Comparison of intra-operative specimen mammography to standard specimen mammography for excision of non-palpable breast lesions: a randomized trial

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Abstract Standard specimen mammography (SSM) is performed in the radiology department after wire-localized excision of non-palpable breast lesions to confirm the presence of the target and evaluate margins. Alternatively, intra-operative specimen mammography (ISM) allows surgeons to view images in the operating room (OR). We conducted a randomized study comparing ISM and SSM. Women undergoing wire-localized excision for breast malignancy or imaging abnormality were randomized to SSM or ISM. For SSM, the specimen was transported to the radiology department for imaging and interpretation. For ISM, the specimen was imaged in the OR for interpretation by the surgeon and sent for SSM. Interpretation time was from specimen leaving OR until radiologist interpretation for SSM and from placement in ISM device until surgeon interpretation for ISM. Procedure and interpretation times were compared. Concordance between ISM and SSM for target and margins was evaluated. 72 patients were randomized, 36 ISM and 36 SSM. Median procedure times were similar, 48.5 (17–138) min for ISM, and 54 (17–40) min for SSM ($p = 0.72$), likely since specimens in both groups traveled to radiology for SSM. Median interpretation time was significantly shorter with ISM, 1 (0.5–2.0) and 9 (4–16) min for ISM and SSM, respectively ($p < 0.0001$). Among specimens with ISM and SSM, concordance was 100% (35/35) for target and 93% (14/15) for margins. In this randomized trial, use of ISM compared with SSM significantly reduced interpretation times, while accurately identifying the target. This could result in decreased operative costs from shorter OR times with use of ISM.

Keywords Mammography · Wire localization · Lumpectomy · Intra-operative imaging

Introduction

Image-guided core needle biopsy has become the standard of care for evaluation of suspicious breast lesions. Surgical excision of breast lesions is often performed for patients diagnosed with malignancy, other high-risk or indeterminate lesions, and lesions not amenable to core needle biopsy. Excision of non-palpable lesions almost always requires percutaneous wire localization.

Wire localization involves placement of a hooked wire under imaging guidance using mammography, ultrasonography, or magnetic resonance imaging (MRI) prior to surgery [1–4]. Standard specimen mammography (SSM) is routinely used to confirm the presence of the target within the excised specimen and to evaluate margin adequacy. This requires transport of the excised specimen to the radiology department for imaging and interpretation by the radiologist, which is then communicated back to the surgeon in the operating room. If the radiologist reports incomplete excision or inadequate margins, the surgeon
may excise additional tissue, potentially reducing the need for future re-operation. The process of specimen transport and radiologist interpretation with SSM can be time-consuming, however, and occurs while the patient remains under anesthesia in the operating room.

Alternatively, intra-operative specimen mammography (ISM) allows surgeons to immediately evaluate the excised specimen while still in the operating room. Specimen images can also be transmitted to the radiology PACS for remote interpretation, bypassing the need for physical transport of the specimen to the radiology department. Compared with use of SSM, ISM has been reported to result in shorter operative times [5–7] with similar rates of positive margins leading to re-operation [5, 7]. Additional studies have reported decreased rates of margin positivity with ISM, which could result in fewer re-excisions [8, 9].

Previous evaluations comparing ISM with SSM have been conducted using data from retrospective and non-randomized studies. We sought to evaluate use of ISM compared with SSM in a prospective, randomized cohort.

**Methods**

**Study design and patients**

Patients were recruited from the outpatient breast clinics at Massachusetts General Hospital. The study was approved by the Massachusetts General Hospital/Partners Healthcare institutional review board [ClinicalTrials.gov NCT01766102]. Women (>18 years old) with a newly diagnosed breast abnormality undergoing an excisional biopsy with wire localization or with a newly diagnosed invasive breast cancer or ductal carcinoma in situ (DCIS) undergoing a lumpectomy with wire localization were eligible for inclusion. Patients were consented and randomized to ISM or SSM. Five dedicated breast surgeons at our institution participated in the study.

