



Post-mastectomy and post-breast conservation surgery pain syndrome: a review of etiologies, risk prediction, and trends in management

Victor E. Chen¹, Benjamin A. Greenberger¹, Zheng Shi², Shefali Gajjar¹, Wenyin Shi¹, Waleed F. Mourad³, Weisi Yan¹

¹Department of Radiation Oncology, Sidney Kimmel Medical College & Cancer Center at Thomas Jefferson University, Philadelphia, PA, USA;

²Department of Radiation Oncology, The University of Texas Health Science Center at San Antonio, San Antonio, TX, USA; ³Department of Radiation Oncology, University of Kentucky, Lexington, KY, USA

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Correspondence to: Weisi Yan, MD, PhD. Department of Radiation Oncology, Sidney Kimmel College at Jefferson University Hospital, 501 South 54th Street, Philadelphia, PA, 19143, USA. Email: Weisi.Yan@jefferson.edu.

Abstract: Postmastectomy pain syndrome (PMPS) or breast conservation surgery (BCS) pain syndrome could be long-term and lead to disability and impairment on body and social function. The pain syndromes are not uncommon in breast cancer patients. It can affect social, psychological, physical and behavioral aspects of a patient. Surgery, radiation, chemotherapy and psychological factors can all contribute to the development of pain syndromes. Axillary dissection is a strong predictor for pain development. Pain medications, ganglion blocks are typically given to the patient for management. Integrative medicine such as acupuncture and psychological management methods are promising modalities in the management arsenal. In this study, we summarized the up-to-date literature to elucidate the etiology, risk factors and management strategies for PMPS.

Keywords: Etiology; detection; early predictor; acupuncture; narrative medicine

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Introduction

Postmastectomy pain syndrome (PMPS) or breast conservation surgery (BCS) pain syndrome can be a debilitating condition leading to long-term disability for patients that undergo definitive interventions for breast cancer. These conditions are a subset of a larger debilitating issue of persistent pain after breast cancer treatment (PPBCT), which is a common side effect with a prevalence following definitive management of breast cancer as high as 50% (1,2). Patients who experience persistent pain are at greater risk for higher levels of perceived stress, anxiety, and depressive symptoms (1). The causes of upper-extremity pain disorders in breast cancer can be multifactorial,

including cervical radiculopathy, brachial plexopathy, rotator cuff tendonitis, adhesive capsulitis, lateral epicondylitis, and edema related pain, though additionally patients may experience a condition analogous to phantom breast pain and sensation (2). The condition is thought to be a chronic neuropathic pain disorder that is particularly associated with operations removing tissue from the upper outer quadrant of the breast or axilla. The condition can be associated with a burning, stabbing, or electric shock type pain or additional neuropathic features of numbness, hyperpathia, allodynia, or paresthesia at the operative site and ipsilateral arm. As paradigms for surgical treatment of breast cancer and adjuvant therapies have evolved in recent

decades, including the increasing use of breast-conservation surgery and sentinel lymph node biopsy (SLNB) in lieu of mastectomy and improved understanding of when surgical procedures with additional potential morbidity such as axillary lymph node dissection (ALND) may be safely avoided (3-5), it is increasingly necessary to understand the potential morbidities of surgical and nonsurgical modalities for definitive breast cancer treatment.

As such we present here a review of PMPS and BCS pain syndrome including the current understanding regarding the etiology of the disorder, recent studies assessing best known predictors of persistent pain, quality of life studies assessing the impact of pain, as well as new trends in both conventional and alternative strategies for the management of the condition.

