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Diagnostic Accuracy of Strain Ratio Elastography on Endoscopic Ultrasound in Detecting Malignant Abdominal Lymph Node Using Fine Needle Biopsy as a Gold Standard

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Abstract

Introduction: The elasticity of the lesion is measured by means of Endoscopic Ultrasound guided elastography (EUS-elastography). Strain Ratio (SR), calculated with EUS, has been proposed in previous studies to differentiate between malignant and benign lesions including LNs. SR may not only improve the accuracy of diagnosing malignant tissue but can also be helpful in attaining targeted biopsies. Moreover, it can access abdominal LNs not approachable by percutaneous route. Our aim was to assess the diagnostic accuracy of strain ratio on EUS-elastography in detecting malignant lymph nodes and differentiating benign from malignant abdominal Lymph Nodes (LNs).

Methods: It was a cross-sectional prospective study. All patients 18 to 60 years undergoing EUS for abdominal lymphadenopathy were enrolled in our study. Patient's demographics, such as age, duration of disease were recorded. Patients who were underwent EUS were administered. EUS was performed after an overnight fast of 8 h by consultant gastroenterologist. EUS-SR elastography calculated. Statistical analysis was performed by SPSS 20.0.

Result: In total 106 patients were included, of which 67 (63%) were male and 39 (37%) were female. Total 36 (34%) had malignant lymphadenopathy, while 70 (66%) had benign lymphadenopathy. Strain Ratio of ≥ 23 was found to be significantly associated with presence of malignant disease with p value of 0.003. At cut off ≥ 23, the Sensitivity, specificity, positive and negative predictive value were 86.11%, 58.57%, 51.67% and 89.13% respectively in predicting malignant lymph nodes on EUS along with diagnostic accuracy of 67.92% (p-value ≤ 0.001).

Conclusion: SR-elastography with EUS can be helpful in differentiating benign from malignant lymph nodes at a cut-off ≥ 23 with a diagnostic accuracy of 67.92%. However, further studies are needed to validate this ratio.

Keywords: Endoscopic Ultrasound; Strain ratio; Lymph node

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Introduction

It is necessary to differentiate benign and malignant Lymph Nodes (LN) in order to stage the tumor, gauge the prognosis and plan best treatment strategy in patients with cancers. An excellent view is provided by LNs close to the gastrointestinal tract by Endoscopic ultrasound [1]. LNs that are unapproachable or present in remote locations such as intra-abdominal and mediastinal LNs, can be better visualized by modalities which are minimally invasive such as EUS [2,3]. In the modern times, the mechanical properties of the tissues have been assessed by means of non-invasive means such as EUS-elastography [4]. This procedure usually involves the basic principle that relies on the degree of tissue distortion in reaction to an external force, so it is used to approximate tissue stiffness [5]. By implying this technique, several organs such as the breast, thyroid, prostate, cervix liver and lymph nodes can be examined [6]. The semi quantitative measure of elastography patterns which comprises of the elastography patterns of the targeted LNs compared to those of a nearby reference tissue is called Strain Ratio (SR) elastography [7]. Currently, Fine Needle Aspiration Cytology (FNAC) is considered gold standard for the diagnosis of malignant cells in a LN with a specificity and a Positive Predictive Value (PPV) approaching 100%. A great level of expertise is required in performing it with a higher risk of multiple complications [8]. This method of diagnosis is quite helpful for tissue diagnosis because it targets the area of a LN with highly suspicious of malignancy. The sensitivity and yield of EUS-FNAC in the existence of multiple LNs, is increased by performing

EUS-elastography as it can help reducing the unnecessary biopsies performed for diagnosis of malignancy [9,10].

Micro metastases may escape detection by EUS-FNAC. Malignancy related changes in tissue stiffness are assessed by elastograpy SR, making this approach extremely useful for detecting early malignant changes so the most suspicious area of LN can be targeted. EUS-elastography SR can also be used if EUS-FNAC is inconclusive or any contraindication to FNAC (technical difficulties or interposed vascular structures) [11].

