Current Physical Medicine and Rehabilitation Reports (2024) 12:383–394
https://doi.org/10.1007/s40141-024-00454-6

REVIEW

Evaluation and Management of Shoulder Dysfunction in Cancer Survivors

Hwajin Lee[1] · **Michael D. Stubblefield**[2]

Accepted: 6 May 2024 / Published online: 13 June 2024

Abstract

Purpose of Review Shoulder dysfunction widely affects function and quality of life of cancer survivors. This paper discusses the etiology, identification, evaluation, and management of the common shoulder impairments seen in cancer survivors, particularly those with breast cancer, head and neck cancer, and Hodgkin lymphoma.

Recent Findings Shoulder dysfunction can be caused by a wide range of sources, often as a sequelae of cancer treatments including surgery, systemic therapy, and radiation therapy. These can change the shoulder biomechanics leading to musculoskeletal disorders such as rotator cuff disease and adhesive capsulitis. Other etiologies include neuromuscular complications, such as post-breast surgery pain syndrome and radiation fibrosis syndrome, and lymphovascular disorders such as lymphedema and axillary web syndrome. Metastatic bone disease and primary bone cancer should be considered for those with intense shoulder pain. Detailed history and physical exam, and in some cases, imaging can assist with evaluation of shoulder issues. Exercise, physical and occupation therapy are essential in managing shoulder dysfunction.

Summary Shoulder dysfunction can limit function and quality of life for cancer survivors. It is important to consider the possible etiologies as accurate diagnosis is critical for optimal treatment.

Keywords Breast Cancer · Head and Neck Cancer · Hodgkin lymphoma · Shoulder Dysfunction · Shoulder Pain · Post-Mastectomy Pain Syndrome

Introduction

According to the American Cancer Society, 1,958,310 new cancer cases are projected for the year 2023 and the five-year relative survival rate has been rising for most types of cancer since 1970s [1]. As such, improving long-term quality of life is an imperative for cancer survivors. Shoulder dysfunction is common in the general population and may be more prevalent in a number of cancer survivor groups such as those with breast cancer [2], head and neck cancer (HNC) [3, 4], and Hodgkin lymphoma (HL) [5]. The modalities used to treat cancer – namely surgery, and radiation therapy (RT) – contribute to the increased incidence and severity of shoulder dysfunction in these groups [6, 7]. About half of breast cancer survivors, for instance, will experience shoulder impairment [8, 9]. For HNC patients, prevalence of shoulder syndrome varies widely depending on the degree of surgical resection and radiation (ranging 9%-100%) [4, 7]. In one study, 73% of 100 HL survivors experienced shoulder dysfunction [5]. In this article, we will discuss the etiology, identification, evaluation, and management of the most common causes of shoulder issues in cancer survivors.

✉ Michael D. Stubblefield
mstubblefield@selectmedical.com

Hwajin Lee
hwajin.lee@rutgers.edu

[1] Department of Physical Medicine & Rehabilitation, Rutgers New Jersey Medical School, Newark, New Jersey, USA

[2] Kessler Institute for Rehabilitation, West Orange, New Jersey, USA

Musculoskeletal Disorders

Post-Surgical Pain

Post-surgical shoulder dysfunction is particularly prevalent in breast cancer survivors as a result of multimodal treatment including surgery, systemic therapy, and RT [2]. Extent of surgery is a major risk factor, with higher risk for pain and slower recovery of shoulder range of motion (ROM)

with total mastectomy and axillary lymph node dissection (ALND) than partial mastectomy and sentinel lymph node biopsy (SLNB) [10–14]. Post-operative shoulder pain may discourage patients from moving their upper extremities, reducing shoulder ROM, ultimately leading to shoulder pathology [2].

When evaluating patients with immediate post-operative pain, it is crucial to rule out acute surgical complications including dehiscence, seroma, infection, and flap necrosis [2]. Post-surgical pain typically has an acute onset, is located around the surgical scar, and limits strength and ROM, with more restriction in active than passive movement. During physical examination, patients may exhibit tenderness at the surgical site.

Exercise enhances surgical recovery, including shoulder ROM and outcomes as measured by the Disabilities of the Arm, Shoulder, and Hand (DASH) score, according to multiple studies [15–21]. Pre-operative exercise can help optimize upper extremity function in patients with breast cancer awaiting mastectomy [22]. Rehabilitation services, including physical therapy (PT) and occupational therapy (OT), are highly recommended after surgery according to a clinical practice guideline [15]. Early rehabilitation with shorter immobilization periods was beneficial, leading to improved shoulder mobility [21]. According to one prospective study of 60 patients who underwent mastectomy and immediate implant-based reconstruction, the group with unlimited shoulder ROM 15 days after surgery yielded better outcomes in pain and function than the group who had limited shoulder ROM until 30 days post-surgery [18]. Moderate to vigorous exercise also improved shoulder function and reduced chronic postoperative pain [20]. Another study noted decreased strength in both the affected and unaffected limbs for post-operative breast cancer patients, thus patients may benefit from therapy that involves bilateral upper extremities [16].

A systemic review examined the effects of perioperative nonsteroidal anti-inflammatory drug (NSAID) administration and found only low-certainty evidence for reduction in postoperative pain and little evidence on its impact on breast hematoma or bleeding [23]. Opioids and interventional procedures are often used to manage severe post-operative pain. One study showed that ultrasound-guided erector spinae plane block after breast surgery decreased postoperative opioid consumption within 24 hours post-surgery [24].

Rotator Cuff Disease (RTC)

RTC disease and shoulder impingement syndrome (SIS) are common in both the general and cancer populations. Cancer treatments can alter shoulder mechanics, leading to RTC pathology, reduced ROM and pain [4, 7, 25]. Late effects of RT, cervical spondylosis, or any disorder that affects the C5-C6 nerve roots and/or upper brachial plexus can cause RTC muscle weakness and referred pain to the lateral shoulder. Weakness of the RTC can result in anterior translation of the humerus (often worsened by mastectomy, reconstruction, radiation, and axillary cording), dynamic impingement of the RTC tendon under the acromial arch, RTC inflammation, and ultimately adhesive capsulitis (AC) with restricted ROM and shoulder pain [2]. Pain from nerve dysfunction, tendonitis, AC, and other pathologies further disincentivize shoulder movement creating a vicious cycle of shoulder dysfunction (Fig. 1 [2]) [2, 7, 26]. Post-surgical pain and pectoralis muscle tightening can also affect scapular kinematics, predisposing breast cancer patients to SIS [25, 27, 28]. One study revealed that biceps tenosynovitis, supraspinatus partial tear, and AC were top three ultrasonographic findings in patients with chronic shoulder pain after breast cancer surgery [29].

Clinical presentation and evaluation for RTC disease are similar for cancer and general populations. Patients have shoulder pain that is worsened by movement, with limited active ROM. Special tests to assess for impingement are helpful (Table 1 [30]) [30, 31].

Routine imaging is unnecessary, but ultrasound, MRI, or MRA can be considered if nonsurgical treatments are ineffective, in cases of trauma, or if suspicious for RTC tear. Ultrasound is the most cost-effective and accurate imaging for full-thickness tears [31].

PT and OT are important for patients with RTC disease. Active and task-oriented exercises are preferred over passive modalities. Manual therapy and acupuncture may be helpful. Therapeutic ultrasound and laser therapy are not recommended although they may slightly reduce pain immediately after the intervention. There is insufficient evidence on the use of proprioceptive taping, transcutaneous electrical nerve stimulation (TENS) stimulation, pulsed electromagnetic fields, interferential currents, or iontophoresis. For second-line treatment, extracorporeal or radial shockwave therapy and calcific lavage can be considered [31].

