methotrexate	
Aromatase inhibitors	Letrozole (Femara)	Joint arthralgias
	Anastrozole (Arimidex)	Osteopenia/Osteoporosis
	Exemestane (Aromasin)	Hot flashes
		Weight gain
		Mood fluctuations
Cytoskeletal disruptors (taxanes)	Paclitaxel (Taxol)	Peripheral neuropathy
	Docetaxel (Taxotere)	Cytopenia
	Abraxane	Acute myocardial infarction
Gonadotropin-releasing hormone agonist	GnRH-A (Cetrorelix)	Osteoporosis
		Weight gain
		Heart failure
		Heart disease
Luteinizing hormone agonist	Goserelin (Zoladex)	Bone pain
	Leuprolide (Lupron)	Sexual dysfunction
	Triptorelin (Trelstar)	Anemia
		Cognitive dysfunction
Kinase inhibitors	Erlotinib (Tarceva)	Hypertension
	Lapatinib (Tykerb)	Acute myocardial infarction
	Imantinib (Gleevac)	Stroke
	Gefinitib (Iressa)	DVT/PE
		Interstitial lung disease
		Bradycardia
Monoclonal antibodies	Trastuzumab (Herceptin)	Cytopenia
	Alemtuzumab (Campath)	Pulmonary inflammation
	Bevacizumab (Avastin)	Congestive heart failure
		Hypertension
		Reduced wound healing
		Skin rash
Platinum-based agents	Carboplatin	Neurotoxicity
	Cisplatin	Ototoxicity
	Oxaliplatin	Rhabdomyolysis
Retinoids	Tretinoin	Increased intracranial pressure
	Alitretinoin	DVT/PE
Selective estrogen receptor modifiers	Tamoxifen (Nolvadex)	Hot flashes
	Raloxifene (Evista)	Weight gain
		Cognitive and memory dysfunction
		DVT/PE
		Stroke

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Table 1 (*continued*)

Drug Category	Common Generic Drugs (Brand Name)	Side Effects*
Topiosomerase inhibitors	Irinotecan (Camptosar)	Cytopenia
	Topotecan (Hycamtin)	Severe diarrhea and dehydration
Vinca alkaloids	Vincristine (Oncovin)	Peripheral neuropathy
	Vinblastine	Dyspnea
		Hypertension
		Angina
		Acute myocardial infarction

DVT = deep vein thrombosis; PE = pulmonary embolism.
* These are known potential side effects. This is not a complete list of side effects.

flora [22]. The Centers for Disease Control guidelines advise against barrier protection except when "the risk of infection from healthcare providers is excessive" [23]. There is no compelling evidence that rehabilitation interventions are contraindicated due to neutropenia, but special consideration should be given to individuals experiencing side effects such as fatigue, malaise, dizziness, or lethargy, and rehabilitation therapy should be self-limited based on patient preferences [16]. Further consideration is warranted to prevent infection by reducing exposure to potential pathogens such as those found in public therapy spaces [24]. Neutropenic infections are a major cause of morbidity and mortality in individuals undergoing cancer treatment [21]. Common infections include sepsis, cellulitis, pneumonia, urinary tract infections and colitis [25,26]. Rehabilitation providers should closely monitor at-risk patients for early signs and symptoms of infection so that medical management can be expedited when needed [27].

Hematological considerations are particularly important in patients undergoing bone marrow transplantation. Pretransplantation induction treatment involves high-dose chemotherapy, frequently with concurrent irradiation. Bone marrow transplantation is typically undertaken after traditional antineoplastic therapies have failed to put an individual into remission. These patients are cytopenic at the time of transplantation and remain so for weeks afterward. There is additional concern, as these individuals have a history of antineoplastic therapies that can result in other adverse effects such as neurotoxicities affecting peripheral nerve function, myopathy due to chronic corticosteroid use, prolonged immobility, nutrition deficits, and cognitive dysfunction [28]. Given the substantial need for rehabilitation services in this population, it is imperative to provide safe rehabilitation interventions. Dimeo et al suggest that exercise not only mediates better physical performance at discharge in this population, but a shorter duration of anemia, neutropenia, thrombocytopenia, and length of hospitalization [29].

Table 2
General rehabilitation considerations in the context of hematological compromise [13,16,19]

Blood Count	Rehabilitation Considerations
White blood cells	>11.0 10^9/L: Symptom-based approach, monitor for fever
	<4.0 10^9/L: Symptom-based approach, monitor for fever
	<1.5 10^9/L (Neutropenia): Symptom-based approach, neutropenic precautions based on facility guidelines
	Mild <1.5 10^9/L
	Moderate 0.5-1.0 10^9/L
	Severe <0.5 10^9/L
Platelets	<150,000 cells/μL (Thrombocytopenia): Symptom-based approach, monitor tolerance to activity
	>50,000 cells/μL: Progressive exercise as tolerated, aerobic, and resistive with monitoring for symptoms associated with bleeding
	>30,000 cells/μL: Active range-of-motion exercises, moderate exercise, aquatic therapy based on immune status
	>20,000 cells/μL: Light exercise, walking, activities of daily living without strenuous effort; assess fall risk and implement safety plan for falls prevention
	<20,000 cells/μL: Understand transfusion status or plan of care, walking, light activities of daily living, symptom monitoring, precaution for falls
Hemoglobin	Reference values
	Male: 14-17.4 g/dL
	Female: 12-16 g/dL
	<11 g/dL (anemia): Establish baseline vital signs; may be tachycardic or present with orthostatic hypertension; symptom-based approach to intervention, monitoring self-perceived exertion
	<8 g/dL (severe anemia): Close monitoring of symptoms and vital signs with intervention; transfusion may or may not be indicated based on individual presentation; short periods of intervention, symptom-limited; education for energy conservation

Cardiopulmonary Toxicity

Malignant tumors are more likely to involve the lungs than the heart—either as primary or metastatic disease. In advanced cancer, there may be significant compromise of pulmonary function due to metastatic disease. Individuals with advanced cancer may have cachexia with severe muscle wasting that may affect cardiac function as well ("cardiac cachexia"). Antineoplastic therapies such as chemotherapy and immunotherapy drugs, as well as radiation therapy to the chest wall, can affect cardiac and pulmonary function, both during and after cancer-directed treatments [30]. One of the most commonly used chemotherapy drug classes, anthracyclines, may have a significant and irreversible impact on cardiac function, primarily resulting in reduced left ventricular function. Over time, this reduces overall ejection fraction and compromises long-term cardiac function. Trastuzumab is a targeted drug that is frequently used in breast and other cancers and has well-known potential for cardiac toxicity. The implications manifest in symptoms of systemic edema, shortness of breath, dyspnea, and lung congestion in severe cases. Bleomycin and methotrexate are agents that commonly lead to pulmonary compromise, including pulmonary inflammation and fibrosis.

