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Title

Complications in DIEP flap breast reconstruction after mastectomy for breast cancer: A prospective cohort study comparing unilateral versus bilateral reconstructions

Running Head

Complications in Unilateral vs Bilateral DIEP flap breast reconstruction

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Presentations

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2. The Italian Society of Microsurgery (SIM) Symposium. Sassari, Italy. October 12th 2012.
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4. The 24th Annual Meeting of the European Association of Plastic Surgeons, (EURAPS). Antalya, Turkey. 23rd-25th May 2013.

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Competing Interests

None declared.

Ethical approval

This study was designed and conducted as an audit so ethical approval was not required. It was registered with code PS2013007 within the database of audits held in the Department of Clinical Audit and Effectiveness of the Norfolk and Norwich University Hospital NHS Foundation Trust.

Synopsis

The demand for bilateral mastectomy and bilateral deep inferior epigastric perforator (DIEP) flap breast reconstruction for breast cancer is rising worldwide. A recent review suggested that adverse events in bilateral DIEP flap breast reconstruction were substantially more common than for unilateral reconstruction and determined that higher quality research was needed. Our prospective cohort study answers this calling and offers robust evidence to support the evolving concept that bilateral DIEP flap breast reconstruction carries a higher risk of adverse outcomes than unilateral DIEP flap breast reconstruction.

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Article word count = 2673

Abstract

Background: The demand for bilateral breast reconstructions is rising worldwide. In the UK, about 30% of breast cancer patients undergoing mastectomy choose autologous tissue breast reconstruction. Although the DIEP flap is gaining popularity, bilateral DIEP flap breast reconstruction remains a complex procedure and reliable outcome data is lacking. In the absence of clinical trials, evidence from cohort studies is needed to better inform clinicians and patients.

Methods: Over a 6-year period, all consecutive patients undergoing DIEP flap breast reconstruction were prospectively included and categorised as unilateral or bilateral reconstruction for comparative analyses of outcomes and complications, with the patient as the unit of analysis.

Results: Overall, 565 DIEP flaps were performed on 468 women. There were 371 unilateral and 97 bilateral reconstructions (194 flaps). Postoperative complications requiring re-operation was twice as likely for bilateral reconstructions (RR 2.1 [95% CI 1.4, 3.4], p=0.002) and mainly due to venous congestion (RR 3.1 [95% CI 1.2, 7.5], p=0.011). The risk of total flap loss was six times greater in bilateral reconstruction (RR 6.4 [95% CI 1.6, 26], p=0.011). The rates of revision breast and abdominal surgery were similar between groups.

Conclusions: Both unilateral and bilateral DIEP flap breast reconstructions are safe, with a low risk of complications. However, bilateral reconstruction was associated with a higher risk of complications and total flap loss. This information should be highlighted to patients requesting bilateral breast reconstruction and particularly those requesting risk-reducing mastectomy and reconstruction.

Level of Evidence: II

Abstract word count: 238

Introduction

The number of bilateral mastectomies is rising worldwide[1-4], and the number of women seeking risk-reducing mastectomy and reconstruction has also increased by 91%[5]. As more women undergoing mastectomy are offered breast reconstruction[6], the increasing demand for bilateral breast reconstruction is becoming a significant and challenging issue[7].

Bilateral breast reconstruction may be considered in cases of: risk-reducing bilateral mastectomy (eg. BRCA1/2 mutation carrier or a strong family history)[8-10]; unilateral mastectomy with contralateral risk-reducing mastectomy for women with similarly high risk of malignancy[4,11-13] or anxiety related illness; synchronous or non-synchronous bilateral mastectomy for cancer or bilateral mastectomy for significant distortion after breast conserving surgery[14].

Following bilateral mastectomy, implant-based breast reconstruction is a valid option particularly in absence of postmastectomy radiotherapy[15]. However, autologous tissue breast reconstruction has been associated with the highest level of patient satisfaction and its use is gaining popularity worldwide[16]. In 2011, approximately 30% of breast cancer patients underwent breast reconstruction with autologous tissue in the UK[17]. Amongst the available autologous tissue options for breast reconstruction, the evolving consensus is that the deep inferior epigastric perforator (DIEP) flap can offer better outcomes due to reduced donor site morbidity[17-20], fewer days in hospital[21], less post-operative pain[22] and superior cosmetic results[23].

