

# Value of shear wave elastography for diagnosis of primary prostate cancer: a systematic review and meta-analysis

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## Abstract

**Aim:** To evaluate the difference in stiffness between prostate cancer (PCa) and benign tissue based on Young's modulus determined by shear wave elastography (SWE). In addition, the diagnostic accuracy of SWE for the detection of PCa was evaluated comprehensively. **Material and methods:** We conducted our systematic review and meta-analysis based on databases of PubMed, Embase and Web of Science. Relevant studies regarding to the diagnostic accuracy of SWE for detecting PCa compared to a reference standard of histopathology were included. The pooled weighted mean difference (WMD) of Young's modulus, sensitivity (SEN) and specificity (SPE), and area under the curve (AUC) were calculated using Stata software. **Results:** Based on our search strategy, 9 studies were ultimately included. The pooled results indicated that the mean Young's modulus for detecting prostate cancer was significantly higher than that for prostate benign tissue (WMD = 38.01, 95%CI = 25.59–50.44,  $p < 0.01$ ). In addition, the pooled SEN was 0.86 (95%CI = 0.75–0.92), and the SPE was 0.89 (95%CI = 0.82–0.93). Moreover, an overall high degree of accuracy was indicated by the summary receiver operator characteristic curve with an AUC of 0.94 (95%CI = 0.91–0.95). **Conclusion:** Our study indicated that SWE is a useful technique for differentiating PCa and benign tissue with a high degree of diagnostic accuracy.

**Keywords:** Shear Wave Elastography; prostate cancer; diagnosis; meta-analysis

## Introductions

Prostate cancer (PCa) is a common diagnosed male cancer throughout the world [1,2]. Although pathologic histology remains the gold standard for the diagnosis of PCa, systematic biopsy (12-core sextant biopsy)

is an invasive method with some risk of complications [3], and its accuracy can be affected by the number and volume of core biopsies [4]. For the screening of PCa in clinical practice, prostate-specific antigen (PSA) [5] and digital rectal examination (DRE) [6] remain as the primary methods, limiting the unnecessary biopsies and reducing the overtreatment, in particular in patients with insignificant PCa [7,8]. However, DRE can lead to rectal discomfort, rectal bleeding and even syncope. In addition, a DRE for suspected PCa relies on the perceived differences in the stiffness of cancer and normal prostate tissue [9]. Hence, an alternative approach for DRE is needed. Transrectal ultrasound (TRUS) is more practical in a clinical setting with the advantage of real-time examination and radiation-free [10,11], and TRUS elastog-

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raphy can improve the detection of stiff prostatic tissues [12,13]. However, TRUS is not sufficiently sensitive or specific for biopsy procedures and whether it definitely improves the diagnostic accuracy of PCa detection remains controversial [11,14]. Hence, shear wave elastography (SWE) was introduced in guiding biopsies and for improving the detection of prostate lesions.

SWE technology has been described in detail by Bercoff et al [15,16]. SWE involves the generation of shear waves in tissue using acoustic radiation force generated by multiple focused ultrasound beams [9]. SWE technology based on measurements of shear wave speed through target tissues, which can be used to dynamically map and reflect tissue stiffness (Young's modulus) properties in real time. It allows the local measurements of prostate tissue stiffness as quantitative elasticity values in kilopascals (kPa). In contrast to strain elastography, SWE requires no compression of the rectal wall. Multiple investigations have indicated the accuracy of SWE in diagnosing breast cancer [17], malignant cervical lymph nodes [18], rectal cancer [19] and pancreatic tumours [20]. In terms of PCa, a previous study indicated that SWE had a higher degree of diagnostic accuracy compared to TRUS [21]; however, Porsch et al showed that SWE yields poor diagnostic selectivity (sensitivity (SEN) of 62%, specificity (SPE) of 35%) with an area under the curve (AUC) of 0.527 [22]. Hence, the value of SWE in diagnosing PC are mains controversial.

Based on the aforementioned, the aim of our study is to evaluate the difference in stiffness between PCa and benign tissue based on Young's modulus determined by SWE. In addition, the overall accuracy of SWE was analysed comprehensively to assess the value of using SWE when compared with histopathology (biopsy or radical surgery).

## Material and methods

Ethical approval and informed consent were waived because the nature of our study was a systematic review and meta-analysis.

### Search strategy

We conducted our systematic review and meta-analysis in accordance with the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (<http://www.prisma-statement.org/>). The final date for study search was March 25, 2019 and the MeSH main key words used in datasets of PubMed, Embase and Web of Science were as following: "prostate," "shear wave", "elastography" and "sonoelastography". In addition, we checked all authors, organizations and the recruitment period in each study to avoid redundant studies.

