TITLE:

Standard Wide Local Excision or Bilateral Reduction Mammoplasty in large-breasted women with small tumours: surgical and patient-reported outcomes

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Running title: A comparative study of unilateral breast conserving surgery and bilateral level II oncoplastic surgery in favourable tumour to breast ratio

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ABSTRACT

Introduction

Oncoplastic breast surgery is used to extend the role of breast-conserving surgery (BCS) to women with an unfavourable tumour to breast volume ratio. However, large-breasted women with a relatively small breast cancer may be offered bilateral reduction mammoplasty (BRM) despite being suitable for standard BCS as the more complex surgery may have advantages in terms of patient satisfaction and reduced adverse effects of radiotherapy.

Patient and methods

This retrospective study evaluated surgical and patient-related outcome measures (PROMs) in large-breasted women with early (<3cm) breast cancer, who have undergone unilateral standard BCS or BRM.

Results

This series included 157 women, 87 in the unilateral BCS group and 70 in the BRM group. Median age was 60.2 years (range: 33-83.9). Median follow-up was 36 months (range: 9.8-76). Tumour size, rates of axillary dissection, adjuvant chemotherapy and tumour bed irradiation boost were significantly greater in the BRM group (p<0.05). The surgical complication rate was not significantly different (43.7%vs.34.3%, p=0.253). Re-excision rates were higher in the standard BCS group (p<0.05). Time to chemotherapy was similar, but time to radiotherapy was longer after BRM surgery (p=0.025). Despite worse prognostic factors, more complex surgery and more aggressive adjuvant treatment, patients report better satisfaction and physical functioning and fewer adverse effects of radiotherapy after BRM than standard unilateral BCS. This difference was not statistically different in this small study (p>0.05).

Conclusion

Limitations of this study mean it can only be regarded as hypothesis-generating. Nonetheless, the trends merit a prospective study to investigate the optimal management of smaller breast cancers in larger-breasted women.

INTRODUCTION

Oncoplastic breast-conserving surgery is used in the developed world for the treatment of early breast cancer, however practice is not currently standardised[1] as oncoplastic guidelines have tended to focus on breast reconstruction[2]. Not all patients with breast cancer are suitable for or require oncoplastic BCS. The usual indication for a reduction mammoplasty (level II oncoplastic approach) is an unfavourable tumour to breast volume ratio or a challenging tumour location, or both, such that a poor cosmetic result might be expected after standard BCS[3,4]. Previous studies have demonstrated that standard and oncoplastic BCS are equivalent in terms of loco-regional control[5,6] Large-breasted women with a relatively small breast cancer may be offered the choice between standard BCS (i.e. wide local excision / lumpectomy) and oncoplastic BCS. In these cases of favourable tumour to breast volume ratio a standard wide local excision is the simplest surgical solution but larger breast size and ptosis are associated with worse cosmetic outcome after BCS and radiotherapy, with an increased rate of asymmetry, fibrosis, retraction and late radiation changes[7-10]. Radiation dose distribution is heterogeneous in larger breasts, and therefore a reduction mammoplasty, while surgically more complex, may lead to improved dose distribution, a reduction in the adverse effects of radiotherapy, and better long term symmetry, cosmesis and patient satisfaction[3,11-14]. Modern Intensity Modulated Radiotherapy (IMRT) reduces the inhomogeneity, but does not eliminate the effect of "large-breastedness" on cosmetic outcome [10]. The risk of subsequent new primary breast cancer is reduced by the extent of breast tissue excised[15,16] thus there is a concomitant advantage in this respect. Furthermore, women may benefit from a bilateral reduction mammoplasty in terms of quality of life, independent of their cancer treatment [17-19]. Long-lasting benefits of reduction mammoplasty are said to include reduction in neck, shoulder, back and breast pain, together with improvement in body posture, sleep, choice of clothing, sexual relationships and ability to work[20,21].

Conversely, bilateral reduction mammoplasty (BRM) could be considered overtreatment for a unilateral tumour; it is a longer procedure and carries the risk of complications in both breasts which may delay adjuvant treatment.[1,3,22].

At our institution bilateral reduction mammoplasty is offered to, and often sought by, suitable patients as an alternative to standard BCS. All patients considering bilateral reduction

mammoplasty for smaller tumours are counselled about the specific complications and potential benefits of both this procedure and the simpler alternative, unilateral standard BCS, hence patient preference plays a large part in decision-making.

