Therapeutic mammoplasties: Full local control of breast cancer in one surgical stage with frozen section


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Therapeutic mammaplasties: full local control of breast cancer in one surgical stage with frozen section.

Background.

Therapeutic mammaplasties have demonstrated their effectiveness in allowing larger excisions and keeping local recurrence rates under control. (1, 2, 3). As these techniques are based on displacements of portions of glandular tissues several concerns can be raised regarding control of margins and possible re-excision in a second operation. The persistence of positive margins even after re-excision would require a mastectomy that should be accomplished through an unusual access with a possible increase in the complication rate (4, 5, 6). A failure in obtaining a complete excision, requiring a second surgical in-stay, may challenge effective identification of positive margins and delay adjuvant treatments; it also may generate a psychological unpleasant feeling of uncontrolled disease (7, 8, 9). The purpose of this work is to demonstrate that intra-operative frozen section can warrant a full local control in a single surgical stage. The re-operative rate and the effectiveness of local control will be tested over a long term follow-up.

Methodology

Admission criteria and surgical techniques employed

Fifty women whose tumour size and location may have compromised effective cosmetic results were admitted to this study. A small number of patients (five) with large breast and small multicentric cancers could also be included. (tab.1). The most common techniques for breast reduction were employed including inferior, superior and supero-medial pedicle breast reductions, Grisotti’s flap for central quadrantectomies, comma shaped mammaplasties and Benelli’s mastopexies. After triple assessment with clinical examination, diagnostic imaging and histological confirmation of cancer, all patients were thoroughly counselled; all the possible surgical options were discussed including uni-lateral operation or mastectomies. All patients included in this study decided to undergo bilateral operations. The surgical operation was performed by a single oncoplastic team of surgeons that performed both the cancer excision and the reshape.
Intra-operative management of margins

Once excised the specimen was sent to pathologists for examination with frozen section. Stitch markings were put for orientation. The margins were inked and the specimen was sliced into 4 mm thick sections perpendicular to the longest axes of tumour mass and mounted on a cryostat and then placed on slides and stained with haematoxylin and eosin. After preparation, the slides were examined by the pathologist, and tumour histology, size of invasive carcinoma, and the distance between inked margins and the neoplastic area were noted. Median duration of frozen section procedure was 20 minutes.

Tumour positive margins were defined as the microscopic presence of cancerous cells at ? 2 mm from the inked edge of specimen. The margins assessment was performed by a team of experienced dedicated pathologists.

The specimen was then fixed in formalin, embedded in paraffin and sections were stained with H & E, so final margin status was obtained by examination of permanent paraffin sections. Intra-operative positive margins mandated an immediate large re-excision; then a second specimen was excised with the aim of leaving at least 1 cm of tissue free of disease. The new slice was marked and oriented once again and sent for permanent histology.

At final sections the margins were considered free of disease when the distance from the tumour burden was more than 2 mm. As re-excision were particularly abundant we applied the same criteria also for the re-excision specimens. Lobular carcinoma in situ in the margins did not mandate re-excision (10). The tumour bed after cancer removal was marked with metallic clips to facilitate the administration of radiotherapy and a possible boost when required.

Adjuvant therapies and follow-up

External post-operative radiotherapy was prescribed to all patients including those affected only by intraductal disease (11,12) at a dosage of 50 Gy with a boost of 10 Gy in the tumour bed (all patients). Adjuvant chemotherapy was indicated in all patients with axillary disease, in patients with overt chemo-sensitive disease (ER-PgR negative) or in younger patients (<35 years) irrespective of hormonal status; patients with hormonal responsive disease were treated with anti-
hormonal therapy for five years. More in details 11 patients received chemotherapy, 16 patients received hormonal therapy and chemotherapy and 23 hormone therapy alone.

