Evaluation of Diagnostic Accuracy of Ultrasound Elastography in Stratifying Breast Lesions In Relation To Histopathological Examination.

Prof.Jishan.Ahmed[1], Dr.Sunil.M.Naik[2]

(Department of general surgery, Assam medical college and hospital, SSUHS, Assam, India)

Abstract

AIM: *To study the role of ultrasound elastography (USE) in differentiating benign and malignant breast masses with FNAC correlation. To analyze and compare the sensitivity, specificity, predictive value and accuracy of USE in diagnosing malignant breast lump.*

Material and Methods: *A total of 106 Patients who presented with breast lesion at the department of Surgery, Assam Medical College and Hospital (AMCH), India, from September, 2017 to march, 2019, were included. Thorough history and detailed clinical examination of all the patients were done. All the patients underwent USE using 12 MHz linear transducer at the department of Radio-diagnosis, AMCH and FNAC at the department of Pathology, AMCH and further subjected to excision biopsy/definitive surgery, the result of which were further compared with the HPE results to determine the sensitivity, specificity, predictive value and accuracy of USE and FNAC.*

Results: *Out of 106 patients, 74(70.48%) benign and 31(29.52%) malignant lesions were found on HPE. FNAC reported 76 benign, 25 malignant and 4 intermediate cases. USE reported 72 benign, 23 malignant and 10 intermediate cases and was unable to detect lump in 1 case, which was excluded from calculation. Sensitivity, specificity, positive and negative predictive values of USE and FNAC in diagnosing malignant breast lump were 88%, 98.57%, 95.65%, 95.79% and 89.28%, 100%, 100%, 96.05% respectively.*

Conclusion: *All interpretation criteria were able to differentiate benign and malignant lesions with statistical significance (p<0.0001). The study showed that sensitivity, specificity and predictive values of FNAC was more when compared to USE and the percentage of intermediate result were also higher with USE. While conventional USG remain the primary modality for investigating the breast masses, USE was found to have a greater sensitivity when compared to USG for diagnosing malignant breast lesions and low suspicion lesions(BI-RADS 3 and 4). Thus USE can complement conventional USG in increasing the diagnostic accuracy and and could be used as a good tool for the classification of breast masses prior to the decision to biopsy a lesion, thus potentially reducing the necessity of biopsy for indeterminate or questionable breast lesions*

Key words: *Carcinoma breast, USE-Ultrasound elastography, FNAC*

I. Introduction

Cancer of breast is the most common cancer affecting women worldwide and is the second most common cause of cancer death next to lung cancer [1]. In developing countries like INDIA, females are unaware of breast pathologies because of social taboo and are hesitant to reveal, hence it is detected usually in advanced stages. Delay in the detection causes malignancy to progress in advanced stage which comprises of inoperable masses, metastasis (bone, brain, and lung) and is a significant cause of morbidity and mortality worldwide[2]. Benign breast diseases need early detection and management because of its high prevalence and its cancerous potential (3-5%). Thus, early detection, diagnosis, and screening of breast lesions have a significant impact on patient management like treatment outcome and survival.

It usually presents as lump or nipple discharges [3]. "Lump" in breast, is therefore, a cause of great anxiety both to the patient and family members. The main motive behind the evaluation of such a newly detected palpable lump is basically to rule out malignancy. The final diagnosis is made by histopathological examination (HPE) of the excised tissue, routine excision of all breast lumps would not be rationale, because as much as 80% of lumps are benign [4]. Thus the need is the utilization of less invasive and cost effective method(s) of diagnosis without resorting to a more painful and invasive surgical biopsy. The modality should also be acceptable to the patient, accurate, easy to apply, reproducible and must not need too much preparations [3].

