Automated Breast Volumetric Sonography Compared to Magnetic Resonance Imaging in Jewish BRCA1/2 Mutation Carriers

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ABSTRACT: Background: Automated breast volumetric sonography (ABVS) is a new technology with various possible applications. Objectives: To compare ABVS and breast magnetic resonance imaging (MRI) in the surveillance of women with a BRCA1/2 gene mutation. Methods: We conducted a prospective study in Jewish female BRCA1/2 mutation carriers who underwent breast MRI and ABVS. The results of both exams performed 6 months apart or less, and relevant clinical data, were reviewed. The BI-RADS results were divided into three subgroups according to subsequent expected management: BI-RADS 1-2 (normal study), BI-RADS 3 (probably benign finding), and BI-RADS 4 and 5 (suspicious findings). BI-RADS 0 and 6 scores were excluded from the study. Distribution of ABVS and MRI BI-RADS scores were compared using McNemar’s test, and concordance was calculated using the Cohen kappa test. Results: Overall, 68 women, 40 BRCA1 and 28 BRCA2 mutation carriers, age range 26–69 (mean 44.55 ± 12.1 years), underwent 79 paired ABVS and MRI examinations. McNemar’s test calculations showed no significant difference between MRI and ABVS BI-RADS score distribution. Cohen’s kappa test resulted in k = 0.158, an agreement that can be described as only "slight agreement" between both modalities. Of 14 discordant cases there was one cancer, revealed by MRI and not by ABVS performed 6 months prior to MRI. Conclusions: ABVS showed slight agreement with MRI in BRCA1/2 mutation carriers. These preliminary results in a small group of healthy high risk patients suggest that the diagnostic abilities of ABVS are inferior to those of MRI. Further studies encompassing larger groups are needed.
Yet not all reports show these superior results. A smaller study by Chang and collaborators [16] compared ABVS in 61 patients with HH-US for the ability to detect breast pathologies and reported that ABVS detected only 57.1–78.6% of the known cancers, and yielded a substantial number of false-positive results (8.3–20.8%) in normal breasts. The purpose of the present study was to compare the accuracy of ABVS and breast MRI in the surveillance of Jewish female high risk BRCA1/2 gene mutation carriers.

**PATIENTS AND METHODS**

This was a prospective study in female Jewish Israeli BRCA1/2 mutation carriers who underwent breast MRI and ABVS at a single follow-up clinic in a tertiary referral medical center in Israel. Results of MRI and ABVS imaging (ACUSON S2000™ Automated Breast Volume Scanner, Siemens Medical Solutions, Inc., CA, USA), performed within 6 months of each other or less (≤ 181 days interval), as well as relevant clinical data, were reviewed. The BI-RADS score results were divided into three groups according to subsequent expected management: BI-RADS 1 and 2 (normal study), BI-RADS 3 (probably benign finding), and BI-RADS 4 and 5 (suspicious finding). BI-RADS 0 and 6 scores were excluded from the study.

The ABVS and MRI studies were interpreted by different radiologists, a single radiologist for each study. The studies were performed as part of the high risk screening, and the interpreting radiologist was not blinded to the previous study result. All the radiologists participating in the study are proficient in breast MRI interpretation. Since ABVS is a new modality, the level of proficiency in its interpretation is lower.

**STATISTICAL ANALYSIS**

The results obtained from the ABVS imaging were compared with those of the MRI (the gold standard). The data were analyzed using descriptive statistics. All statistical analysis calculations were performed using statistical software SPSS (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp, USA). McNemar’s test was carried out to compare the distribution of the BI-RADS results of the two modalities (ABVS and MRI). In addition, classification of the concordance of the ABVS and MRI with the BI-RADS was calculated using Cohen’s kappa test [17]. This test provides a satisfactory estimation of the agreement between the two modalities. We used the magnitude guidelines published by Landis and Koch [18], who characterized the values of $k < 0$ for as indicating no agreement, $k = 0–0.20$ slight, $k = 0.21–0.40$ fair, $k = 0.41–0.60$ moderate, $k = 0.61–0.80$ substantial, and $k = 0.81–1$ as almost perfect agreement. Statistical significance was assumed at $P < 0.05$ for all tests.

