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Basic Original Report

Locoregional Ablative Radiation Therapy for Patients With Breast Cancer Unsuitable for Surgical Resection

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Purpose: Patients with breast cancer who are unsuitable for surgical resection are typically managed with palliative systemic therapy alone. We report outcomes of 5-fraction ablative radiation therapy for nonresected breast cancers.

Methods and Materials: This is a retrospective analysis of an institutional registry of patients with breast cancer who were unsuitable for resection and underwent 35 to 40 Gy/5 fractions to the primary breast tumor or regional lymph nodes from 2014 to 2021. Primary outcomes were cumulative incidence of local failure and grade ≥3 toxicity (Common Terminology Criteria for Adverse Events, version 5.0).

Results: We reviewed 57 patients who received 61 treatment courses (median age of 81 years; range, 38-99). Unresectable tumor (10%), patient refusal (18%), medical inoperability (35%), and metastatic disease (37%) were the causes of not having surgery. Five patients (8%) had previously undergone adjuvant locoregional radiation therapy. Fifty-four percent (n = 33/61) of treatment courses targeted the breast only, 31% (n = 19/61) both the breast and lymph nodes, and 15% (n = 9/61) the lymph nodes only. Sixty-seven percent (n = 35/52) of the courses that targeted the breast were delivered with partial breast irradiation and 33% (n = 17/52) with whole breast radiation therapy (median dose of 25 Gy in 5 fractions) ± simultaneous integrated boost to the primary tumor. Most primary tumors (65%, n = 34/52) and target lymph nodes (61%, n = 17/28) were treated with a dose of 35 Gy in 5 fractions. Most treatments (52%) were delivered with intensity modulated radiation therapy (IMRT). Radiation therapy was delivered daily (20%), every other day (18%), twice weekly (36%), or weekly (26%). The 2-year cumulative incidence of local failure was 11.4% and grade≥3 toxicity was 15.1%. The grade ≥3 toxicity was 6.5% for IMRT treatments, versus 7.7% for non-IMRT treatments targeting partial breast or lymph nodes (hazard ratio, 1.13, P = .92), versus 38.9% for non-IMRT treatments targeting the entire breast (hazard ratio, 6.91, P = .023). All grade ≥3 toxicity cases were radiation dermatitis. No cases of brachial plexopathy were observed.

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Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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Conclusions: Thirty-five to 40 Gy in 5 fractions is a safe and effective breast stereotactic body radiation therapy (SBRT) regimen and may be an attractive option for patients who are not surgical candidates. Highly conformal techniques (ie, IMRT or partial breast irradiation) were associated with a reduced risk of toxicity and should be the preferred treatment approaches.

Introduction

Breast cancer is the most prevalent female malignancy, affecting 13% of all women.[1,2] Surgery is the standard-of-care and currently the only curative-intent treatment for localized disease. However, approximately one-third of patients are diagnosed when they are older than 70 years are more likely to be frail or have significant comorbidities that may contraindicate surgical resection.[1,2] When surgery is not feasible, no alternative local treatment can substitute for resection with curative intent, and patients are typically managed with first-line palliative systemic therapy alone.[3-5]

Primary hormone therapy is the standard treatment for patients with hormone receptor-positive disease.[3-5] However, meta-analyses of randomized clinical trials and retrospective cohorts show that primary hormone therapy provides inferior disease control than surgery,[6-10] and tumor growth is documented in approximately 45% of patients[8] after a median time of 2.8 years.[9] Moreover, locoregional progression is the leading pattern of failure, occurring in ~85% of cases.[7,8] Therefore, most patients with a life expectancy of more than 3 years are likely to experience tumor growth when treated with primary hormone therapy alone.[9] When inoperable patients have hormone receptor-negative disease, management becomes more challenging as the same factors that prevent surgery may contraindicate systemic treatment. Therefore, there is an unmet need to study noninvasive treatment options that can be an alternative to surgical resection.

Stereotactic body radiation therapy (SBRT) is a precise technique that delivers high conformal doses per fraction. This noninvasive treatment has shown excellent outcomes as an alternative to surgery for different primary tumors such as lung, kidney, and prostate.[11-14] Consequently, we hypothesized that SBRT may offer durable tumor control with an acceptable toxicity profile when treating patients with inoperable breast cancer. Therefore, at our institution, patients who decline surgery, are medically inoperable, have unresectable tumors, or have metastatic disease requiring locoregional radiation therapy are offered ablative radiation therapy with 35 to 40 Gy in 5 fractions. This study aims to evaluate the outcomes of this fractionation regimen for nonresected breast cancer.

Methodology

From an institutional database, we retrospectively reviewed consecutive patients with breast cancer who underwent 35 to 40 Gy in 5 fractions to the primary tumor or involved regional lymph nodes (axillary, supraclavicular, or internal mammary) from 2014 to 2021. The institutional research ethics board approved this retrospective review (SUN-2123). Patient, tumor, treatment, and follow-up data were obtained from electronic medical records and treatment planning system.

Treatment technique

Patients underwent computed tomography (CT) simulation for radiation therapy planning and were typically immobilized on a wing board (CIVCO Medical Solutions) and a vacuum cushion (Vac-Lok, CIVCO Medical Solutions) with arms positioned over the head (Fig. E1). A comprehensive simulation process, including 4-dimensional CT (4D-CT) and, since 2020, magnetic resonance (MR) simulation,[15] was recommended to account for breast/chest wall motion and improve gross tumor volume (GTV) contouring, but was not mandatory. Examples of tumors contoured with and without MR simulation are shown in Table E1.

