Positive impact of elastography in breast cancer diagnosis: an institutional experience

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Abstract Elastography (ES) is a technique that, when associated with traditional B mode ultrasound (US), allows the degree of elasticity of tissue to be evaluated according to a color scale system. The aims of the study were to compare the diagnostic characteristics of two widely used techniques adopted in breast cancer screening; US and color Doppler (CD), with those of the same two techniques plus ES, and assessment of the same diagnostic characteristics when the three methods were applied to lesions < or >1 cm. Methods used included subjecting 212 women to investigations aimed at the early diagnosis of breast cancer outside the screening model, whereby 395 lesions were detected by US, ES, and CD, with a definitive diagnosis proved by histological exam. The diagnostic performance of US, ES, CD, and their combinations was calculated. The results showed that comparing the diagnostic characteristics of the three methods with reference to the definitive histological results for malignant breast lesions, the best diagnostic accuracy was obtained when US, ES, and CD were combined (0.837). For lesions <1 cm, diagnostic

accuracy was 0.782, and for those >1 cm, it was 0.886. In the lesions <1 cm, which were more difficult to study, a positive ES score (>4) appeared to be sufficient to deepen the diagnosis, even though 35 % of the ES or US positive lesions were not malignant. By contrast, in lesions >1 cm, the probability of having a malignant lesion when all three tests were positive was very high (97 %). It was concluded that early diagnosis is a key factor in breast cancer, so an economically sustainable, non-invasive pathway is the target of diagnostic breast imaging.

Keywords Elastography · Breast cancer · Screening · ROC analysis · Diagnostic accuracy

Riassunto L'elastosonografia (ES) è una metodica che associata all'ecografia consente di valutare l'elasticità e rigidità dei tessuti utilizzando una scala cromatica. Obiettivi di questo studio sono: confrontare le caratteristiche diagnostiche dell'ecografia (US) e del doppler (CD), due metodiche utilizzate per la diagnosi di tumore al seno, con quelle dell'ES, da sola o in combinazione con le precedenti; valutare le stesse caratteristiche in lesioni < o >1cm. Metodi: 212 donne sono state sottoposte a valutazione per diagnosi precoce di tumore al seno, al di fuori di un programma di screening. 395 lesioni sono state studiate con US, ES, e CD e la diagnosi definitiva è risultata dall'esame istologico. E' stata misurata la performance diagnostica delle 3 metodiche e delle loro combinazioni. Risultati: Dalla comparazione delle diverse metodiche emerge che la più elevata accuratezza diagnostica, per individuare lesioni maligne della mammella, si ottiene utilizzando le 3 metodiche congiuntamente (0.837). Per lesioni <1cm l'accuratezza diagnostica è 0.782, e per quelle >1cm 0.886. Nelle lesioni <1cm, le più complesse da valutare, un punteggio ES>4 sembra essere sufficiente per approfondire l'iter

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diagnostico, sebbene il 35% delle lesioni positive all'ES o all'US siano di tipo benigno. Diversamente, nelle lesioni >1cm la probabilità di avere una lesione maligna quando tutte e tre le metodiche sono positive è risultata molto alta (97%). Conclusioni. La diagnosi precoce rappresenta un fattore chiave nel carcinoma mammario; pertanto, un percorso economicamente sostenibile, e non invasivo è il target dell'imaging diagnostico per la mammella.

Introduction

Breast cancer diagnosis is based on the interpretation of breast lesions as being benign or malignant. Fine needle aspiration cytology (FNAC) and core needle biopsy (CB) are two methods for characterizing breast lesions [1–4]. The use of a non-invasive method, such as the conventional B-mode ultrasound (US), allows nodules to be detected. More recently, elastography ultrasound (ES), a new technique based on tissue elasticity, which is a biological parameter of tissues, has been introduced to characterize a breast lesion more accurately [5–10].

To assess breast lesions by ES, different elasticity systems have been proposed [11, 12]. Giuseppetti et al. [13] proposed the Ueno score, with a sensitivity of 79 % and specificity of 89 %. In another multicenter study, where lesions were classified according to Barr et al. [14–16] the sensitivity range was 96.7–100 % and the specificity was 66.7–95.4 %.

