Introduction

Breast conserving surgery (BCS) is the first-choice treatment for early breast cancer (BC), but tumor-free margins are regarded as an essential prerequisite for correct surgical treatment. BCS provides, if combined with adjuvant radiotherapy, the same (or better) overall survival of mastectomy. It is preferable to combine the two treatments rather than just mastectomy, because it is less invasive and better accepted by patients. Post-operative complications rate (e.g. infections), aesthetic outcome, and patient satisfaction are the advantages of BCS compared to mastectomy. Therefore, BCS is an excellent alternative to mastectomy, but re-operation is sometimes required.

Background: The aim of this study is to evaluate the accuracy of intra-operative specimen mammography (ISM) in surgical margins status assessment and highlight the concordance between the interpretations of the surgeon and the radiologist.

Methods: Our cross-sectional study included 130 patients with early breast cancer, surgically treated between October 2013 and September 2017 in the multidisciplinary breast center of the A.O.U. City of Health and Science (which is a complex of several hospitals) in Turin, Italy. All recruited patients underwent breast conservative surgery. Surgical margins were evaluated intraoperatively, using intra-operative specimen mammography. A standard compression intra-operative specimen mammography was obtained by the surgeon using the dedicated radiological equipment (Faxitron®, BioVision). After the surgeon’s evaluation of the margins, Faxitron images were sent to PACS. All ISMs images were analyzed by the same specialized radiologist in remote access to confirm the surgeon evaluation. We used kappa formula to report concordance.

Results: The discordance rate of positive readings between the surgeon and the radiologist was 5.3% while that of negative readings was 6.9%. The concordance rate between radiologist and pathologist assessments was 100%. Intra-operative specimen mammography specificity was 94% (95% CI: 88–97), and sensitivity was 47% (95% CI: 38–56), with PPV found to be 53% (95% CI: 95% 44-62) and NPV determined to be 92% (95% CI: 86–96), when the assessment was made by the surgeon.

Conclusion: Intra-operative specimen mammography is a helpful tool to identify infiltrated margins and to reduce the rate of secondary surgeries by recommending targeted re-excisions of corresponding orientations in order to obtain a final negative margin status. In our experience, not only radiologists but also surgeons could correctly read Faxitron® intra-operative specimen mammography.
because of infiltrated surgical margins (defined as "positive"). In the literature, there is a wide variability in the frequency of re-excision, from less than 10% to more than 50% of lumpectomies.17 Re-operations after breast conserving surgery adversely affect cosmetic outcome and cause additional stress for patients and their families. According to EUSOMA recommendations (European Society of Breast Cancer Specialist), the proportion of patients who received a re-operation for the primary tumor may not exceed 10%.18 The role of breast imaging is therefore essential not only for a diagnostic purpose, but also for the correct surgical strategy choice in case of non-palpable lesions. Tumor size, its distance from muscular fascia and skin and its precise localization are essential for a complete excision with free surgical margins (pathology report of "no-ink on tumor" for invasive lesions and a clear margin of 2 mm for in situ lesions).

Localization techniques are multiple: metallic hook wire, carbon marking, skin tattoo, clip marker localization and radio-guided localization. During surgery, the surgeon follows the guide (e.i., metallic wire, skin tattoo) to the target area. Nevertheless, margin status assessment of the specimen is mandatory after breast cancer surgery (BCS) of non-palpable breast cancer (BC). Several methods are available that are already part of standard of care for margin detections.19 In Italian hospitals, intraoperative pathology analysis (frozen section or touch cytology) and specimen radiography (intraoperative specimen mammography, ISM) are the most common techniques.

Frozen section use should be considered for margin assessment if reoperation rates at an institution are > 15%.20 Conversely, imaging techniques such as ISM can be used to achieve tumor-free margins in health centers that are specialized in breast cancer treatment. Technological advances have developed a dedicated X-ray equipment for the operating room, such as Faxitron®, which optimize intraoperative specimen analysis times and avoid unnecessary specimen transport to the radiology department.

Faxitron® is a tool that surgeons can use immediately after lumpectomy: the acquired radiographies are read by the surgeon and sent by PACS (Picture Archiving and Communication System) to the radiology department. The exchange of opinion between the surgeon and the radiologist about margins status is a learning opportunity and a moment of professional growth for both medical specialists.

The aim of our study is to evaluate the accuracy of ISM in surgical margins status assessment and highlight the concordance between the interpretations made by the surgeon and the radiologist.

