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CLINICAL TRIAL

New concept for immediate breast reconstruction for invasive cancers: feasibility, oncological safety and esthetic outcome of post-neoadjuvant therapy immediate breast reconstruction versus delayed breast reconstruction: a prospective pilot study

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Abstract Feasibility and oncological safety of post-adjuvant skin-sparing mastectomy (SSM) plus immediate breast reconstruction (IBR) cannot be evaluated by randomized trials. However, comparative study could modify guidelines for the oncosurgical treatment of invasive breast cancer. Our study compared the feasibility, oncological safety and esthetic outcome of SSM plus latissimus dorsi (LD) flap IBR after chemotherapy (CT) and radiotherapy (RT) with the standard management for invasive breast cancer: mastectomy as primary treatment, adjuvant CT and RT, and LD flap delayed breast reconstruction (DBR). Twenty-six selected patients with stages IIA–IIIA breast cancer were offered post-neoadjuvant SSM plus IBR with LD flap plus implant (IBR group). Seventy-eight other patients had primary mastectomy, adjuvant CT and RT, and LD-assisted DBR (DBR group). After 4.1 years (range 1–8) of follow-up, feasibility, oncological safety, and esthetic outcome were compared. Sixteen (61%) early complications were reported for the IBR group versus 44 (56%) for the DBR group ($P = 0.645$). Early implant loss was 0% in IBR versus 12% in DBR. IBR had 8 (30%) late complications versus 17 (21%) for DBR ($P = 0.362$). Capsular contracture and reconstruction failure rates were similar. Local recurrence was 7.7% (2/26) in IBR and 6.4% (5/78) in DBR ($P = 0.823$). Cosmetic evaluation by independent physicians and by the patients themselves was identical in the two groups. Our concept provides a basis for offering more women the opportunity to elect for immediate reconstruction, even in the setting of radiation therapy.

Keywords Breast cancer · Skin-sparing mastectomy · Latissimus dorsi flap · Complications · Local recurrence · Metastases · Cosmetic

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Introduction

Immediate breast reconstruction (IBR) is performed to improve body image and the remaining quality of life for women facing mastectomy [1–4]. Success can be defined as the best possible cosmetic result that does not sacrifice oncological safety [5, 6]. In recent years, skin-sparing mastectomy (SSM) in combination with IBR has gained in acceptance and popularity for early invasive or in situ disease (DCIS) in terms of both oncological safety and acceptable rates of postoperative complications [7–15]. More recent reports have also documented the effectiveness of SSM plus IBR for locally advanced disease [16–24]. These studies showed complication rates comparable to those of a similar group of patients who did not undergo IBR. In addition, these studies found no significant differences in local relapse or distant metastasis rates for patients receiving IBR for locally advanced disease in comparison with patients without immediate reconstruction

[5, 17, 18, 21, 23]. The risk of recurrence thus does not appear to be technique-dependent but instead is stage-dependent, as tumor size and nodal involvement are significant risk factors [25, 26]. Last, overall survival and disease-free survival may not be affected by IBR for T1–T3 tumors in comparison with mastectomy alone [27].

Adjuvant therapy is another concern regarding IBR. The international guidelines have extended the indications for chemotherapy (CT) to include early breast cancers in addition to locally advanced cancers. CT is indicated for both axillary-positive and axillary-negative patients on the basis of high-risk tumor status (diameter, SBR grading, negative hormone receptor status) [28]. It is now acknowledged that when SSM plus IBR is the primary treatment, it does not delay the start of CT [29–31]. On the other hand, randomized studies have demonstrated the usefulness of postmastectomy radiotherapy (PMRT) to decrease local recurrence and increase survival for patients with positive axillary lymph nodes [32, 33]. This situation has increased the complexity of planning for IBR for invasive cancers. First, the need for radiation therapy (RT) cannot always be definitively established before surgery [34]. Second, PMRT is known to increase the surgical complication rate and to decrease the esthetic result of implant-based SSM [34]. Third, some studies have raised the concern that irradiation of the immediately reconstructed breast results in a lower quality of radiation. These studies showed that the majority of radiation plans are unsatisfactory in terms of providing broad coverage of the chest wall and internal mammary nodes while adequately sparing heart and lung [35–37]. Fourth, recent studies reported increased tumor recurrence and patient demise when RT was performed following breast reconstruction in comparison with RT delivered before reconstruction [37–39].

In order to safely integrate RT into the reconstructive algorithm, we have developed the concept of post-neoadjuvant therapy SSM plus IBR over the past 10 years. Essentially, mastectomy and immediate reconstruction are performed once CT and RT have been completed. We believe this concept has some clear advantages. First, SSM plus IBR can be offered to women with locally advanced cancers. Second, since surgery is the final step in the anticancer therapy, it does not interfere with either CT or RT. This study was thus performed to evaluate the feasibility, oncological safety, and esthetic outcome offered by this concept. Patients with invasive breast cancer who had undergone CT and RT followed by SSM plus latissimus dorsi (LD) flap-based IBR were compared with patients who had undergone modified radical mastectomy, adjuvant CT and RT, and finally LD flap-based delayed breast reconstruction during the same time period.

Patients and methods

Since January 2000, 648 consecutive patients underwent mastectomy for malignant disease in the Department of Gynecological Surgery of Arnaud de Villeneuve Teaching Hospital, University of Montpellier, France. All breast cancer patients were routinely managed by primary lumpectomy plus axillary dissection or, in cases of multifocality, core needle biopsy plus axillary dissection. All were evaluated by a multidisciplinary breast cancer team. The need for mastectomy was indicated by conservative treatment failure, discrepancy of tumor size and breast volume, multicentric disease, or invasive tumor associated with extensive DCIS. CT was decided on in accordance with current guidelines regarding patient age, radiologic tumor diameter, SBR grading, and estrogen receptor, Her-2-neu overexpression and axillary node status. RT was decided on in accordance with current guidelines regarding radiologic tumor diameter, multicentric disease, lymphovascular invasion, and axillary node status. Patients with non-metastatic invasive breast cancer and needing mastectomy, radiation therapy, and chemotherapy were candidates to enter the study. One hundred and sixty-four patients who met the inclusion criteria and who were candidates for breast reconstruction were offered the choice between the two oncological managements. Sixty patients were excluded from this study for various reasons (Fig. 1). Twenty-six selected patients with stages IIA–IIIA breast cancer who wanted immediate breast reconstruction were offered post-neoadjuvant therapy SSM plus IBR. These patients received primary CT followed by preoperative RT and final-step SSM plus IBR with an LD flap (IBR group). The 78 patients who did not choose IBR underwent primary mastectomy followed by adjuvant CT and RT and finally LD delayed breast reconstruction (DBR group). The records were analyzed for patient characteristics, tumor patterns, treatment details, and oncological and cosmetic outcomes.

