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ORIGINAL ARTICLE

Diagnostic accuracy of real-time tissue elastography for breast cancer: a meta-analysis

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Abstract

Objective The present study aimed to determine the accuracy of real-time tissue elastography (RTE) for the diagnosis of breast cancer.

Methods The search was conducted in the PubMed, Web of Science, Cochrane Library, and China Biology Medicine databases from inception through December 31, 2014, without language restrictions. The meta-analysis was conducted using STATA version 12.0 and Meta-Disc version 1.4. We calculated the summary statistics for sensitivity (Sen), specificity (Spe), positive and negative likelihood ratio (LR^+/LR^-), diagnostic odds ratio (DOR), and summary receiver operating characteristic (SROC) curve.

Results Ten studies that met all inclusion criteria were included in the meta-analysis. A total of 608 malignant breast lesions and 1292 benign breast tumors were assessed. All breast lesions were histologically confirmed after RTE. The pooled Sen was 0.83 (95% CI = 0.79–0.86); the pooled Spe was 0.86 (95% CI = 0.84–0.88). The pooled LR^+ was 9.87 (95% CI = 2.66–36.71); the pooled LR^- was 0.20 (95% CI = 0.17–0.23). The pooled DOR of RTE for the diagnosis of breast cancer was 62.21 (95% CI = 33.88–114.24). The area under the SROC curve was 0.9334 (standard error = 0.00125). We found no evidence of publication bias (t = –0.57, P = 0.582).

Conclusion RTE may have high diagnostic accuracy for the differential diagnosis of benign and malignant breast tumors. RTE may be a good tool for breast cancer diagnosis.

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Key words: real-time tissue elastography (RTE); breast cancer; diagnostic accuracy; meta-analysis

Breast cancer is a very common malignant disease in women worldwide [1]. Approximately one million women are diagnosed with breast cancer, and more than 110 000 of those affected die from the disease [2]. In Southeast Asia, breast cancer has become the most frequently occurring tumor of all malignant diseases [3]. Despite being the most common cancer, the 5-year relative survival rate of breast carcinoma remains more than 80% when the disease is detected early [4]. To improve survival, a number of screening methods to detect breast cancer have been investigated, including magnetic resonance imaging (MRI), Doppler ultrasonography (US), and computed tomography (CT) [5–7]. Recent studies have suggested that real-time tissue elastography (RTE) could be an effective technique to improve the sonographic diagnosis of invasive breast cancer, and the sensitivity (Sen) of this technique in invasive breast cancer might be similar to those of CT and MRI [8]. A combination of B-mode US and RTE may have predictive value for the differentiation of benign and malignant lesions < 1 cm [9].

RTE has been used for the differential diagnosis of breast, thyroid, and prostate cancers; the basic principle is that tissue compression produces displacement within the tissue, which is smaller in harder tissue than in softer tissue, and the displacement produced in real time is superimposed on the B-mode image as different colors [10]. RTE is a relatively harmless, inexpensive, convenient, radiation-free, and real-time tool compared with CT or MRI [11]. RTE may improve the diagnostic confidence of breast cancer, providing information on the tumor stiffness [12]. Early detection and curative treatment of breast cancer is crucial for patient prognosis [4]. Previous studies have shown that RTE is helpful for the differentiation of benign and malignant breast tumors [10]. However, the results of these studies have been contradictory. Therefore, the present meta-analysis aimed at determining the accuracy of RTE for the differential diagnosis of benign and malignant breast tumors.

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Materials and methods

Literature search

We searched the PubMed, Web of Science, Cochrane Library, and China Biology Medicine databases from inception through December 31, 2014 without language restrictions. The following keywords and MeSH terms were used: ["breast cancer" or "breast neoplasms" or "breast tumor" or "mammary gland cancer" or "mammary gland neoplasms" or "mammary gland tumor"] and ["sonoelastography" or "elastography" or "real-time tissue elastography" or "RTE"]. We also performed a manual search to find any potential articles.