Patient characteristics, clinicopathologic, and treatment-related information for the cohort were collected via medical record review. Patient characteristics included age and Body Mass Index (BMI) at excision. Clinicopathologic information included reason for excision (excisional biopsy vs. atypia vs. invasive carcinoma/DCIS), number of localization wires, localization target, anesthesia type, and pathology of the excised specimen. Excisions with targets including a clip and mass, calcifications, or architectural distortion were classified as clip for the target variable. For cases with invasive carcinoma or DCIS on excision pathology, tumor size, pathologic margin status, number of additional margins taken, type of axillary surgery, number of lymph nodes removed, and number of positive lymph nodes were also collected. The number of patients who underwent re-excision was recorded for those undergoing excision for biopsy-proven invasive carcinoma or DCIS.

For SSM, the excised specimen was oriented and then taken to the radiology department for standard specimen compression mammography. The specimen was oriented with sutures. Surgeons could not see the images and relied on radiologists’ verbal description of interpretation for target lesion and margins. Additional tissue was taken if the radiologist reported involved margins per standard of care at our institution.

For ISM, the excised specimen was oriented as described above and placed inside the ISM digital specimen mammography system (BioVision, Faxitron Bioptics). The images were interpreted by the operating surgeon. After surgeon interpretation with ISM, the specimen was taken to the radiology department for imaging with SSM. Additional tissue was taken if the surgeon or radiologist indicated inadequate excision.

**Outcomes**

Interpretation time for ISM and SSM was recorded and compared. Interpretation time for ISM was defined as time from specimen placement into the ISM device until image interpretation by the surgeon; for SSM, it was defined as the time from when the specimen left the OR until the radiology department called with interpretation results.

Total OR and procedure time were recorded and compared for ISM and SSM. OR time was defined as time from patient entrance to patient exit from the OR, and total procedure time was the time from surgical incision until closure. Given the variety in length and type of operative procedures performed (excisional biopsy versus lumpectomy with ALND), we also recorded and compared time from procedure start (surgical incision made) to time of image interpretation for ISM and SSM.

The presence of the target lesion was interpreted for all specimen images. The specimens containing invasive carcinoma or DCIS were also interpreted for margin status. Interpretation of margin status was recorded by the operating surgeon for ISM or radiologist for SSM. Margins were classified as positive (target lesion present at margin), negative (>2 mm from the target lesion), or close (<0.2 mm from target lesion but not present at margin) both visually and pathologically. At our institution, additional shaved cavity margins are routinely taken at the time of excision for known carcinoma; for this study, we utilized margin status of only the main lumpectomy specimen and excluded the status of shaved cavity margins.

The sensitivity and specificity of ISM and SSM for identifying positive margins were calculated using pathologic margin status of the main specimen. Margins for lesions with both invasive carcinoma and DCIS were
classified according to whichever pathology was closer to the margin (i.e., if negative for invasive carcinoma and close for DCIS, margin was classified as close). A true positive (TP) was defined as a positive margin by imaging (ISM or SSM) and pathology. A false positive (FP) was defined as a positive margin by imaging but negative by pathology. A true negative (TN) was defined as a negative margin by both imaging and pathology. A false negative (FN) was defined as a negative margin by imaging but positive by pathology. The sensitivity (TP/TP + FN), specificity (TN/TN + FP), positive predictive value (TP/TP + FP), and negative predictive value (TN/TN + FN) for identification of positive margins were calculated for ISM and SSM.

The concordance of margin status interpretation by the surgeon using ISM, the radiologist using SSM, and pathologic margin status was also evaluated.

Statistical analysis

The R Project was utilized for statistical analyses, with a p value of less than 0.05 considered statistically significant.

