Elastography for the differential diagnosis of malignant versus benign testicular lesions: a meta-analysis

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Purpose: The aim of this study was to evaluate the value of elastography in the differential diagnosis of benign versus malignant testicular lesions.

Methods: The PubMed, Cochrane Library, and Embase databases were searched for relevant studies. The diagnostic accuracy of elastography was evaluated using pooled sensitivity, specificity, likelihood ratio, post-test probability, diagnostic odds ratio, and by summarizing the area under the hierarchical summary receiver operating characteristic (HSROC) curve.

Results: Seven studies with 568 lesions were included. The pooled sensitivity and specificity were 87% (95% confidence interval [CI], 81% to 92%) and 81% (95% CI, 65% to 90%), respectively. The pooled estimates of the positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio were 4.48 (95% CI, 2.37 to 8.47), 0.16 (95% CI, 0.10 to 0.25), and 28.11 (95% CI, 11.39 to 69.36), respectively. The area under the HSROC curve was 90% (95% CI, 88% to 93%).

Conclusion: Elastography is useful for assessing the stiffness of testicular lesions and for differentiating benign from malignant lesions. Elastography can be an effective supplement to conventional ultrasonography.

Keywords: Testicular lesion; Elastography; Meta-analysis

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Introduction

Testicular cancer is a rare disease in men, accounting for 1% of cases of cancer in males. Young men between the ages of 15 and 35 years comprise 60% of patients with this disease. Because of improvements in diagnostic imaging technology and therapeutic efficacy, the incidence of testicular cancer has increased over the past 20 years, while the mortality rate has declined [1,2].

The most up-to-date research suggests that approximately 75% of testicular lesions are benign, and testis-sparing surgery or periodic follow-up may be performed for these benign lesions [3,4]. In contrast, orchiectomy is commonly used to treat testicular cancer; therefore, failure to distinguish benign from malignant testicular lesions can lead to unnecessary orchiectomies. Thus, more accurate

descriptions of testicular lesions can help to determine whether minimally invasive tissue preservation surgery with follow-up or orchiectomy is required [5,6].

Traditional grayscale and color Doppler ultrasonography, both important methods to diagnose testicular lesions, can keenly distinguish between small tumors and normal testicular tissue [7]. However, other pathologic testicular processes, such as infarcts, hematomas, and dermoid cysts, may resemble testicular tumors on ultrasonographic images. Overlap has been reported in the grayscale ultrasonographic features of benign and malignant testicular tumors, meaning that when abnormal masses are detected on ultrasound images, it may not be possible to distinguish between benign and malignant tumors or even between neoplastic and non-neoplastic lesions [8,9].

In general, testicular malignancies often present with increased peripheral blood vascularization. However, some vascularized lesions, such as inflammatory lesions, are benign, while some malignancies exhibit an avascular pattern due to necrosis and fibrosis. Therefore, a noninvasive technique is required to obtain more detailed information than simply the appearance and blood supply of testicular lesions.

Elastography is a new ultrasonographic technique that can measure the mechanical hardness of biological tissues. It has been widely used in the diagnosis of breast, thyroid, and prostate tumors [10–12]. The elasticity of a tissue depends on its molecular composition and microstructure, and tissue hardness is closely related to tissue pathology. Elastography provides an image of tissue hardness, thereby revealing the tissue characteristics of a lesion. Based on differences in elasticity coefficients between different tissues, as well as the degree of deformation of tissues under external pressure, variations in the movement amplitude of an echo signal before and after application of pressure are presented as a real-time color image. Different elasticity coefficients show different images, and the color of the images reflects the hardness of the tissues. Elastography broadens the information obtained from ultrasonographic images and can compensate for deficiencies in conventional ultrasonography, facilitating more accurate localization and more vivid characterization of lesions [13–15].

