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Series: Breast Reconstruction—The True Multidisciplinary Approach

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Aims and Scope

Annals of Breast Surgery (Ann Breast Surg; ABS; online ISSN 2616-2776) is an open access, peer-reviewed online journal, which provides current and practical information on prevention, diagnosis, and clinical investigations of breast diseases. The journal focuses on cutting-edge findings in the field of breast cancer surgery and reconstruction technique, neoadjuvant therapy, genetic susceptibility and prophylactic mastectomy, including but not limited to, multimodality therapy, biomarkers, imaging, biology, pathology, clinical trial, nursing and technical advances related to breast surgery.

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Editorial

Breast reconstruction—the true multidisciplinary approach

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Breast reconstruction has for the past decade become an integrated and inevitable part of breast cancer treatment and care. To fully integrate and incorporate the reconstructive procedure into the breast cancer treatment pathway, insight into each step of the pathway is mandatory for the wide array of specialists caring and treating breast cancer patient, as well as the increasing number of breast cancer survivors i.e., addressing the late effects and morbidity associated with breast cancer treatment.

Breast cancer treatment as well as prophylactic treatment of individuals carrying an increased risk of acquiring breast cancer is guided by recommendations of the multidisciplinary panel of specialists based on the highest standard of care as well as the highest level of scientific evidence. Recently, the European Society of Breast Cancer Specialist (EUSOMA) published a paper, describing the requirements of a specialist center, with special attention to the multidisciplinary and patient-centered pathways [diagnosis, treatment and late-effects (survivorship)] (1).

In the near future, personalized medicine will inevitably become the main stay in treating breast cancer patient by targeted and tailored imaging techniques, prophylactic therapy/surgery, pathology, oncologic surgery, reconstructive surgery, radiation therapy, chemotherapy and immunotherapy to the individual patient. Furthermore, prevention and treatment of late-effects is developing at a rapid pace (e.g., surgical treatment of lymphedema), thus creating knowledge and data for future evidence-based treatments of these entities as well. Health-care providers, whether being financed by public funds or insurance-based are already defining strict economic limitations, which requires that all health care professionals must seek to balance optimal treatment and innovation against the economic and politics whilst meeting patient-centered demands.

Immediate and delayed breast reconstruction as well as oncoplastic procedures are currently an integrated part of the breast cancer treatment. Oncoplastic surgery i.e., volume displacement and volume replacement—utilizing well-known plastic surgical techniques such as a breast reduction or a mastopexy with or without utilization of local flaps—have paved the way for an increasing number of patients undergoing breast conserving therapy and an increased survival (2,3). Breast reconstruction carried out at any timepoint during breast cancer treatment or as a prophylactic procedure has been shown to benefit the patients, physically and psychosocially as well as improving their quality of life (4-7).

Today, the breast reconstructive procedures encompass the whole reconstructive plethora, ranging from implant-based, acellular (dermal) matrix-assisted one- or two-staged procedures to the entire spectrum of autologous flaps, being perforator-based free flaps or pedicled perforator or axial flaps. Current techniques are targeted and tailored to the individual patient according to morbidity, body habitus, cancer stage and previous or future adjuvant therapies. The techniques/treatments are performed as partial or total breast reconstructions at the optimal time-point of the breast cancer pathway, Moreover, surgical procedures to prevent and treat lymphedema are gaining increased efficacy whilst the anatomical and (patho-) physiological nature of the lymphatic vasculature are

studied and revealed (8,9). The highest goal for breast and reconstructive surgeons is to optimize the reconstructive procedures, diminish and preferably eliminate donor-site morbidity and concomitantly prevent or treat late-effects. However, our obligation extends into innovative studies encompassing robot-assisted reconstructive surgery and super-microsurgery, whereby we may optimize every step of the prophylactic and treatment pathways.

Members of the multidisciplinary breast cancer teams are obliged to offer the patients the highest-level of evidence regarding imaging techniques, pathological assessment, oncologic treatment as well as treatment of late effects.

The aim of this special series in *Annals of Breast Surgery* is to provide the reader with an extensive overview over the current multidisciplinary spearheads in breast cancer treatment and breast reconstruction.

Dear reader, we hope you will enjoy reading this special series, "Breast Reconstruction-The True Multidisciplinary Approach", composed of papers written by some of the most renowned physicians, breast and plastic surgeons, oncologist, radiologist, pathologists from all over the world.

Acknowledgments

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Ethical Statement: The authors are accountable for all aspects of the work to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Original Article

Resource utilization and patient reported outcomes using acellular dermal matrix in breast reconstructive procedures

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Background: The introduction of acellular dermal matrices revolutionized implant-based breast reconstructive procedures. Literature reports both advantages and disadvantages associated to the use of acellular dermal matrix (ADM). The increasing number of breast reconstructive procedures being performed leads to an awareness of improving the psychosocial and functional result and reduce costs associated with these procedures. One-stage implant-based breast reconstruction (BR) with ADM has potential advantages for the patient, but literature shows conflicting results regarding the cost-effectiveness of this approach compared to the two-stage expander-to-implant method. The patient's subjective assessment of the physical and psychosocial effects of BR is extremely important. To contribute to knowledge on the subject, we present a study where the aim was to compare immediate implant-based BR using the ADM assisted one-stage approach with the two-stage expander-to-implant approach regarding resource utilization and patient reported outcomes (PROs).

Methods: The study was designed as an observational cohort study with 44 participants admitted for immediate implant-based BR at Department of Plastic Surgery, Aarhus University Hospital, Aarhus, Denmark. BR was performed with a one-stage technique in 21 patients and with a two-stage technique in 23 patients. Follow-up time was 2 years.

Results: Overall, in favor of the one-stage group was a shorter duration of surgery and furthermore, the reduced need for outpatient visits (for expansions) as well as for additional surgery for implant exchange. In favor of the two-stage approach was reduced cost of materials and fewer interventions to address the aesthetic outcome. Pain, sensory disturbances, physical limitations, health status, quality of life (QoL) and body image were equally favorable between the two groups at 2-year follow-up.

Conclusions: This study does not provide clear evidence for an advantageous use of resources by one method versus the other and further studies should be undertaken to investigate the cost-effectiveness. Considering the equally good results in the two treatment groups regarding PROs the one-stage approach may be preferred if the patient is deemed suitable and is well informed of the potential need for additional interventions to obtain an aesthetically satisfying result.

Trial Registration: ClinicalTrials.gov (NCT04209010).

Keywords: Acellular dermal matrix (ADM); implant-based breast reconstruction (implant-based BR); resource utilization; patient reported outcomes (PROs)

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Introduction

In the western world an increasing part of breast reconstructive procedures is being performed in an increasingly younger population (1,2). This leads to an awareness of improving the psychosocial and functional result and reduce the resource utilization as more women will live for a longer time with the consequences of breast cancer treatment.

In 2005/2006 Breuing and Salzberg were the first to publish the use of acellular dermal matrix (ADM) for immediate implant-based breast reconstruction (BR) following skin-sparing mastectomy (3,4) and in 2007 Bindingnavele *et al.* introduced the use of ADM in tissue expander BR proposing that this would decrease the postoperative pain and allow a faster expansion course (5).

Limited health resources necessitate careful consideration of the implementation of a given treatment modality. ADM products are expensive but may potentially be cost-effective, due to the possibility of reducing expenses as i.e., fewer surgeries and shorter hospital stay, compared to the traditional two-stage expander-implant technique. The literature regarding this subject shows conflicting results. Some suggest that the use of ADM for immediate BR is cost advantageous compared with the two-stage approach and furthermore, that the use of ADM has clinical benefit for patients by allowing a one-stage procedure rather than two separate operations and results in fewer outpatient visits (6,7). Another study has reported that the direct costs of one-stage implant-based BR with ADM were higher than those of two-stage BR, and that health outcomes did not differ between the groups (8).

The advantages of using ADM in BR are improved control of the inframammary fold position (9) and better lower pole projection (10) compared to the traditional expander-to-implant technique. Furthermore, studies indicate that implant-based BR with ADM results in a lower rate of development of capsular contracture, even when the patient has to undergo radiation therapy (11,12). Seroma has, on the other hand, been associated with the use of biological meshes (13,14). The patient's subjective assessment of the aesthetic outcome and the physical and psychosocial effects of BR is extremely important as the overall objective by offering BR is to improve the patients quality of life (QoL).

To contribute to knowledge on the subject, the present study aims at comparing immediate implant-based BR using the one-stage approach with ADM with the two-stage expander-to-implant approach regarding resource utilization and patient reported outcomes (PROs). We present the following article in accordance with the STROBE reporting checklist (available at https://abs.amegroups.com/article/view/10.21037/abs-21-81/rc).

Methods

Study design and participants

The present study was designed as an observational cohort study with 44 participants. Eligible patients were all women admitted for immediate, implant-based BR following skin-sparing mastectomy at the Department of Plastic and Breast Surgery, Aarhus University Hospital, Denmark over a period of 40 months. Patients were diagnosed with either breast cancer, ductal carcinoma in situ (DCIS) or were considered high risk for developing breast cancer. Inclusion criteria were mastectomy weight ≤600 g, patient older than 18 years, tobacco abstinence >4 weeks prior to surgery, ability to complete the study questionnaire, and for the two-stage group; time to achieve 2-year follow-up visit after BR. Follow-up visits were planned 12 and 24 months after insertion of silicone implant where patients completed a study-specific questionnaire regarding PROs. Furthermore, a systematic review of patient records was performed to obtain information for analysis regarding resource utilization. Follow-up time was 24 months.

All participants gave written informed consent. The Ethics Committee of the Central Region of Denmark (1-10-72-572-12) approved this study and it was submitted in ClinicalTrials.gov (NCT04209010). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Recruitment

As the one-stage approach was implemented as a standard

care for immediate implant-based BR following skin-sparing mastectomy, in December 2012, all eligible patients were offered participation in the one-stage group and inclusion continued consecutively until 21 patients were included. The two-stage cohort was established retrospectively. Patients that had undergone immediate implant-based BR following skin-sparing mastectomy with the two-stage expander-to-implant technique were identified using diagnosis- and procedure-related codes, records were examined and patients that fulfilled the inclusion criteria were identified and consecutively offered participation in the two-stage group. Inclusion continued retrospectively until 23 patients were included (see Figure S1). The same study population has been used for the publication entitled "*Comparison of one-stage direct-to-implant with acellular dermal matrix and two-stage immediate implant-based breast reconstruction-a cohort study*" (15) where the outcome was postoperative complications, aesthetic correction procedures and aesthetic outcome.

Study size

Study size was determined upon power calculation on the primary endpoint "reduction in surgery time" as the duration of surgery was considered to have a significant impact on overall resource utilization. Duration of surgery time for bilateral BR with the two-stage technique was, based on own experience, estimated to 300 minutes. The minimum relevant difference the study was aiming to achieve was 60 minutes reduction in surgery time using the one-stage technique (16). With a significance level at 5% and power on 80%, it was calculated that 16 patients were needed in each treatment group. Originally 20 patients were planned in each group, but late secondary review of patients revealed, that one patient had been excluded by mistake from the one-stage group due to conversion to expander-based BR because of vulnerable mastectomy flaps and another three patients were excluded due to removal of implant before inclusion started in the two-stage group. Allocating these patients to their correct study group resulted in 21 patients in the one-stage group and 23 patients in the two-stage group.

Surgical techniques

The surgical technique for one-stage ADM assisted immediate BR and for expander to implant two-stage immediate BR was described in a previous published paper (15). No patients underwent postoperative radiation therapy.

Outcomes

The primary endpoint of the study was resource utilization reported for bilateral and unilateral BRs in the two treatment arms. It was not possible to assign a monetary value on all variables, but the assumption was made that if e.g., number of interventions were higher in one group compared to the other, this would lead to increased resource utilization. The following variables were included: (I) cost of silicone implants, sizers, expanders and sheets of ADM (Strattice™ pliable 8×16 cm) in €. (II) Duration of the breast reconstructive procedure in minutes. In case of unilateral BR with contralateral breast surgery in the same intervention, the duration of the breast reconstructive procedure was estimated by a senior consultant (TD). (III) Number of outpatient visits for expansions in patients who underwent a two-stage procedure. (IV) Number of interventions to address seroma. (V) Number of surgical interventions to address complications. In case several procedures were done during the same surgery it only counted for one intervention. (VI) Number of surgical interventions to address aesthetic outcome. In case of unilateral BR with contralateral breast surgery at the same time as the breast reconstructive procedure, the contralateral procedure counted for one aesthetic intervention. (VII) Duration of hospitalization in days and estimated costs in € and (VIII) duration of sick leave reported by patients (counted as days before work was resumed). These data were obtained for a 2-year period after insertion of the final-size silicone implant. All second stage surgeries for the two-stage group were completed.

Secondary endpoints were PRO measures (PROMs) including Hopwoods body image scale (BIS) and a study specific questionnaire.

Body image was evaluated using Hopwoods BIS (17) at 12- and 24-month follow-up. The scale is validated for use in breast cancer patients and consists of 10 items answered with reference to the past week. The scale has high reliability, good clinical validity, and is sensitive to changes. Items include evaluation of femininity, self-consciousness, physical and sexual attractiveness, and satisfaction with body and scars. Each question has four options for rating body image: "not at all" (score 0), "a little" (score 1), "quite a bit" (score 2) and "very much" (score 3). The 10 item scores were summed to produce an overall score for

each patient, ranging from 0 to 30, with 0 representing no symptom/distress and higher scores representing increasing symptoms/distress.

Furthermore, the patients fulfilled a study specific questionnaire regarding health status, QoL, pain, sensory disturbance and functional sequalae at 12- and 24-month follow-up consisting of items answered at breast level and at patient level. Some of the questions were answered on a scale and were dichotomized prior to analysis as elaborated in the description of questions found in Appendix 1.

Bias

The funders (financial or the ADM supplier) did not participate in study design, data collection, data analysis, or interpretation and writing of the manuscript.

Statistical analysis

Descriptive statistics were used for patients' demographics with mean and standard deviation for continuous variables. Categorical variables were compared between study arms using Fisher's exact test while continuous variables were compared by a *t*-test.

For the resource utilization analysis part, simple linear regression models were used and uni- and bilateral BR were compared separately between the treatment groups. BIS was analyzed using a mixed regression model due to repeated measurements using patient ID as random effect. Due to the small sample size, the Kenward Roger approximation method was used to calculate the degrees of freedom. The regression model assumptions were checked by visual inspection of the diagnostics plots such as QQ plot for the residuals and the scatter plot of residuals and the fitted values. If necessary, a log-transformed outcome was modelled.

PROMs reported at patient level with dichotomized outcomes were analyzed using generalized linear models with log-link function adjusting for repeated measurements by using patient ID as cluster. Regarding health-related limitation of activities the sum score was analyzed using a mixed model, adjusting for the repeated measurements and small sample size as described above.

The original outcomes of PROMs reported at breast level had flooring effect (except the question: Do you feel burdened by sensory disturbances in the area where you were operated?) i.e., many of the answers were "no pain" or similar to that. Therefore, all the outcomes were dichotomized as "no pain" or "yes, pain" (or similar). PROMs reported at breast level with binary outcome were analyzed using a generalized linear model with log-link function. By keeping the smaller sample size in mind, especially those with bilateral surgery, the two breasts were assumed to be coming from two different patients. Therefore, a new ID variable was created at the breast level, assuming that every BR is from one individual, and used as clusters in the model to adjust for the repeated measurements.

The patient (in case of unilateral BR or bilateral BR with bilateral explantation) or the breast (in case of bilateral BR with unilateral explantation) was categorized as lost to follow-up if explantation occurred. Therefore, some patients did not have the opportunity to answer the questionnaire at follow-up visits and were thereby not randomly missing. This was the case for five patients (nine breasts) in the one-stage group and four patients (seven breasts) in the two-stage group (*Figure 1*).

Statistical analyses were performed using STATA® software IC16.1 (Stata Corporation, College Station, TX, USA). Strobe guidelines for reporting observational cohort study were used.

Results

Forty-four patients were included in the study, 21 patients (32 breasts) in the one-stage group and 23 patients (29 breasts) in the two-stage group. Fifteen patients (21 breasts) in the one-stage group and 19 patients (22 breasts) in the two-stage group completed 24-month follow-up (*Figure 1*). The two groups did not differ significantly regarding demographics and clinical characteristics as summarized in *Table 1*.

Regarding the primary endpoint "resource utilization" associated with the two different methods for BR the materials for a one-stage BR (silicone implant, Strattice™, sizer) was 2.6 times more expensive than materials for a two-stage BR (expander, silicone implant, sizer ×2) with a 1,795 € difference in costs for a unilateral procedure (*Table 2*).

The one-stage procedure took longer time than the first operation for the two-stage procedure for both unilateral and bilateral cases. But when the duration of procedures in the two-stage group were summed, the overall surgery time of a unilateral two-stage procedure was 34% longer than a one-stage procedure (P=0.006). For the bilateral groups the overall two-stage procedure took 10% longer (P=0.348) time than the one-stage procedure.

Patients undergoing BR with the two-stage method

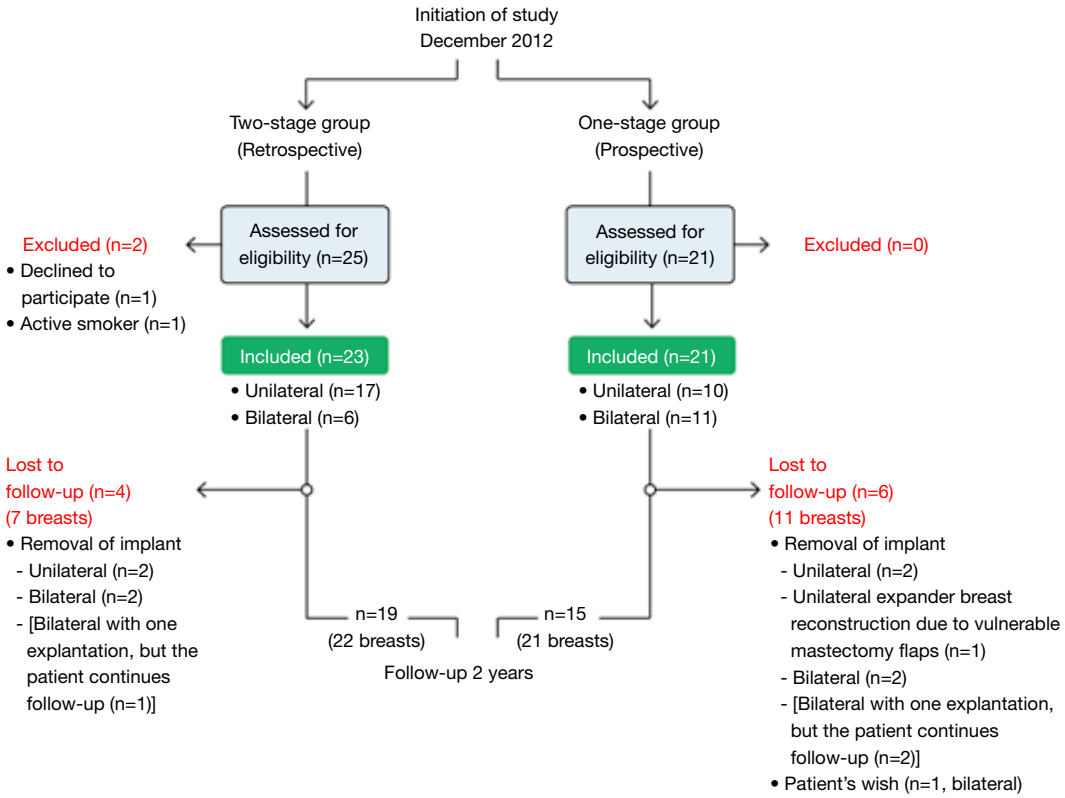

Figure 1 Flow chart of the study participants. This figure has previously been published in a paper regarding the same study population (15).

Table 1 Baseline demographics and clinical characteristics

Variables	One-stage, n=21	Two-stage, n=23
Age (years), mean (SD)	48.3 (10.7)	42.7 (9.9)
BMI (kg/m^2), mean (SD)[†]	23.1 (2.8)	24.7 (3.8)
Comorbidity[†], n	7	3
Laterality of procedure, n		
Bilateral	11	6
Unilateral	10	17
Adjuvant therapy after surgery[†], n		
Endocrine treatment	5	1
None	15	19
Axillary surgery[†], n		
None	13	13
Sentinel node biopsy	7	5
Axillary dissection[‡]	0	2
Indication for mastectomy[†], n		
Cancer	3	0
DCIS	2	6
Prophylactic	15	14

[†], missing values one-stage group n=1, two-stage group n=3; [‡], two patients in the two-stage group were diagnosed with DCIS but underwent axillary dissection due to micrometastasis in sentinel nodes. BMI, body mass index; DCIS, ductal carcinoma in situ.

underwent in average 6.3 (unilateral) and 5.9 (bilateral) expansions. There was no statistically significant difference in mean number of interventions to address seroma between the two treatment groups.

For the variable "surgical interventions to address complications" a flooring effect was observed. For the

Table 2 Resource utilization reported per patient for unilateral and bilateral BRs

Variables	Unilateral				Bilateral			
	One-stage, n=10	Two-stage, n=17	Comparison	P	One-stage, n=11	Two-stage, n=6	Comparison	P
Total cost of materials (€)[†]	2.935	1.140			5.870	2.280		
Duration of operation (min)[‡]								
First operation	136 (116–160)	95 (80–113)			225 (200–253)	151 (112–205)		
Second operation		83 (67–103)				93 (64–135)		
Overall	136 (116–160), M=1	183 (162–207), M=2	1.34 (1.10–1.65)	0.006*	225 (200–253)	247 (207–295), M=1	1.10 (0.89–1.36)	NS
Expansions[§]		6.3 (5.2–7.3), (range, 3–11), M=2				5.9 (4.1–7.7), (range, 4–8.5), M=1		
Interventions to address seroma[§]	0.11 (–0.28 to 0.51), M=1	0.24 (–0.05 to 0.52)	0.12 (–0.37 to 0.61)	NS	0 (–0.15 to 0.15)	0.17 (–0.04 to 0.37)	0.17 (–0.09 to 0.42)	NS
Surgical interventions to address complications[§]	0.56 (–0.002 to 1.11), M=1	0.29 (–0.11 to 0.7)	–0.26 (–0.95 to 0.43)	NS	1 (0.20–1.8)	0.5 (–0.59 to 1.59)	–0.5 (–1.85 to 0.85)	NS
Surgical interventions to address aesthetic outcome[§]	1.57 (1.05–2.09), M=3	0.27 (–0.09 to 0.62), M=2	–1.3 (–1.93 to 0.68)	<0.0001*	0.88 (0.28–1.47), M=3	0.75 (–0.09 to 1.59), M=2	–0.13 (–1.15 to 0.9)	NS
Duration of hospital stay (days)[§]								
First operation	10.4 (9.2–11.7)	6.9 (6.2–7.7)			12.1 (10.4–13.8)	7 (5.7–8.3)		
Second operation		3.2 (2.7–3.7)				2.6 (1.7–3.5)		
Overall	10.4 (9.2–11.7), M=1	10.1 (9.2–11.1), M=2	–0.3 (–1.9 to 1.3)	NS	12.1 (10.4–13.8)	9.6 (7–12.2), M=1	–2.5 (–5.6 to 0.6)	NS
Total cost for hospitalization, 470 € per day[§]	4,909 (4,330–5,488), M=1	4,763 (4,314–5,211), M=2	–146 (–879 to 587)	NS	5,683 (4,870–6,495)	4,512 (3,306–5,718), M=1	–1,171 (–2,625 to 283)	NS
Sick leave (days)[§]	40.5 (9.2–71.8), M=6	42.3 (23.4–61.2), M=6	1.8 (–34.8 to 38.3)	NS	62.6 (39.8–85.4), M=3	59.5 (13.9–105.1), M=4	–3.1 (–54.1 to 47.8)	NS

*, statistically significant P value; [†], one-stage group (silicone implant, Strattice™, sizer), two-stage group (expander, silicone implant, sizer ×2); [‡], median (95% CI). Comparison with the ratio of medians (95% CI, P) with reference to the one-stage group; [§], mean (95% CI). Comparison with the difference (95% CI, P) with reference to the one-stage group. BR, breast reconstruction; M, number of missing data; NS, not significant.

unilateral one-stage group 7 of 9 patients (78%) and 13 of 17 patients (76%) in the two-stage group did not undergo any surgeries due to complications. For the bilateral groups, 6 of 11 patients (55%) and 4 of 6 patients (67%) did not undergo any surgeries due to complications, respectively. By calculating mean number of interventions to address complications there were no significant difference between the two treatment groups for either unilateral BR nor bilateral BR.

Twelve of 15 patients (80%) (2 missing) in the unilateral two-stage group did not undergo further surgical procedures to address aesthetic outcome. With comparison to the one-stage group, where all 7 patients (100%) (3 missing) underwent at least one procedure to address aesthetic outcome, there was a statistically significant difference when comparing the means (P<0.0001). In the bilateral groups there was no significant difference between the mean number of interventions to address aesthetic outcome (P=0.791). By assuming that an intervention entails an expense the significant difference between the unilateral

Table 3 Secondary endpoint PROMs reported at breast level: pain, sensation disturbance, lymphoedema and arm function

Variables	One-stage, n=32[†]		Two-stage, n=29[†]		RR	P
	12 months	24 months	12 months	24 months		
Have you felt pain in the area where you were operated?						
Yes[¶]	6 (29%; 14–57%)	4 (19%; 8–47%)	2 (25%; 7–84%)	7 (32%; 17–59%)	1.67 (0.56–4.94)	NS
Do you feel burdened by sensory disturbances in the area where you were operated?						
Yes[¶]	18 (86%; 72–102%)	18 (86%; 72–102%)	4 (50%; 25–101%)	17 (77%; 61–97%)	0.90 (0.68–1.20)	NS
Mean (SD)	1.38 (0.97)	1.52 (1.12)	1.50 (1.85)	1.33 (1.09)		
Have you felt pain in the arm or shoulder on the operated side?						
Yes[¶]	3 (15%; 5–43%), M=12	3 (14%; 5–41%)	2 (25%; 7–84%)	7 (32%; 17–59%)	2.2 (0.65–7.60)	NS
Do you feel burdened by sensory disturbances in the arm or shoulder on the operated side?						
Yes[¶]	3 (15%; 5–43%), M=12	5 (24%; 11–52%)	4 (57%; 30–109%)	7 (32%; 17–59%)	1.33 (0.50–3.60)	NS
Do you suffer from lymphedema in the arm or hand on the operated side?						
Yes, n	1	0	0	2		
Are you able to use the arm on the operated side as before surgery?						
Yes[¶]	15 (71%; 54–94%)	21	7, M=22	18 (82%; 67–100%)		

[†], missing values one-stage group: n=11 at 12- and 24-month follow-up. Two-stage group: n=21 at 12-month follow-up and n=7 at 24-month follow-up. Exception from this is M; [¶], n (proportion in %; 95% CI) and risk ratio (95% CI, P) for comparison of groups at 24-month follow-up with the one-stage group as reference. PROMs, patient reported outcome measures; M, number of missing data; NS, not significant; N, number.

groups leads to the assumption that there are more expenses in the one-stage group.

Duration of overall hospital stay was the same for the two unilateral treatment groups (10 days) but 2 days longer for the bilateral one-stage patients (12 days) compared to the two-stage patients (10 days). There was no significant difference in self-reported sick leave between treatment arms.

Results concerning the secondary endpoint PRO are described as follows. Attention is drawn to the proportion of missing data especially at 12 months follow-up in the two-stage group and results are provided for 24-month follow-up (*Table 3*). Regarding pain located to the breast region there was no significant difference between groups at 24-month follow-up (RR: 1.67, P=0.354). Nor was there any significant difference within the groups between 12- and 24-month follow-up. Patients were in general mildly burdened by sensory disturbances in the operation field as the means for the outcome (where the outcome is scaled from 1= minimum burden to 5= extreme burden) at 24 months were 1.52 (SD: 1.12) and 1.33 (SD: 1.09) for one- and two-stage group, respectively. There was no statistically significant difference between groups at 24-month follow-up (RR: 0.90, 95% CI: 0.68–1.20, P=0.482) or within groups between 12- and 24- months follow-up. Considering patient reported pain in the arm or shoulder on the operated side no statistically significant differences were observed within the groups between 12- and 24-month follow-up in either of the treatment groups. Even though more pain in the arm or shoulder was reported at 24-month follow-up in the two-stage group (32%) this was not statistically significant different from the one-stage group (14%, P=0.201). Regarding sensory disturbances in the arm or shoulder on the operated side there was no statistically significant difference reported within the groups between 12- and 24-month follow-up in either of the treatment groups or between groups at 24-month follow-up (RR: 1.33, P=0.566).

One patient in the one-stage group reported lymphedema at 12-month follow-up and two patients in the two-stage group at 24-month follow-up. Both patients in the two-stage group underwent axillary dissection before unilateral BR.

All in the one-stage group (of 21 reported) and 82% (of 22 reported) in the two-stage group was able to use the arm on the operated side as before surgery at 24-month follow-up.

Body image improved (BIS score reduction) in the one-

Table 4 Secondary endpoint PROMs reported at patient level

Variables	One-stage, n=21[†]		Two-stage, n=23[†]		Comparison w.r.t. one-stage group	P
	12 months	24 months	12 months	24 months		
BIS[§,‡]	6.9 (4.1–9.7)	5.6 (2.8–8.4)	5.6 (2.3–8.9)	5.6 (3.1–8)	–0.01 (3.88–3.85)	NS
Health related limitation of activities[+,§]	8.8 (7.9–9.7)	8.9 (8–9.8)	8.8 (7.8–9.9)	8.4 (7.5–9.1)	–0.5 (–1.75 to 0.66)	NS
How is your current overall health status?						
Good[¶]	15	15	5 (83%; 58–120%)	18 (95%; 85–106%)		
How is your current overall health status compared to the time of BR?						
Improved[¶]	5 (33%; 16–69%)	7 (47%; 27–81%)	1 (17%; 3–102%)	7 (37%; 20–67%)	0.8 (0.4–1.8)	NS
Was BR the right choice for you?						
Yes, n	14	15	6	19		
With your current experience, would you recommend others to undergo BR?						
Yes, n	15	15	5	19		
How would you describe your current QoL compared to the time before your BR?						
Improved[¶]	9 (60%; 40–91%)	11 (73%; 54–100%)	2 (33%; 11–105%)	10 (53%; 34–81%)	0.7 (0.4–1.2)	NS
Have you been taking painkillers within the past month?						
Yes[¶]	2 (13%; 4–49%)	1 (7%; 1–46%)	2 (33%; 11–105%)	7 (37%; 20–67%)	5.5 (0.7–41.3)	NS
Pain elsewhere in the body?						
Yes[¶]	4 (27%; 11–63%)	3 (20%; 7–56%)	0	5 (28%; 13–59%), M=5	1.39 (0.39–4.98)	NS

[†], missing values one-stage group: n=6 at 12- and 24-month follow-up. Two-stage group: n=17 at 12-month follow-up and n=4 at 24-month follow-up. Exception from this is M; [‡], BIS range 0–30. 0 representing no symptom/distress and higher scores representing increasing symptoms/distress; [§], mean (95% CI) and mean difference (95% CI, P) for comparison of groups at 24-month follow-up with reference to the one-stage group; [¶], n (proportion in %; 95% CI) and risk ratio (95% CI, P) for comparison of groups at 24-month follow-up with reference to the one-stage group; [+], health related limitation of activities, range 0–10, higher scores representing more activities the patient can perform without any health-related limitations. PROMs, patient reported outcome measures; w.r.t., with reference to; BIS, body image scale; BR, breast reconstruction; QoL, quality of life; M, number of missing data; NS, not significant; N, number.

stage group from 12 months (6.9) to 24 months follow-up (5.6), although this was not significant (difference: –1.3 points; 95% CI: –3.2 to 0.5, P=0.144) (*Table 4*). In the two-stage group the mean BIS score was 5.6 at both 12- and 24-month follow-up with no significant difference (P=0.9888). Thereby, the reduction in mean BIS score from 12- to 24-month follow-up were not statistically significant between the groups (P=0.446).

All patients were to a large degree unlimited in their ability to perform physical activities. In both treatment groups a mean score >8 (range, 0–10) at 12- and 24-month follow-up. There was no statistically significant difference between groups at 24-month follow-up (P=0.366).

Furthermore, all patients in the one-stage group and the far majority of patients in the two-stage group (83% and 95%) reported a good current overall health at 12- and 24-month follow-up. An increasing proportion of patients in both treatment groups report a better overall health status compared to the time of BR related to increasing time after surgery. The proportion of patients who report improved health was 27% (95% CI: 0.56–2.85) larger in the one-stage group compared to the two-stage group at 24-month follow-up (P=0.568).

All patients, except for one patient in the one-stage group at 12-month follow-up, thought that BR was the right choice for them and at 24-month follow-up all patients would recommend others in the same situation to undergo BR.

An increasing number of patients in both treatment groups experienced an improved QoL from 12 to 24 months postoperatively, though not statistically

significant. Fifty-three percent of the patients in the two-stage group reported improved QoL at 24-month follow-up compared to 73% in the one-stage group (RR: 0.7, P=0.222).

The use of analgetics was reduced from 13% at 12-month follow-up to 7% at 24-month follow-up in the one-stage group but increased from 33% to 37% in the two-stage group. These changes within the groups were not statistically significant. More patients in the two-stage group had used painkillers within the past month compared to patients in the one-stage group at 24-month follow-up, though not statistically significant (RR: 5.5, P=0.096). At 24-month follow-up 20% in the one-stage group and 28% in the two-stage group report pain in other parts of the body than the operated area within the past month (P=0.614).

Discussion

The objective of this study was to compare two methods for immediate implant-based BR in a resource utilization analysis and furthermore, to discuss the result in conjunction with the patient's subjective report of psychosocial and physical outcome measures.

Sample size of this study was determined upon an expected decrease in duration of surgery on 60 minutes when using the one-stage approach. However, the reduction was 47 minutes in the unilateral group and 22 minutes in the bilateral group and the assumptions made before study start was thereby not met. This leads to concerns whether it is possible to identify any differences between study groups because of sample size limitations. The conclusions to be drawn from the present study may also be limited by the retrospective inclusion of the two-stage group as no baseline measurements of PROs were obtained. Furthermore, the majority of patients in the two-stage group did not complete 12-month follow-up visit but only 24-month follow-up visit leading to a large proportion of missing data. Several additional variables would have been preferred in the resource utilization analysis. For example, total number of outpatient visits for both treatment groups, duration of surgery for additional surgeries due to complications and aesthetic outcome, prize setting of operation time etc. Furthermore, this study did not take into consideration the additional cost for another BR in the case of complications leading to implant loss. At the time of study start no validated Danish questionnaire, as BREAST-Q, for use in patients undergoing breast reconstructive procedures was available. Therefore, a study specific questionnaire was used including questions previously used at our institution (18). With these limitations in mind, the following overall thoughts about the outcome was proposed.

Healthcare cost can be calculated from different viewpoints including using reimbursement tariffs based on diagnosis related groups (DRGs) using average costing. This may not reflect the actual costing as shown by others (6,19) and in this publication the original variables as surgery time, number of additional surgeries and cost of materials were used.

Duration of surgery for the breast reconstructive procedure was longer in the two-stage group compared to the one-stage group (significant in the unilateral comparison) as found by others (8). During surgery for tissue expander-to-implant exchange adjustments such as implant pocket adjustments or revision of the inframammary fold, were often made and this could account for at least some of the extra time spent on surgery used in the two-stage group. This corresponds to the observation of more interventions for aesthetic corrections in the one-stage group compared to the two-stage group (significant in the unilateral comparison). If a one-stage BR ultimately requires additional interventions to obtain an aesthetically satisfying result, the advantage of completing the BR in a single stage is lost seen from both the patient and the hospital's perspective. This paradox has also been noted by others (19,20). A major advantage of the one-stage approach is the possibility to avoid outpatient visits for expansion and the additional cost for outpatient clinic time and utensils may offset part of the cost of using ADM from the hospital's perspective. For the patient there is a huge advantage in avoiding expansions as there are also many indirect costs as sick leave from job, discomfort, risk for adverse events, and the psychological burden of not having completed the BR yet.

It was expected that some patients would report pain located to the breast, arm, or shoulder at the reconstructed side 2-year after BR. In the present study, the one-stage group reported less pain (19% and 14%) than the two-stage group (32% and 32%), although not significantly different. It has previously been shown that up to 20% of patients report persistent pain after breast cancer treatment (PPBCT) located to the mastectomy scar or area of the missing breast (21). It has been suggested that BR increases the risk of chronic pain, but Klit *et al.* found no increased risk of persistent pain in patients having a reconstruction with an implant compared with mastectomy alone (odds ratio: 0.82, P=0.33) (22). A recent meta-analysis confirmed

this observation as there was no significant difference between the mean prevalence of surgically related chronic pain after mastectomy alone (35.6%) or after autologous or implant-based BR (32.8%; P=0.88) (23). In the present study most of the patients in both treatment groups felt burdened (although mildly burdened) by sensory disturbance located to the field of surgery and fewer felt burdened of sensory disturbances located to the arm or shoulder on the operated side. Despite pain and sensory disturbances, all patients in the one-stage group were able to use the arm at 24-month follow-up as before surgery compared to 82% in the two-stage group. None of the patients in the one-stage group, but two patients in the two-stage group underwent axillary dissection which is associated with upper limb morbidity (24). The two patients unfortunately developed lymphedema and were burdened by this to a varying degree. All patients were offered early instruction by physiotherapist and began mobilization of the upper limb after a standardized instruction for breast reconstructive patients. Early mobilization and rehabilitation have been shown to play a significant role in reducing postoperative morbidity of the upper limb (25).

In the present study patients reported a good body image (low BIS score) in both treatment groups at both 12- and 24-month follow-up (BIS: 5.6; range, 0–30). Body image score was lower (better body image) than previously reported for immediate unilateral two-stage BR by our institution, with a mean follow-up time at 3.8 years (16.4, SD: 7.3) (18) but comparable with those found 1 year postoperatively for prophylactic mastectomies with BR (26). Atisha *et al.* observed a persistent good body image for immediate breast reconstructive patients from preoperatively to 2 years postoperatively suggesting that these women seem to have been "protected" from the body image disturbances normally associated with mastectomy (27).

All patients (not lost to follow-up due patient wish or explantation) thought that BR was the right choice for them and would recommend BR to others in the same situation. This is in accordance with other studies with the same study populations (18,28). As the BR was successful for the answering patients, they are supposed to be more likely to answer in a positive way compared to those with an unsuccessful or complicated BR treatment course.

In both treatment groups an increased ratio of patients (from 12- to 24-month follow-up) reported improved health status and QoL compared to the time before BR. In the present study no baseline measurement of health status or QoL was obtained and the design of the two questions may be perceived as a then-test (baseline retrospective measurement) to capture changes in internal standards and adjust for response shift (29). The patient's assessment of an improved health state and QoL may reflect surviving a potentially life-threatening disease as breast cancer or a risk reduction. Thus, the improved QoL and general health may not be ascribed to the breast reconstructive procedure per se.

Despite limitations of this study it is strengthened by the fact that the same team of three plastic surgeons and four breast oncology surgeons performed the surgeries with standardized procedure and technique.

One-stage implant-based BR may entail advantages for the patient, but other, potentially more cost-effective, methods to obtain this has been suggested. The use of autologous dermal flaps to cover the inferior part of the implant in a similar manner than ADM, has been used for immediate one-stage BR of medium and large ptotic breasts (30) making it possibly to reduce costs compared to one-stage BR with the use of ADM (31). Although literature suggest that the risk for short-term complications is not higher than for other forms of implant-based BR, the evidence level for risk of long-term complications such as capsular contracture or PROMs and aesthetic outcome measures compared to other forms of implant-based BR is very limited (32). In 2019, Potter *et al.* found no statistically significant difference between complication rates of implant-based BR with biological mesh, dermal sling or synthetic mesh (33) and synthetic meshes might be a cost-effective alternative to ADM. It has been suggested that meshes as TiLOOP® and TIGR® Matrix Surgical Mesh are safe, in terms on complications, and without any difference in long-term health-related QoL and patient satisfaction in use for one-stage BR compared to BR with the use of biological mesh (34,35). A way to decrease the direct costs of ADM is meshing of the product. This technique has been investigated in a retrospective study by Scheflan *et al.* They found significantly shorter time to drain removal and no difference in complication rates between the two approaches with the use of meshed ADM (36).

In summary, the one-stage approach carries a shorter duration of surgery and in addition reduces the need for outpatient visits (for in average 6 times of expansion) and expander to implant exchange. In favor of the two-stage approach was reduced cost of materials due to the use of ADM in the one-stage group and fewer interventions to address the aesthetic outcome. However, pain, sensory disturbances, physical limitations, health status, QoL and body image were equally favorable between the two groups

at 2-year follow-up.

Conclusions

This study does not provide clear evidence for an advantageous use of resources by one method versus the other even though the one-stage approach makes it possible to avoid outpatient visits for expansions and thereby add value for the patients. Further studies should be undertaken to investigate the cost-effectiveness of one-stage BR with ADM or with synthetic meshes in comparison with the two-stage approach. Considering the equally good results in the two treatment groups regarding PROs the one-stage approach may be preferred if the patient is deemed suitable and is well informed of the potential need for additional interventions to obtain an aesthetically satisfying result.

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Footnote

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Review Article

Donor site morbidity associated with thoracodorsal artery flap breast reconstruction: a narrative review

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Objective: The aim of this paper is to give an overview of the available evidence on shoulder-related morbidity associated with the thoracodorsal artery (TDA) flaps when used for breast reconstruction.

Background: The pedicled TDA flaps are well described for breast reconstruction with the myocutaneous latissimus dorsi (LD) flap being the standard procedure. This flap is well described and considered a safe and reliable reconstructive method. However, use of the flap may be associated with a risk of donor site morbidity—most importantly shoulder dysfunction. Muscle sparring alternatives, including the muscle sparring LD (MS-LD) flap and the thoracodorsal artery perforator (TDAP) flap, has been introduced based on the hypothesis that these would reduce post-operative sequelae.

Methods: We conducted a review presenting the available literature on donor site morbidity after TDA flap harvest with focus on shoulder dysfunction. We found 12 papers dealing with shoulder dysfunction after breast reconstruction with the TDA flaps. Level of evidence (LOE) are highest for LD flaps and lower for the muscle sparring versions.

Conclusions: The available evidence on shoulder morbidity after breast reconstruction with the TDA flaps is scarce and has a low LOE. Furthermore, outcome measures and follow-up time are not uniform and most of the publish studies either lack a control group or simply do not compare the relevant outcomes between groups. However, there is a clear trend showing low functional impairment after reconstruction with the muscle sparring flap types.

Keywords: Breast reconstruction; latissimus dorsi flap (LD flap); thoracodorsal artery perforator flap (TDAP flap)

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Introduction

Modern breast cancer treatment is multifaceted. The main focus is curing cancer, but as the treatment modalities has developed and improved an increased scrutiny on the associated morbidity has emerged concurrently over the last decades. As a natural result the surgical procedures used for tumor removal also carry an important aesthetic aspect as well as an increased focus on the possible negative effects associated with treatment.

The continuous refinement of the abdominal flaps used for breast reconstruction has led to a shift in the surgical approach and is a good example of the evolving focus on

decreasing procedure-related morbidity—from the classical transverse rectus abdominis myocutaneous (TRAM) flap introduced by Hartrampf and colleagues in 1982, to the deep inferior epigastric perforator (DIEP) flap which today is considered a gold standard in autologous breast reconstruction (1-8). Since the introduction of the abdominal free flaps, several alternatives have been developed and introduced (9-11). This has provided a wide armamentarium of options available for autologous breast reconstruction.

However, not all patients are suited for microsurgical reconstruction. Women who have received adjuvant radiation therapy (RT) towards the chest and axilla, and who for some reason are deemed non-eligible for free flap breast reconstruction present a special challenge. RT generally contradicts the use of implant-based reconstruction unless autologous well-vascularized and non-radiated tissue is added to decrease the risk of subsequent capsular contracture and necrosis (12). In these cases, the thoracodorsal artery (TDA) flaps from the back are the workhorse flaps with the latissimus dorsi (LD) flap being the traditional choice (13).

This flap was introduced by Tansini in 1906, but remained dormant until 1977, where it was re-introduced for breast reconstruction by Schneider and colleagues (14,15). The LD flap has since been widely used for breast reconstruction and often combined with an underlying implant to gain sufficient volume (15,16). However, just like advances in the surgical techniques have facilitated a shift to the muscle-sparing versions of the abdominal flaps, alternatives to the conventional myocutaneous flap from the back have also emerged. These flaps may be classified as the TDA flaps and range from the classical LD flap over several muscle sparring versions (MS-LD) to the thoracodorsal artery perforator (TDAP) flap (15,17-23).

The different indications for using the various TDA flaps have recently been described in the literature (24). The TDAP flap represents the most muscle sparring version of TDA flaps, but like the DIEP flap harvest it is more technically demanding to dissect and harvest. The aim of this paper is to give an overview of the available evidence on shoulder-related morbidity associated with the TDA flaps when used for breast reconstruction. We present the following article in accordance with the Narrative Review reporting checklist (available at https://abs.amegroups.com/article/view/10.21037/abs-21-31/rc).

Methods

We performed a review of the existing literature based on a search in the PubMed, Scopus and Web of Science databases. The search included papers published before December 2020 and was based on either of the keywords LD or TDAP combined with the following keywords: flap, breast reconstruction, morbidity.

The results from the search were screened based on title of the paper and if deemed relevant the abstract was read for final inclusion in the review. To be included papers had to be in either English or in a Scandinavian language.

Due to a rather large and heterogenic amount of papers concerning the donor site morbidity after LD flap harvest we choses to include only reviews and meta-analysis that had already discussed the excising evidence. The number of studies describing donor site morbidity after harvest of the remaining TDA flaps was rather scarce and we chose to include all studies that described a population who had been reconstructed by any of the muscle sparring flap versions and included and included an objective assessment of donor site morbidity.

Donor site morbidity

Due to a consistent anatomy and blood supply the LD flap is considered easy to harvest and a safe choice with regard to the risk of necrosis and flap loss (13,25). Harvest does, however, come with some downsides. Raising the flap ultimately leads to release and removal of one of the largest muscles in the body. By this, function of the muscle is compromised and a large donor site defect deep to the skin is formed. These are the key points that contribute to the possible donor site morbidity and the newer versions of the TDA flaps have been developed to diminish these two factors.

Contour and animation deformities

Contour deformity on the back after removal of the muscle along with a visible donor site scar is considered undesirable by some (26,27). In addition, animation deformity of the reconstructed breast due to activation of the LD muscle relative to the pectoralis major muscle may pose both a functional and an aesthetic problem (28). One solution to this problem is transection of the thoracodorsal nerve which does, however, lead to muscle atrophy resulting in volume loss over time. However, there is no consensus about transecting the nerve or not (28-30). When applying the muscle sparing versions of the flap the cavity deep to the skin is reduced considerably alleviating the problem of

volume loss and thereby contour deformity. At the same time, the problems of animation deformity are remedied since muscle transfer is minimal.

Seroma formation

The donor site defect deep to the skin often leads to seroma formation, which can be very uncomfortable to the patient, require prolonged drainage or aspiration, and cause wound dehiscence with healing problems (31,32). Different solutions to this problem have been presented over time with quilting sutures being the most effective way of reducing prolonged seroma (33). Though a nuisance to the patient this problem is always self-limiting and will subside with time.

Shoulder dysfunction

The missing function of the LD muscle is probably what may cause the most problems (34). Although it is believed that activation of agonistic muscles over time will compensate for the lack of LD function, several studies do, however, suggest that harvest of the flap can lead to some degree of impaired shoulder function, chronic pain and discomfort. The extent and severity of any shoulder-related donor site morbidity is, however, debated and the published evidence is both scarce and ambiguous.

The conventional LD flap

Numerous papers of varying quality and with different outcome measures have investigated the possible shoulder-related donor site morbidity associated with harvest of the classical pedicled LD flap; three papers offering the highest LOE exists (35-37).

The latest of these was published by Steffenssen and colleagues in 2019 (35). This paper contains a systematic review and meta-analysis that includes 26 articles published up until May 2017. The majority of these articles deal with the conventional and the extended LD flap. Four of the articles investigated the outcome of reconstruction with the MS-LD. The review included 1,045 patients with level of evidence (LOE) ranging from II–V. The meta-analysis was based on eight articles alone-LOE II–III.

Overall, the authors found many of the published studies to be with small study populations and with great variation in terms of population, follow-up time and included parameters. The conclusion was, however, that there is a clear tendency that LD flap reconstructions can affect shoulder function, but that these limitations seem to be minimal. They found the existing literature on long-term shoulder function impairment to be insufficient to draw any conclusions and advocated further studies with higher levels of evidence and longer follow-up.

The two remaining reviews were published prior to that of Steffenssen *et al.* and include many of the same papers (36,37). Conclusions from these reviews were also that some impairment of the shoulder function can be observed after breast reconstruction with the LD flap. Furthermore, the review by Lee and colleagues found that the extended LD flap (E-LD) showed a relatively high functional morbidity whereas the MS-LD and the TDAP flap introduced minimal impairment (37).

The TDAP flap

Available evidence on donor site morbidity after harvest of the TDAP flap is very limited.

The authors of this paper published the results of a randomized clinical trial (RCT) studying the differences in shoulder dysfunction following a unilateral, delayed breast reconstruction by either the classical LD flap or the TDAP flap (38). The RCT included 40 women—18 in the LD group and 22 women in the TDAP group. The Constant Shoulder Score (CSS) that assesses pain, activity in daily life (ADL), range of motion (ROM) and strength on a combined scale ranging from 0–100 assessed by both patient-reported pain (PRP) and shoulder function.

The proportion of women reporting pain at baseline showed no difference between groups but was significantly higher for LD patients at twelve months after the reconstruction. When applying a logistic regressions model to adjust for pain at baseline, the study showed a significantly decreased risk of experiencing pain at twelve months after the breast reconstruction when reconstructed with the TDAP flap (OR =0.05, 95% CI: 0.005–0.51, P=0.011).

A significant positive impact on the shoulder function measured with CSS score was found both at 6 months (5.6 points, 95% CI: 0.1–11.0 points, P=0.047) and at 12 months (6.2 points, 95% CI: 0.5–12.0 points, P=0.033).

Sub-score analysis showed that the TDAP flap seems to have a significant positive effect on pain and ADL after one year, while there is no significant impact on ROM and strength. The same effect is found at six months after the surgery. At three months, only ADL showed a significant

difference.

A retrospective cohort study including 49 women reconstructed by either the LD or TDAP flaps were published by the same group in 2018 (39). Again the CSS was used for assessment of shoulder function. Comparing LD-reconstructed to TDAP-reconstructed women, a significant reduction in overall shoulder function on the reconstructed side was found, with a mean difference in CSS score of 10.9 points (95% CI: 2.6–19.2 points, P=0.01). There was no difference on the non-reconstructed side. Mean follow-up for these study women was 33.7 months for the LD group and 26.6 for the TDAP group.

Comparison of the reconstructed and non-reconstructed side within each group also showed a highly significant difference for LD patients with a mean of 15.5 points (95% CI: 8.3–22.7 points, P=0.0001). In comparison, the same analysis for the TDAP patients showed a non-significant difference of 4.7 points (95% CI: −2.7 to 12.1 points, P=0.208).

Sub-score analysis was performed for the reconstructed side only. It showed that both pain and range of motion differed significantly between the two groups: Pain score by 3.2 points (95% CI: 1.2–5.2 points, P=0.003) and ROM score by 5.5 points (95% CI: 1.3–9.7 points, P=0.011). Both showed an advantage to the TDAP flap. ADL and strength did not differ significantly (39).

A study conducted by Hamdi and colleagues was published in 2008 as a retrospective cohort study (40). It included 22 patients who had partial breast reconstruction with a pedicled TDAP flap over a two-year period. The mean follow-up time from the reconstructive surgery was 19.4 months, and patients were assessed clinically evaluating LD muscle strength, shoulder mobility and thickness of the LD muscle. Comparison between the operated and non-operated sides was performed.

Results showed no detectable difference in muscle strength or muscle thickness when comparing the two sides. ROM was however, affected. Forward abduction was reduced in both active (range: 120–180° *vs.* 180–180°, P=0.041) and passive (range: 130–150° *vs.* 190–190°, P=0.017) motion, whereas abduction was only affected in passive motion (range: 110–145° *vs.* 180–180°, P=0.018). The remaining motions did not differ significantly and their conclusion was that donor site morbidity after TDAP flap harvest is low and acceptable.

Additionally, Lee and colleagues published a paper in 2016 also presenting a retrospective cohort analysis (41). The study included 293 patients who, over a 12-year period, had a free TDAP flap harvested for various reconstructive purposes. Shoulder function impairment was evaluated using the Quick-DASH tool that ranges from 1–100. This score is based on the patients' subjective evaluation of different disabilities of the shoulder, hand and arm with a high score indicating a high disability; a score below 10 is considered low disability. The study by Lee included 293 cases, 41 flaps (14%) were raised including a segment of LD muscle and could thus be classified as free MS-LD flaps.

Shoulder function impairment was only investigated in patients operated within the last five years of the study period. Out of the 137 possible candidates, 110 responded—the follow-up time was 37 months. Results showed that the mean disability score using Quick-DASH was 2.68 (0–18.2). In 90% of the patients, the disability score was below 10, translating to a low functional impairment of the shoulder.

One further study investigating shoulder function after harvest of the TDAP flap was published in 2018 by Elgohary and colleagues (42). This prospective study used the CSS to evaluate shoulder function before and one year after surgical treatment of hidradenitis suppurativa with resection and following closure with a pedicled TDAP flap. Though well conducted, the results cannot be used for comparison as the disease itself directly affects shoulder function and TDAP flap transfer in part is performed to gain better function. Results of the study does however show high scores for both the total CSS and sub-scores at one year after the surgery dependent on the pre-reconstructive stage of the disease.

The MS-LD flaps

Schwabegger and colleagues were the first to describe the muscle-sparing version of the LD flap in 2003 (17). Their paper presents the first eight cases in seven patients and includes a simple test of muscle strength and function compared to the non-operated side. The authors report normal conditions at two months after surgery.

Saint-Cyr and colleagues published the first retrospective series of twenty cases investigating twenty women who had a breast reconstruction with a transverse MS-LD based on the descending branch of the TDA (19). Patients underwent assessment of the functional and aesthetic outcome, including the DASH questionnaire. The mean follow-up time was 6.3 months (1.4–15.4 months). In unilateral cases (n=12), the operated and non-operated sides were compared. Neither ROM nor strength showed any significant difference between the two sides. The DASH

score showed low disability with a mean score of 7.2 for function/symptoms, 2.9 for sports/music and 4.0 for work.

In 2010, Brackley and colleagues published their prospective series of women reconstructed with a MS-LD type II combined with an implant and a fascial envelope (43). The study included 22 cases in 18 patients. DASH was used to evaluate shoulder function, however, the mean follow-up time is not specified in the paper. Though still acceptably low, the disability scores were somewhat higher than in the series presented by Saint-Cyr with a mean score of 6.4 for function/symptoms, 15.7 for sports/music and 7.8 for work.

The main drawbacks of both studies are that the LOE is low and, furthermore, there is no control group or other group to compare these findings against.

The first study including more patient groups was published by Bonomi and colleagues in 2011 (21). This retrospective study included 82 women who had LD flap-based breast reconstruction over a period of three years. Women were classified into three groups based on reconstruction with either a classic LD flap with implant (n=35), MS-LD type II with implant (n=18) or E-LD for complete autologous reconstruction of the breast (n=29). Two questionnaires were completed by the patients between four and seven months after the operation—one evaluating functional outcome and satisfaction and the DASH questionnaire. Furthermore, a functional assessment of ROM and strength was performed at six months by a physiotherapist. Oddly, the authors did not investigate differences in these outcomes between the three groups. They indicated overall low shoulder function affection with a mean disability score of 7.8 function/symptoms, 19.0 for sports/music and 11.3 for work. 88% of patients reported no change in their ability to perform hobbies/sports and 93% perceived no permanent functional impairment. Objective evaluation showed a difference of less than 10° in ROM between the operated and non-operated side in 11 patients.

The only comparative study dealing with shoulder-related donor site morbidity after MS-LD reconstruction was published in 2013 by Kim and colleagues (22). They presented a retrospective cohort study based on review of medical records, including a total of 73 women who had immediate or delayed unilateral breast reconstruction with a pedicled LD flap. 37 cases were E-LD and 36 cases were MS-LD type II, either alone (n=14), in combination with an implant (n=18) or in combination with fat grafting (n=4). Shoulder ROM had been evaluated at four weeks and six months after the surgery. Limitations of movement, defined as not being able to lift their shoulder above 90°, was found in 9/36 MS-LD patients and 28/37 E-LD patients. At six months after rehabilitation, the same was true for 0/37 MS-LD patients and 3/36 E-LD patients. The multivariate analysis that followed showed how two factors significantly increased the risk of shoulder-movement limitations, these were: E-LD flap reconstruction (OR =7.5, 95% CI: 2.2–25.0, P=0.0011; and higher age OR =0.91, 95% CI: 0.81–0.99, P=0.0488). The paper does not, however, indicate whether analysis was performed on data at four weeks or six months.

Conclusions

In summary, the available evidence on shoulder morbidity following breast reconstruction with the TDA flaps is scarce and has a low LOE. Furthermore, outcome measures and follow-up time are not uniform and most of the publish studies either lack a control group or simply do not compare the relevant outcomes between groups. The heterogeneity of the patient population and the fact that the different flap types are often used in different patient categories further complicated the matter even further. However, there is a clear trend showing low functional impairment after reconstruction with the muscle sparring flap types.

The TDA flaps could be viewed as a spectrum ranging from the extended version of the full LD at one end and the purely perforator-based propeller TDAP flap at the other end. The invasiveness of the procedure relating to flap harvest decreases through the armamentarium of different designs, as less muscle is included in the pedicle. The theoretical extent of damage to muscle function is already minimal by the MS-LD type II. One could thus expect that the donor site morbidities after MS-LD flap harvest and TDAP flap harvest are similar. The available evidence points in that direction, but further prospective studies preferably comparing LD, MS-LD and TDAP flaps is needed to draw final conclusions in this respect.

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Review Article

Alternative flaps for breast reconstruction: a narrative review on using the thigh, buttocks, and back

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Contributions: (I) Conception and design: C Zhou; (II) Administrative support: Both authors; (III) Provision of study materials or patients: Both authors; (IV) Collection and assembly of data: Both authors; (V) Data analysis and interpretation: Both authors; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

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Abstract: As the treatment of breast cancer has dramatically improved in the past decades, so have the techniques for breast reconstruction. Recent innovations in breast implants and the advent of acellular dermal matrices have expanded options for reconstructive surgeons, allowing for cosmetic results previously unattainable in selected cases. However, autologous reconstructive techniques using free flaps remain to provide results that are unparalleled in terms of durability and feel. In this narrative review, the authors share their current experience with free flaps for breast reconstruction harvested from regions other than the abdomen. These include flaps that can be harvested from the thigh, buttocks, and back regions such as upper gracilis myocutaneous flaps, the profunda artery perforator flap, the lateral thigh perforator (LTP) flap, gluteal artery perforator flaps, and the lumbar artery perforator flap. The aim of this article is to improve readers' understanding of the advantages and caveats of each flap, patient selection, and key surgical points. For those interested in learning to perform any of these flaps, a 10-step summary is provided which describes our personal technique in flap harvesting in more detail. Furthermore, knowledge gaps that exist about the clinical outcomes of each technique and future research implications are also highlighted.

Keywords: Breast reconstruction; autologous reconstruction; free flap; thigh perforator flap

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Introduction

As the management of breast cancer has dramatically improved in the past decade, so have our techniques for breast reconstruction. Recent innovations in implants and acellular dermal matrices have expanded options for reconstructive surgeons, allowing for cosmetic results previously unattainable in selected cases (1). However, autologous techniques remain to provide unparalleled results in terms of durability and feel for patients (2). Furthermore, recent refinements in technique and ancillary procedures now permit very good matching of a contralateral ptotic breast (3).

Worldwide, the deep inferior epigastric artery perforator (DIEP) flap is the most popular autologous technique used for breast reconstruction. Many patients have abundant tissue at the abdomen, are satisfied with the post-treatment improvement in donor-site contour and find the resulting abdominoplasty-like scar acceptable. However, not every patient is naturally suited for an abdomen-based free flap. With increased anatomical understanding and surgical skills, many other body regions have now become equally good or even better donor regions in selected patients.

Ever since the first studies on autologous breast reconstruction (4), clinicians have written about the reasons as to why some flaps are their first versus the second choice. Determinants include flap-specific donor-site morbidity, expected volume, flap perfusion, technical

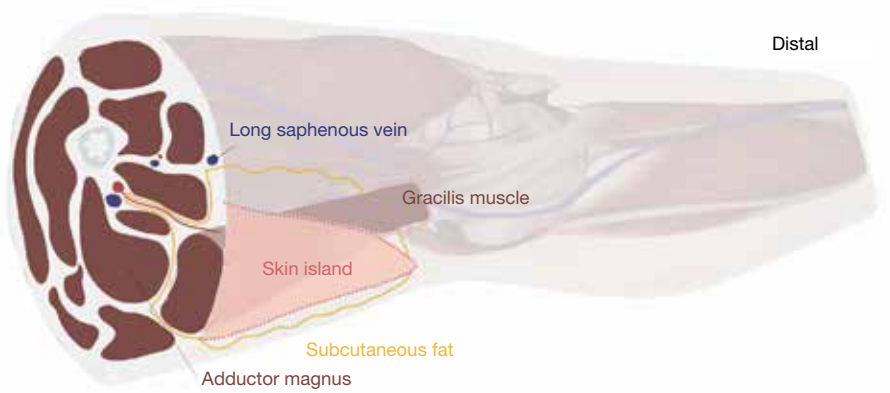

Figure 1 Flap design for the diagonal upper gracilis myocutaneous flap (medial view). Note that only the distal part of the skin island is drawn in relation to the gracilis muscle and other relevant anatomy for clarity purposes. Yellow line denotes dissection plane for additional subcutaneous fat recruitment.

complexity, flap risk profiles, and suitability for bilateral cases. Some have argued that the medial thigh flaps are the ideal "second" choice whereas others prefer the gluteal region. We believe that such discussions are of limited value since the definition of first and second choice depends on patients' habitus, preferences, previous procedures, and many other factors, thus varies from patient to patient. At our institution, an academic tertiary referral centre for autologous breast reconstruction, our vision is to provide the most complete array of autologous options to women (5-7). This includes flaps from the inner thigh, lateral thigh, the gluteal and lumbar region in addition to the abdomen (8-11). After thoroughly assessing the preferences, needs, and body type of a patient, pros and cons are discussed of each technique and a joint decision is made regarding which flap, scar locations, and the need for future additional procedures.

In this article, we provide a narrative review on current non-abdomen-based, free flaps for breast reconstruction and share our experience with these flaps. The pros and cons of each flap, patient selection, and key surgical points are highlighted. We present the following article in accordance with the Narrative Review reporting checklist (available at https://abs.amegroups.com/article/view/10.21037/abs-21-8/rc).

Methods

For this narrative review, we searched PubMed using the following main terms: autologous breast reconstruction, free flap breast reconstruction, alternative flaps for breast reconstruction. We focused on original, English articles that best described surgical technique, perioperative considerations, and outcomes, and used our own experience to complement the findings.

Flaps are grouped by body region and discussed in the following random order: medial thigh, lateral thigh, gluteal region, and lumbar region. Each section provides a short introduction followed by surgical considerations, clinical outcomes, and a future perspective.

Medial thigh I: upper gracilis myocutaneous flaps

Gracilis based myocutaneous flaps are arguably the main flaps that can be harvested from the medial thigh for breast reconstruction (12). Depending on the orientation of the skin island, a transverse upper gracilis (TUG) or a diagonal upper gracilis (DUG) flap can be designed (13). The amount of volume that can be harvested is usually somewhat limited, with reported weights varying between 150–550 grams. In 1992, the musculocutaneous perforators of the TUG were first described and mapped, which led to designing the skin island within the upper third of the gracilis to increase skin viability (14). In the following years, Arnez *et al.* and Schoeller *et al.* popularized the technique with their early successful series of TUG flaps for breast reconstruction (15,16). At our institution, we now prefer orienting the skin island diagonally, which allows for a wider skin paddle, less tension on the closure line, lower risk of damaging the lymphatics, and a better-concealed scar. *Figure 1* provides a schematic illustration of the flap

design and dissection planes.

Surgical considerations

Preoperative planning

Upper gracilis myocutaneous flaps are suited for immediate reconstruction after skin-sparing mastectomy cases. The flap may also be used in a delayed or after implant removal.

Gracilis myocutaneous flaps are based on the medial circumflexa femoral vessels, which branch off the profunda femoris. Its pedicle is on average about 8.5 cm inferior to the pubis, located at the anterior border of the gracilis (17). Pedicle length is about 6.7 cm with an average diameter for artery and vein of 2.2, 2.3 mm respectively.

We believe no preoperative angiography is required unless there is a history suggesting potential trauma to the vasculature. In such cases, CT or MR angiography is the preferred imaging modalities with pros and cons.

The medial thigh is marked with the patient standing and externally rotating the thigh to visualize the inguinal and gluteal crease. A transverse skin paddle of up to 30 cm × 10 cm is possible while a diagonal skin paddle can be even designed larger depending on the inner thigh size of the patient and resulting thigh contour (18,19). However one should be aware that in large designs, some flap edges can be poorly perfused and should be discarded. T-shaped skin paddles have also been reported. For the DUG, we mark a line near the intersection of the adductor longus and the thigh perineal crease (most cranial point) towards the medial aspect of the knee, forming the axis of the flap. A symmetrical ellipse is designed around this axis depending on where the largest volume of fat can be recruited and the final estimated scar location. A pinch test is performed to determine the anterior and posterior borders, while ideally ensuring that (I) the anterior border is medial to the femoral neurovascular bundle, (II) the posterior border does not cross the midline of the posterior thigh and (III) the final scar is not visible when standing from the anterior or posterior position. The most distal portion may be discarded if not needed of poorly perfused.

Flap harvest and transfer

Key in safe and efficient flap harvesting is to identify the gracilis muscle early and its pedicle early on. Avoid fat recruitment lateral to the mid axial line to avoid damage to the posterior cutaneous nerve of the thigh. The muscle is typically inset to form the superior pole of the breast. The relatively short pedicle lowers our threshold for partial rib resection for easier anastomosis. We usually anchor the inferior thigh skin flaps to Colles' fascia to avoid scar problems. *Table 1* describes flap harvesting in 10 steps.

Postoperative key points

Patients recover with knees and hip slightly flexed and head up. Flap monitoring, haemodynamic status, thromboembolic prophylaxis management are performed as with any other free flap breast reconstruction.

Outcomes and future perspective

Upper gracilis myocutaneous free flaps have become an established option for breast reconstruction. These flaps typically have a sufficiently long, predictable pedicle, and are relatively easy to harvest. Its consistency is somewhat similar to that of gluteal free flaps, and it lends itself very well to coning of the flap for more projection (16). Scars, depending on the design of the skin island, can be most times be concealed. They lie somewhat more anterior and superior in comparison with profunda artery-based perforator flaps which are also harvested from the medial thigh area. In comparison, additional volume may be recruited because the gracilis muscle is included.

Flap-specific complications are lymphedema, seroma, wound problems, thigh distortion, bothersome, and aesthetically displeasing scarring. Depending on the definitions used, some groups have reported very high donor-site complication rates up to 62.5% (18-21). We recommend several adjustments we made over the years to reduce such complications (20-22) (*Table 1*).

One of the largest studies of TUG flaps (n=154 flaps) to date employing the previous modifications reported wound healing rates of only 6% and all temporary sensory deficits at the donor-site in about one-third of cases, underscoring their importance (19). Labial spreading is a very rare but serious complication we have not seen ourselves. Finally, it is worth mentioning that the skin of the medial thigh is relatively darker, which can sometimes contrast the lighter native chest skin in delayed cases.

Ancillary procedures that may broaden indications of the upper gracilis myocutaneous flaps for breast reconstruction are similar to those for other free flap options: lipofilling, adding another free flap, and adding an implant to increase volume. Secondary procedures at a later stage include liposuction, lipofilling, skin and scar refinement, fat necrosis excision, contralateral mastopexy/reduction.

One important gap in knowledge that remains in gracilis

Table 1 Ten steps in harvesting myocutaneous gracilis based flaps for breast reconstruction

Step	Description
1	Raise flap using an anterior to posterior approach
2	Dissect through subcutaneous tissue until medial thigh muscles are seen. Usually bevel for more volume. When encountered, preserve the long saphenous vein and preserve femoral triangle lymphatics
3	Continue flap dissection along anterior border, and identify gracilis muscle
	Dissect through thigh fascia, along the gracilis muscle anteriorly until circumflexa femoral branch(s) to the gracilis are seen
4	Reflect fascia and adductor longus muscle medially to further dissect out gracilis vascular pedicle
5	Dissect out pedicle towards origin off the profunda femoris. Clip branches to adductor if needed. Further raise flap in suprafascial plane
6	Raise posterior part of flap, including all the fat above the semitendinosus semimembranosus muscles
7	Dissect underneath gracilis muscle below the skin island, continue more distally in a suprafascial plane towards the knee until required flap volume is met
	Clip minor gracilis pedicles if encountered
8	To fully raise the flap, transect distal gracilis muscle distally and proximally
9	If the flap appears venously congested after raising, position the skin island back to its original position and let it rest to prevent undue tension on the pedicle
10	If ready for transfer, detach the fully elevated flap by clipping the artery and two concomitant veins just distal from their runoff with scissors

based breast reconstructions is flap volume retention over time. It seems reasonable to assume that some muscle atrophy may occur, resulting in loss in original flap volume. Anecdotal evidence and our personal experience suggest this is minimal. However, lack of strong evidence precludes reporting of objective retention outcomes here. Patients should be made aware of this. Nonetheless, gracilis myocutaneous flaps provide natural and pleasing results and we believe that this uncertainty should not preclude women from choosing this option if no other alternatives are available.

Medial thigh II: profunda artery perforator flap

As it is also harvested from the medial thigh, the profunda artery perforator flap is related to upper gracilis based myocutaneous flaps. In comparison with TUG flaps, however, scars lie more posterior and inferior and no muscle is harvested. Moreover, the profunda artery perforator (PAP) flap is a true perforator flap which makes dissection slightly more tedious in our experience. Nevertheless, many women have an unequal fat distribution in the upper medial thigh, on which the decision between a PAP versus gracilis based flap should be based.

The PAP flap builds on previous knowledge on profunda artery-based flaps which had been primarily used for pressure sores and burns (23,24) and uses principles in upper medial thigh lifting. In 2012, Allen *et al.* expanded on this knowledge and reported on the use of a flap based on the first or second vessels running off the profunda femoris artery that pierced the adductor magnus for breast reconstruction (25). Since then the PAP flap has become a popular flap for patients with small to moderate sized breasts, sufficient posteromedial thigh volume, and an insufficient abdomen.

Although there are typically 3–4 perforating arteries originating from the profunda femoris, the dominant perforator for the PAP is consistently found posterior to the gracilis. The most common location is on approximately 5 cm below the gluteal fold and 3.8 cm from the midline (26). The second most common location is 5 cm below the gluteal fold but about 12 cm from the midline near biceps femoris and vastus lateralis, demonstrating a medial and lateral distribution of the perforators.

Figure 2 Flap design for the profunda artery perforator flap (posterior view). Note that only the posterior part of the elliptical skin island is drawn. The superior margin is at or just below the gluteal crease. Inferior margin depends on skin pinch test, typically measuring about 6–7 cm. Skin island orientation is shown in relation to adductor magnus muscle and other relevant anatomy.

Surgical considerations

Preoperative planning

In contrast to gracilis based flaps, we do recommend angiography of the pelvis and lower extremity for PAP flaps to aid in surgical planning. Preoperatively, we note the location at which perforators exit the deep muscular fascia relative to the gluteal fold, the posterior gracilis border and the adjacent muscles. We mark patients standing with an elliptical incision, medially bordered by the adductor longus running laterally along the lateral border of the gluteal fold. Superior border is about 1 cm below the gluteal fold. Inferior border is typically 6, at most 7 cm, below the superior border depending on skin pinch. This is paramount in minimizing wound related problems due to too high tension. Length of the flap varies widely and should also take into account donor-site contour. *Figure 2* shows the skin island design.

Flap harvest and transfer

The procedure is done in supine position with legs in frog-leg position. Key point in effective PAP flap harvesting is careful preoperative planning using imaging and markings. Also be aware of variations in perforator anatomy, and that the dominant perforator runs caudally within the adductor magnus. Furthermore, dissection is often in a tunnel so control of posterior and side-branches is paramount. If the key adductor magnus perforator is not located, a perforator off the descending branch of the inferior gluteal artery can be used. *Table 2* describes each step in PAP flap harvesting in more detail. When raising the flap, we avoid overly aggressive bevelling to avoid postoperative discomfort with sitting on hard surfaces. We routinely use a rib-sparing approach although do not hesitate to resect a rib as needed.

Postoperative key points

Patients are instructed to start sitting on the first postop day and ambulating. Discharge occurs typically at day 4 or 5. Flap monitoring, hemodynamic status, thromboembolic prophylaxis is managed as any other free flap breast reconstruction.

Outcomes and future direction

PAP flaps can deliver great breast reconstruction results in selected patients, with very low failure rates. Compared with gracilis based flaps, it usually has a longer pedicle, and no muscle harvest is required. Projection is easily achieved because the design of the flap allows for great coning. Average flap weights of around 400 grams can be achieved with judicious bevelling, making the flap particularly suited for small to moderate sized breasted patients. Scars are well-hidden and not bothersome particularly if the flap is well designed.

The main disadvantages of the PAP flap relate to the donor site, including wound healing problems, and surgical site infections occurring in 3.6% and 8.2% of cases respectively (27,28). Patients also can report sitting transient discomfort up to 3 months. One of the largest studies to date has reported no lymphedema occurrences following flap harvest. Since it's the first report of its use, the PAP flap has proved to be a great, reliable, and safe option for autologous breast reconstruction. Nonetheless, we feel that few reconstructive microsurgeons consider this flap routinely. We, therefore, believe great opportunity lies with increasing

Table 2 Ten steps in harvesting profunda artery perforator flaps for breast reconstruction

Step	Description
1	Raise flap using a medial to lateral approach
2	Incise at medial tip of the flap first, which is near the groin lymphatics and usually overlies the adductor longus muscle
3	Develop flap towards lateral. Do not bevel superiorly. Bevel inferiorly as needed. Identify gracilis muscle, open fascia in the direction of the fascia fibers at posterolateral portion, and dissection further
4	Retract gracilis anteriorly, identify and dissect through adductor magnus fascia and muscle
5	Proceed subfascial dissection posteriolaterally until perforator is found
6	Continue intramuscular perforator dissection to origin on profunda femoral artery
7	Reposition retractors regularly, and create sufficient exposure. If loose areolar plane behind adductor muscle is reached, pedicle length may be sufficient and dissection may be sufficient in some cases
8	Posterior, suprafascial dissection, flap detachment
9	Perform microsurgical anastomosis
10	Perform flap shaping or coning, inset, and pocket contouring as needed

the awareness about the versatility of this flap both for breast reconstruction and other indications (29).

Gluteal region: superior gluteal artery perforator (SGAP) flap

The first report of using the gluteal region for breast reconstruction was by Fujino *et al.* in 1975 who used a gluteal myocutaneous flap (30). However, despite large initial interest in this flap, it fell out of favour due to the risk of sciatic nerve injury and technical difficulties associated with flap harvest. It was only after the concept of perforator flaps became well-established that the gluteal artery perforator (GAP) flaps made their re-entry (31-33).

