Diagnostic accuracy of ultrasound superb microvascular imaging for breast tumor: a meta-analysis

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Abstract

Aim: This meta-analysis aimed to identify the accuracy of ultrasound superb microvascular imaging (SMI) for the diagnosis of a breast tumor. **Material and method:** We searched PubMed, Web of Science, Google Scholar, Cochrane Library, EBSCO, and CBM databases from January 1st, 2013 until February 1st, 2020 without language restrictions. Meta-analysis was conducted using STATA version 14.0 and Meta-Disc version 1.4 software. We calculated the summary statistics for sensitivity (Sen), specificity (Spe), positive and negative likelihood ratio (LR^+/LR^-), diagnostic odds ratio (DOR) and receiver operating characteristic (SROC) curve. **Results:** Fifteen studies that met all inclusion criteria were included in this meta-analysis. A total of 955 breast neoplasm patients and 1116 patients with benign breast tumors were assessed. All breast lesions were histologically confirmed after SMI. The pooled Sen was 0.81 (95%CI=0.78-0.83); the pooled Spe was 0.71 (95%CI=0.68-0.73) The pooled LR^+ was 3.24 (95%CI=2.27-4.64); the pooled negative LR^- was 0.25 (95%CI=0.18-0.34) The pooled DOR of SMI in the diagnosis of breast tumor was 46.97 (95 % CI=16.72~131.97). The area under the SROC curve was 0.87 (95%CI=0.84-0.90). We found no evidence for publication bias ($t=-0.84$, $p=0.42$). **Conclusion:** Our meta-analysis indicates that SMI may have a high diagnostic accuracy in differential diagnosis between benign and malignant breast tumors. Thus, SMI may be a good tool for the diagnosis of breast tumors.

Keywords: Superb Microvascular Imaging; breast tumor; ultrasound; meta-analysis

Introduction

Breast cancer is a very common malignant disease in women worldwide [1]. It is predicted that more than one million women are diagnosed with breast cancer, and more than 400,000 will die from the disease every year [2]. 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 [3]. To improve the survival, a number of screening methods to detect breast cancer have been studied, including magnetic resonance imaging (MRI), Doppler ultrasonog-

raphy (US) and computed tomography (CT) [4]. The most practical screening method in clinical diagnosis and treatment is US. The shape and distribution of neovascularization in tumors are related to the aggressive growth pattern of cancer cells, which is helpful to distinguish the nature of the tumor [5]. Color Doppler flow imaging (CDFI) is often used to show the blood flow inside the tumor, but CDFI can provide limited data in some low-velocity microvessels [6]. As a novel US technique, Superb Microvascular Imaging (SMI) can quickly, simply and noninvasively study the microvascular distribution in the tumor and evaluate the microvascular perfusion [7]. The SMI adopts a multidimensional filter to eliminate only the clutter and to preserve low-velocity flow signals, whereas conventional Doppler systems use a single-dimension filter and, accordingly, can exhibit a loss of low-velocity flow signals that overlap with clutter [8]. Previous studies have shown that SMI can detect the blood flow signals of neovascularization in tumors and is helpful for the differentiation between benign and ma-

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lignant breast tumors [9]. However, the results of these studies have been contradictory. Therefore, the present meta-analysis aimed at determining the accuracy of SMI in the differential diagnosis between benign and malignant breast tumors.

Material and methods

Literature search

We searched PubMed, Web of Science, Google Scholar, Cochrane Library, EBSCO and CBM databases from January 1st, 2013 until February 1st, 2020 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 ["superb microvascular imaging"]. We also performed a manual search to find other potential articles.

Selection criteria

The following 4 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 SMI for the differential diagnosis of benign and malignant breast tumors; 3) all breast lesions were histologically confirmed after SMI; and 4) published data in the fourfold (2×2) tables must be sufficient. 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 [10]. 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

The STATA version 14.0 (Stata Corp, College Station, TX, USA) and Meta-Disc version 1.4 (Universidad Complutense, Madrid, Spain) softwares were used

for 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. 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. 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 subgroup 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.