In recent years, elastography has been widely used for the diagnosis of testicular lesions; however, no meta-analyses have been performed to assess its overall performance in this context. In 2010, Grasso et al. [16] used elastography to examine testicular lesions, and reported that the higher definition of elastography could provide more relevant information for the diagnosis of tumors in the testis, especially for solid lesions smaller than 10 mm. In 2012, Aigner et al. [17] reported that elastography was effective in distinguishing testicular neoplasms from non-neoplastic lesions. In that study, elastography was used to diagnose testicular tumors based on the increased hardness of testicular tumor tissue. Hard lesions were diagnosed as tumors, and soft lesions were considered non-tumor lesions, with a sensitivity of 100% and a specificity of 81% for the diagnosis of testicular tumors. Trottmann et al. [18] reported statistically significant differences with the use of elastographic imaging for distinguishing benign from malignant testicular tumors. Dikici et al. [19] reported that there were significant differences in the quantitative data obtained from shear wave elastography (SWE) between seminomas and nonseminomatous germ cell tumors.

A series of studies [20–26] have investigated the diagnostic accuracy of elastography for differentiating malignant from benign testicular lesions. In this study, we performed a systematic review and meta-analysis to assess the diagnostic accuracy of elastography in the differential diagnosis of benign versus malignant testicular lesions.

Materials and Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and MetaAnalyses (PRISMA) guidelines. This study involved the collection and study of existing data and documents that were publicly available and were recorded by the investigator in a way that did not identify patients directly or using a patient-related identifier. Therefore, this study was not subject to institutional review board approval and did not require informed consent.

Search Strategy

We searched the literature using Medical Subject Headings (MeSH) and free words in the Cochrane Library, Embase, and PubMed databases up until May 2020. We also searched the reference lists of retrieved systematic reviews and reviews to identify other applicable studies. No language restrictions were applied. The search strategy was as follows: ((Testicular Neoplasms) OR (Testicular cancer) OR (Testicular Neoplasms carcinoma) OR (Testicular tumor) OR (Testicular mass) OR (Testicular lesion) OR ("Testicular Neoplasms" [Mesh])) AND (("Elasticity Imaging Techniques" [Mesh]) OR (elasticity imaging technique OR elastography OR elastogram OR shear wave elastography OR SWE OR elasticity imaging OR ultrasonic elastography OR elastosonography)).

Study Selection

The inclusion criteria included prospective or retrospective studies that used elastography for the diagnosis of testicular lesions. True-positive, false-positive, false-negative, and true-negative values were extracted from 2×2 contingency tables. If no direct data were

provided in the study, the sensitivity, specificity, negative predictive value, and positive predictive value were calculated based on the report.

The exclusion criteria for studies were as follows: the study had been published repeatedly; the study data were incomplete; or the study was a case report, meta-analysis, review, or letter.

Two researchers with similar levels of experience conducted screening and data extraction, respectively. Discrepancies between the two researchers were resolved by consensus.

Data Extraction and Quality Assessment

A unified data collection table was adopted. The main information extracted from each study included the author's name, publication year, country of the study, average patient age, study type, number of lesions, and the number of true-positive, false-positive, false-negative, and true-negative cases. Based on the mechanism of the imaging technology, ultrasound elastography primarily includes real-time tissue elastography (RTE) and SWE. The interpretation criteria for RTE included the elasticity score (ES) and the strain ratio (SR). In contrast, SWE measures the elastic Young modulus of a lesion, including the maximum, minimum, and average Young moduli within an area of interest. For studies using more than one method simultaneously, we selected the indicator with the highest accuracy for our meta-analysis.

Included articles were assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool to evaluate the quality of diagnostic tests. A total of 14 criteria were included. Each criterion was evaluated with an answer of "yes," "no," or "unclear," with "yes" meaning that it conformed to the standard, "no" meaning that it did not conform to the standard or was not mentioned, and "unclear" meaning that there was not enough information to evaluate.

Statistical Analysis

Stata statistical software version 15.0 (Stata Corp., College Station, TX, USA) was used to pool statistical indexes and to draw statistical graphs. The pooled sensitivity, specificity, likelihood ratio, and area under the hierarchical summary receiver operating characteristic (HSROC) curve were used to examine the diagnostic accuracy of elastography.

The heterogeneity of the included studies was assessed using the inconsistency index (I^2) and the Cochrane Q. A Cochrane Q statistical value of $P<0.1$ or $I^2>50\%$ indicated significant heterogeneity, and a random-effects model was therefore used. Otherwise, a fixed-effects model was used.