The most common screening test for breast masses is mammography and ultrasonography (USG), both of which are highly sensitive in detecting breast cancer. However, both methods have some limitations. Though

---

X-Ray mammography is the first line of technique with sensitivity between 69% and 90% and variable specificity in many countries [5], it is reported that this technique has false negative rate (misses lesion) around 10% to 25% in detecting breast cancers in dense breast [6]. In addition, mammogram limitation includes exposure to ionizing radiation. Mammography often yields false negative results in dense breasts [7].

Fine needle aspiration cytology (FNAC) is considered the gold standard method, cost effective and useful for mass lesions [8,9,10]. It has a sensitivity and specificity of > 90% and > 65%, respectively. The positive predictive value (PPV) was reported to be > 99% [11] depending on the skill of person performing the aspiration and expertise of the cytopathologist [12]. Sometimes the problematic cells are missed, resulting in a false negative result. Further, FNAC cannot reliably predict invasion of tumor [13].

Thus, breast Ultrasonography (USG) has evolved as an indispensible problem solving tool in patients with dense breasts, post-radiation breasts, and women less than 35 years of age, pregnant and lactating patients [14]. It is an important technique adjunct to mammography and clinical examination in assessing impalpable breast abnormalities and mammographically occult lesions [15, 16]. It differentiates cystic from solid lesions; benign and malignant breast neoplasm in women when mammography is less sensitive due to dense breasts. The sensitivity of detecting cancer is reported as 65% and 92% [17]. Ultrasound has a high sensitivity in detecting lesions but poor specificity.

To improve specificity, the American College of Radiology (ARC) introduced the Breast Imaging and Reporting Data System (BIRADS) which is used to categorize breast mass [18]. However BI-RADS generated a significant number of false positive results [19] resulting in an increase in biopsies performed with a cancer detection rate of 10-30% [20, 21] causing unnecessary discomfort, anxiety and increased cost to the patient [22]. Ultrasound is also unable to pick microcalcifications which is a strong and sometimes an early finding in cancer of the breast [23].

Ultrasound elastography (USE) was introduced to increase the accuracy of characterizing breast lesions. When a certain amount of force is applied in a tissue, elastic deformation occurs. USE is a technique that applies compression to detect stiffness variation within the scanned tissues. Cancerous lesions are stiffer than non cancerous ones. USE uses this principle to differentiate malignant breast lesions from benign lesion on compression. USE holds promise in improving the differentiation of benign from malignant breast lesions [24, 25].

Given the common occurrence of breast cancer and the importance of accurately diagnosing a clinically palpable breast lump, with non invasive techniques without routinely resorting to formal biopsy which is much invasive, the study is proposed to evaluate the accuracy of USE and FNAC in the diagnosis of newly detected clinically palpable breast lumps in comparison to the final histopathological (HPE) report of the biopsied specimens. Although the accuracies of FNAC and USE in the diagnosis of breast lumps have been tested individually in other studies, study comparing FNAC and USE using upon the same population is not reported in literature. Our study is designed to compare the results of FNAC and USE in the diagnosis of newly detected clinically palpable breast lumps in the same population

II. Aims And Objective
1. To study the role of USE in differentiating benign and malignant breast masses with FNAC correlation.
2. To analyze and compare the sensitivity, specificity, predictive value and accuracy of USE in diagnosing malignant breast lump.

III. Material And Methods
A total of 106 Patients who presented with breast lesion at the department of Surgery, AMCH, India, from September, 2017 to march, 2019, were included. Thorough history and detailed clinical examination of all the patients were done. Recurrent lump at the same site of any previous operation and history of prior irradiation to chest or breast were excluded. Informed consents were obtained and approval of the Institutional Ethics Committee, Assam Medical College, Dibrugarh was taken.

All the patients underwent USE evaluation using TOSHIBA APLIO-500; 12 MHz linear transducer at the department of Radio-diagnosis, AMCH and the reports were grouped into four categories for easy analysis as benign, indeterminate, malignant and otherwise normal based on Breast Imaging and Reporting Data System(BI-RADS). The cases were then sent to Aspiration Cytology at Department Of Pathology, AMCH for Fine Needle Aspiration Cytology(FNAC) examination of breast lump. Reports were collected and grouped into four categories as benign, malignant, indeterminate and inadequate sample. Irrespective of the results of USE and FNAC, all the breast lumps were biopsied (excision and/or incision) and the final HPE report was taken as the gold standard for diagnosis and reports were grouped into benign and malignant for analysis.

