META-ANALYSIS

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Diagnostic Value of Qualitative and Quantitative Endoscopic Ultrasound Elastography for the Evaluation of Lymph Nodes: A Meta-analysis

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ABSTRACT

Background & Aims: The differential diagnosis of benign and malignant deep lymph nodes (LNs) has been a significant challenge up until now. Endoscopic ultrasound (EUS) elastography is a real-time imaging technique evaluated in several studies with diverse results. A meta-analysis was performed to assess the performance of EUS elastography for the differentiation of benign and malignant deep LNs.
Methods: All the eligible studies were searched by PubMed, Medline, Embase, and the Cochrane Library. A meta-analysis was performed to obtain pooled sensitivity, specificity, positive and negative likelihood ratio (LR). The diagnostic odds ratio (DOR) and area under the curve (AUC) were used to examine the accuracy of qualitative and quantitative EUS elastography.
Results: A total of eleven studies including 599 patients and 943 LNs were analyzed. In studies using the qualitative color pattern as the diagnostic standard, the pooled sensitivity, specificity, positive and negative LR were 0.82 [95% confidence interval (CI): 0.77-0.86)], 0.92 (95%CI: 0.89-0.94), 7.83 (95%CI: 3.58-17.09) and 0.22 (95%CI: 0.14-0.34), respectively. In studies using the quantitative value as the diagnostic standard, the pooled sensitivity, specificity, positive and negative LR were 0.80 (95%CI: 0.74-0.86) and 0.87 (95%CI: 0.82-0.92), 5.63 (95%CI: 3.46-9.17) and 0.23 (95%CI: 0.12-0.44), respectively. The summary DOR and the AUC were 48.73 (95%CI: 21.83-108.80) and 0.933 (Q*=0.869) for qualitative EUS elastography, 33.35 (95% CI: 12.81-86.87) and 0.923 (Q*=0.857) for quantitative EUS elastography.
Conclusions: Our meta-analysis shows that both qualitative and quantitative EUS elastography have high accuracy in the detection of malignant deep LNs, which could be used as a valuable complementary method to EUS-FNA for the differentiation of deep LNs in the future.

Key words: endoscopic ultrasound – elastography – lymph nodes – diagnosis – meta-analysis.

Abbreviations: AUC: area under the curve; DOR: diagnostic odds ratio; EUS: Endoscopic ultrasonography; FNA: fine needle aspiration; FN: false negative; FP: false positive; LN: lymph node; LR: likelihood ratio; NPV: negative predictive value; PPV: positive predictive value; QUASAD: quality of diagnostic accuracy studies; SROC: summary receiver operating characteristic; TN: true negative; TP: true positive.

INTRODUCTION

The differentiation between benign and malignant deep lymph nodes (LNs) is important for the diagnosis, treatment and prognosis of malignant tumors. Not all the enlarged LNs are malignant, and lymphadenopathy can also be caused by other causes such as infections, tuberculosis, and other pathologies [1]. Therefore, an accurate diagnosis of LNs is very critical for making therapeutic options. It is well known that superficial LNs are relatively easy to diagnose because histological investigation is available, whereas deep LNs such as mediastinal and abdominal lymph nodes are difficult.

Endoscopic ultrasonography (EUS) is one of the most recent advances in digestive endoscopy and has been widely used in the diagnosis of gastrointestinal and biliopancreatic system disease. It provides both an accurate assessment of tumors and enhances the accuracy of N staging. The current ultrasound criteria suggesting the malignant LNs include rounded shape, hypo-echogenicity, sharp borders, and diameter > 1 cm. However, some of these criteria may be found in benign LNs [2-4]. To increase the accuracy of differential diagnosis, EUS-guided fine needle aspiration (FNA) can obtain cytology or histology and has been advocated. In spite of this, EUS-guided FNA is an invasive procedure and associated with some inevitable complications [5], which can also produce a relatively high false-negative result [6, 7]. Therefore, the differentiation diagnosis of benign and malignant LNs remains a challenge.

