Retrospective Study

Ipsilateral breast tumor recurrence in early stage breast cancer patients treated with breast conserving surgery and adjuvant radiation therapy: Concordance of biomarkers and tumor location from primary tumor to in-breast tumor recurrence

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Abstract

BACKGROUND
Patients with an in-breast tumor recurrence (IBTR) after breast-conserving therapy have a high risk of distant metastasis and disease-related mortality. Classifying clinical parameters that increase risk for recurrence after IBTR remains a challenge.

AIM
To describe primary and recurrent tumor characteristics in patients who experience an IBTR and understand the relationship between these characteristics and disease outcomes.

METHODS
Patients with stage 0-II breast cancer treated with lumpectomy and adjuvant radiation were identified from institutional databases of patients treated from 2003-2017 at our institution. Overall survival (OS), disease-free survival, and local recurrence-free survival (LRFS) were estimated using the Kaplan Meier method. We identified patients who experienced an isolated IBTR. Concordance of hormone receptor status and location of tumor from primary to recurrence was evaluated. The effect of clinical and treatment parameters on disease outcomes was also evaluated.

RESULTS
We identified 2164 patients who met the eligibility criteria. The median follow-up
INTRODUCTION

Breast conserving surgery (BCS) followed by whole breast irradiation (WBI) is an established treatment paradigm for early stage breast cancer with numerous studies showing equivalent outcomes with mastectomy with regard to disease-specific and overall survival (OS) [1-3]. However, despite excellent outcomes with breast conservation, there is still a risk of in-breast tumor recurrence (IBTR). In the EBCTG meta-analysis, the rate of IBTR was 35% with BCS alone and was reduced to 19.3% with adjuvant radiation [4]. In more modern series, the rate of IBTR at 5-years range from 1.1%-3.3% [5-7]. Studies demonstrate that the time to IBTR is not confined to the first few years after surgery and radiation, but that late recurrences do occur, particularly for estrogen receptor (ER) positive disease [9]. Multiple risk factors have been found to increase the risk of IBTR. These include young age [6,7], positive hormone receptor status (HR) [8], the size of the primary tumor, stage, high grade disease [9], and the biology of the tumor [10]. Presence of lymphovascular invasion (LVI) and positive margins have also been associated with increased risk of IBTR [9,10].

CONCLUSION

Among patients with early stage breast cancer who had breast conserving surgery treated with adjuvant RT, HR/PR status and quadrant were highly concordant from primary to IBTR. Tumor size greater than 1.5 cm and use of adjuvant endocrine therapy were significantly associated with decreased risk of IBTR.

**Core tip:** Distinguishing a new primary breast tumor from a true ipsilateral breast tumor recurrence (IBTR) based on clinical features alone is challenging among patients with early stage breast cancer treated with breast conserving surgery and adjuvant radiotherapy. Our aim was to describe primary and recurrent tumor characteristics in patients who experienced an IBTR. We retrospectively analyzed patients with isolated IBTR. Estrogen/progesterone receptor status from primary tumor to IBTR was highly associated, as was the concordance between the quadrant of primary to IBTR. Tumor size greater than 1.5 cm and use of adjuvant endocrine therapy decreased the risk of IBTR.
tumor [approximated by subtype defined by ER, progesterone receptor (PR), and HER-2 receptor status].

Patients with an IBTR after BCS have an increased risk of distant metastasis and disease-related mortality, with older women and those with larger tumors having the highest mortality\[11\]. The management of patients with IBTR represents a complex clinical challenge. In the modern era, local therapy after an IBTR in the setting of prior radiation has evolved from standard salvage mastectomy with axillary dissection. The recently published RTOG 0104 supports a paradigm of salvage lumpectomy and partial breast radiation for patients with small recurrences and favorable tumor biology. In order to spare patients who are clinically node-negative after IBTR from undergoing extensive axillary clearance, repeating sentinel lymph node biopsy may represent a feasible option\[12\]. The role of chemotherapy is often guided by the biomarkers of the tumor\[13\].

One controversy that complicates the decision on how to manage recurrences, particularly late IBTRs, is whether the disease event represents a true recurrence or a new primary. Distinguishing between these two entities based on clinical features and/or outcomes remains a challenge; and the paucity of data with regard to outcomes after IBTR makes distinguishing between the two based on outcomes alone difficult.

