Pilot/Phase II Trial of Hypofractionated Radiation Therapy to the Whole Breast Alone Before Breast Conserving Surgery

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Received 2 August, 2022; accepted 13 October, 2022

Abstract

Purpose: Our purpose was to report the results of a phase II trial of patients with breast cancer treated with hypofractionated whole breast radiation therapy (RT) before breast-conserving surgery (BCS).

Methods and materials: Between 2019 and 2020, patients with cT0-T2, N0, M0 breast cancer were enrolled. Patients were treated with hypofractionated whole breast RT, 25 Gy in 5 fractions, 4 to 8 weeks before BCS. Pathologic assessment was performed using the residual cancer burden (RCB). Toxicities were assessed according to Common Terminology Criteria for Adverse Events (version 4). Quality of life was assessed with Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events, The Breast Cancer Treatment Outcome Scale, Linear Analogue Self-Assessment, and Patient-Reported Outcomes Measurement Information System.

Results: Twenty-two patients were enrolled. Median follow-up was 7.6 months (range, 0.2-16.8). Seven (32%) and 2 (9%) patients experienced grade 2+ or 3 toxicities, respectively. Overall quality of life remained stable. There was no clinically significant change from baseline. No local or distant recurrences have been observed. Only 1 (5%) patient experienced a clinical deterioration that corresponded to a “fair” outcome on the Harvard Cosmesis Scale. At pathologic evaluation, 14 (64%) patients had RCB-0 or RCB-I, including 3 (14%) patients with a pathologic complete response (RCB-0). Eight patients (36%) had RCB-II.

Conclusions: Extremely hypofractionated whole breast RT before BCS is a feasible approach. There were low rates of toxicities and good cosmesis. Further investigation into this approach with RT before BCS is warranted.

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Introduction

Breast-conserving surgery (BCS) followed by adjuvant radiation is the standard of care for early stage breast cancer and results in equivalent outcomes compared with mastectomy alone. Overtime, length of treatment for whole breast radiation has decreased from conventional fractionation (50 Gy in 25 fractions) to moderately hypofractionated (40.05-42.5 Gy in 15-16 fractions) courses based on multiple large randomized trials. Accelerated partial breast irradiation (APBI) is an alternative approach that has also been used successfully in patients with early stage breast cancer. More recently, extremely hypofractionation trials have been reported with promising early results. Of note, all of these trials used post-operative radiation after BCS.

However, preoperative radiation has been successfully used in the treatment of breast cancer both with partial breast irradiation and with treatment to the entire breast or chest wall. Although some of these trials have used extremely hypofractionated courses, they were all partial breast trials. Herein, we report the early results of our single arm phase II trial using extremely hypofractionated preoperative whole breast radiation to 25 Gy in 5 fractions.

Methods and Materials

Study design and patients

This study was a single arm phase II trial that enrolled patients in 2 centers of a single institution. The trial was approved by the institutional review board. Eligible patients included women ≥18 years old with biopsy-proven clinical stage T1-T2, N0, M0 breast cancer. Additional requirements included Eastern Cooperative Oncology Group performance status 0 to 2, no neoadjuvant therapy, and planned BCS with indications for whole breast radiation. Exclusion criteria included prior ipsilateral breast or chest wall radiation, recurrent cancer, or indications for regional nodal irradiation. All patients provided written informed consent.

Treatment

All patients received whole breast radiation to 25 Gy in 5 fractions over consecutive days. Photon treatments were delivered with tangent fields. No tumor bed boost or regional nodal irradiation was allowed. The breast clinical target volume (CTV) was delineated and contoured based on computed tomography simulation according to the Radiation Therapy Oncologic Group consensus guidelines or made based on standard tangent fields to encompass all breast tissue. This volume was limited 5 mm from the skin. The following dose distribution constraints were used: ≥95% of breast CTV received ≥95% of prescription (major violation: 90% of breast CTV received <90% of prescription) and breast CTV max dose <107% of prescription (major violation: max dose >115%). Normal tissue constraints included: heart max dose ≤33% of prescription heart mean dose <1 Gy, and 50% of ipsilateral lung volume received ≤10% of prescription. Daily image guidance was performed with kilovoltage (kV), cone-beam computed tomography (CBCT), or with surface guidance according to institutional guidelines.

BCS was performed 4 to 8 weeks after the completion of radiation. No neoadjuvant or concurrent systemic therapy was allowed. Adjuvant systemic therapy, including hormonal therapy and chemotherapy, was done at the discretion of the medical oncologist.

