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RESEARCH ARTICLE

Color Doppler ultrasonography diagnostic value in detection of malignant nodules in cysts with pathologically proven thyroid malignancy: a systematic review and meta-analysis

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Abstract

Aims Today, the color Doppler ultrasonography is used to further evaluate suspected malignant tumors. This study investigates the malignant thyroid nodules using color Doppler.

Methods After extracting true positive, false positive, false negative, and true negative among included studies, a quality was evaluated by the Quality Assessment of Diagnostic Accuracy Studies-2 tool. Sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio (with 95% confidence interval) were found using a random effect model. Summary receiver operating characteristic curves (SROC) were used to assess relationship between sensitivity and specificity. The area under the curve of the SROC was calculated to estimate the performance of color Doppler ultrasound to distinguish malignant thyroid nodules. Our registration code in PROSPERO is CRD42018111198.

Results Of 1125 articles, 288 articles were selected for the further investigation. After excluding irrelevant and poor articles, 20 studies were included for the meta-analysis. According to a random effect model, the pooled sensitivity and specificity of color Doppler ultrasound to distinguish malignant thyroid nodules were estimated as 0.74 (95% CI 0.62–0.83; I^2 = 89.94%) and 0.70 (95% CI 0.56–0.81; I^2 = 97.79%), respectively. The SROC curve consists of representing the paired results for sensitivity and specificity. According to SROC, AUC = 0.78 (95% CI 0.74–0.81) is between 0.75 and 0.92, so that color Doppler ultrasound has a good accuracy.

Conclusion Color Doppler is a valuable non-invasive method for evaluating thyroid nodules, and it is a high-sensitivity diagnostic tool for assessing thyroid nodules. Resistive index > 0.75 and a pattern III or more in color Doppler predicts malignant with the confidence. Due to its precision, cost-efficiency, easy access, and non-invasive nature, color Doppler should be included in the standard clinical protocol for the decision-making period and the treatment evaluation.

Keywords Color Doppler ultrasound · Thyroid nodule · Malignant thyroid nodule · FNA

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Introduction

Thyroid nodules are very common in the general population. The occurrence of tangible nodules varies from people up to age 50 years from 4 to 21%, while for ultrasound diagnosis of nodules, it varies from 21 to 67% [1–5]. The series of diagnostic modalities consist of biochemical tests such as the measurement of calcitonin, TSH and thyroid autoantibodies which are less suggested in the diagnosis of the common types of thyroid cancer, also ultrasound-guided core needle biopsy (CNB), and fine-needle aspiration (FNA), Doppler sonography, and scintigraphy are done in diagnosis of thyroid nodules [6]. Preventive management of thyroid nodules is a relatively intense process because there is no method with 100% sensitivity and specificity to detect thyroid cancer [7]. The precision aspiration biopsy of the needle under ultrasound guidance (FNA) is a useful method for assessing thyroid nodules. However, there are limitations to the ultrasound guidance for FNA cytology, containing those categorized as uncertain or non-diagnostic aspirated sample [8–10]. Previous studies have shown that the malignancy rates for uncertain or non-diagnostic aspirated samples of ultrasound-guided FNA samples are 60.0% and 10.9% separately [8–10]. This may increase the delay of the final diagnosis of thyroid cancer and the unnecessary thyroidectomy [11]. Today, the color flow Doppler ultrasonography (CFDS) is used to further evaluate suspected malignant tumors. However, there is a wide disagreement among relevant specialists in the validation of the CFDS method for differential diagnosis of benign and malignant thyroid nodules. Some researchers claim that it is very valuable, while others do not agree with this concept [12]. Several studies have pursued to detect ultrasound features that both show sensitivity and specificity for malignancy versus benign illness, but now, it is a question of whether these features are being identified successfully or not [13–15]. Sonographic features that have been detected in previous studies as being indicative of malignancy including irregularities, hypoechogenicity, or microlobulated borders, more tall shape of nodules, intranodular vascularity, and the presence of micro-calcifications [13, 15, 16]. In 2010, Iared et al. did meta-analysis on three articles which showed the overall sensitivity was 96% (95% CI 88–100%), and the specificity was 14% (95% CI 11–18%) [17]. The aim of our study is to investigate the role of CFDS in timely diagnosis and preventive management of malignant thyroid nodules.

Materials and methods

This meta-analysis was performed based on PRISMA guideline, and our registration code in PROSPERO is CRD42018111198.

Search strategy

This research was done by two independent researchers from September 5, 2018 to December 11, 2018, and an information extraction form was used for this purpose. Researchers recognized primary studies and selected studies that were in line with our selection criteria. Any disagreements arising between the two reviewers were decided by discussion with a third reviewer. The following sources of data were searched: Web of Science, International Medical Sciences, Scopus, MEDLINE, PubMed, Index Copernicus, DOAJ, Mbase, Google Scholar, EBSCO-CINAHL, Persian databases including Magiran, and SID using keywords such as: "color doppler ultrasoun*", "thyroid nodule", "malignant thyroid lesion", "malignant thyroid nodule", "follicular thyroid lesion", "thyroid cancer", and "neoplasm".

Inclusion and exclusion criteria

Inclusion criteria were randomized controlled trials or other controlled trials, cohort studies, and cross-sectional studies. Exclusion criteria were letters, reviews, editorials, case reports, articles in abstract form only, articles identified as preliminary reports, irrelevant articles, and articles without the exact quantity information.

Risk of bias (quality) assessment

Selected articles for retrieval are evaluated by two independent reviewers for methodological validation, before entering in the assessment. The Review Manager version 5.0.20 (Cochrane Collaboration, Oxford, UK) was used to calculate sensitivity and specificity, also equivalent 95% Confidence Interval (CIs). The quality of the study was evaluated using 7 items from the Quality Assessment of Diagnostic Accuracy Studies-2 tool. Items that diagnose quality assessment of the list, should be answered the questions by "yes", "no" or "unclear". Items was scored such as "yes" items score 2, "uncertain" items score 1, and "no" items score 0. The highest score was 14, and the lowest score was 0 (Table 1) [18].

Statistical analysis

After extracting true positive (TP), false positive (FP), false negative (FN) and true negative (TN) among included studies, at first sensitivity of studies was evaluated using graphical depiction of residual based such as influence, outlier detection, goodness-of-fit and bivariate normality graph.

