Real-Time Elastography in the diagnosis of prostate cancer: a systematic review

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Abstract

Aim: To evaluate the diagnostic accuracy of real-time elastography as a method for detecting prostate cancer. Material and methods: Relevant studies applying real-time elastography as the diagnostic modality and biopsy as the reference standard, published by March 1, 2018 were retrieved from PubMed, EMBASE, Web of Science and Cochrane Library databases. Two independent reviewers inspected all these articles to confirm the matching of the inclusion criteria. One reviewer with methodological expertise extracted the data from the included studies. Sensitivity, specificity and diagnostic odds ratio (DOR) were used to obtain overall estimates. Randomized effect method, meta-regression and subgroup analysis were performed. Results: Twenty-four studies out of 1156 identified articles met the inclusion criteria. Three groups were set: analysis by patient (Group 1), by core (Group 2), and by image (Group 3) and subgroups set in Group 1. The pooled estimate of real-time elastography sensitivity/ specificity/ DOR calculated with the identical P-value 0.00. Within subgroups “Asia” and “PSA>=10 ng/ml”, the pooled sensitivity, specificity and DOR were 0.83, 0.65 (p=0.01, I²=73.40%; p=0.02, I²=69.5%), 0.80, 0.82 (p=0.66, I²=0.00%; p=0.58, I²=0.00%) and 20.2, 8.67 (p=0.09, I²=54.2%; p=0.20, I²=35.5%), respectively. In these three groups, the areas under the SROC curve were 0.7417, 0.9246, and 0.6213 independently. Conclusions: Real-time elastography is a promising, reliable modality for the non-invasive diagnosis of patients with prostate cancer. The diagnostic accuracy of real-time elastography correlates tightly to the presence of higher PSA level and may help avoid unnecessary biopsy. It seems to be a useful tool in systemic biopsy. Keywords: real-time elastography; prostate cancer; diagnosis

Introduction

In spite of the advances in prostate cancer (PCa) detection and treatment, PCa continues to be one of the leading causes of cancer-related mortality in men [1], with approximately 180,000 new cases diagnosed and 26,000 cancer-related deaths projected in the United States in 2016 [2]. Hence, the diagnostic accuracy is essential to early intervention regarding tumor progression and metastasis, leading to increasing opportunity for surgery and satisfied prognosis.

Improvement has been achieved through different methods, ranging from digital rectal examination (DRE) to prostate-specific antigen (PSA) levels monitoring, computed tomography (CT) and the most widely-used ultrasonography. Magnetic resonance imaging (MRI), in particular, is an important modality in judging disease
localization within prostate and an indicator in diagnosis
along with the subsequent therapy [3]. As a non-invasive
approach, trans-rectal ultrasound (TRUS) is a cost-effective
and readily available imaging modality (MRI is not
popularized in opportunistic screening due to high cost).
Most prostate neoplasms (about 60%-80%) are hypo-
echoic on grey-scale TRUS, whereas 30%-40% are iso-
echoic, and approximately 1.5% are hyper-echoic [2].
The sensitivity and specificity of ultrasound for PCa diag-
nosis vary considerably from 18% to 96% and from 46%
to 91% [1]. Considering the effectiveness and drawbacks
of ultrasound, to develop a new protocol is necessary.

Real-time elastography (RTE) is a unique ultrasound
(US) mode evaluating physical characteristics of tis-
sue and firstly utilized for targeted prostate biopsies by
König in 2005 [4]. The procedure relies on the detection
of variance in tissue compliance by manual compression
and relaxation and is used in conjunction with grey-scale
ultrasound. Nowadays, flexible modalities are well de-
veloped: vibration elastography, acoustic radiation force,
and shear wave elastography (SWE). The two main types
of elastography used in imaging today are compression/strain and SWE. In the fields of breast, liver and prostate,
a series of studies have been reported and meta-analyses
were published [5-7].

The aim of the present study was to perform a meta-
analysis of published papers to assess the overall accu-
ry of RTE targeted biopsy in PCa detection based on
data analysis: 1) Group 1-by patient, 2) Group 2-by core,
and 3) Group 3-by image.

Material and methods

Search strategy
The systematic review and meta-analysis were per-
formed according to the Cochrane diagnostic accuracy
reviews guidelines. Terms and Medical Subject Head-
ings (MeSH) phrases used included: ‘Elasticity Imaging Techniques’ [Mesh], elastography AND ‘Prostatic Neoplasms’ [Mesh], prostate cancer. The search strategy was conducted to find relevant studies from the following databases: Medline (1966 to March 2018), Embase (1980 to March 2018), Cochrane Library (1999 to March 2018), Web of Science (1950 to March 2018).

