ORIGINAL ARTICLE

Usefulness of different ultrasound features of malignancy in predicting the type of thyroid lesions: a meta-analysis of prospective studies

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KEY WORDS

meta-analysis, thyroid, thyroid cancer, thyroid nodules, ultrasonography

ABSTRACT

INTRODUCTION Thyroid nodules are a common medical problem. Thyroid ultrasound remains the most common method for preliminary evaluation and selection of nodules for fine-needle aspiration biopsy (FNAB). Doppler examination and elastography are believed to improve the reliability of ultrasound in predicting malignancy.

OBJECTIVES The aim of this study was to evaluate diagnostic value of common ultrasound markers of malignancy of thyroid lesions.

MATERIALS AND METHODS The PubMed/MEDLINE and Cochrane Library databases were searched to identify studies meeting the inclusion criteria. The random-effects model was used to calculate pooled odds ratio (OR), risk ratio, sensitivity, specificity, and positive and negative predictive values (PPV and NPV) of the individual features of thyroid malignancy on ultrasound. Only the prospective studies published between January 2007 and February 2013, performed using a transducer with the frequency of at least 7.5 MHz have been included in the meta-analysis.

RESULTS The taller-than-wide shape of the thyroid nodule was shown to be the strongest predictor of malignancy (OR, 13.7; PPV, 76.0%); however, its sensitivity was 25.9%. Irregular margins and microcalcifications were also strong predictors of malignancy (OR, 7.2 and 7.1, respectively) and both had higher specificity (79.6% and 75.9%, respectively) than sensitivity (45.5% and 44.1%, respectively). Elastography of the thyroid gland also proved to be a valuable diagnostic tool in detecting malignant lesions (OR, 7.9). Hypoechogenicity, halo absence, and intranodular flow on a color Doppler examination were moderate predictors of malignancy (OR, 3.2, 3.8, and 4.3, respectively).

CONCLUSIONS Ultrasound features considered to be predictors of malignancy seem to be valuable for preliminary evaluation of thyroid nodules and referral for FNAB. However, they should always be interpreted with caution because none of them allows to reliably differentiate malignant from benign nodules.

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INTRODUCTION Nodular thyroid disease constitutes a common medical problem. The prevalence of thyroid nodules differs among various studies, ranging from about 10% to almost 70% of the general adult population, being higher in women, the elderly, subjects with specific nosologic entities such as acromegaly, or with a family history of thyroid disorders.[1-5] The selection of nodules with a high risk of malignancy requiring either surgery or follow-up constitutes an important challenge in endocrine practice. Although there are many new techniques and approaches to estimate the malignancy risk, such as molecular markers, ultrasound thyroid examination remains the most common method of preliminary assessment of nodules and the basis for using fine-needle aspiration biopsy (FNAB) or for selecting nodules for FNAB in multinodular goiter.[6-8] Doppler examination and elastography are believed to improve the reliability of predicting malignancies. The aim of this study was to evaluate and compare the diagnostic value of ultrasound features of malignancy in differentiating benign and malignant thyroid lesions.

TABLE 1 Main characteristics of the studies included in the meta-analysis

Author	Year	Patients	Mean age, y	Nodules	Malignancies
Azizi et al.[10]	2012	706	women, 48.5 men, 47.7	912	86
Bojunga et al.[11]	2012	99 women, 39 men	52.0	158	21
Rossi et al.[12]	2012	1439 women, 417 men	52	2421	233
Trimboli et al.[13]	2012	438 women, 138 men	53.0	498	126
Bhatia et al.[14]	2011	89 patients[a]	not available	89	19
Merino et al.[15]	2011	89 women, 14 men	58	106	10
Ünlütürk et al.[16]	2011	157 women, 37 men	women, 43.7 men, 47.5	237	58
D'Souza et al.[17]	2010	151 women, 49 men	not available (range, 8–74)	200	26
Friedrich-Rust et al.[18]	2010	37 women, 13 men	women, 54 men, 52	53	7
Gietka-Czernel et al.[19]	2010	42 women, 10 men	45	71	22
Yunus et al.[20]	2010	58 women, 8 men	not available (range, 18–75)	78	25
Asteria et al.[21]	2008	54 women, 12 men	women, 51.3 men, 60.5	86	17
Brunese et al.[22]	2008	264 women, 79 men	41.2	479	66
Rubaltelli et al.[23]	2008	25 women, 15 men	55	51	11

a sex not specified

MATERIALS AND METHODS

Data extraction and selection criteria We searched the PubMed/MEDLINE and Cochrane Library databases to identify all relevant research papers. Search terms included: (thyroid cancer OR thyroid nodules) and (ultrasound OR ultrasonography OR elastography OR "power doppler" or "colour doppler"). The following filters were applied: English language as well as publication date between January 2007 and February 2013. The literature search was performed independently by 2 authors (K.W. and M.S.).

