

Extrathyroidal extension on ultrasound in patients with papillary thyroid carcinoma: Is it associated with local lymph node metastasis?

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ABSTRACT

Introduction: The association of extrathyroidal extension (ETE) with local lymph node metastases in patients with papillary thyroid cancer assessed by ACR TI-RADS has not been sufficiently studied. This study aimed to evaluate ACR TI-RADS ultrasonographic features of thyroid nodules in patients with papillary thyroid cancer and define their association with histopathology-confirmed local lymph node metastases. **Material and methods:** This study was a retrospective cohort of patients with surgically treated papillary thyroid carcinoma evaluated preoperatively with thyroid ultrasound. The odds ratio (OR) for all ultrasonographic ACR TI-RADS criteria was calculated with binary logistic regression. The sensitivity, specificity, and accuracy of ultrasound and a ROC analysis to define the optimal cutoff point of tumor size for detecting ETE were calculated. A *p*-value < 0.05 was statistically significant. **Results:** Seventy thyroid nodules from 57 patients with papillary thyroid cancer were included. An association with histopathology-confirmed local lymph node metastases was found in 29 (41.4%) thyroid nodules and ETE demonstrated by ultrasound had an increased risk of local lymph node metastasis (OR 6.50, 95% CI 1.38 - 30.68). ETE detection by ultrasound showed a diagnostic accuracy of 85.7%, a sensitivity of 57.1%, and a specificity of 95.2%. ROC analysis showed that a tumor size of 15.5 mm was the optimal cutoff point for ETE-detection by ultrasound and histopathology. **Conclusions:** This study is the first in Mexico to demonstrate that ultrasonographic findings of ETE in thyroid nodules were associated with local lymph node metastases in patients with papillary thyroid cancer.

Keywords: Diagnostic ultrasound. Extrathyroidal extension. ACR TI-RADS. Papillary thyroid cancer. Lymph node metastasis.

INTRODUCTION

Thyroid cancer is one of the most frequent neoplasms in Mexico with 11,227 (5.7%) of 195,499 cancer cases in 2020¹. Papillary thyroid cancer is the most common type. From a radiological standpoint, a thyroid nodule is a lesion within the gland that is distinct from the surrounding parenchyma². The extension of the nodule margin into the thyroid

capsule and beyond is defined as an extrathyroidal extension (ETE) and is highly suggestive of malignancy². ETE is associated with increased morbidity, tumor recurrence, and decreased 5-year survival³⁻⁵. In patients with papillary thyroid cancer, it is an important prognostic indicator with implications for surgery and postoperative adjuvant therapy⁴⁻⁷.

Ultrasonography is the gold standard for evaluating the thyroid gland². The Thyroid Imaging Reporting and

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Data System (TI-RADS) of the American College of Radiology (ACR) provides a standardized method for evaluating thyroid nodules based on ultrasound⁸. Malignancies tend to spread locally, and an ultrasound scan allows assessment of possible metastatic disease². Features associated with malignancy include solid composition, a hypoechoic nodule, a lobulated or spiculated margin,² ETE, microcalcification, absence of a halo, a nodule shape “taller than wide,” and increased vascularity⁹. On the other hand, larger volume¹⁰ and size¹¹, and the location of the nodule in the isthmus^{4,12-14} have been associated with ETE. There are few reports regarding the association between ultrasonographically detected ETE and lymph node metastasis^{6,11,15-17}. This study analyzed ultrasonographic features of thyroid nodules with ACR TI-RADS criteria in patients with papillary thyroid cancer and defined their association with histopathologically confirmed local lymph node metastasis.

MATERIAL AND METHODS

This retrospective cohort study was conducted from January 2015 to November 2019 at the University Center for Diagnostic Imaging, University Hospital “Dr. José Eleuterio González,” in Monterrey Nuevo Leon, Mexico. Adult patients of both sexes with a diagnosis of papillary thyroid carcinoma were included. Patients with imaging studies performed in other centers, unavailable ultrasound images in the Picture Archiving and Communication System (PACS), or studies performed with the non-standard protocol¹⁸ were excluded. Informed consent was not required for this retrospective observational study of information collected during routine clinical care. The institutional ethics and research committees approved the study protocol.

