Surgical Treatment of Local Recurrence in Breast Cancer Patients

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Jose Vila, Francisco Ripoll, and Oreste D. Gentilini

25.1 Introduction

25.1.1 Definition of Local Recurrence

Local recurrence is defined as the reappearance of an invasive tumor in the ipsilateral preserved breast after Breast-conserving surgery (BCS), or a breast cancer recurrence in the skin, subcutaneous tissue, muscle, or underlying bone after mastectomy. When a local recurrence occurs after a conservative approach, it is called ipsilateral breast tumor recurrence (IBTR) and chest wall recurrence (CWR) when it occurs after mastectomy [1]. Local recurrence tends to occur later after a conservative procedure than after mastectomy, especially in those patients treated by endocrine or chemotherapy [2–4]. Chest wall recurrences are generally diagnosed during physical examination. In contrast, IBTRs are more frequently detected during posttreatment mammographic surveillance [5].

A local failure is considered a marker of aggressiveness as it has been demonstrated to be associated with a three to five times greater risk of distant metastasis and represents the main cause of breast cancer-related death [6]. In the US National Surgical Adjuvant Breast and Bowel Project B-06 (NSABP B-06) study, Fisher et al. demonstrated that patients with IBTR have 3.41 greater risk of developing distant metastasis than patients who do not develop such recurrences [7]. Several factors have been associated with the reappearance of breast cancer such as initial surgery and use of adjuvant therapies (chemotherapy, hormonal therapy, and radiation therapy), residual tumor burden, clinical and pathologic characteristics, and biologic markers of the primary breast tumor [8, 9]. Recently, Shangani et al. updated and validated a web-based predictive model, called IBTR! Version 2.0, to estimate individualized risk of IBTR after breast-conserving therapy. This online tool incorporates seven variables that are routinely assessed and has been associated with increased risk of local failure after conservative surgery, such as age, margin status, lymphovascular invasion (LVI), size tumor, grade, and use of chemo- and/or hormone therapy [10]. This nomogram can be easily implemented in many centers worldwide and may help guide decisions about adjuvant therapies in patients according to their risk of IBTR.

A recent analysis of 86.598 patients from 53 randomized clinical trials showed that isolated local-regional recurrences are now an uncommon event. Advances in the management of early stage breast cancer have significantly reduced the rate of local-regional recurrence from approximately 30% in past studies to 5–15% in recent trials [11]. Even though a rare event, local recurrences are associated with an increased risk of distant metastasis, especially early recurrences occurred within the first 2 years after primary treatment. So, a careful restaging evaluation including a complete blood test, radionuclide bone scan, breast magnetic resonance imaging (MRI), a total body positron emission tomography (PET), and/or chest, abdomen, and pelvis computed tomography (CT) scan may be appropriate in all patients with local recurrence after BCS or mastectomy to rule out the presence of distant disease.

25.1.2 Classification of IBTR

IBTR after BCS comprises a heterogeneous group of tumors with distinct biological behavior and different rates of survival. Although a recognized standard classification for local recurrence after BCS does not exist to date, IBTR has traditionally been categorized as true local recurrence (TR) and new primary tumor (NPT). These two entities were first described by Veronesi et al. in 1995 and were classified basically by its location relative to the primary tumor. TR was defined as the regrowth of invasive disease

J. Vila • F. Ripoll
Hospital Universitario y Politécnico La Fe, Valencia, Spain

O.D. Gentilini (✉)
Breast Surgery, San Raffaele Scientific and Research Hospital, Milan, Italy
e-mail: gentilini.oreste@hsr.it

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at the tumor bed or the boost volume of the treated breast and NPT as a new lesion located at a different site from the primary tumor [12].

Others methods of classifying IBTRs have been proposed by different groups that have attempted to evaluate indicators of prognosis in patients with IBTR. In this sense, Huang et al. classified local recurrences after BCS as either NP or TR based on location and histology [13]. More recently, Sakai et al. have proposed a novel classification of IBTR into four different subtypes based on strict pathologic rules [14]. Initially IBTRs should be classified according to their origin as new primary or true recurrence, similar to others, but subsequently classified again according to the relationship between the IBTR and the primary lumpectomy scar, surgical margin of the primary tumor, and the presence of carcinoma in situ into the IBTR.

