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Scientific Article

Single-Institution Prospective Evaluation of Moderately Hypofractionated Whole-Breast Radiation Therapy With Simultaneous Integrated Boost With or Without Lymphatic Drainage Irradiation After Breast-Conserving Surgery

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Purpose: We report treatment outcomes for patients who received adjuvant moderate hypofractionated whole-breast radiation therapy with simultaneous integrated boost (SIB-mhWBRT) after breast-conserving surgery.

Methods and Materials: SIB-mhWBRT for patients with breast cancer was introduced in our department in July 2017. This prospective evaluation includes 424 consecutive patients treated with SIB-mhWBRT for stage I-III invasive breast cancer (n = 391) and/or ductal carcinoma in situ (n = 33) until December 2021. SIB-mhWBRT was applied with 40 Gy in 15 daily fractions over 3 weeks according to the START B trial, with an SIB dose to the tumor bed of 48 Gy according to Radiation Therapy Oncology Group 1005/UK-IMPORT-HIGH, delivered as 3-dinemsional conformal radiation therapy (RT; n = 402), intensity modulated RT (n = 4), or volumetric modulated arc therapy (n = 18). The mean patient age was 60 years (range, 27-88). Since May 2018, patients with indications for lymphatic pathway RT were included (n = 62). Baseline parameters and follow-up data were recorded and reported, including objective assessment of treatment-related outcomes and subjective patient-reported outcome measures (PROMs).

Results: Mean/median follow-up was 29/33 months (range, 2-60). Acute toxicity grade 0, 1, 2, and 3 was observed in 25.0%, 61.4%, 13.3%, and 0%, respectively, at the completion of RT. Data of 281, 266, 243, 172, and 58 patients were available for 6-month and 1-, 2-, 3-, and 4-year follow-up, respectively. Grade 2 late effects were identified in 8.5%, 6.0%, 4.9%, 2.2%, and 10.2% and grade 3 in 2.8%, 1.1%, 1.2%, 0%, and 0% of patients at 6-month and 1-, 2-, 3-, and 4-year follow-up, respectively. Medical treatment of breast edema was the only grade 3 late effect observed. PROM cosmesis results were evaluated as excellent-good, fair, and poor in 97.2%, 2.5%, and 0.4%; 96.5%, 3.1%, and 0.4%; 97.4%, 2.2%, and 0.4%; 97.5%, 2.5%, and 0%; and 96.5%, 3.5%, and 0.0% at 6 months and 1, 2, 3, and 4 years post-RT, respectively. For all patients, the 3-year overall, cancer-specific, and disease-free survival rates were 98.2%, 99.1%, and 95.9%, respectively. Three-year risk of any locoregional recurrence was 0.6%. No mortality or relapse was observed in patients with ductal carcinoma in situ.

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Conclusions: SIB-mhWBRT demonstrated very favorable side effect profiles and cosmesis/PROMs. Three-year results demonstrate excellent locoregional control. This short-term regimen offers substantial patient comfort and improves institutional efficacy.

Introduction

Until 1990, adjuvant breast radiation therapy (RT) employed a fractionation regimen, which was historically named standard fractionation, known under the name conventional fractionation (CF) today. This regimen involves administering the radiation dose over 5 to 7 weeks with 25 to 35 fractions of 1.8 to 2.0 Gy.[1] By that time, clinical evidence, through in heterogeneous and diverse patient cohorts, as well as radiobiology modeling data, provided indications that breast cancer could have a higher sensitivity to dose per fraction than other common cancers with an α/β ratio close to 3.8 Gy.[2,3] This created the base for trials testing moderate hypofractionation with a breast RT course delivered with 15 to 20 fractions in 2 to 4 weeks, which was thought to provide similarly high tumor control as standard fractionation and have a low toxicity profile. Thus, starting from 1986, multiple clinical trials emerged exploring moderate hypofractionation in settings of adjuvant breast RT. The 7 most significant of them recruited more than 12,000 patients altogether.[4-10] These trials provided evidence of the effective and safe use of moderately hypofractionated whole-breast RT (mhWBRT) regimens instead of a conventional 25-fraction regimen, which allows both to address better the increasing global needs in RT as well as to provide more convenience to the patients. Results of the European Organisation for Research and Treatment of Cancer boost versus no boost trial with a 20-year follow-up demonstrated the importance of boost dose to the tumor bed, which provides a 4.4% reduction of risk of ipsilateral breast recurrence in all age groups and 11.6% in patients younger than 40 years.[11] Boost dose historically was delivered sequentially after WBRT completion both with CF and hypofractionated regimens. With modern RT techniques, the treatment of boost target volume can be integrated into the mhWBRT as a simultaneously integrated boost (SIB-mhWBRT). With this technique, a higher radiation dose is prescribed to the high-risk area (tumor bed), while the lower dose is applied to the whole breast.[12] For the patients, SIB-mhWBRT provides further reduction in the number of sessions, and for the department, an increase in throughput. The phase 3 NRG Radiation Therapy Oncology Group (RTOG) 1005 clinical trial, with a median follow-up of 7.3 years, demonstrated that SIB-mhWBRT is as effective as conventional fractionation with a sequential boost from the point of view of in-breast relapse rates and late adverse effects, for breast cancer patients who do not require regional lymphatic node irradiation.[10] Despite the growing evidence of the safety and efficacy of hypofractionated SIB concept application for adjuvant breast RT,[13-21] this is still not in widespread clinical use.[1,22] In our department, SIB-mhWBRT has been used for the breast since July 2017. Since May 2018, this has also included patients with regional lymphatic treatment.

The aim of this work was to assess treatment outcomes.