Only the prospective studies conducted not earlier than in 2002 and performed with the use of a transducer with the frequency of at least 7.5 MHz were included in the meta-analysis. The aim of those limitations was to avoid underestimation of the diagnostic value of ultrasound markers of malignancy, which might have occurred if older studies, performed with lower-quality equipment, had been included. We also excluded studies in which the diagnosis of malignant, or suspicious, nodules was based only on cytopathology, without subsequent histopathological examination and differentiation between malignant and benign nodules.

Studies focusing only on particular subgroups of patients (e.g., surgical or pediatric patients only) or particular types of nodules (e.g., subcentimeter, palpable, pure cystic or mixed, etc.) were excluded. However, we considered publications that excluded cystic nodules or nodules smaller than the defined diameter.

Statistical analysis We meta-analyzed odds ratios (ORs) and risk ratios (RRs) using a random-effects model using the Statistica v.10 software with medical package. T^2 and i^2 values given in the "Results" section are based on OR calculations. Pooled sensitivities, specificities, positive and negative predictive values (PPV and NPV) of particular markers of malignancy were calculated using a random-effects model according to the methodology described by Borenstein et al.[9]

RESULTS

Fourteen studies met the inclusion criteria and were subjected to a meta-analysis (TABLE 1). These studies encompassed 5439 thyroid lesions – 4712 benign nodules and 727 cancers. The steps of selection are presented in FIGURE 1.

Microcalcifications Thirteen studies provided data on the frequency of microcalcifications, amounting to 5308 nodules (718 malignant, 13.5%). The pooled OR equaled 7.1 (95% confidence interval [CI], 4.3–11.9); RR, 3.8 (95% CI, 3.0–5.0); sensitivity, 44.1% (95% CI, 37.9%–51.3%); specificity, 75.9% (95% CI, 70.3%–82.0%). PPV was 42.3% (95% CI, 33.6%–53.3%) and NPV was 88.6% (95% CI,

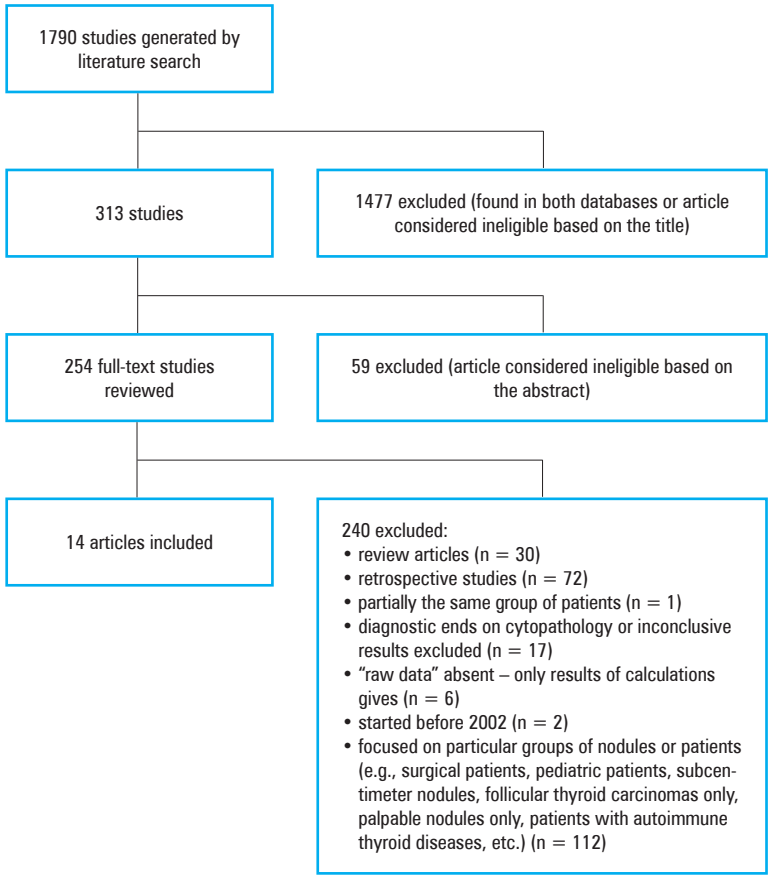


FIGURE 1 Flowchart of literature search and study selection

79.7%–98.5%). There was no evidence of significant heterogeneity (Q = 10.3; degrees of freedom (df) = 12; P = 0.59; i^2 = 0.0%) or publication bias (Kendall's tau, 0.15; 2-tailed P value, 0.46).