Results

Patient cohort

76 patients were consented to the trial between 3/2013 and 5/2014, with four patients subsequently deemed ineligible due to change in operative procedure such that wire-localized excision would no longer be performed. Therefore, 72 patients were included, with 36 randomized to ISM and 36 randomized to SSM. ISM was not performed for 1 of the 36 patients randomized to this arm due to malfunction of the ISM device; this patient was analyzed as intention to treat. 25 (69 %) ISM and 28 (78 %) SSM patients underwent wire-localized excision for biopsy-proven invasive carcinoma or DCIS. Wire-localized excision was performed for atypia in 7 (19 %) ISM and 5 (14 %) SSM patients, and as an excisional biopsy for an abnormal mammogram in 4 (11 %) ISM and 3 (8 %) SSM patients. Four ISM and one SSM patient underwent more than one wire-localized excision during the operation. Only the first specimen excised was included in this study.

Distribution of patient and clinicopathologic characteristics was similar between the two arms, as demonstrated in Table 1.

Operative outcomes

Total procedure time was similar for ISM and SSM, with a median of 48.5 (17–138) and 54 (17–40) min, respectively (p = 0.716). Total OR time was also similar for ISM and SSM, with a median of 68 (29–180) and 74 (35–177) min, respectively (p = 0.676) (Table 2).

Imaging interpretation: target

In the ISM arm, the target was identified in the specimen by the surgeon in 34 of 35 cases. For one specimen, the initial ISM interpretation was that the target was not in the specimen; additional tissue was taken and the target was subsequently identified by the surgeon. In the SSM arm, the target was identified in the specimen for 35 of 36 cases by radiology. For 1 specimen, the target was not identified in the main specimen but was identified in additional margins taken by the surgeon and sent with the main specimen.

The total time for interpretation regarding the presence or absence of the target was significantly shorter for ISM compared with SSM, 1 (0.5–2.0) and 9 (4–16) min, respectively (p < 0.0001). Time from procedure start to imaging interpretation was also significantly shorter for ISM compared with SSM, 19 (6–41), and 31 (16–60) min, respectively (p < 0.0001) (Table 2).

Among specimens with SSM and ISM, concordance between ISM and SSM was 100 % (35/35) for interpretation of target presence or absence in the specimen.

Imaging interpretation: margin status

Interpretation of margin status by the surgeon was available for 22 of 36 ISM patients. Of the 14 patients excluded, 10 had benign pathology and 4 did not have margin interpretation by the surgeon. Surgeon interpretation of margins was 59 % (13/22) negative, 32 % (7/22) close, and 9 % (2/22) positive. Interpretation of margin status was concordant between ISM and pathology for 17 of 22 patients (77 %), with close and negative margins grouped together. Interpretation of margin status was also available for 22 of 36 SSM patients. Of the 14 patients excluded, 7 had benign pathology, 6 did not have margin interpretation by the radiologist, and 1 could not be assessed for pathologic margin status. Radiologist interpretation of margins was 68 % (15/22) negative, 14 % (3/22) close, and 18 % (4/22) positive. Interpretation of margin status was concordant between SSM and pathology for 18 of 22 patients (82 %), with close and negative margins grouped together.

The sensitivity of ISM and SSM for identification of pathologically positive margins was 50 and 20 %, respectively. Specificity of positive margin interpretation was similar for ISM and SSM, 89 and 94 %, respectively. Positive predictive value was 50 % for both ISM and SSM, and negative predictive value was 89 % for ISM and 80 % for SSM (Table 3).
Concordance between margin interpretation by the surgeon using ISM and radiologist with SSM was evaluated for 15 of 36 ISM patients. Of the 21 patients excluded, 9 had no SSM performed, 8 had benign pathology, 3 lacked surgeon margin interpretation with ISM, and 1 lacked radiologist margin interpretation with SSM. Concordance was 93 % (14/15) for margin interpretation between ISM and SSM. One patient was interpreted as having positive margins by ISM but negative by SSM, and had positive margins on pathology (Table 4).

Discussion

In this randomized trial, use of ISM compared with SSM significantly reduced imaging interpretation times while accurately identifying the target within the specimen. Median interpretation time decreased from 9 (4–16) min with SSM to 1 (0.5–2.0) with ISM, and concordance was 100 % (35/35) for target and 93 % (14/15) for margins among specimens that underwent both SSM and ISM with
available data. Based on these findings, use of ISM could result in decreased operative costs from shorter OR and procedure times and improve intra-operative interpretation of margin status.

