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ORIGINAL ARTICLE

Acute Toxicity and Dosimetric Analysis of Ultra-Hypofractionated Radiation Therapy for Breast Cancer

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OBJECTIVE

This study explores ultra-hypofractionated breast radiation therapy in 110 Stage I-III breast cancer patients, focusing on dosimetry, toxicity, overall survival (OS), and disease-free survival (DFS).

METHODS

Conducted from May 2020 to May 2023, the study enrolled patients undergoing ultra-hypofractionated adjuvant radiation therapy post-surgery. Dosimetric parameters were recorded, and toxicity was assessed using SPSS software. Patients underwent either Modified Radical Mastectomy (MRM) or Breast Conservation Surgery (BCS), receiving 26 Gy in 5 fractions over 1 week or a simultaneous integrated boost (SIB) of 6 Gy after BCS. Deep Inspiratory Breath Hold and Surface Guided Radiation Therapy were employed.

RESULTS

The study enrolled 110 patients. Toxicity at the end of treatment included 89% Grade 1 skin toxicity and 18.18% Grade 1 dysphagia, with minimal Grade 2 skin toxicity at the last follow-up. Dosimetric analysis confirmed adequate coverage within organs-at-risk constraints. The 2-year OS was 95.6%, and DFS was 92.7%.

CONCLUSION

The study shows that ultra-hypofractionated breast radiation therapy is feasible and effective, achieving a favorable overall survival of 95.6%. Dosimetric constraints were met with good acceptance. The retrospective nature and absence of a control group present limitations, urging further exploration.

Keywords: Breast cancer; toxicity; ultra-hypofractionation.

INTRODUCTION

Radiotherapy (RT) is an integral aspect of the holistic management of breast cancer, addressing early-stage disease through to metastasis and utilized in nearly 87% of cases.[1] The risk of local recurrence is known to be reduced by postoperative radiation therapy after conservative breast surgery, leading to a survival benefit, as demonstrated in the study by Darby et al.[2] in 2011. Local relapses following breast-conserving surgery and radiation therapy commonly occur in the tumor bed or its immediate vicinity. These relapses have been linked to a heightened risk of distant metastases and diminished survival in breast cancer. This association implies the potential advantages of enhancing the radiotherapy total dose in these regions through an additional boost, aiming to eradicate any remaining subclinical tumor tissue.[3–6]

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The conventional radiotherapy regimen for administering whole-breast irradiation after breast-conserving surgery has been a 50 Gy total dose delivered in 2 Gy fractions over 5 weeks. This is typically followed by a boost dose of 10–16 Gy to the lumpectomy cavity, given sequentially.[7] Taking into account the radiobiological features of breast cancer, over the years, a shift towards hypofractionation emerged, involving the delivery of 40–42.5 Gy in 15–16 fractions over a span of 3 weeks. The safety and efficacy of moderate hypofractionation for whole-breast radiotherapy were established by the UK START trials and the Canadian OCOG trial.[8,9]

As a result of these findings, moderate hypofractionation is now recommended as the standard of care for whole-breast radiotherapy. NRG RTOG 1005 results indicate that a concomitant boost with hypofractionated whole-breast irradiation is non-inferior in terms of in-breast recurrence compared to a sequential boost following conventional whole-breast irradiation in high-risk cases, thereby reducing the overall treatment time.[10] In a randomized, non-inferiority, open-label, phase 3 trial conducted by Wang et al.,[11] it was demonstrated that postmastectomy hypofractionated radiotherapy was non-inferior to conventional fractionated radiotherapy in patients with high-risk breast cancer. Additionally, both approaches exhibited similar levels of toxicities.

Shortened ultra-hypofractionated radiotherapy regimens, such as those employing 5 fractions with weekly periodicity (as observed in the UK FAST trial), every other day (as demonstrated in the HAI trial), or daily administration (as evidenced in the UK FAST-Forward trial), have proven to be feasible and well-tolerated.[12–14]

In this study, our aim is to evaluate dosimetry, toxicity, overall survival (OS), and disease-free survival (DFS) outcomes in breast cancer patients undergoing an ultra-hypofractionated regimen of radiation therapy at our institute. This is particularly pertinent in the Indian context, given the heightened demand for cancer care and prevailing challenges such as the scarcity of radiotherapy centers and limited accessibility.

