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Dual-scale evaluation of pain after hypofractionated post-mastectomy radiotherapy

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ABSTRACT

Background: Post-mastectomy radiotherapy (PMRT) pain encompassing somatic shoulder and chest wall pain (SCWP) and neuropathic pain (NP) is a clinically significant late toxicity following hypofractionated radiotherapy (HFRT) for breast cancer. Limited data exist regarding its incidence, temporal evolution, and determinants across different HFRT regimens.

Objectives: To evaluate the incidence and predictors of SCWP and NP in patients receiving chest wall and regional nodal HFRT, across three HFRT schedules.

Materials and methods: Breast cancer patients were treated with one of three HFRT regimens: 26 Gy in 5 fractions, 34 Gy in 10 fractions, or 40 Gy in 15 fractions. PMRT pain was evaluated using the Common Terminology Criteria for Adverse Events, version 5.0 (CTCAE v5.0) for SCWP, and NP using the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scale. The temporal patterns of both pains were analyzed. Dosimetric parameters of the chest wall (CW), brachial plexus (BP), axillary levels I-III, and supraclavicular fossa (SCF), anatomical parameter (CW thickness), and clinical parameters (age, BMI) were correlated with pain outcomes.

Results: The mean duration of SCWP was 6 months (range, 3-36 months), which was most frequently observed with HFRT-C (40%), followed by HFRT-B (22.9%) and HFRT-A (23.3%) (p=0.09). Patients with Grade≥2 SCWP had significantly thinner CW (p=0.04) and higher CW D_{max} EQD2 values (p=0.04). NP occurred with a mean onset of 12 months (range, 3-24 months) and was most common in HFRT-C (60%), versus 40% in HFRT-A and 28.6% in HFRT-B (p=0.001).On multivariate analysis, Level III axillary dissection (0.049) and higher BP D_{max} EQD2(p=0.001), axillary level III D_{mean} EQD2 (p=0.049) were found to be significant predictors of NP.

Conclusion: HFRT regimen selection and radiation dose distribution significantly influence the incidence and severity of SCWP and NP. Patients with thinner chest walls, higher maximum doses to critical structures, and those undergoing Level III axillary dissection are at greater risk of developing these complications. These findings underscore the importance of refined dose-constraint strategies during HFRT planning to mitigate pain-related morbidity and improve long-term quality of life.

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Introduction

Post-mastectomy radiotherapy (PMRT) pain involving the chest wall (CW), axilla, and upper limb remains one of the most pervasive and functionally debilitating late effects in breast cancer survivors. Following mastectomy and adjuvant radiotherapy (RT), up to 25-60% of patients develop chronic pain that may persist for years, profoundly compromising quality of life and upper-limb function. This persistent PMRT pain constitutes a multifactorial late-toxicity syndrome, originating from the overlap of radiation-induced tissue injury, postoperative musculoskeletal impairment, and neuropathic sensory dysfunction.[1] Both somatic shoulder chest-wall pain (SCWP) and neuropathic pain (NP) frequently coexist in this population, underscoring the heterogeneous nature of PMRT-related pain.[2,3] Radiation-induced chest-wall pain (RICWP) is classically defined as pain originating from irradiated thoracic structures (ribs, intercostal musculature, fascia, subcutaneous tissues), typically presenting months to years after treatment completion.[4,5]

Concurrently, surgical factors, such as sacrifice of the intercostobrachial nerve (ICBN), and the extent of axillary dissection (AD), contribute to neuropathic manifestations, while postoperative musculoskeletal impairments, such as stiffness, reduced strength, and limited range of motion, add functional disability to the clinical picture. RT further exacerbates tissue injury through progressive fibrosis, microvascular compromise, chronic inflammation, and oxidative stress, resulting in reduced tissue compliance, myofascial pain, and impaired shoulder mobility. Dose-dependent injury to the brachial plexus (BP) can manifest as NP, paraesthesia, or upper-limb dysfunction, particularly when BP doses exceed contemporary tolerance thresholds.[6-8]

