e-ISSN 2083–4640
ISSN 1507–1367

RESEARCH PAPER

Reports of Practical Oncology and Radiotherapy
2022, Volume 27, Number 5, pages: 943–953
DOI: 10.5603/RPOR.a2022.0102
Submitted: 15.08.2022
Accepted: 26.09.2022

# Hypofractionated radiotherapy in postmastectomy locally advanced breast cancer: an interim report on acute toxicities and dosimetry

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## ABSTRACT

**Background:** There is a growing interest in the use of hypofractionation in the setting of post-mastectomy radiation therapy (PMRT). Here, we present an interim report on the acute toxicities and the dosimetry of a 15-day hypofractionated regimen.

**Materials and methods:** Patients aged 18–75 years who underwent mastectomy and had pathological stage IIB–IIIC or any clinical stage who had received neoadjuvant chemotherapy were treated with PMRT at a dose of 43.5 Gy in 15 fractions. Acute toxicities were scored using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

**Results:** Between September 2020 and September 2021, 92 patients were enrolled in the study. Majority experienced grade 1 dermatitis during the course of treatment. Skin toxicities peaked two weeks after PMRT in which 57 patients (62%) had grade 2 dermatitis and 6 patients (7%) had grade 3 dermatitis. Most resolved one month after treatment, with all resolving at three months. Grade 2 fatigue occurred in 4 patients (4%). There were no grade 3 fatigue or pneumonitis of any grade. The average V95% for the chest wall, axilla, and supraclavicular fossa were 91.5%, 99.3%, and 97.5%, respectively. Average ipsilateral lung V17 was 43.6%, while the mean heart dose averaged at 3.46 Gy.

**Conclusion:** This interim report showed that hypofractionated PMRT is associated with a low incidence of clinically significant acute toxicities. With the use of the 3-dimensional conformal radiotherapy technique and volume-based planning, adequate target volume coverage and acceptable heart doses were achieved, although with a slightly higher ipsilateral lung dose.

**Key words:** breast neoplasms; radiation dose hypofractionation

*Rep Pract Oncol Radiother 2022;27(5):943–953*

## Introduction

Breast cancer is the most common malignancy worldwide with over 2.1 million new cases in 2018 [1]. Radiotherapy has an established role in its treatment, providing benefit in local control, disease-free survival (DFS), and overall survival (OS) [2–4]. The traditional practice for postmastectomy patients is delivering conventional fractionated postmastectomy radiotherapy (PMRT) of 50 Gy in 25 fractions. However, there is a growing interest in hypofractionated PMRT as explained by radiobiological experiments reporting low $\alpha/\beta$ ratio values for breast cancer [5, 6]. This renders breast cancer theoretically more responsive to higher doses per fraction of radiation.

The role of hypofractionated radiotherapy has been mainly supported by four large randomized

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controlled trials [5–8]; however, the majority of the population in these trials were early-stage breast cancer patients who underwent breast conservation surgery (BCS) and whole breast irradiation. Only 15% of patients in the START-A trial and 8% of patients in the START-B trial underwent mastectomy. Findings from these studies cannot be fully extrapolated to the postmastectomy setting.

An increasing number of retrospective [9, 10] and prospective [11, 12] trials have been conducted that support the use of hypofractionated PMRT, utilizing a variety of fractionation regimens. However, to date, there is only one randomized, phase III trial that compared conventional fractionated PMRT with hypofractionated PMRT [13]. This study conducted by Wang et al. showed no difference in the five-year local control, distant metastasis, DFS, and OS rates between the two fractionation schedules.

In the setting of the coronavirus disease (COVID-19) pandemic, adopting hypofractionated PMRT allows for less risk of exposure, reduced cost, increased convenience to patients, and faster turnover rate allowing resource-constrained settings to treat more patients. This trial was conducted in the era of the COVID-19 pandemic to determine the safety and efficacy of hypofractionated PMRT in locally advanced breast cancer patients and to add to the growing evidence of hypofractionated radiotherapy in this setting. This study is an interim report of the patient profile, dosimetry, and incidence of acute toxicities of patients treated with hypofractionated PMRT.