Systemic therapy varied over time and followed the conclusions in the published literature. Between 2000 and 2004, neoadjuvant (IBR group) and adjuvant (DBR group) CT consisted on FEC 100 [5-fluorouracil 500 mg/m^2 intravenously (i.v.), epirubicin 100 mg/m^2 i.v., and cyclophosphamide 500 mg/m^2 i.v.] every 21 days for six cycles. As of 2005, neoadjuvant CT (IBR group) consisted on FEC 100 every 21 days for four cycles followed by paclitaxel-based CT (175 mg/m^2 every 21 days) for four cycles. During the same period, adjuvant CT (DBR group) consisted on FEC 100 every 21 days for three cycles followed by paclitaxel-based CT (175 mg/m^2 every 21 days) for three cycles. In addition, after 2004, patients with Her-2-neu overexpression (3 + staining by fluorescent in situ hybridization or gene amplification in FISH) received

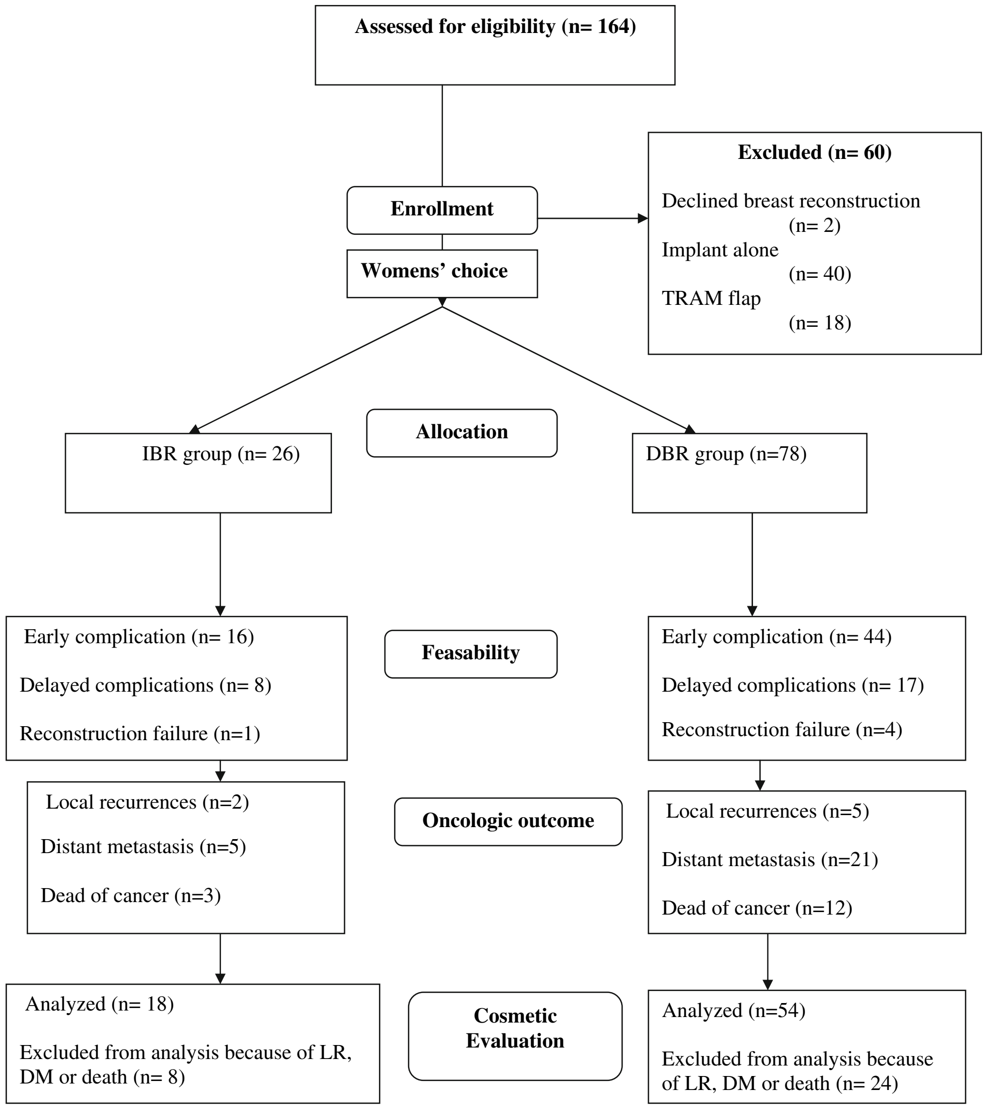

Fig. 1 Study flow chart

trastuzumab for 12 months. Patients who had hormone receptor-positive tumors also received tamoxifen or aromatase inhibitors for 5 years.

For the IBR patients, RT was delivered to the whole breast and the entire thickness of the chest wall by two opposed tangential fields (each field being treated every day) using photons (6MV) to a total dose of 50 Gy in 2-Gy daily fractions 5 days a week. For the DBR patients, RT was delivered to the entire thickness of the chest wall by en-face electrons (9MV) or by two tangential photon (6MV) fields to a total dose of 50 Gy in 2-Gy daily fractions 5 days a week. For both groups radiotherapy treatment was delivered in the supine position to ensure reproducibility during simulation and treatment. The planning target volume included the whole breast and/or the entire thickness of the chest wall and regional lymph nodes (i.e., supraclavicular and infraclavicular nodes, and the internal mammary nodes in the four upper intercostal spaces). The fields were defined on the CT-simulator or, after planning CT, conventional simulator. All shielding blocks were indicated on the digitally reconstructed radiographs or the simulation films, respectively. The field arrangement included the use of an anterior photon field in the supraclavicular region to a total dose of 44–50 Gy, and a mixture of anterior electrons and photons to the internal mammary nodes to a total dose of 44–50 Gy. Each field was calculated wit three-dimensional dosimetry.

