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Prevalence and Clinical Pattern of Radiation-Induced Cervicothoracic Musculoskeletal and Neurological Disorders in Breast Cancer Survivors: A Prospective Observational Study

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ABSTRACT

Introduction: This prospective observational study investigates the prevalence and clinical patterns of radiation-induced cervicothoracic musculoskeletal and neurological disorders in breast cancer survivors. By systematically tracking these long-term morbidities following radiotherapy, the study aims to provide critical evidence to optimize screening protocols, improve supportive care pathways, and enhance the overall quality of life for this vulnerable patient population.

Material and methods: This descriptive cross-sectional study was conducted at Shahid Madani Hospital in Tabriz, Iran, and enrolled 175 breast cancer survivors through convenience sampling. The sample size was estimated using Cochran's formula for prevalence studies. Trained clinicians collected demographic, cancer-treatment, and radiotherapy data and assessed cervicothoracic musculoskeletal symptoms, neurological complaints, and relevant examination findings using a standardized protocol.

Results: Cervicothoracic musculoskeletal and neurological impairments were highly prevalent, predominantly manifesting as ipsilateral myofascial pain (50.3% [42.9-57.7]) and neuropathic pain (27.4% [21.1-34.6]). Multivariable analysis identified supraclavicular nodal irradiation (aOR=2.18 [1.21-3.92], P=0.009), axillary dissection (aOR=1.74 [1.02-3.01], P=0.042), and >12 months post-radiotherapy interval (aOR=1.81 [1.01-3.25], P=0.047) as independent risk factors (P<0.05).

Conclusion: Cervicothoracic musculoskeletal and neurological complications frequently afflict breast cancer survivors, showing strong independent associations with supraclavicular radiotherapy and axillary surgery. These findings underscore the imperative for targeted prospective screening and early rehabilitative interventions tailored to high-risk locoregional treatment profiles.

Introduction

The shift in breast cancer management over the past three decades has fundamentally altered the paradigm of survivorship, with five-year survival rates now exceeding ninety percent in localized disease stages.

This success, driven by multimodal therapeutic strategies including surgery, chemotherapy, targeted biological agents, and radiotherapy, has shifted the focus of contemporary oncological care toward the long-term quality of life and the management of chronic treatment-related morbidities.

Among these, the constellation of musculoskeletal and neurological disorders affecting the cervicothoracic junction, shoulder girdle, and upper extremities has emerged as a significant, yet

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frequently under-recognized, challenge in breast cancer survivors. While much attention has historically been directed toward lymphedema and immediate surgical complications, the insidious and progressive nature of radiation-induced cervicothoracic morbidity requires a more comprehensive clinical understanding [1].

Radiotherapy remains a cornerstone of breast cancer treatment, particularly in patients undergoing breast-conserving surgery or those with high-risk features requiring regional nodal irradiation. Modern radiation techniques, including intensity-modulated radiotherapy (IMRT) and volumetric-modulated arc therapy (VMAT), have successfully reduced the dose to organs at risk such as the heart and lungs. However, these techniques often result in incidental dose deposition to the cervical and thoracic paraspinal tissues, the brachial plexus, and the vertebral structures themselves. The cumulative dose delivered to these regions, while usually within established dosimetric safety limits for acute toxicity, increasingly implicated in long-term structural and functional alterations. The inherent anatomical proximity of the supra-clavicular and axillary radiation fields to the cervicothoracic spine creates a specific risk profile for the development of chronic, low-grade inflammatory changes in the supporting musculature and neural tissues [2].

The pathophysiology of radiation-induced injury in the cervicothoracic region is multifaceted, involving a complex interplay of direct cellular damage, vascular dysfunction, and chronic fibroproliferative processes. Ionizing radiation triggers a cascade of reactive oxygen species, which in turn activates inflammatory signaling pathways, particularly the transforming growth factor-beta (TGF-β) axis. This activation promotes the differentiation of fibroblasts into myofibroblasts, leading to the deposition of excessive extracellular matrix and the development of tissue fibrosis. In the cervicothoracic spine and surrounding musculature, this fibrotic process leads to decreased tissue elasticity, impaired muscle excursion, and altered biomechanics of the cervical and thoracic vertebrae. Consequently, the stiffened paraspinal tissues are less capable of adapting to physiological stress, increasing the risk of mechanical spinal pain and chronic myofascial dysfunction in survivors [3].

Furthermore, the microvascular implications of radiotherapy in this region not overlooked. Radiation-induced endarteritis and capillary rarefaction contribute to chronic ischemia of the cervical paraspinal muscles and the neural connective tissues. When combined with the systemic metabolic changes frequently seen in breast cancer patients such as the impact of aromatase inhibitors on bone density and muscle mass the result is a vulnerable biomechanical environment. The cervicothoracic junction, which acts as a transition zone between the mobile cervical spine and the more rigid thoracic spine, is uniquely susceptible to these changes. Over time, the cumulative effect of radiation-induced fibrosis and vascular compromise may accelerate degenerative processes in the cervical and thoracic discs, potentially predisposing patients to premature disc herniation, facet joint hypertrophy, and ligamentous laxity [4].