Use of ISM allows for immediate evaluation of the excision specimen in the OR for confirmation of target resection and margin interpretation. The operating surgeon can directly interpret the specimen images, and receive rapid radiology consult through remote viewing of intra-operative specimen images. The potential benefits of ISM over SSM include shorter operative times and less anesthesia exposure for the patient, resulting in decreased operative costs and patient morbidity.

Several previous studies comparing ISM with SSM have reported decreased operative time with use of ISM [5–7]. A retrospective chart review of 344 patients by Camp et al. demonstrated a decreased average operative time by 10 min with ISM compared to SSM (68 vs. 78 min, respectively), which correlated with a 20 % increase in surgeon productivity [6]. Similarly, Muttalib et al. found that the mean operating time decreased by 8 min with use of ISM compared to SSM (from 42.7 to 34.7 min) in a non-randomized study of 299 wire-localized excisions [7]. Kaufman et al. evaluated 121 excision specimens that underwent ISM and SSM, and predicted that use of ISM for specimen imaging would shorten operating room time by an average of 19 min [5].

Our randomized study demonstrated a significant decrease in interpretation times for ISM compared to SSM, although operative and procedure times were similar between arms. Median interpretation time was 8 min shorter for ISM compared to SSM (1 and 9 min, respectively) and time from procedure start to interpretation was 12 min shorter (19 and 31 min for ISM and SSM, respectively). The lack of statistically significant reduction in OR and procedure times in our study is likely because ISM specimens were transported to the radiology department for SSM after undergoing ISM and the operation was not concluded until confirmation came from the radiologist. In addition, we evaluated any breast operation that required needle localization and therefore included excisional biopsies for abnormal mammograms, atypia, and lumpectomies which may include sentinel lymph node biopsy or axillary lymph node dissection. These additional procedures added time to the total operation and therefore this added time did not allow the gains from interpretation time to be realized. Based on the significantly shorter interpretation time with ISM compared to SSM, it is reasonable to predict that OR and procedure times would be most affected in those operations that do not have additional procedures.

### Table 2: Operative and imaging interpretation outcomes for ISM and SSM arms

<table>
<thead>
<tr>
<th></th>
<th>ISM (N = 36)</th>
<th>SSM (N = 36)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operative characteristics</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Procedure time</td>
<td>48.5 (17–138)</td>
<td>54 (17–140)</td>
<td>0.716</td>
</tr>
<tr>
<td>OR time</td>
<td>68 (29–180)</td>
<td>74 (35–177)</td>
<td>0.676</td>
</tr>
<tr>
<td>Imaging interpretation&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedure start → interpretation time</td>
<td>19 (6–41)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>31 (16–60)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Interpretation time</td>
<td>1 (0.5–2)</td>
<td>9 (4–16)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

<sup>a</sup> ISM intra-operative specimen mammography, SSM standard specimen mammography, OR operating room

<sup>b</sup> Excludes 1 patient in ISM arm due to device malfunction

### Table 3: Margin interpretation by surgeon with ISM and radiologist with SSM compared to final pathology

<table>
<thead>
<tr>
<th>Margin interpretation</th>
<th>ISM (%) (N = 22)</th>
<th>SSM (%) (N = 22)</th>
</tr>
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<tbody>
<tr>
<td>True positive</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>True negative</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>False positive</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>False negative</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>50</td>
<td>20</td>
</tr>
<tr>
<td>Specificity</td>
<td>89</td>
<td>94</td>
</tr>
<tr>
<td>PPV</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>NPV</td>
<td>89</td>
<td>80</td>
</tr>
</tbody>
</table>

<sup>a</sup> ISM intra-operative specimen mammography, SSM standard specimen mammography, PPV positive predictive value, NPV negative predictive value

### Table 4: Margin interpretation of specimens for which interpretation by surgeon with ISM, radiologist with SSM, and pathology was available