In the recent times, several studies have evaluated the use of EUS-elastography SR in assessing LNs and have revealed that this technique is beneficial for selecting LNs. In proximal gastrointestinal tumors such as esophageal and gastric cancers, the role of strain ratio in nodal staging is judged by using FNAC as a standard in one of the studies [12]. Those authors observed 50 LNs calculated SR cut-off value of 7.5 for malignancy and at this cut off value, the sensitivity, specificity, PPV, NPV, and accuracy was 83%, 96%, 95%, 86%, and 90%, respectively.

One of the studies done by Larsen and his colleagues estimated the yield of EUS guided SR and FNA in the evaluation of LNs associated with upper gastrointestinal tumors, by using invasive (peroperative) biopsy and pathology as a standard. A total of 56 LNs were examined for the SR at a cut-off values of 4.5 the sensitivity 55%, specificity 85%, accuracy 73%, PPV of 71% and NPV of 74% [13].

Hussein Okasha et al. [14] in their study expressed good outcome for predicting malignant LNs, with an approximate sensitivity and specificity of 89.8% and 83.3%, respectively, at a cut-off level of >4.6. For predicting malignant LNs, the SR had a PPV of 82.5% and a NPV of 90.2%. In order to predict benign LN, the SR had a PPV of 85.8%, and NPV of 87.8% [14].

To the best of our knowledge, no studies have been performed in Pakistan and limited data is available regarding utilization of strain ratio in detecting malignant abdominal lymph node. Hence, the current study aims to validate the results of previous studies. The main objective of our study was to assess the diagnostic accuracy of strain ratio on EUS-elastography in detecting and predicting malignant lymph nodes and differentiating benign from malignant abdominal Lymph Nodes (LNs). With the help of this study we can reduce the number of unnecessary biopsies by using the EUS strain ratio elastography and by only targeting the malignant lymph node for biopsy that can't be accessed through percutaneous approach.

Objective

To determine The Diagnostic accuracy of Strain Ratio Elastography on endoscopic ultrasound in detecting malignant abdominal lymph nodes using Fine Needle Aspiration Cytology as a gold standard.

Operational Definitions

Elastography

It is novel radiological modality using ultrasound technique in providing images and measurements estimating tissue stiffness. Color images in B-mode are used to determine elastic properties of tissues. The elasticity modulus, i.e. the tissue elasticity can be obtained from the strain and the stress of the observed structures [11].

Pattern 1: Tissue is labeled as having pattern 1 if 80% of the cross-sectional area was either red or green (i.e., soft).

Pattern 2: Tissue is labeled as having pattern 2 if greater than 50% and less than 80% of the cross-sectional area was either red or green.

Pattern 3: Tissue is labeled as having pattern 3 if greater than 50% and less than 80% of the cross-sectional area was blue.

Pattern 4: Tissue is labeled as pattern 4 if 80% of the cross-sectional area was blue (i.e., hard).

Strain ratio

The Strain Ratio (SR) is the semi quantitative score of elastography which is obtained as R2/R1; where R2 was the elastography of a designated soft (red) reference area outside the target LNs, preferably the gut wall, perinodal tissue or subcutaneous tissue, and R1 was the elastography of the directed LNs [12].

Malignant lymph node

In general, characteristics features of malignancy in FNAC slides are increased cellularity, enlargement of cell, increased Nuclear/Cytoplasmic(N:C) ratio, nuclear hyperchromasia, discohesiveness of cells, prominent and large nucleoli, atypical distribution of nuclear chromatin, increased, irregular mitotic activity and particularly the, nuclear membrane irregularities, and nuclear pleomorphism [15]. Malignant lymph nodes seen in Metastatic lesions, primary lymphoid neoplasm, metastatic squamous cell carcinoma, metastatic adenocarcinoma [15].

Benign lymph node

In the absence of malignant morphological features on FNAC as mentioned above, diagnosis of benign lymph node will be rendered. Benign lymph nodes mostly seen in reactive lymphoid hyperplasia, infectious disease, granulomatous lymphadenitis [16].

Materials and Methods

Study design

Cross-sectional study.

Setting

This study has been conducted in Department of Hepatogastroenterology, Sindh Institute of Urology and Transplantation, Karachi.

Duration of study

Six months (From March 2020 to September 2020).

Sampling technique

Non probability consecutive sampling

Inclusion criteria

- Patient of either gender.
- Age of 18 to 60 years.
- Patients referred for EUS guided evaluation of the abdominal LNs, for TNM staging.