Selection criteria

The following 5 criteria were required for each study: (1) the study design must be a clinical cohort study or diagnostic test, (2) the study must relate to the accuracy of RTE for the differential diagnosis of benign and malignant breast tumors, (3) all breast lesions were histologically confirmed after RTE, (4) published data in the fourfold (2 × 2) tables must be sufficient, and (5) the elasticity images were evaluated using the 5-point scoring method with color mapping of strain images described by Itoh *et al* [13]. If the study did not meet all of these inclusion criteria, it was excluded. The most recent publication or the publication with the largest sample size was included when the authors published several studies using the same subjects.

Data extraction

Relevant data were systematically extracted from all included studies by two researchers using a standardized form. The researchers collected the following data: the first author's surname, publication year, language of publication, study design, sample size, number of lesions, source of the subjects, "gold standard," and diagnostic accuracy. The true positives (TP), true negatives (TN), false positives (FP), and false negatives (FN) in the fourfold (2 × 2) tables were also collected.

Quality assessment

Methodological quality was independently assessed by two researchers based on the quality assessment of studies of diagnostic accuracy studies (QUADAS) tool [14]. The QUADAS criteria included 14 assessment items. Each of these items was scored as "yes" (2), "no" (0), or "unclear" (1). The QUADAS score ranged from 0 to 28, and a score ≥ 22 indicated good quality.

Statistical analysis

STATA version 12.0 and Meta-Disc version 1.4 were used for the meta-analysis. We calculated the pooled summary statistics for sensitivity (Sen), specificity (Spe), positive and negative likelihood ratio (LR^+/LR^-), and diagnostic odds ratio (DOR) with their 95% confidence intervals (CIs). The summary receiver operating characteristic (SROC) curve and corresponding area under the curve (AUC) were obtained [15]. The threshold effect was assessed using Spearman correlation coefficients. The Cochran's Q-statistic and I test were used to evaluate potential heterogeneity between studies [16]. If significant heterogeneity was detected (Q test $P < 0.05$ or I test > 50%), a random effects model or fixed effects model was used. We also performed sub group and meta-regression analyses to investigate potential sources of heterogeneity. To evaluate the influence of single studies on the overall estimate, a sensitivity analysis was performed. We conducted Begger's funnel plots and Egger's linear regression tests to investigate publication bias [17].

Results

Characteristics of included studies

The search with the selected keywords initially identified 335 articles. We reviewed the titles and abstracts of all articles and excluded 94 articles; full text and data integrity were then reviewed, and 231 additional articles were excluded. Finally, 10 studies that met all inclusion criteria were included in this meta-analysis [8, 10, 18–25]. Publication years of the eligible studies ranged from 2007 to 2014. A total of 608 malignant breast lesions and 1292 benign breast tumors were assessed. The Hitachi and Phillips US were used in four studies each, and GE US was used in one study. The QUADAS scores of all included studies were ≥ 22. The study characteristics and methodological quality were summarized in Table 1.

Quantitative data synthesis

The findings of the meta-analysis regarding the accuracy of RTE for the differential diagnosis of benign and malignant breast tumors were provided in Table 2. The random effects model was used because of obvious heterogeneity among the studies. The diagnostic accuracy of RTE was measured as pooled Sen, Spe, LR^+, LR^-, and DOR (Fig. 1). The pooled Sen was 0.83 (95% CI = 0.79–0.86); the pooled Spe was 0.86 (95% CI = 0.84–0.88). Sen and Spe were not significantly correlated ($r_s = 0.418$, $P = 0.229$), indicating no threshold effect. The pooled LR^+ was 9.87 (95% CI = 2.66–36.71); the pooled LR^- was 0.20 (95% CI = 0.17–0.23). The pooled DOR of RTE for the diagnosis of breast cancer was 62.21 (95% CI = 33.88–114.24; Fig. 2a). The results were plotted as a symmetrical SROC curve (Fig. 2b), and the corresponding AUC was 0.9334 (standard error = 0.0125). Subgroup and meta-regression analyses were conducted based on language, sample size, and instrument type to investigate potential sources of heterogeneity. The results of the subgroup analyses re-

