High resolution intra-operative two-dimensional specimen mammography and its impact on second operation for re-excision of positive margins at final pathology after breast conservation surgery

Lokesh Bathla, M.D.,* Ann Harris, M.D., Mary Davey, M.D., Poonam Sharma, M.D., Edibaldo Silva, M.D., Ph.D.

Departments of Surgery, Radiology, and Pathology, Creighton University Medical Center, Omaha, NE, USA and Division of Surgical Oncology, University of Nebraska Medical Center, Omaha, NE, USA

Abstract

BACKGROUND: In the United States, about 50% to 66% of women undergoing breast conservation surgery for cancer undergo subsequent mastectomy for positive margins on initial lumpectomy. This is despite the fact that screening mammography has resulted in a decrease in the size of newly diagnosed breast cancer to 1 cm.

METHODS: A retrospective review of 128 patients who underwent breast conservation surgery for early breast cancer was performed using intraoperative 2-dimensional Faxitron high-resolution specimen mammography without specimen compression as the only margin assessment technique. Of these, 29 patients had histories of lumpectomy with positive margins.

RESULTS: A total of 131 procedures were performed. Margins were histologically clear at initial breast conservation surgery in 84.3% of patients who underwent primary lumpectomy. Subsequent reexcision for positive margins was required in 14.7% of patients. Two-dimensional Faxitron mammographically guided intraoperative reexcision cleared the margins in 95.8% of patients (23 of 24) who would have otherwise required subsequent reexcision.

CONCLUSIONS: Intraoperative 2-dimensional Faxitron high-resolution specimen mammography can decrease rates of margin positivity and has the potential to diminish the number of subsequent undesired mastectomies for positive margins.

© 2011 Elsevier Inc. All rights reserved.

Keywords: Intraoperative margin assessment; Specimen mammography; Reexcision rates; Failed breast conservation
magnetic resonance imaging (MRI) wire localization. These techniques, however, have reported similar high positive margin rates requiring reexcision. McCormick et al showed a remarkable decrease in the reexcision rate from 12% to 5% with a simple approach, namely, 2-view specimen mammography.

Two-dimensional (2D) Faxitron high-resolution specimen mammography (Faxitron X-Ray LLC, Lincolnshire, IL) can alert the surgeon to proceed with reexcision of a potentially positive or close margin when coupled with standardized specimen orientation at the time of BCS. The aim of this study was to evaluate the role of 2D high-resolution intraoperative specimen mammography and its impact on second operation for the reexcision of positive margins after breast conservation.

**Methods**

A retrospective review was performed on 128 consecutive patients diagnosed with breast carcinoma and treated by a single surgeon (E.S.) between 2003 and 2008. Approval of the institutional review board was obtained before collection of the data. A total of 131 procedures were performed during this time period. One hundred one patients (78.9%) underwent preoperative tissue diagnosis with fine needle aspiration or standard core needle biopsy on the day of initial outpatient evaluation at our institution. One patient had negative results on fine needle aspiration as well as core needle biopsy. This patient underwent excision biopsy on the basis of strong clinical and mammographic suspicion. All nonpalpable lesions were marked preoperatively by clip placement and wire localization by the radiologist to guide with identification of the lesion at the time of excision.

Twenty-nine patients underwent excision biopsy at outside hospitals. The histology slides, mammographic findings, and operative records of these patients were reviewed at our institution before reexcision to confirm both the diagnosis of cancer as well as the positive margins. No repeat mammograms were obtained for patients with positive margins on prior lumpectomy to assess for residual disease, because the purpose of 2D specimen mammography is not to confirm the findings of the original diagnostic films but to assess the gross extent of the new margins intraoperatively. Because these cases may confound the measured variables for patients undergoing primary BCS, they have been excluded from the primary analysis.

**Surgical procedure**

BCS was performed concomitantly with sentinel lymph node mapping in all patients. The procedure began with sentinel lymph node mapping. For all patients, lumpectomy was planned as a spherical excision. The goal was to obtain at least a gross 1-cm margin circumferentially on specimen 2D Faxitron images. The pectoral fascia was included in all patients with lesions close to the chest wall. An ellipse of overlying skin was included when the lesions were very close to the skin.