To-date, only a few studies have reported the outcomes of unilateral versus bilateral DIEP flap breast reconstruction and a meta-analysis by our group showed that bilateral reconstruction carried a significantly higher risk of complications than unilateral reconstruction, although the quality of data was generally poor[24]. Given clinicians' influence in the decision making process[25,26], the rising demand for bilateral reconstruction and the paucity of high-quality research on DIEP flap breast reconstruction, robust outcome data is required in order to better inform clinicians and patients[24].

We aimed to investigate the hypothesis that bilateral DIEP flap breast reconstruction is associated with a higher risk of complications than unilateral DIEP flap breast reconstruction.

Methods

Design

Difficulties with recruitment to randomised trials involving breast reconstruction is well known[27-29] and so, a single centre prospective cohort study was planned (Institutional registration number PS2013007). Between January 1st 2009 and December 31st 2014, an electronic database with standardised outcomes was prospectively completed to audit outcomes of all consecutive patients undergoing DIEP flap breast reconstruction. This database was updated using written and electronic patients' notes. Participants were categorised as unilateral or bilateral DIEP flap breast reconstruction for comparative analysis.

Outcomes

Our primary outcome was any postoperative complication requiring a return to theatre. In accordance with the BRAVO study[30], our secondary outcomes were revision surgery on the breast or abdomen, systemic complications (eg. pulmonary embolism) and hospital stay. We also collected demographic data, breast malignancy details and adjuvant therapies. Diameters of the deep inferior epigastric vein (DIEV) and superficial inferior epigastric vein (SIEV) were based on the COUPLER™ size. Complications were defined as adverse events occurring within 30 postoperative days. We defined partial flap loss as necrosis of the flap, which required debridement but not removal of the entire flap. Revision surgeries were planned and occurred after 30 days postoperatively.

Intervention

In our centre, all women undergoing mastectomy for breast cancer are offered discussion regarding breast reconstruction[6]. The choice of timing and type of reconstruction is based on patient's preference and surgical options. About 70% of patients requesting breast reconstruction choose a DIEP flap. When adjuvant radiotherapy is required, our breast multidisciplinary team policy is to offer delayed autologous tissue reconstruction. During the study period we did not perform any pedicled or free TRAM or SIEA flaps.

Patients with a high BMI (>30 kg/m^2) were advised to lose weight[31]. Smokers were advised to stop at least 4 weeks prior to surgery. Neither were exclusion criteria. Hormone therapy, when part of the patient's breast cancer treatment, was continued[32,33].

Before surgery, a Duplex assessment of perforators of the lower abdominal wall is always carried out by the same experienced radiologist. All DIEP flap breast reconstructions are performed by two senior surgeons with a standard technique. We routinely preserve the SIEV for supercharging in case of venous congestion. Our first-choice recipient vessels are the internal thoracic (IT) at the level of the 3rd rib or second intercostal space (rib sparing technique). The thoracodorsal (TD) vessels are used only if the former are considered unsuitable for a patent micro-anastomosis. We perform end-to-end arterial anastomoses with 9-0 Ethilon™ and use a COUPLER™ for venous anastomoses[34,35]. In very slim patients, those with midline abdominal scars or insufficient cross-midline perfusion, unilateral reconstructions are performed using a bipedicled DIEP flap. In such cases, we anastomose both pedicles to the IT vessels, one with anterograde flow and the second with retrograde flow.

