




Thoracic ultrasound for malignant pleural effusion: a systematic review and meta-analysis

Akihiro Shiroshita ^{1,2}, Sayumi Nozaki³, Yu Tanaka², Yan Luo⁴ and Yuki Kataoka^{5,6}

Affiliations: ¹Dept of Respiratory Medicine, Ichinomiyanishi Hospital, Ichinomiya, Japan. ²Dept of Pulmonology, Kameda Medical Center, Kamogawa, Japan. ³Post Graduate Education Center, Kameda Medical Center, Kamogawa, Japan. ⁴Dept of Health Promotion and Human Behavior, Graduate School of Medicine, Kyoto University, Kyoto Japan. ⁵Dept of Respiratory Medicine, Hyogo Prefectural Amagasaki General Medical Center, Amagasaki, Japan. ⁶Dept of Hospital Care Research Unit, Hyogo Prefectural Amagasaki General Medical Center, Amagasaki, Japan.

Correspondence: Akihiro Shiroshita, Dept of Respiratory Medicine, Ichinomiyanishi Hospital, 1 Kaimeihira, 494-0001, Ichinomiya, Japan. E-mail: akihirokun8@gmail.com

ABSTRACT This systematic review aimed to evaluate the diagnostic accuracy of thoracic ultrasound in malignant pleural effusion.

Articles published until December 2019 in MEDLINE, Embase, the Cochrane Central Register of Controlled Trials and the International Clinical Trials Registry Platform were screened by two authors independently to extract data and evaluate the risks of bias and applicability using the modified Quality Assessment of Diagnostic Accuracy Studies-2 tool. We described the forest plots of each thoracic ultrasound finding. We estimated the pooled sensitivity and specificity of pleural nodularity using the bivariate random-effects model.

We included seven articles and found that each thoracic ultrasound finding had low sensitivity. The pooled specificity of pleural nodularity was 96.9% (95% CI 93.2%–98.6%).

In conclusion, thoracic ultrasound is not useful in ruling out malignant pleural effusion. Physicians can proceed rigorously to repeat thoracentesis or other invasive procedures when pleural nodularity is detected.



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This systematic review shows that thoracic ultrasound cannot rule out malignant pleural effusion. Pleural nodularity could be a ruling-in test for performing repeated thoracentesis or other invasive procedures when malignant pleural effusion is suspected. <https://bit.ly/3iuM5z7>

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Introduction

Malignant pleural effusion (MPE) is a common malignancy complication [1]. As patients with MPE usually have poor prognoses, a prompt diagnosis is crucial to allow patients to start optimal treatment as early as possible [2]. A diagnostic thoracentesis is the first step in detecting MPE; however, the initial cytological evaluation only has a sensitivity of approximately 50–70% [1]. If the initial thoracentesis fails to provide a definite diagnosis, pulmonologists or radiologists have to either repeat it or choose another invasive procedure, such as image-guided biopsy or thoracoscopy [3].

Ultrasound is a noninvasive and inexpensive tool; therefore, it is increasingly used by physicians [4]. Its other advantages include lack of radiation exposure and easy personal training because of easy bedside accessibility [5].

The international guidelines recommended ultrasound guidance when performing diagnostic thoracentesis to reduce the risk of complications [6, 7]. Many recent studies have explored the utility of morphological findings of transthoracic ultrasound (TUS) as a tool for detecting MPE [8–14]. However, these studies had a small sample size and were conducted at a single centre; hence, the diagnostic accuracy of TUS remains unclear. Our systematic review aimed to evaluate the diagnostic accuracy of TUS both as a triage test and an add-on test in patients with suspected MPE.

Material and methods

The protocol of this systematic review was registered in the International Prospective Register of Systematic Reviews (CRD42020162846). Our systematic review is based on the Preferred Reporting Items for Systematic Review and Meta-Analysis for Diagnostic Test Accuracy (supplementary table S1). Informed consent from study participants was waived because of the study design. We performed a comprehensive search of MEDLINE, Embase, the Cochrane Library and the International Clinical Trials Registry Platform for publications until December 25, 2019, without any limitations on the language or publication status. Our search terms were based on TUS (index test), MPE (target condition) and specific morphological findings of TUS, including pleural thickening, hepatic metastases, pleural nodules, diaphragmatic thickening, diaphragmatic nodules, solitary pulmonary lesions and swirling (supplementary table S2). We reviewed all the reference lists of the included articles and searched the citations with Web of Science to search for additional relevant articles.

