Treatment of Ipsilateral Breast Cancer Recurrence (IBCR) after Breast Conservation Therapy (BCT)

Therapie des ipsilateralen in-Brust-Rezidivs (IBR) nach brusterhaltender Therapie (BET)

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ABSTRACT

In-breast recurrence or ipsilateral breast cancer recurrence (IBCR) suspected by imaging or palpation, second primary carcinoma and any distant metastases should be ruled out by core biopsy prior to breast surgery. The surgical standard in IBCR management is salvage mastectomy. Increasingly, however, patients express a justified desire for breast conservation in IBCR. In favourable relations of tumour and breast size, long interval between primary disease and IBCR recurrence, favourable tumour biology and ruled out distant metastases, re-BCT may be an option. As patients usually have undergone adjuvant radiotherapy already, re-radiotherapy (brachytherapy/percutaneous RT) should be explored. Systemic management must be based on tumour biology and prior treatment. While the risk of local recurrence increases following re-BCT, overall survival is not compromised.

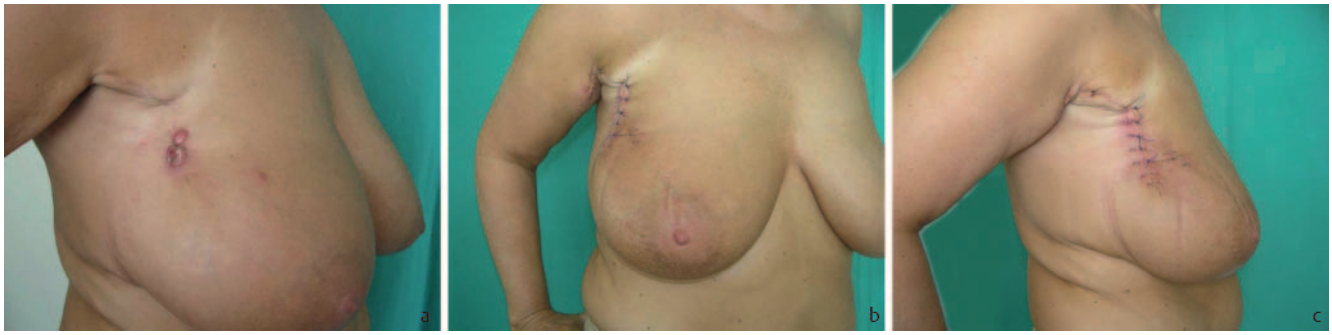
ZUSAMMENFASSUNG

Bei einem durch bildgebende Verfahren oder Tastbefund vermuteten In-Brust-Rezidiv (IBR) sollten vor der Brustoperation durch Stanzbiopsie ein Zweitkarzinom und das Vorliegen von Fernmetastasen ausgeschlossen werden. Den operativen Standard in der Behandlung eines IBR stellt die Salvagemastektomie dar. Immer häufiger wird jedoch der berechtigte Wunsch nach Brusterhaltung geäußert. Bei entsprechendem Wunsch, günstiger Rezidivtumorgröße zur Brustgröße, langem zeitlichem Intervall zur Primärerkrankung, günstiger Tumorbiologie und Ausschluss von Fernmetastasen kann auch eine Re-BET erfolgen. Da in der Regel bereits eine adjuvante Strahlentherapie erfolgt ist, sollte die erneute Bestrahlung (Brachytherapie/perkutane RT) geprüft werden. Die Systemtherapie muss sich an der Tumorbiologie und den Vortherapien orientieren. Nach einer Re-BET ist das erneute lokale Rezidivrisiko zwar erhöht, das Gesamtüberleben wird aber nicht verschlechtert.

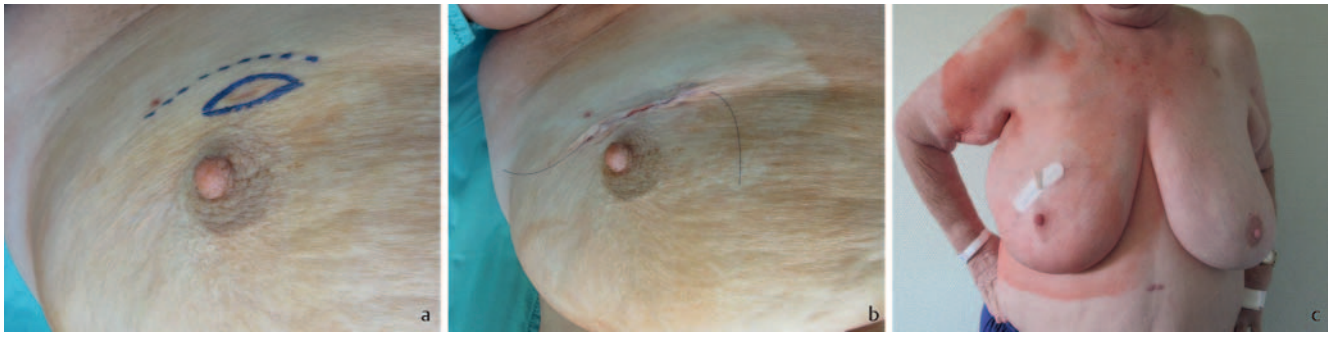
Introduction

With the increasing understanding of the tumour biology in breast cancer, surgery has also changed. In 2017, 86 % of patients with pT1 breast cancer and 71 % with pT2 tumours underwent breast-conserving surgery (https://www.onkozert.de/2019/03/21/jahresberichte-der-zertifizierungssysteme-2019/).