As a noninvasive technique, elastography is a novel real-time imaging technique for measuring tissue elasticity and has shown promising results in the diagnosis of various cancers [8-10]. This method reveals the properties of the tissue by characterizing the difference of hardness. Generally, malignant tumors are harder than benign tumors. EUS elastography is increasingly being used to differentiate between benign and malignant LNs with promising results [11, 12]. Measurements of tissue elasticity would be analyzed either by a qualitative method where blue-predominant represents malignancy or a quantitative method on the basis of hue histograms analysis or strain ratio [13-15]. A previous meta-analysis has shown that EUS elastography is a promising non-invasive technique for differential diagnosis of malignant LNs and can be considered to be a valuable supplementary method to EUS-guided FNA [16]. Nevertheless, there have been many articles published in this field in recent years.

The aim of the present study is to make a thorough search of the published articles and perform a meta-analysis to evaluate the accuracy of qualitative and quantitative EUS elastography for the differentiation of benign and malignant deep LNs.

METHODS

Literature Search

A comprehensive literature search was performed in PubMed, Medline, Web of Science, Embase, and the Cochrane Library for studies published prior to March 2024. The search terms were elastography, elastogram, sonoelastography, endoscopic ultrasonography, EUS, elastosonoendoscopy, EUS elastography, lymph nodes, and lymph node. We also screened the reference lists of eligible articles to expand our study. Language was limited to English. Some meeting abstracts and articles with the same authors were excluded to avoid duplicate data.

Study inclusion/exclusion criteria

Inclusion and exclusion criteria were discussed before the literature search. Studies that met all of the following inclusion criteria were selected: (1) evaluated EUS elastography for the diagnosis of benign and malignant lymph nodes; (2) the use of a reference standard of EUS-guided FNA cytology, surgical histopathology or clinical follow-up of at least 3 months; and (3) reported data necessary to calculate the true positive (TP), false positive (FP), true negative (TN) and false negative (FN) rates of EUS elastography in the diagnosis of malignant LNs. Studies were excluded based on any of the following criteria: (1) did not evaluate LNs by EUS elastography; (2) studies were reviews, editorials, abstracts, case reports or letters; (3) duplicate meeting abstracts and articles; (3) incomplete data available.

Study Selection and Data Extraction

Two authors (C.Z. and F.Z.) independently searched and extracted the data, with disagreements resolved by mutual agreement or in consultation with a third investigator (B.Z.). For each study, the following information was recorded: first author, publication year, country, study design, number of patients, mean age of patients, number of LNs, location of LNs, mean LNs size, reference standard, diagnostic standard, cut-off value, and device used. TP, TN, FP and FN were directly extracted or calculated according to sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

Quality assessment

The quality of the studies was assessed independently by F.Z. and P.L. using a checklist based on the quality of diagnostic accuracy studies (QUADAS) tool [17]. A total of 14 items were designed to evaluate the diagnostic accuracy. Each item was rated "yes" if reported, "no" if not reported, or "unclear" if no sufficient information available to make an accurate decision.

Statistical Analysis

The accuracy of EUS elastography for the differentiation of benign and malignant LNs was performed by calculating the pooled sensitivity, specificity, positive likelihood ratio (LR), negative LR, and diagnostic odds ratio (DOR) with corresponding 95% confidence interval (CI). Pooled results were constructed by using both the fixed-effect model (Mantel-Haenszel method) when significant heterogeneity was absent and the random-effect model (DerSimonian-Laird method) when significant heterogeneity was present. The Chi-square and I-square tests were used to assess the heterogeneity. If I^2>50% or a low p-value (<0.05) of X^2 test, it suggests that there is heterogeneity between studies.

A summary receiver operating characteristic (SROC) curve was plotted to graphically display the results [18]. The area under the curve (AUC) was calculated. An AUC close to 0.5 indicated a poor test, and an AUC of 1.0 indicated a perfect diagnostic tool [19]. The Q* index was used to define the point on the SROC curve where sensitivity equals specificity [20].

The pooled sensitivity, specificity, positive LR, negative LR, DOR, and SROC curve shown in all the figures were performed by using Meta-Disc version 1.4 (Unit of Clinical Biostatistics, Ramony Cajal Hospital, Madrid, Spain), p-value>0.05 was considered to be statistically significant. Publication bias analysis was performed by using STATA 11.0 (Stata Corporation, College Station, TX, USA), p>0.05 was considered that there was no potential publication bias.