In all cases, breast reconstruction was performed by the senior author (PLG) using a standardized LD flap procedure. A transverse skin island was usually designed over the upper portion of the muscle. With the patient in a lateral position, the dissection proceeded in the muscular plane in a caudal direction to the iliac crest and cranially to the scapular bone. The humeral attachment was divided when necessary to obtain adequate excursion. The thoracodorsal nerve was systematically preserved. The flap was passed under the axillary tunnel to the breast region and the patient was turned to the supine position to perform implant positioning and flap shaping. The implant was always placed above the pectoralis major muscle and underneath the LD flap. The LD flap was secured medially to the sternum, superiorly to the pectoralis muscle fascia, inferiorly to the inframammary crease, and laterally to the serratus anterior muscle to avoid lateral displacement of the implant. A suction drain was placed under the flap for 48–72 h, during which time the patient was given prophylactic intravenous antibiotics. The donor site was closed in two layers over the suction drain. Drainage was usually discontinued after three to 5 days or when the output was less than 50 cc within a 24-h period. The patient was then seen 1 week after discharge to review her wounds, after 3 months to assess the need for further surgery, and then every 6 months. Surgery for IBR patients was planned 8–10 weeks after the completion of RT. The mastectomy incision included an ellipse of skin with the nipple-areola excision and the inframammary fold (Fig. 2). The LD flap was harvested through a large transversal elliptical skin incision as needed to exactly match the mastectomy defect (Fig. 3). Surgery for DBR patients was scheduled six to 12 months weeks after RT. The LD flap was harvested through a transversal skin incision and positioned on the anterior chest wall, regardless of the previous mastectomy scar, to place the flap along the lateral, and inferior margins of the reconstructed breast. LD reconstruction was performed using permanent implants (McGhan style 410, McGhan style MLP, Allergan Medical, Marlow, UK) or

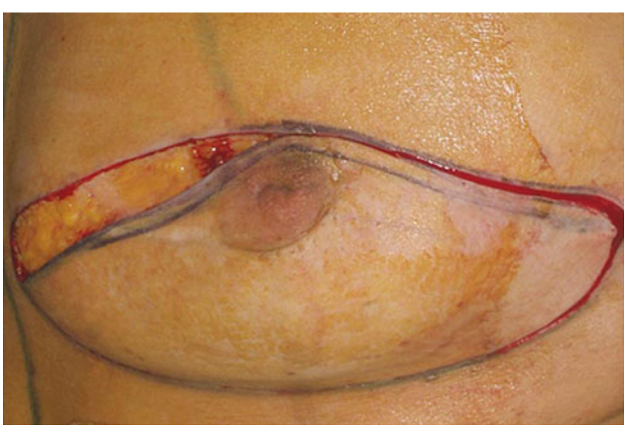

Fig. 2 IBR: design of the mastectomy incision

expanders (McGhan 133 FV, Allergan Medical, Marlow, UK). For all patients in whom expanders were used at the first operation, surgical revision with a change to a definitive silicone implant was performed. During this step, capsulotomy and surgical refinements were performed as needed to obtain the best symmetry between the two breasts.

Tumor response to neoadjuvant therapy was evaluated in the IBR patients, who had no lumpectomy before chemotherapy. The two endpoints were clinical response (determined by physical examination) and pathologic response (determined by histologic examination). Clinical tumor size was ascertained before the initiation of CT and before surgery. When the disease was multifocal, the products of the two greatest perpendicular diameters of the tumor or tumors were calculated, and the sum of these measurements was recorded as "total tumor size." Clinical tumor response was defined as complete (cCR) if there was no clinical evidence of palpable tumor at the time of surgery [40]. A reduction in total tumor size of 50% or greater at the time of surgery was considered to be a clinical partial response (cPR). When there was an increase in total tumor size of more than 50% (compared with pretreatment measurements), the patient was considered to have progressive disease. Mastectomy specimens were analyzed to evaluate the pathologic tumor response. In accordance with recent expert recommendations, patients who had no invasive or in situ ductal cancer in the breast were considered to have had a pathologic complete response (pCR) [41]. In addition to pathologic response to preoperative treatment, the histologic patterns of the mastectomy specimens of IBR patients treated by primary lumpectomy are reported regarding residual in situ invasive carcinoma.

Postoperative outcomes were evaluated by two independent physicians (GR, PB). Follow-up was scheduled at intervals ranging from every 3 months to annually, depending on the length of time since treatment. All follow-up, whether performed by the radiation oncologist, medical oncologist, or surgeon, included physical examination of the breasts and regional lymph nodes. Follow-up also included CT scanning, breast MRI, contralateral mammogram if applicable, and serum tumor markers, at the discretion of the treating physicians. Recurrences and other treatment failures were documented by clinical examination, radiologic test, and/or pathologic assessment. Complications were classified as immediate when occurring within the first 30 days of breast reconstruction. Immediate complications were breast skin envelope necrosis (IBR group) and anterior thoracic wall skin necrosis (DBR group), marginal flap necrosis requiring wound care, hematoma requiring surgical revision, and implant infection requiring surgical revision. Dorsal seroma was defined by the presence of fluid collection at the