The purpose of our study was to identify patients treated with breast conserving surgery and WBBI who experienced an IBTR. The study aimed to characterize features of the primary tumor and recurrent disease and determine which parameters increase the risk for IBTR. It also aimed to better define the relationship between the primary tumor and IBTR in the context of location in the breast and biologic subtype. Finally, this study examined disease outcomes in these patients and determined which if any primary disease characteristics or IBTR characteristics influenced outcome after IBTR.

**MATERIALS AND METHODS**

**Patients**

All women in the cohort were aged > 18 years and diagnosed with pathologically staged 0-II in situ and invasive breast cancer treated with BCS and adjuvant whole-breast radiation at a single institution.

Patients were from four institutional review board-approved prospective clinical trials investigating the use of hypo-fractionated radiation in this patient population (n = 1317) and from an institutional database of breast cancer patients treated at our institution during the period of 2003-2015 (n = 1248). Disease status was updated for all patients from these 4 studies and from the institutional database using study visits, breast imaging, or visits with other breast-cancer physicians. Follow-up, local recurrence, and distant recurrence data were collected by review of electronic medical records or physical charts. Three hundred and thirty-nine patients were enrolled in both the prospective clinical trials and the institutional database and were counted only once in the analysis. Sixty-two women had no physical or electronic charts available and were thus excluded from the list of patients. The final number of patients included in the overall analysis was 2164. This study was approved by the Institutional Review Board (IRB 17-00993).

**Tumor characteristics**

Histopathological and tumor information was obtained through review of pathology reports. The following biological markers were evaluated at initial presentation and at IBTR: grade, LVI, tumor size, nodal status, ER, PR, and HER-2 status, and Ki-67 (< 10% vs > or = 10%). We classified each IBTR as receptor discordant if the IBTR hormone status was ER/PR negative while the original primary was ER/PR positive; or when the IBTR hormone status was ER/PR positive while the original primary was ER/PR negative.

The tumor quadrant in the breast was determined based on mammography and/or magnetic resonance imaging prior to BCS at initial presentation and at recurrence. IBTRs that occurred in the same quadrant of the breast were considered concordant; skin recurrences and recurrences outside the original quadrant were considered discordant.

**Statistical analysis**

Disease and patient characteristics were summarized using descriptive statistics. Local recurrence-free survival (LRFS), disease-free survival (DFS), DFS after IBTR [second recurrence (DFS-SR)], and OS were estimated using the Kaplan-Meier method and follow-up was estimated using the method of Scheper et al\[10\]. All initial event...
and follow-up times were measured from the date of surgery for the primary tumor. Event and follow-up times after IBTR were measured from the date of histologically proven disease at the time of recurrence. The Chi-square test was used to assess the association between receptor subtype concordance and location concordance from primary to IBTR. The univariate Cox proportional-hazards model was used to assess the association between patient age, ER, PR, size, grade, tumor margins, LVI, Ki-67 and completion of hormone or chemotherapy at the time of primary disease, with the time interval to the first IBTR. All statistical tests were two-sided with alpha = 0.05. Statistical significance is expressed as $P < 0.05$. The statistical review of this study was performed by a biomedical statistician.

**RESULTS**

**Patient characteristics**

The median follow-up for all 2164 patients was 3.73 years [Interquartile range (IQR) 2.27-6.07]. Five-year OS was 97.7% (95%CI: 96.8%-98.6%) with 28 deaths. 5-year LRFS was 98.0% (97.2-98.8) with 31 IBTRs.

**IBTR**

Forty patients experienced an isolated IBTR (1.85%), defined as local recurrence without either regional or distant recurrence. Three patients with IBTRs were excluded due to insufficient pathology information.