Analysis

Data was analysed using IBM SPSS v22. Normally distributed continuous variables are presented as means with standard deviations (SD) and compared with independent samples t-tests. Skewed distributions and integer variables are presented as medians with interquartile ranges (IQR), and compared with the Mann-Whitney U-Test. Categorical variables are presented as frequencies (with percentages) and compared with Chi Square or Fisher's Exact test with resampling methods as

appropriate. We preferentially generated risk ratios (RR) with 95% confidence intervals (CI). Following established statistical methodology[36], the patient/woman and not the flap was the unit of analysis as this avoids violating assumptions of independence and RRs can then be directly communicated/translated to healthcare providers and patients alike. To explore potential associations between response variables (our primary and secondary outcomes) and certain explanatory variables, we performed binary logistic regression analyses. This was not to develop prediction models, but instead to test specific hypotheses. There are no known predictors in this context, so we explored outcomes that we felt clinically relevant (eg. operative time, flap ischaemia, etc) and selected variables in an iterative process, with the final model including total operative time in hours and flap ischaemia time in minutes (as scaled predictors), and bilateral versus unilateral DIEP flap reconstruction (as a binary variable) given the magnitude of their effect and fit. Although not required according to the TRIPOD guidance[37], we did perform internal validation by bootstrapping using 1000 resamples for clarity. Models generated odds ratios (OR) with 95% CIs. Significance was set at $p<0.05$.

Results

Overall, 468 women underwent breast reconstruction with 565 DIEP flaps; there were 371 (79.3%) unilateral reconstructions and 97 (20.7%) bilateral reconstruction (with 194 DIEP flaps).

Table 1 summarises patient demographics. All unilateral reconstructions followed cancer related mastectomies. Bilateral cases included: bilateral risk-reducing mastectomy with immediate reconstruction (n=13, 13.4%), delayed contralateral risk-reducing mastectomy with bilateral reconstruction (n=29, 29.9%), simultaneous mastectomy for cancer and contralateral risk-reducing mastectomy with immediate reconstruction (n=39, 40.2%), bilateral mastectomies for synchronous cancers with immediate reconstruction (n=7, 7.2%) and bilateral non-synchronous mastectomies for cancers with delayed reconstruction (n=9, 9.3%). One of the women opting for bilateral risk-reducing

mastectomy and immediate reconstruction was incidentally found to have a ductal carcinoma-in-situ in one breast.

Amongst the unilateral reconstructions, 35 women had a bipedicled DIEP flap (9 immediate and 26 delayed procedures). The IT vessels were used in 558 flaps (98.7%).

The SIEV was absent in 18 women (3.85%). The ipsilateral SIEV supercharged the flap in 50 women (35 unilateral and 15 bilateral). Median COUPLER™ sizes for DIEV and SIEV, location (medial or lateral row) and number of perforators were not different between groups.

In the bilateral reconstruction group, flaps were lighter, operative times and hospital stay longer. Nipple-areola complex reconstruction was more common in bilateral reconstructions (61/97 vs. 184/371 cases, $p<0.001$).

The risk of complications requiring re-operation was higher in the bilateral group (Table 2), as was the risk of total flap failure, associated with venous congestion. We salvaged 14 of 18 congested flaps by rescue SIEV augmentation (n=7) or re-doing the venous anastomoses (n=7).

In the unilateral group, we experienced three total flap failures (0.81%): one patient developed a large pneumothorax, which caused flap congestion and precluded salvage (Figure 1). The other two failures were due to recurrent arterial thrombosis, later proven to be due to hyper-coagulopathy conditions.

In the bilateral group, 5 women experienced unilateral flap failure (5.15%). One case was due to recurrent arterial thrombosis following bilateral synchronous cancer excision and intra-operative findings of occult chest wall spread. Another patient had bilateral risk-reducing mastectomy (Figure 2) and both DIEPs were found dependent on the superficial venous system, which was anastomosed with the IT vein: one flap failed due to kinking of SIEV. The remaining 3 cases had cancer related

mastectomies and developed intra-flap venous congestion in the absence of a SIEV for supercharging. Women who lost one of their bilateral DIEP flaps had a longer median flap ischaemia time (42.8 vs 30 minutes, p=0.043) and longer median operative time (10 hours 6 minutes vs. 8 hours p=0.007), which represents salvage efforts.