Two authors (AS and SN) independently screened the title and abstracts of the listed articles and subsequently reviewed the complete text of potential articles. The inclusion criteria were prospective or retrospective observational studies, case-control studies or case series that assessed the sensitivity and specificity of morphological findings of TUS for MPE. We carefully confirmed that all included studies reported obtaining informed consent from each study participant and protocol approval by an ethics committee or institutional review board. The exclusion criteria were: 1) case reports, review articles, or articles that used animal models; and 2) studies that used ultrasound on lesions other than those in the lung (e.g. abdominal ultrasound). We extracted the following details of the included articles: study design, participants, index tests, reference standards and diagnostic accuracy.

AS and SN independently evaluated the risk of bias and concerns of applicability of the included articles using the modified Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool [14]. During the entire review process, disagreements between the two authors were resolved through discussions and consultations with another pulmonologist, YT. Forest plots were created to illustrate the diagnostic accuracy of each index test in each study. Generally, there are four types of TUS findings in patients with MPE: 1) gross macroscopic findings, including echogenicity and swirling sign; 2) pleural thickness, in which different thresholds may be used; 3) nodularity of parietal or visceral pleura, or the diaphragm; and 4) other findings, such as parenchymal lesions and hepatic metastases. Although we planned to estimate the pooled sensitivity and specificity for each type of finding using a bivariate random-effects model, we expected that the sensitivity and specificity of each TUS finding might vary widely. Therefore, we visually checked the heterogeneity for each finding on the forest plots, moreover, we only calculated the pooled sensitivity and specificity for findings lacking apparent heterogeneity. In addition, we described the hierarchical summary receiver operating characteristic (HSROC) curve for these findings. The overall quality of evidence of pleural nodularity was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach [15].

For statistical analysis, we used R 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria) to generate forest plots; STATA 15 (STATA Corp., College Station, TX, USA) to calculate the pooled sensitivity and specificity; and RevMan v.5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) to summarise the risk of bias and applicability and to create the HSROC curve.

