

# The role of real-time elastography-targeted biopsy in the detection and diagnosis of prostate cancer

## A systematic review and meta-analysis

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### Abstract

**Background:** The role of real-time elastography (RTE)-targeted biopsy in the detection and diagnosis of prostate cancer (PCa) remains controversial.

**Methods:** We searched Medline, Embase, and Cochrane Library from inception to July 31, 2017 and used the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool to assess the quality of the identified studies. We applied the relative sensitivity value to assess the diagnostic accuracy of RTE-targeted biopsy using the 10-core systematic biopsy as the reference standard.

**Results:** Seven studies comprising 5 cohorts and 2 randomized controlled trials (RCTs) were included. Of the 5 cohorts that encompassed 698 participants, we found that RTE-targeted biopsy did not outperform systematic biopsy in either overall PCa detection (69.5% vs 80.5%, relative sensitivity 0.92, 95% CI 0.80–1.06) or for the initial biopsy (56.8% vs 64.0%, relative sensitivity 0.93, 95% CI 0.79–1.11). For the core-by-core analysis, more positive cores were detected by RTE-targeted biopsy than systematic biopsy (21% vs 11%, relative sensitivity 2.17, 95% CI 1.61–2.95). The 2 RCTs showed a favorable trend toward greater PCa detection when a combination of systematic biopsies and RTE-targeted biopsies was used than when systematic biopsy alone was used (45.5% vs 39.5%, risk ratio (RR) 1.18, 95% CI 0.98–1.43).

**Conclusion:** Currently, there is not enough evidence to demonstrate that RTE-targeted biopsy can outperform systematic biopsy, but the combination of systematic and RTE-targeted biopsy may be a promising approach for improving PCa detection.

**Abbreviations:** CIs = confidence intervals, PCa = prostate cancer, PSA = prostate-specific antigen, QUADAS = Quality Assessment of Diagnostic Accuracy Studies, RCTs = randomized control trails, RP = radical prostatectomy, RRs = risk ratios, RTE = real-time elastography, SWE = shear-wave elastography, TRUS = transrectal ultrasound, US = ultrasound.

**Keywords:** meta-analysis, prostate cancer, real-time elastography, targeted biopsy

### 1. Introduction

Prostate cancer (PCa) is regarded as the most common malignancy among men in Western countries. The American

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Cancer Society estimated that 1,688,780 new cases of invasive cancer will be diagnosed in the USA during 2017, including 161,360 cases of PCa, which account for almost 1 in 10 new diagnoses.<sup>[1]</sup> In 2014, the mortality rate of PCa decreased by 51% from that in 1993 owing to advances in early PCa detection and treatment, including prostate-specific antigen (PSA) testing.<sup>[1,2]</sup> However, PCa remains one of the most common causes of cancer-related death in men.

Currently, when PCa is suspected, the gold standard of diagnostic care involves performing Transrectal Ultrasound (TRUS)-guided systematic biopsy.<sup>[3–5]</sup> According to the European Association of Urology guidelines,<sup>[3]</sup> 10 to 12 core biopsies are recommended among men in whom PCa is suspected. However, false-negative rates are estimated to be as high as 20% to 24%.<sup>[6,7]</sup> Furthermore, 50% to 80% of clinically significant prostate cancers may go undetected in systematic prostate biopsy.<sup>[8]</sup> The greater number of cores may improve cancer detection rate but may also increase morbidity and the risk of overdiagnosis.<sup>[9]</sup> Therefore, new biopsy protocols that not only accurately detect PCa but also reduce the number of prostate biopsy specimens and biopsy-related patient complications are required. Ultrasound-based elastography, which primarily comprises real-time elastography (RTE) and the newly introduced shear-wave elastography (SWE), records sonographic images of prostatic tissue at baseline and adds the stiffness status under different degrees of compression. Differences in tissue stiffness can be displayed in real time using different colors on a video-screen.<sup>[10,11]</sup> Cancerous tissue has a much higher cell density with decreased elasticity and can therefore be differentiated from benign tissue.<sup>[8]</sup>

Previous studies have reported that both RTE imaging and SWE imaging showed potential for increased PCa detection.<sup>[12–16]</sup> However, limited data have been obtained with regard to the detection accuracy of image-targeted biopsy. Thus, it remains unclear whether a review of the current literature would elucidate a role for image-targeted biopsy (especially RTE) for PCa detection. Therefore, we performed a systematic review and meta-analysis to assess the diagnostic accuracy of RTE-targeted biopsy compared with systematic biopsy for PCa.