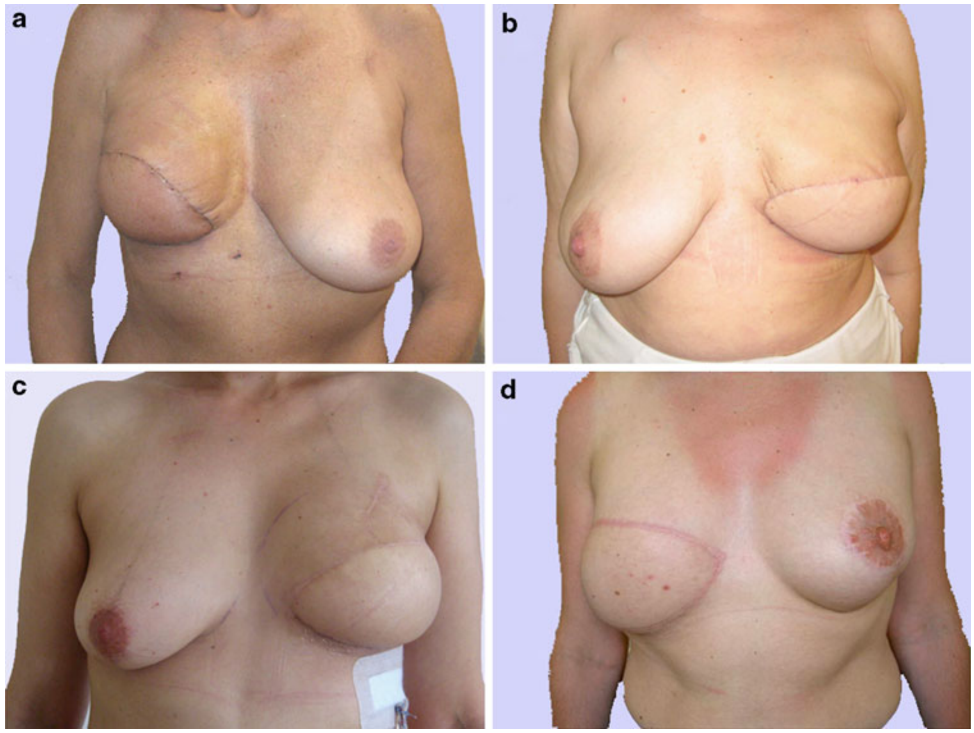

Fig. 3 Early results in IBR patients. The volume of the reconstructed breast may have differed from that of the contralateral breast (**a**, **b**) to anticipate the symmetrization procedure or to follow the patient's wishes

dorsal site after the drain was removed, requiring one or more needle evacuations to relieve the symptoms. Back skin flap necrosis was defined by skin necrosis needing wound care (Fig. 4). The early implant loss rate was recorded. Delayed complications were capsular contracture, back pain, and reconstruction failure. Implant revision was differentiated to distinguish between revision for capsular contracture and for an esthetic indication, which was not recorded as a late complication. The degree of capsular contracture was assessed by the surgeon during patient follow-up using the Baker classification. Breast reconstructions with Baker classes 3 and 4 were classified as capsular contracture complications. Reconstruction failure was defined as breast reconstruction being abandoned or achieved by another surgical procedure. Local recurrence (LR) was defined as histologically proven recurrent tumor in either the ipsilateral breast skin or the chest wall after the mastectomy. Tumor spread to the internal mammary, supraclavicular, infraclavicular, or ipsilateral axillary nodes, or to the nonbreast skin of the ipsilateral chest wall, was classified as other locoregional recurrence. All other sites of tumor recurrence were classified as distant metastases.

The postoperative esthetic results were evaluated by two independent physicians (GR, PB), who reviewed the photographs or saw the patients themselves at the last follow-up visit. Patients who were not disease-free at the visit were not evaluated for cosmetic result. The esthetic result was stratified by subscales according to Gerber et al. [24].

Fig. 4 Aspect of the dorsal scar on an IBR patient after back skin necrosis

Briefly, the volume of the reconstructed breast, shape of the breast mounds, symmetry, ipsilateral and contralateral scars, and the inframammary fold were each evaluated from 0 to 2 points. The results were defined as follows: excellent (Fig. 5): 10–8 points; good (Fig. 6): 7–6 points; fair (Fig. 7): 5–4 points; or poor: fewer than 4 points. In addition, patient satisfaction was assessed by subjective questionnaire using the same grading scale.

Statis tical analysis of the data was performed with StatView software (StatView 512, Brain Power, Inc., Calabasas, CA). The data analyst was blinded to the surgery groups. First, descriptive statistics were performed for the variables. The computed statistics included mean

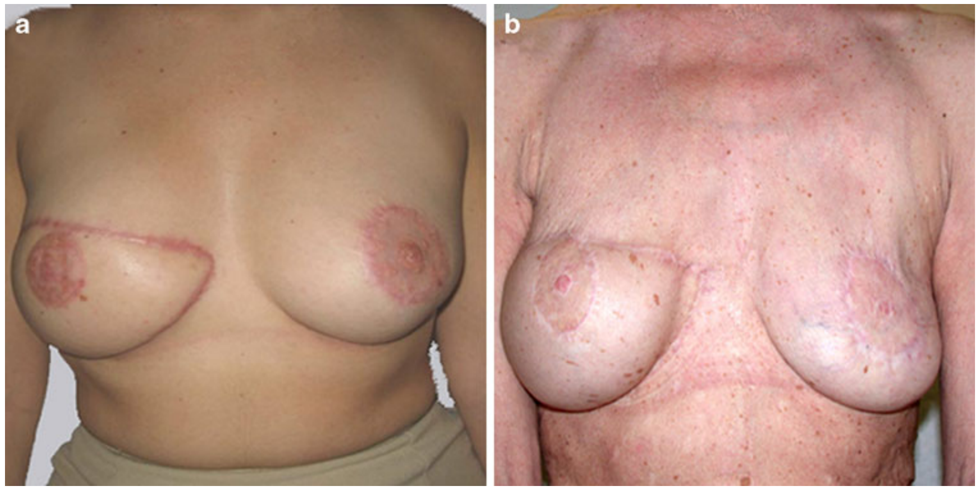

Fig. 5 Cosmetic Results evaluated as excellent. **a** One year post-reconstruction in a 42-year-old patient, and 3 months post-symmetrization and nipple reconstruction. **b** Five years post-reconstruction in a 63-year-old patient