Study selection
The inclusion criteria were as follows: 1) diagnostic
clinical trials evaluating the accuracy of RTE in the
detection of PCa; 2) study population: patients with el-
evated serum PSA (>4 ng/mL), or abnormal DRE, or hy-
po-echoic nodules on TRUS, or low-intensity lesions on
T2-weighted images on MRI; 3) use of surgical specimen
or TRUS-biopsy as the diagnostic reference standard;
4) English articles; and 5) outcome measurements were
in consistency. The exclusion criteria were the follow-
ing: 1) studies unavailable to construct tables for true-
positive, false-positive, false-negative, and true-negative
determinations; 2) overlap with the selected studies (ie,
studies from the same study group, institution, and period
of inclusion); 3) reviews, editorials, case reports, and cor-
responding letters that did not report their own data; and
4) studies were not suitable for the reference standard.

Two independent reviewers inspected the retrieved
studies to identify the conformation with inclusion cri-
tera. Disagreement between two extracting authors was
resolved by consensus involving a third party (one of
the other members of the research team) after the stud-
ies were scrutinized. Values of true positives (TPs), false
positives (FPs), false negatives (FNs), and true nega-
tives (TNs) were retrieved from literature. Additional
data were extracted from the studies, including first
author, publication year, country of origin of the study,
study design, number of patients (cores/images), loca-
tion of biopsy, reference standard for the diagnosis and
imaging technique along with the machine used. One re-
viewer with methodological competence independently
extracted the data from the included studies. Any disa-
greement was resolved by discussion and, if any clarifi-
cation was necessary, the authors of these studies were
contacted.

Statistical methods
Three groups were set in different aspects: Group
1-by patient, Group 2-by core, and Group 3-by image.
Because of significant heterogeneity in Group 1 (analysis
by patient), subgroups were made subsequently.

Meta-analysis was performed for the diagnostic accu-
ry of RTE by calculating pooled estimates of sensitiv-
ity, specificity, and diagnostic odds ratio (DOR) in each
group. Pooling results (included corresponding 95% con-
fidence intervals [CIs]) were conducted by using the fixed
effect model (Mantel-Haenszel method) when significant
heterogeneity was not present; the random-effects model
(Der Simonian-Laird method) was applied in which the
weights were the inverse of variance of each single study.

The pooled results of sensitivity, specificity, DOR and
symmetric receiver operator characteristic (SROC) curve
were conducted by using Meta-Disc version 1.4 (Unit of
Clinical Biostatistics, Ramony Cajal Hospital, Madrid
Spain). The Cochrane Q test was used to detect the het-
egogeneity among studies. When the p values were <0.10
it indicated the presence of heterogeneity. With regard to
inconsistency (I²), the percentage of the variability attrib-
utable to heterogeneity, >50% was considered significant.

Threshold effect was tested with ROC space and
Spearman correlation coefficient [8]. The representation
of atypical “shoulder arm” pattern in a ROC space and a strong positive correlation between the log of sensitivity and log of 1-specificity would suggest presence of threshold effect.

In our study the pooled DORs were obtained calculating the weighted average using the Der-Simonian Laird random effect model. The DORs combined sensitivity and specificity into one measurement of diagnostic performance. The value of a DOR equals to 1 meant the method had no ability to discriminate, while the higher DOR indicated better ability of the test to differentiate subjects with and without the disease of interest. The SROC curve was constructed by using the Moses-Shapiro-Littenberg method to summarize the difference from each study. In addition, the area under the curve (AUC) was calculated, the value ranging from 0.5 to 1.0. When the value closed to 0.5 indicated a poor test while a value of 1.0 indicated a perfect one.

As for a meta-analysis of diagnostic trials, publication bias can be examined by using Deek’s funnel plot. It was conducted by a regression of diagnostic log odds ratio against 1/sqrt (effective sample size [ESS]), weighting by effective sample size, with $P<0.10$ indicating significant asymmetry [9]. Stata (version 12.0) was used for publication bias analysis.

Before performing the statistical analysis, the quality of eligible studies was evaluated with the Quality Assessment of Diagnostic Studies (QUADAS) in Rev-Man (version 5.30). The items of QUADAS were quantified by “yes”, “no”, or “unclear” with 14 questions [10].