Publication Bias

Publication bias was detected using the Deeks' funnel plot asymmetry test generated in Stata. A P-value of <0.10 was considered to indicate significant asymmetry.

Results

Literature Search

The initial database search using the above strategy produced a total of 453 potentially relevant studies. After consideration of the eligibility criteria, 446 records were excluded, leaving seven original papers selected for the meta-analysis. A detailed flowchart of study selection is shown in Fig. 1.

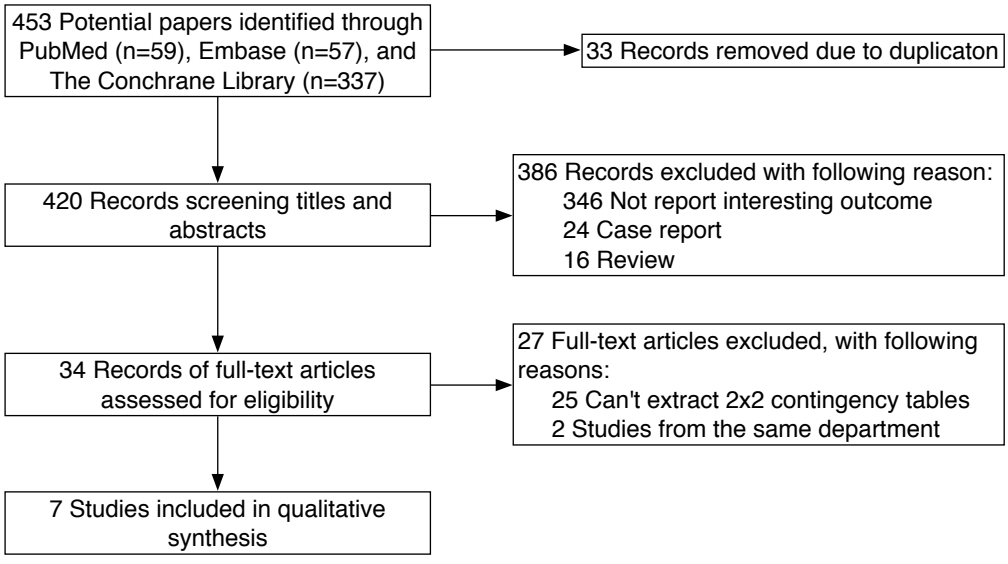


Fig. 1. Flow diagram of study selection.

Study Characteristics

Seven articles were included after screening, including a total of 568 lesions. The basic characteristics of the included studies are shown in Table 1. Most indexes were adequate and resulted in a high QUADAS score (Fig. 2); however, Auer et al.'s study [20] did not mention whether patients were consecutively enrolled, and Pozza et al.'s study [24] did not use a prespecified threshold. Three studies were unclear about whether elastography results were interpreted without knowledge of the reference standard results. Three studies did not mention whether the reference standard results were interpreted without knowledge of the elastography results. None of the studies used the same reference standard.

Data Synthesis and Analysis

The pooled sensitivity and specificity were 87% (95% confidence interval [CI], 81% to 92%) and 81% (95% CI, 65% to 90%), respectively. The pooled estimates of the positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio were 4.48 (95% CI, 2.37 to 8.47), 0.16 (95% CI, 0.10 to 0.25), and 28.11 (95% CI,11.39 to 69.36), respectively (Fig. 3). The area under the HSROC curve was 0.9 (95% CI, 0.88–0.93) (Fig. 4).

A Fagan plot showed that the pretest probability was 20%, the post-test probability was 53%, and the negative probability was 4% (Fig. 5).

As shown in Fig. 3, significant heterogeneity was detected for the pooled sensitivity (I^2=48.53%, P=0.770) and specificity (I^2=83.56%, P<0.001).