Methods and Materials

From July 2017, all patients with breast cancer after breast-conserving surgery, to whom whole-breast RT with tumor bed boost was indicated, received SIB-mhWBRT and were prospectively assessed. Since the ultrahypofractionated whole-breast irradiation was introduced in March 2020, SIB-mhWBRT was only provided for women with an indication for lymphatic pathway irradiation. Additionally, with the clinical implementation of accelerated partial breast irradiation for selected patients with early disease back in August 2016, the latter subgroup was also not treated with SIB-mhWBRT.

The early and intermediate treatment tolerances, patient-reported outcome measures (PROMs), and disease control were accessed in the cohort treated in the time interval between July 2017 and December 2021.

Patients

According to the institutional breast RT protocol, whole-breast irradiation with SIB was indicated for patients with the following characteristics:

- Invasive breast carcinoma and/or ductal carcinoma in situ of the breast
- pT1-4, pN0-3, absent or microscopic residual tumor (R0-1), any lymphatic invasion (L), any vascular invasion (V)
- Prior breast-conserving surgery

Patients aged ≥50 with unifocal tumor pT1-2, £ 30 mm, pN0-1, £ 3 positive axillary nodes, R0, L0, V0 were defined as a low-risk group. Any patients with SIB indications but not fulfilling these criteria were defined as high-risk group. Patients underwent neoadjuvant or adjuvant systemic therapy if indicated. Starting from May

2018, the protocol was adapted to include patients with an indication for lymphatic drainage RT.

Treatment

The RT regimen for patients was chosen according to the test arm of the RTOG trial 1005[23] and the test arm of the UK IMPORT HIGH trial[19] respectively, with 15 × 2.67 Gy and 3.2 Gy = 40.05 Gy whole breast and 48 Gy tumor bed boost, respectively. A dosage of 15 × 2.4 Gy and 3.2 Gy = 36 Gy and 48 Gy was allowed in the protocol for low-risk patients. For patients not receiving adjuvant chemotherapy, RT treatment started within 6 to 12 weeks after the surgery or 4 to 8 weeks after the last chemotherapy cycle. Irradiation of the lymphatic drainage pathways was performed in patients based on the initial status of the tumor for patients with neoadjuvant systemic treatment and on pathologic findings and surgical treatment volume (sentinel lymph node dissection or axillary lymph node dissection) for other patients.[24–31]

RT planning and treatment delivery

The planning computed tomography (CT) scan was acquired natively in the supine position with raised arms. The CT scan region was from midneck to a minimum 5 cm below the breast, mandatory including whole lung volume. The slice thickness was 5 mm. For all patients, CT data were acquired with a Canon Aquilion LB CT scanner (Canon Medical Systems Corporation, Ōtawara, Tochigi, Japan). In the case of left-sided breast treatment or the treatment of internal mammary lymph nodes or medial tumor bed location of any laterality, an additional deep inspiration breath hold CT was acquired in all cooperating patients. Planning CT with the most favorable heart separation from the chest wall was used for the RT planning. The RT plans for all patients were developed with the Eclipse treatment planning system (Eclipse version 15.6, Varian Medical Systems, Palo Alto, CA). Three-dimensional conformal RT with static fields, intensity modulated RT, or volumetric modulated arc therapy techniques were used for treatment.

The boost target volume in most cases was based on intraoperatively placed clip markers or, in the absence of these, on visible postoperative changes and preoperative imaging. The geometric safety margin clinical target volume (CTV) to the planning target volume of 5 mm according to institution standards was added. As general guidance, the boost target volume should not exceed 1 quadrant of the breast. The delineation of the whole-breast CTV was performed according to the standard clinical whole-breast external beam irradiation protocol, and the planning target volume was created with the addition of a 5-mm safety margin. Regional RT of the lymphatic drainage pathways was performed according to the current standard clinical RT guidelines for patients with nodal involvement. In the case of high involvement of axillary lymph nodes, European Society for Radiotherapy and Oncology guidelines were used,[32] and in the case of low involvement of axillary lymph nodes, RTOG guidelines[33] were used for CTV delineation.

Dose constraints for treatment planning for healthy tissue and organs were as follows:

- Ipsilateral lung: <20% of lung volume £ 20 Gy
- Contralateral lung: dose exposure as low as possible
- Contralateral breast: dose exposure as low as possible
- Heart: maximum point dose (Dmax) < 20 Gy
- Arm plexus: dose Dmax £ 40 Gy

All patients were irradiated using a linear accelerator with daily image guidance.

Patient data collection and follow-up

Data collection occurred before RT initiation, at RT completion, 1 to 4 weeks after RT completion (early side effects), after 6 and 12 months, then annually. Interval for outcomes reported is between end of treatment and event. Objective and subjective data on side effects and cosmetic outcomes were collected during follow-up visits and scored according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03, for acute toxicity[34] and the Late Effects in Normal Tissues—Subjective, Objective, Management, and Analytic (LENT-SOMA) scale for late treatment outcomes.[35] Early effects assessment included skin erythema, desquamation, edema, bleeding, and necrosis/ulceration. Late effects (>3 months after RT completion) assessed: breast retraction/atrophy, edema of the irradiated tissue, skin (telangiectasia, hyper/hypopigmentation), radiogenic fibrosis (palpatory and subjective indications), lymphedema of the ipsilateral arm, and any need for treatment of a skin/tissue condition. Subjective data were gathered with the standardized survey of the patients (using a self-assessment questionnaire), which was carried out as a PROM collection according to the LENT-SOMA scale. Pain and its intensity and changes in skin sensation were assessed. To assess the cosmetic outcomes, patient and examiner evaluation data were collected using the Harvard/National Surgical Adjuvant Breast and Bowel Project/RTOG breast cosmesis grading scale.[36] The treated breast was compared with the opposite side. Photo documentation of the breast was also carried out on each clinical visit. The regular oncologic follow-ups were carried out by referring physicians, surgeons, and gynecologists involved according to the usual follow-up standards.