Target volumes and organs at risk were delineated prospectively to guide treatment planning. However, during the initial years, contouring approaches were not standardized, and patients were typically treated with either (1) 25 Gy whole breast or locoregional radiation therapy with a 35 to 40 Gy simultaneous integrated boost to the gross tumor, in 5 fractions, or (2) 35 to 40 Gy in 5 fractions partial breast irradiation. At that time, patients were typically treated with a field-in-field forward-planning technique using a static multileaf collimator and beam energy of 6 MV or combined 6/18MV to achieve uniform dose distribution. Although this technique was previously described in the literature as forward-planning intensity modulated radiation therapy (IMRT),[16-18] we opted to refer to it as 3-dimensional conformal radiation therapy (3D-CRT) because of its limited modulation and moderate conformity compared with inverse-planning IMRT or volumetric-modulated arc therapy (henceforth grouped as IMRT).

As our experience evolved over the years, the treatment technique was refined, and a protocol was implemented to ensure consistent contouring and planning. Patients who underwent 4D-CT and MR simulation typically had the breast GTV contoured on MR and all CT data sets (0%, 50%, average, and maximum intensity projection), and the combination of all GTVs defined the internal tumor volume (ITV). For patients who did not undergo 4D-CT

and MR, GTV was contoured on free-breath CT. In cases of poor GTV definition, a 1 to 5 mm uniform ITV to high-dose clinical target volume (CTV-high) expansion was recommended, and the final volume was adjusted per anatomic barriers (ie, pectoralis muscles) as appropriate. A 5 mm high-dose planning target volume (PTV-high) margin was used for well-visualized and 7 mm for poorly visualized tumors on CT/cone beam CT.[19] The lymph node GTV was contoured on CT/MR for node-positive patients, and a 5 to 7 mm planning target volume margin was applied (PTV-high). A low-dose clinical target volume (CTV-low) was recommended to encompass microscopic disease surrounding the breast tumor, but not mandatory. It consisted of a 20 mm expansion beyond the ITV, which was adjusted per natural barriers, and further expanded in 7 mm to generate the low-dose planning target volume (PTV-low). Inclusion of the entire breast and/or elective nodal areas into the CTV-low was at the physician's discretion. A typical prescription consisted of 25 Gy to the PTV-low with a 35 to 40 Gy simultaneous integrated boost to the PTV-high, in 5 fractions, and IMRT was recommended because of its superior conformity over 3D-CRT. Our treatment planning parameters and dose constraints are detailed in Table E2. Elekta linear accelerators with 5 mm multileaf collimator and robotic couch (HexaPOD, Elekta AB) delivered treatment, verified by pretreatment cone beam CT scans for setup accuracy.

Study outcomes

Patients were monitored weekly during radiation therapy. Posttreatment follow-ups typically occurred within 1 to 3 months and then every 6 to 12 months, or sooner if clinically indicated. A typical radiologic follow-up regimen consisted of mammogram/ultrasound, CT, or MR scans performed every 3 to 12 months as clinically recommended.

The primary endpoints were objective response rate at the last follow-up, local failure (LF), and the cumulative incidence of grade ≥3 toxicity. The secondary endpoints were ipsilateral breast failure (IBF), complete symptom relief among those patients symptomatic at baseline, progression-free survival (PFS), overall survival (OS), and cancer-specific survival (CSS).

Objective response rate was assessed for target lesions (breast or lymph nodes) per Response Evaluation Criteria in Solid Tumors V1.1 (RECIST)[20] and defined as the percentage of treatment courses with partial or complete response. Complete response of the breast tumor was defined as disappearance of the target lesion or absence of residual contrast enhancement on follow-up MR and of the target lymph node as a reduction in the short axis to <5 mm. LF was defined as at least 20% increase in the sum of diameters of target lesions compared with the smallest sum on study (in-field failure). IBF was defined as any in-field or out-of-field breast failure. Complete symptom relief was defined as the disappearance of all baseline breast symptoms (ie, discharge) upon review of patients' charts. Objective response rate, LF, and IBF were analyzed per treatment course for those with at least one follow-up with imaging. Acute and late toxicity was scored per treatment according to the Common Terminology Criteria for Adverse Events, version 5.0. When radiation dermatitis grading was not evident on the patient's chart, any dry desquamation was classified as grade 2 and moist desquamation as grade 3 toxicity. PFS, OS, and CSS were evaluated on a per-patient basis.

Statistical analysis

Descriptive statistics were used for continuous (median and range) and categorical variables (presented as counts and percentages). The time from the start of radiation therapy to the first grade 3 toxicity was used to calculate the incidence of grade ≥3 toxicity, to the progression of the target lesion was used to calculate LF, and to any progression in the ipsilateral breast (in-field or out-of-field) to calculate IBF. The time from the start of radiation therapy to disease progression or death from any cause was used to calculate PFS, to death from any cause to calculate OS, and to death from breast cancer cause to calculate CSS. Cox proportional hazards regression models were used to evaluate the relationship between survival outcomes (PFS, OS, CSS) and potential prognostic factors: age at radiation therapy, TNM Stage (American Joint Committee on Cancer staging manual, seventh edition) at diagnosis, hormone receptor status, previous systemic therapy, locoregional progression at the time of SBRT (yes/no), presence of symptoms (yes/no), the administration of whole breast irradiation (yes/no), and the target tumor size before SBRT. Fine and Gray competing-risks proportional hazards regression models were used to estimate the association of LF, IBF, and grade ≥3 toxicity with potential predictive factors using death as a competing risk. Investigated predictive factors for LF and IBF included TNM stage at diagnosis, hormone receptor status, previous systemic therapy, locoregional progression at the time of SBRT (yes/no), the administration of whole breast irradiation (yes/no), the target tumor size at SBRT, and the prescribed dose to the PTV-high (35 vs 40 Gy). The potential predictors for grade ≥ 3 toxicity included the target tumor size at SBRT, T3/4 disease (yes/no), presence of symptoms (yes/no), daily treatment (yes/no), the prescribed dose to the PTV-high (35 vs 40 Gy), and the treatment technique categorized as follows: 1) all treatments with IMRT versus, 2) treatments with non-IMRT techniques that targeted partial breast or lymph nodes versus, 3) treatments with non-IMRT techniques targeting the entire breast (with or without a simultaneous integrated boost to the primary tumor). Backward stepwise

selection was conducted to identify significant factors on multivariable analysis. All statistical tests were 2-sided, with a P value of $< .05$ indicating statistical significance. The R software (v4.0.2 × 64) was used for all statistical analyses.