In patients with prior lumpectomy or excisional biopsy and positive margins, the goal of reexcision was to ensure adequate circumferential excision of the prior cavity. Subsequently, the treatment algorithm was the same for these patients as for patients undergoing first-time excision. Intraoperative margin assessment of the lumpectomy specimen using 2D Faxitron mammography was done while the histologic evaluation of sentinel nodes was performed. Therefore, intraoperative specimen imaging incurred no significant prolongation in operative time. No intraoperative histologic margin assessment was performed.

**Intraoperative specimen mammography**

Specimen mammography was performed after the surgeon oriented the specimen with a short suture for the superior margin and a long suture for the lateral margin. A single vascular clip was placed for the anterior or superficial surface, and 2 vascular clips were placed for the deep or posterior surface. The oriented specimens were imaged without compression to avoid specimen distortion or compromise of gross margin assessment relative to the centrally located lesion. The specimen imaging was done in the anteroposterior dimension (all vascular marker clips in one plane), and then following 90° rotation of the specimen about the lateral suture with the superficial and deep clip margins now separated on different planes (Figs. 1 and 2). Both the surgeon (E.S.) and the radiologist (M.D.) reviewed all specimen mammographic images. The 5-mm clips served as a measurement standard for the magnified 2D Faxitron images. In patients with less than ideal gross 1-cm margins, an empiric reexcision of the close margins was undertaken without histologic assessment. The reexcision specimen was oriented relative to the main specimen for pathology evaluation.

![Figure 1](image-url) Specimen radiograph in the anteroposterior dimension showing all vascular marker clips in 1 plane.
Pathology

Surgical specimens were prepared for histologic analysis according to a standard protocol. All surfaces were inked in different colors, fixed in formalin, and serially sectioned. A single pathologist (P.S.) reviewed all the cases to confirm the diagnosis and to determine if tumor was present at the margin of the specimen. The distance between the margin of the tumor and the edge of the specimen was measured to the nearest millimeter. A clear microscopic margin was defined as \( \geq 1 \) mm beyond the tumor on inked permanent histologic margin. When the distance was \(<1\) mm, the margin was considered close, and a second procedure was performed for margin clearance.

Results

A total of 128 unselected, consecutive patients undergoing BCS for breast cancer were included in this study. Three patients underwent metachronous excision of separate breast lesions that were newly detected during the study period. Hence, a total of 131 excisions were performed during this study. Of these, 79.4% (104 of 131) had invasive carcinoma and 20.6% (27 of 131) had ductal carcinoma in situ. One hundred thirty of 131 lesions (99.2%) were successfully treated by BCS, and 1 patient decided to undergo mastectomy instead of reexcision for positive margin.

The average tumor size was measured at 1.6 cm (range, 0.3–5.5 cm). Twenty-four specimens (18.3%) were found to have positive margins, and 17 specimens (12.9%) had margin clearance of \(<1\) mm on final histologic examination. The estimated median specimen volume was 120 mL at the first BCS. In those requiring intraoperative 2D Faxitron mammographically directed reexcision, the median additional volume resected was 11.2 mL. Table 1 lists demographic information, excision volumes, and histologic subtypes.

The procedures were divided into 2 groups. The first group included patients who underwent primary BCS by E.S. (102 procedures in 99 patients). The second group consisted of patients who were referred from outside hospitals with histories of lumpectomy or excision biopsy and positive margins (29 procedures in 29 patients).

In these 102 primary procedures, 86 patients (84.3%) had BCS successfully completed as a single surgical procedure. Fifteen patients (14.7%) required second procedures for positive margins (Fig. 3). The breakdown of these patients in terms of their intraoperative margin assessment, reexcision, and final margin assessment by histology is shown in Table 2.

The gross mean margin clearance seen on 2D Faxitron mammography was 8 mm (range, 1–28 mm). Eighteen of 102 excisions (17.6%) had positive margins despite the use of the 2D Faxitron imaging. One patient had positive margin despite reexcision during the first surgery. She elected to undergo mastectomy as the second procedure.