## Material and methods

### Study trial/patient eligibility

A prospective, single-arm phase II trial (UPMREB 2020-184-01) was conducted using a hypofractionated regimen for PMRT. Female patients were eligible if they were 18–75 years old; had a World Health Organization (WHO) performance status of 0-2; had unilateral histologically-confirmed invasive breast cancer; had pathological stage IIB–IIIC disease based on the American Joint Committee on Cancer (AJCC) Staging System 8$^{th}$ edition or any clinical stage who had received neoadjuvant chemotherapy regardless of final pathological stage; had undergone total mastectomy with negative margins and adequate surgical axillary staging; and had received neoadjuvant or adjuvant chemotherapy [14]. A minimum of ten harvested axillary nodes was required; however, for patients who had undergone neoadjuvant chemotherapy, the adequacy of harvested nodes was left to the discretion of the attending surgeon, as neoadjuvant chemotherapy may affect lymph node yield and is not indicative of inadequate surgical staging. Patients were excluded if they had a supraclavicular node, internal mammary node, or distant metastases; had undergone previous irradiation to the ipsilateral chest wall and supraclavicular region; had previous or concurrent malignancy other than non-melanomatous skin cancer; had inflammatory breast cancer at diagnosis; had immediate or delayed ipsilateral breast cancer reconstruction; were pregnant or lactating; or had active collagen vascular disease.

Pre-treatment evaluation included physical examination and imaging (ultrasonography or mammography) to assess the primary tumor and ultrasonography and biopsy of suspicious nodal disease in the neck and axilla. Metastatic work-up included chest x-ray, liver ultrasound, and alkaline phosphatase measurement. Where indicated, further imaging with contrast-enhanced computed tomography (CT) scan of the chest, whole abdomen, or bone scintigraphy were done.

The study protocol was approved by the research ethics board of the University of the Philippines-Manila. This is also registered in the Philippine Health Registry (Registry ID: PHRR210624-003671).

### Radiation treatment planning and technique

A dose of 43.5 Gy in 15 fractions of 2.9 Gy delivered 5 days per week, 1 fraction per day [equivalent dose in 2-Gy fractions ($EQD_2$) of 50 Gy, using an $\alpha/\beta$ ratio of 4] was delivered to the chest wall, axillary, and supraclavicular regions. Either the full axilla (levels I, II, and III) or only level III was treated upon the discretion of the treating physician. Considerations for treating the full axilla included gross extranodal extension, involvement of ten or more nodes on histopathology, a positive lymph node ratio of ≥ 50%, or physician preference. The internal mammary nodes (IMNs) were not intentionally treated, but a retrospective review of the doses received by the IMNs was done. No scar boost, chest wall boost, or axillary boost were per-