## 2. Methods

### 2.1. Systematic search strategy

A systematic search of electronic databases including Medline, Embase, and Cochrane Library (updated to July 31, 2017) was conducted to identify relevant citations for this review and meta-analysis. The terms “elastography,” “elasticity,” and “prostate” were used to search titles, abstracts, and key words (See Information, Supplementary Content, <http://links.lww.com/MD/C174>, which shows the details of search strategy). All studies judged potentially eligible were screened by reading the full text. The references cited in full-text articles were also reviewed to identify additional relevant articles. Two independent authors (XT and SQ) were involved throughout the systematic search, and any discrepancies were arbitrated by a third author (QW).

### 2.2. Inclusion and exclusion criteria

Trials that compared RTE-targeted biopsy and systematic biopsies (cores from the prostate in a random and systematic order, with 10 cores total) were included, regardless of whether or not they were initial or sequential biopsies. The following criteria were also met: the protocol of the RTE-targeted biopsy was as follows: the participants reported in the trials were suspected to have prostate cancer (based on an elevated PSA level or an abnormal digital rectal examination) and then underwent a diagnostic RTE-targeted and systematic biopsy of the prostate. In addition, suspicious areas in RTE were defined as previously reported.<sup>[17]</sup> The available data used to compare the overall detection rate of PCa between the 2 biopsy protocols were listed clearly in the article. The exact statistics of the RTE-targeted and systematic biopsies were identified. If the same population was mentioned in more than 1 published study, we only included the study that had the largest number of cases. We also excluded reports of men with already proven prostate cancer, trials with insufficient or overlapping data, and retrospective studies.

### 2.3. Data extraction

A broad range of data was collected from the articles including the author name, publication year, country, participant details (patient number and prebiopsy parameters), biopsy details (core number, biopsy setting, and biopsy protocol), and results (detection rates between the 2 biopsy methods). Two investigators extracted the data independently (XT and TC).

### 2.4. Quality assessment

The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool, which includes the following 4 domains, was used to evaluate the quality of each trial: patient selection, index test, reference standard, and participant flow and

timing.<sup>[18]</sup> According to the QUADAS-2 guidelines, a study was judged to have a “low risk of bias” if it was evaluated as “low” on all 4 domains relating to bias or the first 3 terms concerning applicability. A study may be interpreted to have an overall high risk of bias if 1 or more domains were judged to be “high” or “unclear.” The assessment was performed by 2 authors (XT and SQ, and any discrepancies were resolved by a third author (QW).

### 2.5. Statistical analysis

There is no perfect reference (gold standard) test for PCa. To compare RTE-targeted biopsy (index test) and systematic biopsy (current reference test), we focused on concordance and discordance of results for the 2 tests. We redefined the positive reference standard as PCa detection in either of the tests.<sup>[19]</sup> The total number of PCa cases was defined as participants with positive either RTE-targeted biopsy or systematic biopsy. The sensitivity of a positive RTE-targeted biopsy was defined as the number of positive RTE-targeted biopsy results divided by the total number of cancers detected. The sensitivity ratio between RTE-targeted biopsy and 10-core systematic biopsy was defined as relative sensitivity. A relative sensitivity value greater than 1.0 suggests that RTE-targeted biopsy detects more cancers than does systematic biopsy and vice versa.

To compare the detection rate of RTE-targeted biopsy and systematic biopsy, Mantel–Haenszel estimates were performed using a fixed or random model among cohorts as appropriate. For randomized controlled trials (RCTs), we used risk ratios (RRs) and 95% confidence intervals (CIs) to compare combined biopsy (systematic biopsy combined with RTE-targeted biopsy) with systematic biopsy alone. Among the included studies, the degree of heterogeneity was evaluated by computing Higgins  $I^2$  index.<sup>[20]</sup> Heterogeneity was considered to be statistically significant at  $P < .05$ . Low heterogeneity of studies was defined as  $I^2 < 25\%$ , moderate heterogeneity was defined as  $I^2 = 25\%$  to  $50\%$ , and high heterogeneity was defined as  $I^2 > 50\%$ . All the analyses were performed using STATA v 12.0 (STATA, College Station, TX).