SCWP may also arise from radiation effects on CW, particularly when a larger irradiated volume is involved. The dose delivered to this region is influenced by factors such as wall thickness, thoracic anatomy, and overall patient morphology. These variables can increase tissue exposure, create dose heterogeneity, and elevate the risk of fibrosis, soft-tissue contracture, and osseous toxicity. Studies consistently demonstrate that increased CW dose directly heightens the risk of chronic pain following hypofractionated radiotherapy (HFRT).[9]

Host-related factors, including younger age, elevated body mass index (BMI), diabetes, and pre-existing pain syndromes, further increase susceptibility to both NP and SCWP. Despite growing recognition of these risk determinants, the contribution of detailed axillary and BP dosimetry, as well as modern CW dose metrics, remains insufficiently characterized for RICWP.[10]

A retrospective cohort study of post-mastectomy patients treated with contemporary HFRT was studied to bridge these knowledge gaps. The primary objective was to observe the incidence of SCWP and NP across the three HFRT regimens and to assess their correlation with patient factors, surgical details, regional nodal doses, and CW anatomy. The overlap of somatic and neuropathic symptoms in PMRT-related pain complicates accurate assessment, with limited evidence differentiating these phenotypes using validated dual-assessment tools in HFRT settings. To address this, a dual evaluation strategy was used: common terminology criteria of adverse events (CTCAE) version 5.0 was used to assess somatic and functional impairments, while LANSS (Leeds Assessment of Neuropathic Symptoms and Signs) scoring identified and quantified neuropathic pain. This combined approach allows precise characterization of both symptom types, enabling a better understanding of the multifactorial nature of persistent PMRT-related pain.

Materials and methods

This retrospective observational cohort study was conducted in the Department of Radiation Oncology, Dr. RPGMC Tanda, from October 2021 to August 2024. The study delineated the incidence and temporal patterns of SCWP and NP. The relationship between regional radiation dose parameters, anatomical, surgical, and clinical factors, and the development of CW pain syndromes in breast cancer patients treated with post-mastectomy radiotherapy (PMRT)was also evaluated.

Study population

Eligible participants were women with histologically confirmed breast carcinoma who underwent modified radical mastectomy (MRM) with AD followed by adjuvant PMRT to CW with regional nodes, availability of complete dosimetric data and planning CT scans, minimum 12-month clinical follow-up, and pain assessments beginning 3 months post RT. Patients were excluded if they had prior ipsilateral breast/thoracic irradiation or developed locoregional recurrence before pain evaluation. Patients received one of the following HFRT regimens: HFRT-A (26 Gy/5 fractions), HFRT-B (34 Gy/10 fractions), or HFRT-C (40 Gy/15 fractions). All patients were treated with 3-dimensional conformal radiotherapy (3D-CRT) with 6 Megavoltage (MV) photons. Treatment planning was performed using the Monaco® treatment planning system (Elekta AB, Stockholm, Sweden). Dose calculation was carried out using MONTE CARLO algorithm by a medical physicist.

Dosimetric, anatomical, and surgical parameters

Dosimetric parameters were derived from each patient's finalized, clinically approved RT plan. BP was contoured in accordance with the Radiation Therapy Oncology Group (RTOG) Brachial Plexus Atlas, and both the maximum dose (BP D_{max}) and mean dose (BP D_{mean}) were recorded (Figure 1A-E). Mean and maximum doses (D_{mean} and D_{max}) of axillary levels I–III and CW were extracted from structures delineated according

to the RTOG Breast Cancer Contouring Atlas (Figure 2A and Figure 2B). All contouring were performed by a single radiation oncologist to ensure uniformity and were independently reviewed by a senior consultant to maintain accuracy and consistency.