The post-operative follow-up was based on clinical examination (every four months for the first 2 years and twice a year subsequently) and annual bilateral mammography. Further examinations were prescribed according to suspicious clinical signs and symptoms. All patients were followed up for a median follow-up of 72.6 months (range: 32-168 months) from February 1996 to February 2010. Data were extracted from medical data records of Humanitas-Centro Catanese di Oncologia.

Results

Fifty-two oncological procedures in fifty patients were evaluated across the study span. The techniques employed were distributed as follows: 18 cases inferior pedicle breast reductions, 8 cases superior pedicle, 11 Benelli's round block technique, 5 comma shaped mammoplasties, 10 miscellaneous.

The overall survival rate was 98% and the disease free survival was 98%; we had a single case of locally recurrent disease (1.9%) that progressed to metastatic disease and patient's death. For what concerns histology we had 33 infiltrating ductal carcinoma, seven infiltrating lobular carcinoma, one pure DCIS, seven infiltrating ductal carcinoma and DCIS and five miscellaneous histology. Lesions were classified according to pT stage: we recorded 2 pTis, 3pT1mic, 3pT1a, 2pT1b, 20 pT1c, 21pT2, and 1 pt4. The medium size of the excised cancers was 17 mm.

The majority of the lesions were G2 (34 cases), 4 G1, 14 G3 and positive for at least one hormonal receptor in 41 cases, 11 cases were ER/PgR negative. We also classified tumour stages according to AJCC and we identified: 2 Stage0, 21 stage I, 13 Stage IIA, 13 Stage IIB, 2 Stage IIIA, 1Stage IIIB (tab.2).

Frozen section as a diagnostic tool for identification of positive margins was tested. In three cases we observed a false positive test, while five were true positive. Only one margin was found to be a false negative while forty four were true negative. In conclusion we report a sensitivity of 0.83 and a specificity of 0.93; the probability of true positive in a positive test (positive predictive value) was 0.62 while the probability of a true negative in a negative test was 0.97, for a final accuracy of 0.94.
Five intra-operative wide re-excisions were performed for true positive margins at frozen section. None of them demonstrated persistent disease. No further excisions or mastectomies were performed.

In the false negative case a single focus of intra-ductal (low-intermediate grade) disease was found in the inferior margin (infra-mammary fold) of a superior pedicled breast reduction for a cancer in the lower pole of the breast. All the other margins were widely free of disease. The multidisciplinary tumour board did not indicate a surgical re-excision or a mastectomy and a radiotherapy boost in the tumour bed was administered. Currently this patient is alive and free of disease.

Discussion

The historical background of therapeutic mammaplasties

Since the end of the nineties oncoplastic breast surgery has changed the technical approach to breast cancer removal and breast reshaping and reconstruction. The long time practised techniques for breast reduction can be employed in the oncological field to excise large portions of breast tissue including the neoplastic lump. After the resection the glandular tissue is displaced to fill the gap left by the excision. The final result is generally very close to that of a cosmetic surgery. The oncological effectiveness of therapeutic mammaplasties is demonstrated by several recent papers: Kaur et al (2) demonstrated that a larger volume can be excised and wider margins can be obtained (oncoplastic group 200cc vs. 117.55 cc no oncoplastic group p=.016 and negative margins 25/30 oncoplastic group, and no oncoplastic 17/30, p=.05); Giacalone et al (1) in 2006 demonstrated that 5 or 10 mm free margins were obtained in the oncoplastic group in a significantly higher percentage of cases; finally Rietjens and coll. (3) in 2008 concluded that this technique keeps local recurrences under control over a long term follow-up. Precisely a 3% rate of local recurrences after five years is reported, no recurrences were observed for lesions up to 2 cm and the risk of relapse for those between 2 and 3 cm became stable after the first three years as for mastectomies in the Milan I trial.

These premises allow to consider oncoplastic resections a safe tool in the hands of the modern oncoplastic surgeon. Furthermore it is assumed that if a correct pre-operative assessment has been performed the oncoplastic excision will be performed on very wide margins. However if a second surgical stage for presence of disease at the edges of the specimen is required this can become challenging once glandular tissue has been displaced.