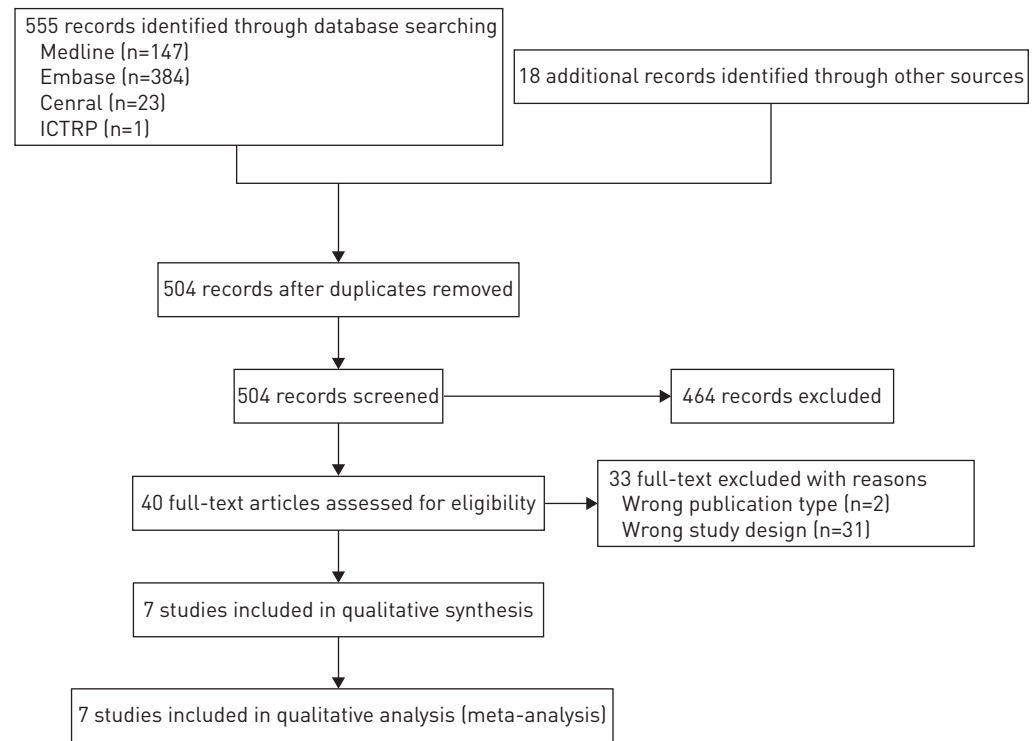


FIGURE 1 Preferred Reporting Items for Systematic Review and Meta-Analysis flow diagram. ICTRP: International Clinical Trials Registry Platform.

Results

Figure 1 illustrates the study selection process. After removing duplicates, we screened 504 articles and included seven studies after applying the exclusion criteria [8–13, 16]. Table 1 summarises the characteristics of the included articles. The included articles assessed 840 patients. All the included articles were prospective studies. Experienced radiologists or pulmonologists performed TUS at a university hospital or tertiary care centre (table 2). Regardless of the follow-up periods, pathological results, including cytology or other biopsy results, were used as a reference standard.

Supplementary figures S1 and S2 summarise the quality of each study using the modified QUADAS-2 tool. Regarding the risk of bias, the reference standard domain was labelled as unclear because we could

TABLE 1 Characteristics of the included studies

First author [ref.]	Year	Participants n	Mean age (sd)	Male %	Prevalence of MPE %	Study design	Country	Study setting
YANG [16]	1992	320	54 (16)	59	35	Prospective cohort	China	University hospital
LOMAS [11]	1993	86	58	64	34	Prospective cohort	United Kingdom	University hospital
MARCUN [12]	2009	40	58	67	23	Prospective cohort	Slovenia	University hospital
QURESHI [13]	2009	52	63	67	60	Prospective cohort	United Kingdom	Tertiary care centre
BUGALHO [9]	2014	133	67 (16)	46	50	Prospective cohort	Portugal	University hospital
ASCIAK [8]	2018	140	Not described	Not described	45	Prospective cohort	United Kingdom	University hospital
FAHEEM [10]	2019	69	50 (16)	42	33	Prospective cohort	Egypt	University hospital

MPE: malignant pleural effusion.

TABLE 2 Detailed information about thoracic ultrasound

First author [ref.]	Machine	Probe	Operators and interpreters	Position
YANG [16]	Aloka SSD 630, SSD 650, Aloka, Tokyo, Japan; Toshiba 100A, Toshiba, Tokyo, Japan	3.5-, 5.0- and 7.5-MHz linear and convex transducers	One of three sonographers performed the ultrasound. The images were recorded on Polaroid film (Polaroid, Cambridge, MA, USA) and were interpreted by the other two sonographers	Sitting or supine
LOMAS [11]	An Aloka SSD-650 or Siemens Sonoline	3.5 MHz transducers	One of the three radiologists performed the ultrasound	Sitting
MARCUN [12]	ATL HDI 5000CV	Phase array P4-2 convex transducer	An experienced pulmonologist conducted ultrasound and the images were stored on hard disc for further evaluation	Sitting or supine
QURESHI [13]	A single Esaote Technos MPX 25	A 3–5-MHz curvilinear probe ± 8–15 MHz linear probe (to visualise the pleura and chest wall in greater detail)	An experienced radiologist performed the ultrasound and the images were stored as anonymised data. Consultant radiologists separately reviewed them	Upright or lateral decubitus
BUGALHO [9]	ACUSON X300 (Siemens, Germany)	A 2- to 5-MHz convex-array probe ± a 5–10-MHz linear-array transducer (to see details of the thoracic wall and parietal pleura)	Pulmonologists with at least 5 years of thoracic ultrasound experience (average of 450 exams per year) conducted ultrasound and the images were stored as 10–20-s digital video clips. At least three other ultrasound operators reviewed them	Sitting or supine (or lateral decubitus)
ASCIK [8]	Hitachi Avius	The abdomen pre-set	The ultrasound reporters held a minimum of Royal College of Radiologists level 1 accreditation, and at least two sonographers performed the pre-procedure ultrasound scan and agreed on the described echogenic qualities of the fluid	Not described
FAHEEM [10]	GE logiq P6 pro	Convex array (3–5 MHz) and linear array (4–11 MHz)	Not described	Supine, prone, lateral or sitting

not ascertain whether the pathologists were blinded in all the articles. In one article by FAHEEM [10], the risk of bias in the index test domain was high because the ultrasound operators were unblinded.