Five patients (3 unilateral and 2 bilateral) required blood transfusion. Pulmonary embolisms were similar between groups (2 after delayed reconstruction vs. 3 after mastectomy with contralateral risk-reducing mastectomy and immediate bilateral reconstruction). Postoperative breast wound infection was more common in the bilateral group (2 vs. 0 cases, p=0.021).

Excluding the need to reconstruct failed flaps in the bilateral group, there were no between-group differences in the rates of revision surgery on the breast or abdomen (Table 3).

The risk of postoperative complications requiring re-operation was higher for those undergoing longer operations (adjusted OR 1.36 [95% CI 1.1, 1.7], p<0.001, fit=83% with 87% predictive ability), which was adjusted for unilateral/bilateral and flap ischaemia time; this was similar when bootstrapped. This means that for every additional hour of operating above the mean (of 4 hours), the odds of postoperative complications requiring a return to theatre increased by approximately 50%. Similarly, the risk of revision surgery was higher in those who developed a postoperative complication (adjusted OR 2.1 [95% CI 1.1, 4.0], p=0.024) and in those with longer operative times for the DIEP flap breast reconstruction (adjusted OR 1.3 [95% CI 1.1, 1.5], p<0.001, fit=59% with 77% predictive ability); these were similar when bootstrapped. This means that the odds of revision surgery increase by 30% per hour over the mean (of 4 hours) and two-fold if a complication is encountered.

Discussion

Despite an increasing demand for bilateral breast reconstruction, few authors have shared the complication rates of their bilateral DIEP flap breast reconstructions[38-44]. Most articles on DIEP flap breast reconstruction report pooled analyses (mixing bilateral and unilateral cases), use the flap as the unit of analysis, mix DIEP flaps with other flaps into a single group and lack coherent subgroup analyses, which makes interpretation problematic[24]. All such publications are weakened by their retrospectivity, the potential for selective outcome reporting and heterogeneous definitions (eg. what constitutes partial flap failure) which is evident when the published rates of total flap failure spans from 0% to 10% and major complications from 6.4% to 27.2%[38-44]. Ideally, randomised trials would be performed to address concerns over poor methodology but the QUEST study showed this to be challenging[29]. Alternatively, well-designed and performed prospective cohort studies, which when sufficiently powered for rare outcomes, can deliver reliable data and this was the basis for our study. Although our study is not exempt from weaknesses, it contemplates a consecutive series of women from a stable population, treated within a single unit by the same surgeons with a standardised technique, using a clear description of methodology to maximise the reliability of findings.

We have shown that the risks of complications requiring re-operation and total flap loss were substantially higher for bilateral cases and after longer surgeries, which reflects previous findings[24]. Interestingly, if we denote the risk of one DIEP flap failure as χ, then one would assume that the probability (aka. risk) of two DIEP flaps failing should be approximately 2χ, but this is not the case. We have observed that unilateral DIEP flap failure in bilateral reconstruction was 6 times as likely (RR=6.4). We should highlight that the CI is very wide, spanning from 1.6 (meaning just less than twice as risky) up to 26 (meaning 26 times as risky) and this width is possibly due to our small sample size. We feel it is both important and equally thought-provoking to state that although our study was under-powered for this outcome (to detect the 4.4% proportional difference in total flap failure, with α=0.05, β=0.9 and 4:1 allocation ratio, we would have needed n=855 women in total), we still found

strong evidence of adverse effect which is in-keeping with the literature[24,44]. None-the-less, we can only speculate on the causes for the higher risk of flap failure and certainly more research is needed.

We believe that DIEP flap failure in bilateral reconstruction is more common due to the obligate need to utilise both sides of the lower hemi-abdomen. This obligation precludes the surgeon from using contralateral lower abdominal tissue to replace or rescue a failing unilateral flap; particularly in cases where the superficial venous system cannot be supercharged and venous congestion occurs. This returns to the importance of considering the capacity of the deep venous system[45-47] and this is perhaps why Rao and colleagues suggested that a muscle sparing-TRAM flap may be more robust[40]. The use of TRAM flaps may also explain why Lin and colleagues found no difference in major complications between their unilateral and bilateral breast reconstructions[39]. Another factor contributing to a higher incidence of complications in the bilateral group may be the surgeon fatigue[48,49] which is associated with longer ischaemia time[50] and suggested from multivariate regression modelling in our dataset, so perhaps we may need to embrace more rest in order to improve outcomes. Equally, perhaps more surgeons could embrace technologies, which reduce operative time such as micro-anastomotic couplers[34,35]. Certainly, our models should be tested on larger and external datasets to confirm or refute their validity.