**Results**

**Eligible studies and quality assessment**

We searched 1156 records and 482 duplicates were removed. After screening titles and abstracts, we identified 104 articles for full-text review. Of these articles, 15 were excluded for type of review articles, 19 for symposiums, 27 for insufficient data, and 19 for different reference standard. Finally, 24 potentially relevant studies were identified as eligible studies [11-34] (fig 1). The quality assessed according to the QUADAS criteria is reported in figure 2.

**Study characteristics**

The studies were published between 2002 and 2018, with seven studies performed in Asia. The main characteristics are reported in Table I. Three groups are set in different dimensions: pooled analysis by patient in 16 studies [12,16,17,19,23-34], by core in 9 studies [11-19] and by image in 3 studies [20-22]. In these studies, 2094 patients, 12145 cores and 2182 images were analyzed respectively. Twenty-three studies had a prospective de-
Table I. Baseline characteristics of studies included in the meta-analysis. Three groups are set in different dimensions: pooled analysis by patient, by core, and by images. In these studies, 2094 patients, 12145 cores and 2182 images were analyzed respectively.

<table>
<thead>
<tr>
<th>Study</th>
<th>Method</th>
<th>Threshold</th>
<th>Golden standard</th>
<th>Design</th>
<th>Number of patients/cores/images</th>
<th>Age, mean / median years</th>
<th>PSA, ng/ml</th>
<th>Machine used</th>
</tr>
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<td>12.0</td>
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<td>230</td>
<td>62.3</td>
<td>NS</td>
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</tr>
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<td><strong>Group 2: By cores</strong></td>
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<td>Needle biopsy</td>
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<td><strong>Group 3: By images</strong></td>
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<tr>
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<td>Surgery specimen</td>
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<td>Blue area</td>
<td>Surgery specimen</td>
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<td>Tsutsumi 2010</td>
<td>Colour pattern</td>
<td>Blue area</td>
<td>Surgery specimen</td>
<td>Prospective</td>
<td>292</td>
<td>65.0</td>
<td>13.3</td>
<td>EUB-8500, Hitachi</td>
</tr>
</tbody>
</table>
sign and fifteen studies clearly stated that the pathologists were blinded to the results of RTE.

**Publication bias and influence analysis**

Deek’s funnel plot (fig 3) showed that $p=0.38$ ($p>0.10$), indicating symmetrical funnel was obtained. It is also observed that the regression line is close to right 90° vertical to the DOR line. Therefore, no significant publication bias was introduced in our study.

Studies were analyzed after excluding each study in turn and no significant changes are observed in newly pooled sensitivity and specificity, which indicated a good stability of enrolled studies along with credible results generated below.

**Pooled analysis by patient (Group 1)**

Significant heterogeneity was found in diagnostic OR (DOR=5.06, Cochrane-$Q=139.52$, df=15, $p=0.00$, $I^2=89.2\%$). The pooled sensitivity, specificity, positive LR and negative LR and its responding $p$-value were 0.76 ($p=0.00$), 0.62 ($p=0.00$), 2.00 ($p=0.00$), and 0.41 ($p=0.00$). Spearman correlation coefficient was 0.032 ($p=0.91$), which means no threshold effect existed. Meta-regression was performed, and “region” resulted in heterogeneity across the studies. The diagnostic value in “Asia” was 6.91 times higher than in “non-Asia” countries (Table II, RDOR=6.91, $p=0.03$).

Subgroups were set for “region”, along with “PSA level”, “age”, “method”, “volume” and “localization (‘peripheral zone’ or ‘whole organ’)” of targeted lesions. No significant heterogeneity was found by DOR in the subgroup “Asia” (Table III, DOR=20.2, Cochrane-$Q=6.54$, df=3, $p=0.09$, $F=54.2\%$) and “PSA>$10ng/ml$” (DOR=8.67, Cochrane-$Q=4.65$, df=3, $p=0.20$, $F=35.5\%$). The pooled sensitivity in two subgroups were 0.83, 0.65 ($p=0.01$, $F=73.40\%$; $p=0.02$, $F=69.5\%$), and specificity 0.80, 0.82 ($p=0.66$, $F=0.00\%$; $p=0.58$, $F=0.00\%$) independently, as shown in figure 4 and 5.

The SROC curve was obtained. The AUC was 0.7417 (fig 6 - line a).

**Pooled analysis by core (Group 2)**

Nine researches were enrolled in this part and there was a heterogeneity. Meta-regression and subgroup-setting were not performed as there were not enough studies in this part. The pooled sensitivity, specificity, positive LR, negative LR, DOR and their responding $p$ values were 0.51 ($p=0.00$), 0.88 ($p=0.00$), 4.30 ($p=0.00$), 0.41 ($p=0.00$), and 11.76 ($p=0.00$). The SROC curve was drawn. The AUC was 0.9246 (fig 6-line b).