Results

Characteristics of included studies

Initially, the searched keywords identified 47 articles. We reviewed the titles and abstracts of all articles and excluded 21 articles; full texts and data integrity were also reviewed and 11 were further excluded. Finally, 15 studies that met all inclusion criteria were included in this meta-analysis [11-25]. Figure 1 showed the selection process of eligible articles. A total of 955 malignant breast lesions and 1116 benign breast tumors were assessed. We summarized the study characteristics and methodological quality in Table I. The QUADAS scores of all included studies were ≥ 22 .

Fig 1. Flow chart of literature search and study selection. Fifteen studies were included in this meta-analysis.

Table I. Baseline characteristics and methodological quality of all included studies

First author	Year	Country	Language	Sample size	Age (Years)	Instrument (Toshiba)	Diagnostic basis	SMI 2×2 table				QUADAS score
								TP	FP	FN	TN	
Wang [11]	2020	China	Chinese	160	54.1±11.2	Aplio 500	Adler classification	97	5	27	31	23
Zhang [12]	2019	China	Chinese	252	46.7±12.5	Aplio 500	Morphology type	105	10	13	124	24
Ni [13]	2019	China	Chinese	123	55.6±9.0	Aplio 500	Adler classification	51	20	2	50	24
Xiao [14]	2019	China	Chinese	105	47.2±10.5	Aplio 500	Adler classification	34	13	7	51	22
Che [15]	2018	China	Chinese	88	48.5±10.5	Aplio 400	Adler classification	30	26	10	22	23
Yao [16]	2017	China	Chinese	102	44.5±11.9	Aplio 500	Adler classification	41	4	26	31	22
Ming [17]	2019	China	English	177	43.9±14.1	Aplio 400	Morphology type	42	6	21	93	24
Zhu [18]	2019	China	English	116	47.1±9.3	Aplio 500	Adler classification	43	56	3	30	23
Zhang [19]	2020	China	English	236	49.4±12.5	Aplio 500	Vascularity index	44	39	29	76	25
Ah [20]	2019	Korea	English	98	45.6±9.7	Aplio 500	Synthesis index	45	14	9	43	22
Suleyman [21]	2019	Korea	English	54	48.5±11.2	Aplio 500	Vascular grading	46	6	2	33	23
Park [22]	2018	Korea	English	191	47(20-83)	Aplio 500	Synthesis index	47	34	16	65	24
Zhao [23]	2016	China	English	135	46.9±10.4	Aplio 500	Vascular grading	48	18	8	76	24
Ma [24]	2015	China	English	123	45.1(15-69)	Aplio 400	Adler classification	49	27	6	39	23
Xiao [25]	2016	China	English	132	44.1(16-78)	Aplio 400	Adler classification	50	48	4	26	25

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

Quantitative data synthesis

Meta-analysis findings on the accuracy of SMI for differential diagnosis between benign and malignant breast tumors were showed in Table II. The random effects model was used due to obvious heterogeneity among the studies. Diagnostic accuracy of SMI was measured as pooled Sen, Spe, LR⁺, LR⁻ and DOR (fig 2). Our meta-analysis revealed that the pooled Sen was 0.81 (95%CI=0.78-0.83); the pooled Spe was 0.71 (95%CI=0.68-0.73). There was no significant correlation ($r=243$, $p=0.610$) between sensitivity and specificity, which indicated that there is no threshold effect. In addition, we observed that the pooled LR⁺ and LR⁻ were 3.24 (95%CI=2.27-4.64) and 0.25 (95%CI=0.18-0.34), respectively. The pooled DOR of SMI in the diagnosis of breast tumor was 15.16 (95% CI=8.24-27.87) (fig 3). The results were plotted as a symmetrical SROC curve (fig 4) and the corresponding AUC was 0.87 (95%CI=0.84-0.90). Subgroup and meta-regression analyses were conducted based on language, instrument type, and diagnostic basis to investigate potential sources of heterogeneity. In the subgroup analyses, the results revealed that SMI exhibited a high diagnostic performance in different subgroups (Table II). Meta-regression analysis results confirmed that no factor could explain the potential sources of heterogeneity (Table III). We found no evidence of obvious asymmetry in the Egger's funnel plots (fig 5). Egger's test also did not display strong statistical evidence for publication bias ($t=-0.84$, $p=0.42$).