Statistics

Descriptive statistical parameters were used for describing patient data and outcomes. Risk ratios (RRs), associated confidence intervals (CIs), and *P* values were estimated using contingency tables, CIs for normal distribution, and *z* tests. The statistical significance of differences in numerical parameters in patient groups with different outcomes was estimated using the Wilcoxon rank-sum statistic. A *P* value of .05 was taken as the significance threshold for rejection of null hypothesis. Disease specific survival, overall survival, disease-free survival, and locoregional relapse risk were calculated using Kaplan-Meier estimates. In disease-specific survival, an event was defined as death caused by the local or distant relapse of breast cancer. In overall survival, an event was defined as any death. In disease-free survival, an event was defined as any relapse of breast cancer. In locoregional relapse risk, an event was defined as any relapse in the ipsilateral breast or in regional lymphatic collectors.

Ethics approval and informed consent

Ethical approval for this study was obtained from the institutional ethical committee (approval number 2020 01008). Written informed consent was obtained from all subjects before the study. All patients included in this analysis initially confirmed their consent for further follow-up controls by us and the further anonymous use of their clinical data (general informed consent of the hospital).

Results

Patients and treatment

Data of 424 consecutive patients treated using the SIB-mhWBRT irradiation regimen at our department between July 2017 and December 2021 was included in this prospective analysis. Table 1 shows the therapy- and tumor-related characteristics of the patient cohort.

RT

RT was performed with 3-dimensional conformal RT in 402 patients (94.8%), intensity modulated RT in 4 patients (0.9%), and volumetric modulated arc therapy in 18 patients (4.2%). Four hundred three patients (95.0%) received a whole-breast dose of 40.05 Gy and the remaining 21 patients (5.0%) of 36.00 Gy. All patients received a dose of 48.00 Gy to the boost volume. The mean irradiated whole-breast volume was 749 ± 385 cm^3 (median, 663; interquartile range [IQR], 470-946 cm^3). The mean boost treatment volume was 98 ± 50 cm^3 (median, 89; IQR, 61-121 cm^3). Mean boost to the whole-breast volume ratio corresponded to 14% ± 5% (median, 14%; IQR, 10%-17%) of the total breast volume. In 408 patients (96.2%), boost volume was less than or equal to one-fourth of breast volume, whereas in 16 patients (3.8%), boost volume exceeded one-fourth of breast volume.

Follow-up

The mean follow-up was 29 ± 16 months (range, 2-60), and the median follow-up was 33 months (IQR, 11-10). Six-month and 1-, 2-, 3-, and 4-year follow-up data were available for 281, 266, 243, 172, and 58 patients, respectively.

Tumor control

To date, 14 patients (3.3%) have presented with ipsilateral breast recurrence or distant relapse and no regional nodal recurrences have been observed. Eleven of 14 patients (2.6% of the entire cohort) recurred with distant metastases only. The median onset of distant metastases was 27 months (range, 5-44). Three patients (0.7%) received a diagnosis of isolated ipsilateral breast recurrence at 3, 10, and 44 months after radiation completion. Eight patients in total died within the observed period, 4 of whom within 8 to 50 months after RT from non−cancer-related causes, including COVID-19 complications. A 3-year locoregional control rate of 99.4% (95% CI, 97.7%-99.9%) (Fig. 1A), a distant metastasis-free survival rate of 97.5% (95% CI, 94.5%-98.9%), and nodal control of 100% were observed. The 3-year disease-free survival was 95.9% (95% CI, 92.7%-97.7%) (Fig. 1B). The 3-year cancer specific survival was 99.1% (95% CI, 97.1%-99.7%) (Fig. 1C), and the 3-year overall survival of the cohort was 98.2% (95% CI, 95.9%-99.2%) (Fig. 1D). To date, no mortality or relapse has been observed in patients with ductal carcinoma in situ.

Objective evaluation of early reactions

Overall, G1 acute reactions were observed in 61.5% of patients (n = 261) and G2 reactions in 13.3% (n = 56) (Fig. 2). Clinically, the most common reaction shortly after completion of SIB-mhWBRT was mild skin erythema. The only patient who presented with G3 acute reactions (ie, bleeding) had surgical wound bleeding before the start of RT. No G3 RT-related early effects were registered.

Table 1 Therapy- and tumor-related characteristics of the patient cohort

Characteristic		Value
Number of patients		424
Age, y	Median [IQR] (range)	59 [51-70] (27-88)
	Mean ± SD	60 ± 12
Side of primary tumor	Left	202 (47.7%)
	Right	222 (52.3%)
Histology	DCIS	33 (7.8%)
	Infiltrating ductal carcinoma	323 (76.2%)
	Infiltrating lobular carcinoma	52 (12.2%)
	Other	16 (3.8%)
Grading carcinoma	G1	46 (11.8%)
	G2	210 (53.7%)
	G3	135 (34.5%)
Grading DCIS	DCIS high grade	27 (81.8%)
	DCIS intermediate grade	5 (15.2%)
	DCIS low grade	1 (3.0%)
Pathologic tumor size, cm	Median [IQR] (range)	1.8 [1.1-2.5] (0.1-12.0)
	Mean ± SD	1.9 ± 1.3
Pathologic T stage	DCIS	33 (7.8%)
	T0	3 (0.7%)
	Tis	2 (0.5%)
	T1	8 (1.9%)
	T1a	5 (1.2%)
	T1b	48 (11.3%)
	T1c	153 (36.1%)
	T2	166 (39.2%)
	T3	5 (1.2%)
	T4a	1 (0.2%)
Extent of axillary staging	Sentinel node biopsy	354 (83.5%)
	Axillary clearance	70 (16.5%)
Pathologic node status	Positive	142 (33.5%)
	Negative	282 (66.5%)
Pathologic N stage	N0	283 (66.7%)
	N0(i+)	10 (2.3%)
	N1	34 (8.0%)
	N1a	38 (9.0%)
	N1mi	32 (7.5%)
	N2	10 (2.3%)
	N2a	8 (1.8%)
	N3	3 (0.8%)
	N3a	4 (1.0%)
	N3b	1 (0.3%)
	N3c	1 (0.3%)

