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Should We Use Magnetic Resonance Imaging for Thyroid Nodules with Indeterminate Cytology?

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Abstract

Background: Although most thyroid nodules with indeterminate cytology (Bethesda III/IV) are benign, they represent a management dilemma possibly leading to unnecessary surgery. This study aims to evaluate the role of magnetic resonance imaging in the risk stratification of thyroid nodules with indeterminate cytology.

Methods: Patients scheduled for thyroidectomy for thyroid nodules with indeterminate cytology were prospectively enrolled. Diffusion-weighted images and T2-weighted images were obtained. Apparent diffusion coefficient values and T2-weighted signal intensities of thyroid nodules, normal thyroid parenchyma, muscle tissue, and spinal cord were recorded.

Results: In the final analysis, 17 nodules (5 malignant and 12 benign) were included. Apparent diffusion coefficient values, nodule-to-spinal cord apparent diffusion coefficient ratio, and nodule-to-muscle T2 signal intensity ratio were significantly lower in malignant nodules (P = .019, P = .019 and P = .037, respectively). Using a threshold of 1.570×10^{-3} mm^2/s, nodule apparent diffusion coefficient value had a sensitivity of 100%, specificity of 75%, positive predictive value of 62.5%, negative predictive value of 100%, and an accuracy of 82.4%. At a threshold of 3.831, nodule-to-muscle T2-weighted signal intensity ratio had a sensitivity of 100%, specificity of 50%, positive predictive value of 45.5%, and negative predictive value of 100%. If falling under both of these threshold values was required for the diagnosis of malignancy, then the sensitivity and negative predictive value would remain unchanged at 100%, but there would be an increase in specificity, positive predictive value, and accuracy to 83.3%, 71.4%, and 88.2%, respectively. Furthermore, 83.3% (10/12) of benign nodules could have been spared from unnecessary surgery.

Conclusion: Magnetic resonance imaging is a very sensitive tool for discriminating benign from malignant thyroid nodules with indeterminate cytology and it may spare patients from unnecessary surgery.

Keywords: Atypia of undetermined significance, diffusion-weighted imaging, follicular lesion of undetermined significance, radiology, thyroid cancer

Introduction

The term thyroid nodule with indeterminate cytology refers to thyroid nodules with fine-needle aspiration (FNA) biopsy result of a follicular lesion of undetermined significance or atypia of undetermined significance (FLUS/AUS, Bethesda category III) or follicular neoplasm/suspicious for follicular neoplasm (FN/SFN, Bethesda category IV). The risk of malignancy of these indeterminate nodules ranges between 10% and 40%.[1] Current guidelines offer the options of repeat FNA, molecular testing, surveillance, and/or diagnostic surgery for thyroid nodules with indeterminate cytology.[2-4] Among these management approaches, only molecular testing aims to further stratify the risk of malignancy. To date, there exists no role for magnetic resonance imaging (MRI) in the risk stratification of thyroid nodules with indeterminate cytology. This study aims to explore the role of MRI in the risk stratification of indeterminate thyroid nodules.

Materials and Methods

After institutional review board approval, patients scheduled to undergo surgery for a thyroid nodule with indeterminate cytology (Bethesda categories III and IV) were recruited in the study.

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The surgical indications were nodule size ≥10 mm and indeterminate cytology on repeat FNA biopsy. None of the patients had compression symptoms (e.g., dysphagia, dyspnea, or hoarseness) or cosmetic complaints related to thyroid nodules, which could qualify as independent indications for resection. All patients signed an informed consent form.

The MRIs were obtained using a 3T scanner (Ingenia; Philips Healthcare, Best, Netherlands). After placing a flex coil on the anterior aspect of the neck, axial turbo-spin echo T2-weighted images (repetition time (TR)/echo time (TE): 2539/90 ms; number of signal averages (NSA): 1; voxel size 0.9 × 0.85 × 3 mm; interslice gap: 0.3 mm; scan time: 56 seconds) were obtained. In addition, respiratory triggered single-shot echo-planar diffusion-weighted images were obtained (TR/TE: 2800/76 ms; b-values: 0 and 1000 s/mm^2; NSA: 2 for b-0 and 6 for b-1000 images; voxel size 1.52 × 1.52 × 3.0 mm; interslice gap: 0.0 mm; scan time: 6 minutes and 36 seconds). In order to reduce the scanning time, the field of view only included sections through the thyroid gland rather than the routine protocol which includes the whole neck. The spinal cord was included in the field of view of all sequences, and the phase direction was set to anterior–posterior. Respiratory triggering was used in diffusion-weighted images (DWI) by means of a pneumatic respiratory belt detecting chest expansion. Apparent diffusion coefficient (ADC) maps were automatically generated.

