Lumpectomy Specimen Radiography: Does Orientation or 3D Tomosynthesis Improve Margin Assessment?

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ABSTRACT

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Purpose: To determine 1) whether 2 orthogonal oriented 2D views of excised breast cancer specimens improves surgical margin (SM) assessment compared to a single unoriented 2D view and 2) whether 2 orthogonal oriented views using 3D tomosynthesis improves SM assessment compared to 2 orthogonal oriented 2D views.

Methods: 41 specimens were imaged using four protocols: single view unoriented 2D image acquired on a specimen unit (1VSU), two orthogonal oriented 2D images acquired on the specimen unit (2VSU), two orthogonal oriented 2D images acquired on a mammogram unit (2V2DMU), and two orthogonal oriented 3D images acquired on the mammogram unit (2V3DMU). Three breast imagers retrospectively and randomly assessed SM of the 41 specimens with each protocol. SM per histopathology was considered the gold standard.

Results: The average area under the curve (AUC) was 0.60 for 1VSU, 0.66 for 2VSU, 0.68 for 2V2DMU, and 0.60 for 2V3DMU. Comparing AUCs for 2VSU vs. 1VSU by reader showed improved diagnostic accuracy using 2VSU, however this difference was only statistically significant for reader 3 (0.73 vs. 0.63, $p = 0.0455$). Comparing AUCs for 2V3DMU vs. 2V2DMU by reader showed mixed results, with reader 1 demonstrating increased accuracy (0.72 vs. 0.68, $p = 0.5984$) while readers 2 and 3 demonstrated decreased accuracy (0.50 vs. 0.62, $p = 0.1089$ and 0.58 vs. 0.75, $p = 0.0269$).

Conclusions: 2VSU showed improved accuracy in SM prediction compared to 1VSU, although this was not statistically significant for all readers. 3D tomosynthesis did not improve SM assessment.

Student Role

I was very closely involved in all stages of this project, from study design and data collection to data analysis and writing. I helped design the reader study together with the other co-authors listed. Once the radiologists read the images, I compiled all reader data. I performed all data analysis along with input from Dr. Brook. Dr. Venkataraman and I wrote the manuscript (she wrote a rough draft which I then edited and expanded on extensively), and all co-authors then contributed to editing the manuscript.

Appendix

INTRODUCTION

Breast-conserving therapy (BCT), or lumpectomy followed by whole breast radiation, has been shown to be equivalent to mastectomy for treatment of stage I and stage II invasive breast cancer [1—3]. However, in order for BCT to be successful, the cancer must be excised with a negative surgical margin to ensure complete tumor removal. The risk of local tumor recurrence is at least two-fold when there is ink on cancerous cells at the edge of the surgical specimen [4]. Histopathologically positive margins are seen in 20-55% of cases [5], with re-excision rates of 10-57%, depending on the institution's practices and desired negative margin width [6, 7]. The lack of consensus on what constitutes a safe margin also contributes to many patients undergoing a second surgery. Repeat surgeries drive up healthcare costs, lead to more stress for the patient, and may result in suboptimal cosmetic results.

In a time of widespread use of screening mammography, most excised cancers are non-palpable and therefore require image-guided procedures both for obtaining the pre-operative diagnosis via biopsy, and to guide surgery. Most imaging centers routinely place a metallic clip at the biopsy site to mark the index lesion. Pre-operative image-guided wire localization of the target lesion (if still present after biopsy), or of the localizing clip, is now routinely employed to enable precise removal of the lesion and to reduce the amount of normal tissue excised. In fact, the American Society of Breast Surgeons' (ASBS) position statement on breast cancer lumpectomy margins (2013) asserts that there must be radiographic confirmation of removal of all non-palpable, image-detected lesions by mammogram or ultrasound, and direct intraoperative communication of specimen imaging results to the surgeon. The ASBS also recommends that the specimen images be made available to the pathologist [8].

Surgical specimen imaging to assess complete removal of the target lesion is commonly done with two-dimensional (2D) mammography. Traditionally this is done using either a

dedicated specimen unit or a digital mammography unit, with acquisition of either a single view or two orthogonal views. The majority of practices obtain a single unoriented view of the excised tissue. The radiologist then communicates to the surgeon whether the targeted lesion has been removed and typically comments on the distance of the lesion from the margin. Studies investigating whether two views are superior to one view have shown mixed results [9, 10]. Moreover, to our knowledge, there has been relatively little research investigating whether two views are superior to one view in regard to margin assessment.

Recently, three-dimensional (3D) digital tomosynthesis (DBT) has shown promise as a superior diagnostic tool compared to 2D mammography because it eliminates tissue superimposition. Several studies have shown increased lesion detection and improved margin assessment with DBT for screening and diagnostic populations [11—14]. Further, DBT is regarded as a superior technique when assessing dense breast tissue [14]. Dense breast tissue may predispose to higher re-excision rates. One study showed that dense breast tissue had a 3.6 odds ratio of repeat surgery [6], while in another study 10 out of 11 (91%) women with dense breasts were recommended to undergo repeat surgery based on positive margins [15].

Given the importance of clear margins in reducing the need for re-excision, and the paucity of research on margin assessment using two orthogonal views and DBT as compared to the standard single unoriented 2D view, our aim was to determine whether two oriented orthogonal views and/or DBT allow for more accuracy in predicting margin status as compared to the standard of care. We hypothesized that orienting the specimen and obtaining two orthogonal images would be superior to a single unoriented image. Our rationale was that two oriented, orthogonal images would provide more anatomic information regarding all six margins. We further hypothesized that DBT would be superior to conventional 2D imaging of the specimen given the ability to “scroll through” the excised tissue in thin slices, thereby eliminating tissue superimposition.

MATERIALS AND METHODS

This retrospective study was approved by the Institutional Review Board at Beth Israel Deaconess Medical Center and was compliant with the Health Insurance Portability and Accountability Act. Our institution funded the study internally. No outside or industry funding was provided.

