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Original Research Article

Ultrasound and Strain Elastography in Evaluation of Suspicious Breast Masses

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Abstract

Breast cancer is the most prevalent type of cancer in Iraq, and the commonest among females worldwide. Ultrasound is an important widely used noninvasive modality in line with mammography and other methods for the detection and characterization of breast masses in routine clinical practice. Elastography is a recent promising method used as an adjuvant to ultrasound that improves performance, increase the specificity of interpretation in differentiating benign from malignant breast masses based on imaging tissue stiffness. We aim to evaluate the accuracy of ultrasound and elastography in diagnosis of suspicious malignant breast masses. A cross sectional study was conducted in Babylon and Kerbala January 15 to August 20, 2017. A consecutive sample of women with breast mass suggestive of malignancy were evaluated with ultrasonography and strain elastography prior to histopathological study. The five point Tsukuba elasticity score were used for differentiation of breast masses. Ethical approval was taken from the Research Ethical Committee in Babylon University- College of Medicine, and verbal consent was taken from each patient prior to enrolment. A total sample of (88) females with breast mass aged 16-69 years with a mean ± SD of 41.33 ± 12.57 years. Ultrasound diagnosed correctly (58) out of the (62) malignant breast masses with a sensitivity and specificity of 93.5% and 100% respectively. By using strain elastography the sensitivity increased to 98.4% with same specificity of 100% were only one malignant mass was missed. By using the ROC analysis, the Area Under the Curve and 95% confidence interval was 0.968 (0.931-1) and 0.992 (0.974-1) for ultrasound and elastography respectively. So when elastography is used with ultrasound, it increases its sensitivity, specificity and accuracy. Efforts needed to adapt and apply its use properly in Iraq through training programs for radiologists.

Key Words: Breast mass, Breast cancer, Ultrasound, Elastography, Strain elastography.

فحص السونار و السترين إلاستوجرافي في تقييم حالات اورام الثدي ذات الشبهة الخبيثة

الخلاصة

سرطان الثدي هو اكثر انواع السرطان انتشارا في العراق، والأكثر شيوعا بين الإناث في جميع أنحاء العالم. سونار الثدي هو وسيلة مهمة وذات استخدام واسع ومضمنة مع اشعة الثدي (الماموجرافي) وغيرها من تقنيات الكشف المبكر وتشخيص اورام الثدي في المؤسسات الصحية. الاستوغرافي هي طريقة حديثة وواعدة تستخدم كفحص مساعد للموجات فوق الصوتية والتي تساهم في تحسن الأداء، وزيادة دقة التشخيص في التفريق بين الاورام الحميدة والخبيثة من الاورام من خلال الاعتماد على تمييز صلابة الأنسجة. هذه الدراسة تهدف الى تقييم دقة الموجات فوق الصوتية والإلاستوغرافيا في تشخيص الاورام الخبيثة في الثدي بالمقارنة مع التحليل النسيجي للورم.

دراسة مقطعية مستعرضة أجريت في بابل وكربلاء للفترة من ١٥ كانون الثاني إلى ٢٠ أغسطس من عام ٢٠١٧. تم اخذ عينة متتالية من النساء المراجعات بعمر ١٥ سنة وما فوق من المصابات بأورام الثدي ذات شبهة خبيثة بالسونار ثم بإلاستوغرافيا قبل الفحص النسيجي واستخدمت مقياس تسوكوبا للمرونة ذي الخمس نقاط لتمييز اورام الثدي. تم استحصال الموافقة الاخلاقية لاجراء البحث من لجنة البحوث الأخلاقية في جامعة بابل- كلية الطب، وتم أخذ الموافقة الشفهية من كل مريض قبل الاشتراك بالبحث. العينة كانت (٨٨) امرأة مصابة بورم في الثدي، وتراوحت أعمارهم بين ١٦-٦٩ سنة بالمعدل ± الانحراف المعياري من ٤١,٣٣ ± ١٢,٥٧ سنة. فحص السونار نجح بتشخيص (٥٨) من (٦٢) اصل ورم خبيث في الثدي مع حساسية وخصوصية ٩٣,٥٪ و ١٠٠٪ على التوالي. ومن خلال استخدام فحص إلاستوغرافي زادت حساسية فحص الامواج الصوتية إلى ٩٨,٤٪ مع نفس درجة الخصوصية ١٠٠٪. باستخدام تحليل روك، كانت المنطقة تحت المنحنى و٩٥٪فسحة الثقة تساوي٠,٩٦٨ (٠،٩٣١ -١) و ٠،٩٩٢ (٠،٩٧٤ -١) للموجات فوق الصوتية والإلاستوغرافي على التوالي. من هذا نستنتج بان استخدام إلاستوغرافي كتقنية مساعدة مع فحص السونار يزيد من حساسية وخصوصية ودقة فحص السونار، وهنالك حاجة لحث الجهود وتركيزها لتعزيز تطبيقه بشكل صحيح في العراق من خلال برامج تدريبية لأطباء الأشعة.