(*continued on next page*)

Table 1 (*Continued*)

Characteristic		Value
Resection margin	R0	415 (97.9%)
	R1	9 (2.1%)
Oncoplastic surgery	Yes	141 (33.3%)
	No	283 (66.7%)
Number of tumor bed clips	0	12 (2.8%)
	1-3	65 (15.3%)
	4-6	329 (77.7%)
	7-9	18 (4.2%)
Estrogen receptors	Positive (>1%)	340 (80.2%)
	Negative	84 (19.8%)
Progesterone receptors	Positive (>1%)	302 (71.2%)
	Negative	122 (28.8%)
Her-2/new	Positive	57 (13.4%)
	Negative	367 (86.6%)
Ki-67	Positive (>1%)	388 (91.5%)
	Negative	36 (8.5%)
Lymphovascular invasion	Present	84 (19.8 %)
	Absent	340 (80.2%)
Neoadjuvant chemotherapy	Yes	90 (21.3%)
	No	334 (78.7%)
Adjuvant chemotherapy	Yes	177 (41.8%)
	No	247 (58.2%)
Adjuvant hormonal therapy	Yes	295 (69.5%)
	No	129 (30.5%)
Lymphatic drainage RT (% of total/% of 402 patients included in modified protocol since May 2018)	Yes	62 (14.6%/15.4%)
	Supraclavicular	53 (12.5%/12.9%)
	Axillary	24 (5.7%/6.0%)
	Internal Mammary	9 (2.1%/2.2%)
	No	362 (85.4%)
DIBH for left-sided breast	Yes	164 (81.2%)
	No*	38 (18.8%)

Abbreviations: DCIS = ductal carcinoma in situ; DIBH = deep inspiration breath hold; G = grade; IQR = interquartile range; RT = radiation therapy.
* Mainly patients aged >75 years.

Subjective late effects and PROMs

Figure 3 presents the frequency distribution of the patient's self-evaluation of pain and its severity before and after RT, arranged according to the time breakdown. The pain was reported postoperatively by 47.6% of the patients before the start of RT. Patients reported experiencing pain sometimes or often in 16.3% after 6 months, 9.6% after 1 year, 10.1% after 2 years, 9.5% after 3 years, and 8.8% after 4 years. Among patients who reported pain, 65.0%, 75.3%, 70.2%, 69.7%, and 44.4% described pain as minimal after 6 months, 1 year, 2 years, 3 years, and 4 years, respectively. None of the patients reported intensive pain at 3- and 4-year follow-ups. Among patients experiencing pain, 9.7% (n = 11) reported any need for analgesics after 6 months, 4.9% (n = 4) after 1 year, 10.3% (n = 6) after

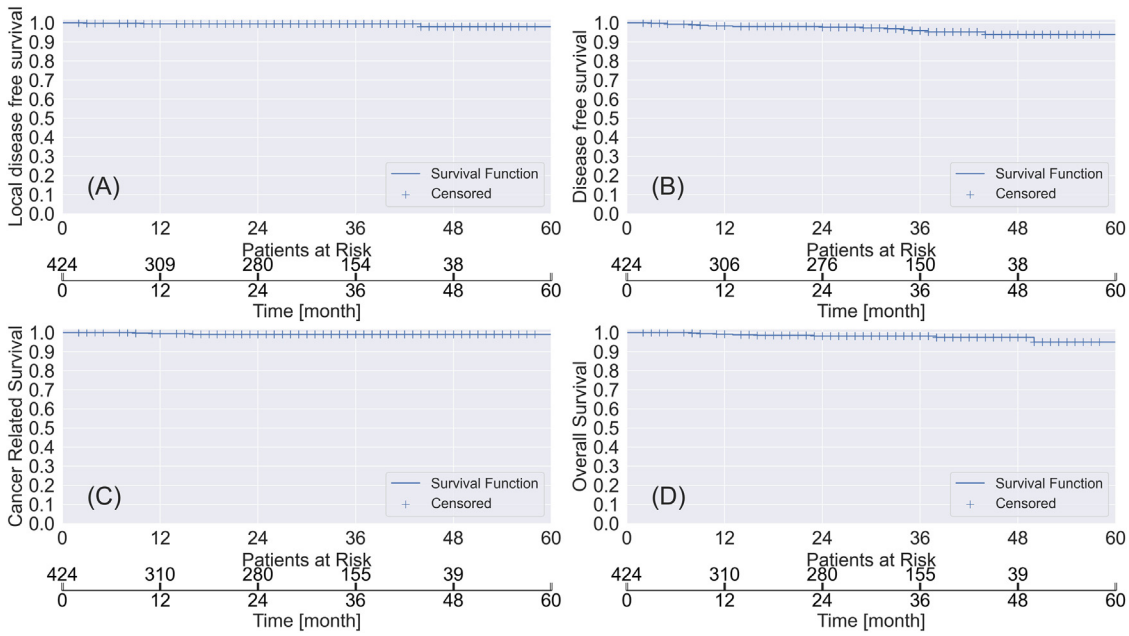

Figure 1 Kaplan-Meier estimation of (A) overall survival, (B) cancer-related survival, (C) local disease-free survival, and (D) disease-free survival.