Heterogeneity was assessed using the Q statistic of the Chi square value test and the inconsistency index ($I^2\% > 50\%$ as heterogenity). Sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) (with 95% confidence interval) were found using a random effect model.

Forest plots were constructed to demonstrate the variations in the sensitivity and specificity estimates combined for color Doppler ultrasound to distinguish malignant thyroid nodules in each study. The sensitivity, specificity and DOR values with 95% confidence intervals (CI) were calculated. Summary receiver operating characteristic curves (SROC) were used to assess relationship between sensitivity and specificity. The area under the curve (AUC) of the SROC was calculated to estimate the performance of color Doppler ultrasound to distinguish malignant thyroid nodules. The $AUC \geq 0.97$ demonstrated excellent accuracy; $0.93 \leq AUC \leq 0.96$ is very good; $0.75 \leq AUC \leq 0.92$ is good, and $AUC < 0.75$ can still be reasonable, but the test

Table 1 Quality assessment of studies that were included in the meta-analysis

Study	Risk of bias				Concerns regarding applicability		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Low risk of bias	9	13	11	11	12	12	12
Unknown risk of bias	7	4	8	5	8	8	8
High risk of bias	4	3	1	4	-	-	-

has obvious deficiencies in its diagnostic accuracy, and it is approaching the random test [19].

Meta-regression was used to assess source of heterogeneity. Deeks' test was applied to detect publication bias. All data analyses used STATA version 14.0 software for Windows (StataCorp, College Station, TX).

Results

Research finding

From 1125 articles found, 288 documents were assessed independently. Duplicate papers were excluded, and 132 articles were examinated. In the next phase, 106 articles such as case report, irrelevant studies, and articles without enough information were excluded. Evaluating the full texts of the remaining papers, 20 papers were confirmed for meta-analysis. Figure 1 shows the evaluation process. Then, the key results of the selected documents were resumed (Table 4). The selected articles included in a study investigated 6272 patients who have malignant and benign thyroid nodules, and all the studies were compared color Doppler ultrasonography with FNA.

Sensitivity analysis

Sensitivity analysis was used for the color Doppler ultrasound to distinguish malignant thyroid nodules and to assess individual study on pooled effect size (Fig. 2). Comparison of pooled diagnostic parameters using all studies except for three outliers [21, 25] showed that excluding the two studies reduced sensitivity from 0.74 to 0.70, specificity from 0.70 to 0.68, DOR from 6.0 to 5.0 and PLR from 2.4 to 2.2, whereas it increased NLR from 0.38 to 0.44 and AUC from 0.82 to 0.91. Specificity in both cases was 0.98. Also, I-square for sensitivity from 89.94 to 88.59% and for specificity from 99.77% to 97.61 changed. As we show these parameters are not essentially changed. Therefore, meta-analysis is performed on the reliable full set of studies.

Heterogeneity

The results showed a high heterogeneity for sensitivity (I^2 = 89.94%), specificity (I^2 = 97.77%), DOR (92.8%), PLR (93.81%), and NLR (92.67%). Therefore, to estimate pooled effect size for each parameter a random effect model was suggested (Table 2).

According to a random effect model, the pooled sensitivity and specificity of color Doppler ultrasound to distinguish malignant thyroid nodules were estimated 0.74 (95% CI 0.62–0.83; I^2 = 89.94%) and 0.70 (95% CI 0.56–0.81; I^2 = 97.79%), respectively. It means that the high diagnostic accuracy (sensitivity = 74%) of color Doppler ultrasound is determined in this meta–analysis (Fig. 3).

To detect source of heterogeneity, meta-regression was used on publication year, country and quality of studies. For three variables, both sensitivity and specificity were

Table 2 Summary estimates of each parameter and their heterogeneity statistics

Parameter	I^2 (95% CI)	Model	Estimate (95% CI)
Sensitivity	89.94 (86.55–93.33)	RE	0.74 (0.62–0.83)
Specificity	97.77 (97.29–98.24)	RE	0.70 (0.56–0.81)
PLR	93.81 (92.81–94.23)	RE	2.4 (1.5–4.0)
NLR	92.67 (89.10–93.19)	RE	0.38 (0.22–0.63)
DOR	92.8 (86.1–98.2)	RE	6.0 (2.0–17.0)

reduced, but quality of studies has more effect on heterogeneity (Table 3).

The SROC curve consists of representing the paired results for sensitivity and specificity. According to SROC, AUC = 0.78 (95% CI 0.74–0.81) is between 0.75 and 0.92, so that color Doppler ultrasound has a good accuracy. Furthermore, the results of PLR = 2.4 (95% CI 1.5–4.0); NLR = 0.38 (95% CI 0.22–0.63) and DOR = 6.0 (95% CI 2.0–17) indicated that color Doppler ultrasound is a reliable methods for detection of malignant thyroid nodules (Table 3 and Fig. 4).

Deeks' funnel plot was depicted for 20 included studies. In the meta–analysis, according to this symmetric diagram and results of Deek's test ($p = 0.54$) for the DOR, there was no evidence of publication bias among included studies (Fig. 5).

We updated our search from September 5, 2018 to December 11, 2018 using search terms in the databases. In this search, 20 papers were updated with diagnostic rate of thyroid nodules by color Doppler. We used a sensitivity analysis for color Doppler ultrasound to evaluate malignant thyroid nodules of studies separately (Fig. 2).

Comparison of diagnostic parameters collected using all studies, except for two cases [21, 25] showed that, irrespective of the two studies, the parameters were decreased for sensitivity from 0.74 to 0.70, the specificity from 0.70 to 0.68, DOR from 6.0 to 5.0, and PLR from 2.4 to 2.2, while the NLR increased from 0.38 to 0.44 and the AUC increased from 0.82 to 0.91. In this study, a significant heterogeneity was found between the sensitivity and specificity of the studies, which was controlled by the meta-regression method. However, the clinical source of this heterogeneity may be due to factors such as the authors, the different locations of studies, the environment and tools, the accuracy and calibration of devices, the skills and training of people working with devices, or technicians. The findings of these studies were consistent with our meta-analysis results. It showed that color Doppler is a valuable method for evaluating thyroid nodules and can be used as a para clinical method for evaluating the risk of malignancy in a patient with palpable and non-palpable thyroid nodules.