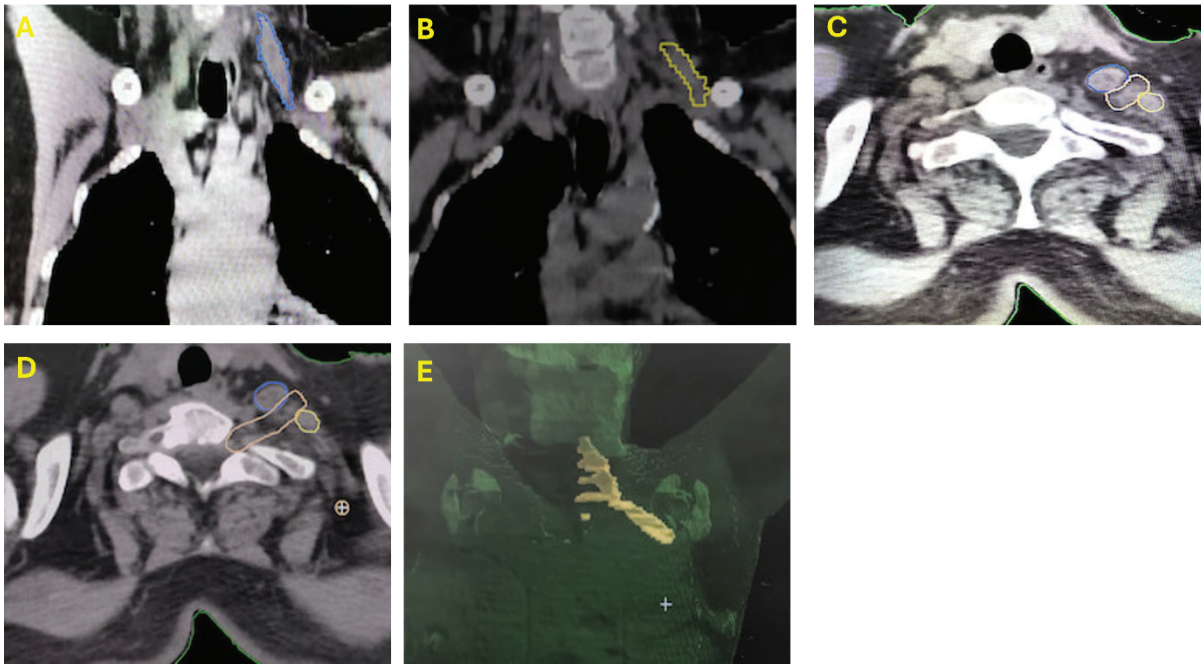

Figure 1. *Brachial plexus contouring per RTOG atlas. A-B: anterior scalene muscle (ASM) in blue color and the middle scalene muscle (MSM) in yellow color were first identified on a coronal view to establish clear anatomical landmarks, C: nerve roots C5-T1 (in dark yellow color) were delineated from each neural foramen into the interscalene space between ASM and MSM, D: when the foramen was not visible, only the scalene fat space was contoured. Below T1, contours followed the plexus posterior to the subclavian-axillary neurovascular bundle to 1-2 slices below the clavicle, E: 3-dimensional view of the contoured BP.*

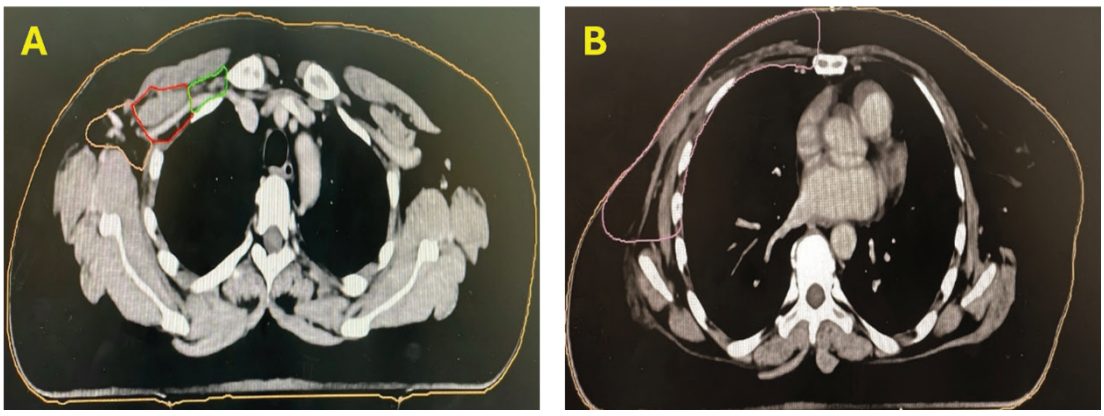

Figure 2. *Contouring of axilla. A: contouring of level I (golden color), level II (red color), and level III (green color), B: contouring of the left-sided chest wall (pink color) according to Breast Cancer RTOG contouring atlas.*