Results

We reviewed 61 treatment courses in 57 patients (Table 1). Three patients had bilateral breast cancer treated simultaneously, and one underwent breast SBRT followed by lymph node SBRT upon regional progression. The median follow-up was 16.8 months (range, 0.2-87.9). The median age was 81.7 years (range, 38-100), and 72% of patients were older than 70 years. The reasons for inoperability include the presence of metastatic disease (37%, n = 21/57), medical inoperability (35%, n = 20/57), patient refusal (18%, n = 10/57), and unresectability of tumor (11%, n = 6/57). When analyzing the characteristics per treatment course, 74% (n = 45/61) of tumors were hormone receptor-positive, and 72% (n = 44/61) had locoregional progression at the time of radiation therapy. A total of 51% (n = 31/61) of tumors invaded the skin and 30% (n = 18/61) caused ulceration. The median diameter of the target breast tumor was 37 mm (range, 8-120) and the target lymph node was 21 mm (range, 7-78).

Fifty-four percent (n = 33/61) of treatment courses targeted the breast only, 31% (n = 19/61) both the breast and lymph nodes, and 15% (n = 9/61) the lymph nodes only. Among the 52 courses that targeted the primary malignancy, 67% (n = 35/52) were delivered with partial breast irradiation and 33% (n = 17/52) with whole breast radiation therapy ± simultaneous integrated boost to the primary. Among the 28 radiation courses that treated lymph nodes, 93% (n = 26/28) targeted the axilla. Most primary tumors (65%, n = 34/52) and target lymph nodes (61%, n = 17/28) were treated with a dose of 35 Gy in 5 fractions. Fifty-two percent (n = 32/61) of treatments were delivered using IMRT, 46% (n = 28/61) using 3D-CRT, and 2% (n = 1/61) using electrons (Fig. 1). The 3D-CRT cohort (n = 28) exhibited a higher percentage of cT3-4 disease (79% vs 47%, $P = .012$), tumors causing skin invasion (69% vs 34%, $P = .010$), or ulceration (45% vs 16%, $P = .009$), and a greater proportion of patients undergoing whole breast irradiation (57% vs 3%, $P < .001$), compared with the IMRT cohort (n = 32). Twenty percent of courses (n = 12/61) were administered daily, 18% (n = 11/61) every other day, 36% (n = 22/61) twice weekly, and 26% (n = 16/61) weekly.

Objective response rate

Tumor response was assessed for 82% (n = 50/61) of treatment courses, with follow-up imaging including CT

Table 1 Patient, tumor, and treatment characteristics

Characteristics per patient	**N = 57**
Female	56 (98%)
Age, y	
Median (range)	81.7 (38-100)
≥70 years old	41 (72%)
Reasons for not undergoing surgery	
Metastatic disease	21 (37%)
Medically inoperability	20 (35%)
Patient refusal	10 (18%)
Unresectable	6 (11%)
Characteristics per treatment course	**N = 61**
Histology	
Invasive ductal carcinoma	57 (93%)
Invasive lobular carcinoma	4 (7%)
T Stage at diagnosis (AJCC 7th edition)	
T0/Tx	3 (5%)
T1	6 (10%)
T2	14 (23%)
T3	7 (11%)
T4	31 (51%)
N stage at diagnosis (AJCC 7th edition)	
N0	20 (33%)
N1	24 (39%)
N2/3	19 (31%)
Clinical stage at diagnosis (AJCC 7th edition)	
I-II	11 (18%)
III	27 (44%)
IV	23 (38%)
Laterality	
Left	37 (61%)
Right	24 (39%)
Receptor status	
ER/PR+, HER2−	37 (61%)
ER/PR+, HER2+	8 (13%)
ER/PR−, HER2+	2 (3%)
Triple-negative	14 (23%)
Prior adjuvant locoregional radiotherapy*	5 (8%)
50 Gy/25 fractions	2 (3%)
42.56 Gy/16 fractions	2 (3%)
Dose and fraction not available	1 (2%)
Prior systemic treatment	
Hormone therapy	45 (74%)
Chemotherapy or target therapy	18 (29%)
None	13 (21%)

(*Continued*)

Table 1 (*Continued*)

Characteristics per patient	N = 57
Locoregional progression at the time of SBRT	44 (72%)
Interval from cancer diagnosis to SBRT, median (range), mo	14.6 (0.5-180)
Size of target breast tumor, median (range), mm	37 (8-120)
Size of target lymph node, median (range), mm	21 (7-78)
Treatment volume	
Breast	52 (85%)
Partial breast irradiation	35/52 (67%)
Whole breast irradiation ± simultaneous integrated boost to the primary tumor	17/52 (33%)
Lymph node	28 (46%)
Axillary node	26/28 (93%)
Internal mammary node	2 /28 (7%)
Supraclavicular node	1/28 (4%)
Dose to the primary breast tumor, Gy	
40	18/52 (35%)
35	34/52 (65%)
Dose to the whole breast, median (range), Gy	25 (20-40)
Dose to the target lymph nodes, Gy	
40	9/28 (32%)
35	17/28 (61%)
30[†]	2/28 (7%)
Dose to the elective nodal areas, median (range), Gy	25 (20-35)
Treatment technique	
Inverse-planned IMRT/VMAT	32 (52%)
3D-CRT	28 (46%)
Electrons	1 (2%)
Fractionation schedule	
Daily	12 (20%)
Every other day	11 (18%)
Twice weekly	22 (36%)
Weekly	16 (26%)

