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Extreme Oncoplasty: Expanding Indications for Breast Conservation

Angelena Crown MD, Ruby Laskin MD, Flavio G. Rocha MD, and Janie Grumley MD

INTRODUCTION: Presence of multiple lesions and/or tumor span ≥ 5 cm are traditional indications for mastectomy. Patient desire for breast conservation has increased the interest in extreme oncoplastic breast conserving surgery (EOBCS) to avoid mastectomy; however, perioperative outcomes in this population have not been well described.

METHODS: This is an observational cohort of breast cancer patients with multiple lesions and disease span ≥ 5 cm who underwent EOBCS. Patient demographics, disease span, margin width, mastectomy and re-excision rates, and cosmesis were evaluated.

RESULTS: One hundred-eleven patients underwent EOBCS between 2012 and 2017. Eighty-two patients presented with multifocal or multicentric disease with an average of 3.2 lesions per breast spanning 57.1 ± 23.6 mm. Eighteen patients presented with unifocal tumors measuring an average of 67.6 mm (range 50-160 mm) on imaging. Eleven patients with an imaging size of < 5 cm had a disease span ≥ 5 cm on final pathology. No tumor on ink occurred in 87 (78.3%) patients. Fifty-seven (51.4%) patients had additional surgery for inadequate margins. Fifteen (12.6%) patients elected to have mastectomy while 42 (37.8%) patients opted for re-excision. Good to excellent cosmetic results were reported in 95% of patients who ultimately achieved breast conservation. Recurrence rate was 1.1% in patients who completed EOBCS and adjuvant radiation therapy.

CONCLUSION: EOBCS can allow for breast conservation in patients who are traditionally counseled to undergo mastectomy. Although the re-excision rate was significant, most patients ultimately achieved breast conservation with adequate margins. Further study is warranted to determine the long-term oncologic outcomes of this approach.

INTRODUCTION

Breast conserving therapy (BCT) consists of wide local excision and axillary staging in conjunction with adjuvant systemic and radiation therapies. Multiple landmark prospective randomized trials have demonstrated similar disease-free and overall survival in BCT compared to mastectomy and have helped to establish BCT as a standard management option for early stage breast cancer.¹⁻⁴ Although survival is equivalent with BCT compared to mastectomy, recent prospective trials have reported local recurrence rates as low as 0.4-1.3% at 5 years for patients treated with traditional BCT.^{5,6} Despite carrying a higher risk of local recurrence, BCT offers advantages such as positive effects on physical appearance and emotional well-being.⁷ Additionally, BCT is associated with less perioperative morbidity and more favorable cosmetic response to radiation therapy compared to mastectomy with reconstruction.^{8,9}

The evolution of oncoplastic surgery has contributed additional advantages, including improved oncologic and aesthetic outcomes through the application of plastic surgery techniques in the resection of breast cancer.¹⁰⁻¹² The spectrum of oncoplastic approaches ranges from simple volume redistribution techniques such as mastopexy to advanced tissue rearrangement techniques such as reduction mammoplasty. Oncoplastic surgery allows for larger resections and may allow patients with large or multifocal disease, traditional indications for mastectomy, to consider BCT.^{13,14} The ability to perform larger resections has also been associated with a reduced rate of inadequate margins and a decreased need for additional operations which can expedite the initiation of adjuvant therapies.^{10,15}

There is a paucity of evidence to support the application of oncoplastic surgery to patients with large tumor span, multifocal and/or multicentric disease, as the current literature generally excludes these patients. Silverstein et al. have advocated for the use of oncoplastic reduction

mammoplasty in patients with multifocal, multicentric tumors, and/or disease span greater than 5cm (coining the term, “extreme oncoplasty”) and have published excellent outcomes on a series of 66 patients with 10% requiring re-excision for inadequate margins and 6% converting to mastectomy.¹⁶

The purpose of the current study is to examine the short-term oncologic and cosmetic outcomes for patients who meet traditional recommendations for mastectomy (with multiple lesions and/or disease span ≥ 5 cm) who underwent extreme oncoplastic breast conserving surgery (EOBCS) performed by breast surgical oncologists.

METHODS

This observational cohort study was approved by the institutional review committee and met the guidelines of our Institutional Review Board; HIPPA compliance was assured. Consecutive patients with invasive or non-invasive breast cancer with multiple lesions and/or disease span ≥ 5 cm treated with EOBCS at Virginia Mason Medical Center between November 1, 2012 and September 15, 2017 were identified from the prospectively collected Multidisciplinary Breast Cancer Database. Demographic, radiologic, histopathologic, operative, perioperative, and recurrence data were entered prospectively and analyzed retrospectively. Additional data were obtained as necessary from review of the medical record.

