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Diagnostic utility of endoscopic ultrasonography-elastography in the evaluation of solid pancreatic masses: a meta-analysis and systematic review

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Abstract

Aim: The accuracy for endoscopic ultrasonography-elastography (EUS-EG) in the evaluation of solid pancreatic masses varies greatly and the pooled results have not been updated since 2013. Also, there still lack a comprehensive comparison among EUS-EG, contrast-enhanced EUS (CE-EUS), and EUS-guided fine needle aspiration (EUS-FNA). **Material and methods:** A thorough search was made for diagnostic trials investigating the role of EUS-EG in solid pancreatic masses. Meta-Disc was used to calculate the pooled sensitivity, specificity, diagnostic odds ratio and summary receiver operator characteristics. **Results:** Finally, 17 studies (1537 patients, 1544 lesions) were selected. The pooled sensitivity and specificity for qualitative methods were 0.97 (95%CI, 0.95-0.99) and 0.67 (95%CI, 0.59-0.74), respectively; the pooled sensitivity and specificity for strain histograms were 0.97 (95%CI, 0.95-0.98) and 0.67(95%CI, 0.61-0.73), respectively; the pooled sensitivity and specificity for strain ratio were 0.98 (95%CI, 0.96-0.99) and 0.62 (95%CI, 0.56-0.68), respectively; the pooled sensitivity and specificity for CE-EUS were 0.90 (95%CI, 0.83-0.95) and 0.76 (95%CI, 0.67-0.84), respectively; the pooled sensitivity and specificity for EUS-FNA were 0.84 (95%CI, 0.77-0.90) and 0.96(95%CI, 0.88-1.00), respectively. **Conclusion:** EUS-EG is reliable for distinguishing solid pancreatic masses; the sensitivity and specificity for different diagnostic methods were very close. Both EUS-EG and CE-EUS can be valuable complementary supplements for EUS-FNA.

Keywords: endoscopic ultrasonography; elastography; contrast-enhanced EUS; EUS-guided fine needle aspiration; pancreatic masses.

Introduction

It is always a great challenge to differentiate solid pancreatic masses; nevertheless, figuring out its final diagnosis is of critical importance, as it will have significant influence on the clinical decision makings. Clinical information, biochemical tests, and imaging techniques may help in the evaluation of solid pancreatic masses [1,2]. A previous study has shown that, magnetic resonance imaging (MRI) was very sensitive to detect pancreatic cystic lesions, while endoscopic ultrasonography (EUS) showed its superiority in solid lesions [3]. Except for conventional B-mode EUS, EUS-elastography (EUS-EG), contrast-enhanced EUS (CE-EUS) and EUS-guided fine needle aspiration (EUS-FNA) all play different but important roles. For those with negative EUS-FNA results or inadequate cells, EUS-EG and CE-EUS could be valuable adjunctive clinical tools [4,5].

The principle of EUS-EG is to evaluate the tissue hardness to help make diagnosis. Generally, malignant tissue is harder than benign tissue [6]. Measurements of elasticity can be divided into qualitative methods and quantitative methods, the former include color pattern

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diagnosis and elastic score, the latter include strain histograms (SH) and strain ratio (SR). The accuracy of EUS-EG in distinguishing solid pancreatic masses has varied greatly in different studies [4,7-9], and several meta-analysis have been published on this issue [10-15]. However, the newly added data since 2013 have not been updated [4,7-9,16], and the results should be pooled separately based on each different measurement. Moreover, there still lacks a comprehensive comparison among EUS-EG, CE-EUS, and EUS-FNA. To answer the above questions, we made a thorough search of the published articles.

Material and methods

Literature search and selection criteria

We searched the three main databases, namely, Pubmed, Embase, and Cochrane Controlled Register Databases, for articles published from inception to 31July, 2016.The following search strategy was used, [(elastograms) OR (elastograms) OR (elastography) OR (sonoelastography) OR (elastographies) OR (sono elastographies) OR elastosonoendoscopy)] AND [(EUS) OR (endoscopic ultrasonography) OR (endoscopic ultrasound) OR (endosonography) OR (echo-endoscopy) OR (ultrasonic endoscopy) OR (endosonographies)] AND [(pancreas OR pancreatic)].