Study development and variables

Patients treated with total thyroidectomy with central and lateral lymph node resection who underwent pre-operative thyroid ultrasound with a histopathologic diagnosis of papillary thyroid carcinoma were specifically selected. Age and sex were recorded. Ultrasonographic features were assessed with ACR TI-RADS using the following criteria: composition, echogenicity, shape, margin, and echogenic foci⁸. Minimal ETE, according to the ACR TI-RADS, was determined sonographically by border abutment, contour bulging, or loss of the echogenic thyroid border⁸.

We do not record extensive ETE (ACR TI-RADS) characterized by frank invasion of adjacent soft tissues and/

or vascular structures, mainly because our interest was the early detection of ultrasonographic findings of ETE and its association with lymph node metastasis. In patients with two thyroid nodules, only one was evaluated for ETE.

A pathologist specializing in thyroid disease (LCF) performed the histopathologic evaluation of the thyroid nodule. Capsular invasion was defined as abnormal cells in the capsule and ETE, an extension of nodule thyroid into adjacent soft tissue and/or vascular structures. The presence or absence of metastasis in local nodes was recorded during neck dissection at the time of surgery. The maximum thyroid nodule size was assessed and recorded on ultrasound and histopathology evaluations.

Ultrasound protocol

Static grayscale and color Doppler thyroid ultrasound images were evaluated from the PAC system of US examinations performed with a standard protocol¹⁸ on Philips Epiq 5qTM Affinity 50gTM equipment (Philips Medical Systems, Amsterdam, The Netherlands) with 12 MHz L12-5 50 mm high-frequency linear transducer and Hitachi HI VISION Preirus equipment (Hitachi Healthcare Americas, Twinsburg, OH, USA) with 13 MHz EUP-L74M 50 mm high-frequency linear transducer. All imaging studies were realized by radiology residents and reviewed by an experienced thyroid radiologist (GOC) with 18 years of experience.

Statistical analysis

Means, standard deviation, minimum, maximum, and medians were calculated for quantitative variables. The chi-square or Fisher's exact test was used for categorical variables. Analysis of thyroid nodule size and its association with ETE was performed with Student's *t*-test and the Mann-Whitney U test. Odds ratios (OR), their corresponding probability, and 95% confidence interval were calculated for the ultrasonographic criteria of the thyroid nodule with binary logistic regression for present or absent local lymph node metastases. The category with an OR = 1.000 corresponds to the reference. Sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, positive predictive value, negative predictive value, and diagnostic accuracy of ultrasound for ETE detection were calculated. The optimal point for thyroid nodule size to detect ETE by ultrasound and histopathologic confirmation were defined by ROC analysis. A *p* - value <0.05 was considered significant. SPSS version 25 (IBM Corp., Armonk, NY, USA) was used.

Table 1. Ultrasonographic findings of 70 thyroid nodules in 57 patients with papillary thyroid carcinoma according to ACR TI-RADS criteria and their risk association (OR) with negative or positive local lymph node metastasis confirmed by histopathology

Thyroid nodules findings	Local lymph node metastasis						OR	95% CI
	Negative (n = 41)		Positive (n = 29)		Total (n = 70)			
	n	%	n	%	n	%		
Composition								
Mixed	5	12.2	2	6.9	7	10.0	1.00	—
Solid	36	87.8	27	93.1	63	90.0	1.88	0.34 a 10.41
Echogenicity								
Hyperechoic or isoechoic	14	34.1	8	27.6	22	31.4	1.00	—
Hypoechoic	22	53.7	14	48.3	36	51.5	1.11	0.37 a 3.34
Very hypoechoic	5	12.2	7	24.1	12	17.1	2.45	0.58 a 10.33
Shape								
Wider than tall	28	68.3	22	75.9	50	71.4	1.00	—
Taller than wide	13	31.7	7	24.1	20	28.6	0.69	0.23 a 2.01
Margin								
Well defined	10	24.4	4	13.9	14	20.0	1.00	—
Poorly defined	22	53.7	5	17.2	27	38.6	0.57	0.13 a 2.58
Lobulated or irregular	4	9.8	7	24.1	11	15.7	4.38	0.81 a 23.69
Extrathyroidal extension	5	12.1	13	44.8	18	25.7	6.50	1.38 a 30.68
Echogenic foci								
Comet tail or none	11	26.8	5	17.2	16	22.8	1.00	—
Macrocalcifications	2	4.9	1	3.4	3	4.3	1.10	0.08 a 15.15
Ring calcification	3	7.3	0	0.0	3	4.3	—	—
Microcalcifications	25	61.0	23	79.3	48	68.6	2.02	0.61 a 6.71