Standard preoperative imaging work up comprised mammogram, ultrasound, and breast MRI, when indicated. Localization clips were placed at the time of breast biopsy. Breast surgical oncologists identified appropriate candidates for EOBCS based on imaging studies, clinical exam, and patient desire for breast conservation. Patients were not excluded based on tumor histology, nodal status, receptor status, smoking history, or presence of comorbidities.

A variety of oncoplastic techniques were employed, ranging from basic techniques such as radial ellipse and mastopexy to more complex techniques including reduction mammoplasty and neoareolar reduction mammoplasty with immediate nipple reconstruction. Patients were offered symmetry procedures for the contralateral side when appropriate. No perforator flaps or musculocutaneous flaps were performed. Each patient was reviewed in a multidisciplinary fashion by the breast cancer team to determine adjuvant treatment recommendations. Patients meeting criteria for radiation therapy were counseled to undergo adjuvant radiation therapy as an integral component of BCT.

Oncoplastic partial mastectomy and symmetry procedures were performed exclusively by breast surgical oncologists. Intraoperative localization of the cancer was achieved with

palpation, intraoperative ultrasound, and/or wire-localization techniques. The operating surgeon inked all surgical specimens. Intraoperative specimen radiograph and gross evaluation by pathologists were performed to assess margins and guide the need for further tissue resection.

Surgical clips were placed circumferentially within the tumor cavity to ensure accurate identification of the tumor bed on subsequent imaging and to help target adjuvant radiation therapy.

In the event of inadequate margins, the surgical clips helped to direct subsequent re-excision. All patients who underwent re-excision had the location of their tumor bed confirmed by intraoperative identification of the surgical clips placed at the time of their index operation. Intraoperative sterile inking along with meticulously mapped pathology reports also aided in the accurate localization of the tumor bed and precise position of the inadequate margins.

The definition of adequate margins changed during the study period; initially margins were considered adequate if ≥ 2 mm for both invasive cancer and DCIS. No ink on tumor was considered an adequate margin for invasive cancers after the SSO/ASTRO/ASCO consensus guidelines were released in 2014.¹⁷ All patients with inadequate margins were counseled to undergo re-excision unless the inadequate margin was the chest wall.

Patients had clinical follow up at 1-2 weeks post-surgery, every 6 months for two years, then annually. As described previously, the operating surgeon assigned cosmesis scores at the six-month follow-up using the Harvard Breast Cosmesis Scale.^{12,18} Surgical complications and interventions were identified through medical record review and the prospectively collected data contained in the Virginia Mason Multidisciplinary Breast Cancer Database. Appropriate imaging surveillance was performed annually in conjunction with clinical exam to monitor for locoregional recurrence.

RESULTS

One hundred eleven patients underwent EOBCS (Table 1). Average age was 58.5 ± 11.7 years (range 38-84). Ninety-four (84.7%) patients had invasive cancers and 17 (15.3%) had pure DCIS. Eighty-two patients presented with multifocal or multicentric disease with an average imaging span of 57.1 ± 23.6 mm (range 35-117mm) and with an average of 3.2 lesions per breast (range 2-13 lesions). Eighteen patients presented with unifocal tumors measuring an average of 76.0 ± 26.7 mm (range 50-160 mm) on imaging. Eleven patients with unifocal disease and imaging size of <5 cm (range 13-49 mm) had a disease span ≥ 5 cm (52-135 mm) on final pathology. Average size on final pathology for unifocal tumors was 73.2 ± 28.4 mm. Largest average single tumor size for multifocal and multicentric tumors was 42.5 ± 35.8 mm on final pathology. Thirty (27.0%) patients had an extensive intraductal component and 23 (20.7%) had lymphovascular invasion present.

Surgical approaches included 49 reduction mammoplasties, 30 racquet mammoplasties, 22 mastopexies and 10 “other” incisions. Ninety-three (83.8%) patients elected to undergo symmetry procedures on the contralateral side. No ink on tumor was achieved in 87 (78.3%) patients. A total of 42 (37.8%) patients had additional surgery for <2 mm DCIS margins and 15 (13.5%) had additional surgery for inadequate margins for invasive cancer. Of the 15 re-excisions for invasive cancer 5 (33.3%) were for <2 mm margins prior to the adoption of the new consensus guidelines for invasive cancer.¹⁷

Fifty-seven (51.4%) patients had additional surgery for inadequate margins as defined at the time of their resection. Of the patients requiring additional surgery for inadequate margins, 15 (26.3%) patients elected to convert to mastectomy while 42 (73.7%) patients opted for re-excision, resulting in an overall re-excision rate of 37.8% and a mastectomy rate of 13.5%.