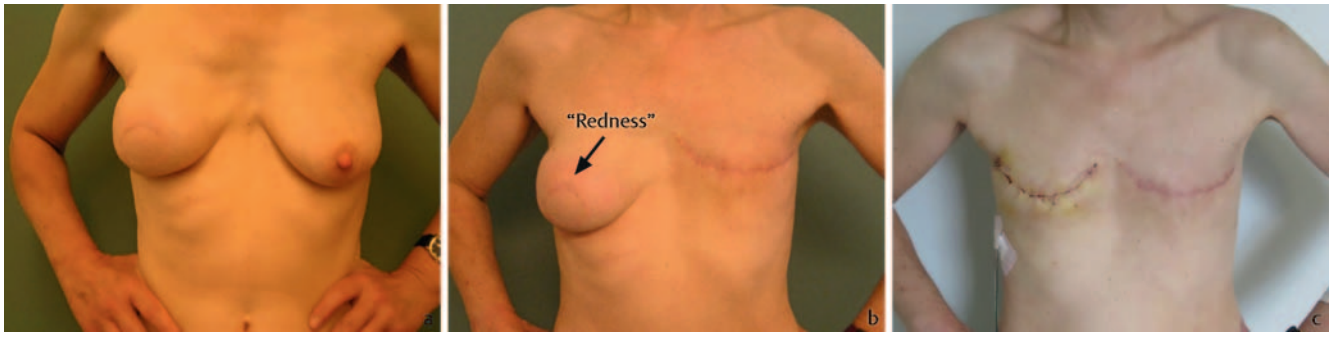
Locoregional recurrence is defined as the recurrence of invasive or non-invasive breast cancer in the [1, 2]:



▶ **Fig. 1** 58-year-old female with prior NAST and BCT for invasive ductal breast cancer ypT1c (10 mm) ypN0 (0/2 sn) cM0 R0; G3, L0 V0, TNBC, Ki-67 40 %; status post radiation **a** after 4.5 years cutaneous recurrence ("ipsilateral breast cancer recurrence"), no IBCR on imaging, cN0 cM0; **b, c** after re-BCT.



▶ **Fig. 2** 70-year-old female with prior BET for invasive ductal right breast cancer pT2 (30 mm) pN0 (0/2 sn) cM0; G2, L0 V0, ER-ICA 12/12, PgR-ICA 10/12, Ki-67 20 %; status post irradiation **a** 2 years later cutaneous metastasis "ipsilateral breast cancer recurrence" cN0 cM0, dashed line old scar, solid line cutaneous recurrence; **b, c** After re-BET, (better excision of cutaneous metastasis).



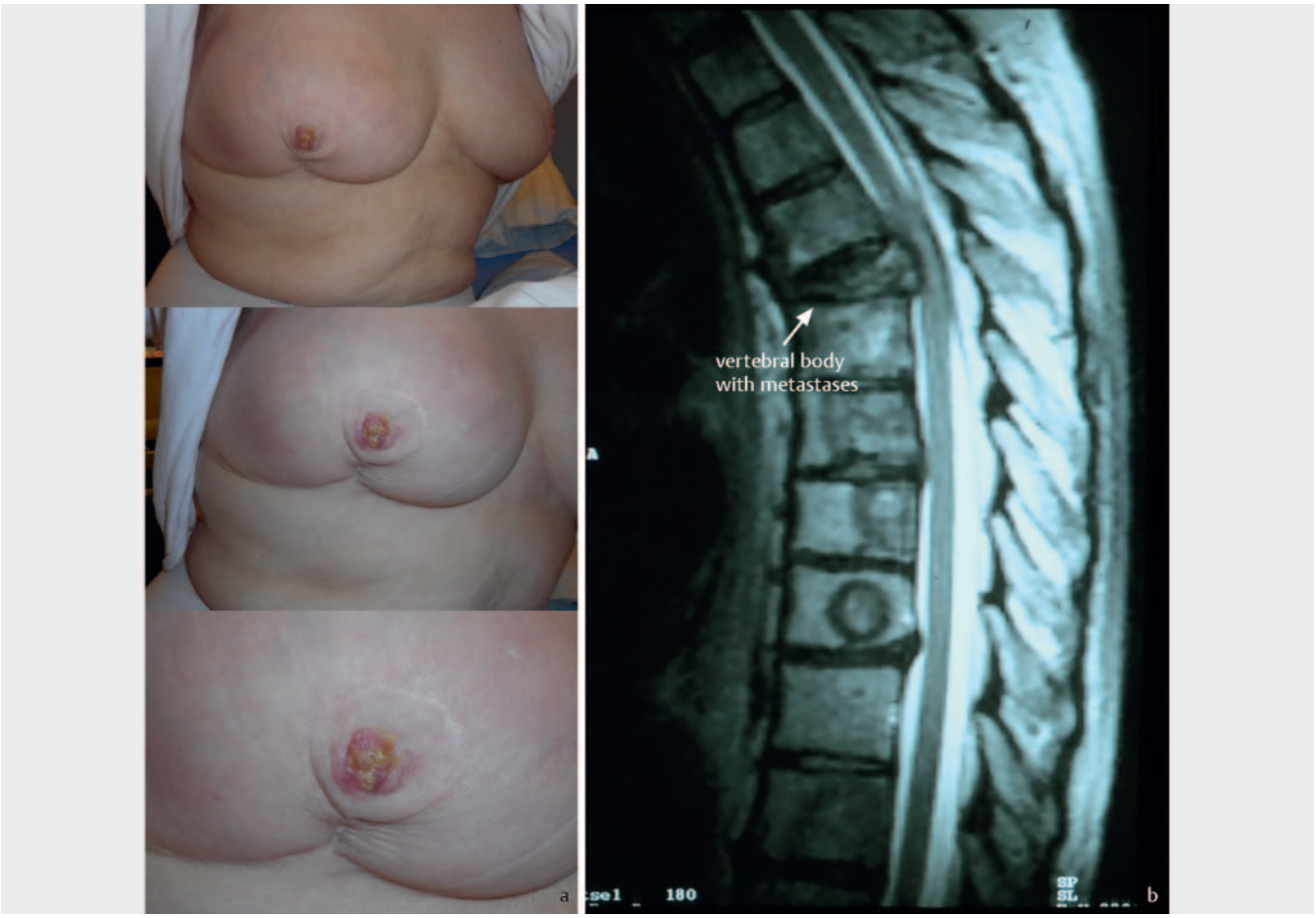
▶ **Fig. 3** 45-year-old female with **a** prior SSM with LADO flap and prosthetic reconstruction for invasive right ductal breast cancer pT1c (m: 20, 13, 6 mm) pN0 (0/1 sn) cM0; G1, L0 V0, ER-ICA 10/12, PgR-ICA 10/12, HER2 negative, Ki-67 20 %; 4 years of tamoxifen **b** 6 years later contralateral multifocal DCIS, mastectomy; **c** after 6.5 years right lymphangial carcinomatosis (redness arrow), **d** after right salvage mastectomy.