Therefore, ES has shown interesting results in the study of axillary lymph nodes [17] and in the study of the stiffness of the tissue surrounding breast lesions, using the fat-to-lesion strain ratio to describe the elastic properties of the breast lesions [18].

The main aim of the study was to compare the diagnostic characteristics of US alone and in combination with color Doppler (CD) with those of the same two techniques, plus ES assessment. All of the proposed techniques were validated with respect to the definitive diagnosis as proved by histological exam. The relationship between the ultrasound characteristics and the size of the lesions (< or >1 cm) was also evaluated.

In this study, the role of mammography, which represents the main exam in breast cancer screening, was not evaluated.

Materials and methods

Three hundred and ninety-five suspicious lesions in 220 women (median age 47 years; range 22–85 years) were examined by US, CD and ES for early diagnosis of breast

cancer outside the screening model. All consecutive patients were visited in a breast unit dedicated to women with suspect lesions, from February 2012 to September 2014, and written informed consent was obtained from each patient. Imaging was performed with a commercially available scanner (ESAOTE MyLab twice, high resolution) equipped with a high-frequency linear probe (LA523 and LA533).

US images were classified according to the Breast Imaging Reporting and Data System criteria (BI-RADS; American College of Radiology, 2003); scores of 1–2 were classified as benign, 3 as indeterminate and scores of 4–5 were classified as malignant. Each lesion was assigned an elasticity score according to the five-point scoring system proposed by Giuseppetti et al. [13]: scores of 1–3 were classified as benign, and scores of 4 or 5 were classified as malignant. CD results were classified as positive (probably malignant) or negative.

All exams were performed during the same session by one operator (AB) with at least 35 years' experience in breast imaging. The final diagnosis was determined by histopathological examination of the surgical or biopsy specimen (Figs. 1–3).

These results were used as the reference standard in assessing the technique outcome.

Statistical measures of test performance

Receiver operator characteristic (ROC) analysis was performed. The areas under the ROC curves (AUC) were calculated to compare the diagnostic performance of the BI-RADS and the elasticity score.

To assess how accurate the techniques were at providing the correct result, sensitivity and specificity were calculated. To estimate the probability of disease in an individual patient, a positive predictive value (PPV) was calculated as well as NPV to estimate the probability of non-disease. Likelihood ratios (LRs) were also calculated. A LR of greater than 1 (LR+) indicates that the test result is associated with the disease. An LR of less than 1 (LR–) indicates that the result is associated with absence of the disease.

The estimates of diagnostic accuracy (DA) were calculated as:

$$DA = (\text{true positive} + \text{true negative}) / \text{total}$$

The diagnostic odds ratio (DOR), a comprehensive evaluation indicator which combines data from sensitivity, specificity, PPV and NPV into a single number, was calculated as:

$$DOR = (\text{true positive/false negative}) / (\text{false positive/true negative}).$$

Fig. 1 Fibroadenoma: oval shape, regular margins, homogeneous pattern, E3 elastosonography, FNAC C2, core biopsy B2

The value of the DOR ranges from 0 to infinity, with higher values implying better discriminative test performance.

Parallel testing was used, with two or more index tests so as to have two or more chances to identify each case (i.e., if any of the tests are positive, the result is considered positive).

To determine if values for sensitivity, specificity, and predictive values vary with the dimension of the lesion, data in the study were stratified into two groups: lesions less than or equal to 1 cm ($N = 194$; 49.11 %), and lesions more than 1 cm ($N = 201$; 50.89 %).

A total of 395 lesions in 212 patients were included in the analysis. Of those, 389 lesions were included to assess US, and 382 were used to assess CD, due to incomplete values.

For the purpose of analysis, a BI-RADS score equal to 3 was classified as benign, since a finding placed in this category has a low rate of malignancy [19].

All statistical analyses were performed using STATA statistical software 11.0.

Results

Pathological analysis showed that 197 lesions were malignant, and 198 lesions were benign. The mean diameter of malignant lesions was 16.37 mm (standard deviation SD = 11.69; range 3–100 mm), and that of benign lesions was 14.25 mm (SD = 9.37; range 0.3–80 mm; p value = 0.048).

