Mammographic and ultrasonographic findings of oxidized regenerated cellulose in breast cancer surgery: a five-year experience

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Authors: R. Rella, M. Giuliani, F. Patrolecco, R. Fubelli, C. Borelli, P. Rinaldi, M. Romani, P. Belli, L. Bonomo; Rome/IT  
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Aims and objectives

Breast-conserving surgery and radiotherapy is firmly established as a good and safe option for most women with early breast cancer.

The purpose of conservative breast surgery is to ensure complete removal of breast cancer, with the same survival rate of mastectomy, preserving the shape and appearance of mammary glands and their natural symmetry [1-4].

Recently, some surgeons have focused their attention on oncoplastic procedures. The purpose of oncoplastic surgery for breast cancer is to improve the cosmetic outcome without impacting local control after resection [5-7]. Generally, oncoplastic surgery consists of two components: wide local excision of the tumor and reshaping of the breast.

In our Institution, over the last 5 years, surgeons started to use oxidized regenerate cellulose (ORC) (Tabotamp fibrillar®, Johnson & Johnson; Ethicon, New Brunswick, NJ, USA) in conservative breast surgery. ORC is a sterile absorbable material, originally used in intra-abdominal or retroperitoneal surgical procedures. It was first proposed as a filling material for volume defects after breast surgery in 2003 [8-9]. When applied in the surgical cavity, ORC swells into a gelatinous brown-black mass, which allows local control of bleeding and reduces the risk of post-operative infections, thus combining the oncological radicality with the aesthetic results.

In our Institution, the technique in use by breast surgeons for placement of oxidized cellulose follows a standard pattern (Fig.1).

This procedure could induce changes in radiological appearance of surgical scar [10-12]. There are few works in Literature about postoperative imaging of ORC [13-14], although the increasing use of this technique in conservative treatment of breast cancer.

Aim of the study is to describe ultrasonographic (US) and mammographic (MX) findings in patients who underwent breast conserving surgery followed by ORC implantation in surgical cavity and their variation in follow-up, in order to avoid misdiagnosis of tumor recurrence and/or additional or unnecessary diagnostic procedures, such as MRI or biopsies.
Fig. 1: After complete tumor excision, adequate reshaping of the gland is performed by dissecting the residual breast parenchyma from the pectoralis major fascia and then from the superficial subcutaneous tissue. With this dissection, two opponent superficial advancement flaps (i.e. skin, subcutis) and two opponent deep advancement flaps (i.e. breast parenchyma) are obtained (a). After careful control of the haemostasis, five separate layers of ORC fibrillar are placed in the residual cavity, topping the pectoralis major muscle (b) and two additional separate layers of ORC are then placed on the surface of the approximated glandular flaps (c)

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Methods and materials

Subjects

We retrospectively reviewed MX and US examinations performed between January 2009 and January 2014 in 262 patients who underwent breast conserving surgery with ORC implantation in the surgical cavity in our Institution.

All patients underwent first postoperative US examination about 6 months after surgery and were then examined with US follow-up every 6 months.

Only 203 patients had also postoperative mammograms about one year after surgery and were then examined with MX follow-up every year.

In this way, a total of 743 US and 417 MX images were reviewed.

The follow-up period ranges from 5 years to six months, depending on the date of surgery.

The study protocol was approved by our Institutional Ethics Committee.

Informed consent, including potential risks and benefits of the procedure, was obtained from all patients.

Although the recall and data analysis were done retrospectively, the patient database was assembled prospectively.

Ultrasonographic and mammographic imaging

US imaging and Colour/Power Doppler was performed with an Antares echograph (Siemens Healthcare, Erlangen, Germany) or with an Aplio 500 echograph (Toshiba Medical Systems Corporations, Otawara-shi, Tochigi-ken, Japan), both equipped with a 5-13 MHz linear transducer.

MX images were obtained by a Senographe DS mammograph (GE Medical System, Milwaukee, WI, USA) and by a Helianthus Bym mammograph (Metaltronica, Pomezia, Italy), including both cranio-caudal and medio-lateral oblique projections.

In our clinical practice, US and MX follow-up evaluations were performed using the same echograph and mammograph for each patient, in order to avoid information bias.