Thirteen (50%) of the 26 patients with lobular histology had inadequate margins; two of these patients converted to mastectomy. Additionally, two patients with triple negative breast cancer and 10 patients with Her2 positive disease, including 2 who were treated with neoadjuvant chemobiologic therapy, required surgery for inadequate margins. Of the 42 patients electing re-excision, 33 (78.6%) patients achieved adequate margins with a single re-excision while 9 (21.4%) patients required multiple re-excisions. Ninety-six (86.5%) patients ultimately achieved breast conservation.

No perioperative deaths or life-threatening complications were reported. Eighteen (16.2%) patients had surgical site complications following EOBCS (Table 2); fifteen (83.3%) complications occurred on the ipsilateral side, 2 (11.1%) complications occurred on the contralateral side, and 1 complication (5.6%) was bilateral. Five (27.8%) of the 18 complications occurred following re-excision. Two (1.8%) patients had operative interventions for management of the complications including one patient who underwent evacuation of a breast hematoma and one who chose to undergo elective scar revision (Table 3). Nine (8.2%) patients required less invasive interventions, ranging from outpatient antibiotic therapy and local wound care to outpatient seroma aspirations. Of the 15 patients who converted to mastectomy, 2 (13.3%) had complications, including 2 post-mastectomy seromas requiring outpatient aspiration. Additionally, there were 2 (1.8%) patients who experienced axillary complications including one axillary hematoma requiring surgical evacuation and one axillary seroma requiring outpatient aspiration.

Good to excellent cosmesis was accomplished in 83 (95%) of 87 patients who had cosmesis scores reported. Of the 18 patients with complications, 15 had cosmetic scores reported with 14 (93.3%) achieving good to excellent cosmesis. Of the 42 patients who

underwent re-excision, 37 had cosmetic scores reports with 34 (91.9%) achieving good to excellent cosmesis.

Thirty-six (32.4%) patients required chemotherapy, including 30 who received adjuvant chemotherapy and 6 who received neoadjuvant chemotherapy (NAC). Eighteen (31.6%) of the 57 patients who obtained inadequate margins at the index operation received chemotherapy, including 3 in the neoadjuvant setting and 15 in the adjuvant setting. Ninety-one (94.8%) of the 96 patients who attained breast conservation completed whole breast radiation therapy. Seventy-two (76.6%) of 94 patients who were advised to take endocrine therapy adhered to that recommendation; five discontinued endocrine therapy secondary to side-effects.

The overall local recurrence rate for the entire study cohort of 111 patients was 2.7%, consisting of 3 patients who recurred locally with invasive cancer. No regional or distant recurrences were documented during the follow-up interval which averaged 36 months (12-60 months). All 3 local recurrences were in patients with breast conservation, leading to a recurrence rate of 3.1% for the 96 patients who completed EOBCS. Two of the patients who recurred locally had declined adjuvant radiation therapy, including one who was 84 years old. Therefore, the recurrence rate for the 91 patients who completed EOBCS and adjuvant radiation was 1.1%.

DISCUSSION

Patients in our study cohort would traditionally be recommended to undergo mastectomy. EOBCS allowed 86.5% of them to achieve breast conservation. The rate of inadequate margins was significant with 51.4% of patients requiring additional surgery to achieve adequate margins. The majority of inadequate margins were for DCIS (73.7%), the full extent of which is frequently challenging to define with preoperative imaging, even with the addition of MRI.¹⁹ This finding is consistent with other studies that have demonstrated higher rates of positive margins for DCIS.^{20,21}

The high inadequate margin rate highlights the importance of having the ability to reliably identify the precise location of margins that require re-excision. In our study, detailed pathology reports and placement of clips within the tumor bed during the index operation provided a map to facilitate re-excisions. Additionally, having a single surgeon perform both the initial cancer resection and tissue rearrangement as well as the subsequent re-excisions aided the localization of inadequate margins.

Of note, the definition of adequate margins changed during the study period following the release of the SSO/ASTRO/ASCO consensus guidelines for invasive cancer in 2014.¹⁷ Had the consensus guidelines been released earlier in the study period, 5 (4.5%) of patients would have avoided additional surgery for inadequate margins for invasive cancer leading to an inadequate margin rate of 46.8%. One of these patients would have avoided mastectomy.

