Review Article
The diagnostic value of virtual touch tissue quantification in the differentiation of renal solid masses: a meta-analysis

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Abstract: Objective: To assess the diagnostic efficiency of virtual touch tissue quantification (VTQ) in the differentiation of malignant and benign renal solid masses through a meta-analysis. Methods: We searched the PubMed, Science Web, Cochrane Library, CNKI, Wanfang, and Medical databases for studies published from January 1, 1990 to January 31, 2020 to identify relevant studies. We also counted the pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and overall diagnostic odds ratio (DOR), and drew summary receiver operating characteristic (SROC) curves to examine VTQ imaging accuracy. Then, we displayed a Fagan plot to evaluate the clinical value of the recognition of malignant renal lesions. Results: A total of 673 lesions in eight studies were included in the meta-analysis. The pooled sensitivity, specificity, PLR, and NLR in differentiating malignant and benign renal solid masses were 0.84 (95% confidence interval (CI) 0.74-0.90), 0.77 (95% CI 0.65-0.85), 3.6 (95% CI 2.3-5.6), and 0.21 (95% CI 0.13-0.35), respectively. The overall DOR was 17 (95% CI 8.37 with an area under the receiver operating characteristic (AUROC) of 0.87 (95% CI 0.84-0.90). VTQ was informative in discriminating malignant renal lesions, when the pre-test probability was 50%, the probability of malignant tumors following a positive measurement was 78%, and the probability of negative measurement was as low as 18%. Conclusions: VTQ has a relatively high application value in distinguishing malignant and benign renal solid masses. It can enrich diagnostic information and broaden ultrasonic diagnoses.

Keywords: VTQ, renal solid mass, ultrasound elastography, meta-analysis

Introduction
Kidney cancer accounts for 5% and 3% of all adult malignancies in men and women, respectively. It is the seventh and tenth most common cancer in men and women, respectively [1]. Renal cell carcinoma (RCC) accounts for 80% of all kidney cancers. Contrast magnetic resonance imaging (MRI) and contrast-enhanced ultrasound (CEUS) play important roles in differentiating RCC and benign renal solid tumors. However, MRI is limited because it has constructed defects, is expensive, and is time-consuming. CEUS is limited to patients with several lesions, and invasive biopsy is not well-accepted by patients. Ultrasound (US) has the irreplaceable role of distinguishing renal cysts from solid masses, and it also has a high detection rate for asymptomatic, early kidney cancer. Nonetheless, one study [2] found that approximately 20% of all small RCC are hyperechoic in US, which is basically the same as angiomylipoma (AML). Fortunately, ultrasonic elasticity-based ultrasound provides a novel diagnostic perspective and can generate disease-related information in addition to the acoustic image features based on traditional ultrasound.

Acoustic radiation force impulse (ARFI) imaging is a developed ultrasonic elastography that measures tissue elasticity and includes virtual touch tissue imaging and virtual touch tissue quantification (VTQ). VTQ is a quantitative diagnostic technique that produces shear waves in tissues by emitting an acoustic radiation pulse, and greater shear wave velocity (SWV) indicates a higher hardness of the measured tissue [3]. VTQ is widely used in thyroid, breast, abdominal, and pelvic organ diseases. Most scholars mainly focus on the diagnosis of renal
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The diagnostic accuracies of VTQ imaging to recognize kidney cancer in a few related studies varied based on the different cut-off values. Therefore, we searched for relevant studies on assembling lesions for this meta-analysis to evaluate the diagnostic efficiency of VTQ in the identification of malignant and benign renal solid masses.

Materials and methods

We comprehensively searched the PubMed, Science Web, Cochrane Library, CNKI, Wanfang, and Medical databases for studies published from January 1, 1990 to January 31, 2020 to identify the relevant studies for evaluating VTQ’s ability to differentiate malignant and benign renal tumors. The appropriate key-words and Medical Subject Heading (MeSH) terms were applied, as follows: (renal solid mass) OR (renal neoplasm) OR (renal cancer) OR (kidney neoplasm) OR (kidney cancer) AND ((ARFI) OR (acoustic radiation force impulse) OR (VTQ) OR (virtual touch tissues quantification) OR (ultrasound elastography)) AND ((diagnosis) OR (differentiation) OR (distinguishing) OR (discriminate)). We also obtained relevant studies using manual searching and omitted duplicate studies after the electronic retrieval. We limited our searches to studies written in Chinese or English.