RESULTS

Search Results and Characteristics of the Studies

A flow chart describing the procedure of study selection is shown in Fig. 1. The initial literature search identified a total of 351 studies. After screening titles and abstracts, 39 studies were identified for full text review. Of these articles, 15 referred to review articles, 3 referred to other detecting methods, 4 were case reports or letters, 4 had no sufficient data for calculation, and 2 had repeated patients. Finally, 11 potentially relevant studies were identified as eligible studies [21-31].

The patients' clinical characteristics of the included studies were summarized in Table I. A total of 599 patients and 943

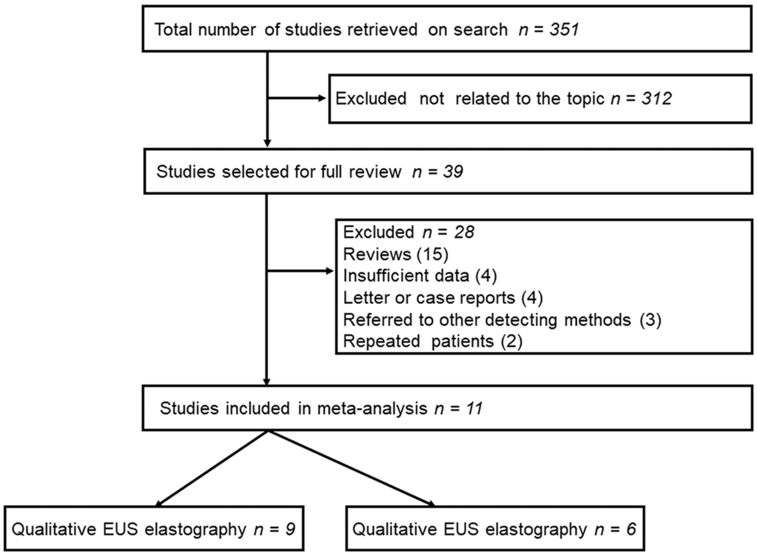

Fig. 1. Literature search flow diagram.

LNs were investigated in the analysis. The mean age ranged between 50.6 and 67.3 years. The mean size of LNs ranged from 13 mm to 43 mm. The location of all the LNs included cervical periesophageal part, mediastinum, and abdomen.

In the current study, the color pattern was defined as qualitative EUS elastography, while hue histogram and strain ratio (SR) were defined as quantitative EUS elastography. Among the included studies, 9 studies used qualitative EUS elastography [21-23, 25, 28-32], 6 studies used quantitative EUS elastography [22, 24, 27, 30-32], and 4 studies used both qualitative and quantitative EUS elastography [22, 30-32]. Of the 6 articles using quantitative EUS elastography, 2 studies used hue histogram [22, 24], and 4 studies used strain ratio [27, 30-32]. For those using SR in our meta-analysis, the cut-off values varied from 4.5 to 7.5.

Quality Assessment Using the QUADAS Questionnaire

Detailed information of the quality assessment is listed in Supplementary file (Table I). All the studies that have a "yes" rating for over 10 items, suggesting a good quality of studies. The studies by Janssen et al. [23], Paterson et al. [27] and Altonbary et al. [30] selected patients who were referred for EUS-FNA, so item 1 concerning spectrum composition and item 3 concerning appropriate reference standard were scored nil. Five studies [21-23, 28, 32] failed to obtain the final diagnosis of all LNs in selected patients and were scored nil for item 5 concerning partial verification bias. For item 11 concerning diagnostic review bias, four studies [29-32] were scored unclear. There were four studies [22-24. 28] which were scored nil for item 14, because they failed to explain the reason for withdrawal from their studies.