Although the color Doppler manifestations cannot alone predicted 100% benign and malignant differentiation, several

Table 3 Results of meta-regression to assess source of heterogeneity

	Sensitivity			Specificity		
	Estimate	I^2	p	Estimate	I^2	p
Year of publication	0.75 (0.64–0.84)	20.0	0.84	0.71 (0.57–0.82)	21.0	0.89
Country	0.73 (0.58–0.85)	0.0	0.97	0.70 (0.52–0.83)	5.0	1.0
Quality of study	0.79 (0.66–0.88)	26	0.47	0.76 (0.60–0.87)	22	0.49

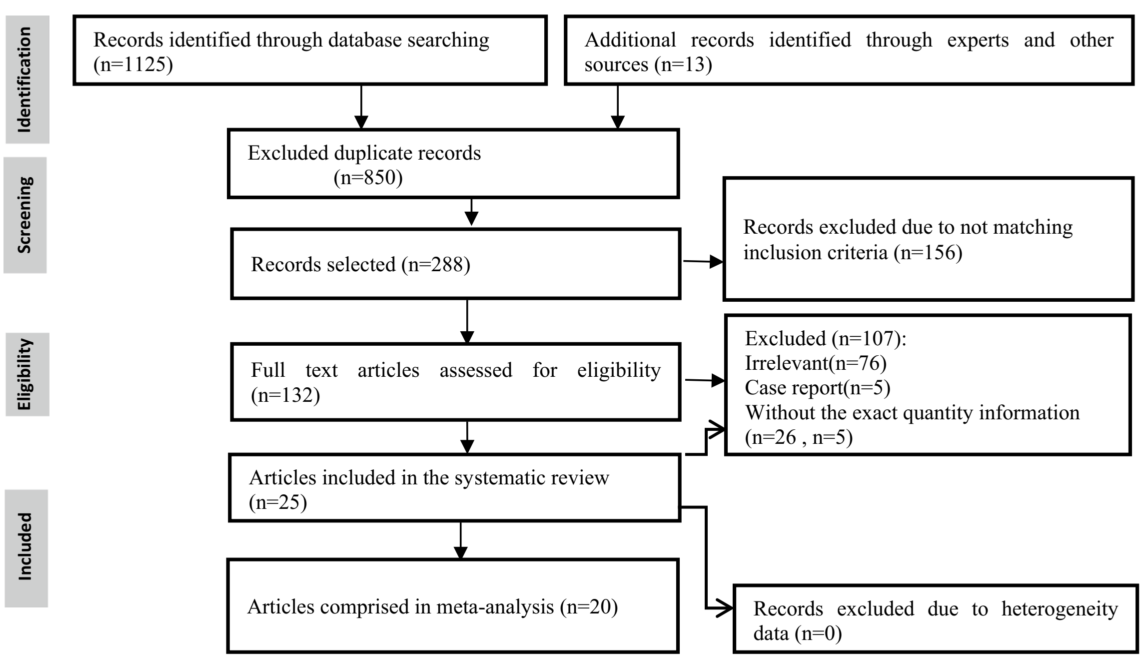

Fig. 1 Flowchart of the study

Table 4 Details of the studies included in this systematic review and meta-analysis

References	Author (year)	Country	Aim	Type of study	Sample size	Scales	Key findings
[20]	Ebeed AE et al. (2017)	Egypt	To assess the role of color flow Doppler ultrasound (CFDS), elastography, and micropure imaging in the evaluation of thyroid nodules	Prospective study	90 (78 women, 12 men)	All patients were tested by color Doppler, B-mode ultrasound, micropure imaging, and ultrasound elastography. All thyroid nodules were exposed to fine-needle biopsy	Color flow Doppler (type III) with absent or slight perinodular blood flow, and obvious intranodular was known in 19 malignant nodules, with sensitivity 79.2%, specificity 95.6%, and the overall accuracy rate was 88.7%
[21]	Appetecchia et al. (2006)	Italy	To evaluate whether conventional ultrasonography (US) and color Doppler ultrasound are able to provide important elements in selecting suspicious nodules	Retrospective study	230 patients	Patients were tested with a CFDS and conventional US. Conventional US examined nodule with echogenicity, size, presence of microcalcifications and halo sign. CFDS assessed the vascular pattern categorized as types I, II and III	The type III flow as identified by CFDS was a statistically important criterion to recommend malignant disease ($p = 0.005$). [Sensitivity 91.7, specificity 34.7, positive predictive value (PPV) 23.2, negative predictive value (NPV) 95.1. Accuracy: 44.8 for CFDS pattern type III]
[22]	Bozbora et al. (2002)	Turkey	To evaluate the usefulness of fine-needle aspiration biopsy (FNAB), color Doppler sonography, and nuclear medicine studies in the assessment of thyroid nodules	Prospective study	81 patients	Intranodular blood flow and perinodular, diameter of inferior thyroid artery and its flow velocity assessment of arterio-venous (A-V) shunt formation were the parameters that were measured by color Doppler sonography	Sensitivity, specificity, negative and positive predictive values of A-V shunt recognition with color Doppler sonography for malignant estimate in hypoactive thyroid nodules are preoperatively calculated as equivalent: 66%, 100%, 89% and 100%

Table 4 (continued)

References	Author (year)	Country	Aim	Type of study	Sample size	Scales	Key findings
[16]	Frates et al. (2003)	USA	To identify if color Doppler examination of a thyroid nodule can help in the forecast of malignancy	Retrospective study	There were 254 nodules. Of these, 177 were benign, 32 were malignant	Color Doppler images of thyroid nodules undertaking sonographically guided fine-needle aspiration	Thirteen of the 32 malignant nodules were solid, as were 18 of the 177 benign nodules. Fourteen of the 32 malignant nodules were color type 4, compared with only 26 of the 177 benign nodules. Among solid nodules, the occurrence of malignancy was greater when the nodule was hypervascular (13 of 31) than when the color type was less than 4 (11 of 77)
[23]	Fukunari et al. (2004)	Japan	To assess the clinical effectiveness of color Doppler imaging for the differential diagnosis of thyroid follicular lesions	Retrospective study	310 patients (266 females, 44 males)	Color Doppler examination was done on patients with a solitary cold nodule in the thyroid gland. All patients undertook surgical resection of the thyroid, and histologic examination was used to approve the diagnosis	Supposing grades 1 and 2 to be benign and grades 3 and 4 to be malignant, 34 of 44 follicular carcinomas and 227 of 266 benign tumors had been accurately diagnosed, yielding a sensitivity of 88.9%, a specificity of 74.2%, and an accuracy of 81%
[24]	Kim et al. (2013)	South Korea	Comparing malignant and benign SITNs base on the color Doppler vascularity pattern, size, and shape. Evaluating the malignancy rate of solid and isoechoic thyroid nodules (SITNs) that do not have sonographic feature of malignant	Retrospective study	Of 382 solid and isoechoic thyroid nodules with the largest diameter ≥ 10 mm in 514 patients	The color Doppler pattern of the thyroid nodules was examined and US-FNA was done after thyroid US examination by the same radiologist using a single-sampling method	Malignant SITNs were identified with deficiency (10%, 1/10) and mixed patterns (12.9, 70.9), but malignant SITNs were not found to have a peripheral (0.31) or central (0.3). There was a significant correlation between Doppler's peripheral color of SITN and benign, but other Doppler patterns showed no significant correlation with malignant or benign nodules