Outcomes

The primary outcome was pathologic response at BCS according to the residual cancer burden (RCB). Specifically, the primary endpoint was patients with RCB-0 or RCB-I. The trial approach would be successful if at least 3 of the first 22 patients had an RCB-0 or RCB-I. Secondary endpoints included toxicities, quality of life (QOL), patient reported outcomes, cosmesis, and disease outcomes. Toxicities were assessed according to Common Terminology Criteria for Adverse Events (CTCAE; version 4). QOL was assessed with The Breast Cancer Treatment Outcome Scale (BCTOS), Linear Analogue Self-Assessment (LASA), and Patient-Reported Outcomes Measurement Information System (PROMIS). QOL was assessed at the following time-points: baseline, end of treatment, 3, 6, and 12 months, and then annually. Deterioration of cosmesis was defined as going from excellent/good to fair/poor or from fair to poor according to the Harvard Cosmesis Scale. Secondary endpoints were assessed at baseline, end of radiation, 3 months after completion of radiation, 6 months after completion of radiation, 12 months after completion of radiation, and then annually.

Statistical analysis

This study was designed as a single arm, single-stage phase II trial to evaluate the pathologic complete response (pCR) rate observed at time of definitive surgery in patients with breast cancer receiving preoperative ionizing radiation. We considered a residual tumor cancer burden of 0 to 1 to be considered a pCR. All patients meeting eligibility criteria who signed a consent form and who had begun treatment were evaluable for the endpoint. The largest success proportion where the proposed treatment
regimen would be considered ineffective in this population is 5%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen would be 20%. The design uses 22 evaluable patients to test the null hypothesis that the proportion of successes is at most 5%. Given this design, we obtained approximately 85% power ($\alpha = 0.10$) to declare that this regimen warrants further studies. Decision rules dictated that if 2 or fewer successes were observed in the first 22 evaluable patients who had a definitive surgical procedure, we would consider this regimen to be ineffective in this patient population. If 3 or more successes were observed in the first 22 evaluable patients, we may recommend further testing of this regimen in subsequent studies in this patient population.

Secondary objectives were analyzed according to protocol. Toxicity is reported as total and proportion of evaluable patients experiencing CTCAE v.5 adverse events at the prespecified timepoints. Similarly, clinical outcomes such as local and distant control as well as overall survival are presented with Kaplan-Meier curves presented where appropriate. QOL and Harvard Cosmesis Scores are presented at each time point as well as modeled using repeated measures mixed modeling to determining whether there are differences in QOL or cosmesis at each time point as well as over time.

Results

Between January 24, 2019, to July 20, 2020, 22 patients were enrolled. Median follow-up was 7.6 months (range, 0.2-16.8). Patient and treatment characteristics can be found in Table 1. Five of 22 patients underwent baseline magnetic resonance imaging (23%). Median age at radiation therapy (RT) was 64.1 years (range, 44.3-76.7). Most patients had clinical T1 disease (21 patients, 95%) and were Estrogen receptor (ER) / human epidermal growth factor receptor 2 (HER2-) (21 patients, 95%). The median and mean tumor diameters were 1.05 and 1.13 cm, respectively. All patients were cN0 and cM0. Furthermore, most patients had invasive ductal carcinoma (15 patients, 68%) and grade 1 disease (12 patients, 55%). There were slightly more right-sided tumors (15 patients, 68%) than left-sided tumors (7 patients, 32%). All patients received 25 Gy in 5 fractions with 3-dimensional conformal RT. Eight patients were treated prone and 14 patients were treated supine. The median time from end of radiation to BCS was 54.4 days (interquartile range, 43, 63) days.

Pathologic responses are shown in Fig. 1. Three patients (14%) had RCB-0, 11 patients (50%) had RCB-I, and 8 patients (36%) had RCB-II. No patient had RCB-III. One patient (5%) was node positive at surgery (1/1 positive sentinel lymph node with a 4-mm deposit of cancer). This patient had RCB-II and was ER+/HER2−. She went on to receive adjuvant hormone therapy with an aromatase inhibitor. No local or distant recurrences have occurred in any patient.

In total, 6 patients (27%) experienced grade 2 toxicity and 2 patients (9%) experienced grade 3 toxicity from end of RT to 1 year follow-up. The grade 2 toxicities included 2 patients (9%) with pain, 2 patients (9%) with fibrosis, and 2 patients (9%) with seromas. The grade 3 toxicities were both infected seromas that occurred 6 months after radiation.