![Figure 2](image)

**Figure 2** Specimen radiograph after 90° rotation of the specimen with superficial and deep clips now separated on different planes.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of excisions</td>
<td>131</td>
</tr>
<tr>
<td>Number of primary excisions</td>
<td>102</td>
</tr>
<tr>
<td>Number of patients with excisions at outside hospitals</td>
<td>29</td>
</tr>
<tr>
<td>Mean age and range (y)</td>
<td>58.6 (36–87)</td>
</tr>
<tr>
<td>Mean tumor size and range (cm)</td>
<td>1.6 (.1–5.5)</td>
</tr>
<tr>
<td>Median lumpectomy volume (mL)</td>
<td>120</td>
</tr>
<tr>
<td>Median reexcision volume during initial operation (mL)</td>
<td>11.2</td>
</tr>
<tr>
<td>Median lumpectomy volume during second operation (mL)</td>
<td>81</td>
</tr>
<tr>
<td>Histologic subtype on final pathology</td>
<td></td>
</tr>
<tr>
<td>Ductal carcinoma in situ</td>
<td>27 (20.6%)</td>
</tr>
<tr>
<td>Infiltrating breast cancer</td>
<td>104 (79.4%)</td>
</tr>
</tbody>
</table>

![Table 1](image)

**Table 1** Demographic data, excision volumes, and histologic subtypes

![Figure 3](image)

**Figure 3** Summary of the outcome of all patients in whom primary breast conservation was attempted.
Twenty-nine specimen radiographs showed the presence of microcalcification at <1 cm from the margin on 2D Faxitron imaging. Frequently, these microcalcifications are not seen on conventional specimen mammography but are highlighted by the 2D Faxitron imaging. Therefore, these patients underwent focused reexcision of this margin during the same procedure. Twenty-four of these 29 excisions had this margin positive or close on histologic assessment, therefore justifying the reexcision (true positive). Seventeen of these 24 were close, and 7 excisions had tumor present at the excision margin. In 23 of these 24 (95.8%), reexcision achieved negative margin and hence successful breast conservation in a single surgery. The remaining 5 reexcisions, which appeared to be close on the basis of 2D Faxitron specimen assessment, were histologically clear on permanent sections (false positive).

Although 73 excisions had adequate margin clearance on specimen imaging, 17 had positive or close (<1 mm) permanent histologic margins (false negative). In summary, of the 41 patients with histologically positive or close margins, 23 (56.1%) avoided return trips to the operating room because of margin clearance obtained on 2D Faxitron imaging.

Our final positive margin rate was 18 of 102 (17.6%). Two of these 18 patients did not undergo repeat surgery despite positive margins on permanent section. One patient had microscopically positive margin with positive axillary lymph nodes. Another patient had microscopically positive margin at the pectoral fascia. This was an 80-year-old woman with multiple comorbidities, and we decided not to perform radical surgery on this patient.

The sensitivity and specificity of the intraoperative margin assessment via 2D Faxitron imaging for patients presenting with primary breast cancer were 58.5% and 91.8%, respectively. The positive predictive value was 82.7%, and the negative predictive value was 76.7%.

The overall sensitivity and negative predictive value for the study were 94.4% and 83.3% when patients who underwent excisional biopsy at an outside hospital were included in the study.

**Table 2**  Results of 2D Faxitron imaging and correlation with histology

<table>
<thead>
<tr>
<th>Margin by 2D Faxitron imaging</th>
<th>Margin by histology</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>24</td>
<td>5</td>
</tr>
<tr>
<td>Negative</td>
<td>17</td>
<td>56</td>
</tr>
<tr>
<td>Total</td>
<td>41</td>
<td>61</td>
</tr>
</tbody>
</table>

Despite many advances in breast imaging, including improved mammographic screening, the overall rates of BCS continue to vary significantly. Often the choice of mastectomy by the patient or the surgeon is due to the presence of positive margins at the initial BCS. In some series, >50% of these women undergo subsequent undesired mastectomy because of the presence of residual cancer at the surgical margin at the time of initial BCS or after a now obsolete diagnostic excision biopsy. This remains a significant problem when current mammographic screening guidelines have led to a decrease in the average size of newly diagnosed breast cancer to <2 cm.

In most of these patients, a second attempt at BCS with repeat lumpectomy can still be performed, with no documented deleterious impact on local recurrence or cosmetic outcome. Yet in more than half of these women, mastectomy is chosen over repeat lumpectomy. Dillon et al reported that in 34% of patients with positive margins at initial BCS, 55% underwent mastectomy as their reexcision procedure. Cellini et al, in an analysis of 276 patients with breast cancer with positive margins at BCS, observed a mastectomy rate of 55% to clear margins. Wallace et al reported a positive margin rate of 43% using MRI-assisted wire localization for breast lesions. In their study, 66% of patients with positive margins elected to undergo mastectomy as the second operation. It appears that positive margins at the time of initial BCS remain a very significant risk factor for undergoing subsequent mastectomy for the treatment of breast cancer. Interestingly, a recent report by O’Sullivan et al showed that even 2 or more reexcisions could be performed to clear margins, with acceptable local recurrence rates of 5.8%.