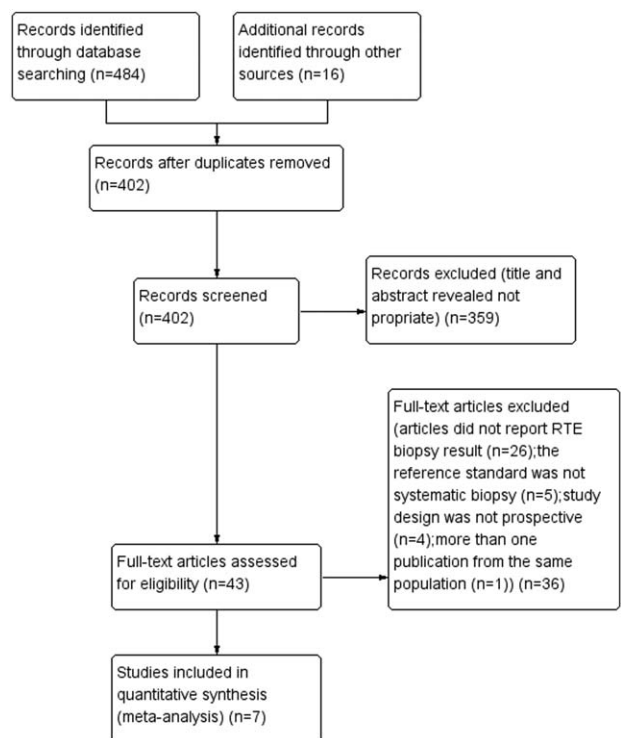
## 3. Results

### 3.1. Description of the meta-analysis

Our literature search initially identified 402 potentially relevant citations. In total, 359 articles, including imaging studies, meeting abstracts, reviews, letters, and other articles, irrelevant to our study were excluded after screening the titles and abstracts. The full texts of the 43 remaining articles were retrieved for assessment. After excluding another 36 articles, 7 prospective studies comprising 5 cohorts, and 2 RCTs were included.<sup>[21–27]</sup> Because the methods are different between cohorts and RCTs, we analyzed the results separately. The systematic search was performed according to the PRISMA statement.<sup>[28]</sup> The exclusion criteria are shown in Fig. 1, and details of the 7 included articles are shown in Table 1.

### 3.2. Details of the technological evaluation and instrument composition

All included studies used the 10-core systematic biopsy as the reference standard. Four studies recruited participants with an initial biopsy,<sup>[21,24,26,27]</sup> 2 studies recruited mixed participants,<sup>[22,23]</sup> and 1 study recruited participants with no data



**Figure 1.** PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flow diagram of identification and selection of studies for the systematic review.

available.<sup>[2,5]</sup> The ultrasound (US) modality and probe used in the studies are presented in Table 2. All the studies included used the free manual compression method to locate the suspicious lesion, which was defined as a blue area on the RTE based on the criteria described by König et al.<sup>[17]</sup> In the 5 cohorts,<sup>[21–25]</sup> the maximum number of cores of the RTE-targeted biopsy varied from 3 to 5. Of the 2 RCTs, Eggert et al.<sup>[26]</sup> performed TRUS-guided 10-core biopsy in both groups and an additional elastographic examination prior to systematic biopsy in the elastography group. However, in Brock study,<sup>[27]</sup> suspicious areas were first sampled by a single targeted biopsy, and a random systematic biopsy was performed if no suspicious area was found in any of

the ultrasound images (hypochoic lesion for TRUS, blue lesion for RTE). Overall, the studies we included seemed to have moderate technological variation in their approaches, which was considered during data analysis.

**3.3. Analysis of different protocols**

**3.3.1. RTE-targeted biopsy versus systematic biopsy.**

**3.3.1.1. Overall analysis of the 2 different biopsy protocols.** Of the 5 cohorts,<sup>[21–25]</sup> there were a total of 698 participants with a sequential sampling design for the RTE-targeted biopsy and systematic prostate biopsy. In total, 298 PCa cases were detected by either RTE-targeted biopsy or by systematic biopsy with a detection rate of 42.7% (298/698). The sensitivity of RTE-targeted biopsy for the detection of PCa was lower (69.5%; 207/298) compared with that of systematic biopsy (80.5%; 240/298). However, the relative sensitivity value of 0.92 (95% CI 0.80–1.06) was not significantly different. Moderate heterogeneity was noted among these trials ( $I^2 = 33.5\%$ ,  $P = .20$ ), but the difference was not statistically significant (Fig. 2A).

**3.3.1.2. Comparison of RTE-targeted and systematic cores for the detection of prostate cancer.** Five studies were used to compare RTE-targeted and systematic biopsy for PCa detection.<sup>[21–25]</sup> For core-by-core analysis, RTE-targeted biopsy detected more positive cores with rates of 21% (463/2216) than did systematic biopsy 11% (715/6794), which resulted in a relative sensitivity value of 2.17 (95% CI, 1.61–2.95). These data suggest that only 5 cores are needed to detect a positive core by RTE-targeted biopsy compared with at least 10 cores that are needed for systematic biopsy. However, considerable heterogeneity was noted among these trials ( $I^2 = 86.5\%$ ;  $P < .05$ ) (Fig. 3).