Methods
Our cross-sectional study included 130 patients with mammography detected early breast cancer (a disease confined to the breast with or without regional lymph node involvement, and the absence of distant metastatic disease), surgically treated between October 2013 and September 2017 in the multidisciplinary breast center of the A.O.U. City of Health and Science in Turin, Italy. Breast cancer (BC) subtypes were grouped into the following categories: luminal A (ER+/PR+/HER2−, Ki−67<20 %), luminal B/HER2+ (ER+/HER2+/any Ki-67/any PR), luminal B/HER2− (ER+/HER2− and at least one of Ki−67≥20 % or PR−), HER2-enriched (ER−/PR−/HER2+), and triple negative (ER−/PR−/HER2−).19,21 All recruited patients underwent breast conservatory surgery. Preoperatively, non-palpable lesions were marked by wire-guided localization (which was performed with a hooked wire through an 18-G spinal needle) or skin tattoo or carbon marking. All surgical procedures were performed by the same specialized breast cancer surgeon. All specimens were direction-oriented using metallic stitches. Surgical margins were evaluated intraoperatively, using ISM. A standard compression ISM was obtained by the surgeon using the dedicated radiological equipment (Faxitron®, BioVision). In 100% of the cases, two orthogonal projections of the specimens were acquired (Figure 1).

The surgeon analyzed ISMs and defined the surgical margins as positive (infiltrated) or negative (tumor-free), according to the presence or the absence of the tumor on surgical margins. Faxitron images were sent to PACS. All ISMs images were analyzed by the same specialized radiologist in remote access to confirm the surgeon evaluation, without knowing the surgeon's conclusions. The procedure took 5 minutes and the communication between radiologist and surgeon took place by phone.

Additional tissue was taken if the radiologist indicated positive margins. Finally, the specimen was sent to the pathology department for pathology analysis, which is the gold standard for the assessment of surgical margins.

We collected pre-operative and post-operative data of all the 130 patients using PACS IDS7 (Sectra Medical Systems, Linköping, Sweden), Synapse (Fujifilm Holdings) systems and TrakCare Information System (InterSystems Corporation, Cambridge, MA, USA).

We used kappa formula to report concordance. BMI data were collected as well and we used the following classification:
- BMI 25-29 kg/m²: overweight
- BMI more than 30kg/m²: obesity

Results
The mean patients’ age was 62 years (range: 27-92 years old.). The mean±SD body mass index (BMI) was 25 kg/m² (over-weight range). The most frequent
mammographic finding was a mass (97 cases out of 130, 74%), following by distortion (11 cases out of 130, 8%), microcalcifications (5 cases out of 130, 4%). Multiple findings were reported in 17 patients out of 130 (13%) and were characterized by the coexistence of radiopacity areas associated with microcalcifications and/or distortions.

Breast lesions were palpable in 84 patients out of 130 (65%). Non-palpable lesions were localized by metallic hook wire (36 lumpectomies out of 46; 78%) or by skin tattoo (10 lumpectomies out of 46; 22%). Fifteen patients were interpreted as having positive margins by the surgeon but only 8 out of 15 patients had a positive margin on pathology (ISM false positive cases). After the surgeon's assessment, 115 lumpectomies were interpreted as having free margins by ISM but 9 lumpectomies out of 115 were histologically involved (ISM false negative cases). The radiologist's assessment agreed with histological results in 130 cases out of 130 (100%), obtaining 17 true positives and 113 true negatives. The concordance rates are shown in Table 1.

The discordance rate of positive readings between the surgeon and the radiologist was 5.3% while that of negative readings was 6.9%.

The concordance rate between radiologist and pathologist assessments was 100%.

ISM specificity was 94% (CI 95% 88–97), and sensitivity was 47% (CI 95% 38–56), with PPV standing at 53% (CI 95% 44-62) and NPV at 92% (CI 95% 86–96), when the assessment was made by the surgeon.

Pathology reports revealed that 6 cases out of 130 (4%) were ductal in situ carcinomas and 124 cases out of 130 were invasive tumours. An in situ component was observed in 31 cases out of 126 invasive tumours (25%). In our case series, 74 BC were Luminal A (57%), 31 BC were luminal B/HER2 negative (23%), 3 BC were luminal B/HER2 enriched (3%), 15 BC were triple negatives (11%), 1 BC was HER2 positive without hormonal receptors expression (<0.5%). Therefore, regarding HER2 status, only four patients (3%) were HER2 positives.

Histological results showed that 66 tumors (51%) were Non-Special Type (NST) carcinomas and 64 tumors (49%) were special type carcinomas (lobular, tubular, micropapillary).

