



Ipsilateral breast tumor recurrence after breast-conserving surgery: insights into biology and treatment

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Abstract

Despite modern surgical and irradiation techniques, ipsilateral breast tumor recurrence (IBTR) accounts for 5–15% of all cancer recurrence in women treated with breast conservative treatment. Historically, this event has been treated definitively with salvage mastectomy and completion axillary clearance. However, many local recurrences are small and without nodal involvement at presentation. Thus, there has been an interest in performing a surgical de-escalation procedure in the breast and the axilla. The current guidelines do not provide detailed descriptions and treatment suggestions for these selected patients, resulting in inconsistent treatment strategies. Moreover, the methods to define true recurrence (TR) and new primary tumor (NP) for IBTR remain controversial. Most developed classification methods mainly rely on clinical and pathological criteria, limiting the accuracy of the description and causing misclassification. In this editorial, we will discuss the current trends in surgical de-escalation for patients with IBTR. Moreover, we will focus on recent IBTR innovations, highlighting molecular-integrated classification and multimodal staging methods for clinical practice and postoperative surveillance strategies.

Keywords Ipsilateral breast tumor recurrence · Surgical de-escalation · Molecular-integrated classification · Multimodal staging method

Abbreviations

BCS	Breast-conserving surgery	PBI	Partial breast irradiation
IBTR	Ipsilateral breast tumor recurrence	PBC	Primary breast cancer
SLNB	Sentinel lymph node biopsy	RFI	Recurrence-free interval
ALND	Axillary lymph node dissection	ASS	Axillary surgical staging
BCT	Breast conservative treatment	cNO	Clinically negative node
TR	True recurrence	HR	Hormone receptor
NP	New primary	SBC	Second breast cancer
APBrI	Accelerated partial breast reirradiation	LRR	Locoregional recurrence
IMB	Interstitial multicatheter brachytherapy	PHBC	Prior history of breast cancer
IORT	Intraoperative radiotherapy	BPE	Background parenchymal enhancement

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Introduction

Even with routine practice of breast-conserving surgery (BCS) and adjuvant radiotherapy, ipsilateral breast tumor recurrence (IBTR) accounts for 5–15% of all cancer recurrence in patients with early-stage breast cancer, which heralds a poor prognosis and accompanies or precedes distant metastasis in a defined proportion of patients [1, 2].

The past decade has witnessed an unprecedented trend of de-escalation for surgical approaches in the management of primary breast cancer [3, 4], including the omission of re-excisions for close margins after BCS, the introduction

of oncoplastic techniques to reduce mastectomy rates, and the replacement of sentinel lymph node biopsy (SLNB) with axillary lymph node dissection (ALND) in patients with low-axillary tumor burden. However, in the setting of local recurrence, these surgical innovations have not yet shed light on the optimal management of the breast and the axilla. An increasing number of treatment strategies are suggested to perform a less aggressive procedure in patients with IBTR after initial breast conservative treatment (BCT). Unfortunately, due to the low prevalence and lack of solid evidence, the current guidelines do not provide detailed descriptions and treatment suggestions for this subset of patients [5, 6]. In this respect, individualized oncologic treatment depends on the rigorous selection of patients to avoid both overtreatment and undertreatment.

Another pressing issue is the precise classification for IBTR defining true recurrence (TR) or new primary (NP) tumor. Many classification methods have been developed, but widely recognized standards are still lacking. Yi et al. classified IBTR as either TR or NP using two conventional methods, wherein patients classified as NP experienced more contralateral breast cancer but had better long-term overall and disease-specific survival rates than those classified as TR. Additionally, patients with TR were more likely to develop metastatic disease after IBTR [2]. However, most classification methods mainly rely on clinical and pathological criteria, limiting the accuracy of the description and causing misclassification [7]. Taking the location of IBTR as an example, for multifocal and multicentric primary tumors, there could be a TR of the same histologic subtype that is not within the same quadrant of the primary tumor but is located outside the treatment field in the ipsilateral breast. Previous studies have shown that some multigene assays, such as the

21-gene recurrence score, were a significant predictor of local recurrence in tamoxifen-treated patients [8, 9] but have not yet been applied in terms of IBTR classification. Therefore, there is great interest in integrating clinicopathological variables and laboratory analyses to provide clinicians with additional information beyond expected outcomes.