The clinicopathologic characteristics of the primary tumor for the patients who experienced an IBTR are summarized in Table 1. The median age at diagnosis was 64 (range 32-91), with 48.6% of patients with invasive disease and 51.4% with ductal carcinoma *in situ* (DCIS). Median whole-breast dose was 40.5 Gy. The median dose with a boost was 48 Gy. Of the patients with invasive disease ($n = 18$), 83.3% had invasive ductal carcinoma (IDC) and 83.3% had an *in situ* component. 55.6% had high-grade disease and 27.8% had LVI. The majority of patients with invasive cancers had disease in the upper outer quadrant (55.6%), were hormone receptor positive (ER 66.7% and PR 66.7%) and HER-2/neu amplification negative (77.8%). The majority of invasive tumors were less than 2 cm (56.3%), node negative (85.0%), and evaluated by sentinel lymph node biopsy (87.3%). 88.9% had negative surgical margins. 61.1% of patients with invasive disease were treated with adjuvant chemotherapy and 61.1% were treated with hormone therapy. 16.7% of patients with invasive disease received anti-HER-2/neu therapy. Of the patients with DCIS (19), 47.3% had high grade DCIS, the majority were ER positive (73.7%) and PR positive (63.2%), with two patients who were ER positive, but PR negative. The majority of patients had negative surgical margins (68.4%), and disease in the upper outer quadrant (63.2%). 36.8% of patients with *in situ* disease were treated with endocrine therapy.

**Clinical and treatment characteristics at the time of IBTR**

Characteristics of the IBTRs are summarized in Table 2. The median time to IBTR was 1.97 (IQR: 1.03-3.5) years. 45.9% of IBTRs were invasive, and 51.4% were DCIS. Of the patients with invasive disease at initial diagnosis, 72.2% had invasive disease at recurrence and 27.8% had pure DCIS at recurrence. Of the patients with DCIS at initial diagnosis, 73.7% had DCIS at recurrence and 26.3% had invasive disease at recurrence. 55.6% of invasive IBTRs had an *in situ* component. At the time of IBTR, 86.5% of patients underwent salvage surgery (43.2% bilateral mastectomy, 24.3% unilateral mastectomy, and 16.2% local excision), 21.6% received chemotherapy, 43.2% received endocrine therapy, and 16.2% (those who had a local excision) underwent re-irradiation of the ipsilateral breast. Median follow-up for all patients was 2.13 years (IQR: 0.97-4.7) following IBTR.

Twenty-five of thirty-two (78.1%) patients had concordant hormone receptor status, and ER and PR receptor status from primary to IBTR were highly associated (ER: $\chi^2 P = 0.006$; PR: $\chi^2 P < 0.05$). Thirteen patients initially had ER or PR positive disease and became ER and PR negative. Four patients were ER and PR negative at diagnosis and were hormone receptor positive at recurrence. Of the patients who were triple negative at diagnosis ($n = 4$), 100% remained triple negative. There were no changes in HER-2 status from primary to IBTR. The concordance between the quadrant of primary to IBTR was 23/37 (62.2%), $\chi^2 P < 0.05$. There was no association between concordance of tumor location or biomarker status with time to IBTR.

Tumor size greater than 1.5 cm (HR: 0.44; 95%CI: 0.22-0.90, $P < 0.05$), and endocrine therapy decreased the risk of IBTR (HR: 0.36; 95%CI: 0.18-0.73, $P < 0.05$) with a median interval to IBTR of 54 wk in patients with tumors < 1.5 cm ($vs$ 119 wk in patients with tumor greater than or equal to 1.5 cm) and a median time to IBTR of 54.5
Table 1  Clinicopathologic characteristics of primary tumors in patients who experienced an ipsilateral breast tumor recurrence