### Inclusion and exclusion criteria

Based on the PICOS criteria (population, intervention, comparison, outcomes and study design), studies included were in accordance with following eligibility criteria: (1) population: patients with primary PCa, with a total number of patients enrolled  $\geq 20$ ; (2) intervention: use of SWE in detecting PCa; (3) comparison: biopsy or radical surgery of histopathology results as a reference standard; (4) outcomes: data applicable based on SEN and SPE to calculate the true-positive, false-negative, false-positive and true-negative rates for the diagnosis of PCa using SWE; (5) study design: prospective or retrospective cross-sectional studies. In addition, the exclusion criteria were: (1) populations including patients with recurrent PCa or other cancers; (2) the use of other techniques based on SWE; (3) the inclusion of other reference standards but not histopathology results; (4) studies with insufficient data; and (5) studies with overlapped populations, reviews or meta-analyses.

### Data extraction and quality assessment of included studies

Two members of our team (YY and XZ) reviewed and assessed each of the included studies independently. In addition, the following information was collected: first author, country, study type, study duration and institution, total number of patients and samples, patient age and PSA value, reference standard and cutoff value of SWE, analysis method and data necessary to calculate the SEN and SPE. In addition, Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) were used to assess the quality of included studies [23]. Moreover, disagreements regarding to information selection, data calculation and quality assessments were resolved through discussions.

### Statistical analysis

Statistical analyses were conducted by using Stata software, version 12.0 (2011; Stata Corp., College Station, TX, USA) and all statistical values were reported with 95% confidence intervals (CI). In our systematic review and meta-analysis, continuous variables were analysed by the weighted mean difference (WMD) using the method of Hozo et al to calculate the mean and SD for analysis [24]. The pooled SEN, SPE, positive (DLR+) and negative (DLR-) diagnostic likelihood ratio, diagnostic odds ratio (DOR) and a likelihood ratio scattergram (LRS) were calculated based on true-positive, false-negative, false-positive and true-negative rates by using the bivariate random effects regression model [25]. In addition, the summary receiver operator characteristic (SROC) curve was plotted, and the pooled AUC value was also calculated [26]. Furthermore, Fagan's nomogram was used to visualize the detection of PCa by SWE

using likelihood ratios to calculate a post-test probability, and Deeks' funnel plot asymmetry test was conducted to assess publication bias. Cochran's Q test and Higgin's I<sup>2</sup> statistic were used to examine heterogeneity, and an I<sup>2</sup> >50% indicated significant heterogeneities among studies [27]. Finally, statistical significance was defined as  $p < 0.05$ .

## Results

### Selected studies and quality assessment

A total of 217 published studies were identified from the datasets in accordance with our search strategy. After removing the duplicates, screening the title and abstract and carrying out further evaluation, 13 studies were identified that use SWE for diagnosis of PCa; however, two studies provided insufficient data [28,29], one study was based on a total number of patients <20 [22] and one study enrolled patients with recurrent PCa [30]; hence, 9 studies were ultimately included in our present study [9,11,31-37] (fig 1). Among the included studies, the study by Ahmad et al [9] was analysed twice according to PSA groupings of 4-20 ng/ml and over 20 ng/ml. Three studies were conducted in Asian countries [34,36,37] and the others in Europe or America. Two studies employed a retrospective design [36,37] and 6 studies were prospective [9,11,31-33,35]. Three studies evaluated the diagnostic accuracy of SWE compared with the histopathology of radical prostatectomy [11,32,35]. The total number

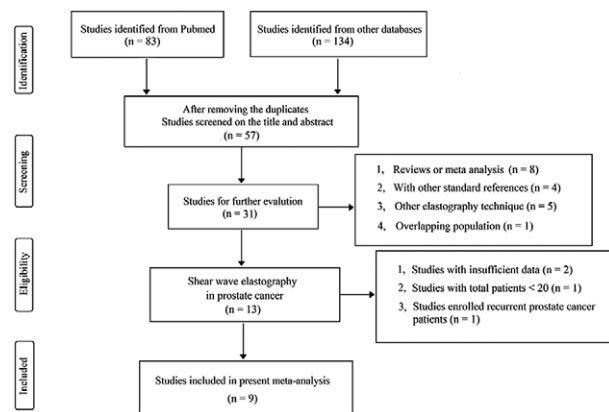


Fig 1. Flow chart of study selection.

of patients enrolled ranged from 30 to 489 and the cutoff values of SWE ranged from 35 to 82.6 kPa. Detailed information on the included studies is summarized in Table I and, quality assessment of included studies are shown in Supplementary figure 1 on the journal site.