The aim of this study was to evaluate surgical outcomes and patient satisfaction in two cohorts of larger -breasted women who underwent either standard BCS or bilateral reduction mammoplasty for a unilateral breast cancer smaller than 3 cm on pre-operative imaging. We chose this cut-off assuming that a tumour of such size could be removed with clear margins from a large breast using standard BCS.

PATIENTS AND METHODS

Institutional Service Evaluation approval was obtained to study the outcome of patients undergoing BRM between June 2009 and November 2014. Eligible patients were sent the BCT Module of the BREAST-Q questionnaire by post and no reminder was sent to patients who did not reply. The comparison cohort of patients who underwent unilateral BCS are a subset of patients involved in an on-going study of outcomes after BCS, for which ethical approval was obtained. The study involved medical photography and completion of the BREAST-Q questionnaire face-to-face at the time of their annual visit for surveillance mammography between 1 and 6 years post-operatively [23]. The subset of patients with larger breasts were identified as women with an estimated bra cup size $\geq$ D on 2D photos and breast volume >500cm^3 on 3D surface imaging of the healthy breast using the VECTRA XT System (Canfield Scientific).

Patients who did not undergo radiotherapy, or who had bilateral or multi-centric cancer were excluded. Patients who went on to have a mastectomy for involved margins, developed distant disease or were lost to follow-up were excluded from the evaluation of patient satisfaction.

Data including patient demographics, clinico-pathological details, surgical outcomes and BREAST-Q scores were collected from a prospectively maintained database and recorded in a Microsoft Excel spreadsheet (Microsoft Corp, Redmond, Wash.).

Surgical outcome measures included complications within 30 days of surgery according to the Clavien-Dindo Classification[24]. We only considered complications occurring in the breast, excluding axillary events. Grade 1 complications include minor deviations from the normal postoperative course without the need for any treatment (eg seroma/haematoma not

requiring drainage, minor skin necrosis, delayed wound healing). Grade 2 complications include patients requiring pharmacological treatment (eg antibiotics for wound infection). Grade 3 complications are divided into 3a, if an intervention under local anaesthesia is required (eg seroma/haematoma which were drained under ultrasound guidance, skin necrosis requiring debridement), or 3b, if general anaesthesia is needed (i.e. major skin necrosis, wound infection requiring debridement, postoperative bleeding). Margin involvement (at the time of this study) was considered negative if greater than 1mm from invasive cancer and 2mm from DCIS). Margin re-excision, length of hospital stay, re-admission within 30 days and delay (>6 weeks) in starting adjuvant treatment were also recorded.

Patient-reported outcomewas evaluated postoperatively using a validated questionnaire (BREAST-Q BCT Module) for both cohorts[25]. A score for each of the nine domains within the questionnaire was derived and then transformed on a scale of 0-100 according to the BREAST-Q protocol with higher scores equating to higher satisfaction.

The mean and standard deviation were calculated for all parametrically distributed variables, whilst the median and the range were calculated for non-parametric ones. Fisher's exact test was applied for categorical data, Student's t-test for continuous data and the Mann-Whitney test for non-parametric data. A p value of <0.05 was considered statistically significant.

RESULTS

In total 157 larger-breasted women were evaluated, 87 in the unilateral BCS cohort and 70 in the bilateral cohort. The median age of patients at the time of surgery was 60.2 years (range: 33-83.9), with a median BMI of 29.6 kg/m^2 (range: 20.3-46.3). The median follow-up was 36 months (range: 9.8-76). The two cohorts were compared for demographics and clinico-pathological characteristics (Table 1). There were no significant differences in terms of patient features, except for the age, which was significantly higher in the unilateral group (p=0.0001). The median breast volume of the unilateral breast cohort was 758,47cm^3 (range: 303,9-1407,3). The tumour size was significantly higher in the bilateral group both on preoperative imaging and postoperative histological analysis (p=0.001, p=0.001) and the central location was more frequent in the bilateral reduction group (p=0.004), indeed, 16 patients underwent nipple-areola complex excision. The excised volume from the index breast was significantly greater in the bilateral group (p<0.001). In the bilateral group the rates of axillary dissection, adjuvant chemotherapy therapy and additional radiation boost to

the tumour bed were significantly greater than in the unilateral group (p=0.002, p=0.0001, p=0.04, p=0.0001 respectively).