Exposure of the chest wall to radiation has the potential to adversely affect both cardiac and pulmonary function and may be progressive over time. Individuals receiving >30-35 Gy exposure to the chest wall are at risk for radiation-associated heart damage [30]. These dose levels are typically eclipsed with standard breast, lung, and various Hodgkin treatments, elevating the risk in these populations. Radiation-related changes include structural damage to the myocardium, coronary arteries, valves, and the conduction system. These complications often lead to diastolic dysfunction and blood flow abnormalities. Cardiac changes typically manifest clinically at least 6 to 12 months after radiation, necessitating awareness and monitoring for symptoms of cardiovascular and pulmonary dysfunction. The impact on cardiac function, however, can be identified even 20 years after the completion of radiation therapy, affecting long-term morbidity and function [31].

Vital sign monitoring throughout the duration of cancer-directed treatments is recommended. A baseline echocardiogram is usually obtained in individuals undergoing cardiotoxic chemotherapeutic regimens and may be repeated at various stages of treatment or after treatment. Low-intensity exercise, administered during chemotherapy cycles, may be protective against anthracycline-induced cardiotoxicity [32], but recommendations regarding timing, frequency, intensity, and mode of exercise are lacking [33]. When prescribing exercise interventions for this population, risk factors such as dose scheduling, prior cardiac comorbidities, and baseline vital signs should be considered. Edema monitoring is necessary to observe and to differentially diagnose cardiopulmonary edema symptoms from the onset of lymphedema.

Late effects of cardiovascular compromise are especially prominent and warrant consideration in adult survivors of childhood and adolescent cancers. The deleterious impact on cardiac function is prevalent; nearly 50% demonstrate cardiac-related comorbidity that compromises function 20-30 years after completion of treatment [34].

Rehabilitation providers seeking to implement a plan of care should be aware of the risk for reduced tolerance to exercise, altered baseline vital signs, and altered physiological responses to rehabilitation interventions. Monitoring during rehabilitative interventions should include a focus on patient self-report of tolerance to exercise via the Borg Scale or another index. Observation for symptoms that may herald undetected cardiac dysfunction or exercise that is too vigorous for someone with known heart disease, include excessive fatigue, sweating, or pallor changes with exercise or activity, and severe shortness of breath.

Neurotoxicity

Chemotherapy-induced peripheral neuropathy is a well-known complication with taxane-based as well as platinum-based chemotherapeutic agents. Acute presentation of neuropathies includes sensory manifestation in the distal extremities. The neuropathic changes are typically progressive with additive chemotherapy cycles. The progression of sensory changes presents in a stocking/glove pattern. In more severe cases, motor disturbance is noted, primarily in the lower extremities.

Although neuropathies occur during chemotherapy cycles, the symptoms tend to abate after the completion of treatment. However, persistent impact on sensation and proprioception are notable and are shown to have a negative impact on balance, gait, and mobility even >5 years after the completion of treatment [35]. Individuals who receive neurotoxic doublets are at greater risk for persistent neuropathic impairment. Of importance is the evidence elucidating the significantly increased risk of falls in the population of individuals treated with neurotoxic chemotherapy agents. Fall risk is 2-3 times greater in the population of individuals with a history of receiving neurotoxic chemotherapeutic agents [36].

There are significant rehabilitation implications for the population of individuals treated with neurotoxic chemotherapeutic agents. Ideally, a baseline assessment of sensation, strength, and balance is completed before initiating chemotherapy. Continued screening for balance change over time, observation of gait deviation, and triage for rehabilitation intervention to manage emerging impairments is recommended [37]. Severe neuropathy with motor changes may affect safety and may necessitate intervention to mitigate balance

deficits and to enhance gait and stability [38]. A comprehensive falls prevention program is an effective strategy that should be proactively implemented to improve functioning [39,40]. Providing assistive devices and/or orthoses may be required to maintain patient safety.

Lymphedema

The natural history of lymphedema is typically a slow, progressive swelling that appears asymmetrically in the limbs after lymphadenectomy or radiation therapy. New-onset lymphedema is an important safety concern primarily because of the risk of deep vein thrombosis, cancer recurrence, or infection [41].

Several studies have examined the safety of exercise in regard to the development and exacerbation of lymphedema and have found that, under controlled circumstances, exercise does not exacerbate this condition or have a significant impact on worsening symptoms [42-44]. There is no strong evidence basis for the use of compression garments during exercise for prophylactic purposes; however, early use of compression therapy in the presence of early, subclinical lymphedema is safe and effective [45]. Individuals with lymphedema should be advised to exercise with some form of compression on their limbs to prevent fluid accumulation. Any signs of redness, erythema, pain, or new onset or exacerbation of swelling should be referred for more extensive medical management. Cellulitis infections are common in individuals with lymphedema and require antibiotic therapy before continuation of rehabilitation interventions.

For individuals in whom lymph nodes have been resected as a standard part of cancer surgery, astute observation of any changes in the limb that indicate an emerging infection should be addressed. An individualized rehabilitation treatment plan should be developed for this at-risk population with precautions to avoid unnecessary strain and injury to the limb that may cause the onset of lymphedema [45].

Frailty

Frailty is a clinical syndrome that may be found in individuals $>$65 years of age and that is characterized by a loss of physiologic reserve secondary to reduced physiological capacity, weight loss, weakness, slow walking speed, self-reported exhaustion, and low physical activity [46,47]. Because cancer occurs disproportionately among people $>$70 years of age, many cancer survivors have frailty symptoms compounded by the negative effects of cancer-directed treatments [48]. Frailty is associated with falls, hospitalizations and increased mortality [49]. A recent study analyzing more than 12,000 patients $\geq$65 years of age found that the prevalence of falls was significantly higher after cancer treatment than before treatment among individuals with prostate and lung cancer, and the prevalence of balance/walking problems were significantly higher after diagnosis in non-Hodgkin lymphoma and breast, prostate, and lung cancer [50]. Frail patients, specifically, pose a challenge to rehabilitation physicians who work with cancer survivors. Frailty has been associated with poorer rehabilitation outcomes and functional gains.

The Comprehensive Geriatric Assessment (CGA) has received attention as a comprehensive battery of tests that assess various domains of functioning and can be used to stratify patients into high- versus low-risk categories to predict their tolerance to cancer therapies and risk for side effects of chemotherapy [51]. The CGA may be a more comprehensive and sensitive indicator to identify functional decline than the current performance status measures used in oncology practice [52]. Interventions such as optimizing nutrition and muscle mass may delay frailty and are safe in the geriatric population [9]. In a review of studies on exercise interventions in frail institutionalized adults, balance and functional training were shown to be effective in improving functional performance, activities of daily living, and quality of life [53].