Selection criteria

Studies that satisfied the following points were included in the meta-analysis: (1) evaluated VTQ imaging for the recognition of benign and malignant renal solid masses, and used VTQ values with the Siemens Acuson S2000 ultrasound system; (2) considered pathology acquired using needle biopsy or surgery, or the image findings included CT, MRI, and CEUS as appropriate diagnostic standards; (3) contained sufficient information to directly or indirectly gain true positive (TP), false positive (FP), true negative (TN), and false negative (FN) results on the basis of the cut-off values; (4) involved large sample sizes with overlapping patient samples.

Study selection and data extraction

The two investigators (Lihong Chen and Yujie Huang) independently assessed and verified the qualified studies and extracted the data. Disagreements were resolved with the help of the third investigator (Haibin Tu). We obtained the necessary information from each study, as follows: first author, year of publication, country, VTQ cut-off value, number of patients and renal lesions for analysis, rate of malignant renal lesions, diagnosis reference standard, and the pathological types of renal lesions. In addition, we calculated TP, FP, FN, and TN in addition to the sensitivity, specificity, and the...
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Table 1. The main information of the included studies

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Country</th>
<th>cut-off (m/s)</th>
<th>No. of patients</th>
<th>No. of tumors</th>
<th>No. of malignant tumors</th>
<th>Rate of malignant lesions (%)</th>
<th>Renal tumor pathological types</th>
<th>Reference standard</th>
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<td>China</td>
<td>2.355</td>
<td>35</td>
<td>35</td>
<td>24</td>
<td>68.57</td>
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<tr>
<td>Zhao J [20]</td>
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<td>139</td>
<td>139</td>
<td>115</td>
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<td>199</td>
<td>199</td>
<td>156</td>
<td>78.39</td>
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</tr>
<tr>
<td>Guo LH [10]</td>
<td>2014</td>
<td>China</td>
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<td>24</td>
<td>24</td>
<td>11</td>
<td>45.83</td>
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<td>Pathology, enhanced imaging, imaging and clinical data</td>
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<td>49</td>
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<td>75</td>
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Table 2. A quality assessment of the included studies

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<th>Q2</th>
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<th>Q6</th>
<th>Q7</th>
<th>Q8</th>
<th>Q9</th>
<th>Q10</th>
<th>Q11</th>
<th>Q12</th>
<th>Q13</th>
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<td>unclear</td>
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<td>yes</td>
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<td>yes</td>
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<td>Liu XH [4]</td>
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<td>unclear</td>
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<td>yes</td>
<td>no</td>
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</table>

Figure 2. Forest sensitivity and specificity of VTQ for the differentiation of liver lesions. Supplementary: PLR 3.6 [2.3, 5.6], NLR 0.21 [0.13, 0.35], DOR 17 [8, 37].

relevant data for each reported VTQ cut-off value.

Quality assessment

We applied the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) questionnaire to determine the quality of the studies included. This tool is used to assess the internal and external validity of the diagnostic accuracy of the studies included in the meta-analysis [7]. The questionnaire includes 14 items. A study that reports related content was registered as “yes”. Otherwise, it was registered as “no”. If an accurate judgment could not be provided using the available information in the study, then it was recorded as “unclear”.

Data synthesis and statistical analysis

We counted the pooled sensitivity, specificity, PLR, NLR, and DOR with a corresponding 95% CI to inspect the VTQ imaging accuracy for the classification of malignant and benign renal
VTQ in the differentiation of renal solid masses. We also plotted a SROC curve to graphically present the results. Moreover, we estimated the heterogeneity across the studies using the inconsistency index ($I^2$) and the Cochrane Q statistic. A $P$ value under 0.10 or an $I^2$ value over 50% was considered evident heterogeneity.

Meanwhile, we conducted a univariate meta-regression analysis to explore the sources of the potential heterogeneity among the studies and conducted a subgroup analysis. The covariates included the following: country (China vs. Turkey), cut-off value ($2.0 \geq m/s$ vs. $<2.0$), rate of malignant hepatic lesions ($\geq50\%$ vs. $<50\%$), and reference standard (pathology only vs. pathology and/or others).

