

# Current Treatment of Isolated Locoregional Breast Cancer Recurrences

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## Keywords

Ipsilateral breast tumor recurrence · Local recurrence breast · Locoregional recurrence breast cancer · Hyperthermia · Radiation therapy · Brachytherapy · Chest wall recurrence · Breast cancer · Re-irradiation breast

## Summary

Patients with isolated locoregional breast cancer recurrences should be treated with curative intent. Mastectomy is regarded as the standard of care for patients with ipsilateral breast tumor recurrence. In a selected group of patients, partial breast irradiation after second breast-conserving surgery is a viable alternative to mastectomy. If a second breast conservation is performed, additional irradiation should be mandatory, especially in patients who had not been irradiated previously. In case of re-irradiation, the largest experience exists for multi-catheter brachytherapy. Prospective clinical trials are needed to clearly define selection criteria, long-term local control, and toxicity. In patients with resectable locoregional breast cancer recurrences after mastectomy, multi-modal therapy comprising complete resection, radiation therapy in previously unirradiated patients, and systemic therapy results in 5-year disease-free and overall survival rates of 69% and 88%, respectively. In radiation-naïve patients with unresectable, isolated locoregional recurrences, radiation therapy is mandatory. In selected patients with previous irradiations and unresectable locoregional recurrences, a second irradiation as part of an individual treatment concept can be applied. The increased risk of severe toxicity should always be weighed up against the potential clinical benefit. A combination therapy with hyperthermia can further improve the treatment results.

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## Introduction

Treatment of locally recurrent breast cancer remains an interdisciplinary challenge since treatment options are limited or at least restricted due to previous treatments. Data from large, randomized trials have demonstrated that locoregional recurrences occur in approximately 5–15% of patients, despite treatment with adjuvant radiotherapy after mastectomy or breast-conserving surgery (BCS) [1–5]. The most common site of recurrence after adjuvant radiotherapy is the ipsilateral breast or the chest wall, comprising 60–95% of all locoregional recurrences [6, 7]. Locoregional recurrences are typically associated with an increased risk of concurrent or subsequent systemic relapse [8, 9]. Especially early recurrences within the first 2 years after primary treatment seem to have a worse prognosis [9]. This publication addresses indications for radiotherapy of isolated locoregional breast cancer recurrences.

## Therapy of Ipsilateral Breast Tumor Recurrence

BCS followed by adjuvant radiotherapy has become the standard of care for the majority of breast cancer patients. Ipsilateral breast tumor recurrence (IBTR) is diagnosed in approximately 5–10% of patients at 10 years after breast-conserving therapy (BCT) [10–13]. International guidelines recommend mastectomy as standard treatment for IBTR after BCT [14–16]. Salvage mastectomy results in locoregional control rates of 69–98% and 5-year survival rates of 53–85% [17, 18]. Nevertheless, this approach is not founded on solid data indicating a clear advantage of radical surgery for IBTR for all patients compared to a second attempt of BCT [19]. There are no published or ongoing prospective studies comparing mastectomy versus repeat BCS alone in patients with IBTR. Published data are limited and most series reporting on a second conservative approach with or without the addition of adjuvant radiotherapy are single-institution retrospective studies. The Radiation Therapy On-

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cology Group (RTOG) introduced in 2010 a phase II prospective trial of repeat BCS adding 3-dimensional (3D) conformal partial breast re-irradiation for local recurrence [20]. Additionally, a mutilating rescue surgery causes enormous emotional and physical distress for the patients [21, 22]. The currently implemented close follow-up routine has led to the detection of IBTR at early stages, technically amenable to a second breast-conserving approach. Thus, the question remains if subgroups of patients can be defined who might benefit from a second breast-conserving approach. Unfortunately, no prospective data have been published so far.