In this editorial, we will decipher the recent advances and emerging trends in de-escalation for IBTR surgery. We will also provide an overview of the most recent innovations in the molecular nature of IBTR, aiming to propose potential diagnostic methods and optimized treatment strategies.

Trends in de-escalation for IBTR surgery: more is not better?

Scenario 1: Local therapy of the breast

Salvage mastectomy has long been considered the standard of care for patients experiencing IBTR after BCS with whole breast irradiation. However, with the early detection of local recurrences, there is a growing surge in evaluating the feasibility of repeat conservative treatment.

Recently, several groups, represented by the Groupe Européen de Curiethérapie and the European Society for Radiotherapy and Oncology (GEC-ESTRO) study, reported their experience with a repeat lumpectomy with accelerated partial breast reirradiation (APBrI) using interstitial multicatheter brachytherapy (IMB) (Table 1). In this series, a 10-year second IBTR rate of 11% was updated, with a 10-year distant metastasis rate of 11% and overall survival of 94% [10]. In the NRG Oncology/Radiation Therapy Oncology Group (RTOG) 1014 trial, Arthur et al. provided

Table 1 Comparison of the available studies on repeat conservative treatment for IBTR

Study	GEC-ESTRO	NRG oncology/RTOG 1014
Patient number	113	58
Patient population	IBTR at least 1 year after primary tumor, excluding in-breast skin and sub-cutaneous metastatic diseases	IBTR tumor ≤ 3 cm, RFI ≥ 1 year after initial BCT, unicentric confirmed by MRI, without evidence of skin involvement, pN0 or pN1 for primary tumor
Study type	Retrospective	Prospective, phase II
Median follow up	121.5 months	5.5 years
Primary endpoint	Second local recurrence and distant metastasis rates	Rate of grade ≥ 3 treatment-related AEs occurring ≤ 1 year from re-treatment completion
Radiation therapy	APBrI (interstitial multicatheter brachytherapy using either low, pulsed, or high-dose rate)	APBrI (3-dimensional conformal external beam radiation therapy, 1.5 Gy twice daily for 30 treatments during 15 days)
Efficacy results	10y-2nd IBTR = 89% (95%CI 83–96) 10y-DMFS = 89% (95%CI 83–96) 10y-DFS = 78% (95%CI 70–87)	5y-2nd IBTR = 5.2% (95%CI 1.4–13.2) 5y-DMFS = 94.8% (95%CI 84.8–98.3) 5y-OS = 94.8% (95%CI 84.8–98.3)

IBTR ipsilateral breast tumor recurrence, RFI recurrence-free interval, BCT breast-conserving treatment, MRI magnetic resonance imaging, pN0 no axillary lymph node involvement, pN1 1–3 axillary lymph nodes involvement, AEs adverse effects, APBrI accelerated partial breast reirradiation, DMFS distant metastasis-free survival; DFS disease-free survival, OS overall survival

consistent and compelling data by using 3-dimensional conformal APBrI in which enrolled patients were restricted to have unicentric tumors smaller than 3 cm, without skin involvement and to be at least 1 year from their initial BCT. Intraoperative radiotherapy (IORT) is another modality of partial breast irradiation (PBI), while preliminary evidence in the setting of primary breast cancer (PBC) is still early for justification [11]. Further study is warranted to inform the outcomes of PBI among patients with IBTR who represent a minority of overall population and to define optimal PBI dose and treatment techniques.

With the encouraging results of the abovementioned studies, panelists of St. Gallen Breast Cancer Consensus (SG-BCC) increasingly took a vote of confidence to second BCT under certain circumstances of IBTR, in which the recurrence-free interval (RFI) seemed to play a major role in decision making. As revealed in the latest voting section, 74% of the panelists regarded salvage mastectomy as the preferred approach in cases of IBTR with a 3-year interval from the primary tumor, while 58% of the voters switched to second BCS plus irradiation when patients were treated 9 years ago. However, given the strictly selected patient population in the NRG/RTOG 1014 trial, we cannot extrapolate it to all patients in routine practice. Further refinement of patient selection criteria is warranted in future studies.