Two radiologists, a fellow and a neuroradiologist with 8 years of experience in neuroradiology who were blinded to the final pathologic diagnosis, did the image analysis. Both readers reviewed the biopsy reports before evaluating the MRI images but they were blinded to each other's measurements. Mean ADC measurements of the nodules, normal thyroid tissue, and spinal cord were recorded, and ADC ratios of the nodule-to-spinal cord and nodule-to-normal thyroid tissue were calculated. On T2-weighted images, signal intensities of the nodules, normal thyroid tissue, and the sternocleidomastoid muscle were recorded, and nodule-to-normal thyroid tissue and nodule-to-muscle signal intensity ratios were calculated. Regions of interest (ROI) were placed on the solid portion of the nodule if it was cystic. No spinal cord pathology was noted on T2-weighted images in any of the patients included in the study, and the spinal cord ROIs included both the gray and white matter.

The final histopathologic diagnosis was made on the evaluation of the surgical specimen.

The data were analyzed using IBM Statistical Package for the Social Sciences using SPSS v26.0 software (IBM Corp.; Armonk, NY, USA). Mann–Whitney *U* test was used to compare the measurements of benign and malignant nodules. The intraclass correlation coefficient (ICC) was used to evaluate interobserver variability in measurements of the 2 radiologists. Receiver operator characteristic (ROC) curves were produced, and threshold values were selected to ensure maximum achievable sensitivity. Accuracy, specificity, positive, and negative predictive values were reported for these threshold values. The significance level was established as $\alpha = 0.05$.

Main Points

- Results of thyroid biopsy are often indeterminate, which constitute a dilemma for managing physicians.
- Diffusion-weighted images and T2-weighted sequences are highly sensitive for distinguishing benign from malignant thyroid nodules with indeterminate cytology.
- Malignant nodules show low signal on T2-weighted images and low signal on corresponding apparent diffusion coefficient maps.

Results

Between September 2019 and March 2020, 22 consecutive patients with 23 nodules scheduled to undergo surgery for thyroid nodule with indeterminate cytology (Bethesda categories III and IV) were included in the study. All patients signed an informed consent form. In total, 27.7% (6/22) were male and the median age of the cohort was 44 years (range, 24-74 years).

Magnetic resonance images were obtained before surgery. The median duration from scanning to surgery was 2 days (range, 0-48 days). The median time from the last biopsy to scanning was 124 days (range, 63-414 days).

Five patients with 6 nodules were excluded from the study. Two were excluded because the nodule biopsied could not be accurately localized on MRI due to multinodular goiter, and the remaining 3 patients were excluded because no nodule was identifiable on MRI. On surgical pathology, none of these patients had a malignant nodule. Hürthle cell adenoma was found in 1 nodule and 5 had adenomatous hyperplasia.

Among the 17 patients included in the final analysis, 10 (58.8%) had Bethesda category III cytology and 7 (41.2%) had category IV cytology. On surgical pathology, 5 (29.4%) had malignant nodules; 3 of them had papillary thyroid carcinoma, 1 had an oncocytic variant of papillary thyroid carcinoma, and 1 had a follicular variant of papillary thyroid carcinoma. Among the 12 benign nodules, 6 had adenomatous hyperplasia, 3 had Hürthle cell adenoma, 2 had microfollicular adenoma, and 1 had follicular adenoma. The median size of the malignant nodules was 17 mm (range, 13-20 mm), and the median size of the benign nodules was 16.5 mm (range, 10-50 mm).