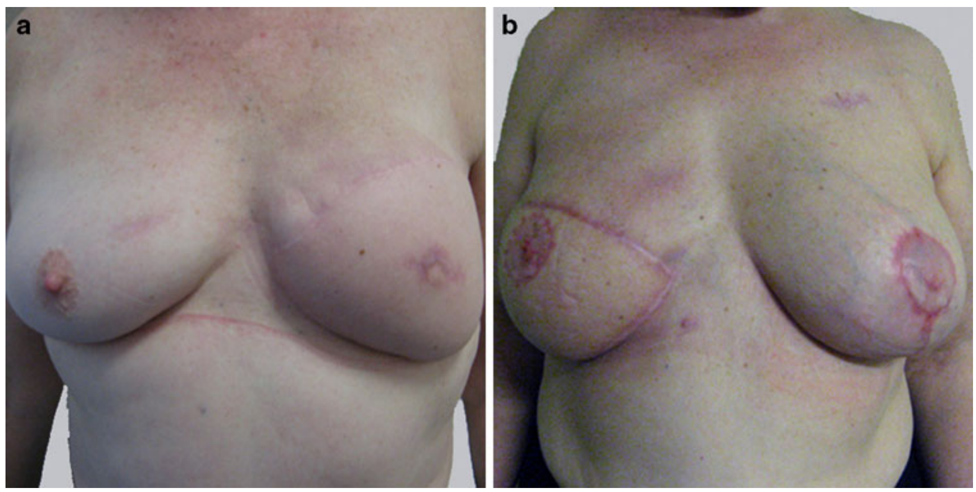

Fig. 6 Cosmetic results evaluated as good. **a** One year post-reconstruction in a 55-year-old patient, and 2 months post-symmetrization and nipple reconstruction. **b** Five years post-reconstruction in a 48-year-old patient

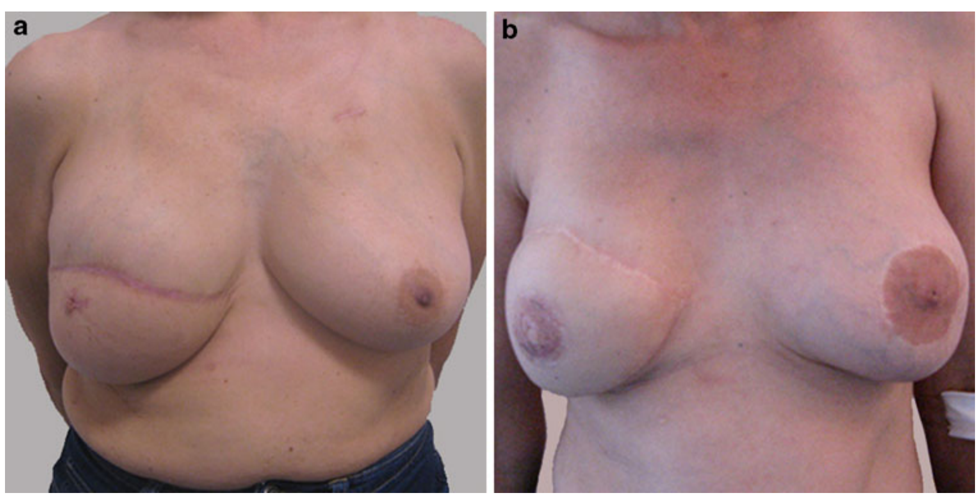

Fig. 7 Cosmetic results evaluated as fair. **a** One year post-reconstruction in a 56-year-old patient, and 3 months post-symmetrization and nipple reconstruction. **b** Five years post-reconstruction in a 50-year-old patient

and standard deviation (SD) of continuous variables, frequencies, and relative frequencies of categorical factors. Baseline preoperative variables were compared using the Chi-square test for categorical data or, when appropriate, Fisher's exact test. The Mann–Whitney *U* test was used to compare the medians of non parametric variables. P value < 0.05 was considered to be statistically significant.

Results

Oncological results

The characteristics of the IBR and DBR groups are detailed in Tables 1 and 2. The two groups were comparable in terms of body mass index, percentages of smokers and diabetic patients, and duration of follow-up. However, the patients who chose IBR were significantly younger than the DBR patients ($P = 0.006$). As expected, the mean (SD) interval between completion of RT and surgery was 8.5 weeks (1.06) in the IBR group versus 29.1 weeks (5.7) in the DBR group ($P < 0.0001$).

Of the 26 breast carcinomas treated in the IBR group, six were lobular carcinomas and 20 were ductal carcinomas. Fourteen were managed by primary lumpectomy plus axillary dissection before initiation of chemotherapy. The remaining 12 were staged by core needle biopsy plus axillary dissection before initiation of CT and were assessable for clinical and pathologic response after neoajuvant therapy. The pre therapeutic histologic characteristics and the post-neoadjuvant therapy changes are reported on Table 3. Clinical complete response was observed in five of the 12 (41%) assessable patients. The overall clinical response rate (cCR + cPR) was 58% (7 of 12 patients). No patient had clinically progressive disease. Two patients had no histologic evidence of cancer in the breast (pCR = 16.6%). For IBR patients who were managed by primary lumpectomy plus axillary dissection, the response to neoadjuvant therapy was not available. However, invasive residual disease was found in two patients and residual DCIS in five patients.

Initial surgery in both the IBR and DBR groups consisted of LD flap plus expanders in five (19.3%) and nine (11.5%) cases, respectively, and silicone implants in 21 (80.7%) and 69 (88.5%) cases, respectively ($P = 0.482$). To obtain a final symmetry that was acceptable to both patient and physician, a contralateral breast operation including reduction or augmentation mammaplasty was performed in seven (26.9%) patients of the IBR group

Table 1 Characteristics of the 93 women in the study

	IBR group $N = 26$	DBR group $N = 78$	P
Age at time of surgery (years)	50.6 (10.4)	56.2 (9.3)	0.006*
Body mass index (kg/m^2)	24.3 (1.62)	24.6 (2.5)	0.357*
Length of follow-up (years)	4.7 (1.91)	4.1 (2.2)	0.132*
Smokers	3 (11.5)	10 (12.8)	0.863**
Diabetes mellitus	1 (3.4)	4 (5.1)	0.786**

Data are presented as mean (SD) or *n* (%)

* Mann–Whitney *U* test

** Chi-square test

Table 2 Details of histologic findings

	IBR group $N = 26$	DBR group $N = 78$	P
AJCC staging[a]			0.235*
Stage IIA/IIB	24 (92.2)	70 (90)	
Stage IIIA	2 (7.8)	8 (10)	
Axillary involvement			0.409*
Negative	0	2	
Positive	26	76	
SBR grading			0.545*
1	1 (3.8)	6 (8.9)	
2	16 (61.5)	39 (50)	
3	9 (34.7)	33 (42.3)	
Multifocality/multicentricity	12 (46.1)	44 (56.4)	0.363*
Extensive DCIS	9 (34.6)	19 (24.3)	0.315*
Lymphovascular invasion	4 (15.3)	15 (19.2)	0.655*
Estrogen receptors			0.909*
Positive	15 (57.6)	34 (43.5)	
Negative	11 (42.4)	44 (56.5)	
Her-2-neu			0.468*
Positive	7 (27)	22 (28.2)	
Negative	13 (50)	46 (58.9)	
Unknown	6 (23)	10 (12.8)	