الكلمات المفتاحية: أورام الثدي، سرطان الثدي، فحص السونار ، فحص إلاستوجرافي، سترين إلاستوجرافي.

Introduction

Breast cancer (BC) is the most common type of cancer among females worldwide, impacting over 1.5 million women worldwide each year. With around 15% of cancer related deaths among women, BC, is the leading cause for cancer-related deaths among women [1- 3].

In Iraq BC is the most prevalent cancer and far from any other cancer representing nearly 19% of all cancer cases registered annually in both genders and more than 30% of female cancers [4 -6].

While the specific causes of breast cancer are unknown, early diagnosis of cancer generally increases the chances for successful treatment by focusing on detecting symptomatic patients as early as possible, and early diagnosis of breast cancer is the main stay in breast cancer prevention and control [7, 8]. However, up to 70% of BC deaths occur in low and middle income countries mostly due to less effective health system and screening programs.

Ultrasound (US) is an important widely used noninvasive adjunctive modality to mammography and other methods for the detection and characterization of breast lesions in routine clinical practice and is established as the first-line guidance modality for percutaneous biopsy [8-10]. Further, US has been advocated and shown to be potentially useful in the examination of women with dense breast or pregnant symptomatic patients [9, 11], However, US suffers from low specificity [12, 13].

Ultrasound elastography (USE) was firstly introduced by Ophir *et al* in 1991 and now considered as a valuable aid to US for visualizing the elasticity characteristics of a lesion. And it has been used to examine several organs, such as the liver, thyroid, prostate, and pancreas as well as breast [8, 14, 15, 16]. Elastography function based on the principle that malignant lesions tend to be harder than benign ones [16, 17,18,19], and studies have shown that the addition of elastography to grey scale US improves the performance and the specificity of US interpretation in differentiating benign from malignant breast masses based on imaging tissue stiffness [16, 20, 21, 22]. Elastography has shown to be highly reproducible, that it could be a promising as an additional diagnostic tool especially in women with symptomatic masses, young women with dense breasts, and those who are recalled because of mass lesions at mammographic screening [23, 24]. Further it shows effectiveness in reducing unnecessary biopsies were studies shows that 70-80% of biopsies shows benign lesions [25, 26, 27]. Thitaikuma *et al* reported an estimation of nearly 1 million unnecessary benign biopsies performed in United States, which leads to a financial cost to the healthcare system of nearly $2 billion annually [28].

There are 2 types of USE, strain elastography (SE) and shear wave elastography (SWE). They differed in the techniques and how they are used in clinical practice. Both SE and SWE have been shown to have high sensitivity and specificity for characterization of breast masses as benign or malignant [15, 18, 29]. Strain elastography (SE) with the color map requires manual compression to be applied to the tissue or a small natural motion to estimate the stiffness of targeted area, thus it is user dependent and sometimes the results are inconsistent. In addition, lack of quantification of the tissue stiffness also limits its application in clinical practice [15, 17, 25, 30].