Patient inclusion

From 7/1/13 to 1/9/14, 72 surgical specimens from 70 patients undergoing breast conservation surgery (BCS) for preoperative diagnoses of ductal carcinoma in situ (DCIS), invasive breast cancer, or other suspicious imaging findings, were imaged using four study protocols. Preoperative diagnoses were based on image-guided percutaneous tissue biopsy. Specimens were imaged consecutively as permitted by the availability of staff and access to the DBT unit. Imaged specimens with benign final surgical pathology (n=22) were not included in the study as margin assessment is not of clinical significance. An additional 9 specimens were subsequently excluded because of incomplete imaging. A total of 41 breast cancer specimens from 39 patients were included in the analysis (**Figure 1***).*

Specimen imaging process

Each patient had wire localization of the breast lesion(s) performed in the breast radiology department prior to surgery. After surgical excision, the excised tissue was immediately sent to the radiology department for conventional 2D imaging by a technologist. The radiologist assessed the specimen radiograph and conveyed the findings to the surgeon, who then proceeded with wound closure or immediate re-excision. The specimen was then imaged using four different protocols by one of three investigators (JM, PS and MK) before being sent to pathology. The specimen remained in a sealed plastic biohazard bag at all times. At a later date, three board-certified breast radiologists independently reviewed the images to assess margin status of each specimen.

Specimen orientation, imaging protocols and technique

Specimen orientation was accomplished using surgical stitches, with the short stitch marking the superior aspect and the long stitch marking the lateral aspect. For the first image, the short stitch faced upward (away from the detector plate) and the long stitch

faced laterally (**Figure 2***).* For the second image, the specimen was rotated 90° such that the short stitch faced towards the imager and the long stitch continued to face laterally.

All surgical specimens were imaged using the conventional protocol as well as 3 additional protocols, for a total of 4 image sets (**Figure 3**), as follows.

1 view specimen unit (1VSU) (conventional protocol)

A single view, unoriented 2D image was acquired on a dedicated specimen unit (*piXarray 100 Digital Specimen Radiography System, 2009, Bioptics Inc., Tucson, AZ).* The technologist placed the specimen on the detector plate without regard to orientation and then shot a single image using pre-set kV and mAs values, with manual adjustments as needed depending on the size of the specimen. kV ranged from 28 to 31 and mAs ranged from 8-10. Standard vendor-specific magnification was used. The specimen was not compressed.

2 view specimen (2VSU)

Two orthogonal, oriented 2D images were acquired on the dedicated specimen unit. The investigator oriented the specimen on the detector plate and shot the first image. The specimen was then rotated 90° to acquire the second image using the same imaging parameters. Pre-set magnification, kV and mAs values were used. kV and mAs was adjusted for larger specimens. The specimen was not compressed.

2 view 3D mammogram unit (2V3DMU)

Two orthogonal, oriented 3D images were acquired on the DBT unit (*Selenia Dimensions System, 2012, Hologic Inc., Marlborough, MA).* In order to achieve the same magnification as the standardized specimen unit, a platform was used to elevate the specimen from the detector plate. Two screening compression paddles (measuring 24 cm x 29 cm and 18 cm x 24 cm, respectively) were first stacked onto the detector plate. The investigator then oriented the specimen on the top paddle surface and lightly compressed the specimen from above using a 10 cm contact paddle before shooting the image. This was then repeated to acquire the orthogonal image. kV was manually set to 28 with slight adjustments made as needed. mAs was manually set and ranged from 75 to 100 depending on the size of specimen.

2 view 2D mammogram unit (2V2DMU)

Two orthogonal, oriented 2D images were acquired on the DBT unit. The same imaging protocol as 2V3D was used, however the digital setting was changed to acquire a 2D, rather than 3D image.

Data collection

Three breast imagers (SV, VFZ, and PJS) with 21, 27, and 25 years of experience, respectively, independently assessed the margin status of each specimen using each of the four study protocol image sets while blinded to final surgical margin status. Each reader was blinded to the other readers. Final margin status per histopathology was considered the gold standard. Image sets were read in random order and there was a 4-week washout period between each protocol reading session for each reader. Specimen reading order was also randomized within each image set.

The radiologist readers recorded margin status and closest margin(s). For our study we defined margins as positive if less than 1 mm, close if between 1 and 5 mm, and negative if greater than 5 mm. All measurements on radiographic images were made using the vendor-specified measurement tool available in PACS or on the *Hologic* viewing station. Each radiologist was provided with a specimen orientation schematic to allow for proper identification of each margin while reviewing images (anterior, posterior, medial, lateral, superior and inferior margins, **Figure 4**). All data were entered into an Excel spreadsheet (*Microsoft Excel 2011, Redmond, WA).*

Author JM correlated reader data with final surgical margin status. The pathology department at our institution defines positive margins as carcinoma at the margin (ink on cancer cells) and reports any distance greater than 0 mm from the margin as negative. The pathologist also specifies distance in millimeters from each of the six margins. In order to properly compare radiologist reader data to pathology data, the pathology margin statuses were converted to match our study definitions using the pathologist-measured distances provided. For example, if the pathologist indicated that there was carcinoma 0.7 mm from the medial margin and therefore “negative” in their report, then the pathological medial margin was considered “positive” for our study.

Statistical methods

For the purposes of analysis, margins read as “close” by the radiologists were counted as negative such that there was a dichotomous outcome of positive or negative. Sensitivity and specificity were then calculated for each modality. Area-under-the-curve (AUC) analyses were used to assess diagnostic performance for each modality. McNemar testing was used to compare sensitivity and specificity for each modality. A Fleiss kappa coefficient was computed to assess inter-reader agreement among the three readers.

RESULTS

Forty-one specimens with malignancy from 39 patients were included. Two patients each contributed 2 separate specimens from different areas of the same breast. All patients were female with a mean age of 60.66 (SD ± 12.67) (**Table 1**). Twenty-six specimens came from the left breast and 15 from the right. Of the 41 specimens, 11 were ductal carcinoma in situ (DCIS), 14 were invasive ductal carcinoma (IDC), 3 were invasive lobular carcinoma (ILC), 2 were IDC and ILC, 2 were invasive cribriform cancer, and 9 were invasive carcinoma not otherwise specified. On histopathology, 25 (61%) had positive margins (< 1 mm) and 16 (39%) had negative margins (≥ 1 mm) per our study definitions. Twelve out of the 39 patients (31%) underwent re-excision at a later date due to cancer found at the edge of the specimen (0 mm).