Osseous Fragility

Osteoporosis and secondary bone loss affect bone health in cancer survivors, most commonly in hormonally driven breast and prostate cancer [54,55]. Osteoporosis worsens with prolonged exposure to hormonal therapies, increasing fracture risk with increased duration of treatment [56,57]. Rehabilitation providers should identify meaningful changes over time that may suggest increased risk and should modify rehabilitative interventions to optimize safety. Weight-bearing exercise may have a protective effect in mitigating bone density depletion during hormonal therapy interventions [58].

Bone metastases occur prevalently in the most commonly occurring cancers; breast, lung, and prostate [59,60]. Bone lesions often result in pain, spinal cord compression, fracture, and hypercalcemia reducing quality of life and limiting functional mobility [61,62]. Although rehabilitative weight-bearing activities can have a positive impact on bone density, mobilizing individuals with bone lesions is challenging due to pain and fracture risk during therapeutic exercise [63].

Metastatic lesions of the long bones and spine present the greatest risk of pathologic fractures, making fracture risk assessment of great importance to rehabilitation providers [60]. A scoring system developed by Mirels et al [64] assigns a severity score to each of 4 factors associated with fracture: namely, site, size, type of lesion, and type of pain reported (Table 3). This system enables an aggregate score that supports fracture risk stratification so that appropriate mobility interventions may be initiated.

Table 3
Mirels criteria for fracture risk assessment

Score	Site of Lesion	Size of Lesion	Nature of Lesion	Pain
1	Upper limb	<1/3 of cortex	Blastic	Mild
2	Lower limb	1/3–2/3 of cortex	Mixed	Moderate
3	Trochanteric region	>2/3 of cortex	Lytic	Functional

According to the recommendation of Mirels et al, prophylactic fixation is indicated for a lesion with a score of ≥9. A lesion with a score of ≤7 can be managed using radiotherapy and drugs. A score of 8 presents a clinical dilemma and requires clinical judgment of the criteria. Functional pain has been identified as the single best predictor of pathological fracture [64].

Another stratification system by Harrington suggests that lytic and blastic lesions in long bones can develop pathologic fractures when >50% of the cortex is destroyed, and lesions of the proximal femur are more likely to fracture if they are >2.5 cm or if they are associated with avulsion of the lesser trochanter. Such lesions should be referred for prophylactic fixation [65].

Rehabilitation is indicated in the presence of bone metastases to maintain function and promote safety and fracture prevention with activities of daily living [66]. Of importance are fall prevention strategies and education for safety with activities that require lifting and carrying heavy objects. A comprehensive mobility assessment is necessary, as the sheer number of bone lesions and location of metastatic sites may not be associated with functional mobility loss in the short term [67]. Rehabilitation interventions are generally safe and effective and do not increase the risk for fractures [66,68-70]. General safety measures are outlined in Table 4 and target restricting excessive resistive, compressive, or rotational torque-like forces on an involved limb or region [71]. Individuals with more severe fracture risk may benefit from offloading the affected limb and using assistive devices or orthoses to safely enhance function and mobility. Caregiver education should be emphasized in the rehabilitation care plan to optimize safety and function in the home environment.

Advanced Cancers

Functional impairments are prevalent in patients with advanced cancer and can lead to disability, increased caretaker dependency, and psychological distress [72]. Safety considerations should be broadened, and rehabilitation assessment should extend beyond the primary functional limitation, as the multisystem impact of advanced cancer jeopardizes safe functioning [73]. Patients with advanced cancer often have a range of comorbid conditions, polypharmacy considerations, and impact functioning, and require a more complex rehabilitative prescription [72,74].

Table 4
General safety measures with bone metastasis

No manual muscle testing in affected limb
No progressive resistive exercises in affected limb
Offloading weight bearing through the affected limb with an assistive device
Avoid excessive spinal flexion, extension, and rotation; clarify need for bracing
Monitor for increasing functional pain

Cachexia is a common condition related to advanced cancer. Symptoms include marked weight loss, loss of lean muscle and muscle atrophy, fatigue, weakness, and loss of appetite, which negatively impact function. Sarcopenia is a condition of lean muscle loss and muscle atrophy. Sarcopenia may also be seen in advanced cancer populations but is a different condition from cachexia; although sarcopenia may be a component of cachexia, not all individuals with sarcopenia are cachectic [75]. Sarcopenia can be identified by low muscle mass and reduced gait speed. This differentiation is important, as exercise, in the absence of appropriate protein and energy balance, may pose a risk for further functional decline in the cachectic population [76]. Rehabilitation interventions should be undertaken with insight and input from an interdisciplinary team that include an understanding of nutritional support and inflammatory profiles of the patient balanced with physical activity and muscle training interventions [77].

Central and peripheral neural structures may be affected by a primary or metastatic tumor as well as oncology-directed treatment (eg, chemotherapy). Neurological changes may be the first presenting sign of metastatic disease and warrant close follow-up and triage for medical management. Neurological symptoms are often consistent with the spinal level or central location of the lesion. Patients may present with cognitive changes, memory loss, affective and personality changes, altered mental status, speech and word finding complications, as well as sensory or motor dysfunction including radiculopathy or myelopathy [78]. Autonomic dysfunction may also occur related to chemotherapy or other antineoplastic treatment issues. Rehabilitation providers should monitor for any neurological status changes during and after intervention, and should monitor pain and vital sign changes during intervention. Caregiver education is also important, as patients may have altered safety judgement, reduced reflexive reactions, poor visual acuity, and word-finding issues that make it difficult to function independently.

Assessment for home modifications and adaptive equipment evaluations should be considered to help reduce the risk of falling and to improve overall safety in the home. Education for compensatory strategies using assistive devices, orthotics, and wheelchairs can improve the safety of individuals while promoting optimal functioning. Partnering with palliative care services to develop patient-centered protocols that span the oncologic spectrum can combine rehabilitation interventions with the treatment of cancer-related pain, anxiety, and psychosocial and spiritual needs [79].

Safety Considerations With Rehabilitation Interventions

Exercise

Exercise has been extensively studied across the cancer care continuum, including interventions before treatment [6,80,81], during active treatment [82,83], and after the completion of treatment [82,84]. Timing and type of exercise affects various biological and physiological markers, psychosocial factors, and functional impairments differently [82,85]. Overall, tolerance to treatment and functional outcomes in a variety of cancer types are improved when exercise is initiated before or during cancer treatment [6,44,81]. Unique considerations are necessary based on the type of cancer and the body structures affected by cancer-directed therapies.