Data were analyzed so as to determine the specificity, sensitivity and predictive values of FNAC and USE taking HPE results as gold standard.

IV. Results And Observations

All together 106 patients with breast lump were included in the study. The demographic profile is shown in [Chart No-1]. The study population included patients above 15 years of age with a mean of 32.34. Most of the cases were noted between 21 -30 years of age (39.62%). The final HPE results of the examined cases are given in [Table no-1]. One case which was reported as normal was not included in the calculations.
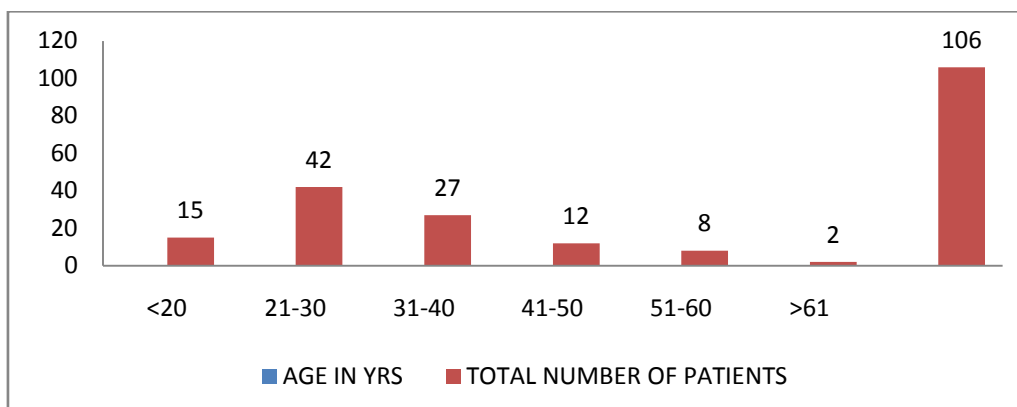

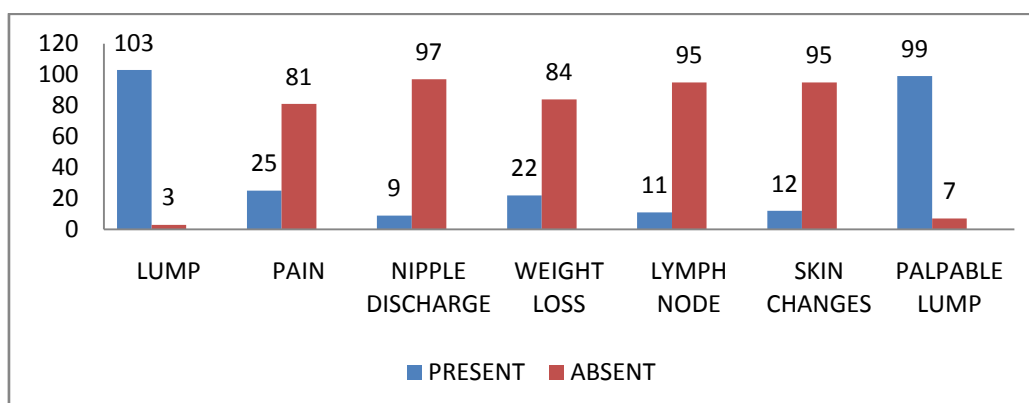**CHART NO-1 :** Demographic profiles of 106 patients.

CHART NO-2:DISTRIBUTION ACCORDING TO PRESENTING SYMPTOMS.