Thin patients seeking autologous reconstruction who accept scars and deformity in the gluteal region are potential candidates. We avoid gluteal artery perforator flaps in the severely obese because the bulk of the flap to pedicle ratio increases. In comparison to other non-abdominal donor sites such as the medial thigh, the gluteal region usually allows for a larger volume harvested. It should be noted that the short pedicle length of the perforator and its size mismatch with recipient vessels can be demanding. Below we describe the SGAP flap. Despite having a shorter pedicle than the inferior gluteal artery perforator (IGAP) flap, we prefer the SGAP because it allows for the entire procedure to be done in supine position in selected cases using the modifications previously published by our group (5).

Surgical considerations

Preoperative planning

Although gluteal perforators are very consistent, we routinely perform contrast angiography for efficiency purposes. Markings are done with the patient in standing and/or prone position using a doppler device. Axis of the flap is slightly oblique or more horizontally oriented. Flap width is usually between 8–12 cm. We mark an elliptical incision, with the medial border usually slightly higher than the mid-gluteal crease. *Figure 3* shows the skin island design.

The superior gluteal artery (SGA) is the largest branch of the internal iliac artery. It exits the pelvis through sciatic foramen above piriformis and inferior to gluteus medius. This exit point is at the junction of the proximal and middle thirds connecting the posterior superior iliac spine (PSIS) to the apex of the greater trochanter. Alternatively, this point is about 6 cm from PSIS, and 4.5 cm lateral to the mid-sacrum. Once the SGA leaves the pelvis, it divides into a superficial and deep branch. The superficial branches that enter below and perforate the gluteus maximus muscle towards the skin are typically dissected in the classical SGA perforator flap. However, if present, we select the septocutaneous perforators that run with the gluteus medius fascia at the superolateral edge of the gluteus maximus (5). This allows harvesting the flap completely in supine position. On average, SGAPs have a pedicle length of 9.8 cm, run intramuscularly for 5.3 cm and a diameter

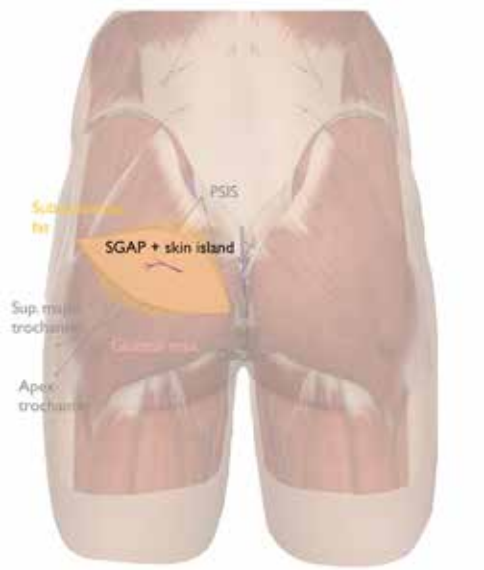

Figure 3 Flap design for the SGAP flap (posterior view). Note that three grey lines are drawn. The point where the SGA exits between piriformis and gluteus medius is about 6 cm from the PSIS and 4.5 cm lateral to the sacral midline. This is at about where the divide is of the proximal third and middle third of the most superior line running from PSIS to the apex of the trochanter. PSIS, posterior superior iliac spine; SGAP, superior gluteal artery perforator.

ranging from 0.9–1.5 mm, which is small in comparison with the medial thigh flaps (34).

Flap harvest and transfer

Key point in effective SGAP flap harvesting is centering the flap over identified perforators, initial suprafascial and later subfascial dissection after the periperforator area is encountered, and meticulous dissection when encountering the subgluteal fat plane for additional length and prevention of deep bleeding. Patients are typically positioned in lateral decubitus for unilateral cases and while a supine-prone-supine sequence is required in bilateral reconstruction. *Table 3* describes the steps in more detail. However, as previously described, the procedure can be done completely in supine position in selected cases.

Postoperative key points

Patients are instructed to start ambulating on postop day 2. Discharge occurs typically at day 4 or 5. Flap monitoring, hemodynamic status, thromboembolic prophylaxis is done as any other free flap breast reconstruction.

Outcomes and future perspective

When used judiciously, SGAP flaps provide aesthetically very pleasing results (35). Gluteal fat is typically firmer than natural breast parenchyma due to a developed reticular system. This allows for great projection but shaping can be more difficult as the tissue is less pliable.

Despite advances in our anatomical understanding and surgical skills, gluteal perforator flaps remain one of the most challenging free flaps with reported flap failure rates up to 8% even in the most experienced hands (33,35). Wound problems may be seen up to 6% of cases, and seroma in as many as 13.5%. A recent observational study found that patients undergoing SGAP reconstruction were less satisfied than those receiving a DIEP flap, concluding that we may have underestimated the donor site morbidity of the SGAP flap (36). The authors reported that the lumbar flap has therefore replaced the SGAP in their practice, while we still routinely perform both in our own. Depending on patient preference and their condition, we do perform one-stage bilateral SGAP reconstructions in suitable cases.

One direction for future studies is to compare the classical method of harvesting SGAP with raising the flap on its septocutaneous perforators, which prevents cumbersome and risky positional changes during surgery. These studies should focus on procedural outcomes such as operative time and donor site related outcomes as we feel that this modification allows more favourable placement the scar.

Lateral thigh: the lateral thigh perforator (LTP) flap

The lateral thigh was introduced as a donor site region for breast reconstruction in 1990 with the musculocutaneous tensor fascia lata free flap (37). In the following years, a variation of this flap without muscle or fascia was popularized as the LTP flap for breast reconstruction (38). Increased understanding regarding perforator anatomy has led us to favour selecting the septocutaneous vessels that run in the posterior septum when possible (5,39). We routinely consider the LTP flap in women with minimal abdominal but abundant upper lateral thigh volume who can accept a scar in this region.

Surgical considerations

Preoperative planning

The lateral femoral circumflex artery forms the basis

Table 3 Ten steps in harvesting superior gluteal artery perforator flaps for breast reconstruction

Step	Description
1	Make incision first superiorly, inferiorly, and laterally. If desired, identify cluneal nerves at superior border and include them for sensate reconstruction
2	Typically, bevel away from flap marking for better contour of the flap and additional volume recruitment
3	Raise flap from a lateral to medial fashion, suprafascially
4	Dissect more medially above gluteus maximus until area of superior gluteal artery perforators is reached
5	Incise fascia in the direction of the fibers at this point for subfascial dissection for better visualisation of perforators [1–3]
6	Reposition retractors regularly, and create sufficient exposure
	Split gluteus muscle in the muscle fiber direction as much as possible
7	Open posterior fascia of the gluteus maximum, expose subgluteal fatpad, place retractors in gluteus medius and/or piriformis muscles when encountered for more exposure
8	Slow down in pedicle dissection, and carefully manage often encountered combinations of intricate small and larger vascular branches
9	If needed, maximize pedicle length but consider that (I) dissection in the subgluteal fat can only provide 2–3 cm additional length, and that (II) the deepest part of the pedicle lies along periosteum of the pelvis which makes it susceptible to difficult bleeding
10	Once the perforator is fully dissected towards the superior gluteal artery, the remainder of the medial incision can be completed, and the flap is isolated
	In closure of the donor site, avoid undermining over greater trochanter and iliac crest

of all variants of the LTP flap. Its septocutaneous perforators are more constant and larger than the musculocutaneous perforators. Average length of the septocutaneous perforators is about 7–8 cm (40). Although the septocutaneous perforators located in the posterior septum between the TFL and gluteus medius muscles are predictable and relatively easy to dissect, the pedicle may be relatively short with typically a small artery and friable vein. *Figure 4* and *Figure 5* show the skin island design and perforator identification, respectively.

Flap harvest and transfer

Key point in effective LTP flap harvesting are accurate preoperative markings. Anterior border of the flap is determined by a line that runs from anterior superior iliac spine (ASIS) to the superolateral patella. Then a horizontal line is marked parallel to the top edge of the symphysis pubis which the height at which most perforators can be found. Further estimation of exact perforator location is based on angiography measurements of distances between the perforators and the ASIS and single endplates penetrating screw (SEPS). Once located, we then design a horizontal elliptical flap which may be designed with either an upward or downward slant towards posterior depending on the fat distribution. Pinch test is used to confirm the markings. *Table 4* details each step.

Postoperative key points

Patients may mobilise on postop day 2–3. Flap monitoring and drains are managed as standard.

Outcomes and future perspective

LTP flaps can be used to achieve very pleasing results, are reliable and offer low failure rates in experienced hands (41). The lateral thigh fat is somewhat firmer than abdominal fat, yet more supple compared to gluteal fat. This firmness allows for good projection to be achieved. With proper patient counselling and selection, the majority of patients find the postoperative scars at the lateral upper thigh very acceptable. Another advantage is, as compared with lumbar or gluteal flaps, no positional change is required, and no interposition grafts are required in spite of the relatively short pedicle. Lastly, we also consider the relative ease of dissection of the septocutaneous perforators a major advantage.

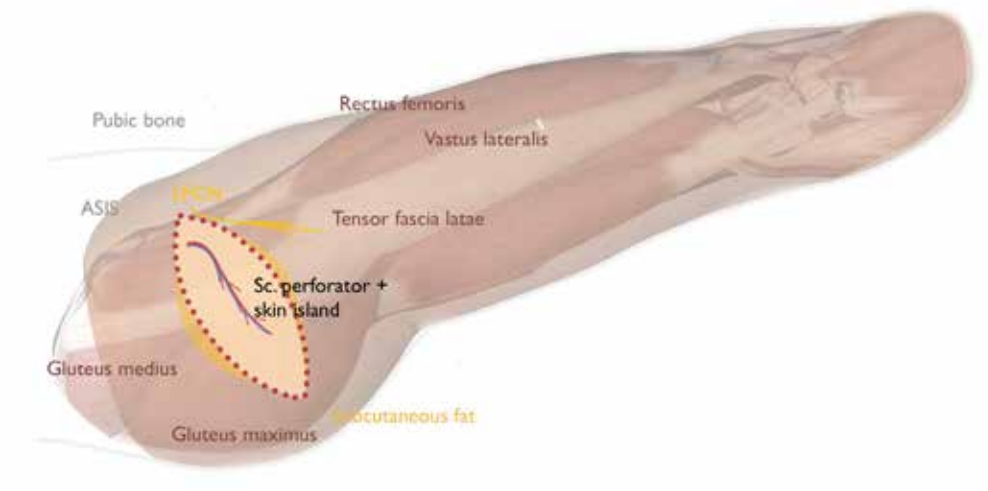

Figure 4 Flap design for the lateral thigh perforator flap (medial view). Note that the LFCN is at risk when raising the flap anteriorly. The Sc. perforator of the lateral circumflexa femoral artery runs between the tensor fascia lata and gluteus medius muscles. ASIS, anterior superior iliac spine; LFCN, lateral femoral cutaneous nerve; Sc., septocutaneous.

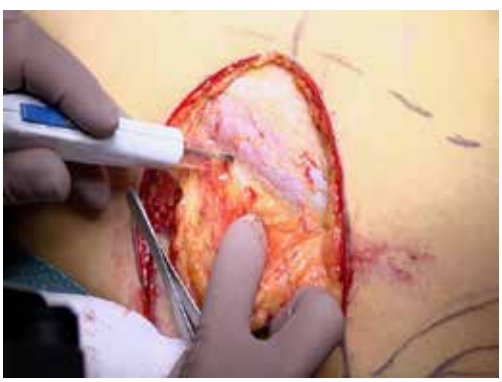

Figure 5 Flap dissection over TFL fascia and perforator identification for the lateral thigh perforator flap. Usually, the contrasting thick and white color of the gluteus medius fascia in comparison to the thinner TFL fascia marks the location of the posterior septum. TFL, tensor fascia lata.

Although we have seen transient numbness in the lateral thigh region, this can be avoided by preserving the lateral femoral cutaneous nerve in most cases. In our experience donor site complaints are fewer and less severe than those of medially based thigh flaps such as the PAP or TUG or gluteal flaps. Secondary corrections such as liposuction or fat grafting both at the breast and donor site are often required to optimize contour and volume. If one LTP flap produces too little volume, two flaps may be stacked to achieve satisfactory volume (42). Bilateral cases can be done in a single stage with relative ease.

As present, we feel that the LTP is somewhat under-recognized as an attractive autologous option for breast reconstruction. Future comparative studies are needed to test the abovementioned advantages in comparison with other non-abdomen-based flaps. We feel that such evidence is needed to increase awareness for this flap, which ultimately may translate into more options for those who lack a suitable abdominal donor site.

Lumbar region: the lumbar artery perforator flap

Before the first report on a lumbar artery perforator flap for breast reconstruction by de Weerd *et al.* in 2003, flaps from the lumbar region were mostly used as pedicled musculocutaneous or fasciocutaneous flaps to treat pressure sores or other defects in this region (43). From early studies on these pedicled flaps, its short pedicle length of about 4 cm became known (44). Since 2003, the free LAP flap has gradually gained popularity, mostly in expert microsurgical centers (45).

Thin patients who have insufficient abdominal tissue and can accept a scar in the lumbar region are potential candidates. Scars usually lie outside the underwear area and, when appropriately placed, allow for aesthetic contouring the flank. In unilateral cases, liposuction is often needed to symmetrize the flanks. Lumbar fat is usually firmer than that from the abdomen but more

Table 4 Ten steps of harvesting lateral thigh perforator flaps for breast reconstruction

Step	Description
1	Raise flaps from anterior tot posterior, dissecting suprafascially over the TFL
2	Preserve lateral femoral cutaneous nerve when encountered, and other cutaneous nerves if possible
3	Continue dissection until the TFL-gluteus medius posterior septum is encountered
4	Divide musculocutaneous perforators of the TFL unless angiography suggests otherwise
5	Identify (septocutaneous) perforator(s) of interest
6	Discontinue further posterior dissection to prevent tension
7	Access posterior septum by incising the TFL fascia
8	Retract TFL, rectus femoris, and Sartorius muscles for sufficient exposure of pedicel dissection
9	Dissect pedicle towards origin of LCFA, although sufficient length is typically achieved before this is reached
10	Close donor site using progressive tension quilting sutures and limited undermining

TFL, tensor fascia lata; LCFA, lateral circumflex femoral artery.

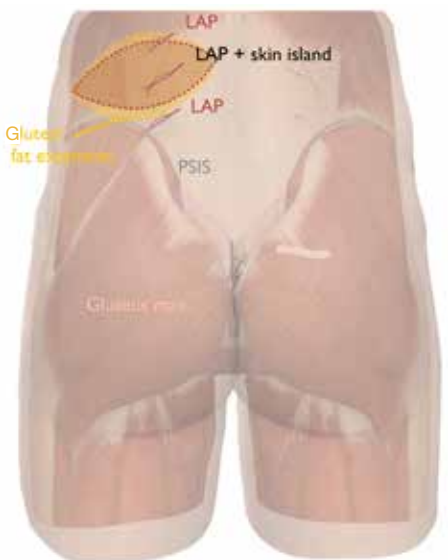

Figure 6 Flap design for the lumbar artery perforator flap (posterior view). Note that multiple lumbar artery perforators are drawn and may be encountered. Only a single perforator is sufficient to raise the flap on. If more volume is required, one can undermine aggressively towards the gluteal region for a "gluteal fat extension" of the flap. LAP, lumbar artery perforator; PSIS, posterior superior iliac spine.

pliable and softer than gluteal fat. We believe that this resembles the feel of breast parenchyma very well. While the possibility for flank contouring and intrinsic tissue feel are clear advantages of the LAP flap, these need to be balanced against the advanced surgical skills required for this flap due to the short pedicle, small perforator diameter, and the need for a vascular interposition graft.

Surgical considerations

Preoperative planning

We perform contrast angiography routinely to assess the position and configuration of the lumbar artery perforators. For bilateral cases, we typically stage the reconstruction with a minimum of 3 months between each side.

Markings are done with the patient in standing position using a doppler device. *Figure 6* shows flap orientation. Perforators are sought and confirmed with doppler with the midline and iliac crest as landmarks. Axis of the flap is slightly oblique oriented. Dominant skin perforators originate from lumbar arteries at the 3rd or 4th vertebra. The maximum skin resection is determined per pinch testing. A gluteal extension is considered for extra volume recruitment. We follow a supine-prone-supine positional sequence.

Flap harvest and transfer

Key point in harvesting LAP flaps include orienting the skin markings based on key landmarks and preparing the surgical team members to ensure efficient, twice repositioning of the patient. We routinely perform the procedure with two teams. *Table 5* describes each step in more detail. As mentioned, the pedicle is typically very short and has a size mismatch with the acceptor vessels. As such, we recommend

Table 5 Ten steps of harvesting lumbar artery perforator flap for breast reconstruction

Step	Description
1	Prepare the operative team for a supine-prone-supine operative sequence
2	Consider a two team approach: the primary surgeon harvesting the composite interposition graft (usually deep inferior epigastric artery and vein harvested as standard), the secondary surgeon starting at the thorax
3	Typically, we plan for ipsilateral harvest. Check skin resection using pinch test, raise flaps from medial to lateral with surgeon standing on the opposite side
4	Bevel caudally to include more gluteal fat for better contour and more upper pole fullness if needed
5	Identify lumbar artery perforators which usually arise from the interval between erector spinae muscles and quadratus lumborum. Note: these perforators are more tightly encased by the fascias so identification is more difficult than other free flaps
6	Once perforator(s) are identified, open surrounding fascias, and complete perforator dissection between or through the muscles. If the pedicle is small or friable, we will harvest it along with a cuff of fascia. As an interpositional graft is typically used, do not pursue maximum perforator length to prevent nerve root injury and difficult deep dissection at the transverse process
7	Perform anastomosis (primary team) between the cranial, smaller caliber end of the interpositional graft to the lumbar artery perforator on a separate table
8	During donor site closure, the other team performs multilayer closure of donor site using quilting sutures, drains, and a vest over pants technique as indicated to prevent high risk of seroma
9	After repositioning the patient to supine position, the second anastomosis between the caudal, larger caliber end of the interpositional graft and the recipient vessels are done as standard
10	Further flap inset and shaping is done, which is only required in a limited amount of cases

using a composite vascular interposition graft such the deep inferior epigastric artery and vein if still available. In tertiary cases, the surgeon can often times harvest the graft through an existing abdominal scar from a previously failed reconstruction.

Outcomes and future direction

LAP flaps can mimic breast greatly because lumbar fat provides an ideal combination of pliability, projection, and firmness that resembles breast parenchyma. However, as mentioned above, its relatively short pedicle and vessel calibre mismatch make it technically a very demanding flap. Opsomer *et al.* have reported a revision rate of 22% and a 9% flap failure rate using this approach in one of the largest series to date (45). Although acceptable, these numbers mandate that we believe a lumbar flap should not be used if the abdomen is suited as a donor site. At our centre, we have used the LAP flap primarily in tertiary cases.

Although great results may be achieved with LAP flaps, surgeons should be aware of several flap-specific outcomes and donor site problems that can occur. Flank seroma is notorious after LAP flaps, which may be minimized through quilting sutures. Furthermore, donor-site pain seems to occur more frequently than with other free flaps, which we aim to minimize through limited undermining of the flanks for closure and timely discontinuation of pedicle dissection once the transverse process of the vertebra is reached. A recent comparative study has reported lower absolute BREAST-Q subdomain scores for donor site well-being and donor site appearance after lumbar flaps as compared with DIEP and SGAP donor sites, suggesting that patients may weigh more heavily on such donor site problems than previously thought (36). With proper patient selection and design, on average, the number of secondary corrections is similar to other flaps such as the DIEP (46). Moreover, LAP flaps can be made sensate by including the superior cluneate nerves. Lastly, although one-stage bilateral breast reconstruction with LAP flaps can be done, the risks of a very long procedure need to be weighed against the disadvantage of having to undergo a second procedure. We recommended to stage bilateral cases with at least 3 months in between the two procedures rather than doing two LAP flaps in one stage. However, with expected improvements in microsurgical techniques in the future, we hope one day to achieve similarly flap success rates with these flaps as with the previously mentioned other free flaps.

General discussion

To date, many surgeons counsel women who seek breast reconstruction yet lack sufficient abdominal tissue for a DIEP flap towards implant-based reconstructions. This article aimed to share a current perspective on flaps that can be harvested from body regions other than the abdomen, such as the upper thigh, gluteal and lumbar regions. For those interested in learning to perform any of these flaps, a 10-step summary is provided describing our technique in flap harvesting in more detail. Furthermore, key findings of influential studies were discussed to highlight the flap-specific advantages and caveats.

With appropriate patient selection, preoperative preparations, and surgical technique all flaps discussed in this article may be used to reconstruct an aesthetically pleasing breast mound (2). Nonetheless, each technique has unique trade-offs. For example, gracilis based myocutaneous flaps are harvested with relative ease and allow for medial thigh contouring (13). However, the extent to which these flaps lose volume over time remains uncertain. In comparison, gluteal artery perforator flaps typically provide greater volume and easier projection but are technically more demanding due to shorter and smaller sized pedicle (35). For some patients, the lumbar artery perforator flap may be the right or even only choice, which allows for a completely hidden scar from a frontal view among other advantages (43,45). However, patients should be made aware that this flap confers the highest flap failure rate because it is technically very demanding even for the most adept microsurgeons. As such, we believe that lumbar flaps are most suited for tertiary cases. The surgeon specializing in autologous reconstruction needs to understand all these flaps and techniques in order to counsel patients to the one best suited to their preferences, habitus, and goals. That said, we acknowledge that it requires years of focused practice to become adept at all of them. We therefore advocate the philosophy where patients should be referred either internally or extramurally to the colleague known to be most skilled at performing a specific technique.

A limitation of the current narrative review is selection bias; it is likely that personal preference has led to inclusion of certain flaps other experienced surgeons would have chosen differently. For example, we are aware that some surgeons favour the IGAP flap over the SGAP because it has a slightly longer pedicle or rarely use the LTP of its impact on the donor site (31). However, this review was intended from the outset as a discussion of different techniques incorporating personal perspectives that were gained through years of microsurgical experience. Nonetheless, to facilitate an objective discussion of the outcomes of each technique, we included key findings from current literature. A second limitation is the lack of randomized trials comparing two or more reconstructive techniques. For example, one may question the validity of comparing the much higher flap failure rate of the lumbar artery perforator flap if these are primarily done in tertiary cases whereas studies examining the other flaps were done in less complex cases. Randomisation would have eliminated this confounding by indication bias, resulting in a more valid comparison. Nonetheless, we are all aware of the practical and ethical issues associated with randomisation at an individual patient level. This is particularly the case in breast reconstruction science as no single patient is exactly the same concerning her preferences and habitus. Future investigators might consider adopting a clustered randomised trial design instead, in which the unit of randomisation is at an institutional level rather than the individual patient (i.e., surgeons or practices that focus on DIEP flaps versus those who perform other flaps) (47,48).

Conclusions

In the past decades, few subfields in plastic surgery have seen the advancements as large as in autologous breast reconstruction. New flaps have been pioneered while old techniques have been refined to the point where we now strive for aesthetic outcomes that parallel those of cosmetic breast and body contouring surgery. As shown in this article, one can harvest regions other than the abdomen to reconstruct natural breasts with acceptable risk, including the thigh, buttocks and back. We are confident that many advancements in design and surgical technique remain to follow, which makes autologous breast reconstruction a hugely exciting field. It is our sincere hope that articles such as the present one will (I) inspire both patients and surgeons to look beyond the abdomen when discussing breast reconstruction and (II) accelerate the learning process for the future generation of reconstructive surgeons in performing these flaps.

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Footnote

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Review Article

Immediate or delayed breast reconstruction: the aspects of timing, a narrative review

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Objective: The objective of this study is to discuss the timing of immediate and delayed breast reconstruction.

Background: The evolution of conservative mastectomy surgical techniques and the introduction of acellular dermal matrix (ADM) have paved the road for the increased popularity of immediate reconstruction, and this also includes use of autologous tissue. Immediate reconstruction holds several benefits, the most important being superior aesthetic outcomes and improved levels of psychosocial wellbeing post-mastectomy. Both immediate and delayed breast reconstruction has been found to be oncologically safe, although high-quality studies are still lacking. Potential delay in adjuvant treatment is a significant concern amongst medical and surgical oncologists, and in addition, a few studies have examined complications in cancer surgery and found negative association with the oncological outcome.

Methods: Narrative literature review and presentation of the authors practice.

Conclusions: Careful patient selection, especially in case of invasive breast cancer is very important. Absolute contraindications for immediate reconstruction include a diagnosis of locally advanced breast cancer or inflammatory breast cancer or active infection in the breast area. Relative contraindications to be carefully considered to keep the risk of complications at a minimum and thus the risk of delaying the adjuvant therapy is: smoking, high BMI, and comorbidities and need of postoperative radiation therapy. Delayed reconstruction should be considered for patients with pressing medical comorbidities, obesity, smoking, inflammatory breast cancer, and for patients distressed regarding their breast cancer diagnosis who are not ready to make treatment decisions. The authors prefer immediate reconstruction if feasible, but it should be remembered that delayed breast reconstruction has been found not to compromise patient-reported outcomes in the long-term. Therefore, the timing and technique of reconstruction should be decided on a case-by-case basis after a thorough discussion with the patient and preferably also in multidisciplinary meetings.

Keywords: Breast reconstruction; relative contraindications for breast reconstruction; complications in immediate breast reconstruction; timing of breast reconstruction

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Introduction

Aside from non-melanoma skin cancers, breast cancer is the most common malignancy affecting women worldwide (1). The last few decades have seen a growth in the number of both immediate and delayed breast reconstruction following mastectomy as breast reconstruction becomes more sought after (2-4). In the United States, the Women's Health and Cancer Rights Act of 1998 compelled payers to provide benefits for mastectomy-related services, including all reconstruction stages and procedures for symmetry (2). These procedures are also covered in tax-funded healthcare systems.

Bilateral mastectomies have become increasingly common, as a risk reduction procedure, often asked by patients (2). As subsequent breast reconstructions also become more popular, choosing when and how to reconstruct the breasts is exceedingly more nuanced. The present study reviews considerations of the aspects of timing when planning breast reconstruction.

Conservative mastectomy, with preservation of the entire skin envelope or nipple sparing procedure, has gained acceptance in recent years, given evidence of comparable prognosis compared to total mastectomy (5-7). Skin preservation allows for optimized reconstructive outcomes by recreating or enhancing breast volume, lower pole contour, symmetry, and appearance (8). By preserving the breast skin envelope, the skin-sparing mastectomy allows for immediate reconstruction closely matched to the preoperative breast's size and shape (9). We present the following article in accordance with the Narrative Review reporting checklist (available at https://abs.amegroups.com/article/view/10.21037/abs-21-44/rc).

Reconstruction options

Breast reconstruction options can be either implant-based or autologous. Implant-based breast reconstruction (IBBR) accounts for approximately 80% of breast reconstructions in the United States, most of which are performed immediately following mastectomy (3,4). IBBR can be completed in either one or two stages following mastectomy. The advent of reconstruction with acellular dermal matrix (ADM) allowed the surgeon to create a breast in one stage immediately. An ideal candidate for single-stage, or direct-to-implant (DTI), reconstruction is a patient undergoing skin-sparing, nipple-sparing mastectomy with small to medium breast size, grade 1 or 2 ptosis, and favorable skin quality (10). Two-stage reconstruction is achieved with tissue expanders that are exchanged for implants at a later date. In the setting of immediate reconstruction with questionable perfusion to the mastectomy skin flaps, placement of a tissue expander that is partially filled may protect the skin flaps from tension (11). Surgeons began ADM utilization in 2001 to provide coverage for either implants or tissue expanders in breast reconstruction (12). The original description was a submuscular placement of the implant with lower pole ADM supporting the device and obviating the need for tissue expansion. ADM was used to extend the submuscular plane, support the implant in an anatomic position, and define the inferior and lateral breast folds (10).

Autologous breast reconstruction can be achieved with abdominal tissue- pedicled transverse rectus abdominis myocutaneous (TRAM) flap, or most commonly today with perforator microsurgical tissue transfer (free TRAM flap, muscle-sparing TRAM flap, deep inferior epigastric perforator (DIEP) flap, superficial inferior epigastric artery (SIEA) flap- and with non-abdominal tissue- gluteal flap, transverse upper gracilis flap (TUG), PAP (profunda artery perforator flap) or DUG (diagonal upper gracilis flap) varieties, or lumbar artery perforator flap. Additionally, autologous reconstruction can be achieved with a combined autologous and implant reconstruction used in conjunction with any of the above or flaps based on the thoracodorsal artery (the Latissimus Dorsi musculo-cutanous flap or variants of this) or a perforator from this (the TAP flap). The indications, operative techniques, and patient selection factors relating to these flaps are beyond the present study's scope and are discussed extensively in the literature (11,13).

Timing considerations and relative contraindications

Historically, less than 25 percent of patients in the U.S. underwent immediate reconstruction (3). The evolution of conservative mastectomy surgical techniques and the introduction of ADM have paved the road for the increased popularity of immediate reconstruction (2,14). In women undergoing mastectomy for early-stage breast cancer, rates of breast reconstruction increased from 11.6% in 1998 to 36.4% in 2011 in the U.S. (15). In Denmark, currently about 20 percent of mastectomized women with invasive breast cancer undergo reconstruction, with a small majority being immediate reconstruction, while most women who undergo mastectomy for in situ cancer are reconstructed immediately (personal message, Hölmich).

Advantages of immediate reconstruction include superior

aesthetic outcomes, improved levels of psychosocial wellbeing post-mastectomy at least short-term, shorter surgical time, fewer surgical procedures, lower costs, and faster social reintegration when compared to delayed reconstruction (16-25). Immediate reconstruction demands better skin flaps than a simple mastectomy followed by a delayed reconstruction and may increase the risk of complications (see below). The main advantages of delayed reconstruction are that potential complications do not compromise adjuvant treatment. In addition, if postmastectomy radiation is needed, it does not compromise the reconstruction site, and it gives patients more time to consider reconstructive options. Disadvantages of delayed breast reconstruction also include more scarring and somewhat less favorable cosmetic outcomes, as well as additional surgical procedures and probably higher cost (19,21,23).

A large multicenter U.S. study found that delayed reconstruction (of all kinds) were associated with a substantial reduction in complications compared with immediate reconstructions (the risk of major complications was halved). Women undergoing delayed reconstruction had significantly worse pre-reconstruction quality of life scores than women with immediate reconstruction; however, 2-year post-reconstruction scores were similar in the two groups (22). Another large register-based U.S. study found a significantly higher incidence of surgical site infection after immediate (8.9%) compared with delayed (6.0%) and secondary (3.3%) implant reconstructions (meaning any secondary procedure), with similar results for noninfectious wound complications. In contrast, the incidence of surgical site infection was similar after immediate (9.8%), delayed (13.9%), and secondary (11.6%) autologous reconstructions. The study concludes that the risks for complications should be carefully balanced with the psychosocial and technical benefits of immediate reconstruction. Selected high-risk patients may benefit from consideration of delayed rather than immediate implant reconstruction to decrease breast complications after mastectomy (26).

Both immediate and delayed breast reconstruction has been found to be oncologically safe, although high-quality studies are still lacking. A meta-analysis including 31 studies (mostly retrospective single-center studies) with almost 140,000 patients compared patients undergoing mastectomy +/– immediate breast reconstruction (27). Most included studies had moderate quality, and selection bias was present; women with reconstruction were younger and had less lymph node metastases than those who only underwent mastectomy, but no difference in tumor size. The pooled data showed a higher occurrence of post-operative infection among women undergoing reconstruction (risk ratio 1.51, 95% CI: 1.22–1.87; P=0.0001); however, no significant difference in total survival or disease-free survival.

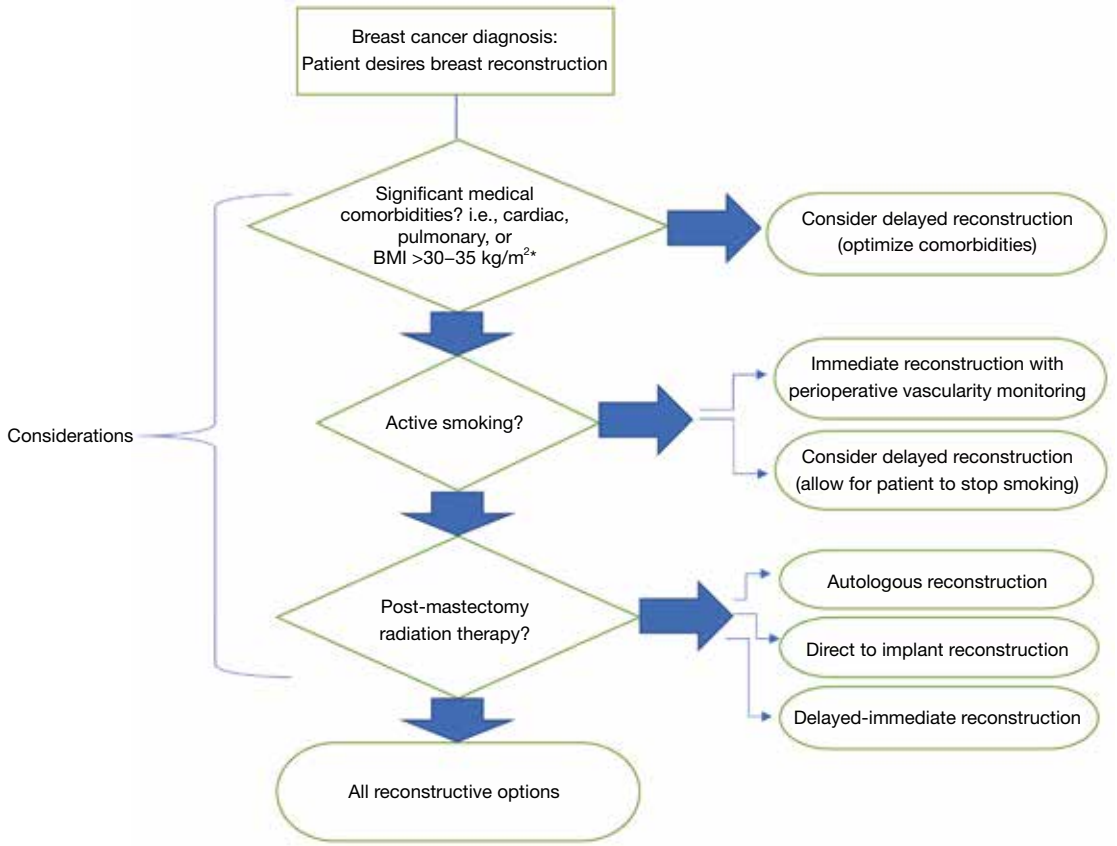
Complications in cancer surgery have been investigated in a few studies and can negatively influence the oncological outcome. The mechanisms involved are unknown but speculated to involve surgical stress, increased inflammatory response with synthesis of growth factors stimulating cancer cells, lowered immune response, and delay of adjuvant treatment (28). These associations have also been found for bowel, lung, and breast cancer surgery (29-32). Of note, two studies evaluated complications in breast reconstruction (33,34). Both studies found more local and distant recurrences in patients with complications compared with those without complications. This is an emerging field; none of the cited studies are large, and the evidence level at best moderate. However, the results call for caution and proper patient selection, in addition to further research protocols.

Potential delay in adjuvant treatment is a significant concern amongst medical and surgical oncologists. A systematic review of 14 studies, including over 5,000 women, of whom about 2,000 had immediate breast reconstruction, evaluated the timing of the adjuvant treatment and found overall that there was no meaningful delay in adjuvant therapy in the reconstruction group (35).

A multicenter prospective cohort study on about 2,500 consecutive patients undergoing mastectomy +/– breast reconstruction (implant-based or autologous) found significantly more complications associated with breast reconstruction than mastectomy alone. However, no overall difference in time to adjuvant therapy was detected. Those with major complications in both groups had their adjuvant therapy significantly later (36). Care should be taken especially in younger women with triple-negative breast cancer, as timely adjuvant therapy has been found to be especially important in this patient group (37,38).

The above allows for the conclusion that immediate breast reconstruction is oncologically safe if adequate precautions are taken; however, care must be taken to avoid complications, and thorough patient selection is therefore critical. If women with risk factors undergo immediate reconstruction, more complications will occur and delay in adjuvant therapy can be expected. Neoadjuvant treatment preoperatively should always be considered.

Despite the numerous benefits, patient selection is therefore critical in evaluating the timing of reconstruction



*In Denmark, the cutoff is BMI above 30 kg/m^2; higher in the U.S. presumably due to cultural differences and demographics.

Figure 1 The authors algorithm for deciding for immediate or delayed breast reconstruction. BMI, body mass index.

as not all patients are suitable candidates for immediate reconstruction. Delayed reconstruction should be considered for patients with pressing medical comorbidities, obesity, smoking, inflammatory breast cancer, patients going to have post-mastectomy radiation therapy, and for patients distressed regarding their breast cancer diagnosis who are not ready to make treatment decisions (22,39,40).

Several absolute and relative contraindications should be considered and discussed in-depth, with the patient and at multidisciplinary tumor board conferences. There is a general consensus that only a few absolute oncologic contraindications for immediate breast reconstruction exist: locally advanced breast cancer and inflammatory breast cancer (9,22). Active infection in the breast area is a surgical contraindication. However, many conditions may present relative contraindications to immediate reconstruction and will be discussed below: increased age, smoking, obesity, comorbidities, risk of delaying adjuvant therapy. *Figure 1* depicts the authors algorithm for deciding for immediate or delayed breast reconstruction. Some cultural and national differences exist among the authors' practice which is included in the algorithm.

Age

There has previously been debate about whether increased age is a contraindication to immediate reconstruction. Studies have found increasing age to be associated with infection and skin necrosis, presumably due to decreased vascularity and comorbidity (41-44). Studies have also shown that immediate breast reconstruction is safe in elderly patients if pre-existing medical conditions are optimized pre-operatively, and thus, a patient's age alone is not a contraindication to immediate reconstruction (45-47).

Smoking

Delaying reconstruction is preferred in patients who are

actively smoking, which will give the patient time to stop. Several studies have found an approximately doubled risk of complications in smokers undergoing breast reconstruction (41-44,48,49). There are also studies indicating that earlier smoking is associated with a higher risk of skin necrosis (48). If reconstruction is performed in an active smoker, peri-operative monitoring of the vascularity of the skin flaps is therefore advisable (50). A large meta-analysis found current smoking and former smoking of 20 pack-years or more to be associated with a significantly increased risk of recurrence and death, both disease-specific and overall (51). Active smoking is therefore considered an important relative contraindication for immediate reconstruction. In Denmark, this also applies to delayed reconstruction. The authors would only consider immediate reconstruction in light smokers without any other risk factors for complications.

BMI

The risk of complications such as infection, skin necrosis and loss of implant is increased in overweight patients and about double the risk of normal weight (41,44,52,53). Overweight patients often have large and broad-based breasts, which will yield a large wound area during the skin-sparing mastectomy. Larger flaps or implants are generally needed; all of these factors are probably adding to the increased risk of complications. In many national guidelines, BMI above 30 kg/m^2 is considered at least a relative contraindication (44,54). Different countries and cultures have different proportions of obese patients and guidelines often reflects this (55,56). Among the authors, discrepancy exists as BMI 30 is used as cut off in Denmark (and generally so in the Nordic countries), while the upper limit in the US is higher.

PMRT

In patients requiring PMRT, the optimal timing and method of breast reconstruction are controversial (57). Generally, plastic surgeons and surgical oncologists advise completion of radiation therapy prior to reconstructing the breast to avoid higher rates of complications of the reconstructed breast receiving PMRT (57-59). The traditional approach calls for tissue expander exchange for the permanent breast implant after the conclusion of PMRT however the authors prefer exchange to implant prior to the radiation, if possible, in order to allow surgery in a non-radiated field. If not possible, the use of a counter incision at the IMF or outside the field is preferred to one over the central portion of the breast. One study found that nearly 50% of implant-based breast reconstruction patients who underwent radiation may require revisions to their reconstruction (60). A meta-analysis evaluating complications including in pre-mastectomy versus postmastectomy radiation therapy generally in two-staged implant reconstruction and found similar and high complication rates and failures (17% versus 20%) (61). The commonly accepted view is that reconstruction with autologous tissue is superior to implant reconstruction within an irradiated operative field. However, autologous tissue reconstructions can also be negatively affected by PMRT (49,57,58). In contrast, a prospective study demonstrated immediate autologous reconstruction in the setting of PMRT to be a safe option that did not negatively affect breast aesthetics nor the patient's quality of life (62). They attribute their findings to advances in radiation techniques such as three-dimensional planning and simple intensity modulation, which allow for greater dose homogeneity within the treatment field (62). There is an abundance of evidence supporting the oncological safety of immediate reconstruction (27). However, the risk a reconstructed breast may pose on comprimising radiation delivery is still a subject of debate (63). The authors generally prefer a delayed autologous reconstruction in case of radiation therapy, but if the patient is not willing to this, an immediate direct-to-implant reconstruction is preferable. We would try to avoid radiation towards an expander, if possible; since it may more difficult to plan the radiation field in a patient with an expander than with a permanent implant, meaning a potentially higher risk of additional radiation to the lungs and the heart or an insufficient dosage distribution (63). In addition, to overcome expansion during chemotherapy which is often given before radiation therapy and performing exchange before radiation therapy can be demanding.

Chemotherapy

As discussed previously, post-reconstruction chemotherapy has not been found to be generally compromised by the reconstruction (35,36). Regarding neoadjuvant chemotherapy in the setting of immediate reconstruction, a recent meta-analysis concluded that immediate reconstruction following neoadjuvant chemotherapy is safe with acceptable post-operative complication levels. The meta-analysis found that neoadjuvant therapy may result in slightly increased implant loss levels; however, there was no

delay in commencement of adjuvant therapy (64).

Conclusions

Patient preference, risk factors and oncologic considerations are always important when planning reconstruction timing. Immediate reconstruction offers many advantages over delayed reconstruction, however, long-term patient-reported outcomes have been found similar, which we should not forget. The authors prefer immediate reconstruction when feasible. The timing and technique of reconstruction should be decided on a case-by-case basis after a thorough discussion with the patient and preferably also in multidisciplinary meetings.

This controversial topic is one that is debated over and over again. Consensus among the surgeons, chemotherapists, and radiation oncologists is the ideal and meetings which encourage this type of dialogue should be routine.

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Footnote

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Review Article

Indocyanine green angiography in breast reconstruction: a narrative review

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Abstract: Sufficient tissue perfusion is important in achieving a successful breast reconstruction to provide the patient with an acceptable result in terms of shape, size, symmetry and possible sensation. Indocyanine green angiography (ICG-A) is a well-known imaging modality which can be applied to visualize the per-operative tissue perfusion assisting the surgeon in intraoperative decision making, flap design and trimming. The consequence of using per-operative ICG-A is reported to correlate with a decreased rate of complications and loss of reconstruction; thus, this technique may be a valuable intraoperative assessment tool for the breast reconstructive surgeon. This paper aims to provide a review of the recent knowledge on the use of ICG-A in breast reconstructive procedures. In addition, an evaluation of the favorable application in implant-based reconstruction, oncoplastic techniques and autologous breast reconstruction. The technique is presented with clinical examples illustrated by per-operative videos, photos and assessment of perfusion to provide the reader with a broader perspective on the application and use of ICG-A. There is a need for further standardization of the per-operative application and perfusion assessment using ICG-A in the field of breast reconstruction, also exploring the use of ICG-A in assessment of postoperative monitoring, microvascular anastomoses and venous insufficiency.

Keywords: Indocyanine green angiography (ICG-A); breast reconstruction; implant-based; autologous breast reconstruction; imaging technique

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Introduction

An increasing number of women seek a breast reconstruction, due to increased survival rate after breast cancer (1). A breast reconstruction aims to increase the quality of life and obtain a new breast with an acceptable size, shape and symmetry (2-5). Sufficient perfusion is important in achieving a successful implant-based, oncoplastic or autologous breast reconstruction. Indocyanine green angiography (ICG-A) is an intraoperative imaging modality visualizing blood flow to the tissue of interest (6-8). The real-time assessment of perfusion supports the surgeon in intraoperative decision making, which consequently leads to a decreased risk of postoperative complications and loss of reconstruction (9-16). We present the following article in accordance with the Narrative Review reporting checklist (available at https://abs.amegroups.com/article/view/10.21037/abs-21-25/rc).

ICG-A—background

ICG-A has been used to assess skin perfusion for the last two decades (17-19) and is a widely used and well described imaging technique for evaluating tissue perfusion (6,8,20).

The modality is not only used to asses arterial perfusion, but has also been described for evaluation of microvascular anastomoses (21,22), venous congestion (23,24), augmentation mastopexy (25), breast reduction surgery (26) and investigation of perfusion zones (27-31).

Scoring and cut-off values in terms of sensitivity, specificity, positive predictive- and negative predictive values have been investigated by several authors (10,11,32-37). In mastectomy flaps, ICG-A has been reported with a sensitivity of 90% and specificity of 100% in reducing skin flap necrosis and overall complication rate (10,38-40). Moyer *et al.* suggested a cut-off perfusion score of 33% in preventing mastectomy flap necrosis (33). In autologous breast reconstruction establishment of a specific cut-off value and perfusion assessment have yet to be determined (15,41-45).

The majority of published studies on ICG-A in breast reconstruction are of lower level of evidence and consists of comparative, case and cohort studies. Only one randomized controlled trial (RCT)-study investigating ICG-A is published (15). The study investigated the use of ICG-A in deep inferior epigastric artery perforator (DIEP)-flaps and found a significant decreased incidence of fat necrosis (15).

A systematic review from 2020 on the use of ICG-A in autologous breast reconstruction, concluded that per-operative perfusion assessment by ICG-A was an effective tool in reducing fat necrosis compared with flaps assessed clinically (46). Mastectomy skin flap necrosis and the risk of repeated surgeries were reported significantly decreased in 2 reviews and 1 meta-analysis (36,37,47). A Cochrane review on ICG-A on mastectomy skin flap perfusion in immediate breast reconstructions was inconclusive due to lack of high-quality evidence (48). Johnson *et al.* investigated the overall use of ICG-A in breast reconstructions, and reported a reduced postoperative tissue loss when applying ICG-A, but emphasized the need for standardization (35).

In the following we present a narrative review and a description on how ICG-A may be used in implant-based, oncoplastic and autologous breast reconstruction demonstrated by clinical examples.

ICG-A—methodology

ICG-A offers an objective, repeatable and real-time imaging of the vascularity and perfusion of tissue (7,49). Indocyanine green (ICG) is a water-soluble molecule excreted via the liver to the bile. The technique is repeatable due to a short half-life of 3–5 minutes. Upon intravenous injection of ICG during surgery a fluorescent near-infrared camera detects the molecule and visualizes perfusion within approximately 20 seconds (6). There is up until now no consensus on the intraoperative dose of ICG which is reported from 2 up to 250 mg (13,50,51).

Several imaging-systems exists among others the Fluobeam Clinical System® (Fluoptics, Grenoble, France, www.fluoptics.com), HyperEye Medical Systems® (Mizuho, Tokyo, Japan, www. mizuhomedical.co.jp) and IC-View® Pulsion Medical Systems. One of the most commonly used systems is the Spy-Elite Fluorescence Imaging System® which is able to quantify perfusion and apply relative values of blood flow in the tissue (33,52). Wearable technology in the form of smart glasses have also been described (53).

Preoperative information

Patients undergoing breast reconstruction should be informed of the rationale and use of per-operative ICG-A. Potential side-effects such as nausea, dizziness, discomfort, rash and sweating occur in up to 0.2–0.34%, and is thoroughly discussed with the patient (32,54-56). Patients allergic to iodine should be excluded due to risk of anaphylaxis (51).

The incidence of anaphylactic shock is rare, and occurs in approximately 1 in 42,000 patients (56). Also, though extravasation is rare, extravasation of ICG may cause reversible discoloration of the skin (*Figure 1*).

ICG-A—intraoperative application

Implant-based breast reconstruction

Immediate reconstruction

Mastectomy, being it nipple-sparing or skin-sparing, is performed in the plane of the subcutaneous fascia to preserve the dermal blood supply. Hemostasis is secured using bipolar diathermia. After removal of the breast tissue, the surgeon evaluates the skin flaps estimating areas in risk of potential hypoperfusion. The breast surgeon should refrain from using vasoconstrictive agents such as Klein's fluid (Ringer lactate, lidocaine and adrenaline) to avoid distortion of the assessment of the ICG-A (*Figure 2*).

A sizer of appropriate size is inserted, and dermis is sutured temporarily. Twenty-five milligrams of ICG are diluted in 10 mL sterile water, an intravenous bolus administration of ICG (Verdye® 5 mg/mL) of 2.5 mg/mL

Figure 1 Patient with discoloration of the leg after extravasation of indocyanine green used per-operatively. The color diminished gradually within 3 months leaving no sequelae.

Video 1 The angiography shows general hypoperfusion of the mastectomy skin flaps due to the use of Klein's fluid for hydrodissection resulting in vasoconstriction.

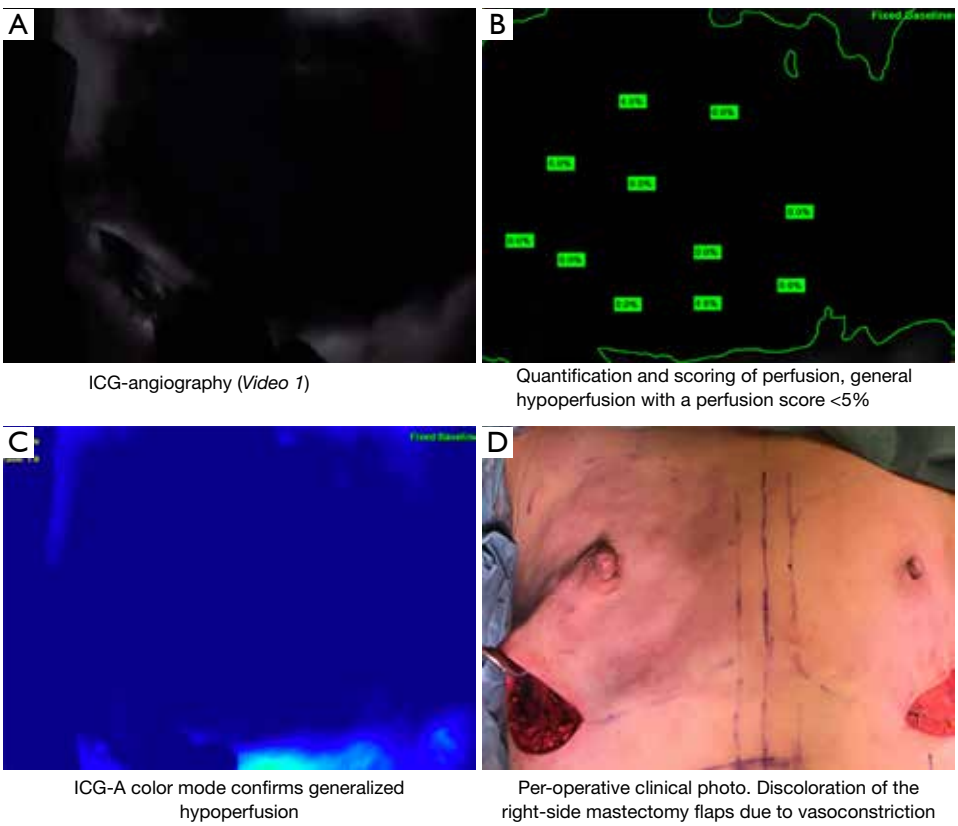


Figure 2 ICG-A performed on mastectomy flaps after a skin-sparing subcutaneous mastectomy using vasoconstrictive agents. (A) The angiography shows general hypoperfusion of the mastectomy skin flaps due to the use of Klein's fluid for hydrodissection resulting in vasoconstriction (*Video 1*). (B) Scoring perfusion by the Spy-Elite Fluorescence Imaging System®, perfusion is <5%. (C) ICG-A color mode showed hypoperfusion indicated by the dark blue color. (D) Per-operative clinical photo of the mastectomy flaps. The patients right side mastectomy flaps are thin and discolored due to the use of vasoconstrictive agents for the hydrodissection during mastectomy. ICG-A, indocyanine green angiography.

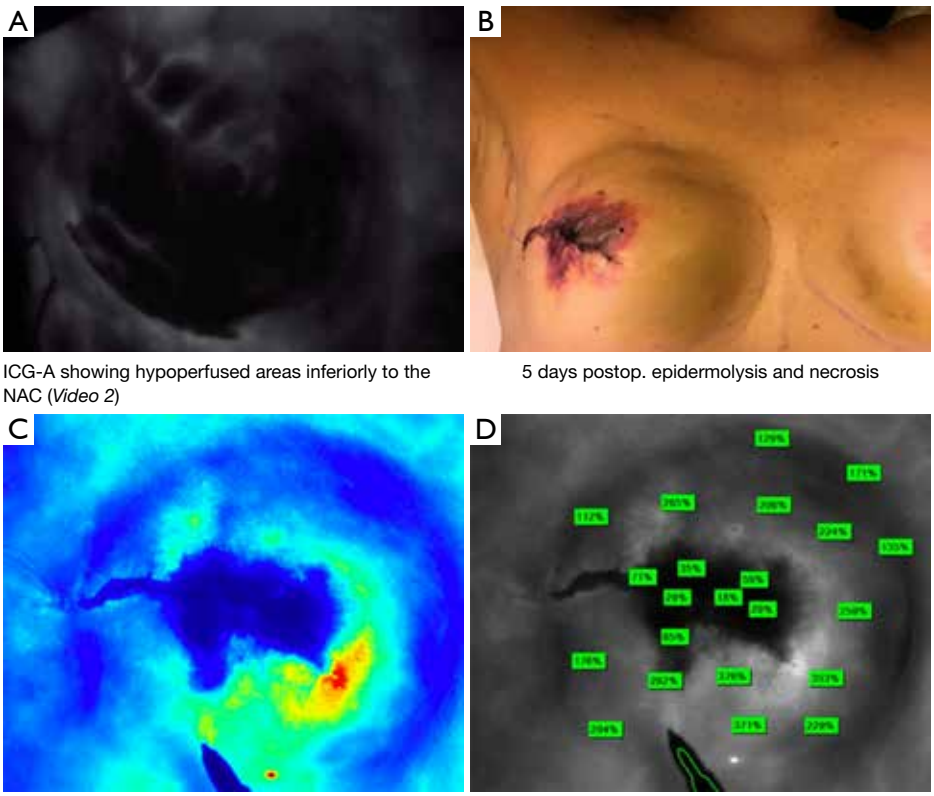
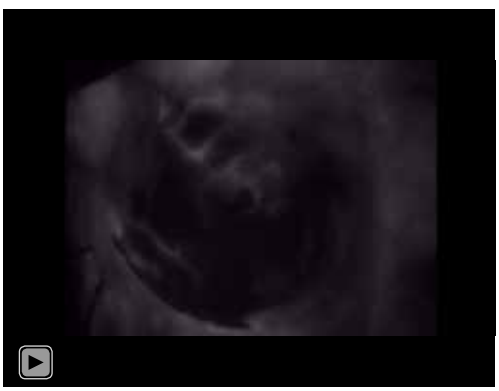


Figure 3 A case where the surgeon chose not to excise the hypoperfused areas indicated by the ICG-A. (A) ICG-A showing hypoperfused areas (<33%) of the mastectomy flap after insertion of sizer before prepectoral breast reconstruction with implant and ADM (*Video 2*). (B) Clinical photo. The patient developed epidermolysis and necrosis 5 days postoperatively corresponding to the ICG-A. The necrotic areas were excised, the implant extracted and the patient underwent 2-stage reconstruction with TE. (C) ICG-A color mode shows central hypoperfusion as seen on the ICG-A. (D) Scoring perfusion by the Spy-Elite Fluorescence Imaging System® 5 days postoperatively, perfusion is centrally <33% corresponding to the clinic. ICG-A, indocyanine green angiography; NAC, nipple areola complex; ADM, acellular dermal matrix.



Video 2 Indocyanine green angiography (ICG-A) showing hypoperfused areas (<33%) of the mastectomy flap after insertion of sizer before prepectoral breast reconstruction with implant and acellular dermal matrix (ADM).

is followed by a 10 mL flush with normal saline (2.5 mL of ICG solution for each administration).

The ICG is injected and the perfusion scored by the SPY-Elite® system. A perfusion below 33% may lead to reevaluation of the reconstructive procedure by reducing volume of the sizer to eliminate the skin tension (33).

In cases with perfusion below 33% on the first ICG-A, the technique is repeated and re-evaluated using the same dose of ICG, after 20 minutes (6). Consequently, a perfusion <33% on the 2. angiography will result in excision of the hypoperfused area (if located near incision area), a smaller implant or result in reconstruction with subpectoral placement of a tissue expander (TE) (*Figure 3*).

In cases with sufficient perfusion, the reconstruction proceeds with either a pre-pectoral implant wrapped in

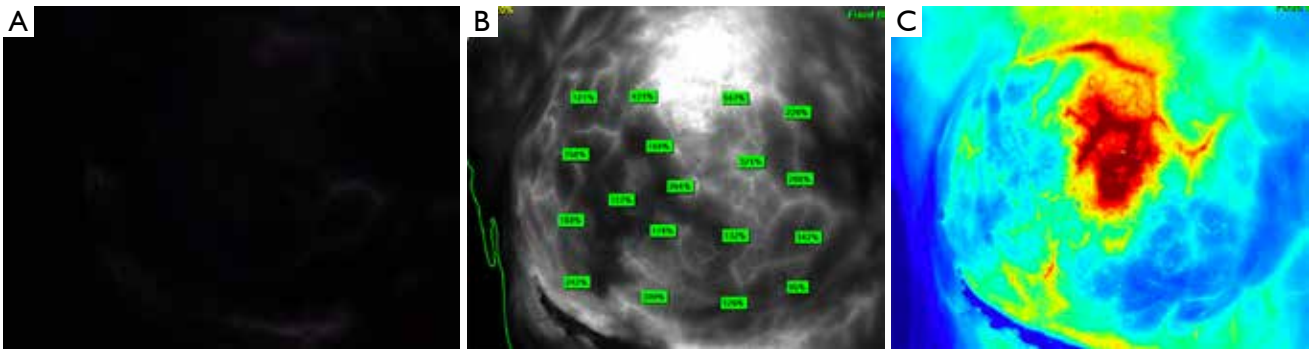
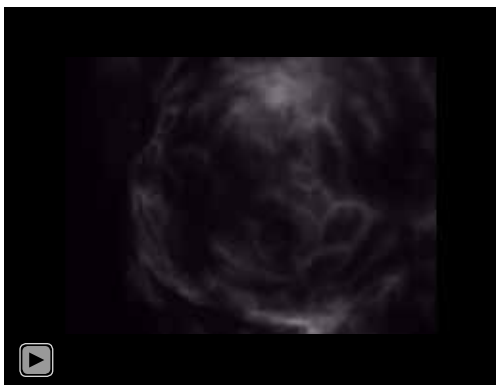


Figure 4 Pre-pectoral breast reconstruction with implant and ADM. (A) ICG-A showing sufficient perfusion after pre-pectoral breast reconstruction with implant and ADM (*Video 3*). (B) Scoring perfusion by the Spy-Elite Fluorescence Imaging System®, perfusion is generally >33% and indicates sufficient perfusion to proceed with the planned reconstruction. (C) ICG-A color mode indicating sufficient perfusion. ICG-A, indocyanine green angiography; ADM, acellular dermal matrix.



Video 3 Indocyanine green angiography (ICG-A) showing sufficient perfusion after pre-pectoral breast reconstruction with implant and acellular dermal matrix (ADM).

acellular dermal matrix (ADM) or a subpectoral implant or TE.

After completing the breast reconstruction, ICG-A is then performed again to confirm and ensure sufficient perfusion (*Figure 4*).

Oncoplastic techniques

Oncoplastic techniques have been used for several decades and can be applied to achieve an acceptable aesthetic result after breast conserving therapy (57-59). Corrective techniques span from Z-plasties and local flaps to larger transposition, advancement and perforator flaps (57). The oncoplastic surgery aims to balance and restore the shape of the breast subsequent to oncologic resection (59). Reshaping and relocation of tissue can compromise perfusion and makes ICG-A a valuable tool in oncoplastic breast surgery (58).

After removing the cancer and intraoperative confirmation of adequate resection, the lateral intercostal artery perforator (LICAP) flap is raised to replace volume and reshape the breast (60). ICG-A can be used per-operatively to assess and score perfusion before after raising the flap, after advancement and before wound closure (*Figure 5*). In oncoplastic displacement (e.g., breast reduction oncoplasty), the ICG-A technique is used as

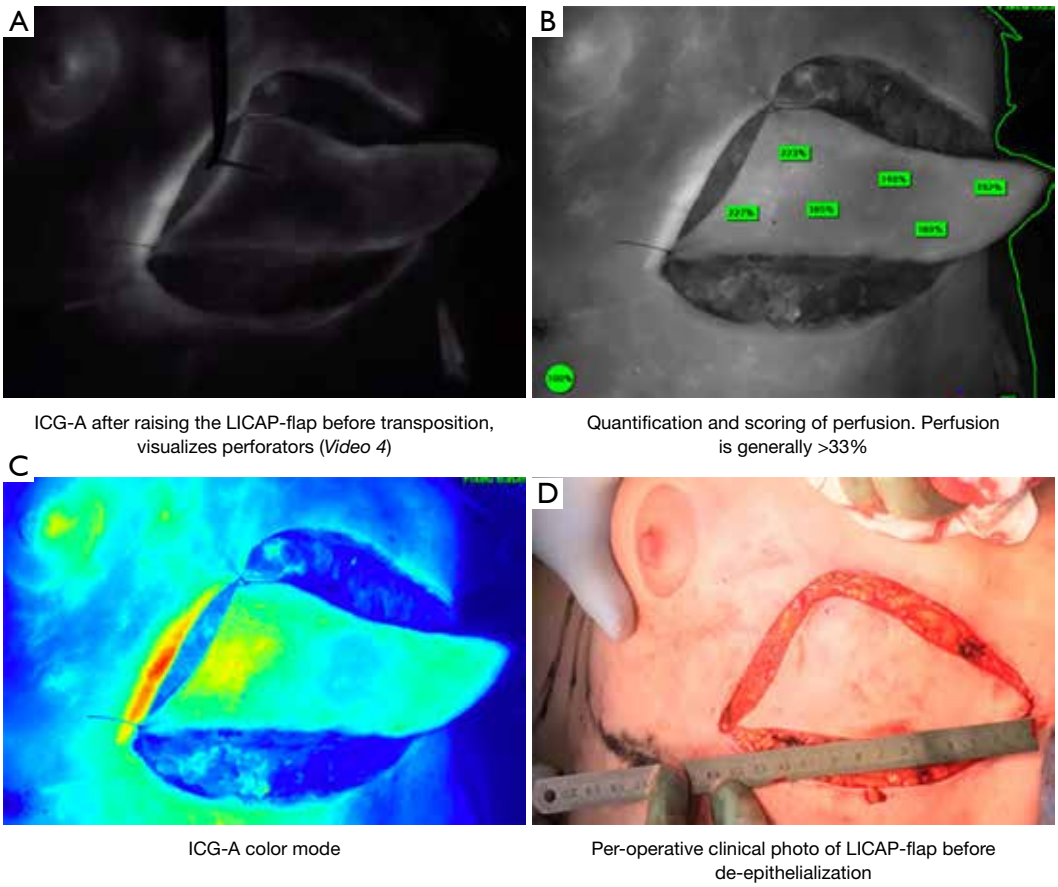
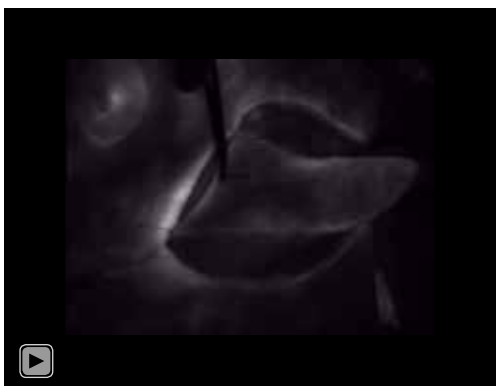


Figure 5 Assessment and scoring of perfusion of LICAP-flap before the flap was deepithelialized and advanced in to the breast. (A) ICG-A after raising the LICAP. Angiography visualizes perforators entering the flap (*Video 4*). (B) Quantification and scoring of perfusion shows sufficient perfusion of the entire flap. (C) ICG-A color mode with sufficient perfusion. (D) Clinical photo of the LICAP-flap before the flap was deepithelialized and advanced in to the breast. ICG-A, indocyanine green angiography; LICAP, lateral intercostal artery perforator.



Video 4 Indocyanine green angiography (ICG-A) after raising the lateral intercostal artery perforator (LICAP). Angiography visualizes perforators entering the flap.

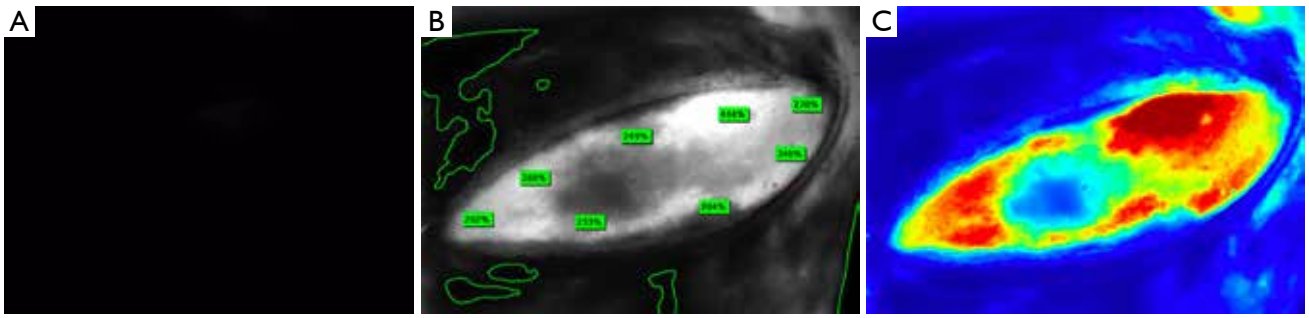


Figure 6 Per-operative ICG-A of a LD-flap after incision around the flap, before flap is elevated on the pedicle. The angiography visualizes the perforators entering the flap. Scoring of perfusion by the Spy-Elite Fluorescence Imaging System®. (A) Intraoperative angiography confirms perforators entering the flap (*Video 5*). (B) Quantification and scoring of perfusion shows sufficient perfusion of the entire flap. (C) ICG-A color mode visualizes perforators and perfusion. ICG-A, indocyanine green angiography; LD, latissimus dorsi.

Video 5 Intraoperative angiography confirms perforators entering the flap.

described for the displacement techniques.

Autologous breast reconstruction

Pedicled flap

Preoperatively a doppler ultrasonography can be used to mark the perforators or artery(ies) if the chosen pedicled flap is a muscle sparing latissimus dorsi (msLD) or a thoracodorsal artery perforator flap (TAP). Perfusion of the flap can then be scored by ICG-A [as described (33)] performed after incision around the flap to the fascia. The angiography indicates the number of perforators within the flap (*Figure 6*).

We recommend repeating ICG-A after the flap is completely raised on its pedicle—before transposition/advancement—which allows assessment of the chosen perforator or artery in order to evaluate possible changes in perfusion—assessing the angiosome if the flap is designed as a perforator flap. The final angiography is performed after the flap is transposed to the recipient site. Areas with hypoperfusion (<33%) should be excised.

The angiographies can aid the surgeon in the intraoperative surgical decision making, and the perfusion measurement may identify areas in risk of postoperative necrosis due to hypoperfusion (*Figure 7*).

Free flap

For breast reconstruction using a free abdominal flap, e.g., deep inferior epigastric artery perforator flap (DIEP), superficial inferior epigastric artery (SIEA) or muscle sparring transverse rectus abdominis (msTRAM) flap, ICG-A can be used to evaluate perfusion of the flap, aiding

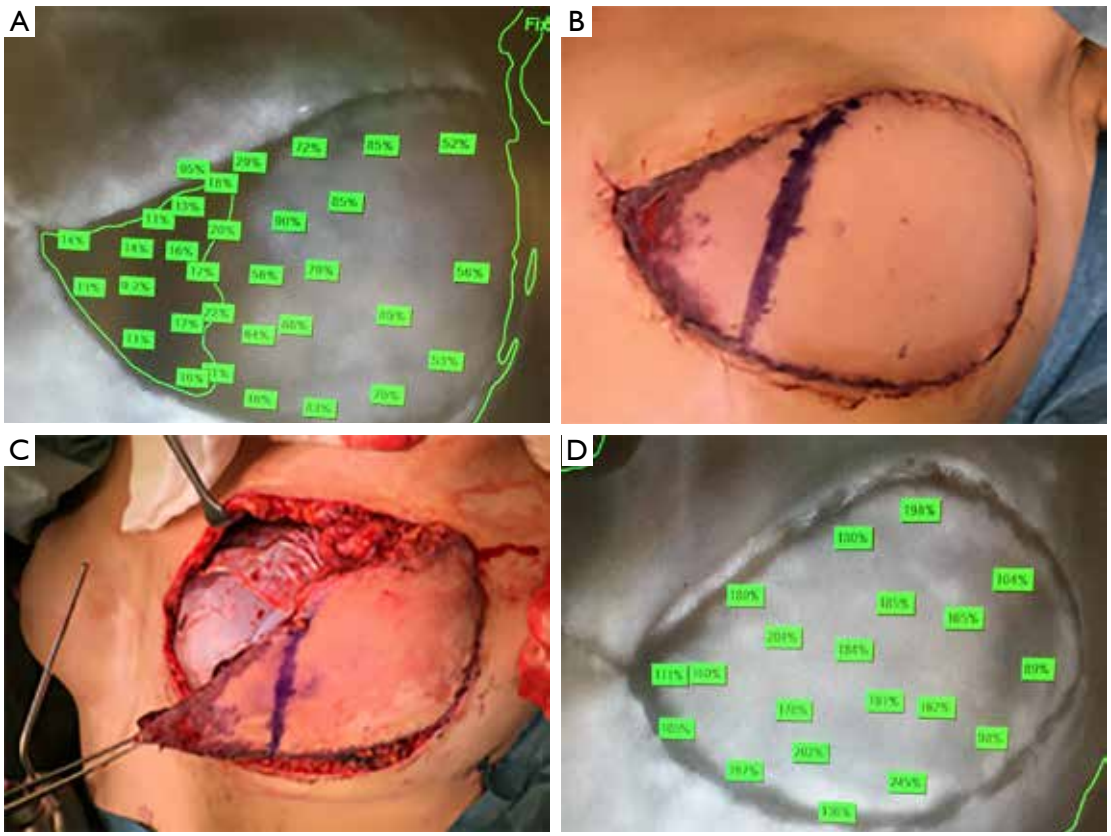


Figure 7 Delayed breast reconstruction using a msLD flap combined with a tissue expander. (A) Intraoperative ICG-A showed hypoperfusion (<33%) of the medial part of the flap, but the area was not excised. (B) Demarcation, epidermolysis and necrosis developed 2 days postoperatively at the medial part of the flap, corresponding to the per-operative ICG-A. (C) Take-back surgery with removal of TE and excision of necrotic tissue. (D) ICG-A confirmed sufficient perfusion and the patient healed uneventfully. Green numbers indicate the relative perfusion score. msLD, muscle sparing latissimus dorsi flap; ICG-A, indocyanine green angiography; TE, tissue expander.

flap design, identification of perforators and assessing perfusion zones, microvascular anastomoses, venous insufficiency etc.

A preoperative computed tomography angiography (CT-A) is done to identify the perforators and the intramuscular course of the vessels in the flap. By performing ICG-A (as described above) upon incision around the flap to the fascial level—before entering the subfascial plane—the complete number of perforators entering the flap can be identified and compared with the preoperative CT-A.

Based on this assessment, the best/most reliable perforators may be dissected, and the angiography repeated, allowing real-time assessment of the perfusion while aiding the intraoperative flap design. If the angiography indicates areas of insufficient perfusion, the surgeon is able to reevaluate and adjust the reconstructive procedure (*Figure 8*).

After the flap is raised with complete pedicle dissection, ICG-A is repeated allowing a final assessment of flap perfusion before transposition to the breast.

Upon completing the microvascular anastomoses, a repeated angiography may display possible hypoperfused areas of the flap, venous insufficiency or insufficient intra-flap perfusion (*Figure 9*).

Using ICG-A intraoperatively informs the surgeon of possible insufficiently perfused areas of the flap and aids in reevaluating the breast reconstruction strategy to prevent

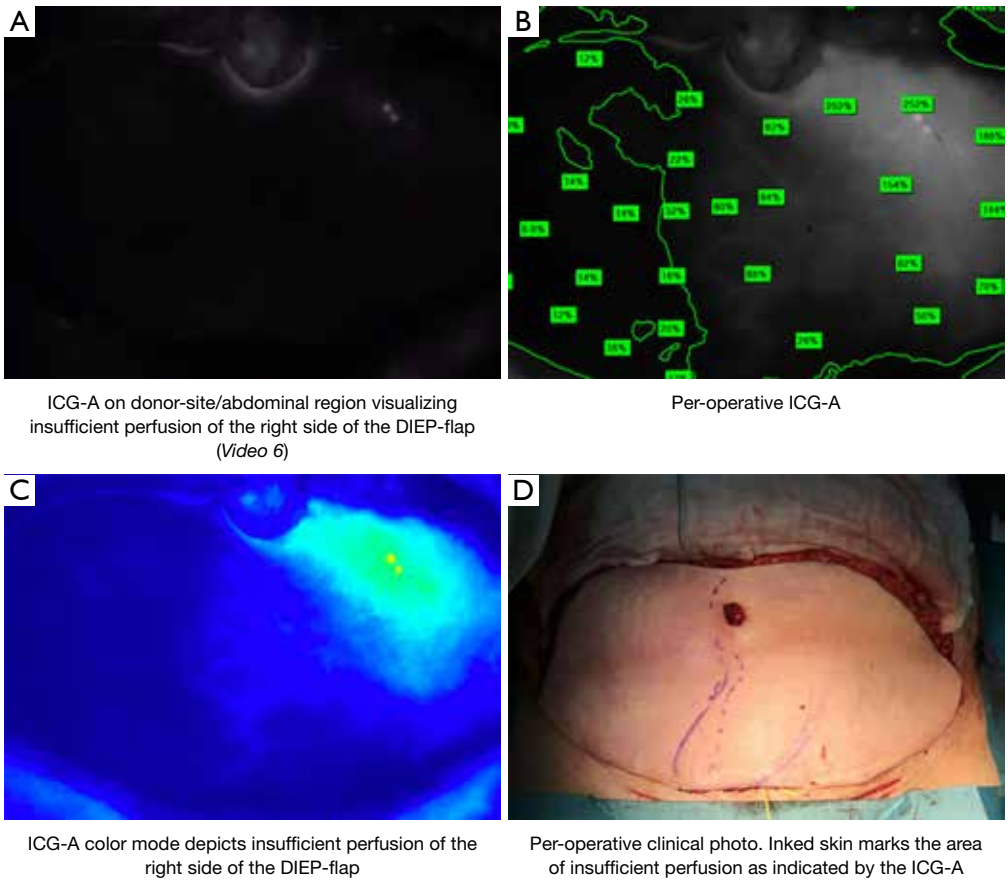
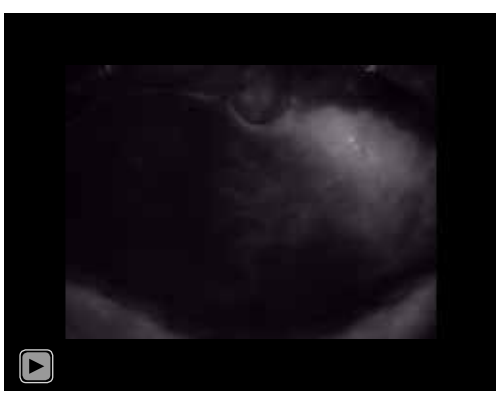


Figure 8 Planned breast reconstruction with bilateral DIEP-flap. ICG-A performed per-operatively at donor-site/abdominal region, after dissection of perforators before entering the abdominal subfascial plane, showed insufficient perfusion of the right half of the flap. The angiography aided the surgeon to reevaluate the reconstructive procedure. (A) Per-operative ICG-A on donor-site/abdominal region visualizing insufficient perfusion of the right side of the DIEP-flap (*Video 6*). (B) Per-operative ICG-A. Scoring of the perfusion shows perfusion <33% on the right side of the flap. (C) ICG-A color mode depicts insufficient perfusion of the right side of the DIEP-flap. (D) Per-operative clinical photo. Area with insufficient perfusion is marked on the skin. ICG-A, indocyanine green angiography; DIEP, deep inferior epigastric artery perforator flap.