Exercise training and maximal and submaximal exercise testing in persons with breast cancer is relatively safe [42,43,86-88]. However, because 35%-58% of breast cancer survivors report persistent shoulder and arm pain [89], it is important to minimize the risk of musculoskeletal injuries that may result from surgical intervention or other therapies. Because women with breast cancer commonly receive cardiotoxic chemotherapeutic agents, awareness of cardiac compromise is warranted. Ideally, a tailored exercise program is developed and initially supervised by a rehabilitation provider [90].

Exercise interventions are generally safe during and after prostate cancer treatment [69,91]. More than 50% of individuals undergoing prostate cancer treatment will receive androgen deprivation therapy (ADT) to alter hormonal impact on tumor growth. ADT is associated with muscle mass depletion and bone density loss, which directly affect safety with rehabilitation interventions. Aerobic and resistive exercise interventions lessen the

Table 5
Modality indications, precautions, and contraindications for cancer survivors

Modality	Indication	Precaution	Contraindication
Heat	Pain relief Muscle relaxation Tissue extensibility	Impaired lymphatic function Scar tissue Open wounds or skin fragility	Unmanaged tumor/active disease Peripheral vascular disease Severely impaired sensation Irradiated tissue
Ultrasound	Tissue extensibility Inflammation management	Impaired sensation Open wounds or skin fragility	Individuals with cancer or with a history of cancer
Cryotherapy	Pain relief Acute management of inflammation Hair loss management	Impaired sensation Open wounds or skin fragility	Ischemic tissue Peripheral vascular disease Raynaud syndrome
Transcutaneous electrical nerve stimulation	Sensory pain management Scar desensitization	Insensate tissue	Unmanaged tumor/active disease Over pacemaker Open wounds
Needle electromyography	Measures muscle response to nerve stimulation	Thrombocytopenia	None
Functional electrical stimulation	Restoration of muscle firing when nerve conduction is intact (eg, ambulation, limb function, swallowing, pelvic floor retraining)	Poor skin condition or indurated tissue	Unmanaged tumor/active disease
Low-level light laser	Oral mucositis Scar tissue extensibility Lymphedema	Open wounds or skin fragility	Acute radiation dermatitis Unmanaged tumor/active disease
Manual therapy	Pain relief Tissue extensibility Joint mobility Soft tissue and radiation fibrosis management Lymphatic stimulation	Impaired sensation Dysvascular tissue Open wounds or skin fragility	Acute radiation dermatitis Unmanaged tumor/active disease Bone fragility due to metastasis or osteoporosis
Spinal manipulation	Spinal mobility and alignment Pain relief	Open wounds or skin fragility	Bone fragility due to metastasis or osteoporosis Radiculopathy, spinal stenosis, myelopathy Spinal cord compromise from tumor or lesion

Table 6
Oncologic emergencies

Condition	Presenting Symptoms	Rehabilitation Implications
Structural or mechanically induced oncologic emergencies		
Spinal cord compression	Localized back pain, primarily in thoracic region Thoracic pain escalating with lying supine, at night, with increased thoracic pressure during sneezing, coughing, or straining Muscle weakness below the area of spinal involvement	Worsening pain in a recumbent position helps to differentiate SCC from other forms of mechanical back pain Pain is the most frequent presenting symptom Identification of SCC before onset of motor or sensory loss improves functional mobility and mortality outcomes Patients with SCC are at risk for urinary tract infections, VTE, decubitus ulcers, and pneumonia Pain assessment should be routine in rehabilitation interactions with concomitant assessment of muscle strength and sensory changes
Malignant pericardial effusion	Due to primary pericardial tumor (rare) or metastatic pericardial disease associated with lung, breast, esophageal, lymphoma, leukemia, melanoma Pericardial effusion results in increased intrapericardial pressure, reduced cardiac output, and cardiac tamponade Dyspnea, cyanosis, engorged neck veins, orthopnea, congested cough, fatigue palpitations, and a drop in systolic blood pressure of $>$10 mm Hg during inspiration Hypotensive, tachycardic, narrow pulse pressure, diaphoretic	Frequent assessment of heart rate, hemodynamic status and respiratory status, including oximetry levels, should be carried out during treatment Assessment of skin color and temperature, capillary refill, and peripheral pulses should be tracked Awareness of mental status changes, confusion, or seizures is necessary due to reduced cerebral blood flow After a cardiac tamponade episode, patients should have medical clearance before re-engaging in rehabilitation care Rehabilitation is indicated to provide strengthening and reconditioning activities, pulmonary hygiene, and postural positioning
Superior vena cava syndrome	Swelling in the upper thorax, face, neck Jugular vein distention. In early stages, edema is worse in the morning and improves throughout the day Dyspnea, dry cough Tachycardia, hypotension, cyanosis, cough, tachypnea, dyspnea Central nervous system symptoms; confusion, headache, vision changes	Onset is typically slow and progressive. Symptom recognition and observance of change over time will support differential diagnosis Avoid Valsalva maneuvers with activity and exercise Heart rate response to activity may be impaired. Use Rate of Perceived Exertion (RPE) scale as a more sensitive self-reported measure during activity
Metabolic oncologic emergencies		
Hypercalcemia	Presentation may be vague and symptoms diffuse Impact on nervous tissue and muscle tissue result in constipation, lethargy, fatigue, bone pain, abdominal pain, polyuria, muscle weakness, confusion, delirium	Diagnostic testing includes serum ionized calcium levels. The rate of increase of calcium level is more important than the absolute serum calcium in correlating with symptoms In severe conditions, individuals are relatively unresponsive, and rehabilitation may not be indicated In mild-to-moderate conditions, weight-bearing activities are recommended along with general aerobic conditioning Consider assistive devices for safety with ambulation Assess and ascertain mental status changes and impact on safety judgement
Tumor lysis syndrome	Symptoms may include nausea, vomiting, weakness, fatigue, lethargy, and arthralgia Typical onset is during acute 6-72 hours after chemotherapy delivery	Awareness of sudden changes in patient's status including weakness, muscle cramping, dysrhythmias, dyspnea, central nervous system changes, and irregular heart rhythms In intensive care settings, early progressive mobility and rehabilitative interventions improve recovery and maintain functional status after discharge

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Table 6 (*continued*)