Figures 2 and 3 illustrate the forest plots of sensitivity and specificity according to each index test. The gross macroscopic findings were assessed and echogenicity, a specific sign of MPE, demonstrated a wide range of sensitivity and specificity. Parietal thickness was evaluated using different cut-off values, 3 mm *versus* 10 mm. Pleural thickness assessment demonstrated low sensitivity and varying specificity. Although only two studies used a cut-off value of 10 mm, they revealed high specificity. We did not calculate the pooled sensitivity and specificity of either echogenicity or parietal pleural thickness given the heterogeneity of the results. Nodularity was assessed in the parietal pleura, visceral pleura or diaphragm. The pooled sensitivity and specificity of nodularity was 42.5% (95% CI 25.3%–61.6%) and 96.9% (95% CI 93.2%–98.6%), respectively, using the bivariate random effect model. Additionally, the HSROC curve revealed high specificity (supplemental figure S3). Finally, we evaluated the overall quality of evidence of pleural nodularity using the GRADE approach, which showed a moderate certainty of evidence (table 3).

Discussion

This systematic review revealed that each macroscopic finding on TUS demonstrated low sensitivity and a wide range of specificity. It demonstrated high specificity and moderate overall quality of evidence for pleural nodularity, including the parietal and somatic pleural nodules and diaphragmatic nodules.

As pleural nodularity has a high specificity and positive predictive value, it can be used as an add-on test for ruling-in MPE. Cytopathological evaluations, such as cytology or cell blocks, can contribute to a definite diagnosis; however, one-time thoracentesis demonstrated low sensitivity [7]. In case chest physicians or radiologists detect pleural nodules during TUS, the pre-test probability of MPE may be increased and repeat thoracentesis or other invasive procedures can be justified. However, physicians