Several factors have been shown to diminish the frequency of positive margins at the time of initial BCS and the rate of potential subsequent mastectomy in patients with breast cancer. Most significant in this regard is the use of preoperative tissue diagnosis with minimally invasive breast biopsy approaches such as fine needle aspiration and core needle biopsy. Numerous reports have recommended various techniques, including the use of intraoperative gross specimen evaluation, empiric reexcision of the lumpectomy cavity, histologic assessment of margins by frozen section, cytologic touch preps, or shavings at the time of BCS. Despite these measures, the rates of margin positivity continue to be high at final histologic assessment. Furthermore, these rates remain high even in patients deemed to have achieved negative margins by intraoperative histology or cytopathology.

Another approach to decrease the need for reexcision at BCS is the use of preoperative chemotherapy, even in women with relatively small tumors who meet criteria for postoperative chemotherapy at presentation. Christy et al showed a margin positive rate of 6% in patients receiving preoperative chemotherapy compared with 37% in those who did not.
Advanced imaging techniques not requiring tedious intraoperative histologic handling of the BCS specimen have also been used to assess margin clearance and decrease the rate of subsequent undesired reexcision and/or mastectomy. These include intraoperative ultrasonography of the breast, specimen radiography, 8–11 2-view specimen mammography,12 and MRI-guided wire localization.4 All these studies, with the exception of the report by McCormick et al,12 observed a reexcision rate >12%. Even the use of preoperative MRI planning of excision at the time of BCS failed to decrease the rate of reexcision for positive margins.35

Multiple reports that have addressed the use of intraoperative specimen margin assessments to diminish the likelihood of positive margins agree that a microscopic clear margin with no transected tumor is the minimum acceptable extent of margin clearance.36,37 Some studies have suggested that a close margin remains at risk for local recurrence and that in as many as 45% of cases, a close margin results in residual tumor being present at the time of reoperation.3

Attempts at intraoperative margin assessment with frozen section examination of the specimen6,16,27,28,30 or the residual cavity32,33 have been associated with high rates of margin involvement on permanent histologic evaluation.14,38 Imprint cytology has also been used to assess the margins at the time of surgery with measurable success.30,31 The histologic or cytopathologic intraoperative margin assessment not only is associated with time delays but also requires pathologic expertise that is not universally available at most community hospitals. Although less complicated, gross specimen examination is associated with a high failure rate and requires reexcision in 22% to 30% of cases.25,29,37 Thus, these difficulties with intraoperative histologic assessment account for a significant number of women who elect to undergo mastectomy for positive margins at initial BCS, because they are fearful of a similar problem at the time of reexcision. Thus, assuming that 60% of women with breast cancer initially elect BCS, nearly half of these may ultimately undergo undesired subsequent mastectomy.

The adequacy of margin clearance has also been related to the total volume of the resection specimen.26 However, very frequently, it is the eccentric or peripheral location of the cancer within the specimen that accounts for a close or positive margins.7 A recent report comparing standard quadrantectomy with an even more generous quadrantectomy requiring oncoplastic approaches for reconstruction showed similar margin width clearance despite a doubling in the volume of the excised specimen.39

The eccentric location of the tumor within the BCS specimen can be addressed by 2D Faxitron imaging, while providing a measure of gross margin clearance, as shown in Figures 1 and 2. The improved resolution and magnification of the specimen by 2D Faxitron imaging allow the identification of worrisome microcalcifications or parenchymal distortions, which are not seen on conventional specimen mammography. It can also show an eccentric location of tumor close to a margin, thereby alerting the surgeon to reexcise the margin before wound closure. These subtle findings, which may harbor microscopic disease, may account for positive margins on final histopathologic review.