- ipsilateral breast (ipsilateral breast cancer recurrence, IBCR),
- the skin or subcutaneous soft tissue of the ipsilateral chest wall (chest wall recurrence; CWR) or
- ipsilateral lymph nodes of the axilla and around the clavicle (regional recurrence).

Nevertheless, not all recurrences, e. g. in the skin of the breast after BCT or breast reconstruction, can be definitively assigned to one of these classifications (▶ **Fig. 1–4**).

Early detection of locoregional recurrence is considered an essential prerequisite for a curative treatment approach. Therefore, one essential component in follow-up is the early detection of locoregional recurrences by clinical examination, mammography, breast ultrasonography and, if necessary, breast MRI.

Diagnostic workup (mammography, ultrasonography, possibly MRI), histological confirmation by core biopsy with repeat receptor testing (ER, PgR, HER2) in IBCR is performed the same as in the initial setting [3]. The significance of grading and Ki-67 testing in recurrence is unclear but may indirectly reflect the aggressiveness of the recurrence.



▶ **Fig. 4** 57-year-old patient 8 years post BET (invasive right ductal breast cancer pT2 (25 mm) pN1 (1/1 sn) cM0; G1, L0 V0, ER-ICA 12/12, PgR-ICA 16/12, HER2 negative, Ki-67 10 %; 6 years of tamoxifen/aromatase inhibitors). **a** Paget disease secondary to central IBCR with caudal skin infiltration. **b** Staging: osseous metastases.

In locoregional recurrence, preoperative staging to rule out distant metastases should always be performed. Depending on the localisation and extent, these are usually more relevant for further management and the course of the disease than the local recurrence itself. For example, in a population of 11 046 patients with breast-conserving surgery within 5 years Neuman et al. found 454 IBCRs [4]. In 27 % of these patients, asymptomatic distant metastases were also detected. Already 35 % of these patients were node positive in the primary situation (▶ **Fig. 4**). Local management of locoregional recurrence should be guided by the prognosis of the distant metastases.

Incidence and prognosis

Valid data on the incidence of locoregional recurrences is rather limited. Most of the data (▶ **Table 1**) refers to publications that refer to regimens from more than 20 years ago and is therefore no longer up to date. For example, since these publications appeared, nationwide mammography screening has resulted in the detection of smaller tumours with less common nodal involvement, and neoadjuvant systemic therapy is an established standard of treatment. In addition, surgery, especially the resection margin, the systemic therapy and also the radiotherapy concepts (partial breast irradiation, hypofractionation) have changed.

▶ **Table 1** Incidence and prognosis of locoregional recurrences [2, 5–7].

location	percentage (%)	5-year survival (%)
ipsilateral breast cancer recurrence (IBCR) ▪ after BCT & radiotherapy	10 (2–20)	65 (45–9)
chest wall (CWR) ▪ after mastectomy	4 (2–20)	50 (24–78)
supraclavicular region/axilla	34	49 (3-year survival)
▪ after ALND	1 (0.1–8)	55 (31–77)
▪ after SLNE	1	93
multiple locations	16 (8–9)	21 (18–23)

In a meta-analysis of 20 qualitatively “proper” trials from around 7000 trials/reports, the incidence of IBCR and contralateral second cancers (CBC) was reported to be 25 % overall [8]. The duration of the follow-up was decisive, as IBCR and especially CBC can still devel-

op even after many years. After staged adjuvant treatment of early breast cancer (pT1–2 N0 M0), the annual incidence of IBCR was 0.6 % (range 0.4–1.1) and of CBC 0.5 % (range 0.2–0.7). However, even in this meta-analysis, the tumour biology and adjuvant therapy actually performed were not known in all patients. Other trials have identified simultaneous CBC in 5 % of patients with IBCR [9].

Risk factors in locoregional recurrence

The development of locoregional recurrence largely depends on the tumour biology – regardless of the location. For example, triple-negative cancers have a 6–8-fold higher risk of local recurrence compared to luminal A-like breast cancers [10, 11]. The tumour biology of the recurrence itself determines the further prognosis after the locoregional recurrence [12, 13]. In this respect, tumour biology should also be included in the discussion of possible re-BCT.

Risk factors for locoregional recurrence include [10, 11, 14–16]:

- Tumour biology
- Tumour size
- Node status
- Young age
- R1/2 resection
- In-site components, and
- inadequate adjuvant therapy.

In a EBCTCG meta-analysis comparing adjuvant versus neoadjuvant systemic therapy with 10 trials from 1983–2002, a significant rise in local recurrence incidence (RR 1.37, 95 %CI 1.17–1.61; p = 0.0001) was found for neoadjuvant versus adjuvant therapy, but this did not affect distant metastasis-free survival and overall survival [17]. A recent GBG meta-analysis with more than 10 000 neoadjuvant patients revealed a significantly lower risk of local recurrence (RR 0.50, 95 %CI 0.39–0.62; p = 0.001) for patients with pathological complete remission (pCR) compared to patients without pCR, which was independent of the type of surgery [18].

Risk factors following locoregional recurrence

For further disease-free survival and also overall survival after locoregional recurrence, in addition to the risk factors already mentioned for developing recurrence, the time from initial surgery, and the location were crucial [19]. Other important factors are adequate radiotherapy and systemic therapy after re-BET of an IBCR.