CW thickness was measured from the planning CT dataset at the 2nd and 5th intercostal spaces, including the narrowest and maximum thickness points, mid-axillary line, and mid-clavicular line. To minimize regional variability and obtain a representative value, the average of all recorded measurements was calculated and used for subsequent analysis.

Equivalent dose in 2Gy fractions (EQD2) was calculated for relevant dosimetric parameters using the linear-quadratic model with an α/β ratio of 3Gy for late responding tissues. The maximum dose and mean dose after EQD2 correction were denoted as D_{max} EQD2 and D_{mean} EQD2, respectively, and were used for further assessment.

Surgical factors were derived from intra-operative reports, with the extent of AD categorized according to the highest level removed (up to level II or up to level III) to account for the potential impact of surgical

manipulation on regional neural and soft-tissue integrity. Patient-related clinical characteristics, including age and BMI, were also extracted from medical records. These dosimetric, anatomical, surgical, and clinical parameters were analyzed as potential determinants of NP and SCWP. BP axillary dose parameters and extent of AD were primarily correlated with NP, whereas CW, axillary dose parameters, and CW thickness were evaluated in relation to SCWP.

Outcome assessment

Pain outcomes were assessed using standardized and validated instruments. Somatic shoulder and chest wall pain (SCWP) was evaluated according to CTCAE, version 5.0, and graded on a scale from 0 to 4, with grades ≥2 considered clinically significant. NP was assessed using the LANSS scale, with scores ≥12 indicating clinically significant NP. All pain assessments were conducted by trained personnel who were blinded to the study objectives and protocol to minimize assessment bias. The primary endpoint was the incidence of SCWP and NP. Clinical evaluations were conducted every three months during the first year and every six months thereafter, beginning three months after PMRT, and continued until SCWP reached Grade ≥2 or the LANSS score was ≥12. The correlations between these pains and patient factors (age, BMI), anatomical factors (CW thickness), extent of AD, dosimetric parameters (doses to axillary levels I-III, BP, supraclavicular fossa, and CW) were also analyzed.

Statistical analysis

Descriptive statistics were used to summarize patient, tumor, and treatment characteristics. Categorical variables were compared using the Chi-square or Fisher's exact test. Continuous variables were analyzed with One-way ANOVA, with post-hoc testing where appropriate. Time-to-event outcomes were estimated using the Kaplan-Meier (KM) method, and survival curves were compared using the log-rank test. Factors associated with pain outcomes were evaluated using Cox proportional hazards regression analysis to estimate hazard ratios with 95% confidence intervals. Variables demonstrating $p<0.10$ in univariable testing were included in multivariable models. A two-sided $p<0.05$ was considered statistically significant.

Results

A total of 90 patients met the eligibility criteria and were included in the final analysis. The median age at diagnosis was 54 years (range: 37-80) with a mean BMI of 22.59±2.3 kg/m^2. The median duration of follow-up was 24 months (range,3-36 months). All patients had previously undergone MRM with AD, followed by HFRT to the CW, supraclavicular fossa (SCF), and axillary levels I–III.

Most patients received HFRT B (38.8%), followed by HFRT-A (33.3%) and HFRT-C (27.7%). A 3D-printed tissue equivalent bolus of thickness 3-5 mm was used in patients with CW thickness <10mm (N=12/90), as per institutional protocol to ensure adequate coverage of planning target volume (PTV), given the potential for underdosage in thin CW patients. Bolus was used every other day in HFRT-B and HFRT-C, and daily in HFRT-A. Baseline demographic, anatomical, surgical, and treatment-related characteristics are summarized in Table 1.

