

## 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**

Juhi M Purswani, Fauzia Shaikh, S Peter Wu, Jennifer Chun Kim, Freya Schnabel, Nelly Huppert, Carmen A Perez, Naamit K Gerber

**ORCID number:** Juhi M Purswani (0000-0003-1068-9449); Fauzia Shaikh (0000-0002-9274-9734); S Peter Wu (0000-0003-1692-6935); Jennifer Chun Kim (0000-0003-3752-6826); Freya Schnabel (0000-0002-6393-7453); Nelly Huppert (0000-0002-0658-4161); Carmen A Perez (0000-0002-6759-5358); Naamit K Gerber (0000-0002-6061-0498).

**Author contributions:** Purswani JM and Gerber NK designed the research; Purswani JM, Gerber NK and Wu SP performed the research; Purswani JM and Wu SP analyzed the data; Purswani JM, Gerber NK, Kim JC, Schnabel F, Huppert N and Perez CA wrote the paper.

**Institutional review board**

**statement:** This study was reviewed and approved by the Ethics Committee of New York University School of Medicine on December 13, 2017. This is an exempt study, annual renewal is not required.

**Informed consent statement:**

Patients were not required to give informed consent to the research study. The analysis used anonymized clinical data obtained after each subject agreed to treatment with written consent.

**Conflict-of-interest statement:**

There are no financial disclosures,

**Juhi M Purswani, Fauzia Shaikh, S Peter Wu, Nelly Huppert, Carmen A Perez, Naamit K Gerber,** Department of Radiation Oncology, New York University School of Medicine, New York, NY 10016, United States

**Jennifer Chun Kim, Freya Schnabel,** Department of Surgery, New York University School of Medicine, New York, NY 10016, United States

**Corresponding author:** Naamit K Gerber, MD, Assistant Professor, Department of Radiation Oncology, New York University School of Medicine, 160 E. 34<sup>th</sup> Street, New York, NY 10016, United States. [naamit.gerber@nyumc.org](mailto:naamit.gerber@nyumc.org)

**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

conflicts of interest, and/or acknowledgments for all the authors.

**Data sharing statement:** No additional data are available.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Invited manuscript

**Received:** March 23, 2019

**Peer-review started:** March 26, 2019

**First decision:** August 2, 2015

**Revised:** October 21, 2015

**Accepted:** November 6, 2019

**Article in press:** November 6, 2019

**Published online:** January 24, 2020

**P-Reviewer:** de Melo FF, Ortiz-Sanches E, Vikey AK

**S-Editor:** Dou Y

**L-Editor:** Webster JR

**E-Editor:** Qi LL



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 estrogen receptor (ER) ( $P = 0.006$ ) and progesterone receptor (PR) ( $P = 0.001$ ) 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,  $P = 0.02$ ) and use of endocrine therapy upfront (HR = 0.36, 95%CI: 0.18-0.73,  $P = 0.004$ ) decreased the risk of IBTR.

### CONCLUSION

Among patients with early stage breast cancer who had breast conserving surgery 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.

**Key words:** : Ipsilateral breast tumor recurrence; Breast conservation; Adjuvant radiation

©The Author(s) 2020. Published by Baishideng Publishing Group Inc. All rights reserved.

**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.

**Citation:** Purswani JM, Shaikh F, Wu SP, Kim JC, Schnabel F, Huppert N, Perez CA, Gerber NK. 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. *World J Clin Oncol* 2020; 11(1): 20-30

**URL:** <https://www.wjgnet.com/2218-4333/full/v11/i1/20.htm>

**DOI:** <https://dx.doi.org/10.5306/wjco.v11.i1.20>

## 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)<sup>[1-3]</sup>. 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 radiation<sup>[2]</sup>. In more modern series, the rates of IBTR at 5-years range from 1.1%-3.3%<sup>[4,5]</sup>. 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, particular for estrogen receptor (ER) positive disease<sup>[6,7]</sup>.

Multiple risk factors have been found to increase the risk of IBTR. These include young age<sup>[8]</sup>, the size of the primary tumor, stage, high grade disease<sup>[9]</sup>, positive margin status<sup>[9,10]</sup>, presence of lymphovascular invasion (LVI) and the biology of the

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<sup>[11]</sup>. 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<sup>[12]</sup>. The role of chemotherapy is often guided by the biomarkers of the tumor<sup>[13]</sup>.