The surgical outcomes are reported in Table 2. The complication rate was 43.7% (38 patients) in the unilateral group and 34.3% (24 patients) in the bilateral groups, this was not statistically significant (p =0.253) (Table 2). The median length of hospital stay was statistically significantly longer in the bilateral cohort being 1 night (range: 0-6) compared with 0 (range: 0-4) in the unilateral group (p<0.001). The unplanned re-admission rate was not significantly higher in the bilateral group (2 versus 1, p value=0.587). Unplanned return to theatre was more frequent after bilateral surgery, while the rate of re-excision of margins was higher after unilateral surgery. Neither of these differences was statistically significant (p values: 0.087 and 0.138). Regarding the time from index surgery to starting first adjuvant treatment, thirteen patients started chemotherapy greater than 6 weeks after primary surgery, 4 being unilateral and 9 bilateral cases (p=0.336), the most common reason being patient's choice, to accommodate pre-arranged holidays etc. A grade 1 complication delayed the start of adjuvant chemotherapy in only two patients, one in each group. Median time to starting radiotherapy was longer after bilateral surgery. This was statistically significant though not oncologically relevant (57 versus 53 days, p=0.025). Index surgery was taken as the starting point because patients undergoing complex bilateral surgery may experience delays owing to complications while those undergoing standard BCS may experience delays as a result of re-excision.

Patient reported outcome measures

The response rate for the unilateral cohort, completing the BREAST-Q within a prospective study, was 100%. The response rate for patients in the bilateral cohort who were sent the questionnaire by post was 55.2% (32 patients out of 58 who were sent the questionnaire). BREAST-Q scores are reported in Table 3. There was no statistical difference in patient-reported outcomeafter unilateral standard BCS or bilateral reduction mammoplasty for any domain (p>0.05) though there was a trend towards better satisfaction with the breast, less concern about adverse effects of radiotherapy and better physical wellbeing.

DISCUSSION

Although oncoplastic breast surgery was initially offered to extend the indications for BCS, there are some women for whom both oncoplastic techniques and standard wide local

excision are options. This study set out to evaluate surgical outcomes and patient satisfaction in the specific subset of larger-breasted women with a relatively small breast cancer, who were suitable for either wide local excision or therapeutic mammoplasty with immediate contralateral symmetrisation.

Therapeutic mammoplasty is the application of breast reduction and mastopexy techniques to treat breast cancer and represents only one option in the wide spectrum of oncoplastic procedures available. Depending on breast and tumour size it often results in asymmetry and necessitates a bilateral procedure. MacMillan et al. divided the ideal candidates for therapeutic mammoplasty into three categories:

1) women who see breast conservation in the form of therapeutic mammoplasty as a preferable alternative to mastectomy and reconstruction.
2) women who need or desire a breast reduction and
3) women with ptotic breasts who are accepting of an altered breast shape but do not necessarily wish to be significantly smaller[26]

However these indications raise the issue of which procedure is the correct gold standard against which to compare results. Many suggest that as therapeutic mammoplasty is predominantly used to extend the role of breast conservation to those who would otherwise require mastectomy, and as the tumour pathology more closely matches a mastectomy cohort, this should be the comparator[27]. Yet in many series including our own[6], there are a number of women with smaller tumours or ptotic breasts i.e. the latter two indications, for whom standard BCS is an option. These should be analysed separately, and in comparison with standard BCS. In order to analyse this scenario, we included larger-breasted women who were suitable for breast reduction and had a tumour smaller than 3 cm so were also suitable for standard BCS. Previous literature about oncoplastic surgery in comparison to BCS highlighted the benefits of the former in cases of unfavourable tumour-breast volume ratio, when wider margins or better aesthetic results were achievable[1,3]. There are currently no published comparative studies of surgical, oncological and patient-reported outcome in the scenario of favourable tumour–breast volume ratio, when the choice for therapeutic mammoplasty is mainly patient-driven.

In our study we identified women with larger breasts and tumours up to 3 cm who opted for either bilateral reduction mammoplasty or standard BCS. Women who underwent standard

BCS were older than those who chose bilateral reduction mammoplasty (table 1), perhaps because younger women were more accepting of bilateral surgery and more likely to desire breast reduction. Regarding tumour characteristics, the bilateral cohort had more aggressive disease, reflected in larger tumour size and higher rates of axillary dissection, adjuvant treatment and boost radiation and, as expected, greater excised volume. As the groups were not well matched for patient and tumour characteristics, oncological outcomes were not evaluated. Margin involvement and hence re-excision were significantly more frequent in the unilateral cohort (*p* values: 0.02, 0.007), but no meaningful conclusions can be drawn because the women who ultimately converted to mastectomy had been excluded from this retrospective study.