Table 4 (continued)

References	Author (year)	Country	Aim	Type of study	Sample size	Scales	Key findings
[13]	Papini et al. (2002)	Italy	To associate the sonographic ultrasound (US)] and color flow Doppler (CFD) outcomes with the results of US-guided fine-needle aspiration biopsy (FNA)	Prospective study	494 following patients with non-palpable thyroid nodules	The US and CFD examinations were done with a real-time scanner with a linear transducer performing at 8.5–13 MHz for morphological study and at 4.7 MHz for CFD assessment, proficient of imagining solid lesions as small as 2 mm in size	Thyroid malignancies were detected in 18 of 195 (9.2%) solitary thyroid nodules and in 13 of 207 (6.3%) multinodular goiters. Cancer occurrence was alike in nodules greater or smaller than 10 mm. cytological measurement which done by FNA on hypoechoic nodules with risk factor had found 87% of cancer in 38.4% of non-palpable lesions
[25]	Rao G et al. (2014)	India	To study the vascular flow pattern and color Doppler outcomes in benign versus malignant nodular thyroid lesions. To find relationship between these findings with cytopathology and surgical histology	Prospective study	80 patients were confirmed to have solitary thyroid nodule (STN)	All the patients undertook ultrasonography and color Doppler earlier to fine-needle aspiration cytology (FNAC)	Resistive index of benign and malignant nodules [$p < 0.0001$] (Fisher's exact test); sensitivity 0.92, specificity 0.99, positive predictive value (PPV) 0.92, negative predictive value (NPV) 0.99
[26]	Tatar et al. (2014)	Turkey	To assess the efficacy of sonographic and elastosonographic parameters to differentiate the malignancy	Prospective study	150 thyroid nodules were assessed. The cytological analysis shows that 141 nodules were benign and 9 nodules were malignant	All patients were examined by color Doppler, gray scale, and elastosonography	In the strain ratio analysis, the best cutoff point was 1.935 to differentiate malignancy with 100% sensitivity, 76% specificity, 100% negative predictive value, 78.5% positive predictive value and 78% accuracy rate. There was a statistically significant association between the elasticity score and malignancy. Most of the benign nodules had score 1, 2, and 3, none of them showed score 5. Most of the malignant nodules show score 5

Table 4 (continued)

References	Author (year)	Country	Aim	Type of study	Sample size	Scales	Key findings
[27]	Yuan et al. (2006)	Taiwan	To evaluate the particular ultrasonic features of papillary thyroid carcinoma and to show the relative frequency of different patterns of papillary carcinoma on color Doppler ultrasonography (CDU) and gray-scale ultrasonography (US)	Retrospective study	51 patients were verified to have papillary thyroid carcinoma. 67 nodules were registered in the study	The features of sonography were investigated based on tumor size, echogenicity, boundary, echotexture, shape, margin, and calcification pattern on patterns of vascularity on CDU and gray-scale US imaging	Mixed perinodular and intranodular blood flow patterns, the absence of halo, micro-calcifications, and margin with a poorly determined and irregular are US features for papillary carcinoma. CDU presented that 56 (84%) lesions had intranodular flow and mixed perinodular patterns. 4 (6%) lesions had inferno-type hypervascular blood flow signals
[28]	Iannuccilli et al. (2004)	USA	To forecasting malignancy risk by associating between color Doppler and results of sonographically guided fine-needle aspiration biopsy	Retrospective study	From 675 patients, 34 malignant and 36 benign thyroid nodules	Individual features and mixtures features of sonography were analyzed for their association with benign or malignant disease	In general, sensitivity and specificity of these criteria for forecasting malignancy in the study population were 35.3% and 75.0%, respectively (PPV: 0.571, NPV: 0.551, $p = 0.497$)
[12]	Sharma et al. (2007)	India	To assess the diagnostic effectiveness of 99mTc-Tetrofosmin scan and color Doppler in the classification of benign and malignant solitary thyroid nodules	Pilot study	Cold solitary thyroid nodules were found in 52 patients	A single-injection dual-phase (30 min and 120 min) 99mTc Tetrofosmin scan was done on all patients. Color Doppler sonography measured intranodular vascularity. Fine-needle aspiration cytology was done on all the patients	Sensitivity, specificity, positive predictive value and negative predictive value of color Doppler were 53.5, 86.4, 61.5 and 82%, respectively

Table 4 (continued)

References	Author (year)	Country	Aim	Type of study	Sample size	Scales	Key findings
[29]	Stacul et al. (2007)	Italy	To associate the diagnosis of benign or malignant thyroid nodules that achieved with color Doppler US, gray-scale ultrasound (US) and with the cytological findings after US-guided fine-needle aspiration	Prospective study	516 thyroid nodules in 420 patients (181 solitary thyroid nodules and 239 multiple nodules)	Thyroid nodules assessed with color Doppler ultrasonography (US), US, and US-guided fine-needle aspiration (FNA). The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy of US and color Doppler US were assessed using FNA as the reference method	For solitary nodules (color Doppler ultrasonography); sensitivity 57%, specificity 67%, positive predictive value (PPV) 34%, negative predictive value (NPV) 84%, and accuracy 65%. For multiple nodules (color Doppler ultrasonography); sensitivity 44%, specificity 57%, PPV 11%, NPV 89%, accuracy 56%
[30]	Brunese et al. (2008)	Italy	To forecast the risk of malignancy by associating between the existence and absent of B flow imaging (BFI) in thyroid nodules with the histologic results of micro-calcifications and sonographically guided fine-needle aspiration	Prospective study	343 patients with 479 suspected nodules	Sonographic and BFI investigations were done with a real-time sonography system, and all patients also received a cytological assessment	Intranodular color Doppler flow; sensitivity 56.1%, specificity 79.9%, PPV 30.8%, NPV 91.9%
[31]	Nicola et al. (2005)	Brazil	To assess whether resistive index (RI) and flow pattern are useful parameters for differentiating benign from malignant thyroid follicular neoplasms (FNs)	Retrospective study	86 thyroid nodules that undertook sonographically guided fine-needle aspiration	Thyroid nodules were detected as cases of FNs were assessed by duplex and color Doppler sonography. The flow pattern seen through power Doppler investigation was ranked for each nodule on a scale of 0–4. For each nodule, the RI value was measured and the average of 1–3 values were found with different flow signals	For forecasting malignancy, an RI cutoff of 0.75 had good accuracy, specificity, and negative predictive value but had low sensitivity and positive predictive value (respectively, 91%, 97%, 92%, 40%, and 67%)