Diagnostic Accuracy of Qualitative EUS Elastography

Nine studies involving 497 patients and 817 LNs reported tissue elasticity by color patterns with blue predominant as malignancy. As shown in Figs. 2a and 3a, the pooled sensitivity, specificity, positive and negative LR for the diagnosis of malignant LNs by qualitative EUS elastography were 0.82 (95%CI: 0.77-0.86), 0.92 (95%CI: 0.89-0.94), 7.83 (95%CI: 3.58-17.09) and 0.22 (95%CI: 0.14-0.34), respectively. The summary DOR was 48.73 (95%CI: 21.83-108.80) (Fig. 4a). The SROC curves and *Q index of qualitative EUS elastography for malignant LNs are shown in Fig. 5a. The AUC and the estimates of Q* index were 0.933 and 0.869, respectively. In the chi-square and I^2 tests, there were statistically significant heterogeneity in the sensitivity (heterogeneity X^2=25.86, p=0.0011; I^2=69.1%), specificity (heterogeneity X^2=44.34, p<0.0001; I^2=82.0%), positive LR (heterogeneity X^2=50.47, p<0.0001; I^2=84.1%), negative LR (heterogeneity X^2=24.87, p=0.0016; I^2=67.8%), and DOR (heterogeneity X^2=17.90, p=0.0220; I^2=55.3%).

Diagnostic Accuracy of Quantitative EUS Elastography

As shown in Figure 2b, the pooled sensitivity and specificity of quantitative EUS elastography for the differentiation of benign and malignant deep LNs were 0.8 (95%CI: 0.74-0.86) and 0.87 (95%CI: 0.82-0.92), which were similar to that of qualitative EUS elastography. The positive and negative LR were 5.63 (95%CI: 3.46-9.17) and 0.23 (95%CI: 0.12-0.44) for quantitative EUS elastography (Fig. 3b). The summary DOR was 33.35 (95%CI: 12.81-86.87) (Fig. 4b), and the AUC was 0.923 (Q*=0.857) (Fig. 5b). In the chi-square and I^2 tests, there were statistically significant heterogeneity in the sensitivity (heterogeneity X^2=20.61, p=0.001; I^2=75.7%), specificity (heterogeneity X^2=10.09, p=0.0728; I^2=50.4%), negative LR (heterogeneity X^2=24.85, p=0.0001; I^2=79.9%), and DOR (heterogeneity X^2=10.46, p=0.0633; I^2=52.2%), while heterogeneity in positive LR (heterogeneity X^2 = 7.11, p=0.2126; I^2=29.7%) was not observed.

Six studies using quantitative elastography were divided into two groups comprising strain ratio and hue histogram. Of these, four studies had used the strain ratio as the diagnostic standard. The pooled sensitivity and specificity were 0.77 (95%CI: 0.68-0.84) and 0.87 (95%CI: 0.81-0.92) respectively (Supplementary file, Fig 1).

Table I. Main characteristics of the included studies

Author	Year	Country	Study design	No.of Patients	No.of LNs	Location of LNs	Mean size of LNs (mm)	Mean age (years)	Reference standard	Diagnostic standard	Cut-off	Device used
Giovannini et al.	2006	France	Prospective, single-center	25	31	Cervical periesophageal part, mediastinum, abdomen	19.7	57	EUS-FNA, surgery, follow-up	Color pattern	Blue predominant	EUB-8500 with Pentax EG38–UT
Saftoiu et al.	2006	Denmark	Prospective, single-center	31	42	Cervical periesophageal part, mediastinum, abdomen	17.26	64.6	EUS-FNA, surgery, follow-up	Color pattern or hue histogram	Blue predominant or 78	EUB-8500 with Pentax EG 3830
Janssen et al.	2007	Germany	Prospective, single-center	50	66	Mediastinum	24.31	63.2	EUS-FNA	Color pattern	Blue predominant	EUB-8500 with Pentax FG 34ux and FG 38ux
Saftoiu et al.	2007	Denmark	Prospective, single-center	54	78	Cervical periesophageal part, mediastinum, abdomen	17.4	61.4	EUS-FNA, surgery, follow-up	Hue histogram	166	EUB-8500 with Pentax EG 3830
Giovannini et al.	2009	France	Retrospective, Multi-center	101	101	Cervical periesophageal part, mediastinum, abdomen	20.1	61.1	EUS-FNA, surgery, follow-up	Color pattern	Blue predominant	EUB-8500 with Pentax EG38-UT and EG38-70UTK
Larsen et al.	2012	Denmark	Prospective, single-center	56	56	Cervical periesophageal part, mediastinum, abdomen	13	66	Surgery	Color pattern or strain ratio	Blue predominant or 4.5	EUB-8500 or 900 with Pentax FG 38ux
Paterson et al.	2012	United Kingdom	Prospective, single-center	48	48	Mediastinum, abdomen	NA	67.3	EUS-FNA	Strain ratio	7.5	EUB-8500
Knabe et al.	2013	Germany	Prospective, single-center	33	33	Cervical periesophageal part, mediastinum, abdomen	NA	64	EUS-FNA, surgery, follow-up	Color pattern	Blue predominant	EUB-8500 with Pentax EG3870 UTK
Sazuka et al.	2016	Japan	Prospective, single-center	35	322	Cervical periesophageal part, mediastinum, abdomen	NA	NA	Surgery	Color pattern	Blue predominant	EUB-7500 with Pentax EG3870 UTK
Altonbary et al.	2018	Egypt	Retrospective, single-center	40	40	Cervical periesophageal part, mediastinum, abdomen	43	52.5	EUS-FNA	Color pattern or strain ratio	Blue predominant or 6.7	Pentax EG3870 UTK
Okasha et al.	2018	Egypt	Prospective, single-center	126	126	Cervical periesophageal part, mediastinum, abdomen	19	50.6	EUS-FNA, surgery, follow-up	Color pattern or strain ratio	Blue predominant or 4.61	EUB-7000 with Pentax EG-3830UT