The importance of establishing an accurate classification of IBTR is due to the prognostic significance related to both entities [15]. A new primary tumor has been associated with a more favorable prognosis than true local recurrences. Smith et al., in a retrospective study on 130 patients with IBTR, 60 of which were classified as a true recurrence and 70 as a new primary according to the site of failure, histologic subtype, and results from the flow cytometry, assessed the prognostic value of this classification. After a median follow-up of 10.4 years, patients with NPT had significantly better 10-year overall survival, distant-free survival, and cause-specific survival than patients diagnosed with TR [16].

25.1.3 Risk Factors of Local Recurrence

As local recurrence after BCS or mastectomy has been associated with a poor prognosis, it is important to identify patients who are at higher risk of recurrence and might benefit from additional adjuvant therapies and close follow-up [17]. In this sense, several risk factors of local recurrence have been identified either in patients treated with primary conservative surgery or mastectomy [18, 19].

– *Patients treated with primary BCS*. Reasonably, the most important predictor of increased risk for IBTR in patients treated with BCS is the failure to achieve optimal local control. Optimal local control includes a margin-negative surgery (no evidence of invasive cells at the inked border on microscopic evaluation) and use of radiation therapy with or without regional nodal irradiation. Other risk factors for recurrence after BCS include (1) tumors with aggressive biology such as triple-negative tumors, high proliferation rate of Ki-67, multicentric disease, tumors with high nuclear grade, etc., (2) young age at diagnosis of primary tumor, and (3) lymphatic invasion and extensive intraductal component at the first tumor.
– *Patients treated initially with mastectomy*. The clinical risk factors associated with increased risk of local failure after mastectomy include (1) young age at diagnosis, (2) tumor greater than 5 cm, and (3) multicentric disease. Histopathologic risk factors for CWR include (1) patients with four or more positive lymph nodes, (2) positive margins, (3) high-grade triple-negative tumors, and (4) presence of lymphovascular invasion.

25.2 Surgical Treatment of Chest Wall Recurrence

The incidence of CWR after mastectomy ranges from 8 to 40% and depends on several factors such as primary tumor characteristics and the use of adjuvant therapies after mastectomy, mainly the use of postmastectomy radiation therapy (PMRT). Several studies have demonstrated that the use of PMRT resulted in better local control of primary tumors by reducing the rate of CWR by up to 70%, especially in patients with node-positive disease in whom the absolute reduction in the recurrence risk is bigger [20]. Similar CWR rates and survival outcome have been found between patients treated with conventional mastectomy versus skin-sparing mastectomy as well as comparing different types of reconstruction [21, 22]. CWR is diagnosed with concomitant distant disease in up to 30% of patients. Absolute contraindications for curative intent resection include extensive local disease with multiple skin nodules and concomitant distant metastasis. Those patients are candidates to receive systemic therapy prior to evaluate the role of salvage surgery [23]. Although CWR may manifest itself as a macroscopically extensive disease or fungating masses, often it is presented as an asymptomatic nodule in the skin or a slight erythematous rash. Hence, diagnosis requires an experienced physician with high index of suspicion, particularly in high-risk patients. Any suspicious lesion mandates a careful evaluation including biopsy and pathologic confirmation.

The surgical management of these patients is complex and requires a preoperative planning between breast surgeons and plastic surgeons to help decide on the best reconstructive option. An estimation of the extent of the disease and the need for skin grafts or rotational flaps are discussed at these meetings. In all cases, achieving clear margins is essential to provide excellent long-term local control.

For no-reconstructed breast patients with isolated CWR confined to the bed tumor or proximal to the scar, a surgical tumor resection followed by primary closure is generally feasible and oncologically safe. However, for extensive recurrence, chest wall reconstruction using coverage with

skin grafts or autologous flaps is usually needed. In some cases, chest wall resection might require resection of the ribs, sternum, and costal cartilages, and the reconstruction technique depends on the site and extent of the chest wall defect [24]. However, it has to be highlighted that the utility of such wide resection is controversial.