Hypoechogenicity Eleven of the 14 selected studies provided data on the frequency of hypoechogenicity, adding up to 5179 nodules (682 malignant, 13.2%). The pooled OR was 3.2 (95% CI, 2.3–4.5); RR, 2.5 (2.0–3.1); sensitivity, 68.7% (95% CI, 58.8%–82.6%); specificity, 60.3% (95% CI, 53.4%–68.2%). PPV was 25.2% (95% CI, 17.6%–36.2%), NPV was 91.4% (95% CI, 78.8%–100.0%). There was no evidence of significant heterogeneity (Q = 16.7; df = 10; P = 0.08; i^2 = 39.9%), or publication bias (Kendall's tau, 0.35; 2-tailed P value, 0.14).

Irregular margins Thirteen studies provided data on the frequency of irregular margins, including a total of 5296 nodules (707 malignant, 13.3%). The pooled OR was 7.2 (95% CI, 4.5–11.5); RR, 4.1 (95% CI, 3.1–5.5); sensitivity, 45.5% (95% CI, 30.9%–66.9%); specificity, 79.6% (95% CI, 71.9%–88.2%). PPV was 40.4% (95% CI, 29.9%–54.7%) and NPV was 88.9% (95% CI, 80.4%–98.3%). There was no evidence of significant heterogeneity (Q = 12.9; df = 12; P = 0.38; i^2 = 7.1%) or publication bias (Kendall's tau, 0.03; 2-tailed P, 0.90).

Elastography Ten studies provided data on lesion stiffness graded according to elastography scores, adding up to 2233 nodules (367 malignant, 16.4%). The pooled OR was 10.5 (95% CI, 6.4–17.2); RR, 6.0 (95% CI, 4.2–8.6); sensitivity, 74.1% (95% CI, 57.7–95.3); specificity, 69.7% (95% CI, 62.8–77.2). PPV was 37.2% (95% CI, 28.4–48.7) and NPV was 91.9% (95% CI, 73.5–100.0). There was no evidence of significant heterogeneity (Q = 13.4; df = 9; P = 0.15; i^2 = 32.9%). The publication bias turned out to be significant (Kendell's tau, 0.64; 2-tailed P value, 0.01). Two studies performed in the smallest groups and presenting the highest study variances[19,21] reported outstanding results (OR, 68.9 and 190, respectively). After the exclusion of these papers, the following results were obtained: OR, 7.9 (95% CI, 5.6–11.2); RR, 5.4 (95% CI, 3.8–7.5); sensitivity, 73.3% (95% CI, 56.6–95.0); specificity, 69.3% (95% CI, 62.4–76.9). PPV was 35.2% (26.5%–46.7%) and NPV was 91.9% (95% CI, 73.0–100.0). Moreover, this step also eliminated the publication bias (Kendell's tau, 0.43; 2-tailed P value, 0.14).

Taller-than-wide shape Three studies provided data on the frequency of the taller-than-wide shape, amounting to 665 nodules (170 malignant, 25.6%). The pooled OR was 13.7 (95% CI, 4.1–45.7); RR, 3.9 (95% CI, 2.5–5.9); sensitivity, 25.9% (95% CI, 12.1%–55.3%); specificity, 95.9% (95% CI, 48.3%–100.0%). PPV was 76.0% (95% CI, 35.0–100.0) and NPV was 77.6% (95% CI, 64.1–94.0). There was no evidence of significant heterogeneity (Q = 2.4; df = 2; P = 0.30; i^2 = 17.3%) or publication bias (Kendell's tau, 0.33; 2-tailed P value, 0.60).

Halo absence Four studies provided data on the halo absence frequency, amounting to 648 nodules (112 malignant, 17.2%). The pooled OR was 3.8 (95% CI, 1.7–8.5); RR, 3.0 (95% CI, 1.5–6.0); sensitivity, 63.8% (95% CI, 38.1–100.0); specificity, 47.5% (95% CI, 33.4–67.8). PPV was 23.5% (95% CI, 15.6–35.6) and NPV was 91.3% (95% CI, 60.0–100.0). There was no evidence of significant heterogeneity (Q = 3.4; df = 3; P = 0.33; i^2 = 10.7%) or publication bias (Kendell's tau, –0.33; 2-tailed P value, 0.50).