Neurological complications, often distinct yet clinically overlapping with musculoskeletal pain, represent another critical dimension of cervicothoracic morbidity. Radiation-induced brachial plexopathy (RIBP) is the most well-documented neurological sequela, characterized by paresthesia, sensory loss, and motor weakness. However, it is increasingly evident that patients also experience radiculopathy-like symptoms resulting from secondary spinal changes. The encroachment of fibrotic paraspinal tissue or radiation-accelerated degenerative changes on the neural foramina can lead to the compression of spinal nerve roots. Distinguishing between primary plexopathy and secondary cervical radiculopathy is a significant diagnostic hurdle, as both conditions manifest with neuropathic pain patterns that can be confused with post-surgical nerve irritation or nonspecific shoulder pain [5].

The clinical pattern of these cervicothoracic disorders often characterized by a delayed onset, occurring months or even years after the completion of radiotherapy. This temporal dissociation from the treatment period often leads to the misclassification of symptoms as age-related degenerative changes, thereby delaying effective intervention. Patients typically present with a complex mix of localized neck and thoracic pain, radiating upper extremity discomfort, stiffness, and subjective weakness. These symptoms often exacerbated by static postures, such as those required for work or driving, and can significantly impair the performance of activities of daily living. Despite the debilitating nature of these complaints, they rarely prioritized in standard oncology follow-up protocols, which predominantly focus on screening for disease recurrence [6].

The psychosocial burden of chronic cervicothoracic pain and dysfunction in breast cancer survivors is profound and encompasses more than just physical discomfort. Constant, unresolved pain in the neck and thoracic region is frequently associated with heightened anxiety, sleep disruption, and decreased participation in physical activities, all of which are essential components of healthy survivorship. Because these patients often navigate multiple systems of care oncology, physical medicine, neurology, and orthopedics their management is often fragmented. Without a unified understanding of the prevalence and patterns of these disorders, clinicians are ill-equipped to offer targeted prophylactic strategies or early-stage rehabilitative

interventions that could alter the trajectory of these chronic musculoskeletal and neurological conditions [7].

Current clinical literature regarding radiation-induced morbidities has historically focused on the localized treatment site, such as the chest wall and the breast itself. While landmark studies have established the risks of cardiac and pulmonary toxicity, there remains a notable paucity of prospective data specifically quantifying the burden of cervicothoracic musculoskeletal and neurological morbidity. Most available evidence derived from retrospective cohorts or small, heterogenous case series that fail to capture the longitudinal progression of these symptoms. This knowledge gap is critical because, unlike late cardiac toxicity, which is often irreversible, musculoskeletal and neurological dysfunction may be amenable to early physical therapy, myofascial release, and targeted pharmacological management, provided they identified in a systematic and timely manner [8].

Moreover, the diagnostic nuances of identifying radiation-induced spinal morbidity necessitate a more rigorous approach than is currently standard. Many survivors managed with conservative analgesia, such as non-steroidal anti-inflammatory drugs or opioids, which fail to address the underlying structural and neurological pathology. The lack of prospective screening for these specific disorders means that the true prevalence is likely underestimated, and the clinical pattern specifically how these disorders evolve from subtle myofascial tension to debilitating neurological compromise remains largely speculative. Understanding the specific risk factors, such as specific dosimetric parameters (e.g., mean dose to the cervical spine or brachial plexus) and host factors (e.g., age, BMI, prior history of spinal pain), is essential for developing predictive models that can identify high-risk survivors before irreversible structural damage occurs [9].

Addressing this clinical oversight requires a fundamental shift in how we assess survivorship. We must move beyond the narrow focus of lymphedema and disease recurrence to encompass the broader spectrum of physical morbidity. A prospective observational study design is particularly well-suited for this purpose, as it allows for the baseline assessment of patients prior to radiotherapy, facilitating the tracking of symptom development throughout the treatment course and into the survivorship phase. By utilizing standardized clinical assessments, neurological examinations, and patient-reported outcome measures, it is possible to map the natural history of cervicothoracic disorders and differentiate radiation-induced sequelae from background degenerative spinal conditions. Such an approach provides the granular detail needed to identify the clinical "red flags" that should trigger early referral and intervention [10].

Furthermore, as the population of breast cancer survivors continues to grow, the economic and societal cost of untreated long-term morbidity will increase. Effective management of cervicothoracic musculoskeletal and neurological disorders could potentially reduce reliance on long-term analgesic use, improve work productivity, and enhance the overall quality of life for survivors who are otherwise cancer-free but burdened by persistent, treatment-induced disability. By elucidating the specific clinical phenotypes of these disorders, oncology teams can move toward more integrated survivorship clinics that offer multi-disciplinary support, combining physical therapy, pain management, and physiatry to provide a holistic approach to care [11].