|                          | Overall | DCIS   | Invasive |
|--------------------------|---------|--------|----------|
| **n**                    | 37      | 19     | 18       |
| **Age [years, mean (SD)]** | 63.08 (14.52) | 65.74 (11.49) | 60.28 (17.05) |
| **Race (%)**             |         |        |          |
| White                    | 27 (73.0) | 13 (68.4) | 14 (77.8) |
| African American         | 7 (18.9)  | 3 (15.8)  | 4 (22.2)  |
| Asian                    | 1 (2.7)   | 1 (5.3)   | 0 (0.0)   |
| Declined                 | 2 (5.4)   | 2 (10.5)  | 0 (0.0)   |
| **ER Positive (%)**      |         |        |          |
| Positive                 | 26 (70.3) | 14 (73.7) | 12 (66.7) |
| **PR Positive (%)**      |         |        |          |
| Positive                 | 24 (64.9) | 12 (63.2) | 12 (66.7) |
| **ILC**                  | 2 (5.4)   | 2 (11.1)  |           |
| **IDC**                  | 15 (40.5) | 15 (83.3) |           |
| **Mixed invasive**       | 1 (2.7)   | 1 (5.6)   |           |
| **Invasive only: DCIS present (%)** |         |          | 3 (16.7) |
| **Invasive only: HER-2 Status (%)** |         |          | 15 (83.3) |
| Negative                 | 14 (77.8) |           |           |
| Positive                 | 5 (16.7)  |           |           |
| Not performed            | 1 (5.6)   |           |           |
| **Invasive only: Pathologic grade (%)** |         |          |           |
| 1                        | 4 (22.2)  |           |           |
| 2                        | 4 (22.2)  |           |           |
| 3                        | 10 (55.6) |           |           |
| **Invasive only: Ki 67 Status (%)** |         |          | 8 (44.4) |
| Low (< 10)               | 8 (44.4)  |           |           |
| High (≥ 10)              | 8 (44.4)  |           |           |
| Not performed            | 2 (11.1)  |           |           |
| **Invasive only: LVI (%)** |         |          |           |
| Not present              | 12 (66.7) |           |           |
| Present                  | 5 (27.8)  |           |           |
| Close                    | 1 (5.6)   |           |           |
| **DCIS only: Nuclear grade (%)** |         |          |           |
| Grade 1                  | 0 (0)     |           |           |
| Grade 2                  | 10 (52.6) |           |           |
| Grade 3                  | 9 (47.3)  |           |           |
| **T - stage (%)**        |         |        |          |
| 0                        | 19 (51.4) | 19 (100.0) | 0 (0.0)  |
| 1                        | 11 (29.7) | 0 (0.0)   | 11 (61.1) |
| 2                        | 7 (18.9)  | 0 (0.0)   | 7 (38.9)  |
| **Positive margins (%)** |         |        |          |
| 8 (21.6)                 | 6 (31.6)  | 2 (11.1)  |           |
| **Chemotherapy (%)**     |         |        |          |
| 11 (29.7)                | 0 (0.0)   | 11 (61.1) |           |
| **Hormone therapy (%)**  |         |        |          |
| 18 (48.6)                | 7 (36.8)  | 11 (61.1) |           |
| **Tumor axis/quadrant (%)** |         |          |           |
| 3:00                     | 1 (2.7)   | 1 (5.3)   | 0 (0.0)   |
| 6:00                     | 1 (2.7)   | 0 (0.0)   | 1 (5.6)   |
| 9:00                     | 1 (2.7)   | 1 (5.3)   | 0 (0.0)   |
| Central                  | 2 (5.4)   | 1 (5.3)   | 1 (5.6)   |
| LIQ                      | 1 (2.7)   | 0 (0.0)   | 1 (5.6)   |
| LOQ                      | 3 (8.1)   | 2 (10.5)  | 1 (5.6)   |
| UOQ                      | 6 (16.2)  | 2 (10.5)  | 4 (22.2)  |
| U0Q                      | 22 (59.5) | 12 (63.2) | 10 (55.6) |
other studies have reported significantly improved post-recurrence recurrence; however, our numbers were small and thus this cannot be stated primary to recurrence did not have a prognostic effect in the context of time to retrospective analyses. In our study, concordance of receptor phenotype from in other series, with discordance of tumor phenotype ranging from 15%-40% in status and a 37.8% discordance in location. Similar rates have also been demonstrated between the primary tumor and IBTR with a 21.9% discordance in hormone receptor tumor sizes. may have explained the longer interval to recurrence among patients with larger tumor size received chemotherapy in our series (85% of T2 patients), which with decreased risk of IBTR may be due to the fact that a majority of patients with [16] = 0.02) Our finding that larger tumor size was associated with reduced DFS following LRR (HR = 1.3, 95%CI: 1.03-1.6, \( P < 0.03 \)) and HER-2 status (\( P = 0.03 \)), absence of gross tumor at the time of radiation (\( P = 0.03 \)), time to initial LRR (\( P = 0.03 \)) after mastectomy included initial smaller tumor size (\( P = 0.03 \)) and first recurrence. There was no effect of concordance of biomarkers, concordance of tumor location, presence of an in situ component at recurrence, invasive vs in situ disease, hormone positive vs hormone negative disease on DFS-SR although the numbers were small.