Table 1 Baseline characteristics and methodological of all included studies

References	Year	Language	Sample size		Age (year)	Instrument	2 x 2 table				QUADAS score
			Malignant	Benign			TP	FP	FN	TN	
Lee JH [18]	2011	English	48	267	–	GE	45	129	3	138	25
Pargjuly SS [10]	2012	English	184	158	44.2 ± 12.7	Hitachi	143	6	41	152	24
Xiao J [19]	2011	Chinese	16	40	20–58	GE	13	7	3	33	22
Shu L [20]	2013	Chinese	23	47	37.1 ± 13.1	Toshiba	19	5	4	42	24
Shen CY [21]	2011	Chinese	41	79	51.8 ± 10.9	Siemens	35	10	6	69	23
Feng X [22]	2007	Chinese	147	450	17–87	Hitachi	120	7	27	443	22
Lin T [23]	2010	Chinese	25	28	36.3 ± 13.6	Siemens	26	3	2	25	23
Fan XF [8]	2009	Chinese	43	109	37.9 ± 11.2	Acuson	36	4	7	105	25
Fan M [24]	2013	Chinese	32	61	19–65	Philips	27	4	5	57	24
Zhang LL [25]	2014	Chinese	49	53	43 ± 2.6	Hitachi	41	6	8	47	22

TP, true positive; TN, true negtive; FP, fasle positive; FN, false negtive; QUADAS, the quality assessment of studies of diagnostic accuracy studies

Table 2 Meta-analysis of the accuracy of real-time tissue elastography for breast cancer

Subgroups	Studies	Sen [95% CI]	Spe [95% CI]	LR^+ [95% CI]	LR^- [95% CI]	DOR [95% CI]
Overall	10	0.83 [0.79–0.86]	0.86 [0.84–0.88]	9.87 [2.66–36.71]	0.20 [0.17–0.23]	62.21 [33.88–114.24]
Language						
English	2	0.81 [0.75–0.86]	0.68 [0.64–0.73]	6.26 [0.05–831.1]	0.20 [0.12–0.36]	39.49 [7.31–213.3]
Chinese	8	0.84 [0.80–0.87]	0.95 [0.93–0.96]	11.04 [5.95–20.49]	0.18 [0.14–0.22]	70.63 [35.82–139.3]
Sample size						
Large	3	0.81 [0.77–0.85]	0.84 [0.81–0.86]	12.70 [4.65–45.83]	0.21 [0.17–0.26]	77.10 [16.20–366.90]
Small	7	0.85 [0.80–0.89]	0.91 [0.87–0.93]	8.24 [5.71–11.89]	0.17 [0.13–0.23]	52.35 [31.67–86.53]
Instrument						
Hitachi	3	0.80 [0.76–0.84]	0.97 [0.96–0.98]	22.70 [14.82–34.78]	0.20 [0.16–0.25]	113.84 [66.52–194.81]
GE	2	0.91 [0.81–0.96]	0.56 [0.50–0.61]	2.83 [1.09–7.34]	0.17 [0.08–0.36]	17.62 [6.93–44.80]
Simens	2	0.88 [0.78–0.95]	0.88 [0.80–0.93]	7.33 [4.31–12.48]	0.14 [0.07–0.26]	52.26 [21.00–130.06]

CI, confidence interval; LR, likehood ratio; DOR, diagnostic odds ratio; Sen, Sensitiviy; Spe, Specificity

Table 3 Meta-regression analysis of source of heterogeneity

Heterogeneity	Coefficient	SE	*P* value	RDOR	95% CI
Language	0.846	0.6745	0.2650	2.33	0.41–13.20
Sample size	0.847	0.6154	0.2271	2.33	0.48–11.35
Instrument	–0.009	0.1951	0.9640	0.99	0.60–1.64

SE, standard error; RDOR, relative diagnostic odds ratio; CI, confidence interval

vealed that RTE exhibited high diagnostic performance in different subgroups (Table 2). The meta-regression analysis results confirmed that no factor could explain potential sources of heterogeneity (Table 3). We found no evidence of obvious asymmetry in the Begger's funnel plots. The Egger's test did not demonstrate strong statistical evidence for publication bias ($t = –0.57$, $P = 0.582$).