Two authors selected the articles independently. The inclusion criteria were: 1) diagnostic trials investigating the role of EUS-EG in solid pancreatic masses; 2) final diagnosis was made through the cytology obtained by EUS-FNA or other method, histology of surgical resection, or more than 6 months' follow-up; 3) true positive (TP), false positive (FP), true negative (TN) and true positive (TP) could be extracted to construct a 2×2 table; 4)references from eligible articles or reviews were also assessed. The exclusion criteria were: a) case reports, editorials or letters; b) without enough data for the 2×2 table; c) cystic lesions; d) review or systematic review; e) quality assessment of diagnostic accuracy studies (QUADAS) score less than 9; f) repeated data (chose the one with better quality).

Study selection and data extraction

The reviewers firstly removed the duplicates, and then reviewed the titles and abstracts to identify eligible articles. Next, full-text was assessed using the inclusion criteria and the exclusion criteria. QUADAS instrument, the well-known criteria for assessing diagnostic trials, was used to measure the quality of each study [17].If any dispute existed, the two reviewers would discuss or ask for help from a third reviewer. Two investigators extracted the data from the final selected studies using a standardized form, mainly for the information about author, publication year, country, study design, information of the patients, QUADAS score, methods, cut-off values, TP, FP, FN, and TN. If the diagnostic utility of CE-EUS or EUS-FNA has also been evaluated, their data were also extracted to construct a 2×2 table.

Statistical analysis

Meta-Disc, Version 1.4 (Ramony Cajal Hospital, Madrid, Spain) was used for data analysis. The pooled sensitivity, specificity, diagnostic odds ratio (DOR) and summary receiver operator characteristics (SROC) for EUS-EG was calculated respectively. For sensitivity, specificity and DOR, 95% confidence interval (CI) was also presented, and for SROC area under the curve, standard error (SE) was calculated. Inconsistency ($I2$) was used to evaluate the heterogeneity among studies [18]. I^2>50% indicating significant heterogeneity, and random-effects model was used, otherwise fixed-effects model was reported. The Spearman correlation coefficient was calculated to figure out whether threshold effect existed. Meta-regression analysis was then performed to explore the possible sources of heterogeneity in the studies. Statistical significance was defined as $p< 0.05$ (two-tailed). Stata MP, Version 14 (StataCorp LLC, Texas, USA) was used to draw the Fagan plot.

Results

Search results and characteristics of the selected studies

In total, 225 articles were identified in the three databases, and 8 more articles were found through reference search. Seventeen studies were finally selected [4,7-9,16,19-30] (figure 1 shows the flow chart of the selection process). Only one was a conference abstract [27], the others were all full-texts. Altogether, 1537 patients (1544 lesions) were evaluated in these studies, of these, 1043 lesions were malignant, and 501 lesions were benign. Characteristics of the selected studies are shown in Table I. Six studies used SH as the diagnostic standard [4,9,22,26-28], 7 studies used SR [7-9,16,19,23,27,30], 3 studies used color pattern[20,23,24],and 3 studies used elastic score [21,25,29]. For those using SH, the cut-off values ranged from 62 to 80, and for those using SR, the cut-off values varied from 3.05 to 24.82. Their cut-off values were decided by using previous published studies, or the one with the highest accuracy rate based on the receiver operator characteristic (ROC) curves. Four studies also evaluated CE-EUS [4,19,20,22], and 4 studies evaluated EUS-FNA [7,8,19,22].

Summary estimates of sensitivity, specificity, and DOR for qualitative methods

The pooled sensitivity (random-effect model) and specificity (random-effect model) were 0.97 (95%CI,