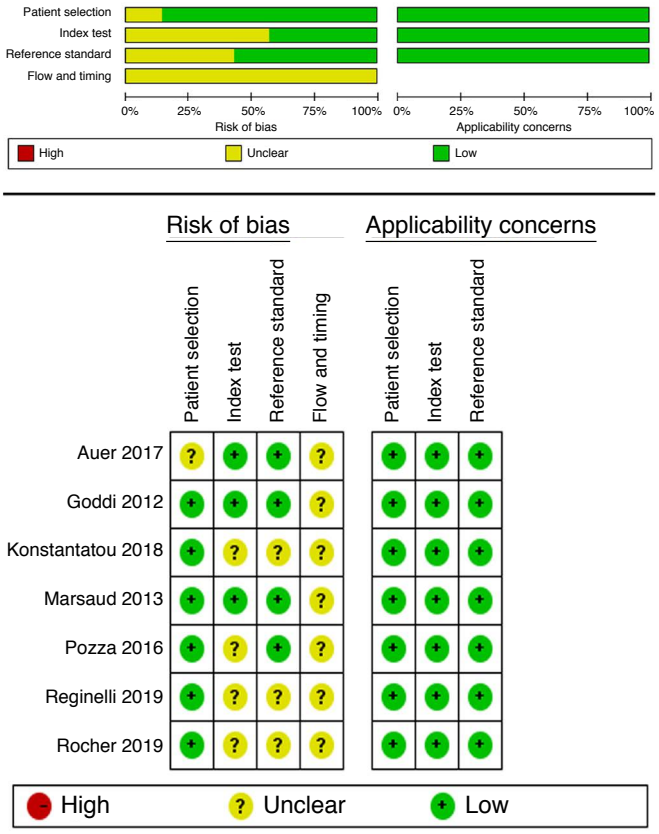
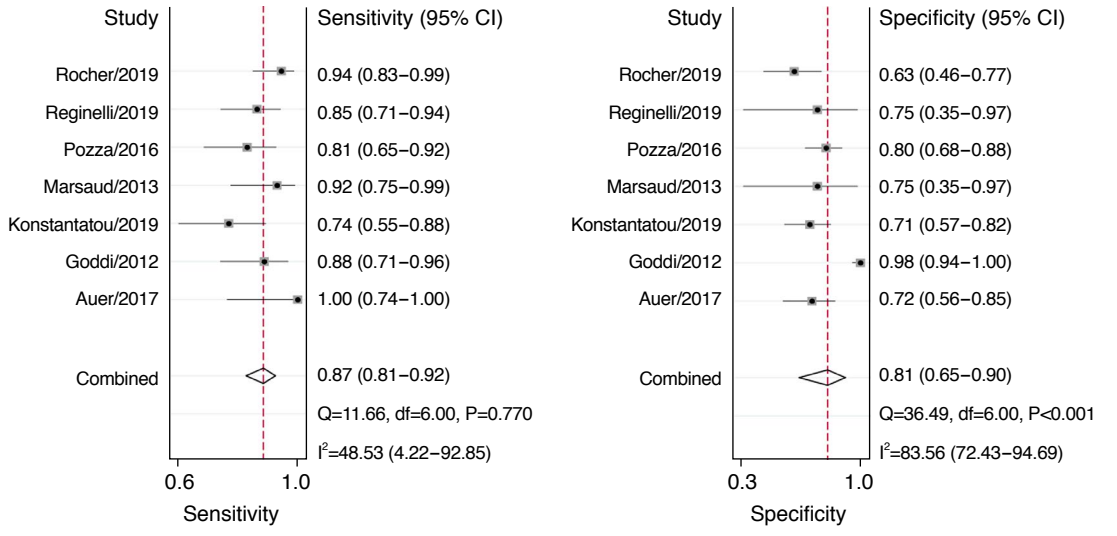


Fig. 2. Quality assessment of included studies using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool. Most indexes were adequate and resulted in a high QUADAS score [20–26].