Inter-reader agreement among the three readers was fair to moderate for the four modalities, with Fleiss kappa statistics of 0.57 (95% confidence interval (CI) 0.48 – 0.72) for 1VSU, 0.47 (95% CI 0.40 – 0.59) for 2VSU, 0.55 (95% CI 0.41 – 0.61) for 2V2DMU, and 0.32 (95% CI 0.18 – 0.44) for 2V3DMU. Area under curve (AUC) analyses of each modality by reader revealed relatively low accuracy, with interpretations ranging from worthless to fair (**Table 2**). The average AUC was highest for 2V2DMU (0.68), followed by 2VSU (0.66), then 2V3DMU (0.60), and then 1VSU (0.60). Sensitivity and specificity of each modality per reader are summarized graphically in **Figure 5.** Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) are provided in **Table 3**. Average sensitivity was substantially higher using all experimental modalities (2V2DMU, 64%; 2V3DMU, 60% and 2VSU, 57.33%) compared to the conventional 1VSU (42.67%).

Average specificity was highest for the conventional 1VSU modality (77.08%). Both average PPV and NPV were highest for 2VSU and 2V2DMU modalities.

Do two oriented images improve accuracy of radiographic margin assessment compared to the standard of care?

Comparing AUCs for 2VSU vs. 1VSU by reader showed overall improved diagnostic accuracy using 2VSU, with AUCs and differences as follows: reader 1, 0.66 vs. 0.60, 0.06, p = 0.3529; reader 2, 0.60 vs. 0.57, 0.03, p = 0.6154; reader 3, 0.73 vs. 0.63, 0.1, p = 0.0455. However, this difference was only statistically significant for reader 3 (**Table 4)**. Average sensitivity was substantially higher for 2VSU compared to 1VSU (57.33% vs. 42.67%) with comparable specificity (75% vs. 77.08%, respectively) (**Table 3)**. McNemar testing to compare sensitivities of 2VSU vs. 1VSU by reader revealed overall improved sensitivity using 2VSU, however these differences were not statistically significant (reader 1, 56% vs. 52%, 4%, p = 1.000; reader 2, 52% vs. 32%, 20%, p = 0.0625; reader 3, 64% vs. 44%, 20%, p = 0.1250). McNemar testing to compare specificities of 2VSU vs. 1VSU by reader revealed mixed results (reader 1, 75% vs. 68.75%, 6.25%, p = 1.000; reader 2, 68.75% vs. 81.25%, -12.5%, p =1.000; reader 3, 81.25% vs. 81.25%, 0%, p = 1.0000).

Does tomosynthesis improve radiographic margin assessment compared to conventional 2D imaging?

Comparing AUCs for 2V3DMU vs. 2V2DMU by reader showed mixed results, with reader 1 demonstrating increased accuracy (0.72 vs. 0.68, 0.04, p = 0.5984) while readers 2 and 3 demonstrated decreased accuracy (reader 2, 0.50 vs. 0.62, -0.12, p = 0.1089; reader 3, 0.58 vs. 0.75, -0.17, p = 0.0269) (**Table 4**). Average sensitivity was lower for 2V3DMU as compared to 2V2DMU (60% vs. 64%, respectively) (**Table 3)**. McNemar testing comparing sensitivities of 2V3DMU vs. 2V2DMU by reader showed mixed results, with reader 1 demonstrating increased sensitivity (76% vs. 68%, 8%, p = 0.6250) while readers 2 and 3 demonstrated decreased sensitivity (reader 2, 44% vs. 56%, -12%, p = 0.3750; reader 3, 60% vs. 68%, -8%, p = 0.6875). Average specificity was substantially lower for 2V3DMU as compared to 2V2DMU (60.42% vs. 72.92%, respectively) (**Table 3)**. McNemar testing to compare specificities of 2V3DMU vs. 2V2DMU showed overall decreased, or equal, specificity without statistical significance (reader 1, 68.75% vs. 68.75%, 0%, p = 1.000;

reader 2, 56.25% vs. 68.75%, -12.5%, p = 0.1250; reader 3, 56.25% vs. 81.25%, -25%, p = 1.000).

Comparing AUCs for 2V3DMU vs. 2VSU by reader showed similar results, with reader 1 demonstrating increased accuracy (0.72 vs. 0.66, 0.06, p = 0.5035) while readers 2 and 3 demonstrated decreased accuracy (reader 2, AUC 0.50 vs. 0.60, -0.10, p = 0.1672; reader 3, AUC 0.58 vs. 0.73, -0.15, p = 0.0442) (**Table 4**). Average sensitivity was slightly higher for 2V3DMU when compared to 2VSU (60% vs. 57.33%, respectively) (**Table 3**). McNemar testing to compare sensitivities of 2V3DMU vs. 2VSU by reader showed mixed results, with reader 1 demonstrating increased sensitivity (76% vs. 56%, 20%, p = 0.1797) while readers 2 and 3 demonstrated decreased sensitivity (reader 2, 44% vs. 52%, -8%, p = 0.6250; reader 3, 60% vs. 64%, -4%, p = 1.000). Average specificity was significantly lower for 2V3DMU compared to 2VSU (60.42% vs. 75%, respectively) (**Table 3**). McNemar testing to compare specificities of 2V3DMU vs. 2VSU showed decreased specificity for all readers, however these differences were not statistically significant (reader 1, 68.75% vs. 75%, -6.25%, p = 0.1797; reader 2, 56.25% vs. 68.75%, -12.5%, p = 0.6250; reader 3, 56.25% vs. 81.25%, -25%, p = 0.1250).

Two view oriented imaging on both the dedicated specimen unit (2VSU) and the mammogram unit (2V2DMU) had both the highest positive predictive values (PPV) (78.07% and 78.65%, respectively) and the highest negative predictive values (NPV) (53.03% and 56.60% respectively) when compared to 1VSU and 2V3DMU (PPVs 74.51% and 69.49%, NPVs 46.44% and 50.40%, respectively) (**Table 3**).