Additionally, both the consensus guidelines for invasive cancer and the 2016 consensus guidelines for the management of DCIS recommended treating DCIS associated with invasive cancer, regardless of DCIS extent, in accordance with invasive cancer standards.^{17,22} They suggested performing selective re-excision of DCIS margins of <2 mm in high risk patients with

invasive disease, such as in patients with multiple close margins and in young patients.^{17,22} If these guidelines had been released earlier in the study period, an additional 20 patients in our study could have avoided additional surgery for inadequate margins based on these criteria. Six of these patients would have avoided mastectomy. In combination, implementation of these guidelines earlier in the study period would have decreased the inadequate margin rate to 28.9% and mastectomy rate to 7.2%.

More aggressive application of neoadjuvant therapies has been suggested as a potential strategy to reduce the inadequate margin rate. Only 5.4% of patients in our study received NAC; more liberal use of NAC may have improved our rate of inadequate margins as well as converted some of our patients with node-positive disease to node-negative disease. Studies of patients with stage III Her2 positive disease have demonstrated an ability to downstage breast cancers with neoadjuvant chemobiologic therapies targeting Her2, reporting pathologic complete response (pCR) rates as high as 40% in the breast.^{23,24,25} Similarly, Liedtke et al evaluated NAC for triple negative tumors and showed the ability to downstage tumors with 22% of patients achieving pCR.²⁶ Despite demonstrating an ability to downstage tumors and allow for smaller volume resections in T2 and T3 tumors, Boughey et al found that use of NAC did not reduce re-excision rates.²⁷

Patients with carcinomas with lobular features had a 50% inadequate margin rate, highlighting the unpredictable and diffuse nature of this histology. In a study of 365 patients with invasive lobular carcinoma, Mukhtar et al advocated for implementation of oncoplastic techniques as a method to decrease the positive margin rate and maximize the chance of successful breast conservation.²⁸ In their study, the mastectomy rate was 25%.²⁸ Use of EOB

in our study resulted in a mastectomy rate of 7.7% in patients with invasive carcinoma with lobular features, confirming a role for oncoplastic surgery in these patients.

Of the 57 patients who required additional surgery for inadequate margins, only 18 (31.6%) required chemotherapy, including 3 patients who were treated in the neoadjuvant setting. Expanding the use of NAC may have also resulted in overtreatment of some patients who did not otherwise require chemotherapy. Additionally, use of NAC would have been unlikely to improve the inadequate margin rate in patients with lobular histology, as the majority were hormone receptor positive and Her2 negative. Petruolo et al previously identified this population of patients as unlikely to downstage in the breast or in the axilla in response to neoadjuvant chemotherapy.²⁹ Finally, because 73.7% of operations for inadequate margins were for DCIS, quantifying the magnitude of the potential effect of NAC on the inadequate margin rate in our study is a challenge.

Multiple studies have demonstrated the effectiveness of neoadjuvant endocrine therapy in downstaging breast cancers and converting patients in whom BCT was not thought to be feasible into candidates for BCT. However, even in these studies, BCT was only possible in 22-46% of patients.^{30,31,32} Although some patients in our study may have benefitted from this approach, neoadjuvant endocrine therapy is typically reserved for elderly patients who have co-morbidities that render them poor surgical or chemotherapy candidates.³³

Patient adherence to multidisciplinary recommendations for both systemic and radiation therapies was high, which is consistent with all patients undergoing breast cancer treatment at our institution.¹² The recurrence rate for the cohort using an intent to treat analysis was 2.7%. When patients who converted to mastectomy were excluded, the recurrence rate was 3.1%. Examining only patients with EOBCS and adjuvant radiation, the recurrence rate was 1.1%.

This underscores the integral role that radiation plays in preventing locoregional recurrence. In combination, these findings suggest that EOBCS has excellent oncologic outcomes and can offer some patients who would otherwise be advised to undergo mastectomy a path toward breast conservation.

EOBCS by breast surgical oncologists was associated with a surgical site complication rate of 16.2%, higher than the 8% complication rate we reported in a previous study evaluating surgical site complications associated with oncoplastic surgery.³⁴ Despite the higher complication rate, the complications reported in this current study were minor and required minimal interventions. Two (1.8%) of patients underwent operative interventions, including one elective scar revision, while the remainder required outpatient management or no interventions.