For patients with previous reconstructed breast, the surgical management depends on the type of reconstruction. If patients with CWR had implant-based reconstruction, removal of the implant is sometimes required, but this is not absolutely indicated and, if technically possible, implant might be left in place. In patients with flap reconstruction (transverse rectus abdominus musculocutaneous, TRAM, or latissimus flap), wide surgical resection preserving the flap may be safe in selected cases of isolated CWR [25].

Postmastectomy radiation therapy (PMRT) has been proven to be a determinant for local control of the disease in patients treated with surgical resection after CWR [26–28]. Recent guidelines recommend a complete course of irradiation to the chest wall and supraclavicular and infraclavicular regions for patients initially treated with mastectomy and no prior radiation therapy. A standard dose of 50 Gy with 1.8/2 Gy fractions followed by an additional boost of 10 Gy should be applied [29]. In selected patients with previous irradiations, a second course of radiation as part of an individual multimodal treatment concept is feasible as is associated with acceptable acute and late morbidity and encouraging local control. Wahl et al. reviewed the toxicity and clinical outcomes of a second course of radiation in a multi-institutional study on 81 patients with CWR who underwent repeat radiation therapy of the breast. After a median follow-up of 12 months (range 1–144 months), only four patients developed grade 3 or 4 toxicity and no treatment-related deaths occurred [30]. A similar report was published by Hannoun-Levi et al. [31] evaluating the effect of chest wall re-irradiation using brachytherapy. The study included 32 patients with local recurrence after BCT treated with mastectomy followed by low- or high-dose rate interstitial brachytherapy. At a median follow-up of 22 months, the second local recurrence rate was low (3%), but the distant metastasis rate was 28%. Grade 3 late skin toxicity was observed only in two patients with no grade 4 toxicity.

25.3 Surgical Treatment of Ipsilateral Breast Tumor Recurrence

Though there have been significant advances in the management of breast cancer patients, the optimal treatment for patients with local recurrence after a conservative surgery is still controversial, and there are no data from randomized trials to guide treatment decisions. According to recent studies, 15% of patients with IBTR after BCT are considered inoperable due to the extensive local disease or concomitant distant metastases. The remaining 85% of patients who are diagnosed with operable tumor recurrence are candidate to surgery. International guidelines still recommend mastectomy as the standard approach for IBTR after BCS [32, 33]. However, several retrospective studies comparing mastectomy and repeating BCS have reported similar survival outcomes between both procedures, suggesting that a second conservative approach may be recommended in selected patients (Table 25.1).

Table 25.1 Outcome by surgical procedure after ipsilateral breast local recurrence

Author (ref.)	Total patients	BCS (n)	M (n)	Follow-up (months)	2nd LR (after BCS)	BCS 5y/10y DFS	BCS 5y/10y OS	M 5y/10y DFS	M 5y/10y OS
Kurtz et al. [34]	118	52	66	84	23%	NA	79%/64%	NA	68%/54%
Dalberg et al. [35]	85	14	65	NA	12.5%	67%/–	NA	88%/–	NA
Salvadori et al. [36]	191	57	134	73 (1–192)	19%	70.2%/–	85%/–	56%/–	70%/–
Alpert et al. [37]	146	30	116	244	7%	–/69.5%	–/58%	–/61.3%	–/65.7%
Fodor et al. [38]	44	28	16	NA	28%[a]	NA	–/81%	NA	–/81%
Chen and Martinez [39]	747	179	568	6	14.8%	NA	67%/–	NA	78%/–
Lee et al. [40]	131	23	108	NA	NA	NA	93.3%/–	NA	85.8%/–
Kolben et al. [41]	170	58	112	49	22.4%	57.3%/–	84.7%/–	61.9%/–	72.6%/–
Yoshida et al. [42]	102	51	51	55	19.3%	83%/–	82%/–	94%/–	92%/–

Abbreviations: *BCS* Breast-conserving surgery, *M* mastectomy, *LR* local recurrence, *DFS* disease-free survival, *OS* overall survival, *y* year
[a]2nd LR rate following salvage excision or mastectomy