The median ADC values and signal intensity ratios of the thyroid nodules for each of the 2 readers are outlined in Table 1. The ADC value of malignant nodules was significantly lower than that of benign nodules ($P = .019$ and $P = .037$ for both readers). The nodule-to-spinal cord ADC ratio was significantly lower in malignant nodules compared to benign nodules ($P = .019$ and $P = .027$ for both readers) (Figures 1 and 2). The signal intensity ratio of nodule-to-muscle on T2-weighted images was significantly lower for reader 1 ($P = .037$), but it did not reach statistical significance for reader 2 ($P = .082$). Excellent interreader agreement was found between the 2 radiologists with an ICC of 0.973 for nodule ADC values, 0.964 for nodule-to-muscle T2 signal intensity ratios, and 0.931 for nodule-to-spinal cord ADC ratios.

There was no significant difference in the nodule-to-normal thyroid tissue T2-weighted signal intensity ratios and the nodule-to-normal thyroid tissue ADC ratios between benign and malignant nodules.

Threshold values for the nodule ADC values, nodule-to-spinal cord ADC ratios, and nodule-to-muscle T2-weighted signal intensity ratios were selected at the value with maximum achievable sensitivity. Specificity, positive predictive

Table 1. Median Values (Min-Max) of MRI Parameters for Both Readers and ICC

	Reader 1			Reader 2			ICC (95% CI)
	Benign (n = 12)	**Malignant (n = 5)**	*P*	**Benign (n = 12)**	**Malignant (n = 5)**	*P*	
Nodule ADC ($\times 10^{-3}$ mm²/s)	1.84 (0.94-2.35)	1.17 (0.86-1.41)	**.019**	1.81 (0.93-2.60)	1.18 (0.81-1.47)	**.037**	0.973 (0.926-0.990)
Normal thyroid ADC ($\times 10^{-3}$ mm²/s)	1.37 (0.86-1.58)	1.05 (0.89-1.46)	.082	1.26 (0.91-1.54)	1.09 (0.90-1.38)	.195	0.829 (0.590-0.935)
Spinal cord ADC ($\times 10^{-3}$ mm²/s)	1.14 (0.83-1.31)	1.25 (0.82-1.32)	.234	1.03 (0.80-1.56)	1.18 (0.81-1.41)	.442	0.833 (0.598-0.749)
Nodule-to-spinal cord ADC ratio	1.23 (0.83-2.44)	0.80 (0.70-1.43)	**.019**	1.27 (0.77-2.62)	0.94 (0.69-1.45)	**.027**	0.931 (0.820-0.974)
Nodule-to-thyroid ADC ratio	1.29 (0.65-2.50)	1.01 (0.81-1.27)	.130	1.39 (0.89-2.55)	0.90 (0.86-1.37)	.104	0.952 (0.873-0.982)
Nodule-to-thyroid T2-weighted signal intensity ratio	1.91 (1.01-2.52)	1.33 (0.36-1.47)	.082	1.92 (1.01-2.66)	1.16 (0.48-1.99)	.104	0.903 (0.752-0.964)
Nodule-to-muscle T2-weighted signal intensity ratio	4.01 (1.46-6.87)	2.29 (1.00-3.44)	**.037**	3.83 (1.36-7.85)	2.52 (1.14-3.56)	.082	0.964 (0.903-0.987)

ADC, apparent diffusion coefficient; ICC, intraclass correlation coefficient.

value, negative predictive value, and accuracy were calculated at these threshold values for both readers as summarized in Table 2. Nodule ADC values of 1.549×10^{-3} mm²/s and 1.570×10^{-3} mm²/s, for readers 1 and 2 respectively, were found to have the best accuracy of 82.4% with a specificity of 62.5%, positive predictive value of 62.5%, and negative predictive value of 100%. Using these threshold values, 75% (9/12) of benign nodules could have been spared from unnecessary surgery.