Video 6 Per-operative indocyanine green angiography (ICG-A) on donor-site/abdominal region visualizing insufficient perfusion of the right side of the deep inferior epigastric artery perforator (DIEP)-flap.

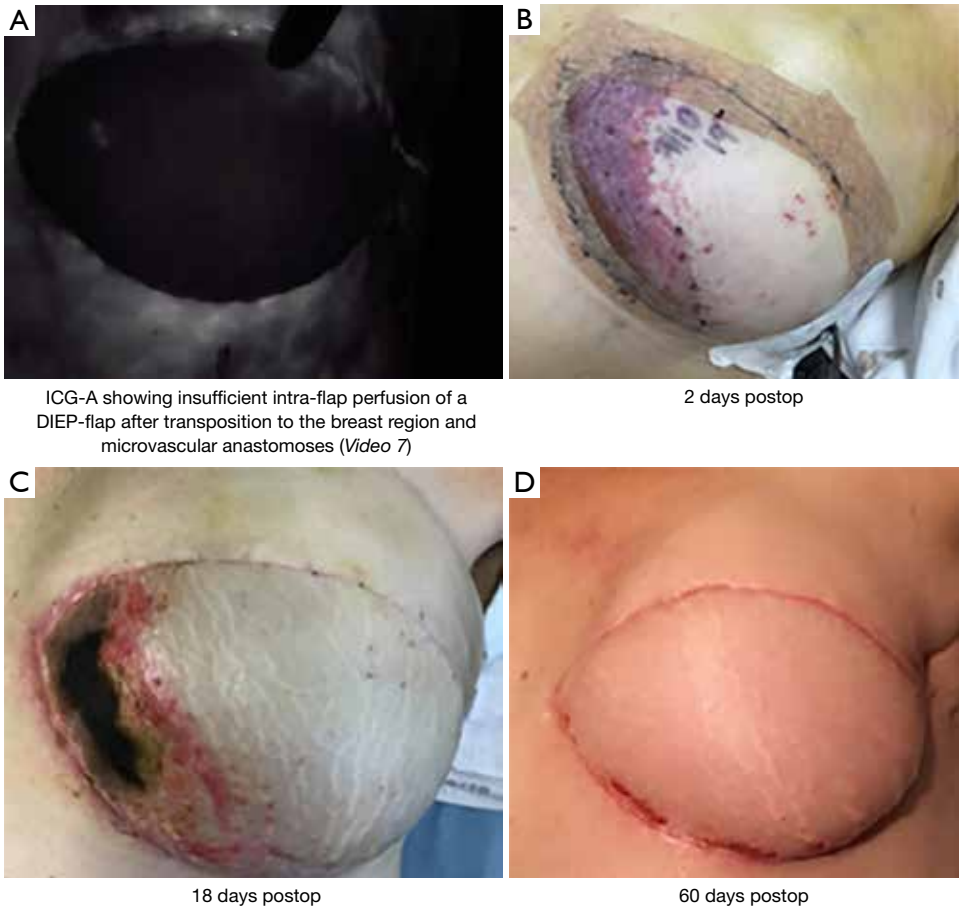
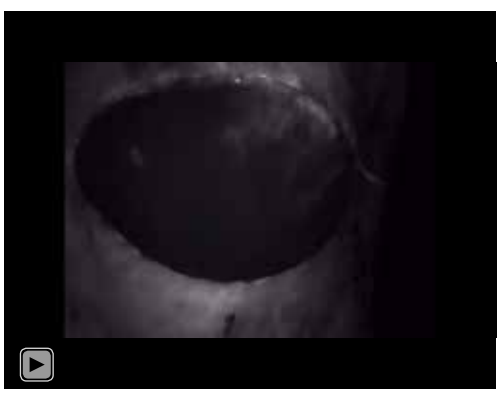


Figure 9 Delayed breast reconstruction with a DIEP-flap (left breast). Pictures of the postoperative complications corresponding to intraoperative ICG-A. (A) ICG-A showing insufficient intra-flap perfusion of a DIEP-flap after transposition to the breast region and microvascular anastomoses. Patient experienced partial flap loss of the medial 20% of the flap corresponding to the intraoperative angiography (*Video* 7). (B) Two days postoperatively, clinical demarcation and epidermolysis of medial segment of the flap. (C) Eighteen days postoperatively, the necrosis of medial segment. (D) After secondary revision and excision of medial segment with necrosis, the patient healed with no further complications. ICG-A, indocyanine green angiography; DIEP, deep inferior epigastric artery perforator flap.



Video 7 Indocyanine green angiography (ICG-A) showing insufficient intra-flap perfusion of a deep inferior epigastric artery perforator (DIEP)-flap after transposition to the breast region and microvascular anastomoses. Patient experienced partial flap loss of the medial 20% of the flap corresponding to the intraoperative angiography.

postoperative complications.

Conclusions

A successful breast reconstruction requires sufficient blood perfusion preventing postoperative complications and loss of reconstruction.

ICG-A provides the surgeon with real-time accurate assessment of the tissue and intraoperative perfusion (7,49). Making information on real-time tissue perfusion available intraoperatively can assist the surgical decision making, providing the opportunity to reevaluate and adapt the reconstruction technique. Repeated intraoperative use of this imaging technique supplies valuable information on perfusion in every step of the reconstruction.

Surgical decision making often relies on clinical experience and judgement. ICG-A can assist the surgeon by providing real-time assessment, scoring and quantification of tissue perfusion.

The role of ICG-A in breast reconstructive procedures is not exhausted.

Determining cut-off values for perfusion, correlating these to postoperative fat necrosis rates or ultimately flap loss remains yet to be investigated. Moreover, further studies, exploring the role of ICG-A in postoperative monitoring, assessment of venous congestion and microvascular anastomoses may further expand the applications of ICG-A in breast reconstructive surgery.

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Review Article

Perspectivising tumescent mastectomy: innovation in preserving mastectomy skin flap perfusion—a narrative review

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Abstract: Mastectomy is used in breast cancer treatment and as risk-reducing in women with genetic high risk of breast cancer. Immediate breast reconstruction including direct to implant but also autologous breast reconstruction is increasingly offered to women planned to have mastectomy. Either simple mastectomy or skin sparring mastectomy followed by immediate breast reconstruction, two specific issues are crucial. (I) Oncologic safety. That is, removal of any diagnosed pathologic finding, but also all breast tissue including the often breast tissue containing Coopers ligaments and thereby minimizing residual breast tissue. (II) Low complication rate. During mastectomy, the skin flaps are dissected from the breast gland. The interruption of blood supply to the skin flaps from below results in diminished perfusion of the skin flaps. This comprises a risk of necrosis and infection and ultimately prolonged time to adjuvant therapy, prolonged recovery, and possible loss of reconstruction. Tumescent technique with epinephrine solution meets both challenges, especially when used under visual guidance. It accentuates breast tissue and makes it easier to dissect the breast tissue and Coopers ligaments free from the subcutaneous fatty tissue. Furthermore, it is atraumatic and preserves the insulating fatty tissue and the blood supply running through this. Maintaining skin flap perfusion diminishes the risk of necrosis and infection. On top of that, tumescent mastectomy leaves more fatty tissue resulting in a more pleasant aesthetic result regardless of either simple or skin sparring mastectomy and regardless of either direct to implant or autologous reconstruction. The powerful ICG-angiography, often used to assess areas with low perfusion and previously shown to be superior to clinical assessment, can, however, not be relied on when tumescent mastectomy technique has been used.

Keywords: Mastectomy; tumescence; skin flap perfusion; immediate breast reconstruction; skin flap viability

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Introduction

Oncologic breast surgery has changed towards breast conserving surgery and neoadjuvant chemotherapy. Despite this, mastectomy is still offered to 1/4–1/3 of all breast cancer women. It is used for extensive or multifocal disease in the breast and is offered in risk-reducing surgery to women with genetic high risk of breast cancer.

The most important issue in mastectomies is the oncologic safety. This requires first of all adequately resection of the breast parenchyma including any diagnosed pathologic findings.

Secondly, mastectomy has to be done with a minimum risk of complications, in order to avoid postponing possible adjuvant therapy, but also to ensure quick recovery and optimized aesthetic result. Frequent complications to mastectomy are skin flap necrosis and infection. A large meta-analysis showed risk of this in direct to implant breast reconstruction on 8.6% and 7.8%, respectively and the ultimate failure—implant loss in 14.4% (1). To avoid these, skin flap perfusion is crucial.

Aesthetic result is essential in both simple mastectomy and when mastectomy is accompanied with breast reconstruction—either immediate or delayed and either

Figure 1 Breast skin flaps including breast dermis, subcutaneous adipose tissue between the dermis and glandular tissue, and breast glandular tissue extending up in a Coopers ligament. Oncologic and surgical safe mastectomy implies removal of all breast tissue including Coopers ligaments and keeping all fatty tissue including vascular supply for the skin flap (HE stain, ×15). The figure kindly supplied by AMB Jylling (Odense University Hospital, Odense, Denmark). HE, hematoxylin and eosin.

implant based or autologous. The thicker subcutaneous coverage of a silicone implant, the more natural and aesthetic pleasant result. The following article is presented in accordance with the Narrative Review reporting checklist (available at https://abs.amegroups.com/article/view/10.21037/abs-21-4/rc).

Oncological safety and breast margins

Performing an oncological safe mastectomy includes removal of all breast tissue, leaving no or a minimum of residual breast tissue in the mastectomy margins (2,3). Residual Breast tissue is especially undesirable in therapeutic mastectomies where radiotherapy is not always included in the adjuvant therapy as with breast conserving surgery. Also in the genetic high risk population, residual breast tissue is unwanted. After risk-reducing mastectomy this group are often no longer offered breast cancer screening, why residual tissue adds additional occult risk. Skin sparring mastectomy in this group can be done with or without sparring the nipple areola complex and associated with either autologous or implant based immediate breast reconstruction. Performing skin sparring mastectomy implies keeping all or most of the skin above the breast parenchyma. This results in leaving a larger resection margin in the patient than with simple mastectomy where an elliptical skin coverage of the breast is resected with the breast tissue. It is therefore even more important that the surgeon is aware of the right dissection plane in order to minimize the residual breast tissue in the skin flap.

An understanding of the anatomy of the breast is prerequisite for avoiding residual breast tissue.

Most agree that the fascia over the pectoral muscle delimits the breast tissue profound. Concerns in interest are: (I) superficial margins in order to find the right clivage between breast tissue and skin flaps and (II) periphery boundaries of the breast tissue in the cranial, lateral, caudal, and medial directions.

Superficial breast margins

Figure 1 shows a slice of breast reduction specimen microscopically. One can see the skin on top consisting of epidermis and dermis overlying a subcutaneous layer of fatty tissue. In the center, stretching through the subcutaneous fatty layer and reaching the skin is a Coopers ligament with glandular tissue. Removing all breast tissue implies removing the majority of Coopers ligaments.

Most breast surgeons find that there exists a superficial macroscopically identifiable oncoplastic plane or dissection plane. This plane separates the breast parenchyma including at-risk duct with the overlying subcutaneous fat and dermis compositing the skin flaps. The dissection should follow this plane. The plane varies in identifiability among women and within the breast. The plane has traditionally been found by incising the skin and subcutaneous tissue and then with counter traction applied to the underlying breast and the skin flaps has consecutively been dissected.

A superficial fascia layer of the body, consisting of connective tissue network between the subdermal planes to the underlying muscle fascia, has been described (4). Controversies regarding the existence of a corresponding superficial fascia in the breast exists. There have been several anatomical studies investigating if a superficial fascia equivalent to the dissection plane exists in the breast (5). A study by Muntan *et al.* found that the superficial fascia layer divides in two layers with the mammary gland in between (6). Beer *et al.* studied breast reduction specimens in 62 breasts and found absence of a superficial fascia in 44% (7). In the group with a microscopically identifiable superficial fascia this was often not detectable macroscopically. Microscopically, however, it contained islands of breast tissue in 42% but no breast tissue above the fascia in the skin flaps. The distance from this superficial fascia to the

dermis was greatly variable but very little in the majority of the women and the authors argued, that following this, would not leave vital skin flaps behind. No breast tissue above the fascia and a wide variability in the distance from the superficial fascia to the dermis was corroborated by Larson *et al.* (8) Furthermore, they found that this distance was not associated with BMI, age or the weight of the breast specimen.

Although newer anatomical studies have revealed interesting evidence of a three dimensional system of a subcutaneous fascia (9), it seems that there is great variability in the presence of a macroscopic detectable superficial layer among women and in distance of this to the skin. It is therefore unpredictable, useless in dissection of the skin flaps and probably not the same as the dissection plane noted by surgeons.

Peripheral breast boundaries

The anatomical boundaries have been described as from the second or third to the sixth or seventh rib inferiorly and from the midaxillary line to the lateral border of the sternum (10). Furthermore, the breast tissue frequently extends into the axilla as the axillary tail of Spence.

As this sounds clearly defined, it seems that the peripheral border is not easily found by the surgeon. Studies find not only residual breast tissue in the skin flaps but also in the periphery including inframammary fold, the infraclavicular region, the axillary tail and especially the upper parasternal region and lower outer quadrant (2,11). Residual tissue depends on the surgeon's expertise, thus every surgeon should evaluate mastectomy quality and comprehensiveness in a close cooperation with his or her pathologist (12).

Vascular anatomy of the breast skin and nipple-areola complex

Even the most elegant mastectomy with or without primary reconstruction is doomed to fail if the overlying skin suffer from necrosis and planed adjuvant therapy is postponed (13).

During mastectomy, a large undermining is done and all blood flow from beneath penetrating through the mammary gland is removed. The skin flap survival is primarily dependent on the blood flow originating from the periphery where the skin flap is attached to the thorax. The blood supply derives from the subdermal plexus and the subcutaneous vessels that are extensions from the intercostal perforators. These vessels lie in the subdermal layer of the mastectomy flaps hence superficial to the dissection plane. Optimizing the blood supply in the skin flaps depends majorly on two essential principles: (I) atraumatic technique in order to minimize injuries in the subdermal plexus during mastectomy, (II) sparring the perforators from the internal mammary artery lateral to the sternum by careful dissection around these.

Tumescent mastectomy technique

Tumescence with epinephrine has been used for local anesthesia for ages and increasingly during the last decade for subcutaneous mastectomy. The technique includes infiltration of epinephrine containing solution with a blunt cannula in the entire breast between the glandular tissue and the skin in the subcutaneous fatty tissue. Using epinephrine results in contractions of the small blood vessels and decreased bleeding enabling a better overview of the surgical field. The technique is described in details and visualized with video previously (14). After infiltration, the mastectomy can be done blindly with blunt dissection or under visual guidance.

When the blind technique is used, the Metzenbaum scissor is simply moved back and forth in the entire breast area with the opposite hand on top of the breast to immobilize the skin flaps and sense the movement of the scissor. This should be as unhindered as possible with only the cutting of Coopers ligament (ligamentum suspensorium mammae) as obstacles in the movement. A longer pair of scissors can be an advantage when inframammary incision is used in nipple sparring subcutaneous mastectomy.

The visual mastectomy dissection technique is done with Metzenbaum scissor and consists of two movements; first, blunt dissection where the two branches of the pair of scissors is separated along the breast tissue detaching the fat lobules from the glandular tissue between the Coopers ligaments. Then, as shown in *Figure 2* the ligaments are cut with the pair of scissors by a sliding movement towards the top of the ligaments to release these from their attachment towards the dermis. The cut has to be as close to the skin as possible in order to remove possible glandular tissue within the ligaments.

The blind technique reduces the surgery time significantly and it is easier for the surgeon. The visual guided technique, which is preferred by the author, has on the other hand several advantages.

First, the epinephrine solution enhances the visual differentiation of glandular tissue including Coopers

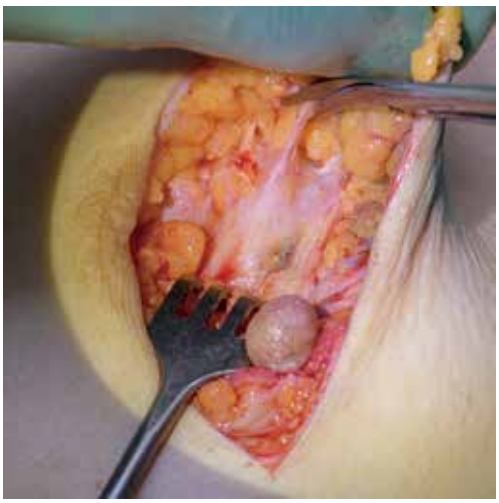

Figure 2 Tumescent mastectomy technique under the guidance of vision. The identification of breast tissue including Coopers ligaments and subcutaneous fatty tissue is greatly improved when using tumescent technique.

ligaments from the subcutaneous fat. These structures become much more visible and it is easy to the surgeon to refine the dissection to keep the fatty tissue on the skin flaps and remove if not all, then as close as possible to all glandular tissue increasing the oncological safety. This is clearly shown in *Figure 2*. Where the yellow fat on the underside of the skin flaps is easily differentiated from the white glandular tissue beneath.

Secondly, the atraumatic technique in the right avascular dissection plane conserves the blood vessels in the dermal layer and ensures optimal blood supply of the skin flaps. The survival of the skin flaps depends on the blood flow to the skin. Keeping this unharmed greatly reduces the risk of postsurgical complications including necrosis, and wound dehiscence but also infections, since the risk of infection is increased if the blood flow to the skin is compromised.

And third, it makes preservation of most of the subcutaneous fatty tissue possible. A thick layer of fatty tissue enables a cosmetic superior result. This is especially important when the mastectomy is immediately followed by breast reconstruction with silicone implants but also ensures an optimal result using autologous flaps. A thick coverage results in a far softer natural and aesthetic acceptable result than thin skin flaps which visualize the implant edges in an unnatural way. Furthermore, a thick skin flap implies a longer distance from the skin surface to the implant, reducing risk of infection.

Risks associated with tumescent has been reported. A meta-analysis based on 4,049 breasts from 5 studies with Level of Evidence III suggested increased risk of skin flap necrosis with tumescent mastectomy technique (15). Stratification into blind and visual technique was not done. This was not corroborated in a later published study with Level of Evidence I by Lautrup *et al.* (16) They randomized 371 breasts to either tumescent mastectomy technique or mastectomy with electrocautery technique. They found no statistically significant difference regarding necrosis, infection, or bleeding. These patients were mastectomized using the blind dissection technique in the tumescent group and extra attention to preserve the blood supply to the skin has therefore not been given. Ng *et al.* reviewed nipple sparing mastectomy and compared necrosis among women having mastectomy with either tumescence and sharp dissection or electrocautery (17). They found statistically significant higher frequencies of both full thickness necrosis (12.8% *vs.* 1.3%) and partial thickness necrosis (33.3% *vs.* 13.0%) among the electrocautery group compared with the tumescent group. Other studies including both autologous and implant based immediate breast reconstruction find neither increased nor decreased risk of skin flap necrosis with the tumescent technique (18-21). These studies do not, however, specify whether blind or visual technique has been used. Surgical time for tumescent technique has been shown to be equal (16) or shorter than compared techniques (17,19).

Indocyanine green laser angiography (ICG) is a modality widely used to describe intraoperative flap perfusion. This has been adapted to mastectomy skin flaps especially when immediate breast reconstruction is planned. Failure to detect perfusion problems may result in postoperative necrosis, reoperation, infection and ultimately implant loss (22). Usage of ICG intraoperative empowers the reconstructive surgeon to detect areas with low perfusion and followed with immediate excision of critically perfused areas before reconstruction, reduces the risk of post-operative necrosis and frequency of reoperation (23,24). Furthermore, ICG- angiography has been shown to be superior to clinical judgement (25).

Using ICG along with tumescent mastectomy technique has, however, been shown to be complicated. Typically, a low score of perfusions is found. When left *in situ* without excision, the tumescent skin flap does not subsequently suffer from necrosis as predicted by the ICG. It seems therefore not advisable to combine ICG with tumescent technique. Indocyanine green laser angiography, however,

do not improve perfusion of mastectomy skin flaps. Neither does it prevent nor reduce risk of necrosis, it just visualizes low perfused tissue areas susceptible to necrosis (26-28).

Even if the differentiation between glandular tissue and fatty tissue is more clearly visualized and makes it possible to also include most of the Coopers ligament in the resected tissue, this technique does not exclude the risk of residual breast tissue completely. Karusseit *et al.* demonstrated small islands of breast tissue in the subcutaneous fatty tissue (29). Some of these might represent breast tissue in cross section of Coopers ligaments, but some might also just be naturally dispersed islands of breast tissue. While the cautious dissection technique described here would eliminate most of the Coopers ligaments it would not eliminate such possible tissue islands located in the subcutaneous fatty tissue. Therefore, the existence of small amount of residual breast tissue cannot be ruled out. The author has, however, on several occasions resected some of the dissected skin flaps, when these were in abundance, and had the pathologist to especially go through this for identification of residual breast tissue. This has not been found in the histologic examination. A more systematic examination of residual breast tissue in dissected skin flaps after tumescent mastectomy remains to be done.

Conclusions

Tumescent mastectomy technique used under the guidance of vision reduces bleeding and thereby enhances visualization of the correct dissection plane. The technique optimizes removal of breast tissue including Coopers ligaments and seems therefore to optimize oncologic safety. It is furthermore a less traumatic technique sparing the subcutaneous fatty tissue and the subdermal layer of blood vessels optimizing skin flap perfusion and thereby possibly reducing the risk of skin necrosis. Intraoperative use of indocyanine green laser angiography to assess tissue perfusion in real time is, however, invalid when tumescent technique has been used. If skin resection and choice of implant in immediate breast reconstruction depend on this, tumescent technique needs to be avoided.

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Review Article

The versatile latissimus dorsi flap: old and reliable or outmoded—with or without an add on?

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Abstract: Latissimus dorsi (LD) myocutaneous flap has long been the golden standard for breast reconstruction. Although free flaps have overrun pedicled flaps as the autologous reconstruction modality of choice for many patients, the LD flap is a good option when microsurgical reconstruction is not suitable or available. Many variations of the flap exist, some aiming to add volume and others to spare muscle function. The traditional LD flap for breast reconstruction has some drawbacks and controversies. The shoulder-related donor site morbidity and the extent of its severity, as well as the optimal management of the thoracodorsal nerve are still debated. To achieve a sufficient size, the LD flap was traditionally combined with implants or expanders. This practice has been questioned during the last decades due to implant-related complications. Instead, large volume fat grating has become a valuable add-on for the LD flap, renewing the LD as a primary total autologous reconstructive alternative. Cost-effectiveness analyses support the use of autologous reconstructive modalities, slightly favoring pedicled flaps. With an increasing number of reconstructive options available, patients and their reconstructive surgeons will need to collaborate in a shared decision-making process. The LD reconstruction warrants thorough patient counselling, but is still a reliable choice for a selected group of patients, especially those for whom other alternatives are not suitable.

Keywords: Latissimus dorsi flap; breast reconstruction; fat grafting

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Introduction

Today's plastic surgeons and post-mastectomy patients are collaborating closely on reconstructive options. In fact, breast reconstruction has become an integral facet on the breast cancer treatment algorithm. Plastic surgeons have several reconstructive methods to choose from. Traditionally, the myocutaneous latissimus dorsi (LD) flap has been considered one of the workhorse flaps for autologous breast reconstruction. It is a reliable reconstructive option with a consistent vascularity, and it is easy to learn as no microvascular anastomosis is needed (1,2). The LD can be used in both immediate and delayed settings (1), in partial breast reconstructions (3-6), in uni- or bilateral cases (7-9), together with implants or expanders, or as an autologous flap—alone or with fat grafting (10).

The LD flap was first described by Iginio Tansini. In 1896, he published a dorsal cutaneous flap to cover the defect after breast cancer surgery, and in 1906 he redesigned the procedure to include the LD muscle in the flap (11-13). His method, a radical mastectomy with the LD flap, was popular throughout Europe between 1910 and 1920 (11).

The flap was reintroduced for breast reconstruction in the 1970's (14-16). In northern Europe, Finland has been one of the forerunners using the LD flap (17). This paper is a narrative review of the different aspects of using the LD flap for breast reconstruction.

Variations of the LD flap

Numerous variations and refinements to the conventional LD flap exist. Some modifications, such as the extended LD, aim to add volume by including fat extensions above or below the muscle, for example the subcutaneous, lumbar and subserratal fat, and parascapular and scapula "fat fascia" (1,18-21). In addition, a fleur-de-lis skin paddle version has been used to carry additional fat on the surface of the LD muscle (22). Other variations aim to decrease donor site morbidity, such as the muscle sparing versions (23-26) and the thoracodorsal artery perforator (TAP) flap (27), to name a few. In addition, endoscopic (28-32) and robotic (33,34) LD muscle harvesting has been introduced.

When to consider an LD?

Although free flaps have overtook pedicled flaps as the primary autologous reconstruction modality, there are cases when a microsurgical reconstruction is not suitable or available. For example, the lack of other suitable soft tissue, comorbidities, obesity, smoking, prior major abdominal surgery, or unavailability of microsurgical services advocate other autologous reconstructive modalities (10,35,36). In these cases, the LD flap offers a good option. In addition, fat grafting has given this traditional flap a new resurgence in popularity as the primary total autologous reconstructive method (10).

Use of the LD flap is also relative to cultural beliefs and geographical constraints. In some countries, the LD has gone almost extinct and is mainly saved for tertiary or palliative purposes, such as for irradiated patients, delayed reconstructions or for the salvage after failed primary or secondary reconstruction (37,38). In other countries, however, the LD is part of the standard repertoire. The LD flap is a good option when microsurgical techniques are not available. In some countries, few patients have access to a practicing microsurgeon (39). Furthermore, a survey showed that only one fourth of practicing US plastic surgeons perform any microsurgical breast reconstruction (40). In addition, the proportion of post mastectomy non-autologous, implant-based reconstructions have grown in the US, whereas the number of autologous reconstructions generally have declined (41). This is, in part, due to the increase in the number of contralateral prophylactic mastectomies, and may, in part, reflect the reimbursement trends (41). Patient education and awareness, leading to a fear of adverse effects in the donor sites, may also contribute to the decline in the use of the LD.

Obesity and the LD

Obesity is considered a risk factor for extensive surgery, including microsurgery. Convincing meta-analyses have shown a clear increase in overall complications, recipient and donor-site complications, and partial flap failure in patients with a body mass index (BMI) ≥30 kg/m^2 (42). According to the recent studies, the LD flap seems to be a safer option in overweight patients. Yezhelyev *et al.* evaluated the influence of BMI on the complications after postmastectomy LD flap reconstruction (43). They concluded that the incidence of both flap and donor site complications after LD reconstruction was not significantly different in overweight (BMI 25–29.9 kg/m^2) and obese (BMI ≥30 kg/m^2) patients compared to the normal weight population. However, obese patients were more likely to develop mastectomy skin flap necrosis (43). In addition, Novak *et al.* compared complication rates between immediately fat-grafted LD and free tissue transfer in obese (BMI ≥30 kg/m^2) population, and found out that the free tissue transfer group had a significantly higher rate of major and systemic complications (44).

Although LD reconstruction appears to be a safer option for overweight patients, one could assume that in breast reconstruction surgeries of approximately the same duration and recovery, the same systemic complications tend to be present—microsurgery or not. Currently, in our own practice, immediate or delayed elective LD-based breast reconstruction, is not recommended for patients with a BMI of 30 or more.

Donor site sequalae

The harvest of the LD flap comes with some drawbacks. The contour deformity of the back after the harvest, together with a long and visible scar, may be undesirable by some (2,45). Seroma formation in the back is the most common complication (46). It is treated with a prolonged suction drainage followed by outpatient aspirations after the drain has been removed (1). To prevent this problem, different solutions have been attempted. A recent prospective randomized controlled trial compared the efficacy of fibrin

glue, triamcinolone acetonide, and quilting sutures in the seroma prevention after LD reconstruction. This study showed that the use of quilting sutures significantly decreases the incidence of donor-site seromas, leads to earlier drain removal and maintains a low complication profile (46).

The shoulder-related donor site morbidity and the extent of its severity is debated. The literature on this subject is quite controversial (47-49). Some state that the effect of the LD harvest on the shoulder function is negligible and minimal, whereas others have found that the impairment of the function is significant (47). A recent systematic review and meta-analysis of functional shoulder impairment after LD breast reconstruction, including 26 articles published until 5/2017, concluded that although the LD flap transfer appears to affect shoulder function, these limitations seem to be minimal. However, many of the studies comprised of small series, and some had a rather short follow-up period. Thus, the authors stated that the existing literature on the long-term shoulder function impairment is insufficient to draw any firm conclusions (47). Lohana *et al.* studied the functional recovery after bilateral extended autologous latissimus dorsi (EALD) breast reconstruction (50). They stated that bilateral EALD breast reconstruction does not appear to cause significant long-term impairment of shoulder function. However, they concluded that women should be appropriately counselled and preoperatively screened, and intensive physiotherapy might be needed.

With regard to the LD flap types, it seems that sparing the LD muscle can result in less functional implications than other types of LD flaps used (47-49). A recent prospective randomized controlled trial compared shoulder function after delayed breast reconstruction by either a LD flap or a TAP flap with assessment at baseline and 3, 6, and 12 months postoperatively. The study showed that patient-reported shoulder-related pain was significantly lower in the TAP group at 12 months after surgery when adjusting for pain at baseline, and the patients had better function of the shoulder 1 year after the reconstruction (51). In addition, patients reconstructed with the LD flap had a higher level of shoulder related pain and a reduced ability to perform normal daily functions while the range of movement and the strength of the shoulder did not seem to be influenced significantly. However, they stated that a longer follow-up period is needed to establish whether the observed difference change with time.

Should we cut the thoracodorsal nerve?

Optimal management of the thoracodorsal nerve in pedicled LD flaps for mastectomy reconstruction is controversial. Animation deformity due to contraction of the muscle may cause a functional and aesthetic problem as well as be distressing for patients (1). To solve this issue, division of the thoracodorsal nerve has been proposed. However, flap denervation has been suggested to cause muscle atrophy leading to poor soft tissue coverage of a possible implant. Kääriäinen *et al.* challenged the idea that the resection of the nerve leads automatically to a volume loss and protects from pain and untoward muscle movement (52,53). Histology of the LD flaps with resected nerves showed that muscle atrophy was replaced with fatty degeneration 1 year post operatively while the volume of the flap was preserved on magnetic resonance imaging (MRI). Furthermore, patients with denervated LD flaps presented with a variety of animation and pain symptoms. The authors concluded that for the interest of operation time and simplicity, there is no need to cut the nerve. However, the possibility of the nerve resection having been too distal in the study subjects was not discussed. A recent retrospective clinical and anatomical study strongly suggests that reanimation does eventually occur despite nerve transection and is often symptomatic. Persistent late onset animation deformity is attributable to anatomical differences in the thoracodorsal branching patterns, rather than patient (age, BMI, smoking) or the therapeutic (oncology or surgery related) factors (54). Other studies may have failed to monitor this, due to short- or nonsystematic follow-up of patients. The thoracodorsal nerve starts to branch about 4 cm proximal to the superior border of the LD muscle and thus careful dissection of the nerve branch as proximally as deemed safe has been recommended. As this is technically arduous, preoperative counselling of the patient that dynamic motion may return years postoperatively is advised (54).

Does the LD flap need an add-on?

To ensure sufficient size, the LD flap was traditionally quite routinely combined with implants or expanders, representing the classical use of the LD myocutaneous flap (*Figure 1*). During the last decades this practice has been questioned due to implant-related complications, such as infection, extrusion, periprosthetic contraction, rupture, and more recently, the suggested association with the anaplastic large cell lymphoma (55,56). Multiple operations related to the implant-based problems seemed overwhelming for the patient and the healthcare system.

Improved technical skills and equipment have led to large volume fat grating (57) resulting in a sufficient, and in

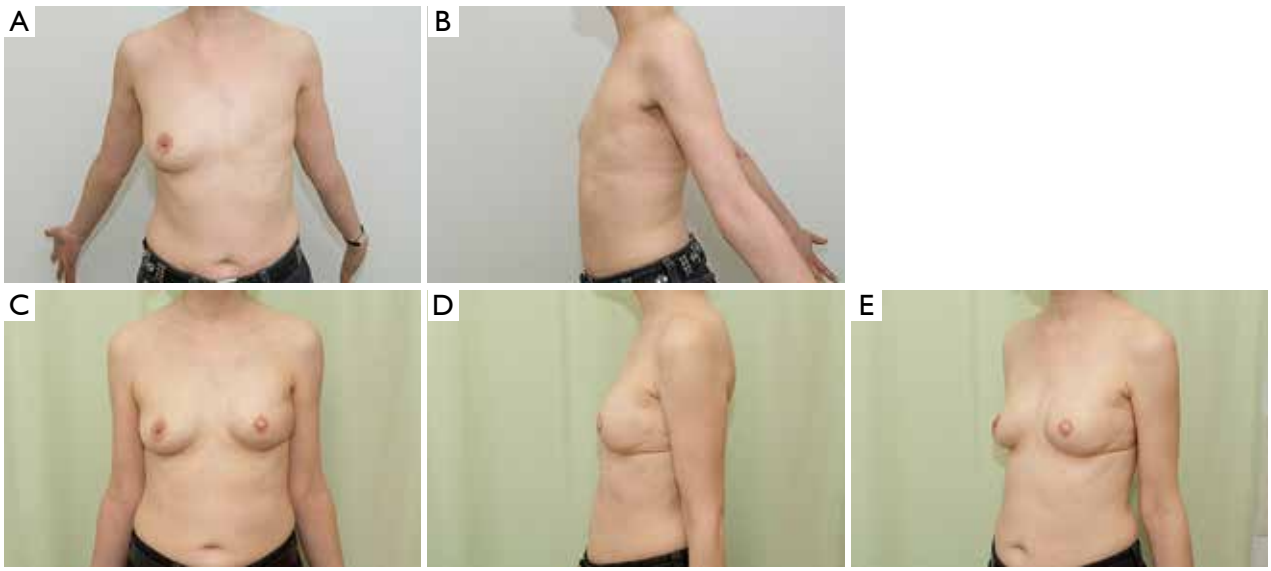


Figure 1 This 60-year-old patient, still disease free, underwent mastectomy and axillary clearance for a bifocal ductal carcinoma in 2005, followed by adjuvant therapy. She had a delayed latissimus dorsi (LD)-reconstruction with an add on of a Mc Ghan ST410 125 cc implant, the custom at the time. (A,B) Preoperative antero-posterior (AP) and side view. (C-E) In 2010, at her so-called final check-up: AP, side and oblique views.

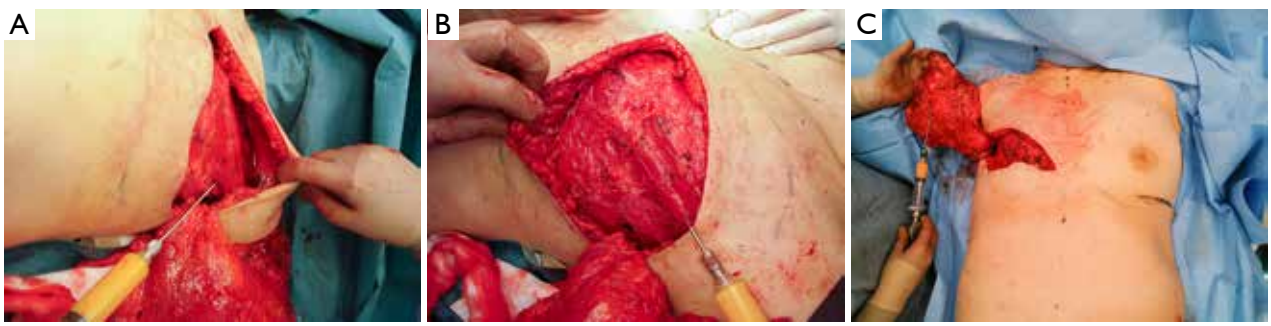
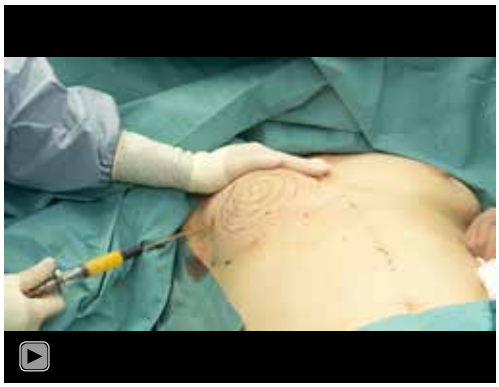


Figure 2 Intraoperative view of fat grafting in the same setting as a delayed latissimus dorsi (LD) reconstruction. Fat can be injected subcutaneously, into the pectoralis major (A,B) and into the flap (C).

many cases predictable, take rate (58). This has increased the use of fat grafting not only for full breast reconstruction (57,59,60), but also for aesthetic augmentation and, for this review interestingly, as an add on to the LD flap. With the LD flap, free fat grafting can be inserted into the muscular and the subcutaneous part of the flap, into the chest wall surface, under the dermis, and especially into the pectoralis major muscle (*Figure 2*, *Video 1*). In our series covering the last 10 years, fewer implants have been used as an add on to the LD flap, but fat grafting has become a more frequent adjunct. The fat grafting can be done either during the LD reconstruction (*Figures 2,3*) or at a later timepoint (*Video 1*).

In a study by Leuzzi *et al.* the number and the type of revision procedures, duration of the hospitalization, the complication rate, and the patient satisfaction were evaluated in a retrospective cohort of patients undergoing LD reconstruction, either with an add on of an implant or with fat augmentation. Patient satisfaction was assessed using the patient-reported outcomes instrument BREAST-Q. Findings concerning the total hospitalization time, overall duration of the reconstruction process, and the distribution of supplementary surgical procedures demonstrated no statistically significant differences between the implant and the fat grafting groups. However, patients in the fat grafting



Video 1 Fat grafting into the latissimus dorsi (LD) flap in a delayed manner due to asymmetry between the autologous LD breast and the contralateral breast. Under the rather scarred circumstances, fat is injected with a blunt cannula into the pectoralis major muscle, into the myocutaneous flap, into the subcutaneous layer and, above all, the very superficial subdermal layer. The videoclip illustrates the angles of approach and teaches the technique.

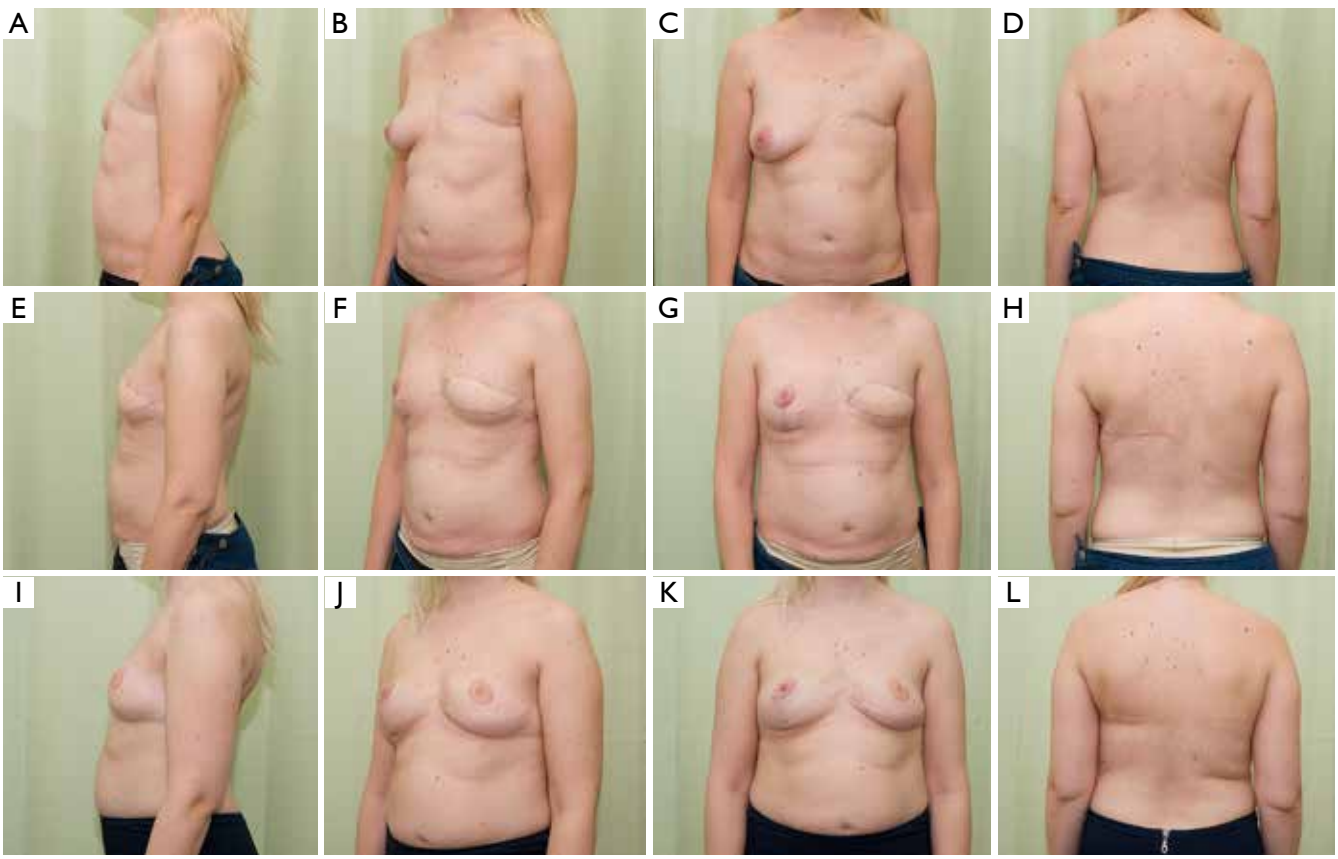


Figure 3 At the diagnosis of breast cancer in 2010, this patient was 31 years old and a mother of three. She opted for a delayed latissimus dorsi (LD) reconstruction in 2012 with an immediate fat enhancement (200 cc) and a symmetrizing mastopexy. An autologous solution with a short recovery and no further refinements suited her. The result has lasted. (A-D) Preoperative; (E-H) 1 month postoperatively; (I-L) in 2015. Side, oblique, antero-posterior and posterior view.

group scored higher in the satisfaction with breast domain of the BREAST-Q. Leuzzi *et al.* concluded that the addition of a breast implant with LD reconstruction does not decrease the breast reconstruction time in terms of number of the revision procedures and hospitalization time, yet exposes patients to a higher complication rate and does not improve patient satisfaction (56). This was supported by Demiri *et al*., who stated that the fat augmented LD flap constitutes an alternative method for delayed autologous reconstruction after post-mastectomy irradiation, avoiding implant-related complications (55). In other studies, the automatic use of an implant as an add on is hardly questioned (51).

Can contralateral reduction mammaplasty promote health?

Despite appropriate patient selection, extensive flap harvesting, and either fat or implant enhancement of the LD reconstruction, a massive breast cannot be achieved. In patients with a hypertrophic contralateral breast, opting for a unilateral LD reconstruction, a symmetrizing reduction mammaplasty has several health promoting effects. Cancer survivors undergoing delayed breast reconstruction may have benefited from oncoplastic surgery or a contralateral breast reduction at the time of the mastectomy. However, the option of a contralateral procedure can be considered also at this later stage. Reduction mammaplasty as such rehabilitates neck-, shoulder- and back-related straining problems (61). Notably, even in healthy, non-cancer subjects, abnormal histopathological findings are revealed in 10% of the patients; of the findings 1% are malignant and 5.5% are high-risk lesions (62). In patients with breast cancer, the figures double (63). Therefore, histopathological analysis of the specimens should be thoroughly considered.

Cost-effectiveness analysis for breast reconstruction; where does the LD flap stand?

Cost-effectiveness analysis guides evidence-based practices of plastic surgeons by quantifying the balance between the risks and the benefits of each treatment strategy from both a patient perspective and a provider perspective (64). If the provider is a public health care facility, the number and the duration of reconstructive procedures, and, above all, the durability of the result plays a major role. On the contrary, if the provider is a private business driven by insurance or industry influences, multiple procedures over the years may give a better profit, enhanced by reimbursement strategies (41). Interestingly, the cost effectiveness analysis on five widely used breast reconstruction techniques clearly favored autologous reconstruction in both radiated and non-radiated patients. In more detail, the pedicled autologous tissue reconstruction was slightly more cost-effective than the free autologous tissue options in both cohorts (64).

Nevertheless, patient centered solutions should be based on the validated patient-reported outcome measures (PROM), available for breast surgeons in many languages to date, so that decision making can be based on solid data (65). For the patient, every surgery is an investment in time and an exposure to morbidity. Thus, cost-efficiency analyses widely applicable to most institutions should be used with prudency, and they are not to be enforced over individual patient preferences (64).

Conclusions

The LD flap is still a worthy choice for breast reconstruction in a selected group of patients, especially when other alternatives are not available. Even in good hands, the LD reconstruction warrants thorough patient counselling and information, as some untoward consequences may appear at a later stage. The implant add-on is associated with the potential of further implant-related sequalae. Fat grafting for flap augmentation and scar correction has resurrected the LD flap as a versatile tool for breast reconstruction.

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Review Article

An update on breast animation deformity grading systems—a systematic review

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Background: Breast animation deformity (BAD) is a motion deformity resulting in displacement of the implant and skin rippling with pectoralis contraction. Animation deformity has recently gained more attention in the literature, however its prevalence and grading has yet to be established. The objective of this study was to systematically assess the existing grading systems of BAD, and the quality of grading systems.

Methods: A systematic literature search was conducted according to PRISMA Guidelines in PubMed, EMBASE Ovid, EMBASE Classic (OVID), and Cochrane Database of Systematic Reviews. The review was registered in PROSPERO with registration number CRD42021223940. For all eligible studies, we evaluated the methodological quality of the studies.

Results: Out of 1,297 studies, a total of 13 studies were retrieved assessing grading systems of animation deformity. Nine grading systems exists in the literature. The prevalence of animation deformity was 73.3% in total, 73.9% of patients with subpectoral implants experienced some degree of animation deformity, in contrast to prepectoral implants where 10.5% experienced some degree of animation deformity.

Conclusions: There is great variability in the present literature regarding quality, reproducibility and validity of the grading systems, as well as the prevalence of animation deformity. We recommend two new grading systems, the qualitative Nipple, Surrounding Skin, Entire Breast (NSE) grading scale and Kim *et al.*'s quantitative grading system—two high quality, reproducible and clinically-relevant assessment methods. The evidence is still inadequate in the existing studies and more studies are needed where the new grading systems are being used for future comparative studies, especially randomized-controlled studies.

Keywords: Breast animation deformity (BAD); motion deformity; breast reconstruction; breast implant

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Introduction

Breast animation deformity (BAD) is a common and afflicting sequelae of breast reconstruction or augmentation, and is estimated to occur with variable severity in anywhere from zero to 75% of reconstructions/augmentation (1). It is characterized by an unsightly deformation, a motion deformity, resulting in displacement of the implant and skin rippling associated with contraction of the pectoral muscle (2). BAD is an aesthetic concern, as well as a functional problem. Muscle twitching, pain, and impaired shoulder function are significant problems, especially in physically active women—thus affecting patient's health-related quality of life (HR-QOL) (3-5).

BAD is seen following submuscular implant placement in both breast augmentation and reconstruction. Concurrently, patients with submuscular breast augmentation or reconstruction have reported more pain compared to patients with premuscular/prepectoral augmentation or reconstruction (6,7). In a previous review from our department we postulated, that the degree of BAD seemed proportional to the degree of muscle involvement in implant-based breast reconstruction or augmentation (8). This means that the degree of BAD seems to be proportional to the surface area of implant covered by muscle. Total coverage seems to be associated with the most severe degree of BAD and gradually diminishes over dual-plane to triple plan techniques and seems negligible with no muscle coverage. However, evidence is still limited regarding the etiology of BAD (9,10). Furthermore, we assessed four different grading systems available at that time, and the surgical techniques used in the included studies (8). None of the existing grading scales were appraised useful for clinical purposes (1,11-13). The topic 'animation deformity' has subsequently gained more attention, and numerous studies have been conducted to assess the etiology, treatment and grading systems of BAD (9,14-18).

This study is the newest update and a further development of our previous systematic review. The aim of this review was to critically appraise the various grading systems available to evaluate BAD, and to investigate the quality and reproducibility of the individual grading systems in the search of the optimal grading scale. In addition, we estimate the prevalence of BAD following either breast augmentation or reconstruction. Finally, we wish to discuss the applicability of BAD assessment tools in daily clinical practice and for scientific purposes. We present the following article in accordance with the PRISMA reporting checklist (available at https://abs.amegroups.com/article/view/10.21037/abs-21-46/rc) (19).

Methods

This review has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number: CRD42021223940.

Literature search strategy

In October 2020 a systematic literature search was conducted according to PRISMA Guidelines (19) in the following electronic databases: PubMed (National Library of Medicine, NLM), Embase Classic (Ovid), and Embase (Ovid). The following terms was used in the search strategy: ((direct-to-implant) OR (breast implant) OR (breast implantation) OR (breast reconstruction) OR (breast augmentation) OR mammaplasty OR mastoplasty OR (breast enlargement) OR (breast prosthesis) OR (breast enhancement)) AND ((implant placement) OR (pre pectoral) OR subpectoral OR (pre pectoral hammock) OR subglandular OR submuscular OR premuscular OR subfascial OR (direct-to implant) OR (pectoralis muscles) OR (dual-plane) OR (triple-plane)) AND (distortion OR deformation OR (animation deformity) OR (breast deformation) OR contraction OR elevation OR displacement OR malposition OR cosmetic OR aesthetic OR appearance OR rippling). Only studies in English, Danish or German were included, with no time limitations.

The reference list of included papers was subsequently hand searched for additional studies.

The literature search was conducted in Covidence (https://www.covidence.org). First, a title and abstract screening was conducted. Studies evaluating "breast animation deformity", "implant-based breast augmentation", or "immediate breast reconstruction" were considered candidate studies for further evaluation based on the inclusion and exclusion criteria established prior to the literature search.

Eligibility criteria

Studies were selected if published as full-text papers and if the objective of the studies were assessment or quantification of BAD. Studies, that did not define how BAD was assessed were not considered eligible.

Inclusion criteria:

(I) Study design: prospective, retrospective, randomized controlled trials, systematic reviews;
(II) Assessment of BAD objective and subjective assessment;
(III) Language requirements: English, Danish, or German.

Exclusion criteria:

(I) Study design: Case-reports;
(II) Other languages then the above named;
(III) Not defining or assessing BAD;
(IV) Studies that focused on most appropriate implant type, and not complications or BAD;
(V) Studies that only included reoperations;
(VI) Studies that focused on treatment of BAD, thus

did not define BAD.

Study selection and data extraction

Full-text of candidate studies were retrieved and screened by two independent authors (J.B.T. and F.D.). Conflicts were resolved by consensus of the two reviewers and, if necessary, a third author (J.A.S). For all eligible studies, the same two reviewers (F.D and J.B.T.) extracted data. All included studies were reviewed using a descriptive checklist including authors, publication country, year, study design, sample size, patient demographics, see *Table 1*. The quality of the included studies was assessed with a checklist developed by our study group in regards of: (I) Description of study sample, (II) rate of participation, (III) surgical technique description, (IV) follow-up period, (V) assessment of BAD, (VI) grading, classification or quantification of BAD, and (VII) reproducibility of the assessment of BAD. The quality of each study is represented with a total score between zero to seven (zero with the lowest quality, and seven with highest quality).

Results

Eligible studies

The literature search yielded 1,297 studies imported for screening, reduced to 1,162 after duplicates were removed. These studies were reviewed as described in methods by two independent reviewers, 13 studies met the inclusion criteria and were included in this systematic review (1,4,8,9,11-18,20). The process of selecting eligible studies is listed in *Figure 1*, PRISMA flowchart.

Study characteristic

Descriptive characteristics of included studies are summarized in *Table 1*. Studies were published from 2004 to 2020. The study designs were retrospective, prospective, cross-sectional, descriptive studies, systematic reviews or overviews. The number of participants in the included studies ranged from 25 to 605. The age of participants was described in seven studies (4,9,11,13-16), with a median age ranging from 33.6 to 49.7 years. There were various variations of BAD assessments from surgeon evaluations, patient self-evaluation to quantification with imaging software (ImageJ) for analysis of BAD. Four of the six studies using patient-reported outcomes used non-validated questionnaires (1,4,13,15), whereas two studies used the validated BREAST-Q (9,16). The follow-up period ranged from three months to 15 years. Out of the 13 included studies, four studies were evaluated in previous review (1,11-13), five new grading systems were suggested (4,14,15,17,18), three studies reused or modified the existing grading systems (9,16,20), and one systematic review (our previous review) did not suggest a new grading systems, but evaluated the quality of the four previously described grading scales (8).

Study quality

Twelve studies had a clear description of the study (1,4,8,9,11-16,18,20), one study presented a grading system without a clear definition of the study (17). The participation rate was described in 11 studies. Two studies consisted of a systematic review and an overview with a description of number of studies or participant rates in the included studies (8,20), while three studies did not define participant rates or number of studies (11,17,18). Three studies did not describe the surgical technique used (4,17,20). Only four studies defined their follow-up period in the group (9,14,15,21), whereas the remaining studies had different follow-up on patients (1,4,8,11-13,16-18,20). BAD was assessed by competent assessors in 10 studies (1,4,8,11,12,14-16,20,21), three studies did not define who assessed BAD (9,17,18), and one study only used patient-self assessment of BAD (13), using a non-validated questionnaire. Six studies assessed patient-reported outcomes (1,4,9,15,16) of which only two studies used validated questionnaires (9,16). Thirteen studies had a well-defined grading system of BAD (1,4,8,9,11-18,20), however three studies reused existing grading systems (9,16,20). Only three studies examined whether their findings were reproducible (14,15,21). The quality of studies is presented in *Table 2*.

Surgical technique

The surgical techniques used varied across studies. The surgical technique of Pelle-Ceravolo *et al.* (12), Spear *et al.* (1), Nigro *et al.* (13), and Bracaglia *et al.* (11) were all subpectoral implant placement and is described in our previous review (8). In brief, Pelle-Ceravolo described breast augmentation using either the Regnault technique or a dual-plane muscle-split technique (12). Spear *et al.* used a dual-plane partial muscle coverage technique (1),

Table 1 Descriptive checklist

Author, year	Country/region	Type of study	No. of participants	Method of data collection	Data assessors	Duration of follow-up (mo)	Outcome variable
Pelle-Ceravolo, 2004, (12)	Italy	Retrospective	348/580	Psychical exam, 6 judgements for each patient	Surgeon, nurse, patient	6	BAD
Spear, 2009, (1)	United States	Case-series	40/40, 69/195	Photographs, questionnaire (non-validated)	Plastic surgery residents, patient	6	BAD, self-evaluation of BAD
Bracaglia, 2013, (11)	Italy	Retrospective	524	Photographs, physical exams	Plastic surgeon	6–180	BAD
Nigro, 2017, (13)	USA	Retrospective	84/108	Questionnaire	Patient	6–72	BAD, level of physical activity
Dyrberg, 2019, (14)	Denmark	Retrospective	37 (74 breasts)	Video	Plastic surgeons	16 (476 days)	BAD, inter- and intraobserver agreement
Vidya, 2018, (18)	United Kingdom	Descriptive, review	N.S.	Photographs, Video	N.S	N.S.	Classification of BAD
Kim, 2019, (15)	Taiwan	Prospective, cross-sectional	88 (145 breasts)	Video	ImageJ analysis Physician	17.7	Quantification of BAD
Becker, 2017, (4)	United States	Cross-sectional study	25	Chart reviews, questionnaire, physical examination	Physical examination by senior author and medical student	N.S.	Classification of BAD, quality of life
Bracaglia, 2020, (9)	Italy	Retrospective	605	Photographs, physical examination	Plastic surgeons	6, 12, 80	Classification of BAD, Breast-Q
Kümmel, 2018, (17)	Germany	Descriptive	N.S.	Physical examination, photographs, N.S.	N.S.	N.S.	Classification of BAD
Dyrberg, 2019, (8)	Denmark	Systematic review	4 studies	Systematic review	Pelle-Ceravolo, Spear, Bracaglia, Nigro grading system	6–180	BAD
Fracol, 2019, (20)	United States	Overview	3 studies	Overview	ImageJ analysis, physician	N.S.	Classification of BAD, treatment of BAD
Fracol, 2020, (16)	Taiwan	Prospective	141	Video	ImageJ analysis, physician	3–113	BAD, BREAST-Q

BAD, breast animation deformity; N.S, not specified; mo, months.

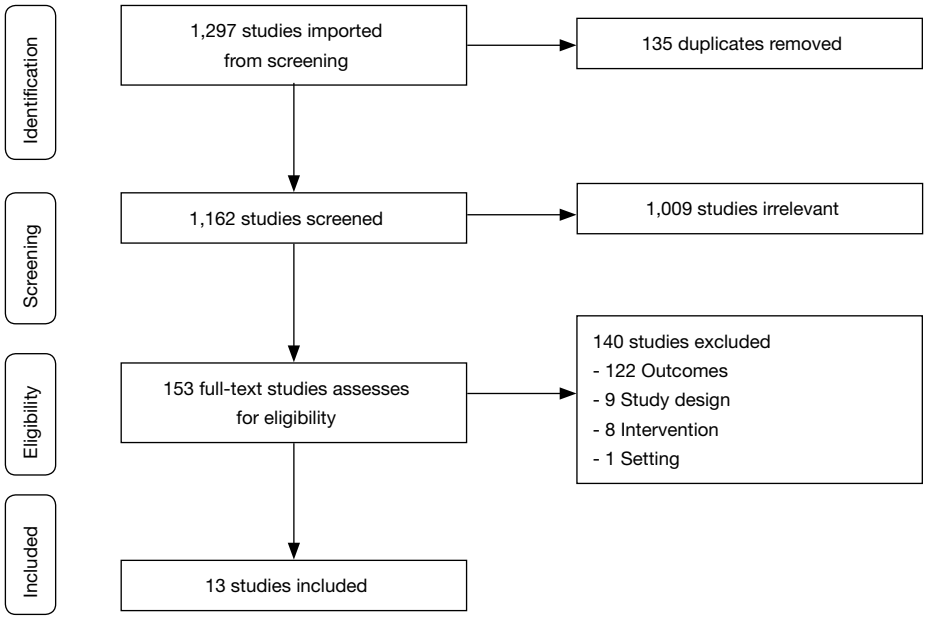

Figure 1 PRISMA flowchart. The study selection process.

Table 2 Quality checklist

Author, year	Clear description of study	Participation rate	Description of surgical technique	Similar follow-up	Competent assessment of BAD	Definition of BAD	BAD definition reproducible?	Total score
Pelle-Ceravolo, 2004, (12)	Yes	Yes	Yes	No	Yes	Yes	No	5/7
Spear, 2009, (1)	Yes	Yes	Yes	No	Yes	Yes	No	5/7
Bracaglia, 2013, (11)	Yes	No	Yes	No	Yes	Yes	No	4/7
Nigro, 2017, (13)	Yes	Yes	Yes	No	Patient self-assessment	Yes	No	5/7
Dyrberg, 2019, (14)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7/7
Vidya, 2018, (18)	Yes	No	Yes	No	No	Yes	No	4/7
Kim, 2019, (15)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7/7
Becker, 2017, (4)	Yes	Yes	No	No	Yes	Yes	No	4/7
Bracaglia, 2020, (9)	Yes	Yes	Yes	Yes	No	Yes	No	5/7
Kümmel, 2018, (17)	No	No	No	No	No	Yes	No	1/7
Dyrberg, 2019, (8)	Yes	Yes	Yes	No	Yes	Yes	No	5/7
Fracol, 2019, (20)	Yes	Yes	No	No	Yes	Yes	No	3/7
Fracol, 2020, (16)	Yes	Yes	Yes	No	Yes	Yes	No	5/7

BAD, breast animation deformity.

and Bracaglia a triple-plane technique (11). Nigro used a dual-plane technique for patients undergoing either direct-to-implant or two-stage immediate breast reconstruction with the use of acellular dermal matrix (ADM) in the lower pole (13). Since then, six new studies described their surgical techniques while assessing or grading BAD (9,14-16,18,22). Bracaglia *et al.* (2019) presents a triple-plane technique, as described in their previous study, and added either a bra flap or an inverted bra flap modified dual plane technique. (9). Vidya *et al.* (2018) and Kim *et al.* both briefly described a subpectoral implant placement using either a bra flap or a hammock-based technique using an ADM (15,18). Fracol *et al.* used a subpectoral implant placement, where the pectoralis major muscle was divided along its inframammary and medial border (16). Dyrberg *et al.* used either a subpectoral (dual-plane) implant placement or prepectoral placement of implant (14), both techniques are recently published in visualized articles (23,24). No other studies evaluated prepectoral implant placement and BAD (1,4,8,9,11-13,15-18,20).

Update on BAD grading systems

In our previous review we described the four existing grading scales available; consisting of Pelle-Ceravolo *et al.* (12), Spear *et al.* (1), Bracaglia *et al.* (11) and Nigro *et al.* (13). None of the available grading systems examined their grading scales for reproducibility. Only Spear's grading system was deemed useful for clinical purpose, as it was the only grading system tested for assessment of BAD in a clinical setting (1). Since then, five new grading systems were suggested; Dyrberg *et al.* (14), Vidya *et al.* (18), Kim *et al.* (15), Becker *et al.* (4) and Kümmel *et al.* (17). Three out of the five new grading systems used a 3-point scale (14,15,17), while two studies used a 4-point scale (4,18). The different grading systems are presented in *Table 3*.

Prevalence of BAD and surgical types

Eight studies assessed the prevalence of BAD in their study population using their suggested grading system (self-assessments were not included in this analysis) (1,4,9,11,12,14-16). The total number of patients assessed for BAD was 1,894 in this systematic review. The total prevalence of patients with some degree of BAD (mild, moderate or severe) was 73.3%. We excluded grading scales where grade 1 consisted of none to minimal BAD in the calculation of the total prevalence of BAD. The degree of BAD varied from 10% (22) to 94.7% (14). See *Table 4* for prevalence of BAD in each study.

The prevalence of BAD in the prepectoral group was 10.5% (14). Eight studies assessed BAD in subpectoral implant placement, where the prevalence of BAD were 73.9% (1,4,9,11,12,14-16). The highest prevalence of BAD was found in subpectoral implant placement; dual-plane muscle splitting technique used in Spear *et al.* (prevalence of 78%) (1), Regnault technique used in Pelle-Ceravolo *et al.* (prevalence of 73%) (12) and Becker *et al.* (prevalence of 76%) where the surgical technique was not further elaborated (4). The Regnault technique had a prevalence of 47% of severe BAD, as in our previous review (12). Dyrberg *et al.* assessed BAD with Nipple, Surrounding Skin, Entire Breast (NSE) grading scale (0–6 points), where the prepectoral group had NSE score on 0.2±0.6, while the subpectoral group had NSE score on 4.3±1.1 (14). With supplementary data from the research group, 18 out of 19 patients with subpectoral implant placement had some degree of BAD, a total NSE score of >2, while only two patients in prepectoral implant placement had a NSE score of >2, resulting in a prevalence of BAD of respectively 94.7% (subpectoral) versus 10.5% (prepectoral) in each group.

Discussion

This systematic review is the newest update on BAD grading systems, an evaluation and quality assessment of the existing grading scales, and the prevalence of BAD in regards of implant placement and type of surgical technique. We retrieved 1,297 studies of which 13 studies were included in this review. Since our previous review, five new grading systems have been presented. Only two grading systems scored a maximum of 7 out of 7 points in the quality assessment of studies and grading system; our own NSE grading scale and Kim *et al.*'s grading system. We found significantly higher prevalence of BAD in the subpectoral implant placement group than the prepectoral implant placement group (73.9% versus 10.5%). There was no evidence of a specific type of surgical technique in the subpectoral group would result in higher prevalence of BAD. The total prevalence of moderate to severe BAD was 73.3% in this systematic review.

The grading systems of Kim *et al.* (15) and Dyrberg *et al.* (14) were both rated high in quality in the quality checklist, with a total score of 7 out of 7 total points with a clear description of the grading systems, competent assessment of BAD, clear definition of BAD and

Table 3 Existing breast animation deformity grading systems

Author, year	Class I	Class II	Class III	Class IV	Other
Pelle-Ceravolo, 2004, (12)	Non-existing or minimal deformity	Moderate deformity with a certain alteration of the breast shape but with limited effect on the aesthetic appearance of the breast	Important and obvious deformity that was definitely aesthetically unacceptable		
Spear, 2009, (1)	No distortion and unable to discern whether the implant lie in front of or behind the pectoralis muscle	One is able to tell that the implant is subpectoral, but there is minimal distortion with an aesthetically pleasing result	Moderate distortion but still an aesthetically acceptable result	Severe distortion with an unattractive result during muscle contraction	
Bracaglia, 2013, (11)	No distortion and unable to discern whether the implant lie in front of or behind the pectoralis muscle	One is able to tell that the implant is subpectoral, but there is minimal distortion with an aesthetically pleasing result	Moderate distortion but still an aesthetically acceptable result	Severe distortion with an unattractive result during muscle contraction	
Nigro, 2017, (13)	Twicthing or movement of the upper pole of the breast with certain muscle movement of the arms or chest	If yes, how bothersome do you find it on a scale of 1 to 10 where 1 is not at all and 10 being disabling			Converted to categories: minimal: 1–2.5; mild: 3–5; moderate: 5.5–7.5; severe: 8–10
Dyrberg, 2019, (14)	TBM/NAC distortion: no distortion (0 points)	TBM/NAC distortion: visible distortion (1 point). TBM/NAC moves upwards, but remains in a vertical position	TBM/NAC distortion: severe distortion (2 points). TBM/NAC moved upwards, horizontalized and kinked inwards		NSE grading system
	Breast skin distortion: no distortion (0 points)	Breast skin distortion: visible distortion (1 point); breast skin is slightly wrinkled, with wrinkles apparent in only on quadrant	Breast skin distortion: severe distortion (2 points). Breast skin was wrinkled with long horizontal lines affecting more than one quadrant		• Distortion of the TBM/NAC (0–2 points); • Distortion of the breast skin surrounding the TBM/NAC (0–2 points); • Distortion of the entire breast (0–2 points)
	Breast movement: no movement (0 points)	Breast movement: visible movement (1 point). Movement of the entire breast, the whole breast lifted upwards, revealing a visible inframammary crease	Breast movement: severe movement (2 point). Movement of the entire breast resulting in the whole breast lifted upwards and revealing more than a visible inframammary crease		Total 0–6 points

Table 3 (*continued*)

Table 3 (*continued*)

Author, year	Class I	Class II	Class III	Class IV	Other
Vidya, 2018, (18)	No visible distortion and displacement of the implant during muscle contraction, both during normal and exercise activity	Minimal visible distortion with displacement of the implant (superolaterally) during muscle contraction both in normal and exercise activity, grooving may be seen, unnoticed by patient	Moderate visible distortion during muscle contraction, with displacement of the implant (superolaterally) during muscle contraction both during normal and exercise activity, often noticed by patient	Severe distortion during muscle contraction with persistent displacement of the implant both in normal and exercise activity, unattractive results disturbing the patient	
Kim, 2019, (15)	Patients have less than 2 cm nipple displacement and less than 25% (one-quarter of the breast mound) are of skin contour irregularity (rippling)	Patients have either greater than 2 cm nipple displacement or more than 25% surface area of skin rippling	Patients have both greater than 2 cm nipple displacement and 25% surface area skin rippling		
Becker, 2017, (4)	Minimal breast distortion, minimal lateral displacement, and minimal to no skin rippling	Moderate breast distortion, moderate lateral displacement or elevation, and minimal rippling	Moderate to severe breast distortion, moderate to severe lateral displacement or elevation, and evident skin rippling	Severe deformity, symmetric breasts with severe lateral or superior displacement, and severe skin rippling	
Bracaglia, 2020, (9)	No distortion and no ability to discern whether the implant lay behind or in front of the pectoralis muscle	Ability to tell that the implant was subpectoral, with mild distortion but an aesthetically pleasing result	Moderate distortion, but still an aesthetically acceptable result	Severe distortion with an unattractive result during muscle contraction	

NSE, Nipple, Surrounding Skin, Entire Breast; TBM, top of the breast mound; NAC, nipple areolar complex.

Table 4 Prevalence of breast animation deformity

Author	Subpectoral and used grading system	Outcome	Prepectoral and used grading system	Outcome
Pelle-Ceravolo, 2004, (12)	Muscle-split prepectoral (n=1,812[a])	I: 69.5 (1,261/1,812); II: 24.9 (452/1,812); III:5.4 (99/1,812); total: 30.4 (551/1,812)		
	Regnault technique (n=276[b])	I: 26.8 (74/276); II: 25.7 (71/276); III: 47.4 (131/276); total: 73.1 (202/276)		
Spear, 2009, (1)	Spear's grading system (n=40)	I: 22.5 (9/40); II: 62.5 (25/40); III: 10 (4/40); IV: 5 (2/40); total II–IV: 77.5 (31/40)		
	Self-evaluation (n=69)	None-mild: 82(56/69); moderate: 10 (7/69); severe: 7 (5/69); total: 24.6 (17/69		
Bracaglia, 2013, (11)	Bracaglia's grading system (n=524)	I: 67 (351/524); II: 29.7 (156/524); III: 3 (17/524); IV: 0 (0/524); total: 33.0 (173/524)		
Nigro, 2017, (13)	Self-questionnaire (n=84)	None: 24.4 (20/84); mild: 50 (41/84); moderate: 14.6 (12/84); severe: 11 (9/84); total: 73.8 (62/84)		
Dyrberg, 2019, (14)	NSE grading system (n=19)	Surgeon 1: 1^{th}: 4±1, 2^{th}: 5.1±1.1 Surgeon 2: 1^{th}: 3.8±1.1, 2^{th}: 4.2±1.2 NSE: 4.3±1.1 Total NSE >2: 94.7 (18/19)	NSE grading system (n=18)	Surgeon 1: 1^{th}: 0.2±0.6, 2^{th}: 0.3±0.6 Surgeon 2: 1^{th}: 0.2±0.7, 2^{th}: 0.1±0.4 NSE: 0.2±0.6 Total NSE >2: 10.5 (2/19)
Kim, 2019, (15)	Kim's grading system (n=145[b])	I: 41.4 (60/145); II: 35.9 (52/145); III: 22.8 (33/145); total: 58.6 (85/145)		
	Subjective grading (Becker's subjective grading) (n=145[b])	Grade 1: 40.0 (58/145); grade 2: 35.2 (51/145); grade 3: 18.6 (27/145); grade 4: 6.2 (9/145); total: 60.0 (87/145)		
Becker, 2017, (4)	Becker's grading system (n=25)	I: 20 (5/25); II: 40 (10/25); III: 24 (6/25); IV: 12 (3/25); total: 76.0 (19/25)		
	Subjective grading (n=20)	Grade 1–2: 25 % (5/20); grade 3–5: 30 (6/20); grade 6+: 45 (9/20); total: 75.0 (15/20)		
Bracaglia, 2020, (9)	Spear's grading system (n=605)	I: 73.8 (444/605); II: 31.1 (188/605); III: 3.3 (21/605); IV: 0 (0/605); total: 34.5 (209/605)		
Fracol, 2020, (16)	Kim's grading system (n=86)	I: 34.9 (30/86); II: 36 (31/86); III: 29.1 (25/86); total: 65.1 (56/86)		

Values are presented in percentage (number cases/number in total). [a], 302 patients × 6 judgements =1,812; [b], 46 patients × 6 judgements =246. NSE, Nipple, Surrounding Skin, Entire Breast.

