Comparing preoperative imaging modalities in patient selection for breast intraoperative radiotherapy

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Background: This study evaluated the relative accuracy of mammography, ultrasound, and magnetic resonance imaging (MRI) in predicting the tumor size of early stage breast tumors in preoperative selection of patients for intraoperative radiotherapy (IORT).

Methods: We identified 156 patients with clinical T1/T2, N0 breast cancer who underwent IORT. Clinical, pathologic, and radiation data were collected. The preoperative tumor size obtained by imaging was compared with tumor pathological size.

Results: The median patient age was 66. The mean tumor size at excision was 1.05 cm (0.1-3.0 cm). Out of the 156 patients, 98 had a reported, nonzero tumor size by mammography, 131 by ultrasound, and 76 by MRI. The mean difference between imaging and the tumor size was +0.062 ± 0.54 cm for mammography, −0.11 ± 0.43 cm for ultrasound, and +0.33 ± 0.55 cm for MRI, with positive values indicating an overestimate of the tumor size. MRI produced more overestimates of tumor size of at least 0.5 cm than mammography or ultrasound in a paired analysis of patients who received both modalities.

Conclusions: Accuracy of imaging modalities in determining tumor size can influence patients’ eligibility for IORT. Mammography and ultrasound showed acceptable accuracy in predicting size. MRI overestimated tumor size and may inappropriately exclude patients from IORT. We would discourage ruling out candidates for IORT on the basis of large size by MRI alone.

Keywords: breast cancer, intraoperative radiotherapy (IORT), magnetic resonance imaging (MRI), mammography, ultrasound

1 | INTRODUCTION

Intraoperative radiotherapy (IORT) is a relatively new partial breast radiation technique used for the treatment of early-stage breast cancers. At the time of lumpectomy, a single fraction of high-dose radiation is delivered to the lumpectomy surface using low-energy photons. The targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A) trial was a noninferiority trial that randomized 3451 women with breast tumors less than 3 cm in size to receive either IORT or a traditional course of external beam radiotherapy (EBRT). In patients aged 40 years or more with small (T1 and small T2), unifocal, hormone-receptor positive invasive cancers, the TARGIT trial demonstrated that IORT resulted in a similar five-year local control to traditional external beam radiation to the whole breast.¹²

This technique makes the tumor size an important component of surgical selection. Patients with a tumor size less than 3 cm are potentially eligible for IORT and breast-conserving lumpectomy,
whereas those with larger tumors are not eligible for IORT, given the increased risk of local disease recurrence. Very few other surgical treatment decisions are made on the basis of narrow preoperative size criteria. This decision can be complicated, as patients may have imaging measurements by mammogram, ultrasound, and magnetic resonance imaging (MRI). The accuracy of MRI, mammography, and ultrasound in predicting tumor size is variable, and this can influence the inclusion or exclusion of patients from IORT. Past studies have indicated that MRI has a tendency to overestimate the size of these larger tumors. Past studies have indicated that MRI has a tendency to overestimate the size of these larger tumors. Past studies have indicated that MRI has a tendency to overestimate the size of these larger tumors.

We therefore studied the relative accuracy of mammography, ultrasound, and MRI in small, unifocal breast tumors preoperatively to aid surgeons in preoperative patient selection for IORT with breast-conserving surgery.

2 | MATERIALS AND METHODS

We performed a retrospective review of patients enrolled in our institutional prospective breast IORT registry under a Columbia University Medical Center IRB approved protocol (IRB-AAAJ8512). We identified patients treated with breast IORT for invasive breast cancer using the Intrabeam System (Carl Zeiss Meditec AG, Jena, Germany) between September 2013 and January 2017. The patients enrolled in our prospective registry were selected using The TARGIT criteria for IORT including screening detected, unifocal, hormone-positive breast cancer less than 3 cm in size on imaging and no evidence of nodal disease. In a small subset of patients, IORT was used as a preplanned upfront boost with additional whole breast radiation planned postoperatively.