The patients with prior excision at outside hospitals deserve special mention. It can be argued that many of these cases had only microscopic or no residual disease at the lumpectomy cavity wall and that specimen mammography is unlikely to have any added value for margin analysis. Yet a generous reexcision of the entire lumpectomy site is required in the absence of any orientation to define the location of the positive margin. High-resolution 2D Faxitron specimen analysis of these lumpectomy walls can ensure adequate gross margin clearance as well as removal of any residual microcalcifications that are often only detected by 2D Faxitron imaging. In this study, all such reexcisions were successful in obtaining negative margin on final histologic assessment. These patients, however, were excluded from the primary analysis to avoid any misleading results.

We used 2D Faxitron imaging to obtain adequate gross margins with no attempt at intraoperative histologic assessment of the specimen. The improved rate of margin clearance, low rate of return to the operating room, and avoidance of subsequent mastectomy are measurably better than described in the literature.

We use this approach for handling surgical specimens in all patients undergoing breast conservation or diagnostic wire localization. This approach does not rely on any kind of intraoperative histologic assessments and their attendant residual persistent positive margins on permanent histologic specimen evaluation. Instead, every effort is made to include a generous margin of ≥1 to 3 cm in a spherical fashion about the primary tumor. The excised specimen is carefully oriented, imaged, and reviewed intraoperatively to ascertain that the gross margins as described in the “Methods” section is >1 cm.

This approach has minimal negative impact on the overall cosmetic result in most patients. The median specimen volume of resection was 120 mL in this study. This compares favorably with more generous oncoplastic BCS approaches using specimen volumes of 200 mL compared with standard quadrantectomy (117 mL) reported by Kaur et al.39 Certainly, it would be anticipated that the cosmetic impact of multiple reoperations to clear margins would be greater than that of a slightly larger initial specimen volume obtained using gross 2D Faxitron specimen assessment. The median 2D Faxitron mammographically directed reexcision volume of 11.2 mL in this study compares favorably with our own median second surgery excision volume of 81 mL, where a more generous specimen is required in the absence of 2D Faxitron mammographic guidance. Thus, a focused intraoperative reexcision on the basis of 2D Faxitron imaging cleared the margin in question with a smaller volume and led to a more favorable cosmetic result. In this series, the 2D Faxitron approach decreased the num-
ber of patients with residual positive margins after first attempt at BCS. In doing so, it decreased the number of individuals at risk for a second operation, which more often than not is a mastectomy. Only .98% of the patients (1 of 102) in this series underwent mastectomy because of positive margins at BCS.

It has been argued that increasing negative margin width may not be related to local recurrence rates.\textsuperscript{20,41,42} We agree that many factors may affect local recurrence rates,\textsuperscript{1,5,43} but the surgeon can control only the rate of margin clearance and its impact on subsequent mastectomy rates. In a report looking at the frequency of margin involvement as a function of measured margin increments, it would seem that margin clearance >5 mm might be preferable.\textsuperscript{3} However, many reports show that increasing margin width beyond a truly microscopically clear margin for invasive cancer does not result in proportionately lesser recurrence rates in patients undergoing BCS with postoperative radiation therapy and systemic therapy.\textsuperscript{38} An image-guided intraoperative removal of an additional margin of 5 to 10 mm could improve rates of breast conservation and have a lesser impact on the cosmetic result. Also, this approach would eliminate the need for reoperation, which often because of patients’ fears or surgeons’ recommendations leads to an undesired subsequent mastectomy.

This approach led to successful BCS in 84.3% of patients (86 of 102) at their first operation. Twenty-nine of the 102 excisions had additional intraoperative margins excised as suggested by close margins on 2D Faxitron imaging. Twenty-three (22.5%) of these would have had to return to the operating room had the margins not been cleared by 2D Faxitron guidance (Fig. 4). Ultimately, 99% of patients

**Figure 4** Study algorithm with details of outcomes of various interventions in patients with primary breast cancer and subsequent management. The number of patients is mentioned in parentheses.
deemed to be BCS candidates underwent successful breast conservation. In conclusion, this approach to gross margin evaluation intraoperatively is easy to reproduce. It has resulted in a low rate of positive margins at initial BCS, thereby reducing the need for a second reexcision and yielding a remarkably low rate of mastectomy. It requires no intraoperative histologic assessment by a pathologist and could be done even faster if the 2D Faxitron unit were located in the operating room. Thus, it would be easy to implement at most facilities caring for patients with breast cancer.

References