Discussion

RTE is a simple, non-invasive diagnostic examination that provides information about the stiffness of a mass [10]. Recent studies have suggested that RTE could be an effective technique to improve the sonographic diagnosis of invasive breast cancer, and the sensitivity of this technique in invasive breast cancer may be similar to those of CT and MRI because of the greater stiffness [7]. Nevertheless, RTE cannot replace other examinations, but only can complement them, because it does not evaluate tumor vascularity, lymph node staging, or chest staging. RTE has not yet been used in routine clinical practice [10]. The conflicting study results could be caused by several factors, including differences in study designs, sample sizes, number of lesions, types of instruments, and statistical methods. The present study aimed to provide a comprehensive and reliable conclusion on the diagnostic accuracy of RTE for the diagnosis of breast cancer.

In the present meta-analysis, we systematically evaluated the technical performance and accuracy of RTE for differential diagnosis of benign and malignant breast tumors. The 10 independent studies were included assessed 608 malignant breast lesions and 1292 benign breast tumors. The pooled Sen, Spe, and DOR of RTE in the diagnosis of breast cancer were 0.83, 0.86, and 62.21, respectively. These results were consistent with the potentially high diagnostic accuracy of RTE for breast cancer, suggesting that RTE may be a good tool for the differential diagnosis

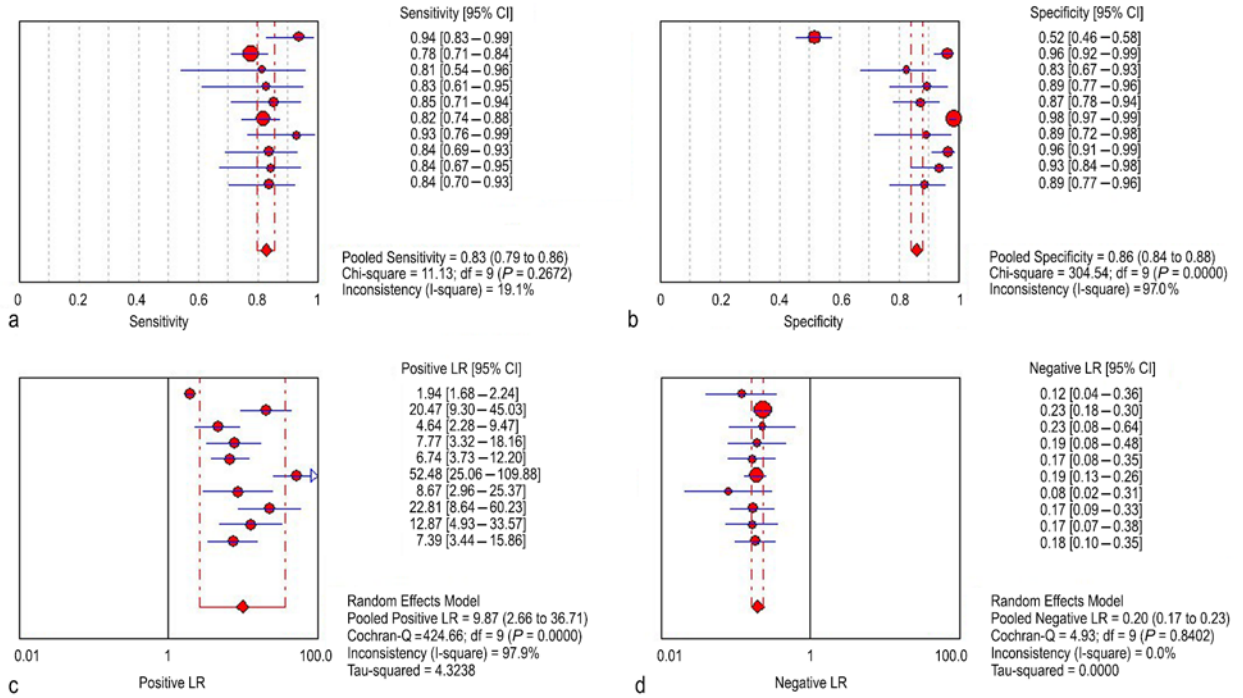

Fig. 1 Forest plots for the accuracy of real-time tissue elastography for the diagnosis of breast cancer