Oral and topical analgesics, such as NSAIDs can be used for pain management. There was no difference in efficacy between COX-2 selective and non-selective NSAIDs [31]. Corticosteroid injection (CSI) can provide short-term relief for severe pain compared to placebo or an anesthetic injection [31]. Multiple CSIs are not superior to a single injection. If there is a full-thickness tear, CSI can increase risk of retear. Hyaluronic acid injections are not recommended because they do not significantly reduce pain compared to placebo [31]. Platelet rich plasma (PRP) injection may help to reduce pain however there is insufficient data on its efficacy for complete tears [31]. While there has been no direct correlation in literature between use of PRP and risk of tumor growth, there is still a theoretical risk of promoting tumor proliferation due to addition of growth factors. Thus,

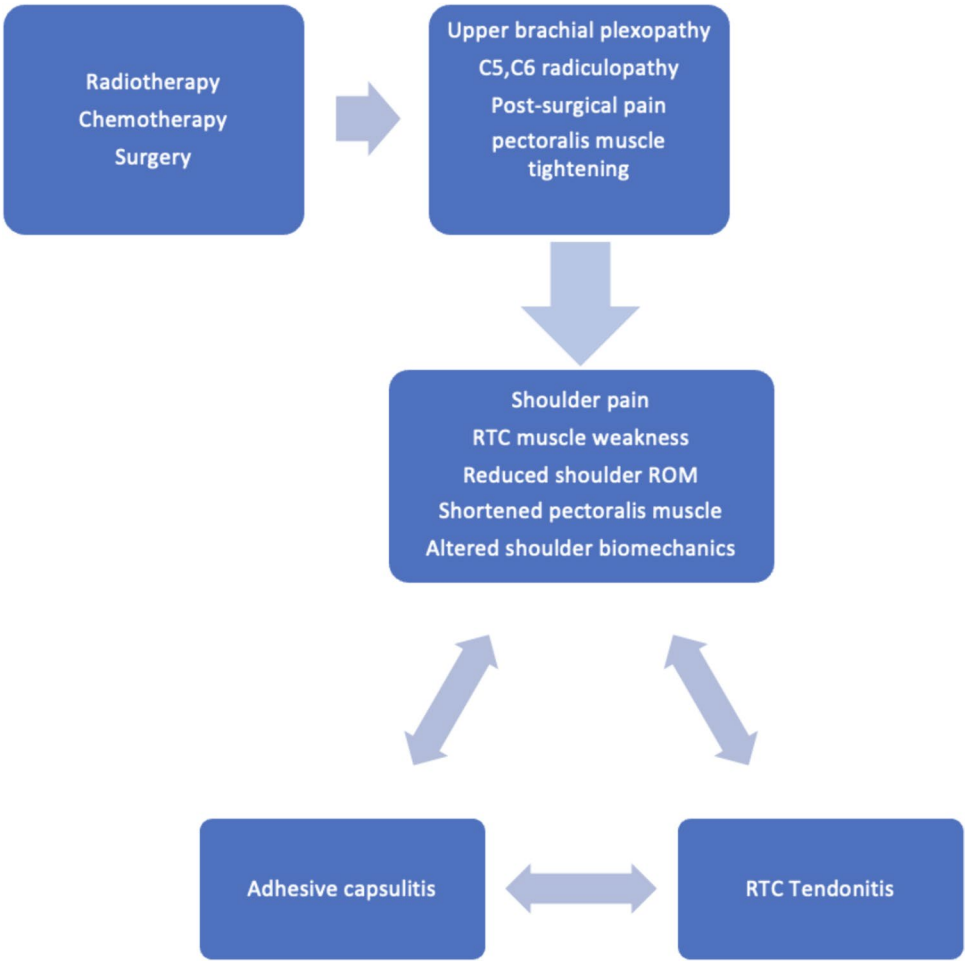

Fig. 1 Shoulder dysfunction and its cycle in cancer patients. This schematic illustrates how cancer treatments can contribute to shoulder disorder, particularly in breast cancer patients although can be applied to understand shoulder dysfunction in other cancer populations

Table 1 Physical exam maneuvers for evaluation of RTC disease

Hawkin's test	Sensitivity: 75-92% Specificity: 44-48% For predicting subacromial bursitis and impingement
Neer's test	Sensitivity: 75-86% Specificity: 48-49% For subacromial bursitis
Empty can test	Sensitivity: 62% Specificity: 54% For partial thickness tear or tendinitis of the supraspinatus tendon
Drop arm test	Specificity: 98% Likelihood ratio: 5.0 For supraspinatus tendinopathy and/or tear

recent malignancy (both solid tumors and hematological diseases) was considered as relative contraindication with a Level 5 level of evidence [32]. Yuan and Gellhorn also concur with this statement, reporting cancer (localized or metastatic) as a contraindication to PRP therapy and history of cancer as a relative contraindication [33]. Thus, discussion with the oncologist prior to considering PRP injection would be necessary.

Early orthopedic referral is advisable for patients with full-thickness tears, particularly those who are young, engaged in physically demanding work, or have a history of traumatic onset [31]. Surgery is generally not recommended for RTC disease secondary to late effects of radiotherapy given the potential progressive nature of radiation fibrosis syndrome.

Adhesive Capsulitis

Commonly referred to as frozen shoulder, AC results in persistent pain and diminished active and passive ROM, accompanied by stiffness in the glenohumeral joint. It may manifest following mastectomy or other surgeries that induce pain, tightness in the pectoral muscles, RTC issues, or alterations in shoulder girdle biomechanics. These factors can lead to protective postures that strain the joint capsule, consequently restricting shoulder mobility and potentially causing secondary AC [34].

Pathophysiology is unclear although it is thought to develop due to an inflammatory process leading to fibrosis and contracture of the glenohumeral joint [28].

AC progresses through three distinct phases [34]: 1) First stage (painful freezing stage) lasts for 2-9 months. Patients report sharp, diffuse shoulder pain with gradual increase in stiffness. 2) Second stage (frozen stage) lasts for 4-12 months. Patients experience peak loss of shoulder ROM and stiffness. 3) Third stage (thawing stage) takes 5 months-2 years to complete. Patients notice gradual regain of shoulder ROM. In most cases, AC is self-limiting and resolves within 2 years however in 20-50 % cases, symptoms may last longer [35]. Risk factors include age, breast reconstruction, lymphedema, lymph node dissection, and aromatase inhibitor therapy [28, 35].

Clinically, patients present similarly to those with SIS. Patients typically have shoulder pain and substantially reduced active and passive ROM in at least two planes, especially with external rotation and abduction [28]. To distinguish AC from SIS, a subacromial injection with a local anesthetic can be used as it should alleviate pain while ROM remains limited in AC [28].

Management of AC focuses on improving ROM and pain. PT and exercise are highly recommended. Progressive banded strengthening exercises and scapular stabilization maneuvers showed improvement of shoulder ROM and overall quality of life [36]. Oral medications can be used for pain, and CSI into the glenohumeral joint can alleviate pain and improve ROM in both short and long term [28, 37]. Other interventions include hyaluronic acid and PRP injections, hydrodistension, extracorporeal shockwave therapy, low level laser therapy and calcitonin although these are not done routinely [38, 39]. If no success with above therapies, surgery can be considered such as manipulation under general anesthetic or arthroscopic capsular release [38].

Arthralgias

Arthralgia is defined as joint pain or stiffness. Certain cancer treatments can cause arthralgia involving multiple joints, including the shoulder [2]. Aromatase inhibitor-associated musculoskeletal symptoms and immune checkpoint inhibitor-induced arthralgias are two common conditions seen in cancer population.

Aromatase Inhibitor-Associated Musculoskeletal Symptoms (AIMSS)

Aromatase inhibitors (AIs) commonly cause musculoskeletal symptoms, specifically AI-induced arthralgia (AIA), affecting 20-70% of patients [40, 41]. Patients often discontinue AIs due to arthralgia. Symptoms can be intermittent or continuous and can involve multiple joints, with symptoms presenting within 2 months and peaking at 6 months [42–44]. Currently, pathophysiology of AIMSS is unknown, although multiple mechanisms have been proposed [42, 43, 45–47]. There are no studies directly comparing AIs (anastrozole, letrozole, exemestane) [47]. Diagnosis lacks standardized criteria, though proposed criteria by Niravath et al in 2013 are available (Table 2 [48]) [42, 45, 47, 48].

Management options include switching AI agents, exercise, oral medications, and acupuncture [42, 43]. Intermittent letrozole treatment, suggested by the Phase III SOLE trial, can be considered, demonstrating comparable disease outcomes [49]. Exercise and PT improve pain and quality of life. Combined aerobic and resistance exercises are recommended [40, 50–54]. Walking, swimming, tai-chi, Pilates and yoga also demonstrated beneficial effects for AIA [45, 47, 52]. NSAIDs and acetaminophen can be used for acute pain control [42, 47]. Duloxetine showed reduced joint pain after 12 weeks and high patient-perceived benefit despite increased rate of adverse events [55]. Bisphosphonate also has potential benefit in preventing AIA as there was a

Table 2 Definition of Aromatase Inhibitor-induced Arthralgia (AIA). Niraveth et al proposed this criteria, in which patients should meet all of the major and 3 of the minor criteria for diagnosis of AIA

Major criteria
Currently taking AI
Joint pain which has developed or worsened since starting AI
Joint pain improves or resolves within 2 weeks of stopping AI
Joint pain returns upon resuming AI
Minor criteria
Symmetrical joint pains
Pain in hands and/or wrists
Carpal tunnel syndrome
Decreased grip strength
Morning stiffness
Improvement in joint discomfort with use or exercise

Adapted with permission from Niravath P. Aromatase inhibitor-induced arthralgia: a review. Ann Oncol. 2013;24(6):1443-9. doi: 10.1093/annonc/mdt037.

significantly lower incidence at 1-year follow-up in patients who received zoledronic acid compared to controls [56]. Prednisone and topical testosterone gel had mixed benefits [47, 57]. Acupuncture showed promising results with several literature reporting its effectiveness in reducing pain and joint stiffness [42, 46, 47]. Nutritional supplements such as vitamin D, omega 3 fatty acid, and herbal remedies had no sufficient evidence for AIMSS [58]. One single-arm, phase II study showed moderate improvement of AI-induced arthralgia with glucosamine/chondroitin which appears promising [59].