Scenario 2: Local therapy of the axilla

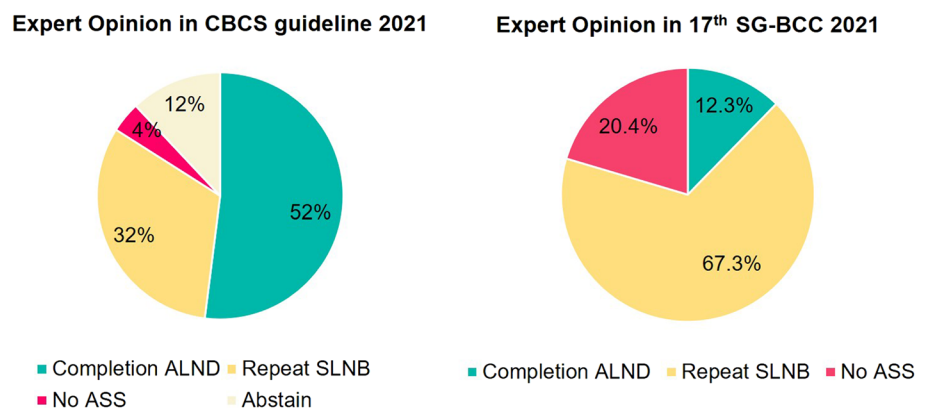
At present, management of the axilla is another controversy that has not been fully addressed in patients with IBTR. Currently, in patients with clinically negative node (cN0) status, it is unclear which axillary surgical staging (ASS) strategy should be adopted, especially in those with previous negative sentinel nodes. This uncertainty is reflected in the heterogeneity of recommendations endorsed by different national and international societies, ranging from repeat SLNB to completion ALND (Fig. 1). In the 2021 SG-BCC vote, repeat SLNB with or without frozen section was predominantly favored by the panel

in the setting of IBTR patients with negative nodes on imaging after previous treatment with negative sentinel node mapping [12]. In contrast, the panelists of the Chinese Anti-Cancer Association Committee of Breast Cancer Society (CBCS) were split 50/50 on offering completion ALND other than repeat SLNB [13].

In the recent past, complete axillary clearance was deemed to be recommended for all patients with IBTR independent of axillary nodal status. With modern multidisciplinary treatment alternatives such as adjuvant systemic therapy and axillary radiation, the rationale for proposing a completion ALND appears to be declining. The concept of repeat SLNB has emerged in recent years, and it remains to be clarified whether second sentinel mapping could safely replace ALND [14, 15]. Lu et al. retrospectively identified patients with IBTR from the Surveillance, Epidemiology, and End Results database and demonstrated that repeat SLNB had a similar long-term overall survival as ALND [16]. Consistently, our single-institution experience revealed that 85% of patients undergoing ASS (repeat SLNB or completion ALND) at the time of IBTR obtained pathologically negative nodes, and a selection bias was observed on the basis of prior ALND, shorter RFI, and concordant molecular subtype favoring no ASS but comparable local control [17]. These findings justified that repeat SLNB might be considered for ASS in patients with IBTR after lumpectomy and initial SLNB.

With the improvement in noninvasive diagnostic options, de-escalation of surgical approaches might be accompanied by an escalation of preoperative staging. Haarsma et al. indicated a low incidence of a tumor-positive repeat SLNB in IBTR patients with a negative FDG-PET/CT and equivalent survival outcome [18]. These results are in line with the aforementioned studies [19, 20], supporting a patient-tailored treatment strategy in which repeat SLNB might also be omitted in cN0 patients with IBTR who underwent optimal clinical staging with FDG-PET/CT.

Fig. 1 Comparison of recommended axilla management in case of IBTR with clinically negative nodes after previous negative sentinel nodes endorsed by CBCS guideline and SG-BCC. *CBCS* Chinese Anti-Cancer Association Committee of Breast Cancer Society, *SG-BCC* St. Gallen Breast Cancer Consensus, *ALND* axillary lymph node dissection, *SLNB* sentinel lymph node biopsy, *ASS* axillary surgical staging



Classification chaos: the elephant in the room

Numerous studies have attempted to classify IBTR into two entities by using tumor location, histologic subtype, or gene-expression profiling data, but no widely recognized size fits all [7]. In our previous comment [21], we used the metaphor of “elephant in the room” for IBTR classifications, which were judged on the basis of clinical and pathological criteria rather than genomic information. Furthermore, the stereotype that biological features are fixed between the primary tumor and the TR should be reconsidered since genomic characteristics might shift due to the clonal evolution nature of “recurrence.”