**Pooled analysis by image (Group 3)**

A heterogeneity was found. The pooled sensitivity, specificity, positive LR, negative LR, DOR and their responding values were 0.77 ($p=0.00$), 0.36 ($p=0.00$), 1.22 ($p=0.00$), 0.52 ($p=0.00$), and 2.38 ($p=0.00$). The AUC was 0.6213 (fig 6-line c).

**Discussions**

Screening, detection and diagnosis of prostate cancer are currently on the basis of DRE, PSA levels, CT, MRI and greyscale ultrasound. However, limitations to these approaches in clinical practice are clear. Digital examination depends mainly on the experience of the physician subjectively and, occult lesions or minor ones cannot be detected effectively; PSA levels can be influenced by infections, hyperplasia, drugs in-taken and so on, following a poor specificity and low predictive value; CT virtually
Table III. Results of subgroup analysis in Group 1 (by patient). No significant heterogeneity was found by DOR in the subgroup “Asia” (DOR=20.2, Cochrane-Q=6.54, df=3, p=0.09, I²=54.2%) and “PSA>=10 ng/ml” (DOR=8.67, Cochrane-Q=4.65, df=3, p=0.20, I²=35.5%).

<table>
<thead>
<tr>
<th>Region</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive LR</th>
<th>Negative LR</th>
<th>DOR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of studies</td>
<td>Pooled estimates, % (95% CI)</td>
<td>p</td>
<td>I-square (%)</td>
<td>Pooled estimates, % (95% CI)</td>
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<td>Asia</td>
<td>4</td>
<td>0.83 (0.76;0.89)</td>
<td>0.01</td>
<td>73.40</td>
<td>0.80 (0.74;0.85)</td>
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<tr>
<td>Non-Asia</td>
<td>12</td>
<td>0.74 (0.71;0.77)</td>
<td>0.00</td>
<td>90.10</td>
<td>0.58 (0.55;0.61)</td>
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<td>PSA</td>
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</tr>
<tr>
<td>≥10 ng/ml</td>
<td>4</td>
<td>0.65 (0.57;0.74)</td>
<td>0.02</td>
<td>69.50</td>
<td>0.82 (0.75;0.87)</td>
</tr>
<tr>
<td>&lt;10 ng/ml</td>
<td>7</td>
<td>0.77 (0.73;0.80)</td>
<td>0.00</td>
<td>92.80</td>
<td>0.59 (0.55;0.62)</td>
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<td>Age</td>
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<tr>
<td>≥65 years</td>
<td>6</td>
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<td>&lt;65 years</td>
<td>10</td>
<td>0.71 (0.67;0.75)</td>
<td>0.00</td>
<td>89.80</td>
<td>0.60 (0.57;0.63)</td>
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<tr>
<td>Method</td>
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<tr>
<td>Colour gradient</td>
<td>14</td>
<td>0.73 (0.70;0.76)</td>
<td>0.00</td>
<td>87.80</td>
<td>0.63 (0.60;0.66)</td>
</tr>
<tr>
<td>SWE</td>
<td>2</td>
<td>0.91 (0.85;0.96)</td>
<td>0.54</td>
<td>0.00</td>
<td>0.54 (0.46;0.62)</td>
</tr>
<tr>
<td>Volume</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥60 ml</td>
<td>3</td>
<td>0.66 (0.58;0.73)</td>
<td>0.01</td>
<td>77.40</td>
<td>0.33 (0.25;0.42)</td>
</tr>
<tr>
<td>&lt;60 ml</td>
<td>7</td>
<td>0.82 (0.78;0.85)</td>
<td>0.00</td>
<td>90.60</td>
<td>0.63 (0.60;0.67)</td>
</tr>
<tr>
<td>Localization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral zone</td>
<td>9</td>
<td>0.75 (0.71;0.80)</td>
<td>0.00</td>
<td>87.50</td>
<td>0.61 (0.57;0.65)</td>
</tr>
<tr>
<td>Whole organ</td>
<td>7</td>
<td>0.76 (0.71;0.80)</td>
<td>0.00</td>
<td>90.70</td>
<td>0.63 (0.59;0.66)</td>
</tr>
</tbody>
</table>
plays no role in the detection of PCa and is not recommended for diagnostic purposes as soft tissues resolution is low and margins of the gland are poorly defined [1]. Conventional MRI is of value in predicting the pathological stage and extra-capsular extension. Prostate MRI used before first prostate biopsy, could identify men who might safely avoid an unnecessary biopsy. However, it is less cost-effective in active surveillance. The use of TRUS has limited diagnostic accuracy, for benign lesions such as prostatitis, infarction, and benign prostate hypertrophy, may be hypo-echoic, resulting to varying sensitivity and specificity.