Bilateral DIEP flap breast reconstruction is challenging and should be not underestimated by surgeons or patients, particularly those seeking risk-reducing mastectomies[16,41,51]. There is a steep learning curve for DIEP flap breast reconstruction and complications usually arise early in practice. Our team now has a collective experience of >2000 DIEP flaps and our practice has plateaued for several years, with no differences between surgeons. Therefore, it is vital that surgeons clearly explain the potential benefits of removing a ‘normal breast’ and the risks of free tissue transfer. Perhaps ‘Breast Cancer Risk Management Multi-Disciplinary Teams’ may be helpful to improve the decision making process[52].

The fact that there were no between-group differences in the numbers of revision surgeries in the breasts or abdomen is interesting, particularly with respect to bulge/hernia and seroma[53] which one would expect to be higher in the bilateral group, given the more extensive dissection. Such findings may reflect a collective practice of rigorous nerve-sparing dissection and rectus sheath repair.

As with all research, our study has limitations. Despite the strengths of the prospective design and data collection methods, various biases still exist. We performed numerous analyses and so the risk of Type 1 error is high and some difference may be found by chance. Equally there is a risk of Type 2 error given the rarity of some outcomes. Therefore, our inferences are cautious in accordance with STROBE[54] and SAMPL[55] guidance. As our follow-up period was variable, a favourable bias towards revision surgery rates could be present. Ideally we would have generated hazard ratios (using Cox's regression) for revision surgery but this cannot be done without the time variable. We lack external data on which to test our models, which weakens their clinical application and equally, our model may be confounded by other variables (such as surgeon fatigue, physiological factors, etc) which we did not measure and this too limits the validity of our model. Moreover, as the study was focused on surgical outcomes, we may be criticised for the lack of patient-related outcome measures (eg. satisfaction, quality of life indices, etc).

Overall, we have demonstrated that DIEP flap breast reconstruction following mastectomy for breast cancer is a safe procedure with a low incidence of flap loss or major complications, in both unilateral and bilateral cases. None-the-less, compared to unilateral procedures, bilateral DIEP flap breast reconstruction does carry a higher risk of postoperative complications and total flap failure, which should be adequately conveyed to patients seeking breast reconstruction.

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Figure Legends

Figure 1. a-c) Prior to unilateral delayed DIEP flap breast reconstruction. The patient underwent left mastectomy and adjuvant chemo-radiotherapy. d-f) 12 weeks after a delayed unilateral DIEP flap which was subject to total failure, excised and the defect skin grafted. g-i) 6 months post secondary breast reconstruction with a pedicled left sided latissimus dorsi flap with implant.

Figure 2. a-c) Pre-operative bilateral risk reducing mastectomy (BRCA1 mutation carrier) with planned immediate bilateral DIEP flap breast reconstruction. d-f) 6 months following failure of the right DIEP flap breast reconstruction, which was excised and closed primarily. g-i) 12 months following secondary right sided breast reconstruction with a pedicled extended latissimus dorsi flap.

Author Contributions

RGW was involved in data collection, undertook the statistical analyses and interpretation of results, and co-authored the manuscript.

SR was involved in data collection, interpretation of results and preparation of the manuscript.

EMS operated on the patients, participated in the interpretation of results and preparation of the manuscript.

RMH operated on the patients, participated in the interpretation of results and preparation of the manuscript.

RSA operated on the patients, participated in the interpretation of results and preparation of the manuscript.

AF led the development and completion of the prospective database, supervised data collection, operated on patients, supervised statistical analyses, led the interpretation of results and co-authored the manuscript.