**DISCUSSION**

This study identified and characterized IBTR in a large cohort of patients treated with BCS and adjuvant radiation. From a cohort of 2164 patients, we identified 40 patients who experienced an IBTR and had sufficient information to study 37 of these patients. We identified high concordance rates between ER/PR status of the primary and recurrent tumor and of the location of the primary and recurrent tumor. We also showed that tumor size greater than 1.5 cm and use of endocrine therapy up-front were associated with decreased risk of IBTR.

In our entire cohort, the OS of 97.7% at 5 years compares favorably with the outcomes of modern trials with early-stage breast cancer patients such as the START B trial and UK IMPORT LOW trial which had 5-year OS rates of 92.1%-95%[11-15]. The LRFS in our study of 98.0% was consistent with modern trials with a LR rate of approximately 2% at 5 years in the START B trial and 1.1% at 5 years in the UK IMPORT LOW trial. The overall low rate of recurrence in this single-institution series demonstrates that excellent local control can be obtained in this population of early stage breast cancer treated with BCS. All patients received radiotherapy and systemic treatment tailored to individual tumor biology.

In our study, there was a decreased risk of IBTR in patients with larger tumor size. Published trials have identified larger tumor size to be a predictor of local recurrence. In the MD Anderson experience, factors associated with improved local control on multivariate analysis among patients with an isolated local regional recurrence (LRR) after mastectomy included initial smaller tumor size (\( P = 0.03 \)), time to initial LRR (\( P = 0.03 \)), absence of gross tumor at the time of radiation (\( P = 0.001 \)) and HER-2 status (\( P = 0.03 \))[15]. In Anderson et al.[15], larger pathologic tumor size was a significant predictor of IBTR (HR = 1.44, 95%CI: 1.22-1.71, \( P < 0.0001 \)) and mortality. A series from Harvard found that larger tumor size was associated with reduced DFS following LRR (HR = 1.3, 95%CI: 1.03-1.6, \( P = 0.02 \))[15]. Our finding that larger tumor size was associated with decreased risk of IBTR may be due to the fact that a majority of patients with larger tumor size received chemotherapy in our series (85% of T2 patients), which may have explained the longer interval to recurrence among patients with larger tumor sizes.

In our study, there was a high rate of biomarker and quadrant concordance between the primary tumor and IBTR with a 21.9% discordance in hormone receptor status and a 37.8% discordance in location. Similar rates have also been demonstrated in other series, with discordance of tumor phenotype ranging from 15%-40% in retrospective analyses[17-19]. In our study, concordance of receptor phenotype from primary to recurrence did not have a prognostic effect in the context of time to recurrence; however, our numbers were small and thus this cannot be stated definitively. Other studies have reported significantly improved post-recurrence

**DCIS:** Ductal carcinoma in situ; \( \text{ER} \): Estrogen receptor; \( \text{PR} \): Progesterone receptor; \( \text{I.L.C} \): Invasive lobular carcinoma; \( \text{IDC} \): Invasive ductal carcinoma; \( \text{LVI} \): Lymphovascular invasion; \( \text{LIQ} \): Lower inner quadrant; \( \text{LOQ} \): Lower outer quadrant; \( \text{UIQ} \): Upper inner quadrant; \( \text{UOQ} \): Upper outer quadrant.
### Table 2  Clinicopathologic characteristics of recurrences

| Characteristic                                                                 | Count (Percentage) |
|-------------------------------------------------------------------------------|--------------------|
| Median time to IBTR (years IQR)                                               | 1.97 (1.03-3.5)    |
| Invasive (%)                                                                   | 18 (45.9)          |
| DCIS (%)                                                                       | 19 (51.4)          |
| DCIS to invasive conversion (%)                                                | 5 (26.3)           |
| Invasive to DCIS conversion (%)                                                | 5 (27.8)           |
| In-situ component in invasive histology (%)                                   | 10 (55.6)          |
| Concordant with original receptor subtype (%)                                  |                    |
| Yes                                                                            | 25/32 (78.1)       |
| No                                                                             | 7/32 (21.9)        |
| Unknown                                                                       | 5/37 (13.5)        |
| ER concordance (%)                                                            |                    |
| Same                                                                          | 25 (75.8)          |
| Change from + to -                                                            | 5 (15.2)           |
| Change from - to +                                                            | 2 (6.1)            |
| PR concordance (%)                                                            |                    |
| Same                                                                          | 22 (66.7)          |
| Change from + to -                                                            | 8 (24.2)           |
| Change from - to +                                                            | 2 (6.0)            |
| HER-2 concordance (%)                                                          |                    |
| Same                                                                          | 16 (100)           |
| Change from + to -                                                            | 0 (0)              |
| Change from - to +                                                            | 0 (0)              |
| Concordant with original location (%)                                         |                    |
| Yes                                                                            | 23 (62.2)          |
| No                                                                             | 14 (37.8)          |
| Salvage surgery (%)                                                           | 32 (86.5)          |
| Bilateral mastectomy                                                          | 16 (43.2%)         |
| Unilateral mastectomy                                                         | 9 (24.3)           |
| Local excision                                                                | 6 (16.2%)          |
| Salvage systemic therapy (%)                                                   |                    |
| Chemotherapy only                                                             | 3 (8.1)            |
| Hormone therapy only                                                          | 11 (29.7)          |
| Both                                                                          | 5 (13.5)           |
| Re-irradiation of ipsilateral breast                                          | 6 (16.2%)          |

