Role of ultrasound in predicting the aggressiveness of breast cancer

Poster No.: C-1640
Congress: ECR 2014
Type: Scientific Exhibit
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Keywords: Cancer, Perception image, Ultrasound, Breast
DOI: 10.1594/ecr2014/C-1640

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Aims and objectives

Breast ultrasound is the most important and reliable diagnostic method in adjunct to mammography in the diagnosis of breast disease [1,2] (Fig. 1).

In 2003 The American College of Radiology has been developed a lexicon of sonographic descriptors of breast masses to standardize terms for lesion characterization and reporting (Ultrasound Breast Imaging Reporting and Data System - BI-RADS) [3].

The sonographic BI-RADS lexicon includes sonographic descriptors for shape, orientation, margins, lesion boundary, echo pattern, posterior acoustic features, and surrounding tissue alterations. On the basis of these descriptors, each lesion was assigned to a final assessment category associated with a certain risk of malignancy.

On sonography, a hypoechoic oval, circumscribed, parallel breast mass with an abrupt interface is probably benign. The ACR BI-RADS-US classifies this type of mass as BI-RADS category 3 based on the assumption that there is less than 2% probability of malignancy. All lesions that do not express typical benign signs are classified as class 4 or 5 depending on the association of the various descriptors. Generally the presence of more highly predictive signs of malignancy allow to assign a lesion to class 5 (more than 95% probability of malignancy) while lesions with intermediate characteristics are assigned to class 4 (2-95% probability of malignancy) [3-5] (Fig. 2).

Innovative features for ultrasound modalities technologies are constantly being developed and recent advanced allow confident characterization of breast masses extracting information regarding tissue structures [6].

However only limited work has been done on establishing correlations between ultrasound imaging features and certain type of biologic behavior of breast cancer [7-12].

The purpose of the present study was to investigate the correlations between ultrasound findings and important prognostic factors in a breast cancer study population.
**Fig. 1:** The ultrasound characteristics of breast cancer have been studied for a long time, which has enabled us to differentiate benign from malignant tumors with some accuracy.

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Fig. 2: On sonography, a hypoechoic oval, circumscribed, parallel breast mass with an abrupt interface is probably benign (BI-RADS 3, less than 2% probability of malignancy). The presence of more highly predictive signs of malignancy allow to assign a lesion to class 5 (more than 95% probability of malignancy) while lesions with intermediate characteristics are assigned to class 4 (2-95% probability of malignancy).

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Methods and materials

We performed a retrospective analysis in 100 consecutive women with invasive breast cancer who underwent US guided core needle biopsy and subsequent surgery in the breast diagnostic centre of Brotzu Hospital (Cagliari, Italy).

Only the patients with definitive histological diagnosis obtained after surgical treatment were included.

DCIS cases were excluded. In patients with multiple breast masses, only the largest lesion was considered.

The ultrasound examination was performed with a Siemens Antares unit (Siemens Medical Solutions, Sweden) using a high-resolution (10- to 13-MHz) linear array transducer.

We analyzed the hard copy of ultrasound examination performed during the US-guided biopsy procedure in order to study morphological features of the lesion.

Two experienced breast radiologists (MC and EF who had 15 and 20 years of breast imaging experience) independently evaluated the US findings. These two investigators were blinded to the clinical history or pathologic results. If there were disagreement in the interpretation of the images, a final decision was reached using consensus evaluation.

Tumor characteristics were assessed using the ACR-BIRADS Ultrasound lexicon [3].

The characteristics considered were shape (round, oval, irregular), margin (circumscribed, indistinct, angular, microlobulated, spiculated), boundary (abrupt interface, echogenic halo), echo pattern (hypoechoic, complex, isoechoic, hyperechoic), posterior acoustic feature (no posterior acoustic feature, shadowing or enhancement or combined pattern).

For echo patter descriptor we have divided the hypoechoic lesions into two groups: markedly hypoechoic lesion and inhomogeneous/middle hypoechoic lesions as Stavros suggests [2].

Each lesion was examined by the same pathologist who assessed histology and tumor grading. For histological examination tissue were fixed in 10% buffered formalin and embedded in paraffin. Section were stained with haematoxilin-eosin stain and if necessary or (indicated) with ck 14, p63, calponin, a-sma and E-cadherin stain [13].