### SWE in differentiating malignant and benign prostate tissue

All of the included studies reported the mean Young's modulus (kPa) for detecting malignant and benign prostate tissue. The pooled results indicated that the mean Young's modulus for detecting prostate cancer was significantly higher than that for prostate benign tissue (WMD = 38.01, 95% CI = 25.59–50.44,  $p < 0.01$ ) (fig 2). In addition, among the included studies, five studies

Table I. Baseline information of included studies

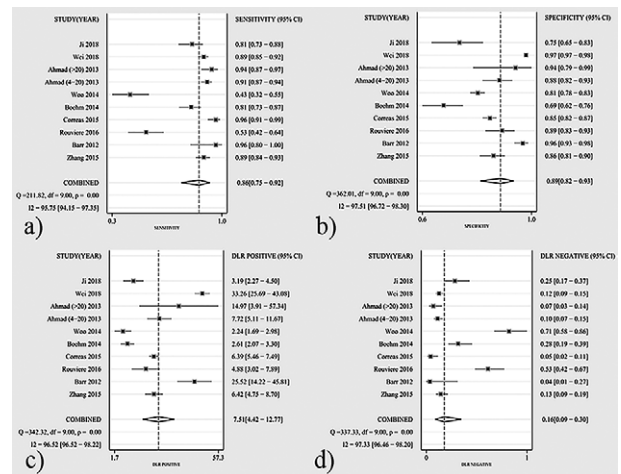
	Author	Country	Study design	Patients number	Samples number	Age (years)	PSA (ng/mL)	Reference standard	Cut-off (kPa)	Analysis method
1	Zhang et al [37]	China	Retrospective	489	NR	mean 70.2	mean 14.5	Biopsy	28.5	Per patient
2	Barr et al [31]	US	Prospective	53	318	mean 64	mean 5.1	Biopsy	37	Per core
3	Rouviere et al [35]	France	Prospective	30	251	median 63	median 6.5	RP	45	Per region
4	Correas et al [33]	France and US	Prospective	184	1040	mean 65	mean 7.4	Biopsy	35	Per core
5	Boehm et al [32]	Germany	Prospective	60	322	NR	median 8.7	RP	50	Per region
6	Woo et al [36]	South Korea	Retrospective	87	1058	mean 66	mean 12.8	Biopsy	43.9	Per core
7.1	Ahmad et al [9]	UK	Prospective	39	485	mean 69	4-20	Biopsy	NR	Per core
7.2	Ahmad et al [9]	UK	Prospective	11	141	mean 69	> 20	Biopsy	NR	Per core
8	Wei et al [13]	UK	Prospective	212	2544	mean 68	mean 11.8	RP	82.6	Per core
9	Ji et al [34]	China	NR	215	NR	mean 71	NR	Biopsy	62	Per patient

US: United States; UK: United Kingdom; NR: not reported; RP: radical prostatectomy; PSA: prostate-specific antigen.

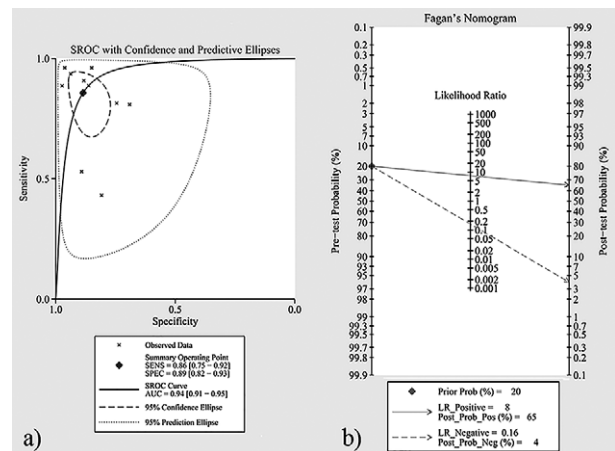
[9,11,33,35,36] reported an association between Young’s modulus and Gleason scores. Although we could not conduct a meta-analysis in terms of this outcome due to the non-uniform data, similar conclusions were observed in these five studies based on a systematic review. Correas et al [33] found a statistically significant difference in stiffness between Gleason scores of 6, 7, 8 and 9 ( $p < 0.01$ ). Meanwhile, Rouviere et al [35] reported that peripheral zone cancers with Gleason scores of 8-9 were significantly stiffer than peripheral zone cancers with Gleason scores of 5-6 or 7. In addition, Ahmad et al [9] showed that the mean Young’s modulus was significantly higher for prostate tissues with a Gleason score of 7 ( $163 \pm 63$  kPa) than those with a Gleason score of 6 ( $95 \pm 28.5$  kPa). Furthermore, Wei et al [11] demonstrated that significant differences were observed of Young’s modulus values for different grades of PCa (Gleason score 6: 91.6 kPa, Gleason score 7: 102.3 kPa and Gleason score  $\geq 8$ : 131.8 kPa). Woo et al [36] indicated that a significant linear trend between Young’s modulus and Gleason scores could be observed (Gleason score  $\leq 6$ :  $32.7 \pm 19.4$  kPa; Gleason score = 7:  $55.4 \pm 48.5$  kPa; Gleason score = 8:  $57.3 \pm 39.4$  kPa; Gleason score  $\geq 9$ :  $88.2 \pm 64.2$  kPa).