While, SWE is a more advanced technique developed to overcome limitations of SE. The SWE measures shear wave velocity or shear wave modules to quantify tissue stiffness by generating acoustic radiation force impulse (ARFI). So, it is more user independent. Further, SWE can provide the elasticity ratio of the breast lesion to the reference fat tissue, similar to the strain ratio obtained from strain elastography technique [15, 17, 30].

This study aims to measure the effectiveness of US and SE in differentiating between malignant and benign breast masses in comparison with histopathology of lesion.

Materials and Methods:

A cross sectional study conducted at Babylon and Kerbala cities \Iraq for the period between January 15, and August 20, 2017, A consecutive sample of women diagnosed with breast mass highly suggestive of malignancy as a provisional diagnosis were eligible for study. They were evaluated with ultrasonography and elastography prior to histopathological study. And results of these procedures were compared. Sociodemographic, personal, and medical history were taken from each women.

A Conventional US examination was done with high frequency linear probe using General Electric (GE) Voluson S8 machine. Breast masses were assessed for side affected, site in breast, size by measuring the biggest diameter, the surface, the surrounding, calcification and involvement of lymph nodes. Patients with multiple masses, the largest one was taken. Then using same probe, a strain elastography survey was done after the conventional US. Both US and SE were done by one investigator with (7) years of experience in US and (6) months with SE following a special training on it.

The five point Tsukuba elasticity score were used for differentiation of breast masses: Score 1 for lesions with similar elasticity to the peripheral breast tissue, and similar strain over the lesion. Score 2 for lesions with mosaic elasticity. Score 3 to express lesions with elastic green surrounding and stiff center. Score 4 was used for nodules that were entirely stiff, excepting the echoic halo. Score 5 was reserved for cases which had no strain over the whole lesion and the nearby tissue [31- 34].

Patient were followed to get the histopathological results, those who fail to get the histopathological results were excluded from study.

Ethical approval was taken from the Research Ethical Committee in Babylon University-College of Medicine. Further, a verbal consent was taken from each patient prior to enrolment in study, after short explanation of the study objectives.

Collected data were entered and analyzed, using statistical package for social science program (SPSS software version 21).

Qualitative data were expressed as numbers (N) and percentages (%), while quantitative variables were expressed as Mean±Standard deviation (SD). Student's t-test were used to test the difference between the means of age and tumor size. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were estimated for US and SE in comparison with histopathologic results.

Then the Receiver operating characteristic (ROC) Curve were measured, to analyzed the accuracy of this assay. The curve, area under the curve (AUC) 95% confidence interval and significance were measured. A P-value of less than 0.05 was considered to be statistically significant.

Results

Out of (99) female evaluated with US and SE, (11) women could not get there histopathologic results, so were excluded from the study. So the sample achieved was (88) females with breast masses. Their age ranges from 16-69 years with a mean ± SD of 41.33±12.57 years. Further, 78.4% were married, (70.5) were housewives, 83% from urban areas, (39.8) had family history of breast cancer, only (2) (2.3%) had previous history of breast cancer and 47.7% had used oral contraceptive pills previously as shown in table-1.

Table (1): Distribution of demographic characteristics of the study sample.

Variable		Frequency N = 88	Percent %
Marital Status	Single	17	19.3
	Married	69	78.4
	Divorced\Widow	2	2.3
Occupation	Housewife	62	70.5
	Employee	20	22.7
	Others	6	6.8
Residence	Urban	73	83.0
	Rural	15	17.0
Family history	Negative	53	60.2
	Positive	35	39.8
Past History	Negative	86	97.7
	Positive	2	2.3
OCP	No	46	52.3
	Yes	42	47.7

Of the 71ever married females their parity range from 0-7 children with a mean of 3.39 ± 1,79 child and the majority (67.6%) had (3) or more children as shown in figure-1.

Majority of masses 52.3% were in the right breast, 63.6% were in the upper quadrant of the breast, 52.3% had smooth surface, 62.5% shows abnormal surrounding tissue. Only 18.2% shows lymph node involvement and 11.4% shows calcification, as shown in table 2.