Table I. Characteristics of the selected studies

Study	Country	Design	No. of patients	Diseases	Age (yrs)	Male ratio	Mass in head ratio	Reference standard	QUADAS score
Iordache, 2016	Romania	Retrospective, single-centered	50	PC, CP	54	86	90	Surgery, EUS-FNA, follow-up	11
Mayerle, 2016	Germany	Prospective, single-centered	63	PC, CP	65	NG	NG	Surgery, EUS-FNA, follow-up	11
Kongkam, 2015	Thailand	Prospective, single-centered	38	PC, CP, AIP, metastasis, others	61	47.37	60	Surgery, biopsy, cytopathology, follow-up	12
Opacic, 2015	Croatia	Prospective, single-centered	149	PC, CP, control, metastasis, NET	63	48.99	51.5	Surgery, EUS-FNA, follow-up	12
Havre, 2014	Norway	Prospective, single-centered	39 (46 lesions)	PC, CP,NET, others	55	51.28	NG	Surgery, EUS-FNA, follow-up	12
Figueiredo, 2012	France	Prospective, single-centered	47	PC, CP, AIP, others	70	53.19	51	Surgery, EUS-FNA,CT, MRI follow-up	12
Hocke, 2012	Germany	NG	58	PC, CP	60	67.24	NG	Surgery, EUS-FNA, follow-up	10
Itokawa, 2011	Japan	Retrospective, single-centered	86	PC, CP, AIP,NET, control	65	64.22	NG	Surgery, EUS-FNA, imaging modalities, blood examinations, follow-up	10
Saftoiu, 2010	Germany	Prospective, single-centered	54	PC, CP	57	79.63	87.04	Surgery, EUS-FNA, follow-up	11
Iglesias, 2010	Spain	Prospective, single-centered	86	PC, CP, NET, metastasis, lymphoma	61	67.44	72.09	Surgery, EUS-FNA,CT, follow-up	12
Iglesias, 2009	Spain	Prospective, single-centered	130	PC, CP, metastasis, NET	62	66.92	76.15	Surgery, EUS-FNA, follow-up	12
Giovannini, 2009	Europe	Multi-centered	121	PC, CP, metastasis, NET	64	63.64	65.29	Surgery, EUS-FNA, follow-up	11
Saftoiu, 2008	Denmark	Prospective, single-centered	68	PC, CP, NET, control	57	69.12	NG	Surgery, EUS-FNA, follow-up, US, CT	10
Lariño-Noia, 2015	Spain	Prospective, single-centered	162	PC, CP, metastasis, NET	63	60.49	66.05	Surgery, radiological assessment, follow-up, EUS-FNA/B	11
Saftoiu, 2011	Europe	Prospective, multi-centered	258	PC, CP	63	66.67	75.58	Surgery, EUS-FNA, imaging data, follow-up	11
Giovannini, 2006	France	Single-centered	24	PC, CP, others, metastasis, NET	60	NG	50	Surgery, EUS-FNA, follow-up	10
Dawwas, 2012	UK	Single-centered	104	PC, CP, others, metastasis, NET	67	54.8	53.9	Surgery, clinical, biochemical and radiological follow-up, biopsy, EUS-FNA	12

PC, pancreatic carcinoma; CP, chronic pancreatitis; AIP, autoimmune pancreatitis; NET, neuroendocrine tumor; NG, not giving; UK, the United Kingdom; EUS-FNA, endoscopic ultrasound-guided fine needle aspiration; CT, computed tomography; MRI, magnetic resonance imaging; US, ultrasonography; EUS-FNB, endoscopic ultrasound-guided fine needle biopsy.

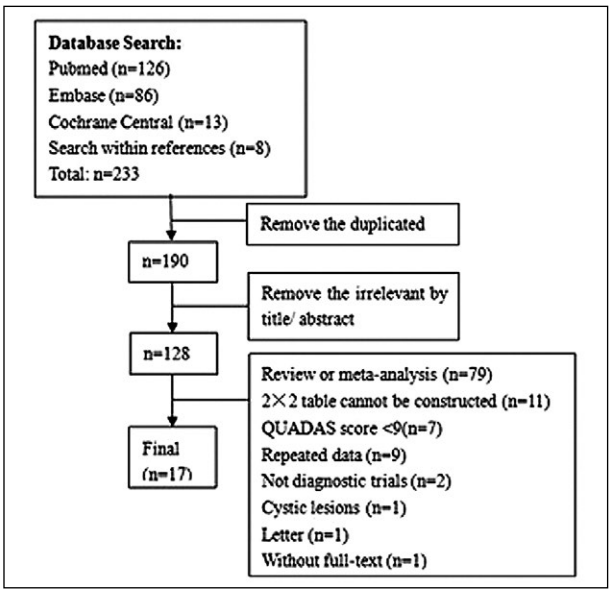

Fig 1. Flow chart of the selection process.

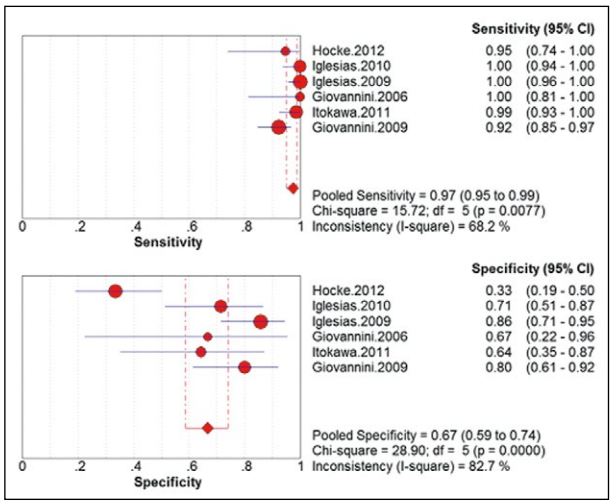

Fig 2. Forest plots showing the sensitivity and specificity for endoscopic ultrasonography – elastography using qualitative methods to differentiate malignant from benign solid pancreatic masses.