Etiology and prevalence

Several risk factors have been identified as contributors to persistent pain >3 months following surgery, including psychosocial factors, age, sex, and genetic factors (6,7). Surgical techniques involving more invasive manipulation within the axilla including complete ALND have been associated with greater upper limb morbidity than SLNB, with associations reported of reduced range of motion at the shoulder, muscle weakness of the arm and hand, increased lymphedema, numbness, and pain (5). A classification scheme for neuropathic pain following breast surgery was proposed by Jung *et al.* (8), taking into account anatomic considerations spanning the typical surgical options for breast cancer, including radical mastectomy, modified radical mastectomy, lumpectomy with ALND, and lumpectomy with SLNB. Of key consideration for risk during procedures involving axillary dissection is the intercostobrachial nerve, which is prone to stretch during retraction or even transected. The telltale symptom of nerve injury would be numbness of the upper inner arm, though few patients present with this. The medial cord of the brachial plexus also gives rise to the cutaneous nerve of the arm, which can be harmed during axillary vein dissection. This injury would lead to sensory loss of the lower medial skin of the upper arm. The neuropathic pain symptoms without associated motor deficit are thought to arise more from damage to nociceptive axons. Jung *et al.* (8) classify neuropathic pain due to surgery, rather than tumor recurrence, radiotherapy, or direct injury into the bins of phantom breast pain, intercostobrachial neuralgia (the classic post-mastectomy pain syndrome), neuroma or scar

related pain (9-11), or other nerve injury pain (outside the distribution of the intercostobrachial nerve) (12). A prospective study of 174 women in Brazil described the incidence of post-mastectomy pain syndrome in their cohort as 52%, with younger women (<40 years) and ALND with 15 nodes excised associated with significantly increased risk of pain syndrome after surgery for breast cancer (relative risk 5.23 with 95% confidence interval, 1.11–24.64) (13). The relative proportion of patients experiencing sensitive alteration in the intercostobrachial distribution appears to be most common, with estimates on the order of 50%, with thoraco-scapular distribution on the order of 25%, and neuroma or phantom breast distribution pain on the order of <5% (14).

Pain mechanisms attributable to radiation include acute radiation dermatitis, damage to nerve fibers, brachial plexopathy, or lymphedema related pain. Concerning breast conservation therapy, both acute and chronic radiation-induced toxicities can modulate late outcomes including cosmetic, function, and pain-related outcomes. A cohort of 159 patients treated in Hannover, Germany was followed for late effects, with 15.1% of patients reporting moderate or severe breast pain and 21.4% reporting moderate or severe pain in the arm or shoulder (15). Breast edema and lymphedema have been found in many studies to be associated with axillary clearance, though in this study chronic shoulder and arm pain was found to be statistically significantly associated with lymphedema of the arm (OR 3.9, $P=0.037$). Radiation dose has also increasingly incorporated the use of tumor cavity boost, with the usual trade-off being a risk of late term fibrosis in order to achieve improved local control, a relationship that has been found to hold across age groups (16,17). Trends have been found toward worsening chronic breast pain associated with the use of boost (OR 1.077, $P=0.060$), though this result has been somewhat inconsistent (15). An appreciation of acute toxicity differences was also pivotal in the recent transition of therapies to incorporate greater dose delivered per fraction. Although initial investigations and reports raised the controversial question of whether pain and functional outcomes would be worse with a hypofractionated course of therapy, randomized data has demonstrated trends toward equivalent or even improved toxicity (18-22). These data have spurred on recent trends toward incorporating improved compliance with hypofractionation for breast conservation therapy in response to ASTRO consensus guidelines (23).

Prevalence reporting of PPBCT has been limited by

the somewhat neglected recognition of the condition, with some authors arguing that the incidence is underreported due to multiple barriers, including anxiety regarding cancer recurrence, fears that pain is inevitable, bothering physicians perceived to be busy, or an overall focus of patients on prioritizing discussions of prognosis/surveillance during limited follow-up visits (14). Before a recent shift in clinical trial design toward patient reported outcomes, estimates regarding incidence of chronic pain relied on such techniques as dedicated phone survey or template forms at time of follow-up. The latter, however, have demonstrated limitations, as one study of French breast cancer survivors demonstrated an incidence of 50% patient reported chronic pain not captured by a standardized World Health Organization Quality of Life (WHOQOL) questionnaire (24). To attempt to get at an estimate of incidence of chronic pain across different treatment types, a large systematic review comprising 177 individual studies and pooling the results of 3,746 post-surgical patients and 15,019 post-RT patients estimated the pain prevalence as 29.8% following surgery and 27.3% following radiation therapy, with inconsistent evidence of improvement in incidence with modern surgical and radiation therapies (7). Pain prevalence was found to be most common following surgery in the breast area, side of the body, axilla, and ipsilateral arm, with four studies specifically included contrasting the pain incidence following ALND and SLNB, with all four studies specifically concluding avoidance of the ALND in favor of SLNB resulting in a reduction in surgical-related morbidity including persistent chronic pain (25-28). One consistent problem in constructing systematic reviews of observational data in this area relate to the inconsistent scales used to grade or assess pain, including standard grade 0-4 CTCAE v3.0 or 4.0 criteria, but alternative publications using qualitative descriptions, Lent-soma, BPI, 11-point NRS, 5 or 6 point Likert, and other measurements that complicate aggregation of data (7).