The biggest diameter of the mass were taken which ranged from 15-68 mm, with a mean of 24.02±8.33 mm. According to histopathological results 62 (70%) of masses were malignant and 26 (30%) were benign.

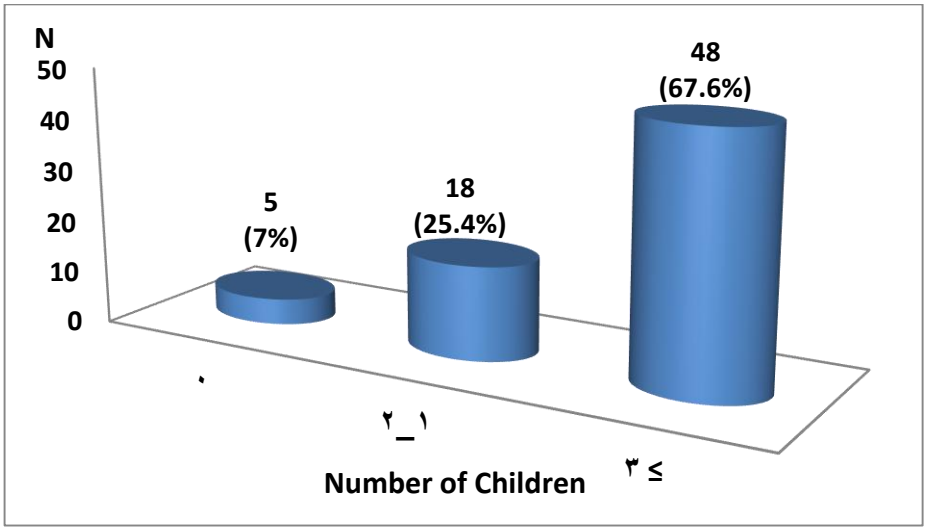

Figure (1): Distribution of married women according to parity.

Table (2): Distribution and ultrasonic characteristics of the breast masses

		Frequency	Percent
Side	Right	46	52.3
	Left	38	43.2
	Both	4	4.5
Site	Upper quadrant	56	63.6
	Elsewhere	32	36.4
Surface	Smooth	46	52.3
	Speculated	42	47.7
Surrounding	Normal	33	37.5
	Abnormal	55	62.5
LN	Negative	72	81.8
	Positive	16	18.2
Calcification	No	78	88.6
	Yes	10	11.4