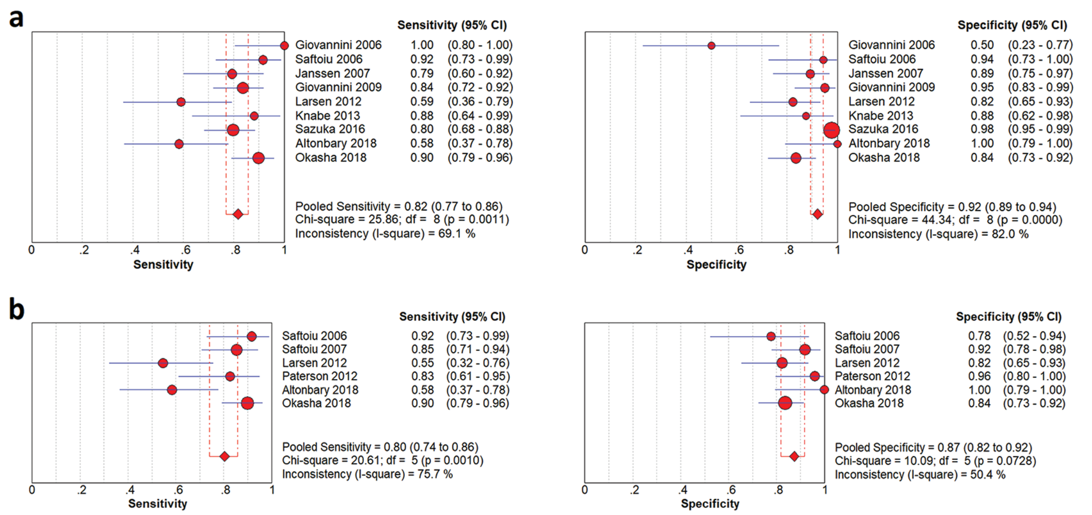

Fig. 2. Forest plot of the meta-analysis for sensitivity and specificity for EUS elastography in the diagnosis of malignant deep LNs. (a) qualitative EUS elastography; (b) quantitative EUS elastography.