Fig 2. Forest plots for the accuracy of SMI for the diagnosis of breast tumors. a Sensitivity. b Specificity. c Positive likelihood ratio. d Negative likelihood ratio.

Fig 3. Forest plot of DOR of SMI for the diagnosis of breast tumors. DOR diagnostic odds ratio

Fig 4. SROC curve for the accuracy of SMI in the diagnosis of breast. SROC summary receiver operator characteristic, AUC area under curve.

Fig 5. Begger's funnel plot of publication bias on the pooled OR. No publication bias was detected

Discussion

With the wide use of high-resolution ultrasound diagnostic instruments, the detection rate of breast nodules has increased significantly [7]. The growth of tumor depends on the complex blood vessels inside the tumor.

Table II. Meta-analysis of the accuracy of SMI for the diagnosis of breast tumors

Subgroup	Studies (n)	Sen (95%CI)	Spe (95%CI)	LR ⁺ (95%CI)	LR ⁻ (95%CI)	DOR (95%CI)
Overall	15	0.81 [0.78-0.83]	0.71 [0.68-0.73]	3.24 [2.27-4.64]	0.25 [0.18-0.34]	15.16 [8.24-27.87]
Language						
Chinese	6	0.81 [0.77-0.84]	0.80 [0.75-0.84]	4.24 [2.02-8.90]	0.23 [0.13-0.42]	20.48 [6.49-64.57]
English	9	0.81 [0.77-0.84]	0.66 [0.62-0.69]	2.72 [1.87-3.94]	0.26 [0.17-0.39]	12.24 [6.20-24.18]
Ultrasound machine						
Toshiba Aplio 500	11	0.83 [0.80-0.85]	0.73 [0.70-0.76]	3.60 [2.23-5.81]	0.22 [0.15-0.33]	18.54 [9.06-37.93]
Toshiba Aplio 400	4	0.76 [0.70-0.81]	0.66 [0.61-0.71]	2.47 [1.40-4.35]	0.34 [0.20-0.58]	8.94 [3.00-26.65]
Diagnostic basis						
Vascularity index	1	0.60 [0.48-0.72]	0.66 [0.57-0.75]	1.78 [1.30-2.44]	0.60 [0.44-0.82]	2.96 [1.61-5.43]
Synthesis index	2	0.79 [0.70-0.86]	0.69 [0.61-0.76]	2.62 [1.69-4.07]	0.30 [0.18-0.53]	8.84 [3.31-23.58]
Vascular grading	2	0.90 [0.83-0.95]	0.82 [0.74-0.88]	4.87 [3.36-7.05]	0.11 [0.03-0.37]	48.42 [10.30-227.71]
Morphology type	2	0.70 [0.61-0.78]	0.81 [0.75-0.87]	11.58 [7.17-18.69]	0.21 [0.07-0.65]	57.02 [18.07-179.94]
Adler classification	8	0.82 [0.79-0.86]	0.58 [0.54-0.63]	2.41 [1.66-3.49]	0.25 [0.17-0.39]	11.52 [6.05-21.93]

95%CI, 95% confidence interval; LR, likelihood ratio; DOR, diagnostic odds ratio; Sen, Sensitivity; Spe, Specificity