Table 4 (continued)

References	Author (year)	Country	Aim	Type of study	Sample size	Scales	Key findings
[5]	Varverakis et al. (2007)	Greece	To assess the claim of color flow Doppler (CFD) sonography in the preoperative supervision of benign and malignant cold thyroid nodules	Retrospective study	85 patients with a cold thyroid nodule larger than 1 cm were evaluated with CFD sonography prior to thyroidectomy	The sonographic features of the nodules used for assessment were: (a) absence of vascularization, (b) existence of peripheral vascularization, (c) existence of central vascularization, and (d) size of the nodule. The associations between the preoperative sonographic features, as defined above, and the histological findings of the nodules were identified	For central vascularization; sensitivity 0.31, specificity 0.67, positive predictive value (PPV) 0.27, negative predictive value (NPV) 0.54
[32]	Sultan et al. (2015)	USA	To assess the role of quantitative Doppler vascularity in distinguishing malignant and benign thyroid nodules	Retrospective study	100 nodules of 99 patients were analyzed	Color Doppler images of 100 nodules were analyzed for three metrics: mean flow velocity index, vascular fraction area, and flow volume index in three regions (nodule center, nodule rim and surrounding parenchyma)	Of the three vascularity metrics considered, the vascular fraction area of the central region was most effective in forecasting malignancy, with a sensitivity of 0.90 ± 0.05, specificity of 0.88 ± 0.13, positive predictive value of 0.84 ± 0.14, negative predictive value of 0.92 ± 0.03 and accuracy of 0.89 ± 0.08
[33]	Singh et al. (2017)	India	To assess the usefulness of US gray scale and color Doppler in different thyroid lesions and to associate these features with histopathological findings	Cross-sectional study	50 patients of all age groups with thyroid nodule	Real-time gray-scale US and color Doppler study were done using high-frequency linear probe of 7–12 MHz	An excellent association was seen in diagnosis of thyroid lesions between sonography [color Doppler flow imaging (CDFI), gray scale, and power Doppler (PD)] histopathology. Sensitivity of color Doppler was 0.83, and specificity was 0.8

Table 4 (continued)

References	Author (year)	Country	Aim	Type of study	Sample size	Scales	Key findings
[34]	Berni et al. (2002)	Rome	To find difference between benign and malignant thyroid nodule base on the vascularization	Retrospective study	Sample sizes were 108 patients with cold thyroid nodule: 54 carcinomas and 54 benign nodules	All patients undertook total thyroidectomy. Diagnosis based on histological analysis of the surgical specimen was compared with ultrasonographic diagnosis	Vascular ultrasonographic investigation produced 10 false positives, 6 false negatives and 92 correct diagnoses, with 88.8% sensitivity, 81.5% specificity, an 82.7% positive predictive value and an 88% negative predictive value
[35]	Gannon et al. (2018)	Philadelphia	To determine whether any ultrasound features alone or in combination could be associated with a low enough risk of malignancy to allow for the same conservative approach currently practiced in adults	Retrospective cohort study	417 subjects were reported to have thyroid nodules, and 152 subjects with 241 unique thyroid nodules	Ultrasound images were reviewed independently by two blinded expert radiologists, and ultrasound features were evaluated to determine optimal reliability and predictive value	Multivariable analyses of these ultrasound features in combination revealed combined sensitivity 58.7%, specificity 91.6%, positive predictive value 78.6%, and negative predictive value of 80.9% for thyroid cancer
[36]	Salehi et al. (2015)	Iran	To compare the results of gray-scale sonography and color Doppler ultrasound in cold thyroid nodules	Cross-sectional study	64 patients with cold thyroid nodule who had the probable diagnosis of malignancy	The patients undertook gray scale and color Doppler sonography studies. The imaging changeable elements that recognized were halo sign, calcification, and parenchymal echogenicity (gray-scale sonography) and resistance index (RI (vascularity and number of nodules (color Doppler sonography)	Favorite central hypervascularity was the most common result on color Doppler sonography in malignant nodules which was found in 17 nodules (68%). Sensitivity was 68% and specificity was 89.7%

Table 4 (continued)

References	Author (year)	Country	Aim	Type of study	Sample size	Scales	Key findings
[37]	Palaniappan et al. (2016)	India	To find the specific gray scale and Doppler characteristics in distinguishing malignant from benign thyroid nodules and to compare it with previous studies	Prospective study	The study sample included 214 thyroid nodules in 194 patients who had undergone ultrasound examination	194 thyroid nodules which were confirmed on FNAC. Each nodule was defined according to size, echogenicity number, contents, halo, shape, margins, calcification, local infiltration and lymphnode enlargement. Each nodule was categorized as benign, indeterminate or malignant based on gray scale and Doppler features	Malignant nodules had a mean pulsatility index (PI) of 1.3 and mean resistive index (RI) of 0.73 which were significantly higher than the benign nodules. Accuracy of identifying malignant thyroid nodules by combining Doppler and gray scale is higher than either of them alone. (Sensitivity 95.34%, specificity 80.4%, PPV 58.57%, NPV 98.34%, accuracy 83.76%)
[38]	Ma et al. (2013)	China	To evaluate the value of color Doppler sonography in differentiating malignant and benign thyroid nodules	Prospective study	The study sample included 172 thyroids in which 78 nodules were benign, and 94 nodules were malignant	Subjects undertook preoperative ultrasound examinations including color Doppler ultrasound (CDUS), gray-scale ultrasound (GSUS), and contrast-enhanced ultrasound (CEUS). All thyroid nodules were evaluated by 14 indicators on GSUS, CDUS, and CEUS. The differences between the benign and malignant thyroid nodules in all indicators were analyzed by the Chi square test	Five positive types of the ten valuable signs on GSUS and CEUS defined the cutoff for the diagnosis of malignant thyroid nodules, with a sensitivity of 89.4% (84/94), specificity of 93.6% (73/78) and accuracy of 91.3% (157/172)