Table 1. Characteristics of the included studies

Author	Year	Country	Average patient age (year)	Size of lesions (mm)	Design	Blinded	Reference standard	Type of elastography	No. of patients	No. of lesions	TP	FP	FN	TN
Auer et al. [20]	2017	Austria	39.5	11.6	Retrospective	Blinded	Histopathologic results/ clinical surveillance	RTE	55	55	12	12	0	31
Goddi et al. [21]	2012	Italy	34	NA	Prospective	Unblinded	Histopathologic results/ clinical surveillance	RTE	NA	144	28	2	4	112
Konstantatou et al. [22]	2018	UK	36	NA	Retrospective	Unblinded	Histopathologic results/ clinical surveillance	RTE	86	86	23	16	8	39
Marsaud et al. [23]	2013	France	NA	NA	Prospective	Blinded	Histopathologic results/ clinical surveillance	RTE	30	34	24	2	2	6
Pozza et al. [24]	2016	Italy	34.5	6	Prospective	Blinded	Histopathologic results/ clinical surveillance	RTE	106	106	30	14	7	55
Reginelli et al. [25]	2019	Italy	42.2	NA	Retrospective	Unblinded	Histopathologic results/ clinical surveillance	RTE	54	54	39	2	7	6
Rocher et al. [26]	2019	France	37.9	20	Prospective	Unblinded	Histopathologic results/ clinical surveillance	SWE	86	89	46	15	3	25

TP, true positive; FP, false positive; FN, false negative; TN, true negative; RTE, real-time tissue elastography; NA, not available; SWE, shear wave elastography.



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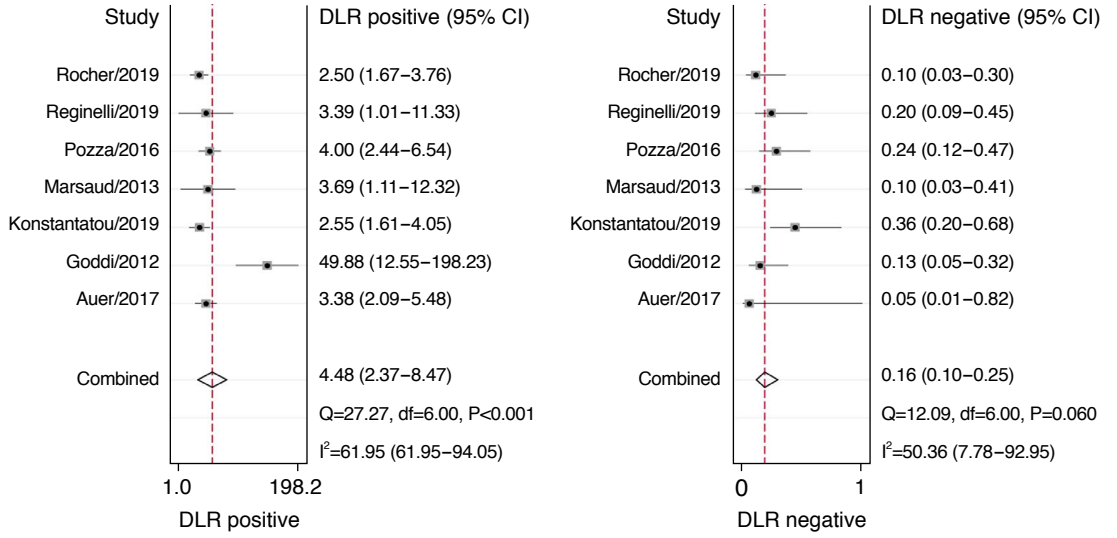

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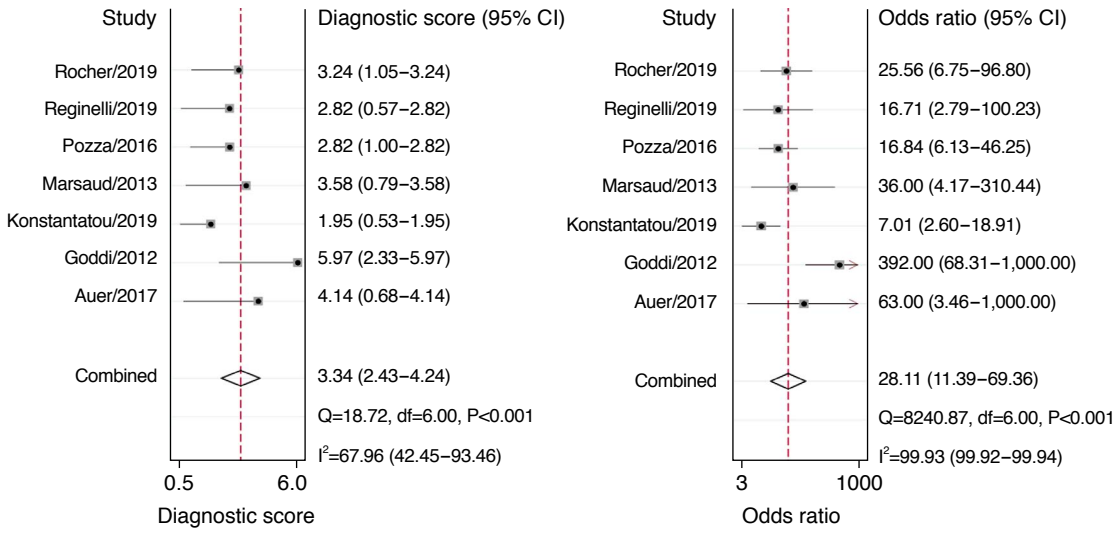