MATERIALS AND METHODS

This study is a pure retrospective review that included Stage I-III breast cancer patients who received ultra-hypofractionated adjuvant radiation therapy to the breast/chest wall, along with regional lymph nodes when indicated, between May 2020 and May 2023.

The inclusion criteria for our study are as follows: participants must be aged over 18 years with pathologically proven invasive breast carcinoma who have undergone mastectomy or breast-conserving surgery for Stage I-III breast cancer. Additionally, complete microscopic excision of the primary tumor with adequate axillary nodal dissection is required, along with written informed consent from the patients.

The exclusion criteria for our study include individuals with a past history of malignancy, excluding basal cell skin cancer, CIN cervix uteri, or non-breast malignancies treated with curative intent and at least 5 years disease-free. Additionally, participants with contralateral and/or previous ipsilateral breast cancer, including DCIS, irrespective of the date of diagnosis, are excluded. Furthermore, individuals with known residual macroscopic nodal disease are also ineligible for participation.

The CIVCO C-Qual™ MT400 Breast Board was the immobilization device used for all patients involved in our study. Radiotherapy planning was carried out using volumetric planning CT scans according to a predetermined simulation protocol. Organs at risk delineated encompassed the ipsilateral and contralateral lungs, heart, and contralateral breast. For patients with left breast cancers, delineation also included the left anterior descending artery (Fig. 1) Patients with node positivity on histopathology or pre-NACT imaging required irradiation to the supraclavicular fossa (SCF). IMN (internal mammary node) radiotherapy was administered to patients with IMN involvement identified on radiological imaging at presentation. Importantly, all of these patients had no radiological evidence of residual IMN at the time of radiotherapy planning.

All patients were treated with the field-in-field forward IMRT technique with bitangential portals. The SCF was treated with a matched single anterior portal.

The following dose constraints were used while planning radiation therapy:

- Planning Target Volume: V95%>90%, V105%≤7%, V107%≤2%, Dmax≤110%
- Ipsilateral Lung: V8Gy<15%
- Contralateral Breast: Mean Dose<3.0 Gy
- Heart: V7Gy<5%, V1.5Gy<30%

All left-sided breast cancer patients were treated with Deep Inspiratory Breath Hold using the Varian RPM respiratory gating system. Surface Guided Radiation Therapy employing the AlignRT (Vision RT Ltd., UK) system was used for patient setup and real-time motion tracking.

Patients who had undergone Modified Radical Mastectomy (MRM) received a planned radiation dose of 26 Gy in 5 fractions over 1 week, whereas all patients

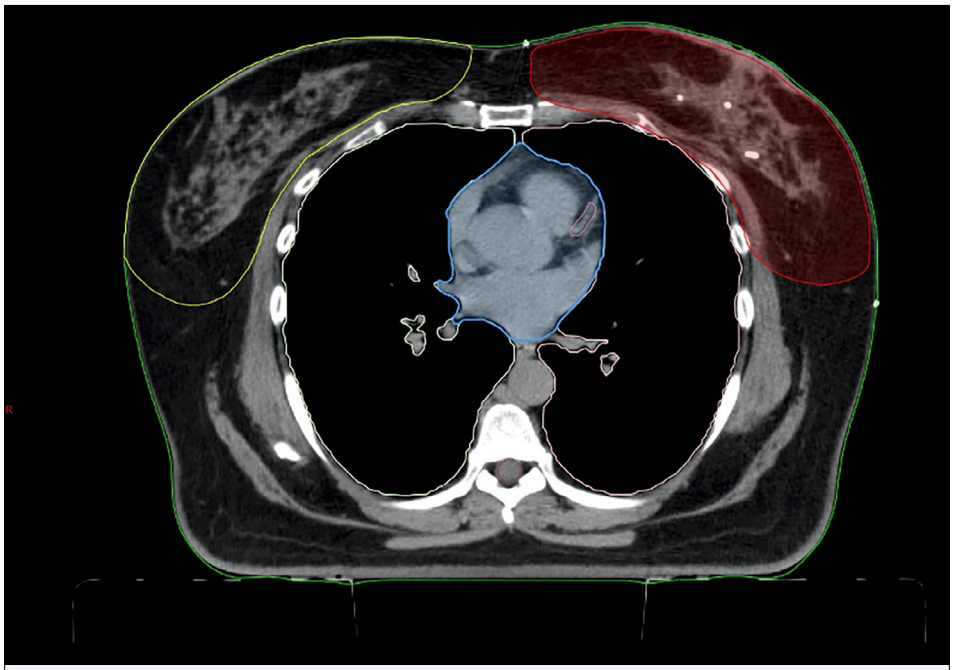

Fig. 1. Delineation included the left anterior descending artery in patients with left breast cancers.