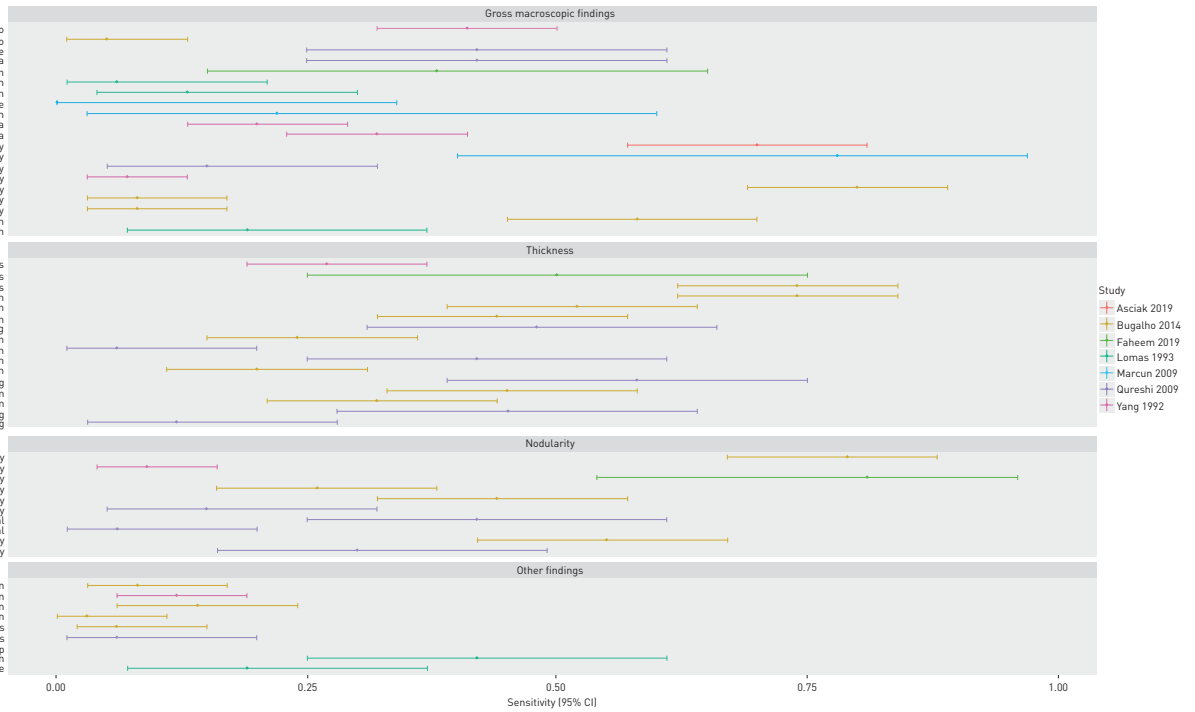


FIGURE 2 Forest plot of the sensitivity for each ultrasound finding in malignant pleural effusion.

should keep in mind that biopsy in pleural or other sites could guide the treatment more precisely based on specific histological subtypes and molecular patterns.

Contrary to pleural nodularity, other index tests demonstrated low specificity and therefore cannot be used as add-on tests. In the current systematic review, we evaluated the diagnostic accuracy of each morphological finding on TUS. Future studies should combine assessments of each of these findings [13].