Data are presented as *n* (%)

* Chi-square test

[a] American Joint Committee on Cancer (AJCC) stage groupings for breast cancer using the T, N, M translated to stage 0, I, II, III & IV

Table 3 Distribution of histological findings before chemotherapy and after neoadjuvant therapy for IBR patients

	Lumpectomy + AD $N = 14$	Biopsy + AD $N = 12$
Pre therapeutic		
Lobular carcinoma	2	4
Ductal carcinoma	12	8
Multifocality	3	9
DCIS	7	2
Post therapeutic		
cCR	ND	5
cPR	ND	2
pCR	ND	2
Residual DCIS	5	
Residual invasive cancer	2	

Data are presented as *n*

AD axillary dissection, *cCR* clinical complete response, *cPR* clinical partial response, *pCR* pathologic complete response

versus 26 (33.3%) of the DBR group ($P = 0.715$). Last, nipple-areola reconstruction was done in 21 (80.7%) IBR patients versus 56 (71.7%) in the DBR group ($P = 0.081$).

Complications

Sixteen (61%) early complications were reported for the IBR group versus 44 (56%) for the DBR group ($P = 0.645$). No differences were found between the two groups for the rate of breast skin envelope necrosis, marginal LD flap necrosis, implant infection, hematoma, or dorsal seroma. Conversely, the rate of marginal back skin flap necrosis was higher in the IBR group than in the DBR group (Table 4). Breast skin envelope necrosis (IBR group), anterior thoracic wall necrosis (DBR group), marginal LD flap necrosis, and back skin flap necrosis were managed routinely by wound dressing. Implant infection required surgical revision, and an attempt to conserve the implant was made using irrigation and drainage. In the IBR group, all infected implants were managed conservatively. In the DBR group, one of the four infected implants was removed after failure of conservative management. The early implant loss rate was 0% in the IBR group versus 12% in the DBR group. Eight late complications were reported for the IBR group (30%) versus 17 (21%) for the DBR group ($P = 0.362$). The rate of capsular contracture (CC) was not different between groups. The total number of implant revisions, including expander change for definitive implant, surgical cure of CC, and revision for esthetic reasons, was not different in the IBR group in comparison with the DBR group. The rate of reconstruction failure was the same in the two groups. Finally, the number of surgical procedures to achieve symmetrization was the same in the two groups (Table 5).

Table 4 Distribution of observed immediate complications

	IBR group $N = 26$	DBR group $N = 78$	*P*
Breast skin envelope necrosis*	1 (3.8)	4 (5.1)	0.786**
Marginal LD flap necrosis	2 (7.6)	7 (8.9)	0.708**
Hematoma	3 (11.5)	10 (12.8)	0.863**
Implant infection	1 (3.8)	4 (5.12)	0.786**
Dorsal seroma	4 (15.3)	14 (17.9)	0.762**
Marginal back skin flap necrosis	5 (19.3)	4 (5.1)	0.04**
Total early complications	16 (61.5)	44 (56.4)	0.645**

Data are presented as *n* (%)

* Breast skin envelope necrosis (IBR group) and anterior thoracic wall skin necrosis (DBR group)

** Chi-square test

Follow-up

The mean (SD) follow-up was 4.7 years (1.9) in the IBR group and 4.5 years (1.8) in the DBR group ($P = 0.751$). No patients were lost to follow-up. The overall LR rates amounted to 7.7% (2 out of 26 patients) in the IBR group and 6.4% (5 out of 78 patients) in the DBR group ($P = 0.823$). For the IBR and DBR patients, four (57%) of the seven LRs were detected clinically and the three others were detected by thoracic tomodensitometry performed because of axillary venous thrombosis (2 cases) and arm lymphedema (1 case). Treatment of LR in the IBR group consisted of local excision for one case and local excision plus CT for the other case. In the DBR group, LR treatment consisted of local excision alone in two cases and excision plus CT in three cases. Five patients (19.2%) of the IBR group developed distant metastasis versus 21 (26.9%) in the DBR group ($P = 0.602$). During the study period, five patients (19.2%) in the IBR group died of cancer disease versus nine (13.5%) in the DBR group ($P = 0.482$).

Table 5 Distribution of delayed complications

	IBR group $N = 26$	DBR group $N = 78$	*P*
Capsular contracture	4 (15.3)	9 (11.5)	0.616*
Back pain	3 (11.5)	4 (8.9)	0.786*
Reconstruction failure	1 (3.8)	4 (5.1)	0.786*
Total late complications	8 (30.7)	17 (21.7)	0.362*
Implant revision capsule	4 (15.3)	9 (11.5)	0.641*
Total implant revision	9 (34.6)	18 (28.1)	0.245*
Symmetrization procedure	7 (26.9)	26 (33.3)	0.715*

Data are presented as *n* (%)

* Chi-square test

At the last follow-up visit, esthetic outcome was evaluated for disease-free patients and patients with no reconstruction failure. Eighteen IBR patients were evaluated versus 54 DBR patients. At this last visit, 77.7% of the IBR patients (14 out of 18) had an overall esthetic result of excellent or good versus 87% (47 out of 54) for the DBR patients. The evaluation by the patients themselves was identical in the two groups (Table 6).

Discussion

This study shows that post-neoadjuvant therapy SSM plus IBR offers the same feasibility, oncological safety, and cosmetic results as DBR.