Other studies about intra-operative assessment
Intra-operative assessment of margins has been tested by several studies. Cabioglu et al. (14) assessed margins intra-operatively in 264 patients undergoing breast-conserving surgery with conventional non-oncoplastic techniques. Fifty-eight patients (29%) with invasive cancer and six (9%) with DCIS had initial positive/close margins, and were rendered margin-negative by intraoperative analysis and immediate re-excision; they report an accuracy of 87.4%. Long term results show the 5-year ipsilateral breast recurrence-free survival rates after BCS and radiation were 99% for invasive cancer (n = 167) and 100% for DCIS (n = 27).

A comparative study by Pinotti (14) was carried out on two groups of patients: in the first one radiological, macroscopic, cytological and histological examination of frozen sections of the breast specimens were performed in the operating room during the surgery, the second group was a control group with no intra-operative assessment. Post frozen section immediate re-excision was indicated and performed in 40.8% cases. Permanent histological sections confirmed all intra-operative results. These patients were followed by a median period of 42 months and we observed 1% of local recurrence while this percentage was 11.4% among patients in the control group, although in a longer period of observation (median of 126 months). Cendan et al,(15) in further a study on 116 operations in which only frozen-section analysis of margins was performed reported an accuracy per-slide of 96% and per-case of 84%.

The only study correlating frozen section and oncoplastic surgery is the one by Rusby et al. 2008 (16). The author evaluated the role of this diagnostic technique in the field of reconstruction with latissimus dorsi mini-flaps after partial mastectomies. Several bed biopsies were submitted for intra-operative frozen section analysis and the flap was harvested only in a demonstrated absence of disease. Frozen sections were positive in 33% of patients with a sensitivity of 83% and accuracy of 96% when compared with paraffin sections. Local recurrence occurred in one case out of 101 (local recurrence rate 0.9%). The median follow-up was 41.4 month.

*Intra-operative assessment in our experience*

These data are quite similar to those reported in our study. Differently from Rusby we reported a lower percentage of positive frozen section; this datum can be due to their tendency to employ the technique of mini-flaps for repairing of excision of large lesions as demonstrated by the average size of the tumor excised (34 mm vs. 17 mm our study). Sensitivity in both studies was 83% while
accuracy was 94% in our study and 96% in Rusby's study who had a shorter median time of observation.

In view of these data the use of intra-operative assessment of margins seems to be a very straightforward tool for the modern oncoplastic surgeon. This practice can improve local control in one surgical stage avoiding complex re-intervention in the field of a manipulated gland. The need for secondary mastectomies can be dramatically reduced (none in our study) avoiding disfiguring procedures that in some cases at final histology demonstrates their usefulness.

Even re-excisions in a second stage could be reduced thanks to our strategy. In this study five patients with true positive margins at frozen section could benefit from a radical intra-operative reexcision. This could have been prescribed in the single false negative case. The location and the characteristics of the residual disease (single focus of low/intermediate grade of DCIS, close to the infra-mammary fold) allowed us to prescribe only a radiotherapy boost in the tumour bed.

A single hospital in-stay can be also beneficial in the psychological point of view for patients that sometimes may feel the need for re-excision as a threat for local control. Other beneficial aspects are the early come back to common activities and the higher efficiency of the technique.

Some aspects are still to be investigated: in our study for instance we observed a low positive predictive value (0.625). This may have led to a number of pointless re-excisions. This of course may affect the cosmetic outcome of conventional wide-local excision; therapeutic mammaplasties with transpositions of large portions of glandular tissue may be more suitable to fill even wider gaps. A further critical aspect of the study relies in the possible longer operating time. This issue is not addressed in this study. However all the frozen sections were performed by the pathologist while the surgeon was dissecting the sentinel node or performing the axillary dissection. This has entirely avoided any waste of theatre time.