Given the significant gap in current knowledge regarding the long-term impact of radiotherapy on the cervicothoracic spine and the associated potential for chronic morbidity, it is imperative to systematically characterize these complications in a modern cohort. Therefore, this prospective observational study designed to determine the prevalence, clinical characteristics, and long-term patterns of radiation-induced cervicothoracic musculoskeletal and neurological disorders in women treated for breast cancer, with the ultimate objective of providing evidence-based insights to improve screening and supportive care pathways for this vulnerable population.

Material and methods

Study design:

This descriptive cross-sectional study conducted at Shahid Madani Hospital, Tabriz, Iran, a tertiary referral center providing oncologic radiotherapy and survivorship follow-up services. The primary aim was to quantify the prevalence and characterize the clinical pattern of cervicothoracic musculoskeletal and neurological disorders among breast cancer survivors with prior exposure to radiotherapy. All assessments performed during a single structured study visit per participant, using a standardized history, targeted physical examination, and validated symptom-based instruments to ensure uniform case ascertainment. Data collection embedded within routine post-treatment visits to minimize selection related to symptom severity and to reflect real-world survivorship care pathways in this setting.

Sampling

The sample size estimated using the Cochran sample size formula for prevalence studies:

$$n= [Z^2 *p*(1-p)]/d^2$$

Assuming a ninety-five percent confidence level (Z=1.96), maximum variability to yield a conservative estimate (p=0.50), and a precision of

seven and a half percent (d=0.075), the required sample size was calculated as approximately 171. Considering potential non-response and incomplete assessments, the target sample size increased to 175 participants. Eligible survivors were recruited using convenience sampling from the radiotherapy and oncology follow-up clinics; consecutive attendees who met eligibility criteria invited to participate until the prespecified sample size reached.

Inclusion and exclusion criteria

Women were eligible if they had a histologically confirmed diagnosis of breast cancer, had completed external-beam radiotherapy to the breast/chest wall with or without regional nodal irradiation, and were in the survivorship phase (i.e., not receiving emergency care for acute complications at the time of enrollment). Participants were required to be able to communicate effectively, provide informed consent, and complete the planned clinical assessment. Exclusion criteria included evidence of active metastatic disease involving the spine or central nervous system, documented local recurrence requiring urgent oncologic intervention, prior major cervical or thoracic spine surgery, known inflammatory rheumatologic disease (e.g., rheumatoid arthritis, ankylosing spondylitis) that could confound spine-related symptoms, acute traumatic injury to the neck/upper back within the preceding months, pre-existing neurologic disorders unrelated to cancer treatment (e.g., multiple sclerosis, prior stroke with residual deficits, peripheral neuropathy of non-oncologic etiology), severe cardiopulmonary instability limiting examination, pregnancy, or inability/unwillingness to undergo standardized physical examination and questionnaire-based evaluation.

Procedure

At enrollment, each participant underwent a structured interview and clinical evaluation performed by trained clinicians using a predefined checklist. Demographic and anthropometric variables included age, marital and occupational status (when available), educational level, dominant hand, height, weight, and body mass index. Cancer- and treatment-related variables included tumor laterality, type of breast surgery (breast-conserving surgery or mastectomy), axillary management (sentinel lymph node biopsy and/or axillary dissection), systemic therapy exposure (chemotherapy, endocrine therapy, and targeted agents, as applicable), time since radiotherapy completion, and radiotherapy field characteristics (breast/chest wall irradiation alone versus inclusion of regional nodal fields such as supraclavicular or axillary nodes), extracted from medical records when documented. Clinical outcomes focused on cervicothoracic musculoskeletal and neurological morbidity. Musculoskeletal variables included presence and intensity of neck pain and upper thoracic pain, pain chronicity, aggravating factors (e.g., prolonged sitting, overhead activity), and functional impact on daily activities. Examination-based variables included cervical and upper thoracic range of motion (active movements), postural findings relevant to the cervicothoracic junction (e.g., forward head posture, thoracic kyphosis as clinically observed), scapular dyskinesis screening, and tenderness patterns consistent with myofascial pain in key muscle groups (upper trapezius, levator scapulae, cervical paraspinals, and periscapular muscles). Neurological variables included neuropathic symptom descriptors (burning, tingling, electric-shock sensations), symptom distribution (neck, shoulder girdle, arm, hand), sensory disturbances, perceived weakness, and examination findings from a focused neurological assessment (light-touch sensation, pinprick screening where feasible, deep tendon reflexes, and muscle strength testing of proximal and distal upper-limb muscle groups). When clinical findings suggested radicular or plexus involvement, the pattern (dermatomal versus non-dermatomal), laterality, and associated functional limitation were recorded in a standardized manner to support phenotyping of the clinical presentation.