2 years, and 2.8% (n = 1) after 3 years. No patients reported any need for analgesics after 4 years. At the follow-up after 6 months, 1 year, 2 years, 3 years, and 4 years, 81.6%, 90.8%, 94.7%, 93.0%, and 91.1% of patients, respectively, had not reported any skin sensation changes.

Objective evaluation of late effects

Figure 4 shows the frequency distribution of objective late effects, arranged according to the time breakdown. Any grade ≥2 (G2+) effects were observed in 11.3% (95% CI, 7.6%-15.0%), 7.1% (95% CI, 4.0%-10.2%), 6.2% (95% CI, 3.1%-9.2%), 3.5% (95% CI, 0.7%-6.2%), and 10.2% (95% CI, 2.5%-17.9%) of patients at 6-month and 1-, 2-, 3-, and 4-year follow-up, respectively. The detailed distribution of the late effects is shown in Table E1. The only

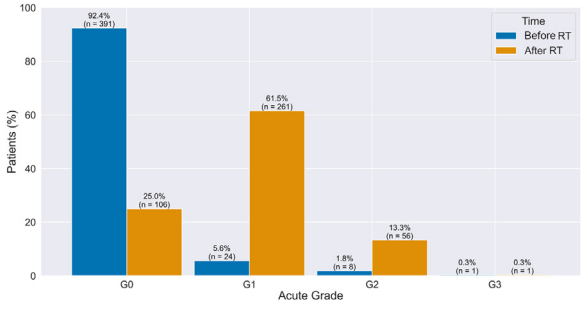

Figure 2 Acute reactions before and 1 to 4 weeks after moderately hypofractionated whole-breast radiation therapy (RT) with simultaneous integrated boost.

G3 effect observed was breast edema treatment (lymphatic drainage as a "medical intervention" is defined as G3 in LENT-SOMA).[35]

Eleven patients (2.6% of the whole cohort) received edema treatment within the observation period. Seven patients (2.5% of observation) received edema treatment within the first 6 months; after 12 months, this was the case for 3 patients (1.1% of observation); after 24 months for 3 patients (1.2% of observation), and after 3 and 4 years for none of the patients. The median breast volume of 66 patients (16%) who developed breast edema of any grade within the observation period was 903 cm^3 (IQR, 687-1229 cm^3; range, 295-2172 cm^3), higher than the median volume of the total collective of 663 cm^3 (IQR, 470-946 cm^3; range, 47-2820 cm^3), and of patients without edema, 629 cm^3 (IQR, 454-880 cm^3; range, 47-2820 cm^3), respectively. The difference between breast volumes in patients with and without edema of any grade was statistically significant ($P < .001$). The risk of G2 edema was not different in patients with or without nodal irradiation (RR, 1.039; $P = .383$; 95% CI, 0.954%-1.132%). The risk of G1+ breast edema was higher in patients with nodal irradiation (RR, 1.286; $P = .022$; 95% CI, 1.037%-1.594%).

The RR forest plot shown in Fig. 4 demonstrates the influence of the presence or absence of nodal irradiation on separate late effect parameters with G2+ complications observed and on cumulative late G2+ complications. There was no statistically significant difference in G2+ complications in patients with or without nodal irradiation (RR, 0.993; $P = .921$; 95% CI, 0.873%-1.131%). Separate evaluation of late skin toxicity only (telangiectasia, pigmentation changes, and fibrosis) demonstrated the

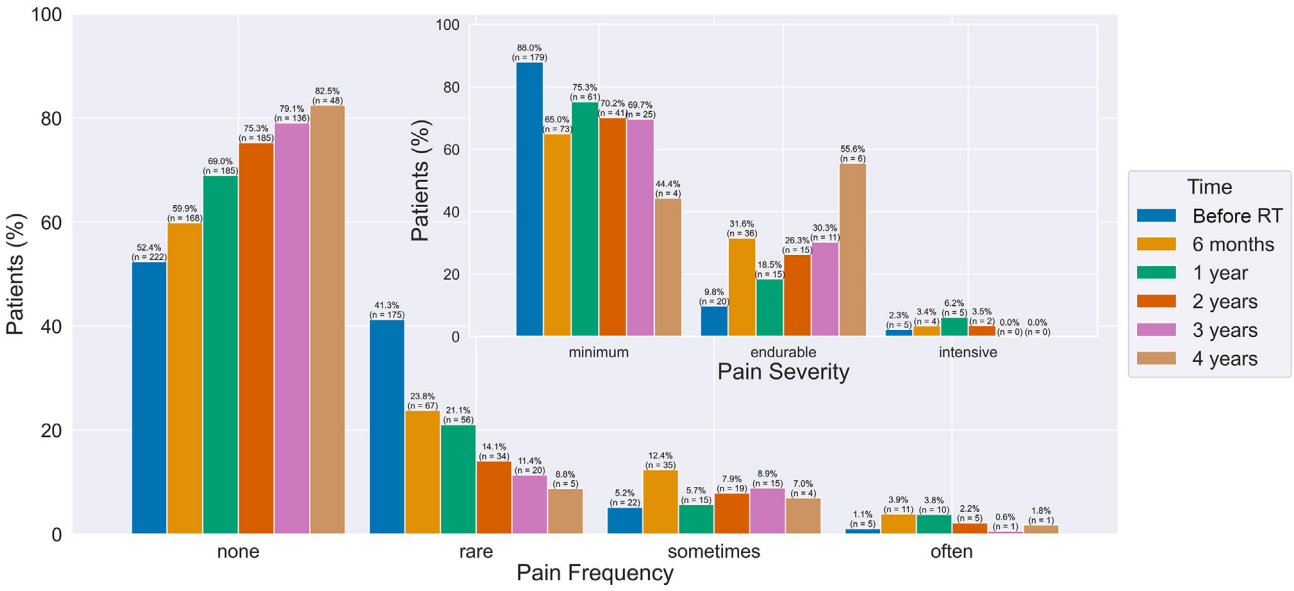

Figure 3 Chest pain and severity of such before radiation therapy (RT) after 6 months and 1, 2, 3, and 4 years.