who had undergone Breast Conservation Surgery (BCS) were planned to receive 26 Gy in 5 fractions over 1 week with a simultaneous integrated boost (SIB) of 6 Gy in 5 fractions over 1 week to the tumor bed. All relevant dosimetric parameters were recorded. The study assessed and documented toxicities observed at the conclusion of treatment and during the last follow-up.

Statistical Analysis

Patient details and dosimetric parameters were recorded and computed using SPSS (IBM SPSS Statistics for Windows, Version 23.0, Armonk, NY; IBM Corp.) software. Survival analysis was performed using the Kaplan-Meier method in STATA 17 (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC).

RESULTS

The study enrolled 110 patients, with a median age of 55 years (Range: 24–89 years). Sixty-four (58.2%) were postmenopausal, 39 (35.5%) were premenopausal, and 7 (6.4%) were perimenopausal. Fifty-three (48.2%) cases were right-sided, while 57 (51.7%) were left-sided. Surgical interventions included breast-conservation surgery for 78 (70.9%) patients, mastectomy for 31 (28.2%) patients, and oncoplastic breast-conservation surgery for 1 patient.

Histologically, 98 (89.1%) patients had invasive ductal carcinoma, 4 (3.6%) presented with invasive lobular carcinoma, and 8 (7.3%) had other histological subtypes. With regard to tumor grading, 7 patients (6.4%) were reported as Grade I, 44 patients (40%) as Grade II, and 55 patients (50%) as Grade III. The mean value of the greatest tumor dimension was 2.6 cm (Range: 0–10 cm), with 44 patients (40%) having node-positive disease.

Among node-positive cases (44), 27 (61.36%) had N1a disease, 1 (2.27%) had N1c, 11 (25%) had N2a, and 5 (11.36%) had N3a disease. Thirty-four patients (30.9%) had Stage I disease, 52 (47.27%) had Stage II, 22 (20%) had Stage III, while staging details were unavailable for 1 patient (0.9%). Lymphovascular space invasion (LVSI) was observed in 35.8% of patients.

Twelve (10.9%) patients received neoadjuvant chemotherapy (NACT), while 46 (41.8%) received adjuvant chemotherapy. Additionally, 86 (78.2%) patients received hormone therapy; among 18 Her2+ positive patients, 17 (94.44%) received induction and maintenance Trastuzumab.

In the cohort of 79 patients who underwent breast-conservation surgery, 78 (98.7%) received a Simultaneous Integrated Boost, consistently delivered using electrons. Radiation therapy to the supraclavicular fossa (SCF) was administered to 53 patients (48.2%), while only 1 (0.9%) patient received internal mammary node (IMN) irradiation (Table 1).

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Table 1 Patient characteristics

	n	%		n	%
Total number of patients	110		Stage		
Median age, years (range)	55 (24–89)		IA	19	17.27
Pre-menopausal	39	35.5	IB	15	13.63
Peri-menopausal	7	6.4	IIA	23	20.90
Post-menopausal	64	58.2	IIB	29	26.36
Laterality			IIIA	5	4.54
Right	53	48.2	IIIB	15	13.63
Left	57	51.7	IIIC	5	4.54
Surgical intervention			Not known	2	1.81
BCS	78	70.9	LVSI		
Mastectomy	31	28.2	Positive	34	30.9
Oncoplastic BCS	1	0.9	Negative	61	55.5
Histology			Not known	15	13.6
Invasive ductal carcinoma	98	89.1	Chemotherapy		
Invasive lobular carcinoma	4	3.6	Adjuvant	46	41.81
Other	8	7.3	Neoadjuvant	12	10.9
Grade			Hormone therapy	86	78.18
Grade I	7	6.4	Anti-Her-2 therapy		
Grade II	44	40	Eligible	18	16.36
Grade III	55	50	Receipt of induction+ maintenance trastuzumab	17/18	94.44
Not known	4	2.3	Regional nodal irradiation		
Mean greatest tumor size, cm	2.6 (0–10 cm)		SCF	53	48.18
Nodal involvement			IMN	1	0.9
N0	65	59	Boost irradiation		
N1a	27	24.54	Eligible	79	71.8
N1c	1	0.9	Boost irradiation receipt	78/79	98.73
N2a	11	10	Modality of boost		
N3a	5	4.54	Electrons	78/78	100
Not known	1	0.9			