Condition	Presenting Symptoms	Rehabilitation Implications
Hematologic emergencies		
Neutropenic fever	Greatest risk is with ANC <500 c/mm^3 Trend of change in ANC count overtime is more important than absolute value Presence of a fever $>101.3^\circ$ F or $>100.4^\circ$ F for >1 hour. Typical symptoms of infection such as redness, swelling, and pus exudate from wounds are frequently absent	Rehabilitation is not contraindicated Considerations for protective wear including gowns, gloves, masks, and reducing risk of transmission of infectious agents by washing hands, keeping equipment clean, and reducing exposure to raw foods and live plants
Venothrombolic events	DVT present with swelling in the extremity, redness and extreme tenderness. More commonly occur in the lower extremity but may also occur in the arms. Pulmonary emboli present with dyspnea, tachycardia, crackles, hemoptysis, chest pain, tachypnea, and anxiety Diagnostic imaging includes Doppler ultrasound for suspected DVT and chest CT, ventilation perfusion scan and pulmonary angiography for suspected PE	Support protocols for VTE prophylaxis including mechanical compression devices including compression hosiery and pneumatic applications Ambulation is encouraged to reduce risk for VTE development in high-risk populations Awareness of pharmacologic interventions that alter platelet activity and clotting

ANC = absolute neutrophil count; CT = computed tomography; DVT = deep vein thrombosis; PE = pulmonary embolism; SCC = spinal cord compression; VTE = venothrombolic event.

impact of ADT and promote restoration of muscle mass and mitigate bone density loss [92].

Numerous prehabilitation and rehabilitation trials have identified positive benefits of exercise as well as its safety and feasibility in the lung cancer population [93]. Exercise is generally well tolerated and beneficial in controlled clinical settings, and evidence supports moderate-intensity exercise for this population [6,94,95]. Vital signs, oximetry, and respiration should be closely monitored during exercise, and individual interventions and testing should be self-limited by the patient [74].

Evidence supports exercise as a safe intervention in women during and after gynecological cancer treatment [96,97]. Lymphedema of the lower extremities may be associated with gynecological cancer and its treatment, warranting consideration of lower-extremity monitoring for individuals who have had inguinal lymph node dissection and/or radiation therapy [41].

Exercise interventions such as walking, stationary cycling, resistance training, and virtual reality-based activities appear to be safe for individuals with leukemia [98-101]. Exercise may be limited by complications of the cancer and its treatment, such as infection, thromboembolic disease, and hemorrhage [102]. Aerobic and strength-training exercises can be safely performed by persons with a stem cell transplant; however, exercises should be less intense, progress slowly, and avoid overtraining [103].

Modalities and Manual Therapy

Physical modalities such as heat [104], cryotherapy [105], electrotherapeutic modalities [106-108], laser [109,110], and manual therapy [104,111] are used as adjuncts to reduce pain and facilitate tissue healing and to minimize pain during rehabilitation interventions [105,112]. Modalities and physical agents require astute understanding of the impact on cancer and the risk of promoting metastatic disease [113,114]. Numerous indications exist for the use of modalities in pain management but should be applied with caution [104]. Table 5 summarizes contraindications to modalities in cancer survivors.

Oncologic Emergencies

During the course of cancer treatment, there may be signs of emergent conditions and the need for care to manage the sudden onset of serious adverse events. These oncologic emergencies should be recognized by rehabilitation providers to promote acute medical management so as to limit the impact on outcomes.

Morris et al categorized oncologic emergencies according to the mechanism of injury and organ system involved, and outlined 3 categories of oncologic emergencies: (1) structural/mechanically induced, (2) metabolic, and (3) hematological [17]. Table 6 outlines the common presenting symptoms of the conditions associated with these categories of emergencies and their implications for rehabilitation providers.

Conclusion

Rehabilitation is generally safe in oncology patients; however, there are numerous important considerations that are unique to this population. Moreover, oncology-directed therapies and protocols are constantly advancing, and rehabilitation specialists need to keep

up to date to ensure the safety of the patients whom they treat. Rehabilitation provides therapeutic interventions that may mitigate loss of function and disability in cancer survivors; however, the frailty of the patients, co-morbid conditions, advanced cancer, side effects of oncology-directed therapies, and a host of other factors contribute to making this one of the most medically complex populations that rehabilitation professionals treat. Assessing each patient through the lens of providing safe rehabilitation interventions in a medically supervised setting is required.