All malignant nodules were below both the nodule ADC threshold value and nodule-to-muscle T2-weighted signal intensity ratio threshold value. Among the 12 benign nodules, only 2 (16.7%) were below both of these 2 thresholds. If falling below both of these 2 threshold values was required for the diagnosis of malignancy, then the sensitivity and negative predictive value would remain unchanged at 100%, but there would be an increase in specificity, positive predictive value, and accuracy

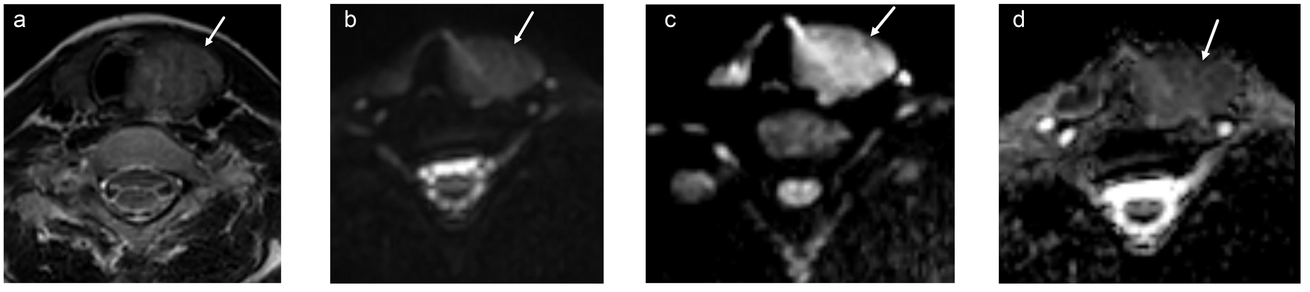

Figure 1. A 26-year-old female with a left thyroid nodule. On FNA biopsy, a follicular lesion of undetermined significance (Bethesda category IV) was reported. (A) T2-weighted image shows a nodule with intermediate signal intensity in the left lobe of the thyroid gland (arrow). The nodule-to-muscle T2-weighted signal intensity ratio is 3.03. (B,C) DWI images at b-0 and b-1000. (D) ADC map showing the thyroid nodule with an ADC value of 1.218 and nodule-to-spinal cord ADC ratio 0.924. The final surgical pathology was papillary thyroid carcinoma. FNA, fine-needle aspiration; ADC, apparent diffusion coefficient; DWI, diffusion-weighted images.

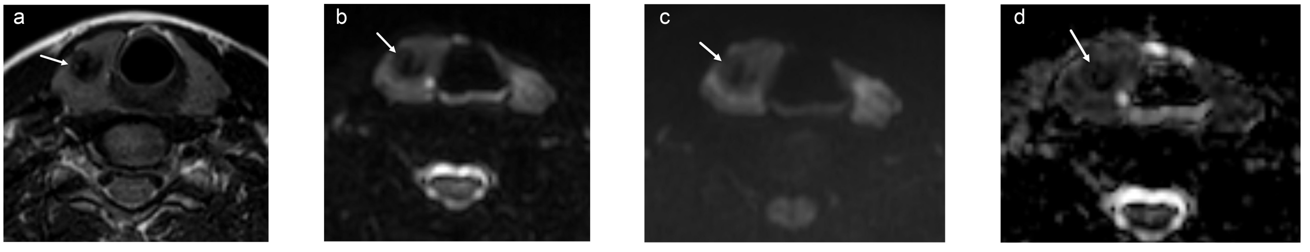

Figure 2. A 24-year-old female with a right thyroid nodule. On FNA biopsy, atypia of undetermined significance (Bethesda category III) was reported. (A) T2-weighted image shows a hypointense solitary nodule in the right lobe of the thyroid gland (arrow). The nodule-to-muscle T2-weighted signal intensity ratio is 0.36. (B–C) DWI images at b-0 and b-1000. (D) ADC map showing the thyroid nodule with an ADC value of 0.856 and nodule-to-spinal cord ADC ratio 0.696. The final surgical diagnosis was papillary thyroid carcinoma. FNA, fine-needle aspiration; ADC, apparent diffusion coefficient; DWI, diffusion-weighted images.

Table 2. Threshold Values and Corresponding Sensitivity, Specificity, Accuracy, Negative, and Positive Predictive Values of Diagnostic Parameters. The Prevalence of Malignancy Was 29.4% (5/17).