**3.3.1.3. Subgroup analysis: participants with an initial biopsy versus participants with a previous negative biopsy.** We included 3 studies in the subgroup analysis.<sup>[21,23,24]</sup> Two studies included participants with an initial biopsy,<sup>[21,24]</sup> and 1 included a mixed population.<sup>[23]</sup> In the initial biopsy group, RTE-targeted biopsy and systematic biopsy displayed similar detection rates of PCa with sensitivities of 68.8% (117/170) and 82.4% (140/170), respectively. The relative sensitivity value of 0.90 (95% CI, 0.74–1.09) was below the threshold for statistical significance. The heterogeneity was large but was not considered statistically

**Table 1**  
**Main characteristics of the included studies.**

Study ID (y)	Country	Study design	No. of participants	Age, y, mean (or median)	PSA, ng/mL, mean (or median)
Cohort					
Pallwein (2007)	Australia	Prospective	230	62.3 ± 8.0*	NA
Aigner (2010)	Australia	Prospective	94	57.4 (35–77)†	3.2 (1.3–4.0)†
Ganzer (2011)	Germany	Prospective	139	65 ± 10	10.8 ± 9.0*
Nygaard (2013)	Norway	Prospective	127	64.2 (38–76)	9.2 (2.2–24.4)
Wang (2015)	China	Prospective	108	71.6 ± 8.5	12.8 (1.24–43.1)
RCT					
Eggert (2008)	Germany	Prospective	189‡	65.3 (39–82)	13.2 (0.4–123.0)
			162§	65.7 (43–82)	12.5 (2.8–97.0)
Brock (2012)	Germany	Prospective	353	64.6	11.1 (0.7–50.0)

bx = biopsy, NA = not available, No = number, RCT = randomized control trial, yrs = years.

\* Mean ± SD.

† Median (range).

‡ Elastography group.

§ Control group.

**Table 2****Details of the technological evaluation and instrument composition.**

Author (y)	Biopsy setting	Systematic bx. (cores)	Core location	RTE-targeted bx. (cores)	Cores per lesion	Machine used	Compression method	Gold standard
Pallwein (2007)	Initial	10	Base (1), mid-gland (1), apex (2), transition zone (1)/each side	5 max.	NA	EUB 8500 Hitachi US with 7.5 MHz probe	Manually free compression	Color pattern: Blue area
Aigner (2010)	Mixed	10	Base (1), mid-gland (1), apex (2), transition zone (1)/ each side	5 max.	NA	EUB 8500 Hitachi US with 7.5MHz probe	Manually free compression	Color pattern: blue areas
Ganzer (2011)	Mixed	10	NA	4 max.	2	EUB 7500 Hitachi US with 7.5 MHz probe	Manually free compression	Color pattern: blue areas
Nygard (2013)	Initial	10	TRUS-guided standard sextant biopsy supplemented with 4 lateral cores from the mid-prostate and the apex.	5 max.	NA	Hitachi Preirus US with V53W end-fire probe	Manually free compression	Color pattern: blue areas
Wang (2015)	NA	10	the paramedian (1), center (1), lateral (1), anterolateral of the peripheral zone (1), and the transition zone (1)/each side	3 max.	NA	HIVISION Preirus US with 5 to 10 MHz probe	Freehand compression	Color pattern: blue areas
Eggert (2008) <sup>[22]</sup>	Initial	10	Apex (1), center (1), base (1), median parts (2)/each side	NA	NA	Vouson 730 US with 7.5 MHz probe	Manually free compression	Color pattern: blue areas
Brock (2012) <sup>[23]</sup>	Initial	10	Base (1), mid-gland (1), apex (1), medial biopsies (2)/ each side	10 max.	1	EUB 7500 Hitachi US with 7.5 MHz probe	Compression scale	Color pattern: blue areas

RCT = randomized control trial, bx = biopsy, NA = not available.

significant ( $I^2 = 55.0\%$ ;  $P = .11$ ) (See Figure 1, Supplemental Content, <http://links.lww.com/MD/C174>, which shows the subgroup analysis for patients with the initial biopsy). Only 1 study of participants with a previous negative biopsy was available.<sup>[23]</sup> The calculated PCa detection sensitivities were 60.4% (29/48) for RTE-targeted biopsy and 91.7% (44/48) for systematic biopsy, which resulted in a relative sensitivity value of 0.66.