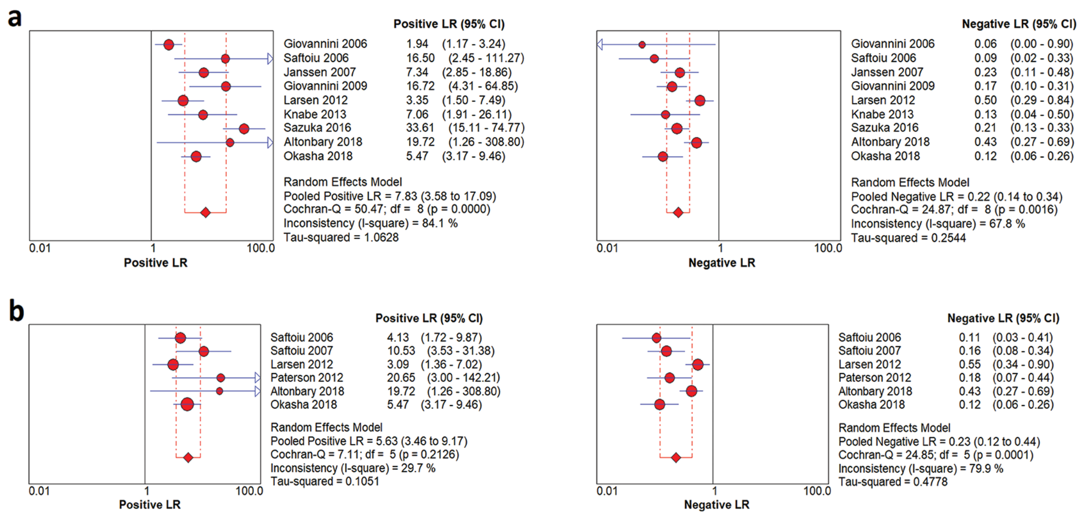

Fig. 3. Forest plot of the meta-analysis for positive LR and negative LR of EUS elastography for differentiation of deep LNs. (a) qualitative EUS elastography; (b) quantitative EUS elastography.

As shown in Supplementary file, Fig 2, the positive and negative LR were 5.64 (95%CI: 2.75-11.59) and 0.29 (95%CI: 0.14-0.60) for the strain ratio group. The summary DOR was 28.15 (95%CI: 6.78-116.93) (Supplementary file, Figure 3). The AUC and the estimate of Q* index were 0.914 and 0.846, respectively (Supplementary file, Fig. 4).

Publication Bias

The Begg's test was used to examine the publication bias. No significant publication bias was found for diagnostic OR of qualitative EUS elastography (p=0.835) and quantitative EUS elastography (p=0.851) in the meta-analyses (Fig. 6).

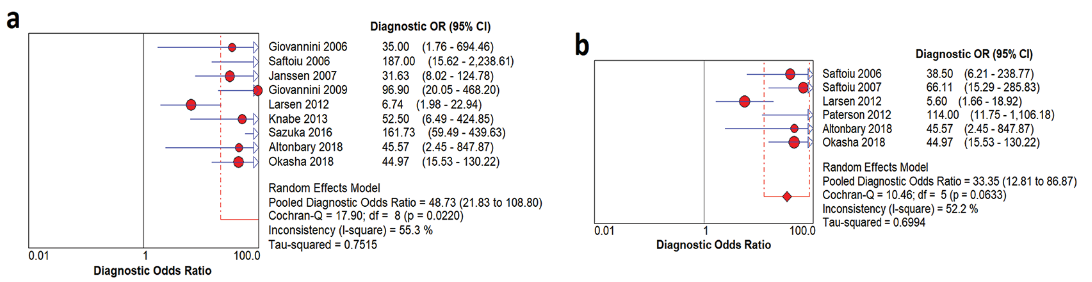

Fig. 4. Forest plot of DOR of qualitative EUS elastography(a) and quantitative EUS elastography (b) used to examine the diagnostic accuracy for the differentiation of benign and malignant deep LNs.