In addition, we created a Fagan plot to evaluate the clinical value of the VTQ imaging [8]. We also analyzed the pre-test probabilities of 25%, 50%, and 75% and the corresponding post-test probabilities. Finally, we investigated the publication bias using Deeks funnel plot asymmetry test, with $P>0.10$ indicating symmetry [9].

Review Manager 5.3 and MIDAS modules in Stata SE 15.0 were used for all the statistical analyses.

**Results**

**Search results and characteristics of the studies**

A total of 224 studies were retrieved initially according to the search strategies; 53 studies were duplicate articles, 150 studies were irrelevant, 21 potentially relevant studies were assessed for eligibility, and 13 studies were excluded due to one of the following: insufficient data ($n=9$), meta-analysis ($n=1$), abstract only ($n=1$), or not Acuson Siemens ($n=2$). Finally, eight articles that satisfied the inclusion criteria were considered in the meta-analysis. A flow chart of the study selection is shown in Figure 1.

The main information from the included studies is listed in Table 1. We collected data on 673 focal renal solid masses in 673 patients, of which 177 were benign lesions and 496 were malignant. The cut-off values ranged from 1.37 m/s to 3.07 m/s. The cut-off was approximately 2.0 m/s in six studies, and the cut-offs were 1.37 and 3.07 m/s in the two remaining studies. Seven studies were completed in China, and the remaining study was completed in Turkey. Siemens Acuson S2000 was used in all the studies on ultrasonic instruments. Four studies used pathological results as the single reference standard, and the other studies adopted the nonsingle reference standard, including MRI, CT, and CEUS. The total proportion of malignant renal lesions was 73.70% (the individual proportions ranged from 54.83% to 82.73%).

In addition, 144 benign lesions were AML. The mean SWV of AML was approximately 1.98 m/s from 2.25 m/s in 112 AML lesions in six studies. The mean SWV of AML was 1.11±0.43 m/s of the 32 remaining AML lesions in the study of Liu [4]. Gou [10] only included 13 pseu-
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Table 3. Results of the meta-regression and subgroup analysis

<table>
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<tr>
<th>Covariates</th>
<th>Subgroup</th>
<th>No. of studies</th>
<th>Sensitivity</th>
<th>P value</th>
<th>Specificity</th>
<th>P value</th>
</tr>
</thead>
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<td>country</td>
<td>China</td>
<td>7</td>
<td>0.81 [0.74-0.89]</td>
<td>0.23</td>
<td>0.80 [0.72-0.87]</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>Turkey</td>
<td>1</td>
<td>0.89 [0.75-1.00]</td>
<td></td>
<td>0.53 [0.26-0.79]</td>
<td></td>
</tr>
<tr>
<td>Cut-off</td>
<td>≥2 m/s</td>
<td>7</td>
<td>0.82 [0.74-0.91]</td>
<td>0.25</td>
<td>0.75 [0.64-0.86]</td>
<td>0.25</td>
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<tr>
<td></td>
<td>&lt;2 m/s</td>
<td>1</td>
<td>0.89 [0.76-1.00]</td>
<td></td>
<td>0.85 [0.67-1.00]</td>
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<tr>
<td>Rate of malignant tumors</td>
<td>≥50%</td>
<td>7</td>
<td>0.82 [0.74-0.90]</td>
<td>0.14</td>
<td>0.78 [0.69-0.88]</td>
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<tr>
<td></td>
<td>&lt;50%</td>
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<td>1.00 [1.00-1.00]</td>
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<td>0.62 [0.26-0.98]</td>
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<td>Reference standard</td>
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<td>0.77 [0.67-0.87]</td>
<td>&lt;0.01</td>
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<td>blinded</td>
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<td>unclear or other position</td>
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<td>0.82 [0.70-0.94]</td>
<td>0.72 [0.57-0.87]</td>
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</table>

Figure 4. A Fagan plot to evaluate the clinical utility of VTQ for the differentiation of renal lesions. A. Pre-test probability =25%; B. Pre-test probability =50%; C. Pre-test probability =75%.

dotumors as benign lesions, and the SWV of the pseudotumor was 3.24±0.75 m/s. A total of 375 malignant lesions were clear cell renal cell carcinoma (ccRCC), and the mean SWV of ccRCC ranged from 2.07 m/s to 2.99 m/s.