The grading was assessed by the Nottingham modification of the Bloom-Richardson grading system in which were evaluated three cancer’s features: the percentage of cancer composed of tubular structures, nuclear pleomorphism and mitotic count [14].
Estrogen and progesterone receptor status was identified using immunoistochemical stains. ER and PR were scored positive if more than 10% of tumor cells were immunoreactive by evaluation of 10 random microscopic fields comprising at least 1000 number of cells [15].

The HER2 status was tested by immustoistochemical stains (Hercept Test, Dako). HER2 status was graded 0, 1+, 2+, and 3+. 3+ was determined as positive [16].

Statistical analysis was made.
Results

Mean age of patients at diagnosis was 56.0 years (range: 36-85 years, Standard Deviation: 13.0 years).

Mean size of target lesion was 21.0 mm (range: 4-80 mm, SD: 14.0 mm).

78 patients had invasive ductal carcinoma, 16 patients had invasive lobular carcinoma, 2 patients had medullary carcinomas, 2 patient had mucinous carcinomas, and 2 patients had tubular carcinomas.

24 patients were G1, 46 patients were G2 and 30 were G3.

57/100 patients were node negatives and 43/100 were node positives.

In all cases ER/PR receptor status, HER2 status, and Ki67 was available.

9 patients had a triple negative breast cancer.

Hystopathological characteristics of breast cancers were analyzed and compared with ultrasound features.

Tumor characteristics stratified by tumor grading were presented in Table 1.

The presence of spiculated margin, echogenic halo and posterior shadowing is significantly associated (p<0.001) with low-grade tumor (G1 and G2) (Fig. 3,4). G1 tumors were highly associated with ER/PgR receptor expression and negative lymph node status.

The presence of microlobulated/angular margin, inhomogeneous/middle hypoechoic echo pattern, absence of echogenic halo and absence of posterior acoustic shadowing is highly associated with high-grade tumor (G3) (Fig. 5). G3 tumors are also associated with ER receptor negativity.

Based on the age we have divided the patients into two groups: patients aged < 50 years and patients aged ≥50 years. The only statistically significant difference concerned the hormone status, more often negative in the young group.

Based on the dimension we have divided the patients into two groups: patients with target lesion <2 cm and patients with target lesion ≥2 cm. Patients with breast lesions lower than 2 cm often have low grade tumor and negative lymph node status.

In our series we had 9 cases of triple-negative tumors. All these cases showed high tumor grade, non spiculated margins, inhomogenous echo pattern and abrupt interface. Most of the cases showed posterior enhancement (Fig. 6).
Table 1: The presence of spiculated margin, echogenic halo and posterior shadowing is significantly associated with low-grade tumor (G1 and G2) \((p<0.001)\). G1 tumors were highly associated with ER/PgR receptor expression and negative lymph node status. The presence of microlobulated/angular margin, inhomogeneous/middle hypoechoic echo pattern, absence of echogenic halo and absence of posterior acoustic shadowing is highly associated with high-grade tumor (G3). G3 tumors are also associated with ER receptor negativity.

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Fig. 3: IDC G2 N0 (m), ER+, PgR+

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**Fig. 4:** IDC G1 N0, ER+, PgR+

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Fig. 5: IDC G3 N1, ER-, PgR-

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Fig. 6: Triple negative breast cancer

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Conclusion

Invasive carcinomas of the breast are different both in term of biological behavior and radiologic appearance [17-23].

Our results showed that the tumor grade on invasive cancers influenced the ultrasound findings. Low tumor grade (G1 and G2) was associated to spiculated margin, posterior acoustic shadowing and hyperechoic halo (Fig. 9). High tumor grade correlates to inhomogeneous/middle hypoechoic echo pattern, abrupt interface and absence of posterior acoustic shadowing (Fig. 10).

Probably these differentiations were related to the stromal reaction and to the cellular microstructure.

Traditionally, a typical malignant breast mass (BI-RADS 5) was expected to exhibit spiculated margins, echogenic halo and posterior acoustic shadowing. However some studies have shown that masses with circumscribed margins and posterior enhancement (BI-RADS 4) are more likely to represent higher grade tumors [7-12] Our results are consistent with these findings.

A limitation of our study is that the results are based on a retrospective analysis. To avoid bias, however, we included all consecutive patients with histologically proven malignant breast tumors. All images were also reviewed by two investigator in consensus blinded to the clinical and pathological data.

Breast cancer aggressiveness appears to correlate with some echographic features. Therefore, further investigations are needed to understood the biological characteristics that may results in imaging differences.
Fig. 7: Ultrasound characteristics of low grade breast tumors

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**Fig. 8:** Ultrasound characteristics of high grade breast tumors

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