We identified 156 patients who were treated with IORT from September 2013 to January 2017. We reviewed all available breast imaging for each patient involved in this study. Of these patients, 155 patients underwent mammography, 150 underwent ultrasound, and 84 patients underwent MRI preoperatively. Imaging reads that included specific radiologic measurements of the study were included in our analysis, including mammography, MRI, and ultrasound. Demographic, preoperative staging, pre- and postoperative pathology, and surgical and radiation data were collected for all patients. Immunohistochemical staining was performed for the estrogen receptor (ER) and progesterone receptor (PR) and interpreted according to the American Society of Clinical Oncology and College of American Pathologists Guidelines. Tumors were considered receptor-positive if either ER or PR demonstrated ≥1% positive staining. We evaluated the need for re-excision and postoperative EBRT and variations between preoperative staging and final pathology. Variability in preoperative tumor size by imaging modalities was compared with the final tumor size as recorded by pathology. The choice of preoperative imaging was at the breast surgeon’s discretion.

2.1 | Imaging modality

MRI was performed on a 3.0 tesla (T) or 1.5-T commercially available system (Signa Excite, GE Healthcare) using a dedicated eight-channel surface breast coil. The imaging sequence included a localizing sequence followed by a sagittal fat-suppressed T2-weighted sequence. A T1-weighted fat-suppressed fast spoiled gradient-echo sequence was then performed before and three times after a rapid bolus injection of gadopentetate dimeglumine (Magnevist, Berlex; 0.1 mmol/L/kg of body weight), delivered through an IV catheter. Image acquisition started after contrast material injection and was obtained consecutively with each acquisition period of 120 seconds. The section thickness was 2.3 mm using a matrix of 256 × 192 and a field of view of 18-22 cm. The frequency was in the anteroposterior direction.

Breast ultrasound was performed by 1 of 5 fellowship trained breast radiologists on a commercially available system (LOGIQ E9, GE Healthcare). Mammography was performed on a commercially available 2D mammography machine (GE Essential, GE Healthcare) and was reviewed on a high resolution picture archiving and communication system (PACS) monitor.

2.2 | Analysis

Patients who did not receive a particular imaging modality had tumor size unreported by that imaging modality or had tumor not seen by that imaging modality were not included in the analyses of that imaging modality. If all the dimensions of a tumor were recorded, on imaging or gross pathology, the largest dimension was used as the tumor size. Descriptive statistics was used to summarize the patients’ characteristics. Categorical variables were reported using frequency (%), whereas continuous variables were presented as mean ± standard deviation or median (interquartile range). For the purpose of comparing the imaging modalities, we defined concordance between size by imaging and final tumor size as an absolute difference of less than 0.5 cm and discordance as an absolute difference of at least 0.5 cm. This classification has been used in other analyses of the predictive power of imaging measurements. Some studies comparing imaging modalities in larger tumors have used a similar method of comparison, defining the boundaries of concordance as ±1.0 cm. McNemar’s test for paired data was used to compare the concordance rates between two imaging modalities, using only patients who received both of those imaging modalities. Statistical analyses were performed using R, version 3.2.1 using a type I error set at 0.05.

3 | RESULTS

Table 1 presents the characteristics of the 156 study participants. The median age was 66 (range 44-91). Ninety percent (140) of the participants were postmenopausal. The histologic subtypes were 90% (140) invasive ductal carcinoma (IDC), 8% (13) invasive lobular...
The findings here were usually described as asymmetry, calcifications, distortion or other findings that revealed the presence of a mass but limited the radiologist’s ability to accurately assess its size. Of the remaining 115 patients, 17 had mammographically occult diseases. The final 98 patients with a reported, nonzero size by mammogram were included in our analyses of the ability of mammogram to predict the tumor size. Of the remaining 115 patients, 17 had mammographically occult diseases. The final 98 patients with a reported, nonzero size by mammogram were included in our analyses of the ability of mammogram to predict the tumor size.

