Factors Predictive of Re-excision After Oncoplastic Breast-conserving Surgery

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Abstract. *Background: Oncoplastic surgery (OPS) consists of breast-conserving surgery (BCS) that allows for oncologically safe breast conservation and breast remodeling, thus reducing postoperative deformities. The purpose of the present study was to identify factors determining the risk of re-excision and complications after OPS. Patients and Methods: A retrospective analysis was conducted on patients who underwent OPS between 2009 and 2013, regardless of whether neoadjuvant chemotherapy was administered. Clinical and pathological factors were evaluated. Recursive partitioning analysis (RPA) was used to build regression trees for the prediction of re-excision. Results: Amongst the 129 patients treated by OPS procedures, 30.3% required re-excision. Predictive factors for re-excision were: being overweight (p=0.02), the presence of microcalcifications on mammography (p=0.003), and tumor multifocality (p=0.03). The RPA identified five terminal nodes based on microcalcifications on mammography, being overweight and the presence of ductal carcinoma in situ. Another model included minimal invasive margins (p<0.001), being overweight (p=0.02) and the presence of microcalcifications (p=0.01) on mammography yielded a model with an area under the receiver operating characteristic curve of 0.875. Conclusion: Microcalcifications, tumor multifocality and being overweight were the factors identified as predictors of re-excision after OPS. These factors can serve as decisional tools before surgery.*

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During the last years, indications for breast-conserving surgery (BCS) for primary breast cancer (BC) have been extended as a result of progress in diagnostic modalities and adjuvant therapies. The development of chemotherapy (CT) regimens (taxanes, for instance) has clearly helped improve pathological complete response rates and BCS rates (1-5). The development of targeted therapies has contributed to widening of the possibilities of BCS application. In selected cases, neoadjuvant CT and neoadjuvant targeted-therapy significantly reduce the tumor size, allowing BCS to be performed in more than 60% of cases (6).

Significant improvements in surgical techniques have also contributed to reducing the mastectomy rate. Furthermore, when mammoplasty techniques are applied to surgery for BC, the risk of aesthetic deformity is almost non-existent (7, 8). In BCS, several studies have demonstrated that excising more than 20% of the breast volume substantially increases the risk of deformity (9-11). Combining plastic surgery techniques with oncological surgery provides access to BCS for larger size tumors with acceptable cosmetic results (8-10).

However, appropriate indications for BCS and oncoplastic surgery (OPS) need to be defined in order to minimize the risk of re-excision. There is an increasing number of arguments supporting the fact that OPS is oncologically safe when applied to primary BC, without negative impact on long-term outcome (12-13). Risk factors for re-excision after BCS have been described (14-16). However, risk factors in OPS have yet to be defined. These parameters would help optimize patient selection for this type of BCS. The purpose of the present study was to identify factors of re-excision after OPS.

Patients and Methods

A retrospective analysis was conducted on all patients who had undergone OPS between January 1st 2009 and February 28th 2013. OPS was defined as lumpectomy performed with a level II oncoplastic technique, according to the classification defined by

Table I. *Demographics of the study population.*

	N=129
Median age (range), years	52 (26-83)
≤50 Years, n (%)	55 (42.6)
>50 Years, n (%)	74 (52.4)
Median BMI, kg/m^2	24.3
Overweight (BMI ≥25 kg/m^2), n (%)	58 (48.7)
Obese (BMI ≥30 kg/m^2), n (%)	23 (20.9)
Mean breast cup size*, n (%)	
A	4 (3.1)
B	45 (34.9)
C	35 (27.1)
D and more	42 (32.6)
Not available	3 (2.3)
Neoadjuvant chemotherapy, n (%)	44 (34.1)

BMI: Body mass index, breast cup size*.

Table II. *Characteristics of the tumors and surgical outcome between groups treated with and without neoadjuvant chemotherapy (CT).*

Characteristic	Primary CT N=44	No primary CT N=85	*p*-Value
Lobular type, n (%)	1 (2.3)	18 (21.2)	0.004
pT, mm	18.6	25.1	0.02
Mean margin width for invasive component, mm	3.3	4.3	0.14
Mean margin width for DCIS, mm	3.4	3	0.60
Frozen section examination, n (%)	34 (77.3)	69 (81.2)	0.60
DCIS component, n (%)	23 (52.3)	60 (70.6)	0.04
Positive or close margins, n (%)	12 (27.3)	25 (29.4)	0.80

DCIS: Ductal carcinoma *in situ* pT; pathological tumor size

Clough *et al*. (9) or surgery with a nipple-areolar complex repositioning. Cases lacking reported details on remodeling of the breast were excluded.