#### Definition of True IBTRs and Selection Criteria for a Second BCT

Veronesi et al. [23] suggested that patients with IBTR constitute a heterogeneous group with true tumor recurrences and new primary tumors. In a large retrospective study on 1,410 patients, Gujral et al. [24] reported a cumulative incidence rate of new primaries after whole-breast irradiation at 5, 10, and 15 years of 0.8%, 2%, and 3.5%, respectively. The authors concluded that whole-breast irradiation approximately halves the rate of new primaries. In a retrospective study on 136 patients with IBTR as the first site of failure, Smith et al. [25] reported a significantly improved 10-year overall survival (OS) in patients with new primaries (75%) compared to patients with true recurrences (55%). This question has been addressed in several studies attempting to differentiate between true recurrences and new primaries [25–28], from which the following conclusions can be derived: The majority of IBTRs are true recurrences, which tend to occur earlier and in the same quadrant as the initial tumor, metastasize earlier and more often

and result in a shorter OS and disease-free survival (DFS) than new primaries. Further retrospective studies [29–31] evaluating IBTRs showed that there are subgroups of patients with improved rates of OS, DFS, and second local recurrence. Based on these retrospective studies, selection criteria for patients who may be candidates for a second breast-conserving approach are summarized in table 1.

However, repeat BCS alone is associated with increased local failure rates, ranging between 19–38% (table 2) [32]. Recent studies showed promising OS rates in selected patients treated with second conservative surgery followed by partial breast irradiation (PBI) [33, 34]. The following survey of techniques and results provides an overview of the different techniques and the current status of radiation therapy for IBTR (table 3).

#### Brachytherapy after BCS for IBTR

The most solid evidence for re-irradiation of IBTRs exists for brachytherapy (BT). The GEC-ESTRO working group [34] (Groupe Européen de Curiethérapie (GEC) combined with the European Society for Radiotherapy & Oncology (ESTRO)) reported on a retrospective collaborative analysis of 217 patients with IBTR treated between 2000 and 2009 in 8 European institutions by multi-catheter BT [34]. The median total dose delivered through low-dose rate (LDR) and pulsed-dose rate (PDR) BT was 46 Gy (range: 30–55 Gy) and 50.4 Gy (range: 49–50 Gy), respectively, and 32 Gy (range: 22–36 Gy) (equivalent dose in 2-Gy fractions (EQD2) 43 Gy) in 5–10 (median: 8) fractions (twice daily) for high-dose rate (HDR) BT. With a median follow-up of 3.9 years (1.1–10.3 years) after IBTR re-treatment, the 5- and 10-year actuarial 2nd local recurrence rates were 5.6% (1.5–9.5%) and 7.2% (2.1–12.1%), respectively. In comparison with salvage mastectomy series, the results were reported to be at least equivalent, with 5- and 10-year actuarial rates for metastatic recurrence of 9.6% and 19.1%, DFS rates of 84.6% and 77.2%, and OS rates of 88.7% and 76.4%, respectively. Further single-institution studies with small patient numbers support these data [35–38].

#### External-Beam Radiotherapy after BCS for IBTR

There is a single report on external-beam radiotherapy (EBRT) for the treatment of IBTR [39] comprising 39 patients. Retreatment was performed by using electrons in single fractional doses of 2 up to 50 Gy to the involved quadrant. At a median follow-up of 51.5

**Table 1.** Possible selection criteria for patients who may be candidates for a second breast-conserving approach

Isolated ipsilateral breast tumor recurrence
Limited size (< 2–3 cm)
Unifocal disease on ultrasound, mammography, and magnetic resonance imaging
Age ≥ 50 years
Long interval between primary treatment and recurrence (≥ 48 months)
Desire of the patient for a second breast conservation followed by radiotherapy
A second breast conservation is technically feasible and will result in acceptable cosmetic results

**Table 2.** Outcomes of patients treated with repeat BCS alone following IBTR

Study/year	Number of patients	Median follow-up, months	Local recurrence rate, %	5-year OS, %
Salvadori et al. 1999 [69]	57	73	19	85
Voogd et al. 1999 [70]	16	52	38	NR
Ishitobi et al. 2011 [71]	78	40	21	NR
Gentilini et al. 2012 [72]	161	81	29	84

NR = Not reported, BCS = breast conserving surgery, OS = overall survival.