Immune Checkpoint Inhibitor (ICI)-Induced Arthralgia

ICIs are monoclonal antibodies targeting immune checkpoints (cytotoxic T-lymphocyte-associated protein-4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed death ligand 1 (PD-L1)) which normally downregulate T-cell activation and prevent autoreactivity [60]. Thus, ICIs can amplify T-cell response, enhancing antitumor effect [61]. This however can lead to immune-related adverse events (irAEs), commonly causing arthralgia with prevalence as high as 43% [62]. Shoulder joint is frequently involved [63].

This is a clinical diagnosis. Other potential etiology of arthralgia should be excluded including gout, pseudogout, infection, rheumatologic or metastatic etiology [64]. Median symptom onset is 3 months after starting ICIs and clinically it may present with various patterns. Imaging at baseline can be useful. MRI and ultrasound are more sensitive than plain radiograph for synovitis and erosions.

Early referral to a rheumatologist is recommended [64]. Mild arthralgia can be managed with oral NSAIDs or a low to moderate dose of corticosteroids. In cases involving only one or two joints, CSI may be performed. If the patient responds well to treatment, there is no need to discontinue ICI. In cases of severe joint pain and swelling, the initial approach involves higher doses of oral corticosteroids (40-60 mg of prednisone) with a gradual tapering over 4-6 weeks. Intravenous corticosteroids are also an option. A review of case reports and case series also supports effectiveness of high dose prednisone [65]. If there is no improvement, disease-modifying antirheumatic drugs (DMARDs), such as methotrexate, should be initiated.

Pectoralis Minor Syndrome (PMS)

Often classified as a subtype of neurogenic thoracic outlet syndrome, PMS has been observed in clinical setting although no studies have yet investigated the connection between PMS and breast cancer [28].

Ahmed et al. provided a comprehensive description of pathoanatomy, diagnosis, and management of PMS [66]. Pectoralis minor muscle originates from the costal cartilage margin of 3rd-5th ribs, inserts onto the superomedial aspect of the coracoid process, and acts as a dynamic stabilizer of the scapula, regulating the retropectoralis minor space. Hyperactivity, spasms, or fibrosis of the muscle can result in its shortening, causing muscle contracture, protracted scapular positioning, and scapular dyskinesia. Brachial plexus passes through the retropectoralis minor space and is subjective to compression.

Shortening of pectoralis minor muscle is common following breast cancer treatment, predisposing patients to PMS [67]. A retrospective study suggested possible pectoralis minor muscle volume change after radiotherapy which can affect scapular movement [68]. Clinically, patients typically present with pain around the shoulder, neck, trapezius, and medial scapula, often with muscle spasms and non-specific paresthesia. Physical exam is notable for scapular dyskinesia, limited ROM, tenderness and positive Tinel's sign over the pectoralis minor muscle, and hand atrophy may be found as a late presentation. Provocative exams such as Adson, Wright, and Roos tests are nonspecific with high false positive rates [66].

PMS is a clinical diagnosis. Pectoralis muscle length and tightness can be assessed indirectly by observing scapular positioning during dynamic exam [66]. Palpation meter (PALM) can be a simple and cost-effective tool to evaluate pectoralis minor length in breast cancer patients [67]. In case of brachial plexus compression, local anesthetic injection into the pectoralis minor muscle is the gold standard approach for diagnosis [28, 66]. Electrodiagnostic studies can be used although it is most commonly within the normal range in PMS [33, 69].

Imaging can exclude alternative causes, such as a Pancoast tumor or other structural abnormalities. MRI of brachial plexus can reveal potential compression sites, nerve edema, fibrosis, or other pathologies that might resemble PMS such as space-occupying lesions or nerve sheath tumors. Ultrasound offers a dynamic assessment of the shoulder, revealing a posterior indentation of the muscle during arm abduction in PMS. This indentation is attributed to the shortened and fibrosed pectoralis muscle pressing against the brachial plexus in the retropectoralis minor space [66].

Conservative treatment with pectoralis muscle stretching, strengthening of scapular retractor muscles, and postural training are first-line management, with the goal to improve pectoralis muscle length and flexibility while retaining scapular mechanics and scapulohumeral rhythm [28, 66]. To keep the shoulders in passive retraction, kinesiotaping and orthotic bracing can be used [66, 70]. Surgical intervention with pectoralis minor release is considered only for refractory cases [28, 66]. Botulinum toxin injection may also play a role in diagnosis and treating PMS. According to a recent

systemic review, while there was limited quality evidence with only one randomized control trial, total of 8 studies were reviewed with 46-63% of primary procedures showing improved symptoms [65].

Bony Metastasis and Primary Bone Cancer

When assessing cancer survivors with new onset or progressively worsening upper extremity pain, it is critical to consider malignancy. A variety of oncologic lesions, including primary sarcomas, benign tumors, and metastatic bone diseases can cause upper extremity pain [71, 72]. Lung, renal, prostate, breast, thyroid cancers, and multiple myeloma often metastasize to bones, with the humerus being a common site [69, 73, 74]. Patients with proximal humeral lesions typically experience dull, consistent shoulder or arm pain, especially at rest and night, often unrelieved by medications [71, 73]. A thorough physical exam is crucial, along with imaging, to exclude malignancy [73]. Clinician should refer patients to an oncologist if metastatic disease or primary bone lesions are suspected.

Managing bone metastasis involves preventing progression and alleviating pain [74]. Regular physical activity is recommended, but there is no standardized exercise protocol for those with metastatic bone disease [75–79]. Supervised exercise is preferable to reduce the risk of fracture [78]. Exercise should be modified based on lesion location, avoiding rapid or forceful movements in affected areas [79]. Untreated unstable osseous sites, like pathological fractures, should be excluded from physical activity [75, 76]. Various fracture risk assessment tools, including the Mirels score, can be used [76, 77, 80].

Local external beam radiation effectively alleviates metastatic bone pain, with a high overall response rate [81]. Zoledronic acid was also shown to be effective [82]. Other treatments include radionuclides, oral medications (opioids, anticonvulsants, antidepressants, corticosteroids), and interventional procedures [83]. For structurally significant lesions in long bones, surgery may be necessary [74]. Impending or complete scapula fractures can be treated conservatively, while most displaced proximal humeral fractures will require surgery [73].

Neuromuscular Disorders

Post-Breast Surgery Pain Syndrome (PBSPS)

PBSPS, often called "post-mastectomy pain syndrome", is commonly seen after breast surgery, affecting 20-68% of breast cancer patients [84]. The updated terminology for this disorder reflects the fact that many of the patients affected by this disorder underwent lumpectomy and not mastectomy [85]. Additionally, breast reconstruction is a common and often major contributor to PBSPS. The disorder has been defined in the literature as a persistent dull, burning, and aching sensations in the ipsilateral chest, axilla, and arm that extends beyond the expected healing period, lasting at least 3-6 months post-surgery [34]. This definition, however, best describes the neuropathic pain component of this disorder. Many patients describe squeezing pain and tenderness in shoulder girdle and other muscles that likely reflects secondary muscle spasm and pain from disruption of neural innervation. The definition and component etiologies of PBSPS are continuing to evolve and remain poorly defined [28]. An article from 2016 proposed a standardized definition of moderate or severe pain persisting for at least 6 months after breast surgery, affecting the ipsilateral breast, chest wall, axilla, and/or arm at least 50% of the time [85]. PBSPS increases risk for subsequent shoulder dysfunction.

Intercostobrachial nerve (ICBN) injury and subsequent neuroma formation is commonly implicated as a contributor to the neuropathic pain component of PBSPS. Damage to other peripheral nerves (medial pectoral, lateral pectoral, thoracodorsal, long thoracic nerve, and 3rd-6th intercostal nerves) are also contributory to both neuropathic and muscular pain [34, 84]. Risk of injuring the ICBN is high during surgery especially when ALDN is performed [2, 28, 84]. Other risk factors include higher BMI, concurrent radiation therapy, lack of social support and younger age [34].