Table III. Meta-regression analyses of potential source of heterogeneity

Heterogeneity factors	Coefficient	SE	p value	RDOR	95% CI	
					UL	LL
Publication year	-0.002	0.3136	0.9962	1.00	0.49	2.03
Language	0.179	1.0684	0.8704	0.84	0.07	9.37
Instrument	0.715	0.9390	0.4641	0.49	0.06	4.09
Diagnostic basis	0.084	0.4321	0.8503	0.92	0.35	2.44

SE, standard error; RDOR, relative diagnostic odds ratio; 95%CI, 95 % confidence interval; UL, upper limit; LL, lower limit

After the proangiogenic and angiogenic stages, the tumor gradually infiltrates and expands to the peripheral tissue. When the tumor is in the proangiogenesis (diameter <2 mm), the invasion range is limited, but when the tumor enters the angiogenic stage (diameter >2 mm), the blood vessels will extend more branches, form a large number of capillaries, infiltrate to the surrounding area and absorb a large amount of nutrients for the survival of the tumor, and at the same time, tumor invasion and metastasis will occur [26]. The vascular morphology and distribution of breast masses are closely related to the nature of the tumor, which can be used as an important supplementary sign in their differential diagnosis [17].

SMI can clearly and completely show the shape and distribution of the vascular network of breast mass without injection of a contrast agent. By observing the number and distribution of blood vessels of breast cancer, SMI can help to judge the nature of the tumor [19]. According to Adler's method, the vascularity was subjectively determined to be absent (grade 0), minimal (grade 1), moderate (grade 2) or marked (grade 3). The blood flow classification of benign tumors is mostly 0-1, while that of malignant tumors is mostly 2-3. Compared with benign tumors, the blood supply of malignant tumors is more abundant and the detection rate of blood flow is higher [24]. SMI can display microvascular architecture patterns of breast tumors. Of that benign masses tend to display the non-vascular pattern, a linear or curvilinear pattern and a treelike pattern, while malignant masses tend to display the root hair-like pattern and the crab claw-like pattern [12]. Smart 3-D SMI can quantitatively assess tumor vascularity via measuring vascularity index (VI) on 2-D SMI images obtained with the qualitative guidance of 3-D SMI images, which is significantly higher in malignant lesions than that in benign ones and may potentially serve as a noninvasive tool to accurately characterize benign versus malignant breast lesions [20]. Present studies have revealed that SMI is more accurate in the detection and characterization of breast lesions comparable with mammography X-ray and conventional CDFI scanning [15]. Nevertheless, each imaging diagnostic examination has its own advantages and disadvantages and only one imaging examination is generally not enough to make an accurate diagnosis of the disease. Therefore, SMI will not replace but can only compliment conventional ultrasound. Although considered as a potentially useful imaging tool, SMI is still not widely used in clinical practice and few reports have discussed its use in the evaluation of breast tumors. This controversy could be caused by several factors, including the differences in study designs, sample size, number of lesions, diagnostic criteria, statistical methods, etc.

In the present meta-analysis, we systematically evaluated the technical performance and accuracy of SMI for differential diagnosis of benign and malignant breast tumors. The 15 independent studies included assessed 955 malignant breast lesions and 1116 benign breast tumors. The pooled Sen, Spe and DOR of SMI in the diagnosis of breast cancer were 0.81, 0.71 and 46.97, respectively. These results were consistent with the potentially high diagnostic accuracy of SMI for breast cancer, suggesting that SMI may be a good tool for the differential diagnosis of benign and malignant breast tumors and could predict the prognosis of breast cancer patients. 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. SMI exhibited a high diagnostic performance in different subgroups for the diagnosis of breast cancer, suggesting that differences in language, diagnostic basis and instrument type did not directly influence the diagnostic accuracy of SMI. Furthermore, our results found no direct evidence of publication bias. Collectively, our findings strongly suggest that SMI 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 SMI 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 SMI. Moreover, the retrospective nature of a meta-analysis can lead to subject selection bias. 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 SMI may have high diagnostic accuracy in the differential diagnosis of benign and malignant breast tumors. Thus, SMI 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: none

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