References

1. Miller KD, Siegel RL, Lin CC, et al. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin 2016;66:271-289.
2. Marchese VG, Morris GS, Gilchrist L, et al. Screening for chemotherapy adverse late effects. Topics Geriatr Rehabil 2011;27:234-243.
3. Partridge J, Harari D, Martin F, Dhesi J. The impact of preoperative comprehensive geriatric assessment on postoperative outcomes in older patients undergoing scheduled surgery: A systematic review. Anaesthesia 2014;69:8-16.
4. Stout NL, Binkley JM, Schmitz KH, et al. A prospective surveillance model for rehabilitation for women with breast cancer. Cancer 2012;118:2191-2200.
5. Carli F, Silver JK, Feldman LS, et al. Surgical prehabilitation in patients with cancer: State-of-the-science and recommendations for future research from a panel of subject matter experts. Phys Med Rehabil Clin N Am 2017;28:49-64.
6. Sebio Garcia R, Yáñez Brage MI, Giménez Moolhuyzen E, Granger CL, Denehy L. Functional and postoperative outcomes after preoperative exercise training in patients with lung cancer: A systematic review and meta-analysis. Interact Cardiovasc Thorac Surgery 2016;23:486-497.
7. McNeely ML, Campbell KL, Rowe BH, Klassen TP, Mackey JR, Courneya KS. Effects of exercise on breast cancer patients and survivors: A systematic review and meta-analysis. Can Med Assoc J 2006;175:34-41.
8. Ahn K-Y, Hur H, Kim D-H, et al. The effects of inpatient exercise therapy on the length of hospital stay in stages I—III colon cancer patients: Randomized controlled trial. Int J Colorect Dis 2013;28:643-651.
9. Singh I, Gallacher J, Davis K, Johansen A, Eeles E, Hubbard RE. Predictors of adverse outcomes on an acute geriatric rehabilitation ward. Age Ageing 2012;41:242-246.
10. Alam E, Wilson RD, Vargo MM. Inpatient cancer rehabilitation: A retrospective comparison of transfer back to acute care between patients with neoplasm and other rehabilitation patients. Arch Phys Med Rehabil 2008;89:1284-1289.
11. Guo Y, Persyn L, Palmer JL, Bruera E. Incidence of and risk factors for transferring cancer patients from rehabilitation to acute care units. Am J Phys Med Rehabil 2008;87:647-653.
12. Fu JB, Lee J, Smith DW, Shin K, Guo Y, Bruera E. Frequency and reasons for return to the primary acute care service among patients with lymphoma undergoing inpatient rehabilitation. PM R 2014;6:629-634.
13. Groopman JE, Itri LM. Chemotherapy-induced anemia in adults: Incidence and treatment. J Natl Cancer Inst 1999;91:1616-1634.
14. Carson JL, Terrin ML, Jay M. Anemia and postoperative rehabilitation. Can J Anaesth 2002;50(6 Suppl):S60-S64.
15. Wing JR. Hematologic complications. In: Stubblefield M, O'Dell M, eds. Cancer Rehabilitation: Principles and Practice. New York: Demos Publishing; 2009, 773-785.
16. Tompkins J, Norris T, Levenhagen K, et al. Academy of Acute Care Physical Therapy Task Force on Lab Values. Laboratory Values Interpretation Resource. Available at http://c.ymcdn.com/sites/www.acutept.org/resource/resmgr/docs/2017-Lab-Values-Resource.pdf. Accessed July 2017.
17. Morris GS, Brueilly KE, Paddison NV. Oncologic emergencies: Implications for rehabilitation. Topics Geriatr Rehabil 2011;27:176-183.
18. Kaufman RM, Djulbegovic B, Gernsheimer T, et al. Platelet transfusion: A clinical practice guideline from the AABBP. Ann Intern Med 2015;162:205-213.
19. Goodman CC, Fuller KS. Pathology for the Physical Therapist Assistant [E-book]. St. Louis, Missouri: Elsevier Health Sciences; 2011.
20. Elter T, Stipanov M, Heuser E, et al. Is physical exercise possible in patients with critical cytopenia undergoing intensive chemotherapy for acute leukaemia or aggressive lymphoma? Int J Hematol 2009;90:199-204.
21. Segal BH, Freifeld AG, Baden LR, et al. Prevention and treatment of cancer-related infections. J Natl Compr Canc Netw 2008;6:122-174.
22. Shelton BK. Evidence-based care for the neutropenic patient with leukemia. Semin Oncol Nurs 2003;19:133-141.
23. Siegel J, Rhinehart E, Jackson M, Chiarello L. US Centers for Disease Control and Prevention. 2007 Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings. Available at www.cdc.gov/infectioncontrol/pdf/guidelines/isolation-guidelines.pdf. Accessed September 1, 2016.
24. Paul KL. Rehabilitation and exercise considerations in hematologic malignancies. Am J Phys Med Rehabil 2011;90(5 Suppl 1):S88-S94.
25. Stern M, Laviano C. Infectious complications of cancer. In: Stubblefield M, O'Dell M, eds. Cancer Rehabilitation: Principles and Practice. New York: Demos Publishing; 2009, 405-409.
26. Shannon SAN, Begal BH. Epidemiology and management of opportunistic infections in immunocompromised patients with cancer. Abstr Hematol Oncol 2005;8:20-30.
27. Mylotte JM, Graham R, Kahler L, Young L, Goodnough S. Epidemiology of nosocomial infection and resistant organisms in patients admitted for the first time to an acute rehabilitation unit. Clin Infect Dis 2000;30:425-432.
28. Gillis TA, Donovan ES. Rehabilitation following bone marrow transplantation. Cancer 2001;92(4 Suppl):998-1007.
29. Dimeo F, Bertz H, Finke J, Fetscher S, Mertelsmann R, Keul J. An aerobic exercise program for patients with haematological malignancies after bone marrow transplantation. Bone Marrow Transplant 1996;18:1157-1160.
30. Bovelli D, Plataniotis G, Roila F, Group EGW. Cardiotoxicity of chemotherapeutic agents and radiotherapy-related heart disease: ESMO Clinical Practice Guidelines. Ann Oncol 2010;21(Suppl 5):v277-v282.
31. Harris EE, Correa C, Hwang W-T, et al. Late cardiac mortality and morbidity in early-stage breast cancer patients after breast-conservation treatment. J Clin Oncol 2006;24:4100-4106.
32. Chicco AJ, Hydock DS, Schneider CM, Hayward R. Low-intensity exercise training during doxorubicin treatment protects against cardiotoxicity. J Applied Physiol 2006;100:519-527.
33. Chen JJ, Wu P-T, Middlekauff HR, Nguyen K-L. Aerobic exercise in anthracycline-induced cardiotoxicity: A systematic review of current evidence and future directions. Am J Physiol Heart Circ Physiol 2017;312:H213-H222.
34. Lipshultz SE, Adams MJ, Colan SD, et al. Long-term cardiovascular toxicity in children, adolescents, and young adults who receive cancer therapy: Pathophysiology, course, monitoring, management, prevention, and research directions. Circulation 2013;128:1927-1995.
35. Winters-Stone KM, Horak F, Jacobs PG, et al. Falls, functioning, and disability among women with persistent symptoms of chemotherapy-induced peripheral neuropathy. J Clin Oncol 2017. JCO2016713552.