PBSPS is diagnosed clinically. Abnormal sensation and possible Tinel's sign in the medial portion of the upper arm can direct to possible ICBN injury [28]. Intercostal and intercostal cutaneous branch neuromas can also be identified by focal tenderness on physical exam with positive Tinel's sign with radiating symptoms along the distribution of the nerve. Frequently, pain is located close to surgical scar lines. Ultrasound can visualize neuromas and is a useful modality for evaluation. "Ultrasound trigger sign," achieved by palpating the neuroma with the transducer, can aid in diagnosis. Confirmation with a nerve block, which also has therapeutic benefits, further supports the diagnosis [28, 86].

Management of PBSPS is well-documented, supporting multidisciplinary approach [28, 87–89]. Exercise and PT were noted to be beneficial, with guidelines recommending beginning exercises as early as one day post-surgery [90, 91]. The focus initially involves gentle ROM, then progresses to strengthening exercises and restoring full ROM over 6-8 weeks [91]. Myofascial release to reduce mechanical traction on neuromas can be extremely helpful [90]. Other treatment options include mindfulness-based cognitive therapy, oral analgesics, antidepressants, capsaicin, laser therapy, botulinum toxin injections, nerve blocks, fat grafting, and neuroma surgery [87, 92].

Radiation Fibrosis Syndrome (RFS)

Radiation fibrosis (RF) is a progressive, irreversible tissue sclerosis caused by radiation therapy, leading to clinical sequelae known as RFS [7]. RFS can affect any structure within the radiation field, including neuromuscular structures, causing myelopathy, radiculopathy, plexopathy, neuropathy, myopathy, or a combination (myelo-radiculo-plexo-neuro-myopathy), ultimately contributing to shoulder dysfunction [7, 93–95].

C5 and C6 radiculopathy and radiation-induced cervical and brachial plexopathy (RICP, RIBP) can result in myotomal-patterned weakness, affecting rhomboids, RTC muscles, deltoid, and biceps [7, 26, 95, 96]. RIBP typically involves the upper trunks and is often accompanied by radiculopathy [7] Symptoms include mild paresthesia, numbness, swelling, weakness, and pain in the upper extremity [7, 97]. Distinguishing RIBP from neoplastic plexopathy is crucial. While RIBP is usually characterized by weakness and paresthesias and neoplastic plexopathy by severe pain, imaging such as gadolinium-enhanced MRI or PET/CT is the only way to exclude malignancy [97]. Shoulder dysfunction may also accompany cervical dystonia, which causes kyphotic deformity and reduced cervical ROM [98].

Mononeuropathies involving dorsal scapular, suprascapular, or long thoracic nerves can cause shoulder dysfunction [96]. Dorsal scapular nerve injury weakens rhomboids, leading to protracted scapula and altered shoulder biomechanics [7]. Neck dissections in HNC patients contribute to shoulder disorder, with extensive lymph node dissection associated with greater impairment [99]. Spinal accessory neuropathy (SAN) is a major contributor to shoulder syndrome in HNC patients given its superficial course across the posterior triangle of the neck, susceptible to surgical injury [4, 100]. Studies noted higher risk with surgical dissections performed at levels 2b and 5, with level 2b-sparing selective neck dissection showing reduced risk for shoulder impairment [100, 101].

Evaluation

This is a clinical diagnosis [93, 95, 96]. Detailed oncologic history is critical, including total radiation dose and dose per fraction [96, 102]. Physical exam should begin with inspection, assessing for any postural abnormality, muscle atrophy, or skin abnormality which may be useful to speculate radiation field and identify structures involved in the field [93]. Musculoskeletal and neurologic exam should also be performed. Electrodiagnostic studies may be useful. In radiculo-plexopathy, fasciculations and myokymic discharges may be seen on EMG whereas radiation-induced myopathy may reveal myopathic motor unit changes [93]. To rule out malignancy, gadolinium-enhanced MRI or PET/CT is typically necessary. In cases where malignancy is still suspected despite normal imaging, serial imaging at 3-month intervals may be warranted [93].

Management

While there is no cure for RFS, ongoing research explores biologic and molecular targets for potential treatments [103]. Current treatment for RFS is largely symptom driven. Nerve-stabilizing medications (gabapentin, pregabalin, duloxetine, and tricyclic antidepressants) are commonly used for neuropathic pain. NSAIDS and opioids can be used for pain [98, 102]. CSI and trigger point injections can target specific pain generators. Botulinum toxin injections can be performed for spasms however caution is needed as injecting to posterior cervicothoracic muscle may exacerbate neck extension weakness [102].

PT and OT play crucial roles in addressing RFS-related shoulder dysfunction. These therapies focus on improving posture, strength, ROM, overall conditioning, function, and independence in daily activities [102]. Evidence supports the effectiveness of interventions such as myofascial release, progressive resistance training, and neuromuscular re-education in improving shoulder dysfunction [93]. Studies in HNC patients advocate early rehabilitation, including scapular control training, EMG biofeedback, and exercise-based interventions [104, 105].

Adaptive equipment, like splints and dynamic orthoses, aids individuals with severe RIBP, potentially preventing subluxation [98]. Acupuncture has limited evidence supporting its effectiveness [104]. Surgery is generally not recommended for RFS, but some literature suggests options like neurolysis, surgical reconstruction with a vascularized flap, and dorsal root entry zone lesioning to alleviate neuropathic pain from plexopathy [98, 106, 107].

Lymphovascular Disorders

Lymphedema

Lymphedema is soft tissue swelling resulting from the accumulation of protein-rich fluid, often caused by radiation damage and lymphadenectomy [108]. ALND and radiotherapy to regional lymph nodes increase the risk of lymphedema [28, 34]. While lymphedema itself does not cause shoulder pain directly, it can contribute to shoulder dysfunction due to upper limb discomfort from swelling and heaviness [28]. A study found higher rates of scapular dyskinesia and decreased pain threshold levels in patients with lymphedema, possibly due to altered scapular biomechanics secondary to arm heaviness [108].

Accurate diagnosis involves baseline and follow-up limb measurements using the relative volume change (RVC), which calculates the percentage volume difference between arms [109]. Breast cancer lymphedema is often defined as RVC ≥10%, more than 3 months post-surgery. Diagnostic tools include volume displacement, circumferential arm measurements, bioimpedance, and perometer [109].

Conservative management with complete decongestive therapy is the gold standard for treatment, consisting of an initial reduction phase with manual lymphatic drainage, compression bandaging, exercise, and skin care, followed by a maintenance phase with compression garments, self-manual lymphatic drainage and continued exercise and skin care [34, 109, 110]. Pneumatic compression devices showed beneficial effects [28]. Surgery, such as lymphatic tissue resection or vascularized lymph node transfers, can be considered if selected cases, though results are mixed [34, 109].

Axillary Web Syndrome (AWS)

AWS, also known as cording, manifests as a single or multiple taut cords in the axilla, extending to the upper arm and chest after breast cancer surgery. It occurs 2-8 weeks post-surgery, limiting shoulder movement and causing pain during abduction. The incidence ranges from 6-86%, often resolving within 3 months but persisting longer in some cases [34, 111]. ALND carries a higher risk than SLNB [34, 111]. AWS can reduce shoulder ROM, potentially leading to long-term movement pattern alterations and dysfunction [111]. Studies identify AWS as a risk factor for impaired function and reduced shoulder motion at 5 years post-surgery [112].

Clinical diagnosis involves noting cord location and number during physical exam. A comprehensive shoulder assessment with a physical therapist, including goniometer measurements of ROM, is recommended [111]. PT is crucial for AWS treatment, focusing on enhancing flexibility, strength, and abduction of the affected limb. Myofascial release, cord manipulation, and stretching can be beneficial [34]. Recent reviews suggest that exercise and stretching are the most effective therapies, though more research is needed to determine the optimal rehabilitation approach [113]. Soft tissue mobilization may improve mobility by "breaking the cord," but its impact on the lymphatic system is unclear, thus gentle manual techniques are generally recommended [111]. NSAIDs may be used for pain.

Conclusion

Shoulder pain and dysfunction can greatly impact quality of life for cancer survivors, affecting their physical, psychological, and social well-being [2, 114, 115]. It is critical to consider multiple etiologies of shoulder impairment, many of which are secondary to cancer treatments, such as post-breast surgery pain syndrome, radiation fibrosis syndrome and inflammatory arthralgia from hormonal and immunotherapy. Accurate diagnosis is crucial for optimal treatment. Clinician should note that multiple underlying causes of shoulder dysfunction can be present concurrently which may evolve over time [2]. Malignancy should also be excluded and close communication with oncology team is essential.