DISCUSSION

Breast conservation therapy is the current accepted therapy for early stage breast cancer. In order for breast conservation therapy to be effective, the excised cancer should have negative margins. Although the relationship between margin status and risk of recurrence is not exact, there is a drive to obtain negative margins either at the time of primary surgery, or with re-excision at a later date. When the first surgery heralds a positive margin, a second surgery is usually recommended. Re-excision is associated with worse

cosmetic results, as well as increased healthcare costs, delay in radiation therapy, and significant additional stress to the patient.

Definitions of what constitutes an adequate negative margin have historically been controversial and range from no cancer at ink to no cancer within 1cm [16—18]. However, Moran et al. [19] published clear guidelines in 2014 on surgical margins following a comprehensive meta-analysis that showed that no ink on tumor cells was associated with low rates of local recurrence. These consensus guidelines, put forth by the Society of Surgical Oncology (SSO) and American Society for Radiation Oncology (ASRO), define a positive margin as ink on invasive cancer or DCIS, and a negative margin as absence of ink. Further, Morrow et al. (2016) recently published clear consensus guidelines of the SSO, ASRO and the American Society of Clinical Oncology (ASCO) that recommend a negative margin width of 2 mm for DCIS and DCIS with microinvasion [20].

Preoperative image-guided localization is done to help ensure complete lesion removal while minimizing removal of large amounts of normal breast tissue. Pre-operative confirmation of diagnosis by percutaneous biopsy with placement of a metallic clip at the index lesion is now standard practice at most institutions. This is especially valuable when the target lesion is small and potentially removed by percutaneous biopsy, for biopsies performed under MRI guidance, and when the patient receives neo-adjuvant chemotherapy. Although other techniques such as radioactive seed localization (instead of wire localization) and intraoperative localization have been described as methods to enhance complete lesion removal, they have yet to be widely adopted [21,22].

Specimen radiography has been shown to be valuable in assessing removal of the target lesion and margin status [9, 23]. In most places, a single unoriented view of the specimen is acquired. Studies evaluating the performance of two views over one view have shown mixed results [9, 10]. However, European guidelines recommend imaging the specimen in two planes intraoperatively to ensure completeness of lesion excision [24].

Although DBT is now widely used in screening and diagnostic imaging, it is not routinely used for specimen imaging. Some studies have shown increased sensitivity with single view DBT specimen imaging and improved performance of DBT in lesion size assessment [13, 25]. Chapgar et al. (2015) also found that intraoperative DBT of the specimen led to a

slight reduction in re-excision rate [26]. Interestingly, a dedicated DBT specimen unit (Kubtec MOZART® with TomoSpec®) was approved by the FDA for specimen radiography in October 2014, and reference two studies supporting DBT specimen radiography on their website. In one study, the breast surgeon subjectively felt that two orthogonal views using DBT provided more anatomic detail and actionable data intraoperatively compared to 2D, thereby facilitating lower re-excisions (Kaufman CS et al., *Visualizing the real difference between 2-D and 3-D specimen mammography,* presented at the 2016 annual meeting of the National Consortium of Breast Centers). The second study, which reviewed 7 specimens, found that DBT provided better clarity of specimen edges compared to 2D and also correlated well with final histopathological margin status (Partain N et al., *Intra-operative Specimen Radiograph Utilizing 2D versus 3D Imaging and Correlation with Final Histopathology,* presented at the 2016 annual Miami Breast Cancer Conference). While these few studies have investigated DBT for specimen imaging, its overall value in this setting has not yet been elucidated, especially given the small size of the study cohort.

Our study revealed a trend of improved margin assessment using two oriented views as compared to a single unoriented view, while DBT did not appear to add diagnostic value for margin assessment as compared to 2D mammography. It is likely that our study was underpowered and could only identify trends rather than statistically significant differences given that there were only 41 specimens included in the analysis.

In regard to two oriented views compared to a single unoriented view, two oriented views did show improved sensitivity across all readers, with an average sensitivity of 57.33% compared to 42.67%, respectively; however, this difference only approached statistical significance for reader 2 ($p = 0.0625$). Average specificity was comparable between the two (2VSU 75%, 1VSU 77.08%). Two oriented views showed an overall higher AUC compared to the single unoriented view across all readers; however, this difference was only statistically significant for reader 3 ($p = 0.0455$). Goldfeder et al. (2006) found that one view had a higher specimen radiography and histopathology concordance rate (including sensitivity, specificity, PPV and NPV), however this was based on comparison of two samples of unequal size, with 66 specimens in the one-view group and 44 specimens in the two-view group [9]. Further, they may have had a sampling bias because cases were excluded from the two-view group when the surgeon left the needle in the specimen.

With regard to DBT compared to 2D mammography, we felt that this was best assessed by comparison of the 2V3DMU and 2V2DMU protocols, as these images were acquired on the same unit, thereby controlling for other variables. There was no clear trend of improved margin assessment with DBT, with mixed results for sensitivity and AUC across the three readers. There was however a trend of decreased specificity when compared to 2D mammography. Urano et al. (2016) recently performed a study comparing DBT to 2D mammography using two views and found that DBT allowed for significantly greater detectability of malignant lesions on a latero-lateral view as compared to 2D mammography [12]. However, this group did not evaluate margin status specifically, and there was only one radiologist reader. Unfortunately, the aforementioned studies comparing DBT specimen radiography to 2D specimen radiography found on the Kubtec website have not yet been published and at this time it is difficult to understand how they arrived at their conclusions given the lack of objective study data.

Our study also showed that overall accuracy of predicting surgical margins using the standard of care of 1VSU was low, with average sensitivity of 42.67%, average specificity of 77.08%, and average AUC of 0.5987. This may be intuitive given that radiographic imaging provides less detail when compared to microscopic evaluation of edges of a specimen, and that a cancer may extend beyond the mammographically visible lesion. The low accuracy appears consistent with the literature on specimen radiography and histopathology concordance for margin assessment, with reported sensitivity and specificity ranging from 55-66% and 60-92%, respectively [27—31]. Mazouni et al. (2006) also found that while there was good correlation between intraoperative radiographic findings and histopathologic features such as lesion size and margin width, specimen radiography was not as useful in predicting margin status alone, with an AUC of 0.62 [32].