C

Fig. 3. Forest plots for sensitivity and specificity (A), positive likelihood ratio and negative likelihood ratio (B), diagnostic score and odds ratio (C) of this meta-analysis.
The pooled sensitivity and specificity were 87% and 81%, respectively. The pooled estimates of the positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio were 4.48, 0.16, and 28.11, respectively [20–26]. DLR, diagnostic likelihood ratio.

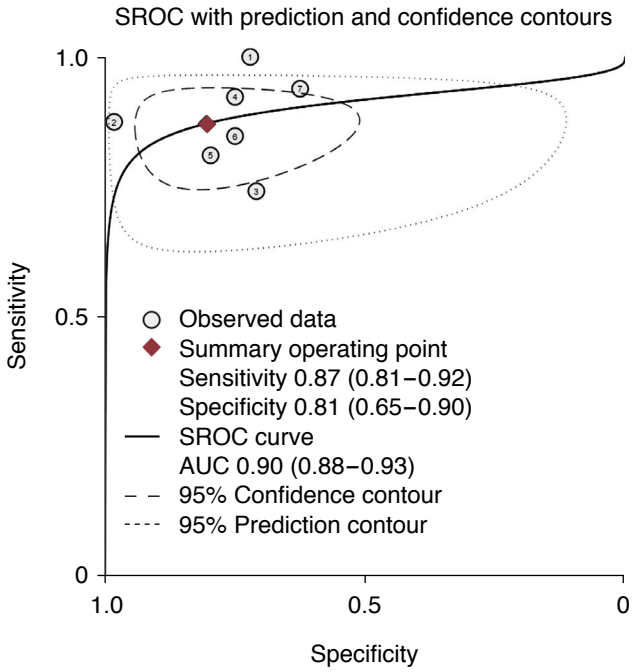

Fig. 4. Summary receiver operating characteristic (SROC) curve. The area under the hierarchical summary receiver operating characteristic curve was 0.9. AUC, area under the curve.

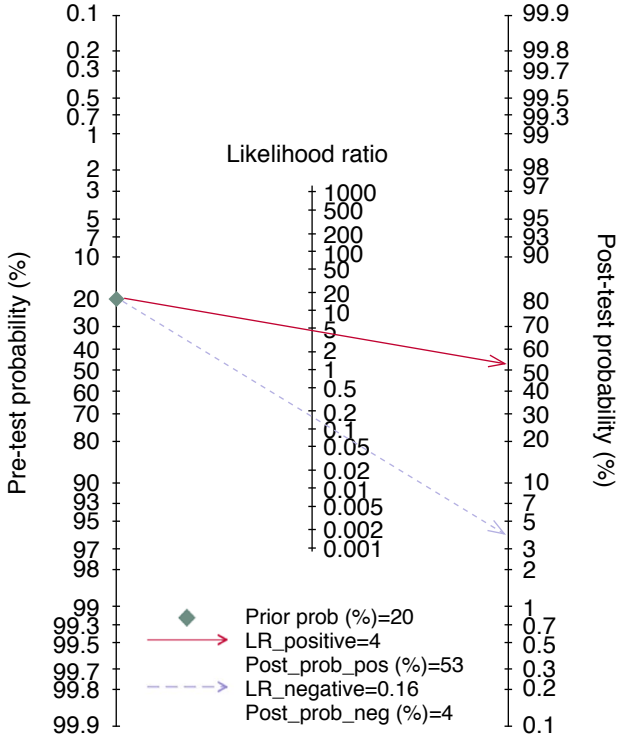

Fig. 5. Fagan plot. The pretest probability was 20%, the post-test probability was 53%, and the negative probability was 4%.