HPE RESULTS	TOTAL NUMBER OF CASES	PERSENTAGE(%)
Abscess (ABS)	4	3.77
CYST	1	0.94
DCIN	1	0.94
Fibroadenoma	60	56.6
Fibroadenosis	5	4.71
IDC	25	23.6
Lipoma	2	1.89
ILC	2	1.89
Medullary Ca	1	0.94
NORMAL	1	0.94
Papillary Ca	2	1.89
Phylloids	2	1.89
Grand Total	**106**	100

TABLE NO-1: Pathological distribution of lesions.

Result of the Fine Needle Aspiration Cytology:

Out of the total 105 examined, 76 (72.38%) breast lumps were reported as benign and 25 (23.80%) were reported as malignant. In 4(3.80%) case the result was indeterminate. Indeterminate reports are neither false positive nor false negative and should be understood as expressing the need of core needle biopsy or open biopsy. So, 4 case of indeterminate result was not included in the calculation. Altogether 101 cases were taken into account. Of these cases 28 turned out to be malignant and 73 cases benign on HPE [Table no-2].

FNAC Report	Number Of Cases	Percentage (%)
Benign	76	72.40
Intermediate	4	3.80
Malignant	25	23.80
Normal	1	
Total	106	100

TABLE NO-2: FNAC Report of all cases

		HPE		
		MALIGNANT	BENIGN	TOTAL
FNAC	MALIGNANT	25	0	25
	BENIGN	3	73	76
	TOTAL	28	73	101

TABLE NO-3: 2x2 table showing results of FNAC v/s HPE taking HPE as gold standard. 4 case of indeterminate result was excluded.

Result of ultrasound Elastography:
Out of 106 cases examined, 72 (68.58%) were reported as benign and 23 (21.90%) as malignant. 10 (9.52%) cases were indeterminate. Like in case of FNAC, here also, the indeterminate cases and cases where USE could not detect the lump were excluded in the calculation. So, altogether 95 cases were taken into account. Of these cases 25 turned out to be malignant and 70 cases benign on HPE [Table no-4].

		HPE		
		MALIGNANT	BENIGN	TOTAL
USE	MALIGNANT	22	1	23
	BENIGN	3	69	72
	TOTAL	25	70	95

Table no-4: 2x2 table showing results of USE v/s HPE taking HPE as gold standard. 10 case of indeterminate result was excluded.

The final comparison of FNAC and USE in the diagnosis of malignant breast lesions is shown in [Table no-5] .

	FNAC	USE
SENSITIVITY	89.28 %	88 %
SPECIFICITY	100 %	98.57 %
Positive predictive value	100 %	95.65 %
Negative predictive value	96.05 %	95.83 %
ACCURACY	97.03 %	95.79

Table no-5: Final comparison of FNAC and USE in the diagnosis of malignant breast lesions.

V. Discussion

Reported sensitivity of FNAC in diagnosis of breast lump in various studies varied from 68% to 97.4% as against our result of 89.28% [2, 5, 6]. These variations could be because of different inclusion criteria of breast lump (like size, palpable or non palpable) in different studies; inclusion of atypia/ suspicious result as malignant in calculation of sensitivity in some studies; and exclusion of inadequate results in some studies. The sensitivity has also been found to be dependent on the skill and experience of the aspirator [4].

Similarly a wide variation in the sensitivity of USG in the diagnosis of malignant breast lesion ranging from 67% to 97% has been reported [7,8] .These wide variations amongst different study could be due to different methods of case selections, different resolution power of ultrasound equipment used, and due to the fact that ultrasound is an operator dependent technique.

A sensitivity result of FNAC of 89.28% in our study suggest that only 10.72 out of 100 cases having malignant lesion would be missed if FNAC is solely used for evaluation of breast lump. Similarly a sensitivity of 88% of USE means that a negative (benign) result of USE does not completely rule out the possibility of malignant nature of the mass. Hence, in the event of a negative result (benign report) of either test, physician should seek for additional investigations to rule out malignancy should his clinical skill and experience suspect malignant nature of the lump.