Author contributions H.L. and M.S. wrote the main manuscript text and H.L. prepared Fig. 1 and Tables 1 and 2. All authors reviewed the manuscript.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Competing Interests The authors declare no competing interests.

References

1. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer Statistics, 2023. CA: a Cancer J Clin. 2023;73(1):17–48. https://doi.org/10.3322/caac.21763.
2. Stubblefield MD, Keole N. Upper Body Pain and Functional Disorders in Patients with Breast Cancer. PM R. 2014;6(2):170–83. https://doi.org/10.1016/j.pmrj.2013.08.605.
3. Cohen EE, LaMonte SJ, Erb NL, Beckman KL, Sadeghi N, Hutcheson KA, et al. American Cancer Society Head and Neck Cancer Survivorship Care Guideline. CA: a Cancer J Clin. 2016;66(3):203–39. https://doi.org/10.3322/caac.21343.
4. Parke SC, Langelier DM, Cheng JT, Kline-Quiroz C, Stubblefield MD. State of Rehabilitation Research in The Head and Neck Cancer Population: Functional Impact vs. Impairment-Focused Outcomes. Current Oncology Reports. 2022;24(4):517–32.
5. Enam N, Chou K, Stubblefield MD. Prevalence of Function-Limiting Late Effects in Hodgkin lymphoma Survivors. PM&R. 2022;14(7):811–7.
6. Stubblefield MD, O'Dell MW. Cancer rehabilitation principles and practice. 2nd ed. New York: Demos Medical; 2007.

7. Lee H, Stubblefield MD. Neuromuscular Complications of Radiation Fibrosis Syndrome. In: Current Physical Medicine and Rehabilitation Reports; 2023. p. 1–8.
8. Rietman JS, Dijkstra PU, Hoekstra HJ, Eisma WH, Szabo BG, Groothoff JW, et al. Late morbidity after treatment of breast cancer in relation to daily activities and quality of life: a systematic review. Eur J Surg Oncol. 2003;29(3):229–38. https://doi.org/10.1053/ejso.2002.1403.
9. Hopwood P, Haviland JS, Sumo G, Mills J, Bliss JM, Yarnold JR, et al. Comparison of patient-reported breast, arm, and shoulder symptoms and body image after radiotherapy for early breast cancer: 5-year follow-up in the randomised Standardisation of Breast Radiotherapy (START) trials. Lancet Oncol. 2010;11(3):231–40. https://doi.org/10.1016/S1470-2045(09)70382-1.
10. Hidding JT, Beurskens CH, van der Wees PJ, van Laarhoven HW, Nijhuis-van der Sanden MW. Treatment related impairments in arm and shoulder in patients with breast cancer: a systematic review. PLoS One. 2014;9(5):e96748. https://doi.org/10.1371/journal.pone.0096748.
11. Vidt ME, Potochny J, Dodge D, Green M, Sturgeon K, Kass R, et al. The influence of mastectomy and reconstruction on residual upper limb function in breast cancer survivors. Breast Cancer Res Treat. 2020;182(3):531–41. https://doi.org/10.1007/s10549-020-05717-z.
12. Nesvold IL, Dahl AA, Lokkevik E, Marit Mengshoel A, Fossa SD. Arm and shoulder morbidity in breast cancer patients after breast-conserving therapy versus mastectomy. Acta Oncol (Stockholm, Sweden). 2008;47(5):835–42. https://doi.org/10.1080/02841860801961257.
13. Min J, Yeon S, Ryu J, Kim JY, Yang EJ, Il Kim S, et al. Shoulder function and health outcomes in newly diagnosed breast cancer patients receiving surgery: a prospective study. Clin Breast Cancer. 2023;23(4):e247–e58. https://doi.org/10.1016/J.CLBC.2023.03.001.
14. McNeely ML, Courneya KS, Al Onazi MM, Wharton S, Wang Q, Dickau L, et al. Upper Limb Morbidity in Newly Diagnosed Individuals After Unilateral Surgery for Breast Cancer: Baseline Results from the AMBER Cohort Study. Ann Surg Oncol. 2023;30(13):8389–97. https://doi.org/10.1245/s10434-023-14316-3.
15. Cardoso F, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rubio IT, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2019;30(10):1674. https://doi.org/10.1093/annonc/mdz189.
16. Min J, Kim JY, Yeon S, Ryu J, Min JJ, Park S, et al. Change in Shoulder Function in the Early Recovery Phase after Breast Cancer Surgery: A Prospective Observational Study. J Clin Med. 2021;10(15):3416. https://doi.org/10.3390/jcm10153416.
17. Bruce J, Mazuquin B, Canaway A, Hossain A, Williamson E, Mistry P, et al. Exercise versus usual care after non-reconstructive breast cancer surgery (UK PROSPER): multicentre randomised controlled trial and economic evaluation. BMJ (Clin res ed). 2021:e066542. https://doi.org/10.1136/bmj-2021-066542.
18. De Almeida Rizzi SKL, Haddad CAS, Giron PS, Figueira PVG, Estevão A, Elias S, et al. Early Free Range-of-Motion Upper Limb Exercises After Mastectomy and Immediate Implant-Based Reconstruction Are Safe and Beneficial: A Randomized Trial. Ann Surg Oncol. 2020;27(12):4750–9. https://doi.org/10.1245/s10434-020-08882-z.
19. Rizzi S, Haddad CAS, Giron PS, Figueira PVG, Estevao A, Elias S, et al. Exercise Protocol With Limited Shoulder Range of Motion for 15 or 30 Days After Conservative Surgery for Breast Cancer With Oncoplastic Technique: A Randomized Clinical Trial. Am J Clin Oncol. 2021;44(6):283–90. https://doi.org/10.1097/COC.0000000000000811.
20. Klein I, Kalichman L, Chen N, Susmallian S. Effect of physical activity levels on oncological breast surgery recovery: a prospective cohort study. Sci Rep. 2021;11(1):10432. https://doi.org/10.1038/s41598-021-89908-8.
21. Kim KH, Yeo SM, Cheong IY, Kim Y, Jeon BJ, Hwang JH. Early Rehabilitation after Total Mastectomy and Immediate Reconstruction with Tissue Expander Insertion in Breast Cancer Patients: A Retrospective Case-control Study. J Breast Cancer. 2019;22(3):472. https://doi.org/10.4048/jbc.2019.22.e40.
22. Yang A, Sokolof J, Gulati A. The effect of preoperative exercise on upper extremity recovery following breast cancer surgery: a systematic review. Int J Rehabil Res. 2018;41(3):189–96. https://doi.org/10.1097/MRR.0000000000000288.
23. Klifto KM, Elhelali A, Payne RM, Cooney CM, Manahan MA, Rosson GD. Perioperative systemic nonsteroidal anti-inflammatory drugs (NSAIDs) in women undergoing breast surgery. Cochrane Database Syst Rev. 2021;11(11):CD013290. https://doi.org/10.1002/14651858.CD013290.pub2.
24. Park S, Park J, Choi JW, Bang YJ, Oh EJ, Park J, et al. The efficacy of ultrasound-guided erector spinae plane block after mastectomy and immediate breast reconstruction with a tissue expander: a randomized clinical trial. The Korean J Pain. 2021;34(1):106–13. https://doi.org/10.3344/kjp.2021.34.1.106.
25. Lang AE, Milosavljevic S, Dickerson CR, Trask CM, Kim SY. Evidence of rotator cuff disease after breast cancer treatment: scapular kinematics of post-mastectomy and post-reconstruction breast cancer survivors. Ann Med. 2022;54(1):1058–66. https://doi.org/10.1080/07853890.2022.2065026.
26. Stubblefield MD. Radiation fibrosis syndrome: neuromuscular and musculoskeletal complications in cancer survivors. PM R. 2011;3(11):1041–54. https://doi.org/10.1016/j.pmrj.2011.08.535.
27. Lang AE, Dickerson CR, Kim SY, Stobart J, Milosavljevic S. Impingement pain affects kinematics of breast cancer survivors in work-related functional tasks. Clin Biomech (Bristol, Avon). 2019;70:223–30. https://doi.org/10.1016/j.clinbiomech.2019.10.001.
28. Chang PJ, Asher A, Smith SR. A Targeted Approach to Post-Mastectomy Pain and Persistent Pain following Breast Cancer Treatment. Cancers (Basel). 2021;13(20) https://doi.org/10.3390/cancers13205191.
29. Kim JH, Kim SH, Kim H-R, Lee S-H, Yoon SY, Yang J-H, et al. Ultrasonographic evaluation of chronic shoulder pain after breast cancer surgery: single center, cross-sectional study. Sci Rep. 2020;10(1) https://doi.org/10.1038/s41598-020-73769-8.
30. Hippensteel KJ, Brophy R, Smith MV, Wright RW. A Comprehensive Review of Physical Examination Tests of the Cervical Spine, Scapula, and Rotator Cuff. J Am Acad Orthop Surg. 2019;27(11):385–94. https://doi.org/10.5435/JAAOS-D-17-00090.
31. Lafrance S, Charron M, Roy JS, Dyer JO, Fremont P, Dionne CE, et al. Diagnosing, Managing, and Supporting Return to Work of Adults With Rotator Cuff Disorders: A Clinical Practice Guideline. J Orthop Sports Phys Ther. 2022;52(10):647–64. https://doi.org/10.2519/jospt.2022.11306.
32. Eymard F, Ornetti P, Maillet J, Noel É, Adam P, Legré-Boyer V, et al. Intra-articular injections of platelet-rich plasma in symptomatic knee osteoarthritis: a consensus statement from French-speaking experts. Knee Surgery Sports Traumatol Arthros. 2021;29(10):3195–210. https://doi.org/10.1007/s00167-020-06102-5.
33. Yuan X, Gellhorn AC. Platelet-Rich Plasma. In: Cooper G, Herrera J, Kirkbride J, Perlman Z, editors. Regenerative Medicine for Spine and Joint Pain. 1st ed. Springer International Publishing; 2020. p. 55–86. https://doi.org/10.1007/978-3-030-42771-9.
34. Marco E, Trépanier G, Chang E, Mauti E, Jones JM, Zhong T. Postmastectomy Functional Impairments. Curr