Exclusion criteria

- Those patients were excluded who were found to be unfit for propofol administration.
- Patients having severe coagulopathy.
- Failure to obtain informed consent.

- Patients with severe life-threatening comorbids like: Congestive cardiac failure, recent history of ischemic heart disease.
- Patient who lost to follow up.

Data collection procedure

All the patients were referred for tumor staging and diagnosis of primary tumor in GI-OPD of Sindh Institute of Urology and Transplantation had undergo EUS strain ratio elastography and informed consent has obtained after explaining the procedure to the patient. A thorough history and clinical examination had done by the researcher for patients who underwent EUS, after taking general anesthesia fitness deep sedation with intravenous propofol has been administered. EUS has been performed after an overnight fast of 8 h by consultant gastroenterologist with more than 3 years of post-fellowship experience An EUS linear array machine (Pentax EG-3830UT Echo-endoscope, HOYA Corporation, PENTAX Lifecare Division, Showanomori Technology Center, Tokyo, Japan) connected to a Hitachi EUB-7000 will be used. Elastography Strain Ratio has calculated by the software as per operational definition.

Biopsy has taken through 22 gauge needle two passes by slow-pull back technique and sent to histopathology department for FNAC. All biopsies specimen had immersed in formalin and then embedded in paraffin. FNAC slides has reviewed by consultant histopathologist having minimum 3 years' experience. Post procedure patient we have observed for bleeding or any other complication and discharged after regain of consciousness. Data has labeled and transferred to pre-designed proforma by researcher. All tests had been performed free of cost as per institutional policy without any ethical issue.

Lymph node with strain ratio ≥ 23 was considered malignant. Diagnostic accuracy compared with gold standard FNAC.

Data analysis

Data entered and analyzed in statistical software (SPSS 20.0). Quantitative data was measured in terms of Mean and standard deviation while categorical values like gender, strain ratio elastography and findings on FNAC i.e. malignant and benign was expressed as frequencies and percentages. The Sensitivity, specificity and positive and negative predictive value and diagnostic accuracy of strain ratio elastography calculated by taking FNAC as a Gold standard using 2 × 2 table. Post stratification chi square test was applied and p value <0.05 was considered as significant.

Result

In total 106 patients were included, Mean age was 46.7 ± 15.4 years, with age range of (18 to 60) and mean disease duration 10 ± 2.5 months. Out of 106 patients, 67 (63%) were males and 39 (37%) were females. Total 36 (34%) had malignant lymphadenopathy, while 70 (66%) had benign lymphadenopathy on histopathology.

On comparison of continuous variables between malignant and non-malignant lymph node groups, Strain ratio was significantly higher in malignant group (p-value ≤ 0.001). While no significant difference was noted in comparison of other continuous variables between two groups (Table 1). Similarly, on comparative analysis of categorical variables between the two above mentioned groups revealed that hypoechoic character of lymph node (p-value 0.01), hard and very hard consistency on elastography (p-value ≤ 0.001) and lymph node size ≥ 2cm (p-value ≤ 0.001) were significantly associated with malignant histology (Table 2) while soft and firm consistency was noted in benign lymph nodes on liver elastography. AUROC was obtained for strain ratio in predicting malignant abdominal lymphadenopathy and it was that of 0.722 (p-value ≤ 0.001) (Figure 1, 2). At cut off ≥ 23, Sensitivity, specificity, positive and negative predictive value was 86.11%, 58.57%, 51.67% and 89.13% respectively in predicting malignant lymph node along with diagnostic accuracy of 67.92% as shown in Table 3, 4.

Table 1: Comparison of baseline continuous variables in terms of malignant lymph nodes on histology.

Variable	Malignant (n=36) Mean ± SD	Benign (n=70) Mean ± SD	p-value
Age	46.8 ± 16.5	46.1 ± 15.2	0.82
Hemoglobin (Hb)	10.8 ±1.28	10.7 ± 1.5	0.73
TLC	8.9 ± 3.1	9.4 ± 3.33	0.492
Platelets	280.7 ± 103	246.3 ± 92.3	0.08
Strain Ratio	96.8 ± 88.6	44.03 ± 61.17	≤ 0.001

Table 2: Comparison of baseline categorical variables in terms of malignant lymph nodes on histology.