According to the QUADAS scale (Table 2), Q1 indicates spectrum composition, Q2 indicates selection criteria, Q3 indicates appropriate reference standard, Q4 indicates disease progression bias, Q5 indicates partial verification bias, Q6 indicates differential verification bias, Q7 indicates incorporation bias, Q8 indicates test execution details, Q9 indicates reference execution details, Q10 indicates test review bias, Q11 indicates diagnostic review bias, Q12 indicates clinical review bias, Q13 indicates intermediate results, and Q14 indicates withdrawals. We investigated two studies that satisfied 11 scale requirements, three studies that satisfied 10 requirements, two studies that satisfied nine requirements, and one study that satisfied eight requirements.

Analysis of the diagnostic efficiency

The pooled sensitivity, specificity, PLR, and NLR for distinguishing malignant from benign renal
solid masses were 0.84 (95% CI 0.74-0.90), 0.77 (95% CI 0.65-0.85), 3.6 (95% CI 2.3-5.6), and 0.21 (95% CI 0.13-0.35), respectively (Figure 2 and Supplementary). A statistically significant heterogeneity was found in the sensitivity (Q=54.34 df=7.00, $P=0.00$, I²=87.12 (70.53-94.71)) and the specificity (Q=19.2 df=7.00, $P=0.01$, I²=63.54 (35.72-91.37)). The overall DOR was 17 (95% CI 8-37) with an AUROC of 0.87 (95% CI 0.84-0.90) (Figure 3).

Meta-regression and subgroup analysis

We searched the sources of possible heterogeneity in the sensitivity and specificity by means of univariate meta-regressions and conducted a subgroup analysis. The results showed that the reference standard and blinded interpretation of VTQ were associated with the heterogeneity of sensitivity ($P<0.01$, 0.02) but not of specificity ($P=0.74$, 0.48). No statistically significant sensitivity or specificity was found for the VTQ cut-off value ($P=0.25$, 0.25), country ($P=0.23$, 0.24), rate of malignant renal lesions ($P=0.14$, 0.49), or the position in the operation ($P=0.32$, 0.79). The grouped data are shown in Table 3.

An assessment of the clinical value of VTQ imaging for renal solid masses

The Fagan plot showed that VTQ imaging is relatively effective at identifying malignant and benign renal solid masses. When the pre-test probability was 50%, a 78% probability of malignant tumors followed a positive measurement, and a probability as low as 18% was obtained under a negative measurement (Figure 4B). However, when the pre-test probability was 25%, VTQ only had a 54% probability of differentiating accurately (Figure 4A). In addition, when the pre-test probability was 75%, the diagnosis would be inaccurate in reaching 39% with a negative measurement. Nevertheless, the probability exceeded 90% for an accurate diagnosis following a positive measurement (Figure 4C).

Publication bias

In accordance with the Deeks funnel plot asymmetry test, the scattered points were distributed on both sides of the regression line, $P=0.30>0.10$ (Figure 5 and Table 4). This finding indicates no evident publication bias in the literature.

Discussion

Elasticity is inherent in biological tissues; it is different in different tissue structures and in the same tissue structures in different pathological states. This theory is fundamental for the elastography diagnosis. VTQ is a quantitative diagnosis elastography and is different from traditional real-time elastic imaging. It can quantify the elasticity and hardness of local tissues. At present, few scholars have studied renal solid masses using VTQ, and their results are varied. Zhao [11] considered the SWV of malignant and benign renal solid masses to be lower than the SWW of the renal cortex, and statistical significance was found in benign and malignant renal lesions ($P=0.013$), ccRCC, and AML ($P=0.022$). However, the question of whether SWV can differentiate RCC from AML is still controversial. Sagreiya [12] did not show a significant differentiation of RCC from AML with an AUROC of 0.62 ($P=0.23$) using the SWV measurements.