The IBR patients were younger than the DBR patients. Although this may have introduced bias in the comparison of safety, other important factors of co-morbidity (BMI, diabetes mellitus, smoking) were comparable between the two groups. According to Lipa et al. [42], age becomes a significant risk factor for perioperative complications in women over 65 years in comparison to younger women. In our study, the mean age of the DBR group was 56 years and, like other authors [42, 43], we believe that the general health status of patients is a better indicator than crude age. For Pinsolle et al. [43], the only factor found to be significantly associated with anterior thoracic wall skin necrosis and flap necrosis was cigarette smoking. This condition was equally distributed between our two groups. Age over 50 years and BMI higher than 25 were not associated with an increased rate of complications. Regarding the hematoma rate, Pinsolle et al. [43] showed that BMI over 25 was a significant risk factor, as was the postoperative use of low-molecular-weight heparin. In our study, these conditions did not differ between the IBR and DBR patients. Last, obesity is another proven risk factor for postoperative infection [42, 44] but was equally distributed in our two groups of patients.

Early complications were mainly benign in both groups. A slight but significant difference was seen regarding back skin necrosis. We believe this difference was not due to the timing of RT, but rather to the surgical technique. Indeed, although the size of the skin island was not recorded at surgery, we assume that the size of the dorsal skin island was larger in the IBR group than in the DBR group. In the IBR group, a large dorsal skin flap was undermined to match the large ellipse of breast skin and the inframammary fold that had been removed. Conversely, the dorsal skin flap was smaller in the DBR group because large skin coverage was unnecessary. Interestingly, complications related to post-radiation skin damage, such as skin necrosis or implant infection, were not over-reported in the IBR group in comparison with the DBR group, indicating that the short time between RT and SSM in the IBR group may not have increased the deleterious effects of radiation. Comparison with the literature was limited by the few reports concerning IBR after CT and RT. However, our concept carries complication rates comparable to those of other published series about implant reconstruction after radiation therapy. An interesting paper by Michy et al. [45] reported a series of 101 patients who had undergone IBR after neoadjuvant CT and RT for invasive breast carcinoma. IBR was accomplished by transverse rectus abdominis musculocutaneous flap (TRAM) in 38 patients, by latissimus dorsi musculocutaneous flap with prosthesis (LDMP) in 32, by autologous latissimus dorsi musculocutaneous flap (ALDM) in 15, and by simple prosthetic implant in 26. The respective complication rates were 50, 37.5, 8, and 62%. The need for additional surgical procedures was, respectively, 29, 15, 6, and 56% [45]. A recent series reported by Tallet et al. [37] concerned 77 patients undergoing IBR with tissue expanders and implants. Of the 55 patients who had received RT, 51% developed postoperative complications versus 14% for the non-irradiated patients. Interestingly, a small sample of eight patients had been irradiated before reconstruction because of ipsilateral recurrence. The complication rate was comparable in this sample, with five of the eight patients presenting a complication [37]. Spear and Onyewu recently found that, of 40 patients treated from 1990 to 1998 who underwent staged breast reconstruction with an expander and implant and received radiation before, during or after the expansion, 47.5% required an additional flap procedure to improve, correct, or save the implant [46]. The overall complication rate was 52.5%, compared with 10% in a control group of 40 patients who did not undergo irradiation who were randomly sampled from 200 such patients treated during the same period. Based on the data from retrospective series of SSM plus IBR, the complication rates range from 14 to 55% when RT is administered versus 7 to 31% for non-irradiated patients [38]. However, the complication rates seem to be comparable when RT is delivered before and after breast reconstruction [37, 38].

Capsular contracture is a common mid- to long-term complication associated with implant-assisted breast

Table 6 Cosmetic evaluation

	Medical evaluation			Patient evaluation		
	IBR	DBR	*P*	IBR	DBR	*P*
Excellent	5 (27.7)	21 (38.8)	0.541*	9 (50)	29 (53.7)	0.723*
Good	9 (50)	26 (48.2)		7 (38.8)	22 (40.7)	
Fair	4 (22.3)	7 (13)		2 (11.2)	3 (5.6)	

Data are presented as *n* (%)

* Chi-square test

reconstruction plus RT and a major concern for the esthetic result. We examined the difference in the rate of CC between our concept (post-neoadjuvant IBR) and other surgical strategies evaluated directly in this comparative study or reported in the literature. Our results demonstrated that the CC rate was similar in the IBR and DBR groups (15.3 and 11.9%, $P = 0.616$), as was the esthetic outcome, which is known to be highly dependent on the CC rate [47]. Furthermore, the capsular formation rate compared favorably with the rates reported in series of immediate breast reconstructions plus adjuvant RT [37, 46–48]. The CC rate varies considerably in the literature—from 17 to 68%—because of the inhomogeneity of the selected patients and the surgical procedures used. The reports in fact concern not only one- or two-stage implant-based reconstructions, but also latissimus flaps plus implants. Another major concern in the validation of our concept was the influence of RT timing on capsular formation. Few data have been published and the debate is not yet closed. Behranwala et al. [49] reported a study of 136 breast reconstructions in 114 patients. A total of 44 patients underwent RT, 15 before breast reconstruction and 29 after reconstruction. The risk of capsule formation was lower for the patients irradiated before reconstruction in comparison with PMRT [HR: 2.23 (0.61–8.2) versus 5.23 (2.31–11.8), $P < 0.001$] [49]. This seems logical because the flap used for the reconstruction, as well as the implant, was unexposed to irradiation. Pinsolle et al. also evaluated the CC rate in relation to the timing of RT in a series of 266 IBR and reported similar results. For patients irradiated before IBR, the CC rate was 24% in comparison with 55% when RT was performed after IBR [43]. Conversely, Contant et al. [50] examined the medical records of 100 women who had undergone a mastectomy followed by IBR with a subpectorally placed silicone prosthesis. Thirteen prostheses were implanted prior to RT and 15 prostheses were implanted after irradiation of the chest wall. The risk of capsule formation did not differ for patients irradiated before reconstruction in comparison with PMRT [HR: 7.5 (3.4–16.6) vs. 6.5 (2.4–15.8)] [50]. However, this series was too small to offer sufficient statistical power. Last, our CC rate seems to be comparable to the reported rates after IBR using LD flaps for salvage mastectomy following conservative treatment failure (surgery plus RT). In a series of 57 patients undergoing salvage mastectomy plus LD-based IBR, Disa et al. [51] reported a CC rate of 17%. Freeman et al. presented a series of 12 patients who underwent LD flap reconstruction after the development of recurrent cancer after breast conserving therapy. Despite previous radiation, the CC rate was 12.5% (median follow-up: 50 months; range: 20–93 months) and all 12 patients had a satisfactory esthetic result [52]. Moreover, the role of the LD flap with a prosthesis in reconstruction of the previously irradiated breast was examined in a retrospective review by Spear et al. [53]. Twenty-eight patients with available charts had undergone LD plus implant reconstruction. The average follow-up was 28.8 months (range: 1 week to 7 years). All patients had soft breasts at follow-up, with no evidence of capsular contracture [53]. The CC rates that we report in our series are closer to the rates for RMD and IBR for salvage mastectomy than for IBR and RT post-IBR. However, these results should be confirmed by direct comparison in much larger series.