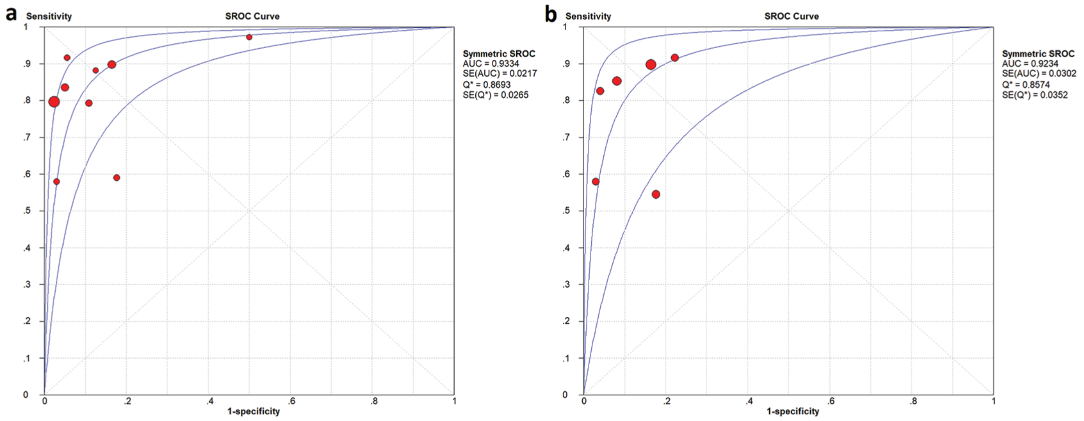

Fig. 5. Summary receiver operating characteristic (SROC) curve of EUS elastography for the differentiation of benign and malignant deep LNs. (a) qualitative EUS elastography; (b) quantitative EUS elastography.

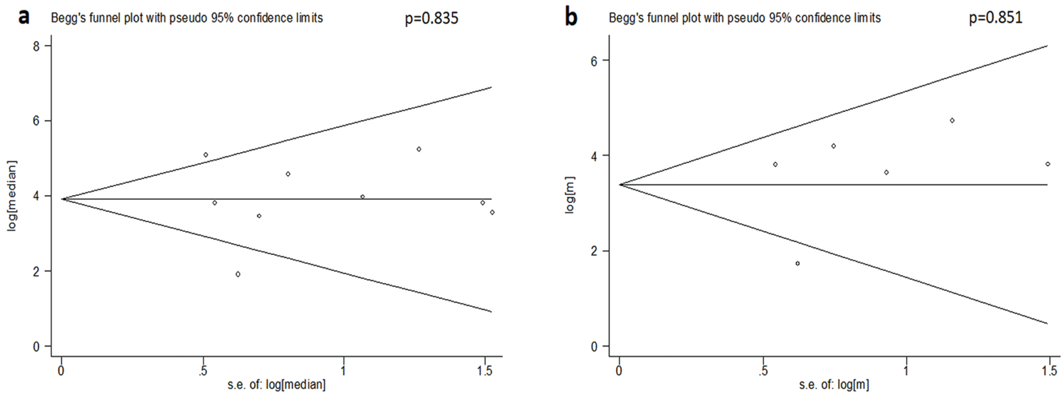

Fig. 6. Funnel plot of the Begg's test used to evaluate publication bias of selected studies. (a) qualitative EUS elastography; (b) quantitative EUS elastography.

DISCUSSION

Differentiating benign and malignant LNs according to EUS characteristics is often difficult and usually necessitates EUS-guided FNA for a more accurate diagnosis. Elastography is a sort of "palpation by imaging", which allows real-time estimation of tissue stiffness. EUS elastography is a new promising technique to complement conventional EUS and may be used as an additional noninvasive technique to help characterizing lesions and LNs in the proximity of the gastrointestinal tract and making further clinical management.

In the current study, we evaluated the performance of EUS elastography for the differentiation of benign and malignant deep LNs. Our meta-analysis found that both qualitative and quantitative EUS elastography performed well as a diagnostic test for LNs. The pooled sensitivities of qualitative and quantitative EUS elastography were 0.82 (95%CI: 0.77-0.86) and 0.80 (95%CI: 0.74-0.86), respectively. In addition, the pooled specificities were also similar and relatively higher, 0.92 (95%CI: 0.89-0.94) and 0.87 (95%CI: 0.82-0.92) for qualitative and quantitative EUS elastography, respectively. The summary DOR of qualitative and quantitative EUS elastography were 48.73 (95%CI: 21.83-108.80) and 33.35(95%CI: 12.81-86.87), respectively. The pooled results implied that the accuracy of quantitative EUS elastography was similar to that of qualitative EUS elastography for the diagnosis of malignant LNs.