TABLE 1  Patient and tumor characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)</th>
<th>N = 156</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmenopausal</td>
<td>140 (90)</td>
<td></td>
</tr>
<tr>
<td>Age, median (range)</td>
<td>66 y (44-91)</td>
<td></td>
</tr>
<tr>
<td>Preoperative pathology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive ductal carcinoma</td>
<td>140 (90)</td>
<td></td>
</tr>
<tr>
<td>Invasive lobular carcinoma</td>
<td>13 (8)</td>
<td></td>
</tr>
<tr>
<td>Mixed ductal/lobular type</td>
<td>3 (2)</td>
<td></td>
</tr>
<tr>
<td>Breast density</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatty</td>
<td>15 (10)</td>
<td></td>
</tr>
<tr>
<td>Scattered fibroglandular</td>
<td>70 (45)</td>
<td></td>
</tr>
<tr>
<td>Heterogeneously dense</td>
<td>69 (44)</td>
<td></td>
</tr>
<tr>
<td>Dense</td>
<td>2 (1)</td>
<td></td>
</tr>
<tr>
<td>Subtype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Her 2+</td>
<td>5 (3)</td>
<td></td>
</tr>
<tr>
<td>Triple negative</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Luminal A</td>
<td>111 (71)</td>
<td></td>
</tr>
<tr>
<td>Luminal B</td>
<td>39 (25)</td>
<td></td>
</tr>
</tbody>
</table>

Of the 156 patients, six did not receive ultrasound, three had ultrasound with the tumor noted but without the tumor size recorded, and 16 did not have tumor detection by ultrasound. The remaining 131 patients were included in our analyses of ultrasound. Seventy-two patients did not have MRI, five had had MRI reads noting an abnormality but not specifying a size, and in three patients, MRI was not able to detect a tumor. Seventy-six patients had a reported, nonzero tumor size by MRI. For our paired analyses comparing two imaging modalities, 80 patients had a reported, nonzero size for both mammography and ultrasound, 46 patients had a reported, nonzero size for both mammography and MRI, and 64 patients had a reported, nonzero size for both ultrasound and MRI.

### 3.1 Mammographic findings

All patients had breast density described using breast imaging reporting and data system (BI-RADS) criteria. Of all the patients, 10% (15) had fatty breasts, 45% (70) had scattered fibroglandular breasts, 44% (69) had heterogeneously dense breasts, and 1% (2) had dense breasts. Increased breast density did not hinder the ability of any of the imaging modalities to predict tumor size based on a Chi-squared test comparing the proportion of imaging measurements within a half centimeter of tumor size in breasts of different densities. Of the 98 patients with recorded, nonzero tumor measurements by mammography, the mean difference from tumor size was +0.062 ± 0.54 cm, indicating a slight average overestimate of tumor size. Based on a paired, two-sided t test, there was no statistically significant difference between the mean tumor size and the mean size by mammography in patients receiving mammography (P = 0.25).

### 3.2 Ultrasound findings

Of the 131 patients with nonzero size by ultrasound, the mean difference in size between preoperative ultrasound measurement and tumor size was −0.11 ± 0.43 cm. The P-value that this consistent
underestimate was due to chance was 0.0033 based on a paired t-test.

3.3 | MRI findings

Of the 76 patients with nonzero size by MRI, on average preoperative MRI measurement overestimated final tumor size by +0.33 ± 0.55 cm. The P-value that this consistent overestimate was due to chance was 9.8 × 10⁻⁷ based on a paired t-test. Two patients in this cohort had size greater than 3.0 cm by MRI, and might have been considered poor candidates for IORT based on MRI alone. Given that MRI was not required in the TARGIT-A trial, patients with size greater than 3.0 cm by MRI could be eligible for IORT if they met selection criteria by ultrasound or mammogram. Furthermore, both of these patients had a final surgical size less than 3.0 cm.