Our study has several limitations. One important limitation is that there are an unknown number of patients that underwent immediate re-excision or shavings of the surgical cavity after the initial findings of the conventional image acquired on the specimen unit were conveyed to the surgeon. Therefore, a patient may have theoretically converted from a positive to a negative margin, such that the specimen radiograph shows a positive margin while final surgical pathology shows a negative margin. These would represent false

positives in our dataset. Another important limitation is that the readers had varying years of experience, which may have contributed to inter-reader variability.

Additionally, there are limitations related to the specimen imaging itself. The specimen was lightly compressed in order to acquire an image on the DBT unit, while the specimen was not compressed on the specimen unit. With regard to orienting the specimen, there were multiple potential errors, including inaccurate orientation given the irregular shape of the specimen, incorrect orientation of the specimen by the radiographer, inaccurate surgical stitches marking the superior and lateral aspects, as well as other potential errors such as radiologist misinterpretation of radiographic orientation markers, and technical issues with inking of the specimen and ink tracking into the specimen from its surface, which may distort pathology measurements of lesion distance to margin [31, 33].

In summary, orientation of surgical specimens may increase sensitivity and accuracy of margin assessment, although this did not reach statistical significance for all readers in our study. Clearly, more research is needed to determine whether orientation of the specimen should be integrated into routine clinical practice. With regard to DBT, this did not seem to add much value in imaging surgically excised tissue. Given the considerable added cost for a practice to acquire a dedicated DBT specimen unit, as well as the comparably higher cost of a DBT specimen unit versus a 2D unit, more research is needed to justify this added expense.

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Table 1. Patient and specimen characteristics.

Patient and specimen characteristics	
Age, mean (SD), years	60.66 (12.67)
Gender, no. (%)	
Female	39 (100)
Breast laterality, no. (%)	
Left	26 (63.41)
Right	15 (36.59)
Lesion type, no. (%)	
Mass	20 (48.78)
Calcifications	11 (26.83)
Mass with calcifications	7 (17.03)
Other	3 (7.32)
Lesion size, no. (%)	
< 5 mm	3 (7.31)
5 - 10 mm	19 (46.34)
11 - 15 mm	10 (24.39)
16 - 20 mm	2 (4.88)
21 - 25 mm	3 (7.32)
> 25 mm	4 (9.76)
Cancer type, no. (%)	
DCIS only	11 (26.83)
Invasive carcinoma	30 (73.17)
Invasive ductal CA	*8 (19.51)*
Invasive lobular CA	*3 (7.32)*
Invasive ductal + lobular CA	*2 (4.88)*
Invasive cribriform CA	*2 (4.88)*
Invasive CA – not specified	*7 (17.07)*
DCIS + invasive ductal CA	*5 (12.20)*
DCIS + microinvasive CA	*1 (2.44)*
DCIS + invasive CA – not specified	*2 (4.88)*
Margin status, no. (%)	
Positive	25 (60.98)
Negative	16 (39.02)

Re-excision at later date, no. (%)	
Yes	12 (30.77)
No	27 (69.23)

Table 1. Patient and specimen characteristics. 41 specimens from 39 patients are reflected. *SD,* standard deviation**.** Cancer type is according to final surgical pathology. Margin status is based on study definitions using final surgical pathology data, with a positive margin defined as cancer < 1 mm from the edge of the specimen.

Table 2. Area Under Curve (AUC) by modality, reader and average AUC per modality with qualitative interpretations.

Modality	Reader	AUC	95% Confidence Intervals	Interpretation	Average AUC	Average AUC Interpretation
1VSU	1	0.6037	0.44966 - 0.75784	poor	0.5987	worthless
	2	0.5662	0.43038 - 0.70212	worthless		
	3	0.6262	0.48620 - 0.76630	poor		
2VSU	1	0.6550	0.50713 - 0.80287	poor	0.6616	poor
	2	0.6037	0.44966 - 0.75784	poor		
	3	0.7262	0.58851 - 0.86399	fair		
2V3DMU	1	0.7237	0.57865 - 0.86885	fair	0.6021	poor
	2	0.5012	0.34120 - 0.66130	worthless		
	3	0.5813	0.42200 - 0.74050	worthless		
2V2DMU	1	0.6838	0.53387 - 0.83363	poor	0.6846	poor
	2	0.6238	0.47008 - 0.77742	poor		

	3	0.7463	0.61038 - 0.88212	fair		

Table 2. Area Under Curve (AUC) by modality, reader and average AUC per modality with qualitative interpretations.

Table 3. Sensitivity, Specificity, PPV and NPV for each modality and reader.

	Sensitivity, %				Specificity, %				PPV, %				NPV, %			
Modality	**1V SU**	**2V SU**	**2V3 DMU**	**2V2 DMU**	**1V SU**	**2V SU**	**2V3 DMU**	**2V2DMU**	**1V SU**	**2V SU**	**2V3 DMU**	**2V2 DMU**	**1V SU**	**2V SU**	**2V3 DMU**	**2V2 DMU**
Reader 1	52.00	56.00	76.00	68.00	68.75	75.00	68.75	68.75	72.22	77.78	79.17	77.27	47.83	52.17	64.71	57.89
Reader 2	32.00	52.00	44.00	56.00	81.25	68.75	56.25	68.75	72.73	72.22	61.11	73.68	43.33	47.83	39.13	50.00
Reader 3	44.00	64.00	60.00	68.00	81.25	81.25	56.25	81.25	78.57	84.21	68.18	85.00	48.15	59.09	47.37	61.90
Average	42.67	57.33	60.00	64.00	77.08	75.00	60.42	72.92	74.51	78.07	69.49	78.65	46.44	53.03	50.40	56.60

Table 3. Sensitivity, Specificity, PPV and NPV for each modality and reader. PPV, positive predictive value; NPV, negative predictive value.

Table 4. Comparison of Modalities using Area Under Curve (AUC).