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 WBI 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 Schemper *et al*<sup>[14]</sup>. 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
<i>n</i>	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 (%)	26 (70.3)	14 (73.7)	12 (66.7)
PR 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 (%)			
No			3 (16.7)
Yes			15 (83.3)
Invasive only: HER-2 Status (%)			
Negative			14 (77.8)
Positive			3 (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 (%)			
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)
UIQ	6 (16.2)	2 (10.5)	4 (22.2)
UOQ	22 (59.5)	12 (63.2)	10 (55.6)

DCIS: Ductal carcinoma *in situ*; ER: Estrogen receptor; PR: Progesterone receptor; ILC: Invasive lobular carcinoma; IDC: Invasive ductal carcinoma; LVI: Lymphovascular invasion; LIQ: Lower inner quadrant; LOQ: Lower outer quadrant; UIQ: Upper inner quadrant; UOQ: Upper outer quadrant.

wk in patients who did not receive endocrine therapy (*vs* 138.1 wk in patients treated with endocrine therapy). The primary tumor grade, chemotherapy up-front, margins, ER, PR, and patient age were not associated with the time interval to IBTR (Table 3). Among patients with invasive primary tumors, HER-2 receptor status, LVI, 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 the time interval to IBTR.

Seven patients (18.9%) with an isolated IBTR experienced a second disease event during the follow-up period. The 5-year DFS after IBTR [second recurrence (DFS-SR)] was 81.1%. There were four patients who experienced an isolated LR after the first IBTR, two who developed a distant recurrence and 1 who developed a regional recurrence. Of the 4 who had an isolated LR after the first IBTR, 2 had undergone lumpectomy at the time of first recurrence, 1 had undergone mastectomy and 1 did not undergo further surgery. Among all four patients, the second recurrence had concordant biomarkers with the primary tumor and the first recurrence. Among three patients, the second recurrence also had concordant tumor location with the primary 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%<sup>[4,5]</sup>. 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 ( $P = 0.03$ )<sup>[15]</sup>. In Anderson *et al*<sup>[11]</sup>, 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,  $P = 0.02$ )<sup>[16]</sup>. 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<sup>[17-19]</sup>. 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

**Table 2 Clinicopathologic characteristics of recurrences**

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.

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<sup>[17]</sup>. 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<sup>[20]</sup>.

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,  $P < 0.0001$ )<sup>[21]</sup>. Haffty *et al*<sup>[22]</sup> classified an NP based on the fulfilment 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<sup>[22]</sup>. 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*<sup>[16]</sup>, there was a 68% concordance of biologic subtype from primary tumor to IBTR approximated by ER, PR, HER-2 and tumor

**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*<sup>[23]</sup>, 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 ( $P = 0.003$ )<sup>[23]</sup>. 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 recurred 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 = 0.36, 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 wk in patients who did not receive endocrine therapy (*vs* 138.1 wk in patients treated with endocrine therapy). The primary tumor grade, chemotherapy up-front, 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 *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 recurrence 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.