The most frequent tumoral staging was pT1c (60 cases out of 130, 46%), followed by pT2 (32 cases out of 130, 24%), pT1b (23 cases out of 130, 18%) and pT1a (9 cases of 130, 7%).

Figure 1. Pre-operative mammography revealed a group of microcalcification in upper-external quadrant of the right breast (a, b, c, d). During VABB (vacuum assisted breast biopsy) a metallic clip was placed. A metallic hook wire was placed for intraoperative localization of the tumor. ISM confirmed the complete removal of the residual microcalcifications (e, f).
Sixteen patients out of 130 underwent wider resection because of margins status (12%): targeted re-excision was always performed intraoperative. Additional tumoral cells were found only in 50% of them (8/16).

Discussion

The principal disadvantages related to BCS include the possibility of re-intervention because of positive margins. This eventuality causes discomfort for the patient, higher cost for the health system, an increased risk of poor aesthetic outcomes, and delays adjuvant therapies (radiotherapy or chemotherapy). Efforts are necessary to avoid re-intervention for positive margins.

On the other hand, false positivity may affect aesthetic outcome because of unnecessary wider breast resection. In the literature, some elements are recognized as risk factors for re-intervention after BCS. Most of them are intrinsic factors such as dense breast, young age, low BMI, and HER2 positivity.

In our sample, re-operation rate was 0%, probably because of scarce representation of these risk factors: our patients set was old, overweight, and rarely HER2 positive. These features are related to tumor biology and patient characteristics and can not be changed, but the improvement of intraoperative margin status assessment techniques can reduce re-operation rate. ISM represents a valid tool to identify intra-operatively positive margin after lumpectomy. If tumors are not detectable with mammography, ultrasound could be used for surgical margins assessment instead of mammography. PACS system allows a rapid and effective communication with the radiology department, avoiding the transport of the specimen from the operative room to the radiology department, thereby reducing operator time. Nevertheless, the possibility that the surgeon may read ISM by himself represents a further advantage in term of costs and operative times. ISM interpretation requires the radiologist to dedicate time and to discontinue other activities that are not related to the operating room (screening mammography, second look mammography, breast ultrasound).

Furthermore, it should be noted that ISM is prone to sources of error such as specimen orientation, resulting in false positive findings and consequently aesthetic and economic disadvantages. When the surgeon reads ISM of the specimen that has been removed and oriented with metallic stitches, the interpretation of the specimen orientation is easy and accurate: this is essential in case of positive margin because the surgeon knows better than anyone where metallic stitches are located and, therefore, can remove the target margin with extreme precision. Thus, among the advantages of Faxitron®, the surgeon's desirable independence in ISM reading must certainly be included.

Discordance rate between surgeon and radiologist evaluations was found to be very low. Only 5% of the surgical margins were considered to be involved by the surgeon but non-involved by the radiologist (and the pathologist). FPs cases were non-palpable in the 86% (6/7): six cancers out of seven were NSTs and one case was a special types carcinoma (papillar).

In 7% of the cases, the surgeon false negatives could cause a successive re-intervention for involved margins if not compared with radiologist evaluation. FNs cases were non-palpable in the 88% (2/9): five cancers out of nine were NST, three cancers were special types tumors (1 mucinous; 1 papillar, 1 tubular) and one DCIS.

Analyzing the cases of discrepancy between the surgeon and radiologist, the tumors manifestation was calcifications: thus, we could suggest that the surgeon can read alone ISM images in case of mass lesion, but surgeons need the radiologist's support in case of calcifications.

In conclusion, ISM is a helpful tool to identify infiltrated margins and to reduce the rate of secondary surgeries by recommending targeted re-excisions of corresponding orientations in order to obtain a final negative margin status. In our experience, not only radiologists but also surgeons could correctly read Faxitron® ISM. Intrahospital refresher courses could increase surgeons' experience and accuracy in surgical margins status assessment by Faxitron ISMs.

Conflict of Interest

No conflict of interest or funding source to declare.

References


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Table 1. Concordance between surgeon, radiologist and pathologist assessment of surgical margins status

<table>
<thead>
<tr>
<th>Margin status</th>
<th>Surgeon</th>
<th>Radiologist</th>
<th>Pathologist</th>
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<tbody>
<tr>
<td>True Negative</td>
<td>106 (81.5%)</td>
<td>113 (87%)</td>
<td>113 (87%)</td>
</tr>
<tr>
<td>True Positive</td>
<td>8 (6%)</td>
<td>17 (13%)</td>
<td>17 (13%)</td>
</tr>
<tr>
<td>False Negative</td>
<td>9 (7%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>False Positive</td>
<td>7 (5%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
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