**IBTR**: Ipsilateral breast tumor recurrence; **IQR**: Interquartile range; **DCIS**: Ductal carcinoma in situ; **ER**: Estrogen receptor; **PR**: Progesterone receptor.

In order to further classify IBTRs, studies have tried to distinguish between new primaries (NP) and true recurrences (TR) incorporating multiple factors including receptor subtype with the theory that NPs will have improved outcomes compared to TRs and that NPs are less likely to have concordant biomarkers and/or tumor locations. Patients with NPs tend to have a longer median time to relapse than TR patients (7.3 vs 3.7 years, \( P < 0.0001 \))[21]. Haffty et al.[22] classified an NP based on the fulfillment of at least one of the following three criteria: New location, histological subtype, or conversion from aneuploidy primary to a diploid relapse using DNA flow cytometry. In their series, 62% of patients had an isolated IBTR with a concordant location, and 74% with a concordant histology at a median follow-up of 10.2 years.[23] Post-breast recurrence survival rate for TRs was 3.16% compared to 5.42% for NPs (\( P < 0.05 \)). In a series by Braunstein et al.[16], there was a 68% concordance of biologic subtype from primary tumor to IBTR approximated by ER, PR, HER-2 and tumor survival and OS among patients who maintain their tumor phenotype. In a retrospective analysis of 139 patients, the loss of hormone receptor positivity resulted in a worse post-recurrence survival (\( P = 0.01 \)) and OS (\( P = 0.06 \)), compared with the corresponding concordant-positive cases[17]. A small prospective study of 29 patients demonstrated that changes in hormone status from primary to recurrent disease led to a 20% change in disease management[20].
Table 3 Results of univariate Cox model assessing the association of clinical variables with risk of the first ipsilateral breast tumor recurrence

| Clinical variable                  | Hazard ratio (95%CI)     | P value |
|-----------------------------------|--------------------------|---------|
| Patient age (continuous)          | 1.004 (0.98-1.02)        | 0.73    |
| ER negative                       | 1                        | -       |
| ER positive                       | 0.53 (0.26-1.11)         | 0.093   |
| PR negative                       | 1                        | -       |
| PR positive                       | 0.75 (0.38-1.50)         | 0.423   |
| Tumor grade: Low                  | 1                        | -       |
| Tumor grade: Intermediate         | 0.791 (0.25-2.5)         | 0.689   |
| Tumor grade: High                 | 1.624 (0.54-4.8)         | 0.385   |
| Margins negative                  | 1                        | -       |
| Margins positive                  | 0.793 (0.36-1.75)        | 0.565   |
| No chemotherapy                   | 1                        | -       |
| Chemotherapy up-front             | 1.282 (0.63-2.6)         | 0.499   |
| No endocrine therapy up-front     | 1                        | -       |
| Endocrine therapy up-front        | 0.362 (0.18-0.73)        | 0.004   |
| Biomarker not concordant          | 1                        | -       |
| Biomarker concordant              | 1.04 (0.95-1.10)         | 0.92    |
| Location not concordant           | 1                        | -       |
| Location concordant               | 1.265 (0.63-2.53)        | 0.506   |
| Size < 1.5 cm                     | 1                        | -       |
| Size ≥ 1.5 cm                     | 0.442 (0.22-0.90)        | 0.023   |
| Invasive primary tumors           |                          |         |
| LVI none                          | 1                        | -       |
| LVI present                       | 0.617 (0.20-1.92)        | 0.404   |
| HER2 negative/equivocal           | 1                        | -       |
| HER2 positive                     | 0.837 (0.28-2.55)        | 0.754   |
| Ki-67 (continuous)                | 1.002 (0.99-1.02)        | 0.745   |