With the increasing use of systemic agents, including taxanes, platinum agents, and vinca alkaloids on the chemotherapy side and aromatase inhibitors (AI's) on the hormonal therapy side in the treatment of breast cancer, conditions called persistent pain in breast cancer treated with chemotherapy and hormonal therapy (PPBCC and PPBCHT) have been described (14). Compared with the use of tamoxifen, AI's such as anastrozole, letrozole, and exemestane have demonstrated increased disease-free survival benefits, prompting their increasing use as standard of care for adjuvant endocrine therapy in the

setting of estrogen receptor positive early breast cancer (29). Compared with tamoxifen, however, the use of AI's has been associated with increased arthralgias, with figures of AI-related joint pain on the order of 40-50% in the hands, arms, feet, pelvic, and hip bones (30). The etiology of the pain is unknown, though there is some suggestion that the mechanism could be through estrogen depletion itself (31). Reports suggest these symptoms have been implicated in 13-22% of episodes of noncompliance, with unfortunately systematic reviews pointing to little definitive evidence of efficacy of vitamin D, yoga, exercise, acupuncture, omega-3, prednisolone, duloxetine, or other interventions significantly improving AI related arthralgia (32). With the long-term results of NRG Oncology/NSABP B-30 now reported, data from 1,512 patients treated with doxorubicin (A), cyclophosphamide (C), followed by docetaxel (T) (AC- > T regimen), concurrent ACT, or AT in early of peripheral neuropathy on the order of 41.9% are now reported, with AT and ACT regimens associated with less severe long-term peripheral neuropathy incidence compared to AC- > T (33). Also associated with the incidence of worsening neuropathy were pre-existing peripheral neuropathy, older age, obesity, mastectomy, and greater number of positive involved lymph nodes. Similarly, to post-radiation and -surgical persistent pain, studies assessing persistent pain following chemotherapy and hormone therapy have found profound long-term quality of life alterations (34-37).

Predictors of persistent pain

Persistent pain can produce a long-term impact on quality of life for patients undergoing breast cancer surgery. Elucidation of the predictors of persistent pain after breast cancer surgery is important in order to develop prevention and early intervention strategies.

Persistent post-surgical pain (defined as pain >3 months post-surgery) (PPSP) affects approximately 40% of patients. Risk factors for PPSP include the presence of preceding pain, psychosocial factors, age, sex, type of surgery, analgesic used, and genetics (38,39). A large database search reviewed 171 out of 9,077 published studies on persistent pain after breast cancer surgery showed that younger age, radiation therapy, axillary lymph nodes dissection, and acute postoperative pain are factors that are associated with PPSP (7).

ALND has been shown to cause more morbidity than sentinel lymph node biopsies (SLNB) (source needed). In addition to surgery, adjuvant therapies such as radiation and

systemic treatments can also contribute to the development of PPSP. For example, radiation therapy can cause skin reactions, damage nerve fibers, and can cause lymphedema which can all contribute to the development of pain (40). Axillary dissection is being performed less frequently as ACOSOG Z0011 showed sentinel lymph node dissection compared to ALND in patients with early stage breast cancer did not result in inferior survival (41). Thus, a shift towards increased use of SLNB can potentially lead to a decrease in persistent pain (42,43). Acute postoperative pain was managed with patient-controlled analgesia (PCA) and a dedicated acute pain service, this better management of acute pain lead to a decreased rate of chronic postsurgical pain (44).

Some of the risk factors for post-treatment pain syndrome are measurable. Interestingly, when analysis was made to prospectively examine list of risk factors for persistent pain after breast cancer surgery, increased diastolic blood pressure was reported to be associated with reduced pain at 12 months. The inverse relationship between blood pressure and pain was observed before and was believed to be modulated by alpha-2 adrenergic receptors in animal works. Thus, blood pressure might be an interesting indicator for prediction of persistent pain (45).