## REFERENCES

- 1 **Fisher B**, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, Jeong JH, Wolmark N. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002; **347**: 1233-1241 [PMID: 12393820 DOI: 10.1056/NEJMoa022152]
- 2 **Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**. Darby S, McGale P, Correa C, Taylor C, Arriagada R, Clarke M, Cutter D, Davies C, Ewertz M, Godwin J, Gray R, Pierce L, Whelan T, Wang Y, Peto R. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet* 2011; **378**: 1707-1716 [PMID: 22019144 DOI: 10.1016/S0140-6736(11)61629-2]
- 3 **Veronesi U**, Zucali R, Luini A. Local control and survival in early breast cancer: the Milan trial. *Int J Radiat Oncol Biol Phys* 1986; **12**: 717-720 [PMID: 3519549 DOI: 10.1016/0360-3016(86)90027-1]
- 4 **Coles CE**, Griffin CL, Kirby AM, Tittle J, Agrawal RK, Alhasso A, Bhattacharya IS, Brunt AM, Ciurlionis L, Chan C, Donovan EM, Emson MA, Harnett AN, Haviland JS, Hopwood P, Jefford ML, Kaggwa R, Sawyer EJ, Syndikus I, Tsang YM, Wheatley DA, Wilcox M, Yarnold JR, Bliss JM; IMPORT Trialists. Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial. *Lancet* 2017; **390**: 1048-1060 [PMID: 28779963 DOI: 10.1016/S0140-6736(17)31145-5]
- 5 **START Trialists' Group**. Bentzen SM, Agrawal RK, Aird EG, Barrett JM, Barrett-Lee PJ, Bentzen SM, Bliss JM, Brown J, Dewar JA, Dobbs HJ, Haviland JS, Hoskin PJ, Hopwood P, Lawton PA, Magee BJ, Mills J, Morgan DA, Owen JR, Simmons S, Sumo G, Sydenham MA, Venables K, Yarnold JR. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet* 2008; **371**: 1098-1107 [PMID: 18355913 DOI: 10.1016/S0140-6736(08)60348-7]
- 6 **Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**. Davies C, Godwin J, Gray R, Clarke M, Cutter D, Darby S, McGale P, Pan HC, Taylor C, Wang YC, Dowsett M, Ingle J, Peto R. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet* 2011; **378**: 771-784 [PMID: 21802721 DOI: 10.1016/S0140-6736(11)60993-8]
- 7 **Colleoni M**, Sun Z, Price KN, Karlsson P, Forbes JF, Thürlimann B, Gianni L, Castiglione M, Gelber RD, Coates AS, Goldhirsch A. Annual Hazard Rates of Recurrence for Breast Cancer During 24 Years of Follow-Up: Results From the International Breast Cancer Study Group Trials I to V. *J Clin Oncol* 2016; **34**: 927-935 [PMID: 26786933 DOI: 10.1200/JCO.2015.62.3504]
- 8 **Fourquet A**, Campana F, Zafrani B, Mosseri V, Vielh P, Durand JC, Vilcoq JR. Prognostic factors of breast recurrence in the conservative management of early breast cancer: a 25-year follow-up. *Int J Radiat Oncol Biol Phys* 1989; **17**: 719-725 [PMID: 2777661 DOI: 10.1016/0360-3016(89)90057-6]
- 9 **Dewar JA**, Arriagada R, Benhamou S, Benhamou E, Bretel JJ, Pellae-Cosset B, Marin JL, Petit JY, Contesso G, Sarrazin D. Local relapse and contralateral tumor rates in patients with breast cancer treated with conservative surgery and radiotherapy (Institut Gustave Roussy 1970-1982). IGR Breast Cancer Group. *Cancer* 1995; **76**: 2260-2265 [PMID: 8635030 DOI: 10.1002/1097-0142(19951201)76:11<2260::aid-encr2820761113>3.0.co;2-d]
- 10 **Findlay-Shirras LJ**, Outbih O, Muzyka CN, Galloway K, Hebbard PC, Nashed M. Predictors of Residual Disease After Breast Conservation Surgery. *Ann Surg Oncol* 2018; **25**: 1936-1942 [PMID: 29748884 DOI: 10.1245/s10434-018-6454-1]
- 11 **Anderson SJ**, Wapnir I, Dignam JJ, Fisher B, Mamounas EP, Jeong JH, Geyer CE, Wickerham DL, Costantino JP, Wolmark N. Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in patients treated by breast-conserving therapy in five National Surgical Adjuvant Breast and