Overall QOL LASA, PROMIS, and BCTOS over time is shown in Fig. 2. QOL was evaluated at various timepoints, including baseline, end of treatment, 3 months, 6 months, and 12 months in 21 (95%), 21 (95%), 18 (82%), 19 (86%), and 6 (27%) patients, respectively. Overall, QOL LASA and PROMIS did not change significantly from baseline ($P = .21$ and $P = .72$, respectively). Additionally, there was no clinically significant change (≥1 point) in any of the BCTOS domains. Patient satisfaction with treatment was high, with over 90% of patients saying they would do RT again. Cosmetic outcomes can be seen in Fig. 3. Only 1 (5%) patient experienced a clinical deterioration corresponding to “fair” on the Harvard Cosmesis Scale.

Discussion

This single arm phase II trial of preoperative extremely hypofractionated whole breast radiation demonstrates a feasible approach for early-stage breast cancer. Pathologic responses were encouraging, with 64% of patients having RCB-0 or RCB-I at the time of surgery. Furthermore, no patient had RCB-III.

Our pCR (RCB-0) rate of 14% is similar to the results from other preoperative breast trial rates of 10% to 42%, 14-16,18,24,25 For example, the Preoperative Accelerated Partial Breast Irradiation (PAPBI) trial enrolled patients with early stage breast cancer (T1-2 ≤3 cm and pN0 after sentinel lymph node biopsy).12-15 Patients were treated with preoperative APBI to either 40 Gy in 10 fractions over 2 weeks or 30 Gy in 5 fractions over 1 week. BCS was performed 6 weeks after the end of radiation. They reported a (nearly) pCR in 23% (15/66) of patients.14 Our time from radiation to surgery was similar to this trial and yielded similar results. This is in contrast to Vasmel et al.,16 who performed a single arm trial using single fraction (20 Gy to the gross tumor volume and 15 Gy to 20-mm margin) preoperative APBI. Importantly, BCS was performed much later, at either 6 or 8 months after radiation. This resulted in 42% (15/36) of patients achieving a pCR. There was a difference in pCR numerically between the 6- and 8-month cohorts, with pCR rates of 33% (5/15) and 48% (10/21), respectively. These higher pCR rates could be at least partially due to the longer time interval between radiation and BCS compared with most other preoperative breast trials that have used days to
weeks. The optimal time for BCS after preoperative radiation is not known but should be investigated in future studies.

The low toxicity observed in our trial is reassuring and is comparable to other extremely hypofractionated trials. Only 2 patients (9%) in the current trial had a grade 3 toxicity, both of which were infected seromas. The United Kingdom FAST-Forward trial used a similar fractionation to ours except that it was done postoperatively.\textsuperscript{10,11} They randomized patients with early staged breast cancer after BCS to 1 of 3 fractionation regimens: 40 Gy in 15 fractions, 27 Gy in 5 fractions over 1 week, or 26 Gy in 5 fractions over 1 week. The only CTCAE acute skin grade 3 toxicity was in the 27 Gy arm and consisted of 1 (2.4%) patient. With longer follow-up, normal tissue effects in the breast or chest wall showed no difference between the 40 and 26 Gy arms, at 9.9% and 11.9%, respectively. Low toxicity rates have also been reported in preoperative breast radiation trials. For example, Vasmel et al\textsuperscript{16} reported 31% grade 2 and 3% grade 3 toxicity after single fraction preoperative partial breast irradiation. Likewise, the PAPBI trial reported about 90%, with none to mild fibrosis after 2 years and no differences whether the patient was treated with 40 Gy in 10 fractions over 2 weeks or 30 Gy in 5 fractions in 1 week.\textsuperscript{12} Similarly, in their 38.5 Gy twice daily fractionated APBI trial, Nichols et al\textsuperscript{18} reported 15% grade 3 seromas and 4% grade 3 wound infection.

Cosmetic outcome can be affected by several factors including fractionation regimen, timing of radiation in relation to BCS, and treated volume (partial breast irradiation vs whole breast). As noted previously, extreme hypofractionation has been used in the preoperative setting, but with partial breast irradiation. The PAPBI trial reported cosmetic outcomes improved over time and were good-to-excellent in 68% at 6 months and 92% at 5 years.\textsuperscript{12} Furthermore, no difference was noted between fractionation regimens. Horton et al\textsuperscript{17} enrolled patients with early staged breast cancer and treated them with single fraction preoperative partial breast irradiation to 15, 18, or 21 Gy. Because of their study protocol, a few women received postoperative radiation, but 100% of the women treated with preoperative partial breast irradiation reported good-to-excellent cosmesis throughout follow-up. Nichols et al\textsuperscript{18} also treated patients with early-stage breast cancer preoperatively with partial breast irradiation to 38.5 Gy in 10 fractions delivered twice daily. Cosmetic outcome was good-to-excellent in 79% at a median follow-up of 3.6 years. However, in the postoperative setting, some have reported worse cosmesis with APBI,\textsuperscript{8} and others have reported improved cosmesis with APBI.\textsuperscript{5} The current trial is unique in that it is the only preoperative trial using extreme hypofractionation and whole breast radiation. Our cosmesis compares favorably to the other preoperative breast trials.