ACR TI-RADS: American College of Radiology Thyroid Imaging Reporting and Data System[®]; OR: Odds Ratio; CI: Confidence interval.

RESULTS

Fifty-seven patients with papillary thyroid cancer were included. There were 50 (88.0%) women and 7 (12.0%) men. Their mean age was 40.8 ± 12.6 and 50.9 ± 12.3 years, respectively. Forty-four (77.2%) patients had a single thyroid nodule, and 13 (22.8 %) two nodules. A total of 70 thyroid nodules were included. The ultrasonographic findings of 70 thyroid nodules and their association with lymph node metastasis based on histopathologic findings are shown in Table 1. Twenty-nine nodules had associated positive local lymph node metastasis with histopathological confirmation. ETE detected on ultrasound had a significantly increased risk of lymph node metastasis histopathologically confirmed (n=13, 44.8%; OR 6.50, 95% CI 1.38 - 30.68). Thirteen cases with ETE by ultrasound and lymph node metastases histopathologically confirmed corresponded to 13 patients. ETE was not observed with ultrasound in 10 (34.5%) of 29 thyroid nodules with histopathologically confirmed lymph node metastases. No significant differences were found in composition, echogenicity, shape and echogenic foci of thyroid nodules and lymph nodes with or without metastasis.

The histopathologic findings of capsular invasion and ETE in 70 thyroid nodules and their relationship to positive or negative local lymph node metastases are shown in Table 2. Eighteen (62.1%) thyroid nodules with positive capsular invasion and ETE by histopathology were significantly associated with positive local lymph node metastasis (OR 7.56, 95% CI 2.18-26.24), whereas 21 (51.2%) of 41 thyroid nodules with negative local lymph node metastases did not have capsular invasion or ETE. Figure 1 is a grayscale ultrasound scan of a 32-year-old female patient with a solid nodule of the left thyroid lobe with capsular disruption by ETE (ACR TI-RADS 5). The histopathologic diagnosis was papillary thyroid carcinoma with lymph node metastasis.

True-positive ultrasound results identifying ETE confirmed by histopathology as the gold standard were found in 16 thyroid nodules, true-negative results were found in 40 nodules. False-positive ETE was seen in two and false-negative in twelve thyroid nodules. Ultrasound accuracy in detecting ETE in thyroid nodules was 85.7%, sensitivity 57.1%, and specificity 95.2%, compared to the gold standard of histopathologic