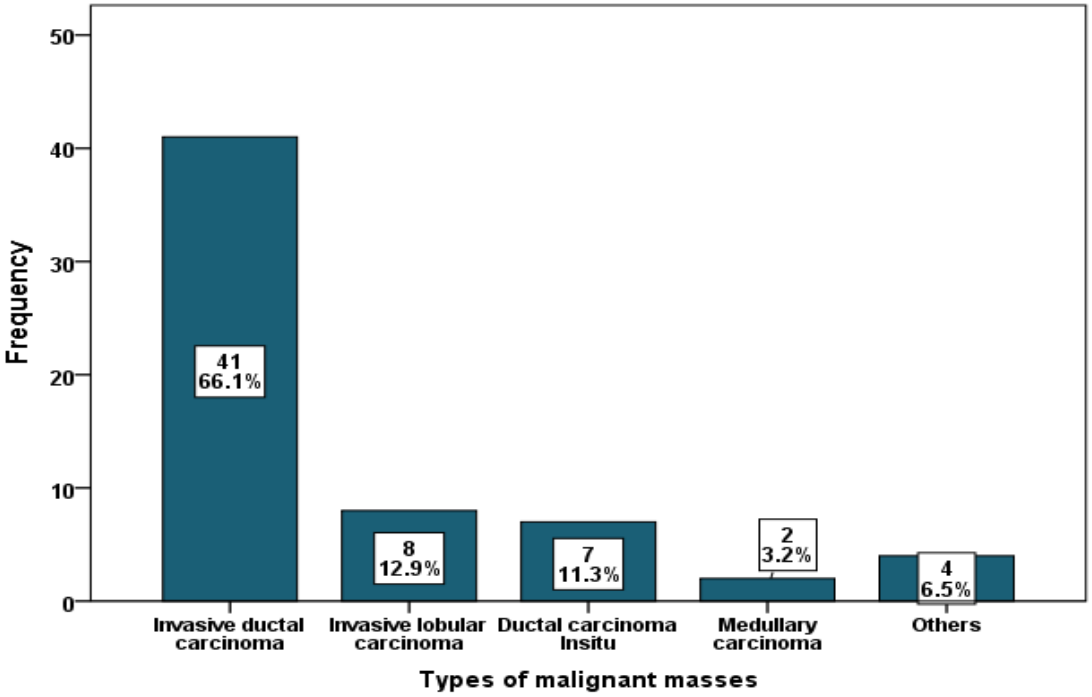

Figure (2): Histopathological types of malignant breast masses

All benign tumors were fibroadenomas. While the most prevalent type of cancer was invasive ductal carcinoma, which represents 66.1% of the malignant cases as shown in figure 3. The mean age of women with malignant lesion was 46.82 years that is much higher and significantly different from those with benign lesion. While the mean size of benign masses was slightly higher but it was not significantly different as shown in table 3.

Table (3): Comparison between women with benign and malignant masses in regards to age and mass size

		N	Mean	SD	P value
Age/ years	Benign	26	28.23	8.22	< 0.001
	malignant	62	46.82	9.69	
Size/ mm	Benign	26	26.38	13.35	0.085
	malignant	62	23.03	4.75	

All the benign masses were diagnosed correctly. However, of the (62) malignant (61 cases the B mode US had positively diagnosed (58) and (4) false negative, and the SE had correctly diagnose and only one false negative case as shown in figure 3.

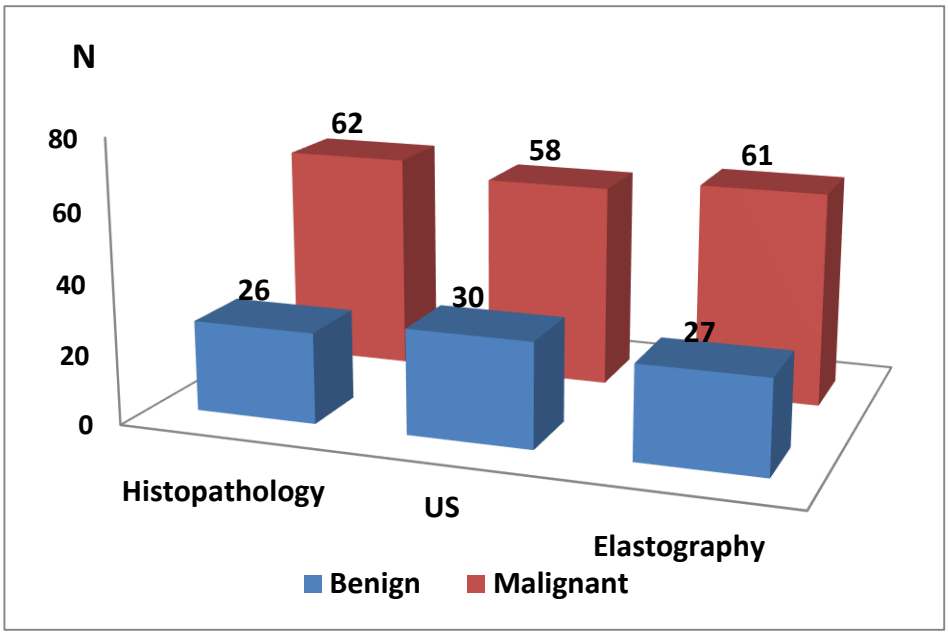

Figure (3): Comparison of histopathological results of masses with US and SE evaluation.

Discussion

Ultrasound elastography was recently entered into practice in Iraq and is of very limited use as well as experience with it. Up to our knowledge this is the first study in Iraq to estimate the role of strain elastography in differentiation between malignant and benign breast masses.