EUS elastography uses a qualitative method or a quantitative method. Elastography began as a qualitative technique, where blue areas indicative of stiff tissues were considered more likely malignant [14, 15]. This method is highly operator dependent and cannot provide an objective diagnosis. The sensitivities of nine studies included in our study using qualitative elastography rage from 41.7% to 100%. Most studies reported the sensitivity was more than 80%, and only two studies reported the sensitivities were nearly 50% [30, 32]. All but one of the articles using qualitative elastography had a specificity of more than 80%. There are two options for quantitative elastography evaluation, a hue histogram or strain ratio calculation. The hue histogram is a graphical representation of the color distribution in a selected image field, which can minimize the operator bias to make an objective evaluation. The number of studies using hue histogram in our study is small, and there were only two studies published by the same author using hue histogram values for the differentiation of benign and malignant LNs [22, 24]. Strain ratio was calculated by comparing the mean strain measurement for the target of the lymph node with a surrounding tissue, and a higher ratio indicates a higher probability of malignancy. The use of a strain ratio is an objective measure that is not limited by the inter-observer variability. A total of four studies used the strain ratio for the diagnosis of malignant LNs [27, 30-32]. The sensitivity of each study varied greatly, but all the specificities of the four studies were over 80%. For those using SR in our study, the cut-off values varied from 4.5 to 7.5. The optimal cut-off value has not yet been determined and more researches are required to confirm in the future.

For qualitative EUS elastography, heterogeneity was found in the sensitivity (heterogeneity X^2=25.86, p=0.0011; I^2=69.1%), specificity (heterogeneity X^2=44.34, p<0.0001; I^2=82.0%), positive LR (heterogeneity X^2=50.47, p<0.0001; I^2=84.1%), negative LR (heterogeneity X^2=24.87, p=0.0016; I^2=67.8%), and DOR (heterogeneity X^2=17.90, p=0.0220; I^2=55.3%) in our meta- analysis. While for quantitative EUS elastography, heterogeneity was found in the sensitivity (heterogeneity X^2=20.61, p=0.001; I^2=75.7%), specificity (heterogeneity X^2=10.09, p=0.0728; I^2=50.4%), negative LR (heterogeneity X^2=24.85, p=0.0001; I^2=79.9%), and DOR (heterogeneity X^2=10.46, p=0.0633; I^2=52.2%). This could be explained by the large variations of patients' LN lesions between the included studies. The location of LNs included cervical periesophageal part, mediastinum, abdomen, and others. Of these, in some cases only mediastinum LNs of esophageal cancer were assessed, while in others all LNs around the entire upper digestive tract were assessed. Secondly, the reference standard was different, and most studies used EUS-FNA, surgery, or follow-up. Three studies used EUS-FNA as the reference standard [23, 27, 30], while two studies used surgery [29, 32]. In addition, the size of LNs can also affect the results. Other important explanations could be the different kinds of ultrasound machine, methodology and design of studies.

There were some limitations in this meta-analysis. Firstly, EUS elastography has intra- and inter-observer variability owing to endoscopists with different levels of experience. Secondly, varied diagnostic standards for EUS elastography were applied in the enrolled studies, and the studies about quantitative EUS elastography were relatively rare. Thirdly, the malignant LNs detection rate of EUS elastography is dependent on the LNs size, localization and histological type. Another limitation is unpublished studies were not identified in our meta-analysis, and articles written in other languages besides English were not included.

CONCLUSIONS

Our meta-analysis demonstrated that either qualitative or quantitative EUS elastography could be used as a promising noninvasive identification tool for benign and malignant deep LNs. This might be used as a valuable complementary method to help characterize LNs after negative EUS-guided FNA even before EUS-guided FNA. Nevertheless, the preferable quantitative EUS elastography for LNs requires further evaluation.

Conflicts of interest: None to declare.

Authors contributions: C.Z., F.Z., P.L., B.Z conceived the study and designed the methodology. C.Z., F.Z. extracted the included studies. C.Z., F.Z., P.L. performed a quality assessment and the statistics. C.Z. drafted the manuscript. B.Z. resolved disagreements, offered the technique support and revised the paper. All the authors read and approved the final version of the manuscript.

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Supplementary material: To access the supplementary material visit the online version of the *J Gastrointestin Liver Dis* at http://dx.doi.org/10.15403/jgld-5754

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