Oncol Rep. 2023;25(12):1445–53. https://doi.org/10.1007/s11912-023-01474-6.
35. Wong CJ, Tay MRJ, Aw HZ. Prevalence and Risk Factors of Adhesive Capsulitis in Asian Breast Cancer Patients Undergoing an Outpatient Community Cancer Rehabilitation Program. Arch Phys Med Rehabil. 2021;102(5):843–8. https://doi.org/10.1016/j.apmr.2020.10.105.
36. Aboelnour NH, Kamel FH, Basha MA, Azab AR, Hewidy IM, Ezzat M, et al. Combined effect of graded Thera-Band and scapular stabilization exercises on shoulder adhesive capsulitis postmastectomy. Support Care Cancer. 2023;31(4):215. https://doi.org/10.1007/s00520-023-07641-6.
37. Challoumas D, Biddle M, McLean M, Millar NL. Comparison of Treatments for Frozen Shoulder: A Systematic Review and Meta-analysis. JAMA Netw Open. 2020;3(12):e2029581. https://doi.org/10.1001/jamanetworkopen.2020.29581.
38. Redler LH, Dennis ER. Treatment of Adhesive Capsulitis of the Shoulder. J Am Acad Orthop Surg. 2019;27(12):e544–e54. https://doi.org/10.5435/JAAOS-D-17-00606.
39. Haider SI, Awais MZ, Iqbal MT. Role of Platelet-Rich Plasma in the Treatment of Adhesive Capsulitis: A Prospective Cohort Study. Cureus. 2022;14(10):e30542. https://doi.org/10.7759/cureus.30542.
40. Cathcart-Rake EJ, Ruddy KJ. Evidence-Based Guidance for Breast Cancer Survivorship. Hematol Oncol Clin North Am. 2023;37(1):225–43. https://doi.org/10.1016/j.hoc.2022.08.019.
41. Beckwee D, Leysen L, Meuwis K, Adriaenssens N. Prevalence of aromatase inhibitor-induced arthralgia in breast cancer: a systematic review and meta-analysis. Support Care Cancer. 2017;25(5):1673–86. https://doi.org/10.1007/s00520-017-3613-z.
42. Christensen HS. Aromatase Inhibitor Musculoskeletal Syndrome and Bone Loss: a Review of the Current Literature. Curr Oncol Rep. 2023;25(7):825–31. https://doi.org/10.1007/s11912-023-01413-5.
43. Gupta A, Henry NL, Loprinzi CL. Management of Aromatase Inhibitor–Induced Musculoskeletal Symptoms. JCO Oncol Pract. 2020;16(11):733–9. https://doi.org/10.1200/op.20.00113.
44. Menas P, Merkel D, Hui W, Lawton J, Harper A, Carro G. Incidence and management of arthralgias in breast cancer patients treated with aromatase inhibitors in an outpatient oncology clinic. J Oncol Pharm Pract. 2012;18(4):387–93. https://doi.org/10.1177/1078155211434853.
45. Tenti S, Correale P, Cheleschi S, Fioravanti A, Pirtoli L. Aromatase Inhibitors—Induced Musculoskeletal Disorders: Current Knowledge on Clinical and Molecular Aspects. Int J Mol Sci. 2020;21(16):5625. https://doi.org/10.3390/ijms21165625.
46. Grigorian N, Baumrucker SJ. Aromatase inhibitor–associated musculoskeletal pain: An overview of pathophysiology and treatment modalities. SAGE Open Med. 2022;10:205031212210787. https://doi.org/10.1177/20503121221078722.
47. Hyder T, Marino CC, Ahmad S, Nasrazadani A, Brufsky AM. Aromatase Inhibitor-Associated Musculoskeletal Syndrome: Understanding Mechanisms and Management. Front Endocrinol. 2021:12. https://doi.org/10.3389/fendo.2021.713700.
48. Niravath P. Aromatase inhibitor-induced arthralgia: a review. Ann Oncol. 2013;24(6):1443–9. https://doi.org/10.1093/annonc/mdt037.
49. Jerusalem G, Farah S, Courtois A, Chirgwin J, Aebi S, Karlsson P, et al. Continuous versus intermittent extended adjuvant letrozole for breast cancer: final results of randomized phase III SOLE (Study of Letrozole Extension) and SOLE Estrogen Substudy. Ann Oncol. 2021;32(10):1256–66. https://doi.org/10.1016/j.annonc.2021.07.017.
50. Bae K, Lamoury G, Carroll S, Morgia M, Lim S, Baron-Hay S, et al. Comparison of the clinical effectiveness of treatments for aromatase inhibitor-induced arthralgia in breast cancer patients: A systematic review with network meta-analysis. Crit Rev Oncol Hematol. 2023;181:103898. https://doi.org/10.1016/j.critrevonc.2022.103898.
51. Boing L, Vieira MCS, Moratelli J, Bergmann A, Guimaraes ACA. Effects of exercise on physical outcomes of breast cancer survivors receiving hormone therapy - A systematic review and meta-analysis. Maturitas. 2020;141:71–81. https://doi.org/10.1016/j.maturitas.2020.06.022.
52. Lu G, Zheng J, Zhang L. The effect of exercise on aromatase inhibitor-induced musculoskeletal symptoms in breast cancer survivors :a systematic review and meta-analysis. Support Care Cancer. 2020;28(4):1587–96. https://doi.org/10.1007/s00520-019-05186-1.
53. Baglia ML, Lin IH, Cartmel B, Sanft T, Ligibel J, Hershman DL, et al. Endocrine-related quality of life in a randomized trial of exercise on aromatase inhibitor–induced arthralgias in breast cancer survivors. Cancer. 2019;125(13):2262–71. https://doi.org/10.1002/cncr.32051.
54. Roberts KE, Rickett K, Feng S, Vagenas D, Woodward NE. Exercise therapies for preventing or treating aromatase inhibitor-induced musculoskeletal symptoms in early breast cancer. Cochrane Database Syst Rev. 2020;2020(1) https://doi.org/10.1002/14651858.cd012988.pub2.
55. Henry NL, Unger JM, Schott AF, Fehrenbacher L, Flynn PJ, Prow DM, et al. Randomized, Multicenter, Placebo-Controlled Clinical Trial of Duloxetine Versus Placebo for Aromatase Inhibitor-Associated Arthralgias in Early-Stage Breast Cancer: SWOG S1202. J Clin Oncol. 2018;36(4):326–32. https://doi.org/10.1200/JCO.2017.74.6651.
56. Santa-Maria CA, Bardia A, Blackford AL, Snyder C, Connolly RM, Fetting JH, et al. A phase II study evaluating the efficacy of zoledronic acid in prevention of aromatase inhibitor-associated musculoskeletal symptoms: the ZAP trial. Breast Cancer Res Treat. 2018;171(1):121–9. https://doi.org/10.1007/s10549-018-4811-1.
57. Traish A, Bolanos J, Nair S, Saad F, Morgentaler A. Do Androgens Modulate the Pathophysiological Pathways of Inflammation? Appraising the Contemporary Evidence. J Clin Med. 2018;7(12):549. https://doi.org/10.3390/jcm7120549.
58. Anand K, Niravath P. Acupuncture and Vitamin D for the Management of Aromatase Inhibitor-Induced Arthralgia. Curr Oncol Rep. 2019;21(6) https://doi.org/10.1007/s11912-019-0795-1.
59. Greenlee H, Crew KD, Shao T, Kranwinkel G, Kalinsky K, Maurer M, et al. Phase II study of glucosamine with chondroitin on aromatase inhibitor-associated joint symptoms in women with breast cancer. Support Care Cancer. 2013;21(4):1077–87. https://doi.org/10.1007/s00520-012-1628-z.
60. Alturki NA. Review of the immune checkpoint inhibitors in the context of cancer treatment. J Clin Med. 2023;12(13):4301.
61. Ghosh N, Tiongson MD, Stewart C, Chan KK, Jivanelli B, Cappelli L, et al. Checkpoint Inhibitor-Associated Arthritis: A Systematic Review of Case Reports and Case Series. J Clin Rheumatol. 2021;27(8):e317–e22. https://doi.org/10.1097/RHU.0000000000001370.
62. Cappelli LC, Gutierrez AK, Bingham CO 3rd, Shah AA. Rheumatic and Musculoskeletal Immune-Related Adverse Events Due to Immune Checkpoint Inhibitors: A Systematic Review of the Literature. Arthritis Care Res (Hoboken). 2017;69(11):1751–63. https://doi.org/10.1002/acr.23177.
63. Kostine M, Truchetet M-E, Schaeverbeke T. Clinical characteristics of rheumatic syndromes associated with checkpoint inhibitors therapy. Rheumatology. 2019;58(Supplement_7):vii68–74. https://doi.org/10.1093/rheumatology/kez295.