Selection of surgical procedure was based on the 'quadrant per quadrant atlas', as described by Clough *et al*. (11). Briefly, inferior pedicle mammoplasty was used for tumors located in the upper quadrant junction. Lateral mammoplasty and V mammoplasty were used for tumors of the upper outer quadrant and upper inner quadrant, respectively. For the inferior aspect of the breast, superior pedicle mammoplasty was used for tumors of the lower quadrant junction, J mammoplasty for tumors of the lower outer quadrant, while round block or batwing technique were used for tumors of the lower inner quadrant.

At our Center, contraindications for oncoplastic techniques match contraindications for BCS, namely inflammatory BC, multi-centric BC and extensive microcalcifications. An OPS is performed as first intervention or after neoadjuvant CT. Axillary dissection is preferred over sentinel lymph node biopsy for tumors measuring 20 mm or more. In March 2012, this criterion was modified by our group and has since applied to tumors measuring 30 mm or greater. In the neoadjuvant treatment setting, axillary lymph node dissection was systematically performed.

When patients received neoadjuvant CT, surgery was performed within three weeks following the last CT treatment. In these cases, indications for BCS were based on an estimated clinical and radiological response. All indications for surgery and neoadjuvant CT were discussed by a dedicated multidisciplinary tumor board. Neoadjuvant CT consisted of four cycles of anthracyclines, cyclophosphamide and 5-fluorouracil (5-FU) followed by four docetaxel cycles. Trastuzumab was added to CT in case of human epidermal growth factor receptor 2 (HER2-)overexpressing BC. Pathological complete response (pCR) was defined as complete disappearance of invasive carcinoma in both breast and axillary lymph nodes. Residual ductal carcinoma *in situ* was included in the pCR category.

When the pathological tumor margin was positive or less than 1 mm, a re-excision was proposed. The technique used for the secondary surgical revision was decided by the referent surgeon according to the size of the residual breast and in agreement with the patient.

For statistical analysis, the Chi-square test was used to compare the distribution of demographic characteristics between groups, whereas the Mann–Whitney test was used for the continuous variables. A 5% significance level was used and all *p*-values were two sided. Recursive partitioning analysis (RPA) was used to build regression trees for the prediction of the re-excision. Recursive partitioning is a statistical method which groups patients into distinct cohorts based on maximizing the value of log-rank tests for the clinical end point of interest (17). RPA was performed using R, an open source statistical package (http://www.r-project.org/) using the rpart function (The R Foundation for Statistical Computing, Vienna, Austria) (18).

Results

Demographics. Between January 2009 and February 2013, 129 patients with an operable breast tumor underwent OPS. The patient and tumor characteristics are shown in Table I. The majority of patients were more than 50 years old, and almost half of patients were overweight. The distribution of histological sub-types were as follows: luminal A sub-type in 72.9%, luminal B sub-type in 10.9 %, HER2 sub-type in 5.4% and triple-negative breast cancer in 10.9%. Invasive ductal carcinoma was found in 110 cases (85.3%) while invasive lobular carcinoma was found in 19 cases (14.7%). More than one-third of patients received neoadjuvant CT (34.1%).

Surgical outcomes. Surgical techniques used were distributed as follows: Round block in 45 cases (34.9%), superior pedicle in 30 (23.2%), lateral mammoplasty in 25 (19.4%), V mammoplasty in 11 (8.5%), inferior pedicle in eight (6.2%), Batwing technique in seven (5.4%), sillon using Crescent technique in two cases (1.6%), and J mammoplasty in one case (0.8%).