IBTR: Ipsilateral breast tumor recurrence; HR: Hormone receptor; ER: Estrogen receptor; PR: Progesterone receptor; LVI: Lymphovascular invasion.

grade at a median follow-up of 105 mo. Patients with triple negative breast cancer who developed LRR were at high risk of subsequent recurrence with significant worse DFS after IBTR compared with women with luminal A disease (ER and PR positive, HER-2 negative and grade 1 or 2 disease) (37.5% vs 88.3% at 5 years, P < 0.005). In a series by Komoike et al[23], classification of TR/NP was based on location of the primary and secondary tumor, initial surgical margin, and histological features. The 5-year survival rates were 71.0% in TRs vs 94.7% in NPs (P = 0.022). NP was a prognostic risk factor for a second local relapse (P = 0.003)[13]. In light of these findings, further research is warranted to identify prognostic factors for post-recurrence DFS and OS given that different studies are using variable definitions for TRs and NPs. In our study, there were too few events after IBTR to effectively determine an association between outcomes after IBTR and quadrant concordance, biomarker concordance, or the presence of an in situ component.

There are multiple limitations in this study. This was a retrospective study of patients enrolled in prospective clinical trials as well as in a large institutional database. The overall low rate of local recurrence in our cohort could be due in part to a lack of follow-up and missing information. There is also possible selection bias in that it is possible that patients with inferior outcomes (e.g., recurrence) were more likely to seek care at outside institutions and therefore be more likely to have missing follow-up information than those patients who did not experience a recurrence. Another limitation of this study is the lack of statistical power to determine associations between tumor or patient characteristics and outcomes given our small number of patients who experienced IBTR. Finally, this is a single institutional series which may also limit its applicability and generalizability.

Our study found an overall low rate of IBTR in a large series of patients treated with BCS and adjuvant radiation. We found that tumor size and endocrine therapy at
initial diagnosis correlated with decreased risk of IBTR, and biomarker and tumor location were highly concordant from primary tumor to IBTR. We did not find an association between disease outcomes after IBTR and quadrant concordance, biomarker concordance or the presence of an in situ component though our numbers were small. Early vs late IBTR, biomarker and quadrant concordance may serve as useful classifiers; however, more evidence is necessary to accurately classify IBTRs in a way that is prognostic of outcomes. In an era where options for the management of IBTRs often represents a complex clinical challenge, a better understanding of what is a recurrence and what may represent a new primary will refine our treatment paradigms.

ARTICLE HIGHLIGHTS

Research background

Patients with an in-breast tumor recurrence (IBTR) after breast conserving therapy have a high risk of distant metastasis and disease-related mortality. The management of patients with IBTR represents a complicated clinical challenge. Local therapy after an IBTR in the setting of prior radiation has evolved in the modern era from standard salvage mastectomy with axillary dissection. Recent literature supports salvage lumpectomy and partial breast irradiation for patients with small tumor recurrences that have favorable tumor biology. The role of chemotherapy is guided by the biomarkers of the tumor.

Research motivation

One controversy that complicates the decision on how to manage recurrences is whether the disease event represents a true recurrence or a new primary. Distinguishing these processes based on clinical features alone remains a challenge given the dearth of data with regard to outcomes after the first recurrence.

Research objectives

The purpose of our study was to identify patients treated with BCS and whole breast irradiation who experienced an IBTR. We aimed to characterize the features of the primary tumor and the recurrence and determine the factors that increase the risk for IBTR. The study also aimed to better define the relationship between the primary tumor and the ipsilateral breast recurrence with respect to location of recurrence in the breast and the biologic subtype based on histopathology markers. Lastly, the study investigated the disease outcomes in these patients and elucidated whether any primary disease characteristics or IBTR characteristics influence outcomes after the first recurrence.