		Cutoff (Threshold) Value	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Accuracy (%)	AUC	Standard Error	*P*
Reader 1	Nodule ADC ($\times 10^{-3}$ mm²/s)	1.549	100	75	62.5	100	82.4	0.867	0.089	.020
	Nodule-to-spinal cord ADC ratio	1.436	100	66.7	55.6	100	76.5	0.867	0.090	.020
	Nodule-to-muscle T2 ratio	3.495	100	66.7	55.6	100	76.5	0.833	0.101	.035
Reader 2	Nodule ADC ($\times 10^{-3}$ mm²/s)	1.570	100	75	62.5	100	82.4	0.833	0.100	.035
	Nodule-to-spinal cord ADC ratio	1.542	100	58.3	50	100	70.6	0.850	0.097	.027
	Nodule-to-muscle T2 ratio	3.831	100	50	45.5	100	64.7	0.783	0.116	.073

ADC, apparent diffusion coefficient; AUC, area under the ROC curve; ROC, receiver operator characteristics.

Table 3. Outcomes of Molecular Tests in Discrimination of Malignant from Benign Thyroid Nodules

Test Name	Study	Bethesda Category	Number of Nodules	Prevalence of Malignancy (%)	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	AUC
Afirma GSC	Patel et al. 2018	III and IV	190	23.7	91.1	68.3	47.1	96.1	
Afirma GSC	Vuong et al. 2020	III and IV	807	18.1	93.6	25.1	41.6	86.1	
ThyroSeq v3 GC	Steward et al. 2018	III and IV	247	28	94	82	66	97	
ThyroSeq v3 GC	Nikiforova et al. 2018	III, IV, and V	115	52.6	98	81.8			0.931
ThyroSeq v3 GC	Desai et al. 2020	III and IV	127	55.1	92.9	45.6	53.7	83.9	
ThyGenX Oncogene Panel/ThyraMIR miRNA Classifier	Labourier et al. 2015	III and IV	109	32	89	85	74	94	
microRNA-based assay	Yanai et al. 2016	III and IV	150	20.1	74	74	43	92	

AUC, area under the ROC curve; ROC, receiver operator characteristics; GSC, genomic sequence classifier; GC, Genomic Classifier.

up to 83.3%, 71.4%, and 88.2%, respectively. In addition, 83.3% (10/12) of benign nodules could have been spared from unnecessary surgical excision.

Discussion

It is estimated that about 600 000 thyroid FNA biopsies are performed every year in the United States,[5] and this figure has been increasing annually by approximately 22%.[6] Although thyroid FNA biopsy can classify most nodules as benign or malignant, about 20% will be considered to have indeterminate cytology (Bethesda categories III and IV)[7] which is associated with a risk of malignancy ranging between 10% and 40%.[1] Current guidelines offer several management options for these patients which include repeat FNA, molecular testing, surveillance, and/or diagnostic surgery.[2-4] Surgical excision is eventually performed in about 39% and 70% of patients with Bethesda categories III and IV nodules, respectively.[7] Despite the low risk of serious complications, the cost of thyroid surgery may amount up to $11 265 for initial total thyroidectomy and $6549 for hemithyroidectomy. In addition, there is a potential lifelong cost for treatment of hypothyroidism after surgery which may reach up to $860 per patient per year.[8] Therefore, there exists a need for tests to further stratify the malignancy risk of thyroid nodules with indeterminate cytology.

Over the last 2 decades, several panels of genetic mutations and gene expression were marketed and they were recommended by various guidelines for the management of thyroid nodules with indeterminate cytology.[2-4] Initial data for the currently commercially available panels of molecular testing reported strikingly high sensitivity and negative predictive values, as shown in Table 3.[9-12] This allowed ruling out malignancy and avoiding unnecessary diagnostic surgery in up to 85% of the cases.[10] However, subsequent meta-analysis and validation studies reported less favorable outcomes.[8,13-15] A possible disadvantage of these molecular tests is their high cost which is estimated at more than $5000 per nodule.[16] But it should be acknowledged that tissue samples for these molecular tests can be easily shipped to laboratories where experts are available for interpretation, whereas MRI parameters need to be standardized across different scanning systems and vendors.