64. Suarez-Almazor ME, Pundole X, Abdel-Wahab N, Johnson DB, Gupta D, Glezerman I, et al. Multinational Association of Supportive Care in Cancer (MASCC) 2020 clinical practice recommendations for the management of immune-mediated cardiovascular, rheumatic, and renal toxicities from checkpoint inhibitors. Support Care Cancer. 2020;28(12):6159–73. https://doi.org/10.1007/s00520-020-05710-8.
65. Kök M, Schropp L, Van Der Schaaf IC, Vonken E-J, Van Hattum ES, De Borst GJ, et al. Systematic Review on Botulinum Toxin Injections as Diagnostic or Therapeutic Tool in Thoracic Outlet Syndrome. Ann Vasc Surg. 2023;96:347–56. https://doi.org/10.1016/j.avsg.2023.05.009.
66. Ahmed AS, Graf AR, Karzon AL, Graulich BL, Egger AC, Taub SM, et al. Pectoralis minor syndrome – review of pathoanatomy, diagnosis, and management of the primary cause of neurogenic thoracic outlet syndrome. JSES Rev Rep Techniques. 2022;2(4):469–88. https://doi.org/10.1016/j.xrrt.2022.05.008.
67. Harrington SE, Hoffman J, Katsavelis D. Measurement of Pectoralis Minor Muscle Length in Women Diagnosed With Breast Cancer: Reliability, Validity, and Clinical Application. Phys Ther. 2020;100(3):429–37. https://doi.org/10.1093/ptj/pzz174.
68. Seo A, Hwang J-M, Lee J-M, Jung T-D. Changes in Pectoral Muscle Volume During Subacute Period after Radiation Therapy for Breast Cancer: A Retrospective up to 4-year Follow-up Study. Sci Rep. 2019;9(1) https://doi.org/10.1038/s41598-019-43163-0.
69. Ryan C, Stoltzfus KC, Horn S, Chen H, Louie AV, Lehrer EJ, et al. Epidemiology of bone metastases. Bone. 2022;158:115783. https://doi.org/10.1016/j.bone.2020.115783.
70. Lai CC, Chen SY, Yang JL, Lin JJ. Effectiveness of stretching exercise versus kinesiotaping in improving length of the pectoralis minor: A systematic review and network meta-analysis. Phys Ther Sport. 2019;40:19–26. https://doi.org/10.1016/j.ptsp.2019.08.003.
71. Arguello AM, Houdek MT, Barlow JD. Management of Proximal Humeral Oncologic Lesions. Orthop Clin North Am. 2023;54(1):89–100. https://doi.org/10.1016/j.ocl.2022.08.008.
72. Lee DH, Hills JM, Jordanov MI, Jaffe KA. Common Tumors and Tumor-like Lesions of the Shoulder. J Am Acad Orthop Surg. 2019;27(7):236–45. https://doi.org/10.5435/JAAOS-D-17-00449.
73. Voskuil RT, Mayerson JL, Scharschmidt TJ. Management of Metastatic Disease of the Upper Extremity. J Am Acad Orthop Surg. 2021;29(3):e116–e25. https://doi.org/10.5435/JAAOS-D-20-00819.
74. Coleman R, Hadji P, Body JJ, Santini D, Chow E, Terpos E, et al. Bone health in cancer: ESMO Clinical Practice Guidelines. Ann Oncol. 2020;31(12):1650–63. https://doi.org/10.1016/j.annonc.2020.07.019.
75. Keilani M, Kainberger F, Pataraia A, Hasenöhrl T, Wagner B, Palma S, et al. Typical aspects in the rehabilitation of cancer patients suffering from metastatic bone disease or multiple myeloma. Wien Klin Wochenschr. 2019;131(21-22):567–75. https://doi.org/10.1007/s00508-019-1524-3.
76. Crevenna R, Hasenoehrl T, Wiltschke C, Kainberger F, Keilani M. Prescribing Exercise to Cancer Patients Suffering from Increased Bone Fracture Risk Due to Metastatic Bone Disease or Multiple Myeloma in Austria—An Inter- and Multidisciplinary Evaluation Measure. Cancers. 2023;15(4):1245. https://doi.org/10.3390/cancers15041245.
77. Wilk M, Kepski J, Kepska J, Casselli S, Szmit S. Exercise interventions in metastatic cancer disease: a literature review and a brief discussion on current and future perspectives. BMJ Support Palliat Care. 2020;10(4):404–10. https://doi.org/10.1136/bmjspcare-2020-002487.
78. Weller S, Hart NH, Bolam KA, Mansfield S, Santa Mina D, Winters-Stone KM, et al. Exercise for individuals with bone metastases: A systematic review. Crit Rev Oncol Hematol. 2021;166:103433. https://doi.org/10.1016/j.critrevonc.2021.103433.
79. Campbell KL, Cormie P, Weller S, Alibhai SMH, Bolam KA, Campbell A, et al. Exercise Recommendation for People With Bone Metastases: Expert Consensus for Health Care Providers and Exercise Professionals. JCO Oncol Pract. 2022;18(5):e697–709. https://doi.org/10.1200/op.21.00454.
80. Mirels H. Metastatic disease in long bones. A proposed scoring system for diagnosing impending pathologic fractures. Clin Orthop Relat Res. 1989;249:256–64.
81. Rich SE, Chow R, Raman S, Liang Zeng K, Lutz S, Lam H, et al. Update of the systematic review of palliative radiation therapy fractionation for bone metastases. Radiother Oncol. 2018;126(3):547–57. https://doi.org/10.1016/j.radonc.2018.01.003.
82. Lorange JP, Ramirez Garcia Luna J, Grou-Boileau F, Rosenzweig D, Weber MH, Akoury E. Management of bone metastasis with zoledronic acid: A systematic review and Bayesian network meta-analysis. J Bone Oncol. 2023;39:100470. https://doi.org/10.1016/j.jbo.2023.100470.
83. Lo Bianco G, Lanza E, Provenzano S, Federico M, Papa A, Imani F, et al. A Multimodal Clinical Approach for the Treatment of Bone Metastases in Solid Tumors. Anesthesiol Pain Med. 2022;12(3) https://doi.org/10.5812/aapm-126333.
84. Gong Y, Tan Q, Qin Q, Wei C. Prevalence of postmastectomy pain syndrome and associated risk factors: A large single-institution cohort study. Medicine (Baltimore). 2020;99(20):e19834. https://doi.org/10.1097/MD.0000000000019834.
85. Waltho D, Rockwell G. Post–breast surgery pain syndrome: establishing a consensus for the definition of post-mastectomy pain syndrome to provide a standardized clinical and research approach—a review of the literature and discussion. Can J Surg. 2016;59(5):342.
86. Causeret A, Lapegue F, Bruneau B, Dreano T, Ropars M, Guillin R. Painful Traumatic Neuromas in Subcutaneous Fat: Visibility and Morphologic Features With Ultrasound. J Ultrasound Med. 2019;38(9):2457–67. https://doi.org/10.1002/jum.14944.
87. Chappell AG, Yuksel S, Sasson DC, Wescott AB, Connor LM, Ellis MF. Post-Mastectomy Pain Syndrome: An Up-to-Date Review of Treatment Outcomes. JPRAS Open. 2021;30:97–109. https://doi.org/10.1016/j.jpra.2021.07.006.
88. Yuksel SS, Chappell AG, Jackson BT, Wescott AB, Ellis MF. Post Mastectomy Pain Syndrome: A Systematic Review of Prevention Modalities. JPRAS Open. 2022;31:32–49. https://doi.org/10.1016/j.jpra.2021.10.009.
89. Salati SA, Alsulaim L, Alharbi MH, Alharbi NH, Alsenaid TM, Alaodah SA, et al. Postmastectomy Pain Syndrome: A Narrative Review. Cureus. 2023;15(10):e47384. https://doi.org/10.7759/cureus.47384.
90. Kannan P, Lam HY, Ma TK, Lo CN, Mui TY, Tang WY. Efficacy of physical therapy interventions on quality of life and upper quadrant pain severity in women with post-mastectomy pain syndrome: a systematic review and meta-analysis. Qual Life Res. 2022;31(4):951–73. https://doi.org/10.1007/s11136-021-02926-x.
91. Tait RC, Zoberi K, Ferguson M, Levenhagen K, Luebbert RA, Rowland K, et al. Persistent Post-Mastectomy Pain: Risk Factors and Current Approaches to Treatment. J Pain. 2018;19(12):1367–83. https://doi.org/10.1016/j.jpain.2018.06.002.
92. Murugappan A, Khanna A. Interventional Treatment Options for Post-mastectomy Pain. Curr Oncol Rep. 2023;25(10):1175–9. https://doi.org/10.1007/s11912-023-01435-z.
93. DiFrancesco T, Khanna A, Stubblefield MD. Clinical Evaluation and Management of Cancer Survivors with Radiation Fibrosis Syndrome. Semin Oncol Nurs. 2020;36(1):150982. https://doi.org/10.1016/j.soncn.2019.150982.