BCS: Breast conservation surgery; LVSI: Lymphovascular space invasion; SCF: Supraclavicular fossa; IMN: Internal mammary node

Toxicity

At the conclusion of treatment, 98 patients (89%) exhibited Grade 1 skin toxicity, with only 2 patients experiencing Grade 2 skin toxicity, and 10 patients reporting no skin reactions. Twenty patients (18.18%) experienced Grade 1 dysphagia at the conclusion of treatment. At the last follow-up, 4 (4.5%) patients had Grade 1 skin toxicity.

Dosimetry

All radiation treatment plans were evaluated and found to have adequate coverage while respecting organs-at-risk dose constraints. Results are depicted in Table 2.

Oncological Outcomes

The median follow-up was 22 months. Among the 91 patients (82.7%) available for follow-up, 83 (91.2%) were alive and disease-free. Three patients (3.2%) were alive with locoregional recurrence, while 2 (2.19%) were alive with distant metastases. One (1.09%) patient died after developing locoregional recurrence, while 2 (2.19%) died after developing distant metastasis (Table 3).

The 2-year overall survival (OS) was 95.6%. The 2-year disease-free survival (DFS) was 92.7% (Figs. 2, 3).

DISCUSSION

The landmark FAST-Forward Trial aimed to establish a five-fraction adjuvant radiotherapy schedule delivered in one week, demonstrating non-inferiority in local cancer control and safety compared to the standard 15-fraction regimen after primary surgery for early breast cancer. The 5-year results, presented in 2020, revealed that 26 Gy in five fractions over one week is non-inferior to the standard 40 Gy in 15 fractions over

Table 2 Dosimetric arameters

Parameter	Measure	Median value
Planning target volume (PTV)	D90% (Gy)	24.08 Gy (IQR: 23.67–24.47)
Heart	Mean dose (Gy)	1.39 Gy (IQR: 0.78–2.18)
Left anterior descending artery (LAD) in left sided breast cancer	Mean dose (Gy)	1.79 Gy (IQR: 1.12–4.33)
Ipsilateral lung	V8Gy (cc)	17.9 cc (IQR: 13.89–21.27)
Contralateral lung	Mean dose (Gy)	2.31 Gy (IQR: 1.92–2.75
	V5Gy (cc)	0.00 cc (0.00–0.00)
Contralateral breast	Mean dose (Gy)	0.098 Gy (IQR: 0.062–0.139)

IQR: Interquartile range

Table 3 Summary of relapses, pathological features, and disease-related deaths in the study cohort

	Pathological stage	Molecular status	Pattern of relapse	Status
Patient 1	ypT0N1a	Triple negative	Locoregional recurrence	Dead
Patient 2	T2N0	Triple negative	Distant metastases	Dead
Patient 3	T2N1a	Luminal A	Distant metastases	Alive
Patient 4	T4bN1a	Triple negative	Distant metastases	Alive
Patient 5	T2N3a	Luminal B	Locoregional recurrence	Alive
Patient 6	T1cN0	Luminal A	Locoregional recurrence	Alive
Patient 7	T3N2a	Triple negative	Distant metastases	Dead
Patient 8	T2N0	Triple negative	Locoregional recurrence	Alive

three weeks for local tumor control, with no significant differences in the physician's assessment of late effects between the two schemes.

Zerella et al.[15] assessed the toxicity, local control, overall survival, and disease-free survival among elderly breast cancer (BC) patients who underwent adjuvant once-weekly ultra-hypofractionated radiotherapy (RT) with either intensity-modulated radiotherapy (IMRT) or 3D conformal radiotherapy (3DCRT). The study focused on BC patients who received 5.7 Gy once a week for 5 weeks to the entire breast following breast-conserving surgery. Notably, the sole severe acute toxicity observed at the conclusion of RT was erythema, which occurred in 0.4% of cases within the 3DCRT group, with no instances of Grade 3 edema or epitheliolysis recorded.