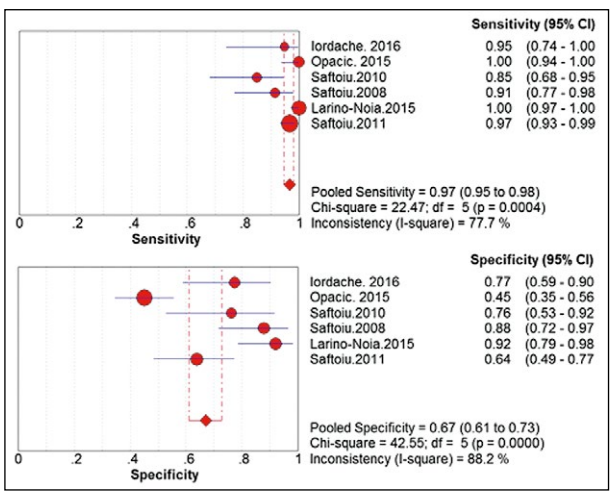

Fig 3. Forest plots showing the sensitivity and specificity for endoscopic ultrasonography – elastography using strain histograms to differentiate malignant from benign solid pancreatic masses.

0.95-0.99, I^2=68.2%) and 0.67 (95%CI, 0.59-0.74, I^2=82.7%), respectively (fig 2). The pooled DOR (fixed-effect model) was 71.24 (95%CI, 29.64-171.22), with moderate heterogeneity (I^2=40.3%). The SROC area under the curve was 0.9195 (SE=0.1027). The Q* index was 0.8528 (SE=0.1178). The Spearman correlation coefficient was -0.406 (p= 0.425), suggesting no threshold effect existed. Area, disease coverage, malignant proportion was taken into consideration for meta-regression, while no factors was found to be the possible source of heterogeneity. Forest plots showed that, two studies were outliers [20, 25], after excluding the outliers, the heterogeneity diminished, suggesting that the outliers might be the sources of heterogeneity. Based on subgroup analysis excluding the outliers, the pooled sensitivity (fixed-effect model) and specificity (fixed-effect model) were 1.00 (95%CI, 0.98-1.00, I^2=0%) and 0.77 (95%CI, 0.67-0.85, I^2=24.0%), respectively. The pooled DOR (fixed-effect model) was 272.04 (95%CI, 71.53-1034.69), without heterogeneity (I^2=0%). The SROC area under the curve was 0.8126 (SE=0.9182). The Q* index was 0.7469 (SE=0.8159).

Summary estimates of sensitivity, specificity, and DOR for SH

The pooled sensitivity (random-effect model) and specificity (random-effect model) were 0.97 (95%CI, 0.95-0.98, I^2=77.7%) and 0.67(95%CI, 0.61-0.73, I^2=88.2%), respectively (fig 3). The pooled DOR (fixed-effect model) was 68.61 (95%CI, 36.05-130.59), without significant heterogeneity ($I2$=48.2%). The SROC area under the curve was 0.9163 (SE=0.0434). The Q* index was 0.8491 (SE=0.0492).The Spearman correlation coefficient was -0.029 (p=0.957), suggesting no threshold effect existed. Meta-regression was performed to explore the possible sources of heterogeneity. We took male ratio, disease coverage, malignant proportion into consideration, while it still could not show the sources of heterogeneity. Three studies [4,22,26] used the same cut-off value, and their pooled sensitivity (fixed-effect model) and specificity (fixed-effect model) were 0.90 (95%CI, 0.81-0.95) and 0.81 (95%CI, 0.71-0.89), respectively. The heterogeneity disappeared (I^2=0%), suggesting that differ-

ent cut-off values might be the sources of heterogeneity. Based on subgroup analysis using the same cut-off value, the pooled DOR (fixed-effect model) was 39.24 (95%CI, 15.91-96.74), with minor heterogeneity (I^2=5.1%). The SROC area under the curve was 0.9187 (SE=0.0696). The Q* index was 0.8519 (SE=0.0796).