**Table 3.** Outcomes of patients treated with repeat BCS and radiotherapy following IBTR

Study/Year	Patients, n	Median follow-up, months	RT technique	Repeat RT dose, Gy	Toxicity grade 3/4, %	Local control, %	OS, %
Deutsch 2002 [73]	39	51.5	EBRT	50	NR	77	78
Kraus-Tiefenbacher et al. 2007 [41]	15	26	IORT	20	0	100	93
Chadha et al. 2008 [37]	15	36	BT	30 or 45	0	89	100
Guix et al. 2010 [42]	36	89	BT	30	0	89 <sup>a</sup>	97 <sup>a</sup>
Kauer-Dorner et al. 2012 [36]	39	57	BT	50	17/0	93	87
Hannoun-Levi et al. 2013 [34]	217	46.8	BT	LDR 46 PDR 50.4 HDR 32	11	93 <sup>a</sup>	76 <sup>a</sup>

RT = Radiotherapy, OS = overall survival, EBRT = external-beam radiotherapy, IORT = intraoperative radiotherapy, BT = brachytherapy, LDR = low dose rate, PDR = pulsed dose rate, HDR = high dose rate, NR = not reported, BCS = breast conserving surgery.  
<sup>a</sup>10-year actuarial.

**Table 4.** Outcomes of patients with locoregional chest wall recurrences treated with repeat irradiation ± hyperthermia

Study	Patients, n	Initial dose, Gy	RT technique	Repeat dose, Gy	Complete remission, %	Toxicity grade (%)
Delanian et al. [74]	11	45–65	BT	60	81.8	2/3 (45%) 4 (9%)
Harms et al. [65]	58	36–70	BT	2 × 20	79.3	3 (60% <sup>b</sup> ) 4 (7%)
Laramore et al. [53]	13	40–50	EBRT	40–50	61.5	3 (0%) 4 (0%)
Phromratana-pongse et al. [56]	44	35–66	EBRT + HT	16–56	40.9	3 (25%) 4 (NR)
Li et al. [75]	41	58	EBRT	43	56	4 (8%)
Jones et al. <sup>a</sup> [67]	52	NR	EBRT	30–66	42.3	3 (2%)
Kouloulis et al. [76]	56		EBRT + HT	60–70	66.1	3 (5%)
	15	60	EBRT + HT	30.6	20	3 (NR) 4 (7%)
Linthorst et al. [60]	198	48	EBRT + HT	8 × 4	78 <sup>c</sup>	3/4 (11.9% <sup>d</sup> )
Linthorst et al. [68]	248	49	EBRT + HT	8 × 4	39 <sup>c</sup>	3 (1% <sup>d</sup> )

RT = Radiotherapy, BT = brachytherapy, EBRT = external-beam radiotherapy, HT = hyperthermia, NR = not reported.

<sup>a</sup>Breast cancer and other tumor entities.

<sup>b</sup>Predominantly telangiectasia.

<sup>c</sup>5-year local control rate.

<sup>d</sup>5-year rate.

months, 30 women (76.9%) had an intact breast free of tumor. The RTOG started a phase II study of repeat breast-preserving surgery and 3D conformal partial breast re-irradiation (PBI) for local recurrence of breast carcinoma with single doses of 1.5 Gy in 15 fractions twice daily for a total dose of 45 Gy [40]. The study has reached the accrual goal of 61 patients and is closed, but not published.

#### *Intraoperative Radiotherapy after BCS for IBTR*

There is only 1 publication considering intraoperative radiotherapy (IORT) for re-irradiation of IBTR [41]. 15 patients were treated applying IORT with 50-kV X-rays in single dosages of 14.7–20 Gy (applicator surface). At a medium follow-up of 26 months (1–60 months), no local recurrence occurred.

#### *Toxicity Assessment/Cosmetic Outcome*

In all publications, acute toxicities of the respective method were reported to be low while the most frequent late reaction pattern was fibrosis. Especially when assessed by standardized scoring systems, grade 1–2 sequelae in terms of fibrosis, telangiectasia and/or pain ranged between 44 and 79%, respectively [41–43]. Grade 3 late reactions were observed in 0–17% (table 3) and in most of the cases comprised breast tissue fibrosis and breast pain [34, 42]. The range may be explained by the application of different treatment techniques and regimes and small patient numbers. Severe late reactions like skin necrosis or ulceration were hardly ever stated. In the GEC-ESTRO series of 217 patients, 141 patients (65%) developed late complications: cutaneous and subcutaneous fibrosis

(67%), telangiectasia (16%), hyperpigmentation (9%), and ulceration (1%). Grade 3 and 4 complications were reported in 10% and 1%, respectively. The cosmetic results in the GEC-ESTRO series were assessed in 109 patients (50.2%) and were rated excellent in 52 (48%), good in 40 (37%), fair in 14 (13%), and poor in 2 (2%) patients [34].