Reader	Modalities compared	Respective AUCs	Difference	P value
1	1VSU vs. 2VSU	0.6037 < 0.6550	- 0.0513	0.3529
	2VSU vs. 2V3DMU	0.6550 < 0.7237	- 0.0687	0.5035
	2V2DMU vs. 2V3DMU	0.6838 < 0.7237	- 0.0399	0.5984
	2VSU vs. 2V2DMU	0.6550 < 0.6838	- 0.0288	0.7064
2	1VSU vs. 2VSU	0.5662 < 0.6037	- 0.0375	0.6154
	2VSU vs. 2V3DMU	0.6037 > 0.5012	0.1025	0.1672
	2V2DMU vs. 2V3DMU	0.6238 > 0.5012	0.1226	0.1089
	2VSU vs. 2V2DMU	0.6037 < 0.6238	- 0.0201	0.6600
3	1VSU vs. 2VSU	0.6262 < 0.7262	- 0.1000	**0.0455**
	2VSU vs. 2V3DMU	0.7262 > 0.5813	0.1449	**0.0442**
	2V2DMU vs. 2V3DMU	0.7463 > 0.5813	0.1650	**0.0269**
	2VSU vs. 2V2DMU	0.7262 < 0.7463	- 0.0201	0.7769

Table 4. Comparison of Modalities using Area Under Curve (AUC). Reader 3 had better diagnostic accuracy with 2VSU when compared to 1VSU, 2VSU when compared to 2V3DMU, and 2V2DMU when compared to 2V3DMU, showing general improved diagnostic performance with 2 2D oriented views.

Figure 1. Consort flow diagram for patient inclusion in study.

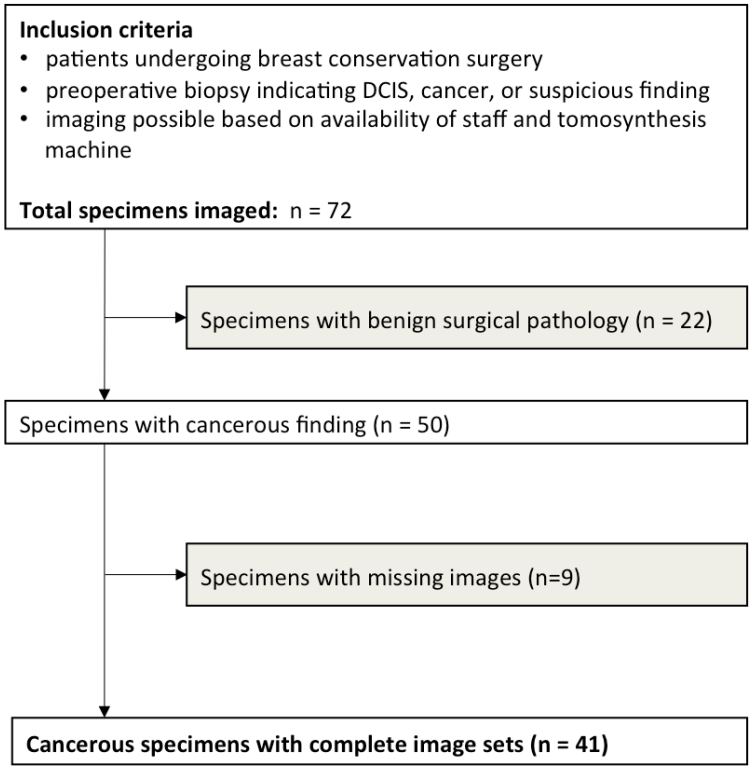

Figure 1. Consort flow diagram for patient inclusion in study. Consort flow diagram showing the selection of cases for inclusion in the study.

Figure 2. Specimen Orientation Diagram. Top down photograph and drawing of left breast specimen on detector plate. Short stitch marks superior aspect, long stitch marks lateral aspect. In first image, long stitch faces laterally (in this case left because left breast specimen), and short stitch faces up (away from detector plate). In the second image, the specimen has been rotated 90˚ up towards the imager so that the short stitch now faces the imager and the long stitch continues to face laterally. The first image is marked with 1 BB (blue sticker) to indicate the posterior aspect (chest wall), and a paper clip to indicate the lateral aspect. The second image is marked with 2 BB's (blue and pink stickers) to indicate the superior aspect, and a paper clip to indicate lateral aspect.

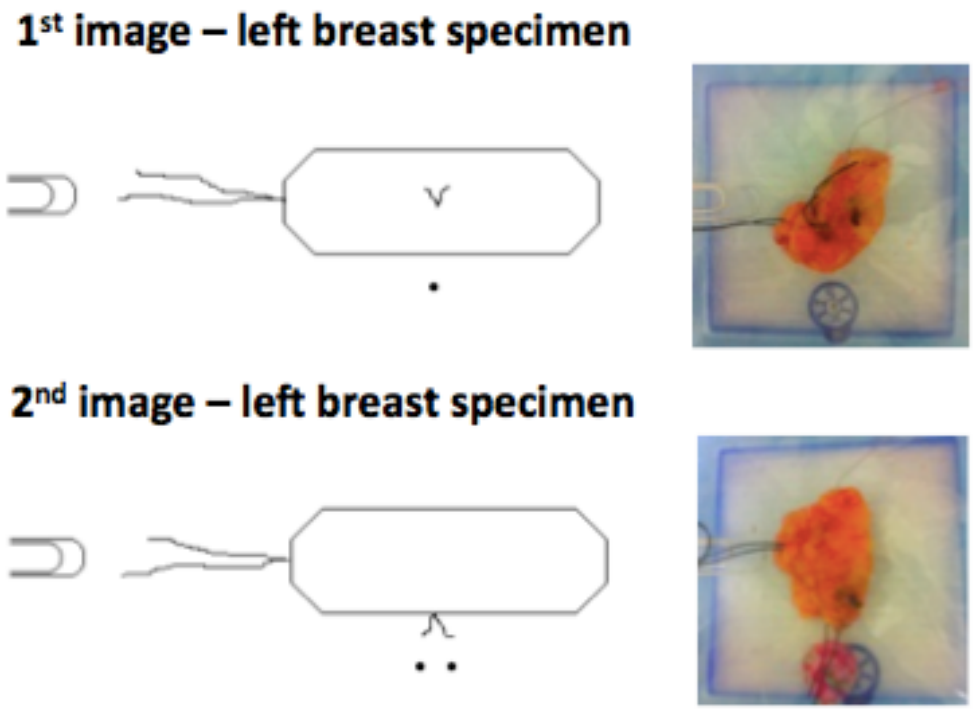

Figure 3. Specimen imaging using four different study protocols.