Variable		Malignant (n=36) n(%)	Benign (n=70) n(%)	p-value
Gender	Female	13 (36.1)	29 (41.4)	0.596
	Male	23 (63.9)	41 (58.6)	
Lymphnode character	Hyperechoic	3 (8.3)	31 (44.2)	0.01
	Hypoechoic	30 (91)	23 (33)	
	Mixed	2 (5.6)	2 (3)	
	Isodense	1 (2.7)	14 (20)	
Lymphnode Site	Peripancreatic LN	6 (16.7)	10 (14.2)	0.37
	Porta LN	19 (53)	33 (47)	
	Mediastinal LN	1 (2.7)	11 (16)	
	Para-aortic LN	8 (22.2)	14 (20)	
	Celiac LN	2 (5.6)	2 (3)	
Lymphnode shape	Oval	5 (13.9)	14 (20)	0.76
	Round	20 (55.6)	33 (47)	
	Triangular	8 (22.2)	15 (21)	
	Semilunar	3 (8.3)	6 (8.6)	
	Horseshoe	0 (0)	2 (3)	
LN size	≥ 2 cm	20 (55.7)	13 (18.5)	≤ 0.001
	<2 cm	16 (44.5)	57 (81.4)	
Elastography	Soft	1 (5.6)	20 (28.5)	≤ 0.001
	Firm	2 (5.6)	25 (35.7)	
	Hard	19 (41.7)	12 (17.1)	
	Very hard	17 (47.2)	13 (18.5)	

Table 3: Chi square test showing association of high strain ratio with malignant lymphnodes.

Variable		Lymphnode characteristics		p-value
Strain Ratio		Malignant	Benign	≤ 0.001
	≥ 23	31	29	
	<23	5	41	

Discussion

The skill of EUS-elastography to categorize and differentiate benign and malignant LNs was primarily gauged by Giovannini et al. [17], on LNs with different sites. The conclusion was based on FNAB

Table 4: Showing sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of strain Ratio in predicting malignant lymphnodes.

Statistic	Value
Sensitivity	86.11%
Specificity	58.57%
Positive Predictive Value (PPV)	51.67%
Negative Predictive Value (NPV)	89.13%
Diagnostic accuracy	67.92%

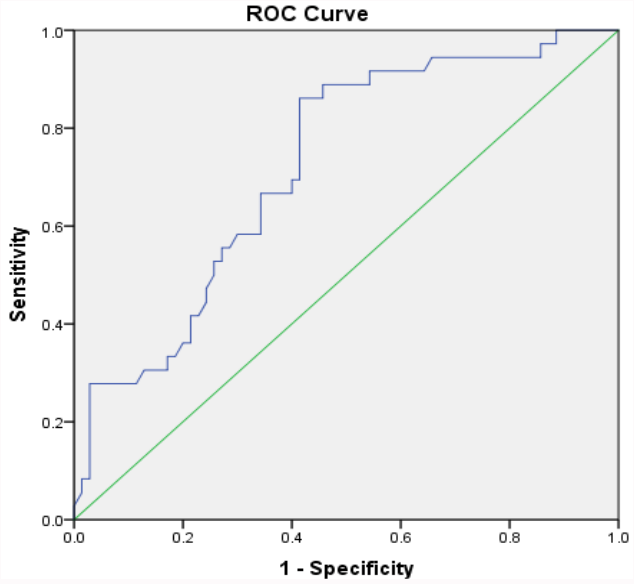

Figure 1: Area under ROC curve for Strain ratio is 0.722(p-value ≤ 0.001).

samples or surgical specimens with a sensitivity and a specificity of 100% and 50% respectively using a color-coded scale, with blue designated for malignant tissue and green for fibrosis while yellow color was for normal tissue, and red represented fat. They highlighted the need for improvement in specificity, emphasizing the capable result of EUS-elastography for guiding the biopsy [17]. In 2009, a multicentric study was carried out by Giovannini et al. [18], which was the sequela of the previous one including 101 LNs in the same number of patients with different malignancies. The evaluation relied upon the same real-time elastographic pattern, and the results were compared with the classification based on the B-mode EUS images, using EUS-FNAB and/or surgical pathology as reference standard (44 benign LNs and 57 malignant LNs). They found better results as compared to the previous study, with a specificity of 82.5% as compared to 50% in the first study [18].