Table 4 (continued)

References	Author (year)	Country	Aim	Type of study	Sample size	Scales	Key findings
[39]	Kalantari (2018)	Iran	To study the diagnostic value of color Doppler US and gray scale in forecasting thyroid nodules malignancy.	Analytical cross-sectional	63 patients with thyroid nodules	The patients with nodular goiter were evaluated by color Doppler and gray-scale US, fine-needle aspiration and surgery was done in all the subjects. The sensitivity, specificity, positive predictive value, and negative predictive value of the finding in US, and their cutoffs were calculated	For intranodular and perinodular vascularity (sensitivity 77, specificity 48, PPV 20, NPV 92)
[40]	Cantisani et al. (2013)	Italy	To estimate whether pattern III of color Doppler ultrasonography may recognize malignant nodules	Retrospective study	1090 patients (230 males, 860 females)	Correlation between histological features and color Doppler features	164/273 (60.1%) patients with malignant disease were related to vascularization pattern III. Pattern III of vascularization was found in 152/268 (56.7%) patients with benign disease. No association was found between pattern III and malignancy

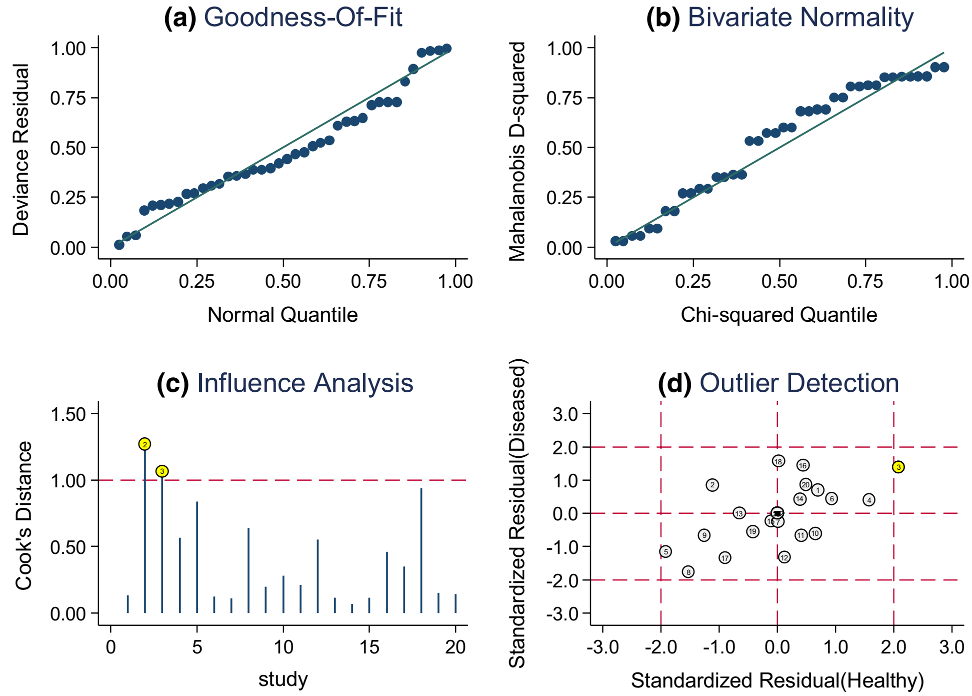

Fig. 2 Sensitivity analysis of included studies in diagnostics meta-analysis: **a** graphical depiction of residual-based goodness-of-fit, **b** bivariate normality, **c** influence analysis, **d** outlier detection

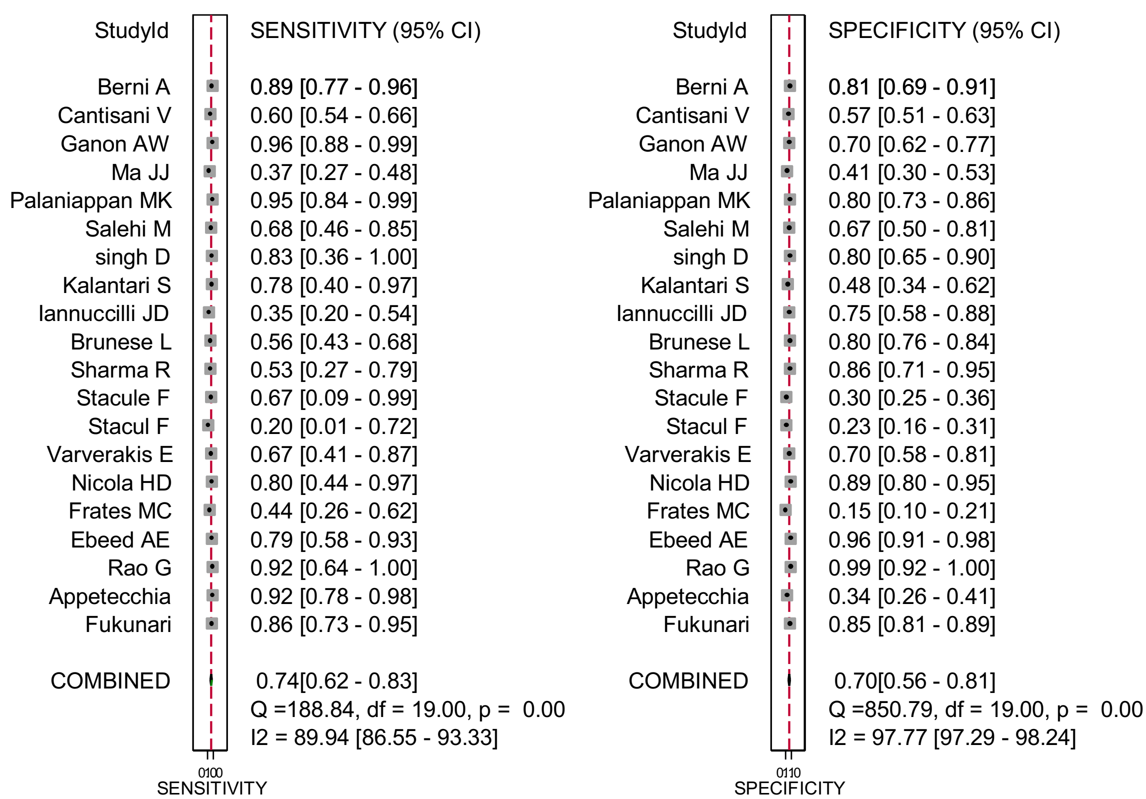

Fig. 3 Forest plot for the pooled estimates of sensitivity and specificity of color Doppler ultrasound to distinguish malignant thyroid nodules