A sensitivity analysis was also performed, with the results showing significant heterogeneity for the studies by Goddi et al. [21] and Reginelli et al. [25] (Fig. 6). Meta-regression and subgroup analyses showed that neither the study design nor the interpretation method had a significant impact on the diagnostic accuracy nor the heterogeneity of studies (Table 2).

Publication Bias

No apparent publication bias was identified based on the Deeks' funnel plot, with a P-value of 0.770 (Fig. 7).

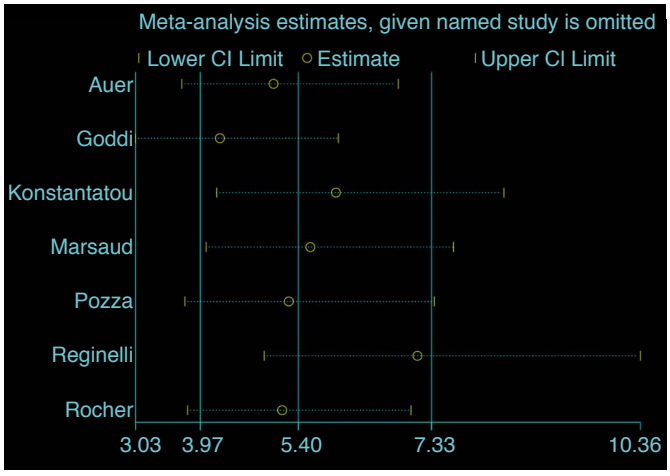

Fig. 6. Sensitivity analysis. The studies by Goddi et al. [21] and Reginelli et al. [25] had significant heterogeneity [20–26]. CI, confidence interval.

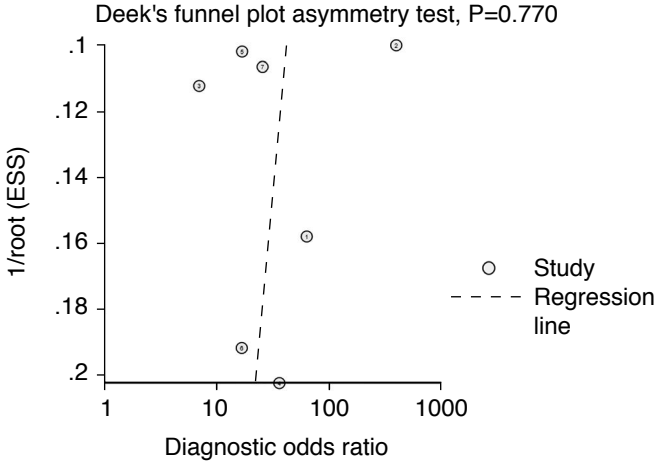

Fig. 7. Deeks' funnel plot. No significant bias was found.

Table 2. Subgroup analysis

Parameter	Category	No. of studies	Sensitivity	P-value	Specificity	P-value
Prospective design	Yes	4	0.89 (0.83–0.94)	0.052	0.85 (0.72–0.97)	0.671
	No	3	0.83 (0.75–0.91)		0.73 (0.51–0.95)	
Blinded	Yes	3	0.89 (0.80–0.98)	0.190	0.77 (0.55–0.98)	0.422
	No	4	0.86 (0.79–0.93)		0.83 (0.69–0.98)	

Discussion

In this study, we conducted a meta-analysis to assess the diagnostic accuracy of elastography for the differential diagnosis of benign versus malignant testicular lesions. Our meta-analysis ultimately revealed a pooled sensitivity of 87% and a pooled specificity of 81% for differentiating between malignant and benign testicular gland lesions. With reference to related elastography values in other medical fields, we consider that elastography showed a satisfactory performance for diagnosing malignant testicular lesions. For example, Li et al. [27] performed a meta-analysis to assess the diagnostic accuracy of elastography in the differential diagnosis of benign versus malignant salivary gland lesions, and reported a pooled sensitivity and specificity of 76% and 73%, respectively. Dong et al. [28] conducted another meta-analysis to investigate the diagnostic performance of elastography for differentiating between malignant and benign thyroid nodules, with a pooled sensitivity of 86% and specificity of 89%.