Continuous variables were described as median with a range. Age was presented in years, time intervals in months, tumor size in mm, and radiation therapy dose in Gy.
Abbreviations: 3D-CRT = 3-dimensional conformal radiation therapy; AJCC = American Joint Committee on Cancer; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; IMRT = intensity modulated radiation therapy; PR = progesterone receptor; SBRT = stereotactic body radiation therapy; VMAT = volumetric-modulated arc therapy.
[*]The median interval between prior adjuvant radiation therapy and breast/lymph node SBRT was 6 years (range, 3-20).
[†]Two patients who received a dose of 30 Gy/5 fractions to the lymph node were included in this analysis as they simultaneously received 35 to 40 Gy to the primary breast tumor.

scan (70%, n = 35/50), ultrasound/mammogram (18%, n = 9/50), and MR (12%, n = 6/50). At last follow-up, the objective response rate was 54% (n = 27/50), being 8% (n = 4/50) complete and 46% (n = 23/50) partial responses, 36% (n = 18/50) had stable disease, and 10% (n = 5/50) had local progression (Figs. 2 and 3).

Local failure

The cumulative incidence of LF at 1 and 2 years was 0% and 11.4%, respectively (Fig. 4). The median time to LF among those who recurred was 18.2 months (95% confidence interval [CI], 12.3 not reached). When stratified by the treatment site, the LF rate at 2 years was 10.6% for breast versus 11.5% for lymph nodes. On multivariable analysis, independent predictors of increased risk of LF included lymph node involvement (hazard ratio [HR] >100 and $P < .001$) and radiation therapy for locoregional progression (HR>100 and $P < .001$, Table E3). The 2-year LF was 0% for N0 versus 13.5% for N + disease ($P < .001$) and 0% for tumors not progressing versus 12.7% for those progressing at the time of SBRT ($P < .001$, Fig. E2).

Ipsilateral breast failure

The cumulative incidence of IBF rate at 1 and 2 years was 8.6% and 20.5%, respectively (Fig. E3), with the median time to failure being 14.3 months (95% CI, 5-20.1). On multivariable analysis, independent predictors of increased risk of IBF included lymph node involvement (HR >100 and $P < .001$) and radiation therapy for locoregional progression (HR >100 and $P < .001$, Table E3). The 2-year IBF was 0% for N0 versus 25.2% for N + disease ($P < .001$) and 0% for tumors not progressing versus 23.8% for those progressing at the time of SBRT ($P < .001$, Fig. E4).

Toxicity

Grade 1 toxicity was observed in 46% (n = 28/61), grade 2 in 20% (n = 12/61), grade 3 in 13% (n = 8/61), and grade 4 in 2% (n = 1/61) of treatments. One patient experienced a grade 1 rib fracture after 35 Gy in 5 fractions partial breast irradiation with 3D-CRT. The grade 2 toxicities consisted of radiation dermatitis in eleven (18%, n = 11/61) and pneumonitis in one (2%, n = 1/61) case. The case of pneumonitis was reported in a 92-year-old woman with chronic obstructive pulmonary disease who developed progressive shortness of breath 1 year after completing radiation therapy (25 Gy locoregional radiation therapy with 40 Gy simultaneous integrated boost to the primary tumor and an enlarged axillary lymph node, in 5 fractions, using 3D-CRT). Although the cause of her symptoms remained unclear, with exacerbation of chronic