Resection margins were examined on frozen sections in 103 patients (79.8%). This perioperative evaluation led to tumor

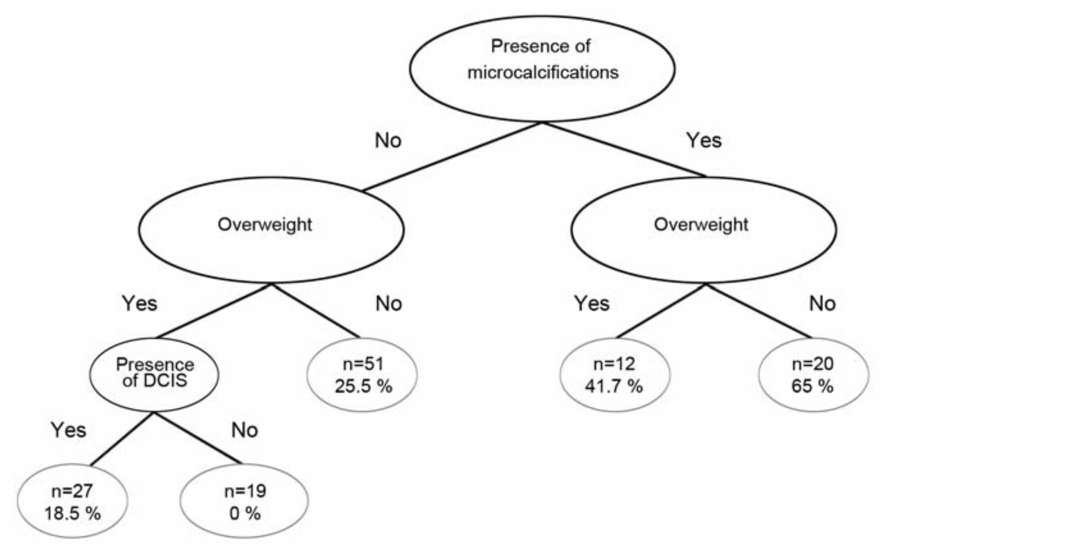

Figure 1. *RPA analysis identifies fives groups at risk for re-excision after OPS.*

bed re-excision in 50 patients (38.8%). The mean pathological size of the tumor was 22.9 mm (range=0-100 mm). Positive axillary nodes were found in 43.4% of cases. The mean and median margin widths were 4 mm and 5 mm for invasive component (range=0-15 mm) and 3.2 mm and 3.5 mm (range=0-11 mm) for the DCIS component. Out of the 44 patients who received neoadjuvant CT, nine (7%) achieved pCR. Surgical outcome, tumor features and pathological findings were compared according to administration of primary CT (Table II). In the group treated with neoadjuvant CT, lobular type was rare (p=0.004), tumor size on surgical specimen was smaller (p=0.02) and a DCIS component was less frequently found (p=0.04).

Amongst the 129 patients, a second surgery for close or positive margins was proposed to 37 patients (28.7%). Two of them refused surgery. Thus, 35 surgical re-excisions were performed, consisting in eight tumor bed re-excisions (22.9%) and 27 completion mastectomies (77.1%). Thus, mastectomy was performed in 20.9% of the total cohort. Of the 18 patients who required mastectomy, eight patients (44.4%) underwent immediate breast reconstruction. When comparing the patients that underwent re-excision to the rest of the cohort that did not need re-excision, multifocality and presence of a DCIS component was more frequent. In the group treated with neoadjuvant CT, pCR was more frequent (p=0.04), as shown in Table III. Pathological tumor (pT) size was higher in the group with re-excision (p=0.05). Type of OPS technique did not differ between the two groups (p=0.25).

In univariate analysis (Table IV), predictive factors for surgical re-excision were: overweight (OR=0.36, p=0.02), presence of microcalcifications on mammography (OR=5.64, p<0.001), multifocal tumor (OR=5.37, p=0.01), size of minimal invasive margins (p<0.001) and presence of DCIS (OR=3.8, p=0.007); pCR did not reach significance (p=0.99). In multivariate analysis, overweight (OR=0.25, p=0.02); size of minimal invasive margins (OR=0.49, p<0.001) and presence of microcalcifications on mammography (OR=4.4, p=0.01) were predictive for the risk of re-excision while presence of DCIS was not significant (OR=2.9, p=0.11).