Recent evolutions in next-generation sequencing make it possible to identify the clonal origin and relatedness of tumor pairs in the genomic profile. Nakagomi et al. revealed that PIK3CA-AKT pathway abnormalities predominantly act in developing long-term residual recurrences, thus, subdividing IBTR into two groups with respect to the existence of shared mutations in both tissue of PBC and IBTR [22]. Tommaso et al. employed proteogenomic to reveal that breast tumors evolve into different IBTRs depending on hormonal status and proliferation levels, possibly enhanced by *APOBEC3B*, and pinpointed that immune cell infiltration and significantly elevated Ki-67 in primary tumors might serve as a starting point to predict IBTR formation [23].

Notably, local recurrences of hormone receptor (HR)-positive breast cancer are featured with a favorable prognosis and late occurrence compared with other molecular subtypes [1]. These clinical characteristics raised the question of whether this kind of ipsilateral second breast cancer (SBC) is a TR or NP tumor. Rassy et al. unveiled this issue in a group of patients with HR-positive breast cancer by comparing the mutational profile of PBC with those of patient-matched ipsilateral SBC [24]. The final analysis revealed that approximately 18% of patients exhibited common gene variants (*ARID1A*, *NSD2*, *SETD2*, etc.) in the first and ipsilateral SBC tumor and could be considered TR. Further analysis using larger cohorts, preferably using single-cell analyses to account for clonality, might better select patients with TR and thereby inform the decision-making process.

Second recurrences after IBTR: an inconvenient truth

Locoregional recurrence (LRR), including IBTR, chest recurrence and regional nodal recurrence, has been historically considered an independent risk for distant

recurrence and is associated with a poorer overall prognosis [25]. In retrospective studies, 15–23% of patients with LRR were reported to have nonsynchronous distant metastases (DM) [1, 25, 26]. With that in mind, Murata et al. identified seven risk factors associated with DM after LRR, in which progesterone receptor negativity in recurrent tumors and RFI < 24 months exhibited the largest hazard ratios [27]. A risk prediction model was therefore developed based on the number of detected risk factors: low-, intermediate-, high-, and the highest-risk groups with 0 to 1, 2, 3 to 4, and 5 to 7 factors, respectively. In line with that, Wu et al. constructed an integrated nomogram to guide clinical decision-making, in which post-LRR patients could be divided into two groups and had tailored therapeutic strategies (local treatment for the low-risk group and systemic therapies for the high-risk group) [28].

Apart from risk prediction models, noninvasive imaging seems to be more appealing for stratifying the risk of second recurrence after IBTR. Previous studies have consistently demonstrated that the addition of breast magnetic resonance imaging (MRI) to mammography and ultrasound in the preoperative workup of IBTR allows for more accurate size estimation and higher sensitivity for the detection of multifocality [29, 30]. As a result, the American College of Radiology recommends annual breast MRI surveillance for women with a prior history of breast cancer (PHBC) [31]. Lee et al. demonstrated that mild, moderate or marked background parenchymal enhancement (BPE) at surveillance breast MRI was associated with future second breast cancer risk in women with a PHBC [32]. Further studies in larger multi-institution data sets are needed to validate BPE at surveillance breast MRI as an imaging marker for establishing personalized imaging surveillance strategies.

Conclusion

There is a growing trend of de-escalation for breast and axilla surgical strategies in patients with IBTR after initial BCT. Considering urgent clinical needs and the lack of standard guidelines, future large-scale studies are warranted to validate novel techniques for axilla staging, explore potential benefits of no ASS, and assess the potential use of IORT for these patients. A certain proportion of IBTR patients exhibited the common nature of gene variants in primary and IBTR tumors. Such complexity suggests the importance of implementing both clinicopathological and genomic information to design treatment strategies in a personalized fashion. Simultaneously, caution for second recurrences should be applied when treating patients with this disease.

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Declarations

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