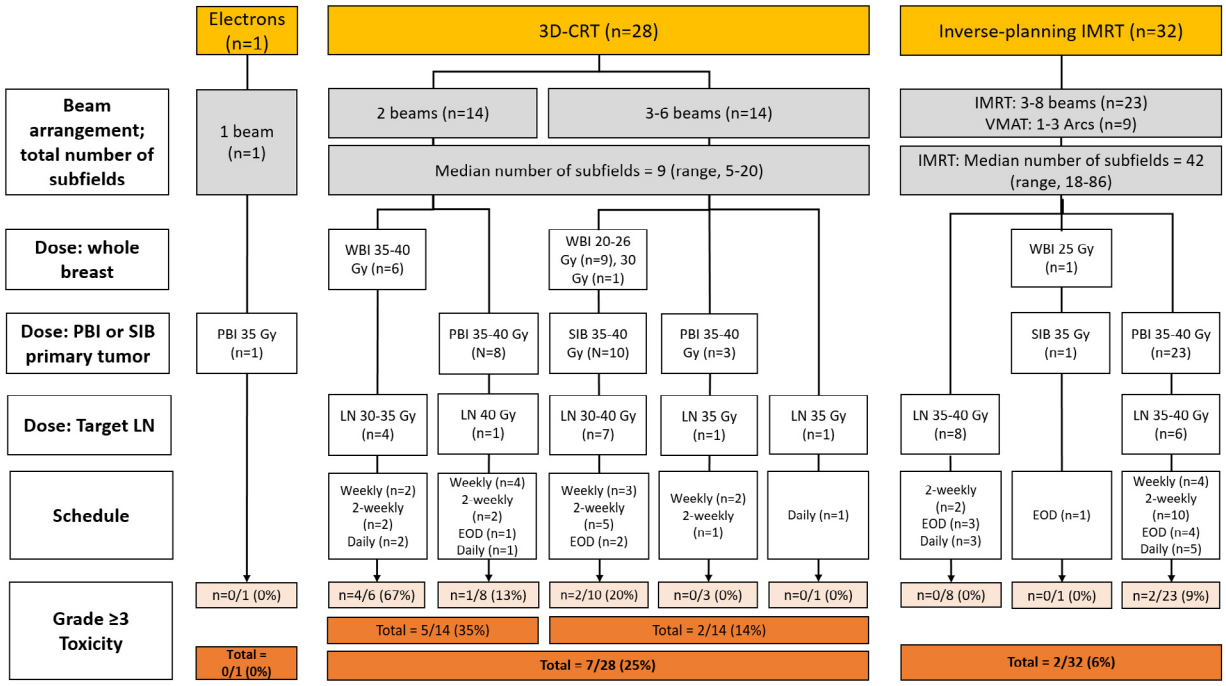

Figure 1 Detailed treatment characteristics of the studied population. *Abbreviations*: 2-weekly = twice weekly; 3D-CRT = 3-dimensional conformal radiation therapy; EOD = every other day; IMRT = intensity modulated radiation therapy; LN = lymph nodes; n = number of treatment courses; PBI = partial breast irradiation; SIB = simultaneous integrated boost; VMAT = volumetric modulated arc therapy; WBI = whole breast irradiation.

obstructive pulmonary disease being one of the potential differential diagnoses, it was deemed possibly related to radiation therapy.

All events of grade ≥3 toxicity consisted of radiation dermatitis, and 7 of 9 (78%) occurred in patients treated with 3D-CRT. The only grade 4 toxicity consisted of skin necrosis in the axilla. This occurred in a patient who received 25 Gy locoregional radiation therapy, 35 Gy to an enlarged axillary lymph node, and 40 Gy to the primary tumor, in 5 fractions, using simultaneous integrated boost and 3D-CRT. Notably, this is an exceptional case where the patient was immobilized with arms facing down, which likely increased the risk of self-bolus formation and subsequent toxicity. No cases of brachial plexopathy were reported in our study.

The 1-, 2-, 3-, 12-, and 24-month cumulative incidence of grade ≥3 toxicity was 1.6%, 11.5%, 15.1%, 15.1%, and 15.1%, respectively (Fig. 5). Treatment volume and technique were the only predictors of grade ≥3 toxicity on univariate and multivariable analyses. The 12-month cumulative incidence of grade ≥3 toxicity was 6.5% for IMRT treatments versus 7.7% for non-IMRT treatments targeting partial breast and/or lymph nodes (HR, 1.13; 95% CI, 0.11-11.8; P = .92) versus 38.9% for non-IMRT treatments targeting the entire breast with or without a simultaneous integrated boost to the primary tumor (HR, 6.91; 95% CI, 1.31-36.4; P = .023). In the latter subgroup, we observed an elevated risk of toxicity in 6 patients who received ≥30 Gy to the entire breast (grade ≥3 = 71%, n = 5/7) compared with those who were prescribed ≤26 Gy with a simultaneous integrated boost to the primary (grade ≥3 = 11%, n = 1/9, Fig. 1).

Symptom relief

One-third of tumors (27.8%, n = 17/61) caused symptoms at baseline, with discharge (22.9%, n = 14/61), bleeding (16.4%, n = 10/61), and pain (14.8%, n = 9/61), being the most common ones. All patients experienced at least partial symptom relief within 3 months of radiation. The cumulative incidence of complete symptom relief was 28.8%, 28.8%, and 52.8% at 3, 6, and 12 months, respectively. The median time to complete symptom relief among those who achieved this outcome was 6.6 months (95% CI, 2.7-10.7).

Survival outcomes

Among patients with M0 disease, 8.3% (n = 3/36) had locoregional progression, 22.2% (n = 8/36) had distant progression, and 55.6% (n = 20/36) died, with nonbreast cancer being the leading cause of death (80.0%, 16/20 deaths). Among those with M1 disease, 23.8% (n = 5/36) had locoregional progression, 66.7% (n = 14/21) had distant progression, and 47.6% (n = 10/21) died, with breast cancer being the leading cause of death (90.0%, 9/10 deaths).

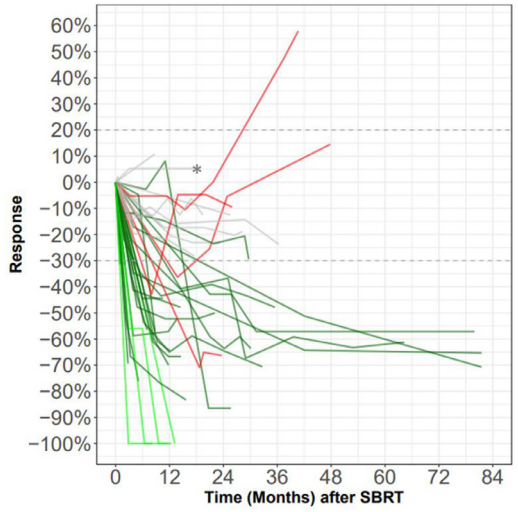

Figure 2 Spider plot indicating the percentage change in the size of target tumor from baseline (red = progressive disease, gray = stable disease, dark green = partial response, light green = complete response, asterisk = one patient developed clinical progression of disease in the overlying skin with no increase in the size of target tumor on computed tomography).

The median PFS was 22 months (95% CI, 16-28) and the 1-, 2-, 3-, and 4-year PFS was 69.9%, 39.4%, 26.2%, and 17.5%, respectively. The median OS was 31 months (95% CI, 22-38) and the 1-, 2-, 3-, and 4-year OS was 75.2%, 51.8%, 38.8%, 28.4%, respectively. No prognostic factors for PFS or OS were identified on multivariable analysis.