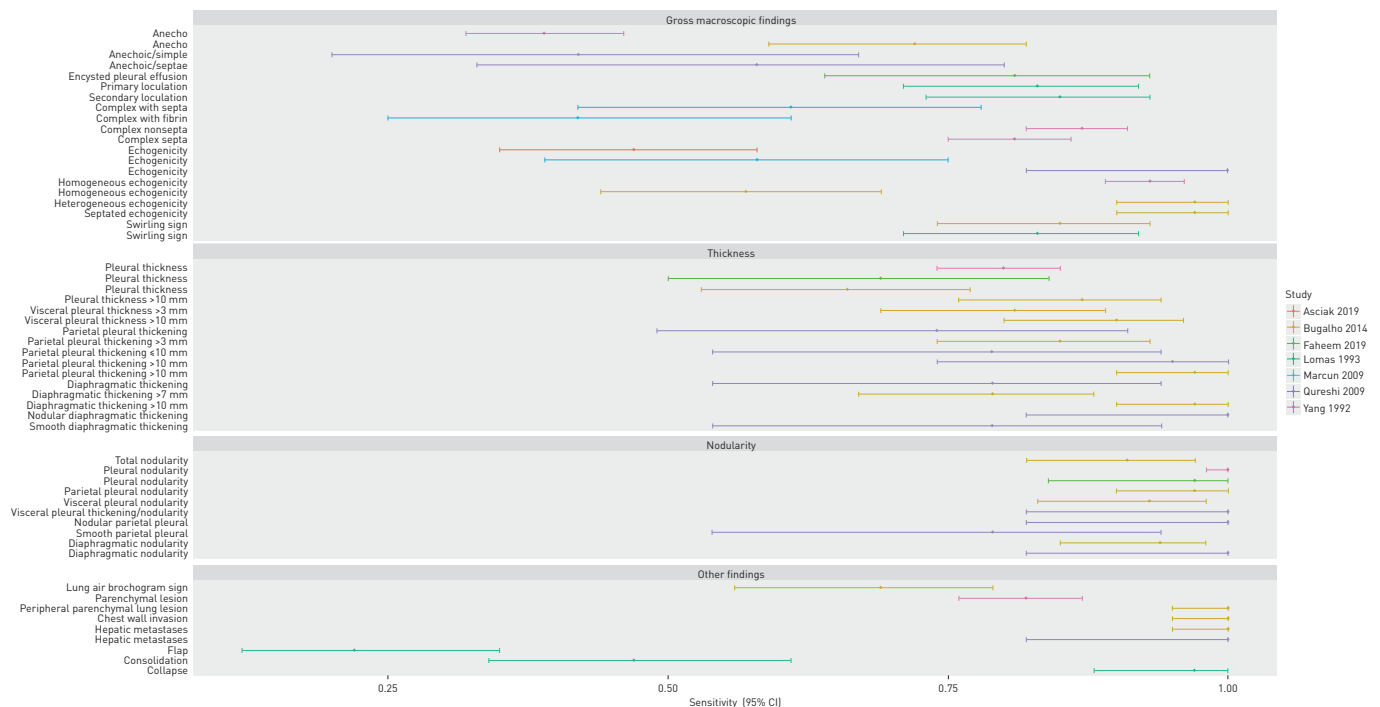


FIGURE 3 Forest plot of the specificity for each ultrasound finding in malignant pleural effusion.

TABLE 3 Findings with the pleural nodularity *via* thoracic ultrasound using the Grading of Recommendations, Assessment, Development and Evaluation approach

Question	Should pleural nodularity <i>via</i> thoracic ultrasound be used in diagnosing malignant pleural effusion in patients with pleural effusion who are suspected to have malignancy?										
Sensitivity	0.42 (95% CI 0.25–0.62)							Prevalence	10%	20%	40%
Specificity	0.97 (95% CI 0.93–0.99)										
Outcome	No. studies (no. patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 10%	Pre-test probability of 20%	Pre-test probability of 40%	
True positives (patients with MPE)	Four studies (459 patients)	Cohort and case-control type studies	Serious [#]	Not serious	Not serious	Not serious	None	43 (25–62)	85 (51–123)	170 (101–246)	⊗⊗⊗○ moderate
False negatives (patients incorrectly classified as not having MPE)								57 (38–75)	115 (77–149)	230 (154–299)	
True negatives (patients without MPE)	Four studies (545 patients)	Cohort and case-control type studies	Serious [#]	Not serious	Not serious	Not serious	None	872 (839–887)	775 (746–789)	581 (559–592)	⊗⊗⊗○ moderate
False positives (patients incorrectly classified as having MPE)								28 (13–61)	25 (11–54)	19 (8–41)	

MPE: malignant pleural effusion; CoE: certainty of evidence. [#]: In all the included studies, it was unclear whether the pathologists were aware of the patients' backgrounds or other test results, including thoracic ultrasound. In some studies, the ultrasound operators were aware of the patients' background information before performing the thoracic ultrasound scan.

QURESHI *et al.* [13] calculated the sensitivity and specificity of combining nodularity, pleural thickening >1 cm and hepatic metastasis. They found that this combination demonstrated extremely high specificity compared with contrast-enhanced computed tomography (sensitivity 73%, specificity 100%). We could not identify any other articles that reported the overall diagnostic yield. Currently, physicians cannot use any other single morphological pattern except pleural nodularity for ruling-in MPE.

TUS cannot be used as a triage test for ruling out MPE among patients with pleural effusion who are suspected to have malignancy. The result is plausible because thoracentesis is a relatively easy and safe procedure; therefore, it only has a few contraindications, such as the presence of small pleural effusion or inability to maintain the position [17]. When MPE is suspected, it is reasonable to proceed to histopathological tests, such as thoracentesis or thoracoscopy.

This systematic review has several limitations. First, in each article, experienced radiologists or pulmonologists performed TUS in university hospitals. TUS is operator-dependent and a relatively new module. Physicians and ultrasound practitioners require further education and experience to popularise the use of TUS. There is a need for future studies in primary or secondary care settings. Second, five of the seven studies were conducted in Europe, which is not an endemic region for tuberculosis. Pleural tuberculosis, among the most common forms of extrapulmonary tuberculosis, can be visualised as pleural nodules on computed tomography [18]. There are concerns regarding the applicability of pleural nodularity in patients in tuberculosis endemic areas. Third, we could not assess publication bias and heterogeneity using statistical methods. Currently there is no valid method to test for publication bias; further, the methodology of meta-analyses for diagnostic accuracy comprises a substantial risk of bias.

In conclusion, the morphological findings of TUS were not useful as a ruling-out test. Nevertheless, pleural nodularity on ultrasound could motivate us to proceed with repeat thoracentesis or other invasive procedures when MPE is suspected.

Conflict of interest: None declared.

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