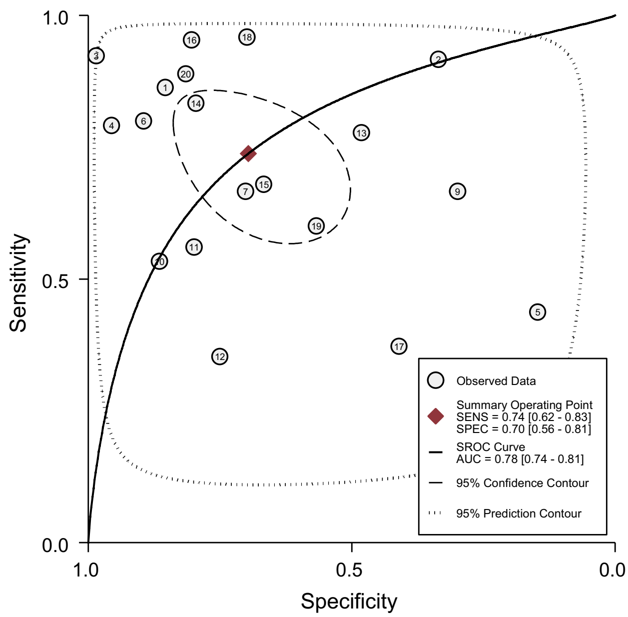

Fig. 4 SROC curve for color Doppler ultrasound to distinguish malignant thyroid nodules. Each circle represents an individual research study. The size of the circle is proportional to the sample size of the study. The best-fitting curve lies between the other two curves demarcating its 95% confidence interval [summary receiver operating characteristic (SROC), area under the curve (AUC)]

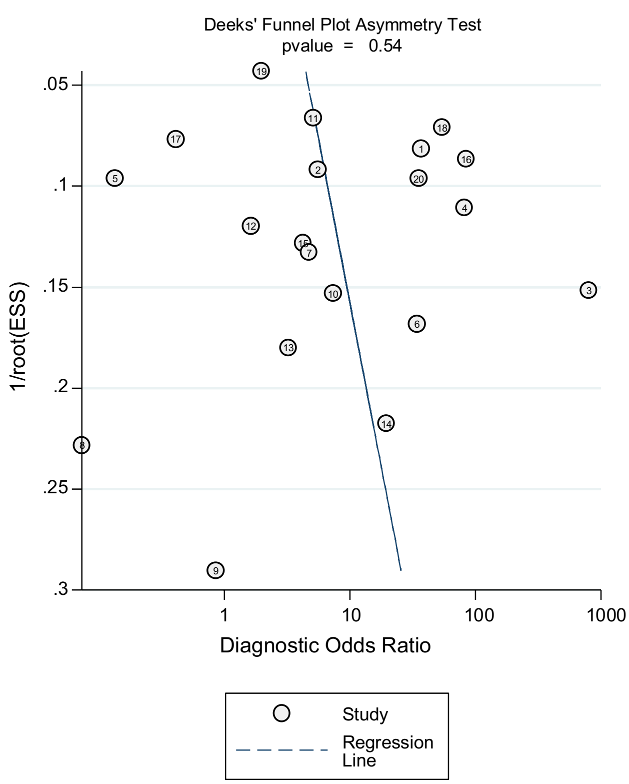

Fig. 5 Deeks' funnel plot for the assessment of publication bias among 20 included studies

features found in a thyroid nodule increase the probability of diagnosis of the thyroid papillary carcinoma [41].

Color Doppler can be useful in managing fine-needle aspiration cytology (FNAC) patients with non-diagnostic or indeterminate results, which is the main limitation of FNAC from thyroid nodules. Non-diagnostic cytology can be detected in cystic or hemorrhagic lesions due to the lack of sufficient number of cells. Ultrasound is valuable in separating solid and cystic lesions. Wienke et al. [42] reported that 60% of benign thyroid nodules are solid, and 40% of them have cystic structure, but these results contradicted with a few authors' studies (Lanonchicchi et al. and Appetecchia). In general, the presence of multiple cystic components can almost eliminate the probability of papillary cancers, which can help to identify benign cystic nodules that required a rapid FNAC or biopsy, especially if the patient has a risk factor of thyroid cancer, including a family history of thyroid cancer and head and neck cancer [41].

Calcification can be detected in about 10–15% of all thyroid nodules, but the location and pattern of calcification are more effective in prognosis of benign from malignancy. Perhaps, calcification is the most reliable feature of benign nodules, but unfortunately, it can occur in the small percentage of benign nodules. When calcifications are large and coarse, the nodule is more likely to be benign. When calcifications are small and dotted, there is a more probability of malignancy. Pathologically, these fine calcifications may be come from psammoma bodies, which are commonly seen in papillary cancers. In all studied articles, except for two cases, micro-calcification was significantly associated with malignancy in the nodules. Fortunately, color Doppler had an ability to determine the presence of calcification ($p < 0.05$). Some studies have shown that micro-calcification has a high specificity (95%) and a low sensitivity (29-36%) of thyroid malignancies [33].

Irregular margins with deterioration or micro-lobulations are a common histopathologic finding in malignancy [15]. In studies conducted by Papini et al. [13] and Lu et al. [43], the poorly defined boundary was found in 77.4% and 79% of the cases. The display of this irregular border represents the malignant nature of the lesions. Similarly, Solbiati et al. [44] found that 82% of the thyroid nodules were benign with regular margins, and 55% of the thyroid nodules were malignant with irregular margins [33]. In Kalantari's study, irregular margin of nodules had the least sensitivity (33%) among cases that were investigated by color Doppler [39].