Summary estimates of sensitivity, specificity, and DOR for SR

The pooled sensitivity (random-effect model) and specificity (random-effect model) were 0.98 (95%CI, 0.96-0.99, *I*2=72.7%) and 0.62(95%CI, 0.56-0.68, *I*2=87.5%), respectively (fig 4). The pooled DOR (random-effect model) was 57.35 (95%CI, 17.80-184.74), with significant heterogeneity (*I*2=55.8%). The SROC area under the curve was 0.9284 (SE=0.0655). The Q* index was 0.8632 (SE=0.0780). The Spearman correlation coefficient was -0.024 (P= 0.955), suggesting no threshold effect existed. Area, malignant ratio, disease coverage was taken into consideration for meta-regression, while no factors was found to be the possible source of heterogeneity. Forest plots showed that, three studies were outliers [23,27,30]; after excluding the outliers, the heterogeneity diminished, suggesting that the outliers might be the sources of heterogeneity. Based on subgroup analysis excluding the outliers, the pooled sensitivity (fixed-effect model) and specificity (fixed-effect model) were 0.94 (95%CI, 0.90-0.97, *I*2=29.7%) and 0.54 (95%CI, 0.46-0.62, I^2=27.2%), respectively. The pooled DOR (fixed-effect model) was 29.42 (95%CI, 12.62-68.62), without heterogeneity (I^2=0%). The SROC area under the curve was 0.8707 (SE=0.0752). The Q* index was 0.8012 (SE=0.0742).

Summary estimates of sensitivity, specificity, and DOR for CE-EUS

The pooled sensitivity (fixed-effect model) and specificity (fixed-effect model) were 0.90 (95%CI, 0.83-0.95, I^2=0%) and 0.76 (95%CI, 0.67-0.84, I^2=0%), respectively (fig 5).The pooled DOR (fixed-effect model) was 25.84 (95%CI, 11.83-56.44, I^2=0%). The SROC area under the curve was 0.8819 (SE=0.0656). The Q* index was 0.8124 (SE=0.0666).

Summary estimates of sensitivity, specificity, and DOR for EUS-FNA

The pooled sensitivity (fixed-effect model) and specificity (fixed-effect model) were 0.84 (95%CI, 0.77-0.90, *I*2=0%) and 0.96 (95%CI, 0.88-1.00, *I*2=50.8%), respectively (fig 6). The pooled DOR (fixed-effect model) was 70.50 (95%CI, 22.36-222.32, *I*2=0%). The SROC area under the curve was 0.8695 (SE=0.0858). The Q* index was 0.8000 (SE=0.0845). The Spearman correlation coefficient was -0.400 (p=0.600), suggesting no threshold effect existed. Due to the small number of the studies included, it was impossible to do the meta-regression, and forest plots implied that one study was the outlier [19]. Excluding the outlier, the heterogeneity disappeared, suggesting that the outliers might be the sources of heterogeneity. Based on a subgroup analysis excluding the outliers, the pooled sensitivity (fixed-effect model) and specificity (fixed-effect model) were 0.85 (95%CI, 0.77-0.92, I^2=0%) and 1.00 (95%CI, 0.92-1.00, I^2=0%), respectively. The pooled DOR (fixed-effect model) was 165.26 (95%CI, 29.06-939.76, I^2=0%). The SROC area under the curve was 0.9621 (SE=0.0837). The Q* index was 0.9076 (SE=0.1245).

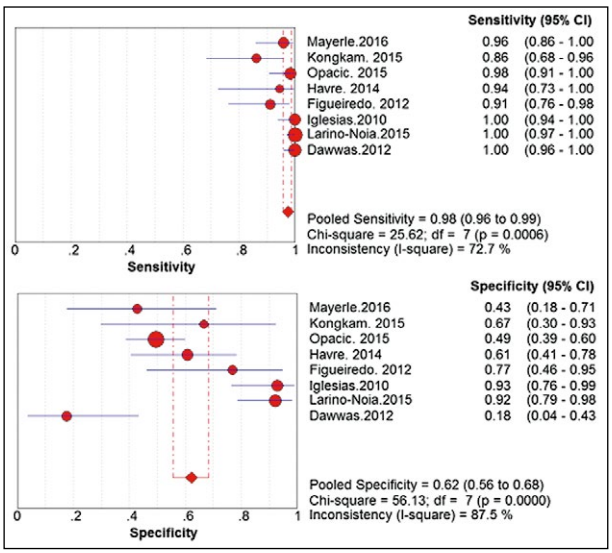

Fig 4. Forest plots showing the sensitivity and specificity for endoscopic ultrasonography – elastography using the strain ratio to differentiate malignant from benign solid pancreatic masses.