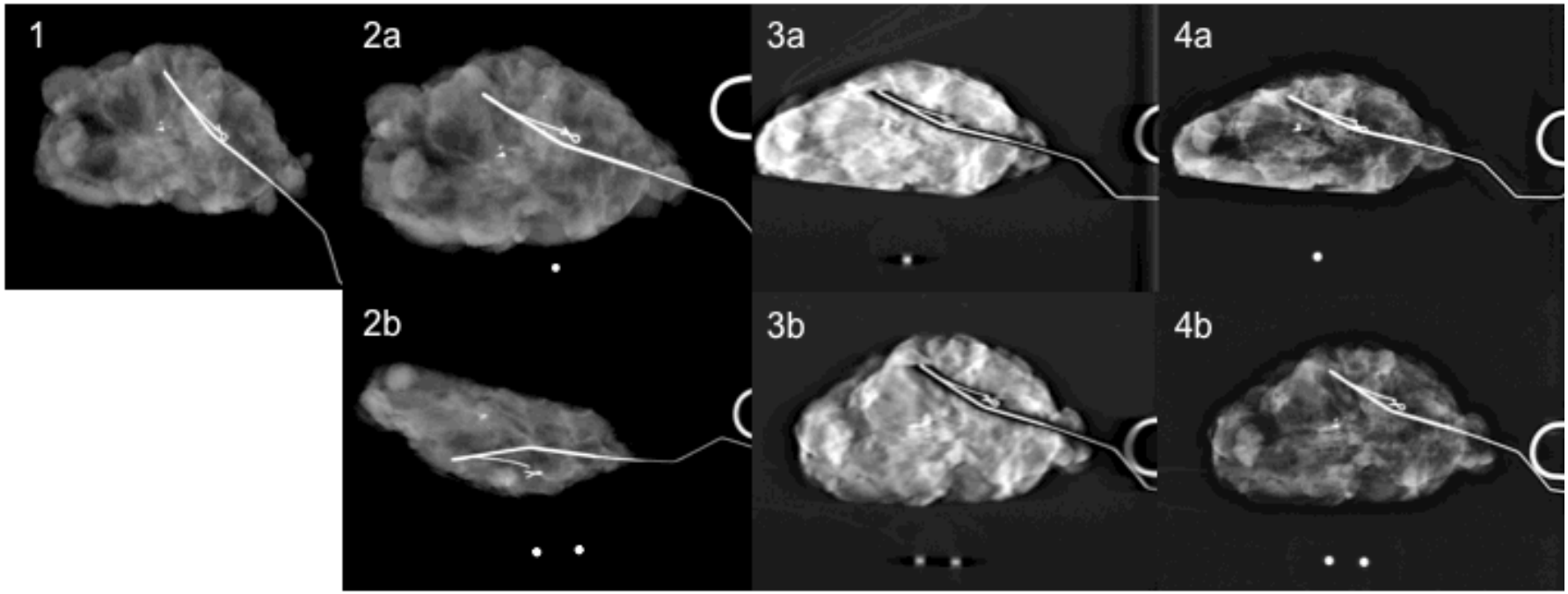

Figure 3. Specimen imaging using four different study protocols. Specimen radiographs from an 81-year-old woman who underwent preoperative needle localization of a mass with calcifications in her right breast, shown to be DCIS on initial biopsy. In this case, all readers called the margin positive with all modalities, however note that in the oriented image 2b it is more readily apparent that the calcifications extend to inferior margin. Final surgical pathology revealed invasive carcinoma with a positive inferior margin. The patient ultimately did not have re-excision. **Image 1.** Single unoriented 2D image acquired on a dedicated specimen unit (1VSU). **Image 2a and 2b.** Two orthogonal, oriented 2D images acquired on specimen unit (2VSU). **Image 3a and 3b.** Two orthogonal, oriented 3D images acquired on mammogram unit (2V3DMU). **Image 4a and 4b.** Two orthogonal, oriented 2D images acquired on mammogram unit.

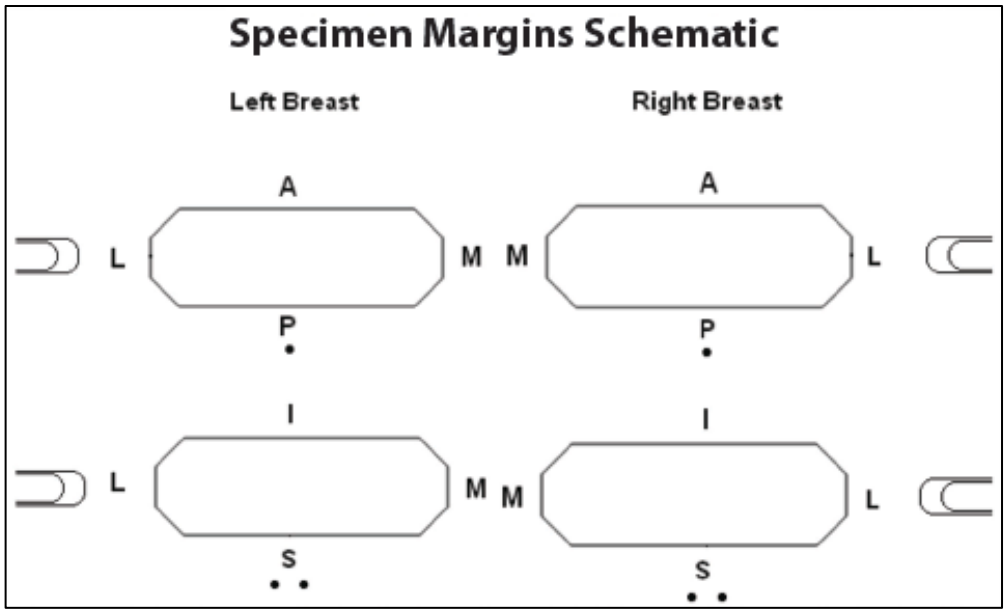

Figure 4. Specimen Margins Schematic. All radiologists used this schematic as a reference tool to correctly identify each margin while reading specimen images. BBs and paperclips were used to label the margins. The first image was marked with 1 BB to indicate the posterior aspect (chest wall), and a paper clip to indicate the lateral aspect. The second image was marked with 2 BBs to indicate the superior aspect, and a paper clip to indicate lateral aspect. A = anterior, P = posterior, L = lateral, M = medial, S = superior, I = inferior.