The mean age for women in our study was 41.33 years which is lower than the 47.25 years of Salih *et al* [35], as well as many other studies in different countries Fleury *et al*, (44) years, Cho *et al*, 44.3, Gheonea *et al*, 46.6, Xiao *et al* 47, Wojcinski *et al*, 48.0, Cho *et al*, 48.6, Halim *et al*, 49.5, Atabey *et al*, 50 [36, 29, 34, 10, 26, 37, 16, 25]

Further the mean age for those with malignant tumor was 46.82 and was significantly higher than those with benign mass, this age difference goes with studies of Li *et al*, 56.8 vs 39, Olgun *et al*, 56 vs 47.8, Cho *et al* 47.7 vs 44 and Lee *et al*, 51.7 vs 42.2 for malignant and benign cases respectively [15, 38, 29, 39]. This

agrees what is reported that breast cancer in Iraq and middle east region tend to affect women at younger ages [6, 40, 41].

The right side was mostly affected by 52.3% which similar to the 49% Alwan (2017b) while Li *et al* (2016) reported 53.3% on left side. Further Li *et al* (2016) reported 18.9% of calcifications present which is higher than our 11.4% [42, 15].

The mean of mass size which represents the biggest diameter was 24.02 mm which close to Mutala *et al* 22 mm, Elkharbotly and Farouk 21.9 mm [30, 43] and higher than Ikeda *et al* 19.2 mm, Wojcinski *et al* 14mm, Cho *et al* 11.9 mm [44, 26, 37]. However, the mass size for benign masses were bigger than that for malignant masses though it was not significant as shown in Table 3. and this goes with Elkharbotly and Farouk [43], but in contrast with several other studies who reported bigger sizes for malignant masses [16, 34, 37, 38, 39, 44, 45]. Further the mean mass size for the malignant masses in our study was 23.03 mm which is close to Elkharbotly and Farouk 22.9 mm [43] and bigger than the malignant breast masses reported by others [44, 39, 37, 16, 45, 38], except for Gheonea *et al* who reported a bigger size of 27.3 mm for malignant cases [34]. This could be accidental or also could be related to late diagnosis and diagnosis of advanced cases in our community and region [6, 40, 41, 46].

The percentage of malignant cases was higher than benign in our study, and this is expected as we already selected suspicious masses, and masses that obviously benign through history or clinical examination were excluded from study. However, Invasive ductal carcinoma was the most prevalent type representing 66.1% and this agrees with other studies as it represents the most common type of breast cancer in Iraq as well as other countries with various prevalence [6, 16, 25, 37, 38, 39, 42]. The second most prevalent type was invasive ductal carcinoma followed by carcinoma in situ and this goes with other studies [6, 25, 38, 42]. While in other studies ductal carcinoma in situ appeared as the more prevalent type [3, 10, 16, 29, 34, 39] and this could be related to genetic, community and geographical factors, or it could be related to better screening and early detection programs in that countries.

In this study, the B mode ultrasound examination succeed in diagnose (58) out of (62) malignant masses and failed with only (4) cases while it correctly diagnose all the benign lesions producing high readings for sensitivity, specificity, PPV and PNV. The sensitivity was 93.5%, that is higher than Cho *et al*, Cho *et al*, Elkharbotly and Farouk, results that was 93.1%, 84.9%, 72.2%, respectively [37, 29, 43]. But lower than, Stachs *et al*, Marcomini *et al*, Ikeda *et al* who reported 97.4%, 97.0% and 93.9 respectively [47, 48, 44].

The specificity was very high (100%), and higher what other researchers reported Ikeda *et al*, Elkharbotly and Farouk, Halim *et al*, Marcomini *et al*, Stachs *et al*, Lee *et al*, Cho *et al* 88.3%, 76.2%, 67.7%, 42.6%, 42.3%, 30% and 25.3%. Also the PPV of 100% was higher than other studies [44, 43, 16, 48, 47, 39, 37].