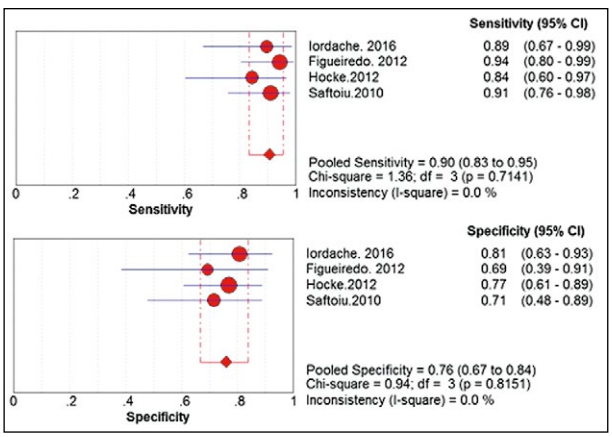

Fig 5. Forest plots showing the sensitivity and specificity for contrast-enhanced endoscopic ultrasonography to differentiate malignant from benign solid pancreatic masses.

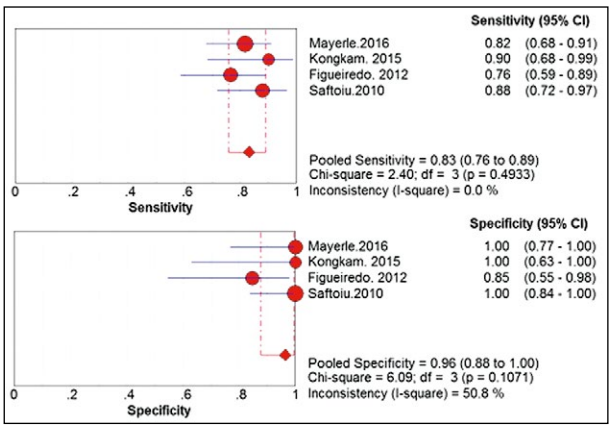

Fig 6. Forest plots showing the sensitivity and specificity for endoscopic ultrasound-guided fine needle aspiration to differentiate malignant from benign solid pancreatic masses.

The summary estimates of sensitivity, specificity, DOR and Q* index of each method were listed in Table II. To make a visual presentation, we drew a Fagan plot to evaluate the clinical utility of each method (fig 7). With pre-test probability of 20% to develop malignant masses, the post-test probability of malignancy gave a negative result; using the qualitative method it was 0%, and 44% with a positive result, 1% and 53% for SH, 1% and 42% for SR, 3% and 48% for CE-EUS, 4% and 95% for EUS-FNA, in sequence.

Publication Bias

Since the number of studies in each method group was small (less than 10) it is difficult to draw the funnel plot and reveal the publication bias. But an exhaustive search was made through the Pubmed, Embase, and Cochrane Controlled Register Databases and the references of related issues to minimize the publication bias.

Table II. Summary estimates of sensitivity, specificity, DOR, and Q* for different methods

Method	Pooled Sensitivity	Pooled Specificity	DOR	Q*
Qualitative				
Overall	0.97 (0.95-0.99)	0.67(0.59-0.74)	71.24 (29.64-171.22)	0.8528
Subgroup	1.00 (0.98-1.00)	0.77(0.67-0.85)	272.04 (71.53-1034.69)	0.7469
SH				
Overall	0.97(0.95-0.98)	0.67(0.61-0.73)	68.61(36.05-130.59)	0.8491
Subgroup	0.90(0.81-0.95)	0.81(0.71-0.89)	39.24(15.91-96.74)	0.8519
SR				
Overall	0.98(0.96-0.99)	0.62(0.56-0.68)	57.35 (17.80-184.74)	0.8632
Subgroup	0.94(0.90-0.97)	0.54(0.46-0.62)	29.42(12.62-68.62)	0.8012
CE-EUS				
Overall	0.90 (0.83-0.95)	0.76(0.67-0.84)	25.84 (11.83-56.44)	0.8124
EUS-FNA				
Overall	0.84(0.77-0.90)	0.96(0.88-1.00)	70.50(22.36-222.32)	0.8000
Subgroup	0.85 (0.77-0.92)	1.00(0.92-1.00)	165.26 (29.06-939.76)	0.9076

DOR, diagnostic odds ratio; SH, strain histograms; SR, strain ratio; CE-EUS, contrast-enhanced endoscopic ultrasonography; EUS-FNA, endoscopic ultrasound-guided fine needle aspiration.