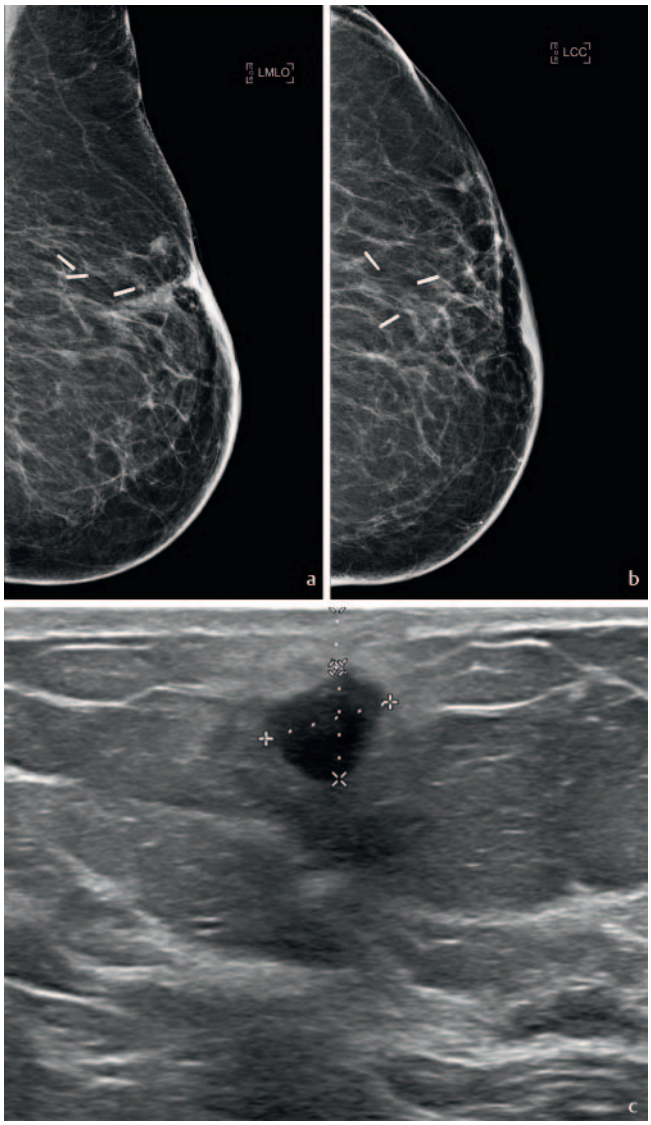
Differential diagnosis of IBCR vs. second primary cancer

The differentiation of IBCR versus true second primary cancer is of considerable clinical significance but can be difficult in some cases (▶ **Table 2**; ▶ **Fig. 5, 6**).

"Genuine" second primary cancer again can undergo breast-conserving surgery and adjuvant therapy according to the tumour biology, just as in primary cancer. The prior treatment modalities

▶ **Table 2** Criteria for differentiating IBCR and second primary cancer after BCT.

ipsilateral breast cancer recurrence:	ipsilateral second primary cancer:
▪ 80 %–90 % of all IBCR	▪ 10 %–20 % of all "recurrences"
▪ close to primary location	▪ distant from primary location
▪ similar tumour biology	▪ different tumour biology
▪ inadequate adjuvant therapy	▪ adequate adjuvant therapy
▪ early occurrence	▪ long time interval
▪ treatment as in recurrence	▪ treatment as in primary disease



▶ **Fig. 5 a–c** 79-year-old patient with prior left BCT (invasive solid-left ductal breast cancer craniolateral pT2 (23 mm) pN0 (sn0/2; n 0/6) cM0 V0 L0 R0 G2, ER IRS 12, PR IRS 12 HER2 negative Ki67 18 %. As part of the follow-up 18 months later: Local left recurrence rcT1b (8 mm) with same tumour biology as primary cancer.

(systemic treatment, radiotherapy) must be considered. The extent to which neoadjuvant therapy is beneficial, e. g., in the case

of new triple-negative and/or HER2-positive cancer, is unclear. However, in some cases this is an alternative to improve the surgical options, e. g., if the size of the tumour and the volume of the breast differ considerably.

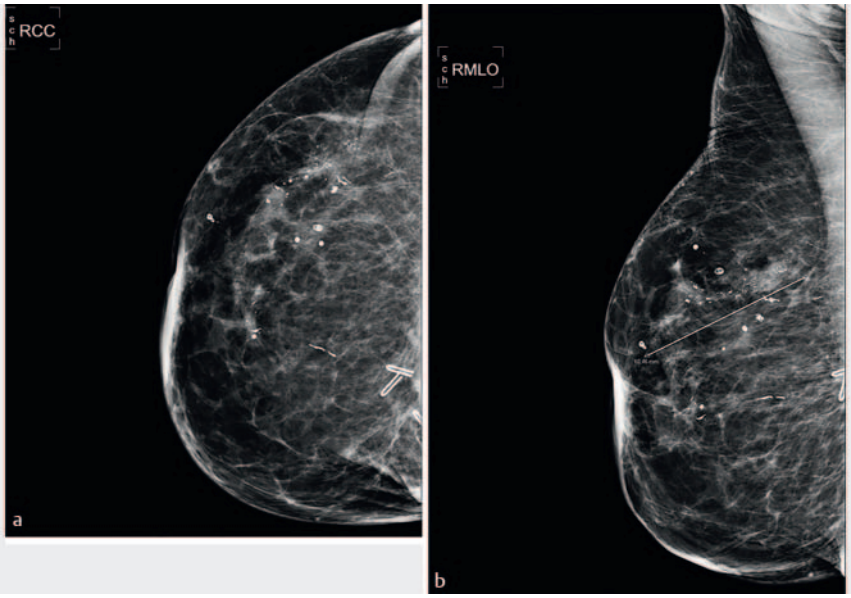
Surgery in IBCR

Increasingly, women with prior breast-conserving therapy for breast cancer and IBCR want to have another breast-conserving operation (re-BCT). However, due to the lack of prospective randomised trials, the data on oncological safety is inadequate [20].