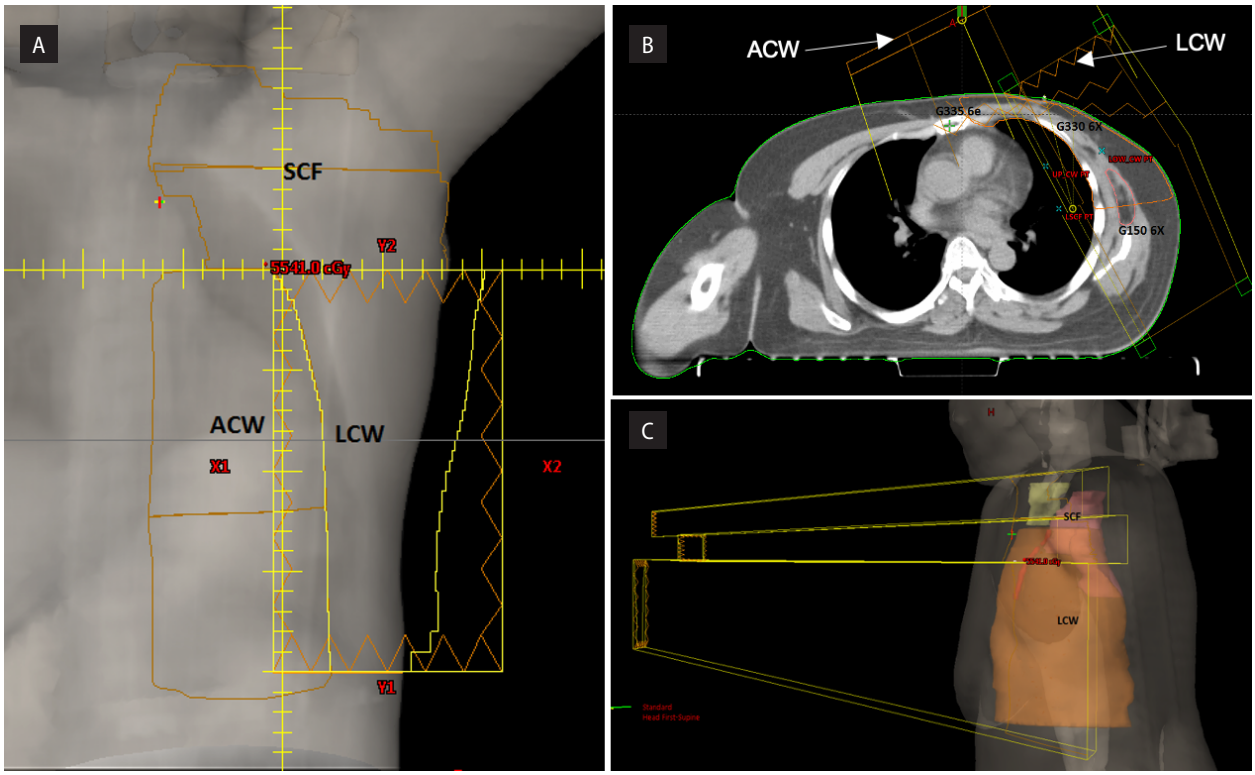


**Figure 1.** Three-dimensional (3D) conformal radiotherapy technique showing (**A**) beam's eye view of the chest wall field, (**B**) axial view of the field geometry of anterior chest wall (ACW) and lateral chest wall (LCW) plans, and (**C**) sagittal view of the supraclavicular (SCF) and LCW field matching

mitted. A 5mm chest wall bolus was used for all patients on the first ten days of treatment. CT-based planning was done for all patients, with the treatment planning scan of 5 mm thickness spanning the mandible to the inferior edge of the liver. Target delineation followed the RTOG Breast Cancer Atlas for Radiation Therapy Planning: Consensus Definitions.[15] A three-dimensional conformal radiotherapy technique (3D-CRT) was used. This involved matching three plans for the anterior chest wall, lateral chest wall, and supraclavicular/axillary region (Fig. 1). Half-beam opposed lateral oblique tangential photon fields with gantry angles ranging from 350° to 300° were utilized for the lateral chest wall field; opposed fields with gantry angles from 350° to 340° for the supraclavicular/axillary field, avoiding as much as possible the trachea, larynx, esophagus, and the spinal cord; and a single fixed source-to-surface distance (SSD) electron fields with energies ranging from 6–12 MeV for the anterior chest wall field. Field-in-field technique was used in all photon fields to improve dose homogeneity. An acceptable planning objective was for ≥ 90% of the target volumes to receive 95% of the prescribed dose (Fig. 2). The maximum point dose was no more than 130% of the prescribed dose since electrons and photons were mixed for a composite plan [16]. Dose constraints to normal organs were based on the NSABP B51/RTOG 1304 protocol and QUANTEC recommendations but converted to $EQD_2$. These dose constraints were soft and applied according to clinical priorities reflecting the risk and severity of a given side effect.

## Toxicity management and monitoring

Patients were periodically assessed once per week during radiotherapy and at two weeks, one month, and three months post-RT in the acute setting. Acute radiation toxicities were assessed and scaled according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. If patients could not physically come for assessment, they were contacted by phone to assess and grade acute toxicities through structured interviews. Patients were advised to apply an alcohol-free moisturizer to the treated region during the course of treatment. When moderate to brisk erythema and pruritus developed, topical cortico-

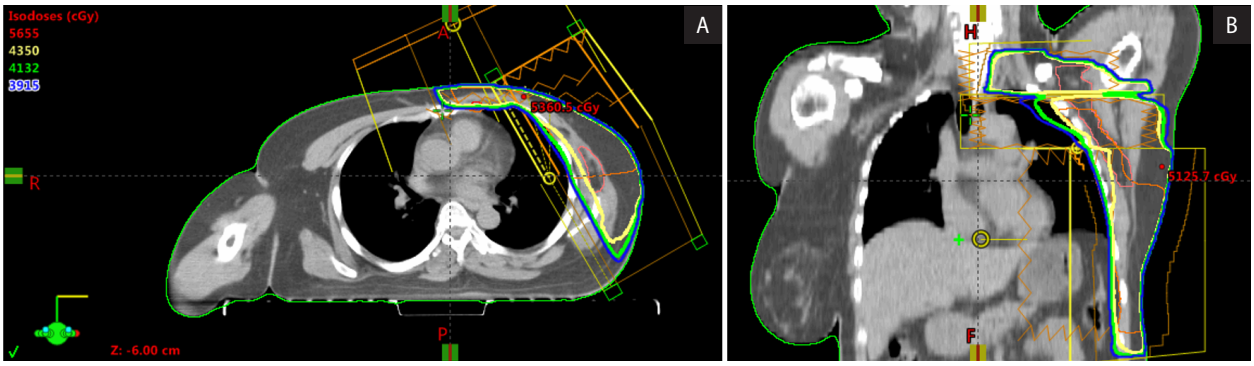


**Figure 2.** Transverse (**A**) and coronal (**B**) dose distribution of the 3D conformal radiotherapy technique in a representative patient

steroids of medium potency (i.e., mometasone furoate 0.1% cream) were prescribed for two weeks, whereas silver sulfadiazine creams were advised for areas with moist desquamation.