In this meta-analysis, we assessed the performance of VTQ in distinguishing 673 renal masses, where the pooled sensitivity (0.84) and specificity (0.77) were relatively high. The overall DOR was 17 with an AUROC of 0.87. This finding is consistent with the finding Hu [13] reported for liver lesions. Some studies [14, 15]
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considered that the difference was not statistically significant between VTQ and CEUS in differentiating renal solid masses. Wu [14] reported that VTQ can correct misdiagnosis of the benign lesions of oxyphilic adenoma reported as malignant tumors using CEUS. VTQ imaging is easily and inexpensively integrated into the ultrasound systems and can be performed with one conventional probe. Moreover, the operator can easily master the system with a high repeatability, and the region of interest can be positioned manually at the specific location inside the kidney. Thus, VTQ is only slightly affected by obesity. In addition, patients easily find it acceptable because it is faster and less expensive. Furthermore, VTQ imaging can observe several lesions simultaneously without causing any discomfort. Therefore, VTQ imaging is a promising elastic technology and plays an important role in clinical practice.

However, a network meta-analysis [16] showed that the pooled sensitivity and specificity were 0.87 and 0.84 for CEUS, respectively, for differentiating malignant and benign renal solid masses. The PLR and NLR were 5.55 and 0.12, respectively, and the overall DOR was 53.44 with an AUROC of 0.95. Evidently, the diagnostic efficiency of VTQ was less than that of CEUS. On the one hand, the likely reason is that VTQ imaging has some technical limitations, including a maximum probe depth of approximately 8 cm, a sampling fixed frame of (10 mm × 6 mm), and it’s vulnerable to breathing and angle of measurement. In addition, old and weak patients cannot hold their breath, and some renal lesions have pathological changes with necrosis, liquefaction, and calcification. On the other hand, our study has several potential limitations that should be considered. First, the number of articles reviewed was small. Second, the range of the VTQ cut-off was wide. Liu [4] explained that cpRCC and rapRCCs were bloodless tumors compared with ccRCC, the mesenchymal cells were few, and the small vacuoles of the intracytoplasms were large in cpRCC [17]. Hemorrhage, necrosis, and cystic degeneration are common in rapRCCs [18]. These factors were responsible for the low SWV. In addition, only the study of Guo [10] differentiated between ccRCC and pseudotumors. The SWV of the pseudotumors was higher than the SWW of the other benign tumors and RCC. Third, seven out of eight studies were completed in China, indicating a large regional bias. Fourth, all eight studies included evaluated the diagnostic performance of VTQ, but other studies on elastic technology were excluded in this meta-analysis.

Meanwhile, the subgroup analysis showed that the sensitivity of the studies using only pathology as a reference standard was less than it was using pathology and other factors (0.77 vs. 0.88), and the sensitivity of the blinded interpretation of VTQ was lower than it was with the unclear or unblinded interpretations (0.80 vs. 0.87). And there was no statistically significant differences in the sensitivity and specificity found between the VTQ cut-off values, countries, rates of malignant renal lesions, or the positions in the operations. We believe that this finding is mainly related to the small number of articles examined, the imbalance of the locations, and the imbalance of the malignant and benign renal lesions covered in articles included in the meta-analysis. We expect future studies on the clinical value of VTQ to obtain more reliable results.

In conclusion, as a novel imaging technology, VTQ has a high application value in distinguishing renal solid masses. It can represent elastic information of tissues. It is safe, non-invasive, simple, inexpensive, and fast; it also has high repeatability, and obtains objective results. In addition, it has a wide range of applications, can more comprehensively locate lesions, distinguishes the nature of the lesion, enriches the diagnostic information of the disease, broadens the ultrasonic diagnosis, and perfects the modern ultrasonic technology.

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Disclosure of conflict of interest

None.

Table 4. Stata publishing bias evaluation form

| yb     | Coef.  | Std. Err. | t     | P>|t|   | [95% Conf. Interval] |
|--------|--------|------------|-------|-------|----------------------|
| Bias   | 16.75672 | 14.82302  | 1.13  | 0.301 | [-19.5139, 53.02734]  |
| Intercept | .7726507 | 1.867431  | 0.41  | 0.693 | [-3.796789, 5.34029]  |
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