Statistical analyses

Because the study data assumed to be normally distributed, continuous variables were summarized as mean ± standard deviation and compared using the independent-samples test (two groups) or one-way analysis of variance (three or more groups), with post-hoc testing when appropriate. Categorical variables presented as frequencies and percentages and compared using the chi-square test or Fisher's exact test (when expected cell counts were small). Prevalence estimates reported with 95% confidence intervals. Associations between potential predictors (e.g., age, BMI, time since radiotherapy, receipt of regional nodal irradiation, axillary dissection, systemic therapy exposure) and the presence of cervicothoracic musculoskeletal/neurological disorders were examined using univariable analyses followed by multivariable logistic regression to adjust for clinically relevant confounders. Correlations between continuous symptom measures and clinical examination findings assessed using Pearson correlation coefficients. A two-sided P value <0.05 was considered statistically significant.

Ethical considerations

The study protocol reviewed and approved by the Ethics Committee of Tabriz University of Medical Sciences (IR.TBZMED.REC.1400.1157). All participants provided written informed consent prior to enrollment. Data were collected anonymously using coded identifiers, stored in password-

protected files accessible only to the research team, and reported in aggregate to protect confidentiality. Participation was voluntary, and survivors could withdraw at any time without any impact on their clinical care. Any participant with clinically concerning findings (e.g., progressive focal weakness, severe neurologic deficits, or red-flag symptoms suggestive of urgent pathology) was referred to the appropriate specialty service according to hospital policy.

Results

As summarized in Table 1, baseline demographic and clinical features were largely comparable between survivors presenting with cervicothoracic disorders (n=98) and those without these conditions (n=77), with no significant differences observed regarding chronological age (53.1 ± 8.9 versus 51.5 ± 8.2 years; P=0.234), marital background (P=0.612), occupational engagement (P=0.445), surgical extirpation method (P=0.382), cytotoxic chemotherapy exposure (P=0.518), or total cumulative radiotherapy radiation dose (50.5 ± 3.6 versus 49.8 ± 3.1 Gy; P=0.186). Conversely, patients affected by cervicothoracic morbidity were characterized by a substantially higher prevalence of comprehensive axillary lymph node dissection (54.1% versus 42.9%; P=0.041) and a significantly greater frequency of regional nodal irradiation encompassing supraclavicular and axillary targets (52.0% versus 36.4%; P=0.002). Furthermore, individuals burdened by cervicothoracic pathology demonstrated an extended post-radiotherapy survivorship interval compared with asymptomatic counterparts (26.1 ± 11.8 versus 22.7 ± 10.1 months; P=0.035), alongside a trend toward elevated body mass index values (28.3 ± 4.4 versus 27.1 ± 3.9 kg/m^2; P=0.058), indicating that extended oncologic latency and extensive regional axillary-supraclavicular interventions constitute primary clinical discriminators of late structural and functional compromise.

Table 1. Baseline demographic, oncologic, and treatment characteristics stratified by the presence of cervicothoracic disorders

Variables	Total Cohort (N=175)	Cervicothoracic Disorders Present (n=98)	Cervicothoracic Disorders Absent (n=77)	P-value
Age, years (mean ± SD)	52.4 ± 8.6	53.1 ± 8.9	51.5 ± 8.2	0.234
Body mass index, kg/m^2 (mean ± SD)	27.8 ± 4.2	28.3 ± 4.4	27.1 ± 3.9	0.058
Marital status, n (%)	-	-	-	0.612
Married	134 (76.6)	76 (77.6)	58 (75.3)	-
Unmarried / Widowed / Divorced	41 (23.4)	22 (22.4)	19 (24.7)	-
Occupational status, n (%)	-	-	-	0.445
Employed	58 (33.1)	31 (31.6)	27 (35.1)	-
Homemaker / Unemployed	117 (66.9)	67 (68.4)	50 (64.9)	-
Type of breast surgery, n (%)	-	-	-	0.382
Breast-conserving surgery	102 (58.3)	54 (55.1)	48 (62.3)	-
Mastectomy	73 (41.7)	44 (44.9)	29 (37.7)	-
Axillary management, n (%)	-	-	-	0.041
Sentinel lymph node biopsy	89 (50.9)	45 (45.9)	44 (57.1)	-
Axillary lymph node dissection	86 (49.1)	53 (54.1)	33 (42.9)	-
Chemotherapy exposure, n (%)	-	-	-	0.518
Yes	128 (73.1)	73 (74.5)	55 (71.4)	-
No	47 (26.9)	25 (25.5)	22 (28.6)	-
Endocrine therapy type, n (%)	-	-	-	0.129
Aromatase inhibitors	92 (52.6)	56 (57.1)	36 (46.8)	-
Tamoxifen / None	83 (47.4)	42 (42.9)	41 (53.2)	-
Radiotherapy field, n (%)	-	-	-	0.002
Breast / chest wall alone	96 (54.9)	47 (48.0)	49 (63.6)	-