On conventional MRI, T1-weighted signal intensity does not help differentiating benign from malignant thyroid nodules, but malignant nodules were shown to have a significantly lower signal intensity on T2-weighted images compared to benign nodules.[17] Noda et al[17] reported that a threshold value of 1.91 the nodule-to-muscle signal intensity ratio on T2-weighted imaging had a sensitivity and specificity of 93% in differentiating benign from malignant thyroid nodules.

Several studies[17-26] and meta-analyses[27,28] focused on the role of diffusion-weighted MRI in the discrimination of benign from malignant thyroid nodules. Although different DWI parameters, diagnostic reference (FNA biopsy vs surgical histopathology), inclusion and exclusion criteria were used, all studies reported that malignant thyroid nodules had significantly lower ADC values compared to benign nodules as summarized in Table 4. However, DWI was unable to differentiate between different types of malignant thyroid tumors.[18,19] Hemorrhage, identified by its high signal on pre-contrast T1-weighted images, was recognized as one cause for low ADC value in benign nodules which could lead to false-positive results.[18,22] However, it is not known whether all nodules demonstrating high signal on pre-contrast T1-weighted images may be safely considered benign nodules.

To our knowledge, only a single study reported the FNA cytology results of resected thyroid nodules and described their MRI features. In this study, significantly lower ADC values were found in nodules with indeterminate cytology that were proven to be malignant on resection (mean ADC value was 1.27×10^{-3} mm^2/s for malignant nodules and 1.95×10^{-3} mm^2/s for benign nodules). However, no threshold ADC value, sensitivity, or specificity were calculated for this subset of patients.[18]

The current study aimed to evaluate the ability of DWI and T2-weighted MRI in risk stratification of thyroid nodules with indeterminate cytology which constitutes a management dilemma for the clinician and may eventually lead to unnecessary surgery. Like previous studies, the current study demonstrated that malignant nodules have significantly lower ADC and nodule-to-muscle T2-weighted signal intensity ratios. Since the malignancy ratio of thyroid nodules with indeterminate cytology may reach up to 40%,[1] an optimal diagnostic test must have high sensitivity and negative predictive value for the detection of malignancy. This approach allows the clinician to select patients who may safely undergo active surveillance rather than surgery. The high sensitivity of diagnostic tests usually comes at the cost of lower specificity, which translates into patients with benign nodules being misclassified as malignant. On ROC analysis, the authors chose threshold values that sacrifice specificity for optimal sensitivity. Although the specificity of the thresholds reported in the current study was lower than those reported in previous MRI studies (Table 4), using a combination of 2 threshold values (the nodule-to-muscle T2-weighted signal intensity ratio and the ADC threshold values) to classify the nodule as malignant resulted in a specificity of 83.3% which is comparable to that of the currently available molecular tests (Table 3) and other MRI studies. Using this approach could have saved 10 of 12 patients with benign nodules from unnecessary surgery. To our knowledge, previous studies did not attempt this 2-test approach on MRI.

ADC values are known to demonstrate significant differences between various MRI systems and sequences.[29] The spinal cord normally demonstrates low signal on ADC maps and it is rarely involved by other diseases. Therefore, the spinal cord was found to be an appropriate tissue with reproducible and less variable ADC values which can be used for internal reference in head and neck imaging.[29] Tumor-to-spinal cord ADC ratios were reported for other tumors.[30,31] These ratios may be more useful than ADC values when comparing results from studies conducted on different MRI scanners. For these reasons, the authors calculated the thyroid nodule-to-spinal cord ADC ratio which also was significantly lower in malignant tumors compared with benign tumors. To our knowledge, no other studies reported nodule-to-spinal cord ADC ratio for thyroid nodules.