## Statistical analysis

The primary endpoint of the main study was locoregional recurrence. The present study is an interim report on the patient profile, acute toxicity, and dosimetry. Statistical tests were not performed as this was planned after the completion of the specified follow-up period. A minimum of 85 patients was required for this study. This was based on the 96% prevalence of good local control in patients treated with hypofractionated radiotherapy after 44 months of follow-up.[12]loco-regional recurrence; distant metastasis and survival rates were recorded for comparison.Results: Twenty-five patients were enrolled in each arm with baseline characters well matched. At median follow up of 44 months, OS was 80% in HF arm against 64% in CF arm (p-value: 0.292 Critical value approach (hypothesis testing) applying two-tailed distribution was used to derive the sample size, which accounted for a power of 80% and a 5% level of significance. The null hypothesis was that hypofractionated PMRT leads to local control rates of 96%, while the alternative hypothesis was that it does not lead to local control rates of 96%. The proportion for the alternative hypothesis was set at 88% based on the prevalence of patients treated with conventional fractionation who had good local control.[12]loco-regional recurrence; distant metastasis and survival rates were recorded for comparison. Results: Twenty-five patients were enrolled in each arm with baseline characters well matched. At median follow up of 44 months, OS was 80% in HF arm against 64% in CF arm (p-value: 0.292 This resulted in critical values of 77 and 84, implying that if the number of patients with good local control is equal to or greater than 84, or less than or equal to 77, then the null hypothesis may be rejected. For this study, a sample size of 92 was used to account for attrition.

# Results

## Demographic, clinical, and treatment-related characteristics

Between September 2020 and September 2021, 92 patients were enrolled in the study. Table 1 shows their demographic, clinical, and treatment-related characteristics. Median age was 50 (range: 28–71) years. Fifty-three percent of patients were ≤ 50 years of age. A majority had N1 disease (57.6%) and were anatomic stage IIIB at diagnosis (39.1%). All patients received adjuvant (53.3%) or neoadjuvant (46.7%) chemotherapy of anthracycline plus taxane-based regimens, with a median of eight cycles. Of 43 patients (46.7%) who underwent neoadjuvant chemotherapy, pathologic complete response was achieved in one (2.3%) in the breast only, 13 (30.2%) in the nodes only, and one (2.3%) in both the breast and nodes. The median time between surgery and start of radiotherapy was 11.8 months for those who received adjuvant chemotherapy and 2.97 months for those who received neoadjuvant chemotherapy.

## Dose-volume analysis

Dosimetry data is available in Table 2. The average volume receiving 95% of the prescribed dose