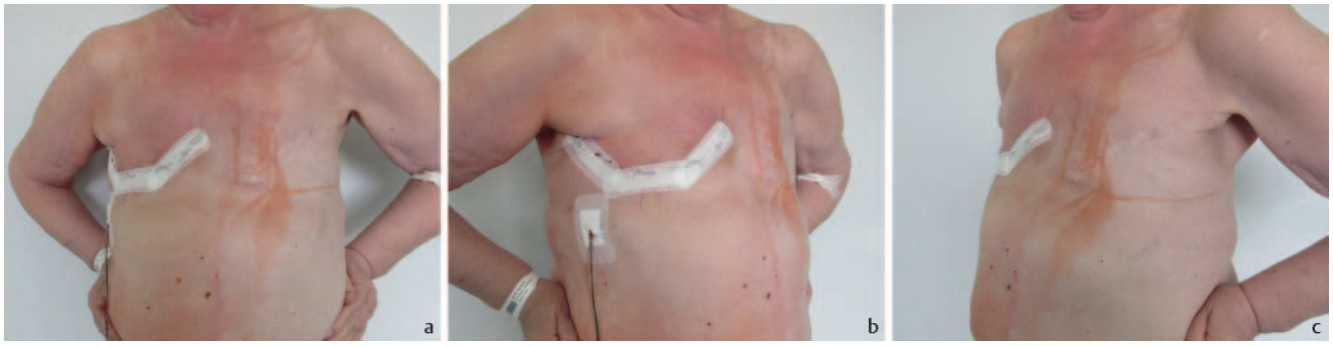
For ethical reasons, it will also not be possible to randomise patients with IBCR, different recurrence and breast sizes, time intervals, tumour biology, surgical options and particularly the personal wishes of the patients, into prospective trials. Most knowledge is therefore based on experience, observational and retrospective analysis, with considerable bias. Fittingly, a statement from the American College of Radiology reads: "… where evidence is lacking or inconclusive, expert opinion should be provided as a recommendation …" [21].

The standard treatment for IBCR today is (still) salvage mastectomy (▶ **Fig. 3, 7**) [10]. In the current guidelines and therapy recommendations (AGO, S3 guideline, NCCN), breast-conserving repeat surgery with consideration of repeat radiotherapy reserve is recommended as an option according to the "expert consensus" [22–24].

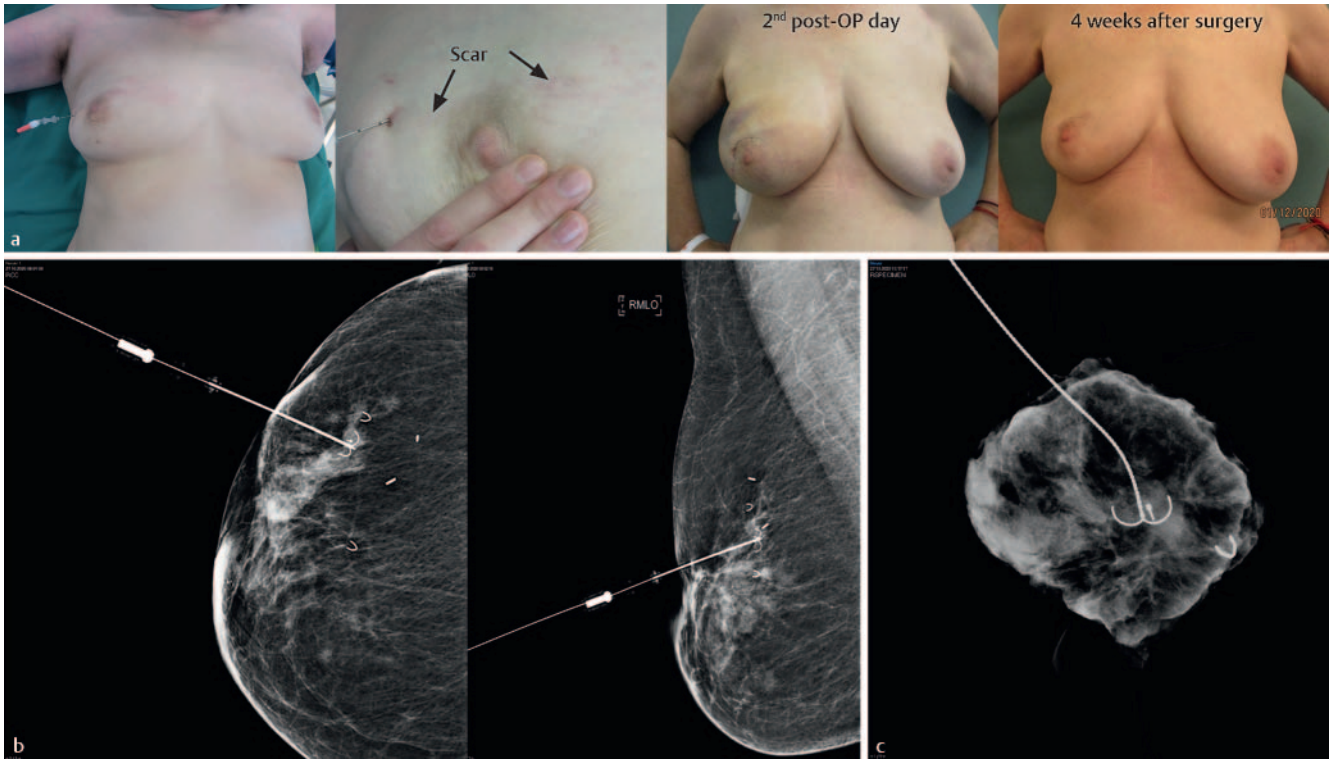
If the patient requests re-BCT, she should be informed that because of the R1/2 resection the risk of a second operation increases compared to salvage mastectomy (▶ **Fig. 7**). Detailed counselling regarding renewed IBCR after re-BCT is therefore mandatory. In principle, however, a resection is also possible within the framework of re-BCT. From the point of view of a possible resection, it should be noted that these are often "older" women, or women with comorbidities, who request rapid and permanent surgical treatment of