The study was approved by the Institutional Review Board and informed consent was obtained from all participants.

**RESULTS**

Overall, 68 Jewish women, 40 BRCA1 and 28 BRCA2 mutation carriers, age range 26–69 years (mean 44.55 ± 12.1), underwent 79 pairs of breast imaging by ABVS and MRI examinations between May 2012 and April 2014. Two pairs of ABVS and MRI examinations were excluded from the study due to ABVS BI-RADS category 0. Table 1 displays the distribution of the BI-RADS scores using the two modalities − ABVS and MRI. Of these, 65 examination pairs (82%) had complete concordant BI-RADS scores in the two modalities. In the remaining 14 pairs, in 10 MRI scored a higher BI-RADS score (five BI-RADS category 3 and five BI-RADS category 4) compared with the ABVS score, and in 4 the ABVS BI-RADS score was higher (one BI-RADS category 3 and three BI-RADS category 4) than MRI [Table 1]. The ABVS BI-RADS category 3 follow-up ultrasound exam was not performed, and a matching small lesion was seen in the consecutive MRI unchanged in size. Three of the MRI BI-RADS category 3 lesions disappeared on the follow-up MRI, one was unchanged, and one was lost to follow-up in our institute. Biopsy results in the mismatching pairs when either

<table>
<thead>
<tr>
<th>MRI BI-RADS score</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1+2</td>
<td>3</td>
</tr>
</tbody>
</table>

**Table 1. Distribution of the BI-RADS results using the two tested modalities: ABVS and MRI**

<table>
<thead>
<tr>
<th>ABVS BI-RADS score</th>
<th>MRI BI-RADS score</th>
<th>Order of examination: 1: US 1st, MRI 2nd; 2: MRI 1st, US 2nd</th>
<th>Time interval between exams (days)</th>
<th>Lesion size (cm)</th>
<th>Benign (0) or malignant (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>4</td>
<td>1</td>
<td>120</td>
<td>180</td>
<td>0, 1</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>1</td>
<td>167</td>
<td>3.5</td>
<td>0, 1</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>1</td>
<td>103</td>
<td>0.5</td>
<td>0, 1</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>2</td>
<td>156</td>
<td>1.3 x 0.3</td>
<td>0, 1</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>2</td>
<td>34</td>
<td>0.5 (US 1, MRI)</td>
<td>0, 1</td>
</tr>
</tbody>
</table>

*Non-mass enhancement
‡A different benign lesion was reported in each modality
ABVS = automated breast volumetric sonography, US = ultrasound, MRI = magnetic resonance imaging
contribute to the lack of agreement. Only one 0.8 cm lesion was proved to be cancer, an invasive ductal carcinoma, detected only by MRI and not by ABVS performed 6 months prior to the MRI. This lesion was seen on second-look hand-held ultrasound and consequently underwent biopsy using ultrasound guidance, raising the possibility that if ABVS was performed simultaneously with MRI the lesion might have also been detected by ABVS.

These preliminary results that are based on a small group of healthy high risk patients show slight agreement between ABVS and breast MRI. However, most of the biopsies yielded benign results, suggesting that false-positive findings can occur with both modalities. The one cancer that was detected by MRI 6 months after ABVS, and which was subsequently found (and very obviously) at second-look ultrasound, would have been seen on ABVS also had it been performed at the same time as the MRI. Therefore, we may speculate that ABVS can down-grade high BI-RADS MRI lesions.