Table 25.2 Suggested selection criteria for second Breast-conserving surgery

Suggested selection criteria for a second breast-conservative approach
Age ≥50 years
Small cancer ≤2 cm
Late recurrence (>48 months)
Absence of multifocality and/or multicentricity on clinical and conventional imaging examination including breast MR
Desire of the patient for conservative approach
Acceptable cosmetic results

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Patient selection criteria are crucial and represent a guide to selecting the best candidates for consideration of second conservative surgery. Vila et al. in a recent review proposed six clinical conditions that should be taken into account to help select the subset of patients who might benefit of less radical surgery with acceptable long-term survival outcome and local-regional control [43]. The selection criteria are listed in Table 25.2. Careful restaging workup of patients with local recurrence after BCS is mandatory to exclude distant disease and to identify patients who can be managed with curative intent.

25.3.1 Mastectomy

Although breast cancer treatment is becoming more conservative, mastectomy still remains the standard treatment for ipsilateral breast tumor recurrence after breast-conserving surgery [44]. Mastectomy for IBTR provides excellent local control that ranges from 69 to 98% [45]. The benefit of chest wall or regional nodal irradiation in patients treated with post-recurrence mastectomy has not been addressed but generally is not recommended in previously irradiated patients. However, regional nodal irradiation should be considered in high-risk patients who initially did not receive irradiation of the regional nodes. Ideally, mastectomy should be followed by immediate breast reconstruction using either a breast implant or autologous tissue.

25.3.2 Second Breast-Conserving Surgery ± Radiation Therapy

Retrospective studies addressing the role of a second conservative procedure have shown similar survival outcome when compared with mastectomy. Clinical outcome of patients treated with a second lumpectomy with or without re-irradiation is listed in Table 25.3. The largest series evaluating second BCS alone for in-breast local relapse was reported by Gentilini et al. This retrospective study evaluated 161 patients who underwent a second conservative alone approach after BCS and whole breast irradiation [55]. With a median follow-up of 81 months after IBTR, the 5-year overall survival was 84% (95% confidence interval [CI] 78–89) and a 5-year cumulative incidence of a further local reappearance of the tumor of 29%. This rate was lower than previous series and may be related to the small tumor size in the second BCS cohort (60% of the tumors were <1 cm). However, for patients with the diagnosis of a small relapse (<2 cm) occurring late after primary treatment (>48 months), the cumulative incidence of a further in-breast event was 15%. This finding suggests that motivated patients with the early diagnosis of a second primary tumor might be considered for a repeat BCS as an alternative to mastectomy. The local control after repeat BCS in the published series is similar to the outcome achieved by conservative surgery alone without radiotherapy. Therefore, due to improved radiotherapy treatments, a second course of radiation treatment should be carefully considered in those patients undergoing a second conservative procedure for the treatment of IBTR [56].

The largest experience evaluating the combination of a second conservative procedure followed by radiation therapy in patients with previously irradiated breast exists for multicatheter brachytherapy. As shown in Table 25.3, the addition of a second course of irradiation resulted in better local control. For patients treated with second lumpectomy alone, the

Table 25.3 Outcome of BCS ± re-irradiation for ipsilateral breast tumor recurrence

Author (ref.)	Total patients	Re-irradiation (type)	Follow-up (months)	2nd LR	5-year OS
Maulard et al. [46]	38	Yes (BT)	48	21	55
Voogd et al. [5]	16	No	53	38	NA
Deutsch [47]	39	Yes (EBRT)	51	20.5	77.9
Resch et al. [48]	17	Yes (BT)	59	24	88
Kraus-Tiefenbacher et al. [49]	17	Yes (IORT)	26	NA	94
Chadha et al. [50]	15	Yes (BT)	36	7	100[a]
Trombetta et al. [51]	26	Yes (BT)	38	4	88.5[b]
Guix et al. [52]	36	Yes (BT)	89	3	96.7[c]
Ishitobi et al. [53]	78	No	40	21	NA
Kauer-Dorner et al. [54]	39	Yes (BT)	57	NA	87
Gentilini et al. [55]	161	No	81	29	84
Hannoun-Levi et al. [56]	217	Yes (BT)	47	7	88.7

Abbreviations: *ref* reference, *LR* local recurrence, *OS* overall survival, *BT* brachytherapy, *EBRT* external beam radiation therapy, *NA* not available

[a]3-year OS

[b]3.2-year OS

[c]10-year OS

second LR rate ranged from 19% to as high as 39%, while in patients treated with a second course of irradiation, the second LR rate ranged from 3 to 21%. However, OS was less influenced by the effect of the re-irradiation as similar 5-year OS rates were observed.