Image analysis
Two radiologists, with more than 5-years-experience in breast imaging, retrospectively reviewed in consensus a total of 417 Mx and 743 US images.

Either the presence or the absence of abnormal findings was evaluated on US and MX images.

Interpretation of breast US and MX imaging was based on the American College of Radiology Breast Imaging Reporting and Data System criteria (BI-RADS) [15].

US findings of the implanted ORC were classified into three patterns:

1. Complex masses: well-encapsulated hypo-isoechoic lesions with circumscribed margins with internal hyperechoic nodules, that we named "ile-flottante" (Fig. 2a);
2. Hypo-anechoic lesions without internal hyperechoic nodules (Fig. 2b);
3. Completely anechoic collections (Fig. 2c).

Moreover, Doppler ultrasound examination was performed in all the patients.

In order to study lesional vascularization with Color/Power Doppler, we use the following scheme:

- Pattern 0: absence of Color/Power Doppler signals
- Pattern 1: perilesional flow
- Pattern 2: presence of intra and perilesional vascularization

Four main MX patterns were identified:

1. Round or oval opacity with circumscribed margins (Fig. 3a);
2. Round or oval opacity with indistinct or ill-defined margins (Fig. 3b)
3. Irregular opacity with indistinct or spiculated margins and features of expansive lesion (Fig. 3c);
4. Architectural distortion or focal asymmetry (Fig. 3d).

Sequential changes in lesion's size were analyzed in patients who had at least US imaging follow up at 6, 12 and 18 months after surgery, by comparing the data achieved at 6 months examination with those of 12 and 18 months after surgery examinations. Lesion's size was measured in a transverse scan and marked as the longest diameter.
In the same way, temporal changes in lesion's size on MX were evaluated in patients who had at least MX imaging follow-up at 1, 2 and 3 years after surgery, by comparing the data achieved at 1 year examination with those of 2 and 3 years after surgery examinations.

We classified lesions as decreased (decline > 3 mm on follow-up MX or US), stable (#3 mm change on follow-up imaging) or increased (increase > 3 mm on follow-up imaging) in size.

**Statistical analysis**

Statistical analysis (general linear models-repeated measures) was used to assess any significant difference in number of reduced, increased and stable lesions.

Statistical analysis was performed for all cases that showed a reduction in lesion's size at US follow-up comparing the data of 6 months after surgery examination with those of 12 and 18 months and, for all cases that had a decrease in lesion's size at follow-up MX, comparing the data of 1 year after surgery examination with those of 2 and 3 years.

Repeated measures general linear models (GLM) analysis was performed to determine whether there was a statistically significant decrease in lesion's size at US and MX follow-up examinations.

We also evaluated the decrease in lesion size during the first follow-up period (12-24 months and 6-12 months for MX and US examinations, respectively), and in the second follow-up period (24-36 months and 12-18 months for MX and US examinations, respectively). For both US and MX imaging, we compared the decrease in lesion size between the first and second follow-up period using a t-test analysis.

All data were included in a dedicated electronic database, periodically checked. Continuous variables are presented as mean ± standard deviation, and categorical variables as percentages. All analyses were conducted using the SPSS software version 19.0 for Windows (Statistical Package for Social Sciences, SPSS, Chicago, IL, USA). P value was considered statistically significant at a value of less than 0.05.
Fig. 2: Ultrasonography performed after breast conservative surgery with ORC implantation revealed three different patterns, respectively a well-encapsulated isoechoic lesion with internal hyperechoic nodule, called "ile-flottante" (pattern 1, a), an hypo-anechoic lesions without internal hyperechoic nodule (pattern 2, b) and a completely anechoic collection (pattern 3, c)

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Fig. 3: Mammography performed after breast conservative surgery with ORC implantation revealed four different patterns, respectively a oval opacity with regular margins (pattern 1, a), a round opacity with ill defined and indistinct (pattern 2, b), an irregular opacity with spiculated margins (pattern 3, c), low-density architectural distortion, without any opacity evidence (pattern 4, d)