Within the stages including the occurrence and progression of neoplasms, cancerous lesions became harder and less elastic, following the changes histologically: increased cellular density, rising micro-vascularity, a loss of glandular tissue architecture [35], and increased collagen deposition in the stroma [36]. Real-time elastography is applied in detecting abnormal lesions by images accessing of tissue elasticity or stiffness, involving many fields like thyroid, liver, kidney, breast, pancreas and prostate [37-43]. As a modality of great importance, however, the sensitivity and specificity are variously reported. Our study was designed to analyze pooled data and evaluate the diagnostic value of RTE in the detection of prostate cancer.

Though meta-analyses have been performed before [6,7,43], updates based on new and large-scale data is still necessary, with setting of subgroups and deeper exploration. As an invasive procedure, TRUS-guided biopsy may cause infections and hematuria. Over the past decade, there has been a trend to obtain larger numbers of biopsy specimens, with most clinicians taking 8 to 12 biopsy cores and most current studies recommending a 12-core biopsy scheme [44]. According to our study, real-time elastography will decrease the rate of unnecessarily performed cores with lower health care costs and side effects.

Subgroups were set in Group 1 by considering region, PSA levels, age, prostate volume, method and tumor localization based on the results of meta-regression and clinical perspectives. Total serum PSA, prostate volume and age have been found to be clinically significant predictors of positive biopsy findings [45]. Within the subgroup of PSA level >=10 ng/ml and region of Asia, the pooled sensitivity was 0.65, 0.83 and specificity 0.82, 0.80. No significant heterogeneity was found in specificity (p=0.66, $I^2$=0.00%; p=0.58, $I^2$=0.00%). This indicated that patients in Asia counties and/or with higher PSA may be more likely to be precisely diagnosed by RTE. The values of RTE climbed as the PSA level increased, meaning the progression of tumor, and that RTE is a reliable indicator in the detection of abnormal lesions. As to the data in Asian areas, the diagnostic odds ratio is six times higher than that in non-Asian countries, but with a $I^2$-square (54.2%) which indicated the inconsistency.
within this group. Not many relevant studies (only 4) that conform with our standards were well performed in Asia, and this is the principal reason leading to the high DOR in this subgroup. More studies and following updates are still required.

To our knowledge, this is the first meta-analysis introducing analysis of RTE with three dimensions: by patient, by core and by image respectively, along with both reference standard of TRUS-guided biopsy and radical-prostatectomy biopsy. According to the results of our study, the diagnostic accuracy of RTE quantified by AUC is 0.9246 for the diagnosis of prostate cancer in the group “analysis by core”. Our meta-analysis indicated that RTE can be used with a high diagnostic accuracy to detect malignant prostate lesions.

There are several limitations to our study. First, only three studies were included in the analysis by image. Second, though high sensitivity, specificity and DOR are obtained with fine consistency in subgroup “Asia” and “PSA>=10 ng/ml”, the small number of studies as a factor cannot be neglected which will give rise to higher estimates. Third, as data on Gleason score were not well described in research the analysis was not performed unfortunately. Fourth, RTE is a modality dependent on physicians’ performance. Though colour-gradient scale was applied in ultrasound system, the judgment of the right images and localization is still influenced by the pressure given by doctors and their experience. Reproducible results cannot be obtained satisfactorily. Modalities like SWE which uses acoustic radiation force and are less dependent on performers need to be popularized. In addition, in this paper, the publication bias cannot be excluded, even though the analysis of the Deek’s plot indicated small risk.

In conclusion, in our study, RTE achieved an exciting efficiency in PCa detection, with the analysis of sensitivity, specificity and diagnostic odds ratio. Furthermore, it showed quite correspondence with the PSA elevation, indicating its value as a potential marker. Due to the obtained results and to their non-invasive characteristics, RTE is a promising modality for the early characterization in patients with prostate cancer and may reduce the unnecessary biopsies in the future, along with digital rectal examination, serum indicator, greyscale US and MRI. Large-scale trials are warranted to further explore the diagnostic value of RTE in the diagnosis of prostate cancer and other fields.

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Conflict of interest: none

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