RPA. By using standard clinical and pathological factors, the recursive partitioning was used to stratify sub-groups of predictive factors for re-excision. The RPA identified five terminal nodes based on presence of microcalcifications on mammography, overweight and presence of DCIS in the specimen (Figure 1). The most important predictive factor was the presence of microcalcifications on screening mammography. After four partitions, there were three groups of clinical relevance: the presence of microcalcifications and not being overweight (probability of re-excision=65%, n=20); the presence of microcalcifications and being overweight (probability of re-excision=41.7%, n=12); and the absence of microcalcifications and not being overweight (probability of re-excision=25.5%, n=51). For the last partitions, the presence of DCIS in the specimen was considered and resulted in the following groups: absence of microcalcifications, overweight and no DCIS (probability of re-excision=0%, n=19); and absence of microcalcifications, being overweight and the presence of DCIS (probability of re-excision=18.5%, n=27). Receiver

Table III. *Characteristics of patients with and without re-excision.*

Characteristic	Re-excision N=37	No re-excision N=92	*p*-Value
Lobular type, n (%)	8 (21.6)	11 (12)	0.16
Presence of DCIS, n (%)	31 (83.8)	52 (56.5)	0.003
Multifocality, n (%)	7 (18.9)	4 (4.3)	0.007
Neoadjuvant CT, n (%)	12 (32.4)	32 (34.8)	0.80
Frozen section examination, n (%)	31 (83.8)	72 (78.3)	0.48
pT, mm	27.1	21.2	0.05
pCR, n (%)	0 (0)	9 (28.1)	0.04

DCIS: Ductal carcinoma *in situ*; CT: clinical tumor size; pT: pathological tumor size; pCR: pathological complete response.

operating characteristic curve (ROC) analysis yielded an area of 0.751 for the RPA group affiliation.

A second analysis including the size of minimal invasive margins identified six terminal nodes based on the size of minimal invasive margins, being overweight and the presence of microcalcifications on mammography. The most important predictive factor was the size of minimal invasive margins, for which thresholds identified were 1.3 and 3 mm. After five partitions, the groups of clinical relevance were: margins <1.3 mm and no microcalcifications (probability of re-excision=72.2%, n=18); margins <1.3 mm and micro-calcifications (probability of re-excision=100%, n=9); margins 1.3-<3 mm and microcalcifications (probability of re-excision=14.3%, n=7); margins ≥1.3 mm and microcalcifications with margins >3 mm (probability of re-excision=50%, n=16); margins <1.3 mm and no micro-calcifications, and being overweight (probability of re-excision=0%, n=38); and margins <1.3 mm and no microcalcifications, and normal weight (probability of re-excision=12.2%, n=41). ROC analysis yielded an area of 0.875 for the RPA group affiliation.

Discussion

The association of plastic surgery principles with surgery for BC is considered a safe and optimal approach. Multiple previous reports emphasize the specific safety aspect of these procedures: oncologically safe when considering local recurrence, disease-free survival and overall survival; surgically safe entailing few complications, few surgical re-excisions and short adjuvant therapy delay; and esthetically beneficial, especially for large or sub-optimally localized tumors, thus reducing risks of postoperative deformities (11, 19). These techniques allow for optimal initial management which improves care and outcomes for patients with BC, especially in terms of quality of life (20). In recent years, the addition of OPS techniques to the surgical armada allowed for extension of plastic surgery indications in BC beyond the minimization of poor esthetic results. An OPS allows wider excision combined with a filling of the glandular defect with adjacent breast tissue. This permits direct closure of the excision cavity and a better remodeling of the gland. In a recent meta-analysis, Losken *et al*. report that patients treated by OPS had tumors of larger volume than did patients treated solely with BCS techniques (12). Thus, OPS offers the possibility of resecting greater volumes of mammary tissue than in BCS alone. But along with the possibility of resecting a larger tumor comes the risk of narrower or positive margins.

In the literature, the positive margin rate following BCS ranges from 20 to 60% (21, 22). In this study, excision rate after OPS was close to one-third of the patients. This proportion is higher than those of previously reported series. The fact that there-excision procedure is not uniformly defined certainly contributes to widening the range of reported re-excision rates. Clough *et al*. performed a re-excision in 10.9% of patients after OPS (11). Rates from smaller series vary between 0 to 29% (9, 23-25). Chang *et al*. reported that the positive margin rate was significantly lower with OPS compared to standard lumpectomies. Furthermore, completion mastectomies are rarely needed. (26). This observation is highly dependent on tumor size and the tumor size/breast size ratio. The high percentage of patients who received neoadjuvant CT in our series indirectly confirms the management of larger tumors, thus increasing the risk of re-intervention. Moreover, the definition of close margins and the indication of re-excision are still matters of debate. At our Department, re-excision is systematically performed for positive or close margins (less than 1 mm), even for focally involved margins. In the literature, indications for re-excision are not precisely specified.