The NPV was 86.7% that was close to Elkharbotly and Farouk 86.5% [43] but less than Lee *et al*, Halim *et al*, Zhi *et al*, Stachs *et al*, who reported 100%, 98.4%, 97.3%, 93.9% [39, 16, 3, 47].

This wide variation in the readings of the sensitivity, specificity, PPV and NPV of B mode US is not unexpected, as it could be related to difference in US machines used, probes, frequencies and persons use it and their experience. Also could be due to different patients, types of tumors, stages of disease, size of masses and grading approaches as well as difference in research methodologies and patient selection.

By adding the US elastography to the B mode US (3) out the (4) false negatively diagnosed were discovered. As a result the sensitivity had increased from 93.5% to 98.4% as well as the NPD that increased from 86.7% to 96.3% while we already have a specificity and PPV of 100%. This sensitivity is higher than what Cho *et al*,

Stachs *et al*, Gheonea *et al*, Elkharbotly and Farouk, Atabey *et al*, Lee *et al*, Ikeda *et al*, Wojcinski *et al* reported of 92.5%, 90.7%, 85.3%, 83.3%, 83%, 80.8%, 76.8% and 62.5% respectively [37, 47, 34, 43, 25, 39, 44, 26]. But lower than Marcomini *et al* who find 100% sensitivity [48]. As mentioned above this variation could be related to difference in instruments, difference in evaluator as well as different in lesions and patients. Further there is more variation in types of strain elastography and wide range reading evaluation and classification of results with more interpersonal variation adding to that the lower experience with the newly invented technique.

Further, Elkharbotly and Farouk and Marcomini *et al* find an increase in sensitivity by adding USE to US [43, 48] while others indicates decrease in sensitivity [44, 47, 39]. This could be related partially to that some investigators evaluated USE alone to compare with US results not as an adjuvant to it. However, most investigators reported increase in specificity by adding the USE to conventional US [37, 39, 43, 47, 48].

Measurements of the Receiver Operating Characteristics (ROC) curves and estimating the area under the curve (AUC) which was 0.968 for the US with the 95% Confidence Interval of 0.931-1.000. which is higher than 0.861, 0.835, 0.822, 0.745, 0.650 reported by Marcomini *et al*, Cho *et al*, Stachs *et al*, Elkharbotly and Farouk (2015), and Lee *et al* respectively [48, 29, 47, 43, 39] but lower than 0.951 reported by Ikeda *et al* [44].

For USE the AUC was 0.992 with a 95% Confidence Interval of 0.974-1.000 and this is higher than 0.908, 0.904, 0.879, 0.869, 0.859, 0.851 and 0.608 that was reported by Gheonea *et al*, Marcomini *et al*, Ikeda *et al*, Stachs *et al*, Elkharbotly and Farouk, Cho *et al* (2010), Lee *et al* respectively [34, 48, 44, 47, 43, 29, 39].

So, this indicate a high accuracy for conventional US in differentiation of breast masses that increased by adding the USE as reported by other researchers [29, 43, 47, 48].

Of the limitations that we are using qualitative type of elastography as the more recent quantitative such as SWE is much expensive and not available in public Iraqi hospitals. Where the qualitative is more prone to be influenced by personal technique and hand as well personal judgment and subjectivity in scoring the lesion depending on images. Also it's not a blinded study, so the researchers knows the history and other clinical manifestation that might affect the decision in diagnosis.

Conclusion

Breast US is a useful and effective noninvasive technique that is very helpful in diagnosis, screening and follow up of breast masses with high sensitivity, specificity and accuracy. Further. USE is helpful adjuvant that increases the sensitivity, specificity and accuracy of US in differentiation between benign and malignant breast masses. Invasive ductal carcinoma was the most common type of malignancy followed by invasive lobular carcinoma. And that Iraqi women are affected breast cancer at younger ages than women in other regions of the world. We recommend the need for USE to be adapted and used in clinical practice in Iraq, with the most recent quantitative elastography including breast cancer screening as well as other fields by implementing training courses for radiologist on elastography as well as other recent modalities.

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