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Results

US Findings

In 170/262 patients (65%), US examinations showed abnormal findings; in 92/262 patients (35%), no significant alterations were detected. In the initial US examinations performed about 6 months after breast conservative surgery, 95/170 cases (56%) showed US pattern 1, 40/170 cases (24%) revealed US pattern 2 and 35/170 cases (20%) showed US pattern 3 (Table 1). In the evaluation of dimensional changes of the abnormalities observed at US examinations, we considered only patients (107/170) who underwent three radiological follow-up controls (6, 12 and 18 months): of these, 43 cases (40%) showed no changes in lesion size and 64 cases (60%) showed a size decrease (Fig 4). Statistical analysis was performed in 64 patients who showed a reduction in lesion size at US follow-up comparing the data of 6 months with those of 12 and 18 months after surgery examinations and our results are shown in Table 2: follow-up US examinations revealed that the percentage of decrease in size was 29.4% between 6 and 12 months and 46.5% between 6 and 18 months, and this variation was statistically significant (p value < 0.01). Moreover, the mean reduction of lesion size on US examination in early follow up period (6-12 months) and in late one (12-18 months) was 9.8 mm (95% CI: 7.7-11.8, p<0.01) and 5.7 mm (95% CI: 3.7-7.6, p<0.01), respectively. Our data also revealed that the mean reduction in lesion’s size assessed on ultrasound analysis was significantly higher in the early follow up period compared to late one (p<0.01). The Color and Power Doppler showed in all the patients a perilesional vascularization, without intralosomal signals (pattern 1).

MX Findings

Of 262 patients, only 203 performed follow-up MX examinations at our radiology department. In all the patients, slight architectural distortion due to postoperative changes was noted in MX imaging, but it was not considered as a significant alteration (Fig. 5). So that, MX examinations showed abnormalities in 95/203 patients (47%) while they were considered normal in 108/203 cases (53%). At the earliest MX examinations performed about 12 months after breast surgery, 55/95 cases (58%) showed pattern 1, 16/95 cases (17 %) showed pattern 2, 9/95 cases (9%) revealed pattern 3 and 15/95 cases (15%) showed pattern 4 (Table 3). Occurrence of calcifications was noted in 18 cases, but they were considered typically benign in all of cases. In the evaluation of changes in those alterations observed at MX examinations, we have considered only patients (61/95 patients) who had undergone three mammographic follow-up controls (12 months, 24 months and 36 months); of these, 22 cases (36%) showed no changes in size while 39 cases (64%) showed a size decrease at follow-up examinations (Fig. 6). Statistical analysis was performed for 39 cases that showed decrease in lesion size at MX follow-up
comparing the data of 1 year control with those of 2 and 3 years after surgery controls as illustrated in Table 4. Follow-up mammography revealed that the percentage of decrease in lesion's size was 23.3% between 12 and 24 months and 44.5% between 12 and 36 months, and this difference was statistically significant (p value <0.01).

Moreover, the mean reduction of lesion's size on MX examinations in follow up periods of 12-24 months and 24-36 months was 9.8 mm (95% CI: 6.8-12.9, p<0.01) and 9.1 mm (95% CI: 6.8-11.2, p<0.01), respectively. Our data also revealed, therefore, that the mean lesion's size reduction on MX analysis was significantly greater in the late follow up period compared to early follow up period (p<0.01).
Table 1: US Findings

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Fig. 4: The US follow-up at 6 (a), 12 (b) and 18 months (c) after surgery showed a progressive reduction in size of the lesions.

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Table 2

<table>
<thead>
<tr>
<th></th>
<th>Mean decrease (mm)</th>
<th>CI 95%</th>
<th>% decrease</th>
<th>p value</th>
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<td>12.6-18.1</td>
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</table>
**Table 2:** Variation of lesion size on follow up US examination at 6, 12 and 18 months

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**Fig. 5:** MX examination of two different patients shows slight architectural distortion due to postoperative changes, not considered as a significant alteration.

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Table 3: MX Findings

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Number of Patients</th>
<th>Percentage (%)</th>
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<tbody>
<tr>
<td>Pattern 1</td>
<td>55/95</td>
<td>58%</td>
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<tr>
<td>Pattern 2</td>
<td>16/95</td>
<td>17%</td>
</tr>
<tr>
<td>Pattern 3</td>
<td>9/95</td>
<td>9%</td>
</tr>
<tr>
<td>Pattern 4</td>
<td>15/95</td>
<td>15%</td>
</tr>
</tbody>
</table>

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**Fig. 6:** The MX follow-up at 12 (a), 24 (b) and 36 months (c) after surgery showed a progressive reduction in size of the lesion, in both MX projections.