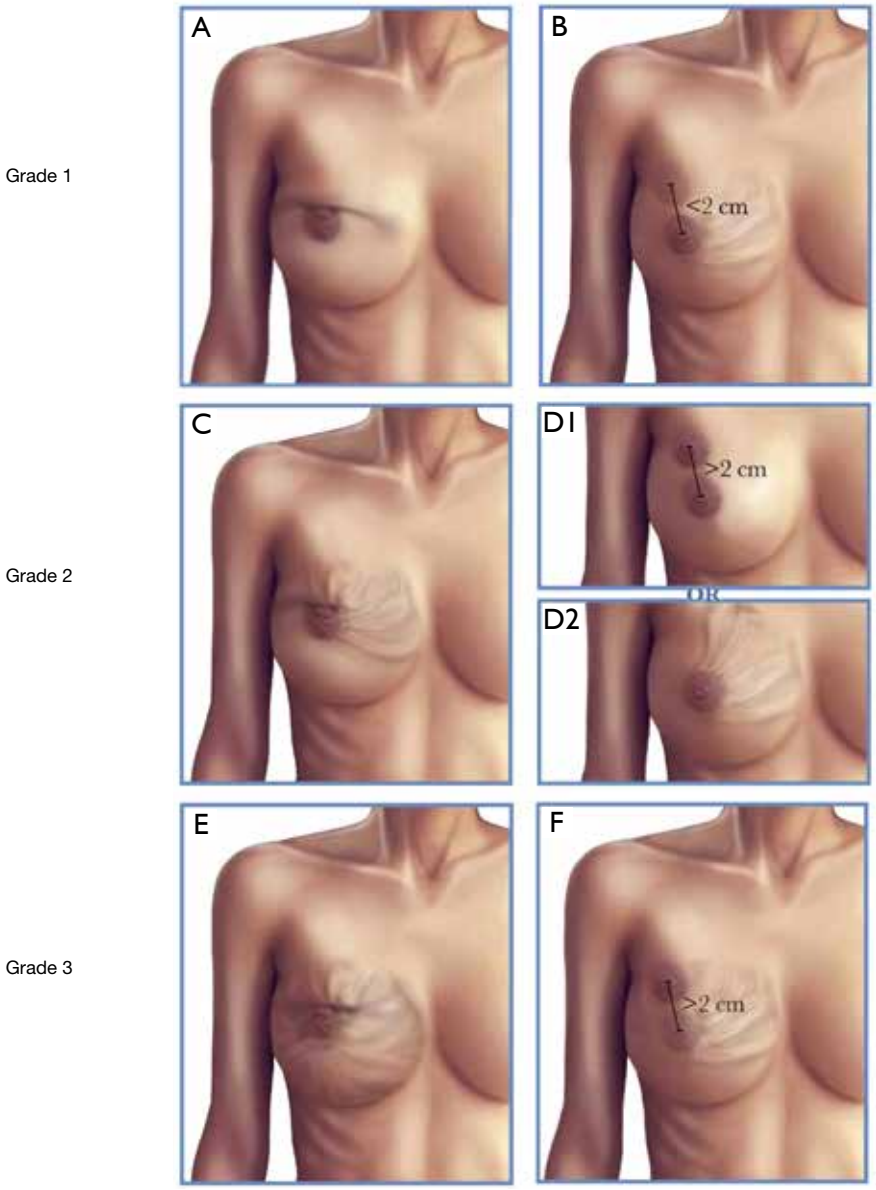

Figure 2 A comparison and our interpretation of the two recommended BAD grading systems. The NSE grading scale (14) (left) and Kim *et al.*'s grading system (15) (right) both consisting of a 3-point grading scale illustrating the severity of BAD. The NSE grading scale: (A) distortion of the TBM/NAC; (C) distortion of the breast skin surrounding TBM/NAC; (E) distortion of the entire breast. Kim *et al.*'s grading system: (B) <2 cm nipple displacement and <25% (of the breast mound) skin contour irregularity; (D1) >2 cm nipple displacement or; (D2) >25% skin contour irregularity; (F) >2 cm nipple displacement and >25% skin contour irregularity. BAD, breast animation deformity; NSE, Nipple, Surrounding Skin, Entire Breast; TBM, top of the breast mound; NAC, nipple areolar complex.

reproducible grading systems. Both grading systems consist of 3-point scales. See *Figure 2* for our interpretation of the two grading systems. Kim *et al.* used an imaging software (ImageJ) for assessment of BAD, an objective, quantitative and reproducible method, however time-consuming and not easy to use in the everyday clinic (15). Dyrberg *et al.* presented the NSE grading scale, evaluating the degree of tissue distortion in these three areas of the breast by two plastic surgeons. They used video recordings for assessment of BAD, and found moderate (74%) to strong (88%) inter-

and intraobserver agreements. Overall the grading system was rated simple, reproducible and useful for clinical use (14). The NSE grading scale, is qualitative and therefore more subjective than Kim *et al.*'s grading scale, however Kim *et al.*'s grading scale is more time-consuming for clinical use. Both studies were limited by the small sample sizes. Consistent with the findings of Kim *et al.*, Cheffe *et al.* suggested a demarcation of topographic landmarks and linear segments between landmarks to quantify breast distortion (21). However, they did not define, how BAD could be assessed with this objective demarcation, thus the study was not included in this review. Furthermore, there were no statistically significant differences between the quantified demarcation and the degree of deformity. Further modifications are therefore needed for the use of Cheffe *et al.*'s method for quantifying the degree of BAD with a grading scale or numerical severity scale for either clinical or research purposes. As BAD has attained more attention in recent years, the use of standardized grading scales is needed for comparative research (8,25-28).

An optimal grading system is based on objectivity, reproducibility and applicability for every-day clinical use. However, a significant aspect of the grading systems is the patient-perception of BAD and the correlation between the clinically graded severity and the patient-perceived deformity (4,13,29). Six studies assessed patient-reported outcomes either for HR-QOL assessments or assessment of the patient's evaluation of the degree of BAD (1,4,9,13,15,16). Four studies used a self-developed, however not validated questionnaires for assessing the degree of BAD (1,4,13,15). Despite the methodological limitation of the questionnaires, patients reported a prevalence of BAD between 25% to 75% and patients evaluated the degree of BAD higher than the clinical evaluations in three studies (4,13,15). Hence, more studies are needed where the patient's perspective are included in the assessment of BAD using validated questionnaires. Two studies used the validated BREAST-Q for assessment of HR-QOL (9,16). Bracaglia *et al.* (2019) used BREAST-Q for assessment of the surgical techniques, and not to the degree of BAD (9). Fracol *et al.* (2020) however, correlated their quantitative grading system of BAD against BREAST-Q patient-reported outcomes. Surprisingly, their findings suggested that patients with increasing severity of animation deformity (grade 3) had better physical well-being scores, than grade 1 patients. Grade 3 patients had significantly less pulling, less nagging and less aching pain in the breast area compared to grade 1. Additionally, grade 1 patients had significantly higher rates of revision surgery than grade 2. Nonetheless, grade 3 patients had the highest number of revisional surgery than grade 1 and grade 2 patients (16). This finding is contradictory of other studies, where BAD was suggested to have a negative impact on HR-QOL (3-5). Correspondingly, a systematic review and meta-analysis found no difference of BREAST-Q scores for HR-QOL and satisfaction with the outcome in the prepectoral and subpectoral groups (28). However, Cattelani *et al.* showed significantly better psychosocial well-being and satisfaction with the outcome in the prepectoral group (30). While, Baker *et al.* compared short-term outcomes of subpectoral and prepctoral immediate breast reconstruction, and found significantly more patients in the prepectoral group, that reported more visible implant rippling than in the subpectoral group, and were overall more dissatisfied (31).

The disparity of varying reported rates of BAD is speculated to be due to numerous factors; (I) the subjectivity of current assessment scales, apart from NSE and Kim *et al.*'s grading system (14,15); (II) inconsistent categorization of mild to severe BAD, (III) the various surgical techniques used, (IV) the size and study types used for the assessment of BAD, and (V) the placement of the implant (sub- or prepectorally pocket). The subjectivity and inconsistency of grading scales may have resulted in over- and underestimation of BAD, depending on the grading system. The subjectivity is however minimized with the use of standardized, high-quality grading scales such as Kim *et al.* and the NSE grading scale (14,15) and more consistent categorization of the degree of BAD will be possible (8) in future studies.

We developed the NSE grading scale due to the limitation of existing grading systems. The interpretation of the NSE-grading scale has been further developed as the scores can be accumulated for a more consistent categorization of mild to severe BAD. The NSE grading scale scores from zero to two points in each of the three features (nipple, skin, and the entire breast) were 0 represents no visible distortion, 1 represents visible distortion, and 2 represents severe distortion, resulting in a total of zero to six points for all features. For more consistent categorization of BAD the summed scores of all features represents the severity of BAD; a total of 0–2 points represents mild BAD, 2–4 points represents moderate BAD, and 4–6 points represents severe BAD (14). This point accumulation for the degree of BAD was used for the calculation of the prevalence of BAD in the subpectoral

implant placement group versus the prepectoral implant placement group (94.7% versus 10.5%). Surprisingly, we found the prevalence of BAD to be 10.5 percent in patients reconstructed using the prepectoral technique, which we had not expected. However, the number of high-quality studies reporting BAD is scarce and future studies will show if the prevalence is true. Dyrberg *et al.* is to our knowledge the first study using a high-quality grading scale to evaluate both subpectoral and prepectoral implant pocket placements in relation to BAD (14).

The evidence is conflicting regarding the various surgical techniques and the impact on the degree of BAD (5,26-28,32-35). Most studies have assessed subpectoral implant placement when assessing BAD (1,9,11-13,16,36). In our previous review, we postulated, that the degree of muscle involvement in the breast reconstruction may be proportional with the degree of BAD, as the Regnault technique had the highest prevalence of severe BAD (12). A meta-analysis was not possible to conduct, as most studies assessed subpectoral implant placement (and the various techniques used in subpectoral plane) and only one study assessed prepectoral implant placement. Nonetheless, a total of 2 patients had some degree of BAD in the prepectoral group out of 19 patients, while 1,345 patients had some degree of BAD in the subpectoral group out of 1,819 patients. The prevalence of BAD was significantly higher in the subpectoral group compared to the prepectoral group with a relative risk (RR) of 0.14, 95% CI: 0.04–0.53; P value <0.004. This study is to our knowledge the first to quantify the prevalence of BAD in relation to implant pocket placement. In a meta-analysis Li *et al.* compared prepectoral to subpectoral implant-based reconstruction regarding various outcomes (capsular contraction, quality of life, pain, skin necrosis, and implant loss), however they found no cases of BAD and therefore could not conduct an analysis of BAD regarding implant placement (10). Yang *et al.* found a prevalence of BAD on 8.5% in the subpectoral group versus 0% in the prepectoral group (37), they however did not define, how BAD was graded. We found a significantly higher prevalence of BAD in both the subpectoral and prepectoral group, however, the findings of Yang *et al.* were consisting to our findings regarding higher prevalence of BAD in subpectoral implant placement compared to prepectoral implant placement.

Subpectoral implant placement has been the gold standard of breast reconstruction for more than five decades (32). Several studies have recently suggested correction of BAD by converting the implant from a subpectoral plane to a prepectoral placement, particularly with the use of ADM (5,25-27,32-35,38). It is theorized that repositioning of the implant to a prepectoral plane separates the contracting muscle from the overlying skin and thereby reversing the animation deformity (5,25,39). Hammond *et al.* described a 100% resolution of BAD by changing to a prepectoral plane in 19 breasts (35). The etiology of BAD, the impact of surgical techniques, and implant placement may not be as simple, as described in previous studies. In this review, we have shown that prepectoral implant placement has significantly lower prevalence of BAD, however prepectoral implant did not result in complete elimination of BAD with a prevalence of 10.5%. A simple change from a subpectoral to prepectoral plane may therefore not solve the BAD-related problems. The degree of BAD in patients reconstructed by partial submuscular technique may differ between those reconstructed with or without mesh/ADM. However, the limited number of high-quality studies reporting on BAD does not allow for subgroup analysis between partial sub-muscular reconstruction with or without the use of mesh/ADM. (5,25,32,33).

Prepectoral implant placement may provide more natural aesthetic results, reduce postoperative pain, and shortens the recovery period (27,40). Prepectoral implant placement is associated with a higher incidence of capsular contracture (41). However, we do not know if the associated higher incidence of encapsulation is true after the introduction of ADM. In addition, prepectoral breast reconstruction requires the mastectomy/reconstructive flaps to be of sufficient thickness and vitality and it increases the risk of rippling and implant edge visibility (22,37). Subpectoral implant placement has lower rates of capsular contraction and flap thickness is not as crucial as in prepectoral implant placement (29,37,41). Although the prevalence of BAD is higher in the subpectoral group compared to the prepectoral group in this review, the studies have significant limitations with insufficient number of patients, the use of non-standardized grading systems, and only three studies assessing prepectoral implant placement (14,22,37). The evidence is insufficient to advocate one implant pocket placement over another with the existing literature. We can merely advocate for a more comprehensive and individualized selection of implant plane depending on patients/breasts (29,42), as limited studies have examined the differences of implant pocked placement and surgical technique on BAD with the use of standardized and high-quality grading systems (1,9,11-16,18,20,22,37).

There are some limitations in this review. A meta-analysis was not conducted, as the methods of assessing BAD were not comparable, due to variations from 4-point scales to 3-point scales, from surgeon to patient-self assessment, and variation of type of surgery. Only one retrospective study compared the two implant pocket planes, and the study was limited by a small sample size. However, BAD was assessed with the use of the high-quality NSE grading scale (14). Further limitations are that only retrospective-, prospective studies and reviews were included in this review, as no RCT studies have been published assessing BAD. Various surgical techniques and pocket implant placements were presented in breast reconstruction and augmentation (1,11-15,18). However, only few comparative studies were available with clear description of study design, participants and standardized grading systems (1,14-16). The sample sizes of the included studies were small, with only two larger studies comprising of 580 and 605 patients (9,12). Large, multicenter, randomized-controlled trials are needed for further evaluation of the etiology and prevalence of BAD with the use of standardized grading systems.

Conclusions

This systematic review is the newest update on the various BAD grading systems available, and the quality and reproducibility of the individual grading systems. We recommend two grading systems, the qualitative NSE grading scale and Kim *et al.*'s quantitative grading system—two high quality, reproducible and clinically-relevant assessment methods. Patients with prepectoral implant placement have a significantly lower prevalence of BAD compared to patients with subpectoral implant placement (10.5% versus 73.9%). The total prevalence of some degree of BAD was 73.3% regardless of implant placement and surgical techniques. The evidence is still inadequate in the existing studies and more studies, especially randomized-controlled trials are needed were these reliable and high-quality grading systems are used in combination of validated patient-reported outcome measures to further investigate and understand the etiology of BAD.

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Footnote

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Review Article

Current imaging techniques and impact on diagnosis and survival—a narrative review

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Abstract: Imaging plays a central role in the detection and assessment of breast cancer. Breast cancer screening programmes have been well established, as even in the era of modern therapies early detection has a major impact on survival. Time interval and method of breast cancer surveillance programme depends greatly on the individual risk factors and a correct selection and/or combination of methods proved to be useful in women with higher than average risk or in women with dense breasts. In women with clinical symptoms, imaging methods provide reliable differentiation between benign and suspicious processes that need to be evaluated with a biopsy. Each of the three basic imaging methods of the breast—mammography, breast ultrasound and magnetic resonance imaging (MRI) has its advantages and limitations. Additionally, appropriate preoperative marking is a mandatory part of imaging that helps transfer the information from imaging to surgery. In this review, we summarize the data on the use of breast imaging in prevention, diagnostics and staging with a clinical perspective. We emphasize the multimodality approach with combined evaluation of all imaging methods and multidisciplinary team work with close cooperation of various medical specialties, which is essential for planning the proper execution of patient management to ensure the best possible outcome. Practical examples are given in a series of clinical scenarios.

Keywords: Breast cancer; imaging; mammography; ultrasound; breast magnetic resonance imaging (breast MRI)

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Introduction

Diagnosis of breast cancer occurs for a woman either during a surveillance imaging programme (breast cancer screening) when there are no symptoms present or in a diagnostic setting when the cancer causes clinical problems. Imaging plays a central role in detection, staging and follow-up. The methods of breast imaging are evolving and their strengths and weaknesses are re-evaluated constantly to formulate recommendations and guidelines beneficial for clinical practice. In this review we summarize the data from current literature, guidelines and emerging research and discuss advantages as well as possible pitfalls of the imaging methods and future prospects. This text should also help to understand image interpretation and the use of each of the methods and their combinations in various clinical situations as described in the final section of exemplary cases.

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We present the following article in accordance with the Narrative Review reporting checklist (available at https://abs.amegroups.com/article/view/10.21037/abs-21-22/rc).

Literature search and selection of sources

A bibliographical search was performed in PubMed using combinations of key words relating to "breast cancer", "breast imaging", "mammography", "digital breast tomosynthesis", "breast cancer screening", "breast MRI", "breast ultrasound". The eligible criteria included studies in English language published between 2010 and 2021. We included studies referring to breast cancer imaging modalities and their use, breast cancer screening, treatment and survival related to imaging, and guidelines of special focus groups, medical societies and healthcare authorities. In particular, we focused on available meta-analyses and systematic reviews, large epidemiological studies, cohorts and case-control studies and randomized control trials. Reference lists from selected articles were also manually checked to identify additional relevant report.

Preventive versus diagnostic imaging

Mammography screening programmes have been running in many countries and detect on average 5 cancers per 1,000 screens (1). Attendance of mammographic screening has proven effective by randomized control trials in reducing the mortality of breast cancer by approximately 30% (2). Even in the era of modern therapy, detection of breast cancer in the early stages is the key to a better chance of survival (3). The greatest benefit achieved by screening mammography has been demonstrated for women between 50 and 69 years of age with up to a 40% reduction of mortality for women attending the screening programme (4). For the population between 40 and 49 years of age, the value of preventive mammography surveillance is still being discussed, but the evidence of the benefits for this age group has been increasing (5,6). The recommended screening interval is 2 years for the age category of 50–69 years and 1 year for women of 40–49 years of age, due to a higher mammographic density and greater aggressiveness of tumours in younger women (7).

Mammography screening programmes have been thoroughly scrutinized to evaluate potential adverse outcomes; mainly false positivity and overdiagnosis. The programme efficacy varies slightly in different countries, but in general the benefits outweigh the harms (8,9). The false positivity of mammographic screening is relatively low, reaching a maximum of 20% per 20 years of surveillance (10 screen rounds), and most of the findings are solved without any need for an interventional procedure; less than 1% of false positive findings require a core biopsy per screening round (4). Overdiagnosis (i.e., the rate of screen-diagnosed cancer which would otherwise go unnoticed during the patient's lifetime), is estimated to additional 6.5% of cancers on average (ranging from 1% to 10%) (10).

Intensive preventive programmes in shorter time intervals (annual or even more frequent) are recommended for women with risk factors, especially a family history of breast/ovarian cancer and for genetic mutation carriers (11) with impact on improved survival (12,13). The protocols for women with an elevated or high risk of breast cancer involve multiple imaging modalities combining mammography with ultrasound and/or MRI which help detect more cancers in the earlier stages (14).

Diagnostic assessment is carried out on women of any age with clinical symptoms. These usually include a palpable lump in the breast or axilla, nipple discharge (especially when serous or bloody), skin changes or nipple or skin retraction. Clinically manifesting cancers typically comprise cancers in women of ages outside the screening period, women who do not attend preventive surveillance and interval cancers. Tumours manifesting clinically are usually larger and more advanced than tumours diagnosed in screening, with a higher risk of lymph node involvement, resulting in poorer prognosis (15).

Mammography

The basic imaging modality of the breast is mammography. This method uses low doses of ionizing radiation, therefore radiation exposure is minimal, ranging from 1.5 to 4 mGy, varying across countries and device manufacturers (16). Two views from each breast are obtained—one in cranio-caudal view, one in medio-lateral oblique view, which also enables evaluation of part of the axilla. Compression of the breast is necessary to reduce superposition of structures and decrease radiation dose (17). Additional views including magnification views, spot compression, rolled or extended views can be used to more clearly depict abnormalities.

Tumours are seen in mammography as mass lesions of higher density, with irregular or spiculated margins (*Figure 1*). Sometimes cancers can manifest as asymmetrical densities, distortions of breast parenchyma or smoothly contoured masses (which are otherwise more typical for

benign processes such as cysts or fibroadenomas). The presence of microcalcifications, especially if these are clustered, follow ductal anatomy, are new or progress in time can also indicate malignancy. These typically represent ductal carcinoma in situ (DCIS) (18).

The performance of mammography is dependent on the breast density, which is determined by the proportion of glandular parenchyma and fat. The density is scored by the BI-RADS system from A (fatty) to D (dense) (*Figure 2*) and the sensitivity of mammography varies accordingly. In fatty breasts almost no cancer goes undetected, while in dense breasts the sensitivity can drop down to 50% (19). High breast density is an independent risk factor for breast cancer (20) and is also associated with higher proportion of interval cancers as smaller cancers can be masked by the dense parenchyma during screening (21). The density tends to change during life, decreasing with age. Mammography is therefore used and is more efficient in women over 40 years of age (22).

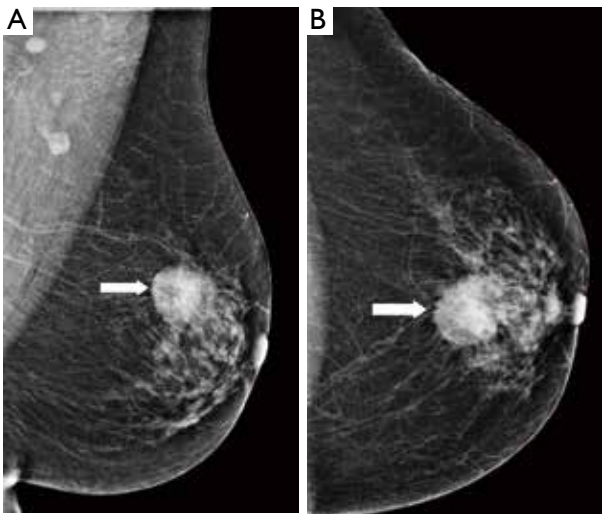

Figure 1 Mammography of the left breast in medio-lateral oblique (A) and cranio-caudal (B) view. A mass with irregular margins can be seen, located in 12 o'clock position representing a cancer (arrows).

Technical innovations

Digital breast tomosynthesis (DBT) is a novel approach in mammography that has the potential to overcome the limits of conventional mammography. It acquires several low-dose images of the breast, and reconstructs a synthetic 2D image with enhanced parenchymal distortion features and multiple slabs/slices of the breast, to enable exploration of 3D anatomy of the breast tissue (*Figure 3*). DBT detects approx. 15–30% more cancers, which would otherwise be hidden in the breast parenchyma in conventional mammography, and also helps to reduce the false positivity caused by superposition of normal structures mimicking pathology by 15–20% (23). Although very promising, DBT

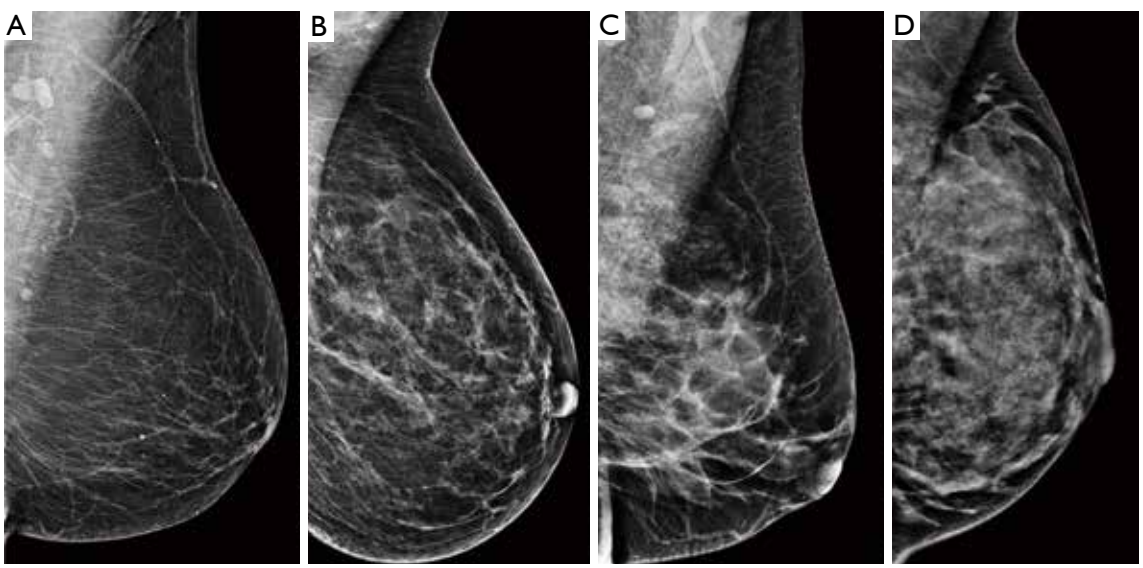

Figure 2 Breast density categories. (A) Almost entirely fatty, (B) scattered areas of fibroglandular density, (C) heterogeneously dense, (D) extremely dense.

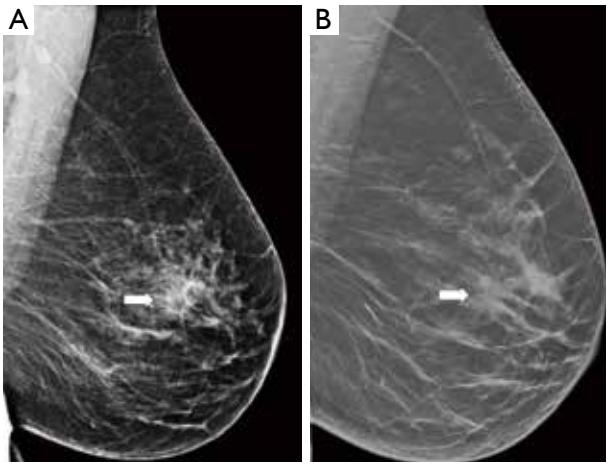

Figure 3 Difference between mammography (A) and DBT (B), arrow showing a cancer (arrows) which is more clearly visible in DBT. DBT, digital breast tomosynthesis.

is still used mainly within clinical trials and its broader use as a screening method is still not routinely adopted. In comparison with mammography, DBT requires longer reading time, the radiation dose can be slightly higher and achievement of the main goal—reduction of interval cancers—has not yet been confidently demonstrated (24).

As a diagnostic tool DBT provides improved diagnostic accuracy compared with mammography and helps better localization of the lesions, distinguishing between benign and malignant features or detecting multifocality.

Staging with mammography

In staging, mammography is mainly important for evaluation of microcalcifications, as these may not be seen in other modalities and can represent a DCIS component.

Digital breast tomosynthesis can be useful for assessment of lesion size and identification of additional lesions in multifocal processes (25).

Breast ultrasound

Breast ultrasound has improved significantly during the last decades due to the advances in the technology and resolution of the devices. This method uses reflection of acoustic waves in the tissue and is a safe and well tolerated method for every patient. The main disadvantage is that a hand-held ultrasound is an operator dependent method, therefore the results of the examination may vary. Automated breast ultrasound systems (ABUS) might bring more reproducible and objective results (26).

Ultrasound should not be used as a standalone screening method (27) but is a valuable adjunct and diagnostic tool. In combination with mammography, ultrasound helps detect more cancers especially in the population of women with dense breasts where up to 4 additional cancers per 1,000 screened women can be found (28). Therefore, ultrasound can be recommended as a supplemental method to the mammography in women with breast density category D (very dense) and category C (heterogeneously dense) (29) and also in women with elevated risk (14). However, the data also consistently suggests that the addition of ultrasound brings increased false positivity and necessity for additional procedures or check-ups. Its routine role in the screening systems is therefore still being evaluated, as additional costs and the capacity of ultrasound centres must also be taken into account (30).

For evaluation of young, pregnant and breastfeeding patients with clinical symptoms breast ultrasound is used as the first (and usually sufficient) method. In this population, ultrasound reliably differentiates benign findings from those requiring a biopsy (31).

Breast ultrasound is also very helpful for evaluation of abnormities detected by mammography or MRI and navigation interventional methods such as biopsies and needle aspirations (32).

Breast cancer usually appears in ultrasound as hypoechoic (dark) mass with irregular margins, with vertical orientations and/or accompanied by posterior, acoustic shadowing. Some tumours can have an infiltrative pattern of growth appearing as non-circumscribed areas of decreased echogenicity (darker than normal parenchyma) (*Figure 4*). Ultrasound reliably differentiates between cystic and solid lesions.

Staging of breast cancer with ultrasound

Breast cancer frequently occurs as multiple lesions in one quadrant (multifocal) or multiple quadrants (multicentric) (33). In evaluation of patients with breast cancer ultrasound is a useful method for assessment of the extent of the disease and detection of additional lesions. Most additional lesions occur in the same quadrant, however detection of more distant additional lesions or even contralateral pathology is not rare and may alter the planning of the treatment.

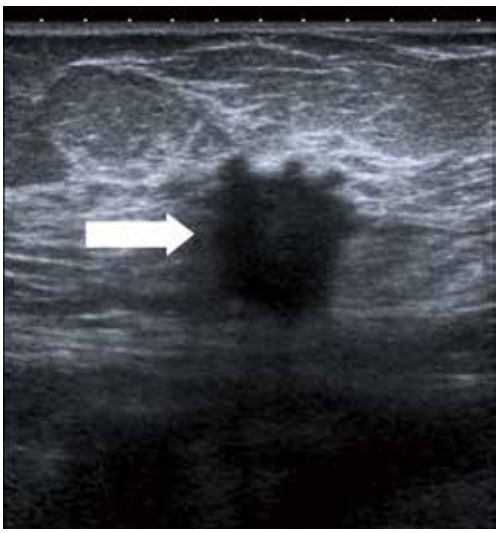

Figure 4 Breast cancer in ultrasound. A hypoechoic mass with irregular margins and posterior shadowing (arrow).

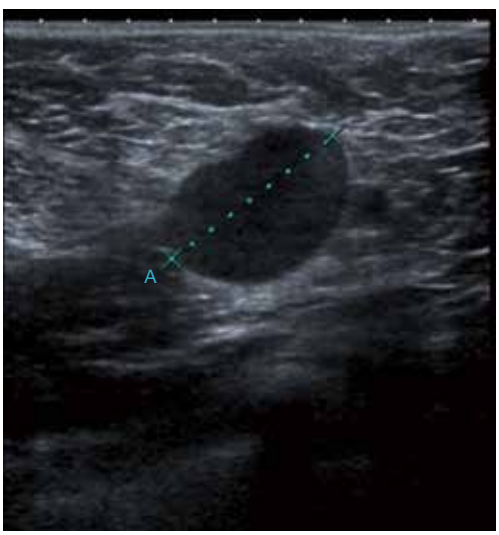

Figure 5 Infiltrated lymph node. Oval hypoechoic shaped node with displaced and compressed hilum.

Ultrasound of the axilla (axillary ultrasound) is mandatory for staging of the disease. Various features of lymph nodes are considered suspicious of metastatic involvement: cortical thickening of more than 3mm, irregular cortex width, displacement or absence of the fatty hilum or round shape of the lymph node (*Figure 5*). Ultrasound is also the method used to navigate the fine needle aspiration biopsy (FNA/FNAB) to confirm the status of the lymph node (34), with high sensitivity (79.6%), specificity (98.3%) and PPV 97.1%

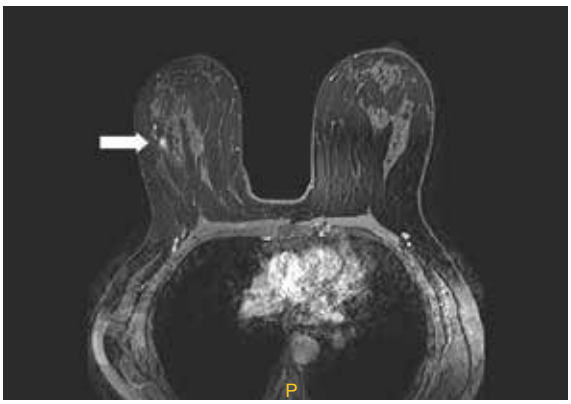

Figure 6 Breast MRI in high-risk patient (*BRCA1* gene carrier). A small lesion with marked enhancement and irregular margins is seen in the right breast (arrow). MRI, magnetic resonance imaging.

for identification of axillary involvement. With decreasing radicality of axillary surgery, the main advantage of axillary ultrasound is its ability to reliably identify or exclude a major axillary tumour burden (35).

Breast magnetic resonance imaging (MRI)

Breast MRI is an established valuable method that helps detect lesions that are not visible for other modalities. The sensitivity of dynamic contrast-enhanced MRI (DCE-MRI), 93%, is very high for every type of breast (including dense breasts) with relatively good specificity of 71% (36). The examination requires the application of a gadolinium-based contrast agent intravenously, and there are several contraindications as this method uses a high-intensity magnetic field.

The clinical indications for the use of breast MRI include high-risk screening, staging of breast cancer, evaluation of the effect of neoadjuvant chemotherapy, detection of occult breast cancer, evaluation of implants, evaluation of nipple discharge and assessment of equivocal lesions in conventional imaging methods (37).

In gene mutation carriers and in women with a high risk (>20%) of breast cancer, MRI is superior to all other breast imaging methods for the early detection of cancer and is recommended for surveillance of this population (38,39) (*Figure 6*).

MRI also detects more early cancers than mammography in women with a family history of breast cancer but without proven genetic mutation (40) and in women with extra dense breast tissue. In the DENSE trial (41) with MRI used as a

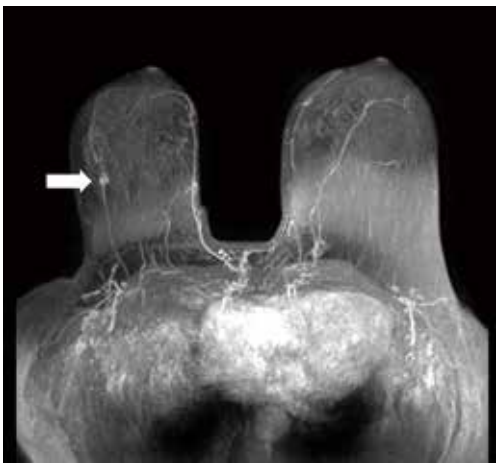

Figure 7 Abbreviated MRI protocol with MIP image showing both whole breasts at once. Small cancer in the right breast (arrow). MRI, magnetic resonance imaging; MIP, maximum intensity projection.

supplemental method to mammography, the ultimate goal of significantly reducing interval cancers (2.5/1,000 with MRI versus 5/1,000 for mammography only) was reached. Interestingly, MRI also achieves a high cancer detection rate in the average risk population of variable densities (42). The additional detection rate of 15.5 per 1,000 is much higher than that of any other imaging methods. Most of these studies however also suggest a higher proportion of false positive results than with mammography, which need further evaluation including interventions under MRI guidance.

The availability, price and duration of the examination and the interpretation time have always been raised as issues which have prevented wider use. Abbreviated protocol, shortening both image acquisition and study evaluation time while maintaining the same diagnostic accuracy, could help solve these issues and make MRI available to more patients (43) (*Figure 7*).

In MRI, cancer typically appears as a mass with irregular shape, lobulated or spiculated margins and inhomogeneous structure, or as non-mass-like areas with ductal or segmental distribution, both with marked and/or early enhancement in dynamic post-contrast sequence which decreases in later phases. The dynamic contrast-enhanced sequence is the most important sequence for detection of malignant lesions, the additional MRI sequences [T2-weighted sequences, diffusion-weighted imaging (DWI), spectroscopy] can further characterize the pathology and help differentiate malignant lesions from benign processes. The combined use of multiple parameters of MRI further increases specificity of the method to up to 75–89% (44).

Staging with MRI

In staging of a biopsy-proven breast cancer, MRI is often used for the assessment of the extent of the disease and detection of additional lesions in the same or in the contralateral breast, which potentially influence the patient´s subsequent management. Due to its high sensitivity MRI is superior to mammography and ultrasound in identification of a DCIS component or multifocality. MRI is frequently used in lobular histology of the cancer, in patients with dense breasts, younger in age, in case of discrepancy of the lesion size in mammography, ultrasound or clinical findings and in uncertainty of the extent or suspected multifocal/multicentric disease detected with mammography and ultrasound.

While the value of MRI has been questioned in the past as increased mastectomy rate was observed and the benefits affecting reexcision and survival rates had not been demonstrated previously (45), recent studies support the use of MRI in various scenarios with a proven reduction in the breast reoperation rate from 15% to 5% (46).

Biopsy techniques

Each lesion found in imaging where malignancy cannot be ruled out must be biopsied. Various procedures under imaging guidance are available (47). The FNA/FNAB obtains clusters of cells, enables differentiation of malignant from benign findings and evaluates metastatic involvement of axillary lymph nodes. The core biopsy (12–16G with standard 14G) retrieves pieces of compact tissue, thus enabling the additional assessment of the biological and prognostic markers of the tumour, which possibly have an impact on the treatment choices. The vacuum-assisted biopsy (VAB) uses larger-gauge needles, providing samples with a larger amount of tissue.

Imaging is used for precise navigation of the procedure. The modality where the lesion is most visible is always used for guidance. The easiest way to target a biopsy needle

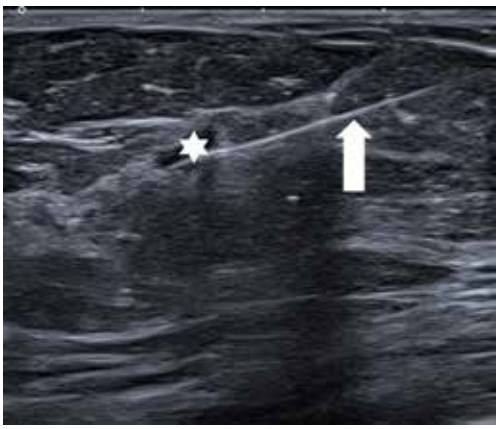

Figure 8 A lesion (star) is biopsied by a core needle (arrow) visualized directly by ultrasound.

is under ultrasound guidance, which enables real-time navigation (*Figure 8*). The VAB is frequently navigated by mammography for a biopsy of microcalcifications that are not visible by ultrasound. The VAB can also be used under MRI guidance for lesions visible only by MRI.

The multimodality approach for staging and management

No modality stands alone in the evaluation and staging of breast cancer. Clinical information about the patient, clinical findings, imaging studies and patient's preferences must all be combined in planning strategy.

In many patients the combination of mammography and ultrasound provide sufficient information about the breast and the axilla for planning of the strategy. In some cases, MRI is necessary to help detect additional lesions or to evaluate the extent of the disease (see examples of clinical scenarios below). Each lesion that is found in additional imaging and which would alter the treatment plan must undergo further evaluation and a biopsy. Lesions detected by MRI must be evaluated with special caution, as a potentially false positive finding, due to the high sensitivity of this method, may result in unnecessarily radical surgery.

Clinical practice has shown that patients benefit from therapeutic management based on a multidisciplinary approach, which involves multiple specialties and a patient´s perspective. The multidisciplinary team (MDT) includes the radiologist, pathologist, surgeon, oncologist, radiation oncologist and the breast nurse/psychologist. Regular MDT meetings where each breast cancer case is discussed help review all the information from imaging, relevant clinical patient data and patients' preferences and help to plan how to proceed. The complexity of the combined multidisciplinary approach, which does not bring merely a summary of findings, translates into an 18% increase in the survival rate, as shown by a United Kingdom study (48).

Preoperative marking

Preoperative or pretreatment marking of non-palpable tumour lesions, and possibly also axillary involvement, are vital for transferring information from imaging to surgery. The method of marking is dependent on the centre's preferences and is discussed in a multidisciplinary team meeting. A variety of localization wires, clips visible by ultrasound, detectable by magnetic or scintillation probe are available, supplemented by skin or carbon markings. For larger lesions, marking with multiple wires/clips/marks ("bracketing") is necessary to ensure proper localization and delineation of the extent of the pathological finding. Protocols and standard practices with close cooperation of the radiologist and the surgeon are used to ensure the best outcomes. Each lesion is marked under guidance of the method where both the localization and whole extent is most visible. Ultrasound is the easiest method for any intervention, however in cases of microcalcifications which are not visible by ultrasound, mammography (stereotactic) guidance might be necessary. For MRI-only detected lesions, biopsy and localization might be more challenging, but it is necessary in order to ensure an optimal outcome (49).

If neoadjuvant chemotherapy is planned for the patient, with a subsequent scheduled attempt at breast conserving surgery, early marking is mandatory for all the lesions, as these may disappear during the treatment. The same applies for the affected lymph nodes if a targeted lymph node dissection is to be attempted (50).

Examples of clinical scenarios

(I) Screening, a patient of 50 years in age, no clinical finding, mammography with fat predominance (density A), new dense nodule with spiculated margins and microcalcifications is present on the left side.

The lesion is biopsied under ultrasound guidance with result of low grade carcinoma, lymph nodes negative. No further assessment necessary, the patient is scheduled for breast conserving surgery with a sentinel node biopsy (*Figure 9*).

(II) Screening, an asymptomatic woman of 65 years old, in mammography an architectural distortion is detected in the lateral part of the left breast. The ultrasound findings are subtle with suggested areas of decreased echogenicity. The biopsy under ultrasound guidance reveals DCIS grade 2. The extent of the disease however is not certain. MRI is indicated. MRI shows an extensive process in the lateral part of the left breast resulting in the need of mastectomy (*Figure 10*).

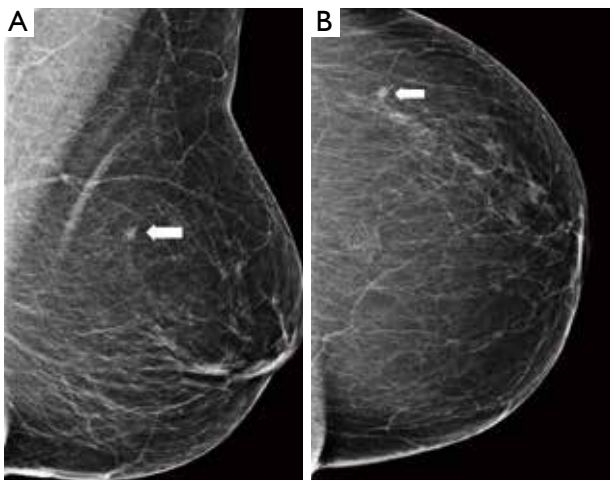

Figure 9 Mammography of the left breast in medio-lateral oblique (A) and cranio-caudal (B) view. Small cancer is detected in upper outer quadrant (arrows).

(III) Diagnostic assessment, a patient of 45 years of age with a palpable lump on the right side for 2 months. In mammography with higher proportion of fibroglandular tissue (category C) several areas of increased density with irregular margins and architectural distortions are visible. Ultrasound confirms more than one lesion. MRI demonstrates a large area of enhancement up to 7 cm (*Figure 11*).

(IV) A patient of 50 years of age evaluated for enlarged lymph nodes in the axilla. Mammography and ultrasound show enlarged pathological lymph nodes in the axilla, otherwise no pathological finding in the breast on initial evaluation despite the low mammographic density. The largest lymph node is biopsied proving metastatic invasive carcinoma NST of breast origin. MRI is indicated to search for an occult lesion in the breast. MRI shows the enlarged

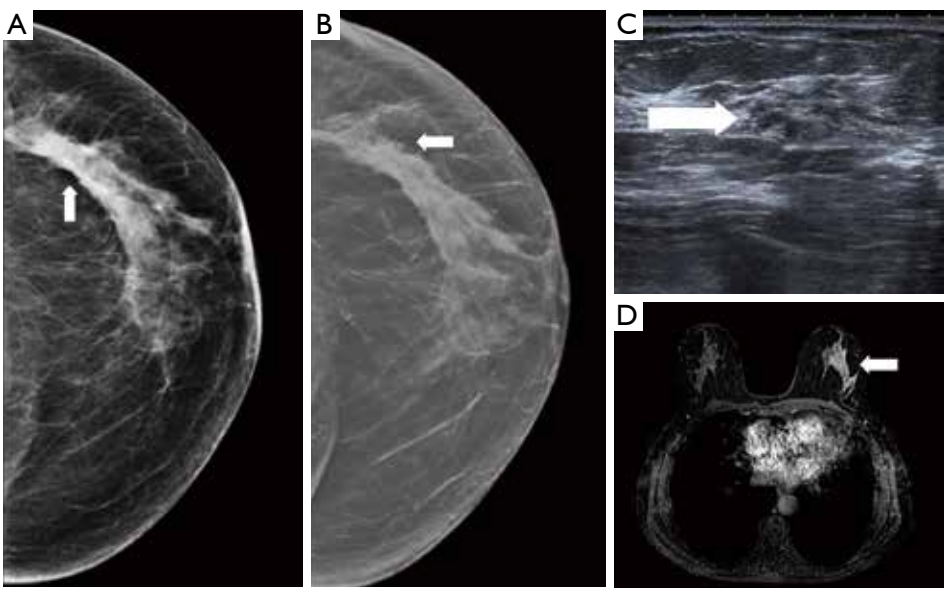

Figure 10 Mammography of the left breast in cranio-caudal view (A) with architectural distortion (arrow). The distortion is more visible in DBT (B) (arrow). Ultrasound (C) reveals subtle finding of irregular area of decreased echogenicity (arrow). MRI (D) shows extensive area of non-mass-like enhancement in the whole lateral part of the breast (arrow). DBT, digital breast tomosynthesis; MRI, magnetic resonance imaging.

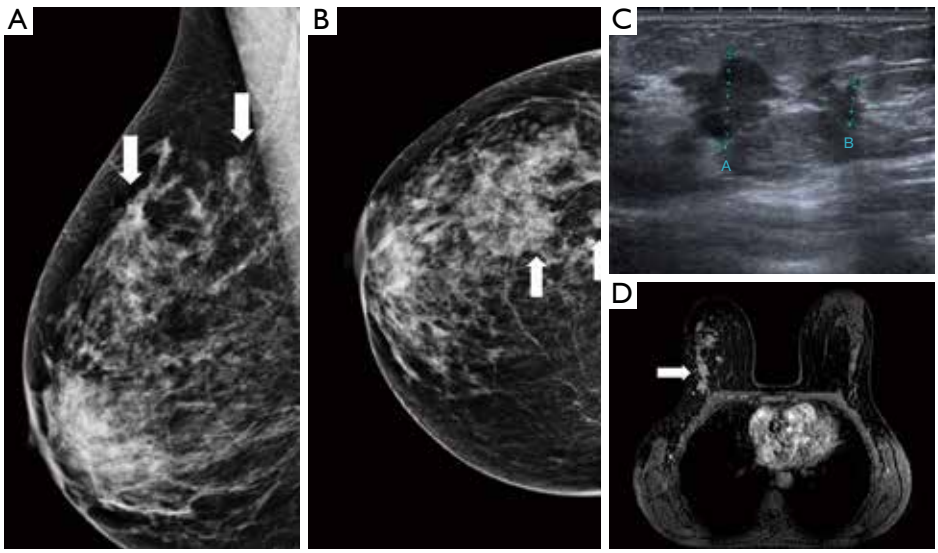

Figure 11 Mammography of the right breast in medio-lateral-oblique (A) and cranio-caudal view (B) with multiple densities with irregular margins and architectural distortions (arrows). Ultrasound (C) shows more than two hypoechoic lesions of suspicious features. In MRI (D) an extensive area of tumour involvement is revealed. MRI, magnetic resonance imaging.

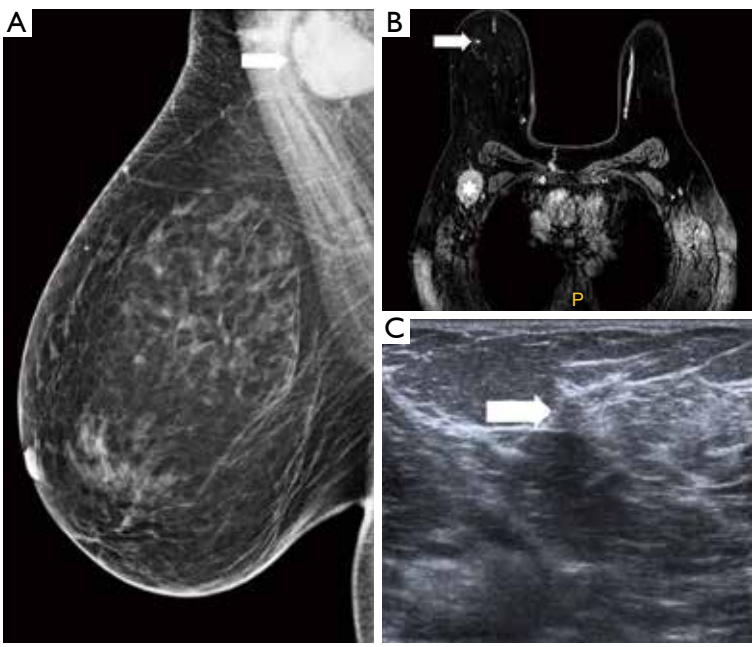

Figure 12 Enlarged lymph node in the right axilla is seen in mammography (A). In MRI (B) enlarged lymph nodes (star) are confirmed and a small mass with early intense enhancement in the upper outer quadrant (arrow). In ultrasound (C) the lesion is very subtle (arrow). MRI, magnetic resonance imaging.

lymph nodes and a small lesion in the right breast in upper outer quadrant. A second-look, targeted ultrasound with the knowledge of the location of the lesion is performed to reveal a small suspicious lesion, which is subsequently verified as the primary tumour in the breast (*Figure 12*).

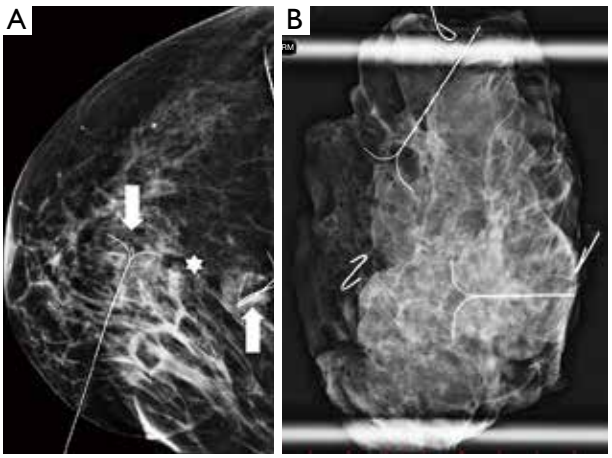

Figure 13 In mammography (A) microcalcifications are visible in the centre of the breast (star). The extent is delineated by two wires placed to the ventral and dorsal edge of the microcalcifications (arrows). A specimen mammography (B) confirms both wires and microcalcifications present in the removed tissue, the microcalcifications do not reach the margins of the specimen.

(V) Preoperative marking. Microcalcification with ductal distribution biopsied by vacuum—assisted biopsy under mammography guidance as DCIS grade 2; the extent of the calcifications is approximately 30 mm. Marking by two wires is performed to delineate the extent of the disease. A specimen mammography of the resected tissue shows both wires with microcalcifications between them that do not reach the margins (*Figure 13*).

Summary

Breast imaging is complex and still evolving. Preventive programmes are seeking more effective ways of detecting more cancers in the earlier stages. For staging purposes, a multimodality approach using a combination of multiple imaging methods is necessary for proper planning of the patient's subsequent management. Preoperative marking ensures transfer of the information from imaging to surgery.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Review Article

Narrative review of breast reconstruction with a latissimus dorsi flap—is there a price to pay?

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Contributions: (I) Conception and design: Both authors; (II) Administrative support: Both authors; (III) Provision of study materials or patients: Both authors; (IV) Collection and assembly of data: Both authors; (V) Data analysis and interpretation: Both authors; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

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Abstract: The musculocutaneous latissimus dorsi flap (m. latissimus dorsi flap) is a stable workhorse in reconstructive plastic surgery. It is commonly used as a safe and viable alternative to the deep inferior epigastric perforator (DIEP) flap and possesses the advantage that it does not require microsurgical expertise. It offers a natural and aesthetically satisfying result, the complications rates are generally low and the postoperative length of hospitalization is short. Although investigated numerous times through the past decades, the functional effect of raising a latissimus dorsi flap remain debatable. We performed a review of the literature and identified studies that have investigated the functional effects after breast reconstruction with a m. latissimus dorsi flap. A reduction in shoulder strength for motions to which the muscle contributes could be intuitively expected following its dissection and have been reported by some authors. However, range of shoulder motion is unaffected in most studies and the subjective effect of the procedure on shoulder function remains ambiguously reported. The following article presents an overview of functional outcomes such as range of motion, shoulder strength and patient reported ability to perform activities of daily living following breast reconstruction with a latissimus dorsi flap. We also discuss other important factors regarding the outcome after m. latissimus dorsi flap, that should ideally be considered, when choosing and informing the patients about strategy for breast reconstruction.

Keywords: Reconstructive surgery; breast surgery; breast reconstruction; plastic surgery

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Introduction

The predecessor of the modern musculocutaneous latissimus dorsi flap (m. latissimus dorsi flap) was initially described more than 100 years ago by Italian surgeon Ignicio Tansini as an option for coverage of large defects after breast surgery (1). Since the 1970s when the flap technique was modernized and adapted for breast reconstruction, it has become increasingly popular and today remains a workhorse in reconstructive plastic surgery (2).

Breast cancer incidence has been rising for decades and today more than 1 out of 10 women are diagnosed with breast cancer. Fortunately, the increased knowledge about diagnosis and adjuvant therapies to surgical treatment have left the 5-year survival rate at more than 85% (3), thus creating an increased need for reconstructive procedures in order to help alleviate the physiological and psychological trauma related to a cancer diagnosis (4).

Autologous breast reconstruction is the preferred option of many surgeons for patients in need of secondary reconstructive procedures after radiation therapy (5). Radiotherapy can result in hard, fibrotic tissue in the

area of the removed breast, which makes implant-based reconstructions difficult and necessitates the addition of healthy tissue (6). The latissimus dorsi (LD) flap supplies a natural skin island and underlying soft tissue to the damaged area, and provides a natural appearance and texture of the reconstructed breast.

The impact on shoulder function following LD-flap breast reconstruction has been discussed for years, and numerous studies have examined the effect of LD harvest through the past five decades (7-17). Despite different authors presenting some degree of measurable loss of shoulder strength following LD transfer, the subjective functional outcome and effect on patient's ability to perform activities of daily living (ADL) remains unresolved (8-12,17-20).

Clarity regarding factors other than donor-site morbidity, such as the length of postoperative hospitalization, complication-rates, aesthetic outcome, and the expected need for corrective procedures is needed in order to properly evaluate the benefits and drawbacks of breast reconstruction with an LD-flap.

The following narrative review aims at presenting an overview of the impact on shoulder function following breast reconstruction with a latissimus dorsi flap, with respect to measurable changes in shoulder motion and strength as well as ability to perform activities of daily living. We present the following article in accordance with the Narrative Review reporting checklist (available at https://abs.amegroups.com/article/view/10.21037/abs-21-30/rc).

Surgical technique

The patients are typically placed in the lateral position, with the arm elevated and pointed forward to allow dissection in the axillary area. The surgery is usually initiated with dissection of the thoracodorsal vessels, that constitutes the vascular supply. This should be done with caution as previous lymph node dissection or radiation therapy to the area may have left the thoracodorsal vessels surrounded by fibrotic scar tissue. In rare cases, the thoracodorsal vessels might have been damaged during lymph node dissection, which would necessitate an alternative reconstructive strategy. Some surgeons advocate the pre-operative use of color-doppler ultrasonography, which may be a very useful tool to detect vascular anomalies and plan an alternative approach. The vascular pedicle is dissected from its insertion into the latissimus dorsi muscle and toward the axilla until the desired length of the pedicle is achieved—often about 8–10 cm, but can reach up to 15 cm.

The nerve is the identified and, may be ligated, depending on the surgeon's preferences, in an attempt to avoid jumping breast syndrome (21). The flap is then dissected, with respect to the desired size of skin island, in its entity from its origin at the lower back and the dissection continues towards its most inferior part at the iliac crest, from where the last part of the dissection is performed in direction of the axilla. Some surgeons prefer to initiate the dissection from the lumbar origin of the muscle and proceed towards the axilla, which may be a time-sparing option, if the thoracodorsal vessels have been identified as functional preoperatively. The humeral insertion may then be detached, and the flap is transposed through the axilla, to its new position at the chest.

A number of variations to this technique has been described throughout the years and the alternatives include the extended myocutaneous LD flap where a portion of the lumbar fat is included in the flap, in order to provide sufficient volume for complete breast reconstruction (22). On the other hand is the muscle-sparing LD flap where a strip of muscle is kept to protect the vessels and constitute a pedicle based on the descending branch of the thoracodorsal artery, while the remaining part of the muscle is left functional at its original place (23). The perforator-based alternative, the thoracodorsal artery perforator (TDAP) flap, is this donor-area's analogue to the deep inferior epigastric perforator (DIEP) flap, that consists of skin and underlying fascia and is supplied by perforators from the thoracodorsal artery. It is usually "propelled" to the its new position at the site of breast reconstruction (24).

Range of motion (ROM)

Change in ROM is a popular and easy-to-asses method for determining change of shoulder function following LD breast reconstruction. It is typically measured using a goniometer (25), but different, digital, assessment methods have emerged in recent years, which provides an option that does not necessitate any equipment in excess of a smartphone and can be performed at any place by the physician (26). ROM should ideally be performed pre- and postoperatively, and with a follow-up that respects the physiological changes and maturing of scar-tissue after surgery. The LD muscle primarily contributes to the shoulder motions extension, adduction, and internal rotation (*Figure 1*).

Several studies have examined the changes in ROM after LD transfer, although only three studies report the specific

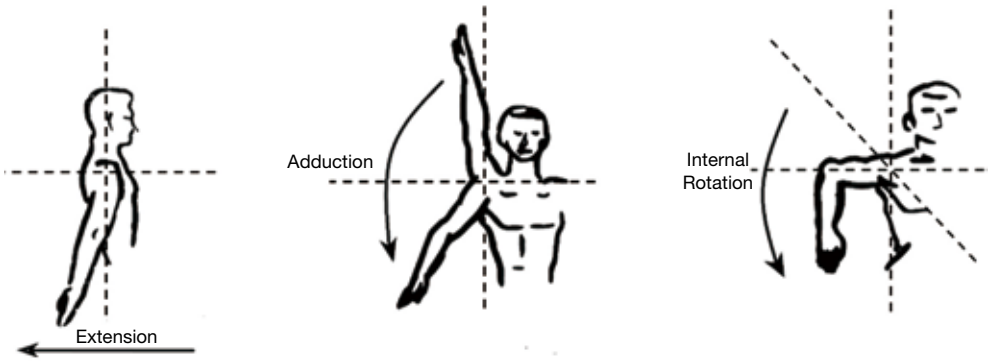

Figure 1 Degrees of shoulder motion to which the LD muscle contributes. LD, latissimus dorsi.

Table 1 Change in ROM after breast reconstruction with an LD flap

Study	Number	Follow-up	Measurement	Change	P
Glassey *et al*. (in 2008)	22	12 months	Adduction	0	NA
			Extension	+4.4°	NA
			Internal rotation	+8.0°	NA
Sowa *et al*. (in 2017)	18	12 months	Extension	+3.1°	ns
		36 months	Extension	+6.4°	ns
		12 months	Internal rotation	–2.0°	ns
		36 months	Internal rotation	+0.9°	ns
Russel *et al*. (in 1986)	23	16 months	Adduction	0	ns
	–		Extension	5.6%	ns
	7*		Internal rotation	13.5%	ns

*, specified for breast-reconstruction patients. ROM, range of motion; LD, latissimus dorsi; NA, not applicable; ns, no statistical significance.

changes following breast reconstruction with the pedicled LD flap (*Table 1*). Russell *et al.* investigated 24 patients of which 7 had breast reconstruction performed (7). The patients with breast reconstruction had a 13.5% decrease in internal rotation and a decrease of 5.6% for extension across the cohort. No change was detected for abduction. Glassey *et al.* investigated 22 patients with a 12-month follow-up and found an increase of shoulder extension of 4.4 degrees and an increase of 8.0 degrees for internal rotation (10). Sowa *et al.* examined 18 patients and found a non-significant increase in extension of 3.1 degrees and 6.4 degrees at 12 and 36 months respectively. Internal rotation was limited by 2.0 degrees at 12 months but had improved by 0.8 degrees at 36 months follow-up but was not statistically significant (16). de Oliveira *et al.* found no significant change in ROM 1 year after immediate breast reconstruction with an LD flap, but investigated shoulder flexion and abduction, motions to which the LD muscle is not usually considered to contribute (13). Other studies have reported some changes in shoulder ROM but have not reported quantified results as Garusi *et al.* (14) report that 96% of their cohort of 86 patients had recovered shoulder ROM of 80–100% for extension and 94% had recovered 80–100% of internal rotation at the end of follow-up which ranged from 1–14 years. Saint-Cyr *et al.* investigated ROM between the operated and non-operated side in 20 patients and found no difference between the sides for any motions of the shoulder (11). Rindom *et al.* performed a randomized trial comparing LD to TAP flap breast reconstruction and found a decrease in Constant shoulder score of three points for the LD group at 12-month follow-up (17). The Constant score is system for assessment of

Table 2 List of studies investigating shoulder strength after LD reconstruction

Study	n	Follow-up	Motion	Measurement	Change	P
Rindom *et al*. (in 2019)	18	12 months	NA	Isometric	–18%	NA
Sowa *et al*. (in 2017)	20	36 months	Adduction	Isometric	–36%	<0.05
		36 months	Extension		–7%	ns
		36 months	Internal rotation		–14%	<0.05
Van Huizum *et al*. (in 2016)	12	3.5 years	Adduction	Isometric	16.2%	<0.05
			Extension		–22.4%	<0.05
			Internal rotation		–14.4%	<0.05
Forthomme *et al*. (in 2010)	20	6 months	Adduction	Isokinetic	–31%	<0.05
			Internal rotation		–19%	<0.05
Glassey *et al*. (in 2008)	22	12 months	Adduction	Spring balance	–0.3 kg	NA
			Extension		–0.06 kg	NA
Fraulin *et al*. (in 1995)	13	4.4 years	Adduction	Isokinetic	–39%	<0.05
			Extension		–32%	<0.05
			Internal rotation		–19%	ns
Russel *et al*. (in 1986)	23	16 months	Latissimus function	Manual	–18%	NA

*, specified for breast-reconstruction patients. LD, latissimus dorsi; NA, not applicable; ns, no statistical significance.

shoulder function, that investigates ROM (0–40 points), pain (0–15 points), strength (0–25 points) and ability to perform activities of daily living (0–20 points) and scores the function from 0–100, with a score of 100 meaning no shoulder impairment at all.

The vast heterogeneity of reporting measures, study design and follow-up time makes it difficult to compare the effect of LD breast reconstruction on shoulder ROM, and whilst some report a decrease and others an increase, a definite conclusion remain unclear.

Shoulder strength

Shoulder strength can be measured in a number of different ways but the gold standard for muscle testing is isokinetic dynamometry (27). The major drawback of the isokinetic dynamometer is its large size and immobility, but handheld devices for isometric dynamometry has shown good results regarding reproducibility and is often the preferred choice in studies of breast reconstruction patients. Measurements have also been performed using a spring balance or manual muscle testing (7,10), but these do not provide the same accuracy as the dynamometers. An overview of studies examining muscle-strength is shown in *Table 2*.

Rindom *et al.* found a decrease in Constant score for shoulder strength of 2.2 points after measurements with a dynamometer, but evaluated against patients undergoing TAP flap reconstruction, and found no significant difference between the groups (17).

Sowa *et al.* used isometric testing of shoulder strength and found a significant decrease in adduction strength of 36% at 3-year follow-up and a significant decrease of 14% for internal rotation. Extension strength was decreased by 7% but insignificantly (16).

In 2016, van Huizum and colleagues performed a study of 12 women who had undergone LD breast reconstruction at an average of 3.5 years prior to the study (15). They investigated the loss of synergistic muscle strength and controlled to the contralateral arm. They found a significant decrease of shoulder strength for extension, adduction, and internal rotation of on the operated side compared to the non-operated and reported 19% higher scores for overall torque of the motions performed by the latissimus muscle, on the non-operated side. Forthomme *et al.* performed a study measuring shoulder strength with an isokinetic dynamometer in 20 women undergoing LD breast reconstruction with a follow-up of 6 months (12). They found a significant reduction of peak torque for

internal rotation (19%) and adduction (31%) at the end of follow-up. The results were compared to the non-operated site, and the significant reductions were only present on the operated side. Fraulin *et al.* examined 13 women using isokinetic testing (9). Mean time from reconstruction was 4.4 years and strength were measured between the operated and the non-operated side. They found that shoulder strength was significantly reduced by 32% for extension and 39% for adduction. An insignificant decrease of 19% for internal rotation was also recorded. They also included isotonic functional strength tests using a Baltimore therapeutic equipment (BTE), that simulates activities such as ladder climbing, painting and ability to push up from a chair. The ability to utilize the shoulder for the mentioned activities was significantly reduced in breast reconstruction patients, while simulation of skiing was unaffected.

Other authors have utilized less reproducible methods for testing shoulder strength. Glassey and colleagues found a decrease in shoulder strength for extension of 0.06 kg and a reduction in adduction of 0.3 kg at 12-month follow up, but measured strength using a spring balance, and did not provide any statistical considerations alongside the results (10). Russell *et al.* used manual muscle testing and found that the operated side was statistically weaker in all patients. The average weakening when they specifically tested for strength of the latissimus dorsi muscle was 18%, which surprised they recorded some degree of strength "even though the muscle was gone" (7).

The results of the studies clearly show that some degree of measurable shoulder weakening should be expected following LD breast reconstruction, although it also appears that the agonistic muscles of the shoulder to some extent compensate for the loss as there seem to be an increase in strength from the earliest measurements (1–3 months) to 12-month follow-up.

Patient-reported shoulder function

One issue is the determination of measurable shoulder weakening after LD breast reconstruction, another is whether this loss actually affects the patient's everyday life and ability to perform daily activities. A wide variety of assessment options for patient-reported outcome measures (PROMs) is available when examining the functionality of the shoulder function. Most often has questionnaires been used and the preferred har traditionally been the *Disabilities of the Arm, Shoulder and Hand* (DASH) questionnaire, although different questionnaires and interviews have been individually designed in several different studies. Furthermore, the Constant score includes a section of the patients' ability to perform ADL.

The studies by Forthomme *et al.* and Rindom *et al.* found a decrease in Constant score for ADL of 40% (6 months post-op) and 8% respectively (12 months post-op) (12,17) and the change in the latter study was significantly larger than for patients undergoing TAP reconstruction.

The DASH questionnaire has been developed by the American Academy of Orthopedic Surgeons (28) and has been utilized to evaluate shoulder function after LD breast reconstruction with varying results. The patients are assigned scores corresponding to their answers were 0 represents no disability and a 100 represents total disability. Two prospective studies found no statistical or clinical difference before and 1 or 3 years postoperatively (10,18) and one prospective found a significant increase in DASH score from 2.74 to 13.8 at 12-month follow-up (20). One study found significantly higher average DASH score compared to a control group, but the mean DASH score for the LD group was 16.5, which corresponds to mild impairment (15). Two retrospective studies without controls found mean DASH scores of 7.2 and 16.0, that were assessed to be low, and concluded that LD reconstruction led to minimal subjective functional disability (11,19). These retrospective studies are limited by the nature of their design and cannot consider any impairment that might have existed prior to reconstruction.

Brumback *et al.* and Fraulin *et al.* used non-commercialized questionnaires and found that 40% and 33% complained of some degree of shoulder limitations although they first study primarily attributed the complaints to tightness of axillary or back (8,9).

Another aspect of the patient's perception of the procedure is related to whether denervation of the thoracodorsal nerve has been performed or not. Previous studies have shown relatively high incidence-rates of involuntary contractions of the reconstructed breast or jumping breasts (29), although to our knowledge, no studies have investigated any correlation between discomfort associated with breast contractions and functional impairment.

No systematic decrease in the patient's self-reported ability to perform activities of daily living has been documented in previous reports. This may be attributable to the possible compensation from the shoulder agonists for the movements to which the LD muscle contributes.

Other aspects

Perioperative optimization and hospitalization

A well-documented benefit of LD breast reconstruction is the possibility for introduction of *Enhanced Recovery After Surgery* programs which provides the possibility of short postoperative hospitalisation and is associated with low perioperative complication-rates (30). Breast reconstruction with an LD flap has previously been shown to be possible in an ambulatory setting, if an extensive outpatient system is established and cooperation with an in-hospital ward is present, should complications arise (31). A postoperative length of stay (LOS) of 3–4 days have been shown in departments without the need for specialized outpatient centers (30). This advantage offers the possibility of a shorter hospital stay, which may be associated with a positive impact on quality of life (32).

Surgical refinement

In recent years, a trend toward perforator-based flaps has emerged and while the DIEP is well established as the gold standard for autologous breast reconstruction, the use of the LD flap continues to be the first-choice alternative for many surgeons. Since its introduction in the early 90's, the TDAP (33) flap for breast reconstruction has been gaining increasing popularity as an alternate flap originating from the back. Like the case for different myocutaneous/perforator flap pairs such as the transverse rectus abdominis myocutaneous (TRAM)/DIEP flaps, it is tempting to seek out muscle-sparing alternatives. The preference of the TAP flap by many surgeons may be contributable to the intuitively sensible in avoiding transplantation of a muscle when it is not necessary. As mentioned above, Rindom *et al.* demonstrated positive effects of the TDAP flap regarding shoulder-related donor-site morbidity, which favors the choice over conventional LD (17). Hamdi *et al.* likewise reported minimal donor-site morbidity following TDAP flap reconstruction, but had no basis for comparison with the LD flap (34). Nonetheless a total transition to perforator-based flap has not been seen despite that the TDAP-flap has been an option for almost 30 years. Even though the distinct difference between different variations of the LD-flap and the TDAP-flap lies in the absence of muscle transfer during TDAP-flap reconstruction, there are several other factors that should be considered when planning reconstructive modality and informing the patients ahead of surgery. First of all, as a perforator-based flap, success is highly dependent on surgical expertise and experience in locating the right perforator (which requires equipment in form of ultrasound or doppler verification) and assessing the viability of how big a reconstruction the given perforator can support. Secondly, in patients with comorbidities, the use of the LD flap has been advocated as the safer alternative (35). Furthermore, ERAS programs for patients undergoing reconstruction with the TDAP flap, has not been published and postoperative LOS traditionally has been reported with a median of 7 days, although an LOS of down to 2 days was demonstrated, which illustrates a potential for shorter hospitalizations in standardized settings (24). A common challenge for these patients has traditionally been the relatively large drain output that is associated with the placement of a synthetic or allogenic mesh, which necessitates hospitalisation if the department does not have a well-established plan for discharging patients with drains, although the introduction of procedures omitting the use of a mesh or using a low-irritant mesh (i.e., a vicryl mesh) may reduce the drain output drastically, thereby allowing early drain-removal.

Conclusions

The LD flap remains a safe and reliable option for breast reconstruction. The heterogeneity of the studies regarding measurement methods, reporting outcomes, follow-up time, adjuvant therapies administered to the patients and timing of the procedure makes a relevant comparison of the studies difficult and warrants long-term prospective studies of the patients, starting at the time before any surgical procedures affecting the shoulder area. The LD flap may still be considered a viable option for breast reconstruction but further comparative studies on benefits and drawbacks of both the LD and the TDAP flap should be encouraged.

As many things in life, the raising of a latissimus dorsi flap for breast reconstruction comes with a cost as the price to pay for an LD flap may be a considerable loss of measurable shoulder strength of up to 40% for some motions. Nonetheless, the patient's ability to perform activities of daily living does not seem to be radically impaired, leaving the price the patients perceived by the patients, lower than else expected.

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Footnote

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Review Article

The interface between breast conserving surgery with oncoplastic techniques and mastectomy: when to perform one or the other—a narrative review

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Objective: The aim of this review is to describe different oncoplastic surgery techniques and indications versus mastectomy.

Background: Oncoplastic breast surgery has emerged in last 2 decades as an alternative to mastectomy. It refers to the resection of the breast tumour with clear margins followed by the reconstruction of the defect using surgical plastic techniques. Oncoplastic breast surgery allows women to keep their breast with tumours that otherwise would imply a mastectomy performed. The concept of oncoplastic breast surgery requires in one side a complete oncological surgical technique and in the other performing that surgery using plastic surgery techniques. If a breast symmetry is needed or demanded by the patient it should be performed in the same operation. Oncoplastic breast surgery is a safe oncological option, and it maintains the shape of the breast without the secondary effects of foreign bodies, re-do surgery and its complications. In oncoplastic breast surgery there are two different groups of techniques available to correct the defect created after the surgical excision of the tumour: volume displacement and volume replacement. In the volume displacement technique following the resection, the defect is filled with the rest of the available breast. In volume replacement technique, autologous flaps and tissue are dissected and transposed from a close or distant place. It requires special training program that must be facilitated to all breast surgeons. Mastectomy remains the main option for patients who wish their breast to be removed or for those when breast conserving surgery is not suitable.

Methods: We have searched the most relevant publications in PubMed from 1981 up to date using the keywords.

Conclusions: Oncoplastic breast surgery techniques have become the best new surgical options to treat breast cancer.

Keywords: Conservative breast surgery; oncoplastic breast surgery; mastectomy; indications; contraindications

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Introduction

Rationale

The dilemma between conserving breast surgery with oncoplastic techniques and mastectomy is difficult to solve. The final decision has to be taken by the patient after detailed information of both procedures and before the consent has been signed.

Breast surgery has evolved over the past two decades. What it used to be considered a "simple" surgical procedure has become sophisticated techniques that require high level of skills and training. Mastectomy has been the surgical procedure for a T3 tumour for decades. However, currently, the same tumour has a variety of surgical options all of which have excellent cosmetic results. Mastectomy, therefore is not always mandatory.

The patient wishes after a detailed information will always remain the main factor to decide the technique.

Surgical skills, training, knowledge and experience will remain the pillars that will move the balance and the surgeon has to be able to explain all the different options to the patient.

Breast conservative surgery (BCS) followed by radiotherapy (RT) have become the gold standard for patients with small breast carcinomas achieving good oncological and aesthetic outcomes in most patients (1). The most important goal of BCS comprises the complete cancer resection with clear margins maintaining cosmesis. Mastectomy would therefore remain as the gold standard only for large and locally advanced tumors always considering the relation between the size of the tumor and the size of the breast.

Prospective randomized trials have compared mastectomy with BCS and no survival difference was observed between both techniques (2,3). Recent reviews (4) observational studies (5) and population-based studies or revies (6,7) have pointed a better survival after BCS compared with mastectomy. We present the following article in accordance with the Narrative Review reporting checklist (available at https://abs.amegroups.com/article/view/10.21037/abs-21-35/rc).

Objectives

The aim of this review is to describe different oncoplastic surgery techniques and indications versus mastectomy.

Methods

The most relevant publications in PubMed from 1981 up to date related to breast conservative surgery, oncoplastic breast surgery techniques and mastectomy have been searched including meta-analysis. Case reports and short series have been excluded.

Discussion

Oncoplastic breast surgery (OBS)

OBS was introduced by Audretsch in the 1990s (8). OBS comprises the resection of the tumour with clear margins followed by the reconstruction of the defect using surgical plastic techniques. This eventually will improve the cosmetic results avoiding deformities after BCS and RT. However, BCS may have complications. Deformities in the operated breast originating asymmetry with the contralateral side have been described in 30% of the patients after the operation. These complications will affect the quality of life and distress on the body image (9).

OBS allows women to keep their breast with large tumors that otherwise would imply a mastectomy performed. It comprises the complete resection of the tumor and the immediate reconstruction of the operated breast using plastic replacement or displacement techniques. If the patient requires contralateral symmetry, it can be performed at the same time (10). Eventually, it will avoid the secondary effects of the mastectomy or the prolonged multistage reconstruction with autologous tissue or implants techniques. It should be delivered by surgeons trained as breast oncoplastic specialists with knowledge of both surgical disciplines and oncological principles.

So far there are no published studies comparing the overall survival, disease-free survival and local recurrence between standard BCS and mastectomy with OBS. There is a growing evidence that OBS is safer from the oncological point of view. A recent systematic review has confirmed its safety for T1–T2 invasive cancer, as the patients show a high rate of disease free and overall survival and also low local and distant recurrence rates. These data suggest that OBS is safe for invasive tumors up to 5 cm. (11).

Rietjens *et al.* published long term results in patients with T1–T3 with OBS (12). There was no local recurrence in the T1 patients. Patients with T2–T3 had a 5-year local recurrence rate of 3% comparable with the 14.3% local recurrence in the NSABP trial (13) and the 0.5% local recurrence in the Milan study (14) where only T1 tumors were included.

The main indication for OBS is women whose cancer is

not small enough to be treated by a simple technique and not large enough to dictate mastectomy (1). The concept also sits well with the increasing use of neo-adjuvant therapy to downsize cancers that previously have been managed with mastectomy.

OBS can improve the outcomes of BCS in four aspects:

(I) It allows removal of large tumors, without risking major local deformity;
(II) For surgical procedures where a high percentage of the breast needs to be excised (20%) with adequate margins and cosmetic outcomes, OBS is the standard procedure;
(III) OBS techniques are able to correct deformities after breast conservative surgery in patients treated also with radiotherapy (15);
(IV) OBS optimizes the breast radiation therapy of patients with macromastia (16).

Mastectomy remains the main option for patients who wish their breast to be removed or for those whom breast conserving surgery is not suitable. However, all women undergoing mastectomy should be offered the opportunity to discuss reconstruction.

OBS techniques avoid secondary surgery for reconstructions as prevent major deformities of the breast (17). It is essential to perform all the reconstructions at the same time in order to avoid reconstructive surgery of important defects after radiotherapy (18).

Clasification of oncoplastic procedures

Clough classified oncoplastic procedures within two levels (19)

Level I procedures include resections in which up to 20% of breast tissue needs to be removed. This includes glandular re-approximation and re-positioning of the nipple-areolar complex (NAC). Lumpectomy through low-visibility incisions and extramammary incisions for lateral resection with NAC mobilization are included. This technique should be performed by all breast surgeons.