When we compare FNAC and USE in the diagnosis of malignancy in breast mass, both was found to have 100% and 98.57% specificity and 100% and 95.65% positive predictive value respectively.

Sensitivity of FNAC was found higher than that of USE (89.28% v/s 88%). These values give an impression that FNAC is a better tool than USE in ruling out the probability of malignancy in breast mass. However, the percentage of indeterminate result was much higher in USE than in FNAC (4 out of 105 in FNAC and 10 out of 105 in USE). In addition 10 cases where USE was indeterminate, FNAC could correctly diagnose the lesions in 8 and in 2 cases of indeterminate USG results; FNAC was wrong in diagnosing the lesions. Thus

both the diagnostic tools should be considered complementary and the physician should use the basis of his clinical findings and experience in choosing either one of or both the tools.

In similar study, to evaluate the role of USE in diagnosing palpable breast lesions, following results were obtained.

Author	USG/USE	PATIENTS	SENSITIVITY	SPECIFICITY	PPV	NPV	ACCURACY
Hatzung et al 2010	USG	97	97	82	71	98	87
	E		71	48	39	78	-
	USE		100	38	43	100	58
Evans et al[26] 2012	USG	175	95	77	88	90	89
	E		95	69	84	91	86
	USE		100	61	82	100	86
Sahacfer et al[30] 2011	USE	193	96.9	96	-	-	-
Dujim et al	USE	-	92	97.7	68	99.6	-
Ataby et al	USE	-	83	89	79	91	-
Cho et al[27]	USE	100	82	84			-
Jan em at al [28]2012	USG	200	100	96.4	66.7	100	-
Takhellambam et al[29] 2013	USG	60	94.74	100	100	97.22	-
OUR study	USE	105	88	98.57	95.65	95.83	95.79

#USG- Ultrasonography, E- Elastography, USE- Ultrasound elastography

In the studies showed by Hatzung et al and Evans et al, sensitivity and NPV of combined Ultrasonography and Elastography are 100%, which is higher when compared to data analyzed individually in both the studies. Thus a positive result (malignant report) of test can be considered confirmatory and further treatment decision can be made solely on this report without any further additional diagnostic investigation.

Another important finding is that when we consider only younger patients (≤35 year of age), the sensitivity, specificity, positive and negative predictive values of USE in diagnosis of malignant breast mass were all 100% against the respective values of 93%, 100%, 100% and 91% when considering those older than 35 years. Again the chances of missing the lump or indeterminate result were less in ≤35 year of age group. This clearly shows the more accurate value of USE in younger patients.

There are certain limitations of our study. First, the size of the breast lump was not taken into account. Larger sized lumps are less likely to be missed in USG. Secondly, the indeterminate reports were excluded in calculation of specificity and sensitivity. The rate of inconclusive report was higher in case of USE than in FNAC. So, the calculated value of sensitivity did reflect this limitation of USE as against FNAC. Thirdly, age of the patient is known to largely affect the USE result and is also shown in this study. In actual clinical practice USG is seldom preferred in aged patient. However, we subject the patient to USG, bound by our protocol, irrespective of age. Such an approach appears clinically irrelevant.

There are certain strong points also of our study. First, the gold standard test used in our study is histopathological report which is valid, reproducible and has been accepted as the gold standard internationally. For a good study, the reference test against which the diagnostic test in evaluation is compared should be gold standard [10]. Secondly, cystic lesions and abscess were included in the study as they were treated mainly by aspiration and drainage and hence tissue sample could be obtained for Histopathological examination. This non-selectiveness of cases may not limit the generalization of the findings in clinical practice. A very strong point, again of our study, is the fact that both the cytopathologist performing the FNAC and USE radiologist belonged to different departments of the institute and hence were blinded from each others' results. Nor, they were given the clinician's impression about the lump. Finally both the diagnostic tools in questions were tested upon the same study population.