36. Wildes TM, Dua P, Fowler SA, et al. Systematic review of falls in older adults with cancer. J Geriatr Oncol 2015;6:70-83.
37. Stubblefield MD, Burstein HJ, Burton AW, et al. NCCN task force report: Management of neuropathy in cancer. J Natl Comp Cancer Network 2009;7(Suppl 5):S-1-S-26.
38. Kerckhove N, Collin A, Conde S, Chaleteix C, Pezet D, Balayssac D. Long-term effects, pathophysiological mechanisms, and risk factors of chemotherapy-induced peripheral neuropathies: A comprehensive literature review. Front Pharmacol 2017;8:86.
39. Gu Y, Dennis SM. Are falls prevention programs effective at reducing the risk factors for falls in people with type-2 diabetes mellitus and peripheral neuropathy: A systematic review with narrative synthesis. J Diabetes Complications 2017;31:504-516.
40. Stubblefield MD, McNeely ML, Alfano CM, Mayer DK. A prospective surveillance model for physical rehabilitation of women with breast cancer. Cancer 2012;118:2250-2260.
41. Cormier JN, Askew RL, Mungovan KS, Xing Y, Ross MI, Armer JM. Lymphedema beyond breast cancer: A systematic review and meta-analysis of cancer-related secondary lymphedema. Cancer 2010;116:5138-5149.
42. Schmitz KH, Ahmed RL, Troxel A, et al. Weight lifting in women with breast-cancer-related lymphedema. N Engl J Med 2009;361:664-673.
43. Schmitz KH, Ahmed RL, Troxel AB, et al. Weight lifting for women at risk for breast cancer-related lymphedema: A randomized trial. JAMA 2010;304:2699-2705.
44. Cheema B, Gaul CA, Lane K, Fiatarone Singh MA. Progressive resistance training in breast cancer: A systematic review of clinical trials. Breast Cancer Res Treat 2008;109:9-26.
45. Shaitelman SF, Cromwell KD, Rasmussen JC, et al. Recent progress in cancer-related lymphedema treatment and prevention. CA Cancer J Clinic 2015;65:55.
46. Winters-Stone KM, Bennett J, Mick D. Preventing frailty in older cancer survivors. Topics Geriatr Rehabil 2015;31:241-245.
47. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: Evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146-M156.
48. Handforth C, Clegg A, Young C, et al. The prevalence and outcomes of frailty in older cancer patients: A systematic review. Ann Oncol 2015;26:1091-1101.
49. Retornaz F, Monette J, Batist G, et al. Usefulness of frailty markers in the assessment of the health and functional status of older cancer patients referred for chemotherapy: A pilot study. J Gerontol A Biol Sci Med Sci 2008;63:518-522.
50. Huang MH, Blackwood J, Godoshian M, Pfalzer L. Prevalence of self-reported falls, balance or walking problems in older cancer survivors from Surveillance, Epidemiology and End Results-Medicare Health Outcomes Survey. J Geriatr Oncol 2017;8:255-261.
51. Mohile SG, Magnuson A. Comprehensive geriatric assessment in oncology. Cancer Aging 2013;38:85-103.
52. Jolly TA, Deal AM, Nyrop KA, et al. Geriatric assessment-identified deficits in older cancer patients with normal performance status. Oncologist 2015;20:379-385.
53. Weening-Dijksterhuis E, de Greef MH, Scherder EJ, Slaets JP, van der Schans CP. Frail institutionalized older persons: A comprehensive review on physical exercise, physical fitness, activities of daily living, and quality-of-life. Am J Phys Med Rehabil 2011;90:156-168.
54. Stubblefield MD, Schmitz KH, Ness KK. Physical functioning and rehabilitation for the cancer survivor. Semin Oncol 2013;40:784-795.
55. van Londen G, Taxel P, Van Poznak C. Cancer therapy and osteoporosis: Approach to evaluation and management. Sem Oncol 2008;35:643-651.
56. Poulsen M, Frost M, Abrahamsen B, Gerke O, Walter S. Osteoporosis among men with prostate cancer during treatment with androgen deprivation therapy. Eur Urol Suppl 2016;15:e70.
57. Bouvard B, Soulié P, Hoppé E, et al. Fracture incidence after 3 years of aromatase inhibitor therapy. Ann Oncol 2014;25:843-847.
58. Zerzan S, Smoot B, Lee JQ, Lui A, Allen DD. The effect of bone-loading exercise on bone mineral density in women following treatment for breast cancer: A systematic review and meta-analysis. Rehabil Oncol 2016;34:144-155.
59. Eastley N, Newey M, Ashford RU. Skeletal metastases—the role of the orthopaedic and spinal surgeon. Surg Oncol 2012;21:216-222.
60. Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. Clin Cancer Res 2006;12:6243s-6249s.
61. Costa L, Badia X, Chow E, Lipton A, Wardley A. Impact of skeletal complications on patients' quality of life, mobility, and functional independence. Support Care Cancer 2008;16:879-889.
62. Healey JH, Brown HK. Complications of bone metastases: Surgical management. Cancer 2000;88(12 Suppl):2940-2951.
63. Silver JK, Baima J, Mayer RS. Impairment-driven cancer rehabilitation: An essential component of quality care and survivorship. CA Cancer J Clin 2013;63:295-317.
64. Mirels H. Metastatic disease in long bones. A proposed scoring system for diagnosing impending pathologic fractures. Clin Orthop Relat Res 1989:256-264.
65. Harrington KD. Impending pathologic fractures from metastatic malignancy: Evaluation and management. Inst Course Lect 1986;35:357-381.
66. Bunting RW, Shea B. Bone metastasis and rehabilitation. Cancer 2001;92:1020-1028.
67. Cheville AL, Murthy NS, Basford JR, et al. Imaging and clinical characteristics predict near-term disablement from bone metastases: Implications for rehabilitation. Arch Phys Med Rehabil 2016;97:53-60.
68. Bunting R, Lamont-Havers W, Schweon D, Kliman A. Pathologic fracture risk in rehabilitation of patients with bony metastases. Clin Orthop Relat Res 1985:222-227.
69. Cormie P, Newton RU, Spry N, Joseph D, Taaffe DR, Galvao DA. Safety and efficacy of resistance exercise in prostate cancer patients with bone metastases. Prostate Cancer Prostatic Dis 2013;16:328-335.
70. Cormie P, Galvao DA, Spry N, Joseph D, Taaffe DR, Newton RU. Functional benefits are sustained after a program of supervised resistance exercise in cancer patients with bone metastases: Longitudinal results of a pilot study. Support Care Cancer 2014;22:1537-1548.
71. O'Toole GBP, Herklotz M. Bone metastases. In: Stubblefield M, O'Dell M, eds. Cancer Rehabilitation: Principles and Practice. New York: Demos Publishing; 2009, 773-785.
72. Pergolotti M, Deal AM, Lavery J, Reeve BB, Muss HB. The prevalence of potentially modifiable functional deficits and the subsequent use of occupational and physical therapy by older adults with cancer. J Geriatr Oncol 2015;6:194-201.
73. Silver JK, Raj VS, Fu JB, Wisotzky EM, Smith SR, Kirch RA. Cancer rehabilitation and palliative care: Critical components in the delivery of high-quality oncology services. Support Care Cancer 2015;23:3633-3643.
74. Jones LW, Eves ND, Mackey JR, et al. Safety and feasibility of cardiopulmonary exercise testing in patients with advanced cancer. Lung Cancer 2007;55:225-232.
75. Muscaritoli M, Anker S, Argiles J, et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: Joint document elaborated by special interest groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". Clin Nutr 2010;29:154-159.
76. Hopkinson JB. The nursing contribution to nutritional care in cancer cachexia. Proc Nutr Soc 2015;74:413-418.
77. Aapro M, Arends J, Bozzetti F, et al. Early recognition of malnutrition and cachexia in the cancer patient: A position paper of a