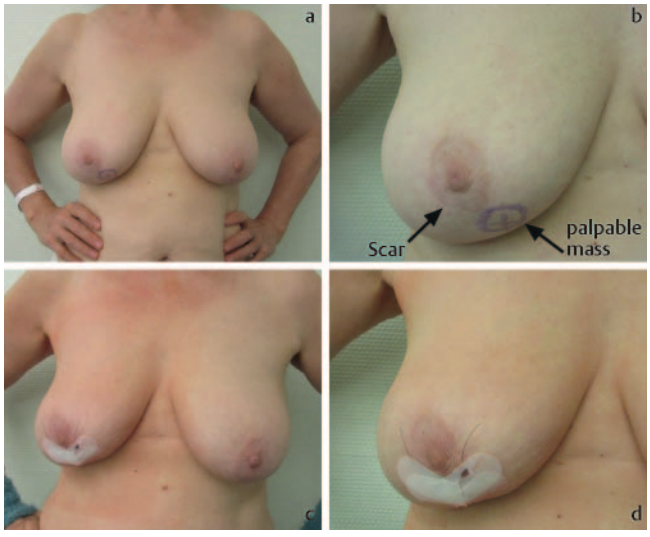
▶ **Fig. 6 a, b** 71-year-old female with prior right BCT 7 years earlier for invasive ductal Ma-Ca pT2 (29 mm) pN0 (sn0/3) cM0 V0 L0 R0 G1, ER-IRS 12/12, PgR-IRS 12/12, HER2 negative Ki-67 18 %. Mammogram of right breast showing extensive new microcalcifications distant from the primary tumour. Core biopsy of high-grade DCIS with invasive ductal components G3, ER-IRS 4/12, PgR-IRS 0, HER2 negative Ki-67 34 % (second primary cancer).



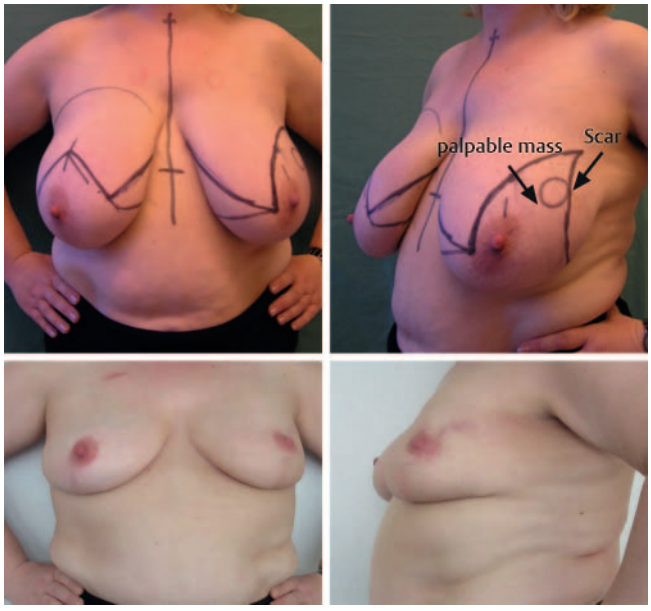
▶ **Fig. 7 a–c** 70-year-old female with invasive IBCR after DCIS on the right 13 years after mastectomy for breast cancer on the left. Salvage mastectomy was performed another 13 year later after re-BCT with SLNB on the right and R1 resection.



▶ **Fig. 8** 48-year-old female with invasive IBCR after breast cancer on the right and BCT (caution: incision!) in another hospital. Refusal of radiotherapy and systemic therapy. After 22 months invasive IBCR at the same location and re-BCT. **a** patient images, **b** mammography findings, **c** specimen radiography re-BCT.