In our study we calculated the strain ratio using EUS-elastography and also used the cutoff values for the SR. Furthermore, in our study, we had better specificity and accuracy in indistinguishing benign from malignant lymph node, the EUS-SR was more efficient in representing tissue stiffness, although it measures only the relative stiffness of the lymph node.

However, our study had several limitations. The most noticeable one was that the acquirement of elastograms, as well as the analysis depended upon on the observer performing the procedure. The degree of initial compression could alter the elasticity map. Furthermore, the study was based on fixed B-mode images instead of video clips, which makes it even more observer dependent &

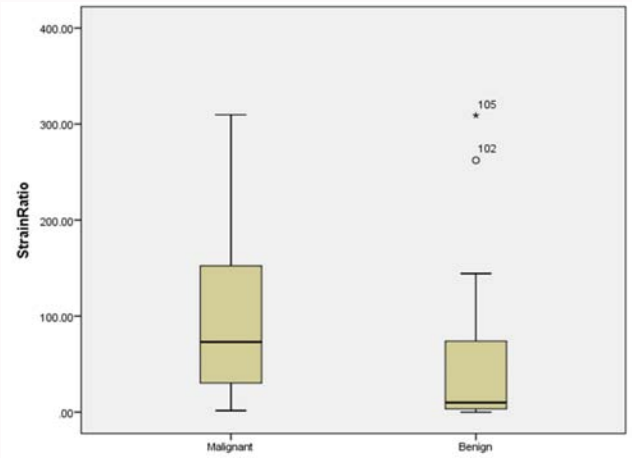

Figure 2: Box plot showing association of high strain ratio with malignant lymph nodes.

addition, inter-observer or intra-observer variability in performing and interpreting elastography was not analyzed. One might point to this shortcoming as a relevant issue in clinical settings, particularly with different levels of experience between observers. Performance of elastography relies on multiple aspects, such as lymph node size, texture, echogenicity and closeness of a lymph node to surrounding tissue, making it challenging to achieve regularly accurate image quality. All these reasons are responsible for the variations in the results obtained in our study. It might be beneficial to address these limitations in larger studies, so that new methods can be applied to provide more quantitative elasticity assessment which will further improve the sensitivity and specificity of elastography in detecting malignant lymph nodes.

Our study has shown that strain ratio of ≥ 23 were found to be associated with 34% of malignant lymphadenopathy with AUROC=0.72. At cut off ≥ 23, Sensitivity, specificity, positive and negative predictive value were 86.11%, 58.57%, 51.67% and 89.13% respectively in predicting malignant lymph nodes on EUS along with diagnostic accuracy of 67.92% (p-value ≤ 0.001). EUS elastography has a potential skill of describing characteristics of benign and malignant lesions, but needs improvement of the specificity and clear definitions of the criteria is essential for an accurate elastographic estimation of the lymph node. This can be achieved by improving the grading system [19]. Elastographic strain ratio is hopeful, as it seems to overcome some of problems in categorizing the LNs in the scoring system. Studies have revealed that percutaneous US-elastography has shown improved sensitivity when using a strain ratio [20], in contrast to the values acquired by using visual scoring systems, which displayed better specificity [21]. This was also revealed in a meta-analysis comprising of nine studies using qualitative elastography score and five studies with strain ratio. The results on the utility of using a strain ratio over a visual scoring system were discordant as far as EUS-elastography studies are concerned [22]. Thus, the efficacy of the 'elasticity ratio' should be tested in larger prospective studies, with an emphasis on cut-off points. The existence of central necrosis may also alter the differentiation of lesions by a subjective analysis of the elastography score according to the strain ratio [23]. The strength of our study is that no such study has been conducted in this part of world and large small size of greater than 100 along with that we have derived our own cutoff for strain ratio in characterizing malignant lymph nodes.

Conclusion

In order to differentiate between benign and malignant lymph nodes, EUS-elastography and the strain ratio can be used as prognostic indices a diagnostic accuracy of approximately 67.62%. However, further studies are required to validate the role of SR in predicting malignant lymph nodes.

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