Color Doppler examination Three studies provided data on the frequency of intranodular flow in color Doppler examination, including 1048 nodules (214 malignant, 20.4%). The pooled OR was 4.3 (95% CI, 3.1–6.1); RR, 2.6 (95% CI, 1.6 – 4.0); sensitivity, 44.2% (95% CI, 33.6–58.2); specificity, 81.5% (95% CI, 67.8–98.0); PPV, 41.3% (95% CI, 28.4–60.2); NPV, 82.4% (95% CI, 67.6–100.0). There was no evidence of significant heterogeneity (Q = 1.8; df = 2; P = 0.41; i^2 = 0.0%) or publication bias (Kendell's tau with continuity correction, 0.0; 2-tailed P value, 1.0).

Power Doppler: pattern 3 flow (intensive central with lower peripheral blood flow) Six studies provided data on the frequency of pattern 3 flow in power

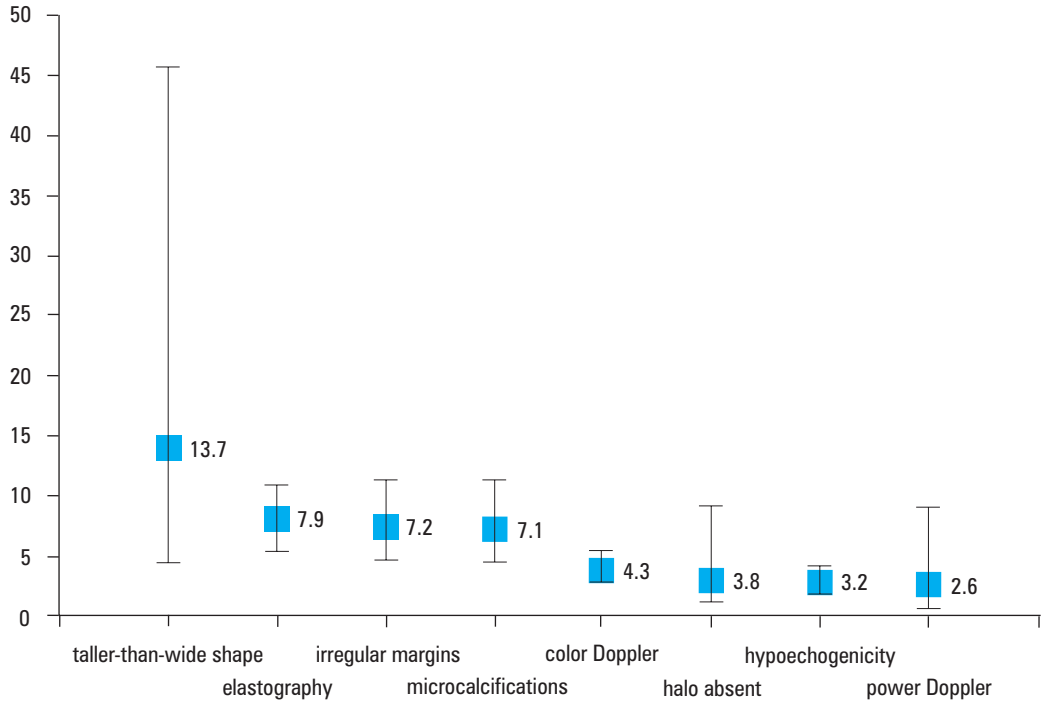


FIGURE 2 Pooled odds ratios with 95% confidence intervals for significant ultrasound markers of malignancy