We found no significant difference between the two cohorts in terms of total complication rate (*p* value: 0.253) or specific grade of complication (*p* value>0.05) (Table 2). However there were differences in the specific types of grade 1 complications, mainly seromas (n=11) in the unilateral group and delayed wound healing (n=15) in the bilateral group. These may be very different in impact on patients, for example, delaying the start of adjuvant radiotherapy. Grade 2 complications were mostly represented by infections in both groups and grade 3 by ultrasound-guided aspiration of seroma/haematoma. There is a trend towards a higher rate of grade 3b complications (requiring intervention under general anaesthesia) in the bilateral group, which is reasonable as the surgical technique of breast reduction yields a higher risk of specific complications (e.g. nipple necrosis, flap necrosis, haematoma) requiring further surgery.

Although the length of hospital stay is one night longer in the bilateral group as expected from more complex surgery, the difference is mitigated by the lower rate of readmission for re-excision of margins. Previous studies of oncoplastic surgery showed that it did not delay any adjuvant treatment[28,29], but our results confirm this finding for chemotherapy only. Our cohorts did not differ significantly in the median time interval from surgery to chemotherapy ($p = 0.825$), but the median time to radiotherapy is significantly longer in the bilateral cohort ($p = 0.002$). As this difference is 53 versus 57 days, it is unlikely to be oncologically relevant. Furthermore almost 30% of the complications were on the symmetrising side which would not affect the timing of radiotherapy.

The strength of this study is the evaluation of PROMs using the BREAST-Q questionnaire. The breast-conserving therapy module is the most recent module to be introduced and this is

the first report of its use to compare standard BCS with oncoplastic BCS. Despite the difference in surgery, the two cohorts' scores were not statistically significant in any domain. The power of our study is limited by the smaller numbers responding to the questionnaire in the bilateral reduction cohort. When planning PROMs studies, thought should be given to the mode of distribution. The bilateral cohort was sent questionnaires in the post once, no reminder was sent in case of no response, to respect the patient's choice. This could have led to bias, but the lower quartile was 57 in both cohorts, suggesting that unsatisfied women did participate in both studies. The overall response rate was 55.2% and 81.3% of these completed the psychosexual domain. Conversely, the unilateral group participated as part of a prospective study and met an investigator face-to-face[23]. The completion rate was 100%, but paradoxically only 62.1% completed the psychosexual domain. This raises the possibility that response rates, and possibly answers, are different according to the context in which patients complete the questionnaire. We are now also examining the option of online completion of PROMs questionnaires by patients (ePROMs).

Notwithstanding bilateral surgery, larger tumour size and more adjuvant treatment the bilateral cohort showed a clear trend towards higher patient satisfaction (80 versus 68) and less concern about adverse effects of irradiation (100 versus 89). There is also a more subtle trend towards better physical well-being (perhaps owing to reduction of back / neck pain) in the bilateral group, and worse psychological well-being (possibly linked to the worse prognosis of their disease). All of these hypotheses should be tested on a larger and better-matched prospective sample. Median values for other domains are too close to draw any conclusion. The heterogeneity of methods of evaluation of patient satisfaction in the literature makes it difficult to compare our results with previously published studies which have suggested better satisfaction after therapeutic mammoplasty compared to standard BCS[30,31]. One limitation of this study is that we only assessed postoperative patient satisfaction, and pre-existing dissatisfaction could impact post-operative satisfaction. For example, wide local excision aims to maintain the same breast shape as before surgery, but if a larger-breasted patient had poor body image pre-operatively, she would be dissatisfied after surgery as well. Conversely, dissatisfaction with breasts is likely to be a factor swaying a larger-breasted woman with a favourable tumour-breast volume ratio towards more complex surgery in the form of bilateral reduction mammoplasty and the change in size and the shape of breasts as a result of surgery is likely to lead to greater satisfaction with the outcome.

CONCLUSION

This cohort study demonstrated that larger-breasted women with favourable tumour to breast volume ratio have similar complication rates and achieve high levels of satisfaction after both standard breast conserving surgery and bilateral reduction mammoplasty. Despite not reaching statistical significance, these data are hypothesis-generating for future prospective studies with larger and better-matched cohorts and health economic evaluation which could eventually provide clear evidence of advantages and disadvantages of therapeutic mammoplasty compared with standard BCS.

Conflict of interest

All authors of this paper disclose any conflict of interest.