3.4 | Comparison of imaging modalities

For the purpose of comparing the imaging modalities, we defined concordance between size by imaging and tumor size as an absolute difference of less than 0.5 cm and discordance as an absolute difference of at least 0.5 cm. This classification has been used in other analyses of the predictive power of imaging measurements. We then examined the subsets of our patient population with specified, nonzero measurements of tumor size by both preoperative mammography and ultrasound (N = 80), mammography and MRI (N = 46), and MRI and ultrasound (N = 64) and compared the concordance rates of the two imaging modalities in each of these groupings using a McNemar’s test for correlated proportions. Results of these comparisons are shown in table 3. There was no significant difference between the rates of concordance in mammogram and ultrasound in patients receiving both modalities (76% vs 77%). Mammogram produced nonsignificantly more readings concordant with tumor size than MRI in patients receiving both imaging modalities (80% vs 70%, P = 0.20). Ultrasound produced nonsignificantly more readings concordant with tumor size than MRI in patients receiving both imaging modalities (80% vs 69%, P = 0.13). Of 24 discordant predictions of surgical size by MRI, 22 were due to overestimates of surgical size of at least 0.5 cm. MRI had more instances of overestimating tumor size than mammography (13% vs 26%, P = 0.058) or ultrasonography (8% vs 30%, P = 0.000047) in patients who received MRI and the other imaging modality.
**FIGURE 2** Comparison of size by imaging to surgical size. These graphs compare surgical size with size by imaging in mammography, ultrasound and MRI for invasive and in situ tumors. The solid line is \(x = y\) and represents the relationship between size by imaging and the final surgical size in an ideal imaging modality. The dotted line is the best fit line for the given subset of the data. This figure includes the 98 patients who had a reported, nonzero tumor size by mammography, 131 by ultrasound, and 76 by MRI. MRI, magnetic resonance imaging.

**TABLE 3** McNemar’s pairwise analysis comparing the concordance rates between imaging modalities

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Proportion discordant modality 1</th>
<th>Proportion discordant modality 2</th>
<th>(P)-value</th>
<th>Proportion overestimate modality 1</th>
<th>Proportion overestimate modality 2</th>
<th>(P)-value</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammography versus ultrasound</td>
<td>24%</td>
<td>23%</td>
<td>1</td>
<td>15%</td>
<td>6%</td>
<td>0.2</td>
<td>80</td>
</tr>
<tr>
<td>Mammography versus MRI</td>
<td>20%</td>
<td>30%</td>
<td>0.20</td>
<td>13%</td>
<td>26%</td>
<td>0.13</td>
<td>46</td>
</tr>
<tr>
<td>Ultrasound versus MRI</td>
<td>20%</td>
<td>31%</td>
<td>0.13</td>
<td>8%</td>
<td>30%</td>
<td>0.0005</td>
<td>64</td>
</tr>
</tbody>
</table>

Abbreviation: MRI, magnetic resonance imaging.

Concordance between size by imaging and final surgical size is defined as an absolute difference of less than 0.5 cm and discordance as an absolute difference of at least 0.5 cm. Overestimates are defined as overestimates of at least 0.5 cm of final surgical size.
Of the 64 patients who received all three imaging modalities, the concordance rates were 81% by mammogram, 84% by ultrasound, and 70% by MRI.

3.5 | Occult disease

Ultrasound produced concordant predictions of tumor size in 53% of patients with mammographically occult disease, compared with 78% in other patients, $P = 0.033$. Mammography produced concordant predictions of tumor size in 53% of patients with disease undetectable by ultrasound, compared with 76% in other patients, $P = 0.08$.

4 | DISCUSSION

There is a large body of radiology literature on the specificity and sensitivity of breast imaging modalities in detecting tumors.\(^9,10\)

However, very few treatment decisions are made on the basis of narrow preoperative size criteria, and there is very limited prior literature on the ability of mammography, ultrasound, and MRI to accurately predict breast tumor size in small, low grade breast tumors. The ability to predict tumor size in this group of patients is vitally important for preoperative selection of patients for IORT with breast conserving surgery, to minimize the risk of local recurrence which is more frequent in larger tumors.

Our work compares the ability of mammography, MRI, and ultrasound to predict tumor size in patients who underwent IORT. We found that while mammogram on average slightly overestimates tumor size and ultrasound slightly underestimates tumor size, both of these imaging modalities provide very close approximations of tumor size and are equally likely to provide tumor measurements within half a centimeter of tumor size. We found that MRI on average overestimates surgical size by 0.33 cm, and was more likely than mammography or ultrasound to overestimate tumor size by at least 0.5 cm.