Silverstein et al argue that patients who complete BCT in a single operation have improved quality of life and cosmesis while also experiencing lower levels of pain and generate lower health care costs compared to patients who undergo multiple operations.¹⁶ A significant number of our patients (48.6%) achieved adequate margins in a single operation. An additional 29.7% of patients achieved adequate margins after a single re-excision. Additional studies evaluating time to initiation of adjuvant therapies and health care costs associated with EOBCS are clearly needed.

The overwhelming majority of our patients achieved favorable cosmetic outcomes with 95% of patients with documented cosmesis scores achieving good or excellent outcomes. Cosmetic outcomes remained favorable with over 90% of patients achieving good or excellent outcomes even in the setting of re-excisions and surgical site complications.

One of the limitations to this study is that it is a retrospective review of patients from a single institution. Additionally, there were only two breast surgical oncologists who were

included in the study. Finally, the pathology department at our institution performs gross evaluations of margins intraoperatively and provides detailed maps of surgical specimens which enhances our ability to achieve adequate margins as well as to identify inadequate margins for re-excision. These elements may reduce the generalizability of our study.

CONCLUSION

This study demonstrates that EOBCS can be performed safely by appropriately-trained breast surgical oncologists with an acceptable complication profile and achieve favorable oncologic and cosmetic outcomes. Application of these techniques offers patients who are traditionally counseled to undergo mastectomy an opportunity to consider breast conservation. However, further study is warranted to examine the long-term oncologic and cosmetic results of this approach.

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Table 1. Patient, tumor, and surgery characteristics.

	Patients n=111	%
Patient Characteristics		
Age (years)	58.5 ± 11.7	
Tumor Characteristics		
Node positive	38	34.2%
<i>Size on Imaging</i>		
Unifocal Tumors	76.0 ± 26.73 mm	
Span of multifocal and multicentric tumors	57.1 ± 23.6 mm	
<i>Size on Final Pathology</i>		
Unifocal Tumors	73.2 ± 28.4 mm	
Largest size of multifocal and multicentric tumors	42.5 ± 35.8 mm	
<i>Histology</i>		
Invasive Ductal Carcinoma	68	61.2%
Invasive Lobular Carcinoma	17	15.3%
Invasive Carcinoma with Ductal and Lobular Features	9	8.1%
Ductal Carcinoma-in-situ	17	15.3%
<i>Grade</i>		
Grade 1	13	11.7%
Grade 2	50	45.0%
Grade 3	48	43.2%
<i>Focality</i>		
Unifocal	29	26.1%
Multi-focal	65	58.6%
Multi-centric	17	15.3%
<i>Receptor Status</i>		
ER positive	94	84.7%
PR positive	72	64.9%
Her2 positive	16	14.4%
Triple negative	8	7.2%
Presence of lymphovascular invasion	23	20.7%
Presence of extensive intraductal component	30	27.0%
Surgical Techniques		
Reduction Mammoplasty	49	44.1%
Mastopexy	22	19.8%
Racquet Mammoplasty	30	27.0%
Other	10	9.0%
Contralateral Symmetry Procedure	93	83.8%
Surgery Characteristics		

No ink on tumor	87	78.3%
<2mm margins for DCIS	42	37.8%
Re-excision	42	37.8%
Mastectomy	15	13.5%
Adjuvant Therapies		
Chemotherapy	36	32.4%
Neoadjuvant Chemotherapy	6	5.4%
Adjuvant Chemotherapy	30	27.0%
Whole Breast (of 96 who achieved BCS)	91	94.8%
Endocrine Therapy (of 94 who were recommended)	72	76.6%

Table 2. Complications associated with EOBCS

Complication Type	N = 111
Seroma	3 (2.7%)
Dehiscence	8 (7.2%)
Fat necrosis	1 (0.9%)
Cellulitis	2 (1.8%)
Hematoma	4 (3.6%)
Total	18 (16.2%)

Table 3. Interventions for complications associated with EOBCS.

Intervention Type	N = 111
Aspiration	3 (2.7%)
Negative Pressure Dressing	1 (0.9%)
Evacuation of hematoma	1 (0.9%)
Wound care	2 (1.8%)
Antibiotics	4 (3.6%)
Surgical scar revision	1 (0.9%)
Total	11 (9.9%)

- 1) Oncoplastic surgery can allow patients with multiple lesions and/or large tumor span to avoid mastectomy
- 2) Although re-excision rate may be high, most patients can achieve breast conservation
- 3) Short-term oncologic and cosmetic results are favorable

ACCEPTED MANUSCRIPT