Table 1. Patient, tumor, and surgical characteristics.

Characteristics	N
Age (years)	
<50	47
≥50years	43
Stage	
IIB	22
IIIA	33
IIIB	10
IIIC	25
Axillary dissection	
Level I and II	51
Level I, II, and III	39
Chemotherapy	
Yes	65
No	25
Hormonal therapy	
Tamoxifen	35
Letrozole	45
None	10
Radiotherapy	
34 Gy in 10 fractions	35
26 Gy in 5 fractions	30
40 Gy in 15 fractions	25
Histology	
Invasive ductal carcinoma	50
Infiltrating ductal carcinoma	36
Mucinous carcinoma	4
Laterality	
Right	51
Left	39
BMI (kg/m^2)	
<18	35
≥18	55

Somatic shoulder and chest wall pain (SCWP) outcomes

The overall incidence of Grade ≥2 SCWP was 30% (N=27). The incidence varied across HFRT regimens, with the highest frequency observed in HFRT-C (48%), followed by HFRT-A (23.3%), and HFRT-B (22.8%). However, the difference did not reach statistical significance ($p=0.09$).

KM analysis demonstrated a temporal pattern of SCWP occurrence across the three HFRT regimens, with

no statistically significant difference (log rank p=0.098) (Figure 3A). Median onset of SCWP was reached only in the HFRT C at approximately 18 months, while it was not reached in the HFRT B or HFRT C. The mean duration of SCWP was 6 months (range, 3-24 months).

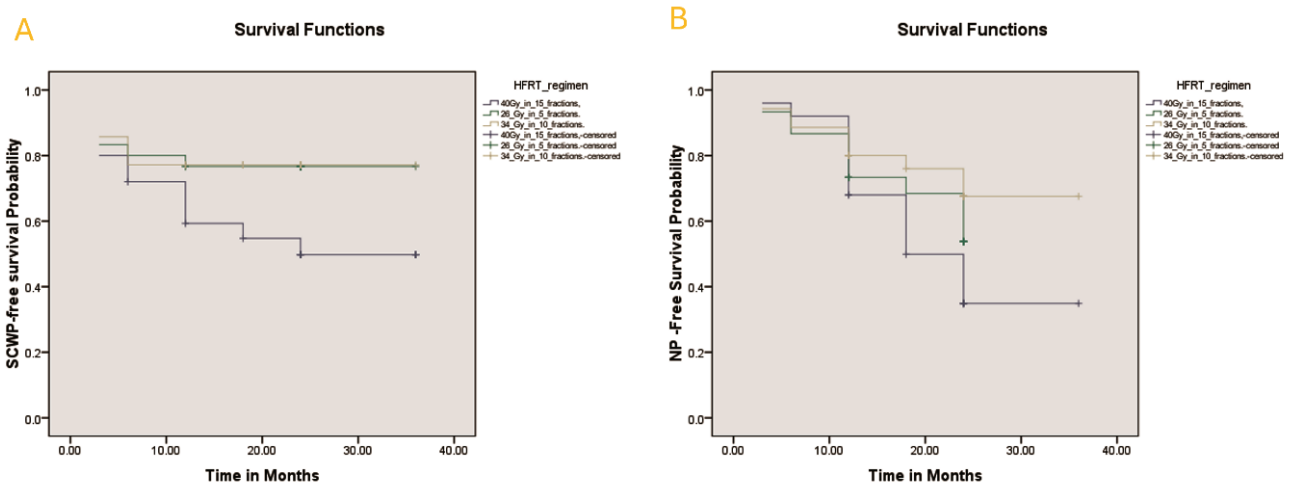

Figure 3. *KM curves. A: SCWP-free survival, B: NP-free survival according to the HFRT regimen. The plot compares Survival outcomes for patients treated with different HFRT regimens:40 Gy in 15 fractions (blue), 26 Gy in 5 fractions (green), and 34 Gy in 10 fractions (golden). ⁺censored observations.*

Patients developing Grade ≥2 SCWP had significantly thinner CW thickness and higher CW D_{max} EQD2.On Cox regression multivariate analysis, CW thickness (HR = 0.895; p = 0.04) and CW D_{max} EQD2(HR 1.45;0.04) were significantly associated with SCWP. No significant correlations were identified between SCWP and BP doses, BMI, age, level of AD, or dosimetry to axillary nodal levels (Table 2).