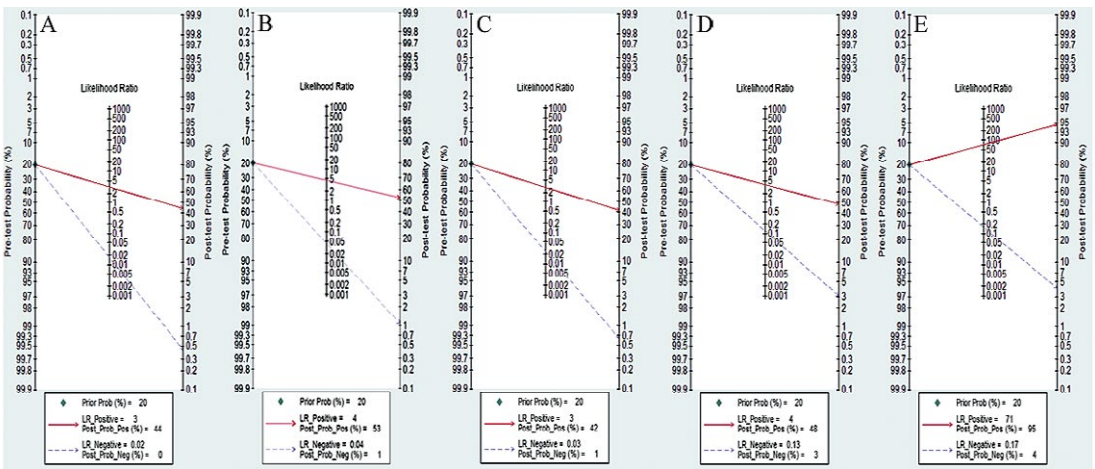

Fig 7. Fagan's plots to evaluate the clinical utility of each method: A, qualitative method; B, strain histograms; C, strain ratio; D, contrast-enhanced endoscopic ultrasonography, and E, endoscopic ultrasonography-guided fine needle aspiration.

Discussions

Diagnosing solid pancreatic masses is sometimes confusing, since we cannot get the cytology or histology specimens of the pancreas as easily and directly as the stomach or colon. The emergence of EUS-FNA has helped in obtaining the cells or tissues of the pancreatic mass; however, it is technically demanding, invasive, and the result may be inconclusive [31]. To make up for these flaws, EUS-EG has arisen as a new diagnostic technique in the diagnosis of pancreatic masses.

EUS-EG can aid in making the final diagnosis during conventional EUS examination by measuring the tissue stiffness; there is no need to perform a needle puncture or inject a contrast agent, which is much more convenient, and avoids the incidence of acute pancreatitis, hemorrhage, and infection [34,35]. In the elastographic images, different elasticity values are coded with different colors, where blue indicates hard tissues, red indicates soft tissues, and yellow or green indicates intermediate tissues [36]. In the color pattern diagnosis, the evaluation is made on the basis of major color tones and its distribution [36-38]. Giovannini et al [29] developed an elastic score to assign the elastographic images. A score ranged from 1 to 5 was used, and each stood for a kind of color pattern. In fact, the elastic score did not differ greatly from the color pattern diagnosis, except for using a number to show the pattern, and both are qualitative methods.

Color pattern diagnosis is subjective and hard to reproduce, and more objective methods are needed to decrease the dependence on the examiner [4]. Hence, SH emerged, through conversion of the elastographic images; a gray scale (0 to 255) is used to mark the color tone of the elastography image. There is a special type of SH called neural network, in which the selection of images is automatically done by computer, and selection bias can be reduced to some degree [4]. Another common quantitative method is SR, which compares the SH of two regions of interest, usually the ratio of peripheral tissue and the lesion [7,36]. The methods used and the results in the previously published studies are still in dispute [4,7-9,16], so we made a systematic review and meta-analysis of the published articles based on the different evaluation methods they used. At the same time, a comparison with EUS-FNA and CE-EUS was also made.

Our meta-analysis demonstrated that, EUS-EG was very sensitive to differentiate the solid pancreatic masses, with a pooled sensitivity of no less than 0.97; however, the specificity was not satisfactory (0.70). Different methods can be used to evaluate the elasticity of the masses; the pooled results imply that the difference in sensitivity and specificity among them was not obvious. The role of CE-EUS was similar to that of EUS-EG, also high in sensitivity (0.90), while low in specificity (0.76). For sensitivity, EUS-EG was higher than CE-EUS, while for specificity, it turned out the opposite. The results further pointed out that EUS-FNA was complementary to both EUS-EG and CE-EUS, as it was high in specificity (0.96). Nevertheless, it had a defect in the sensitivity (0.84).