**Table 1.** Demographic, clinical, and treatment-related characteristics of patients

| Characteristic | Hypofractionated radiotherapy (n = 92) |
|---|---|
| **Age [median]** | **50** |
| ≤ 40 | 18 (19.6) |
| 41–50 | 31 (33.7) |
| 51–60 | 31 (33.7) |
| 61–70 | 11 (12) |
| > 70 | 1 (1.1) |
| **WHO status** | |
| 0 | 88 (95.7) |
| 1 | 4 (4.3) |
| Laterality | |
| Left | 47 (51.1) |
| Right | 45 (48.9) |
| **Histology** | |
| Invasive ductal carcinoma | 17 (18.5) |
| Invasive lobular carcinoma | 6 (6.5) |
| Invasive mammary carcinoma, NOS | 61 (66.3) |
| Others | 8 (8.7) |
| ***Tumor size** [median, IQR] | 5.8 (2–18) |
| **LVSI** | |
| Positive | 57 (62) |
| Negative | 33 (35.9) |
| Not stated | 2 (2.2) |
| Grade | |
| 1 | 11 (12) |
| 2 | 47 (51.1) |
| 3 | 29 (31.5) |
| Not stated | 5 (5.4) |
| **Number of axillary lymph nodes dissected** (median, IQR) | 15 (0–30) |
| **Number of positive lymph nodes** (median, IQR) | 2 (0–25) |
| **†N Stage** | |
| N0 | 4 (4.3) |
| N1 | 53 (57.6) |
| N2 | 27 (29.3) |
| N3‡ | 8 (8.7) |
| **†Anatomic stage** | |
| Stage IIB | 22 (23.9) |
| Stage IIIA | 26 (28.3) |
| Stage IIIB | 36 (39.1) |
| Stage IIIC | 8 (8.7) |
| **Clinical/Pathologic Prognostic Stage** | |
| Stage IA | 2 (2.2) |
| Stage IB | 13 (14.1) |
| Stage IIB | 12 (13) |
| Stage IIIA | 18 (19.6) |
| Stage IIIB | 37 (40.2) |
| Stage IIIC | 5 (5.4) |
| Cannot be determined | 5 (5.4) |
| **ER status** | |
| Positive | 66 (71.7) |
| Negative | 26 (28.3) |
| **PR status** | |
| Positive | 54 (58.7) |
| Negative | 38 (41.3) |
| **Her2-neu** | |
| Positive | 33 (35.9) |
| Negative | 59 (64.1) |
| **Hormonal therapy** | |
| Yes | 65 (70.7) |
| No | 27 (29.3) |
| **Trastuzumab** | |
| Yes | 28 (30.4) |
| No | 64 (69.6) |
| **Chemotherapy** | |
| Adjuvant | 49 (53.3) |
| Neoadjuvant | 43 (46.7) |
| **Number of chemotherapy cycles** (median, IQR) | 8 (4-8) |
| **For patients who underwent neoadjuvant chemotherapy, conversion to pathologic complete response?** | |
| Breast only | 1 (2.3) |
| Nodes only | 13 (30.2) |
| Both breast and nodes | 1 (2.3) |
| None | 28 (65.1) |
| **Interval of surgery and radiotherapy (months)** | |
| Adjuvant chemotherapy | 11.83 |
| Neoadjuvant chemotherapy | 2.97 |
| **Axillary radiotherapy volume** | |
| Full axilla | 73 (79.3) |
| Level III only | 19 (20.7) |

WHO — World Health Organization; NOS — not otherwise specified; IQR — interquartile range; LVSI — lymphovascular space invasion; ER — estrogen receptor; PR — progesterone receptor. *For patients who did not receive neoadjuvant chemotherapy, tumor size on pathology was used. For patients who received neoadjuvant chemotherapy, tumor size was based on imaging and/or clinical examination prior to initiation of chemotherapy. †For patients who did not receive neoadjuvant chemotherapy, pathological stage was used. For patients who received neoadjuvant chemotherapy, either clinical or pathological stage was used, whichever was higher. This included pathologic N3 disease; patients with clinical N3 disease were excluded from the study

**Table 2.** Dosimetry of treatment plans

| **Coverage (%) of 95% of the prescribed dose of 43.5 Gy** | |
|---|---|
| Chest wall | 91.49 ± 1.56 |
| Axilla (Level III) | 99.34 ± 1.49 |
| Supraclavicular fossa | 97.54 ± 2.47 |
| IMN* | 36.74 ± 27.60 |
| V17† of ipsilateral lung | 43.55 ± 6.16 |
| V17† of bilateral lung | 22.61 ± 4.37 |
| **V21.2‡ of heart** | 2.65 ± 2.77 |
| **Heart Dmean** | |
| Gy | 3.46 ± 1.64 |
| EQD2 | 4.09 ± 1.93 |
| **Esophagus Dmean** | |
| Gy | 6.60 ± 3.57 |
| EQD2 | 7.79 ± 4.21 |
| **Spinal cord Dmax** | |
| Gy | 14.01 ± 11.10 |
| EQD2 | 16.53 ± 13.10 |
| **Larynx Dmean** | |
| Gy | 4.79 ± 5.06 |
| EQD2 | 5.65 ± 5.97 |
| Hotspot§ (%) | 123.93 ± 3.35 |

Data are mean ± standard deviation. EQD2 — equivalent dose in 2 Gy fractionation; Vx — relative volume receiving more than x Gy; *Retrospectively gathered. †V17 is biologically equivalent to V20 in this study. ‡ V21.2 is biologically equivalent to V25 in this study. §Dose received by the maximally irradiated 0.03cc of the target volumes, expressed in percentage

was 91.5% for the chest wall, 99.3% for the axilla, and 97.5% for the supraclavicular fossa. Average ipsilateral lung V17 was 43.6%, and average bilateral lung V17 was 22.6%. Average heart dose (Dmean) was 3.46 Gy ($EQD_2$ 4.09 Gy), while average heart V21.2 was 2.65%. Average esophagus and larynx doses were 6.60 Gy ($EQD_2$ 7.79 Gy) and 4.79 Gy ($EQD_2$ 5.65 Gy), respectively, while maximum dose to the spinal cord averaged at 14.01 Gy ($EQD_2$ 16.53 Gy). The mean hotspot was 123.93%.