Some authors have recommended sampling from nodules larger than 1.0 or 1.5 cm [16, 45]. Clinicians usually refer patients to the fine-needle aspiration biopsy (FNAB) if the nodule size is greater than 1 cm. However, a larger thyroid nodule is not a risk factor for malignancy [46]. Papillary thyroid cancers that smaller than 1–1.5 cm may show metastasis to the primary lymph node or spread around [15]. Varverakis et al. concluded that nodules less than 2.5 cm have more vascularity, although the vascularity pattern (central or peripheral) does not have relationship with nodule size. Generally, the size of the nodule cannot be a good criterion for diagnosing benign from malignancy. According to the examined articles, if only the size is considered (< 15 mm) as a sign of the malignancy, we will lose 50% of the papillary carcinoma nodules [27].

The vascular nodule models in color Doppler have been suggested as a diagnostic tool for the prevention of thyroid malignancies, assuming that peripheral vessels represent a benign grade, while the central vessels represent malignancy grade [16]. Several studies have shown that central vessels are associated with malignant solid thyroid nodules [13, 16]. In particular, Frates et al. reported that the central vascularity was seen in a greater percentage of malignant nodules than benign nodules (42% and 14%). In a Kalantari et al. study of color Doppler ultrasonography, there was no significant correlation between blood flow intranodular and perinodular vascularity from benign and malignant nodules.

According to the studies on papillary and follicular lesions, the RI pattern of malignancy (> 0.75) was always associated with a vascular type that indicated malignancy in the Doppler. Follicular lesions in the FNAC can have a particular challenge; therefore, the pattern of vascular flow and color Doppler can help us in this scenario. Papillary carcinoma does not usually show a vascular pattern, probably because of some papillary carcinomas tend to be fibrotic, thus they have non-vascular patterns. In contrast, in all of the follicular cells, there was an increase in the central vascularity, so in the follicular carcinoma nodules that FNA is challenged, the color Doppler can be helpful, and it seems that both methods can be complement each other.

Varverakis et al. [5] found that nodules smaller than 2.5 cm have more vascularity than the larger nodules. Although, the vascularization pattern (central or peripheral) was not correlated with nodule size. Peripheral vascularity is a high feature of benign. Central vascularity is a feature of moderate malignancy. Several authors have suggested that vascular pattern III may be associated with malignancy, as was shown in Bakhshaee's and his colleagues' work [47].

Rago et al. [48] reported that among 74 patients with benign nodules, 38 patients had pattern III (51.8%). While among 30 patients with malignant nodules, 20 patients had pattern III. Studies done by Moon et al., Argalia et al., Tamsel et al., and Rosario et al., showed that there is no association between intravenous and malignant vessels [49–52]. Moreover, Clarke et al. [53] reported by examining color Doppler ultrasonography that cold nodules are mainly introduced with peripheral coronary arteries, and hot nodules are introduced with central vessels. They concluded that color Doppler ultrasonography could not properly detect benign from malignant thyroid nodules. According to the studies, thyroid nodules do not require interferences with the elastography grade I and II. Nodules with grade III which diagnosed by color Doppler are suspicious nodules, and we recommend FNAC. However, nodules with grade IV and V are highly suspected of malignant, and we recommend surgery.

Color Doppler ultrasonography in various studies has shown that halo sign is a thin and complete area, which strongly represents benign nodules. A halo sign of blood vessels is located around the periphery of the lesion (the basket pattern). Solbiati et al. [44] reported that halo sign is found in 36% of thyroid nodules and mostly found in benign than malignant cases (86% versus 14%). Halo sign seems to be a parenchyma of the normal thyroid, especially for fast-growing cancers, which are often thick, irregular, and imperfect. It is shown in a hypo-vascular or avascular color Doppler scan which Singh and colleagues also confirmed this.

Palaniappan et al. also showed that comet tail artifacts are seen in 23 nodules, all of them are benign (100%). Hence, this is a specific criterion for thyroid benign nodules. These findings are comparable with the findings of Wang and Ahuja, which conclude that the trace of the comet tail artifacts is a sign of benign [54].

In the reviewed articles, the prevalence of malignancy in hypoechoic nodules was higher than those of the hyperechoic and isoechoic nodules. In the study of Kalantari et al. [39], micro-calcification of tissue and hypoechogenicity are the most and the least predictive factors for malignancy in nodules (77% sensitivity, 76% specificity versus 24%, 41% PPV versus 14%, and 94% NPV vs. 86%), respectively. A study by Papini et al. on cytological examination of the non-palpable nodules showed that the appearance of hypoechoic is correlated with at least one independent statistical ultrasonography risk factor. It has been able to detect the majority of non-palpable tumors of the thyroid nodules [13].

Various studies have found that the risk of thyroid cancer with several nodules is less than the individual nodules. Brown in his study reported that ultrasonography included multiple nodules in 28% of the glands, and none of the nodules that had multiple nodules were malignant [55].

85% of patients with nodular diseases were female [23] and other epidemiological studies show that the incidence of palpable thyroid nodules is about 5% in women and 1% in men. But, studies show that age and sex are not the most important criteria for differentiating benign and malignant thyroid nodules.

According to the surveys that were done, certain malignant features grow stronger in the color Doppler including: micro-calcification, hypoechoic, thick, weak and irregular halo, lymphadenopathy, and additional local thyroid stimulation. Other features, such as the absence of a halo and macro-calcification, are less likely to be useful, but its side effects may be helpful.

Conclusion

However, needle aspiration cytology is the most accurate, sensitive, and specific diagnostic tool in preoperative thyroid evaluation and can be very helpful. Though when FNAC provides an undesirable number of cells for the removal of malignant cells, and there is no clinical feature for identifying the malignancy, another test with similar strength can be helpful under such conditions. Color Doppler is widely available, easily applied in practice, and as a diagnostic tool for evaluating thyroid nodules. Also, it has high sensitivity and specificity.

Resistive index > 0.75 and a pattern III or more in color Doppler predicts malignancy with the confidence. Finally, we recommend that the thyroid nodules with positive result of ultrasonography are required to take FNAC. Doppler can play a complementary role in FNAC for evaluation of individual thyroid nodules, due to its precision, cost-efficiency, easy access, and non-invasive nature. Not only it can be avoid unnecessary FNAC, it also increases diagnostic ability and helps the surgeon in conducting the surgery to do the necessary design for the malignant neoplasm before surgery. This method can prevent important problems, such as repeated biopsies and delays in detection.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval (research involving human participants and/or animals) This work has no human or animal participants.

Informed consent There is no consent for this work.

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