The median CSS was 49.7 months (95% CI, 34-not reached) and the 1-, 2-, 3-, and 4-year CSS was 88.8%, 82.5%, 66.0%, and 52.8%, respectively. On multivariable analysis, M1 stage (HR, 7.38; 95% CI, 1.87-29.2; $P = .004$) and hormone receptor-negative disease (HR, 3.37; 95% CI, 1.12-10.13; $P = .030$) were prognostic for worse cancer-specific survival (Table E3). The 1-, 2-, 3-, and 4-year CSS was 96.0%, 85.7%, 85.7%, and 85.7% for patients M0 versus 76.2%, 76.2%, 38.1%, and 0% for those with M1 disease ($P = .004$), and 94.1%, 90.3%, 67.7%, and 59.3% for patients with hormone receptor-positive disease versus 74.3%, 61.9%, 61.9%, and 30.9% for those with hormone receptor-negative ($P = .019$), respectively. PFS, OS, and CSS are shown in Fig. E5.

Discussion

We report the largest contemporary cohort of ablative radiation therapy for nonresected breast cancer. This study provides much-needed evidence suggesting radiation therapy as a safe, effective, and promising noninvasive treatment option for patients unsuitable for tumor resection.

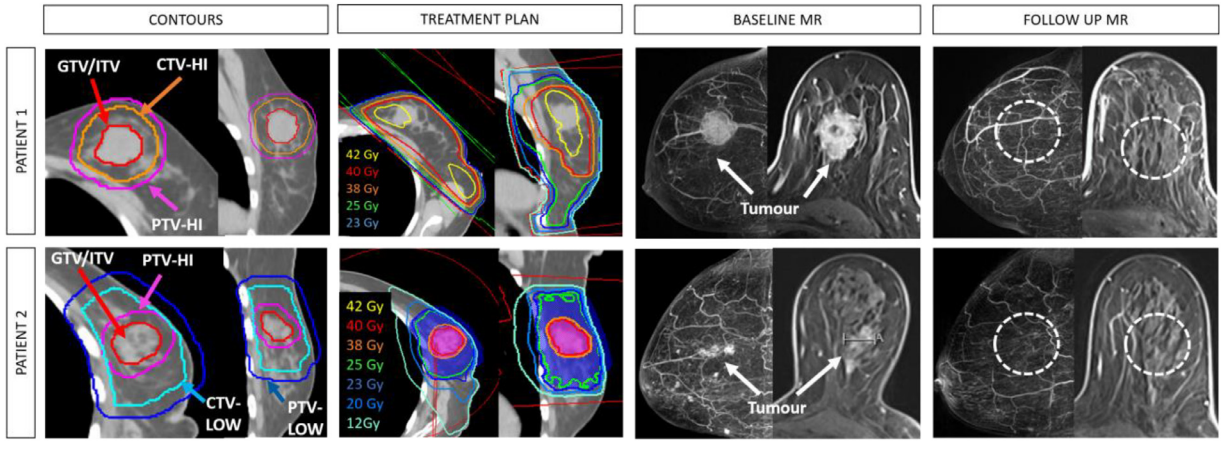

Figure 3 Examples of patients who achieved a complete response after ablative radiation therapy. Patient 1 is a 75-year-old woman with a T2N0M0 triple-negative breast cancer who was deemed not a candidate for surgical resection or systemic therapy because of comorbidities. She was treated with 25 Gy whole breast irradiation and 40 Gy simultaneous integrated boost to the primary tumor in 5 fractions, using 3D-CRT. The patient died of nononcological causes 3 years after radiation therapy, with complete response of the primary tumor and no evidence of distant metastases. Patient 2 is a 94-year-old woman with a T2N0M0 hormone receptor-positive HER2-negative breast cancer who was considered inoperable due to frailty and declined hormone therapy. She was treated with 25 Gy partial breast irradiation and 40 Gy simultaneous integrated boost to the primary tumor in 5 fractions, using volumetric modulated arc therapy. The patient had a complete response and was on surveillance with no evidence of distant metastases 12 months after radiation therapy. *Abbreviations:* CTV-Hi = high-dose clinical target volume; CTV-Low = low-dose clinical target volume; GTV = gross tumor volume; ITV = internal tumor volume; MR = Magnetic resonance imaging; PTV-Hi = high-dose planning target volume; PTV-Low = low-dose planning target volume.

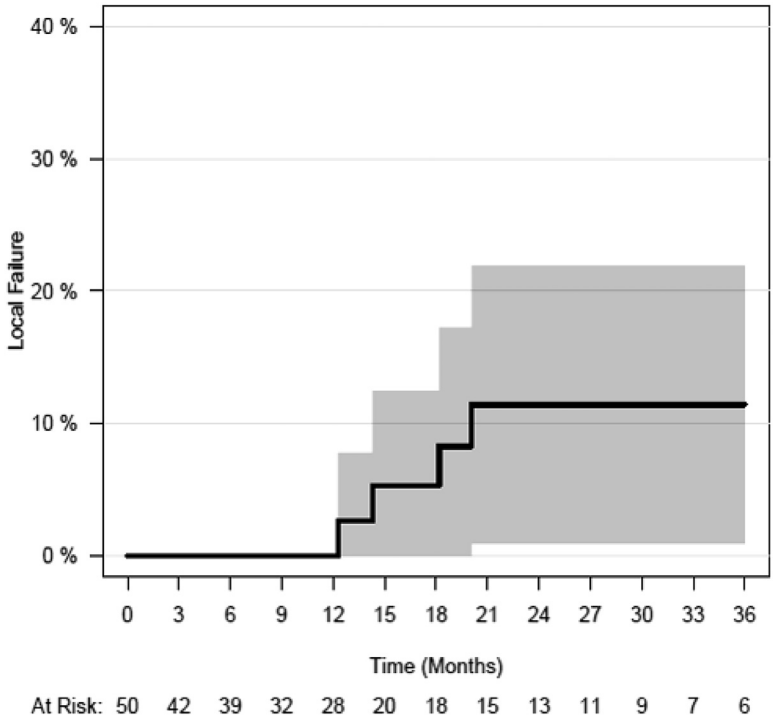

Figure 4 Cumulative incidence of local failure.