94. Kline-Quiroz C, Nori P, Stubblefield MD. Cancer Rehabilitation: Acute and Chronic Issues, Nerve Injury, Radiation Sequelae, Surgical and Chemo-Related, Part 1. Med Clin North Am. 2020;104(2):239–50. https://doi.org/10.1016/j.mcna.2019.10.004.
95. Stubblefield MD. Neuromuscular complications of radiation therapy. Muscle Nerve. 2017;56(6):1031–40. https://doi.org/10.1002/mus.25778.
96. Stubblefield MD. Clinical Evaluation and Management of Radiation Fibrosis Syndrome. Phys Med Rehabil Clin N Am. 2017;28(1):89–100. https://doi.org/10.1016/j.pmr.2016.08.003.
97. Karri J, Lachman L, Hanania A, Marathe A, Singh M, Zacharias N, et al. Radiotherapy-Specific Chronic Pain Syndromes in the Cancer Population: An Evidence-Based Narrative Review. Adv Ther. 2021;38(3):1425–46. https://doi.org/10.1007/s12325-021-01640-x.
98. Jones N, Stubblefield MD. Evaluation and Management of Radiation-Induced Plexopathies. Curr Phys Med Rehabil Rep. 2022;10(4):345–54. https://doi.org/10.1007/s40141-022-00374-3.
99. Wang K, Moon DH, Amdur RJ, Dagan R, Sheets NC, Shen CJ, et al. Shoulder symptoms and quality of life impact of limited neck dissection after de-intensified chemoradiotherapy: Secondary analysis of two prospective trials. Head Neck. 2019;41(5):1213–9. https://doi.org/10.1002/hed.25535.
100. Dziegielewski PT, McNeely ML, Ashworth N, O'Connell DA, Barber B, Courneya KS, et al. 2b or not 2b? Shoulder function after level 2b neck dissection: A double-blind randomized controlled clinical trial. Cancer. 2020;126(7):1492–501. https://doi.org/10.1002/CNCR.32681.
101. Barber B, Seikaly H, Ming Chan K, Beaudry R, Rychlik S, Olson J, et al. Intraoperative Brief Electrical Stimulation of the Spinal Accessory Nerve (BEST SPIN) for prevention of shoulder dysfunction after oncologic neck dissection: a double-blinded, randomized controlled trial. J Otolaryngol Head Neck Surg. 2018;47(1):7. https://doi.org/10.1186/s40463-017-0244-9.
102. Kline-Quiroz C, Byrd H, Dovgan J, Lockney N. Pathophysiology of Radiation Fibrosis Syndrome. Curr Phys Med Rehabil Rep. 2023:1–10.
103. Kline-Quiroz C, Fricke B. Molecular and Biologic Targets for Radiation Fibrosis: Implications for Rehabilitation. Curr Phys Med Rehabil Rep. 2021;9(3):127–35. https://doi.org/10.1007/s40141-021-00321-8.
104. Almeida KAM, Rocha AP, Carvas N, Pinto ACPN. Rehabilitation interventions for shoulder dysfunction in patients with head and neck cancer: Systematic review and meta-analysis. Phys Ther. 2020;100(11):1997–2008.
105. Chen Y-H, Liang W-A, Lin C-R, Huang C-Y. A randomized controlled trial of scapular exercises with electromyography biofeedback in oral cancer patients with accessory nerve dysfunction. Support Care Cancer. 2022;30(10):8241–50. https://doi.org/10.1007/s00520-022-07263-4.
106. Jammeh ML, Yang A, Abuirqeba AA, Ohman JW, Thompson RW. Reoperative Brachial Plexus Neurolysis After Previous Anatomically Complete Supraclavicular Decompression for Neurogenic Thoracic Outlet Syndrome: A 10-Year Single-Center Case Series. Oper Neurosurg (Hagerstown). 2022;23(2):125–32. https://doi.org/10.1227/ons.0000000000000252.
107. Gebreyohanes AMH, Ahmed AI, Choi D. Dorsal Root Entry Zone Lesioning for Brachial Plexus Avulsion: A Comprehensive Literature Review. Oper Neurosurg (Hagerstown). 2021;20(4):324–33. https://doi.org/10.1093/ons/opaa447.
108. Korucu TS, Ucurum SG, Tastaban E, Ozgun H, Kaya DO. Comparison of Shoulder-Arm Complex Pain, Function, and Scapular Dyskinesia in Women With and Without Unilateral Lymphedema After Breast Cancer Surgery. Clin Breast Cancer. 2021;21(3):e285–e93. https://doi.org/10.1016/j.clbc.2020.10.008.
109. Montagna G, Barrio AV. Managing the Morbidity: Individualizing Risk Assessment, Diagnosis, and Treatment Options for Upper Extremity Lymphedema. Surg Oncol Clin N Am. 2023;32(4):705–24. https://doi.org/10.1016/j.soc.2023.05.004.
110. McLaughlin SA, Brunelle CL, Taghian A. Breast Cancer-Related Lymphedema: Risk Factors, Screening, Management, and the Impact of Locoregional Treatment. J Clin Oncol. 2020;38(20):2341–50. https://doi.org/10.1200/JCO.19.02896.
111. Koehler L, Haddad T, Hunter D, Tuttle T. Axillary web syndrome following breast cancer surgery: symptoms, complications, and management strategies. Breast Cancer: Targets Ther. 2018;11:13–9. https://doi.org/10.2147/bctt.s146635.
112. Koehler LA, Hunter DW, Blaes AH, Haddad TC. Function, Shoulder Motion, Pain, and Lymphedema in Breast Cancer With and Without Axillary Web Syndrome: An 18-Month Follow-Up. Phys Ther. 2018;98(6):518–27. https://doi.org/10.1093/ptj/pzy010.
113. González-Rubino JB, Vinolo-Gil MJ, Martín-Valero R. Effectiveness of physical therapy in axillary web syndrome after breast cancer: a systematic review and meta-analysis. Support Care Cancer. 2023;31(5) https://doi.org/10.1007/s00520-023-07666-x.
114. Macdonald ER, Amorim NML, Hagstrom AD, Markovic K, Simar D, Ward RE, et al. Evaluating the effect of upper-body morbidity on quality of life following primary breast cancer treatment: a systematic review and meta-analysis. J Cancer Survivors. 2023;2023:1–31. https://doi.org/10.1007/S11764-023-01395-0.
115. Stubblefield MD, Custodio CM. Upper-extremity pain disorders in breast cancer. Arch Phys Med Rehabil. 2006;87(3 Suppl 1):S96–1. https://doi.org/10.1016/j.apmr.2005.12.017.