Level II are procedures with the resection of more than 20% of the breast volume. This Level also requires re-shaping the contours and, nearly always, symmetrization of the contralateral breast. Within level II OBS, we identified patients with extreme oncoplasty. Extreme oncoplasty is defined as surgical procedures, which most of the surgeons would consider a mastectomy instead of BOS. These techniques are based in breast reduction mammoplasty and require specific oncoplastic surgical training.

Volume replacement/volume displacement techniques

Volume replacement and volume displacement are the two different group of plastic technique procedures used by breast surgeons for immediate reconstruction of resection defects.

In volume replacement procedure, tumourectomies larger than 20% of the breast volume are performed and the defect is repaired with the transposition of autologous tissue from elsewhere.

In volume displacement surgery after the high volume tumourectomy the defect is filled with the tissue left after the excision of the tumour.

Volume replacement

It is most appropriate for patients with small to medium size tumors that cannot be repaired by volume displacement techniques, or who wish to avoid contralateral surgery.

Transpositions flaps

(I) The latissimus dorsi flap: it is a musculocutaneous flap that can be used to fill lateral, superior, inferior and medial defects. It should have a bigger volume that the defect to cover as the surgical de-innervation and radiotherapy will create atrophy of the flap.
(II) Chest wall perforators flap only use de-epithelised skin with adjacent fat. The main advantage over other methods of reconstruction is the use of well-vascularized tissues to spare the underlying muscles in order to reduce the site morbidity and the seroma formation (20). They are classified according to the source of the vessel from which the perforator arises (21).
    (i) Thoracodorsal artery perforator (TDAP) flap: the flap is raised from a septocutaneous perforator from the thoracodorsal artery at the anterior border of the latissimus dorsi muscle and more commonly as a musculocutaneous perforator. The base of the flap in its medial part is placed at the lateral breast crease. The perforators have to be identified with the patient in a lateral decubitus position using a 5- to 8-MHz hand-held acoustic Doppler close to the medial border of the latissimus dorsi muscle and the rest of the flap, as in the other perforator flaps, has to be drawn with account of perforator position, size of flap required and availability skin laxity (22). Usually, the height of the flap has a maximum of 8 to 10 cm and can be as long as 30 cm always trying to conceal it with the bra strap line. Usually, these flaps are used to fill defects close to

100 cc. Dissection has to be careful with the patient in lateral decubitus position, the same as when the perforators where identified. The shoulder abducted onto a support and in some cases a complete lateral position is needed to dissect the flap and close the incision. The dissection is performed medial to lateral. All perforators have to be identified eliminating only those that can restrict the movement of the flap. Once the flap has been de-epithelised it can be transposed into the defect. Sometimes a suture is placed trying to avoid the movement of the flap induced by gravity but in most of the cases it is not necessary. Identification of the perforators by doppler, marking the skin, dissection of the flap from medial to lateral and filling the defect with the flap are all required steps for theses procedures.

(ii) Lateral thoracic artery perforator (LTAP) flap (22). This flap is based on single or multiple perforators of the lateral thoracic vessels that are usually found 1–2 cm lateral to the breast crease and in the 3rd to 4th intercostal spaces in the inferior outer quadrant of the breast and the surface of the flap can be very similar to the TDAP flap.

(iii) Intercostal artery perforator (ICAP) originating from the lateral region (LICAP) or from the anterior region upon the rectus muscle (AICAP). The LICAP perforators are commonly found between the 5th and 7th intercostal spaces. The patient´s position is the same as for the LTAP and TDAP and sometimes it will be difficult to differentiate these perforators and the final decision of the type of flap used will be based on perforator exploration. In the AICAP flaps are based on perforators originated from the rectus muscle and are used to fill defects in the superior or inferior interior quadrants. The scar will remain in the inframammary fold.

(iv) The branch to the serratus anterior perforator (SAAP). If this branch can be identified and it comes from the artery to the Serratus Anterior side branches should be ligated and the pedicle dissected with the fascia of the Serratus.

(v) The superior epigastric artery perforator (SEAP). There are usually four to six SEAPs from the superior epigastric artery and the biggest perforator are usually localized in an area 2 cm from the midline and 0–10 cm below the xiphoid (23).

(vi) Local fascio-cutaneous flaps can also be used in the case of small lateral defects (<10% of the breast size).

(vii) Other less common volume replacement techniques are omental flaps first used in 1963 (24). This technique initially did not achieve popularity because of the severe laparotomy-associated complications that sometimes occurred. In 1998, however, Costa reported the successful performance of breast reconstruction with a laparoscopically harvested omental flap (25).

Autologous fat graft

Autologous fat graft is a common technique also used to improve aesthetic outcomes after conservative surgery. The fat is obtained with hand held syringes and special cannulas or ultrasound assisted in continuous aspiration from different part of the body such as abdomen, flanks and thighs. Tumescent anesthesia with saline, lidocaine and adrenaline in donor area before liposuction reduces pain, blood loss and far removal is easier to perform. Larger diameter cannulas (5 mm) fat grafts demonstrated better histologic integrity when compared with 2–4 mm cannulas (26). There are different processing techniques; centrifugation, washing, gravity separation and filtration. Once the processed lipoaspirates are obtained they have to be delivered at the recipient side. Coleman originally described the placement with a Luer-Lock syringe connected to a 17-gauge blunt cannula (27). Fatty tissue is injected while withdrawing slowly the cannula in different directions.

Fat grafting can be used to protect the skin after radiotherapy and at the same operation of exchanging the expander by the permanent implant, to fill conservative surgery defects and it has also been described its use in the breast to create breast in successive operations until the desired volume is reached.

Volume displacement techniques (28)

(I) The ideal technique for medium to large breasts with ptosis is probably mastopexy or therapeutic mammoplasty (29). The tumour is included within the breast resection pattern and the remaining breast tissue is used to re-shape the breast. Using a Wise pattern any tumour can be operated irrespectively to its location.

(II) Inferior pedicle approach. After a resection of a

tumor in the upper pole and a thin superior or superomedial pedicle performed an inferior pedicle can be used to cover the defect after a vertical or Wise pattern.

(III) Round block approach (upper pole, inner quadrant, outer quadrant) is a technique more suitable for upper pole tumours close to the areola in ptotic breasts, which will be improved with mastopexy at the same time through the round block.

(IV) Grisotti flap technique is useful for retro-areolar tumors. It uses an inferiorly based dermal-glandular pedicle to advance a skin island intro the central defect. Once the flap has been done the skin island is suitable for a nipple reconstruction with a skin flap or tattooing.

(V) J mammoplasty is useful for lower outer pole tumors. It avoids lateral retraction of the breast and deviation of the nipple-areola complex. It comprises a central and lateral breast flap, which is rotated towards the defect and the nipple-areola complex is re-positioned with a superior pedicle.

(VI) V-mammoplasty (lower inner quadrant). The tumour is excised "in block" with a pyramidal section of the gland with the apex of the pyramid in the areola and the base in the inframammary fold.

(VII) Superior pedicle approach (lower pole). A superior or supero-medial pedicle, similar to the one used for reduction mastoplasty, obtains good aesthetic results as the inferior pole is usually part of the breast excised during those procedures.

(VIII) Batwing technique (upper inner, central and outer quadrant). It combines resection of a crescent-shaped area of skin and gland above the nipple-areolar complex plus two adjoining triangle or winglike areas of the skin and breast parenchyma extending from both sides of the areola. It is useful for large volume glandular resection of tumors in the central upper pole between 8H and 4H position

(IX) Incisions in the lateral border of the breast are used with lateral mammoplasty for the outer quadrants and are associated with very good cosmetic outcomes.

Indications for oncoplastic breast surgery

Excision volume

OBS is indicated when the breast volume excised is over 20% of the overall breast tissue as there is a high probability of deformity, asymmetry and poor cosmetic results (17). It is also indicated when the resection of the parenchymal tissue exceeds 70–100 cc or a tumour-to-breast weight ratio is over 10%. Patient satisfaction rates are over 90% if 5% or less of breast tissue is excised, but only 25% satisfaction is reached if 20% of breast volume is lost (19). For excisions higher than 20% of the total breast volume a standard tumourectomy would lead to a major deformity.

Tumor location

In some areas of the breast, it is more difficult to resect tissue maintaining at the same time good cosmesis. Unfavourable tumour locations are medial, superomedial, central or inferior parts of the breast. Excision of tumors on the upper inner quadrant may lead to scars in the cleavage or indentation as there is less parenchymal volume. Excision of tumors from these areas may also result in nipple malposition due to scar retraction. Resection of inferiorly sited tumors may also cause a bird's beak deformity. Tumors closer than 2 cm to the nipple may require nipple sacrifice (30). If the resection includes the nipple and is performed as an ellipse, it will flatten the breast shape. Oncoplastic techniques allow better cosmesis following resection of this areas.

Multifocal and multicentric disease

Expert consensus supports the technical feasibility of OBS as a therapeutic mammoplasty for surgical treatment of multiple ipsilateral breast carcinomas (31). Nonetheless, the evidence for clinical equivalence in terms of outcomes such as locoregional recurrence, breast cancer-specific outcomes and overall survival rates compared to mastectomy is of only of moderate quality (32).

Re-operation after conservative surgery

Before radiotherapy

If the patient needs a re-excision for one or more affected margins and where a simple re-excision may end up in shape deformity (33).

If the margins are free but the patient seeks correction of deformity for cosmetic reasons after BCS.

After radiotherapy

When corrections of the defect after BCS and RT are needed, caution is mandatory as these patients will be at higher risk of wound healing problems and pedicle hypo-

vascularity. The oncological safety of these procedures is not supported by high-level evidence

Extensive DCIS

It is possible to perform therapeutic mammoplasties for extensive DCIS tumors up to 5 cm with a small percentage of margins involved (1.9%). This percentage increases when the tumor size is over 5 cm (64%) (34). For tumors over 50 mm better preoperative localization is recommended.

Invasive lobular carcinoma

Invasive lobular carcinoma grows in a diffuse pattern and it is sometimes very difficult to perform a complete surgical excision with adequate margins. Oncoplastic techniques and selective margins shavings is associated with a lower rate of positive margins and conversion to mastectomies (35).

Poor response to neoadjuvant chemotherapy

Oncoplastic breast surgery after neoadjuvant chemotherapy is as effective as standard breast conservative surgery allowing similar rates of re-excision (2% *vs.* 9%) and mastectomies (18% *vs.* 24%) (P=0.22 and P=0.30) with similar probabilities of survival and recurrence. Volume was larger in the oncoplastic group (180 cc) compared to the conservative group (98 cc) (P>0.0001) (36).

Macromastia

Women with large breasts may be technically challenging for the administration of whole breast radiotherapy. Many of them will suffer significant complications such as breast oedema and skin reactions.

Therapeutic mammoplasty is the term for the oncoplastic application of breast reduction and mastopexy techniques to treat selected breast tumors by breast conserving surgery enabling OBS for larger breast cancers (34). The majority of studies of therapeutic mammoplasty for macromastia in breast cancer achieve low rates (8%) of incomplete excision (35). Given the rates of involved margins reported for invasive cancer (15–20%) and DCIS (30%), this benefit is worthwhile. The tumor may be excised in bloc with the reduction sample but special care must be taken with margins marking and orientation. Recurrence rate from studies analyzing oncological outcomes following therapeutic mammoplasty are between 0% and 9.2% (33).

A detailed review (36) concluded that therapeutic mammoplasty has oncological outcomes comparable to BCS. However, they note that no randomized trials have been performed and the evidence in support of these techniques is all derived from case series and cohort studies.

Contraindications of oncoplastic breast surgery

(I) Inflammatory breast cancers: treatment of inflammatory breast cancer includes trimodal therapy with chemotherapy, surgery (with modified radical mastectomy enhancing survival outcomes) and radiation.

(II) Recurrent cancer following BCS and whole breast RT: these patients are at high risk of fat necrosis and vascular insufficiency of the pedicle and wound edges due to the previous RT.

(III) Oncological contraindications: if there is no possibility to achieve free margins after multiple operations even with the use of OBS. Multicentric invasive lobular disease: in these cases, there is higher risk of margin involvement due to the diffuse spreading nature of this subtype of cancer and the poor response to neoadjuvant chemotherapy. Failure of neoadjuvant chemotherapy: when there is no response to NAC or progression is noted during the treatment OBS is not a safe possibility if the patient didn't have an indication for conservative surgery initially.

(IV) Cosmetic contraindications: unfavorable tumor to breast size ratio.

(V) Inability to deliver indicated radiotherapy (37).

(VI) Small breast without ptosis and conical breast.

(VII) Special comorbidities: such as diabetes, heavy smoking, obesity and concomitant physical and psychological illness as they have an increased risk of complications.

Complications

The major concern for complications of oncoplastic techniques is not interfering with the time of adjuvant therapies (38). A meta-analysis comparing oncoplastic and standard breast-conserving surgery showed that early complications rates in the oncoplastic surgery group did not delay the initiation of adjuvant therapies (39).

Overall complications following volume replacement

techniques are slightly higher (2–77%) (39) than in volume displacement techniques (3–15%) (40).

Cosmetic sequelae are also an event that can affect up to 17% of patients who undergo OBS. Most of them appear during the first 5 years of follow-up. Insufficient re-shaping, fat necrosis, and postoperative complications are the main risk factors for deformity (41).

Follow up

Follow up for OBS is the same as for CS. Ultrasonography combined with MRI can identify cancer recurrence. Qualitative changes seen in the mammography are similar between lumpectomy and oncoplastic techniques (42). The time required for OBS to achieve radiologic stability tends to be 25.2 months (43).

Conclusions

After reviewing the literature there are key points to be highlighted.

All decisions related to oncoplastic techniques in breast cancer patients must go through an MDT meeting that will inform the patient about different treatments available.

Mastectomy is an option for women who desire it after a complete informed discussion.

OBS is a safe oncological option and it maintains the shape of the breast without the secondary effects of foreign bodies, re-do surgery and its complications.

OBS involves appropriate oncologic surgery, immediate homolateral reconstruction using plastic surgery techniques and correction of the contralateral breast, whenever a symmetry procedure is required.

Training in oncoplastic surgery must be facilitated to all breast surgeons.

Limitations of the study come mainly from the absence of prospective randomised trials comparing conservative surgery directly with oncoplastic breast surgery in similar populations and studying overall survival and recurrence in similar populations. However, those studies seem to be difficult to perform.

Future research should concentrate in the long term oncoplastic surgery data related to survival, local recurrence and quality of life of patients.

Oncoplastic breast surgery techniques have become the best new surgical options to treat breast cancer. Specific training is needed for breast surgeons to learn and apply all surgical options that oncoplastic surgery offers to treat breast cancer.

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Review Article

The propeller thoracodorsal artery perforator flap—designs for breast reconstruction and perspectives

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Abstract: The propeller thoracodorsal artery perforator flap (pTDAP) is a further development and simpler version of the classic TDAP pioneered by Angrigiani C in 1995. The pTDAP can be used for immediate and delayed breast reconstruction in combination with an implant, fat grafting or in combination with other perforator flaps as an alternative to the latissimus dorsi flap. The pTDAP breast reconstruction can be performed and designed in several different ways regarding: (I) flap design, (II) axilla design and (III) breast design. The aim of this paper is to describe and illustrate different pTDAP designs and perspectives. We present the indications for use of the propeller TDAP in delayed as well as immediate breast reconstruction. The TDAP can be harvested from the back in various ways, horizontal and two different oblique techniques, upwards and downwards angled. The flap can be raised as an extended flap to include as much subcutaneous fat adjacent to the skin island as possible, either in the entire length of the flap or as the "Saturn"-design. The location of the dominant perforator(s) is predictable in most cases, but variations due occur and flap harvest can preferably be targeted by color Doppler ultrasonography for perforator identification. The propeller flap pedicle can be tunneled or left visible below/in the axilla. The flap can be augmented by an expander/direct to implant technique or combined with fat grafting or other perforator flaps, an internal mammary perforator flap from the contralateral breast, a superior epigastric artery perforator (SEAP) flap or with a free TDAP as stacked flaps. The pTDAP can and should be designed, targeted and adapted to the individual patient when used for breast reconstruction. This entails the flap size and shape in the back, the choice and use of perforators, the design and rotation in the axilla and the breast reconstruction when using the flap for augmentation, shaping and draping using expanders, implants, fat grafting or in combined with other flaps.

Keywords: Thoracodorsal artery perforator flap (TDAP); propeller flap; breast reconstruction; perforator

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The latissimus dorsi flap without muscle or the thoracodorsal artery perforator (TDAP) flap was introduced by Angrigiani in 1995 (1). This was the first time the TDAP flap was used for breast reconstruction. The TDAP in one variant from a range of TDAP flaps: (I) the extended lattisimus dorsi flap (ELD), (II) the latissimus dorsi flap (LD), (III) the muscle sparing latissimus dorsi flap (MSLD), (IV) the propeller thoracodorsal artery perforator flap (pTDAP) and (V) the classic thoracodorsal artery perforator flap (cTDAP). The different indications for use of these flaps in breast reconstruction have recently been described as well as the different designs of these flaps (2). The pTDAP itself can be designed in many different ways, the location, orientation and size and outline of the skin island. The rotation/

tranposition of the pedicle as well as ways to use the flap for shaping, draping and augmentation in the recipient site can also be designed in multitude of different ways. The pTDAP is often used instead of the LD flap for breast reconstruction to leave the upper body's largest muscle intact and to avoid the possible morbidity of the shoulder and arm associated with the use of the LD muscle (3,4). The indications for using the pTDAP flap for breast reconstruction is similar to the indications for using the LD flap (2,5). The flaps can be used for both immediate and delayed breast reconstructions and often in women who previously had radiation therapy to the chest, where the damaged unpliable skin and subcutis can be replaced by the more pliable flap tissue, which enables a better cosmetic and functional result in the long run (6). The aim of this paper is to describe and illustrate different pTDAP flap designs for breast reconstruction and the perspectives.

Indication for breast reconstruction

Delayed breast reconstruction

The pTDAP is used to add extra tissue to enable the breast reconstruction and often in combination with an implant. The skin and subcutis or the remainders of the mastectomy flap in the anterior part of the thorax is raised as a musculocutaneous flap with the pectoralis major muscle. In a few cases, where the subcutis is particularly thick or if the radiation damage to the muscle is severe, the flap can be raised as a cutaneous flap without muscle (6-8). The two flaps are combined to shape and drape the reconstruction.

Immediate breast reconstruction

In women who previously have had radiation therapy in combination with a lumpectomy, the skin of the lower quadrants is often removed after the mastectomy or as part of the mastectomy specimen. The aim is to replace the tissue damaged by radiation therapy by the pliable tissue of the pTDAP (6). It sometime seems odd to excise skin and tissue which at a first glance seems unaffected by radiation, but there is a substantial risk of capsular contracture in cases, where the damaged breast skin in not replaced by pliable skin. The alternative to the pTDAP in these cases is multiple fat graftings of the radiated mastectomy flaps, however in many cases it is only a matter of time before the contractures calls for a flap solution.

The pTDAP can also be used for partial breast reconstruction or salvage of reconstructed breasts (6).

Designs

Overall, there are three steps to designing a breast using a pTDAP flap: (I) flap design, (II) axilla design and (III) breast design. The designs are described below.

Flap design

In unilateral cases the flap is raised with the patient in the lateral position. The flap can be raised simultaneously with dissection of the axilla and recipient site (7,9). In bilateral cases, the recipient site is prepared first with the patient in the supine position. The patient is then turned to the prone position to raise the flaps and subsequently turned once again to the supine position for the breast reconstruction (10).

The skin island for the TDAP flap is harvested from the back and can be designed in many different ways. The base of the skin island is marked above and around the perforator(s). The flap can be designed in various ways and in different angles, however, there are three main designs: (I) horizontal (H), (II) oblique upwards (OU) and (III) oblique downwards (OD) (9,11-14), *Figure 1A*.

The scars of the first two options, H and OU can be hidden under clothing, whereas the third option leaves a scar in the lower part of the back, which can be difficult to hide. The flaps of the H and OU designs have to be rotated 180° or more to the recipient site, whereas the OD design only needs to be rotated in angle of 120–135° (9,11,12,15). Thus, the pedicles of the H and OU designs needs to be dissected more thoroughly and often all the way through the muscle to enable relocation of the flap from the donor site to the recipient site (9,12,15). The flap length of the oblique flap designs, the OU and the OD, can be up to 35 cm long compared to 25 cm of the H design (11). However, this also means that the distal part of the OU/OD flaps can only be used if the blood supply is reliable, when tested by fluorescence using indocyanine green or similar techniques (16). The distal 5 cm of the tip of the flap often has to be removed due to insufficient perfusion (2). The size of the flap, thickness, width and length, depends on the size and proportions of the individual patient. In skinny patients, the flap width can usually only be 6–7 cm compared to 10–11 cm in larger patients. The lengths of the flaps may variate from 18 cm up to almost 40 cm in large patients (7). The thickness and amount of subcutaneous tissue to be harvested varies a lot depending on BMI and the looseness of the skin. The

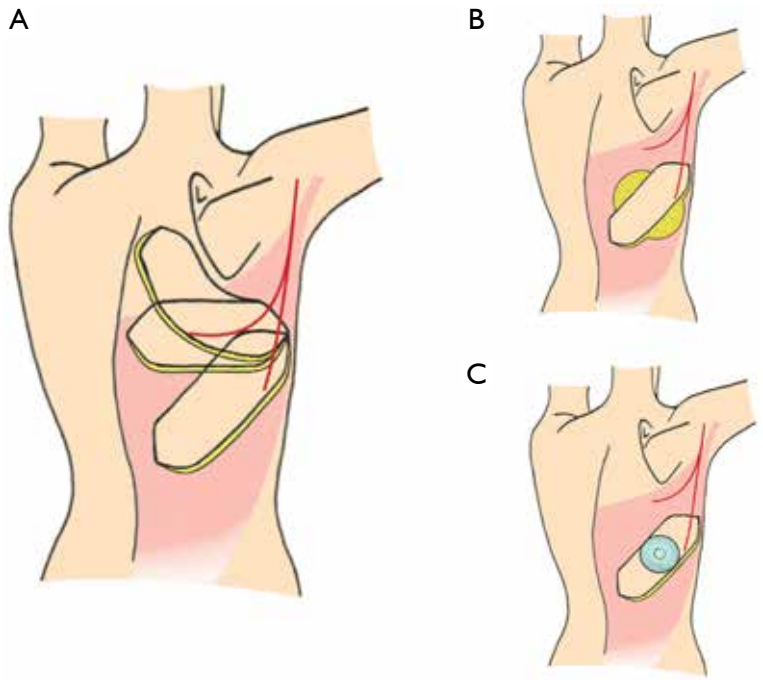

Figure 1 Designs of the pTDAP in the back. (A) The three main designs of the pTDAP flaps. (B) The extended Saturn design. (C) Expander placed under the pTDAP for preexpansion. pTDAP, propeller thoracodorsal artery perforator flap.

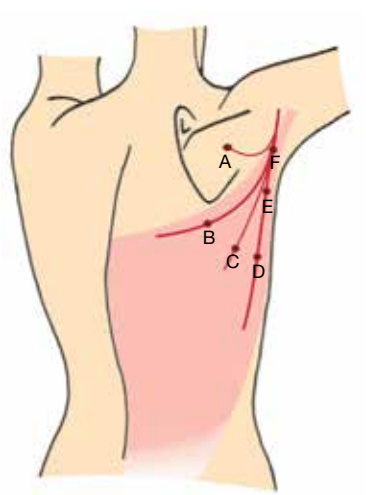

Figure 2 Location of TDA perforators. Perforators E and D are usually the dominant perforators. TDA, thoracodorsal artery.

largest flaps can be harvested in massive weight loss patients, where the tissue is often very loose and the perforators are relatively sizable compared to patients who have not lost weight. The flaps can be harvested as extended flaps including as much of the subcutaneous tissue under and adjacent to the skin island as possible (6,17,18). This can be designed in different ways, however in many patients the location of the subcutaneous fatty tissue allows for a "Saturn" design of the flap as illustrated in *Figure 1B*. The harvest of the subcutaneous tissue is often limited by the fascia of Scarpae, which should preferably be saved for closure of the donor site. Maybe this limitation can be overcome by pre-expansion, *Figure 1C*.

Raising the flap from the tip towards the base can be recommended using a scalpel in combination with bipolar cautery or a monopolar cautery. The skin is incised and bevelled outwards in the subcutis to add additional subcutaneous tissue to the flap volume if possible and necessary (7-9,14). The flap can be raised with or without the muscle fascia. The thickness of the muscle fascia variates and is often very thin almost as an epimysium. The argument for leaving the fascia intact is allegedly less seroma formation, however, regardless of the design there is no need for drains in the donor site as there is hardly any seroma formation (7). The advantage of raising the flap with the fascia is that it can be used to drape the implant when performing the reconstruction. The first three quarters of the flap can be raised very quickly until a close proximity to the perforators is reached (*Figure 2*), unless

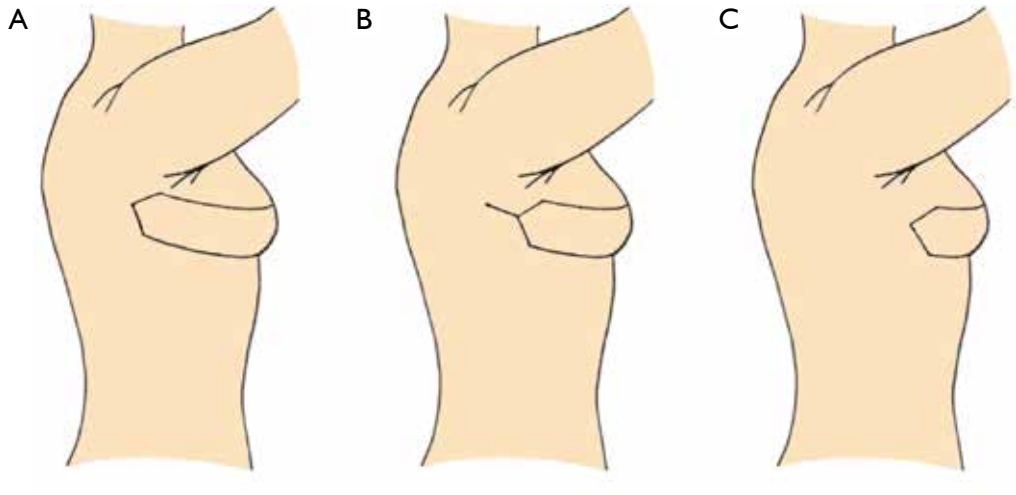

Figure 3 Axilla designs. (A) Simple rotation and base of flap visible. (B) VY design. (C) Base of flap tunneled.

preoperative color Doppler ultrasound has revealed a sizable perforator outside the usual location (A, B, C in *Figure 2*). In the majority of cases the dominant perforator(s) will be located close to the anterior border of the latissimus dorsi muscle (E in *Figure 2*). However, the location and the size of the perforator variate and preoperative color Doppler ultrasound is recommended for identification of the perforators (6,10,19,20). In the majority of cases there are one to two sizeable perforators located at the most prominating anterior part of the LD muscle, approximately 8–12 cm from the top of the axilla and 3–5 cm from the anterior border of the LD muscle (7,9) (D, E in *Figure 2*). The dominant perforator(s) can be located more distal along the descending or the horizontal branches of the TDA. Sometimes the dominant perforator can be placed in unexpected locations due to scars, which has redirected the original blod flow to the skin (2) (A, B, C in *Figure 2*). In these cases, the CDU is a very good tool for a targeted approach (19). Once in a while there are no obvious dominant perforator and three or more smaller perforators have to be included in the flap pedicle (21).

The flap area can be expanded in the back using an expander (*Figure 1C*), which has not been described for breast reconstruction, but for coverage of severe scarring in the cervicofacial regions (22). However, this could also be an option for breast reconstruction in patients with damaged or very thin skin in the recipient site.

The donor site is closed in three layers using absorbable sutures adapting the fascia of scarpae, the deep dermis and the subcutis. No drains are needed (7).

Axilla design

The pedicle of the pTDAP can be placed and designed in different ways depending on the location of the perforators.

(I) In patients where the perforator(s) is located 5–7 cm or more behind the anterior edge of the LD muscle and if the skin in the axilla is tight it is often advantageous to incise the skin between the flap and the recipient site and simply place the base of the flap in the gap to release the tight skin in the axilla and to ensure unaffected blood perfusion through the flap (10) (*Figure 3A*). Another reason for this approach is that the base of the flap can sometimes be quite bulky and difficult to cover by the axillary skin. The procedure not only releases the tight axillary skin, but also makes the donor site closure easier simply by providing more skin for the axilla and adjacent area, which can be somewhat tight when harvesting a big flap from the back.

(II) In cases where the perforator(s) perforates the muscle 3–4 cm behind the anterior edge of the LD muscle, the base of the pTDAP flap above the perforators can be deepithelialized and covered by the adjacent axillary skin (8,14). Often the skin is incised all the way from the flap to the recipient site and subsequently, when you know how much tissue is at hand the posterior base of the flap can be covered by the adjacent axillary skin in a VY manner (*Figure 3B*).

(III) When the perforator(s) is located anterior to or close the anterior edge of the LD muscle, the

pTDAP can be tunneled under the axillary skin to the recipient site (*Figure 3C*). The tunneled base of the TDAP flap can be used to replace the missing tissue in the axilla of women who had an axillary lymph node dissection (7,14). The added tissue often leaves a satisfying cosmetic as well as functional result as the scar tissue following the axillary procedure is removed and released as part of the procedure. This often enables better movement of the shoulder and arm as perceived by the patient.

The axillary skin and base of the TDAP flap will loosen over time and in approximately 50% of cases a lateral liposuction, shape and drape procedure is needed to debulk and tighten the tissue lateral to the reconstructed breast (6,7).

Breast design

The patient is placed in the supine position for breast reconstruction. In delayed breast reconstructions, the pTDAP flap can be placed where the scar was placed following mastectomy. However, the scar is often placed quite cranially and when the relatively thick pTDAP flap is placed in the middle of the breast reconstruction with a thin tissue layer bordering both sides of the flap, this often leaves a rather abrupt transition from the mastectomy flaps to the pTDAP flap simply due to the differences in flap thickness (8,14). This can successfully be corrected by several additional fat grafting procedures (23).

However, the pTDAP flap can also be placed in the neo-inframammary crease, where it is much easier to make a smooth transition for pTDAP flap to mastectomy flap (7,10,18). The mastectomy flap is raised as a musculocutaneous flap with the major pectoralis muscle, which makes the thickness of the flap similar to the pTDAP and the extended subcutis of the pTDAP flap can be used to shape a smoother transition between the flaps (7). In cases where the mastectomy scar is placed in the lower part of the chest, the skin between the neo-inframammary crease and the mastectomy scar can be removed to avoid a third scar. However, when the scar is placed more cranially, the skin is needed for the breast reconstruction leaving three scars, the mastectomy scar, the cranial pTDAP scar and the caudal pTDAP/neo-inframammary crease scar. The latter procedure enables the best possibility for shaping and draping the reconstructed breast and eventually the best cosmetic result despite the additional third scar. There is a risk of insufficient blood supply to the mastectomy skin below the mastectomy scar. In a few cases, we have had to remove this skin in a secondary procedure.

Shaping and augmentation of the pTDAP breast reconstruction

Direct to implant

In many cases the pTDAP flap can be immediately combined with a permanent implant for breast reconstruction (8,9,24). The implant can be placed and supported in the desired location by use of a biologic or a synthetic mesh (8). In some cases, the extended fascia around the pTDAP flap can be used to support the implant and in those cases a mesh is not needed.

Expander to implant

In the last couple of years, we have increasingly used expanders for pTDAP reconstruction (10) (*Figure 4A*). One reason for this is that we are using the pTDAP for breast reconstruction in patients with lower BMIs, where an expander seems to be the safer option to ensure sufficient blood supply. Another reason is that the expansion enables a sufficient and sizable cavity for a correct sized permanent implant (9,14,24,25). The majority of pTDAP reconstructions are, however, still reconstructed by a direct to implant technique using a permanent implant (*Figure 4B*).

Expander-fat

When a patient wishes a breast reconstruction with a pTDAP in combination with fat grafting, the fat augmentation can preferably be combined with an expansion using an expander for preshaping the breast prior to fat grafting (23,26). In the subsequent procedures the water volume of the expander is deflated simultaneously with fat grafting of a similar amount of fat replacing the water volume in the expander with fat injected into the tissue surrounding the expander. This enables better shaping of the reconstruction and also there seems be a better take of the transplantation fat as the loose preexpanded tissue seems more susceptible to the injected fat.

Internal mammary artery perforators (IMAP)

The implants alone, in combination with fat grafting or fat grafting alone has been the mainstay for augmenting

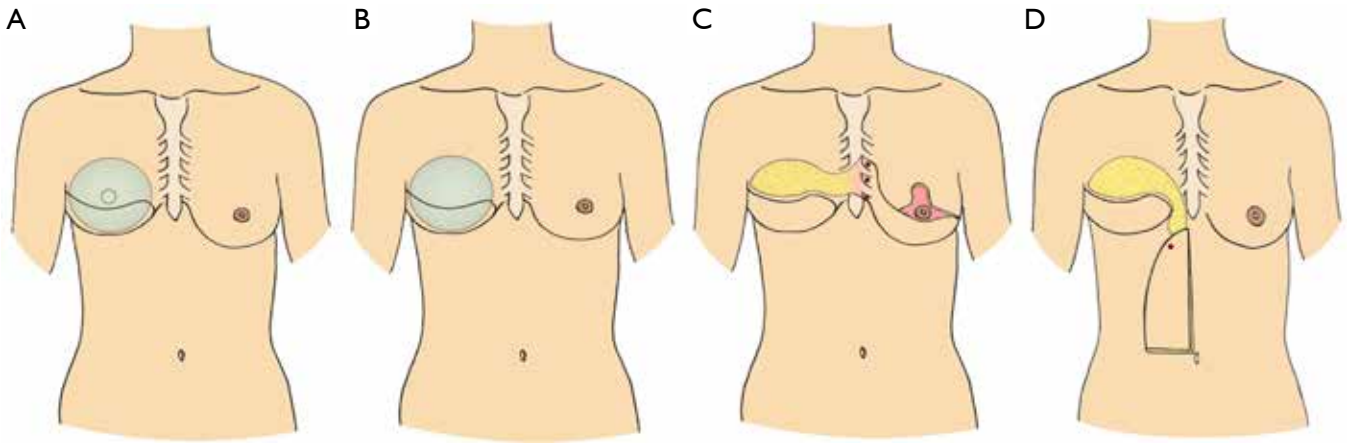

Figure 4 Design of the breast reconstruction. (A) Expander placed under flap. (B) Permanent implant placed under flap. (C) pTDAP flap combined with IMAP flap from the opposite breast. (D) pTDAP flap combined with SEAP flap from the abdomen. pTDAP, propeller thoracodorsal artery perforator flap; IMAP, internal mammary artery perforator; SEAP, superior epigastric artery perforator.

the breasts reconstructed with pTDAP flaps. However, there are other novel options, which can also be used. The pTDAP can be combined with other flaps for augmentation and added volume.

In unilateral breast reconstructions, where the patient has a large contralateral breast, which needs to be reduced, the deepithelialised skin and subcutis can be utilized as a flip over flap based on IMAPs (*Figure 4C*). This is only possible if a sizable perforator(s) can be identified in intercostal spaces of the caudal part of the sternum. Preoperative imaging, MRI, CDU and preferably a combination of these two imaging modalities is mandatory for preoperative identification of the perforators, which enables a targeted reconstructive procedure (19,20). When raising the IMAP flap consisting of skin and subcutaneous fat, the plastic surgeon has to be experienced in finding the correct dissection plane between the glandular tissue and the subcutaneous tissue (27). The procedure is not intended to be a breast-sharing technique, but rather to use a cutaneous flap for augmentation in order to avoid transposition of glandular tissue from one breast to the other. The flap perfusion needs to be examined by indocyanine green to ensure sufficient blood flow in the distal part of the IMAP flap prior to tunneling of the flap to the recipient site (16). The flap can be placed and used for augmentation of the cranial part of the breast reconstruction and the shaping of the flap can be supported by a reabsorbable mesh. The combined pTDAP/IMAP flaps can be augmented further by fat grafting in subsequent procedure(s) along with the lateral correction of the pTDAP pedicle (7,23). A total of 3–4 fat graftings should be anticipated, when using this approach. The bulkiness of the pedicles of both the TDAP and IMAP flaps needs to be corrected by liposuction in one of these subsequent procedures to finalize and shape the reconstruction and areas adjacent to the reconstruction.

Superior epigastric artery perforator (SEAP)

In patients with abundant loose abdominal subcutaneous tissue, who are candidates for a vertical abdominoplasty, the vertical SEAP flap can be used to augment the breast reconstruction in combination with pTDAP flap (*Figure 4D*). The location and size of the SEAP perforator has to be confirmed by CDU prior to surgery for a targeted procedure (19,20). The length of the flap goes from a couple of centimetres above the xiphoid process to 3–5 cm cranial to the umbilicus and the width from the midline and laterally based on a pinch test using the usual markup for a vertical abdominoplasty. The perfusion has to be checked by ICG prior to tunneling of the flap to the recipient site (16). The combined TDAP/SEAP flaps needs to be augmented by fat grafting, shaped and corrected in the same manner as the TDAP/IMAP flaps (6,7,23).

Free TDAP

The pTDAP can also be combined with a free TDAP as stacked flaps breast reconstruction (2).

Perspectives

We expect that the use of the pTDAP in combination with expanders, implants and fat for breast reconstruction will increase in the years to come. We also expect to see an increase in the use of combined flaps from the thorax, pTDAP, IMAP and SEAP, for breast reconstruction in a selected group of patients. Preexpansion of the pTDAP in the back prior to breast reconstruction is also an obvious possibility in selected cases.

Conclusions

The pTDAP can and should be designed, targeted and adapted to the individual patient when used for breast reconstruction. This entails the flap size and shape in the back, the choice and use of perforators, the design and rotation in the axilla and the breast reconstruction when using the flap for augmentation, shaping and draping using expanders, implants, fat grafting or in combined with other flaps.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Review Article

Radiation therapy in breast cancer: a narrative review on current standards and future perspectives

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Abstract: Mastectomy and reconstructive procedures have been refined over the decades, allowing for aesthetic outcomes close to the native breast shape and in symmetry with the contralateral intact breast or even to improve breasts appearance and symmetry. Similarly, improvements in radiation oncology can help reduce treatment related toxicity and improve outcomes. However, postmastectomy radiation therapy (PMRT) is associated with poor cosmetic outcomes and increased rate complications in patients who undergo breast reconstruction. Radiation therapy planning should be guided by disease stage, risk of recurrence, correct definition of the target volumes and treatment objectives. Currently, there are guidelines endorsed by European Society for Radiotherapy and Oncology (ESTRO) for target volume delineation for breast cancer and elective nodal volumes, including after immediate reconstruction. Correct target volume delineation, along with meticulous radiation planning, total dose and fractionation, dose homogeneity, and organs at risk (OAR) doses are significant for reducing radiation-induced toxicity. Currently, tremendous efforts are done by different groups to improve aesthetic outcomes without compromising disease outcomes in breast cancer patients who are candidates for mastectomy and radiation therapy. The current paper summarizes key principles in PMRT, considering new surgical techniques for immediate breast reconstruction and new, partly experimental radiation techniques including future trials and proton beam irradiation.

Keywords: Breast cancer; mastectomy; reconstruction; radiation; radiotherapy; postmastectomy

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Introduction

Breast cancer treatment should be supported by a multidisciplinary team from time of breast cancer diagnosis until end of follow up (1,2), and the team should recommend therapy based on evidence-based guidelines. This approach may not-only increase patient's satisfaction from treatment but also facilitate treatment decision and management and possibly lead to a better outcome (2). Careful evaluation by the multidisciplinary team including breast radiologists, plastic and breast surgeons, pathologists, radiation, and medical oncologists should guide the treatment approach to improve outcomes (3). Factors such as tumour related findings (e.g., tumour size, molecular subtype), distance of the tumour foci from skin/subcutaneous and/or nipple areola complex, benefit from systemic therapy (pre *vs.* postoperative), breast size and shape, tumour-size/breast-size ratio and location of the tumour lesion within the breast,

patient's comorbidities, body habitus and contralateral breast shape, patient's wishes and expectations, and surgeon's expertise, have significant implications on the treatment approach (3).

Surgical techniques change constantly to improve aesthetic results (4-6). Mastectomy and reconstructive procedures have been refined over the decades, allowing for aesthetic outcomes close to the native breast shape and in symmetry with the contralateral intact breast or even to improve breasts appearance and symmetry (4). Furthermore, in many cases this can be achieved at the time of the mastectomy [i.e., immediate breast reconstruction (IBR)] (7). Nevertheless, the most important notion guiding the team is to maintain oncological safety as a priority and clearly communicate it to the patient. Thus, the treatment approach should not lead to a delay or compromise on oncological treatment (8).

For years, IBR was considered a contraindication if postmastectomy radiation therapy (PMRT) was planned, mainly due to a concern of reconstruction failure and major complications (9,10). Lately, the number of patients receiving PMRT in the setting of IBR increases (11-13). In this changing reality, along with advances in radiation therapy techniques, we should work together to improve PMRT outcomes in the setting of mastectomy and IBR (14,15). The current paper summarizes key principles in radiation therapy and PMRT, considering new surgical techniques for IBR and new, partly experimental PMRT techniques. We present the following article in accordance with the Narrative Review reporting checklist (available at https://abs.amegroups.com/article/view/10.21037/abs-21-16/rc).

Key principles of current radiation techniques

The key principles for any radiation therapy planning is to clearly define radiation "target volumes" (i.e., areas at risk of subclinical tumour spread), organs at risk (OAR) (i.e., healthy tissues placed in proximity to the target volume whose irradiation could cause damage), dose and fractionation. These should be also applied in the setting of PMRT (16-18).

The radiation oncologist should clearly define the radiation planning objectives, considering patient, disease, and treatment related factors. Patient related factors such as age and comorbidities can dictate the dose constraints to various OARs and/or planning objectives for the target volume coverage (e.g., compromising medial coverage if the tumour bed is lateral, to reduce the cardiac dose) (16,17,19). By performing a mindful physical examination at initial patient visit prior to radiation planning and considering the physical properties of the radiation beam (photons *vs.* electrons *vs.* protons), the radiation oncologist can to some extent predict potential side-effects and difficulties in covering target volumes/avoiding OARs (e.g., the area of infra-mammary fold, medial contralateral breast, heart, lung) and which radiation technique should provide a potential advantage in treatment (fewer side effects with adequate target coverage).

Correct delineation of the target volumes in some cases can reduce the OARs doses (20).

When deciding on radiation technique, the radiation oncologist should keep in mind the different dose distribution, low *vs.* high dose regions and exposure of OARs, and uncertainties in treatment planning, as these may differ significantly by different techniques such as tangential alignment versus volumetric intensity modulated radiation therapy (IMRT) with potential low dose bath. The radiation technique should be decided after considering pro and cons of each approach. A recent publication led by physicists and clinical oncologists from the Danish Breast Cancer Group (DBCG) in collaboration with a multidisciplinary group of international experts nicely shows how different radiation techniques used for planning PMRT cases with implant-based IBR can significantly differ in dose distribution, mainly exposure of OARs, even when planning the same patient case and the same target volumes (16). Therefore, radiation planning should be done meticulously, and decisions should be taken with consideration of disease control and reducing potential toxicity.

PMRT indications and therapeutic value

In the setting of mastectomy, nodal disease is the main indication for PMRT (21). The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis is a landmark publication to establish the role of PMRT in reducing the rate of locoregional recurrences (LRR) as first event after 10-year. The impact of PMRT in reducing the 10-year rate of LRR was correlated with nodal disease stage. For nodal disease stage pN0, the LRR rate was 1.6% for the no-PMRT group versus 3% in the PMRT-group; for the pN1-3 group the LRR rate was 20.3% for the no-PMRT group versus 3.8% for the PMRT group; and for the pN4+ group the LRR rate was 32.1% for the no-PMRT group versus 13% for the PMRT group (21,22). Therefore, for many years, advanced nodal involvement remained the

key indication for PMRT (22,23). However, current trials support de-escalation of surgical intervention in patients with low nodal tumour load, and there is an increased application of PMRT to eradicate potential subclinical disease within the regional lymphatics in patients treated with less radical axillary lymph node dissection (24,25). Additionally, there is an increase in the rate of patients who are eligible for breast conserving therapy, but opt for mastectomy and IBR, leading to increased number of PMRT in the setting of IBR. Even though there is no robust data from randomised controlled trials for the use of sentinel node biopsy instead of axillary dissection in mastectomy patients, nor that regional nodal irradiation is sufficient in mastectomy patients with low nodal tumour burden, some of the data guiding this approach is extrapolated from enrolling patients after breast conserving therapy. The landmark EBCTCG PMRT publication (21) also showed the impact of PMRT to the chest wall and regional lymph nodes in 870 patients, with T3 (>5 cm) pN0 who underwent axillary sampling. PMRT to chest wall and regional lymphatics showed statistically significant advantage for reducing the 10-year risk of LRR or any recurrence and a trend towards reducing the breast cancer mortality or any mortality at 20-year. Therefore, along with trials that established the role of regional irradiation instead of axillary dissection in patients with low-nodal disease burden, the EBCTCG subgroup analysis provides additional support for this approach (21).

Furthermore, other clinical and histological factors were suggested to be associated with a high risk for LRR after mastectomy. These include young age at diagnosis (26-29), T3 tumour (30-35), tumour muscle invasion (35,36), high tumour grade (29,35,37), lymphovascular invasion (28,35,37), negative hormone receptor (29-31,38,39), extracapsular nodal tumour extension (32), and a high 21-gene-recurrence score (40,41). Therefore, these factors should be taken into account when considering postoperative radiation but their significance as a sole indicator to support PMRT is not reported in the literature, and therefore unknown.

A thought provoking issue is that in the trials establishing the role of PMRT, the surgical approach included more radical types of mastectomies (i.e., without skin preservation) and axillary clearance (21) thus, less probability for residual breast tissue and less dermal lymphatics (42). Current mastectomy techniques aim to facilitate breast reconstruction by skin sparing (with/without nipple sparing), there is tendency to leave various amounts of residual glandular tissue to facilitate breast reconstruction and allow for better aesthetic outcome of the neo-breast (42). However, as the native skin and subcutaneous tissue are preserved in these surgeries, the dermal plexus, an important lymphatic route for draining the mammary region and may harbour tumour cells, is left intact (43). Thus, the local recurrence risk might be increased in high-risk node-negative patients in which PMRT is not performed (44). Many of the guidelines for breast reconstruction do not provide information in-which cases these procedures should be avoided or in-which PMRT is indicated in patients who are without nodal involvement (45). Using new RT techniques (e.g., imaging-based, deep-inspiration breath hold) and defining the volumes according to ESTRO delineation guidelines (16-18) can contribute reducing the dose to OARs without compromising the target coverage (20). Therefore, the potential therapeutic benefit of PMRT in this setting might be greater comparted to RT based on bony landmarks (46-48). However, PMRT techniques may vary significantly in OAR exposure and target coverage (47,49), and more sophisticated advanced techniques might not necessarily provide an advantage, so careful evaluation of RT plans is recommended. Therefore, it is encouraged to use techniques to reduce the OARs dose such as deep inspiration breath-hold or continuous air way pressure mask (CPAP) and mindfully consider the pros and cons of each RT technique used (47,48). Especially as most of these patients will have a long-term survival which puts them at risk for recurrences or/and RT-related complications.

The target volumes

The target volumes are areas that potentially harbour subclinical disease. Contouring target volumes for chest wall and elective nodal irradiation according to guidelines will help avoiding excessive radiation to adjacent tissues (17,18). In case of IBR, the implant (tissue expander or permanent implant) may be positioned *ventral* or *dorsal* to the major pectoral muscle. The ESTRO-ACROP guidelines for PMRT in early breast cancer indicate that the target volume includes the residual subcutaneous glandular tissue and the subcutaneous lymphatics and that the major pectoral muscle serves as the anatomical *dorsal* border for mastectomy. Therefore, the breast glandular tissue position is dependent of the implant location. In case of muscle invasion, local inclusion of that part of the pectoral muscle is advised, and in case of rib cage invasion the ribs/intercostal muscles should also be focally included in the target volume, although these patients are usually not candidates for

IBR (17). We recommend using these guidelines when planning early breast cancer radiation therapy, but the delineation should be adopted per case accordingly, using available preoperative/pre-systemic therapy imaging for planning and identifying the risk areas for recurrence.

The timing of PMRT in the setting of reconstruction

Reconstructions can be immediate, delayed, or delayed–immediate. Immediate reconstructions are performed at mastectomy, whereas delayed reconstructions are usually performed 6–12 months (or years) after the completion of mastectomy and adjuvant therapy, when the patient is recovered from treatment related toxicity (50). Different factors dictate the timing of reconstruction (50). Immediate reconstruction is facilitated by skin sparing (SSM) or nipple sparing mastectomy (NSM, i.e., sparing of the skin and nipple and areola complex). By contrast, delayed-breast reconstruction was the common approach after non-skin sparing procedure, especially if patients were planned for PMRT prior to surgery. This approach allowed for the irradiated skin to be replaced with healthy skin from a donor site.

Delayed-immediate reconstruction involves placing tissue expanders at the time of mastectomy (50). This may allow to maintain or expand the skin and pectoralis muscle to create a pocket for the implant. Additionally, the decision on PMRT can be based on the final pathology report. Usually, patients not planned for PMRT complete reconstruction with an implant or flap, whereas patients planned for PMRT undergo PMRT with a tissue expander followed by later definitive reconstruction. The immediate-delayed approach permits the opportunity to avoid irradiating an autologous flap (if planned), gradually expand the pectoralis muscle to serve as a pocket for a permanent implant, and the benefits of providing an immediate breast mound for the patient after mastectomy.

In the past, immediate reconstruction was considered contraindicated if PMRT was planned, however, recently more studies are reporting its use (11,12,50).

Unfortunately, there is no consensus regarding the timing of the reconstruction (immediate, delayed, or delayed-immediate) in the setting of PMRT and the treatment approach varies significantly among centres and countries. The rate of reconstruction failure varies substantially from 0% to 40%, depending on whether PMRT was delivered to the tissue expander or to the permanent implant. Recent publications suggest that PMRT to tissue expander is associated with a higher rate of complications while others did not find significant differences (51-53).

Therefore, further trials are needed to determine the optimal approach for reconstruction in the setting of PMRT with regards to timing if a two-stage expander/implant reconstruction is planned.

Bolus

Bolus was commonly used for PMRT chest wall irradiation (without reconstruction) to serve as a tissue equivalent material placed on the skin to shift the 95–100% isodose line to the skin and subcutis to reduce the local recurrences in these volumes (54). However, bolus was the most important independent risk factor for severe skin toxicity in case of PMRT without strong evidence for lower rates of local recurrence (55,56). Importantly, its use in the setting of SSM/NSM, varies between institutions, and little data is available with regards to complications/failure of the reconstruction (55,56). Therefore, until further data become available, the routinely use of a bolus in these cases is not recommended and should be considered on an individual basis if there is a concern for a high-risk area that is not getting full coverage (55,56).

Radiation boost

Historically, radiation boost in the setting of PMRT was aimed to provide an additional radiation dose to the mastectomy scar to reduce local recurrences in this area (57). A study by Massachusetts General Hospital (57), evaluated whether a chest wall boost was independently associated with reconstruction complications in the setting of breast reconstruction. The study cohort included patients who had delayed reconstruction procedures. Radiation boost was significantly associated with infection, skin necrosis, and implant exposure. For implant-based reconstruction, the addition of the boost was independently associated with higher risks of implant failure. Most importantly, the addition of the boost was not associated with improving local tumour control, even in high-risk subgroups (57). Therefore, we do not recommend routine use of boost in case of IBR.

Dose and fractionation

Practice patterns vary widely among centres and countries

with regards to total dose and fractionation schedule for breast cancer patients who underwent mastectomy with/without IBR. The most common used fraction sizes in case of IBR is 1.8–2 Gy to a total dose of 50–50.4 Gy (58). However, some countries adopted the moderate hypofractionation regimens (e.g., 40 Gy delivered in 15 fractions over 3 weeks) to the chest wall and regional nodes, even in the setting of IBR, based on long-term data from the START A/B trials, showing reduced toxicity of hypofractionation scheme compared to normo-fractionation (1.8–2 Gy per fraction to 50–50.4 Gy) (59). Even though there is little data from clinical trials specifically evaluating hypofractionation in the setting of IBR to support its use, and there are several ongoing clinical trials, based on the long-term data of hypofractionation in breast conserving therapy, there is no reason to believe that its outcome will be inferior to conventional fractionation (58-61).

Proton-based RT

Proton therapy has not been widely used nor investigated for adjuvant breast cancer RT, because there are only few proton centers across the world. However, due to the properties of proton therapy it is possible to achieve optimal dose coverage of relevant targets and at the same time ensure low dose to OAR compared with photon RT. The use of volumetric based-photon planning (i.e., arc-based intensity modulated radiation therapy, vIMRT) for breast cancer might not achieve dosimetric advantage over tangential field-based planning (49). The use of vIMRT often results in large volumes receiving a low dose "bath", which may result in unexpected toxicity (if these organs were not contoured and taken into consideration while planning) (62), and possibility for secondary cancer as many of these patients are long-term survivors (63).

In an energy-dependent manner, proton therapy will deposit the majority of its dose in tissue depths defined by the Bragg peak (64). In practice, this translates into (I) the ability to deliver the peak energy to target volumes of irregular 3-dimensional shape using pencil-beam scanning technology, (II) a sharp dose fall-off following deposition of energy in the target and (III) reduction of the integral dose to the patient. Within millimeters, the exit dose drops off from 90% to 10%, resulting in the virtual absence of an exit dose. The effectiveness, safety and feasibility of proton therapy has been reported in few small cohort studies with limited follow up, and there is a lack of clinically controlled randomised trials documenting benefit from proton therapy, evaluated either as higher tumour control and/or as fewer morbidities.

The potential of proton therapy for PMRT is to lower the dose to heart and lung without a compromise on dose to chest wall target on regional nodes. However, proton therapy has an estimated 10% higher radiobiologic effective dose (RBE), and studies imply that the relative effect may be even higher, leading to a higher risk of morbidities from OAR than anticipated (65). Most studies on proton therapy in early breast cancer have been single-institution and retrospective with no formal research plan (66,67), but fortunately, well-designed trials are also made. Seventy patients requiring loco-regional RT including internal mammary node irradiation were treated with proton therapy in a phase II trial from Boston 2011–2016 (68). Inclusion criteria were >20 Gy was received by >5% of the heart or >20 Gy to the left anterior descending artery with conventional photon RT. The doses were 1.8–2.0 Gy (RBE), 25–28 fractions. The primary endpoint was grade 3 or worse radiation pneumonitis or any grade 4 toxicity within 3 months from proton therapy. Mastectomy was done in 93%, and 83% of these pursued reconstructions. At median 55 months follow-up, and the 5-yr LRR and OS were 1.5% and 91%, respectively, and only one patient developed grade 2 pneumonitis as the highest morbidity score. As of 2021, there are 2 phase III randomised controlled clinical trials investigating gain and risk from proton therapy in breast cancer patients. The RadComp trial (NCT 02603341) is a pragmatic randomised trial testing proton *vs.* photon RT for patients with stage II–III breast cancer with an indication for loco-regional RT including internal mammary node irradiation (69). The primary endpoint is major coronary event reduction by proton therapy, hypothesizing a reduction in the 10-year major coronary events rate from 6.3% to 3.8% compared to photons. The trial aims for 1,278 patients accrued during 2016–2022. The other trial open for inclusion since 2020 is the DBCG Proton trial (NCT04291378), where patients operated for breast cancer or DCIS can be included if photon treatment planning with strict criteria for dose coverage of breast, chest wall and nodal volumes reveals a mean heart dose ≥4 Gy and/or V20lung ≥37% (trial protocol is available on Google). The primary endpoint is 10-year risk of heart disease, hypothesizing a 10-year reduction from 10.2% (photon) to 6.3% (proton). The baseline 10-year risk of heart disease in Danish women 60 years old is 5.8%. The trial aims for 1,502 patients. Both the RadComp and the

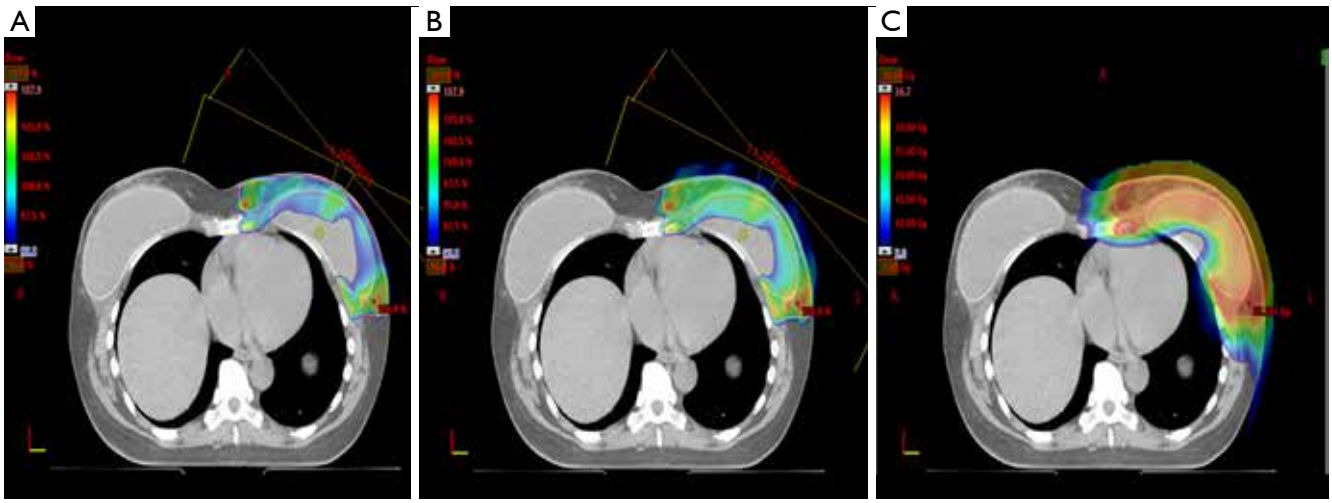

Figure 1 Patient operated with bilateral mastectomy, and with an indication for postmastectomy radiation therapy on the left side. The treatment planning is based on proton therapy 50 Gy/25 fractions. The target (pink line) is the tissue ventral to the implant and the internal mammary nodes. The implant is highlighted with a yellow line. The dose distributions indicate 95% (A), 90% (B), and 5 Gy doses (C). The two en face beam angles are indicated in (A,B). The plan emphasizes the dosimetric properties of proton plan, that the peak dose is deposit at a certain depth at the location of brag-peak without an exit dose as opposed to photon-based planning.

DBCG trials have several secondary endpoints including extensive reporting of loco-regional radiation associated morbidities and documenting the pattern of recurrence.

Since proton therapy requires a higher precision in daily therapy due to the properties of the beam (*Figure 1* to show en face beam arrangement and dose very close to heart), and one of the main reasons for using proton therapy in breast cancer is concern of heart disease, it is likely that future reporting of results from proton trials will include reporting of doses to substructures of the heart. An automated atlas for delineating 25 substructures of the heart has been reported from Denmark, but other countries are likely to develop similar atlases (70). However, providing RT on a single planning-CT-scan according to strict institutional guidelines does not guarantee that the treatment is reproducible. For example, by using cine images recorded during each radiation fraction, it is possible to detect a quite substantial variation in the heart position in some patients, whilst for other patients the position of the heart is robust during the whole treatment period (71).

Future trials

Currently there are several trials aiming to improve the outcomes of patients who are planned for mastectomy, reconstruction and are candidates for PMRT (*Table 1*). Some are aimed to evaluate the fractionation protocols as FABREC (NCT03422003) and RTCharm (NCT03414970) that are planned to compare conventional *vs.* hypofractionated regimens in breast cancer patients with IBR. The DBCG RT Recon trial is aimed to evaluate the timing of reconstruction (immediate *vs.* immediate-delayed) and fractionation (allows for conventional and moderate-hypofractionation). While trials such as Primary Radiotherapy And DIEP flAp Reconstruction Trial (PRADA) (NCT02771938), aim to evaluate preoperative radiation in patients who are planned for mastectomy and autologous-based reconstruction.

Conclusions

Breast cancer treatment evolved significantly with improvement in surgical and RT techniques. Radiation planning should be guided by disease stage, risk of recurrence, correct definition of the target volumes and treatment objectives. Meticulous RT planning, total dose and fractionation, dose homogeneity, and OAR doses are significant for reducing RT toxicity. The multidisciplinary team should work together in aim to improve the outcomes of mastectomy patients in both in clinic and in planning future trials.

Table 1 Ongoing trials of postmastectomy radiation therapy for patients who are planned for reconstruction

Trial name (NCT)	Accrual targets (number of patients)	Accrual study start year	Design	Primary end point
DBCG RT Recon trial NCT03730922	590	2020	Prospective randomized	Surgical complications of immediate-delayed versus delayed reconstruction in patients who are planned for PMRT
FABREC (NCT03422003)	400	2018	Prospective randomized	Patient reported outcomes (note: reconstruction complications and oncological outcome are secondary endpoints)
RTCharm (NCT03414970)	880	2018	Prospective randomized	To evaluate whether the reconstruction complication rate at 24 months post radiation is non-inferior with hypofractionation
PRADA (NCT02771938)	60	2016	Interventional non-randomized	Number of participants with presence of open breast wound at 4 weeks after DIEP surgery

NCT, ClinicalTrials.gov Identifier; PMRT, postmastectomy radiation therapy; PRADA, Primary Radiotherapy And DIEP flAp Reconstruction Trial; DIEP, deep inferior epigastric perforator.

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Footnote

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Review Article

Standards in oncoplastic breast-conserving surgery

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Abstract: Oncoplastic breast-conserving surgery is becoming more widely accepted as a standard of care in management of breast cancer, with both oncologic and aesthetic benefits for patients. Significant geographic and specialty-specific variability exists regarding the availability, understanding, and application of oncoplastic reconstructive techniques. Providing high-quality care for patients with breast cancer requires streamlined multi-disciplinary communication; care of patients undergoing oncoplastic breast-conserving surgery is no exception, as surgeons from different specialties are often called upon to work together in order to optimize oncologic efficacy and aesthetic results. Standardization of oncoplastic terminology and classification systems as well as a shared understanding of available outcomes data will help patients undergoing these procedures achieve the best possible results regardless of their geographic location or health care system. In this article, we review oncoplastic standards and highlight variations with regard to terminology, classification systems, and training in oncoplastic techniques. Regional differences regarding the preference for and involvement of plastic surgery providers are highlighted. Safety, efficacy, and patient satisfaction outcomes are presented with the goal of establishing a commonly understood baseline to aid in pre-operative patient counseling. With increased acceptance and generalizability of oncoplastic standards, high-quality oncoplastic reconstructive procedures will be available to a more diverse patient population.

Keywords: Oncoplastic surgery; breast reconstruction; breast conservation; standards; breast cancer

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Introduction

Oncoplastic breast-conserving surgery refers to the surgical management of breast cancer which combines oncologic techniques for partial mastectomy with plastic surgical techniques to optimize breast aesthetics and symmetry. The goals of oncoplastic breast-conserving surgery therefore include (I) oncologic efficacy comparable to partial mastectomy alone, (II) improved breast aesthetics and symmetry compared to partial mastectomy alone, (III) a favorable safety profile regarding complications and need for re-operation, and (IV) improved overall patient satisfaction compared to partial mastectomy alone.

Oncoplastic techniques have increased in popularity over time with greater acceptance of their effectiveness and safety profile, as well as greater surgeon comfort with the technical aspects of the operations. A recent retrospective cohort analysis of data from the ACS-NSQIP database demonstrated an increase in use of oncoplastic breast reconstruction of 241%, a rate of increase of 11% per year, while the rate of partial mastectomy without reconstruction remained relatively constant (1). Oncoplastic breast reconstruction is now considered by many to be the "gold standard" following partial mastectomy (2,3). However, there remains disagreement among experts regarding several aspects of oncoplastic reconstruction

including the nomenclature used to describe, classify and bill for oncoplastic surgical procedures (4), the importance of dedicated training programs in oncoplastic surgery (5,6), and the necessity of plastic surgeon involvement in oncoplastic reconstruction cases (7). In many cases, points of view vary significantly by geographical location. All stakeholders recognize the urgent need for standardization of these items in order to improve communication between breast and plastic surgeons worldwide, to facilitate data sharing and generalizability, and most importantly to improve patient outcomes. In this review, we aim to summarize current standards as they pertain to oncoplastic terminology, techniques, and safety.

Standard terminology in oncoplastic surgery

In April 2019, to improve consistency and minimize confusion among patients and surgeons, the American Society of Breast Surgeons (ASBrS) published a consensus definition of oncoplastic surgery as, "*a form of breast-conservation surgery that includes oncologic resection with a partial mastectomy, ipsilateral reconstruction using volume displacement or volume replacement techniques with possible contralateral symmetry surgery when appropriate*" (8). Regional differences in the acceptance of this definition may exist; though some surgeons may consider oncoplastic surgery to include any method of breast reconstruction after partial or total mastectomy (9,10), others (particularly in the United States) use the terms "oncoplastic surgery" and "oncoplastic breast conservation" interchangeably. For the remainder of this paper, the term "oncoplastic surgery" will refer specifically to methods of breast reconstruction after partial mastectomy.

Fundamentally, oncoplastic surgery involves tumor removal, preservation of breast tissue and reconstruction of the defect. The oncoplastic approach was pioneered by Audretsch *et al.* as a way of addressing not only the oncologic resection but also as a way of reconstructing the breast to a reasonable form (11,12). This intent was further reinforced by Clough *et al.* whose classification system heavily influenced the ASBrS definition (13). This has been supported by both breast and plastic surgeons (14-18), and oncoplastic surgery has becomes a third standard of surgery offered to breast cancer patients. Along with the previous two traditional options of standard partial mastectomy and mastectomy, oncoplastic surgery is now a third option for the appropriate breast cancer patient.

Classification systems

Most classifications differentiate oncoplastic surgery into volume displacement and volume replacement techniques (8,19,20). A level 1 volume displacement oncoplastic operation involved less than 20% of the breast tissue being removed in the partial mastectomy and then reconstructed with a local tissue rearrangement design such as a doughnut mastopexy or a crescent mastopexy (8). A Level 2 volume displacement oncoplastic operation involved 20% to 50% of the breast tissue being removed in the partial mastectomy followed by a reconstruction design that typically uses breast mastopexy or reduction designs (see *Figures 1-4*). Lastly, a volume replacement oncoplastic operation occurs when greater than 50% of breast tissue is removed as part of the partial mastectomy followed by reconstruction using local/regional flaps or implants. The ASBrS classification is meant as a guide; however, the final surgical plan is always made as a shared decision between the patient and the recommendations of the surgical team. Selection of operation depends on the oncologic features of the breast cancer as well as the patient's pre-morbid breast appearance; these features are balanced against the patient's preferences and expectations. For example, a patient with a small breast cancer in the inferior pole, moderate sized breasts and Grade 3 ptosis may benefit from an oncoplastic mastopexy design even with the possibility that less than 20% of the breast tissue may be removed as part of the partial mastectomy; selection of a mastopexy reconstructive design in this scenario would prevent the development of a bird beak deformity (21). Nevertheless, the majority of oncoplastic operations may be able to use this classification system as a useful algorithm for guiding selection of surgical technique.

Multidisciplinary team approach

A multidisciplinary approach to the care of patients undergoing oncoplastic procedures is essential, as in the care of any patient with breast cancer. Multimodal therapies and an individualized approach to treatment will mandate coordination of care between team members from radiology, surgical oncology, hematology, radiation oncology, pathology, and others. Communication between these teams in the preparation/planning stages of treatment in a multidisciplinary tumor board setting is a widely recognized standard of care, with the overarching goal of achieving the

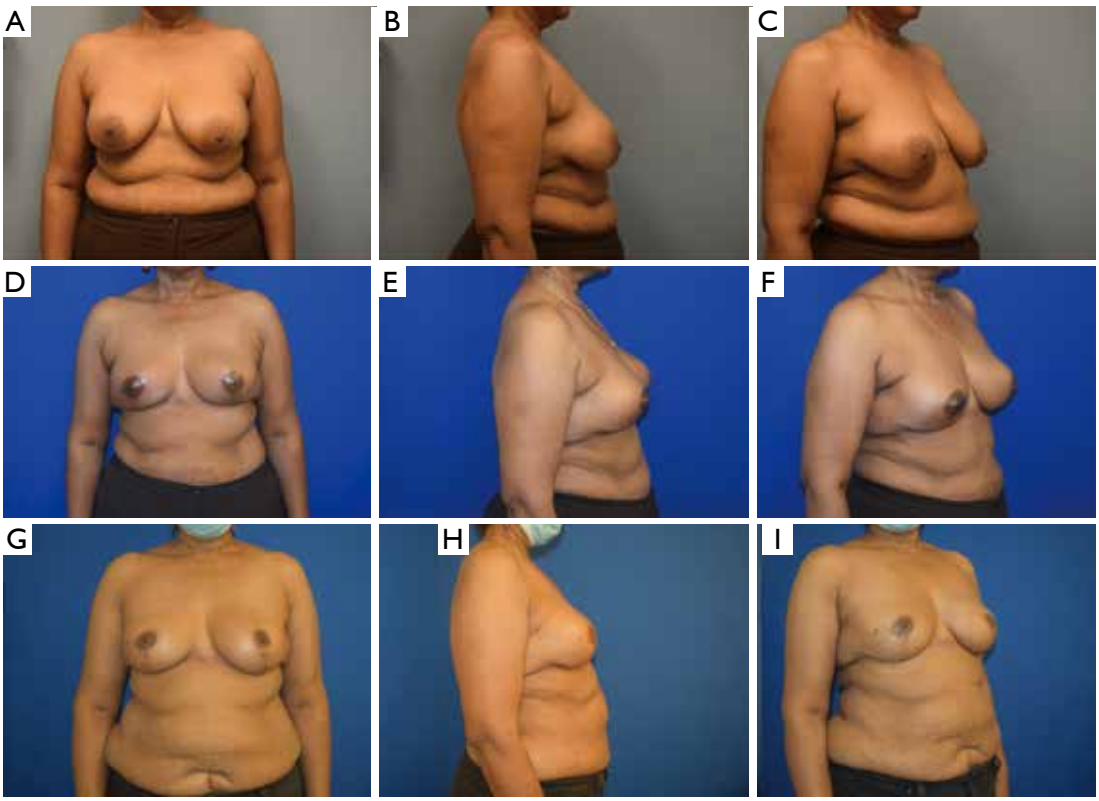

Figure 1 Case #1. Sixty-seven-year-old with right breast infiltrating ductal cancer in subareolar position. Right central lumpectomy with partial resection of areola was performed. Right breast oncoplastic reconstruction achieved using extended superior pedicle with wedge closure of areolar defect. Contralateral circumvertical mastopexy was performed for symmetry. (A-C) Preoperative, (D-F) 2 months and (G-I) 3 years post-op. Patient received intraoperative radiation therapy.

best possible oncologic outcome while maintaining the best possible breast aesthetic. Though final breast cosmesis is obviously important in overall patient satisfaction, opinions among specialists regarding the necessity of plastic surgeon involvement in oncoplastic procedures vary significantly. In some specialized breast surgery practices, a general or oncologic surgeon performs both the ablative and reconstructive portions of oncoplastic surgeries. In other institutions, a two-team approach with ablation performed by surgical oncology followed by reconstruction by plastic surgery is the accepted standard.

Preference for and opinions regarding the necessity of a single team versus a two-team approach vary depending on specialty, training experience, and geographic location. For example, in the United States, a two-team approach has traditionally been employed (22). Many breast surgeons feel comfortable performing Level 1 volume displacement local tissue rearrangements after smaller partial mastectomy operations, and the importance of hidden incisions and aesthetics is now being taught in the breast surgery curriculum. The majority of breast surgeons presently do not perform Level 2 volume displacement oncoplastic surgery themselves and require the partnership of a plastic surgeon to safely perform such operations.

A recent survey of members of the American Society of Breast Surgeons and the American Society of Plastic Surgery was performed to ascertain differences in opinion regarding partial breast reconstruction at the time of tumor resection between breast surgeons and plastic surgeons (7). This survey found that while plastic surgeons were more likely to favor a two-team approach overall, the preference for either two-team approach or a mutually agreed upon team combination was favored by both breast and plastic surgeons, and only 7.5% of respondents felt that it was appropriate for a breast surgeon alone to perform more complex reconstructions. Plastic surgeon availability was not felt to be a major barrier to partial breast reconstruction by either group. A subsequent American Society of Breast

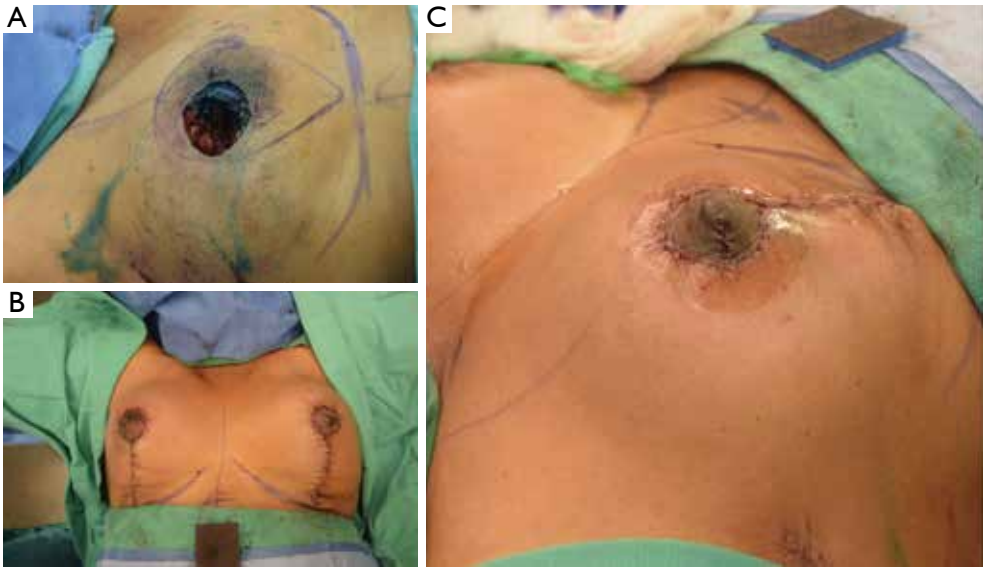

Figure 2 Case #1. (A) Intraoperative picture demonstrating central lumpectomy with partial areolar defect. (B) On-table result following right breast oncoplastic tissue rearrangement with contralateral circumvertical mastopexy. (C) Close-up of wedge repair of areolar defect.