In terms of oncological outcomes, at a median follow-up of 2.9 years, 91.9% of patients (249/271) were alive and free from any events, and only 1.8% experienced isolated locoregional recurrences. The 3-year disease-free survival and overall survival rates were 94.9% and 97.8%, respectively.[15]

Ivanov et al.[16] randomized 60 early breast cancer patients post-conserving surgery, assigning 27 to ultra-hypofractionated whole-breast 3D conformal radiotherapy (26 Gy in 5 fractions over 1 week) and 33 to moderate fractionation during the COVID-19 pandemic (March–July 2020). Comparable Grade 1 acute skin toxicity (p=0.18), RESS subcutaneous tissue toxicity (p=0.18), RESS late skin toxicity (p=0.88), and cosmetic results (p=0.46) were observed. Dosimetric analysis showed significantly lower median lung doses in the 5-fraction group (p<0.01), with lower median heart and left anterior descending artery doses for left breast cancer patients (p<0.01).[16]

Othman et al.,[17] at Princess Margaret Hospital, Toronto, Canada, evaluated their institutional experience of ultra-hypofractionated breast RT in a real-world setting at a large academic cancer center. Stage 0–II breast cancer patients who received adjuvant whole-breast irradiation (WBI) or partial breast irradiation (PBI) between May 2020 and March 2021 were compiled. Patients were divided into two cohorts: Ultra-HFRT (26 Gy in 5 daily fractions) and Moderately-HFRT (40.05 Gy in 15 fractions). Grade 1 RTOG skin toxicity significantly improved over time for patients who received U-HFRT: 37% during RT, 57% within 90 days post-RT, and 6% >1 year post-RT (p<0.001). Grade 2 toxicity was minimal (5% within 90 days post-RT), and there were no Grade 3 toxicities. Increased toxicity was observed for patients who received a boost (p<0.001).[17]

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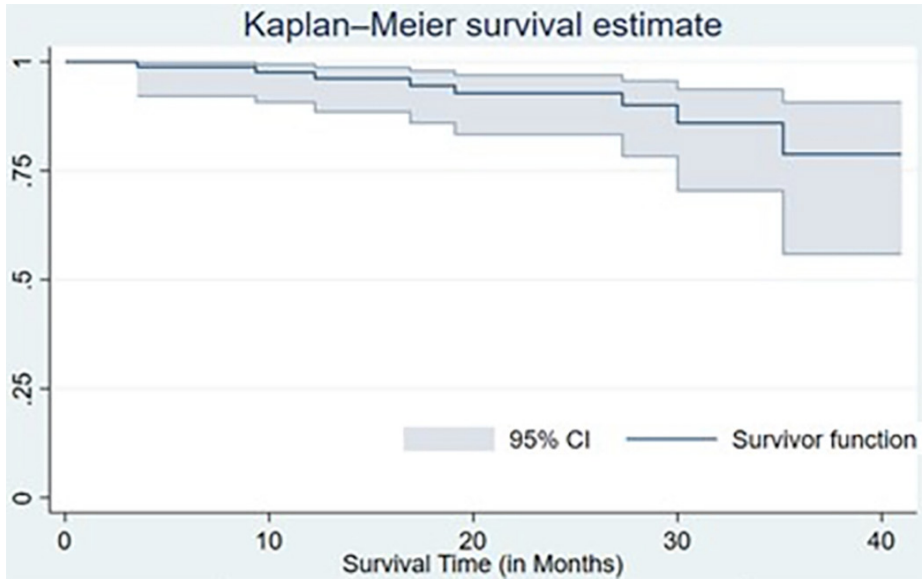

Fig. 2. Shows the Kaplan-Meier survival estimates for any kind of recurrences from the date of surgery till next 40 months. A total of 8 recurrence were seen.
CI: Confidence interval.