Several limitations have been associated with these retrospective studies such as patient selection for second conserving surgery and the fact that no prospective studies or randomized trials have been performed comparing both procedures. So, the most important question still remains unanswered: Are all patients with operable tumor recurrence forced to undergo mastectomy instead of a second conservative procedure? The answer is no.

25.4 Surgical Axillary Management in Local Recurrence of Patients with Prior BCS

Although sentinel lymph node biopsy (SLNB) has replaced axillary lymph node dissection (ALND) in primary early stage breast tumors for women with clinically negative axilla [57], the axillary surgical management of women diagnosed with IBTR is highly controversial. Widely consulted guidelines still suggest that prior axillary surgery due to oncological reasons is a contraindication to the use of SLNB as the draining lymphatic channels are thought to be disrupted caused by the fibrosis directly related to the surgery resulting in unacceptable false-negative rates [44]. However, data from several retrospective series showed that SLNB is a technically feasible and an oncologically safe procedure to restage the axilla in patients with IBTR (Table 25.4). The success rate of second SLNB ranges from 53.7 to 92.5%. The numbers of the lymph nodes removed during the first surgery is one of the most important factors for successful identification when a second SLNB is performed [58]. In case of previous axillary lymph node dissection, no further treatment of the axilla should be necessary although several studies have reported that SLNB is feasible even in these patients. However, previous ALND is associated with the lowest detection rate of sentinel nodes.

Table 25.4 Experience with the use of second sentinel lymph node biopsy in locally recurrent breast cancer

Author (ref)	*N*	Success rate of sSLNB	Percentage of extra-axillary drainages
Port et al. [58]	54	74.1% (40/54)	5.5% (3)
Cox et al. [59]	56	80.4% (45/56)	2.2% (1)
Schrenk et al. [60]	15	80.0% (12/15)	14.3% (2)
van der Ploeg et al. [61]	36	72.2% (26/36)	47% (17)
Maaskant-Braat et al. [62]	41	53.7% (22/41)	25% (10)
Intra et al. [63]	212	92.5% (196/212)	8% (17)
Uth et al. [64]	73	65.7% (48/73)	8.2% (6)
Matsumoto et al. [65]	22	81.8% (18/22)	4.5% (1)

Abbreviations: *ref* reference, *sSLNB* second sentinel lymph node biopsy

The prognostic value of axillary restaging and the role for treatment decision making process has not been fully elucidated yet. A recent study by Ugras et al. from Memorial Sloan Kettering Cancer Center evaluated the value of axillary restaging in 83 patients with local recurrence (79 IBTR and 4 CWR) and clinically negative nodes at diagnosis. Axillary surgery was performed in 47 patients and 36 patients did not undergo axillary staging. Both groups of patients were similar according to primary tumor characteristics and adjuvant therapies received; however, time to local recurrence in the non-axillary surgery group was significantly shorter (median 3.5 vs. 6.5 years; $p < 0.05$). After a median follow-up of 4.2 years, both groups of treatment had similar rates of axillary failure, non-axillary recurrence, distant metastasis, and death. The authors concluded that preoperative SLNB, although technically feasible, may not be necessary in some cases and should be confirmed in larger cohort of patients [66].

Conclusions

The surgical management of local recurrences after BCS or mastectomy requires integration of health professionals providing multidisciplinary care that comprises breast and plastic surgeons, oncologists, and radiotherapists. Factors such as time to recurrence, site of relapse, initial nodal status, and clinical characteristics of the primary tumor have been shown to predict for differences in overall survival, disease-free survival, and local-regional control. A summary of the surgical options for breast tumor recurrence is represented in Fig. 25.1.