The LR and cancer-related death rates were not significantly different in the two groups and compared favorably with the findings of other published series of patients who underwent SSM and patients with locally advanced disease who were treated by mastectomy with or without reconstruction [5, 54, 55]. The recurrence rates reported in the literature increased with stage, from 3% for stage I to 11.1% for stage III, from 3.7% for T1 to 9.9% for T2–T4, and from 0% for stage I to 25% for stage III [9, 11, 13]. Recurrence appeared to be stage-dependent and independent of the use of IBR. In addition, this wide range is possibly due to potential bias because of inadequate axillary sampling, incomplete surgical technique, and suboptimal systemic therapy [56]. A recent pooled analysis by Jatoi and Proschan of six randomized trials comparing mastectomy and breast conservation in the treatment of primary breast cancer examined mortality and LR [57]. The rates of LRR after mastectomy in these trials ranged from 2 to 16% [57]. Slavin et al. [8] did not observe an increased risk of LR in a series of 51 IBRs with autologous tissue. Kroll concluded from the IBR series from M.D. Anderson that SSM did not increase the risk of LR [54]. Sandelin found an 8% LR rate in a series of 100 IBRs with a mean follow-up of 36 months [58]. Thus, the literature clearly demonstrates that the type of reconstruction has no influence on the clinical outcome of the disease, as was noted in our series. We conclude that our surgical procedure is a safe option, and after these preliminary results we found no difference in comparison with standard approaches using delayed breast reconstruction. However, our study findings would be strengthened by a longer follow-up, as LR rates and cancer-related death are known to increase over time [20, 55, 59, 60].

The combination of autogenous tissue/prosthetic reconstruction has several advantages in the setting of previously irradiated tissues. Autogenous tissue flaps provide pliable, well-vascularized soft tissue, which can facilitate both wound healing and the process of tissue expansion. The elective use of flaps alongside breast prostheses in patients irradiated before reconstruction is supported by many authors [61]. However, data on long-term esthetic outcomes are needed, particularly after RT, which is known to affect the esthetic results with time.

Geber et al. reported the cosmetic results in a series of SSM patients after a mean follow-up of 59 months and, more recently, after a mean follow-up of 101 months [24, 62]. The surgeons' re-evaluation of the esthetic results revealed a significant shift from 78.4% excellent results after 59 months of follow-up to 47.9% after 101 months [24, 62]. Similarly, Clough et al. [47] reported deterioration in the esthetic outcome following implant-based IBR in a series of patients in whom only 8% had RT: from 86% acceptable results at 2 years to 54% at 5 years. Last, Thomson et al. [63] reported a prospective study of cosmetic outcome in immediate LD breast reconstruction with and without RT. The cosmetic outcome of all reconstructions deteriorated over time, with the non-irradiated reconstruction producing the best long-term esthetic outcome and the irradiated implant reconstructions faring worst. Adjuvant RT was the most important factor for the long-term decreased cosmetic score, although factors other than capsule formation, such as the natural aging of the contralateral breast parenchyma and the overlying skin envelope, as well as overall weight change, are likely to significantly influence the long-term score [63].

This study was limited by the possibility of selection bias and the short median follow-up. It would have been powerful to compare IBR group with a control group composed of patients treated with mastectomy and IBR followed by RT. However, in our practice, patients who have undergone mastectomy plus IBR for invasive disease have had false negative sentinel node status at introperative pathologic examination and had not received preoperative chemotherapy. In addition, in these cases, IBR was routinely performed using an implant alone or with expanders and not a LD flap. These conditions explain the lack of a control group. In the current study, the CT regimens used the same drugs in the two groups. However, since 2005, the total number of cycles administered has differed depending on whether CT is used as neoadjuvant therapy (IBR group, 8 cycles) or adjuvant therapy (DBR group, 6 cycles). This condition may have introduced a bias in the comparison of oncological outcome. A meta-analysis from Maury et al. [64] nevertheless showed that neoadjuvant and adjuvant CT had equivalent rates of survival and disease progression. Another limitation was the comparison of tumor response to treatment in each group. A close comparison of clinical and pathologic responses between groups was irrelevant because the DBR patients underwent mastectomy as the primary step and CT as adjuvant treatment. In addition, the number of patients assessable for tumor response to neoadjuvant treatment was small, as only 12 IBR patients had no lumpectomy before induction of CT. However, our study was not performed to assess and compare the responses to CT in the two groups. In the IBR group, neoadjuvant CT and RT were not performed to shrink tumor size and allow conservative treatment but to integrate IBR for patients needing both mastectomy and CT plus RT. An analysis of the LR rate by disease stage was not done because of the relatively low patient numbers. Although the majority of local failures occurred within the first 5 years of treatment, distant failure may occur later, and the patients in our study remain at risk for both locoregional and distant failure. Similarly, severe CC may not develop until several years after treatment [63] and the short median follow-up time of our study may give a falsely reassuring picture concerning our concept. As well, cosmesis outcome is known to decrease with time, particularly when RT is used. Thus, differences between the two groups in terms of LR and/or distant metastasis, CC rate and cosmesis outcome may appear at a later time. Despite these limitations, this report presents convincing evidence that our concept provides a basis for offering more women the opportunity to elect for immediate reconstruction, even in the setting of radiation therapy.

Conclusion

IBR is indubitably a valuable addition to the oncological surgical armamentarium for primary treatment of breast cancer. Our study shows that the feasibility and oncological safety of IBR are comparable to DBR. Our concept should be further analyzed in larger comparative studies in order to confirm our preliminary finding that IBR can be safely integrated into the global management of locally advanced breast cancer patients.

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