Multishot-echoplanar imaging (MS-EPI) DWI sequences and parallel imaging techniques are less vulnerable to blurring and suitability artifacts compared to single-shot echo-planar DWI sequences.[32] Therefore, these sequences could provide superior image quality of the thyroid gland which is especially vulnerable to these artifacts due to its proximity to air within the

Table 4. Review of Reported Outcomes of Diffusion-Weighted Imaging in Discrimination of Malignant from Benign Thyroid Nodules

Study	Study Design	Number of Nodules	Patients Excluded Due to Image Quality, %	Reference	Prevalence of malignancy (%)	Nodule Size (cm)	Field Strength (T)	b-Values (s/mm^2)	ADC Cutoff Value ($\times10^{-3}$ mm^2/s)	Sensitivity (%)	Specificity (%)	Accuracy (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	AUC
Noda Y et al. 2015	Retrospective	42	6.7 (3/45)	Both	33.3	0.6-9.5	1.5	0 and 1000	1.12	93	93				0.929
Nakahira et al. 2012	Retrospective	42	4.4 (2/45)	Surgery	45.2	1.0-7.2	1.5	0 and 1000	1.60	94.7	82.6	88.1	81.8	95	
Abdel Razek et al. 2008	Prospective	63	6 (4/67)	Surgery	11.1	0.8-4.2	1.5	0, 250, and 500	0.98	97.5	91.7	98.9			0.970
Bozgeyik et al. 2009	Prospective	93	11.6 (10/86)	FNA	5.4	1.0-4.3	1.5	100	2.05	88.5	100				0.997
								200	0.65	100	80.0				1.00
								300	0.62	90.2	100				0.884
El-Hariri et al. 2012	Prospective	56	15.2 (7/46)	Both	34	0.7-3.4	1.5	0 and 500	1.5	94	95		94	95	
Mutlu et al. 2012	Prospective	51	None	Surgery	9.8	0.9-6.0	1.5	0, 50, 400, and 1000	1.00	80	97	96	80	97	
Ilica et al. 2013	Prospective	28	Not specified	Both	37.9	0.8-8.9	3	0, 50, 100, 500, 1000, and 1500	0.905	90	100				0.972
Shi et al. 2013	Prospective	111	None	Surgery	20.1	>1.0	1.5	150, 300, and 500	1.704	92.3	87.5	86.9			0.942
Wu et al. 2013	Prospective	42	Not specified	Surgery	33.3	>1.0	1.5	0 and 300	2.17	77	100				0.876
Wang Q et al 2018	Prospective	114	2.9 (4/138)	Both	45.6	>1.0	3	0, 800, and 2000	1.16	96.2	85.5				0.944
						<1.0	3	0, 800, and 2000	1.16	93.9	85.5				0.940
Song M 2020	Prospective	46	Not specified	Surgery	47.8	>1.0	3	0 and 600	1.49	90.9	91.7	89.1	90.5	88.0	0.970
								0 and 990	1.35	95.5	87.5	91.3	87.5	95.5	0.939

ADC, apparent diffusion coefficient; AUC, area under the ROC curve; FNA, fine-needle aspiration; ROC, receiver operator characteristics.

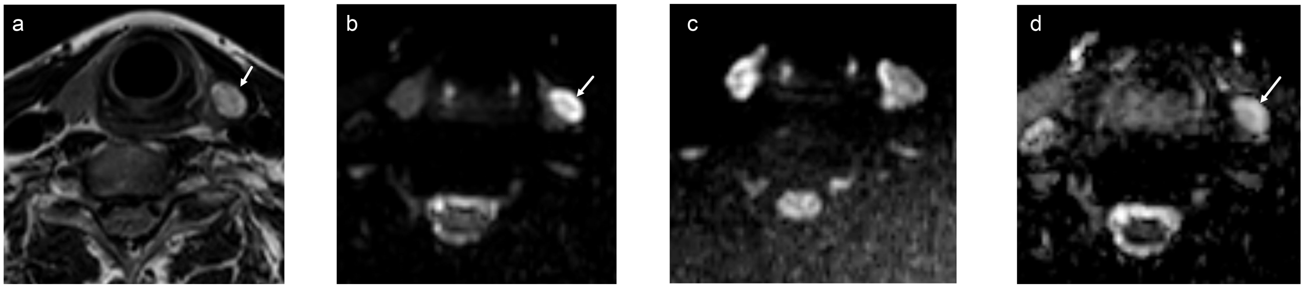

Figure 3. A 43-year-old female with a left thyroid nodule. On FNA biopsy, atypia of undetermined significance (Bethesda category III) was reported. (A) T2-weighted image shows a hyperintense solitary nodule in the left lobe of the thyroid gland (arrow). The nodule-to-muscle T2-weighted signal intensity ratio is 5.592. (B,C) DWI images at b-0 and b-1000. (D) ADC map showing the thyroid nodule with an ADC value of 2.157 and nodule-to-spinal cord ADC ratio 1.893. The final surgical diagnosis was microfollicular adenoma. FNA, fine-needle aspiration; ADC, apparent diffusion coefficient; DWI, diffusion-weighted images.