The final focus of this study is on oncological local control of disease. Although in this study no comparisons are made with conventional wide local excisions, oncoplastic resections and intra-operative frozen section demonstrated to keep effectively under control the local recurrence rate (1.9% during six years of follow-up) very close to that reported by Rusby and coll. and by far in keeping with international standards. Only one patient experienced a recurrence in the breast; the same patient subsequently deceased due to progressive disease.
Conclusion
Therapeutic mammaplasties are expected to prevent cosmetic failures in breast conserving surgery. Wider excisions performed using surgical techniques derived from cosmetic surgery could also allow wider margins reducing the re-interventional rates.
In this study we pursued this goal using frozen section as a complimentary tool to avoid further operations. We demonstrated that intra-operative assessment of margins can be effective in preventing a second surgical look with concurrent optimal local control of disease. None of the patients in this series required a delayed mastectomy that, although not directly demonstrated by the results of this report, could be due to wider excisions allowed by the surgical technique.
Further prospective comparative studies should be warranted to demonstrate the effectiveness of this strategy.
REFERENCES

<table>
<thead>
<tr>
<th>Admission criteria:</th>
<th>Technique</th>
</tr>
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<tbody>
<tr>
<td>Breast cancer located in the lower pole of the breast</td>
<td>Superior pedicle breast reduction</td>
</tr>
<tr>
<td>Centrally located breast cancers</td>
<td>Grisotti’s Flap or Inf. Pedicle reduction (skin island on the inferior pedicle)</td>
</tr>
<tr>
<td>Tumours in the upper outer quadrant of small- to medium sized breast</td>
<td>Conventional quadrantectomy with Nipple-areola complex repositioning (Benelli’s Technique)</td>
</tr>
<tr>
<td>Tumours in the lower outer quadrant of small to medium size breast</td>
<td>Bilateral Regnault mammoplasties</td>
</tr>
<tr>
<td>Multicentric lesions in large breasts</td>
<td>Inferior or supero-medial breast reductions (technique tailored to lesion locations)</td>
</tr>
</tbody>
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Tab. 1: Surgical techniques employed.
<table>
<thead>
<tr>
<th>Patients/ n.cases</th>
<th>50/52</th>
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</thead>
<tbody>
<tr>
<td>Mean follow-up time (months; range)</td>
<td>72.6 months (range 32 /168)</td>
</tr>
<tr>
<td>Tumour type</td>
<td></td>
</tr>
<tr>
<td>Invasive ductal carcinoma</td>
<td>33 (63.4%)</td>
</tr>
<tr>
<td>Invasive lobular carcinoma</td>
<td>7 (13.4%)</td>
</tr>
<tr>
<td>DCIS</td>
<td>2 (3.8%)</td>
</tr>
<tr>
<td>Invasive ductal/lobular+DCIS</td>
<td>6 (11.5)</td>
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<tr>
<td>Various (tubular, medullary, anaplastic)</td>
<td>4 (7.6%)</td>
</tr>
<tr>
<td>Stage 0</td>
<td></td>
</tr>
<tr>
<td>T 0, N0, M0</td>
<td>2 (3.8%)</td>
</tr>
<tr>
<td>Stage I</td>
<td></td>
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<tr>
<td>T1, N0, M0</td>
<td>21 (40.3%)</td>
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<tr>
<td>Stage II A</td>
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<tr>
<td>T1, N1, M0</td>
<td>5 (9.6%)</td>
</tr>
<tr>
<td>T2, N0, M0</td>
<td>8 (15.3%)</td>
</tr>
<tr>
<td>Stage II B</td>
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<tr>
<td>T2, N1, M0</td>
<td>13 (25%)</td>
</tr>
<tr>
<td>Stage III A</td>
<td></td>
</tr>
<tr>
<td>T1, N2, M0</td>
<td>2 (3.8%)</td>
</tr>
<tr>
<td>Stage III B</td>
<td></td>
</tr>
<tr>
<td>T4, N0, M0</td>
<td>1 (1.9%)</td>
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Tab.2 Oncological characteristics