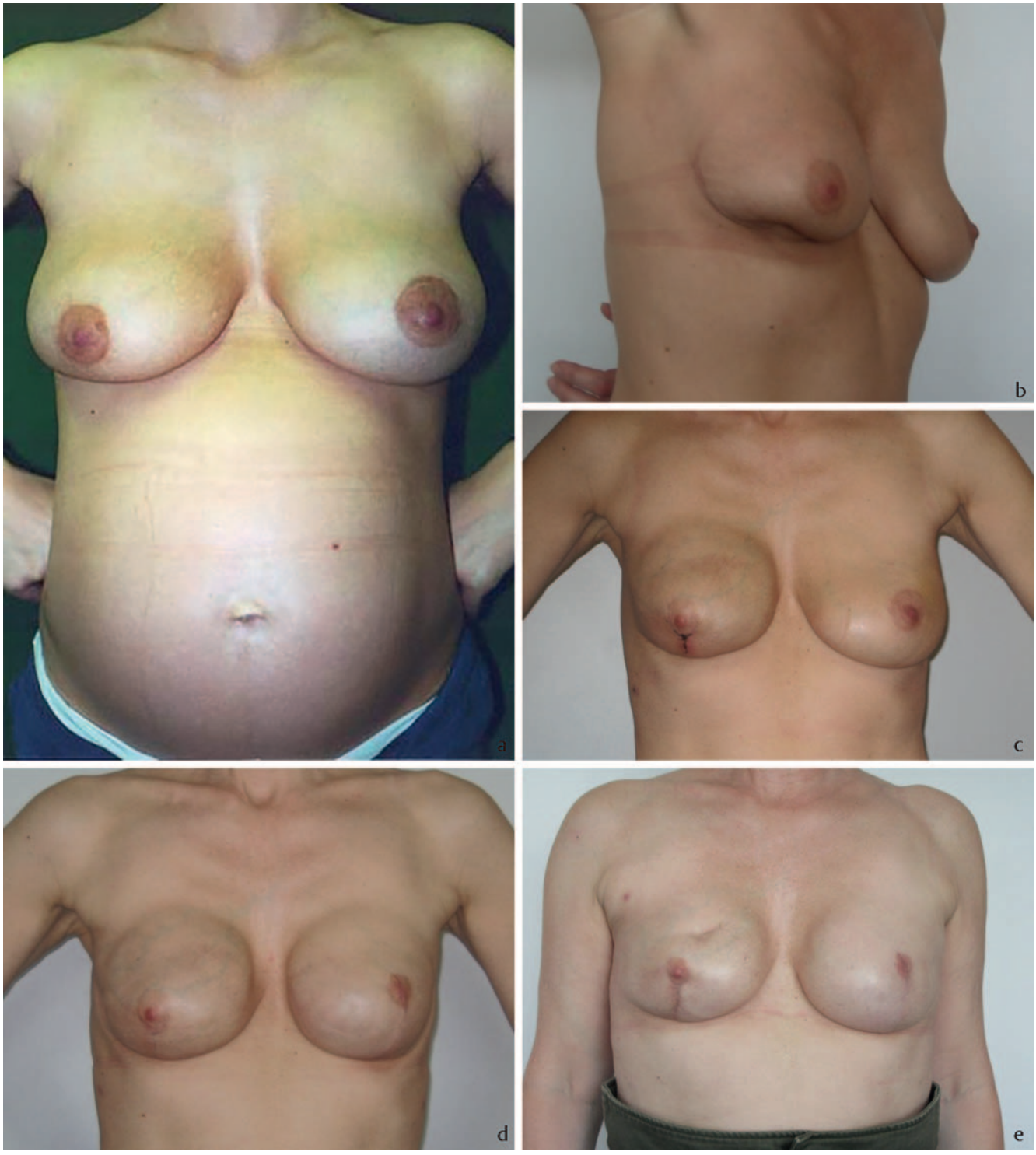
▶ **Fig. 9** 49-year-old female with invasive IBCR after breast cancer on the right (BCT 50 months ago) and re-BCT.



▶ **Fig. 10 a–d** 48-year-old female with invasive IBCR (close to the skin) after BCT LUOQ 4 years ago. Request for breast conservation. In bilateral macromastia, tumour-site adapted breast reduction surgery on the left and adaptation on the right (cost reimbursement confirmed by health insurance provider).

their IBCR. These women often also refuse repeat radiotherapy and systemic therapy, thereby worsening their overall survival.

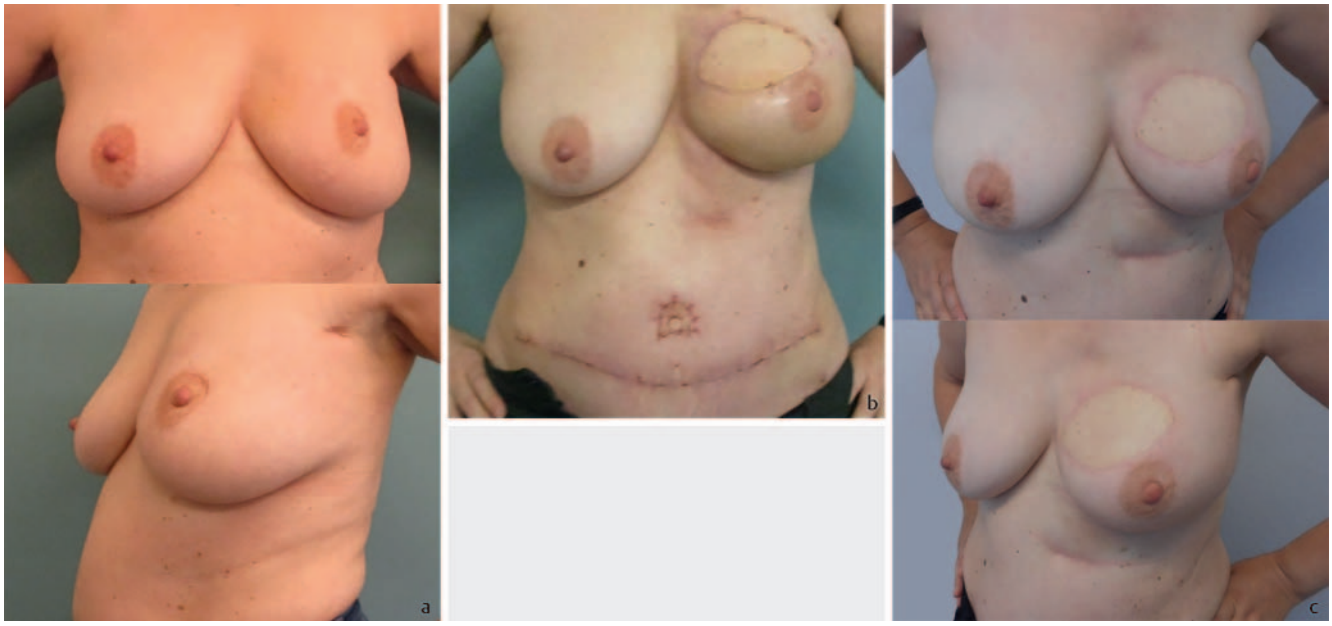
If a patient wishes to undergo re-BCT, the local conditions (e. g., radiotherapy, relation of tumour size to breast size, concomitant diseases) and the prognosis must be considered. The surgical technique of re-BCT is identical to primary BCT, where ideally the old incision should be used (▶ **Fig. 8, 9**). In the



▶ **Fig. 11** **a** 26-year-old female with right breast cancer in pregnancy. **b** after 15,5 years: right IBCR and re-BCT. **c** another 4,5 years later: 2. IBCR and NSM with prosthetic reconstruction. **d** Contralateral breast cancer with NSM and prosthetic reconstruction on request. **e** another 5,5 years later: right axillary recurrence.

case of "large" breast volume, tumour-site adapted breast reduction may be contemplated (▶ **Fig. 10**). It should be noted, however, that the patients had already prior radiotherapy and therefore wound healing and cosmetic results are worse than after primary surgery. Before surgery on the contralateral breast, the health insurance provider should confirm cost reimbursement.