Definitive breast radiation therapy was first studied in the 2- and 3-dimensional era.[21-26] Arriagada et al[21] published a collaborative study in which 463 patients were treated with doses as high as 80 Gy in 2 Gy fractions and demonstrated that dose-escalated regimens were associated with a lower risk of LF, being ~69% with 51 to 60 Gy, ~55% with 61 to 70 Gy, and ~24% with ≥80 Gy.[21,27] Moreover, Maher et al[25] and Courdi et al[26] reported their experience of treating primary breast tumors with 5 to 8 weekly fractions of 6.5 Gy (total dose of 32.5-52 Gy), comprising 5 fractions to the involved breast and 0 to 3 additional fractions to the tumor. The authors observed LF rates of ~14% at 3 years[25] and ~22% at 5 years,[26] with a trend toward lower LF among those treated with ≥35 Gy.[25]

One of the first attempts to use modern techniques for definitive breast radiation therapy was published by Shibamoto et al.[28] The authors treated 18 patients with 50 Gy in 25 fractions whole-breast irradiation followed by 18 to 25.5 Gy/3 fractions SBRT or 20 Gy/8 fractions IMRT boost and reported a ~8% failure rate at 3 years.[28] Karasawa et al treated early-stage breast cancer with carbon ion radiation therapy (52.8-60 Gy relative biologic effectiveness in 4 fractions) and reported only one local progression among 14 treated patients (crude ~9% LF),[29] and more recently, Zabrocka et al[30] reported a ~7% LF rate at 2 years after 40 Gy in 5 fractions SBRT regimen. Therefore, taken together, these data serve as a benchmark for our observed excellent 11.4% LF rate at 2 years.

Primary hormone therapy is the standard of care for patients with hormone receptor-positive disease.[3-5] However, LF remains the leading pattern of relapse among those treated with hormone therapy alone[7,8] and typically occurs after a median time of 2.8 years.[9] Therefore, a therapeutic opportunity exists to incorporate SBRT early in the disease course to provide durable tumor control for patients expected to live more than 3 years, and validated tools exist to help estimate patients' life expectancy.[3,31-33] By controlling the site most likely to progress, radiation could delay or even avoid the need for subsequent lines of systemic therapy. Additionally, this approach might offer the added advantage of reducing the likelihood of developing breast symptoms, such as pain or discharge, secondary to tumor progression. In our cohort, 28% of our patients underwent SBRT when they already had significant local symptoms, and despite high-dose radiation, complete symptom relief was achieved by only ~53% of patients at 12 months. This is consistent with other studies, which indicate that radiation therapy may take considerable time to eliminate symptoms completely once developed.[34]

We observed an overall cumulative incidence of grade ≥3 toxicity at 15.1%. Particularly, our analysis revealed a strong association between treatment technique and toxicity, with the lowest risk of grade ≥3 toxicity among patients treated with IMRT (6.5%) and those treated with partial breast irradiation or lymph node radiation therapy using non-IMRT techniques (7.7%). It is worth noting that 3D-CRT was the primary treatment modality when we initially began treating patients with ablative breast radiation therapy. At that time, we often treated patients with more advanced disease (ie, cT3-4) compared with our current