**3.3.2. Systematic biopsy combined with RTE-targeted biopsy versus systematic biopsy only.** The 2 RCTs,<sup>[26,27]</sup> which recruited 704 participants, compared the diagnostic efficiency between systematic biopsy combined with RTE-targeted biopsy (367 participants) and systematic biopsy only (337 participants). There was a trend toward greater PCa detection sensitivity in the combination biopsy group with an overall detection rate of 45.5% (167/367) compared with 39.5% (130/337) in the systematic biopsy only group. However, the relative risk value of 1.18 (95% CI 0.98–1.43) was not significant. Furthermore, no significant heterogeneity was detected ( $I^2 = 0.0\%$ ;  $P = .84$ ) (Fig. 2B).

### 3.4. Assessment of study quality (QUADAS-2), risk of bias, and heterogeneity

The systematic biopsy approach addressed in this work was not likely to differentiate the target status correctly, and thus the reference test was judged to be at high risk of bias. Each of the included studies was judged to be at an overall risk of bias because systematic biopsy was chosen as the reference standard. Most of the other factors were judged to be at a “low risk of bias” (Table 3).

We identified moderate heterogeneity ( $I^2 = 33.5\%$ ,  $P = .20$ ) in an overall analysis of different biopsy protocols. We performed sensitivity analysis by eliminating Nygard study,<sup>[24]</sup> which decreased the degree of heterogeneity ( $I^2 = 0.0\%$ ,  $P = 0.46$ ). However, the relative sensitivity value of 0.98 (95% CI 0.84–1.15) was also not significantly different, which indicates that our previous results were robust (See Figure 2, Supplemental

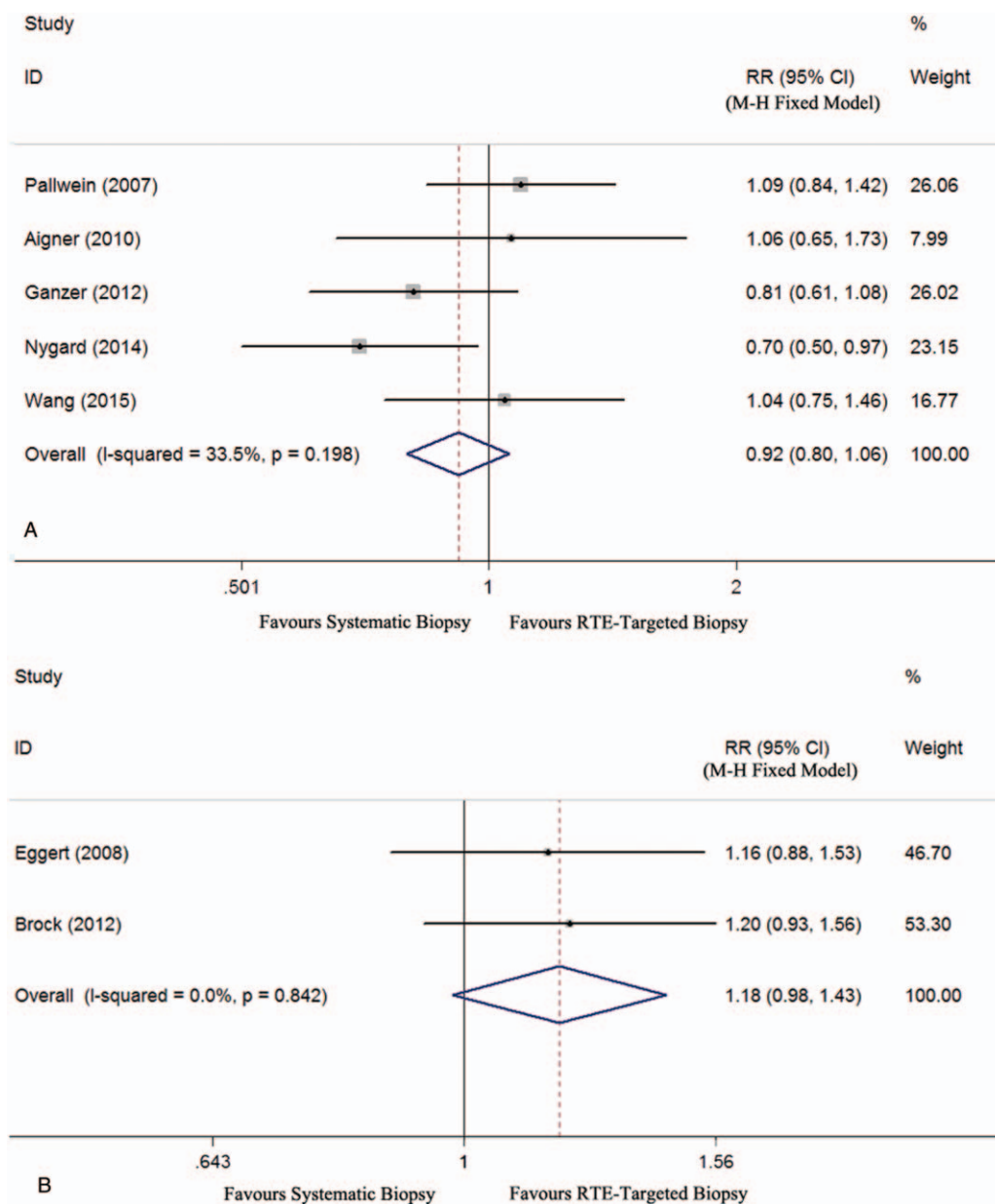
Content, <http://links.lww.com/MD/C174>, which shows the sensitivity analysis by removing Nygard’s study). Per-core detection analysis was performed using the random effects model of Mantel–Haenszel estimates because we found significant heterogeneity ( $I^2 = 86.5\%$ ;  $P < .05$ ) (Fig. 3).