## Acute toxicities

Table 3 shows the acute toxicity of patients as reported over time. The main toxicity was radiation dermatitis. The worst CTCAE grade experienced by patients is as follows: grade 1: 23 patients (25%), grade 2: 63 patients (68%), and grade 3: 6 patients (6.5%). Grade 2 toxicity was primarily due to moderate to brisk erythema and moist desquamation confined to skin folds. Figure 3 presents the CTCAE toxicity scores documented at each time point during radiotherapy and post-radiotherapy. Majority of patients experienced grade 1 dermatitis during the treatment course. Two weeks after radiotherapy (week 5), majority [57 (62%) patients] had grade 2 dermatitis, while six patients (6.5%) had grade 3 dermatitis. Most resolved after one month of radiotherapy (week 7), with all resolving three months post-treatment (week 15). Grade 2 fatigue occurred in four patients (4%). One patient experienced shortness of breath during the last week of radiotherapy but this resolved after symptoms were managed conservatively. No patient in the treatment cohort developed grade 3 fatigue or pneumonitis of any grade.

# Discussion

This is the first study on hypofractionated PMRT involving the Filipino cohort and one of the few studies in the Asian population. These acute tox-

**Table 3.** Acute toxicities of treatment based on *Common Terminology Criteria for Adverse Events (CTCAE)* version 4.0

| | Week 1 | Week 2 | Week 3 | End of treatment | 2 weeks post-treatment | 1 month post-treatment | 3 months post-treatment |
|---|---|---|---|---|---|---|---|
| **Skin toxicity** | | | | | | | |
| Grade 1 | 81 (88%) | 84 (91.3%) | 78 (84.8%) | 77 (83.7%) | 24 (26.1%) | 62 (67.4%) | 84 (91.35) |
| Grade 2 | | | 2 (2.2%) | 4 (4.3%) | 57 (62%) | 21 (22.8%) | |
| Grade 3 | | | | | 6 (6.5%) | 1 (1.1%) | |
| **Fatigue** | | | | | | | |
| Grade 1 | 81 (88%) | 84 (91.3%) | 79 (85.9%) | 80 (87%) | 86 (93.5%) | 84 (91.3%) | 82 (89.13%) |
| Grade 2 | | | 1 (1.1%) | 1 (1.1%) | 1 (1.1%) | | 2 (2.2%) |
| **Pneumonitis** | | | | | | | |
| Grade 1 | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |

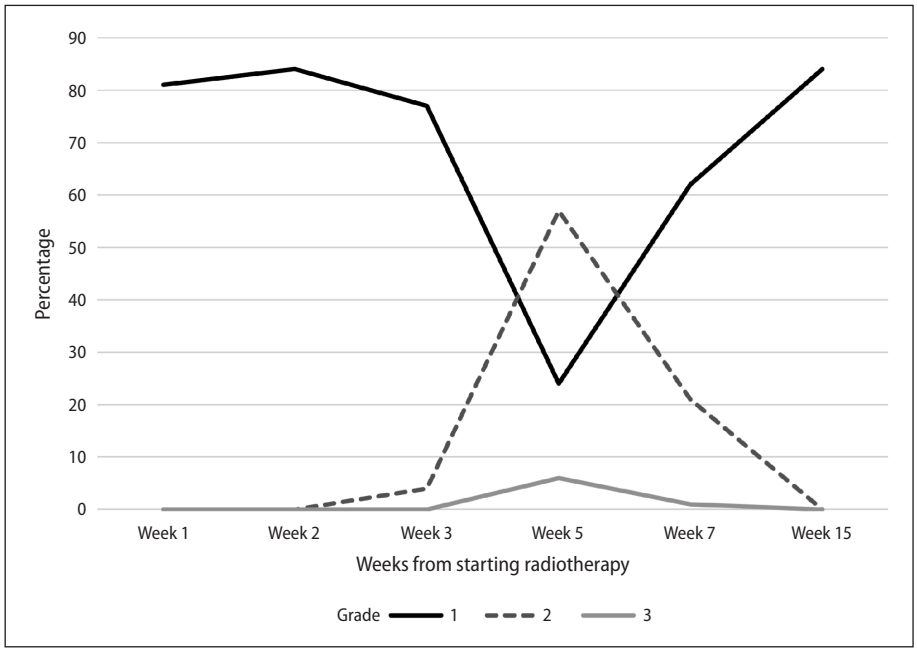


**Figure 3.** Acute skin toxicity — prevalence of grade 1, grade 2, and grade 3 using Common Terminology Criteria for Adverse Events (CTCAE) scoring system at various time points

icity and dosimetry reports were not designed to involve statistical hypothesis testing but rather to determine the incidence of clinically significant toxicities associated with this hypofractionated regimen. Based on these results, hypofractionated radiotherapy of 43.5 Gy in 15 fractions is associated with a low incidence of clinically significant acute toxicities. As summarized in Table 3, the majority of patients experienced grade 2 dermatitis which peaked at two weeks post-treatment and settled one month after treatment. Furthermore, despite relatively high V17 lung doses, no acute pneumonitis was reported in this subset of patients.