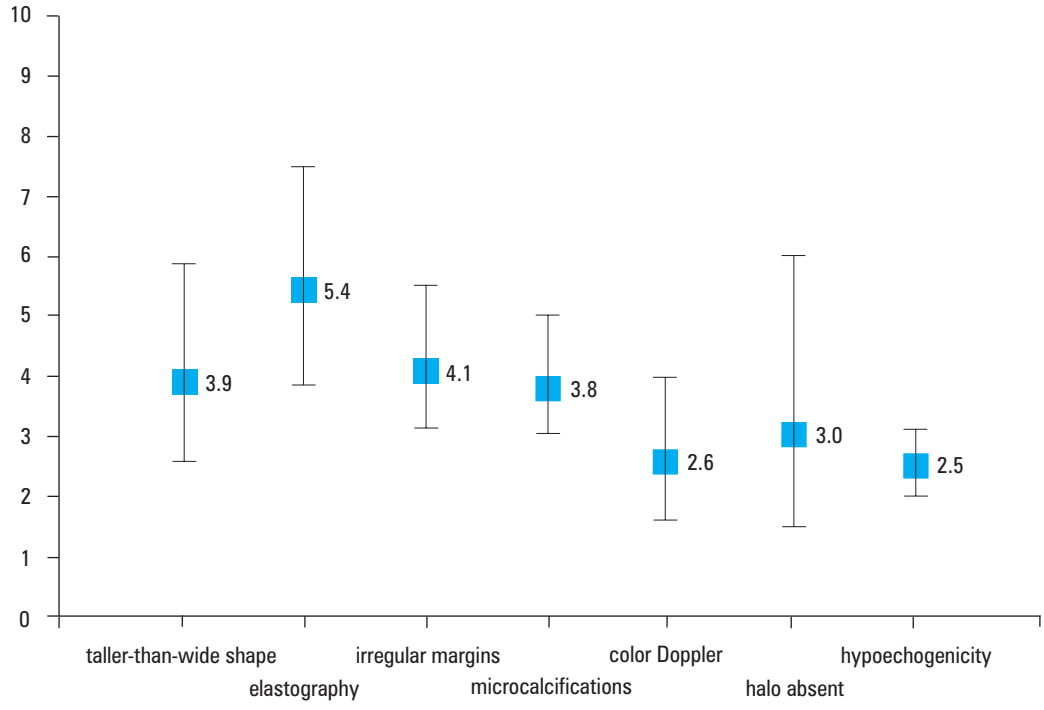


FIGURE 3 Pooled risk ratios with 95% confidence intervals for significant ultrasound markers of malignancy

Doppler examination, adding up to 1419 nodules (204 malignant, 14.4%). The pooled OR was 2.6 (95% CI, 0.8–8.3) and the result was statistically insignificant. There was no evidence for significant heterogeneity (Q = 5.9; df = 5; P = 0.32; i^2 = 15.2%) or publication bias (Kendall's tau, 0.2; 2-tailed P value = 0.57). The results are presented in FIGURES 2–5.

Logarithm of risk ratios The binary logarithms of RRs of individual malignancy markers are shown in TABLE 2. It is possible to compare the malignancy risk of several nodules, for instance in multinodular goiter, by adding the values of the logarithm of RRs for the features present. With the assumption that particular markers are independent variables, the highest obtained value would indicate the nodule presenting the highest risk of malignancy.

DISCUSSION The fourteen studies included in the meta-analysis contain data on 4479 patients with 5439 thyroid nodules that were subject to FNAB (and eventually postsurgical histopathology). Of all nodules, 727 turned out to be cancers (13.4%). The smallest malignancy ratio was 9.4%[10,15] and the highest – 32.1%.[19] This ratio was somewhat higher than expected. It might have

FIGURE 4 Pooled sensitivity and specificity with 95% confidence intervals for significant ultrasound markers of malignancy