## 4. Discussion

In this systematic review and meta-analysis, we evaluated the diagnostic accuracy of RTE-targeted biopsy compared with systematic biopsy for PCa detection by analyzing the current clinical evidence. Our principle findings were that RTE-targeted biopsy did not outperform systematic biopsy in either overall PCa detection or in the subset of initial biopsies in men with suspected prostate cancer. However, RTE-targeted biopsy only required an estimated 5 cores to detect a positive core compared with at least 10 cores needed for systematic biopsy. Additionally, there was a trend of enhanced detection rate when systematic biopsies were combined with RTE-targeted biopsies, albeit the difference between the combined biopsy and systematic biopsy alone was not statistically significant.

Previous studies have attempted to assess the diagnostic performance of RTE imaging for the detection of PCa. Zhang et al<sup>[12]</sup> reported that RTE imaging has high accuracy when the histopathology of the radical prostatectomy specimen is used as the reference standard (sensitivity of 0.72 and specificity of 0.76). Aboumarzouk et al<sup>[14]</sup> thoroughly assessed the detection role of RTE imaging using histopathology of the radical prostatectomy (RP) specimen and TRUS biopsies (minimum of 10) as the reference standards. Although both comparisons showed positive results for RTE imaging, the studies failed to demonstrate a role for RTE-targeted biopsy in PCa detection.<sup>[14]</sup> Another study published in 2012 assessed the overall accuracy of RTE-targeted biopsy for PCa detection and found that the pooled sensitivity of RTE-targeted biopsies was 62% and that specificity was 79%. However, the reference standard in their study was not clearly stated, and they failed to include studies restricted to RTE-targeted biopsy, which made it difficult to evaluate the true efficacy.<sup>[13]</sup> As far as we know, only 1 systematic literature review





**Figure 2.** A, Effect of overall detection rate of prostate cancer with RTE-targeted biopsy and systematic biopsy. B, Effect of overall detection rate of prostate cancer with systematic biopsy combined RTE-targeted biopsy and systematic biopsy only. Squares indicate relative risk. Diamonds represent summary measures (center of diamond) and associated confidence intervals (lateral tips of diamond).

has sought to synthesize the current evidence based on well-designed, controlled studies to compare the effectiveness of RTE-targeted biopsies with systematic randomized biopsies in the diagnosis of PCa. However, because of variable results and the lack of quantitative analysis, that review failed to draw a clinically relevant conclusion.<sup>[29]</sup>

Our meta-analysis showed that RTE-targeted biopsy and systematic biopsy did not significantly differ in terms of overall PCa detection. However, RTE-targeted biopsy outperformed systematic biopsy in a core-by-core analysis with a relative sensitivity of 2.17. In other words, RTE-targeted biopsy can make a nearly equivalent diagnosis with fewer cores (5 cores max) compared with systematic biopsy, which requires at least 10 cores. Previous reports have shown that an increased number of sampled cores may result in increased morbidity and a greater

risk of overdiagnosis.<sup>[30–32]</sup> Moreover, prostate biopsy with fewer cores reduces patient discomfort and may decrease costs for specimen processing, pathologic evaluation, and cancer therapy.<sup>[5]</sup>

In the subgroup analysis, we found no significant difference between RTE-targeted biopsy and systematic biopsy for the overall detection of PCa in participants with an initial biopsy. Furthermore, the number of studies with sufficient data to analyze the detection rate in participants with previous negative biopsy is currently limited. Therefore, we could not draw any definitive conclusions regarding this subset of the patient population.