LIMITATIONS

There are several notable limitations to this study:

- This was a small group of patients with a limited spectrum of germline mutations all evaluated in a single medical center
- ABVS is a new technology, and the ABVS cases in this study were reported by several different radiologists with varied experience in ABVS reporting, so interobserver differences may have affected accuracy
- In most cases ABVS and MRI were not performed on the same day, with an interval of up to 181 days apart, allowing for “interval tumor,” a tumor detected in the period between annual breast imaging examinations, to become detectable. The variable temporal gap between the two tests limited the ability to accurately compare between them
- The lifetime risk for developing breast cancer is substantially lower in healthy individuals than in patients with high-risk mutations, which may affect the overall concordance between imaging modalities

DISCUSSION

Previous studies report that MRI has higher sensitivity and specificity than mammography alone or in combination with hand-held ultrasound in BRCA mutation carriers [9,19]. Some previous reports have also shown ABVS to be a sensitive modality for breast cancer detection [13-15] in the general and dense breast population. To the best of our knowledge this is the first study to compare between ABVS and MRI in BRCA mutation carriers. Using MRI as the gold standard, ABVS showed only “slight agreement,” with MRI findings in BRCA1/2 mutation carriers using a validated comparison scheme.

Most biopsies in this study (11 of 12, average size 0.8 cm) were benign lesions. This high prevalence of benign biopsies was noted using both modalities, but each modality identified different benign lesions in different tested women, thus contributing to the lack of agreement. Only one 0.8 cm lesion was proved to be cancer, an invasive ductal carcinoma, detected only by MRI and not by ABVS performed 6 months prior to the MRI. This lesion was seen on second-look hand-held ultrasound and consequently underwent biopsy using ultrasound guidance, raising the possibility that if ABVS was performed simultaneously with MRI the lesion might have also been detected by ABVS.

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higher in BRCA gene mutation carriers than in the general population by a factor of up to sevenfold, yet even among cases at a substantially increased breast cancer risk, a large group of patients should be examined in order to evaluate and compare cancer detection rates between modalities. Subsequent larger studies in ethnically distinct populations with longer follow-up are needed to further evaluate ABVS ability for early detection of breast cancer.

In conclusion, the current study shows that in high risk BRCA mutation carriers ABVS and MRI have a high false-positive rate in detecting clinically relevant lesions. However, given the small number of participants and the limited number of imaging-related anomalies, more studies are clearly needed before any firm conclusion can be drawn.

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email: osnatx@gmail.com

References
1. Israel National Cancer Registry. 2011.
2. Antoniou A, Pharoah PD, Narod S, et al. Average risks of breast and ovarian cancer related anomalies, more studies are clearly needed before any number of participants and the limited number of imaging-in detecting clinically relevant lesions. However, given the small

Capsule
Prevention of tumor formation by latent gamma herpes virus infection
Recent reports suggested that chronic herpes virus infection, as a constituent of the so-called virome, may not only exert harmful effects but may also be beneficial to the host, for example mediating increased resistance to secondary infections or to tumors. To further challenge this concept, specifically regarding increased resistance to tumors, Raffegerst et al. infected chimeric HLA-DR-H2-E (DR4) mice, a mouse strain which spontaneously develops hematological tumors, with the rodent herpes virus murine gamma herpes virus 68 (MHV-68). Using this model, the authors observed that infection with wildtype MHV-68 completely prevented tumor formation. This happened, however, at the cost of hyposplenism. In contrast to wildtype infection, infection with a latency-deficient mutant of MHV-68 neither prevented tumor formation nor induced hyposplenism. The underlying mechanisms are not known but might be related to an infection-mediated priming of the immune response, resulting in the suppression of a tumor promoting endogenous retrovirus. Thus, under certain circumstances, chronic herpes virus infection may prevent the development of tumors.

“I am so clever that sometimes I don’t understand a single word of what I am saying”
Oscar Wilde (1854-1900), Irish playwright, novelist, essayist, and poet who became one of London’s most popular playwrights in the early 1890s. He is remembered for his epigrams, his novels, his plays, as well as the circumstances of his imprisonment and early death.