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Table 1 Patient demographics and clinico-pathological characteristics

	Unilateral n(%) or median (IQR)	**Bilateral n (%) or median (IQR)**	**p value**
Total	87	70	
Mean age ± SD, (years)	63.3±9.1	56.1±9.0	0.0001
BMI (kg/m^2)	30(27-33)	29.3(25.2-32.5)	0.584
Median follow-up (months)	36(22-49)	36.5(22.3-51)	0.357
Smoking history (ex or current)	40(46.0)	34(48.6)	0.75
Ethnicity			
White	76(87.4)	56(80)	0.278
Other	11(12.6)	14(20)	0.278
Location of tumour			
Central	4(4.6)	14(20)	0.004
Upper Outer	46(52.9)	30(42.9)	0.148
Upper Inner	17(19.5)	8(11.4)	0.191
Lower Outer	12(13.8)	13(18.6)	0.512
Lower Inner	8(9.2)	5(7.1)	0.774
Neo-adjuvant chemotherapy	8(9.2)	14(20)	0.065
Median preoperative tumour size (mm)	15(10.5-23)	22(16.25-27)	0.001
T1a	1(1.2)	5(7.1)	0.09
T1b	21(24.1)	5(7.1)	0.005
T1c	40(46)	21(30)	0.008
T2	25(28.7)	39(55.8)	0.001
Median histological tumour size (mm)	20(14-28)	28(17-40)	0.001
pT1a	4(4.6)	3(4.3)	1
pT1b	10(11.5)	4(5.7)	0.26
pT1c	37(42.5)	16(22.9)	0.11
pT2	36(41.4)	47(67.1)	0.001
Specimen weight (g)	42(29-59.5)	250(124.75-453)	<0.001
Axillary dissection	10(11.5)	23(32.9)	0.002
Sentinel Lymph Node Biopsy	67(77.0)	45(64.3)	0.110
No axillary treatment	10(11.5)	2(2.9)	0.067
Pathology			
IDC	12(13.8)	17(24.3)	0.102
IDC+DCIS	53(60.9)	37(52.9)	0.334
ILC	8(9.2)	6(8.6)	1
DCIS	10(11.5)	4(5.7)	0.265
other	4(4.6)	6(8.6)	0.343
ER+	76(87.4)	58(82.9)	0.499
PR+	66(75.9)	54(77.1)	1
Her2+	6(6.9)	9(12.9)	0.276
Patients with positive axillary nodes (macro-metastases)	17(19.5)	23(32.9)	0.0002
Adjuvant Treatment			
Chemotherapy	15(17.2)	31(44.3)	0.001
Endocrine Therapy	71(81.6)	56(80)	0.84
Radiation Boost	16(18.4)	36(51.4)	0.0001

Table 2 Surgical outcomes

Complications	Unilateral Cohort n=87 (%)	Bilateral Cohort n=70 (%)	*p* value
grade 1 grade 2 grade 3a grade 3b	24(28) 17(20) 4(5) 0	20(29) 6(9) 1(1) 3(4)	1 0.069 0.382 0.087
Number of patients with a complication	38 (44)	24 (34)	0.253
Length of hospital stay in nights	0(0-0.5)	1(1-2)	<0.001
Readmissions for complications **Return to theatre for complications** **Margin involvement** **Return to theatre for margin re-excision**	1(1) 0 14(16) 14(16)	2(3) 3(4) 3(4) 2(3)	0.587 0.087 0.02 0.003
Time to chemotherapy (days) **Time to radiotherapy (days)**	40 (36-50) 53 (46-63)	39 (33-48) 57 (53-71)	0.551 0.025

Table 3 Patient satisfaction: BREAST-Q median score and interquartile range

BREAST-Q	Unilateral Cohort (n=87)	Bilateral Cohort (n=32)	*P* value	No answer (%)
Satisfaction with the breast	68(57-82.5)	80(57-95.5)	0.320	0
Adverse effects of RT	89(80-100)	100(80-100)	0.099	1(0.8)
Psychosocial well-being	82(69-100)	76(63-100)	0.705	0
Sexual well-being	57(49.5-69)	46(36-58)	0.079	39(26.9)
Physical well-being	75(67-92)	81(70.5-92)	0.422	2(1.4)
Satisfaction with Information	75(65.5-100)	84(72-100)	0.153	3(2.1)
Satisfaction with Surgeon	100(98-100)	100(96-100)	0.595	3(2.1)
Satisfaction with Team	100(100-100)	100(100-100)	0.287	0
Satisfaction with Office	100(100-100)	100(96.5-100)	0.245	0

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