**Diagnostic accuracy of SWE in the detection of PCa**

The diagnostic accuracy of SWE in the detection of PCa is shown in figure 3. The pooled SEN was 0.86 (95% CI = 0.75–0.92) (fig 3a) and the SPE was 0.89 (95% CI = 0.82–0.93) (fig 3b). Meanwhile, the pooled DLR+ was 7.51 (95% CI = 4.42–12.77) (fig 3c) and the DLR- was 0.16 (95% CI = 0.09–0.30) (fig 3d). Based on the results of DLR+ and DLR-, the LRS is shown in Supplementary figure 2, on the journal site. In addition, the pooled DOR was 46.64 (95% CI = 16.56–131.36) (Supplementary figure 3, on the journal site). Moreover, an overall high



**Fig 3.** Diagnostic accuracy of shear wave elastography. A, pooled sensitivity; B, pooled specificity; C, positive diagnostic likelihood ratio; D, negative diagnostic likelihood ratio.



**Fig 4.** A, Overall accuracy was revealed by the summary receiver operator characteristic curve; AUC: area under the curve; B, Results of Bayesian analyses showing the pre- and post-test likelihoods for PCa detection.

Study ID	WMD (95% CI)	Weight (%)
Zhang	18.50 (16.90, 20.10)	12.49
Barr	36.80 (28.71, 44.89)	11.88
Rouviere	22.00 (15.18, 28.82)	12.06
Correas	32.00 (15.44, 48.56)	10.24
Boehm	46.00 (36.29, 55.71)	11.63
Woo	21.20 (11.00, 31.40)	11.54
Ahmad	58.80 (26.44, 91.16)	6.77
Wei	75.70 (65.97, 85.43)	11.62
Ji	41.00 (32.22, 49.78)	11.78
Overall (I-squared = 95.9%, p = 0.000)	38.01 (25.59, 50.44)	100.00

NOTE: Weights are from random effects analysis

**Fig 2.** Pooled weighted mean difference (WMD) of Young’s modulus (kPa) between prostate cancer and benign tissues.

degree of accuracy was revealed by the SROC curve with an AUC of 0.94 (95% CI = 0.91–0.95) (fig 4a). Finally, a Fagan nomogram was constructed to illustrate the pre- and post-test probability of SWE to predict PCa based on the included studies (fig 4b). Based on the results, we found that without taking into account the results of SWE, a PCa episode had a “pre-test” probability to be detected of 20%. When detection of PCa was based on a SWE-positive result, there was a 65% “post-test” probability of detecting a subsequent PCa episode. With a negative SWE, the “post-test” probability of detecting PCa dropped to 4%. In our analysis, the Spearman’s correlation coefficient was 0.40 ( $p = 0.27$ ), which indicated that there was no heterogeneity arising from a threshold effect.

### Publication bias

Deeks' funnel plot asymmetry test was conducted to evaluate the publication bias. Based on the results (Supplementary figure 4 on the journal site), there was no significant publication bias among our included studies ( $p=0.167$ ).