#### *Conclusions for the Therapy of Ipsilateral Breast Cancer Recurrences*

Even though mastectomy is regarded as the standard of care for patients with IBTR, in a selected group of patients PBI after second BCS is a viable alternative to mastectomy. This approach yields high breast preservation rates and does not seem to compromise oncologic safety. If a second breast conservation is performed, additional irradiation should be mandatory, even more so in patients who had not been irradiated previously. In case of re-irradiation, so far the largest experience exists for multi-catheter BT. There is only limited information on the effectiveness of EBRT or IORT, which should be preferentially performed in clinical trials. Prospective clinical trials are needed to clearly define selection criteria, long-term local control, and toxicity.

### **Therapy of Isolated Locoregional Recurrences after Mastectomy**

#### *Definition and Patterns of Recurrence*

A locoregional breast cancer recurrence after mastectomy is defined as the appearance of tumor in the ipsilateral chest wall or in axillary, internal mammary, or supraclavicular lymph nodes [8]. The Early Breast Cancer Trialists' Collaborative Group analysis revealed a 10-year risk of an isolated locoregional recurrence as the first event after mastectomy of 20.3% for patients with 1–3 positive axillary lymph nodes, and of 32.1% for patients with 4 or more positive nodes. The addition of radiotherapy significantly reduced the risk to 3.8 and 13%, respectively [2, 44–46]. In a retrospective study, Katz et al. [47] reported on the local recurrence patterns of 1,031 women treated in 5 prospective trials with mastectomy and adjuvant chemotherapy without radiation therapy. After a median follow-up of 116 months, the most common sites of isolated locoregional recurrences were at the chest wall and the supraclavicular lymph nodes.

#### *Treatment of Resectable Recurrences*

If no previous irradiation has been performed, the optimal treatment consists of complete excision of the gross disease followed by irradiation [8, 39]. This approach has improved local control [48] and may have an effect on survival [49]. In a retrospective study on 159 patients with an isolated locoregional recurrence after mastectomy, Skinner et al. [50] reviewed the effects of a dose escalation on local control and survival. The patients in the standard treatment group were treated to a dose of 50 Gy plus a boost of 10 Gy, while the dose escalation group was treated to a dose of 54 Gy plus a 12 Gy boost. The authors observed for the

entire group a 77% locoregional control rate (LCR) and a 55% OS rate at 5 years. OS and LCR were not significantly improved in the dose escalation group. In summary, patients with an isolated locoregional recurrence after mastectomy should undergo surgical resection of the local recurrence and radiation therapy to the chest wall and supraclavicular lymph nodes. If no previous irradiation has been performed, a standard dose of 50–50.4 Gy with 1.8/2-Gy fractions should be applied. An additional boost dose of 10 Gy can be applied, especially if risk factors are present.

For systemic management, endocrine therapy should be administered to all receptor-positive patients [51]. In a prospective randomized study, Aebi et al. [52] investigated the effects of chemotherapy in 162 patients with completely resected isolated locoregional breast cancer recurrences. The authors found that adjuvant chemotherapy in addition to radiation and endocrine therapy prolonged the DFS and OS, in particular in patients with estrogen receptor-negative locoregional relapse. The 5-year DFS and OS rates were 69% and 88%, respectively. This result challenges the current practice of inconsistent use of chemotherapy and provides evidence in favor of offering adjuvant chemo- and radiotherapy to women with completely resected isolated locoregional relapse of breast cancer.

#### *Treatment of Unresectable Recurrences*

In patients with unresectable, isolated locoregional recurrences who were not previously irradiated, radiation therapy is mandatory. In a retrospective study, Skinner et al. [50] reported that patients with gross disease at the time of radiation had a significantly lower 5-year local control (63%) and survival rate (34%) compared to patients with no residual disease after surgery or systemic therapy (81% and 62%, respectively). If a complete remission after radiation therapy was accomplished, the 5-year survival rate increased from 27% to 62% [50]. Therefore, the same recommendations for radiation and endocrine therapy apply as for resectable disease. The boost dose can be increased depending on the size and the location of the recurrence. The indication for an additional chemotherapy should be defined on an individual basis since no prospective data are available. In summary, multi-modal therapy including systemic therapy and radiation therapy has the potential to cure selected patients [9, 49].