The distributions of elasticity score, BI-RADS category, and CD result, separately in benign and malignant lesions are presented in Table 1. The AUC of BI-RADS was 0.848 (95 % CI 0.810–0.886), and that of the elasticity score was 0.775 (95 % CI 0.733–0.817).

The diagnostic performance, measured by sensitivity, specificity, PPV and NPV and LR $\pm$ of US, ES, CD, and their combinations, is reported in Table 2 and compared with definitive histological results. If a malignant lesion is considered, whether any of the tests is positive, then sensitivity is 88 % and NPV 84 %, but specificity falls to 64 % and PPV to 71 %. The DA and DOR are 0.759 and 12.9, and 0.620 and 17.6, respectively.

Fig. 2 IDC: irregular margins, hypoechoic pattern, E4 elastosonography, FNAC C5, core biopsy B5

In Table 3, values for sensitivity, specificity, predictive values, LR+ and LR– are presented separately, according to the size of the lesions. In the group of lesions less than or equal to 1 cm, there were 194 cases; histological exams proved positive in 87 cases (44.16 %) and negative in 107 (54.04 %). In the group of lesions greater than 1 cm, there were 201 cases and the histological exam was found to be positive in 110 (54.84 %), and negative in 91 (45.96 %) (p value = 0.05). No differences emerged in ES sensitivities and positive predictive values combined with US and/or CD values for different lesion sizes when the method of parallel testing (US or ES positive versus either negative; US or ES or CD positive versus all three methods as negative) was chosen. When the results of the three methods were combined, percentage FN was lower than 8 and 4 %, LR+ was 2.16 and 2.71, while LR– was 0.29 and 0.12, respectively, for lesion sizes less than or equal to 1 cm or more than 1 cm. In lesions >1 cm, DA was 0.807 (lesion size <1 cm, DA = 709), and DOR displayed a better discriminative test performance (DOR = 24.07) than in small lesions (DOR = 7.47).

Discussion

Elastography is an established technique that can differentiate benign from malignant lesions, and allows suspected/malignant lesions to be detected at an early stage. The aim of our study was to investigate the relation between elastography alone, or combined with other tests such as US and CD, used to achieve the correct diagnosis of nature, and the definitive pathological results as benign or malignant lesions. In our experience, the best result was obtained when US, ES, and CD were combined, choosing the “or” formula. As expected, using more independent tests in parallel, the sensitivity increased, and the specificity decreased. When the three combined techniques were used, the FN cases decreased ($N = 15$; 8 %). Parallel testing is mostly used when missing a case of disease, which is a serious risk.

Recurrence rates and mortality rates can be reduced by early breast cancer diagnosis; therefore, an economically sustainable, non-invasive pathway is the target of diagnostic breast imaging. However, it is important to

Fig. 3 ILC: irregular margins, hypoechoic pattern, E4 elastosonography, FNAC C4, Core Biopsy B5

Table 1 Distribution of elasticity scores ($N = 395$), BI-RADS categories ($N = 389$), and CD results ($N = 388$) in benign and malignant breast lesions

	Benign lesions		Malignant lesions		<i>P</i> value
	<i>N</i> ^a	%	<i>N</i> ^a	%	
Elasticity score					
1	8	4.04	3	1.52	<0.001
2	120	60.61	34	17.26	
3	9	4.55	0	0.00	
4	58	29.29	116	58.88	
5	3	1.52	44	22.34	
BI-RADS categories					
1	1	0.51	0	0.00	<0.001
2	97	49.49	18	9.33	
3	78	39.80	34	17.62	
4	11	5.61	47	24.35	
5	9	4.59	94	48.70	
CD					
Negative	179	92.75	137	70.26	<0.001
Positive	14	7.25	58	29.74	

^a Total can vary due to missing values

remember that US is an operator-dependent technique, and so the operator's experience is essential for maximizing results.

In agreement with the literature, our study has shown that elastography is a test characterized by high sensitivity (81 %; US = 73 %; CD = 30 %, whereby the data are derived from data in Table 1).