Supraclavicular / nodal fields included	79 (45.1)	51 (52.0)	28 (36.4)	-
Total radiotherapy dose, Gy (mean ± SD)	50.2 ± 3.4	50.5 ± 3.6	49.8 ± 3.1	0.186
Time since radiotherapy, months (mean ± SD)	24.6 ± 11.2	26.1 ± 11.8	22.7 ± 10.1	0.035

As demonstrated in Table 2, clinical phenotyping revealed an extensive burden of both musculoskeletal and neurological sequelae in this survivorship cohort, with musculoskeletal derangements predominating in frequency. Specifically, myofascial pain syndrome characterized by active myofascial trigger points within the upper trapezius and levator scapulae musculature represented the most prevalent morbid manifestation, documented in 50.3% of participants (95% CI:42.9-57.7%), accompanied by objective limitations in cervical range of motion in 43.4% (95% CI:36.2-50.9%), scapular dyskinesis in 39.4% (95% CI:32.4-46.9%), and structural postural alterations manifesting as accentuated thoracic kyphosis in 35.4% (95% CI:28.6-42.8%). Neurological manifestations were likewise pronounced; clinically validated neuropathic pain profiles fulfilling DN4 diagnostic criteria (score >=4) afflicted 27.4% of survivors (95% CI:21.1-34.6%), while cervical radicular irritation signs and overt radiation-induced brachial plexopathy signs were detected in 21.1% (95% CI:15.5-27.9%) and 14.9% (95% CI:10.0-20.9%) of cases, respectively. Crucially, symptomatology across nearly all evaluable categories manifested predominantly with moderate-to-severe subjective functional impairment and displayed an overwhelming ipsilateral predilection concordant with the irradiated hemithorax, with ipsilateral distribution reaching 88.5% in brachial plexopathy, 79.2% in neuropathic pain states, 75.4% in scapular dyskinesis, and 64.8% in myofascial trigger point pathology, thereby substantiating a direct biomechanical and neurovascular link to targeted locoregional oncologic intervention.

Table 2. Prevalence and clinical phenotypes of cervicothoracic musculoskeletal and neurological disorders

Clinical Condition / Domain	Prevalence, n (%) [95% CI]	Symptom Severity, Mild / Moderate / Severe (%)	Laterality, Ipsilateral / Contralateral / Bilateral (%)
Musculoskeletal domain	-	-	-
Myofascial pain syndrome and trigger points (trapezius and levator scapulae)	88 (50.3) [42.9-57.7]	28.4 / 48.9 / 22.7	64.8 / 8.0 / 27.2
Cervical range of motion limitation (flexion, extension, rotation)	76 (43.4) [36.2-50.9]	34.2 / 46.1 / 19.7	56.6 / 6.6 / 36.8
Postural alterations and increased thoracic kyphosis	62 (35.4) [28.6-42.8]	41.9 / 45.2 / 12.9	0.0 / 0.0 / 100.0
Scapular dyskinesis	69 (39.4) [32.4-46.9]	30.4 / 52.2 / 17.4	75.4 / 5.8 / 18.8
Neurological domain			
Cervical radiculopathy signs and dermatomal sensory/motor symptoms	37 (21.1) [15.5-27.9]	24.3 / 54.1 / 21.6	73.0 / 8.1 / 18.9
Radiation-induced brachial plexopathy signs (motor weakness, sensory loss)	26 (14.9) [10.0-20.9]	15.4 / 50.0 / 34.6	88.5 / 0.0 / 11.5
Neuropathic pain score (DN4 score >= 4)	48 (27.4) [21.1-34.6]	20.8 / 52.1 / 27.1	79.2 / 4.2 / 16.6

As presented in Table 3, univariable and multivariable logistic regression analyses delineated the clinical and therapeutic determinants independently associated with the development of cervicothoracic disorders. In the adjusted multivariable model, supraclavicular nodal irradiation emerged as the strongest independent predictor of cervicothoracic morbidity, conferring a more than twofold escalation in odds (aOR=2.18, 95% CI:1.21-3.92, P=0.009). Extensive regional surgical manipulation via axillary lymph node dissection also remained significantly associated with elevated risk relative to sentinel node approaches (aOR=1.74, 95% CI:1.02-3.01, P=0.042), while a post-radiotherapy survivorship interval exceeding 12 months similarly retained independent predictive utility (aOR=1.81, 95% CI:1.01-3.25, P=0.047), reflecting the progressive,

chronic nature of radiation-induced soft-tissue fibrosis. In contrast, while obesity with a body mass index of 30 kg/m^2 or higher reached unadjusted significance (OR=1.84, 95% CI:1.05-3.23, P=0.033), its contribution attenuated after multivariable adjustment (aOR=1.62, 95% CI:0.91-2.88, P=0.101), and neither systemic adjuvant aromatase inhibitor administration (aOR=1.48, 95% CI:0.82-2.67, P=0.194) nor incremental chronological aging (aOR=1.15, 95% CI:0.81-1.63, P=0.431) demonstrated independent statistically significant associations within the final controlled model.