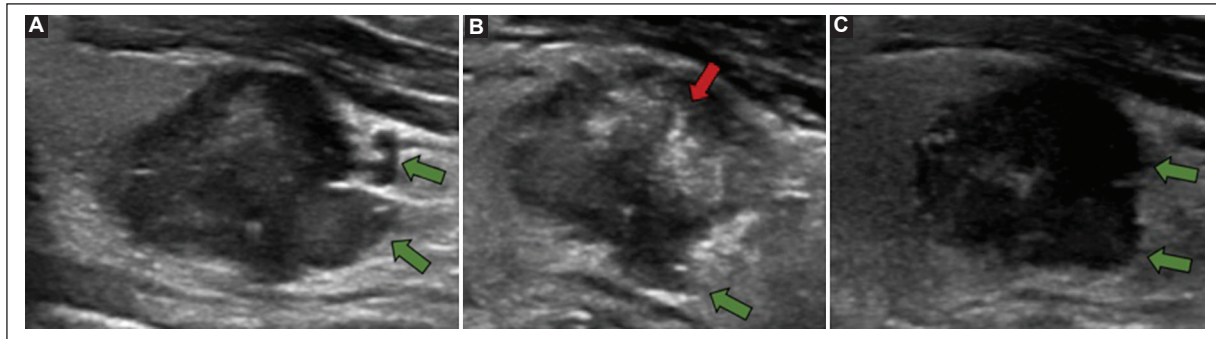


Figure 1. Grayscale ultrasound in a 32-year-old woman: Solid nodule in the left thyroid lobe. **A:** transverse section. **B:** sagittal section. Hypoechoic with internal calcifications (green arrow). **A-C:** disruption of the thyroid capsule by ETE and lobulated margins (red arrows). ACR TI-RADS 5 with histopathological diagnosis of papillary thyroid carcinoma with ETE.

ACR TI-RADS: American College of Radiology Thyroid Imaging Reporting and Data System; ETE: Extrathyroidal Extension.

Table 2. Histopathological findings of capsular invasion and ETE in 70 thyroid nodules and their association with local lymph node metastasis in patients with papillary thyroid cancer

Thyroid nodule findings	Local lymph node metastasis				Total (n = 70)	
	Negative (n = 41)		Positive (n = 29)			
	n	%	n	%	n	%
Positive capsular invasion, positive ETE ^a	10	24.4	18	62.1	28	40.0
Positive capsular invasion, negative ETE	10	24.4	6	20.7	16	22.9
Negative capsular invasion, negative ETE	21	51.2	5	17.2	26	37.1

ETE: Extrathyroidal extension; ^aOR 7.56, 95% CI 2.18-26.24.

Table 3. Diagnostic accuracy of ultrasound for the detection of ETE compared with the reference standard of histopathological study of the nodule in patients with papillary thyroid cancer

Description	Parameter	95% CI
Accuracy	85.7	75.3-92.9
Sensitivity	57.1	37.2-53.5
Specificity	95.2	83.8-99.4
Positive Likelihood Ratio	12	2.99-48.18
Negative Likelihood Ratio	0.45	0.39-0.69
Positive Predictive Value	80.0	49.9-94.1
Negative Predictive Value	86.9	81.2-91.1

ETE: Extrathyroidal extension; CI: Confidence interval.

examination in patients with papillary thyroid carcinoma (Table 3).

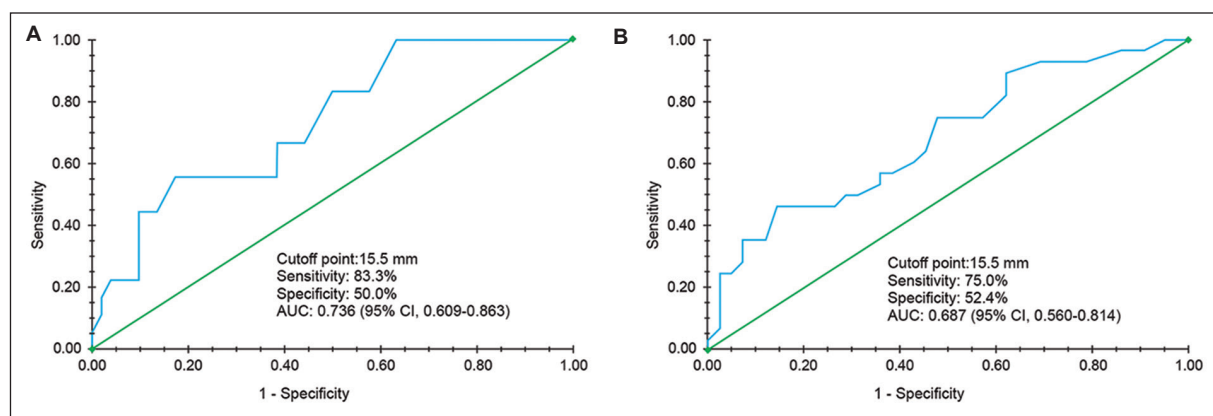
The thyroid nodule size was significantly larger in ultrasound-detected ETE cases (mean 32.11 ± 17.93 mm; $p = 0.002$) and histopathological confirmation (mean 29.00 ± 18.14 mm; $p = 0.006$) (Table 4). In contrast, no