toxicity of G2 in 5.7%, 4.5%, 4.5%, 3.5%, and 6.8% of patients after 6 months and 1, 2, 3, and 4 years, respectively. No higher-grade toxicity was observed. The risk of G2 skin toxicity was not different in patients with or without nodal irradiation (RR, 0.961; P = .317; 95% CI, 0.888%-1.040%) risk of skin toxicity of G1+ was higher in the subgroup with nodal irradiation, but this difference was not statistically significant (RR, 1.439; P = .080; 95% CI, 0.958%-2.163%). The risk of G2 postradiation fibrosis was lower in patients with nodal irradiation (RR, 0.941; P = .022; 95% CI, 0.893%-0.991%). There was no statistically significant difference in the risk of G2 arm lymphedema (RR, 1.018; P = .369; 95% CI, 0.979%-1.059%), as well as in the risk of G1+ arm lymphedema (RR, 1.100; P = .068; 95% CI, 0.993%-1.218%) in patients with or without nodal irradiation.

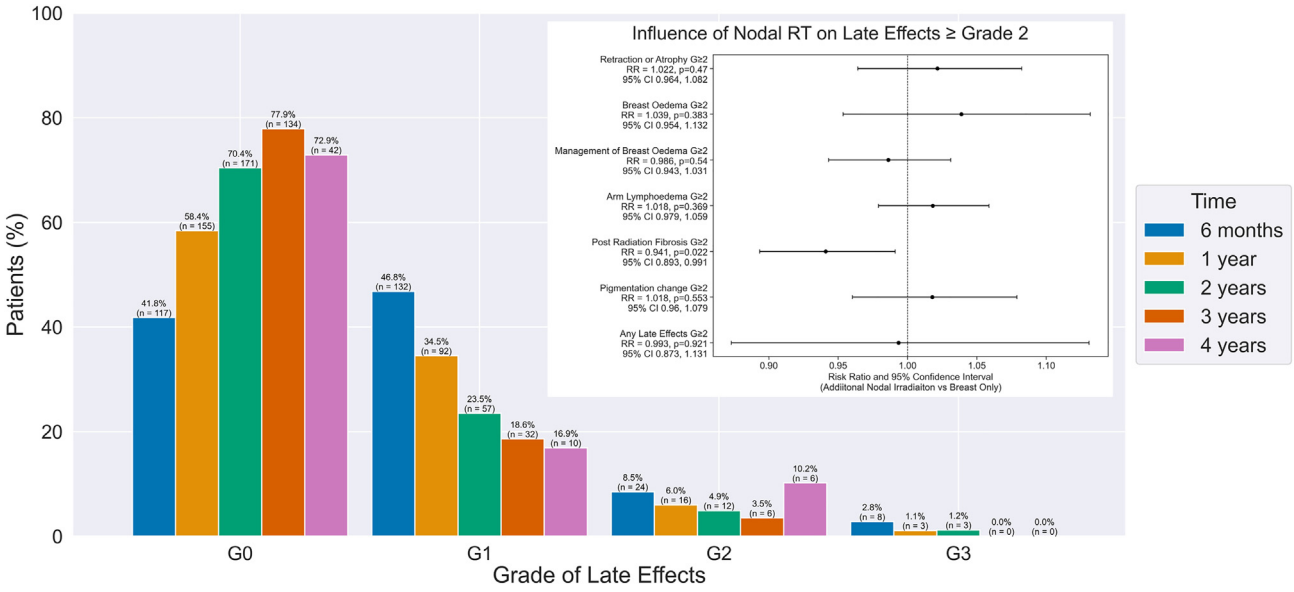

Figure 4 Frequency distribution of objective late effects. Insert shows forest plot of risk ratios (RR) demonstrating the influence of the presence or absence of nodal irradiation on selected late effects with grade ≥2 and on cumulative late effects of grade ≥2 (n = 52). *Abbreviation*: RT = radiation therapy.

Cosmetic result

Patients rated the cosmetic result as "good to very good" in 97.2% (n = 273), 96.5% (n = 257), 97.4% (n = 273), 97.5% (n = 168), and 96.5% (n = 56) cases after 6 months and 1, 2, 3, and 4 years, respectively. There was no statistically significant influence of oncoplastic surgery, chemotherapy, or any other patient or treatment-related factors on cosmetic outcomes. Figure E1 shows the results of the cosmetic self-evaluation before RT and during follow-up appointments.

Discussion

The aim of this prospective analysis was the subjective and objective assessment of acute and intermediate tolerance and cosmetic outcome after postoperative SIB-mhWBRT in our patients with organ-preserving breast cancer. In summary, we found a high early and intermediate therapy tolerance as well as a high degree of subjective satisfaction in the PROM evaluations, with still relatively short follow-up. The tumor control rate was high; in contrast to most of the studies listed in Table 2, advanced tumor stages were also included in our patient cohort. The mean age of 60 years in our cohort is comparable to that of the studies mentioned.