Figure 5. Summary of sensitivity and specificity for each modality and reader.

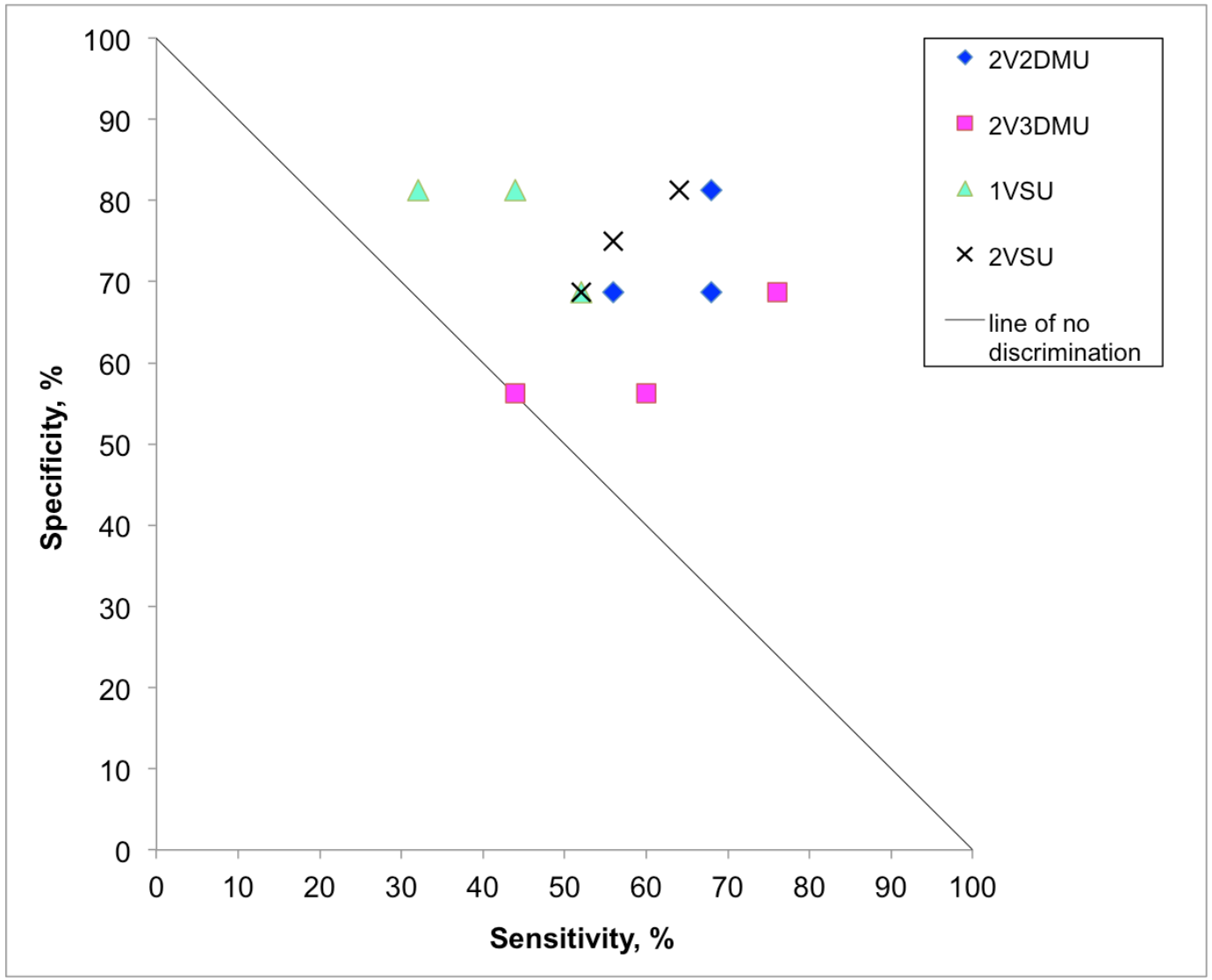

Figure 5. Summary of sensitivity and specificity for each modality and reader.

Table 5. McNemar test results comparing sensitivities of each modality.

Modalities compared	Reader	Respective sensitivities, %	Difference, %	McNemar p value
1VSU vs. 2VSU	1	52.00 < 56.00	- 4.00	1.0000
	2	32.00 < 52.00	- 20.00	0.0625
	3	44.00 < 64.00	- 20.00	0.1250
2VSU vs. 2V3DMU	1	56.00 < 76.00	- 20.00	0.1797
	2	52.00 > 44.00	8.00	0.6250
	3	64.00 > 60.00	4.00	1.0000
2V2DMU vs. 2V3DMU	1	68.00 < 76.00	- 8.00	0.6250
	2	56.00 > 44.00	12.00	0.3750
	3	68.00 > 60.00	8.00	0.6875
2VSU vs. 2V2DMU	1	56.00 < 68.00	- 12.00	0.4531
	2	52.00 < 56.00	- 4.00	1.0000
	3	64.00 < 68.00	- 4.00	1.0000

Table 5. McNemar test results comparing sensitivities of each modality.

Table 6. McNemar test results comparing specificities of each modality.

Modalities compared	Reader	Respective specificities, %	Difference, %	McNemar p value
1VSU vs. 2VSU	1	68.75 < 75.00	- 6.25	1.0000
	2	81.25 > 68.75	12.50	1.0000
	3	81.25 = 81.25	0.00	1.0000
2VSU vs. 2V3DMU	1	75.00 > 68.75	6.25	0.1797
	2	68.75 > 56.25	12.50	0.6250
	3	81.25 > 56.25	25.00	0.1250
2V2DMU vs. 2V3DMU	1	68.75 = 68.75	0.00	1.0000
	2	68.75 > 56.25	12.50	0.1250
	3	81.25 > 56.25	25.00	0.1250
2VSU vs. 2V2DMU	1	75.00 > 68.75	6.25	1.0000
	2	68.75 = 68.75	0.00	1.0000
	3	81.25 = 81.25	0.00	1.0000

Table 6. McNemar test results comparing specificities of each modality.