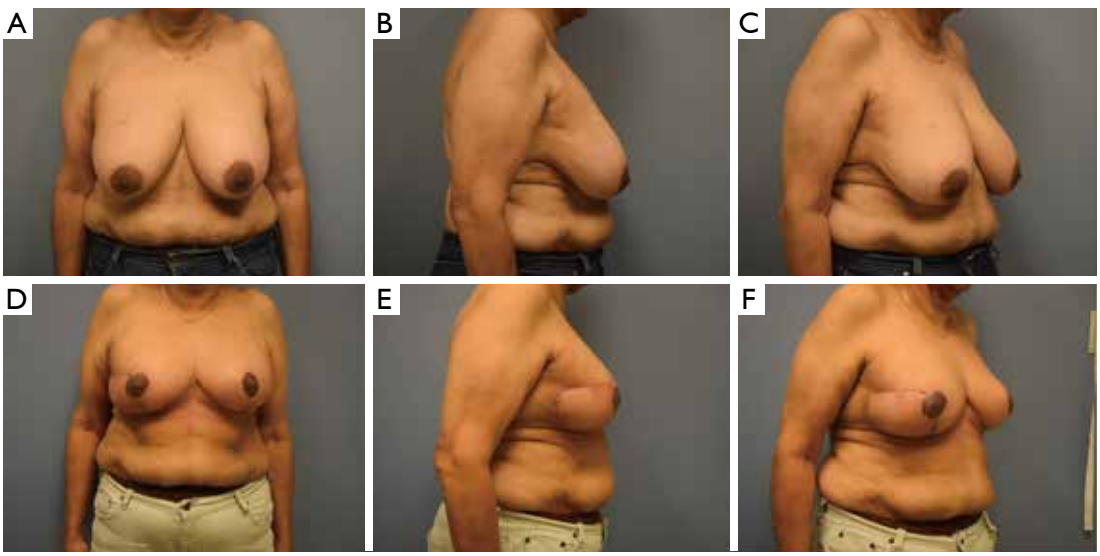

Figure 3 Case #2. Sixty-seven-year-old with right breast cancer. Large right upper outer quadrantectomy was performed resulting in significant volume deficiency and skin defect. Nipple-areola preserved with superior-medial pedicle. An inferiorly-based secondary pedicle was created to replace missing skin and obliterate upper pole dead space. (A-C) Preoperative and (D-F) 6 months post-op (3 months after completion of adjuvant radiation).

Surgeons survey in the following years noted that 99% of breast surgeons surveyed were interested in oncoplastic surgery and approximately 19% of those had independently performed a Level 2 volume displacement oncoplastic operation using a mastopexy/reduction design (23). Regardless of the single surgeon versus two-team approach, such interests underscore the need for further oncoplastic surgery adoption with particular emphasis on safety and appropriate training.

The single surgeon model has been popular in the UK

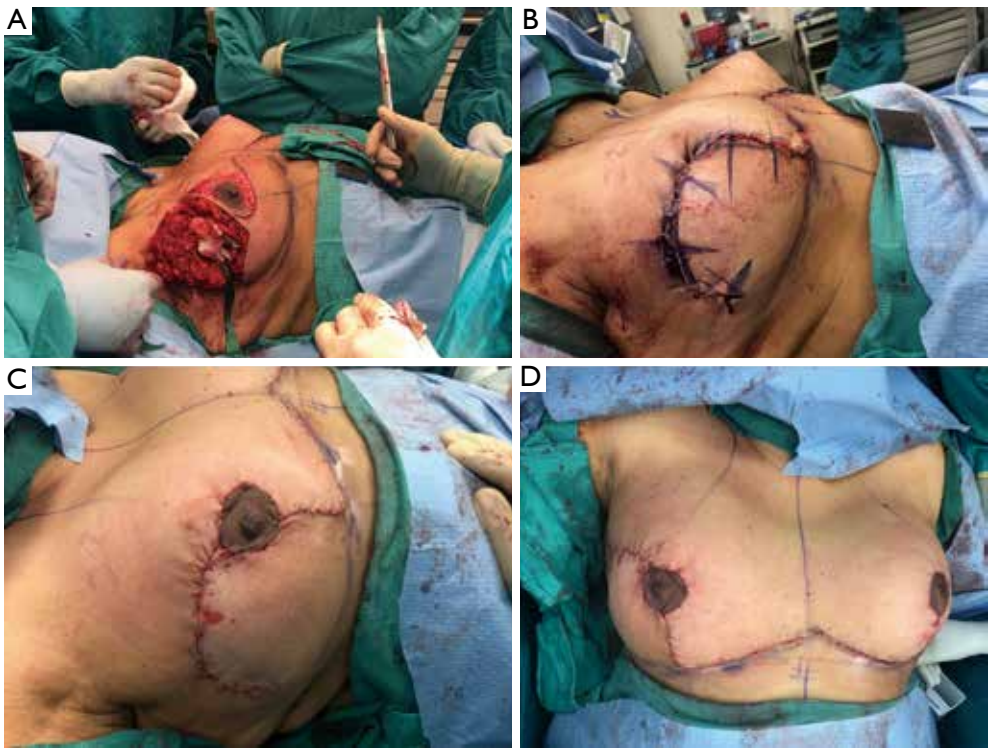

Figure 4 Case #2. (A) Intraoperative photos demonstrating right breast upper outer quadrant defect. (B) Inferiorly-based pedicle of skin and breast parenchyma was created and advanced into defect to eliminate volume deficiency and replace missing skin. (C) Nipple-areola was preserved on a superior-medial pedicle and brought out at the most projecting point of the new breast mound. (D) On-table result, contralateral wise-pattern reduction performed for symmetry.

and in parts of Europe and now, thanks to "dual training" opportunities, is used in the US as well. A recent survey in the United Kingdom regarding changing practice patterns in oncoplastic surgeries suggested a threefold decrease in oncoplastic procedures performed using a two-team approach (5). The proportion of general and breast surgeons in the UK who performed breast mastopexy and reduction procedures increased by 26%, and the proportion who performed latissimus dorsi flaps increased by 15% between 2010 and 2015. The authors of this study theorized that fewer plastic surgeons and high cross-specialty demand limited plastic surgery availability and participation in oncoplastic procedures.

A practice survey of general surgeons in Ontario, Canada found that less than 50% of respondents performed oncoplastic procedures, and that most commonly, plastic surgeons were involved in breast conserving surgeries rarely (44.0% of respondents) or never (44.6% of respondents) (6). Lack of specific training in oncoplastic techniques and lack of plastic surgeon availability were cited as the major barriers to more widespread adoption.

In the only study to compare oncoplastic surgical outcomes following a single team versus two-team approach, Blankensteijn *et al.* retrospectively evaluated the NSQIP database for patients undergoing oncoplastic reconstruction between 2005 and 2017 (24). A total of 4,350 patients met criteria; of these, 3,759 had undergone oncoplastic reconstruction by a breast surgeon alone, and 591 by a plastic surgeon and breast surgeon together. There was no significant difference in the rate of post-operative complications between the two groups, though the authors found that plastic surgery involvement likely correlated with more complex reconstructive procedures. The authors concluded that neither a single or two-team approach was associated with increased surgical morbidity. However, it should be noted that the majority of single-surgeon oncoplastic surgeries performed were Level 1 volume displacement with less complex techniques compared to oncoplastic operations utilizing the two-surgeon model that used a greater proportion of Level 2 volume displacement

techniques.

Regardless of surgical specialty or country of origin, all parties can agree that achieving the best possible aesthetic breast appearance is in the best interest of the patient. In practice settings where plastic surgeons are readily available, a two-team approach makes sense and has several advantages. In situations where ability to coordinate with plastic surgery is limited, patients should not have to settle for a lower standard of care. In these situations, additional training for general or breast surgeons in advanced oncoplastic techniques in order to deliver a high quality oncologic and reconstructive procedure should be the goal.

Training in oncoplastic surgery

To ensure acceptance and patient safety, training is critically important when it comes to oncoplastic surgery regardless of which model is utilized.

The "single-surgeon model" implies that the treating surgeon has expertise in both the oncologic treatment of breast cancer as well as reconstruction of partial mastectomy defects. In the United States, there are different options for obtaining training and expertise in these areas. One potential track involves training in an integrated plastic surgery program followed by a one-year American Society of Breast Surgeons/Society of Surgical Oncology approved breast surgery fellowship. Another option involves general surgery residency followed by formal plastic surgery training and then a one-year American Society of Breast Surgeons/Society of Surgical Oncology approved breast surgery fellowship. It is expected that plastic surgery training in the United States would involve exposure to oncoplastic breast reconstruction. Potential options in the future to shorten training would be a 2–3 year oncologic and reconstructive breast oncoplastic training fellowship after general surgery. Collaboration between the major surgical societies is key to success of these programs.

The "two-surgeon model" requires that both breast surgeon and plastic surgeon understand the nuances of oncoplastic surgery. Training is acquired in a formal setting through surgical residency programs in either breast or plastic surgery, or through societal training courses.

Outside of the United States, other countries have developed oncoplastic training opportunities that uniquely suit their particular needs and resources. Given that some of the first adopters of oncoplastic surgery came from Europe, it is not surprising that formal oncoplastic training programs have since been developed in European countries. For example, in Britain, the Joint Committee on Surgical Training has established a formal oncoplastic breast surgery fellowship that is overseen by the Association of Breast Surgery and the British Association of Plastic, Reconstructive and Aesthetic Surgeons. Applicants for this fellowship can come from both general surgery or plastics surgery training backgrounds (25). In Australia and New Zealand, the Breast Surgeons of Australia and New Zealand (BreastSurgANZ) have developed a two-year post fellowship training program that formally trains breast fellows in both Level 1 and Level 2 volume displacement oncoplastic surgery (26). In Brazil, specialized oncoplastic training centers have developed specialized courses where practicing surgeons with backgrounds in either oncology, breast surgery or plastic surgery can apply to learn new skill sets required to be safe in practicing oncoplastic techniques (27).

Safety of oncoplastic surgery

Oncoplastic surgery aims to optimize the final cosmetic appearance of the breast following partial mastectomy; however, breast aesthetics are secondary in importance to oncologic efficacy and safety. Many oncoplastic techniques involve extensive rearrangement of local tissues, creation of additional incisions on the breast, or transposition of regional tissues into the tumor cavity. Legitimate concerns have been previously raised about how these techniques may affect overall risk of complications, subsequent delivery of adjuvant therapy, margin positivity, local recurrence, and survival. Preoperative counseling of patients considering oncoplastic breast surgery should include a thorough discussion of the risks and benefits of these techniques. Surgeons who perform or participate in oncoplastic surgeries should have a shared understanding and agreement about the safety profile of these procedures.

Surgical complications following oncoplastic breast reconstruction

Oncoplastic breast reconstruction can be directly compared to alternative therapies including standard breast conservation without reconstruction, as well as total mastectomy with or without reconstruction. In primarily retrospective analyses, these comparisons have been performed demonstrating a favorable risk profile for oncoplastic techniques. The overall complication rate following oncoplastic surgery ranges from 14–16% in systematic review and meta-analysis of the literature (28,29).

Common complications include delayed wound healing, fat necrosis, infection, nipple necrosis, seroma and hematoma, with individual incidence ranging from <1–4% (28,30). Overall, the rate of complication requiring reoperation is likely around 3% (29,31). In their NSQIP database analysis, Cil *et al.* identified multiple factors independently associated with a higher likelihood of developing a complication within 30 days of surgery including obesity, smoking, American Academy of Anesthesiologists (ASA) category 3 or 4, diabetes, bleeding disorder, chronic obstructive pulmonary disease (COPD), and a longer operative time. The presence of bleeding disorder had the highest association with post-operative complications (odds ratio 1.8) (32).

Smoking in patients undergoing breast reconstruction increases perioperative morbidity and mortality as well as cost to the healthcare system (33). Smoking in patients undergoing oncoplastic breast reconstruction is a situation that demands special consideration; though smoking increases the risk of post-operative complications, the risk of attempting reconstruction on a radiated breast in a delayed setting may be even greater (34). Therefore, patients with smoking history must be counseled regarding the risks and benefits of undergoing immediate oncoplastic reconstruction for their ipsilateral (cancer) breast. Smoking remains an important modifiable risk factor, and cessation counseling is appropriate. If needed, the contralateral symmetry operations can be delayed until the patient stops smoking, providing yet another incentive for smoking cessation.

Overall, oncoplastic reconstruction may have a comparable or slightly lower rate of complications compared to standard breast conservation therapy alone. A meta-analysis performed by Losken *et al.* demonstrated a rate of complications of 15.5% in patients undergoing oncoplastic reconstruction, compared to 25.9% in patients undergoing standard breast conservation therapy, though the average follow-up of patients in this analysis was longer for patients undergoing breast conservation alone (64 *vs.* 37 months) (29). In their NSQIP review, Cil *et al.* found that the 30-day rate of complications was similar between patients undergoing oncoplastic reconstruction (1.7%) *vs.* standard breast conservation therapy (1.9%) (32).

When complications do occur, significant delay in initiation of adjuvant therapy is possible. Kapadia *et al.* retrospectively reviewed 118 patients who underwent oncoplastic reconstruction at a single institution (35). Twenty-two percent of patients developed a complication including delayed wound healing, seroma, infection, and wound dehiscence. There was a statistically significant delay in initiation of radiation in patients who developed a complication versus those who did not (74 *vs.* 54 days, P<0.001). Similarly, in a retrospective review of 150 patients undergoing oncoplastic reconstruction published by Hillberg *et al.*, initiation of adjuvant radiotherapy was delayed in 8.2% of patients due to a post-operative complication, though the overall complication rate was high in this study (37.5%) (36).

Breast reduction or mastopexy is often considered for the contralateral or non-cancer breast in order to improve breast symmetry and optimize aesthetic appearance following oncoplastic reconstruction. Concerns have been raised that this additional surgery may increase the rate of post-operative complications and potentially delay adjuvant therapy. In a recent retrospective review published by Deigni *et al.*, 429 patients underwent oncoplastic reconstruction followed by either immediate contralateral symmetry procedure, or symmetry procedure performed in a delayed fashion (37). There was no significant difference in overall complications between the two groups. Though complications resulted in a delay in adjuvant therapy in 4.2% of patients overall, complications attributable to the contralateral symmetry procedure accounted for a delay in only 0.7% of patients.

Surgical margins following oncoplastic reconstruction

Positive margins following breast conservation are known to correlate with cancer recurrence. One theoretical benefit of oncoplastic reconstruction compared to standard breast conservation is that the enhanced ability to aesthetically reconstruct large breast defects may encourage the extirpative surgeon to perform more generous tumor resections, resulting in lower rates of positive margins. In a retrospective review by Losken *et al.* of 207 patients undergoing breast conservation, positive margin rates were compared in patients who had lumpectomy followed by oncoplastic reconstruction versus those who had lumpectomy alone (38). The authors found that patients undergoing oncoplastic reconstruction had significantly lower positive margin rates (defined as <1 mm), lower rates of re-excision, and lower completion mastectomy rates compared to lumpectomy alone despite more advanced cancers in the oncoplastic group. This finding was confirmed in a meta-analysis of more than 8,500 patients performed by the same group; the overall rate of margin positivity was 12% in the oncoplastic group compared to 21% in

patients undergoing standard breast conservation (29). A similar systematic literature review in early stage breast cancer patients reinforced a low positive margin rate in oncoplastic surgery of 10% by De La Cruz *et al.* (28). Invasive lobular tumor histology, ductal carcinoma in-situ tumor histology, obesity, tumor multifocality and presence of microcalcifications on mammogram have been shown to predict margin positivity and need for re-excision following oncoplastic surgery (39-41).

Local recurrence, disease free and overall survival

To be considered a safe surgical option for patients with breast cancer, oncoplastic techniques must not sacrifice the oncologic efficacy achievable with standard breast conservation or mastectomy. Given that oncoplastic breast reconstruction techniques have only become a mainstream treatment option in the last 2 decades, long term data about recurrence and survival are somewhat lacking. As previously mentioned, margin positivity following partial mastectomy is known to predict local recurrence; however, tumor biology is also an important predictor of oncologic outcome. Oncoplastic surgical techniques extend the indications for breast conservation, including patients with larger and more aggressive tumors. Concerns have been raised that this phenomenon may affect the rate of cancer recurrence in patients treated with oncoplastic techniques. In a retrospective cohort study of 1,800 patients with breast cancer who underwent either standard breast conservation or oncoplastic breast conservation, Niinikoski *et al.* addressed this question (42). After a median follow-up of 75 months, there was no difference in local recurrence-free survival between the two groups. Of particular note, patients treated in the oncoplastic group had significantly larger tumors which were more often palpable and multifocal; in addition, their breast cancers had significantly higher histologic grade, T-stage and lymph node involvement. There was no difference in positive margin rate between groups in this study.

In a systematic review performed in 2016, De La Cruz *et al.* analyzed 6,011 oncoplastic reconstruction patients with a mean follow-up of 50.5 months. Among 871 patients with at least 5 years follow-up, the rates of overall survival, disease-free survival, local recurrence and distant recurrence were 93.4%, 85.4%, 6% and 11.9% respectively (28). The authors noted that these rates appear to correlate favorably with recurrence and survival rates after standard breast conservation, suggesting that surgical technique is not the primary predictor of oncologic outcome.

In general, it appears that oncologic reconstruction techniques do result in a generous resection and improved margin control, however, this does not translate into a recurrence benefit compared to standard breast conservation. Tumor recurrence, however, is not increased by the immediate reconstruction of these defects. Oncoplastic surgery may be offered to patients with a broader range of tumor size and pathology, and the aesthetic benefits of this approach do not appear to compromise cancer recurrence and survival.

Patient satisfaction following oncoplastic surgery

The primary perceived advantage of oncoplastic surgery is the aesthetic improvement in the final breast appearance compared to standard breast conservation, in which the rate of unacceptable breast cosmesis may be as high as 40% (43). Though oncoplastic surgeries have in common reconstruction of a partial mastectomy defect, the techniques by which this is accomplished and the oncologic situation in which they are applied may significantly affect how patients perceive benefit following surgery. For example, a patient who undergoes volume displacement/mastopexy for reconstruction of a relatively small partial breast defect will likely have a different experience than a patient who undergoes volume replacement with autologous tissue reconstruction of a large defect followed by adjuvant therapy for locally advanced disease. Treatment of the contralateral breast may also have a large impact on patient satisfaction, as breast symmetry is highly correlated with overall cosmesis. An analysis of patient reported outcomes after oncoplastic surgery using standardized, validated questionnaires will inform patient counseling and surgical decision making in the pre-operative setting.

Patient satisfaction following oncoplastic reconstruction has been shown to exceed satisfaction following standard breast conservation therapy (44,45), mastectomy alone (46), and mastectomy with reconstruction (47-49). Veiga *et al.* compared the patient reported satisfaction scores from 45 women undergoing breast conservation and oncoplastic reconstruction with 42 women who underwent breast conservation alone using validated questionnaires (45). He found that patients who underwent oncoplastic reconstruction reported higher levels of perceived health and physical functioning, higher social-emotional well-being and self-esteem compared to the standard breast conservation group. In addition, he noted that patients

in the oncoplastic reconstruction group actually had improvement in their satisfaction scores in follow-up compared to before surgery. Rose *et al.* published the results of a survey study comparing patient reported outcomes after oncoplastic surgery (107 patients) or standard breast conservation (657 patients) (44). Subjects were administered the Breast-Q validated questionnaire an average of 60.8 months from the time of surgery. The authors found that despite having on average more advanced cancers, patients in the oncoplastic group had significantly higher self-reported psychosocial well-being. A comprehensive literature review of patient reported outcome measures including Breast-Q was performed by Char *et al.* and found that oncoplastic surgery in general had the highest patient satisfaction scores among breast reconstructive choices (49). Forty three articles were included in this study looking at all forms of autologous tissue and implant based reconstruction.

The method of oncoplastic reconstruction or extent of surgery seems to have little impact on patient satisfaction. High levels of patient satisfaction have been reported after volume displacement techniques (46,50) as well as volume replacement techniques (51,52). In their survey of 624 patients undergoing a variety of different oncoplastic procedures, Rezai *et al.* demonstrated that there was no significant correlation between the method of oncologic reconstruction and the patient perception of the aesthetic result. Oncoplastic reconstruction with a reduction mammaplasty approach may have a particularly large impact on patient-reported quality of life after surgery. Losken *et al.* performed a retrospective review of 353 patients undergoing oncoplastic breast reconstruction with a breast reduction technique (53). The average reduction weight of patients in this study was 545 g. The authors used the Breast-Q validated questionnaire to show that, compared to pre-operative baseline, women undergoing oncoplastic reduction had increased self-confidence, feelings of attractiveness, emotional health and satisfaction with sex life over 1 year post-operatively.

There is some evidence that suggests that oncologic status may affect patient reported outcomes more than surgical technique. In their study of 120 patients undergoing oncoplastic breast reconstruction with volume displacement techniques, Gardfjell *et al.* showed that lower patient satisfaction appeared to correlate with need for axillary dissection and neoadjuvant chemotherapy (50). In their comparison of 379 patients undergoing oncoplastic surgery or breast conservation alone, Ojala *et al.* showed that larger tumor diameter, multifocality, and oncoplastic reconstruction were predictive of poor patient-reported aesthetic result; however, in this study, patients undergoing oncoplastic reconstruction were more likely to have larger, multifocal tumors with lymph node involvement (54).

Taken together, it can be said that patients undergoing oncoplastic reconstruction have high levels of satisfaction with their appearance, mental well-being, and overall perception of health, comparing favorably to other surgical breast cancer treatment modalities. This effect is somewhat expected and may be secondary to the attention to breast aesthetics and symmetry that are the focus of oncoplastic techniques. The quality-of-life benefit that accompanies breast reduction may also be a contributing factor. This data can assist with patient counseling and decision making.

Conclusions

Oncoplastic breast reconstruction is now a globally accepted option for treatment of breast cancer. This approach has a favorable safety profile and equivalent oncologic efficacy compared to standard breast conservation, but has the major advantage of improved aesthetic outcomes. By utilizing techniques of volume displacement, volume replacement, and contralateral breast reduction/mastopexy, the oncoplastic approach can reduce the rate of post-lumpectomy breast deformity while optimizing breast symmetry.

The oncoplastic approach mandates multidisciplinary communication and coordination in order to provide the highest quality care for patients. Inter-specialty discussion in the pre-operative planning phase, particularly between surgical oncology and plastic surgery, will optimize the plan of care from both oncologic and reconstructive standpoints.

When considering the delivery of oncoplastic reconstructive care from a global viewpoint, one size does not fit all. Breast surgeon comfort with oncoplastic techniques and the involvement of a plastic surgeon in oncoplastic operations may vary significantly by geographic location depending on availability of training and subspecialty resources. While there is no accepted standard for who should be performing oncoplastic surgery, the goal should be that all involved have appropriate training and education in order to deliver the highest possible quality of patient care.

Currently available data suggest excellent outcomes in oncologic efficacy, aesthetic result, overall safety and patient satisfaction. Previously limited given the relative novelty of

oncoplastic techniques, data quality is improving with larger series and longer follow-up.

As international acceptance of oncoplastic reconstruction continues to increase, providers should continue to evaluate outcomes, refine techniques, and streamline care delivery through better interspecialty communication with the goal of optimizing results and overall patient satisfaction.

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Review Article

Breast conserving surgery revisited: a narrative review

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Background and Objective: Breast cancer surgery has seen a reverse evolution particularly over the last decade. There has been a universal acceptance of the fact that tumour biology and response to systemic treatment dictates risk of breast cancer recurrences and not surgical radicalism. The role of surgery has been "risk adapted" over the years to maintain function, contour and body image without compromising on the principles of surgical oncology. In this article we explore the first major transition from radical ablative mastectomies to breast conserving surgery (BCS) as we know it today comparing the different cancer specific and health related outcome measures for BCS and mastectomy.

Methods: We undertook comprehensive search using Ovid Medline from 1946 till May 2021 to identify complete papers published in English, primarily comparing the clinical outcomes of BCS and mastectomy using keywords such as "mastectomy", "breast conserving surgery" to name a few. Particular emphasis was given to data from randomised controlled trials and meta-analyses looking at the safety of breast conserving treatment. The oncological characteristics and results from key studies identified are analysed and summarised in this review.

Conclusions: BCS in conjunction with radiotherapy in appropriately selected cases gives results comparable to mastectomy for overall survival and relapse free survival. Current data suggest that in both node negative and node positive patients, breast conservation therapy (BCT) is a safe option with higher levels of favourable patient related outcomes.

Keywords: Breast conserving surgery (BCS); breast cancer; mastectomy; survival

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Introduction

Globally, breast cancer is the most diagnosed cancer and the leading cause of cancer-related deaths in women. The Surveillance, Epidemiology and End Results (SEER) programme estimates that 281,550 new breast cancers will be diagnosed in 2021 (129.1 per 100,000 women per year), accounting for 14.8% of all new cancers in the United States. In developed countries, approximately 1 in 8 (12.9%) women are likely to develop breast cancer during their lifetime (1). The GLOBOCAN 2018 survey showed that although developing countries had a lower overall incidence, it has been steadily increasing over the years (2).

Surgical management of breast cancer has evolved in the past decades with a reverse evolution, from heroic

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radicality to careful conservatism. In the past, Halsted's radical mastectomy was considered the standard of care for many decades. Although most modern breast surgeons consider it extremely radical, preceding studies assessed even more radical approaches in a desperate attempt to provide a cure and prevent local recurrences (LRs) and distant metastasis (3-5). These extended radical procedures did not show additional benefit and soon fell into disrepute due to the associated morbidity. Bernard Fisher introduced his novel hypothesis that invasive breast cancer is a systemic disease at inception (6). This new school of thought prompted a shift in practice towards a more conservative surgical approach, leading to the initiation of landmark trials like the NSABP B-04 that showed no advantage of radical mastectomy over a more conservative mastectomy (7). This paved the way for even more conservative surgical approaches leading to landmark trials in breast conservation (8,9).

The transition from radical mastectomy to breast conserving surgery (BCS) has been a scientific and systematic de-escalation process validated through several randomised controlled trials (9-16). Offering BCS, where appropriate, was an essential step towards improving the quality of life (QOL) in breast cancer survivors. The rapidly evolving sub-speciality of oncoplastic breast surgery (OPBS) has allowed for even more generous tumour excision volumes while at the same time enhancing the cosmetic appearance of the breast by adopting the aesthetic principles of plastic surgery. The realisation that breast cancer is a heterogeneous disease has led to a multidisciplinary approach to its management where each treatment modality contributes significantly to improved cancer outcomes. Recent advances in medical and radiation oncology have contributed significantly to improved cancer-specific outcomes following BCS by facilitating superior local and systemic control. The remit of surgical management has expanded to include optimal cosmesis and QOL in addition to achieving improved long-term survival and local control.

In this narrative review, we have explored breast conservation from its inception and looked at key trials in literature that enabled this transition from radicality. We have also considered several essential aspects: margins, adjuvant and neoadjuvant treatments, and their impact on survival. We present the following article in accordance with the Narrative Review reporting checklist (available at https://abs.amegroups.com/article/view/10.21037/abs-21-98/rc).

Methodology

Literature search was conducted using Ovid MEDLINE from 1946 to May 2021 combining relevant Keywords and MeSH headings to identify papers published mainly in the English language, primarily comparing BCS and mastectomy clinical outcomes. We gave particular emphasis to outcomes reported from randomised controlled trials and meta-analysis of relevant trials. In addition, the bibliography of these key publications was used to identify further relevant papers to be included in this narrative review.

The transition from mastectomy to breast conservation for invasive breast cancer

Six key randomised trials conducted in the 70s and 80s of the last century, many with long term follow up, showed no difference in overall and disease-free survival between BCS and mastectomy. They established the pivotal role of radiotherapy in decreasing the unacceptable high LR rate after breast conservation (9-12,15,16) (*Table 1*).

Of particular interest is the NSABP B-06, as this key trial reported outcomes of 1,851 women with stage 1 or 2 breast cancer and a tumour diameter of less than 4 cm, randomised to receive either total mastectomy (n=589) lumpectomy alone (n=634) or lumpectomy followed by radiotherapy (n=628). For patients undergoing a lumpectomy, tumours were resected with adequate surrounding normal breast tissue to ensure negative pathological margins. Approximately 10% of patients in the lumpectomy arm had positive margins and subsequently underwent a total mastectomy and received no further treatment. All patients identified with positive axillary nodes on axillary nodal dissection received adjuvant chemotherapy. At 20-year follow-up, the overall cumulative survival was comparable in the conservation and mastectomy arm. The cumulative incidence of death from any cause was 47.7% in women with no lymph node involvement versus 63.3% in women with axillary nodal disease. The conclusion was that lumpectomy and radiotherapy can be considered safe if the tumour resection margins are negative (9).

A meta-analysis conducted by Early Breast Cancer Trialists' Collaborative Group (EBCTCG) consisting of 3,100 patients from seven randomised trials reported no difference in the 10-year survival rate comparing BCS to total mastectomy (13). Another meta-analysis by Morris *et al.* included studies comparing BCS and total mastectomy

Table 1 Randomized controlled trials of BCS versus mastectomy in early breast cancer

Trial	Time period	Sample size	Median years of follow-up	T size (cm), inclusion criteria	Margins defined as	RT boost administered	LR		Overall survival		
							BCT (%)	Mastectomy (%)	BCT (%)	Mastectomy (%)	P value
NSABP B-06 (9)	1976–1984	1,851	20	4	Free	No	14	10	46	47	0.57
Milan (16)	1973–1980	701	20	2	–	Yes	9	2	42	41	1.0
NCI (12)	1979–1987	247	18	5	Grossly free	Yes	22	6	59	58	0.67
EORTC (15)	1980–1986	868	10	5	1 cm gross	Yes	20	12	65	66	0.23
Danish (11)	1983–1989	793	20	Any	Grossly free	Yes	NR	NR	58	51	0.24
IGR, Paris (10)	1972–1979	179	15	2	2 cm gross	Yes	9	14	73	65	0.16

BCS, breast conserving surgery; RT, radiation therapy; LR, local recurrence; BCT, breast conservation therapy; NSABP, National Surgical Adjuvant Breast and Bowel Project; NCI, National Cancer Institute; EORTC, European Organization for Research and Treatment of Cancer; IGR, Institute Gustave Roussy; NR, no response.

in early breast cancer, demonstrated a pooled odds ratio (OR) of 0.91 at 10 years. When more than 50% of node-positive patients in both the mastectomy and BCS arms received adjuvant radiation, both arms had similar survival rates. When less than 50% of node-positive patients in both arms received adjuvant nodal radiation, the OR was 0.69, and patients receiving breast conservation therapy (BCT) had a survival advantage (14).

This survival advantage was also seen in a recent prospective cohort study for the Swedish National Cancer Registry that included 48,986 women with T1–2, N0–1 breast cancer, treated outside clinical trials undergoing breast surgery between 2007 and 2018. Three groups were compared: mastectomy without radiation (Mx – RT), mastectomy with radiation (Mx + RT) and BCS with radiation (BCS + RT). At a median follow-up of 6.28 years and after adjustment for covariates notably comorbidities and socio-economic status, overall survival and breast cancer specific survival were significantly worse after Mx – RT [hazard ratio (HR), 1.79; 95% confidence interval (CI): 1.66–1.92 and HR, 1.66; 95% CI: 1.45–1.90, respectively] and Mx + RT (HR, 1.24; 95% CI: 1.13–1.37 and HR, 1.26; 95% CI: 1.08–1.46, respectively) than after BCS + RT. Studies with radiation following BCS have a better long-term outcome than Mx – RT, especially for triple negative breast cancer (TNBC) (17). This better survival with BCS is more likely to be associated with an inherent unavoidable selection bias in most non-randomized reported series. Mastectomy is more likely to be offered to relatively advanced cases with adverse clinical and radiological features. The effect of post-BCS radiation and other adjuvant therapies, especially when compared with mastectomy without indications for adjuvant radiotherapy, may be another possible explanation.

Following the findings of the key initial clinical trials, a gradual change in practice was observed and the SEER data reported an increase in the BCS rate from 23.9% in 1985 to 34.6% in 1989 (18). In 1991, the National Institute of Health (NIH) published a consensus statement acknowledging BCS in conjunction with radiation therapy (RT) as an acceptable treatment for appropriately selected patients with early breast cancer (18,19). Following the NIH Consensus recommendation, the BCS rate increased to 53.4% in women with stage 1 & 2 breast cancers (18,19) and in 2005, the National Cancer Database (NCDB) reported a breast conservation rate of approximately 65%. The contraindications to BCS mainly concern appropriate case selection and the inability to receive adjuvant radiotherapy. A high percentage of patients are suitable for BCS and the adoption of the new OPBS techniques have extended these. However, of late it has been observed that the mastectomy rates seem to be increasing in certain parts of the world for various reasons such as patient choice, surgeon preference, non-availability of RT, RT-related patient anxiety, better reconstruction options, younger age, mutation status and patient anxiety related to their family

history (20).

Factors affecting locoregional recurrence (LRR) rate post BCT

The primary goal of breast conservation is to achieve long term local control with an acceptable risk of LR. A pooled analysis of updated long-term results of all six trials showed that the LRR rate was higher for BCT compared to mastectomy at a median follow-up of approximately 14.6 years (OR, 1.561; 95% CI: 1.289–1.890; P<0.001). The LRR rates varied from 4.6% to 25.6% across the 6 studies (21). However, the mortality rates were no different in the two groups (OR, 1.070; 95% CI: 0.935–1.224; P=0.33). Due to the difference in the definition of "LRR" within the six trials (the NSABP B-06 trial classified supraclavicular recurrence as a LRR, whereas the EORTC trial classified them as a distant recurrence) (9,22) results were calculated for both locoregional and total recurrences separately. Four out of the six trials showed a lower LRR, and three out of four (with total recurrence data) showed a lower total recurrence rate with mastectomy. However, there were variations in surgical procedures among these trials that might have attributed to the heterogeneity for risk LRR. In the Milan study the surgeons performed quadrantectomies while in the Danish and US NCI study wide excision was performed with no gross margin involvement. Another key point to note about the Danish trial was that nearly 248 patients did not follow their randomisation. The trialists excluded these patients from the final analysis, resulting in non-adherence to the principle of intention-to-treat analysis. However, the pooled analysis results did not change even after the exclusion of the Danish study. The most notable finding was that the increase in LRR rates did not translate to a rise in mortality (21).

The high rate of LRR in these studies may be attributed to the era in which they were conducted and factors such as non-uniform reporting of pathological margins, non-availability of modern systemic chemotherapeutic regimes and older radiation techniques with no consistency of tumour bed boost. With the advent of better systemic treatment and radiotherapy protocols, several recent studies have shown a further decrease in the incidence of LRR post BCS with a reported rate of <5% (23,24).

An interplay of several factors contributes to the risk of LR that are either patient-related, tumour-related, or treatment-related factors. Amongst patient-related factors, young age is an independent risk factor for increased LR (25-27). Young age is frequently associated with biologically aggressive cancers that result in higher rates of local relapse. A family history of breast cancer and/or positive germline mutation status confer a higher risk of ipsilateral recurrences and an increased risk of second primaries (28). There are tumour related factors that increase the risk of LRR not only in BCS patients but also for patients with a mastectomy such as tumour size, grade, molecular subtype and disease burden in the axilla. Some features like extensive intraductal component (EIC) was for long considered as an independent risk factor for LR in BCS before routine inking of margins (29). However, recent evidence shows that is not true, provided it is adequately excised (30-33). EIC is an indicator of the potential residual burden of ductal carcinoma in situ (DCIS); however, the need for further re-excision should be gauged based on the extent of DCIS in proximity to the margin and post excision imaging.

A positive resection margin is the most important risk factor associated with a higher rate of LR. Adjuvant radiation with boost and adequate systemic therapy are also of paramount importance in reducing the risk of LR post BCS. Adjuvant chemotherapy and endocrine treatment further decrease the rate of LR. For example, a 66% decrease in LR was observed in patients who received adjuvant hormonal therapy in the NSABP B-13 trial (34). While the node negative, ER negative patients in the NSABP B-13 study, were randomised to receive chemotherapy versus no-treatment and the 8-year recurrence rate in the ipsilateral breast was 2.6% in the chemotherapy arm versus 13.4% in the non-treatment arm.

Margin assessment in BCS for invasive cancer

Involved resection margins is an important factor that contributes to the increased risk of LR as patients with positive surgical margins are at an increased risk of LR varying between 5% and 25% at a median follow up of 5–9 years (31,35-41). Historically, the definition of "an adequate margin/optimal surgical margin" following BCS has always been controversial due to the heterogeneity of results from various studies reported in the literature. For quite some time there was a lack of a clear consensus on adequate margin width, and this was examined by several authors (42-44). It is critical to understand that a negative margin does not rule out residual tumour in the breast but suggests that the residual tumour burden is low enough to be controlled with adjuvant radiotherapy. At the same

time, radiotherapy cannot compensate for inadequate surgery; instead, it serves to sterilise the operative field of microscopic residual disease. The guidelines for adequate margins vary in different parts of the world. They also tend to differ in some guidelines for invasive carcinoma and DCIS due to differences in their patterns of growth and the subsequent adjuvant therapy recommendations, which could potentially impact the risk of LRR (45-47).

NSABP B-06 (9) was one of the prospective randomised trials that defined microscopic margin as "no ink on tumour" and established the safety of BCT in invasive carcinoma. In 2014, "no ink on tumour" was accepted as a negative margin for invasive disease following the consensus guidelines recommended by the Society of Surgical Oncology (SSO) and the American Society for Radiation Oncology (ASTRO) (46). A meta-analysis by Houssami *et al.* looked at the effect of margin status and margin width on ipsilateral breast tumour recurrence (IBTR) in patients with early-stage invasive breast cancer (48). They included 21 studies that identified 1,026 LRs in 14,571 patients, which showed the OR for recurrence was 2.42 (P<0.001) for positive versus negative margins even after they had controlled for the use of tumour bed boost or endocrine therapy. They observed that increasing the width of a negative margin did not reduce the risk of local relapse. They concluded that a negative margin of "no ink on tumour" optimises local control and obtaining a wider margin does not alter outcomes. The National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology, the American Society of Breast Surgeons, and the St. Gallen International Expert Consensus group also accepted this definition (49). Considering the high risk of LR, patients with positive margins should at least undergo a margin revision or then a mastectomy (50).

The publication in 2017 of the national margins audit in the UK showed lots of variation in the different units, many accepting the Association of Breast Surgery (ABS) guidelines (1 mm for both invasive disease and DCIS), while some accepted SSO-ASTRO guidelines ('no ink on tumour' for invasive and 2 mm for DCIS) and some following other guidelines. The re-excision rate was 17.2% across the units and the interesting point was that if all units followed the ABS guidelines the re-excision rate would be 15% and if all followed the SSO-ASTRO this would be 14.8%, so, in essence whatever guidelines you follow the variation in the re-excision rate will be small and not significant (44).

There is no robust data to support the guideline of "no ink on tumour" in patients following neoadjuvant chemotherapy (NACT) but most units will use the same margin policy that they use for post-NACT patients. The expert panel at the 15th St. Gallen's Consensus conference in 2017 voted that "no ink of tumour" would be an acceptable margin in patients undergoing BCS following NACT (49). The majority also voted that a further re-excision of margins need not be undertaken provided the margins of the resection are clear even in cases where the specimen shows multifocal residual cell nests. Wimmer *et al.* retrospectively studied 406 women with invasive breast cancer that underwent BCS following NACT between 1994 and 2014. They concluded that there was no significant difference in LR risk, disease-free survival, or overall survival when comparing close, wide or unknown margins and that the "no ink on tumour" was acceptable following NACT (51).

Role of BCS and margin status in DCIS

Although DCIS has a mortality rate of under 1% after BCT, local control is vital as half of the local relapses are invasive cancers, impacting breast cancer-specific mortality (52). There are no randomised controlled trials that have evaluated the role of breast conservation in DCIS. Most guidelines have accepted wide excision with negative margins as a valid treatment option for localised DCIS based on the data from studies for invasive breast cancer. However, young age, symptoms at presentation, extensive disease, presence of necrosis, margin width and use of adjuvant therapy are all identified as risk factors for LR in patients undergoing BCS for DCIS (53). Margin width and utilisation of adjuvant therapy are modifiable risk factors. The Van Nuys Prognostic Index utilises margin width to risk stratify DCIS (54). The trials conducted to evaluate the benefit of radiotherapy post BCS in DCIS were not designed to assess the association of margin width to LR (53). Hence, there is no guidance on optimal margin width for DCIS. There is a lot of heterogeneity on multiple surveys showing margin width ranging from "no tumour on ink" to >1 cm as acceptable for patients with DCIS treated with BCT. The most widely accepted margin width for DCIS is based on the SSO-ASTRO guidelines which recommends a margin width of 2 mm for DCIS. The recommended margin width for DCIS is more than that in invasive cancer due to the adverse histological features of DCIS, such as the occurrence of skip lesions and multifocality (47).

A meta-analysis including 6,353 women that evaluated the

impact of margin status on LR in women with DCIS treated with BCT (55) reported no additional benefit for margins greater than 2 mm. Subsequently, in 2015, an SSO-ASTRO-ASCO multidisciplinary consensus panel concluded that a 2 mm margin minimises LR risk compared to narrower negative margins. More widely clear margins do not further reduce the risk of LR (47) as demonstrated also in two large single institution studies (55,56) reporting that close margins (<2 mm) were non-inferior to wider negative margins in this cohort of patients. The SSO-ASTRO-ASCO panel took all this evidence into account along with long term favourable outcomes of NSABP trials using no ink on tumour as their margin definition and recognising that minor differences in local control do not impact overall survival in DCIS. Hence, although 2 mm is the desired negative margin, they emphasised that re-excision of margins <2 mm may also be an individualised decision based on the volume of disease near a margin, post excision image findings, the cosmetic impact of re-excision, patient age, tumour size and grade, life expectancy and patient tolerance of risk with accentuation that a negative margin <2 mm is not by itself an indication for mastectomy (53).

In early breast cancer, is BCT a better option than mastectomy?

As discussed above, an earlier pooled analysis of updated data by Jatoi *et al.* in 2005 showed a higher LR rate in four of the six randomised trials, which was also shown in the pooled data. But when looking at the pooled data for mortality there was no significant difference noted (21). Dixon *et al.*, contend that consequent to the availability of better imaging modalities, greater attention to resection margins and better and more effective systemic adjuvant therapies administered in some cases for longer durations, the recurrence rates post BCT are comparable to those of mastectomy in early breast cancer (57). Several large, population-based cohort studies have shown BCT to be superior to mastectomy with respect to breast cancer specific and overall survival, independent of tumour characteristics (17,58-60). A more recent prospective cohort study with a median follow-up of 6.28 years suggests, that conservable node negative patients could potentially benefit from a significantly better breast cancer specific survival were they to undergo BCT as opposed to a mastectomy without radiotherapy. The benefit persists in node positive patients with a lower axillary burden undergoing mastectomy with radiotherapy but is lost in patients with a heavily node positive axilla (17). The better outcome persisted even after adjusting for age, tumour size, tumour grade, year at diagnosis, race, socio-economic status (17,61). Although a smaller proportion of the overall percentage of women affected, there has been some debate about young women <40 years and the increased risk of LR following BCT. Notwithstanding that there have been no randomised controlled trials comparing BCT to mastectomy in this cohort of young women, reported population based and institutional studies have shown no inferiority in overall survival (62). TNBC is deemed to be a more aggressive biological subtype with a higher risk of recurrence, metastasis and lower overall survival that affects typically younger women. Considering these factors, it is vital to maximise local control through risk adapted surgery. A recent SEER based retrospective population study reported that in patients with T1–2N0M0 patients with TNBC, BCT was associated with superior OS and BCSS when compared with mastectomy with or without radiotherapy (63).

Recent studies suggest that the long-held paradigm of the non-inferiority of BCT when compared with mastectomy, needs to change. With the advent of better systemic therapy, targeted therapies, longer endocrine adjuvant manipulation, margin assessment, improved radiotherapy planning and delivery systems the authors suggest that on balance BCT is probably equivalent or in some selected cases even superior to mastectomy in the modern era of multidisciplinary management. The lower complication rate and better QOL following BCT makes BCT a more patient centric option when compared to mastectomy for all patients who are suitable for both surgical options. However, the decision of BCT versus mastectomy is a more complex one and the rising rate of mastectomy and bilateral mastectomy in North America irrespective of BRCA status is a reminder of the same (64). In developing countries, this is confounded by cost of additional radiation and non-availability of radiation centres in smaller cities. Decision aids for shared decision making in this setting may improve decisional conflict as well as BCS rates (65).

BCS post-NACT

There has been a steady increase in the use of NACT in the treatment of breast cancer. This practice initially started with a view to downstaging locally advanced disease prior to surgery. Today it has evolved to down-sizing tumours with an unfavourable tumour to breast volume ratio to facilitate

BCS with a cosmetically acceptable result. Historically, BCS was achieved in up to 25% of cases following NACT (66). The NSABP B-18 study showed that an absolute 8% gain in BCS rate is observed in post-NACT cases. However, the fear of a patchy response to chemotherapy and a slightly increased risk of IBTR makes a reduction in the volume of resection a little difficult to comprehend in such cases.

Since smaller resection volumes are correlated with better cosmetic outcomes, it follows that downsizing with NACT may result in a better QOL. However, there are few prospective studies evaluating patient-related outcome measures. In a systematic review by Volders *et al*. (67), 26 studies were included after screening 1,219 studies, treating 5,379 patients with chemotherapy and 10,110 patients without chemotherapy. The margin positivity rate (2–39.8%), second surgery rate (2–45.4%), specimen excision volume rate (43.2–268 cm^3) showed significant heterogeneity. Only two studies reported on the cosmetic outcomes. The authors concluded that there was no evidence to suggest that preoperative chemotherapy improved surgical outcomes following BCS. This is further confounded by the presumed higher LR rate in BCS post-NACT, as seen in the latest EBCTCG analysis (68). However, it must be stressed the final analysis did include trials where patients did not undergo any surgery following NACT. The rate of LRR is between 4 and 10% across most recent studies of BCT post-NACT (69). In the BrighTNess randomised trial, a 53.2% conversion from BCS ineligibility to BCS eligibility was observed as a part of the secondary outcome analysis (64). However, only around 60% of these patients who were eligible for BCS actually underwent BCS. The decision was largely influenced by the prevailing use of bilateral mastectomy, especially in North America, irrespective of germline BRCA mutation carrier status.

Role of adjuvant radiotherapy

Postoperative whole breast radiation is a critical component of BCT. As mentioned earlier, it is instrumental in eradicating residual occult microscopic disease in the breast. Six randomised trials (9-12,15,16) and two meta-analyses (13,70) have demonstrated the role of lumpectomy with adjuvant radiotherapy in achieving locoregional control and organ preservation while providing survival outcomes that are equivalent to mastectomy. NSABP B-06 (9) is the largest trial with a follow up of 20 years to report a statistically significant decrease in local failure with a trend toward improved disease-free survival in the group that received radiotherapy versus the group that received lumpectomy alone. The lumpectomy plus radiotherapy group also showed no difference in survival compared with the mastectomy group, which was confirmed by the Milan (16), Danish (11) and EORTC trials (15).

Several prospective randomised trials of BCS have been conducted with or without radiotherapy for patients with stage I or II breast cancer. All trials have demonstrated a significant reduction in the risk of IBTR with the addition of radiotherapy at follow up of 5 years or more. The risk of IBTR after 5 years was between 6–39% without radiation compared with 1–14% with radiation (9,71-80) (*Table 2*). After BCS, the omission of radiotherapy is associated with a small but clinically significant increase in breast cancer mortality and decreased overall survival of between 0.5% to 5% within 10 years. The most notable difference was observed in node-positive patients in the Milan quadrantectomy trial (71) with a 10-year overall survival rate of 82% with RT versus 62% without RT. However, a pooled analysis of 15 prospective randomised trials with 9,422 women found the relative risk of mortality to be 1.086 (95% CI: 1.003–1.175), or an 8.6% excess risk of mortality, if radiotherapy was omitted (81). In 2011, the EBCTCG (82) published a meta-analysis of individual patient data for 10,801 from 17 randomised radiotherapy trials versus no radiotherapy after BCS. 8,337 women had pathologically confirmed nodal status as either node-negative (pN0) or node-positive (pN+) disease with a median follow up of 9.5 years, and 25% of women were followed up for more than a decade. In this meta-analysis, six trials were of radiotherapy after lumpectomy and included low-risk and high-risk women (category A, 4,398 women). Four were of radiotherapy after sector resection or quadrantectomy (category B, 2,399 women), and seven more recent trials were of radiotherapy after lumpectomy in low-risk women (category C, 4,004 women). It reported a 10-year risk of any (locoregional or distant) first recurrence to be 19.3% in women who received radiotherapy versus 35% in women who received BCS without radiotherapy, corresponding to an absolute risk reduction of 15.7% (95% CI: 13.7–17.7; P<0.00001) and a 3.8% absolute risk reduction in 15-year risk of breast cancer death from 25.2% to 21.4% (95% CI: 1.6–6.0; P=0.00005). In women with pN0 disease, the absolute recurrence reduction varied according to age, grade, oestrogen-receptor status, tamoxifen use, and extent of surgery, and these characteristics were used to predict large (≥20%), intermediate (10–19%), or lower (<10%) absolute reductions in the 10-year recurrence. The meta-

Table 2 Overall survival and LR rates comparing breast conservation surgery alone to breast conservation surgery and RT

Trial	Sample size	Tumour size (cm)	Tamoxifen (%)	Chemo (%)	Percerntage of LR risk		Follow up (years)
					BCS	BCS + radiotherapy	
British 1996 (78)	418	≤5	If ER positive	If ER negative	35	13	5
Ontario 1996 (73)	837	≤4	0	0	35	11	8
Scottish 1996 (75)	585	≤4	73	26	24.5	5.8	6
Uppsala-Orebro 1999 (72)	381	≤2	0	0	24	8.5	10
Milan 2002 (71)	579	≤2.5	12	17	23.5	5.8	10
NSABP B-06, 2002 (9)	1137	≤4	0	37	39.2	14.3	20
NSABP B-21, 2002 (74)	673	≤1	All	0	16.5	2.8	8
	336	≤1	0	0	–	9.3	–
Canadian 2004 (80)	769	≤5	All	0	7.7	0.6	5
GBCSG 2004 (76)	173	≤2	0	0	29.1*	4.3*	5.9
	174	≤2	All	0	2.5*	3.2*	–
ABCSG 2007 (77)	869	<3	All	0	5.1	0.4	5
CALGB 2013 (79)	636	≤2	All	0	8.5*	1.8*	12

*, crude result. LR, local recurrence; RT, radiation therapy; BCS, breast conservation surgery; NSABP, National Surgical Adjuvant Breast and Bowel Project; GBCSG, German Breast Cancer Study Group; ABCSG, Austrian Breast and Colorectal Cancer study Group; CALGB, Cancer and Leukaemia Group B; ER, estrogen receptor.

analysis concluded that about one breast cancer death was avoided by year 15 for every four recurrences avoided by year 10. The mortality reduction did not differ significantly from this overall relationship in any of the three categories for pN0 or pN+ disease.

Similar to that seen in invasive breast cancer, whole breast radiation reduces the risk of LR after BCS for DCIS (53). However, prognostic indices allow one to choose those low-risk patients with DCIS in whom radiation may be safely avoided. Between 17% and 44% of women with a diagnosis of DCIS are treated by wide excision alone without adjuvant radiotherapy (83). The SEER data for example reported that 31% of women underwent wide excision alone for DCIS between 1988–2011 (83). Several studies showed a significant disparity in the margin width that was adequate to decrease LR in wide excision alone for patients with DCIS (84-90).

Role of tumour bed boost

A tumour bed boost implies an extra dose of radiation applied to cover the primary tumour bed. The rationale behind a boost is to reduce LR that is most observed adjacent to the previous tumour bed site by eliminating remaining microscopic tumour foci. Tumour bed boost remained controversial for many years due to the results of the NSABP B-06 trial (9), which did not incorporate a boost compared to trials that used the boost. In 1997, a French trial (91) that randomised 1,024 patients with a tumour size of 3 cm or less to receive a 10-Gy boost to tumour bed versus no boost reported a statistically significant reduction in LR at 5 years in women receiving a boost (3.6%) compared with women who did not receive a boost (4.5%; P=0.044). The EORTC trial first published its results in 2001 (92) and again in 2007 (93) of 5,318 patients with stage I or II breast cancer and microscopically negative margins with a median follow up of 10.8 years. Patients were randomised to receive 50 Gy of radiation to the whole breast, followed by a 16 Gy boost versus no boost, confirming local control benefit from the addition of a boost. Seventeen-year updated results of the EORTC trial (94), reported that a boost dose of 16 Gy reduced the LR rate from 13.1% to 8.8% at 15 years and from 16.4% to 12% at 20 years (HR, 0.65). This relative risk reduction was seen across all age groups, with the largest absolute benefit (12%) observed in younger patients. A recent Cochrane review (95) of 8,325 women from 5 randomised control trials reported better local control

(HR, 0.64; 95% CI: 0.55–0.75) with tumour bed boost when compared to no boost. However, this did not translate into an overall survival (HR, 1.04; 95% CI: 0.94–1.14) or disease-free survival (HR, 0.94; 95% CI: 0.87–1.02) benefit. There was no difference in late toxicity scored by means of percentage of breast retraction assessment (mean difference, 0.38; 95% CI: –0.18 to 0.93). Cosmesis scored by an expert panel was better for the no boost group (OR, 1.41; 95% CI: 1.07–1.85) but showed no difference when scored by a physician (OR, 1.58; 95% CI: 0.93–2.69).

QOL studies

The multidisciplinary management of breast cancer and early diagnosis driven by screening and breast awareness have significantly improved overall survival rates. With an increasing number of survivors, maintaining a good QOL becomes vital. BCS was introduced to facilitate organ preservation and to move away from more ablative and defeminising surgery. A meta-analysis (96) included six studies comparing the quality-of-life following BCT and mastectomy without reconstruction (2 from Asia-Korea, Taiwan, and 4 from Europe, Turkey, Netherlands, and Germany) EORTC QLQ-BR23 questionnaire. The random effects model showed a statistically significant better QOL in 3 of the 8 aspects of the questionnaire, i.e., in the body image outcome, systemic therapy side effects outcome, and future perspective outcome in patients who underwent BCS compared to those that underwent mastectomy. However, the meta-analysis did not show any difference in QOL aspects such as sexual functioning, sexual enjoyment, upset by hair loss, arm symptoms and breast symptoms. This suggests that QOL with respect to sexual satisfaction is a complex process that is influenced by demographic, biological, psychological, and sociocultural factors. Most systematic reviews (97) report a significant heterogeneity across studies and hence the difficulty in interpreting results.

Conclusions

BCT is a safe treatment modality for patients with early breast cancer without any detriment to long-term oncological outcomes, with acceptable local and regional recurrence rates. Appropriate case selection, achieving adequate resection margins, timely and appropriate adjuvant therapies are crucial to successful outcomes. OPBS, which uses plastic surgical principles to reconstruct partial or total breast defects, is being increasingly preferred as it results in a better QOL and quicker psychosocial rehabilitation of patients.

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Review Article

The neoadjuvant systemic treatment of early breast cancer: a narrative review

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Background and Objective: The use of neoadjuvant systemic therapy for breast cancer is on the rise. Neoadjuvant treatment is equally effective as adjuvant treatment in preventing disease recurrence and death. The role of neoadjuvant treatment is unique for each breast cancer subtype. Neoadjuvant systemic therapy can improve surgical outcomes, provide valuable prognostic information and the response can guide post operative systemic treatment decisions. There is a growing need for all disciplines involved in the treatment of early breast cancer to discuss with patients the potential role of neoadjuvant treatment for their tumor subtype. To better guide the use of neoadjuvant systemic treatment we aim to detail its unique role in the three breast cancer subtypes with a focus on patient selection, surgical and oncological benefits, and future directions.

Methods: We performed a search of the PubMed, Cochrane Review, and Clinical Trials.gov databases. We used the search terms "neoadjuvant chemotherapy" AND "breast cancer" and then conducted a thorough manual review of all bibliographies and relevant studies to identify additional potentially eligible studies.

Key Content and Findings: To improve surgical outcomes, neoadjuvant therapy can be considered in all patients with operable breast cancer deemed to require adjuvant systemic treatment. For patients with human epidermal growth factor receptor-2 (HER-2) positive and triple negative breast cancer (TNBC) the presence of residual tumor can prompt a postoperative treatment change. For postmenopausal women with hormone receptor (HR) positive HER-2 negative tumors neoadjuvant endocrine treatment should be considered to help facilitate breast conservation. The use of preoperative gene expression profiles can be considered to decide whether to administer neoadjuvant chemotherapy (NACT) to patients with HR positive HER-2 negative tumors who require mastectomy or axillary lymph node dissection (ALND) upfront, however the role of these tests in the neoadjuvant setting is still unclear. Neoadjuvant therapy offers a unique window of opportunity to research additional biomarkers and systemic treatments.

Conclusions: The role of neoadjuvant systemic therapy in early breast cancer is continuing to develop with the likelihood that its applications will continue to expand, further emphasizing the importance of multidisciplinary communication to provide the best outcomes for our patients.

Keywords: Neoadjuvant; pathological complete response (pCR); triple negative (TN); human epidermal growth factor receptor-2 positive (HER-2 positive); hormone receptor positive (HR positive)

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Introduction

Over the last decade, the use of neoadjuvant chemotherapy (NACT) for the treatment of early breast cancer, particularly locally advanced breast cancers, has significantly increased (1). There is a growing need for all disciplines involved in the treatment of early breast cancer to understand and discuss with patients the potential role of neoadjuvant treatment for their tumor subtype. Results of the NSABP-B18 trial demonstrated that NACT provides similar disease-free survival (DFS) and overall survival (OS) as adjuvant chemotherapy. Patients receiving NACT experienced an increased likelihood of breast conserving surgery (BCS) and of pathologically negative nodes (2). A 2018 meta-analysis by the early breast cancer trialists collaborative group (EBCTCG) showed that NACT increases BCS rates compared to adjuvant chemotherapy (3). NACT may also spare clinically node positive patients the long-term morbidity associated with an axillary lymph node dissection (ALND). The SENTINA (4) and ACOSOG Z1071 trial (5) showed that clinically node positive patients who respond to NACT can be accurately staged by sentinel lymph node biopsy (SLNB) alone and the use of dual tracers and removal of at least three sentinel nodes provides a clinically acceptable false negative rate (FNR) of <10%, while placing a clip in the biopsy proven node and removing it at surgery further reduces the FNR (6). Beyond surgical advantages, neoadjuvant systemic therapy provides important prognostic information. A pooled analysis of 12 neoadjuvant trials involving almost 12,000 patients showed that on an individual patient level a pathological complete response (pCR) defined as no residual invasive tumor in the breast or lymph nodes was significantly associated with event free survival (EFS) and OS (7). This association was strongest in patients with human epidermal growth factor receptor-2 (HER-2) positive and triple negative (TN) tumors compared to hormone receptor (HR) positive tumors. While pCR is dichotomous, a graded index known as the residual cancer burden (RCB) has also been shown to be prognostic of long term survival (8) with pCR classified as RCB-0, minimal residual disease as RCB-1, moderate residual disease as RCB-2 and extensive residual disease as RCB-3 (9). This index has also been shown to be continuously prognostic independent of other clinicopathological variables for 10-year relapse free survival in all 3 breast cancer subtypes, with a greater prognostic impact in the TN and HER-2 positive subtypes (8). The prognostic insight provided by pCR has been translated into positive postoperative treatment escalation studies using residual disease to predict which patients may benefit from additional postoperative systemic therapy (10,11). The primary surgical and oncological advantages of neoadjuvant systemic treatment are shown in *Table 1*. Ancillary advantages of neoadjuvant treatment include increased time for genetic testing and consideration of reconstructive or prophylactic surgical options prior to breast surgery. Despite the adoption of a multidisciplinary approach to the treatment of early breast cancer, for many patients it is still unclear who stands to benefit most from a neoadjuvant approach, limiting its clinical implementation. In this review we aim to provide all clinicians involved in the treatment of early breast cancer with a comprehensive assessment of the role of neoadjuvant systemic therapy in HR positive, HER-2 positive and TN breast cancer, focusing on patient selection, surgical and oncological benefits, and future directions. We present the following article in accordance with the Narrative Review reporting checklist (available at https://abs.amegroups.com/article/view/10.21037/abs-21-109/rc).

Methods

We performed a search of the PubMed, Cochrane Review, and Clinical Trials.gov databases. Only English language publications were included. The search terms were as follows: "neoadjuvant chemotherapy" AND "breast cancer". We conducted a thorough manual review of all bibliographies and relevant studies to identify additional potentially eligible studies (*Table 2*).

HER-2 positive breast cancer

Anti-HER-2 therapy administered with chemotherapy in patients with HER-2 positive breast cancer has led to a significant reduction in tumor recurrence and death, and when given preoperatively, is associated with high rates of pCR (12,13). Nevertheless, not all patients require such intensive treatment and de-escalation of anti-HER-2 targeted therapies and chemotherapy in appropriately selected populations has been an area of increased research. Currently, patients with stage 1 HER-2 positive breast cancer have excellent outcomes with adjuvant single agent paclitaxel and trastuzumab (14) and unless breast tumor downstaging is required to optimize surgery these patients do not require neoadjuvant treatment. Neoadjuvant treatment can be considered in all medically fit patients with stage 2 or 3 HER-2 positive breast cancer regardless of their pretreatment eligibility for BCS as their response to

Table 1 Goals of neoadjuvant systemic treatment

1. Improve patient DFS and OS similarly to adjuvant therapy
2. Improve surgical outcomes (breast conservation rates, spare axillary dissection)
3. Provide prognostic information
4. Enable escalation or de-escalation of postoperative systemic treatment

DFS, disease-free survival; OS, overall survival.

neoadjuvant treatment may affect postoperative treatment decisions (15).

Pivotal trials

The adjuvant NSABP B-31/NCCTG-N9831 trials demonstrated that the addition of one year of trastuzumab to anthracycline/taxane based chemotherapy resulted in a 40% reduction in breast cancer recurrences and a 37% reduction in mortality (12). Following the success of trastuzumab in the adjuvant setting, phase 2 trials showed impressive pCR rates in the neoadjuvant setting in patients with stage 2 and 3 HER-2 positive breast cancer treated with trastuzumab and chemotherapy (15-17). In the phase 3 NOAH (Neoadjuvant Herceptin) trial the addition of trastuzumab to chemotherapy yielded a response rate of 81% and a significantly superior pCR rate compared to chemotherapy alone (13) translating into a 36% relative improvement in 5-year EFS (18). The HER-2 dimerization inhibitor pertuzumab further improved outcomes when incorporated into both neoadjuvant and adjuvant trastuzumab/chemotherapy regimens and received accelerated approval in the neoadjuvant setting based largely on data from the phase 2 NeoSphere trial (19,20). This trial compared pCR rates between docetaxel/trastuzumab/pertuzumab (THP), docetaxel/trastuzumab (TH), docetaxel/pertuzumab (TP) and trastuzumab/pertuzumab (HP) in patients with stage 2 or 3 HER-2 positive breast cancer. All patients received additional anthracycline-based chemotherapy after surgery, regardless of response. Among arms, the THP combination was superior and demonstrated a pCR rate of 46%. Notably, even with the combination of trastuzumab and pertuzumab, without chemotherapy, 17% of patients experienced pCR, suggesting that for selected patients, treatment may potentially be de-escalated to exclude chemotherapy (20). To spare patients the potential long-term cardiac and myelotoxicity of anthracycline based regimens, the phase 2 TRYPHAENA trial examined the safety and efficacy of the anthracycline-free regimen TCHP (docetaxel, carboplatin, trastuzumab, pertuzumab) (21). This combination yielded a pCR rate of 66% with fewer declines in left ventricular ejection fraction compared to the anthracycline-based regimens. Further evidence supporting the use of an anthracycline-free regimen comes from the phase 3 TRAIN-2 trial demonstrating that a neoadjuvant platinum/taxane based regimen in combination with trastuzumab and pertuzumab provides equivalent 3-year EFS rates compared to a traditional anthracycline containing regimen (22). Overall, these pivotal neoadjuvant trials in HER-2 positive breast cancer show that between 50–80% of patients with HER-2 positive tumors will experience pCR following NACT with dual anti-HER-2 blockade and approximately 90% of patients who experience pCR will remain disease free 4 years after surgery (23).

Postoperative/adjuvant treatment escalation

Despite the significant improvements described above, between 20–50% of patients do not experience pCR. This patient population is at a higher risk for disease recurrence and death (HR with pCR, EFS: 0.39, 95% CI: 0.31–0.5; OS: 0.34, 95% CI: 0.24–0.47) (7) and thus warrants modification of the postoperative adjuvant therapy. The phase 3 KATHERINE trial randomized 1,486 HER-2 positive patients with residual disease following NACT and trastuzumab (approximately 18% in each arm received pertuzumab as well) to either standard adjuvant trastuzumab or T-DM1 [an antibody drug conjugate of trastuzumab (T) and the cytotoxic agent emtansine (DM1)] to complete 1 year of treatment. Patients receiving T-DM1 experienced a significant reduction in 3-year invasive disease-free survival (iDFS) (88.3% *vs.* 77%, P<0.001) (11). Given the results of this trial, neoadjuvant treatment in HER-2 positive breast cancer is now indicated not only to improve surgical outcomes and provide prognostic information, but also to predict a benefit for switching treatment from trastuzumab to T-DM1 in the postoperative setting. While the seminal neoadjuvant trials included only patients with stage 2 or 3 breast cancer the KATHERINE trial also included a small number of patients with stage 1 disease, suggesting a potential benefit of neoadjuvant treatment in this population as well. In the final efficacy results of the ExteNET trial which examined the role of 1 year of adjuvant treatment with the pan-HER tyrosine kinase inhibitor neratinib after one year of trastuzumab; among

Table 2 Narrative review search methods

Items	Specification
Date of search	July 2021 repeated March 2022 for updated data
Databases and other sources searched	PubMed, Cochrane Review, Clinical Trials.gov
Search terms used	Neoadjuvant chemotherapy and breast cancer
Timeframe	From July 1997 to February 2022
Inclusion and exclusion criteria	English only
Selection process	Selection conducted by all authors together
Additional considerations	A manual review of bibliographies identified additional relevant studies; newly published data was updated during the manuscript writing process

295 HR positive patients with residual disease post-NACT, one year of neratinib resulted in a 9.1% improvement in 8-year OS (91.3% *vs.* 82.2%, P=0.031) (24). These results are yet another example of how a HER-2 targeted agent can be personally tailored to improve patient outcomes based on their response to neoadjuvant treatment.

De-escalating treatment

As described, some patients have excellent responses to anti-HER-2 antibodies with single agent chemotherapy or without chemotherapy altogether, setting the stage for potential strategies for de-escalation of toxic chemotherapy in the neoadjuvant setting. The patient sub-groups that benefit from de-escalation still need to be defined (see biomarker discussion below). The ongoing Compass and Decrescendo trials are examining whether single agent taxane plus dual HER-2 inhibition with THP given for 4 cycles will be sufficient in patients who experience pCR (25,26). Patients with residual disease at surgery will receive adjuvant T-DM1 ± additional chemotherapy per investigator's choice. The KRISTINE trial which randomized 444 patients with stage 2–3 HER-2 positive breast cancer to 6 cycles of neoadjuvant T-DM1 with pertuzumab or TCHP showed inferior pCR rates and increased rates of locoregional progression before surgery with T-DM1 (27). With the results of this trial, the use of T-DM1 in the neoadjuvant setting has not been incorporated into standard clinical practice.

Biomarkers for response

De-escalation strategies should optimally rely on biomarkers for response to the targeted treatment. One possible biomarker is HR negativity as it is consistently correlated with superior pCR rates in HER-2 positive breast cancer (*Figure 1*). For example, in NeoSphere patients with HR negative disease treated with THP or the chemotherapy free HP combination had pCR rates of 63% and 27% respectively (20). In TRYPHAENA, HR negative patients receiving TCHP had a pCR rate of 83% compared to 50% among those with HR positive tumors (12). Lastly, in the phase 2 West German Study Group (WSG) ADAPT trial HER-2 positive HR negative patients were randomized to trastuzumab with pertuzumab ± paclitaxel. For the 42 patients receiving paclitaxel with trastuzumab and pertuzumab the pCR rate was 90.5% (28). Another potential predictor of response to anti-HER-2 treatment is intratumoral HER-2 heterogeneity. Filho *et al.* explored the role of intratumoral HER-2 heterogeneity in a single arm phase 2 trial of neoadjuvant T-DM1 with pertuzumab (29). Patients were biopsied in 2 different areas of the tumor with 3 cores taken from each area. Intratumoral HER-2 heterogeneity was defined as at least one of the six cores demonstrating either HER-2 positivity by flourescence in situ hybridization (FISH) in >5% and <50% of tumor cells or an area of tumor that tested HER-2 negative. Among 164 patients enrolled, none of the patients with HER-2 heterogenous tumors experienced pCR, suggesting that these patients may not be appropriate candidates for omission of chemotherapy. Molecular subtyping may also provide additional predictive information; in the phase 2 PAMELA trial 151 patients with HER-2 positive stage 1–3 breast cancer were treated with dual anti HER-2 blockade using lapatinib and trastuzumab for 18 weeks and the association between molecular subtype as defined by the PAM50 assay and pCR was evaluated (30). In this study 101/151 (67%) of the HER-2 positive patients were of the HER-2 enriched subtype. Notably 41% of these had pCR at surgery while 10% of the

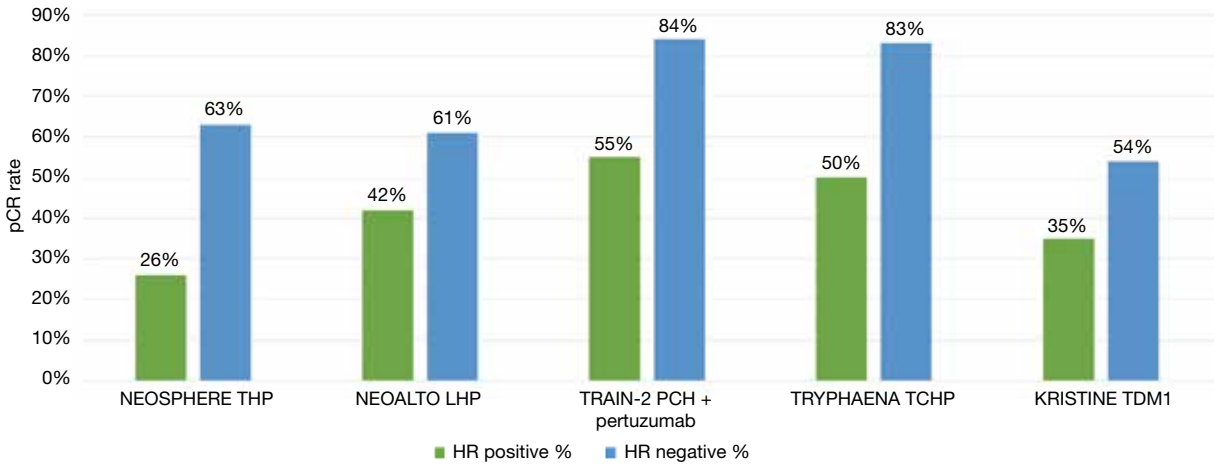

Figure 1 pCR rates in major trials of neoadjuvant dual HER2 inhibition by HR status. THP, docetaxel, trastuzumab, pertuzumab; LHP, lapatinib, trastuzumab, pertuzumab; PCH, paclitaxel, carboplatin, trastuzumab; TCHP, docetaxel, carboplatin, trastuzumab, pertuzumab; TDM-1, trastuzumab emtansine; HR, hormone receptor; pCR, pathological complete response.

non-HER-2 enriched tumors showed a pCR.

While these biomarkers are promising, until large randomized trials provide definitive evidence that certain populations can be spared multiagent chemotherapy without compromising long term outcomes, patients with HER-2 positive breast cancer undergoing neoadjuvant treatment should receive standard anthracycline based or platinum/taxane based chemotherapy combined with dual anti HER-2 inhibition with trastuzumab and pertuzumab (15).

Triple negative breast cancer (TNBC)

HR negative and HER-2 negative breast cancer known as TNBC composes approximately 15% of all cases of breast cancer, is more commonly diagnosed in women younger than 40 years and is considered to be more aggressive with worse prognosis (31,32). NACT may be offered to all chemotherapy eligible TNBC patients with tumors above 2 cm or positive lymph nodes, regardless of BCS eligibility (15). A pCR following NACT is of particular significance in TNBC as the association between long-term outcomes is strongest in this patient population (HR for EFS with pCR 0.24, 95% CI: 0.18–0.33) (7).

Historically anthracycline/taxane based regimens have been preferred in the treatment of TNBC (32). In the adjuvant setting in the combined analysis of the Anthracycline in Breast Cancer (ABC) trials the anthracycline-free regimen of docetaxel and cyclophosphamide (TC) was found to be inferior to standard anthracycline/taxane based chemotherapy, particularly for patients with TNBC or positive lymph nodes, reinforcing the continued role of anthracyclines in TNBC (33). In contrast in the WSG Plan B study adjuvant TC was found to be noninferior to a standard anthracycline/taxane regimen regardless of HR expression or lymph node status (34). In the neoadjuvant setting, there are some data suggesting that a taxane/platinum combination may provide similar pCR rates to the anthracycline/taxane based regimens. Sharma *et al.* (35) reported that pCR rate was 55% following NACT with docetaxel and carboplatin concluding that this regimen yields promising efficacy. Further support is seen in the phase 2 NeoSTOP trial where patients randomized to receive 6 cycles of docetaxel and carboplatin demonstrated an identical pCR rate as those that received 4 cycles of paclitaxel and carboplatin followed by 4 cycles of doxorubicin and cyclophosphamide (36). However, large neo-adjuvant trials comparing these regimens with EFS as an endpoint are lacking. Thus, anthracycline containing NACT regimens remain the standard in TNBC. For patients who are not eligible for anthracyclines due to a history of cardiac disease or major risk factors for cardiac toxicity the use of an anthracycline free regimen may be warranted.

The order and nature of the taxane

It appears that the sequence of treatment does not matter and the anthracyclines can either be followed or preceded by a taxane (37). In addition, there is no overwhelming evidence

that the nature of the taxane influences outcomes (38). In the adjuvant setting weekly or every 2 weeks solvent based paclitaxel appears to have the most efficacy (38,39) While nab-paclitaxel (nanoparticle albumin bound paclitaxel) has shown superiority to solvent-based paclitaxel in some studies, others have failed to show a significant difference. GeparSepto demonstrated improved pCR with nab-paclitaxel compared to paclitaxel in all breast cancer subtypes including TNBC (pCR entire cohort 38.4% *vs.* 29%, P=0.00065, TNBC 48% *vs.* 26%, P=0.00027) (40). This improvement in pCR translated to a significantly improved 4-year iDFS (41). In contrast, the ETNA trial which also compared these 2 taxanes in the neoadjuvant setting failed to show a significant difference in pCR rates (42).

Addition of carboplatin

The addition of carboplatin to standard anthracycline/taxane based NACT in TNBC is controversial. A meta-analysis of 9 randomized clinical trials including 2,109 patients found that the addition of platinum increased pCR rates significantly from 37% to 52.1% (P<0.001) with an increase in hematological toxicity (43). While effectively increasing pCR, its effect on long-term outcomes is uncertain. In GeparSixto the addition of carboplatin to the anthracycline/taxane backbone significantly improved pCR rates (53.2% *vs.* 36.9%, P=0.005) translating into an improvement in 3-year DFS (86% *vs.* 76%, P=0.022) (44,45). In contrast the addition of carboplatin to doxorubicin and paclitaxel in CALGB 40603 provided similar improvements in pCR yet failed to demonstrate an improvement in DFS (46,47). Notably, in GeparSixto patients with germline BRCA1/2 mutations did not experience improvements in pCR from the addition of carboplatin with exceptional pCR rates irrespective of carboplatin treatment (48). While current guidelines allow for the consideration of carboplatin as part of the neoadjuvant treatment of TNBC (15), the lack of definitive data demonstrating its effect on long term outcomes has prevented it from becoming a standard of care worldwide.