Table 2. Multivariate Cox regression analysis showing independent predictors of NP following PMRT.

Variable	SCWP (N=27)	NO SCWP (N=63)	HR (95% CI)	*p* value
CW thickness	18.3±8.9 mm	30.15±6.7 mm	0.895 (0.709-0.956	0.04
Mean CW D_{max}EQD2	55.3±1.63 Gy	48.23±1.89	1.456 (1.23-1.567)	0.04
Mean CW D_{mean} EQD2	44.98±2.3 Gy	43.4±1.65	1.12 (0.89-1.23)	0.5
AD level	Level III	Level II	1.01 (0.66-1.4)	0.79
Axillary level II D_{mean} EQD2	49.8±1.45	48.9±1.76	1.02 (0.89-1.2)	0.1
Axillary level III D_{mean} EQD2	51.2±1.89 Gy	50.5±1.3 Gy	1.015 (0.904-1.14)	0.089

Note: HR: hazard ratios, CI: confidence interval, EQD2: equivalent dose in 2 Gy fractions, D_{max}: maximum dose, D_{mean}: mean dose, AD: axillary dissection, SCWP: somatic chest wall and shoulder pain, CW: chest wall.

Neuropathic pain (NP) outcomes

The overall incidence of NP was 41.1% (N=37) with a significantly higher incidence observed in the HFRT C (60%) compared with HFRT A (40%) and HFRT B (28.57%) (p=0.001). KM analysis for time to NP onset demonstrated significant differences among the three HFRT (log rank p=0.01) (Figure 3B). Median onset of NP occurred exclusively in the HFRT C at 18 months. In contrast, HFRT A and HFRT B did not reach a median onset within the follow-up period. The mean duration of onset of NP was 12 months (range, 3-24 months).

NP was significantly associated with higher LANSS scores, AD up to level III, higher BP D_{max}EQD2, and higher axillary level III D_{mean} EQD2. Supraclavicular, chest wall doses, as well as clinical factors including age and BMI, were not significantly associated with NP (Table 3).

Table 3. Multivariate Cox regression analysis showing independent predictors of NP following PMRT.

Variable	NP (N=37)	No NP (N=53)	HR (95% CI)	*p* value
LANSS score	16.37±4.74	7.44±3.76	1.1 (1.08-1.23)	0.002
BP D_{max}EQD	46.85±2.4 Gy	43.26±2.14 Gy	1.08 (1.02-1.15)	0.001
BP D_{mean}EQD2	21.3±4.35 Gy	20.15±3.25 Gy	1.06 (0.75-1.56)	0.2
AD level	Level III	Level II	1.5 (1.3-1.67)	0.049
Axillary level II D_{mean} EQD2	50.5±1.23 Gy	45.03±2.33	1.03 (0.9-1.08)	0.05
Axillary level III D_{mean} EQD2	54.1±1.34 Gy	45.05±2.06	1.262 (1.109-1.3)	0.03
SCF D_{mean} EQD2	51.4Gy±1.5 Gy	47.3±4.8	1.1 (0.7-1.2)	0.056

Note: HR: hazard ratios, CI: confidence interval, EQD2: equivalent dose in 2 Gy fractions, D_{max}: maximum dose, D_{mean}: mean dose, BP: brachial

Discussion

PMRT-related pain remains an under-recognized but clinically significant toxicity that adversely affects long-term quality of life in breast cancer survivors.[13] The present study demonstrates that PMRT pain is not a homogeneous entity; rather, it represents a composite syndrome comprising both somatic and neuropathic elements.