significant association was found between thyroid nodule size and the presence or absence of local lymph node metastasis (24.21 ± 17.52 mm vs. 20.80 ± 14.58 mm, respectively; $p = 0.380$). In the ROC analysis (Figure 2A), a nodule size of 15.5 mm, measured in its maximum diameter, was defined as the optimal cutoff point for the identification of ETE by ultrasound with a sensitivity of 83.3%, a specificity of 50.0%, and an area under the curve of 0.736 (95% CI 0.609 - 0.863; $p = 0.003$). Similarly (Figure 2B), a nodule size of 15.5 mm was the optimal cutoff point with a sensitivity of 75%, a specificity of 52.4%, and an area under the curve of 0.687 (95% CI 0.560 - 0.814; $p = 0.008$) for the detection of positive histopathological extrathyroidal invasion.

Table 5 shows the comparison of ultrasonographic and histopathologic findings of 70 nodules from patients with papillary thyroid carcinoma and their relationship to ETE, nodule size, and ACR TI-RADS criteria. Forty-two nodules were ACR TI-RADS 5, and ETE was detected by ultrasound in 18 ($p = 0.007$), while histopathology showed extrathyroidal invasion in all 23 nodules ($p = 0.015$). None of the ultrasound-positive ETE

Table 4. Thyroid nodule size in patients with papillary thyroid carcinoma and its association to ETE on ultrasound and histopathological confirmation

Description	Extrathyroidal extension, ultrasonographic findings ^a		Extrathyroidal extension, histopathological findings ^b	
	Absent (n = 52)	Present (n = 18)	Absent (n = 42)	Present (n = 28)
Thyroid nodule size, mean, mm \pm SD	18.79 \pm 13.62	32.11 \pm 17.93	17.69 \pm 12.36	29.00 \pm 18.14
Thyroid nodule size, median, mm (range)	15.5 (2-56)	33 (11-72)	14.5 (2-56)	23.5 (4-72)

ETE: Extrathyroidal extension; ^ap = 0.002; ^bp = 0.006.**Figure 2. A:** in the ROC analysis, a nodule size of 15.5 mm was defined as the optimal cutoff point for identification of ETE present by ultrasound. **B:** a nodule size of 15.5 mm was the optimal cutoff point for detection of positive extrathyroidal invasion by histopathology.

ETE: Extrathyroidal Extension; ROC: Receiver operating characteristic.

nodules were smaller than 1 cm, while histopathology showed only one nodule, which had extrathyroidal invasion, smaller than 1 cm. The probability of extrathyroidal invasion was high in ACR TI-RADS 5 with nodules larger than 1 cm and very low in smaller nodules. Twenty-six nodules were ACR TI-RADS 4, and none had ETE on ultrasound, regardless of size. In contrast, histopathology showed extrathyroidal invasion in five nodules: three nodules were smaller than 1.5 cm, and two were larger than 1.5 cm. In two nodules ACR TI-RADS 3, no ETE was observed either on ultrasound or histopathology.

Figure 3 is a grayscale ultrasound scan of a 39-year-old woman with a solid, hypoechoic nodule with irregular margins, calcifications, and ETE (ACR TI-RADS 5). The histopathologic diagnosis was papillary thyroid carcinoma. Figure 4 is a grayscale ultrasound scan of a 59-year-old male patient with a solid, hypoechoic nodule with irregular margins and evidence of capsular disruption by ETE (ACR TI-RADS 5). The diagnosis was papillary thyroid carcinoma.