### Discussions

In the recent years SWE has provided quantitative information on tissue elasticity in real time, which has generated interest in its potential applicability in the detection of PCa. This approach is based on the fact that the structure of benign tissue in the prostate differs from that of cancerous tissue [32]. Based on differences in elasticity, the stiffness of various tissue types may be an indicator of cancer [32]. In addition, SWE allows the calculation of elasticity ratios between benign and malignant tissue, which may result in user-independent imaging of the prostate. However, the SEN of SWE in the detection of PCa varies from 53% to 96% and the SPE varies from 69% to 96% based on previous investigations [9,11,31-37]. Our results indicated that the mean Young's modulus in the detection of PCa was significantly higher (mean 38 kPa) than that in prostate benign tissue. In addition, the pooled SEN was 0.86, the SPE was 0.89, the DLR+ was 7.51 and the DLR- was 0.16. Moreover, the pooled DOR was 46.64 and an overall high degree of accuracy was revealed by the SROC curve with an AUC of 0.94. Based on the aforementioned results, we consider SWE to be a novel and non-invasive imaging technique for the assessment of tissue stiffness to facilitate detection of PCa and biopsy guidance.

Compared with MRI and CT, TRUS is more practical in the clinical setting with the advantage that the results can be examined in real-time and it is cost-effective and radiation-free [10,11]. A previous meta-analysis [38] regarding real-time elastography reported that the pooled SEN was 0.72, the SPE was 0.76, and the pooled DOR was 12.59. The results of our meta-analysis yielded a pooled SEN, SPE and DOR that were higher than the above meta-analysis. Although our study did not conduct a comparative analysis directly between TRUS and SWE, a similar conclusion could also be observed from previous evidence [21]. In addition, the presence of suspicious SWE findings is an independent predictor of clinically significant PCa [39]. Therefore, SWE may be helpful in selecting patients for biopsy, although TRUS-guided systematic biopsy is currently standard in clinical practice. Nonetheless, the per-core detection rate for SWE-targeted cores has not been shown to be significantly higher than the detection rate of systematically

sampled cores [39]. Hence, a combination of systematic and SWE-targeted biopsy may be a promising approach for improving PCa detection.

Based on the diagnostic accuracy of SWE, novel SWE-based techniques and systems have been utilized. Su et al [40] reported a novel 11-point scoring system based on SWE and other clinical parameters (TRUS, DRE, total PSA, PSA density and free PSA/total PSA ratio). The results showed that the AUC of the scoring system based on SWE plus the clinical parameters (0.911) was significantly more diagnostically efficient than the scoring systems based on SWE alone (0.842) or clinical parameters alone (0.868). In addition, Shoji et al [29] indicated that combining Prostate Imaging Reporting and Data System Scores (PI-RADS) with measurement of Young's modulus by three-dimensional SWE improved the diagnosis of clinically significant prostate cancer. Moreover, Zhang et al [41] also demonstrated that multiparametric TRUS including greyscale imaging, colour Doppler imaging, SWE and contrast-enhanced ultrasound yielded a higher SEN, negative predictive value and accuracy than did multiparametric MRI (97.4% versus 94.7%, 96.9% versus 92.3% and 87.2% versus 76.9%, respectively) for detecting localized PCa. Hence, based on the aforementioned findings, novel SWE-based techniques and systems with improved diagnostic accuracy have provided direction and evidence for the detection of PCa in the future.

The primary benefit of our study is to provide a quantitative analysis of Young's modulus for PCa and benign tissue. In addition, the overall analyses of diagnostic accuracy have provided valid evidence for the clinical application of SWE in the detection of PCa. However, there are some limitations to our study. Firstly, the heterogeneities in patient baseline information across the included studies could not be eliminated. Ji et al [34] enrolled patients with a mean age of 71 and all other included studies enrolled patients with a mean age of less than 70. Zhang et al [37] enrolled patients with a mean PSA of 14.5 ng/mL, while Barr et al [31] enrolled patients with a mean PSA of 5.1 ng/mL. Secondly, two included studies [36,37] were retrospective in nature and two included studies [34,37] were analysed based on per patients. The types of study design included may bias our overall analyses; hence, we may need to acquire individual data to update our findings in the future. Finally, most of the studies included used TRUS-guided biopsy data as a reference standard for PCa detection, and three studies [11,32,35] used radical prostatectomy. However, biopsy data yielded poor accuracy in locating PCa in comparison with the histopathology of the radical prostatectomy specimens. Therefore, we might need

large-scale prospective investigations to further explore the value of SWE when compared to histopathology of radical prostatectomy.

### Conclusions

Our study indicated that SWE is useful for differentiating prostate cancer and benign tissue with a high SEN and SPE for the detection of PCa. Hence, we suggest that SWE could improve guiding capability for diagnosis in clinical practice. The pooled results indicated that the mean Young's modulus for detecting prostate cancer was significantly higher than that for prostate benign tissue of 38kPa.

### Conflict of interest: none

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