In the trial by Wang et al., hypofractionated PMRT had less frequent grade 3 acute skin toxicity than conventional fractionated PMRT with an incidence of 3% (14 patients) [13]. Comparing this with our study, our cohort had a slightly higher incidence at 6.5% (6 patients). Nevertheless, results are comparable as with other studies demonstrating that most patients experience grade 1–2 dermatitis [11, 17, 18]. The observed trend of a higher incidence of grade ≥ 2 dermatitis two weeks after hypofractionated radiotherapy is also anticipated. In the acute skin toxicity report of the UK FAST-Forward Trial [19], the peak of grade ≥ 2 dermatitis was observed at week 5 (i.e., two weeks after treatment) among patients treated with a three-week regimen of 40 Gy in 15 fractions. Grade 3 toxicity also appeared during this period. A factor that may have affected the rates of acute grade ≥ 2 skin toxicity in our study is the standardized use of bolus which was shown to be significantly associated with acute radiation dermatitis in several studies [20]. Recent findings however have shown that bolus may not be necessary for all patients, and an international consensus recommendation has been published regarding its indications [21]. Other contributory factors to acute radiation dermatitis may also be considered in the hypofractionated setting including body mass index of ≥ 25 kg/m$^2$, smoking habits, breast volume, and diabetes [22].

The per protocol dose constraint for the ipsilateral lung according to the NSABP B-51 trial is V20 ≤ 15%, with V20 ≤ 40% considered acceptable.[16] The average ipsilateral lung V17 (biologically equivalent to V20) in our study was 43.6%, slightly higher than the acceptable lung dose constraint. Despite this, there was no pneumonitis observed in the treatment cohort. This finding is consistent with results of previous hypofractionated PMRT trials showing low incidence of acute pneumonitis [11, 13, 23]. For cases of increased ipsilateral lung dose, potential methods of decreasing the dose include use of prone positioning or breathing adaptation techniques [24].

With respect to radiotherapy planning, one of the challenges encountered was achieving an acceptable ipsilateral lung dose. The phase III trial by Wang et al. achieved an ipsilateral lung V20 of 17.8% in the hypofractionated arm [13], while the phase II trial by Poppe et al. attained an ipsilateral lung V15 (biologically equivalent to V20 in their study) of 24.8% [11]. However, it is important to consider the type of treatment planning techniques employed. In both studies, volume-based planning was not standard. The trial by Wang et al. described their radiotherapy techniques in an earlier published article where majority of patients were treated using 2-dimensional planning without CT simulations. Patients were treated with a 6–10 MeV electron beam, depending on the thickness of the chest wall measured by ultrasonography [25]. In the trial by Poppe et al., majority of patients (74%) were treated with partially wide tangents and ipsilateral lung dose constraints were not predetermined. Rather, the ipsilateral lung width visible at any level on the tangent beam's eye view was limited to < 3 cm. Although target volume coverage and organs-at-risk doses were not evaluated pre-treatment, they were retrospectively collected and showed adequate planning target volume coverage (V95% = 97% for chest wall and V95% = 92% for axilla) and acceptable ipsilateral lung parameters (V15 = 24.8%, V18 = 23.5%) [11]. The release of the RTOG Breast Cancer Atlas and the application of CT-based planning have proven useful in optimizing target volume coverage and monitoring OAR doses. As information on dosimetry becomes more evident, efforts have been made to develop more sophisticated planning techniques to achieve improved dosimetry than would otherwise be expected from traditional techniques. With volume-based planning, use of partially wide tangents in hypofractionated radiotherapy yielded ipsilateral lung V20 values of 41% in a treatment planning study [26]. In our study, with the use of 3D-CRT and volume-based planning, we were able to achieve adequate target coverage and acceptable heart doses although with a slightly higher ipsilateral lung dose than intended.