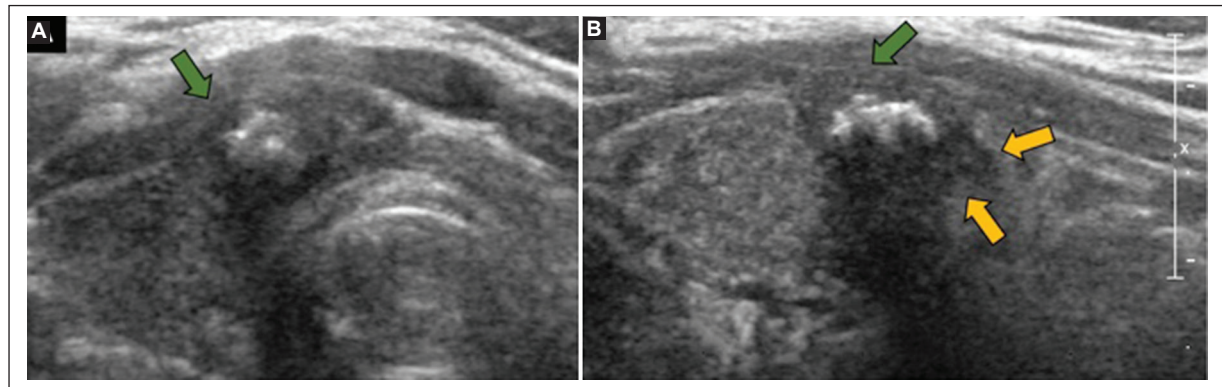
DISCUSSION

This study is the first in Mexico to demonstrate that ETE detected on ultrasound was associated with an increased risk of local lymph node metastasis with histopathological confirmation in patients with papillary thyroid carcinoma. The finding of ETE on preoperative ultrasound and the prediction of local lymph node metastasis are critical for planning surgical treatment.

Papillary thyroid carcinoma usually has an excellent prognosis although, it has been reported that approximately 30% of patients have metastases to local nodes and it is associated with increased tumor recurrence¹⁰. ETE on ultrasound has a 6.5-fold higher risk of lymph node metastasis than thyroid nodules with well-defined margins (absent ETE)^{6,17}. We used the ACR TI-RADS criteria of minimal ETE to define an association with local lymph node metastases, more than the extensive ETE finding. In a report of patients with papillary thyroid carcinoma, metastatic lymph nodes were more frequent in 62 (38.0%) of 163 patients with ETE compared

Table 5. Ultrasonographic and histopathologic findings in 70 nodules of patients with papillary thyroid carcinoma and their association with ETE according to ACR TI-RADS classification

ACR TI-RADS	Thyroid nodule size	Ultrasonographic findings, extrathyroidal extension		Total (n = 70)	p-value	Histopathological findings, extrathyroidal invasion		Total (n = 70)	p-value
		Absent n = 52 (%)	Present n = 18 (%)			Absent n = 42 (%)	Present n = 28 (%)		
TI-RADS 5	≤ 1 cm	8 (33.0)	0	42	0.007	7 (37.0)	1 (4.0)	42	0.015
	> 1 cm	16 (67.0)	18 (100)			12 (63.0)	22 (96.0)		
	Total	24	18			19	23		
TI-RADS 4	≤ 1.5 cm	14 (54.0)	0	26	1.000	11 (52.0)	3 (60.0)	26	1.000
	> 1.5 cm	12 (46.0)	0			10 (48.0)	2 (40.0)		
	Total	26	0			21	5		
TI-RADS 3	≤ 2.5 cm	1 (50.0)	0	2		1 (50.0)	0	2	
	> 2.5 cm	1 (50.0)	0			1 (50.0)	0		
	Total	2	0			2	0		

ETE: Extrathyroidal extension; ACR TI-RADS: American College of Radiology Thyroid Imaging Reporting and Data⁸.**Figure 3.** Grayscale ultrasound of a 38-year-old woman. **A-B:** a solid thyroid nodule; hypoechoic, irregular margins in the isthmus (yellow arrows) with calcifications, anterior bulging, and evidence of capsular disruption (green arrow) contacting the posterior margin of the muscle by ETE (ACR TI-RADS 5). Histopathologic diagnosis of papillary thyroid carcinoma.