Interestingly, in the present series, the second surgery was completion mastectomy in 20.9% of cases. When margins are found to be positive, two surgical options are conceivable, namely breast preservation and mastectomy. In this series, mastectomy was proposed in more than two-thirds of patients. A detailed analysis was unable to identify factors decisive in preferring one procedure over the other. Multiple re-excision procedures are known to be associated with a higher risk of local relapse (14, 15). No local relapse was detected in the present cohort, probably in part due to the short follow-up period.

The search for factors influencing the risk of re-excision clearly identified three significant variables, namely being overweight (p=0.02), the presence of microcalcifications on mammography (p=0.003), and tumor multifocality (p=0.03). Body mass index has been showed to influence locoregional control (27). In cases of multifocality the BCS option is debated. It is considered an acceptable option if tumors are in

Table IV. *Univariate analysis of predictive factors for re-excision*.

Factor	OR (95% CI)	*p*-Value
Age increase	0.99 (0.96-1.02)	0.41
Breast size increase	0.74 (0.48-1.15)	0.18
Overweight (BMI ≥25 kg/m^2) *versus* normal weight	0.36 (0.16-0.83)	0.02
Microcalcifications on mammography	5.64 (2.37-13.41)	<0.001
Neoadjuvant chemotherapy *versus* no	0.95 (0.42-2.15)	0.91
Lobular component *versus* others	0.50 (0.17-1.43)	0.20
pT ≥30 mm *versus* < 30 mm	0.98 (0.84-1.14)	0.79
Multifocal tumor *versus* unifocal	5.37 (1.47-19.7)	0.01
Presence of DCIS in specimen *versus* no	3.8 (1.43-9.93)	0.007
Size of minimal invasive margins (increase)	0.53 (0.42-0.68)	<0.001

BMI: Body mass index; pT: pathological tumor size; DCIS: ductal carcinoma *in situ*

the same location. These observed factors are in accordance with previously reported factors for re-excision. Previous studies reported further factors as being significant, namely the presence of non-palpable tumor, positive preoperative N-stage, high breast density, lobular histological type, high histological grade; a nomogram based on these factors was recently proposed to predict the risk of positive margins (28). In a recent study, Jeevan *et al*. reported rates for re-intervention and factors influencing type of surgery after BCS in patients with BC in England (29). This study exposed an increased risk of re-intervention in cases which presented a DCIS component, but this finding did not influence the choice for mastectomy. Authors also reported influence of age, and co-morbidity that were not significant in the present series. When the minimum size of invasive margins was added to our model, DCIS was not a significant parameter, but minimal margin size, the presence of microcalcifications, and weight enabled patients to be classified into five groups. Interestingly this model yielded a higher value for AUC (0.875).

The mobilization of large glandular flap on which OPS is based necessarily entails a significant risk of postoperative local complications. The 14.7% rate observed was mainly related to infectious or hemorrhagic processes. In previous series, immediate complication rates were found to have a similar spectrum. Fitoussi *et al*., recorded a 16.3% rate of complications but only 3.3% required surgical intervention (10). Similarly, in a smaller series of 50 patients, Mc Culley *et al*. reported a 16% complication rate, essentially in relation to fat necrosis (30). Interestingly, complications in the present study were significantly more frequent in obese patients. This could be due to the fact that breasts are composed of a greater proportion of fat in this sub-population.

In the present study, the RPA identified microcalcifications on mammography, and presence of DCIS on specimen as significant predictors for re-excision, and overweight as protective factor. In this specific analysis, the model based on these three factors yielded a good AUC. The advantage of tree representation of predictive risk resides in its visual depiction of risk categories, allowing a better understanding of the re-excision risk. The recorded AUC of 0.751 and 0.875 according to the model represent high levels of predictive accuracy. This pilot model being based on a rather small cohort, further work on a larger sample size from different institutions would definitely strengthen its validity. The accuracy of our model could probably be further improved by integrating additional predictor variables or existing biomarkers. Future work will focus on validating this model, also integrating the use of current imaging to improve the choice of surgical modality.

Conclusion

OPS improves the breast conserving rate in BC surgery. Our model allows better targeting of patients who could safely benefit from this technique, therefore reducing the rate of re-excision.

Conflicts of Interest

No conflict of interest to disclose.

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