Interestingly, the 2 RCTs showed an increase in the PCa detection rate when systematic and RTE-targeted biopsies were combined.<sup>[26,27]</sup> In their trial, Brock et al randomized participants

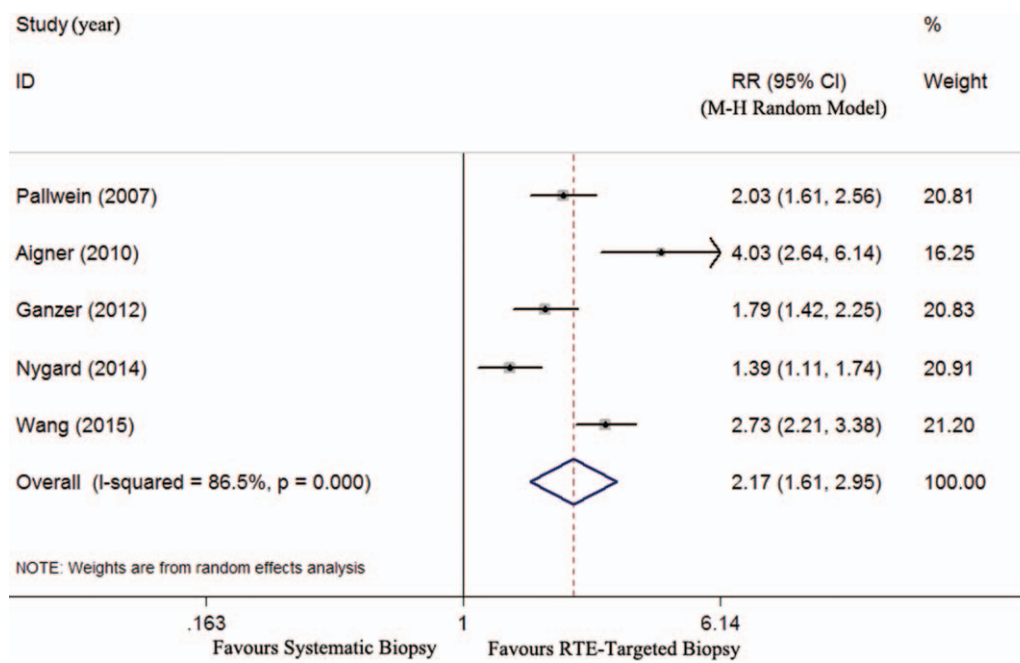


Figure 3. Core detection rate of RTE-targeted biopsy versus systematic biopsy: relative risk (RR) of positive core rate.

into 2 groups (A: systematic biopsy combined with elastography-targeted cores with 10 cores in all; B: 10 systematic cores without elastography-targeted biopsy). This study observed a 12% higher PCa detection rate in the group where elastography-targeted cores were added to a 10-core biopsy scheme (51%) compared with the standard systematic 10-core scheme (39%).<sup>[27]</sup> Eggert et al<sup>[26]</sup> also found out a higher cancer detection rate (40.2%) when elastographic examination was added to the classic TRUS-guided 10-core biopsy compared with the control group (TRUS-guided 10-core biopsy only) (37.7%). This collection of evidence suggests that the combination of systematic and RTE-targeted biopsies may be a promising approach for more efficient detection and diagnosis of PCa.

Traditionally, the diagnostic performance of RTE imaging or RTE-targeted biopsy originated from comparisons with the histology of RP specimens.<sup>[12-14]</sup> Additionally, TRUS is widely used in the visualization of the distal ejaculatory duct system to detect potential lesions in men with hematospermia,<sup>[33]</sup> to monitor prostate growth during testosterone therapy in hypogonadic men and detect abnormalities related to impaired male reproductive health.<sup>[34]</sup> With the property of conventional gray-