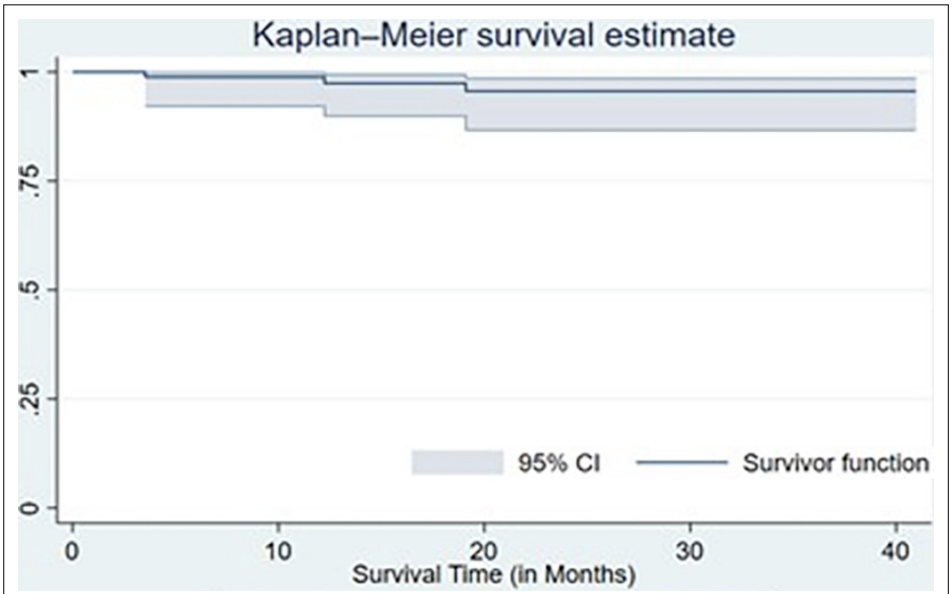

Fig. 3. Kaplan-Meier survival estimates for mortality outcomes from the date of surgery till next 40 months. A total of 3 deaths were observed.
CI: Confidence interval.

Sigaudi et al.[18] reported the early clinical outcomes of a prospective series of early breast cancer patients treated with ultra-hypofractionated postoperative whole-breast irradiation after breast-conserving surgery and axillary management. The maximum detected acute skin toxicities were Grade 2 erythema (6.7%), Grade 2 induration (4.4%), and Grade 2 skin color changes. No early in-breast tumor recurrences were observed. Ultra-hypofractionated whole-breast irradiation provides favorable compliance and early clinical outcomes in early breast cancer after breast-conserving surgery in a real-world setting.[18]

Corrigan et al.,[19] at MD Anderson Cancer Center, Texas, analyzed the adoption of ultra-hypofractionated whole-breast irradiation (ultra-HF-WBI) for DCIS and early-stage breast cancer. Among 249 patients, 37.4% received ultra-HF-WBI, with a significant increase from 4.3% in March–April 2020 to 45.5% in July–August 2020 ($p<0.001$). Factors associated with increased ultra-HF-WBI use included age ≥50, low-grade WBI without axillary inclusion, no radiation boost, and longer travel distance ($p<0.03$).

Yahya et al.[20] conducted a local study at University Hospital Birmingham to evaluate the practical experience of patients undergoing an ultra-hypofractionated schedule, comparing feasibility and toxicity to the FAST-Forward trial during the COVID-19 pandemic. The study included 211 patients with early-stage breast cancer who received adjuvant radiotherapy between March 23, 2020, and May 31, 2020. Data were retrospectively collected for treatment dose, boost dose, and toxicity. Among the 85 patients treated with 26 Gy in 5 fractions, 15.9% reported no skin toxicity, while 63.5% reported RTOG Grade 1, 15.9% had Grade 2, and 1.6% reported Grade 3 skin toxicity. Of the 19 patients who received a boost, 10.53% reported no skin changes, 78.9% reported Grade 1 skin toxicity, and Grades 2a and 2b were reported by 5.26% each.

Krug et al.[21] emphasized that in the FAST-Forward trial, the option for boost irradiation was available. This boost was administered as a sequential boost, involving 5–8 fractions of 2 Gy each. Specifically, patients under 40 years and those aged 40–59 years with adverse risk factors, such as grade 3 tumors and/or lymphovascular invasion, received a tumor bed boost. Notably, patients aged ≥60 years generally did not receive a boost. The authors justified this approach by citing prudence in not altering both the fractionation of whole-breast and boost irradiation simultaneously, a strategy akin to the approach in the START trials. However, they expressed reservations about the decision to extend the overall treatment time significantly to deliver a tumor bed boost in 2 Gy fractions to a considerably smaller volume, deeming it unconventional.[21]

A possible way of overcoming this issue of prolongation of treatment due to the administration of a boost dose to the tumor bed could be addressed by incorporating a simultaneous integrated boost (SIB) to the tumor dose during the 5 fractions of ultra-hypofractionated radiation therapy.