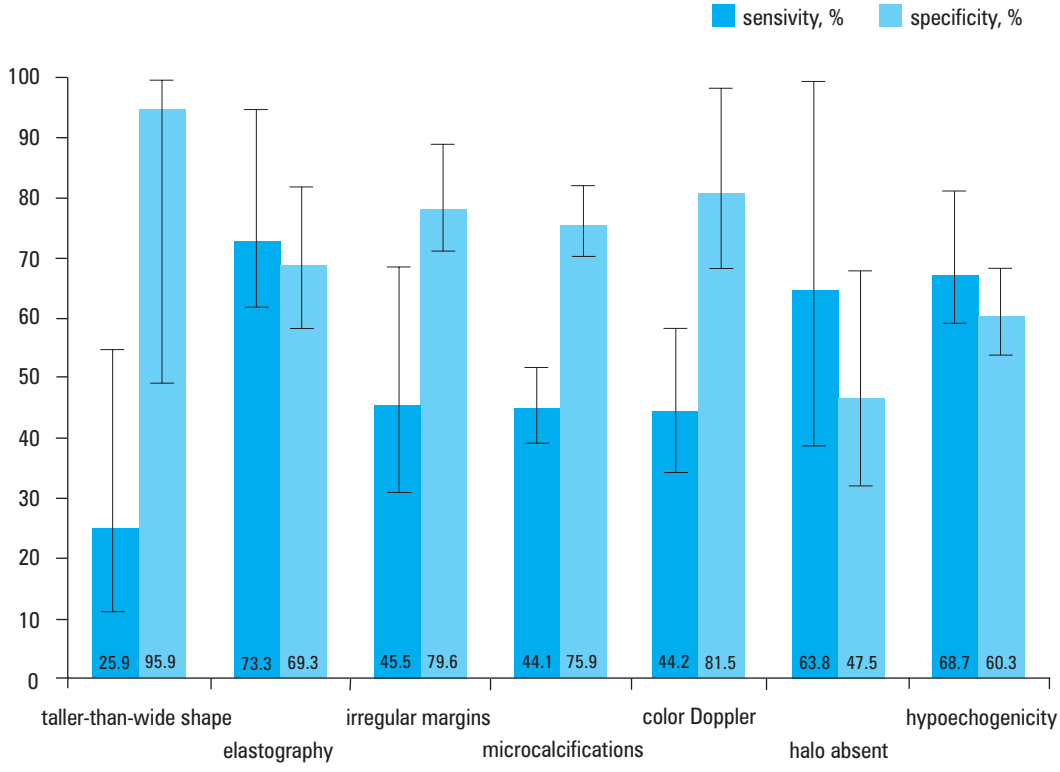
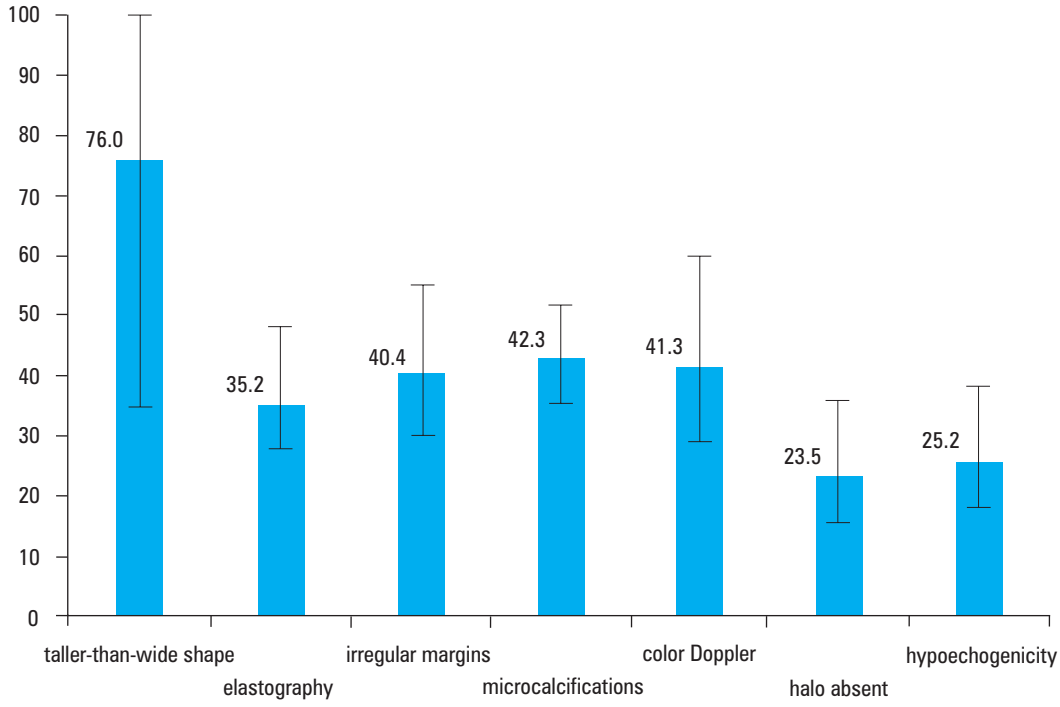


FIGURE 5 Pooled positive predictive values with 95% confidence intervals for significant ultrasound markers of malignancy



been partially caused by the fact that most studies excluded certain groups of nodules (e.g., pure cystic) with the expected low malignancy rate. Additionally, we cannot exclude the possibility that, in some studies, patients with nodules characterized by suspicious appearance on ultrasound were preferentially included.

The taller-than-wide shape turned out to be the strongest predictor of malignant thyroid nodules; however, its sensitivity was low. Microcalcifications and irregular margins were also suspicious findings suggestive of malignancy, but similarly to the taller-than-wide shape, they showed rather poor sensitivity and slightly better specificity.