In some cases – again considering prior treatment, tumour biology and the patient's wishes – a nipple/skin sparing mastectomy with prosthetic reconstruction may also be performed. Espe-



▶ **Fig. 12** 52-year-old female **a** 4 years after NAST (pCR) and BCT LUOQ for TNBC, now with ipsilateral second primary cancer pT2 (23 mm, 60 mm is) cN0M0 G1, L0 V0, ER-ICA 8/12, PgR-ICA 8/12, HER2 negative, Ki-67 20 % UIQ **b, c** after SSM and TRAM reconstruction.

cially in slim patients with prior radiations, the cosmetic results are somewhat disappointing (▶ **Fig. 11**). Autologous reconstruction in IBCR is possible in principle, but the risks and benefits, follow-up treatment and the prognosis of the recurrence should be assessed in advance (▶ **Fig. 12**).

There is practically no data for a second re-BCT, but according to our own experience this can be performed on a case-by-case basis with the patient's consent.

With the surgical treatment of IBCR, the question arises as to how to proceed in the axilla. Axillary intervention (ALND or SLNE) is not indicated in clinically (palpatory and ultrasonographical) unremarkable lymph nodes. Only if no SLNE had been performed so far – e. g., invasive IBCR after prior DCIS – can SLNE be performed in a cN0 cM0 situation. The rate of false negative SLNE in IBCR is reported to be less than 10 % even in re-SLNE [25]. The clinical benefit for further treatment planning and the clinical outcome of the patient has not been established [26]. Clinically suspect or positive lymph nodes, on the other hand, should be resected as a debulking procedure.

Breasts with autologous or heterologous reconstruction present a special problem. Most of these cases present with prior "mastectomy". This is basically the same situation as with patients with prior mastectomy, in other words the resection must have a safe margin. As a rule, this means salvage mastectomy including the autologous tissue or implant (▶ **Fig. 3**); in some cases, R0 resection with preservation of the reconstructed breast may be performed.

There is no data on the potential of "preoperative" systemic therapy (chemotherapy, hormone/anti-HER2 therapy, etc.) – analogous to neoadjuvant systemic therapy – in operable IBCR. All guidelines agree that R0 resection in IBCR should be followed by adequate systemic therapy [22, 27].

From an oncological point of view, re-BCT in radiotherapy-induced sarcoma of the breast post BCT must be avoided at all costs [28, 29].

Outcome after re-BET in IBCR

All guidelines confirm that the local risk of recurrence increases following re-BCT, but overall survival does not deteriorate [30]. The cosmetic outcome (retractions, dents, asymmetry, etc.) is usually less favourable following re-BCT and radiotherapy than after primary surgery (▶ **Fig. 11b**). In contrast, complications post re-BCT tend to be lower (19.2 %) compared to mastectomy with or without reconstruction (30.8 % and 34.3 %, respectively) [30].

A US observational study analysed 166 ipsilateral IBCRs following breast-conserving therapy in 2038 patients [31]. Salvage mastectomy was performed in 116 of the 166 patients, while 50 patients underwent re-BCT. At 64.5 % (mastectomy) there was no significant statistical difference in 10-year overall survival compared to 58 % (re-BCT). However, the authors also point to biases such as time interval to first surgery, tumour size, nodal status, tumour biology, patient wishes, and other prognostic parameters that were considered in the decision for re-BCT. The authors therefore announced a prospective randomised trial comparing salvage mastectomy with re-BCT and breast radiotherapy as early as 2005. Such a trial is still not underway today and the authors regard it as ethically untenable!

The question of oncological safety of re-BCT in IBCR is addressed by a strikingly large number of trials from the Asian region [32]. In an analysis from China of 2075 patients with BCT, 475 (22.9 %) underwent re-BCT, while 1600 (77.1 %) underwent mastectomy [33]. After a median follow-up of more than 10 years,

breast cancer-specific survival (BCSS) and overall survival (OAS) did not differ significantly between the two groups before and also after statistical matching of both collectives. In multivariate analysis, AJCC (American Joint Committee on Cancer) stage, size of recurrence, tumour biology, and re-radiotherapy were independent predictors of BCSS and OAS. In a similar trial from Korea with 335 IBCR patients, 90 matched patients were treated by re-BET or mastectomy [34]. After a median follow-up of more than 10 years, no significant differences were found for the 10-year OAS (hazard ratio [HR] 1.08, 95 % confidence interval [CI] 0.49–2.39) and BCSS (HR 0.83, 95 % CI 0.35–1.95).

Radiotherapy of the tumour bed following re-BCT seems to be crucial. If re-BCT is not followed by partial breast radiotherapy, the overall survival is significantly worse compared to re-BCT plus radiotherapy, but also compared to mastectomy alone [35, 36].

CONCLUSION

In summary, the following can be stated for ipsilateral breast cancer recurrence:

- Differential diagnosis IBCR or second primary cancer
- Salvage mastectomy is standard
- Re-BCT is possible in selected cases (caution: breast and recurrence size, time interval to primary disease, tumour biology, surgical options, and patient preferences)
- Preoperative restaging to exclude distant metastases
- Check possibility of re-radiotherapy, systemic therapy depending on tumour biology
- Higher risk of local recurrence following re-BCT, but no decline in overall survival

Umberto Veronesi, a pioneer of de-escalation of therapy in breast cancer, said back in 2005: *"In-breast-recurrences or second ipsilateral carcinoma of restricted size can be treated with a second conservative surgery."* [37]

Conflict of Interest

The authors declare that they have no conflict of interest.

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