There is some evidence that QOL is improved with hypofractionated breast radiation.\textsuperscript{28,29} Although our trial is a single arm study, QOL was high, with overall LASA

**Table 1 Patient and treatment characteristics (n = 22)**

| Median age, y (range) | 64.1 (44.3-76.7) |
|----------------------|------------------|
| Clinical stage       |                  |
| Tis                  | 1 (5%)           |
| T1                   | 21 (95%)         |
| N0, M0               | 22 (100%)        |
| Receptor status      |                  |
| ER+/HER2−            | 21 (95%)         |
| ER+/HER2+            | 1 (5%)           |
| Histology            |                  |
| Invasive ductal carcinoma | 15 (68%)       |
| Invasive lobular carcinoma | 3 (14%)        |
| Ductal carcinoma in situ | 1 (5)           |
| Other                | 3 (14%)          |
| Tumor grade          |                  |
| 1                    | 12 (55%)         |
| 2                    | 9 (41%)          |
| 3                    | 1 (5%)           |
| Laterality           |                  |
| Right                | 15 (68%)         |
| Left                 | 7 (32%)          |
| Radiation dose       | 25 Gy            |
| Modality             |                  |
| Photon               | 22 (100%)        |
| Median time from RT to surgery, wk (range) | 8 (4-9) |
| Axillary surgery     |                  |
| None                 | 2 (9%)           |
| SLNB                 | 19 (86%)         |
| SLNB + ALND          | 1 (5%)           |
| Node positive at surgery | 1 (5%)      |
| Residual cancer burden |               |
| 0                    | 3 (14%)          |
| I                    | 11 (50%)         |
| II                   | 8 (36%)          |
| Negative margins     | 22 (100%)        |
| Adjuvant chemotherapy|                  |
| None                 | 21 (95%)         |
| Yes                  | 1 (5%)           |

**Abbreviations:** ALND = axillary lymph node dissection; ER = Estrogen receptor; HER2 = human epidermal growth factor receptor 2; RT = radiation therapy; SLNB = sentinel lymph node biopsy.
and PROMIS not changing over time from baseline, and no significant change was seen in BCTOS. This is further supported by the fact that most patients in our trial reported they would receive radiation again.

There are several limitations to our trial, including the small sample size and it being nonrandomized. Although this study does not have long-term follow-up, we hypothesize one of the advantages of preoperative RT will be lower rates of fibrosis. We extrapolate this hypothesis from extremity sarcoma trials in which preoperative radiation demonstrated lower rates of fibrosis versus postoperative radiation.\textsuperscript{30,31} Rate of fibrosis in these studies may be attributable to higher radiation dose delivered postoperatively. Therefore, we suspect that lower doses, especially in the preoperative setting for breast cancer, may allow for equal tumor control but lower rates of fibrosis compared with standard postoperative radiation.

**Figure 1** Pathologic response at the time of breast-conserving surgery after preoperative hypofractionated radiation therapy.

**Figure 2** Overall quality of life (QOL) Linear Analogue Self-Assessment (LASA), Patient-Reported Outcomes Measurement Information System (PROMIS), and The Breast Cancer Treatment Outcome Scale (BCTOS) over time in patients undergoing preoperative hypofractionated radiation therapy and breast-conserving surgery.
Future clinical trials will need to address how preoperative RT may affect outcomes for specific breast cancer subtypes. Furthermore, it is difficult to directly compare to other preoperative breast radiation trials given the differences in fractionation regimens, time to surgery, and treated breast volumes. Lastly, longer follow-up is also needed to assess late toxicity, long-term cosmetic outcomes, and QOL.

This phase II trial of extremely hypofractionated whole breast radiation before BCS demonstrates a potentially successful alternative to the current standard of postoperative radiation after BCS for early-stage breast cancer. The preoperative approach in this trial yielded excellent pathologic responses with low rates of toxicities and good cosmesis. These results are being used to develop the next preoperative breast radiation trial at our institution. Further research into this approach is warranted.

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