Prior studies on larger tumors have also noted tumor size overestimation by MRI. Grimsby et al studied 190 patients who had received MRI before breast resection. This paper had a mean tumor size of 3.8 cm and found that MRI produced overestimates of more than 0.5 cm in 32% of cases, underestimates of more than 0.5 cm in 15% of cases, and concordance in 53% of cases. They noted that 65% of MRI overestimates involved satellite lesions, ductal carcinoma in situ (DCIS), or lymphovascular invasion.\(^5\) Williams et al\(^3\) also only looked at MRI and concluded that MRI correlated well with the final tumor size. However, this study had a median tumor size of 3.75 cm and included tumors as large as 10.4 cm.

Several studies have compared the ability of ultrasound, mammography, and MRI to predict tumor size, in tumors larger than those normally considered for IORT. Gruber et al compared mammography, ultrasound, and MRI to tumor size in a retrospective study of 121 patients, with the tumor size as large as 8 cm. They found that ultrasound significantly underestimated tumor size, MRI nonsignificantly overestimated the final pathologic size and mammography measurements did not significantly differ from tumor size at excision.\(^6\) Dummin et al\(^4\) compared the prediction ability of ultrasound and mammography in patients with breast tumors as large as 7.5 cm and found that mammography was a better predictor of tumor size and ultrasound tended to underestimate the final tumor size.

Bosch et al compared the predictive value of physical examination, mammography, and ultrasound in patients with an average tumor size of 1.7 cm. They found that ultrasound underestimated the tumor size by 0.3 cm on average, but correlated significantly better with the tumor size than mammography or physical examination.\(^11\)

Consistent with previous studies, in our study MRI tended to overestimate the extent of disease.\(^12\) Our study is unique in demonstrating this phenomenon in a cohort of patients with small, low-grade tumors, and demonstrating similar predictive abilities of mammography and ultrasound. Physicians should be careful when ruling patients out for IORT based on size by MRI alone. MRI may still be useful in IORT candidates if used to rule out multifocal or contralateral disease. Patients with diseases which are undetectable by mammography or ultrasonography are at an increased risk of having a measurement by the other imaging modality which is discordant with the tumor size. Increased caution should be taken when selecting these patients for IORT.

Major limitations of our study include a small sample size and the retrospective nature of the study. Only 64 subjects received all three imaging modalities. Only patients who underwent IORT for invasive breast cancer were included; a large subset of patients may have been excluded on the basis of imaging size before referral. Although our selection process led to the exclusion of many patients with larger tumor sizes by imaging, we focus specifically on the utility of imaging modalities in a cohort of patients who meet the selection criteria for IORT. Another limitation is that size by imaging and tumor size were determined by multiple radiologists and pathologists who were not blinded to previously reported imaging sizes of the tumor. A concern was that the use of biopsies could decrease the size of the tumors. However, this was unlikely a significant effect, given that ultrasound underestimated the final tumor size on average. MRI is often performed after biopsy at our institution, so it is possible that post-biopsy inflammation or hematomas contributed to the overestimation of the final tumor size by MRI. However, the hematoma size was generally reported separately to tumor size if present and in this case did not influence the recorded size by MRI.

5 | CONCLUSIONS

This study affirms the ability of ultrasound and mammogram to predict breast tumor size with acceptable accuracy, with ultrasound on average slightly underestimating tumor size. Previous studies have shown overestimation of tumor size by MRI.\(^5,6\) Our study confirms this result in patients with small, low-grade tumors. We would therefore recommend against ruling out otherwise good
candidates for IORT on the basis of large size by MRI alone. However, MRI still plays an important role in patient selection for IORT with regard to ruling out patients with multifocal or contralateral disease. We also found that patients with disease undetectable by mammography or ultrasound are at increased risk of having a measurement by the other modality that is discordant with final tumor size. Increased caution should be exercised in such candidates for IORT.

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