The average hotspot was 123.93%, which is considered acceptable following the NSABP B51/RTOG 1304 protocol, where the ideal maximum dose should not exceed 130% of the prescription when electron and photons are mixed for a composite plan. Hotspots are relevant since they are penalized more severely in a hypofractionated setting owing to the "triple trouble" phenomenon [27]. That is, hotspots in a hypofractionated treatment receive not only a higher dose per fraction but also a higher total effective dose, much more than what a hotspot of a conventional fractionated treatment would otherwise incur. This raises concerns for increased late toxicities; however, hotspots of this intensity are tolerated in the junction of the electron and photon fields to avoid underdosage of the chest wall during field matching. Likewise, in this study, hotspots were confined to a very limited volume.

The radiotherapy regimen utilized in this study was adopted from Wang et al. as it is the only phase III study on hypofractionated PMRT. Furthermore, on the basis of an $\alpha/\beta$ value of 4 Gy for breast cancer [5], the use of 43.5 Gy in 15 fractions ($EQD_2$ 50 Gy) for locally advanced breast cancer is slightly higher than the doses used in the START B Trial [40 Gy in 15 fractions ($EQD_2$ 44.4 Gy)] [8] and the Canadian trial [42.56 Gy in 16 fractions ($EQD_2$ 47.2 Gy)] [7] which mainly included low-risk, early-stage patients who had BCS.

A distinction of our study from that of Wang et al. is the treated axillary volume. In the study by Wang et al., only the level III axilla was treated, whereas our study had a variation in treated axillary volumes. Some had undergone full axillary irradiation while some were treated to the axillary level III nodal region alone. While this subject on the appropriate axillary nodal volume remains to be settled, it would be interesting to determine and compare these two volumes (full *vs.* limited axillary irradiation) in terms of late toxicities, particularly lymphedema and brachial plexopathy, in the hypofractionated setting. A prospective screening trial has shown that the combination of axillary lymph node dissection (ALND) and regional lymph node radiation (RLNR) led to higher rates of lymphedema compared with sentinel lymph node biopsy (SLNB) alone, SLNB + RLNR, and ALND alone [28]. Moreover, most of the patients in our treatment cohort had clinical/pathologic N1 disease at diagnosis. The presence of four or more positive axillary nodes (N2+) remains to be an absolute indication for PMRT, whereas the benefit of PMRT in patients with one to three axillary nodes remains

to be unclear [29]. In patients receiving neoadjuvant chemotherapy, post-pathology results, however, may not accurately reflect the actual tumor burden at diagnosis. Pathologic staging has not been validated for these patients, hence prognosis is still determined based on pretreatment clinical stage. In our cohort, a considerable proportion of patients underwent neoadjuvant chemotherapy suggesting that the proportion of N2+ disease may have had been higher had these patients undergo upfront ALND. It would also be worthwhile to examine the effects of hypofractionated radiotherapy with regional nodal irradiation in this subset of patients considered to have low nodal burden.

In the context of the COVID-19 pandemic, oncologists in Europe and Canada began to adopt more hypofractionated breast radiotherapy regimens. On the other hand, an international practice patterns survey showed that the utilization of hypofractionated PMRT was the lowest in the Asia-Pacific at 36.2% compared to the Middle East's utilization rate of 70.4% [30]. In addition to lack of long-term evidence and toxicity concerns, reimbursement was reported as a barrier by Asia-Pacific respondents. Furthermore, they showed that low- and lower-middle-income countries were significantly less likely to adopt hypofractionation than high-income countries. This is counterintuitive since a recent study showed that breast hypofractionation is more cost-effective, especially for developing countries with low-resource facilities [31].

Hypofractionated PMRT is particularly relevant in our country where locally advanced cases are one of the most common indications for treatment. During the COVID-19 pandemic, hypofractionation has helped in reducing the infection risk of patients and allowed our facilities to cope with limited operational hours and reduced manpower brought about by surges in COVID-19 infection rates. While we await long-term follow-up results of the patients in this study, initial toxicity reports are reassuring and favorably support adoption of the hypofractionated postmastectomy regimen for our patients. Future studies can delve on facilitators and barriers to the use of hypofractionation in our setting to further understand the impact of hypofractionated treatment on reimbursement and cost-efficiency.

## Conclusion

Hypofractionated radiotherapy for postmastectomy breast cancer patients is associated with a low incidence of clinically significant acute toxicities. The majority of patients experienced grade 2 dermatitis which peaked at two weeks after radiotherapy and settled one month after treatment. There were no reported acute pneumonitis, and the incidence of clinically significant fatigue was also very low. Furthermore, with the use of 3D-CRT and volume-based planning, adequate target coverage and acceptable heart doses were achieved, although with a slightly higher ipsilateral lung dose.

### Conflict of interest

None declared.

### Funding

None declared.

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