European School of Oncology Task Force. Ann Oncol 2014;25:1492-1499.
78. Giglio P, Gilbert MR. Neurologic complications of cancer and its treatment. Curr Oncol Rep 2010;12:50-59.
79. Raj VS, Silver JK, Pugh TM, Fu JB. Palliative care and physiatry in the oncology care spectrum: An opportunity for distinct and collaborative approaches. Phys Med Rehabil Clin N Am 2017;28:35-47.
80. Schmid D, Leitzmann MF. Association between physical activity and mortality among breast cancer and colorectal cancer survivors: A systematic review and meta-analysis. Ann Oncol 2014;25:1293-1311.
81. Singh F, Newton RU, Galvao DA, Spry N, Baker MK. A systematic review of pre-surgical exercise intervention studies with cancer patients. Surg Oncol 2013;22:92-104.
82. Speck RM, Courneya KS, Masse LC, Duval S, Schmitz KH. An update of controlled physical activity trials in cancer survivors: A systematic review and meta-analysis. J Cancer Surviv 2010;4:87-100.
83. Fong DY, Ho JW, Hui BP, et al. Physical activity for cancer survivors: Meta-analysis of randomised controlled trials. BMJ 2012;344:e70.
84. De Backer IC, Schep G, Backx FJ, Vreugdenhil G, Kuipers H. Resistance training in cancer survivors: A systematic review. Int J Sports Med 2009;30:703-712.
85. Mishra SI, Scherer RW, Geigle PM, et al. Exercise interventions on health-related quality of life for cancer survivors. Cochrane Database Syst Rev 2012;8:CD007566.
86. Cheema BS, Kilbreath SL, Fahey PP, Delaney GP, Atlantis E. Safety and efficacy of progressive resistance training in breast cancer: A systematic review and meta-analysis. Breast Cancer Res Treat 2014;148:249-268.
87. Johansson K, Klernas P, Weibull A, Mattsson S. A home-based weight lifting program for patients with arm lymphedema following breast cancer treatment: A pilot and feasibility study. Lymphology 2014;47:51-64.
88. Bloomquist K, Karlsmark T, Christensen KB, Adamsen L. Heavy resistance training and lymphedema: Prevalence of breast cancer-related lymphedema in participants of an exercise intervention utilizing heavy load resistance training. Acta Oncol 2014;53:216-225.
89. Kootstra JJ, Dijkstra PU, Rietman H, et al. A longitudinal study of shoulder and arm morbidity in breast cancer survivors 7 years after sentinel lymph node biopsy or axillary lymph node dissection. Breast Cancer Res Treat 2013;139:125-134.
90. Galantino ML, Stout NL. Exercise interventions for upper limb dysfunction due to breast cancer treatment. Phys Ther 2013;93:1291-1297.
91. Bourke L, Smith D, Steed L, et al. Exercise for men with prostate cancer: A systematic review and meta-analysis. Eur Urol 2016;69:693-703.
92. Gardner JR, Livingston PM, Fraser SF. Effects of exercise on treatment-related adverse effects for patients with prostate cancer receiving androgen-deprivation therapy: A systematic review. J Clin Oncol 2013;32:335-346.
93. Granger CL, Chao C, McDonald CF, Berney S, Denehy L. Safety and feasibility of an exercise intervention for patients following lung resection: A pilot randomized controlled trial. Integr Cancer Ther 2013;12:213-224.
94. Driessen EJ, Peeters ME, Bongers BC, et al. Effects of prehabilitation and rehabilitation including a home-based component on physical fitness, adherence, treatment tolerance, and recovery in patients with non-small cell lung cancer: A systematic review. Crit Rev Oncol Hematol 2017;114:63-76.
95. Crandall K, Maguire R, Campbell A, Kearney N. Exercise intervention for patients surgically treated for non-small cell lung cancer (NSCLC): A systematic review. Surg Oncol 2014;23:17-30.
96. Newton MJ, Hayes SC, Janda M, et al. Safety, feasibility and effects of an individualised walking intervention for women undergoing chemotherapy for ovarian cancer: A pilot study. BMC Cancer 2011;11:389.
97. Babatunde OA, Adams SA, Orekoya O, Basen-Engquist K, Steck SE. Effect of physical activity on quality of life as perceived by endometrial cancer survivors: A systematic review. Int J Gynecol Cancer 2016;26:1727-1740.
98. Zhou Y, Zhu J, Gu Z, Yin X. Efficacy of exercise interventions in patients with acute leukemia: A meta-analysis. PLoS One 2016;11:e0159966.
99. Smith-Turchyn J, Richardson J. A systematic review on the use of exercise interventions for individuals with myeloid leukemia. Support Care Cancer 2015;23:2435-2446.
100. Alibhai SM, O'Neill S, Fisher-Schlombs K, et al. A pilot phase II RCT of a home-based exercise intervention for survivors of AML. Support Care Cancer 2014;22:881-889.
101. Jarden M, Adamsen L, Kjeldsen L, et al. The emerging role of exercise and health counseling in patients with acute leukemia undergoing chemotherapy during outpatient management. Leuk Res 2013;37:155-161.
102. Bergenthal N, Will A, Streckmann F, et al. Aerobic physical exercise for adult patients with haematological malignancies. Cochrane Database Syst Rev 2014:CD009075.
103. Tsuda K, Sudo K, Goto G, et al. A feasibility study of virtual reality exercise in elderly patients with hematologic malignancies receiving chemotherapy. Intern Med 2016;55:347-352.
104. Cheville AL, Basford JR. Role of rehabilitation medicine and physical agents in the treatment of cancer-associated pain. J Clin Oncol 2014;32:1691-1702.
105. Pfalzer LA. Physical agents/modalities for survivors of cancer. Rehabil Oncol 2001;19:12.
106. Boon AJ, Gertken JT, Watson JC, et al. Hematoma risk after needle electromyography. Muscle Nerve 2012;45:9-12.
107. Pearl ML, Fischer M, McCauley DL, Valea FA, Chalas E. Transcutaneous electrical nerve stimulation as an adjunct for controlling chemotherapy-induced nausea and vomiting in gynecologic oncology patients. Cancer Nurs 1999;22:307-311.
108. Crary MA, Carnaby GD. Adoption into clinical practice of two therapies to manage swallowing disorders: Exercise based swallowing rehabilitation and electrical stimulation. Curr Opin Otolaryngol Head Neck Surg 2014;22:172.
109. Migliorati C, Hewson I, Lalla RV, et al. Systematic review of laser and other light therapy for the management of oral mucositis in cancer patients. Support Care Cancer 2013;21:333-341.
110. E Lima JGM, de Andrade MFC, Bergmann A. Low-level laser therapy in secondary lymphedema after breast cancer: Systematic review. Lasers Med Sci 2014;29:1289-1295.
111. Corbin L. Safety and efficacy of massage therapy for patients with cancer. Cancer Control 2005;12:158-164.
112. French SD, Cameron M, Walker BF, Reggars JW, Esterman AJ. A Cochrane review of superficial heat or cold for low back pain. Spine 2006;31:998-1006.
113. Sicard-Rosenbaum L, Danoff JV, Guthrie JA, Eckhaus MA. Effects of energy-matched pulsed and continuous ultrasound on tumor growth in mice. Phys Ther 1998;78:271-277.
114. DeLisa JA, Gans BM, Walsh NE. Physical Medicine and Rehabilitation: Principles and Practice. Vol 1. Philadelphia: Lippincott Williams & Wilkins; 2005.

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