In the lesions <1 cm, which are more difficult to study, a positive ES score (>4) appeared to be sufficient to deepen the diagnosis, even though 35 % of the ES- or US-positive lesions would not be malignant.

In the lesion size <1 cm, it is less likely that two or three tests would be positive (sensitivity of 59 and 5 %, respectively); these lesions are too small to have a specific vascular netting and a modified tissue elasticity.

When all three tests were positive, two lesions out of six were found to be non-malignant. By contrast, in lesions >1 cm, the probability of having a malignant lesion when all three tests were positive was very high (97 %). The combination of ES, US, and CD in detecting breast cancer should be considered for inclusion in the clinical routine since it will detect more cancer cases than by US alone. The target in breast disease diagnosis is the

Table 2 Sensitivity, specificity, predictive values (positive, PPV; negative, NPV), likelihood ratios (positive, LR+ and negative, LR−) of ultrasound (US), elastography (ES), and color doppler (CD) techniques, combined or not, compared with definitive histological result

Method (test)	N	TP	FP	FN	TN	Sensitivity	Specificity	PPV	NPV	LR+	LR−
US	389	141	20	52	176	73	89	88	77	6.52	0.30
USIES ^a	389	165	61	28	135	86	69	73	83	2.75	0.21
USIESICD ^b	382	168	69	23	122	88	64	71	84	2.43	0.19
US and ES ^c	389	132	19	65	179	67	90	87	73	6.98	0.36
US and ES and CD ^d	382	42	3	155	195	21	98	93	56	14.0	0.80

LR+ = sensitivity/(100−specificity); LR− = (100−sensitivity)/specificity

Cutoff US, BI-RADS score ≥ 4 ; ES elasticity score ≥ 4 ; CD positive

TP true positive cases, FP false positive cases, FN false negative cases, FP true negative cases, PPV positive predictive value, NPV negative predictive value

^a US or ES positive (≥ 4) versus either negative (≤ 3)

^b US or ES or CD positive versus all three methods as negative

^c US and ES positive (≥ 4) versus US and/or ES negative (≤ 3)

^d US and ES and CD positive versus US and/or ES and/or CD negative

Table 3 Sensitivity, specificity, predictive values (PPV, NPV), and positive and negative likelihood ratio (LR+ and LR−) of ultrasound (US), elastography (ES), and color doppler (CD) technique, by combined result or not (compared with definitive histological result), separately by lesion size (≤ 1 cm, $N = 194$; >1 cm, $N = 201$)

	N	TP	FP	FN	TN	Sensitivity	Specificity	PPV	NPV	LR+	LR−
Lesion size ≤ 1 cm											
US	193	55	13	31	94	64	88	81	75		
USIES ^a	193	70	38	16	69	81	65	65	81		
USIESICD ^b	189	70	40	15	64	82	62	64	81	2.16	0.29
US and ES ^c	194	51	12	36	95	59	89	81	73		
US and ES and CD ^d	194	4	2	83	105	5	98	67	56		
Lesion size >1 cm											
US	196	86	7	21	82	80	92	92	80		
USIES ^a	196	95	23	12	66	89	74	81	85		
USIESICD ^b	192	98	29	8	57	92	66	77	88	2.71	0.12
US and ES ^c	201	81	7	29	84	74	92	92	74		
US and ES and CD ^d	201	38	1	72	90	35	99	97	56		

LR+ = sensitivity/(100−specificity); LR− = (100−sensitivity)/specificity

TP true positive cases, FP false positive cases, FN false negative cases, FP true negative cases, PPV positive predictive value, NPV negative predictive value

^a US or ES positive (≥ 4) versus either negative (≤ 3)

^b US or ES or CD positive versus all three methods as negative

^c US and ES positive (≥ 4) versus US and/or ES negative (≤ 3)

^d US and ES and CD positive versus US and/or ES and/or CD negative

early detection of cancer, through a screening model that depends on the age of the patients; therefore, an additional technique associated with ultrasound that can provide more information on the lesion, especially of small size, must be considered as a valid support to routine investigations.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest for this study.

Ethical statement The study was conducted in accordance with the Declaration of Helsinki.

Informed consent A written informed consent was obtained from all participants.

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