Table 2 summarizes major SIB-mhWBRT studies from the perspective of tumor control and tissue tolerance at the time of implementation of the SIB-mhWBRT regimen at our center. Compared with the data of Janssen et al[39] for mhWBRT according to START A with the sequential boost (13 fractions, 41.6 Gy whole-breast dose applied 4 days of the week, 1 × weekly boost irradiation with 3 Gy each on the fifth day, total treatment duration 3 weeks) or the analysis of Giani et al[40] according to START B with the sequential boost (15 fractions, whole-breast dose of 40 Gy, boost irradiation sequentially after completion of whole-breast mhRT with 8-10 × 2 Gy, duration 4.5-5 weeks), we found, as in other SIB studies, similarly good tolerance results for the SIB concept also with 40 Gy whole-breast dose applied in 3 weeks.

The proportion of 62% G1 early reactions (predominantly erythema) observed in our study is broadly in line with other collectives: Scorsetti et al (64%),[14] Chadha et al (70%),[17] Giani et al (sequential boost, 70%),[40] Formenti et al (72%),[16] and Janssen et al (sequential boost, 82%).[39]

The hypothesis of the ARO-2013-04 phase 2 study was a maximum G2+ acute dermatitis of 20%. The results[41] collected from 143 patients from 12 centers in the period of November 2013 through July 2014 show a G2+ rate of 14.7%, as well as 11% G3 skin reactions. In our cohort, we observed 13.3% G2 skin reactions, which is within the range and comparable with other analyses, such as Scorsetti et al with 0%, Janssen et al (sequential boost) and Chadha et al with 5% each, Formenti et al with 10%, Giani et al (sequential boost) with 22%, and Van Parijs et al[20] with 27%. We saw no RT-related G3 early reactions, comparable to Formenti et al, Scorsetti et al, and Giani et al (sequential boost) at 1% each and Van Parijs et al with slightly higher values (8%). In the recently reported HYPORT adjuvant trial, where around 70% of patients underwent nodal irradiation (12.5% in our study), no Grade 3 toxicity was reported among patients who received the 3-week SIB treatment.[37] These patients had an identical dose fractionation schedule to our study.[38]

The absence of G2 late skin toxicity and 0.3% G3 skin toxicity were reported on up to 3 years of follow-up by Franceschini et al.[42] Separate evaluation of late skin toxicity only (telangiectasia, pigmentation changes, and fibrosis) in our analysis shows that G2 was observed in 5.7%, 4.5%, 4.5%, 3.5%, and 6.8% of patients after 6 months and 1, 2, 3, and 4 years, respectively. No higher-grade toxicity was observed. The risk of G2 skin toxicity was not different in patients with or without nodal irradiation (RR, 0.96; P = .317; 95% CI, 0.89%-1.04%); the risk of any skin toxicity was higher in the group with nodal irradiation, but this difference was not statistically significant (RR, 1.44; P = .080; 95% CI, 0.96%-2.16%). Recent results of the NRG RTOG 1005 trial demonstrated low rates of any G3+ treatment-related toxicity after a median follow-up of 7.3 years, such as 3.5% in Arm II, which has used the same fractionation regimen as the current study.[10] In our study, medical treatment of G3 late-toxicity edemas was observed in 2.6% of patients to date after a median follow-up of 2.8 years.

A combined analysis of 5 years of follow-up data of the ARO-2010-01 and ARO-2013-04 studies recently reported a cumulative G3 late toxicity rate of 0.7% (related to breast lymphedema and telangiectasia).[21] In this analysis, after a median follow-up time of 33 months, no lymphedema of the breast or telangiectasia of G3 was observed. The cumulative G3 late toxicity rate of 2.6% observed in this analysis was related only to breast edema medical treatment.

Similar intermediate tissue toxicity was found by Janssen et al after a sequential boost after 12 months (n = 180 patients; no 6-month control), with a comparable frequency of edema formation, telangiectasia, and pigmentation changes with slightly less postradiogenic fibrosis.

The PROMs recorded in our study document a high level of patient satisfaction with the SIB-mhWBRT treatment. More than 97% of all patients rated the cosmetic result at 3-year follow-up as good to excellent. The poor breast appearance was observed in our study in 0.7%, 0.4%, 0.4%, 0.4%, 0.0%, and 0.0% of patients after 6 months and 1, 2, 3, and 4 years, respectively. This excels results of Arm II of the NRG RTOG 1005 trial, which used the same fractionation regimen as the current study and reported 84% of excellent or good cosmetics results on a 3-year follow-up.[10]

Besides RT, the cosmetic outcome is known to be influenced by surgical intervention, tumor location and