ETE: Extrathyroidal Extension; ACR TI-RADS: American College of Radiology Thyroid Imaging Reporting and Data System.

with 50 (26.2%) of 191 patients without ETE ($p < 0.020$)⁶. Papaioannou et al.¹⁶ reported a retrospective study that included 102 patients who underwent thyroidectomy for papillary thyroid microcarcinoma. Preoperative thyroid and neck ultrasound was performed in all patients and compared with the histopathology report. Multifocality ($p < 0.03$), tumor size ($p < 0.05$), and ETE ($p \leq 0.001$) were significantly associated with lymph node metastasis. Our study included 70 thyroid nodules from 57 patients with papillary thyroid carcinoma. In these, an increased risk of positive local lymph node metastasis was found in 13 (44.8%) of 29 thyroid nodules with ultrasound-detected ETE with confirmation by

histopathology (OR 6.50). ETE was the only ultrasonographic feature of the thyroid nodule associated with local lymph node metastases in patients with papillary thyroid carcinoma.

The diagnostic accuracy of preoperative thyroid ultrasound in detecting ETE in patients with papillary cancer has not been sufficiently studied. Papaioannou et al.¹⁶ reported a sensitivity of 53.6% and a specificity of 100% in nodules with suspected ETE in a retrospective study using preoperative ultrasound. Another study¹⁹ reported that capsular disruption had a diagnostic accuracy of 81.3% for ETE detection with a sensitivity of 61.6% and a specificity of 87.1%. Preoperative ultrasound findings

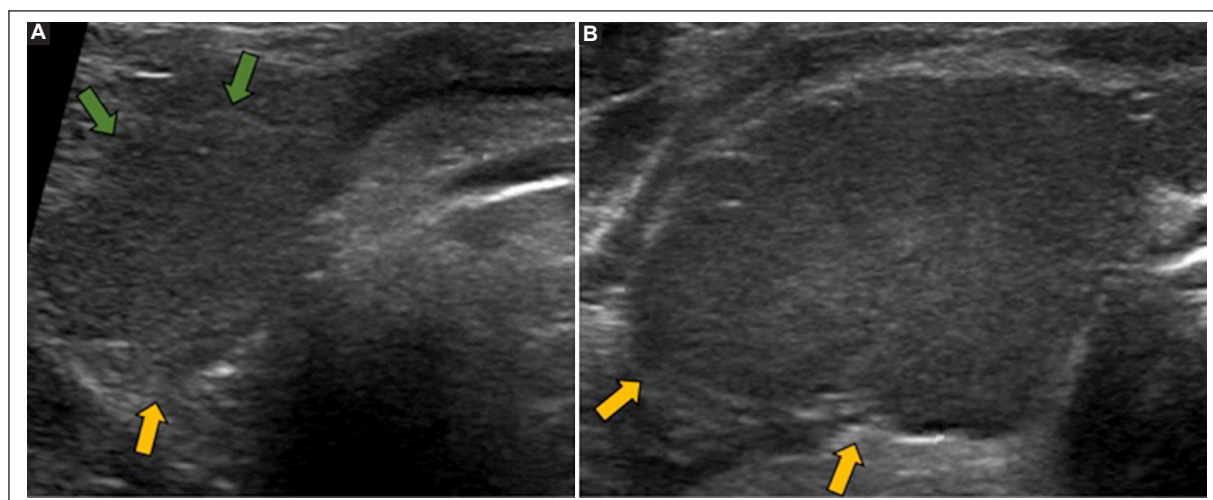


Figure 4. Grayscale ultrasound in a 59-year-old man. **A-B:** with a solid, hypoechoic thyroid nodule in the right lobe with an irregular posterior margin (yellow arrows) and capsular disruption (ETE) (green arrows); ACR TI-RADS 5 with a histopathologic diagnosis of papillary thyroid carcinoma with ETE.