A current study using over 500 parameters to feed supervised machine learning is able to exclude the possibility of persistent pain with a certainly over 90% (46). This machine learning tool is only partly good for predicting persistent pain. Furthermore, the majority of parameters are pain-related factors, suggesting that this current tool is still focused on using acute pain to predict persistent pain. There is a need for more parameters for machine learning as a tool to accurately predict persistent pain.

Impact of pain in breast cancer patients

The impact of pain is not only limited to a clinical syndrome, but also an important factor in patient's quality of life and well-being. The JACS study revealed a prevalence of 53–70% of musculoskeletal pain in the patient group that had breast cancer related surgery and adjuvant therapy (47).

SF-36, a measure of health-related quality of life, is used in this study. Musculoskeletal pain is noted to have a statistically significant negative association with quality of life such as lower physical functioning, general health, vitality and mental health on the SF-36. This was also reflected on the FACT-G and B, cancer-focused quality of life scales, where women with these pains again reported

lower quality of life.

Chronic pain affects work, general activities and relationships (48). Chronic pain also leads to negative effects on physical, cognitive, and emotional function (49). Majority of studies attribute chronic pain (lasting over 3 months) to neuropathic causes, however, they did not include a detailed review of clinical presentation for the nature or type of pain (50).

Psychological factors such as higher pretreatment trait anxiety, depression, sleep disturbance and perceived stress are shown to be associated with persistent postmastectomy pain (51).

In retrospective studies, persistent post-mastectomy pain is readily associated with psychological factors such as anxiety, depression and stress (52,53). Psychological factors are typically not addressed with traditional pain management strategies. However, there is evidence to suggest improved physician-patient relationships positively impact pain control and quality of life.

Narrative medicine has been shown to decrease pain intensity and improve sense of well-being in cancer patients. During this narrative course, a physician listens to a patient's life picture and applies scientific knowledge to provide individualized management strategies. Furthermore, emotional rapport and support built through patient narrative may improve pain and well-being as shown by the results of a randomized controlled trial in patients with cancer pain (54).

There is also a role for the multidisciplinary team to reduce negative feelings such as anxiety, depression and nurture the patient's capacity to cope with pain by providing emotional support (55). Thus, holistic care which addresses patients' psychological, social and behavioral aspects could influence the patient's post treatment chronic pain issues.

Current management techniques for post-mastectomy and -BCS pain syndrome

A variety of management techniques are currently utilized by healthcare practitioners in order to aid breast cancer survivors in reducing their level of discomfort associated with the side effects of surgical intervention, radiotherapy, and systemic treatment in the months to years following their initial diagnosis and treatment for breast cancer. In a review published by Wijayasinghe *et al.*, neural blockade for treatment of neuropathic pain syndrome following breast cancer surgery was examined (56). As described previously, they attributed pain after breast cancer surgery

to a neuropathic origin, stating that injury to nerves such as the intercostobrachial nerve and intercostal nerve, often inevitable during BCS or mastectomy, was the cause of patient pain and discomfort. This literature review identified seven studies that had previously examined neural blockade techniques. Four of these studies were case series examining intercostal nerve blocks, with fifteen patients total across the four studies (11,57-59). In each one of these papers, the neural blockade was used only as a singular component of the patient's overall pain management strategy, which generally involved further surgical intervention or neurolytic treatment. Therefore, given the small number of patients as well as the fact that intercostal nerve blocks seem to have only been used as a bridge to further, more invasive therapies, it is difficult to conclusively state whether intercostal nerve block serves a role in current management techniques for post breast conservation pain syndrome.

Two other studies evaluated in the review looked at stellate ganglion blocks; a paper by Hoseinzade *et al.* demonstrated that in a group of sixty patients, while this type of nerve block provided statistically significant pain relief, lasting up to 3 months, pain reduction was in fact inferior to administration of gabapentin, 300 mg three times a day (60). Another study evaluating the efficacy of stellate ganglion blocks via both an oblique fluoroscopic approach versus an anterior paratracheal approach demonstrated that both were equally safe and effective in a group of fifty patients, but there was no comparison to other forms of pain management (61). Finally, a single study examining only ten patients who underwent paravertebral neural blockade had a twenty percent success rate in completely eliminating pain at the 5-month follow-up time point (62). Given the low power associated with each of these studies examining nerve blockade and the lack of consistent comparators, it is difficult to make any conclusions on comparing their efficacy to more common techniques such as gabapentin, venlafaxine, and capsaicin.