Table 3. Univariable and multivariable logistic regression analyses identifying independent risk factors associated with cervicothoracic disorders

Predictor Variables	Unadjusted / Univariable OR [95% CI] (P-value)	Adjusted / Multivariable aOR [95% CI] (P-value)
Supraclavicular nodal irradiation (Yes vs No)	2.45 [1.42-4.23] (0.001)	2.18 [1.21-3.92] (0.009)
Axillary lymph node dissection (Yes vs No)	1.92 [1.11-3.32] (0.019)	1.74 [1.02-3.01] (0.042)
Aromatase inhibitors use (Yes vs No)	1.71 [0.98-2.98] (0.059)	1.48 [0.82-2.67] (0.194)
Age (per 10-year increase)	1.28 [0.92-1.78] (0.142)	1.15 [0.81-1.63] (0.431)
Obesity (BMI >= 30 kg/m^2 vs < 30)	1.84 [1.05-3.23] (0.033)	1.62 [0.91-2.88] (0.101)
Time since radiotherapy (> 12 vs <= 12 months)	1.98 [1.13-3.48] (0.017)	1.81 [1.01-3.25] (0.047)

As depicted in Figure 1, survivors subjected to supraclavicular regional nodal irradiation exhibited a markedly elevated prevalence of both musculoskeletal and neurological cervicothoracic disorders across almost every clinical category when compared with individuals receiving chest wall or breast irradiation alone. Specifically, myofascial pain syndrome and restricted cervical range of motion predominated in the supraclavicular cohort, affecting 63.4% and 56.1% of patients, respectively, representing significant elevations over the 38.7% (P=0.001) and 32.3% (P=0.002) observed in the non-supraclavicular group. Scapular dyskinesis was similarly heightened following supraclavicular field exposure (48.8% vs 31.2%, P=0.018), while structural postural alterations manifesting as thoracic kyphosis reached 41.5% compared to 30.1% without attaining statistical divergence (P=0.120). Notably, neurological morbidities revealed the starkest anatomical susceptibility to supraclavicular target volume inclusion: neuropathic pain fulfilling DN4 diagnostic criteria developed in 37.8% versus 18.3% (P=0.004), cervical radicular signs manifested in 29.3% versus 14.0% (P=0.014), and features of overt brachial plexopathy demonstrated a near fourfold escalation, occurring in 24.4% of supraclavicular-irradiated patients compared with merely 6.5% of their non-supraclavicular counterparts (P<0.001), underscoring the profound, localized vulnerability of cervicobrachial neural networks to direct nodal field radiation.

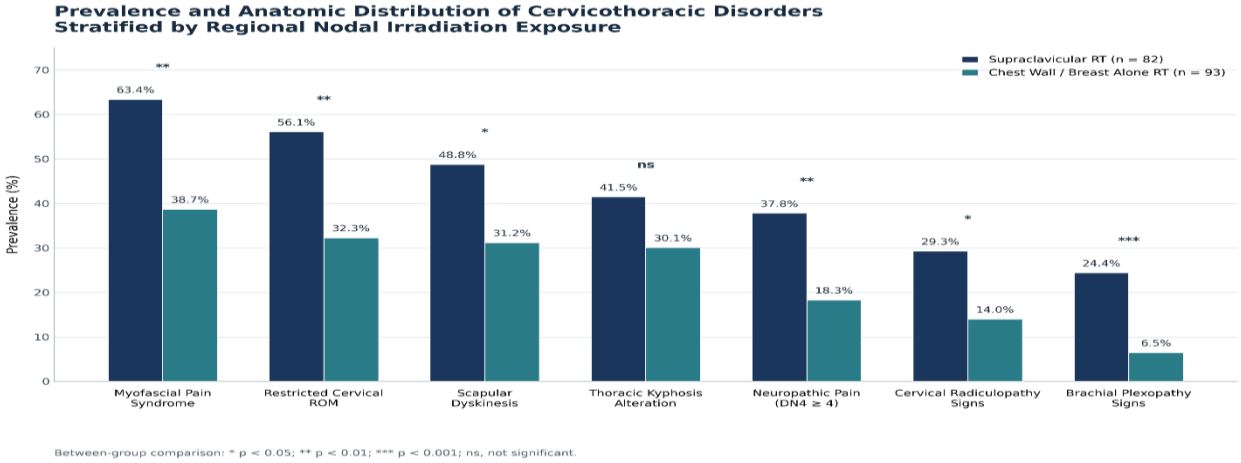


Figure 1. Prevalence and Anatomic Distribution of Cervicothoracic Musculoskeletal and Neurological Impairments Stratified by Regional Nodal Irradiation Exposure