- Bowel Project protocols of node-negative breast cancer. *J Clin Oncol* 2009; **27**: 2466-2473 [PMID: 19349544 DOI: 10.1200/JCO.2008.19.8424]
- 12 **Wong SM**, Golshan M. Management of In-Breast Tumor Recurrence. *Ann Surg Oncol* 2018; **25**: 2846-2851 [PMID: 29947005 DOI: 10.1245/s10434-018-6605-4]
- 13 **Aebi S**, Gelber S, Anderson SJ, Láng I, Robidoux A, Martín M, Nortier JW, Paterson AH, Rimawi MF, Cañada JM, Thürlimann B, Murray E, Mamounas EP, Geyer CE, Price KN, Coates AS, Gelber RD, Rastogi P, Wolmark N, Wapnir IL; CALOR investigators. Chemotherapy for isolated locoregional recurrence of breast cancer (CALOR): a randomised trial. *Lancet Oncol* 2014; **15**: 156-163 [PMID: 24439313 DOI: 10.1016/S1470-2045(13)70589-8]
- 14 **Schemper M**, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials* 1996; **17**: 343-346 [PMID: 8889347 DOI: 10.1016/0197-2456(96)00075-X]
- 15 **Skinner HD**, Strom EA, Motwani SB, Woodward WA, Green MC, Babiera G, Booser DJ, Meric-Bernstam F, Buchholz TA. Radiation dose escalation for loco-regional recurrence of breast cancer after mastectomy. *Radiat Oncol* 2013; **8**: 13 [PMID: 23311297 DOI: 10.1186/1748-717X-8-13]
- 16 **Braunstein LZ**, Niemierko A, Shenouda MN, Truong L, Sadek BT, Abi Raad R, Wong JS, Punglia RS, Taghian AG, Bellon JR. Outcome following local-regional recurrence in women with early-stage breast cancer: impact of biologic subtype. *Breast J* 2015; **21**: 161-167 [PMID: 25559656 DOI: 10.1111/tbj.12371]
- 17 **Dieci MV**, Barbieri E, Piacentini F, Ficarra G, Bettelli S, Dominici M, Conte PF, Guarneri V. Discordance in receptor status between primary and recurrent breast cancer has a prognostic impact: a single-institution analysis. *Ann Oncol* 2013; **24**: 101-108 [PMID: 23002281 DOI: 10.1093/annonc/mds248]
- 18 **Saedi Saedi H**, Ghavam Nasiri MR, ShahidSales S, Taghizadeh A, Mohammadian N. Comparison of hormone receptor status in primary and recurrent breast cancer. *Iran J Cancer Prev* 2012; **5**: 69-73 [PMID: 25628823]
- 19 **Li BD**, Byskosh A, Molteni A, Duda RB. Estrogen and progesterone receptor concordance between primary and recurrent breast cancer. *J Surg Oncol* 1994; **57**: 71-77 [PMID: 7934066 DOI: 10.1002/jso.2930570202]
- 20 **Simmons C**, Miller N, Geddie W, Gianfelice D, Oldfield M, Dranitsaris G, Clemons MJ. Does confirmatory tumor biopsy alter the management of breast cancer patients with distant metastases? *Ann Oncol* 2009; **20**: 1499-1504 [PMID: 19299408 DOI: 10.1093/annonc/mdp028]
- 21 **Smith TE**, Lee D, Turner BC, Carter D, Haffty BG. True recurrence vs. new primary ipsilateral breast tumor relapse: an analysis of clinical and pathologic differences and their implications in natural history, prognoses, and therapeutic management. *Int J Radiat Oncol Biol Phys* 2000; **48**: 1281-1289 [PMID: 11121624 DOI: 10.1016/s0360-3016(00)01378-x]
- 22 **Haffty BG**, Carter D, Flynn SD, Fischer DB, Brash DE, Simons J, Ziegler AM, Fischer JJ. Local recurrence versus new primary: clinical analysis of 82 breast relapses and potential applications for genetic fingerprinting. *Int J Radiat Oncol Biol Phys* 1993; **27**: 575-583 [PMID: 8226151 DOI: 10.1016/0360-3016(93)90382-6]
- 23 **Komoike Y**, Akiyama F, Iino Y, Ikeda T, Tanaka-Akashi S, Ohsumi S, Kusama M, Sano M, Shin E, Suemasu K, Sonoo H, Taguchi T, Nishi T, Nishimura R, Haga S, Mise K, Kinoshita T, Murakami S, Yoshimoto M, Tsukuma H, Inaji H. Analysis of ipsilateral breast tumor recurrences after breast-conserving treatment based on the classification of true recurrences and new primary tumors. *Breast Cancer* 2005; **12**: 104-111 [PMID: 15858440 DOI: 10.2325/jbcs.12.104]



Published By Baishideng Publishing Group Inc  
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA  
Telephone: +1-925-2238242  
E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
Help Desk: <https://www.f6publishing.com/helpdesk>  
<https://www.wjgnet.com>