Smith *et al.* examined the few double-blind, randomized placebo-controlled trials that have been done involving these drugs (63). In a randomized controlled crossover trial of capsaicin versus placebo, capsaicin was demonstrated to be associated with greater pain relief and reduction in sharp, sudden pains, although no reduction in constant pain sensation was identified (64). For chronic pain, gabapentin and venlafaxine have been shown to be effective in randomized clinical trials (65,66). In fact, studies have even been done to examine the effect of pre-operative

administration of gabapentin on reducing immediate post-operative pain as well as long-term pain sensation, but these trials were negative (67-69). Amitriptyline has also been shown to be effective in a randomized controlled crossover trial, but the side effect profile of amitriptyline was demonstrated to be overly burdensome to some patients (70).

New trends in management for post-mastectomy and -BCS pain syndrome

As noted previously, there remain significant challenges in identifying a medication or a procedural intervention such as nerve block that can effectively treat most or all patients with post breast conservation pain syndrome. In some instances, this is due to the lack of large randomized trials assessing their efficacy versus placebo; however, even when these studies have been done, the results have been mixed. Therefore, it should come as no surprise that physicians are looking into new directions to try to treat this increasingly prevalent syndrome. Hershman *et al.* evaluated the effect of acupuncture on joint pains commonly experienced by breast cancer survivors taking AI's and found that there was a statistically significant reduction in joint pain as evaluated by pain inventory scores (71). Most notably, this study also included a "sham acupuncture" arm where acupuncture needles were placed in non-acupuncture points, or locations that were thought to have no effect. In this study of 226 patients, true acupuncture significantly improved pain scores on pain inventory measures as compared to both sham acupuncture and the arm without any intervention at all. However, whether this difference is clinically meaningful is debatable, and other limitations include patient acceptance of nontraditional techniques such as acupuncture and availability of acupuncture, particularly in more rural areas.

A pilot trial was performed in South Korea by Jeong *et al.* evaluating the effectiveness of acupuncture for treatment of peripheral neuropathy, a common side effect of the taxane-based chemotherapy regimen (72). In this single-arm observational study, after twelve acupuncture treatments over four weeks, not only was neuropathic pain reduced on a symptom inventory score, but neural function as evaluated by nerve conduction study also improved in three of seven patients who had abnormal nerve conduction at baseline. Furthermore, there was functional improvement associated with these two findings—on a quality of life questionnaire, patients in the study endorsed improvement in their physical health problems, social functioning,

and perception of their general health after the 4-week acupuncture therapy. Limitations of the study include the sample size and study design (a total of ten participants were enrolled in this single-arm observational trial) as well as the applicability of this Korean study in Western health care environments, where, as noted previously, patient acceptance and availability of acupuncture are more limited. Nevertheless, exploratory studies such as these deserve further investigation given the prevalence of issues such as chemotherapy-induced peripheral neuropathy and arthralgias from hormone therapy for breast cancer treatment.

Conclusions

Early prediction and prevention of pain would be crucial to avoid or decrease the persistent pain in breast patient population. Different methods from current or traditional medical practice have been utilized to cope with pain, and there is an ongoing journey to standardize the best strategies for pain management. What may ultimately be most important, however, is emphasizing the development of a strong physician-patient relationship. Not only will this allow for patients to become more comfortable in expressing their concerns with each treatment modality before, during, and after treatment, but giving physicians a more holistic view of each individual patient will also lend itself to treating the entire body rather than just a pain score (73).

More focus can be given to oft-overlooked psychosocial and spiritual factors that play into each individual patient's perception of pain. As the study of post-breast conservation pain syndrome management continues to evolve and grow, as necessitated by our increasingly effective techniques at treating breast cancer, we must ensure our focus is on "treating the patient" rather than "treating the pain".

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