There is data regarding the safety and efficacy of incorporating an SIB with moderately hypofractionated regimens. The findings from the randomized IMRT-MC2 trial, which compared an intensity-modulated radiotherapy (IMRT) scheme with SIB to the same scheme with 3D conformal radiotherapy (3D-CRT) and a sequential boost, indicated no significant differences in late cosmesis appearance at the 2-year follow-up. However, IMRT-SIB demonstrated slight superiority over 3D-CRT with a sequential boost in terms of quality of life, attributed to the shortened overall treatment time.[22]

IMPORT HIGH aimed to compare a simultaneous integrated boost with a sequential boost, seeking a shorter treatment duration while maintaining control and similar or reduced toxicity. The control group underwent 40 Gy in 15 fractions to the entire breast and a sequential photon tumor bed boost of 16 Gy in 8 fractions. Test group 1 received 36 Gy in 15 fractions to the whole breast, 40 Gy in 15 fractions to the partial breast, and a concomitant photon boost of 48 Gy in 15 fractions. Test group 2 had 36 Gy in 15 fractions to the whole breast, 40 Gy in 15 fractions to the partial breast, and a concomitant photon boost of 53 Gy in 15 fractions. In all groups, the 5-year incidence of in-breast tumor recurrence was lower than the expected 5%. Adverse event rates at 5 years were low with small boost volumes. Simultaneous integrated boost in IMPORT HIGH was deemed safe and reduced patient visits.[23]

In the NRG RTOG 1005 trial, high-risk post-lumpectomy patients with stages 0, I, and II breast cancer were randomly assigned to two radiotherapy arms. Arm I received 50 Gy in 25 fractions or 42.7 Gy in 16 fractions plus a sequential boost. Arm II received 40 Gy in 15 fractions with a concomitant boost. After a median follow-up of 7.3 years, the 5- and 7-year in-breast recurrence rates were comparable between the two arms. The non-inferiority comparison favored Arm I, meeting criteria (HR: 1.32, $p=0.039$). Adverse events were low and similar between arms, with no significant difference in 3-year excellent/good cosmesis (86% vs. 84% for Arm I vs. Arm II, $p=0.61$).[10]

In contrast to moderate hypofractionation, only a limited number of ultra-hypofractionated regimens incorporate a simultaneous integrated boost. Machiels et al.[24] investigated outcomes in 102 patients using a radiotherapy schedule similar to FAST-Forward but with the inclusion of a single-fraction sequential boost of 6 Gy for patients requiring it. The occurrence of Grade 1 and 2 acute skin toxicity was documented at 74% and 2.7%, respectively.[24]

The HAI5 trial assessed the acute tolerance of a 5-fraction schedule administered every other day for 12 days in 95 breast cancer patients. The treatment in-

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cluded 28.5 Gy/5.7 Gy to the breast/chest wall and 27 Gy/5.4 Gy to the lymph node areas, with a simultaneous integrated boost (SIB) given in 66% of patients at doses of 32.5 Gy/6.5 Gy or 34.5 Gy/6.9 Gy based on surgical margins. With a median follow-up of 5.6 months, the authors observed a 17.6% incidence of Grade 2–3 acute skin toxicity in the SIB arm, compared to 0% when an SIB was not administered.[13]

From the same research team, the YO-HAI5 (Young-Old Highly Accelerated Irradiation in 5 fractions) trial randomly assigned breast cancer patients following lumpectomy to two treatment arms: whole breast irradiation (WBI) in 5 fractions of 5.7 Gy with a simultaneous integrated boost (SIB) of 6.2 Gy over 12 days, or WBI in 15 fractions of 2.67 Gy with a simultaneous boost of 3.12 Gy/day. The researchers noted a notably higher occurrence of acute breast edema, breast pain, asthenia, and skin toxicity in patients subjected to moderate hypofractionation compared to those receiving ultra-hypofractionation.[25]