Research methods

Patients were identified from institutional databases of patients treated from 2003-2017 at our institution. All women in the cohort were > 18 years diagnosed with pathological stage 0-II in situ and invasive breast cancer treated with lumpectomy and adjuvant radiation. Histopathological and tumor information for the primary tumor and the ipsilateral breast recurrence were obtained through review of pathology reports. We classified each IBTR as receptor discordant if the IBTR hormone status was estrogen receptor/progesterone receptor (ER/PR) negative, while the original primary tumor was ER/PR positive; or when the IBTR hormone status was ER/PR positive, while the original primary tumor was ER/PR negative. The tumor quadrant in the breast was determined based on mammography and/or magnetic resonance imaging prior to BCS at initial presentation and at recurrence. IBTRs that recur in the same quadrant of the breast were considered concordant; skin recurrences and recurrences outside the original quadrant were considered discordant. Overall survival (OS), disease-free survival, and local recurrence-free survival (LRFS) were estimated using the Kaplan Meier method. We identified patients who experienced an isolated IBTR. Concordance of hormone receptor status and location of tumor from primary to recurrence were evaluated using the Chi-square test. The effect of clinical and treatment parameters on disease outcomes was evaluated using a univariate Cox proportional-hazards model. All statistical tests were two-sided with alpha = 0.05.

Research results

We identified 2164 patients who met the eligibility criteria. The median follow-up for all patients was 3.73 [Interquartile range (IQR) 2.27-6.07] years. Five-year OS was 97.7% (95% CI: 96.8%-98.6%) with 28 deaths; 5-year LRFS was 98.0% (97.2-98.8) with 31 IBTRs. We identified 37 patients with isolated IBTR, 19 (51.4%) as ductal carcinoma in situ and 18 (48.6%) as invasive disease, of whom 83.3% had an in situ component. Median time from initial diagnosis to IBTR was 1.97 (IQR: 1.03-3.5) years. Radiotherapy information was available for 30 of 37 patients. Median whole-breast dose was 40.5 Gy and 23 patients received a boost to the tumor bed. Twenty-five of thirty-two (78.1%) patients had concordant hormone receptor status, HER-2 receptor status, and ER ($P = 0.006$) and PR ($P = 0.001$) receptor status from primary to IBTR were significantly associated. There were no observed changes in HER-2 status from primary to IBTR. The concordance between quadrant of primary to IBTR was 10/19 [(62.2%), $P = 0.008$]. Tumor size greater than 1.5 cm [$HR = 0.44$, 95% CI: 0.22-0.90, $P < 0.05$], and endocrine therapy decreased the risk of IBTR ($HR = 0.56$, 95% CI: 0.18-0.73, $P < 0.05$) with a median interval to IBTR of 54 wk in.
patients with tumors < 1.5 cm (vs 119 wk in patients with tumor greater than or equal to 1.5 cm) and a median time to IBTR of 54.5 wk in patients who did not receive endocrine therapy (vs 138.1 wk in patients treated with endocrine therapy). The primary tumor grade, chemotherapy upfront, margins, ER, PR, and patient age were not associated with time interval to IBTR. Among patients with invasive primary tumors, HER-2 receptor status, lymphovascular invasion, and Ki-67 were not associated with a shorter time interval to IBTR. The presence of an in situ component at the time of invasive recurrence was not associated with time interval to IBTR.

Research conclusions
The OS rate in our entire cohort compares favorably with the outcomes of modern trials with early stage breast cancer patients. Among patients with early stage breast cancer who had BCS treated with adjuvant RT, ER/PR status and quadrant were highly concordant from primary to IBTR. Tumor size greater than 1.5 cm and use of adjuvant endocrine therapy were significantly associated with decreased risk of IBTR. We did not find an association between disease outcomes after IBTR and quadrant concordance, biomarker concordance or the presence of an in situ component, although our numbers were small.

Research perspectives
In order to further classify IBTRs, studies have attempted to distinguish between new primaries and true recurrences with the idea that new primaries will have improved outcomes compared to true recurrences. Early vs late IBTR, biomarker and quadrant concordance may serve as useful classifiers; however, more evidence is necessary to accurately classify IBTRs in a way that is prognostic of outcomes. In an era where options for the management of IBTRs often represent a complex clinical challenge, a better understanding of what is a recurrence and what may represent a new primary will refine our treatment paradigms. These questions should be further investigated in larger multi-institutional prospective clinical studies with the statistical power to determine associations between the characteristics of primary tumor and IBTRs, treatment and disease outcomes.

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