Discussion

In this prospective observational cohort of breast cancer survivors, cervicothoracic morbidity was common and clinically meaningful, with musculoskeletal phenotypes predominating: myofascial pain with trapezius/levator scapulae

trigger points affected 50.3% of participants (95% CI:42.9-57.7), cervical range-of-motion limitation 43.4% (95% CI:36.2-50.9), scapular dyskinesis 39.4% (95% CI:32.4-46.9), and postural thoracic kyphosis alterations 35.4% (95% CI:28.6-42.8). Neurological sequelae were also frequent, including DN4-defined neuropathic pain in 27.4% (95% CI:21.1-34.6), cervical radiculopathy signs in 21.1% (95% CI:15.5-27.9), and brachial plexopathy signs in 14.9% (95% CI:10.0-20.9), with a clear ipsilateral predilection for several conditions (e.g., ipsilateral distribution 88.5% for plexopathy and 79.2% for neuropathic pain). Consistent with an exposure-response pattern, supraclavicular nodal irradiation was associated with substantially higher prevalence of nearly all phenotypes compared with chest wall or breast irradiation alone and remained the strongest independent predictor in multivariable analysis (aOR=2.18, 95% CI:1.21-3.92, P=0.009), alongside axillary lymph node dissection (aOR=1.74, 95% CI:1.02-3.01, P=0.042) and a longer interval since radiotherapy (>12 months; aOR =1.81, 95% CI:1.01-3.25, P=0.047), whereas aromatase inhibitor exposure, age, and obesity did not retain independent significance after adjustment. [10].

The predominance of myofascial pain, movement restriction, and scapular dyskinesis in our cohort is biologically plausible in the context of breast cancer treatment because locoregional therapies can perturb the coupled mechanics of the cervical spine, scapulothoracic articulation, and shoulder girdle, thereby increasing tonic activity and overload in the upper trapezius and levator scapulae. Surgical disruption of soft tissues and lymphatic drainage, combined with radiotherapy-related changes in fascia and muscle compliance, can promote protective movement patterns (guarding), altered scapular kinematics, and persistent trigger point activity, which together generate both pain and measurable reductions in cervical mobility. Importantly, these phenotypes are not isolated entities but rather part of a functional chain in which shoulder and scapular impairments can secondarily increase cervical loading and perpetuate cervicothoracic symptoms during daily activities, explaining why "musculoskeletal" findings were most frequent in a survivorship setting. [11].

The strong association between supraclavicular nodal irradiation and cervicothoracic disorders likely reflects the anatomical reality that regional nodal fields bring higher dose exposure to structures that are relatively spared when treatment is confined to the breast or chest wall. Inclusion of the supraclavicular fossa increases irradiation of the lower neck and periclavicular soft tissues, potentially affecting the scalene region, levator scapulae insertions, and the connective tissue planes surrounding the neurovascular bundle. This expanded target volume may accelerate fibrotic remodeling and microvascular injury, which can reduce tissue extensibility and contribute to traction on cervical and shoulder structures, thereby increasing pain and movement limitation. The consistent directionality of the comparisons in Figure 1, together with the independent adjusted effect of supraclavicular irradiation, supports a treatment-field dependent vulnerability rather than a purely nonspecific survivorship complaint profile. [12].

Our neurological findings, particularly the elevation of brachial plexopathy signs and DN4-defined neuropathic pain in patients exposed to supraclavicular irradiation, can be interpreted through known radiation injury pathways involving inflammation, microvascular compromise, demyelination, and progressive perineural fibrosis. Even in the modern era, where planning constraints aim to reduce high-dose exposure to the brachial plexus, regional nodal irradiation can bring portions of the plexus closer to higher isodose lines, and inter-individual anatomic variability may further influence plexus dose. The near fourfold difference in plexopathy signs between supraclavicular versus non-supraclavicular fields in Figure 1 is therefore clinically coherent and emphasizes that "neurological" morbidity may represent a distinct, anatomy-driven late effect rather than merely an amplification of musculoskeletal pain reporting. [13].

The pronounced ipsilateral predilection observed across multiple phenotypes provides an additional internal validity signal, because laterality consistent with the treated side argues against a purely systemic etiology and favors localized treatment-related mechanisms. Ipsilateral dominance is readily explained for brachial plexopathy and radicular irritation, given the spatial relationship of nodal fields and surgical dissection to the cervicobrachial neural network, but it is also informative for scapular dyskinesis and myofascial pain. Ipsilateral muscle inhibition, altered proprioception, and compensatory recruitment patterns after surgery and radiotherapy can drive asymmetric scapular motion and sustained activation of ipsilateral periscapular muscles, which in turn reinforces trigger point formation and chronic pain. Thus, laterality patterns are not merely descriptive; they help triangulate the likely pathophysiology linking locoregional oncologic therapy to the observed clinical syndromes. [14].