On the other hand, hypoechogenicity and absent halo were slightly but significantly more common in thyroid cancers than in benign nodules with poor specificity.

Pattern 3 flow on power Doppler ultrasound turned out to be more frequent in thyroid cancers, but this result was statistically insignificant. Intranodular blood flow on color Doppler ultrasound seemed to be more reliable and statistically significant. However, sensitivity of this

TABLE 2 Binary logarithms of risk ratios of individual predictors of malignancy

	Logarithms of risk ratios	
	yes	no
microcalcifications	1.94	0
hypoechogenicity	1.30	0
irregular margins	2.05	0
elastography	2.42	0
taller-than-wide shape	1.95	0
halo absent	1.60	0
color Doppler – intranodular flow	1.40	0

marker was unsatisfactory. According to the available data, decreased elasticity of a lesion was also a potent predictor of malignant thyroid nodules, with the second highest OR (after the taller-than-wide shape). This finding is in line with the results of our previous study including patients referred for thyroid surgery, which indicated a very high diagnostic value of shear-wave elastography (OR of up to 54.5 depending on the threshold).[24]

Although we did not have enough data to meta-analyze the average size of both malignant and benign nodules, the available results are interesting. According to Rossi et al.,[12] 144 of 233 malignant nodules (61.8%) were smaller than 1 cm in the maximum diameter, while in the report by Azizi et al.,[10] this was observed in 39 of 86 cancers (45.3%). In this context, leaving subcentimeter nodules without undertaking further diagnostic measures might have led to misdiagnosis and treatment delay in a considerable number of cancers. There was also not enough information to meta-analyze the presence of macrocalcifications. However, the available data suggest a rather low diagnostic value of this parameter. According to Azizi et al.,[10] macrocalcifications were insignificantly more prevalent in cancers (OR, 1.6; 95% CI, 0.7–3.6), while in the study performed by D'Souza et al.,[17] they occurred slightly less frequently in malignancies (OR, 0.12; 95% CI, 0.02–1.02). The data on nodule composition were also insufficient to perform a meta-analysis. Nevertheless, the available statistics are divergent. In the study performed by Bhatia et al.,[14] all 19 thyroid cancers and 5 metastases from other organs were solid, while 53% of benign nodules were partially cystic. According to Azizi et al.,[10] solid nodules had a statistically insignificantly increased risk of malignancy (73.3% of malignant and 66.0% of benign nodules were solid; OR, 1.4; 95% CI, 0.9–2.3). D'Souza et al.[17] reported similar results (65.4% of cancers and 59.2% of benign nodules were solid; OR, 1.3; 95% CI, 0.5–3.1). However, unlike cancers, 10.3% of benign lesions were purely cystic.

There were also some new ultrasound markers that could not be meta-analyzed owing to an insufficient number of studies but should be considered in future research. Azizi et al.[10] distinguished 2 levels of microcalcifications (level 1, up to 3 foci, and level 2, 4 foci or more). The authors indicated that only the presence of level 2 microcalcifications was correlated with malignancy. Brunese et al.[22] described B-flow imaging twinkling sign as a very strong predictor of malignancy (OR, 384.2).

Another approach to improve diagnostic accuracy is to combine classic ultrasound markers of malignancy. In the simplest version, this would mean to assess several markers together, and, in a more advanced form, to evaluate the risk (including information about all ultrasound markers) and to find out how it affects the *a priori* malignancy risk with the use of, for example, the Bayesian network.

Of note, most cancers assessed in the studies included in our meta-analysis were papillary thyroid carcinomas. In those studies which provided the exact information on the final histopathological results, about 89% of cancers on average were papillary thyroid carcinomas. Therefore, the above ultrasound markers of malignancy might not be similarly reliable in the case of other thyroid carcinomas. A study on follicular carcinomas revealed that certain classic predictors of malignancy were frequent in this group (e.g., hypoechogenicity, 82%; halo absent, 64%), while others were rare (e.g., calcifications, 14%).[25] The few available studies on medullary thyroid cancer report rather divergent results; yet, they indicate that this subgroup of thyroid cancers might present a relatively benign appearance on ultrasound.[26,27] To sum up, data on ultrasound features of nonpapillary thyroid cancer are limited.