scale imaging, its value in malignancy detection is low as PCa tissue typically appears hypoechoic; however, it may also appear echoic or isoechoic.<sup>[35]</sup> However, based on the properties of noninvasion and accuracy for TRUS in the assessment of the prostate-vesicular region, the transrectal ultrasound approach to guide a biopsy is now a standard of care, and 10 to 12 core biopsies are recommended as part of the systematic biopsy for the initial PCa diagnosis.<sup>[3]</sup> TRUS-guided systematic biopsy also has the advantage of easy clinical accessibility and cost-effectiveness. The role of RTE-targeted approaches for the detection of PCa can be comprehensively assessed by direct comparison between RTE-targeted biopsy and systematic biopsy. Our study demonstrated that RTE-targeted biopsy had a higher per-core detection rate and indicated that combining the 2 protocols may improve the accuracy of PCa detection. Despite this finding, the limited data available for analysis hinders any opportunity to draw further conclusions. There is a clear need for additional well-designed RCTs to delineate the diagnostic role of RTE-based protocols in PCa detection.

A strength of this review includes a focus on trials that have applied sequential sampling using both RTE-targeted biopsy and

Table 3

Risk of bias assessment of each study using the Quality Assessment of Diagnostic Studies-2 tool (QUADAS-2).

Study ID (y)	Risk of bias				Application concerns		
	Patient selection	Index test	Reference test	Flow and timing	Patient selection	Index test	Reference standard
Pallwein (2007)	?	-	+	-	-	-	+
Aigner (2010)	?	-	+	-	-	-	+
Ganzer (2011)	?	-	+	-	-	-	+
Nygard (2013)	-	-	+	-	-	-	+
Wang (2015)	?	-	+	-	?	-	+
Eggert (2008)	-	-	+	-	-	-	+
Brock (2012)	-	-	+	-	-	-	+

- = low risk, + = high risk, ? = unclear risk.

systematic biopsy in the same patient, which allows a comparison of the PCa detection rate in the most objective manner. Furthermore, we applied a strategy to redefine the PCa detection rate and adjust differences in cancer prevalence across their own control cohorts using relative sensitivity. Another strength of our study was the application of strict inclusion criteria that restricted our assessment to studies that directly compared the diagnostic efficacy between image-targeted biopsy and systematic biopsy. To our knowledge, this is the first thorough systematic review and meta-analysis that has attempted to delineate the diagnostic accuracy of RTE-targeted biopsy using systematic biopsy as the reference standard.

The limitations of the present study are largely related to the limited number of available studies that could be used to draw a valid conclusion despite the incorporation of all the studies that met the inclusion criteria. First, we restricted the meta-analysis to prospective studies, which increased the quality of evidence that we examined. Second, we detected differences in many of the variables that may contribute to heterogeneity when RTE-targeted and systematic biopsies are conducted. Nevertheless, upon inspection, our overall analysis was subject to insignificant and moderate heterogeneity. Third, the current study did not assess the use of SWE approaches for targeted PCa biopsy. However, several recently published studies, such as those by Woo and Sang, demonstrated that SWE imaging played a positive role in PCa detection.<sup>[15,16]</sup> Moreover, differences exist between RTE and SWE technology (shear-wave speed can be converted into Young modulus used to define a suspicious lesion, whereas RTE is mainly based on a color pattern), which may add technological variation to the study. Nevertheless, future interest should focus on answering whether elasticity-based methods can improve targeted PCa biopsy success rates based on proper synthesis and meta-analysis. Finally, the included studies had insufficient data regarding the PCa detection rates designated as clinically significant or insignificant. Therefore, it was challenging to determine the more clinically useful approach that reduces the risks of underdiagnosis or overdiagnosis of PCa.

In summary, we analyzed the current clinical evidence to evaluate RTE-targeted biopsy for the detection of PCa. We found that RTE-targeted biopsy did not outperform systematic biopsy in either overall PCa detection or in initial biopsies for men with suspected PCa. With regard to the core-by-core analysis, RTE-targeted biopsy had an approximately 2-fold greater detection rate of positive cores than did systematic biopsy, and there was a trend toward an increased PCa detection rate when systematic biopsies were combined with targeted biopsies. We therefore conclude that currently there is insufficient evidence that shows that RTE-targeted biopsy can outperform systematic biopsy, but the combination of systematic and RTE-targeted biopsy may be a promising approach for improving PCa detection. Moreover, moving forward, focus needs to shift toward objective comparisons between systematic and RTE-targeted biopsy approaches to detect clinically significant PCa.

## 5. Author contributions statement

QW and LY contributed to the conception and design of the study. XT, SQ, and TC wrote the main manuscript text. TC and KJ prepared Figs. 1 to 3, Tables 1 to 3 and supplementary Figs. 1 and 2 and Checklist. XT, KJ, and YB participated in the acquisition of data and statistical analysis. All authors reviewed the manuscript.

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