VI. Conclusion

Evaluation of breast lump is important to rule out malignancy. USE is an imaging technique and FNAC a tissue diagnostic technique.

All interpretation criteria were able to differentiate benign and malignant lesions with statistical significance (p<0.0001). The study showed that sensitivity, specificity and predictive values of FNAC was more when compared to USE and the percentage of intermediate result were also higher with USE. While conventional USG remain the primary modality for investigating the breast masses, USE was found to have a greater sensitivity when compared to USG for diagnosing malignant breast lesions and low suspicion lesions(BI-RADS 3 and 4).

In addition, reference studies have shown that USE yield a better result when compared to USG and Elastograpgy individually. Thus Elastography can complement conventional USG in increasing the diagnostic

accuracy and could be used as a good tool for the classification of breast masses prior to the decision to biopsy a lesion, thus potentially reducing the necessity of biopsy for indeterminate or questionable breast lesions

Specificity of both the diagnostic tools in diagnosing malignant breast lump was found to be high in our study, thereby giving the inference that a positive (malignant) result of either test can alone solely form the treatment decision without much additional diagnostic investigation.

The exact place of these diagnostic tools in the evaluation of beast lump would depend on the expertise and availability of these modalities in a clinical setup and also on the age factor of the patients as well as on the clinicians' degree of suspicion of nature of the lump.

In aged, clinician may place USE at lower level of preference as it is less accurate in less denser breast of the adult. On the other hand a malignant report of FNAC of a hard, irregular lump in breast in adult nulliparous women may be better credited by the dealing clinician. The reverse may be true in younger patients where carcinoma is rare. Thus, both these diagnostic tools should be considered complementary.

Further advancement in the technique with expertise and addition of Doppler in USE may increase the accuracy. Also with the gaining experience in characterization of solid breast mass using USE, the accuracy of USE in the diagnosis of breast lump is increasing. Certainly, more studies are required, addressing these recent advancements, to properly define the place of FNAC and USE in the management of breast lump.