### **Therapy of Isolated Locoregional Recurrences after Mastectomy and Adjuvant Radiotherapy**

In patients with isolated locoregional recurrences after mastectomy and adjuvant radiotherapy, the treatment options are limited. If a complete resection is possible, surgery should be accomplished, but heroic surgery with problems to cover the tissue defect or prolonged wound healing problems should be avoided. Unfortunately, most of the patients present with advanced disease. Systemic therapy is a treatment option, especially when concurrent distant metastases are present. Re-irradiation is used with caution due to an increased normal-tissue complication probability. Thus, only few series using EBRT alone [53–55] or in combination with hyperthermia for re-irradiation of the chest wall have been published so

far [56–61]. Additionally, simultaneous radiochemotherapy as a further treatment option has been investigated in a limited number of trials [62–64].

#### Re-Irradiation

Laramore et al. [53] reported on 13 patients treated with conventionally fractionated electrons for chest wall recurrences. All patients had received previous postoperative chest wall irradiation of 40–50 Gy. 62% of the patients were alive and free of local disease after a median follow-up of 12 months. The skin reactions were restricted to temporary erythema and dry or moist desquamation. In a retrospective study, Harms et al. [65] reported on 58 patients treated with PDR BT molds. The local control rate was 79%. 10% of the patients experienced grade 3 fibrosis and 7% grade 4 late effects.

#### Re-Irradiation in Combination with Hyperthermia

A further approach to enhance radiation effectiveness is the additional use of hyperthermia. This combination has improved clinical response and local control in several phase II studies and randomized trials [66]. Jones et al. [67] enrolled 109 patients with superficial tumors (70 patients with breast cancer) in a prospective randomized trial comparing irradiation of chest wall recurrences with irradiation and additional hyperthermia. The complete response rate was 66.1% in the hyperthermia arm and 42.3% in the irradiation alone arm. Previously irradiated patients had the greatest incremental gain in complete response: 23.5% in the non-hyperthermia versus 68.2% in the hyperthermia arm. No OS benefit was seen. The authors concluded that adjuvant hyperthermia conferred a significant local control benefit to patients with superficial tumors receiving radiation therapy. In a retrospective analysis on 198 patients who underwent either R0 (n = 107) or R1 resection (n = 91), hyperthermia was used as an adjunct to re-irradiation (8 × 4

Gy) [60]. After a median follow-up of 42 months, the 5-year LCR was 78%. The 5-year grade 3/4 late toxicity rate amounted to 11.9% (n = 15 skin ulcerations, n = 5 osteoradionecrosis of the ribs). The same working group investigated 248 patients with macroscopic breast cancer recurrence treated with re-irradiation and hyperthermia [68]. After a median follow-up period of 32 months, 70% of the patients had a complete remission. The 5-year local control rate was 39%. 23% of the patients developed thermal burn, which healed with conservative measures. The incidence of 5-year late grade 3 toxicity was 1% (table 4).

#### Conclusions for the Therapy of Locoregional Recurrences after Mastectomy

Multi-modal therapy including systemic therapy, surgery, and radiation ± hyperthermia achieves a high rate of local control and can be curative with long-term survival in a subset of patients. In previously not irradiated patients, the chest wall and regional lymph nodes should be treated with doses of 50–50.4 Gy (1.8–2 Gy per day). A boost dose of 10 Gy may be applied. Further dose escalation does not seem to improve the treatment results.

In selected patients with previous irradiations and unresectable locoregional recurrence, a second irradiation as part of an individual multi-modal treatment concept can be applied. The increased risk of severe acute and late toxicity should always be weighed up against the potential clinical benefit. Especially in previously irradiated patients, a combination therapy with hyperthermia can further improve the local control rates and spare dose.

#### Disclosure Statement

W.H., A.G., C.C., M.B., D.K., and B.A. declare no conflict of interest.

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