<table>
<thead>
<tr>
<th>Number of Patients (n = 15)</th>
<th>ISM</th>
<th>SSM</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concordant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>3</td>
<td>Negative</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>1</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Discordant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
</tr>
</tbody>
</table>
The accuracy of ISM for target identification and interpretation of margin status has been reported to be equivalent or superior when compared with SSM [5, 10]. We previously reported that expert radiologist review of 100 pairs of breast specimen radiographs obtained with ISM and SSM demonstrated high diagnostic confidence for target verification using ISM [10]. Kaufman et al. reported identification of the target within the excision specimen in 98 % of ISM and 99 % of SSM cases [5]. We similarly found that the target was identified in the excision specimen in 97 % of ISM and 97 % of SSM cases. Among specimens that underwent both SSM and ISM, concordance was 100 % (35/35) for interpretation of target presence or absence within the excision specimen. These findings suggest that intra-operative target verification by the surgeon does not result in diminished accuracy when compared with radiologist interpretation using SSM.

Similar or improved re-operative rates have been reported with the use of ISM compared to SSM, with several studies also reporting reduced rates of positive margins with use of ISM [5, 8, 9, 11]. Muttalib et al. reported a reduction in re-excision rates from 31.5 to 19.8 % with use of ISM compared to SSM, respectively [7]. We previously showed that review of specimen images by expert radiologists resulted in similar concordance rates, PPV, and NPV for identification of positive margins using ISM and SSM when compared to pathologic margin status [10]. Kim et al. reported a decrease in the rate of positive margins from 19 % with SSM to 6.2 % with ISM, with the type of specimen imaging an independent predictor of margin positivity on multivariate analysis [9]. In a retrospective review of 128 lumpectomies, Bathla et al. found that excision of additional tissue based on ISM margin evaluation was able to clear the margins in 95.8 % of patients who would otherwise have required re-excision [8]. Additionally, authors reported a sensitivity of 58.5 % and specificity of 91.8 %, PPV of 82.7 % and NPV of 76.7 % for detection of positive margins with ISM. In our study, the concordance rates for margin interpretation compared to pathologic margin status were similar for ISM and SSM (77 and 82 %, respectively). In specimens that underwent both ISM and SSM, there was a 93 % (14/15) concordance rate between margin interpretation by the operating surgeon using ISM and radiologist with SSM. For the one case of discordance, the margin status was correctly interpreted as positive by the surgeon using ISM but read as negative by radiology with SSM. Prior studies evaluating surgeons’ ability to accurately interpret margins on imaging have demonstrated a similar PPV of specimen imaging compared to histologic examination between radiologists and surgeons [12, 13]. Similar to other studies, we found a 50 % sensitivity and 89 % specificity, 50 % PPV and 89 % NPV for identification of positive margins with ISM [5, 8]. These values were similar or improved when compared with use of SSM in our study. We were unable to compare re-operation rates between the ISM and SSM arms, since specimens randomized to ISM also underwent SSM. We were also unable to evaluate rates of margin positivity for ISM compared to SSM, since margins were evaluated based on the main lumpectomy specimen, and at our institution shaved cavity margins are routinely taken during lumpectomy and represent the true margin status. However, our findings indicate that as with target verification, surgeon interpretation of margin status using intra-operative mammography does not result in decreased accuracy when compared with radiologist interpretation using SSM, and further studies may demonstrate additional benefits including reduced re-operation rates.

Strengths of the current study include randomization, side-by-side comparison of ISM and SSM regarding presence of the target and margin evaluation, and the ability to evaluate concordance between the operating surgeon using ISM and radiologist with SSM regarding target and margins. Limitations in our study include the small number of specimens available for evaluation of concordance between ISM and SSM regarding target verification and margin status, and inability to compare rates of re-excision and margin positivity between the ISM and SSM arms.

In this randomized study, use of ISM compared to SSM resulted in significantly shorter interpretation times, suggesting the potential for reduced operative costs from decreased OR and procedure times. Additionally, ISM enabled accurate identification of the target within the excision specimen and comparable margin evaluation by the operating surgeon when compared to radiologist interpretation with SSM.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest or financial disclosures to report.

References