The pattern of PMRT pain observed aligns closely with previously documented toxicity profiles following HFRT, where 10-30% of patients may develop moderate chest wall discomfort within the first year of treatment.[14,15] SCWP occurred early after RT, with most cases appearing within the first 3-6 months and gradually decreasing over time. This suggests that SCWP is likely related to acute or subacute RT-induced inflammation and tissue injury, which tends to improve as healing occurs. In contrast, NP developed later, most commonly at 12 months or beyond, and persisted longer. The delayed onset of NP indicates progressive radiation-related nerve damage or fibrosis, which evolves rather than immediately after treatment.[16-18] A pronounced inverse relationship between CW thickness and SCWP severity echoes prior analyses demonstrating that thinner CW is associated with higher effective dose deposition in superficial nociceptive structures (ribs and intercostal nerves). Dosimetric evidence indicates that patients with a “thin” CW are at particularly high risk for RICWP and rib-periosteum toxicity. In phantom and clinical-planning studies, thin CW geometry (≤15 mm) has been shown to alter dose deposition significantly. Furthermore, emerging evidence from advanced dosimetric and computational modelling demonstrates that the use of partial bolus techniques, combined with high-precision dose-calculation algorithms such as Monte Carlo, substantially improves dose accuracy in patients with thin CW and mitigates excessive dose deposition to the skin and underlying ribs, thereby potentially reducing toxicity in this high-risk subgroup.[19] This dosimetric effect has been reported in severe planning studies, demonstrating that thin CW anatomy contributes to elevated D_{max} values, higher rib doses, and increased heterogeneity within high dose regions. Clinically, it may manifest as a greater incidence of rib tenderness, costochondral pain, and CW discomfort.

SCWP was correlated strongly with higher CW D_{max} increased toxicity was observed in the 50-55 Gy equivalent dose range. The observed association between elevated CW D_{max} EQD2 and clinically significant SCWP is consistent with established dose-response relationships, which demonstrate a heightened risk of CW tenderness, fibrosis, and rib pain in areas exposed to high-dose CW hotspots. [20] In contrast, BP dosimetry showed no association with SCWP, consistent with the distinct anatomic pathways governing somatic CW sensation.

NP was most frequently observed in patients treated with 40 Gy in 15 fractions, followed by those treated with 26 Gy in 5 fractions, reflecting the well-established sensitivity of neural structures to higher biologically effective doses (BED). This aligns with the modelling study by Lee et al., which demonstrated that BP tolerance is strongly dependent on BED; a BP D_{max} of approximately 26 Gy delivered in 3-4 fractions (≈EQD2 ≈45-50 Gy for α/β=3 Gy) already produced a ~10% risk of plexopathy, with the probability rising steeply at higher BED levels-consistent with the dose-dependent neuropathic effects observed in current study. This is further supported by evidence showing that BP injury rates vary from less than 1 % to over 70 % as fraction sizes increase to 2.2-4.58 Gy (total doses 43.5-60 Gy), highlighting the remarkable sensitivity of the plexus to dose-per-fraction escalation.[21-23] Although BP D_{max} EQD2 values in the present study remained within conventionally accepted tolerance limits, the observed association with neuropathic pain suggests the presence of subclinical neural injury and/or cumulative multimodal effects rather than overt radiation-induced plexopathy. Neural tissue exhibits a spectrum of radiation responses, ranging from reversible functional disturbances to irreversible structural damage. At lower dose levels, radiation may induce microvascular endothelial injury, neuroinflammation, Schwann cell dysfunction, and altered axonal conduction, which can manifest clinically as NP without meeting radiographic