Many ultrasound features seem to be valuable markers of malignancy. However, it is worth noting that although the results of individual studies usually demonstrate the same trend, the estimation of the effect size (e.g., OR) is widely varied. For instance, among 13 studies assessing the regularity of nodule margins, the lowest reported OR was 1.8, while the highest was 39.9. 95% CIs are wide (OR, 4.5–11.5). Similarly, the results referring to pattern 3 in power Doppler examination varied significantly.[24] Only in 6 studies, OR was between 0.8 and 50.4, 95% CI of the pooled result was also wide (0.8–8.3); nevertheless, it may partially be a consequence of a small number of studies. The taller-than-wide shape is a strong marker of malignancy (OR, 13.7; 95% CI, 4.1–45.7). However, the sensitivity (25.9% with 95% CI, 12.1%–55.3%) and specificity (95.9%, 95% CI, 48.3–100.0) are, in fact, difficult to determine.

According to our results, many ultrasound features are valuable markers of malignancy and should not be omitted when interpreting ultrasound results. Although the Society of Radiologists in Ultrasound recommends mainly calcifications and solid or predominantly solid composition as features prompting biopsy,[28] our meta-analysis reveals that other ultrasound features, such as the taller-than-wide shape or irregular margins, are also strong predictors of malignancy.

To conclude, certain ultrasound characteristics of thyroid nodules seem to be valuable for the preliminary assessment of thyroid nodules and referral for FNAB. The presence of the taller -than-wide shape, decreased elasticity, microcalcifications, irregular margins, or intranodular blood flow on color Doppler examination strongly increases the risk of malignancy. If the lesions have at least 1 of those features, FNAB should be considered. However, ultrasound markers of malignancy should always be interpreted with caution because none of them reliably differentiates malignant from benign nodules.

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ARTYKUŁ ORYGINALNY

Przydatność sonograficznych markerów złośliwości w przewidywaniu charakteru zmian ogniskowych w tarczycy – metaanaliza badań prospektywnych

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SŁOWA KLUCZOWE

guzki tarczycy, metaanaliza, rak tarczycy, tarczyca, ultrasonografia

STRESZCZENIE

WPROWADZENIE Zmiany ogniskowe w tarczycy stanowią częsty problem medyczny. Badanie ultrasonograficzne (USG) tarczycy pozostaje najpowszechniej stosowaną metodą wstępnej oceny oraz wyboru zmian ogniskowych wymagających biopsji cienkoigłowej (*fine-needle aspiration biopsy* – FNAB). Badanie doplerowskie oraz elastografia są uważane za techniki mogące przyczynić się do zwiększenia przydatności USG w różnicowaniu guzków łagodnych i złośliwych.

CELE Celem pracy była ocena wartości diagnostycznej powszechnie stosowanych sonograficznych markerów złośliwości zmian ogniskowych tarczycy.

MATERIAŁ I METODY Przeszukano bazy danych PubMed/MEDLINE oraz Cochrane Library w celu odnalezienia prac spełniających kryteria włączenia. Użyto modelu efektów zmiennych do obliczenia ilorazów szans (*odds ratio* – OR), ryzyka względnego, czułości, swoistości oraz wartości predykcyjnej wyniku dodatniego (*positive predictive value* – PPV) i ujemnego (*negative predictive value* – NPV) poszczególnych sonograficznych markerów złośliwości. Jedynie badania prospektywne, opublikowane między styczniem 2007 i lutym 2013 roku, wykonane aparatami z częstotliwością ≥7,5 MHz, włączono do metaanalizy.

WYNIKI Cecha *taller than wide* okazała się najsilniejszym predyktorem złośliwości (OR = 13,7; PPV 76,0%); jednak czułość tej cechy wyniosła 25,9%. Nieregularne granice oraz mikrozwapnienia również były silnymi predyktorami złośliwości (OR odpowiednio 7,2 oraz 7,1). Obie cechy wykazywały większą swoistość (odpowiednio, 79,6 oraz 75,9%) niż czułość (45,5 oraz 44,1%). Elastografia tarczycy również okazała się wartościowym narzędziem diagnostycznym w wykrywaniu zmian złosliwych (OR = 7,9). Hipoechogenność, brak *halo* oraz przepływ krwi wewnątrz guza w badaniu metodą kolorowego Dopplera okazały się umiarkowanie silnymi predyktorami złośliwości (OR odpowiednio 3,2, 3,8 oraz 4,3).

WNIOSKI Cechy sonograficzne uważane za predyktory złośliwości wydają się wartościowe we wstępnej ocenie zmian ogniskowych tarczycy oraz w podjęciu decyzji o FNAB. Powinny one jednak być interpretowane ostrożnie, gdyż żadna z nich nie pozwala na definitywne zróżnicowanie guzków łagodnych i złośliwych.

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