The management of isolated CWR depends on accurate assessment of many variables, such as age, comorbidities and desire of the patients, initial treatment, and size and location of the recurrence. For patients with previously non-irradiated mastectomy, wide resection with clear margins followed by radiation therapy should be indicated. In patients who previously received PMRT, a second course of irradiation may be considered when patients have a high risk of second recurrence. In case of IBTR, motivated patients with the early diagnosis of a second primary tumor might be considered for a repeat BCS as an alternative to mastectomy. Careful preoperative workup including breast MRI should be performed for the best patient selection. A second course of radiation treatment should be carefully considered in those patients undergoing a second conservative procedure for the treatment of IBTR. Although a second sentinel lymph node biopsy has demonstrated to be technically feasible and oncologically safe, little is known about the value of axillary restaging in these patients. Further prospective studies involving patients with local recurrences after BCS and mastectomy are needed to provide solid data that help guide physicians' treatment decisions.

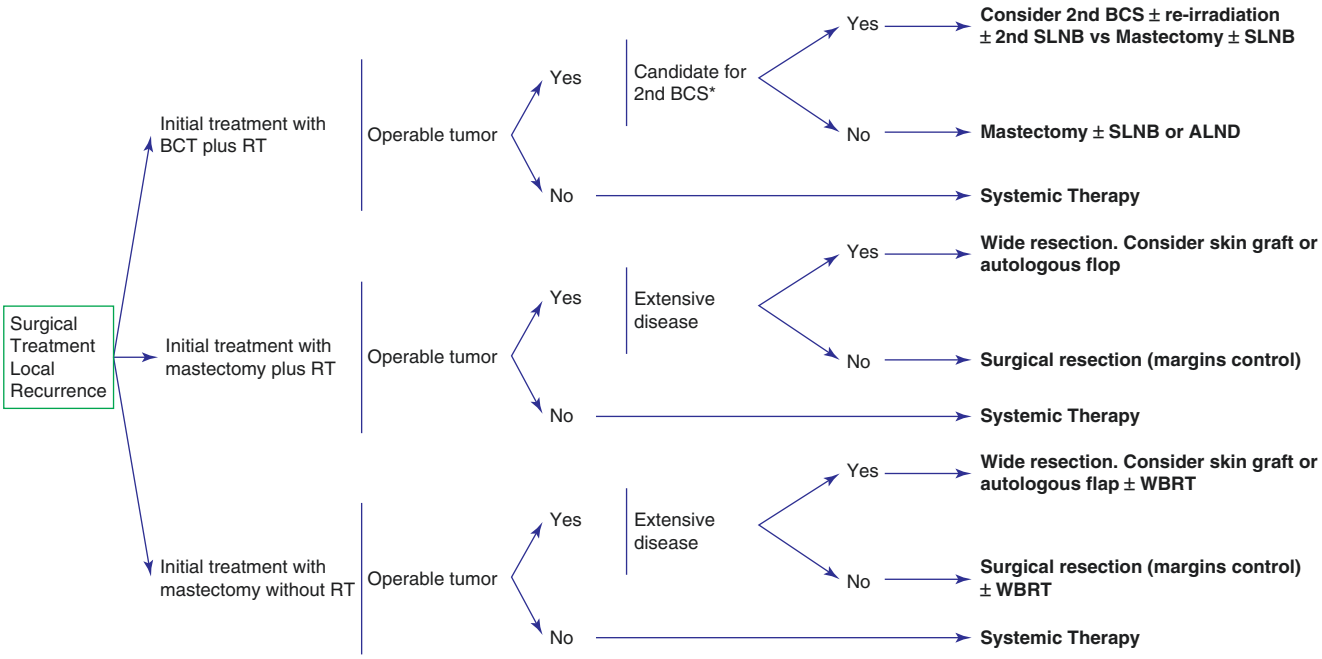

Fig. 25.1 Summary of surgical approach for breast local recurrence. Abbreviations: *BCT* breast-conserving therapy, *RT* radiation therapy, *BCS* breast-conserving surgery, *SLNB* sentinel lymph node biopsy, *ALND* axillary lymph node dissection, *WBRT* whole breast radiation therapy (including chest wall and regional nodal irradiation). *According to suggested selection criteria of Table 25.2 or following own institutions guidelines

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