Before our research, 6 systematic reviews and meta-analysis focused on this subject [10-15]. Among them, 3 studies [10,11,15] made a subgroup analysis based on qualitative and quantitative interpretations of the EUS-EG. One study indicated that, the color pattern showed preferable pooled estimates rather than the use of SH [10]. While the other two demonstrated that there was no significant difference in sensitivity or specificity between the qualitative and quantitative diagnostic standard [11,15]. Our results were in accordance with the latter. The inconsistency may lie in the disease category, as Li et al [10] evaluated the value of EUS-EG in differentiating pancreatic ductal adenocarcinoma from chronic pancreatitis, and the other three evaluated distinguishing malignant from benign lesions.

The roles of EUS-EG, CE-EUS and EUS-FNA in differentiating solid pancreatic masses are not the same but let us consider the combination of them? Three studies investigated the value of combing EUS-EG with CE-EUS [4,20,22], and the pooled sensitivity and specificity was 0.85 and 0.88, respectively, indicating that the combination of EUS-EG and CE-EUS help in increasing specificity. Hard and hypovascular masses suggests malignancy, while soft and iso/hypervascular indicates benign lesions. This is extremely vital for negative EUS-FNA, as the above two subgroup patients could be assigned to either surgery or follow-up. For intermediate patients, repeated EUS-FNA may be required [4]. Only one study evaluated the combination of EUS-EG with EUS-FNA [8], and in their study, the sensitivity and specificity for EUS-EG is 0.86 and 0.67, for EUS-FNA it is 0.90 and 1.00, and for EUS-EG +EUS-FNA it is 0.95 and 0.75, in sequence. This demonstrates that the combination of EUS-EG with EUS-FNA can make up for the demerits both in the specificity of using EUS-EG alone and in the sensitivity of using EUS-FNA alone. However, the sample size was not large enough; hence, the results should be validated in more multi-central randomized-controlled trials with a large sample-size, and what also should be figured out is whether EUS-EG guided EUS-FNA is superior to conventional EUS-FNA.

Each diagnostic method is similar to a double-edged sword; each have advantages and disadvantages. For EUS-EG, high sensitivity and non-invasiveness is its

obvious superiority. But there are still limitations [39]. The selection bias and the reproducibility of interpretation of EUS-EG is the main concern, especially among endoscopists with different experience levels. Soares et al [40] found that, EUS-EG was reproducible regardless whether the endoscopist had rich or limited experience in these techniques, and that an experienced endoscopist might have an increase in the reproducibility and diagnostic accuracy rate. The interobserver agreement κ value and areas under ROC curves (AUROC) for experienced endoscopists were 0.80 and 0.83, and for endoscopists with limited experience it was 0.54 and 0.77, respectively. Larger studies are needed for external validation. Other limitations include limited penetration depth (lesions in near field or small in size have better result); inadequate presentation of surrounding tissues, such as vessels, cysts, and so forth; hard to control the pressure application (especially excessive); and relatively low specificity [40].

In this meta-analysis, we not only updated the previous data, but also conducted the calculation based on each different method and divided them into several groups, not only the qualitative method and quantitative method. On the other hand, to our knowledge, this is the first comprehensive meta-analysis evaluating the role of EUS-EG, CE-EUS and EUS-FNA in solid pancreatic masses, which may help in clinical decisions. Undeniably, there are some limitations in this study; unpublished studies were not identified, full-text of one study was not obtained, significant heterogeneity presented in some method groups, but can be diminished in subgroup analysis, publication bias was difficult to evaluate, exhaustive search was done to make the publication bias as small as possible. To be judicious, these data must be interpreted cautiously.

In conclusion, EUS-EG is reliable and promising for distinguishing malignant from benign solid pancreatic masses with a high sensitivity. The sensitivity and specificity for different diagnostic methods are very close, and both EUS-EG and CE-EUS can be a valuable complementary supplement for EUS-FNA, for those with positive EUS-EG or/and CE-EUS. EUS-FNA helps to increase the positive predictive value of diagnosing malignancy, and what is more important, for patients with negative EUS-FNA, the combination with EUS-EG or/and CE-EUS will show a high negative predictive value to exclude malignancy. In the future, EUS-EG guided FNA, hybrid techniques and 3D elastography might also be feasible [39,41].

Conflict of interest: none

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