or electrophysiologic criteria for classical plexopathy. Importantly, the pattern of NP in our cohort suggests contributions from not only direct BP irradiation but also surgical and regional irradiation factors, particularly given that BP doses in this study remained well below established tolerance constraints. This interpretation is strongly reinforced by the findings of Lundstedt et al., who identified a clear dose-response relationship, with paraesthesia rates rising sharply only when the BP D_{max} exceeded approximately 55 Gy. Their results compellingly suggest that symptoms observed at lower dose levels are unlikely to be radiation-induced and are instead more plausibly explained by alternative mechanisms, most notably ICBN injury associated with extensive AD.[24-27] Apart from this, surgical manipulation can cause traction-related plexus stress and postoperative fibrosis, creating a vulnerable neural substrate. Subsequent regional nodal irradiation may then act as a biological sensitizer, amplifying inflammatory and fibrotic processes and lowering the effective tolerance of neural structures. This concept of reduced neural reserve following surgery provides a plausible explanation for the significant correlation between BP D_{max} EQD2 and LANSS scores observed in our cohort, despite doses remaining below traditional thresholds for overt plexopathy. In the present study, a borderline yet consistent positive association emerged between axillary nodal D_{mean} EQD2 and NP This pattern is biologically credible and strongly suggests a contributory role of non-BP neural structures within the axilla, highlighting a potential dose-sensitive mechanism beyond classical brachial plexopathy. Previous evidence has demonstrated that regional nodal irradiation, particularly when incorporating a posterior axillary boost (PAB), can precipitate late-onset neurotoxicity and brachial plexopathy. This supports the hypothesis that axillary irradiation may injure small sensory nerves, with effects potentially amplified by prior surgical trauma.[28,29] NP was more pronounced in patients undergoing level III AD, consistent with analysis, which showed that a greater number of removed lymph nodes markedly increases susceptibility to BP neuropathy, highlighting the synergistic impact of surgical disruption and regional nodal irradiation on neural injury risk.[30] Collectively, the evidence underscores that NP following PMRT is a multifactorial phenomenon driven by a combination of surgical factors, particularly extensive AD and the cumulative radiation dose delivered not only to BP but also to axillary nodal regions, underlining the importance of meticulous optimization of regional dose distribution in HFRT protocols.

While the current follow-up period captured most early and subacute toxicities, radiation-induced neuropathic complications are known to have a delayed onset, sometimes several years after treatment. Hence, extended follow-up would be necessary to fully characterize the long-term incidence of NP across HFRT regimens. Overall, our findings highlight the importance of optimized dose distribution, hotspot control, and adherence to organ at risk constraints during HFRT planning to minimize treatment-related morbidity while maintaining optimal therapeutic outcomes. Furthermore, with respect to SCWP, validation in larger, adequately powered cohorts is essential to derive statistically robust and clinically generalizable conclusions.

Limitations

As a retrospective, single-institution study, the findings may have limited generalizability to centers employing different radiotherapy planning techniques, dose calculation algorithms, contouring practices, and patient populations. Nevertheless, the homogeneity of treatment delivery and follow-up within a single institution allows for a consistent evaluation of dosimetric-toxicity relationships. This study did not evaluate individual rib dose parameters and ICBN involvement, which may further contribute to PMRT pain. The limited sample size and further subdivision into HFRT regimens may have reduced statistical power and restricted generalizability. Prospective studies with detailed nerve contouring and larger cohorts are needed

Conclusion

PMRT-related pain following HFRT is multifactorial, with somatic symptoms associated with higher CW dose and neuropathic symptoms influenced by surgical extent and regional noal irradiation. Given the larger equivalent doses delivered to late-responding tissues with hypofractionation, meticulous optimization of CW hotspots, regional nodal coverage, and BP dose during HFRT planning is recommended. A longer follow-up is warranted to better characterize the evolution of late pain outcomes and validate these dosimetric associations

Ethical approval

As this was a retrospective analysis of existing clinical data with no direct patient intervention, formal ethical committee approval was not obtained

Funding

None

Conflict of interest

None

CRediT authorship contribution statement

Pratibha Prashar: conceptualization, study design, data curation, formal analysis, writing: original draft; **Brish Bhanu Bhardwaj**: methodology, statistical analysis, writing: review and edit; **Vandana Thakur**: data collection, data curation; **Poorva Vias**: patient follow-up, data verification; **Hardik Sharma**: writing:

review and edit; **Kulbir Singh:** supervision, data curation; **Ankita Pandey**: writing: review and edit; **Vivek Kumar**: data curation.

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