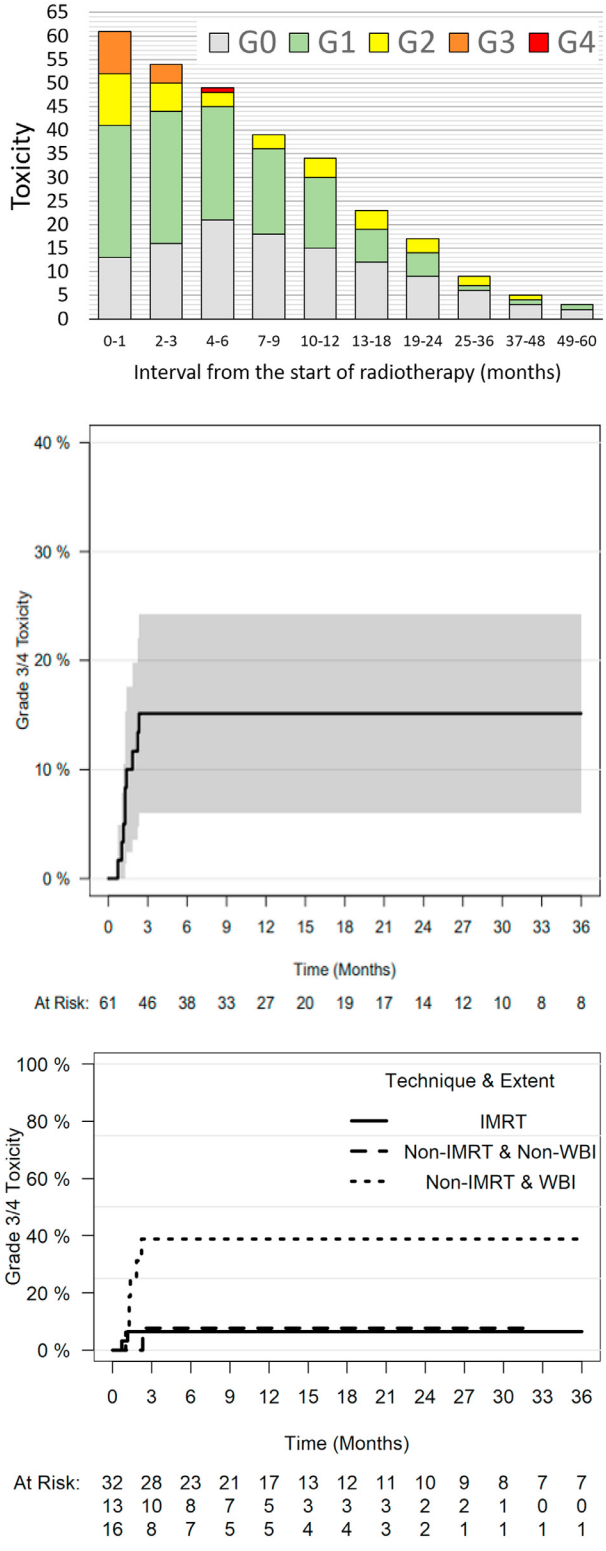

Figure 5 Treatment toxicity. (A) Worst toxicity at different time intervals from the start of radiation therapy in absolute numbers; (B) cumulative incidence of grade ≥3 toxicity for the entire population; (C) cumulative incidence of grade ≥3 toxicity stratified per treatment volume and technique. Non-IMRT includes patients treated with 3-dimensional conformal radiation therapy or electrons. Non-WBI includes patients who received partial breast irradiation or lymph node radiation therapy alone. *Abbreviations*: G0 = grade 0; G1 = grade 1; G2 = grade 2; G3 = grade 3; G4 = grade 4; IMRT = intensity modulated radiation therapy; WBI = whole breast radiation therapy.

practice. This difference in patient characteristics explains the higher proportion of patients treated with whole breast radiation therapy in the 3D-CRT (57%) compared with the IMRT cohort (3%). Furthermore, we observed that toxicity among those undergoing whole breast radiation therapy was primarily derived from patients who were prescribed >30 Gy to the entire breast for treating locally advanced disease (grade ≥3 in 5/7 patients = 71%), whereas those who received doses of ≤26 Gy (plus simultaneous integrated boost to the primary) exhibited a safer toxicity profile (grade ≥3 in 1/9 patients = 11%). These findings emphasize the importance of contouring and planning strategies to minimize normal breast tissue exposure to high-dose radiation therapy and a dosimetric analysis is warranted to identify predictors of radiation dermatitis and refine breast and skin dose constraints.[35]

Nonetheless, our practice evolved toward selecting more suitable candidates for breast SBRT and developing a treatment protocol to standardize contouring and planning strategies. Consequently, our current treatment approach with partial breast radiation therapy and IMRT demonstrates a remarkably improved safety profile, with less than 8% of treatments causing grade ≥3 radiation dermatitis. This aligns with the study by Rahimi et al,[36] which reported a 6.6% risk of grade 3 adverse events among 45 patients treated with 35 to 40 Gy/5 fractions partial breast irradiation in the adjuvant setting, the study by Zabrocka et al,[30] which reported 8.7% grade 3 toxicity when treating nonoperable breast tumors with 40 Gy in 5 fractions, and the phase 1 BOMB trial[37] that reported no cases of significant toxicity among 10 patients undergoing definitive radiation therapy with 40 Gy in 5 fractions. Therefore, we have confidence in the safety profile of this regimen.

The most compelling evidence to corroborate the use of partial breast irradiation for definitive radiation therapy comes from studies in the adjuvant setting. Phase 3 randomized controlled trials[38-40] showed that partial breast irradiation is as effective as whole breast irradiation when given adjuvantly to early-stage tumors. This is supported by most of their locoregional recurrences occurring near the primary disease site.[41,42] Therefore, it is reasonable to extrapolate these findings for patients with unresectable early-stage tumors. However, as our population was heterogeneous regarding tumor burden, partial breast irradiation was often delivered for patients with advanced disease, which justifies a slightly higher, but acceptable, 20% risk of IBF compared with an 11% risk of LF at 2 years. Therefore, this suggests that the decision on treatment volume should be based on T and N stages per partial breast irradiation guidelines[43-45] and individualized for those not fitting these criteria. When deciding on whole breast radiation therapy, the prescription should be limited to 26 Gy as its safety is supported by prospective studies,[46,47] while simultaneously boosting the primary tumor.

The strengths of our study encompass the largest contemporary cohort of ablative definitive radiation therapy and a comprehensive report of outcomes after a single fractionation regimen of 35 to 40 Gy/5 fractions. However, our study also holds limitations. Among those patients whose retrospective toxicity grading was not clear, we cautiously labeled any moist desquamation as grade 3 and possibly overgraded cases of confined moist desquamation. Our population comprised heterogeneous tumor volumes, with some undergoing radiation for sizeable progressive disease. Consequently, our data may underestimate the local control and overestimate the toxicity rates expected if treatment had been initiated earlier when tumors were smaller. The follow-up imaging modality was variable and relied mainly on nonfunctional modalities (ie, CT scan), which cannot distinguish residual disease from replacement fibrosis. Therefore, we may have underreported complete responses, particularly if MR had been used instead. Moreover, 18% of patients were followed with ultrasounds/mammograms, which are not recommended for assessing tumor response by RECIST 1.1.

Conclusion

We report excellent local control and a favorable toxicity profile associated with definitive breast radiation therapy. This highlights ablative radiation therapy as an attractive, noninvasive treatment option for patients unsuitable for tumor resection. Additionally, highly conformal techniques such as IMRT and partial breast irradiation were associated with a reduced risk of toxicity, making them the recommended treatment approach for breast SBRT. A dose-escalated phase 1 clinical trial (ClinicalTrials Identifier: NCT03585621) is underway at our intuition to determine prospectively the optimal dose and toxicity profile of primary breast SBRT.

Disclosures

HS reports honoraria from Elekta for educational activities.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.prro.2023.12.003.

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