In this meta-analysis, the included studies were statistically heterogeneous in their estimates of sensitivity (I^2=48.53%, P=0.770) and specificity (I^2=83.56%, P<0.001). Therefore, meta-regression, subgroup, and sensitivity analyses were performed. The meta-regression and subgroup analyses showed that neither the study design nor the interpretation method had a significant impact on the diagnostic accuracy nor the heterogeneity of studies. The sensitivity analysis showed that the studies by Goddi et al. [21] and Reginelli et al. [25] had significant heterogeneity, potentially due to differences in ultrasound scanning equipment or the histological diversity of lesions.

Theoretically, malignant lesions are harder than benign ones [29]; however, some benign lesions with calcification may have higher measurements of stiffness, while some malignant lesions with necrosis and liquefaction may have lower measurements of stiffness [30]. These conditions can lead to overlap in the elasticity imaging characteristics of benign and malignant lesions and may have affected the results of this study. Therefore, it is important to analyze the elastography of lesions of the same pathological type; however, due the limited number of current studies, this heterogeneity could not be adequately analyzed or excluded in this study. Furthermore, when a malignant testicular mass is small, elastographic images may actually show some benign features. In addition, some malignant testicular tumors are formed by local malignancy in otherwise benign tumors. At the early stages of development, these lesions may show similar elastographic characteristics as benign tumors. Some low-grade malignant testicular tumors may also be surrounded by membranes, which can easily lead to misdiagnosis. The above factors may have caused heterogeneity in the articles included in this meta-analysis.

Of the seven studies included in our meta-analysis, three used the ES to evaluate testicular lesions, one used SWE quantitative values, and three used ES, SR, and image structural features simultaneously. Theoretically, SWE should be more accurate than RTE in assessing the hardness of tumors since RTE is usually performed with a rating system that is subjectively used by the operator and therefore is more operator-dependent. Instead, SWE only needs the assistance of the ultrasonic probe and does not require the user to pressurize the external force at all to conduct objective and quantitative evaluations of tissue elasticity. It also has better repeatability and consistency, while avoiding the limitations of traditional external pressure ultrasound elastography, which is affected by subjective experience and lacks objective quantitative indexes. However, our findings suggest there is no significant difference between SWE and RTE in differentiating benign and malignant testicular tumors. We hypothesize that perhaps because the testis is a relatively small organ, the RTE operator can apply pressure to the entire tissue more evenly than is possible for organs such as the breast or liver, and can better compare the difference in stiffness between the lesion and the surrounding normal tissue. These advantages make RTE as effective as SWE in detecting testicular lesions. However, due to the limited number of existing studies, this study could not fully compare the performance between the two techniques for testicular lesions.

This study had several limitations. First, due to the limited number of articles, we elected to include studies that used different ultrasonographic equipment. Second, ultrasound elastography findings can differ based on the pathological type of the testicular lesion; however, we were not able to analyze this factor more closely due to the limited relevant data in the identified literature. Third, only articles published in English were included, resulting in a

linguistic bias. Due to these limitations, more rigorous studies with larger sample sizes should be designed for further verification in future research.

In conclusion, elastography is useful for differentiating malignant from benign testicular lesions and can be a useful supplement to conventional ultrasonography.

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Author Contributions

Conceptualization: Lin Z, Lin R, Wu H, Xu J. Data acquisition: Lin Z, Lin R, Wu L, Zeng J. Data analysis or interpretation: Lin R, Dong F. Drafting of the manuscript: Lin Z, Lin R, Wu H, Wu L. Critical revision of the manuscript: Lin Z, Lin R, Zeng J, Xu J, Dong F. Approval of the final version of the manuscript: all authors.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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