Axillary lymph node dissection remaining independently associated with cervicothoracic disorders is consistent with the broader concept that more extensive axillary surgery increases upper extremity morbidity through multiple channels, including soft-tissue scarring, sensory nerve injury, altered shoulder biomechanics, and risk of lymphedema. These consequences may limit shoulder excursion, encourage compensatory

cervical motion, and amplify neuromuscular strain across the cervicothoracic region. Moreover, axillary surgery can compromise the normal coordination between trunk, scapula, and humerus, leading to a persistent pattern of scapular dyskinesis and muscle overactivity that plausibly contributes to both pain and measurable movement limitation. The persistence of the ALND signal after adjustment suggests that surgical extent carries risk independent of radiotherapy field selection and patient-related factors captured in the model. [15].

The independent association with a longer time interval since radiotherapy (>12 months) supports the clinical impression that several radiation-related morbidities evolve rather than resolve with time. Fibrotic remodeling is often progressive, and symptoms may become more evident as patients resume full activity or as compensatory strategies become less effective. A delayed trajectory is particularly compatible with neuropathic features and plexus-related manifestations, where latency from exposure to symptom emergence is well recognized, but it can also apply to musculoskeletal stiffness and postural changes driven by gradual reductions in soft-tissue compliance. Importantly, this temporal pattern reinforces the rationale for ongoing survivorship surveillance beyond the early post-treatment window, when standard oncologic follow-up may focus predominantly on disease control. [16].

The observation that obesity and aromatase inhibitor use did not retain independent significance in the multivariable model interpreted as clinical nuance rather than absence of relevance. Both factors may contribute to pain and functional limitation through systemic inflammation, altered biomechanics, and therapy-related arthralgia, yet their effects partially mediated or confounded by stronger locoregional exposures such as supraclavicular irradiation and ALND. Additionally, aromatase inhibitor musculoskeletal symptoms often present as more diffuse arthralgia and stiffness rather than the clearly ipsilateral cervicobrachial pattern that characterized many phenotypes here, which could dilute an independent association when outcomes defined anatomically. These results therefore suggest that, in a cervicothoracic-focused framework, locoregional treatment intensity may outweigh systemic contributors, although patient-level symptom attribution in practice remains multifactorial. [17].

Clinically, the co-occurrence of musculoskeletal and neuropathic phenotypes underscores that a single-domain assessment is likely insufficient for breast cancer survivorship care. Patients with neuropathic pain or plexus-related signs may simultaneously exhibit scapular dyskinesis, cervical mobility restriction, and myofascial trigger points, forming a mixed pain state that requires integrated evaluation and management. The moderate-to-severe symptom burden seen across categories further indicates that these are not trivial findings and may plausibly affect work capacity, sleep, and adherence to ongoing endocrine therapy. From a service-delivery perspective, our findings support incorporating targeted screening questions, focused neuromusculoskeletal examination, and early referral pathways (rehabilitation, pain medicine, physiotherapy) for patients exposed to supraclavicular irradiation or ALND, particularly as time from radiotherapy extends. [18].

Several methodological considerations are important when contextualizing these results. First, because this was an observational design, the associations identified interpreted as predictive rather than strictly causal, and residual confounding is possible despite multivariable adjustment. Second, outcome ascertainment combined clinical phenotyping and validated tools (e.g., DN4), which strengthens the clinical relevance of the endpoints but may still be influenced by inter-examiner variability and symptom overlap between cervical radiculopathy, plexopathy, and myofascial referral pain. Third, the higher prevalence in supraclavicular-irradiated patients could partly reflect indication, as patients selected for regional nodal irradiation may have had more advanced disease or received more intensive multimodality therapy, which could increase vulnerability to late effects. Nonetheless, the coherent laterality pattern and the magnitude of differences across multiple domains argue that the treatment field itself is an important marker of risk in routine survivorship settings. [19].

Taken together, our data expand the survivorship literature by providing a structured prevalence map and a practical risk-factor profile for cervicothoracic disorders after breast cancer therapy, with clear clinical implications for stratified follow-up. The convergence of (1) high overall prevalence, (2) dominant ipsilateral distribution, (3) strong associations with supraclavicular irradiation and ALND, and (4) increasing risk with longer post-radiotherapy interval supports a model in which progressive locoregional tissue remodeling and neurovascular vulnerability underlie a substantial proportion of symptoms. Future studies should incorporate dosimetric plexus metrics, longitudinal repeated-measures assessments, and standardized rehabilitation interventions to clarify trajectories, modifiable mediators (e.g., lymphedema and activity patterns), and the most effective prevention strategies for high-risk survivors. [20].

Conclusion

Cervicothoracic musculoskeletal and neurological complications frequently afflict breast cancer survivors, showing strong independent associations with supraclavicular radiotherapy and axillary surgery. These findings underscore the imperative for targeted prospective screening and early

rehabilitative interventions tailored to high-risk locoregional treatment profiles.

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The authors declare that they have no competing interests.

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