Addition of immune checkpoint inhibitors

Programmed cell death 1 (PD-1) is a transmembrane protein expressed on T cells, B cells, and NK cells. This protein binds to PD-1 ligand (PD-L1) and has an inhibitory effect, particularly on cytotoxic T cells (49). PD-L1 is expressed on the surface of multiple tissue types, including tumor cells and tumor infiltrating immune cells (50). Inhibition of the interaction between PD-1 to PD-L1 may restore the ability of T cells to identify and attack cancer cells (49). Various immune check point inhibitors (CPI) inhibiting PD-1 (pembrolizumab, nivolumab) or PD-L1 (atezolizumab, avelumab, durvalumab) have been approved for use in various tumor types. TNBC is considered the most immunogenic of all the breast cancer subtypes (51) and in the metastatic setting the combination of a CPI with chemotherapy has been shown to improve progression free survival (PFS) and OS in patients expressing PD-L1 on tumor cells or tumor infiltrating immune cells (52,53).

The beneficial role of the addition of CPI to NACT in TNBC is currently unfolding. The phase 3 KEYNOTE-522 trial examined the effect of adding pembrolizumab to an anthracycline/taxane based regimen including carboplatin in the neoadjuvant setting. At the first interim analysis the addition of pembrolizumab showed a 13.6% improvement in pCR (64.8% *vs.* 51.5%, P=0.00055) (54). A recently reported analysis of 3-year EFS demonstrated a significant improvement in favor of patients who received pembrolizumab (84.5% *vs.* 76.8%, P=0.00031) (55). In an exploratory subgroup analysis based on response to neoadjuvant treatment, patients who experienced pCR in both groups had excellent 3-year EFS outcomes [94.4% *vs.* 92.5%, P value not reported (NR)] while the patients who did not experience pCR appeared to derive a clinically significant benefit from the addition of pembrolizumab to the NACT regimen (3-year EFS: 67.4% *vs.* 56.8%, P value NR) (55). Based on these latest results the FDA has recently approved the use of pembrolizumab combined with NACT for neoadjuvant treatment of high risk TNBC. The phase 3 IMpassion031 trial examined the effect of adding atezolizumab to anthracycline/taxane based NACT without carboplatin. The addition of atezolizumab significantly increased pCR by 17% (58% *vs.* 41%, P=0.0044). EFS and OS results are immature (56). Smaller phase 2 trials have shown mixed results with CPI in the neoadjuvant setting. Both NeoTRIPaPDL1 which examined the addition atezolizumab to NACT and GeparNuevo which examined the addition of durvalumab to NACT did not demonstrate a statistically significant improvement in pCR (57,58), however the long term results of the GeparNuevo trial demonstrated a significant improvement in both DFS and OS despite the modest improvement in pCR (59). Thus, while pCR rates are highly correlated to prognosis after NACT treatment the correlation of pCR with neoadjuvant CPI treatment is not as clear. Importantly, CPI treatment may be associated with potentially severe and sometimes

long-term toxicity, particularly endocrinopathies requiring lifelong medication (60). As more long-term results become available in the next year, we expect that CPIs will be regularly incorporated into the neoadjuvant treatment regimens of TNBC.

Addition of poly-ADP-ribose polymerase (PARP) inhibitors

Up to 20% of patients with TNBC harbor a germline BRCA1/2 mutation (61). Carriers of deleterious BRCA1/2 mutations lose expression or function of BRCA1/2 proteins in cancer cells resulting in damage to the homologous DNA repair mechanism responsible for repairing double strand DNA breaks (62). The PARP are key players in repair of DNA single strand breaks (63). PARP inhibitors (PARPi) promote death of BRCA deficient cells by a "synthetic lethality" mechanism. These drugs prevent repair of single DNA strand breaks eventually causing accumulation of double strand breaks. In tumors without proper function of BRCA proteins these double strand breaks cannot be repaired causing death of the cancer cells (64).

PARPi are used in the treatment of metastatic breast cancer patients who carry a germline BRCA 1/2 mutation where they improved PFS (65,66) and possibly OS when used in first line (67). Recently, the phase 3 Olympia trial demonstrated that 1 year of adjuvant Olaparib significantly improves 3-year DFS (85.9% *vs.* 77.1%, P<0.001) in germline BRCA1/2 mutant breast cancer patients with at least stage 2 tumors that did not receive NACT or did not experience pCR following NACT (68).

The role of PARPi in the neoadjuvant setting is currently being explored. The adaptive phase 2 ISPY2 trial demonstrated that adding carboplatin and the PARPi veliparib to standard anthracycline/taxane NACT improved pCR compared to the standard anthracycline/taxane alone in patients with TNBC (51% *vs.* 26%, P value NR) (69). These results led to the phase 3 BrighTNEss trial which randomized 634 patients (15% germline BRCA 1/2 mutation) to either neoadjuvant paclitaxel plus carboplatin plus veliparib, paclitaxel plus carboplatin or paclitaxel alone. After receiving one of these three regimens all patients received 4 cycles of anthracycline based treatment. While both the carboplatin-veliparib combination and carboplatin monotherapy arms achieved increased pCR rates compared to paclitaxel alone, the addition of veliparib failed to improve pCR beyond that of carboplatin alone (70); suggesting that PARPi may not have a role in the neoadjuvant setting in patients already receiving a platinum agent. In a small study by Litton *et al.* (71) 10 out of 19 (53%) patients carrying germline BRCA 1/2 mutations who received single agent talazoparib for 6 months had a pCR. In the phase 2 NEOTALA study of 48 evaluable TNBC patients with germline BRCA1/2 mutations 45.8% demonstrated a pCR after 24 weeks of talazoparib treatment (72). These data are promising and various larger clinical trials using neoadjuvant PARPi as single agents or in combination with CPIs are planned. Use of neoadjuvant PARPi outside of clinical trials is currently not recommended.

The pCR rates for the major TNBC neoadjuvant trials are summarized in *Table 3*.

Post-operative treatment for patients not achieving pCR

The CREATE-X trial randomly assigned 910 patients with HER-2-negative residual invasive breast cancer after NACT to postsurgical treatment with capecitabine or placebo. Among patients with TNBC, the addition of capecitabine significantly improved DFS and OS (10). Similar to the KATHERINE trial in HER-2 positive patients (11) and Olympia in germline BRCA1/2 related breast cancer (68), CREATE-X demonstrated how postoperative treatment can be tailored to improve outcomes based on the response to NACT in TNBC.

HR positive breast cancer

NACT

While chemotherapy in HER-2 positive and TNBC is routinely used, the decision to administer NACT in HR positive breast cancer is more complex, as many patients are not expected to derive a significant survival benefit from chemotherapy (73). While it has been reported that following NACT over 70% of HR positive patients have a clinical and pathological response in the breast and up to 21.1% have been shown to have a complete pathological axillary response (74), it is still unclear which patients will be able to avoid mastectomy or the sequelae of an ALND (75) after NACT. The pCR rates are very low, with an expected rate of less than 10% in low grade tumors and less than 20% in high grade tumors (7). Moreover, the prognostic value of pCR in HR positive disease is questionable, especially in low grade luminal A like disease [defined clinically as high estrogen receptor (ER) and progesterone receptor (PR) levels, negative HER-2 and Ki-67 <15%] indicating a need for better pathologic response measures

Table 3 pCR rates in major neoadjuvant trials in TNBC

Study	Study design	pCR	Treatment arms	Number of TNBC patients	pCR	P value	DFS/EFS	P value
GeparSixto (44,45)	Phase II	ypT0pN0	P + Dox + Bev + Cb	158	53.2%	0.005	86.1%	0.0224
			P + Dox + Bev	157	36.9%		75.8%	
CALGB 40603 (46,47)	Phase II	ypT0/is	P + Cb → ddAC ± Bev	221	60%	0.0018	NR	
			P → ddAC ± Bev	212	46%		NR	
Keynote 522 (54,55)	Phase III	ypT0/TisypN0	Pembrolizumab + P + Cb → AC	784	64.8%	<0.001	84.3%	0.0003
			Placebo + P + Cb → AC	390	51.2%		76.2%	
IMpassion031 (56)	Phase III	ypT0/is ypN0	Atezolizumab + NabP → AC	165	58%	0.0044	Immature	
			Placebo + NabP → AC	168	41%		Immature	
GeparNuevo (58,59)	Phase II	ypT0 ypN0	Durvalumab + NabP → EC + durvalumab	88	53.4%	0.224	85.6%	0.0398
			Placebo + NabP → EC + placebo	86	44.2%		77.2%	
BrighTNess (70)	Phase III	ypT0pN0	P + Cb + veliparib → AC	316	53%	0.36*	78%	
			P + Cb + placebo → AC	160	58%	<0.001**	79%	
			P + placebo → AC	158	31%		69%	0.02

*, P + Cb + veliparib *vs.* P + Cb; **, P + Cb + veliparib *vs.* P + placebo. pCR, pathological complete response; TNBC, triple negative breast cancer; DFS, disease-free survival; EFS, event free survival; P, paclitaxel; Dox, doxorubicin; Bev, bevaciumab; Cb, carboplatin; dd, dose dense; AC, adriamycin-cyclophosphamide; NR, not reported; NabP, nabpaclitaxel; EC, epirubicin + cyclophosphamide.

of neoadjuvant treatment in this patient population (76). Efforts have been made to define HR positive subgroups that will derive benefit from NACT. Gene expression profiles such as Oncotype Dx and MammaPrint, commonly used to support adjuvant chemotherapy decision-making in HR positive breast cancer are being explored in the neoadjuvant setting. There is a growing amount of evidence showing the concordance of gene expression profiles derived from preoperative core needle biopsies to surgical specimens (77,78) and their ability to potentially predict response to neoadjuvant systemic therapies (*Tables 4-6*) (79-94). For instance, in the NACT portion of the WSG ADAPT trial, Oncotype Dx recurrence scores (RS) performed on presurgical biopsies were predictive of pCR (82). While pCR rates were low overall, patients with an RS >25 had a significantly higher pCR rate than patients with an RS ≤25 (16.1% *vs.* 7.2%, P=0.006). This difference was most evident amongst premenopausal patients (17.2% *vs.* 4.8%, P=0.03) while the difference among postmenopausal patients was not significant (15.2% *vs.* 12.2%, P=0.8). Therefore, if a patient has a preoperative genomic risk score predicting long term benefits from chemotherapy it may be reasonable to administer NACT particularly if tumor or axillary downstaging is required to improve surgical outcomes. Notably, while gene expression profiles may be used in the clinic to guide clinical decision making regarding NACT (95) current guidelines do not recommend their routine use in this setting (15).

Neoadjuvant endocrine treatment (NET)

For post-menopausal HR positive patients in need of surgical downstaging who are either not candidates or are not predicted to benefit from chemotherapy, another option is NET. Currently, due to a limited amount of data in premenopausal patients, NET should not be regularly recommended in this patient population. Although pCR is rarely achieved with NET, clinical response rate (CRR) and BCS rates, while varying between trials, appear to be comparable to NACT and with less toxicity (96).

The pivotal trials in NET have demonstrated the superiority of aromatase inhibitors (AIs) over tamoxifen

Table 4 Neoadjuvant oncotype studies with 11 and 25 RS cutoffs

Author	Gene expression profile	Study type	Patient population	Number of patients	Treatment	Endpoints	Low risk <11	Low risk <25	Intermediate risk 11–25	High risk >25	P value
Morales Murillo *et al.* 2021 (79)	Oncotype Dx	Prospective	HR pos HER2 neg	60	NACT NS	RCB 0/1	NA		PostMp: 6.7%, PreMp: 0%, RS (11–20)	PostMp: 52.6%, PreMp: 42.9%, RS >20	NA
Bear *et al.* 2017 (80)	Oncotype Dx	Prospective	HR pos HER2 neg	64	Anthracycline/ taxane NACT or ET	CRR, BCS, pCR	ET: 83.3%, 75%, 0%		ET: 50%, 72.2%, 0%, CT: 72.7%, 63.6%, 0%	CT: 92.9%, 57.1%, 14.3%	0.049, NA, NA
Sella *et al.* 2021 (81)	Oncotype Dx	Retrospective	HR pos HER2 neg age <40	76	Anthracycline/ taxane NACT	pCR		5%		21%	0.09
Kuemmel *et al.* 2020 (82)	Oncotype Dx	Prospective	HR pos HER2 neg	864	Anthracycline/ taxane NACT	pCR		7%, PostMp: 12.2%, PreMp: 4.8%		16%, PostMp: 15.2%, PreMp: 17.2%	0.006, 0.8, 0.003
Thekkekara *et al.* 2019 (83)	Oncotype Dx	Retrospective	HR pos HER2 neg	110	NACT NS	CRR, pCR		32.5%, 0%		81.4%, 16%	NA, NA

RS, recurrence score; HR, hormone receptor; pos, positive; neg, negative; NACT, neoadjuvant chemotherapy; NS, nonsignificant; RCB, residual cancer burden; NA, not available; PostMp, postmenopausal; PreMp, premenopausal; ET, endocrine therapy; CRR, clinical response rate; BCS, breast conserving surgery; pCR, pathological complete response; CT, chemotherapy.

in terms of response rates and surgical outcomes. P024 randomized 337 postmenopausal BCS-ineligible patients to 4 months of NET with letrozole or tamoxifen (97) with superior CRRs (55% *vs.* 36%, P<0.001) and BCS rates (45% *vs.* 35%, P=0.022) associated with the letrozole. In PROACT, 451 postmenopausal patients were randomized to 12 weeks of preoperative anastrozole or tamoxifen (98) with concomitant chemotherapy allowed. Among the 262 patients treated with NET alone and ineligible for upfront BCS the CRR was significantly superior with anastrozole (49% *vs.* 36%, P=0.04). There were no significant differences in BCS between the two groups (38% *vs.* 30%, P=0.11). PROACT also provided data on axillary downstaging. Amongst the 201 patients with node positive disease, 43.4% of patients in the letrozole group and 38.5% of patients in the tamoxifen group experienced clinical downstaging of the axilla. To date there are limited prospective data regarding the approach to the axilla following NET with retrospective data indicating between a 10–15% axillary pCR rate (99). The IMPACT trial randomized 330 postmenopausal patients to 12 weeks of preoperative anastrozole, tamoxifen or the combination (100). CRRs were similar between groups and amongst the 124 patients initially ineligible for BCS, 44% of those treated with anastrozole had BCS compared with 31% receiving tamoxifen (P=0.23). Additionally, the rate of patients deemed eligible by their surgeons for BCS were significantly higher following anastrozole than tamoxifen or the combination (46%, 22% and 26% respectively, P=0.03). This study also provided early biomarker data as higher levels of ER were shown to correlate with response. Additionally, tumor cell proliferation as measured by a decrease in Ki-67 levels 2 weeks following treatment was significantly improved in the anastrozole group (101) and was associated with improved recurrence free survival (102).

NACT vs. NET

The largest trial comparing NACT to NET randomized 239 postmenopausal women to NET with an AI (exemestane or anastrozole) or to NACT with doxorubicin and paclitaxel (103). CRRs were 64% in both the NET and chemotherapy arms, pCR rates were low in both arms (3% and 6% respectively) and there was a non-statistically significant numerical difference in BCS rates in favor of NET (33% *vs.* 24%, P=0.058). Kim *et al.* (104) randomized

Table 5 Neoadjuvant oncotype studies with 18 and 30 RS cutoffs

Author	Gene expression profile	Study type	Patient population	Number of patients	Treatment	End points	Low risk <18	Intermediate risk 18–30	High risk >30	P value
Pardo *et al.* 2021 (84)	Oncotype Dx	Retrospective	HR pos HER2 neg	158	NACT not specified	Axillary pCR	10.7%	9.7%	27.5%	0.0268
Iwata *et al.* 2019 (85)	Oncotype Dx	Prospective	HR pos HER2 neg	295	Letrozole	CRR, BCS	54%, 79%	42%, NA	22%, 60%	<0.001, 0.009
Pivot *et al.* 2015 (86)	Oncotype Dx	Prospective	HR pos HER2 neg	81	Anthracycline/ taxane NACT	pCR	0%	6.2%	8.6%	0.004
Yardley *et al.* 2015 (87)	Oncotype Dx	Prospective	HER2 neg	108	Ixabepilone/ cyclophosphamide	pCR	0%	0%	17% (HR neg) 31% (HR pos)	0.002
Ueno *et al.* 2014 (88)	Oncotype Dx	Prospective	HR pos	64	Exemestane	CRR	59.4%	58.8%	20%	0.015
Akashi-Tanaka *et al.* 2009 (89)	Oncotype Dx	Prospective	HR pos	43	Tamoxifen or anastrazole	CRR	64%	31%	31%	0.11
Chang *et al.* 2008 (90)	Oncotype Dx	Prospective	Locally advanced all subtypes	97	Docetaxel	CRR	0%	NA	21.4%	NA

RS, recurrence score; HR, hormone receptor; pos, positive; neg, negative; NACT, neoadjuvant chemotherapy; pCR, pathological complete response; BCS, breast conserving surgery; CRR, clinical response rate; NA, not available.

Table 6 Additional neoadjuvant gene expression profile studies

Author	Gene expression profile	Study type	Patient population	Number of patients	Treatment	End points	Low risk	Intermediate risk	High risk	P value
Dubsky *et al.* 2020 (91)	Endopredict	Retrospective	HR pos HER2 neg	134	Anthracycline/ taxane NACT ± tecemotide	RCB 0/1	0%	NR	26.4%	0.112
Dubsky *et al.* 2020 (91)	Endopredict	Retrospective	HR pos HER2 neg	83	Letrozole ± tecemotide	RCB 0/1	27.3%	NR	7.7%	
Whitworth *et al.* 2017 (92)	Mammaprint/ Blueprint	Prospective	HR pos HER2 neg	474	Anthracycline/ taxane NACT	pCR	2%	NR	13%	0.001
Mathieu *et al.* 2012 (93)	BCI	Retrospective	All subtypes	150	Anthracycline/ taxane NACT	pCR, BCS	1.6%, 14%	21%, 46%	29%, 44%	0.0001, 0.0002
Straver *et al.* 2010 (94)	Mammaprint	Retrospective	All subtypes	167	Anthracycline/ taxane NACT ± trastuzumab	pCR	0%	NR	20%	0.015

HR, hormone receptor; pos, positive; neg, negative; NACT, neoadjuvant chemotherapy; RCB, residual cancer burden; NR, not reported; pCR, pathological complete response; BCI, breast cancer index; BCS, breast conserving surgery.

187 premenopausal women to anthracycline/taxane based NACT or NET with goserelin and tamoxifen with the primary endpoint of CRR at 24 weeks. While there were no differences in BCS (13.8% *vs.* 11.5%, P=0.531), patients receiving NACT had a significantly better CRR (84% *vs.* 71%, P=0.046). In GEICAM/2006-03, 95 patients, 51 of

which were premenopausal, were randomized to NET with exemestane (+ goserelin if premenopausal) or NACT (105). Similarly, premenopausal women experienced significantly greater CRR to NACT (75% *vs.* 44%, P=0.027), while no difference was seen among post-menopausal women (57% *vs.* 52%, P=0.78). The pCR rates were exceptionally low in both groups (NACT: 2%, NET: 0%) and there were no differences in BCS or axillary nodal status after surgery.

Potential biomarkers of response to NET

With pCR being a rare occurrence, data from the earlier NET trials supported the development of a distinct surrogate pathologic marker of response to NET known as preoperative endocrine prognostic index (PEPI) (106). This score was developed by analyzing post treatment factors associated with survival in P024 and independently validated in a cohort of patients from IMPACT. PEPI is based on the post-NET surgical specimen and calculated as the sum of points given to 4 categories: tumor size, nodal status, Ki-67 level, and ER expression. Patients with a PEPI of 0 (pT0/1, N0, Ki67 <2.7%, and positive ER), have very favorable outcomes without chemotherapy. In ACOSOG Z1031 377 postmenopausal patients were randomized to 16–18 weeks of NET with an AI (letrozole, anastrozole or exemestane) (107) with comparable CRR and BCS rates between arms. The PEPI score was a secondary endpoint and tumors were subtyped by a PAM-50 analysis. CRRs were 62.9%, 74.8% and 69.1% for exemestane, letrozole, and anastrozole, respectively. In patients designated as requiring a mastectomy before treatment 51% were subsequently able to undergo BCS, and 83% of patients who were considered marginal for breast conservation underwent BCS. There was no difference between CRR or BCS rates between luminal A and luminal B cancers, however significantly more patients with luminal A disease had a PEPI score of 0 (27.1% *vs.* 10.7%, P=0.004). At a median follow-up of 5.5 years, of 421 patients from Z1031 eligible for long-term analysis, 119 (25.9%) had a PEPI 0 response and only 4 (3.3%) recurrences were identified in this group as opposed to 49 (14.4%) in patients with a PEPI score >0 (108).

NET in premenopausal women

As discussed, 2 studies comparing NACT to NET showed a significantly greater CRR in premenopausal patients receiving NACT. The phase 3 STAGE trial randomized 197 premenopausal patients to 24 weeks of preoperative goserelin with anastrozole or tamoxifen (109). Patients in the anastrozole group had a CRR of 70.4% *vs.* 50.5% in the tamoxifen group (P=0.004). Despite this promising trial, data is still limited on the role of NET in this patient population and more studies are needed to properly identify premenopausal patients who are most likely to benefit from this treatment approach.

The main findings of the major NET trials are summarized in *Table 7*.

NET combined with CDK4/6 inhibitors

CDK4/6 inhibitors (abemaciclib, palbociclib, ribociclib) in combination with endocrine therapy have become a standard of care in metastatic HR positive breast cancer (110). Their role in the neoadjuvant/adjuvant setting is still under investigation. The NeoPAL study randomized 106 Prosigna defined luminal A or B stage 2 or 3 patients ineligible for BCS to either letrozole plus palbociclib or standard anthracycline and taxane based chemotherapy (111). The pCR rates were low in both arms (two patients in the palbociclib arm and three in the chemotherapy arm) and the CRRs and BCS rates were identical. The single arm NeoPalana trial (n=50) examined whether the addition of palbociclib to anastrozole increased the rate of complete cell cycle arrest (CCCA) defined as Ki67 <2.7% (112). CCCA was observed among 26% of patients following anastrozole as opposed to 87% after combined treatment (112). Similar improvements in CCCA were observed with abemaciclib in the neoMONARCH trial (113). Thus, while current data indicate that the addition of CDK4/6 inhibition may increase the antiproliferative effect of endocrine treatment and dramatically decrease Ki-67 expression, to date no study has shown an improvement in CRR or BCS rates which are the primary goal of NET. The optimal endpoint to neoadjuvant CDK4/6 trials and their effect on long term outcomes is also unclear. In the adjuvant setting, early results from the MonarchE study comparing adjuvant endocrine therapy with an AI with or without 2 years of abemaciclib in high risk patients showed a significant improvement in 2-year iDFS (114). In contrast two adjuvant trials using palbociclib failed to show an improvement in DFS (115,116). While promising, in the neoadjuvant setting these agents should currently only be used within a clinical trial.

Conclusions

Over the last two decades, we have come to understand

Table 7 Major NET trials

Trial	Year	Treatment arms	Patient population	Number of patients	CRR	BCS rate	P value (CRR, BCS rate)
Eiermann *et al.* (97)	2001	Letrozole *vs.* tamoxifen, 4 months	Post-menopausal, stage II/III, BCS ineligible	337	Letrozole =55%, tamoxifen =37%	Letrozole =45%, tamoxifen =35%	<0.001, 0.022
Cataliotti *et al.* (98)	2006	Anastrozole *vs.* tamoxifen ± CT, 12 weeks	Postmenopausal, tumor size >3 cm	262 (ET alone)	Anastrozole =49%, tamoxifen =36%	Anastrozole =38%, tamoxifen =30%	0.04, 0.11
Smith *et al.* (100)	2005	Anastrozole, tamoxifen or both, 3 months	Postmenopausal	330	Anastrozole =37%, tamoxifen =36%, combination =39%	Anastrozole =44%, tamoxifen =31%	0.87, 0.23
Semizaglov *et al.* (103)	2007	A + T *vs.* exemestane or anastrozole, 3 months	Post-menopausal, stage II/III	239	ET =64.5%, CT =63.6%	ET =33%, CT =24%	>0.5, 0.058
Kim *et al.* (104)	2020	AC-T *vs.* goserelin + tamoxifen, 24 weeks	Pre-menopausal, stage II/III	187	84%, 71%	13.8%, 11.5%	0.046, 0.531
Alba *et al.* (105)	2012	AC-T *vs.* exemestane ± goserelin, 24 weeks	Pre/post-menopausal, stage II/III	95	Premenopausal: ET =44%, CT =75%; postmenopausal: ET =52%, CT =57%	ET =56%, CT =47%	0.78, 0.2369
Ellis *et al.* (107)	2011	Anastrozole, letrozole, exemestane	Postmenopausal, stage II/III	377	Anastrozole =69%, letrozole =75%, exemestane =63%	Anastrozole =77%, letrozole =61%, exemestane =68%, 51% BCS ineligible underwent BCS in entire cohort	NA, NA
Masuda *et al.* (109)	2012	Goserelin + tamoxifen or anastrozole, 24 weeks	Premenopausal	197	Anastrozole =70%, tamoxifen =50%	Anastrozole =86%, tamoxifen =68%	0.004, NA

NET, neoadjuvant endocrine treatment; CRR, clinical response rate; BCS, breast conserving surgery; CT, chemotherapy; ET, endocrine therapy; A, doxorubicin; T, taxane; C, cyclophosphamide; NA, not available.

that neoadjuvant systemic therapy is as safe and effective as adjuvant therapy (2). In patients with operable breast cancer neoadjuvant therapy can be considered for all patients determined upfront to require systemic adjuvant treatment. If given preoperatively this treatment may improve surgical outcomes. In patients with TN and HER-2 positive tumors, neoadjuvant systemic therapy should also be considered not only for the improvement of surgical outcomes, but also for the prognostic and predictive information the response to treatment will provide. Neoadjuvant therapy also offers a window of opportunity to research novel biomarkers allowing for a more tailored approach to patient care. At present, the role of neoadjuvant systemic therapy in early breast cancer in both contemporary clinical practice and the research setting is continuing to develop with the likelihood that its applications will continue to expand, further emphasizing the importance of multidisciplinary communication to provide the best outcomes for our patients.

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Review Article

The development of autologous breast reconstruction and the impact of enhanced recovery after surgery (ERAS): a narrative review

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Background and Objective: Enhanced recovery after surgery (ERAS), or fast-track surgery, was first described almost 20 years ago as a peri- and postoperative care concept that aims to achieve a pain- and risk-free operation. Since then, many surgical specialties have embraced the concept, and it is widely accepted that enhanced recovery programs (ERPs) can be superior to conventional care for a wide range of surgical procedures, including microsurgical reconstructive procedures. However, many published ERAS protocols are complex and difficult to apply.

Methods: A literature search based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses was performed in PubMed, Embase and Web of Science for the period of 2000 till 2020. Only English language papers were included for consideration.

Key Content and Findings: We present an overview of ERAS in relation to autologous breast reconstruction (ABR), with selected recent data based upon personal ERAS experience of ABR with both deep inferior epigastric perforator (DIEP) flaps and latissimus dorsi (LD) flaps over the last 10 years. Based on our experience with ERAS in ABR we suggest using 9 core elements to successfully apply an ERAS protocol.

Conclusions: The concept of ERAS can and should be applied to ABR with both free (DIEP) and pedicled (LD) flaps. The goal is improved patient recovery with no increase in flap loss or complications. Length of stay can be safely reduced, with a typical discharge on postoperative day (POD) 3 after ABR. To achieve this, implementation of an ERAS protocol could focus on team effort, the 9 procedure-specific core elements, and the use of functional discharge criteria. Our ERAS protocol is no longer a research tool but the standard of care in ABR.

Keywords: Enhanced recovery; autologous breast reconstruction (ABR); core elements

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Introduction

Functional, social, and psychological rehabilitation are an essential part of breast cancer treatment. Even with breast-conserving surgery as an available alternative, many women with breast cancer still undergo a mastectomy.

More than 80% of the women so treated show interest in breast reconstruction after the initial treatment (1), and, with a 5-year survival rate of more than 85% (2), it has become an integrated part of breast cancer treatment. As the incidence of breast cancer is growing and the use of radiotherapy limits implant-based reconstruction, the demand for reconstructions using autologous tissue has

increased.

Autologous breast reconstruction (ABR) can be performed in both irradiated and nonirradiated patients. However, patients who have undergone radiotherapy should ideally have autologous reconstruction, as complication rates in irradiated patients are unacceptably high (3).

Either or both breasts can be reconstructed in the same procedure, and the reconstruction can be performed either at the time of the mastectomy or as a delayed procedure. The goal of the surgery is to remove the bothersome external prosthesis and, more importantly, to provide women with the feeling of wholeness, thus helping to alleviate the physiological and psychological trauma related to breast cancer (4). The importance of ABR for psychological well-being is well-documented, but whether it can offer additional benefits for pain, lymphedema, and other complaints is still being investigated.

The deep inferior epigastric perforator (DIEP) flap has been the gold standard in ABR for well over a decade. This perforator-based flap from the abdomen delivers the best possible tissue, allows for excellent shaping, and has very low complication rates. Flap survival is typically reported to be above 98%, and the treatment is well established worldwide (5-7). The musculocutaneous latissimus dorsi (LD) flap with a permanent implant is another workhorse in reconstructive plastic surgery. In our unit, it is a commonly used, safe, and viable alternative to the DIEP flap or other free flaps.

Enhanced recovery after surgery (ERAS), or fast-track surgery, was described almost 20 years ago as a peri- and postoperative care concept with the aim of achieving a pain- and risk-free operation (8). Since then, many surgical specialties have embraced the concept, and it is widely accepted that enhanced recovery programs (ERPs) can be superior to conventional care for a wide range of surgical procedures, including microsurgical reconstruction, and can provide substantial economic benefits (9-14). However, many published ERAS protocols are convoluted and difficult to apply.

Prior to the introduction of ERAS in plastic surgery, ABR was often seen as a complex procedure, and patients could expect a long postoperative hospital stay with a slow recovery.

In our initial paper, we demonstrated that the application of a simple, inexpensive, early ERAS protocol could reduce patient length of stay (LOS) by more than 1 day for those undergoing unilateral ABR with an abdominal flap. We did this by comparing the historical data from 292 patients [1994–2003] to that of 177 ERAS patients [2006–2011]. Applying an ERAS protocol significantly reduced LOS from 7.4 to 6.2 days (P=0.0002). In 2016, our established ERP setup for ABR with free abdominal flaps (15) was published. Analyzing 16 consecutive patients, we demonstrated a significant reduction in LOS: from 6.2 to 3.1 days (P<0.001). We have just published our 5-year follow-up of 147 unilateral ABRs with abdominal flap, in which a mean LOS of 3 days was achieved. In our department, ERAS is no longer a research tool but the standard of care in microsurgical breast reconstruction.

We here present an overview of ERAS, with recent data selected and based on our personal ERAS experience in ABR with DIEP flaps and LD flaps over the last 10 years. We present the following article in accordance with the Narrative Review reporting checklist (available at https://abs.amegroups.com/article/view/10.21037/abs-21-26/rc).

Methods

The search for the literature cited in this paper was conducted based on guidelines suggested by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. The search was performed by the main author as described in the *Table 1*.

ERAS: implementation and challenges

With millions of operations performed each year worldwide, postoperative complications remain a significant problem in the 21st century. The concept of ERAS, previously known as fast-track surgery, is a peri- and postoperative care concept first described in detail by Kehlet (8) in 1997. ERAS is based on identifying and adjusting important factors that contribute to the successful treatment of a surgical patient. ERAS is a multidisciplinary approach involving the surgeons, anesthesiologists, nurses, and physiotherapists as they manage patient treatment. ERAS standardizes and limits variation in postoperative patient care while providing a multimodal approach to controlling perioperative pathophysiology. It thereby mitigates the risk of organ dysfunction and enhances recovery. The goals of ERAS are to improve postoperative recovery and reduce perioperative risk, LOS, morbidity, and mortality, with the ultimate aim of achieving pain- and risk-free surgery (16). Several studies and meta-analyses comparing the ERAS concept with conventional care have been published in most surgical specialties, including orthopedic surgery, abdominal/hepatic surgery, and gynecology, and all clearly

Table 1 The search strategy summary

Items	Specification
Date of search	1 March 2021
Databases and other sources searched	PubMed, Embase, Web of Science
Search terms used	"ERAS", "enhanced recovery after surgery", "breast reconstruction", "postoperative care", "breast"
Timeframe	2000–2020
Inclusion and exclusion criteria	All types, English text only
Selection process	CB selected all references

show ERAS to be superior to traditional protocols (17). However, the literature on the use of ERAS in plastic surgery and microsurgical procedures is more limited. Nonetheless, evidence accumulated over the 5 years suggests that ERAS can improve postoperative recovery by shortening LOS and reducing medical complaints without increasing the risk of surgery-related complications and readmissions, even after major reconstructive procedures like ABR (18).

First introduced by Holmström in 1979, microsurgical breast reconstruction with use of a free abdominal flap has become a well-established practice (19). The procedure has since been modified and today is mostly performed as a perforator-based reconstruction (20), aided by computed tomographic or magnetic resonance angiograms (21-24). The musculocutaneous LD flap was described over a hundred years ago (25) and has been extensively used in ABR since the 1970s (26).

In 2015, we published one of the first reports of an ERP in microsurgery (27); in 2016, we published our final ERP setup for ABR with free abdominal flaps (15), which was followed by the publishing of our experience in applying the same protocol for ABR with LD flaps (18). We showed that by adhering to a few simple, easy-to-measure, functional discharge criteria (FDC), it was possible to safely discharge the patients by the third postoperative day (POD).

An important step in the popularization of ERAS was the establishment of the ERAS Society (28). In 2001, a group of surgeons formed the ERAS study group with the goal of developing perioperative care protocols. The ERAS study group subsequently established a nonprofit international society (the ERAS Society; http://www.erassociety.com/) to further develop the ERAS concept. In 2017, the ERAS Society endorsed a set of guidelines for breast reconstruction (29), which described 18 care elements in the pre-, peri-, and postoperative periods. These included minimal fasting, carbohydrate loading, multimodal pain and nausea prophylaxis, judicious fluid administration, early refeeding, and early ambulation. While useful and relevant, the guidelines highlighted one of the challenges of implementing a clinically effective ERAS: many protocols are overly complicated, often with more than 15 to 25 recommendations required for successful implementation. Extensive guidelines can hinder progress because they require changes that might not be realistic in most hospital departments in terms of either the resources or the staff available. We believe that to ease implementation, the content of an ERP should be limited. One way to achieve this is to define the most impactful elements first.

Because ERAS is a dynamic process, it can originate, evolve, and become successful by including relatively few core elements, as explained below.

Applying the eras principles to ABR

As mentioned above, the numerous interventions recommended in many ERPs makes it hard to apply them in most hospital settings outside large, resource-strong university hospitals. Another challenge is the interpretation of the different studies using ERAS in ABR. In most publications on ERAS in ABR, the patient populations are quite heterogenous, and both primary and secondary, as well as unilateral and bilateral reconstructions, are analyzed interchangeably (30-32). Our considerations are based on studies performed exclusively on unilateral, secondary reconstructions, as these are the most homogenous autologous reconstructions performed and treats the population for whom the ERP principles are the easiest to apply and maintain. Based on our previous studies and the ERAS principles, we suggest that the treatment pathway can be divided into 3 distinct phases: pre-, peri-, and

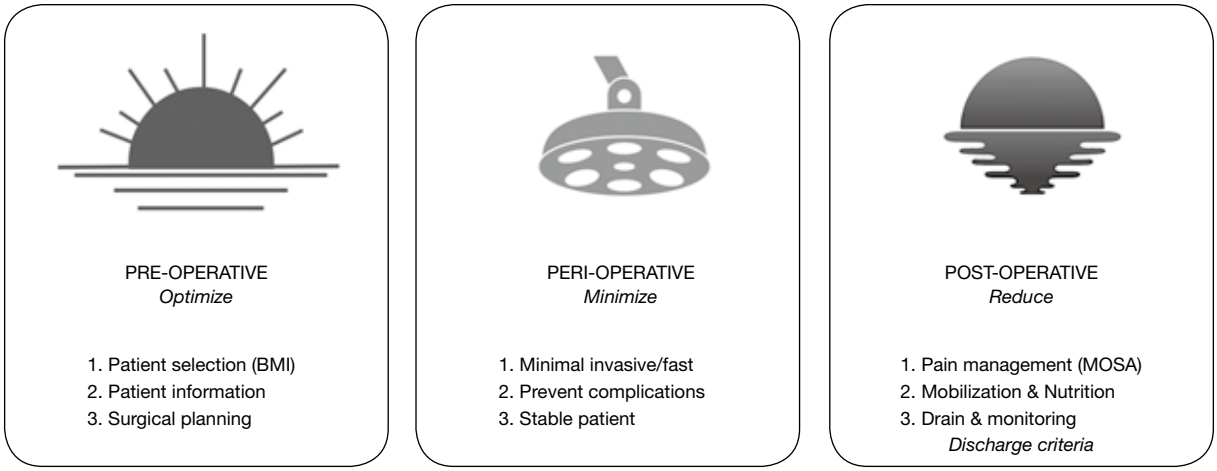

Figure 1 The core elements of ERAS in ABR. The treatment pathway can be broken up into 3 distinct phases: pre-, peri- and postoperative. Within each phase, the 3 easy-to-apply core elements have been identified. BMI, body mass index; MOSA, multimodal opioid-sparing analgesia; ERAS, enhanced recovery after surgery; ABR, autologous breast reconstruction.

postoperative. Within each phase, we put forward 3 easy-to-apply core elements that we believe will have the greatest impact (*Figure 1*). These core elements will help achieve results and provide a practical protocol and not simply act as academic exercise. However, it is vital to remember the single most important point when implementing an ERAS: that it is a team effort. For an ERP to succeed, all professional groups involved in the treatment—nurses, physiotherapists, and doctors—must accept and support the changes so the treatment pathway is coherent and uniform. As for the individual core elements, we are aware that not all recommendations can be applied in all centers due to national or regional differences or regulations, but such variation is inevitable.

Preoperative core elements (optimize)

A common denominator for the core elements in the preoperative phase is optimization. Patients should be psychologically and physically well prepared. Providing them with sufficient information about the surgery should help enhance the later phases.

Patient selection

Only patients with American Society of Anesthesiologists (ASA) scores of 0 or 1 (33) are accepted for reconstruction. We do not accept patients with more than 1 complication from ASA group 1. Smokers are asked to stop smoking 2 months before the procedure as we do not perform reconstruction in active smokers. It is well-documented that smoking increases the risk of complications, which can include delayed wound healing and infection. In purely elective ABR, except for primary reconstructions, it is acceptable to require the patient to make every possible effort to minimize the risk of complications. The same applies to body mass index (BMI). We do not perform elective surgeries in patients with a BMI >28 kg/m^2. Patients with more comorbidities, including obesity (BMI >30 kg/m^2), are likely to have more complications and thus be less suited for an ERP (34). The number of complications increases with a higher BMI, and recently, an analysis of over 4,000 DIEP flap reconstructions found more complications in the higher BMI groups and shorter LOS in the lower BMI groups (35).

Patient information

From the initial consultation, the information the patient receives should prepare them for surgery and enhanced recovery. In the early days of microsurgery, patients were often told that this was an advanced procedure that required an extraordinary amount of care and monitoring.

Patients undergoing ABR would receive multiple suction drains and be immobilized for several days. Today, the patient must be involved as an active participant and should receive a realistic overview of the whole treatment pathway. A figure illustrating the treatment timeline and a diagram detailing the operation (*Figure 2*) will help the patient prepare mentally. They should be carefully informed about the practical aspects of the treatment (e.g., expected arrival time in recovery, timing for the removal of drains, mobilization). We take

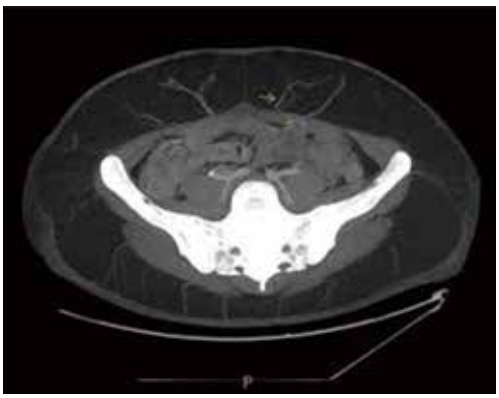

Figure 2 An example of a computed tomography angiogram.

patients on a mental journey where we explain what is going to happen at every step of the treatment during the hospital admission. For example, patients are told that the first night after surgery will be difficult due to the nurses having to check the flap perfusion every hour, which will make sleep difficult and the patient tired the next morning. Knowing this makes it easier for patients to handle. Due to our knowledge of postoperative pain levels, we can prepare patients for what to expect. They are also told that discharge will happen on the evening of the second POD or the morning of the third. This creates a self-fulfilling prophecy, and, again, helps the patient prepare mentally.

Surgical planning

Since 2006, we have routinely performed computed tomography (CT) angiograms in all patients undergoing ABR with abdominal flaps (*Figure 3*). When selecting the perforator(s) to be used, the main goal is to choose a vessel that allows for both sufficient flap perfusion and the easiest dissection with the shortest possible intramuscular course. During surgery, the strategy is to go directly for the main selected perforator and ignore all other vessels on that side unless another perforator is found to be larger or better placed, despite the initial CT angiogram. This approach allows us to save time raising the flap and therefore shortens the total operating room (OR) time. Based on the CT angiogram, the likelihood of having to convert from a DIEP flap to a muscle-sparing transverse rectus abdominis myocutaneous (MS-TRAM) flap can also be preoperatively determined. The damage done to the rectus muscle from the dissection of 3 or more perforators for a DIEP flap is often comparable to performing an MS-TRAM flap (36). However, any decision to convert the procedure to an MS-TRAM flap should be made as early as possible to save surgical time.

Before starting the procedure, the surgeons assign tasks to each team member (this includes any trainees), so they can work independently. Any special requirements, for example, a preference for short (12 cm) or long (15 cm) micro-instruments, are also decided upon and requested when booking the surgery. Preoperative markings are performed the day before, and the position of the planned perforator is checked with a Doppler ultrasound pencil probe and marked on the skin. Markings for the mastopexy or reduction are also drawn the day before surgery.

Core perioperative elements (minimize)

Minimize is the word that encapsulates the core perioperative elements. Minimizing the surgical stress that the patient is subject to, limiting OR time, and reducing the likelihood of complications all increase the probability of a successful postoperative recovery.

Minimally invasive surgical techniques

There has been a gradual evolution from using muscle flaps to using perforator flaps over the last two decades. By removing as little as possible (preferably none) of the abdominal muscles and conserving the motor nerves to the rectus muscle, damage to the donor site can be minimized (20). Of course, surgeons should be well trained in microsurgery and perform a sufficient annual number of microsurgical procedures to maintain surgical proficiency.

Marginal gain is a concept introduced into microsurgery by professor Venkat Ramakrishnan although it was originally coined by Sir David John Brailsford, a British cycling coach. The concept revolves around having everything under control and functioning at optimum levels while striving toward continuous betterment by focusing on small improvements in any conceivable area 1% at a time. Professor Ramakrishnan *et al.* "process mapped" the entire surgical process of performing ABR with a DIEP flap. By breaking down the operation into 100 streamlined steps, they enhanced operative efficiency without compromising outcomes (37).

We have successfully implemented other aspects, such as being highly verbal throughout the operation and informing anesthesiologists about the progress and upcoming steps of the procedure. Muscular relaxation during the flap elevation should be interrupted as soon as the fascia is closed. We close the umbilical hole in the flap before moving it to the

Timeline for autologous breast reconstruction using a free DIEP flap

When	What
First visit	Outpatient visit, information, etc.
Prior to surgery	CT angiogram
The day before surgery	Preoperative information by surgeon, anesthesiologist and nurse
Day of surgery	Operation, including any contralateral procedures
Hours after surgery	Recovery, return to ward, mobilization
POD 1	Urinary catheter removal, patient ambulating
POD 2	Drain removal considered, end of flap monitoring
POD 3	Planned discharge (if possible)
POD 14	Outpatient control (nurse)
3-month post-operative	Follow-up by surgeon
After 3 months	Nipple reconstruction (local) followed by tattoo and final control

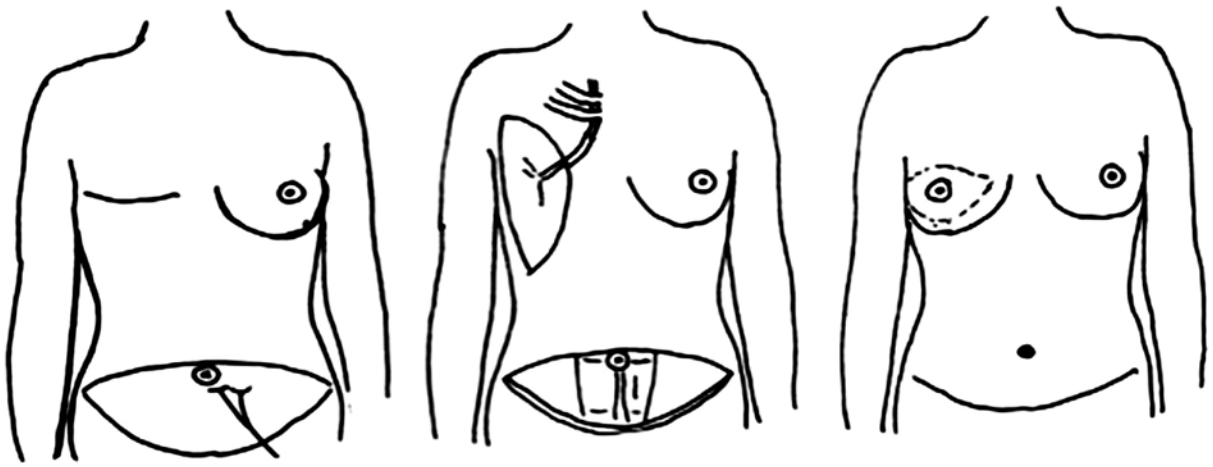

Illustration from the written patient information explaining the procedure

Figure 3 An example of preoperative patient information, including a timeline and schematic drawing of the surgery. CT, computed tomography; POD, postoperative day; DIEP, deep inferior epigastric perforator.

recipient area and place the suction drain in the recipient area before performing the anastomosis. By considering each small step, each can be improved and the surgery performed more quickly and safely.

Prevention of surgery-related complications

We always use a 2-team approach: one team (usually a consultant and a trainee) will raise the flap, while the other team will prepare the recipient vessels and perform corrections on the contralateral side (mastopexy/reduction). With this setup, symmetrizing surgery can be carried out in parallel operating processes without affecting overall operative times.

The anastomosis is performed by the surgeon who prepares the recipient vessels. We routinely employ 3 diathermy devices, each equipped with monopolar and bipolar diathermy. This requires preoperative planning for the placement of electrodes and an understanding of how the diathermies are directed to each surgical field (*Figure 4*). This is most often not recommended by the manufacturers but may depend on the brand of diathermy equipment. However, after operating with this setup for over a decade, we have yet to experience any related technical problems. Meticulous hemostasis allows us to use a single abdominal drain, and we refrain from the use of any fibrin glue or quilting sutures. Perioperative antibiotics and measures to

Figure 4 An illustration of the placement of the diathermy equipment. Also the abdominal markings of the perforators and intramuscular course. This image is published with the patient's consent.

prevent thromboembolic (TE) complications should be used.

Stable patient (thermo-, fluid, and pain regulation)

During surgery, when several areas are being worked on at the same time, the patient is very exposed and at risk of hypothermia. They should be placed on a heating blanket, as this will help to keep them normothermic. Fluid replacement should be conservative, and blood products should not be needed. Close teamwork with the anesthesiologist responsible for the microsurgical unit is crucial.

Core postoperative elements (reduce)

The primary focus in the postoperative phase should be on reducing the amount of time spent in bed and in hospital and limiting the time that the patient has a urinary catheter and drains inserted. These goals are supported by the following 3 core elements.

Effective dynamic pain treatment

Multimodal opioid-sparing analgesia (MOSA) is one of the central aspects of ERAS in ABR. A synergetic combination of analgesics and mechanisms that affect different sites in the nervous system results in a lower rate of adverse effects than do higher doses of an individual analgesic. Our published MOSA (38) includes a standard oral cocktail of a COX-2 inhibitor (celecoxib, 200 mg/12 hourly; STADA Nordic, Herlev, Denmark), gabapentin (300 mg/8 hourly), and paracetamol (1 g/6 hourly). Opioids are only administered on request. Aspirin (150 mg) is prescribed 1 day before surgery and for the first 14 PODs. Patients receive standard thromboprophylaxis (3,500 IU of low-molecular-weight heparin (Innohep, Celgene Corp., Boulder, CO, USA) from the day of surgery until discharge. Antibiotics are given only during surgery. The decision to use a COX-2 inhibitor instead of nonsteroidal anti-inflammatory drugs (NSAIDs) is founded on both our clinical results and the well-documented effects of NSAIDs on thrombocyte aggregation. Due to the blockade of prostaglandin synthesis at the COX-1 receptor, NSAIDs can increase the risk of bleeding from the operative site and the gastrointestinal mucosa. Prior to our study, documentary evidence regarding the use of COX-2 inhibitors after free flap surgery was extremely limited due to the concerns about TE complications, which followed the withdrawal of rofecoxib (Vioxx) from the market (39-41). At the time, the only relevant published study suggested a flap loss rate of 29% when the patients were treated with COX-2 inhibitors (42). We demonstrated that a MOSA with a COX-2 inhibitor does not increase flap loss when given postoperatively for no longer than a week and that COX-2 inhibitors may be superior to NSAIDs as they carry a smaller risk of postoperative hematomas.

Early ambulation and oral nutrition

Patients are encouraged to ambulate as early as possible. Preoperative fasting will leave the patient energy-depleted after surgery. Therefore, oral nutritional intake starts on the evening following the procedure. The urinary catheter is removed on the morning of the first POD, and a supportive bra and abdominal compression are worn constantly during the first 3 weeks.

Due to the preoperative information they receive, patients know that the first day is going to be challenging, but by the second POD, all patients are eating and free of pain [visual analogue scale (VAS) <4] (15). Furthermore, both the MOSA and early oral nutrition can help reduce the incidence of ileus (43). Although immobilization is a major pathogenic factor for deep vein thrombosis and pulmonary embolism, we have not observed these complications in any of our ABR patients after the implementation of our ERAS protocol. This is most likely due to early postoperative mobilization, which is supported by reports on ERAS in hip and knee arthroplasty that suggest long-term TE prophylaxis may not be required (44-46).

Rational use of drains and flap monitoring

In analyzing our ERAS data, we found that the main reason for LOS >3 days after ABR was the use of drains (unpublished data, article under review). Individual preferences of the doctor doing the rounds will often determine when drains are removed, with output ranging from <10 to <100 mL. According to our ERAS protocol, nurses remove the drains without consulting the doctors on day 2 if total production is less than 50 mL, and on day 3 if total production is less than 100 mL (15). This strategy eliminates any personal preferences regarding drain removal and is supported by the literature: Miranda *et al.* (47,48) found no difference in total complications, seroma, dehiscence, or hematoma rates between late and early drain removal for ABR with both LD and DIEP flaps.

Flap monitoring is performed every hour in the first 24 hours, and every 2 hours for the following 24 hours. While most vascular complications will occur within the first 24 hours after microsurgery, the benefits of early detection gained from reliable flap monitoring over 48 hours may well outweigh the additional cost and relatively low workload associated with the extra 24 hours of monitoring (49).

FDC

A final concept that supports these core elements is the development of FDC. A well-defined set of functional endpoints will make it clear to all staff exactly how long the patient is to remain hospitalized. FDC can vary depending on the surgical specialty and specific procedure. For example, our FDC for ABR are different from our FDC for microsurgical head and neck reconstruction (50). In the case of ABR, we use a simple set of 7 functional parameters, defined to help establish when the patient is ready for discharge (15). The FDC can be evaluated once or twice a day, and when all 7 criteria are met, the patient should be discharged unless there is another specific reason for extending their stay. In such a case, the cause should be registered. The parameters of the FDC are the following: mobilization (more than 4 hours/day); oral feeding (eating normally), drains (all drains removed), freedom from pain (VAS score less than or equal to 4), flap monitoring (laser doppler/hand held ultrasound doppler monitoring discontinued at 6 pm on POD 2), personal hygiene (ability to shower and use the toilet), and gastrointestinal function (patient has gastrointestinal function).

Although the most commonly reported aspect of ERAS is LOS, there has been recent skepticism about its relevance as an appropriate marker of having achieved a pain- and risk-free operation (51). While easily measurable, it is only valuable if precise discharge criteria, similar to our 7 points, and the destination of discharge are taken into account.

The 9 core elements described above have been used primarily for DIEP flap reconstructions although similar results have also been obtained when using the LD flap. Although the surgical procedures are different, the principles remain the same, and most of the core elements are identical, the exception being that no CT angiograms are performed in LD flap reconstructions.

Our experience and the future

When preparing to implement an ERAS protocol, it is important for any department to review their traditional care regimen and procedural results to establish a baseline and ascertain what challenges they typically face during postoperative hospitalization. In 2006 we reviewed our traditional recovery after surgery (TRAS) experience for ABR (7). After a preparatory pilot study, the full ERAS protocol was implemented on January 1, 2006.

The first 2 publications on enhanced recovery in plastic surgery, both focusing on microsurgical breast reconstruction, were published by Batdorf *et al.* and by our group within a few months of each other in 2015 (27,52). Both studies reported a statistically significant reduction of LOS by about 1 day in the ERAS group compared to the TRAS group.

Prior to these 2 studies, ABR was considered a complex and advanced procedure. Patients would have multiple suction drains and an epidural catheter, be hospitalized for extended periods of time, mobilized late, and prepared for a late discharge (*Table 2*).

Our first 5-year analysis [2006–2011] consisted of 177 unselected consecutive patients treated with unilateral ABR, with use of an MS-TRAM or DIEP flap. This ERAS group was then compared to the 277 patients treated under the TRAS. Results were modest but clear: by introducing a simple peri- and postoperative care program, it was possible to reduce LOS after microsurgery by at least 1 day (from 7 to 6 days) with no increase in complications or flap loss (27). Over the following years, we developed the ERAS further and were the first to define a set of FDC for ABR with free abdominal flaps (15). Our final ERP setup was published in 2016, and we demonstrated that LOS after ABR with

Table 2 Postoperative protocol changes after ERAS [2006]

	Pre-ERAS (<2006)	Post-ERAS (>2006)
Drains (No.)	4	2
Drains removed	30 mL or POD 7	<50 mL or POD 3
Flap monitoring period	3 days*	2 days**
Epidural	Yes, removed POD 3	No
Urinary catheter removed	Day 3	Day 1
Mobilization	Day 3	Day 0/1
Planned discharge	Day 7	Day 3

*, every 30 min, 72 hours; **, every hour in the first 24 hours and every second hour for the following 24 hours. ERAS, enhanced recovery after surgery; POD, postoperative day.

DIEP flaps could be reduced to approximately 3 days. Since our follow-up study was published in 2016, reports of using ERAS in ABR have steadily grown in number and acceptance.

Two of the challenges of interpreting studies using ERP in ABR are the heterogeneity of many patient populations and the need to clearly distinguish between primary and secondary as well as between unilateral and bilateral reconstructions. Another issue is assessing the stability of the ERAS protocol results when they are no longer used in a closely monitored research setup but rather as the standard of care.

We recently reviewed our 5-year results of using our ERAS as the standard of care and found them to be consistent with our early experience. More than 80% of the patients undergoing unilateral secondary breast reconstruction with a free abdominal flap were able to be discharged directly to their home on the third POD. Discharging patients with drains on the second POD could further reduce LOS since drains are the main reason for a prolonged LOS.

In our unit, the main alternative to a DIEP for ABR is the pedicled LD flap. We also use the thoracodorsal artery perforator (TAP) flap, but since the majority of our reconstructions are secondary, the TAP perforator can be damaged, thus necessitating the use of the full LD.

Using the same ERAS protocol and MOSA (38), we expanded our implementation to cover breast reconstructions with LD flaps and a permanent implant (18). We reviewed our past results (53) and compared these data to those of the ERAS program for LD reconstructions as well those from another surgical team who continued to perform LD reconstructions without implementing the ERAS (TRAS). LOS was significantly shorter in the ERAS group (3.2 days) when compared to the historical (6.9) and TRAS (6.3) groups. Drains were removed significantly faster in the ERAS group (day 3.9) in comparison to the historical (day 6.3) and TRAS (day 7.0) groups.

In summary, our standard ERAS protocol reduced LOS from 6 to 3 days without increasing complications in unilateral breast reconstructions using both DIEP and LD flaps.

We are currently using our ERAS protocol for primary and bilateral ABR and awaiting the results. Patients in these cases face additional surgical procedures—mastectomy and/or two free flap reconstructions—thus generating greater surgical stress and, in theory, a higher risk of complications and an extended LOS.

Finally, we have recently described the most common postoperative challenges for recovery in patients who have undergone microvascular reconstruction for head and neck cancer using a modified version of our ERP for this complex procedure (50). These findings now serve as the core of our ERP for microsurgical reconstructions.

As seen above, in uncomplicated cases, LOS after ABR should be around 3 days. It might be possible to reduce this to just 2 days in large international centers, but we are unlikely to be able to reduce it much further due to the nature and extent of the surgery.

National and regional differences and traditions that are not based on science can hinder the implementation of even the best protocols, and profit is sometimes dependent on longer hospital stays, which works against an early discharge.

However, with health care under constant pressure to deliver improved results despite financial restrictions, significant potential exists for improving the clinical pathway for a wide variety of surgical procedures, including ABR. There is a need for more evidence-based procedure-specific studies to evaluate the effects of individual interventions on relevant procedures. ERAS recommendations should be well-documented from rigorous, relevant studies, and these studies should focus on the core elements of enhanced recovery to benefit the patients. Protocols and studies should specify the type of procedure (unilateral or bilateral), the destination of the patient at discharge, and the indication for surgery (primary or secondary). This would allow readers to easily differentiate patients and compare the results.

The goals of ERAS are to reduce the incidence of complications and readmissions, and to improve patient quality of life after surgery. Future investigations should begin to shift the focus from reducing LOS to the avoidance of post-discharge problems.

The concept of ERAS is becoming more widely accepted and applied in various areas of reconstructive surgery. We are currently using or investigating the possibilities of applying ERAS in our primary and bilateral ABR, in our microsurgical head and neck reconstructions, and in our orthoplastic collaborations. Further analysis in other aspects of plastic surgery with long, complex pathways, such as pressure sores and perhaps even transgender surgeries, will define the future role of ERAS.

Conclusions

The concept of ERAS can and should be applied to ABR with both free (DIEP) and pedicled (LD) flaps. The goal is to see improved patient recovery with no increase in flap loss or complications and a reduced LOS with discharge on POD 3 after ABR.

To achieve this, any implementation of an ERAS protocol should focus on team effort, the 9 procedure-specific core elements, and the FDC. Our ERAS protocol is no longer a research tool but the standard of care in ABR.

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Footnote

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Review Article

Current concepts of lymphedema treatment for the breast cancer patient: a clinical practice review

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Abstract: Lymphedema is a progressive disease caused by insufficient lymphatic drainage leading to abnormal accumulation of interstitial fluid within soft tissues. The most common cause for secondary lymphedema in the developed world is treatment for breast cancer. In the past, almost a forgotten disease, frequently overlooked, nowadays we can provide patients with treatment and relief. We discuss the current approach to lymphedema treatment for the breast cancer patient from clinical diagnosis through different imaging modalities with their advantages and disadvantages. Possible conservative and operational treatments aimed to restore lymphatic function and reduce adipose hypertrophy are described. From reductive techniques such as resection or liposuction to physiologic techniques involving reconstructive microsurgery such as lymphatico-venous anastomosis (LVA), vascularized lymph node transfer (VLNT) and other lymphatic free flaps. A review of our constructed approach and guidelines for managing secondary lymphedema in the breast cancer patient from 2005 to present days is presented. It is based on our growing experience and evolving techniques. Management of lymphedema in the breast cancer patient is multi-disciplinary and involves both the general and plastic surgeons, oncologists, physical therapists, social workers and many more. A holistic approach to the patient is advocated. This is best performed by adjusting and tailoring the appropriate treatment for each patient.

Keywords: Breast cancer related lymphedema; lympho-venous anastomosis (LVA); vascularized lymph node transfer (VLNT); surgical treatment

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Lymphedema is a progressive disease of the lymphatic system characterized by accumulation of proteins in the interstitium leading to chronic inflammation, adipose deposition and ultimately fibrosis of the skin and subcutaneous tissues. The most common cause of secondary lymphedema in the developed world is cancer treatment with breast malignancy in the lead. It is estimated that as many as 50% of breast cancer patients treated with axillary lymph node dissection go on to develop lymphedema (1,2). In the case of the less invasive sentinel lymph node biopsy (SLNB), it is estimated to be around 5% (3). This rate of lymphedema may be secondary to disruption of arm lymphatics during an SLNB procedure. Identifying and preserving the arm nodes with reverse axillary mapping may translate into a lower incidence of lymphedema with SLNB and axillary lymph node dissection (4). Lymphedema may arise at any time, months or even years after breast cancer surgery, but approximately 75% of cases occur in the

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Table 1 Clinical staging of lymphedema

Stage 0: subclinical condition in which swelling is not evident despite impaired lymph transport
Stage 1: early reversible pitting edema; limb elevation will reduce swelling
Stage 2: irreversible lymphedema; pitting is no longer present
Stage 3: end-stage lymphedema with elephantiasis; pitting is absent and trophic skin changes (acanthosis, fat deposits, and wart overgrowths) develop

The diagnosis and treatment of peripheral lymphedema: 2013 Consensus Document of the International Society of Lymphology (updated 2020).

first year after surgery (5,6). The treatment for lymphedema in breast cancer patients should be multi-disciplinary and targeted on balancing this chronic illness. Patients should be informed nowadays that there are vast treatment options for treating lymphedema.

Clinical features and evaluation

Lymphedema is a progressive process with worsening symptoms. At first, patients describe a sense of discomfort and heaviness. This may later proceed by chronic swelling, pitting edema and recurrent cellulitis. With time, patients may go on to develop non-pitting edema and eventually elephantiasis. This shift, from pitting to non-pitting edema, represents hypertrophy and fat deposition of the interstitium which, at the end stage, can result in overt fibrosis.

There are numerous classification systems for grading lymphedema. Some like The International Society of Lymphology staging system (ISL) rely primarily on clinical features of the disease (7). Other classifications are aided on imaging based on indocyanine green (ICG) findings (8,9). The ISL system is the most widely used and portray clinical findings of the limb (*Table 1*, *Figure 1*). Patients with stages 1 and 2 lymphedema may benefit from a microsurgical reconstruction.

Those with a graver stage (2 and 3), characterized by fat hypertrophy and fibrosis, were once limited to debulking surgery alone but today, with evolving knowledge of the disease and treatment options, the surgical treatment is tailored to the patient and different surgical modalities are proposed and combined in the same surgery.

Pre-op assessment of a swollen limb should consider other possible pathologies and risk factors. Obesity is a great contributor of secondary lymphedema. Studies have shown an almost linear correlation with higher baseline weight and the development of lymphedema after axillary lymph node dissection for breast cancer (2). For this reason, obesity must be addressed with weight loss ahead of surgical treatment whenever possible (10). Other risk factors for the development of secondary lymphedema include axillary lymph node dissection or dissection of four or more nodes. Radiotherapy alone, and to a greater extent when combined with ALND, is another major risk factor.

The diagnosis of lymphedema is clinical and high suspicion is sufficient. Imaging is a very useful tool to explore the extent of the disease, but it is not mandatory for the diagnosis. A thorough medical history should be recorded, emphasizing on the above-mentioned risk factors. Measurements of the limb are performed using optoelectronic limb volumeter (Perometer). This is a reliable and convenient tool for measuring limb volume with each measurement taking only a few seconds.

The psychosocial impact on the patient is often neglected. These women, some of whom are still very young, have been confronted with breast cancer and its deleterious effect on their well-being, self-esteem, and sexuality. On top of their oncological treatments, they suffer a major complication that warrants further treatments and more time away from home, friends, and work. This issue needs to be addressed with sensitivity and these patients should receive professional help from therapists and social workers. A multi-disciplinary, holistic approach should guide the course of treatment.

Conservative therapy

The standard nonsurgical therapy for lymphedema is complete decongestive physiotherapy (CDT). This multimodality approach combines the use of manual lymphatic drainage, bandaging, exercise, and skin care. CDT comprises two consecutive phases: Phase 1 is the initial reduction phase in which patients are subjected to five therapy sessions per week, in times combined with

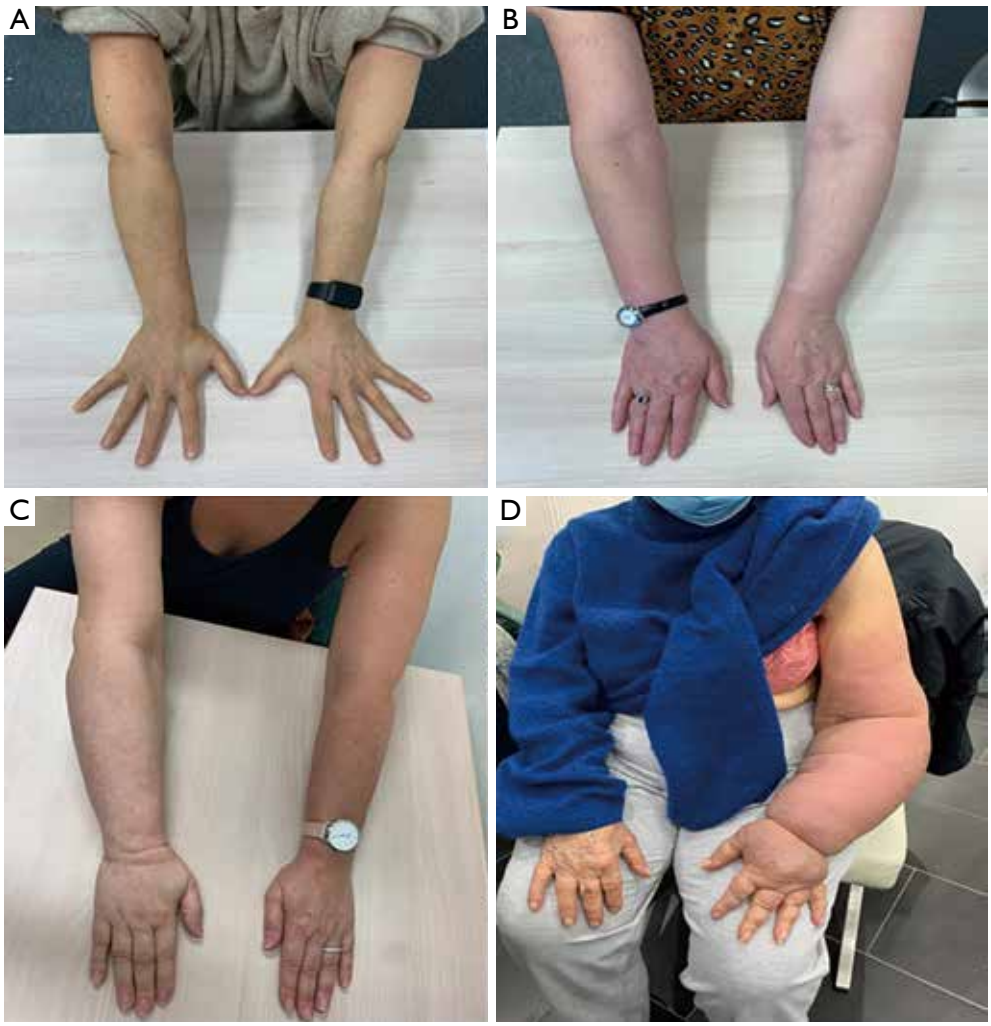

Figure 1 Clinical stages of lymphedema (international society of lymphology). (A) Stage 0, (B) stage 1, (C) stage 2, and (D) stage 3.

Figure 2 Elastic banding applied after manual lymphatic drainage.

elastic bandaging (*Figure 2*). It usually takes 4 to 8 weeks for the reduction in fluid to reach a plateau. Phase 2 is the maintenance phase where the aim is to preserve the reduction obtained. At this stage, manual lymphatic drainage is less frequent (1–3 times/week) and compression garments are applied. This time consuming, lifelong commitment is aimed to reduce the progression of the disease with its complications. Although recent studies have raised doubts regarding its impact, it is still considered first-line therapy for lymphedema (11). All patients are requested for a minimum of 6-month trial of decongestive therapy prior to considering a possible surgical intervention, especially in the early stages of the disease.

Assessment and imaging

Diagnostic imagining techniques are essential tools to determine the scale of disease progression in order to tailor

an appropriate therapeutic strategy for each patient. It can also be helpful for assessing post-operative improvement. The three main imaging modalities for lymphedema patients are radionuclide lymphoscintigraphy (LSG), near infra-red (NIR) fluorescence, and magnetic resonance lymphangiography (MRL).

Radionuclide lymphoscintigraphy (LSG)

Lymphoscintigraphy is an imaging test that gives a global evaluation of the functionality of the lymphatic system and is the reference standard for confirming the diagnosis of lymphedema. It uses technetium-labeled colloid and nuclear scanning through a recommended protocol for LSG. The colloid is injected sub-dermally in one or more web spaces of the hand. A minimum of 3 images are obtained: 30 minutes after injection, another after 15 minutes of finger exercises, and one 60 minutes after normal activity. The radiologic images are then assessed to include: (I) the course of the radioactive tracer from the injection site to the axilla, (II) the transition time to the axilla, (III) the absence or presence of major lymphatic basins, (IV) the number and size of vessels and nodes, (V) the presence of collaterals, (VI) reflux, and (VII) relative symmetry compared with the opposite limb. The transport index represents the uptake of the colloid and how quickly it reaches the nodal basin. Leakage out of damaged lymphatic vessels is reflected by reflux of the dye (12). Typical images of lymphoscintigraphy can be seen in *Figure 3A,3B*. The ability to assess flow velocity of the lymphatic system, quantification and nodal basin is the main advantage of LSG. It can also provide comparative information for postoperative assessment. Its downfalls include poor anatomic resolution for it does not provide any anatomic information in 3D. It is unable to assess interstitial tissues nor give indication of fat hypertrophy and it is a lengthy procedure. For this reason, information must often be complemented with ICG-lymphography and MR-lymphangiography.

Near infra-red (NIR) fluorescence imaging—indocyanine green (ICG) lymphography

NIR fluorescence visualizes real-time function of the superficial lymphatic vessels. The tracer, ICG, is injected subcutaneously at the web spaces of the hand followed by a near-infrared camera scan. The images can identify the location and functional status of superficial lymphatic vessels. In a healthy limb, flow through lymphatic vessels is detected spontaneously, even with minimal mobilization. In a failing lymphatic system however, the dye migration may be slowed down or fully impaired, might necessitate manual drainage or extravasate through the lymphatic vessel walls. In patients with diseased lymphatics, the number of functional vessels is reduced, and reflux (dermal backflow) might be seen. These findings were gathered to form a staging system developed by Yamamoto *et al.* where normally functioning lymphatic vessels appear as linear structures (13). With disease progression, the pattern visualized will shift from a linear pattern through a splash pattern, a stardust pattern and finally a diffuse pattern in advanced cases (*Figure 4*). The procedure is limited by its ability to only visualize lymphatics that are less than 12 mm deep to skin surface and the field can be totally obliterated by the tracer, making the mapping difficult. It does not provide information regarding the interstitial tissues such as deep edema accumulation or fat hypertrophy and does not visualize venous patterns (14). For this reason, MR-lymphangiography, is advocated in selected cases.