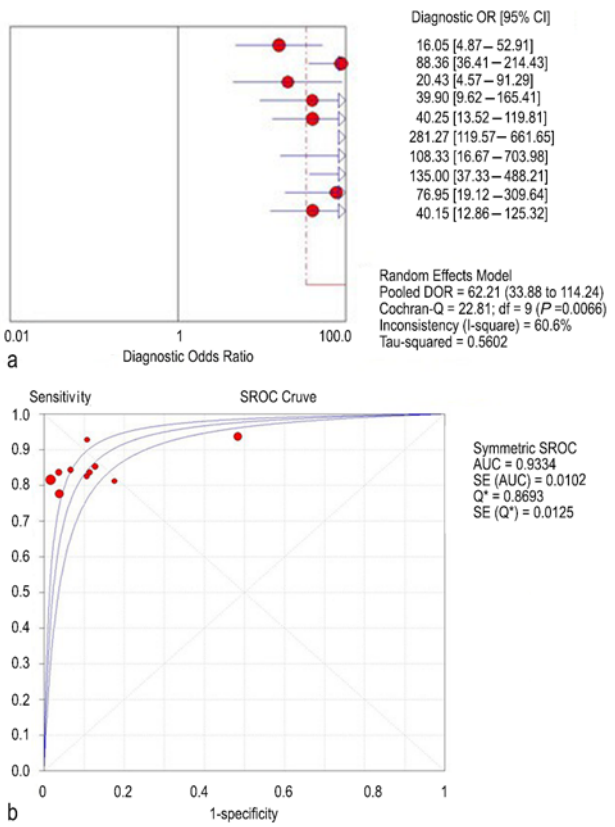

Fig. 2 Forest plot of DOR and SROC curve of real-time tissue elastography for the diagnosis of breast cancer. OR, odds ratio; CI, confidence interval; SROC, summary receiver operator characteristic; AUC, area under curve; SE, standard error

of benign and malignant breast tumors and could predict the prognosis of breast cancer patients. Although RTE has high diagnostic accuracy for breast cancer, a breast biopsy is still necessary to diagnose benign and malignant breast tumors [26]. The threshold effect is usually interpreted as a sudden and radical change in a phenomenon that often occurs after surpassing a quantitative limit. Our findings showed no significant relationship between Sen and Spe within the studies, providing no evidence of a threshold effect. Because heterogeneity existed in the individual studies, subgroup analyses were conducted. Similar results were demonstrated in these subgroup analyses. RTE exhibited high diagnostic performance in different subgroups for the diagnosis of breast cancer, suggesting that differences in language, sample size, and instrument type did not directly influence the diagnostic accuracy of RTE. Furthermore, our results found no direct evidence of publication bias. Collectively, our findings strongly suggest that RTE is a highly accurate and non-invasive tool for the qualitative diagnosis of breast cancer, consistent with previous studies.

Despite the demonstrated diagnostic accuracy of RTE for breast cancer, our study has certain limitations. First, owing to the relatively small sample sizes and low level of quality of the included studies, there were insufficient data to assess the accuracy of RTE. Moreover, the retrospective nature of a meta-analysis can lead to subject selection bias. Third, we failed to obtain all of the original statistics from the included studies, which further limits the assessment of RTE for the diagnosis of breast cancer.

Importantly, the majority of included studies originated from China, which may adversely affect the reliability and validity of our results.

In conclusion, our meta-analysis suggests that RTE may have high diagnostic accuracy in the differential diagnosis of benign and malignant breast tumors. Thus, RTE may be a good tool to diagnose breast cancer. However, due to the limitations, further detailed studies are required to confirm the present findings.

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Conflicts of interest

The authors indicated no potential conflicts of interest.

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