References

[1].   Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J of Cancer. 2010; 127(12):2893-917.
[2].   Garcia M et al. Global Cancer Facts & Figures; 2007. Atlanta, GA: American Cancer Society.
[3].   Tiwari M. Role of fine Needle aspiration cytology in diagnosis of breast lumps. Kathmandu Univ Med J. 2007;5(2):215-17.
[4].   Pruthi S. Detection and evaluation of a palpable breast mass. Mayo Clin Proc. 2001; 76: 641-48.
[5].   Houssami N et al. Accuracy of combined breast imaging in young women. The Breast, 2002; 11: 36-40
[6].   Martelli G et al. Diagnostic efficiency of physical examination, mammography, fine needle aspiration cytology (triple test) in solid breast lumps: an analysis of 1708 consecutive cases. Tumori, 1990; 76: 476-79.
[7].   Saarenmaa I, Salminen T, Geiger U, Heikkinen P, Hyvärinen S, Isola J, Kataja V, Kokko ML, Kokko R, Kumpulainen E, Kärkkäinen A, Pakkanen J, Peltonen P, Piironen A, Salo A, Talviala ML, Hakama M: The effect of age and density of the breast on the sensitivity of breast cancer diagnostic by mammography and ultasonography. Breast Cancer Res Treat 2001, 67:117–123.
[8].   Giard RW and Hermans J. The value of aspiration cytologic examination of the breast. A statistical review of the medical literature. Cancer, 1992; 69: 2104-10.
[9].   Jayaram G et al. Cytological analysis of breast lesions: A review of 780 cases. Malaysian Journal of Pathology, 1996; 18: 81-87.
[10].   Tiwari M. Role of fine Needle aspiration cytology in diagnosis of breast lumps. Kathmandu Univ Med J., 2007; 5: 215-17.
[11].   Kocjan G. Needle aspiration cytology of the breast: current perspective on the role in diagnosis and management. Acta Med Croatica, 2008; 62: 391-401.
[12].   Karin L. Breast. In: Svante RO, Greogory FS, Darrel W, editors. Fine Needle Aspiration Cytology. 4th ed. India: Elsevier Ltd; 2005; 165-225.
[13].   Tse GM and Tan PH. Diagnosing breast lesions by fine needle aspiration cytology or core biopsy: which is better? Breast Cancer Res Treat., 2010; 123: 1-8.
[14].   Ghazala M et al. Sonomammography for evaluation of solid breast masses in young patients. J Ayub Med Coll Abbottabad, 2006; 18: 34-37.
[15].   Stavros AT et al. Solid breast nodules: use of sonography to distinguish between benign and malignant lesions. Radiology, 1995; 196: 123-13
[16].   Gordon PB. Ultrasound for breasts cancer screening and staging. Radiol. Clin. North Am., 2002; 40: 431-41.
[17].   Kailash S et al. The accuracy of Ultrasound in characterization of palpable breast lumps. JK Science, 2008; 10: 186-88.
[18].   Liberman L, Menell JH: Breast imaging reporting and data system (BI-RADS). Radiol Clin North Am 2002:409–430.
[19].   Athanasiou A, Tardivon A, Tanter M, Sigal-Zafrani B, Bercoff J, Deffieux T, Gennisson J-L, Fink M, Neuenschwander S: Breast lesions: quantitative elastography with supersonic shear imaging--preliminary results.Radiology 2010, 256:297–303.
[20].   Duncan JL, Cederbom GJ, Champaign JL, Smetherman DH, King TA, Farr GH, Waring AN, Bolton JS, Fuhrman GM: Benign diagnosis by image-guided core-needle breast biopsy. Am Surg 2000, 66:5–10.
[21].   Chiou SY, Chou YH, Chiou HJ, Wang HK, Tiu CM, Tseng LM, Chang CY: Sonographic features of nonpalpable breast cancer: A study based on ultrasound-guided wire-localized surgical biopsies. Ultrasound Med Biol 2006, 32:1299–1306.
[22].   Poplack SP, Carney PA, Weiss JE, Titus-Ernstoff L, Goodrich ME, Tosteson ANA: Screening mammography: costs and use of screening-related services.Radiology 2005, 234:79–85.
[23].   Baker R, Rogers KD, Shepherd N, Stone N: New relationships between breast microcalcifications and cancer.Br J Cancer 2010, 103:1034–1039.
[24].   Raza S, Odulate A, Ong EMW, Chikarmane S, Harston CW: Using real-time tissue elastography for breast lesion evaluation: our initial experience.J Ultrasound Med 2010, 29:551–563.
[25].   Tohno E, Ueno E: Current improvements in breast ultrasound, with a special focus on elastography. Breast Cancer 2008, 15:200–204.
[26].   Evans A, Whelehan P, Thomson K, McLean D, Brauer K, Purdie C, et al. Quantitative shear wave ultrasound elastography: initial experience in sold breast masses. Breast cancer Res 2010; 12(6):R104.
[27].   Cho N, Jang M, Lyou CY, Park JS, Choi HY, Moon WK. Distinguishing Benign [24] from Malignant Masses at Breast US: Combined US Elastography and Color Doppler US—Influence on Radiologist Accuracy Radiology. 2012;262:1.
[28].   Jan M et al. Triple assessment in the diagnosis of breast cancer in Kashmir. Indian J Surg., 2010; 72: 97-103.
[29].   Takhellambam YS et al. Comparison of ultrasonography and fine needle aspiration cytology inthe diagnosis of malignant breast lesions. J Clin Diagn Res., 2013; 7: 2847-50.
[30].   Schafer FK, Hooley RJ, Ohlinger R, Hahne U, Madjar H, Svensson WE, et al. ShearWave elastography BE1 multinational breast study: additional SWE features support potential to downgrade BIRADS(R)-3 lesions. Ultraschall Med 2013;34:254-259.