Magnetic resonance lymphangiography (MRL)

MRL combines magnetic resonance imaging technology with a lymphatic dye to allow precise anatomic imaging. It shows both the superficial and deeper lymphatic structures and provides high-quality images of the lymphatics, venules, and subcutaneous tissues. Mapping lymphatic vessels in relation to veins is difficult with standard imaging techniques. MRL has been shown to be accurate and sensitive compared in detecting anatomical abnormalities in the lymphatic system of patients with extremity lymphedema (15). Gadolinium is injected sub-dermally to all web spaces and is preferentially taken up by the lymphatics. The information gained includes the functionality of the lymphatic channels and visualization of the lymph node basin. The interstitial tissue along with presence and location of the edema is also demonstrated (16). This aids in disease staging and surgical planning. The combination of the functionality, location and quality of the lymphatic channels and its comparison to the interstitial tissues will determine the choice of surgical technique. With worsening lymphedema, the interstitial tissues will progress from fluid dominant edema to adipose dominant and finally to fibrosclerotic dominant. Microsurgical

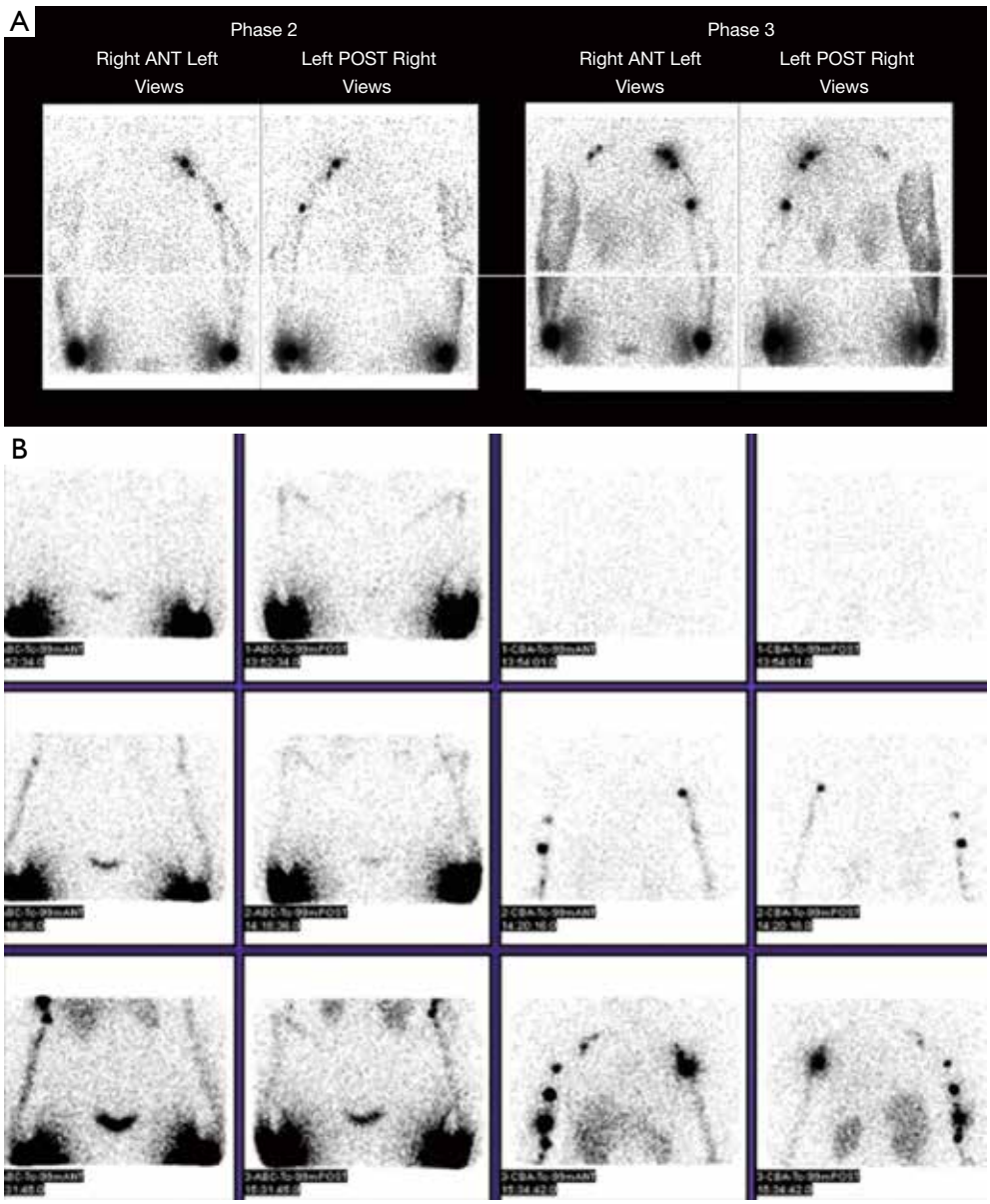

Figure 3 Typical images of lymphoscintigraphy. (A) A patient with right side severe upper limb lymphedema. On the second phase, only a beginning progression can be seen on the right side with beginning diffuse tracer diffusion, whereas on the left side the tracer has reached the axilla through linear lymphatic channels. On phase three a massive dermal back-flow can be seen over the whole right upper limb, with little axillary nodes. (Images courtesy of Pierre Bourgeois. Dept of dermatology, Erasme University Hospital, Brussels, Belgium). (B) Moderate right upper limb lymphedema. Bilateral lymphatic insufficiency at rest (no tracer progression). Recruitment of deep lymph nodes seen on the right side. (Images courtesy of Pierre Bourgeois. Dept of Dermatology, Erasme University Hospital, Brussels, Belgium).

reconstruction remains an option for patients with fluid dominant edema with a relatively healthy subcutaneous tissue. Liposuction is used for those with adipose dominant limb swelling. Identifying the location and quality of the lymphatic vessels and venules helps to select the most suitable lymphatic channels for creating shunts during lympho-venous anastomosis. It has been demonstrated that MR lymphangiography is a good and accurate technique for pre-operative mapping of functional lymphatics and adjacent veins in the lymphedematous limb, thus improving

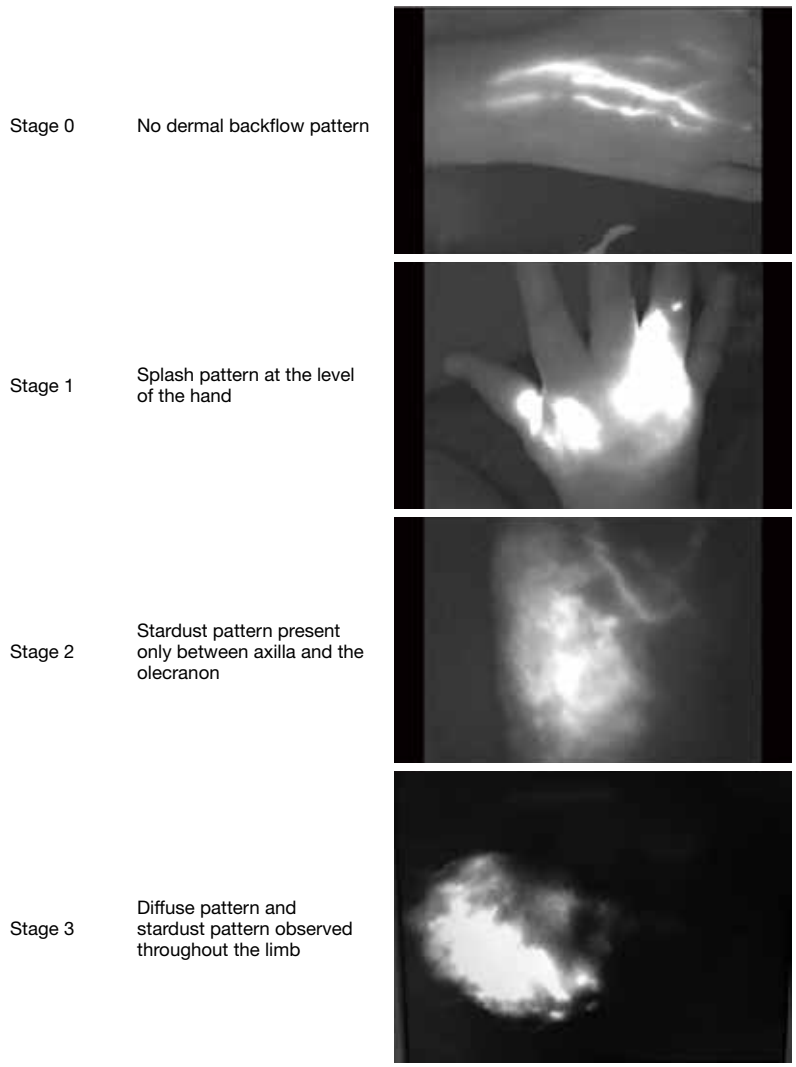

Figure 4 Yamamoto's arm dermal backflow staging for lymphedema using ICG lymphography. (Images courtesy of A. Zeltzer). ICG, indocyanine green.

patient selection for a feasible LVA (17). The examination gives us important anatomic information based on one imaging modality, that other examinations fail to give in such extent. In comparison with CT mapping of perforator flaps [e.g., deep inferior epigastric perforator (DIEP) flap], it makes surgery more predictable and swifter by giving exact coordinates for the place of incision in LVA (18). The downfalls of MRL are that it is time-consuming, requires a high level of expertise and is relatively expensive. On the other hand, information gathered from the MRL is that of both the LSC and the NIR fluorescence imaging, thus it might even be more cost effective.

Advantages and disadvantages of the different imaging techniques are listed in *Table 2*.

Selection of treatment

Surgical management

Lymphedema treatment is aimed to restore lymphatic function and reduce adipose hypertrophy when installed. Surgical treatment for lymphedema is divided into reductive or physiologic techniques. Reductive techniques include resection or liposuction, and physiologic techniques involve reconstructive microsurgery.

Table 2 Advantages and disadvantages of the different imaging techniques of the lymphatic system

	Lymphoscintigraphy	Infra-red fluorescence (ICG)	MR lymphography
Lymphatic channels	+	+	+
3D localization	–	+/–	+
Lymph nodes	+	–	+
Dermal backflow	+	+	+
Velocity progression	+	+/–	+/–
Fat deposition/fibrosis	–	–	+
Info veins	–	–	+
Info depth of lymphatic channels	–	Maximum 10–12 mm (sub-dermal)	Deeper lymphatic channels seen, and exact depth can be measured

ICG, indocyanine green; MR, magnetic resonance.

Physiologic treatment

Microsurgical reconstructive techniques

Lymphatico-venous anastomosis (LVA)

Lymphatic fluid in the lymph vessels drains into the venous system via the thoracic ducts. LVA involves suturing superficial lymphatics to subdermal venules, creating peripheral shunts within the diseased limb, allowing a draining gradient between the congested high pressure lymphatic system and the lower-pressure venous system. Intact and functional lymphatic vessels are key components in LVA, and these can be confirmed with ICG prior to surgery. MRL can map the optimal locations to perform LVA where healthy lymphatics and venules are in proximity. These are also located during surgery using ICG and patent blue. Using this GPS mapping created by pre-operative MRL, two to four short incisions (2–3 cm long) are made just over the sites of healthy lymphatics, and when an adjacent venule is located, the anastomosis is performed using super-microsurgery techniques. The most used is an end-to-end anastomosis but other techniques have been described (19). The patency of the anastomosis can be tested with ICG or patent blue or by performing the 'milking test'. The ideal number of anastomoses is yet to be determined; however, it is recommended to have as many as possible. As described, healthy functioning superficial lymphatics are essential for LVA, thus suitable candidates have stage 0 or 1 with minimal irreversible tissue fibrosis. At later stages LVA can sometimes still be performed but will not reverse fat hypertrophy or hard fibrosis. Studies have demonstrated volumetric improvements and symptoms relief including decreased incidence of cellulitis (9). Some patients were even able to completely discontinue use of compression garments, even over long-term follow-up (20). Some groups have embraced a prophylactic surgery that involves the anastomosis of arm lymphatics with a collateral branch of the axillary vein at the time of nodal dissection for the prevention of lymphedema (21). Lymphatic microsurgical preventing healing approach (LYMPHA) involves the injection of blue dye into the upper arm to map and preserve the arm lymphatic drainage during ALND and thus diminish lymphedema. Lymphatics coming from the arm (usually 2 to 4) are visible and by using multiple LVA's between them and a secondary branch of the axillary vein, prevention of lymphedema is feasible. It is better considered in high BMI patients, those with 4 or more positive lymph nodes and those who require combined radiotherapy and LND. Boccardo *et al.* reported that only 3 out of 74 patients undergoing this procedure developed lymphedema. This 4% risk is much more favorable in comparison to up to 50% incidence of lymphedema in women undergoing ALND (22). Despite these results further study is needed to determine its efficacy on the long term.

Vascularized lymph node transfer (VLNT)

VLNT replenishes the missing lymph nodes by delivering vascularized tissue-containing lymph nodes from one area of the body to the affected limb as a free tissue transfer. For the upper limb lymphedema, the groin is the most popular donor site where the superficial inguinal lymph nodes are harvested based on either the superficial circumflex iliac or the superficial inferior epigastric vessels. Logically a lymph node flap is transferred anatomically to the axilla (where the nodes have been removed) although nodes can be placed extra-anatomically (elbow or wrist). The theory behind

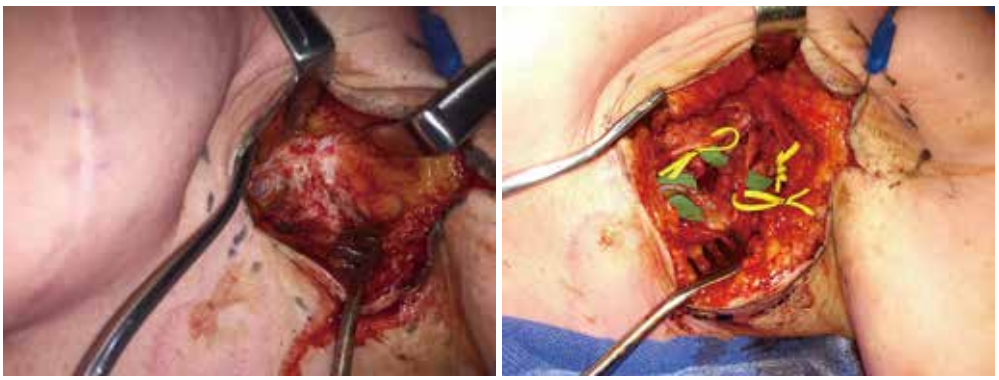

Figure 5 Extensive release of axillary scar. View of a scarred 'hostile' axilla with extensive scarring impairing lymphatic passage, entrapping nerves and tethering the muscles. Same axilla after a full scar removal, neurolysis (with yellow loops), preparation of the vascular recipient vessels for the axillary anastomosis (green field on the left), and release of the axillary vein (seen top right).

placement in a non-anatomic site is that the relocated lymph nodes act as a pump directing interstitial fluid into the venous network. This concept is also supported by post VLNT radionucleotide lymphoscintigraphy that visualizes the rerouted lymph fluid flowing into the recipient vein via the free flap nodes (23). Distal recipient sites may be more efficacious (24) and they allow gravitational drainage of the limb through the potential opening of old lymphatic channels once interstitial pressures normalize. As mentioned, upper extremity lymphedema is usually the result of prior surgery and is often followed by radiation to the axilla, thus creating a 'hostile axilla'. An essential step of approaching the axilla as a recipient bed is a full release of the scar that might envelope the recipient vessels, nerves and even tether the muscle. This ensures a healthy bed for lymphangiogenesis and bridging of lymphatics in the recipient bed (*Figure 5*).

VLNT is reserved for patients with stage 1 and 2 lymphedema, regardless the presence of healthy superficial lymphatic vessels. It can both treat patients with damaged lymphatics or decreased lymph node function and can be combined with LVA, liposuction or a simultaneous breast reconstruction. Alternative donor sites include the lateral thoracic lymph nodes, submental lymph nodes, supraclavicular lymph nodes, and omentum lymph node flap (25,26).

Vascularized groin lymph node flap (VGLNF)

The first and most commonly used option for a lymph node flap is the groin. Becker *et al.* reported treating upper extremity lymphedema by transferring inguinal lymph nodes to the axillary region (27). The flap is designed in accordance with essential anatomic landmarks and bony prominences described as the golden triangle (28) and it is an ellipse with its central axis parallel to the vascular pedicle [superficial circumflex iliac vein/artery (SCIV/A)]. Increased number and density of the harvested nodes may improve the efficiency of the flap (29). The main concern is that secondary lymphedema may arise in the lower limb after groin VLN harvest. This complication has been reported to be as high as 13.5%, thus extreme caution and profound anatomical knowledge is mandatory for a safer flap design (30). To reduce this hideous complication, it is cardinal to preserve the deeper lymphatics and nodes that are responsible for draining the lower extremity. Harvesting of groin lymph nodes should therefore be superficial to the deep fascia, staying cephalad to the groin crease and lateral to the femoral artery (28). Classically, the reversed lymphatic mapping can be used (31). We currently use a modified reverse lymphatic mapping, using patent blue to map the lower limb draining nodes and distinguish between nodes that drain the limbs and the ones suitable for harvest (32). This gives us a visual advantage during surgery. The golden triangle provides guidelines to optimize the safety (in preventing donor-site lymphedema) and efficacy (enough nodes in the flap) for groin lymph node harvesting (*Figure 6*). It can also be used for lymph node reconstruction other than breast-cancer related (33).

Lateral thoracic lymph node flap

The second choice for harvesting lymph nodes is the lateral thorax. With anatomical variations, it can be raised based on different pedicles: the lateral thoracic vessels, an accessory lateral thoracic vessel, or a branch of the thoracodorsal artery. Knowing that the number of transplanted lymph nodes correlates positively with an improved lymphatic

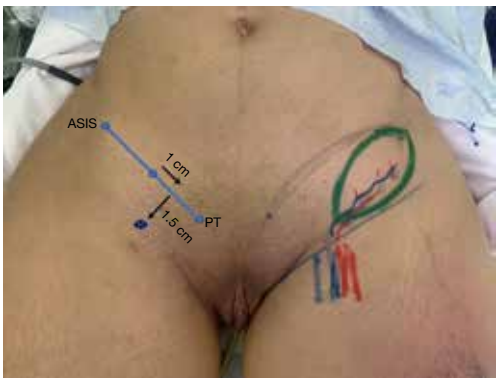

Figure 6 Anatomic landmarks for the planning of a VGLNF. VGLNF, vascularized groin lymph node flap.

drainage function, the lateral thoracic donor site, with an average of 13 lymph nodes is considered a good alternative (34). The lateral thoracic artery, however, can be hypoplastic or even absent and then it needs to be harvested on the thoracodorsal artery (35). These high anatomical variations seem to hinder its widespread use. Reverse lymphatic mapping is used to visualize lymphatic drainage of the breast and upper extremity, and aids to ensure a safe flap dissection. This flap possesses favorable features, such as fair pedicle length, abundance of lymph nodes and a cosmetically acceptable donor site scar.

The DIEP flap with lymph nodes

Nowadays, the gold standard for abdominally based autologous reconstruction is a DIEP free flap. After breast cancer treatment, if the patient is not interested in breast reconstruction, a solitary lymph node transfer should suffice. However, some patients require both breast reconstruction and VLNT for treating lymphedema. These patients often have irradiated and scarred axillary region accompanied with lymphedema of the upper limb. This can be addressed with a chimeric flap composed of an abdominal flap for breast reconstruction (DIEP) and a lymph node flap from the groin (VGLNF), targeting both problems in one operation. In this setting, the abdominal flap is based on the deep inferior epigastric vessels and the lymph node flap is based on the superficial circumflex iliac or the superficial inferior epigastric vessels. Using CT scan mapping with measuring distances to anatomic landmarks, the flap is designed in accordance with the safe "golden triangle" zone. The groin lymph nodes are harvested en-bloc with the abdominal flap. When designing the flap, it is recommended to lower the scar down go get better access to the groin and better aesthetic result, much like an aesthetic abdominoplasty. Choosing the perforator for DIEP must consider the breast size. For a small breast, ipsilateral perforator and lymph nodes are harvested and for a bigger breast, a contralateral perforator to the lymph nodes is harvested. In flap setting, if the lymph node harvest in the groin is contralateral to the breast, flipping the flap upside down and setting it in a horizontal fashion is best. When the lymph node harvest is ipsilateral to the breast, setting of the flap is vertical. Placement of the breast reconstruction flap medial on the chest wall and the lymph node flap lateral in the axilla allows using a separate set of anastomoses for each one. It is important to perform an extra anastomosis for the lymph nodes, on top the one to the DIEP and put the nodes in contact with the axillary vein (36). It is crucial to perform extensive scar removal in the axilla releasing vessels and nerves in order to create an open system the flap could integrate in. For the donor-site, seroma formation is a major complication, with higher rates for the combined flap than when harvesting lymph node flap alone. This is due to the big dead space left after a VGLNF and DIEP harvest. Minimizing or avoiding this requires meticulous planning with a prehending reversed lymphatic mapping and use of patent blue. More techniques for reducing seroma include leaving a superior deepithelialized flap for a good closure, using quilting sutures in the groin to minimize dead space, clipping lymphatic vessels, using separate drains for the DIEP and for the groin, donor site compression and the use of fibrin glue (37).

Reductive techniques

Direct excision of the diseased interstitial tissues or skin is an aggressive measure that in western population, is rarely used, if ever, for the upper limb due to its mutilating and disfiguring effect.

Liposuction is a method that permits effective volume reduction in therapy-resistant lymphedema of the limbs. It is performed using power-assisted liposuction aimed at removing the pathological hypertrophied fat from the interstitium. A tourniquet and tumescent can be used to minimize blood loss. Described by Brorson (38), full liposuction is performed circumferentially from wrist to shoulder and was demonstrated to be an effective method for the treatment of chronic, nonpitting, arm lymphedema resistant to conservative treatment (39). It is reserved for patients with an important circumferential fat hypertrophy of the limb. When residual pitting edema is seen in limb, selective liposuction can be performed in specific resistant regions to reduce adipose tissue deposits. It is essential to catch the disease on time, before it progresses irreversibly

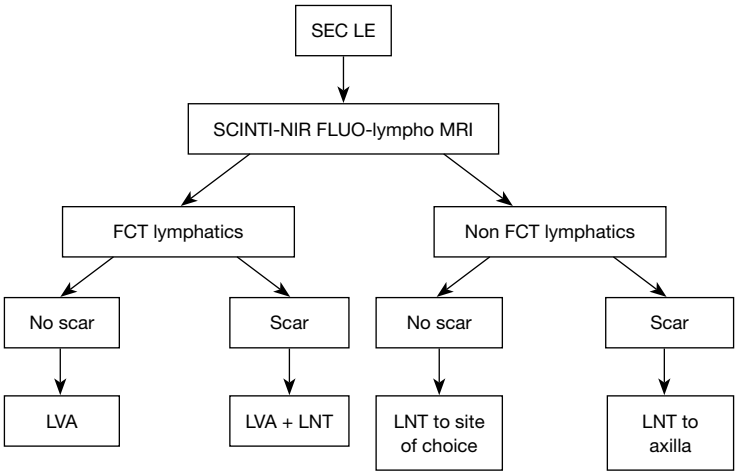

Figure 7 Approach to surgical treatment of upper limb lymphedema. SEC, selected; LE, lymphedema; SCINTI, lymphoscintigraphy; NIR, near-infrared; FLUO, fluoroscopy; FCT, functional; LVA, lympho-venous anastomosis; LNT, lymph node transfer.

and liposuction is the only possibility. Those who present with advanced stage or fail conservative therapy and are not candidates for microsurgical reconstructive surgery may benefit from liposuction. It will provide volume reduction and diminished circumference of the limb, but once performed, liposuction mandates the patient to wear lifelong compression garments. In selected cases, 6–12 months after liposuction was done, an additional lymph node transfer can be performed in order to stabilize the result.

Treatment algorithm

The approach to lymphatic limb surgery should focus on tailoring the best matched procedure to each patient. Lymphedema patients with pitting lymphedema are worked up by preoperative imaging with lymphoscintigraphy and near infra-red fluorescence, and in recent years lympho-MRI has been incorporation for selected cases. When lymphatics are functional, the patient is a candidate to perform lympho-venous anastomosis (LVA). When there is no scar in the root of the limb, the axilla, LVA alone is performed. In the presence of a scar, lymph nodes transplantation to the debrided scar is combined with LVA distally. In the event there are no functional lymphatics in a patient with pitting lymphedema and there is no scar, lymph node transplantation in performed to the site of choice, either anatomic or non-anatomic. When the axilla is scarred however, the root of the limb must be addressed and then the lymph node transplantation goes to the axilla. This protocol is described in *Figure* 7.

Post-surgery care

Post-op treatment is again tailored specifically to each patient and her needs. Remembering that lymphedema is a progressive chronic disease with its ups and downs might require adjustments, even after a corrective surgery. Compression garments are advised and CTD and manual lymphatic drainage are started 10 days after surgery. We continue routine follow-ups, making and recording measurements using the Perometer. The same preventive measures as for each lymphedema patient are suggested (skin care, infection prevention and hygiene, no direct shocks to the affected limb, etc.).

A possible adjunct in the follow up of patients is the low energy extracorporeal shockwave therapy (ESWT). These are acoustic, electromagnetic pulses transmitted into the human tissue inducing an intracellular biological reaction (40). It was demonstrated to stimulate angiogenesis and lymphangiogenesis, reducing inflammatory response and upregulating cell proliferation (41). This method is as an alternative noninvasive treatment for residual, end-stage, secondary upper limb lymphedema. It has been demonstrated that upper limb circumference measurements were significantly reduced after 4 weeks of treatment (42). This is also in concordance with studies that reported of 30% and even higher mean total circumference reduction (43). Given this data, ESWT can be considered an additional treatment option to improve the clinical outcome of refractory, long-standing secondary lymphedema.

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Footnote

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Review Article

Barcelona lymphedema algorithm for surgical treatment (BLAST)

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Abstract: Upper limb lymphedema after breast cancer treatment is a progressive and disabling condition that can significantly impair the quality of life of affected individuals. Consequently, managing breast cancer-related lymphedema (BCRL) is a major challenge for patients and healthcare professionals. In the last few decades, various techniques have been developed for the treatment of BCRL, but the surgical approach to this condition remains in a state of constant evolution. Currently, the three main pillars for the surgical treatment of BCRL are lymphatic-venous anastomosis (LVA), functional vascularized lymphatic tissue transfer (FVLTT), and liposuction. The choice of one or other of these techniques usually depends on the presence or absence of a functional lymphatic system of the upper limb and axilla, and the degree of hypertrophy of the subcutaneous adipose tissue. A combination of techniques may sometimes be employed, either in the same intervention or in stages. However, the most recent trend is to identify transected lymphatic channels during axillary lymph node dissection and to immediately restore lymphatic drainage through LVA at the axillary level to prevent the development of BCRL. This article provides an overview of the clinical diagnosis and staging of BCRL, the imaging techniques used to assess the lymphatic system, a brief description of surgical techniques, and an update of the Barcelona lymphedema algorithm for surgical treatment (BLAST).

Keywords: Breast cancer-related lymphedema (BCRL); lymphatic-venous anastomosis (LVA); functional vascularized lymphatic tissue transfer (FVLTT); liposuction; targeted-lymphatic axillary repair (T-LAR)

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Introduction

Female breast cancer, with an estimated 2.3 million new cases diagnosed in 2020, remains the most commonly diagnosed cancer worldwide (1). After breast cancer treatment, upper limb lymphedema is a chronic and progressive sequela that impairs patients' quality of life (2,3). The overall estimated incidence of breast cancer-related lymphedema (BCRL) is around 21% but, due to the lack of diagnostic criteria, ranges from as much as 5% to 30% (4). Because long-term survival rates in women with proper breast cancer treatment are as high as 80% at 15 years (5), adequate management of BCRL represents a major challenge for both patients and healthcare professionals.

BCRL typically results from the interruption of the lymphatic drainage produced by surgical dissection of the axillary lymph nodes. A well-established risk factor for this complication is regional lymph node radiation (6). Nevertheless, the incidence of BCRL may gradually be decreased by current trends in less invasive axillary therapy in patients with a positive sentinel node biopsy (7) and less aggressive radiotherapy protocols (8-10).

Traditional treatment for patients with BCRL has typically involved conservative methods including a combination of manual lymphatic drainage, compression

Table 1 Staging of lymphedema of the ISL

ISL stage	Features
0	Latent or sub-clinical condition where swelling is not evident despite impaired lymph transport. It may exist months or years before overt edema occurs
I	Early accumulation of fluid relatively high in protein content and subsides with limb elevation. Pitting may occur
II	Limb elevation alone rarely reduces tissue swelling and pitting is manifest. Late in Stage II, the limb may or may not pit as tissue fibrosis supervenes
III	Lymphostatic elephantiasis where pitting is absent and trophic skin changes such as acanthosis, fat deposits, and warty overgrowths develop

ISL, International Society of Lymphology.

garments, exercises, and skin care (11). However, the efficacy of these therapies alone is limited, as the existence of structural damage to the lymphatic system continues to impede adequate lymph drainage of the affected upper limb.

Over the last five decades, our understanding of the anatomy and pathophysiology of the lymphatic system has been enhanced by advances in imaging techniques and higher microscope magnification, leading to the development of various surgical techniques for the treatment of BCRL. However, the surgical management of BCRL is constantly evolving and there is no established consensus on the optimal treatment of these patients. Consequently, we would like to share an update of the therapeutic algorithm used in our centers, which has yielded highly encouraging results and could potentially be used to guide decision-making when planning the surgical treatment of BCRL.

Clinical considerations

According to the International Society of Lymphology (ISL), accurate clinical history and physical examination are essential for a proper diagnosis of BCRL and its staging (*Table 1*) (12). The main clinical manifestation of lymphedema is swelling of part or all of the limb, which may be accompanied by sensations of tightness, heaviness or fullness, and sometimes by pain in the affected area.

On physical examination, it is important to distinguish between pitting and non-pitting edema. Swelling in the early stages of lymphedema is characterized by the presence of pitting, resulting from the accumulation of protein-rich fluid in the interstitial space. Subsequently, as the inadequate lymph drainage persists, the continued state of lymph overload leads to a failure of the lymphatic pump (13). Consequently, the permanent lymph stasis generates a chronic inflammatory response, inducing progressive degeneration of functional lymphatic channels (from the site of the interruption to the distal area), and a proliferation of adipose and connective subcutaneous tissue (14-16). Thus, as lymphedema progresses, upper extremity swelling will transition from pitting to non-pitting edema due to progressive hypertrophy of the subcutaneous tissue. Therefore, the more advanced stages of lymphedema are characterized by the absence of pitting, which is often accompanied by the presence of trophic skin changes, and the increased arm volume may even restrict range of motion.

Clinical assessment should also include measurement of limb circumference and volume. Girth measurements may be obtained by multiple circumference measurements of both limbs using a spring-loaded tape measure (5-cm intervals starting at the elbow, then progressing down to the dorsum of the hand, and then up to the shoulder). Volume measurements can be obtained using circumference measurements through the truncated cone model (17). However, other methods can also be used, including plethysmography and perometer. Based on the difference in limb volume, severity can be assessed as minimal (<20% increase), moderate (20–40% increase), or severe (>40% increase) (12). Understanding the clinical manifestations and pathophysiological processes of lymphedema is essential to comprehend the principles underlying the surgical treatment of this disease.

Diagnostic imaging techniques

After clinical diagnosis and ISL staging, imaging techniques play an essential role in assessing the structural and functional features of the lymphatic system. One of the main diagnostic imaging techniques is indocyanine green

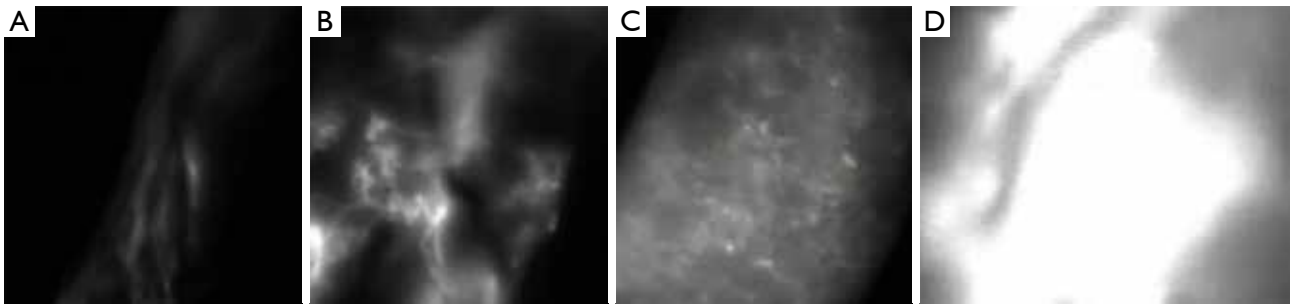

Figure 1 Indocyanine green lymphography images. Linear pattern (A): represents the normal lymphatic channel. Splash pattern (B): is observed as scattered dye twinkling in tortuous lymphatic channels. Stardust pattern (C): is observed as dimly luminous, spotted fluorescent signals. Diffuse pattern (D): a widely distributed dye is observed without twinkling or identifiable spots.

lymphography (ICG-L), which can be used to assess the functionality of the superficial lymphatic system. The findings can be classified into linear or dermal backflow patterns. Linear patterns correspond to normal active subdermal lymphatic channels (up to a depth of 1.5 to 2 cm), while nonlinear or dermal backflow patterns represent the accumulation of lymphatic fluid in the interstitial space. Dermal backflow patterns can be further divided into splash, stardust, and diffuse patterns, which correspond to the degree of severity of lymphedema (*Figure 1*) (18,19).

The other main diagnostic imaging technique for the assessment of the lymphatic system is lymphoscintigraphy (LS). This imaging modality allows qualitative assessment of the functionality of the deep lymphatic system. Among the main parameters evaluated are tracer uptake and migration speed, visualization of major lymphatic collectors and axillary lymph node basins, as well as the time taken by the tracer to reach them, and calculation of the transport index (*Figure 2*) (20).

Generally, ICG-L and LS provide sufficient information to determine the most appropriate surgical strategy. However, a third imaging technique, magnetic resonance lymphography (MRL), has been introduced in the last decade, which we request in our center to complement certain limitations of the two previous imaging techniques or resolve discrepancies between their findings. MRL provides three-dimensional high-resolution anatomic images of the superficial and deep lymphatic systems, including lymph node basins, as well as useful information on the function of the lymphatic system. This imaging modality also provides detailed characterization of lymphedema-associated soft tissue changes and detailed limb circumference measurements that can be used to calculate limb volume (21,22). More recently, ultra-high frequency ultrasound (UHFUS) has also been introduced, which provides more acurate imaging of the structure of the subdermal lymphatic vessels. This technique can even detect the lymphatic vessels, where dermal backflow patterns were revealed by ICG-L. However, acquisition of accurate images by UHFUS is highly operator-dependent (23,24).

Surgical techniques

Surgical techniques for BCRL treatment can be divided into physiologic procedures, which attempt to re-establish lymphatic drainage and increase lymphatic fluid clearance, and ablative procedures, which aim to remove excess subcutaneous tissue in order to reduce limb volume. Currently, the three main pillars for the surgical treatment of BCRL are lymphatic-venous anastomosis (LVA), functional vascularized lymphatic tissue transfer (FVLTT), and liposuction (25). The three techniques have different therapeutic aims and their indications depend on the pathophysiological changes of the affected upper limb.

LVA is a supermicrosurgical physiologic procedure that connects lymphatic channels to nearby subdermal veins to redirect lymph drainage to the venous system in the limb (26). We recommend the use of this technique when functional lymphatic channels remain throughout the limb. Patient suitability for LVA can usually be determined by ICG-L. ICG-L or MRL can be used for preoperative planning. However, the combination of these two techniques allows for better location and selection of the most suitable functional lymphatic channels for LVA (*Figure 3*) (27). Moreover, if UHFUS is available, it may be employed for a more accurate preoperative identification of the subdermal lymphatic channels and nearby veins to be

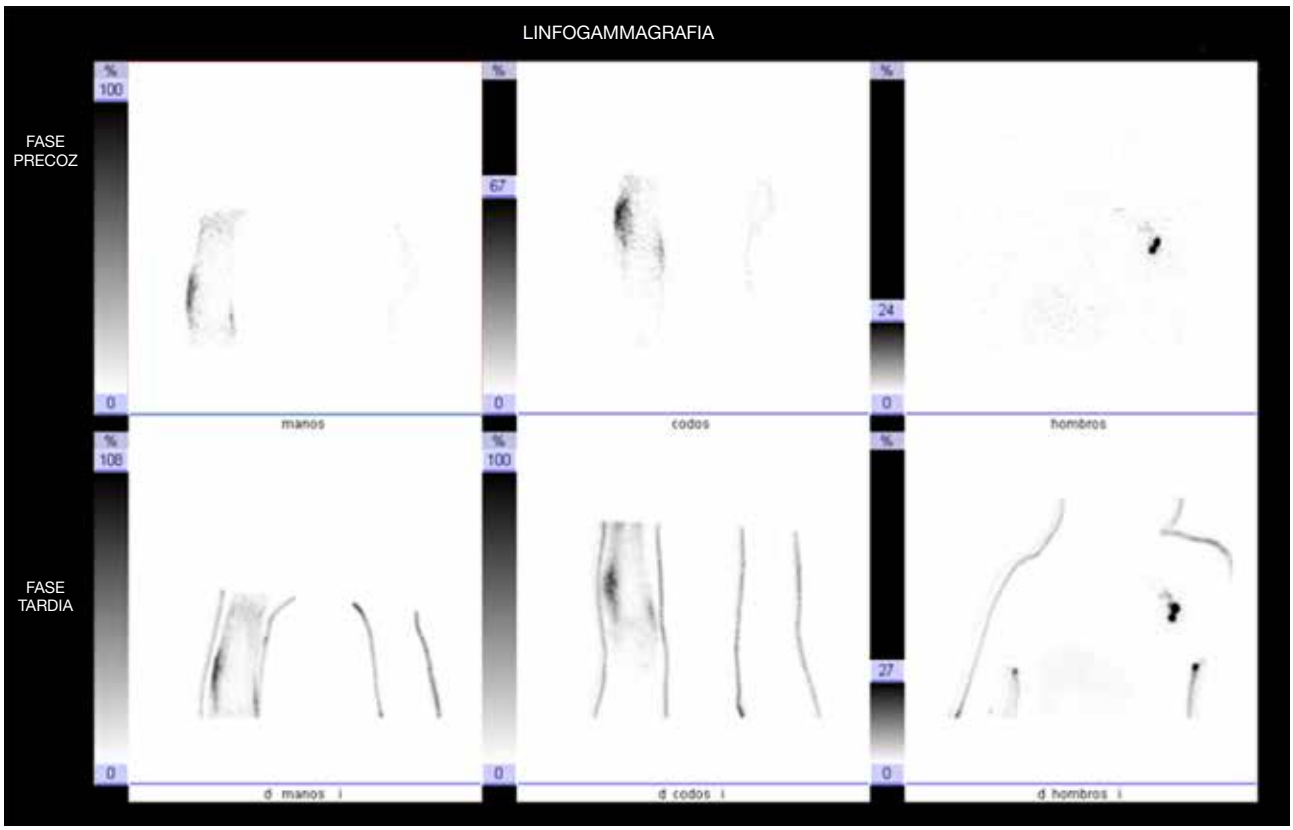

Figure 2 Lymphoscintigraphy images of the upper limbs of a patient with right-side lymphedema: early phase (above) and late phase (below).

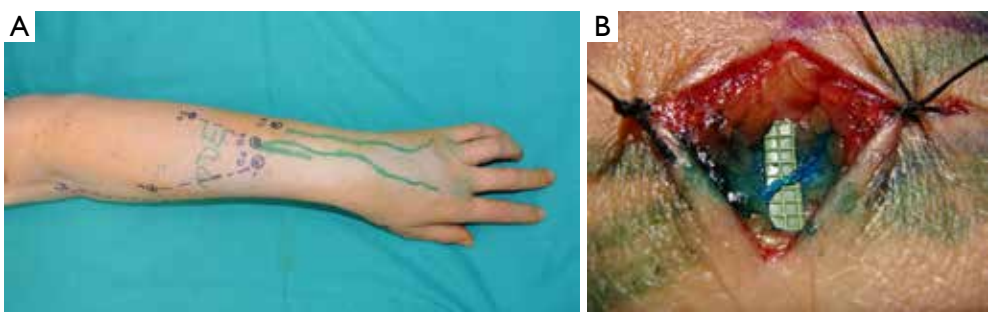

Figure 3 Lymphatic-venous anastomosis technique. (A) Pre-operative indocyanine green lymphography (green) and magnetic resonance lymphography (blue) markings. (B) End-to-end lymphatic-venous anastomosis.

anastomosed (23,24).

FVLTT is a microsurgical physiologic procedure involving the transfer of a vascularized flap with a functional lymphatic network. This functional lymphatic tissue flap is transferred from another region of the body to an area where the native lymph node basins and/or lymphatic channels are no longer functional. The exact mechanism of FVLTT is still under debate. One hypothesis is that the transferred functional lymphatic tissue may induce lymphangiogenesis and act as a wick to bridge gaps between the proximal and distal lymphatic vessels in the recipient site (28,29). The other hypothesis proposes that the vascularized lymphatic tissue acts as "lymph pumps". These pumps absorb lymph fluid from the surrounding interstitial

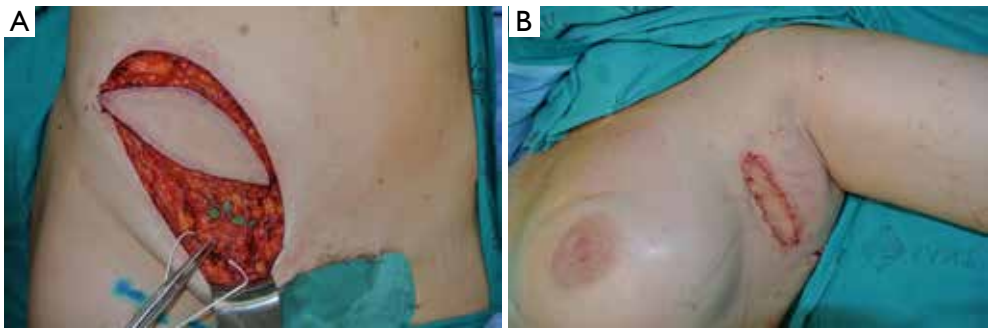

Figure 4 Functional vascularized lymphatic tissue transfer technique. Flap harvesting from the groin (A). Skin island of the functional vascularized lymphatic tissue flap transferred to the axillary region, anastomosed with the thoracodorsal vessels (B).

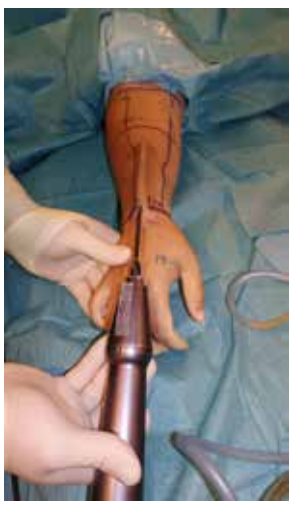

Figure 5 Liposuction technique with vibration-assisted device.

tissue and then expel it into the venous circulation by means of lymphovenous communication within the nodes in the transferred flap (29,30).

Various donor sites can be used for the FVLTT technique, with the most common being the iliac-inguinal region, with the superficial circumflex iliac vessels being used as the vascular pedicle. When planning FVLTT through the use of a groin flap, computed tomography angiography is needed to provide information on the location of the vascular pedicle of the flap and inguinal lymph nodes. In our practice, the recipient area for the FVLTT is the axillary region and proximal part of the limb (*Figure 4*). Both LS and ICG-L are usually needed to assess the functionality of the lymphatic system of the proximal part of the arm, and to determine whether the patient is suitable for FVLTT. In some cases, FVLTT can even be combined with autologous breast reconstruction. For this purpose, the ideal donor site is the lower abdominal region. For lymphatic tissue transfer, tissue is taken from the iliac-inguinal region, with the superficial circumflex iliac vessels providing a vascular pedicle. For breast reconstruction, tissue is taken from the lower abdomen, with the deep inferior epigastric vessels providing a pedicle. The two flaps are then harvested as one and positioned in the thorax (31). This combined reconstructive procedure is known as total breast anatomy restoration (TBAR) (32).

Despite the revolutionary concept of restoring the functionality of the lymphatic system together with effective maintenance decongestive therapy, neither of these techniques completely reduces limb circumference in more advanced stages of lymphedema, because the excess volume is mostly related to fat hypertrophy and fibrosis. In this context, liposuction is the preferred surgical procedure to remove excess subcutaneous tissue. This reductive technique helps to achieve similar circumference measurements to those of the contralateral limb, improve patient comfort, and reduce the incidence of erysipelas episodes (33). For this procedure, we recommend the use of power-assisted liposuction with vibrating cannulas (*Figure 5*). The liposuction technique is executed circumferentially from the wrist to the shoulder. Postoperative compression therapy is crucial to obtain favorable results (34).

The Barcelona lymphedema algorithm for surgical treatment (BLAST)

Because both the speed and severity of the pathophysiological changes of lymphedema are unpredictable and vary widely among patients, the surgical management of BCRL is complex. Therefore, the approach should be individualized

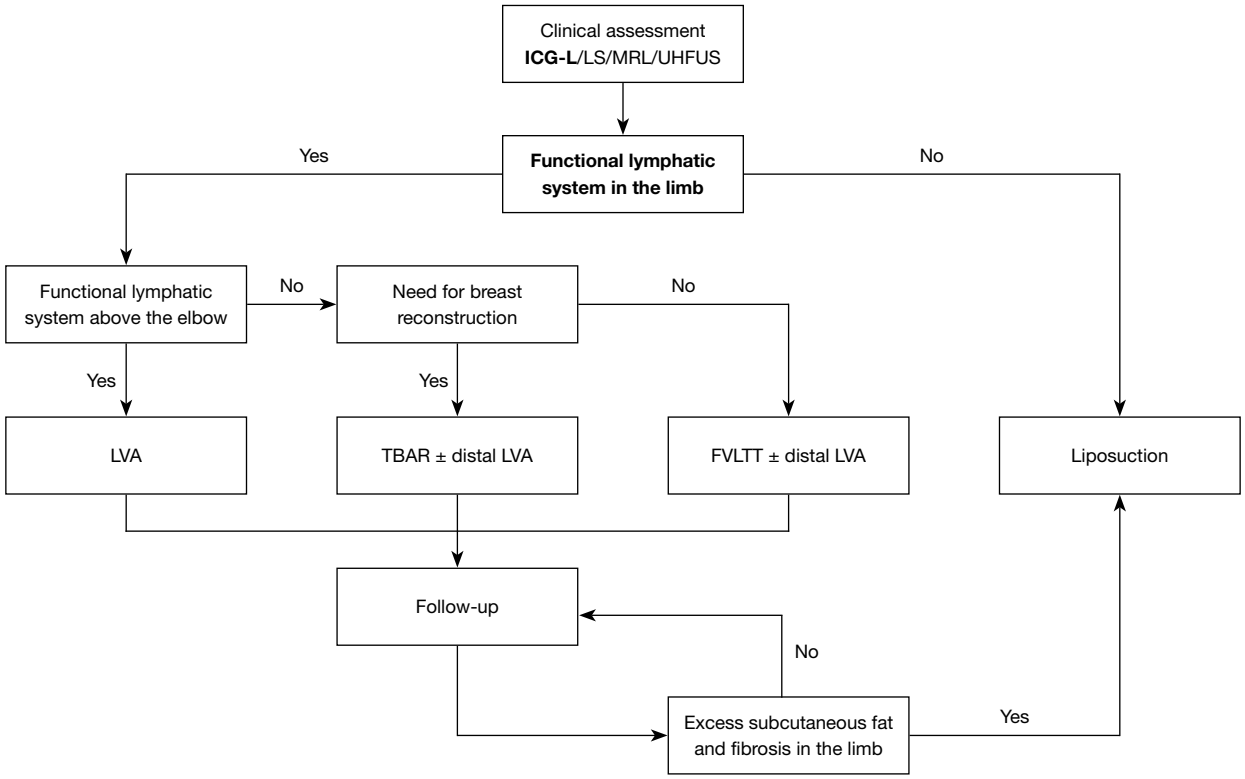

Figure 6 Barcelona lymphedema algorithm for surgical treatment. ICG-L, indocyanine green lymphography; LS, lymphoscintigraphy; MRL, magnetic resonance lymphography; UHFUS, ultra-high frequency ultrasound; LVA, lymphatic-venous anastomosis; TBAR, total breast anatomy restoration; FVLTT, functional vascularized lymphatic tissue transfer.

based on the degree of involvement of the lymphatic system and hypertrophy of the subcutaneous tissue (32,35). The surgical strategy may often involve a combination of techniques, either in the same intervention or in two stages. Below, we summarize the main clinical scenarios that can arise, depending on the findings of diagnostic imaging techniques and clinical assessment, and our surgical approach to the treatment of BCRL (*Figure 6*).

- Functional lymphatic system above the elbow on ICG-L/MRL: these findings generally correspond to ISL stages I–II. We recommend performing the LVA technique to improve lymph drainage by redirecting the flow of the functional lymphatic channels to the venous circulation in the limb itself. Subsequent periodic follow-up is also needed to assess the response to treatment and outcomes.
- Functional lymphatic system up to or below the elbow on ICG-L/MRL: these findings usually correspond to ISL stage II. We recommend a combined surgical approach using the FVLTT technique to improve lymph drainage of the proximal part of the limb, and the LVA technique at the level of the functional lymphatic channels to improve lymph drainage of the distal part of the limb. This combined approach can be performed either in the same intervention or in two stages. It should also be considered if the patient needs a breast reconstruction, to assess the possibilities of performing the TBAR technique. Subsequent periodic follow-up is also needed to assess the response to treatment and outcomes.
- Non-functional lymphatic system on ICG-L/LS/MRL: these findings generally correspond to ISL stage III. In patients with a moderate (20–40% increase) or severe (>40% increase) difference in the volume of the limb, and a history of erysipelas, pain, or reduced arm mobility, we recommend liposuction.
- Patient with previous physiologic procedures (LVA, FVLTT ± LVA or TBAR ± LVA) and excess subcutaneous fat and fibrosis. In some patients who

have undergone successful physiological surgical interventions, the volume of the limb may not decrease to that of the contralateral side. This is due to the development of excess subcutaneous fat and fibrosis. These patients may correspond to ISL late stage II. In patients with a moderate (20–40% increase) difference in the volume of the limb that affects the quality of life, we recommend performing liposuction as a complementary surgical procedure.

Risk reducing lymphedema surgery

The earlier reconstructive procedures are performed, the greater their effectiveness. Accordingly, the most recent trend is BCRL risk reducing surgery. This new approach involves intraoperative evaluation of the axillary lymphatic system in patients undergoing lymph node dissection and immediate surgical repair of the sectioned lymphatic channels.

This innovative approach was first reported by Boccardo *et al.* (36) and was named the lymphatic microsurgical preventive healing approach (LYMPHA). The surgical technique consists of injecting a blue dye to visualize the afferent lymphatic channels during axillary lymph node dissection and the sectioned lymphatic channels are then introduced inside the nearby veins cut end using a U-shaped stitch.

The reported incidence of BCRL with the LYMPHA was highly encouraging (4.34% in the LYMPHA group *vs.* 30.43% in the control group not undergoing surgical prevention) (37). However, some studies show that the lymphatic-venous implantation technique is associated with a very high rate of blood clot formation and subsequent blood vessel obstruction (38,39).

More recently, a similar surgical approach was developed by our team for the prevention of upper limb lymphedema secondary to breast cancer treatment, the targeted-lymphatic axillary repair (T-LAR) approach. This technique involves axillary reverse mapping using ICG-L and blue patent V dye to identify afferent lymphatic channels during axillary lymph node dissection. When interruption of lymphatic channel is confirmed, an immediate bypass is performed between the transected lymphatic channel and small tributaries of axillary veins through end-to-end lymphatic-venous anastomosis. Because of the high precision of axillary reverse mapping in identifying sectioned afferent lymphatic channels and the feasibility of lymphatic venous bypass through "true" anastomoses that maintain the continuity of the intima of the vessels, the T-LAR approach is a promising procedure to significantly reduce the incidence of BCRL (40).

Conclusions

The key to successful management of BCRL is optimal patient selection and individualized surgical treatment based on the structural and functional involvement of the lymphatic system. Screening for BCRL by ICG-L in patients with previous axillary lymph node dissection should be standard practice for early diagnosis and prompt surgical treatment. Nevertheless, risk-reducing lymphedema surgery is becoming a highly promising approach to decrease the incidence of this debilitating condition.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Editorial Commentary

Timing of post mastectomy radiotherapy in immediate or delayed-immediate breast reconstruction: an algorithm to the sentinel first principle

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Introduction

About one out of eight women will be dealing with breast cancer throughout their life. The prevalence of this disease has jet-fueled breast cancer research, causing an immense leap in treatment modalities over the last decades. A better understanding of the disease, its subtypes, its genome and its treatment strategies has allowed us to evolve from aggressive to targeted, from debulking to breast conserving and from avoiding death to ensuring quality of life after survival. Despite major advances in medical therapy, surgery remains an indispensable step in breast cancer treatment. The novelties in breast conserving surgery and reconstructive surgery have made the treatment more versatile, which allows the oncoplastic team to provide a tailor-made surgical plan for each patient. The treatment regimen must aim for synergism between the different treatment modalities, without compromising either the oncological or reconstructive objective. While adjuvant therapy may downstage the tumor and make breast conservative surgery possible, adjuvant treatments like radiotherapy might also compromise the reconstructive outcome. Most patients who undergo breast conserving surgery are treated with radiotherapy, whereas the indication for postmastectomy radiotherapy (PMRT) is mainly based on tumor stage and the extent of lymph node involvement. Radiotherapy of the breast is indicated after breast conserving surgery for all invasive tumors, most ductal carcinoma *in situ* and Paget's disease. It will also be applied when mastectomy margins were not clear from disease or when the tumors appeared to be more than 4 cm in diameter. Locoregional radiotherapy is indicated when nodal disease is confirmed (≥ N1) and will be more extensive according to the degree of nodal disease.

In patients needing PMRT, the definite reconstruction can be delayed by placing an expander in the mastectomy pocket. Although the consequences of radiotherapy on the autologous reconstructed breast is the subject of discussion, the literature suggests a higher occurrence of fat necrosis, late flap failure and decreased esthetic outcome from radiotherapy after free flap breast reconstruction (1). Since autologous breast reconstruction requires proper organization regarding surgery time and available surgeons, it is not advisable to rely on a preoperative diagnosis to decide whether or not to proceed with an autologous reconstruction.

A problem arises in clinical node-negative breast cancer patients, where the definite tumor and nodal staging is not complete until full tumor and sentinel node resection. It is logistically not feasible to foresee both immediate and delayed reconstructive surgery depending on an intra-operative decision. Therefore, the sentinel first principle was introduced in our center.

This paper outlines the algorithm applied in our center, in which the sentinel procedure is done in a separate surgery before the mastectomy for definite staging. This method, called the "sentinel first procedure", allows the oncoplastic team to decide whether immediate or delayed-immediate reconstruction is indicated. This paper describes an algorithm for this principle, which was introduced in our center in 2017, and reviews thirteen cases. The objective

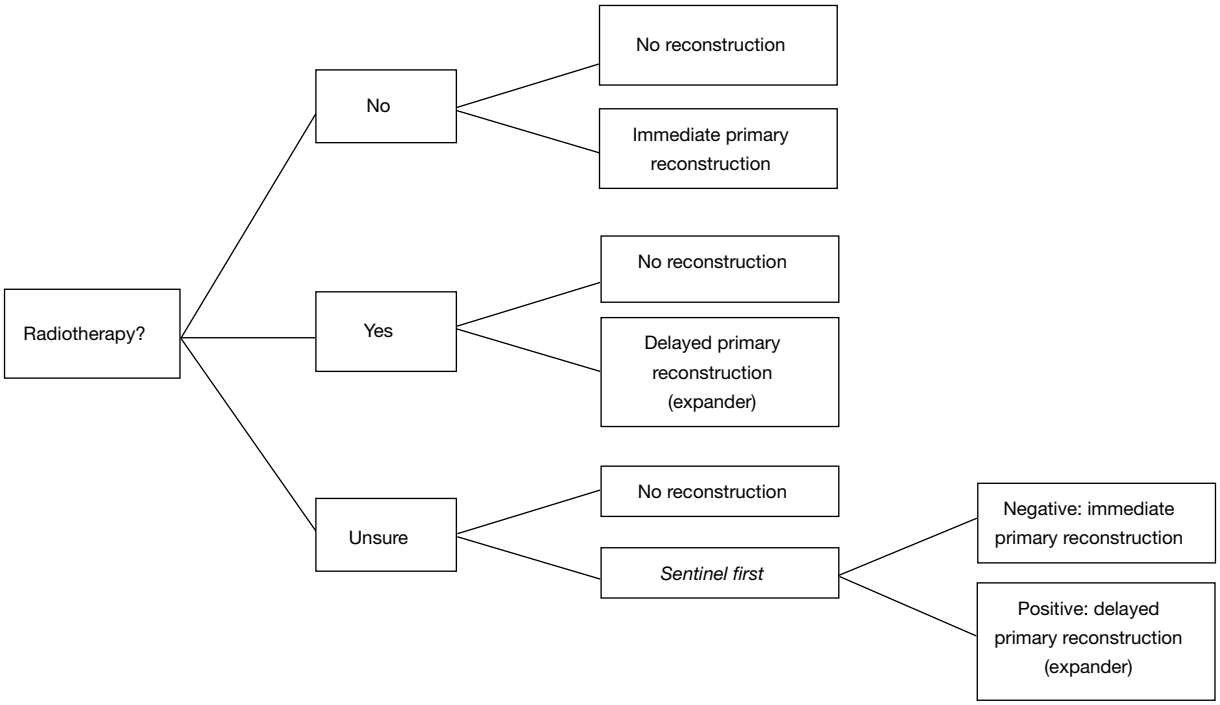

Figure 1 Decision tree for breast reconstruction according to the need for radiotherapy. Sentinel first is indicated when the decision to add PMRT relies almost solely on the nodal status of the patient. PMRT, postmastectomy radiotherapy.

of this principle is to improve the oncoplastic orchestra of breast reconstructive surgery.

Protocol

Patients with a ductal carcinoma in situ (DCIS) tumor or a tumor that is smaller than 3 cm with a clinically negative node status are candidates for mastectomy with immediate reconstruction if the node is confirmed to be negative after resection. These patients will be included in what is called the "sentinel first" procedure. These patients are scheduled for sentinel node biopsy in the surgical day clinic. When no cancerous cells are found in the resected sentinel nodes, skin sparing mastectomy with immediate autologous or allogenous reconstruction is planned as second surgery. When one or more sentinel nodes are invaded, de patient is scheduled for mastectomy with expander prosthesis reconstruction and the definitive reconstruction will be completed after adjuvant radiotherapy. This is called delayed immediate reconstruction (*Figure 1*).

Radiotherapy can be initiated between six weeks and two months after the placement of the expander and when the skin is properly healed. In the case of adjuvant chemotherapy, the initiation of radiotherapy is between two and six weeks after the last chemotherapy session. Completion of the free flap reconstruction can be planned as soon as the skin is sufficiently healed from radiotherapy which varies between 6–12 months.

When autologous reconstruction is not possible or when the patient prefers it, an implant-based reconstruction is second choice. In that case, the timing of radiotherapy will be in a two-stage setting with an expander prosthesis that is similar to autologous reconstruction. Both the expander as the definite prosthesis will be placed in a subpectoral plane. Patients that are initially advised to get a delayed or delayed immediate reconstruction are evidently no candidate for the sentinel first procedure.

Cases

Between 2017 and 2021, a total of thirteen patients were candidates for the sentinel first procedure. Patients were between 45 and 61 years old (mean: 52.1) and they were all diagnosed with either invasive or *in situ* ductal type carcinoma. The indication for mastectomy was multifocality in four patients, recurrence in three patients, BRCA1

positivity in one patient and unfavorable tumor/breast ratio or esthetic outcome in five patients. Four patients received neoadjuvant chemotherapy for triple negativity which downstaged the tumor to an ypT0N0 stage in three patients. The sentinel was positive (malignant cells found) in two cases, in which an expander was placed to preserve the breast pocket during radiotherapy. The reconstruction was completed as an immediate delayed procedure six months after the completion of the radiotherapy treatment regimen. Nine patients were reconstructed with a DIEaP (Deep Inferior Epigastric artery Perforator) flap, one patient with a PAP (Profunda Artery Perforator) flap, one patient with TMG (Transferse Myocutaneous Gracilis) flap, one patient with implants and one patient with an expander that is not reconstructed yet. *Figure 2* shows a 69-year-old patient with history of breast reduction who was diagnosed with multifocal ductal carcinoma *in situ* in the left breast. A sentinel first procedure was done two weeks after the diagnosis. The sentinel showed no nodal disease, so the patient was planned for a unilateral DIEaP flap reconstruction of the left breast three weeks later. The sentinel procedure leaves a 2 cm scar in the axilla, as seen in *Figure 3*.

Discussion

Post mastectomy radiotherapy has become an indispensable part of the therapy regimen, since the EBCTCG meta-analysis reported that it improves disease free and breast cancer survival for patients with involved axillary lymph nodes (2). Also, the introduction of the sentinel lymph node biopsy procedure with axillary and thoracic wall radiotherapy has become an alternative to axillary lymph node dissection in patients with limited nodal disease (3,4). PMRT reduces the risk of local recurrence, which most often occurs subcutaneously in the chest wall, followed by the skin itself and mostly at the area around the mastectomy scar. It is postulated that the latter is the result of tumor cell seeding during the surgical procedure (5).

The surgical technique of mastectomy should eliminate as much breast tissue as possible without disrupting surrounding structures that are important for reconstructive outcome. The skin flap should ideally contain only subcutaneous tissue without residual breast tissue, since the skin above the tumor site contains a high risk of recurrence especially in DCIS type breast tumors (6). Patients that are candidates for primary breast reconstruction after mastectomy, the need for adjuvant radiotherapy will determine whether an immediate or delayed immediate reconstruction can be performed. The delayed immediate principle was introduced to decrease the complications associated with radiotherapy on the reconstructed breast, but this also delays reconstruction in patients that turn out to be in no need of radiotherapy. The psychological burden of breast reconstructive surgery is less in immediate procedures compared to immediate delayed. Also, an unnecessary delay of final reconstruction in sentinel negative patients is psychologically challenging for the patient. The need for PMRT cannot be excluded until the final pathological evaluation is done, being after surgery. Although a systematic review from 2014 concluded that there were similar complication rates between patients receiving radiotherapy before and after autologous reconstruction, the overall incidence of flap loss was 1% in patients who received radiotherapy before reconstruction *vs.* 4% in patients who received radiotherapy after reconstruction (7). A meta-analysis of 12 observational studies concluded the same about complication rates, but stated that women who received radiotherapy after reconstruction had a significantly higher incidence of revisional procedures compared to women receiving radiotherapy before their reconstruction (8). In implant based reconstruction, radiotherapy on the permanent implant is associated with a higher incidence in capsular contracture, but the rate of reconstructive failure is subject to debate. Studies that show an increase in reconstructive failure in patients that receive radiotherapy on their implant are contradicted by a meta-analysis from 2017 that shows no difference between radiotherapy to the tissue expander versus radiotherapy to the permanent implant. Conclusive high-quality evidence from randomized clinical trials is lacking, according to Ho *et al.* (1). Still, autologous reconstruction is reported to have lower rates of complications and better cosmetic outcomes in the setting of PMRT, compared to implant-based reconstruction (9).

Studies show that there were no differences in complication rate when the autologous reconstruction was performed either before or after six or twelve months post-radiotherapy. Implant reconstruction after prosthesis did show a higher rate of implant failure when the exchange was done within six months of radiotherapy according to a study by Peled *et al.* (10). In implant-based reconstruction, capsulectomy and Acellular Dermal Matrix can be used to prevent implant failure and improve the surgical outcome.

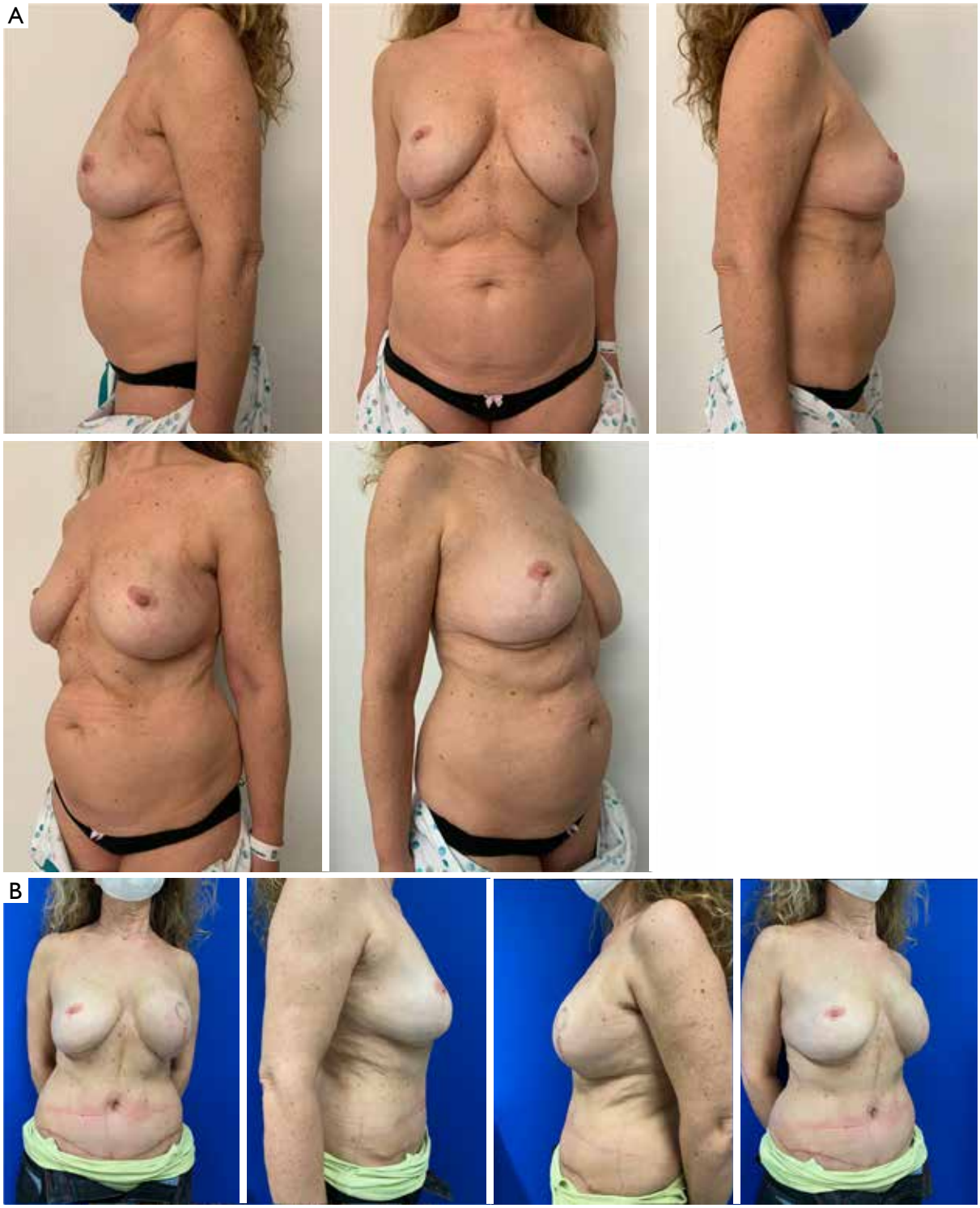

Figure 2 A 69-year-old patient with history of breast reduction who was diagnosed with multifocal ductal carcinoma *in situ* in the left breast. (A) Preoperative pictures of a 69-year-old patient with history of breast reduction who was diagnosed with multifocal ductal carcinoma in situ in the left breast; (B) postoperative results two months after DIEaP flap reconstruction of the left breast. DIEaP, Deep Inferior Epigastric artery Perforator. These images are published with the patient's consent.

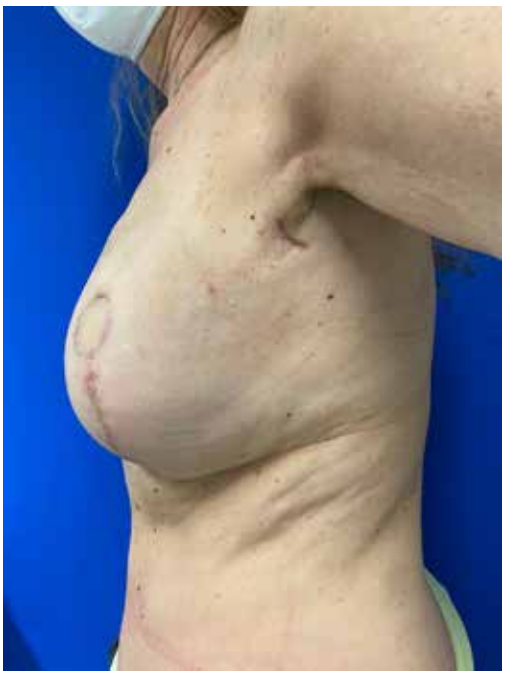

Figure 3 Scar from the sentinel first procedure in the axilla. This image is published with the patient's consent.

Conclusions

Immediate postoperative complications might delay the administration of adjuvant therapy administration, while late complications impact the safety of oncological surveillance, cost/effectiveness and aesthetic outcome of the reconstruction. In a certain subpopulation of early stage breast cancer patients in whom tumor size does not require PMRT after mastectomy, the need for PMRT will be almost solely based on the nodal status of the patient. For this purpose, the *sentinel first* procedure was introduced in our center as a staging tool that allows the surgical team to decide whether immediate or delayed reconstruction should be applied. The long-term outcomes and benefits of this procedure should be determined in larger case series.

Acknowledgments

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Footnote

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Editorial Commentary

The immediate-delayed deep inferior epigastric perforator (DIEP) flap: is it worth the extra step?—an expert's opinion

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Introduction

Breast cancer is the most common cancer in women worldwide (1). An increasing number of patients decide to undergo breast reconstruction after mastectomy (2). On local, regional, national and international level, a large variety exists among type and timing that are offered in breast reconstruction surgery. In general, autologous breast reconstructions are considered to provide a more natural and permanent outcome, resulting in higher patient-reported satisfaction rates when compared to implant-based reconstructions (3,4). Due to lower complication rates than other autologous flaps, the deep inferior epigastric perforator (DIEP) flap has become the golden standard for autologous breast reconstruction (5). The increasing number of DIEP flaps each year (6), requires a novel approach combining the most optimal oncological treatment on the one hand, while resulting in the most aesthetically pleasing breast(s) on the other hand. Moreover, in order to keep up with the increasing demand of DIEP flaps, efficient planning of the operation in support of reduction of surgical time is needed.

Immediate, immediate-delayed and delayed DIEP flap reconstruction

Following mastectomy, a DIEP flap reconstruction can be performed in an immediate, immediate-delayed (i.e., immediate tissue expander placement, followed by staged DIEP flap reconstruction) or delayed fashion. Several factors contribute to the decision-making process of the timing of the breast reconstruction, including medical considerations such as a history of breast surgery, comorbidities, patients' anatomy or a possible indication for adjuvant radiotherapy (3,5,7,8). Moreover, patients' preference, surgeons' expertise and hospitals' recourses are to be considered. For example, many hospitals do not have access to sufficient capacity to offer immediate breast reconstruction due to logistical challenges (9,10).

Given the varying risks and benefits of the different types of breast reconstructive options, the decision-making process can be highly complex and overwhelming for patients. This can lead to feelings of anxiety and/or distress in already uncertain times in which they are already confronted with the diagnosis of (increased risk at) breast cancer (11). Moreover, the Dutch guideline for breast cancer treatment advices a maximum period of six weeks between diagnosis and mastectomy (with or without breast reconstruction) (12), thereby putting a time constraint on the decision-making process. Previous literature showed that women who are struggling with their decision on what type of breast reconstruction to choose, experience additional emotional pressure due to this six week window (4). In order to buy time for decision-making process without delaying oncological treatment (i.e., the mastectomy, radiotherapy or adjuvant therapy) while preserving the skin envelop (13,14), immediate-delayed breast reconstruction might offer a solution to a possible lack of hospital capacity and/or perceived emotional pressure. In case the mastectomy was performed previously, a way to simulate a skin envelop, an extra procedure can be offered to pre-expand the breast skin that is left before performing the delayed breast reconstruction. DIEP flap reconstructions are cost-effective

when considering health-related quality of life and patient satisfaction (15,16). However, comparative data on costs of pre-expansion of the breast before DIEP flap reconstruction is limited. Comparing immediate, immediate-delayed and delayed DIEP flap reconstruction, similar incidences of recipient site complications and flap re-explorations were observed (3).

The major advantage of pre-expansion of the breast is better cosmetic outcomes, in terms of better native shape of the breast, more sensate skin envelope and less scarring (5,7,8). This is important, because aesthetics play an important role in the quality of life and well-being of the patient and strongly influences the choice for additional reoperations (8). In addition, pre-expansion results in a shorter duration of reconstructive surgery for the autologous breasts.

However, there are also disadvantages to pre-expansion. First, an extra element of surgery during or after mastectomy is added, and the patient must live for a considerable amount of time with a tissue expander before definitive operation. This might lead to postponement of oncological therapy, may lead to longer hospitalization and increased risk of social or emotional difficulties due to complaints of the tissue expander or a prolonged time until completion of the treatment trajectory (5,8). Moreover, some patients experience the many out-clinic visits for expansion of the tissue expander as (emotionally) intensive. Last, the risk of early explantation of the tissue expander due to infection or erosion.

Clinical experience

Pre-operative consultation is crucial. Patients have a 30 minutes consultation at the plastic surgeon to show a standard PowerPoint with principles, examples of outcomes including a diverse range of photos, complications and treatment protocols. In case a patient is not convinced about her decision offering the option of pre-expansion after mastectomy might support patients in experiencing less pressure and stress during the decision-making process.

Indications for pre-expansion included all patients who underwent unilateral DIEP flap reconstruction between January 2013 and December 2019 or patients with the desire of a DIEP flap reconstruction who had their initial surgery (mastectomy) in another hospital, combined with patient-preference. The approach of pre-expansion consists of a skin sparing mastectomy followed by an immediate subpectoral placement of alloplastic material in form of a tissue expander and using them as spacers inside the breast skin envelop to avoid the skin to stick back to the thoracic wall after mastectomy has been performed. The tissue expander can be filled to enlarge the breast skin until the start of radiotherapy or adjuvant therapy, thereby not delaying oncological treatment. Once the oncological treatment is completed, the tissue expander can be filled until it is sufficient and substituted with the DIEP flap. During DIEP flap reconstruction, the tissue expander was removed and partial capsulectomy was performed. Premature explantation of the tissue expander due to infection or erosion occurred in seven patients (12.5%).

In our community hospital, the mean duration of surgery for unilateral DIEP flaps with pre-expanded breasts was 308 minutes (SD 81) and the mean duration of surgery for unilateral DIEP flap without pre-expanded breasts was 334 minutes (SD 85) (P=0.0126). Although not significant, it is clinically relevant. The duration of a DIEP flap in a pre-expanded breast is approximately 30 minutes shorter (*Figures 1,2*) with no more major complications, thereby creating opportunity to perform two unilateral DIEP flap reconstructions in one day.

Postoperative, patients with pre-expanded breasts were more satisfied with the aesthetics of the breast because of better native shape of the breast, more sensate skin envelope, no need for a (large) skin island, and less scarring. Hence a lower number of complementary surgeries were required to achieve satisfying aesthetic result.

Recommendation

According to previous literature and our clinical experience, the author's opinion is that pre-expansion is worth the extra procedure. Pre-expansion of the breast leads to a shorter duration of reconstructive surgery with higher patients' satisfaction rates and a comparable rate of complications. However, important factors to consider remain hospital capacity and costs. In future research, it would be valuable to include a costs-benefit analysis of both surgical modalities and to include patient-reported outcome (PRO) scores with a validated and breast cancer specific questionnaire such as

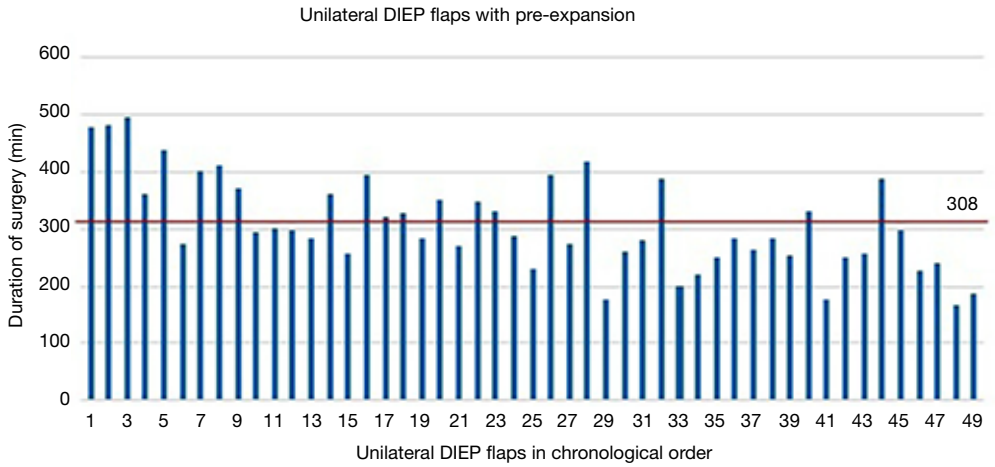

Figure 1 Unilateral DIEP flaps with pre-expansion. The duration of surgery per patient in chronological order. The red line illustrates the mean duration of surgery in minutes. DIEP, deep inferior epigastric perforator.

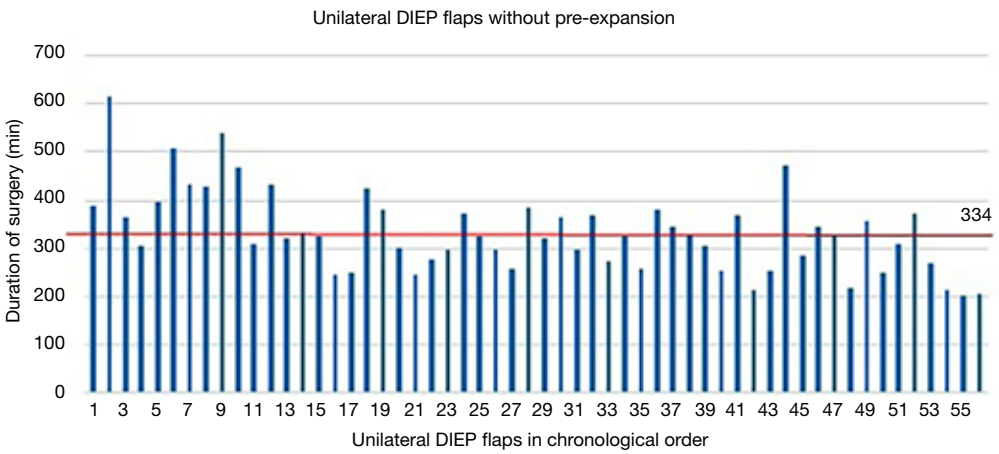

Figure 2 Unilateral DIEP flaps without pre-expansion. The duration of surgery per patient in chronological order. The red line illustrates the mean duration of surgery in minutes. DIEP, deep inferior epigastric perforator.

BREAST-Q.

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