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**Table 4**: Variation of lesion size on follow up MX examination at 12, 24 and 36 months

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<table>
<thead>
<tr>
<th>Decrease 12→24</th>
<th>Mean decrease (mm)</th>
<th>CI 95%</th>
<th>% decrease</th>
<th>p value</th>
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<td>Decrease 24→36</td>
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<td>6.8-11.2</td>
<td>27.6</td>
<td>p&lt;0.01</td>
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<tr>
<td>Decrease 12→36</td>
<td>18.9</td>
<td>14.8-22.9</td>
<td>44.5</td>
<td>p&lt;0.01</td>
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</table>
Conclusion

Breast-conserving surgery is an excellent option for early stage breast cancer, providing it can be performed without compromising the effectiveness of treatment whilst achieving an acceptable cosmetic result.

Reconstruction using ORC has been introduced in recent years to optimize oncologic safety and cosmetic outcomes.

In Literature there are few works with small number of cases about the postoperative imaging of ORC [9].

In the present study, we have analyzed MX and US patterns most frequently observed after conservative breast surgery followed by ORC implantation in surgical cavity.

The most frequent finding at US examinations is a complex mass: well-encapsulated hypo-isoechoic lesion with circumscribed margins and internal hyperechoic nodules (95 patients, 56%). The presence of hyper-isoechoic nodules within complex cystic mass can be explained as typical granulomatous foreign body reaction induced by the presence of ORC. We named this finding "ile-flottante". The presence of hyper-isoechoic nodules within complex cystic mass could be misdiagnosed as tumor recurrence at the peripheral zone of the surgical scar if interpreted by radiologists not experienced in recognizing breast changes caused by the use of ORC.

Use of Color/Power Doppler should be considered as part of the ultrasound procedure. A perilesional vascularization is probably indicative of compression exerted by Tabotamp on neighboring tissues or connected to the presence of granulation tissue around the surgical site.

The most frequent MX pattern (55 patients, 58%) is a round or oval opacity with circumscribed margins. In 9 cases in which mammography revealed opacities with irregular morphology and spiculated margins (MX pattern 3), that could simulate a local recurrence, 6 cases showed no evidence of suspicious lesions at following ultrasound examination so that the diagnostic question was solved, while 3 patients were referred to undergo additional radiological examinations, such as breast MRI, core needle biopsy or both, but however, there was no evidence of tumor recurrence in all of these cases, according to the Literature [12]. In 18 cases mammography showed occurrence of calcifications but the majority of these showed typically benign pattern (punctate, dystrophic, rim or eggshell calcifications), so no further examination was needed, in agreement to the Literature [14].

In our study size of lesions gradually decreased in follow-up examinations in most of patients (60% and 64% at US and MX imaging respectively). This reduction in lesion size
is probably connected to the gradually absorption of the fluid and to progressive fibrosis with retraction of the lesion [10].

Moreover, data showed that, in MX follow up, the lesion size reduction in the late period is bigger than in the the first one while in US follow-up we could find that the reduction in the early period was bigger than in the second one. This difference can be explained by different follow up times cause of the longer duration of MX follow up (36 months MX follow up vs 18 months US follow up). Whether there is a doubt about local tumor recurrence, reduction in size of alterations showed at MX and US follow-up examinations could be an additional criteria to help breast radiologists to properly assess these changes as benign.

In conclusion, when applied to surgical residual cavity, ORC helps controlling of local hemorrhage and reducing the risk of post-operative infections, but it could lead alterations in surgical scar. Thus, US and MX examinations during follow-up should be performed by radiologists who well know peculiar properties of this material and understand the corresponding mammary and scar changes and can correctly interpret them, in order to avoid misdiagnosis of tumor recurrence and additional or unnecessary diagnostic examinations such MRI or biopsies.
Personal information

rossella.rella@gmail.com
References