ACR TI-RADS: American College of Radiology Thyroid Imaging Reporting and Data System; ETE: Extrathyroidal Extension.

were confirmed in a histopathologic report¹⁹. In our study, we found comparable results. The diagnostic accuracy of ultrasound for detecting ETE was 85.7%, sensitivity 57.1%, and specificity 95.2%. Ultrasonography has a high specificity, allowing ETE to be excluded with greater accuracy. On the other hand, the absence of ETE on ultrasound should be interpreted with caution because the reported sensitivity was low.

It has been reported that thyroid nodule size ≥ 10 mm is significantly associated with an increased risk of ETE^{6,20}. Rim et al.⁵ compared the accuracy of different tumor sizes, 9 mm, 10 mm, and 11 mm, in patients with papillary thyroid carcinoma. A ROC analysis of tumor size to distinguish present and absent ETE showed a sensitivity of 51.9%, 47.3%, and 42.7% and a specificity of 65.6%, 70.8%, and 76.4%, respectively. In our study, a ROC curve analysis showed an optimal cutoff point of 15.5 mm for identifying ETE by ultrasound and histopathology with a sensitivity of 83.3% and a specificity of 50.0% by ultrasound. In contrast, sensitivity by histopathology was 75.0% and specificity 52.4%. Thus, in our study, the larger nodule size (15.5 mm) was a cutoff point for defining ETE, increasing sensitivity compared with smaller size but reduced specificity with an increase of false-positive ETE results. We consider that with the current evidence, it is not possible to recommend an optimal cutoff point for tumor size to define ETE in patients with papillary thyroid carcinoma.

A large nodule is significantly associated with the high aggressiveness of thyroid carcinoma²⁰. Our study of the Mexican population found a larger mean tumor size of

thyroid nodules compared to other reports in non-Mexican populations^{5,11,20}. The mean nodule size was 32.11 mm with ETE on ultrasound and 18.79 mm without ($p = 0.002$). The mean nodule size on histopathology was 29.0 mm in patients with ETE and 17.69 mm without ETE. Our results regarding tumor size are comparable to a previous study in a Mexican population that included 278 patients with thyroid cancer (267 cases corresponded to papillary and 11 to follicular cancer) from a national cancer referral center that treats patients in our country²¹. The authors reported 154 (55.4%) cases with tumor size equal to or larger than 20 mm associated with an increased risk of ETE (relative risk [RR] 5.5). The larger size of the thyroid nodules in patients with thyroid cancer in the Mexican population could be related to the delay in seeking medical attention by patients and the lack of early detection of thyroid cancer.

The strengths in our study were related to the confirmed histopathological diagnosis of papillary thyroid cancer in all included patients. The presence of ETE and positive local lymph node metastasis were confirmed by histopathology. Ultrasonographic evaluation of all thyroid nodules was performed using ACR TI-RADS. This classification was shown reproducible and with good to excellent interobserver and intraobserver agreement²². On the other hand, the weaknesses of our study were related to its retrospective design, small sample size, and ultrasonographic evaluation of static images, which could have limited the accuracy of detecting ETE. In addition, tumor volume, which has been proposed as a

significant independent predictor of local lymph node metastasis in the neck¹⁰, was not recorded.

CONCLUSION

In our study, ultrasonographic findings of ETE were associated with an increased risk of lymph node metastasis in patients with papillary thyroid cancer. The radiologist's role is critical in the detection of ETE on preoperative ultrasonography of thyroid nodules suspicious for malignancy. We suggest that finding ETE on ultrasound should be highlighted in the radiology report so that clinicians can use this information in planning surgical treatment. The detection of larger thyroid nodules in Mexican patients compared to other populations reported in the literature is relevant. It is necessary to implement public policies with efficient strategies for detecting malignant thyroid nodules, allowing early diagnosis and timely treatment.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

Ethical Disclosures

Protection of Individuals. This study was conducted in compliance with the Declaration of Helsinki (1964) and its subsequent amendments.

Confidentiality of Data. The authors declare that they followed their center's protocol for sharing patient data.

Right to privacy and informed consent. Informed consent was not required for this retrospective observational study of information collected during routine clinical care.

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