Table 2 Major SIB-mhWBRT studies indicating tumor control and tissue tolerance

Authors/trial/ publication year/ study [reference]	Patients, no.	FU (mo), median	Tumor characteristics	Patient characteristics	SIB-mhWBRT schedule	% Local recurrency	Tolerance
Mondal et al, 2017, phase 1/2 [13]	10	24	pT1-2, N0-1	≥18 y.o.	VMAT: 15 Fr 40.5/ 48 Gy/3 wk	0% @ 2 y	No G3
Scorsetti et al, 2012, phase 1/2 [14]	50	12	pT1-2, N0-1	36-88 y.o.	VMAT: 15 Fr 40.5/ 48 Gy/3 wk	0% @ 1 y	1 acute G3, late complications not assessed
De Rose et al, 2017, phase 2 [15]	787	47	DCIS or IDC stage I-II <3 cm, N ≤3	≥18 y.o.	VMAT: 15 Fr 40.5/ 48 Gy/3 wk	0% @ 2 y	No acute G2, no late G3
Formenti et al, 2011, phase 1/2 [16]	141: 90 51	61	Stage I-II	-	IMRT: 15 Fr 40.5/48 Gy/3 wk Control: 46 + 14 Gy/6 wk	1% @ 3.5 y	No late G3
Chada et al, 2012, prospective cohorts [17]	124: 50 74	42	pTis, pT1-2, 3 cm, pN0/i	-	IMRT: 15 Fr 40.5/45 Gy/3 wk Control: 46.8/ 1.8 + 14 Gy/2 Gy/6 wk	1% @ 3.5 y	No late G3
Cievide et al, 2012, NYU 01-51 and NYU 05-181 combined [18]	145: 59 86	60	DCIS	Any	15 Fr 3D-CRT: 42 Gy IMRT: 40.5/48 Gy/3 wk	4.1% @ 5 y	PROMs: 91% good-excellent, 9% fair-poor
UK IMPORT HIGH, 2019, phase 3 [19]	2617	49	pT1-3, pN0-3a	≥18 y.o.	IMRT: 15 Fr 36/40/48 vs 53 Gy/3 wk	-	After 3-y comparable late effects in SIB-IMRT and WBRT + sequential boost
RTOG 1005, 2022, phase 3, [10]	2262: 1124 1138	87	DCIS or stage I-II, N0-1	≥18 y.o.	3D-CRT IMRT Arm I: 50 Gy/25 Fr or 24.7 Gy/16 Fr + 12-14 Gy Arm II: 15 Fr 40/48 Gy/3 wk	2.0% @ 5 y 2.2% @ 7 y 1.9% @ 5 y 2.6% @ 7 y	3.3% rate of late G3+ toxicity 3-y excellent/good cosmesis: 86% 3.5% rate of late G3+ toxicity 3-y excellent/good cosmesis: 84%
Van Parijs et al, 2012, University Hospital Brussels, phase 3 [20]	69: 37 32	72	pT1-3, N0-1	Any	IMRT: 15 Fr 42/51 Gy/3 wk Conventional: 50 Gy/25 Fr 18 Gy/9 Fr boost	0% @ 4 y 0% @ 4 y	Conventional arm with 2 × more late effects

(*continued on next page*)

Table 2 (*Continued*)

Authors/trial/ publication year/ study [reference]	Patients, no.	FU (mo), median	Tumor characteristics	Patient characteristics	SIB-mhWBRT schedule	% Local recurrency	Tolerance
Pfaffendorf et al, 2022, ARO-2010-01 and ARO-2013-04 combined [21]	274	60	R0, no lymphatic RT indications	≥18 y.o.	IMRT (54.7%), 3D-CRT (43.8%): 16 Fr 40/ 48 Gy/3 wk	1.1% @ 5 y	14.7% G2-3 acute, no influence on cosmetic 0.7% rate of late G3 toxicity 7.3% rate of G2 toxicity
HYPORT-Adjuvant SIB cohort, 2022 [37,38]	104: 52 52	Ongoing since March 2019	R0, M0, no DCIS	Any	15 Fr 40/48 Gy/3 wk 5 Fr 26/32 Gy/1 wk	Ongoing	9.6% G2 dermathitis 1.9% G2 dermathitis
Present analysis, 2023	424	33	pT1-4, N0-3, R1-0	Any	15 Fr 3D-CRT: 40/48 Gy/3 wk	0.6% @ 3 y in whole cohort 0.6% @ 3 y in patients with follow-up >3 y	No RT-related acute G3 @ 3 y: no late G3, PROMs 97% good-excellent

Abbreviations: 3D-CRT = 3-dimensional conformal radiation therapy; DCIS = ductal carcinoma in situ; Fr = fractions; FU = follow-up; G = grade; IDC = invasive ductal carcinoma; IMRT = intensity modulated radiation therapy; PROMs = patient-reported outcome measures; RT = radiation therapy; RTOG = Radiation Therapy Oncology Group; SIB = simultaneous integrated boost; SIB-mhWBRT = moderately hypofractionated whole-breast radiation therapy with simultaneous integrated boost; VMAT = volumetric modulated arc therapy; WBRT = whole-breast radiation therapy; y.o. = years old.

size in relation to the breast, and individual tissue reaction. The differentiation of actinic versus the other influencing factors is not possible.

Studies by other authors that collected PROMs, such as those by Scorsetti et al (100% satisfaction at 12 months), Franceschini et al (97.2% at 3 years and 98.3% at 5 years), ARO-2013-04, and Ciervide et al[18] (91% 6 months and 90.5% at 5 years, respectively) showed similar high PROM satisfaction rates, as did the cohorts of patients after sequential mhRT boost by Janssen et al (99% satisfied to very satisfied at 12 months) and Giani et al (98% at 1 year and 95% at 2 years).

No tangible influence of oncoplastic interventions on any outcomes was found.

Limitations and deficits of the work

There were patients lost to follow-up for the questionnaire/data collection, known as being alive and nonrelapsed from other sources: 34% after 6 months, 14% after 12 months, 13% after 24 months, and 3% after 36 months. The drop in 6-month follow-up data was mainly related to the COVID-19 pandemic (April 2020-December 2021). Later, some of these patients were followed up with on annual assessments. Otherwise, because the therapy is very well tolerated, patients no longer necessarily have any incentive to visit the doctor for follow-up only.

The observation period is still too short for a conclusive assessment of the long-term outcomes.

Conclusion

Based on the data presented herein as well as on the increasing number of results available from other centers, SIB-mhWBRT of the breast is confirmed as effective, well tolerated, patient friendly, and economically advantageous.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2023.101270.

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