Montero et al.[26] in Spain recently reported their findings on acute skin toxicity in patients with early breast cancer undergoing ultra-hypofractionated radiotherapy with simultaneous integrated boost (SIB). With a median follow-up of 18 months (range: 7–31), all patients remained alive without any signs of local, regional, or distant relapse. The observed acute tolerance was deemed acceptable, with minimal to mild toxicity: 182 (48%) and 15 (4%) patients experienced skin toxicity of Grade 1 and 2, respectively; 9 (2%) and 2 (0.5%) patients had breast edema of Grade 1 and 2, respectively. No other acute toxicities were noted.[26]

The HYPORT adjuvant trial, a randomized phase III non-inferiority study, compared a standard moderate hypofractionated three-week radiotherapy regimen to an extreme hypofractionated one-week radiotherapy regimen with all breast-conserving surgery (BCS) patients receiving a boost. For patients with a simultaneous integrated boost (SIB), the total dose to the tumor bed volume (BTV) was 48 Gy in 15 fractions (3 weeks) in the control arm and 32 Gy in 5 fractions (1 week) in the experimental arm. Analysis of the first 271 patients, including 104 with an SIB boost, showed that all mandatory dosimetric criteria were met, except for one patient with a higher contralateral breast dose due to optimal internal mammary nodal coverage. Three patients (1.1%) experienced Grade 3 radiation dermatitis (none with SIB), and no other Grade 3 or higher toxicities were reported.[27]

Kılıç Durankuş et al.[28] conducted a study in Turkey evaluating early skin toxicity in breast cancer patients treated with the FAST-Forward radiotherapy protocol. The study included 60 patients who received 26 Gy in five fractions over one week. Their findings demonstrated low acute skin toxicity rates, with 11.6% experiencing Grade 1 reactions and 1.6% experiencing Grade 2 reactions by the second week, highlighting the protocol's safety and feasibility within a Turkish cohort. These results support the adoption of hypofractionated schedules in breast cancer radiotherapy.[28]

The outcomes of our study align with the aforementioned literature, supporting the trends and conclusions observed in the broader research landscape.

We recognize the limitations and contentious aspects of our study. The retrospective nature and absence of randomization and a control group may impact data interpretation, although comparisons with historical data do not indicate worse tolerance with ultra-hypofractionated Whole Breast Irradiation + Simultaneous Integrated Boost (SIB). The limited number of patients and short follow-up may obscure some results, hindering the establishment of long-term tolerance certainty.

The authors acknowledge that the ultra-hypo fractionated regimen is currently not standard for locally advanced breast cancers or those requiring regional nodal irradiation or those treated with BCS requiring SIB. The study includes patients treated from May 2020 to May 2023, which coincided with the period of Covid19 pandemic. There were significant challenges for patient treatment during this period and many patients would not have been able to take the standard 20 fractions radiotherapy. The urgency to optimize treatment delivery while ensuring patient safety prompted us to explore alternative regimens. While acknowledging that the ultra-hypofractionated regimen may not be considered standard practice for LABC, RNI, or SIB treatments, we made the decision based on the available data and clinical judgment. We also acknowledge the importance of thoroughly documenting both acute and late toxicities, particularly in the context of a non-standard treatment approach. While acute toxicities were meticulously recorded during the study, we encountered challenges in documenting late toxicities. The impact of the COVID-19 pandemic and logistical issues, including patients residing out of the study area, posed significant challenges in ensuring comprehensive follow-up and documentation of late toxicities and breast cosmesis. These circumstances limited our ability to monitor patients adequately for late toxicities, including fibrosis, other late effects and cosmesis.

CONCLUSION

Our study demonstrates that ultra-hypofractionated breast radiation therapy is not only feasible and effective, with mild reported toxicities, but also achieves favorable dosimetric outcomes with good acceptance. While we acknowledge the short follow-up period, the survival results observed thus far include a 95.6% overall survival rate, underscoring the potential of this approach. Further studies with longer follow-up are warranted to validate these findings.

Ethics Committee Approval: The study was approved by the Sir H. N. Reliance Foundation Hospital Ethics Committee (no: IEC/2022/DNB-RDOC-20, date: 24/06/2023).

Authorship contributions: Concept – P.R.D., R.K., A.G.; Design – P.R.D., R.K., A.G.; Supervision – P.R.D.; Materials – P.R.D., N.A.S., A.K., V.H., R.B.; Data collection and/or processing – R.K., M.D., A.G.; Data analysis and/or interpretation – P.R.D., A.G.; Literature search – A.G.; Writing – A.G., P.R.D.; Critical review – P.R.D.

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