trachea. Wang et al[25] used an MS-EPI DWI sequence with readout segmentation of long variable echo-trains and generalized autocalibrating partially parallel acquisitions with a 3 mm slice thickness to evaluate papillary thyroid carcinoma and they included nodules smaller than 10 mm (microcarcinomas). Using this technique, only 2.9% (4/138) of patients were excluded due to bad image quality. Very high sensitivity and specificities were obtained both for microcarcinomas and papillary carcinomas larger than 10 mm (as shown in Table 4). However, in this study, 15 papillary microcarcinomas were excluded because the nodules were undetectable on MRI and 4 nodules were excluded because they were not measurable.[25] Therefore, both the referring physicians and the interpreting radiologists should be aware of size limitations for MRI even when small slice thickness and optimal technique are employed.

In the current study, respiratory gating was used and no patients were excluded because of bad image quality or motion artifacts. Although a few other studies similarly reported that no patients were excluded because of image quality issues,[22,33] most authors reported patient exclusion due to bad image quality and motion artifacts at a rate of 2.9%-15.2%.[17-21,25] Among 5 patients excluded from the current study, 2 were excluded because they had multinodular goiter and the authors could not accurately localize the biopsied nodule. In addition, 3 patients were excluded because the nodule biopsied could not be visualized on MRI. None of these 5 nodules was found to be malignant on final pathology. More research is needed to determine whether it is safe to avoid surgery and follow-up patients having indeterminate nodules larger than 10 mm on ultrasound that is not detectable on thyroid MRI.

In the current study, the nodule-to-thyroid tissue ADC ratios for malignant nodules were 1.03 and 1.04, whereas they were 1.38 and 1.43 for benign nodules (Table 1). Although the difference between these values did not reach statistical significance, the authors believe that the detection of small malignant nodules on ADC maps can be challenging due to the overlap in signal characteristics of malignant nodules and the surrounding normal thyroid tissue. Moreover, since benign nodules have higher ADC values, they are more readily detectable (Figure 3). A potential pitfall would be making measurements on the conspicuous benign nodule rather than the obscure malignant nodule if both existed in the same thyroid lobe. This potential pitfall may be overcome by correlating the MRI findings with ultrasound imaging. In addition, T2-weighted images have better contrast between the nodule and its surrounding thyroid tissue (Table 1). Hence, it may be helpful to first look at T2-weighted images to detect nodules followed by evaluation of DWI images and ADC maps.

A recent study reported that intravoxel incoherent motion had better accuracy, sensitivity, and specificity (97.8%, 95.5%, and 91.7%, respectively) than ADC values (91.3%, 95.5%, and 87.5%, respectively) in differentiating malignant from benign thyroid nodules.[26] However, this study did not report the preoperative cytology results of its cohort. Another recent study reported that ADC values less than 1.85×10^{-3} mm^2/s could discriminate between more aggressive papillary thyroid carcinomas with extrathyroid extension from those without extrathyroid extension[34]; but it should be noted that this study included a few microcarcinomas (measuring 0.5 mm, 3 mm, 8 mm, and 8 mm)[34] which may fall below the MRI resolution at the slice thickness they utilized (5 mm). Therefore, these findings need to be validated in future studies. Another study also reported that mean ADC values of undifferentiated thyroid cancers were significantly lower compared to differentiated tumors.[35] In another study, using ADC histogram skewness and kurtosis diffusion-weighted MRI could differentiate between reactive and metastatic lymph nodes in thyroid carcinoma patients.[36] Therefore, in addition to its ability to discriminate benign from malignant thyroid nodules, diffusion-weighted MRI could possibly provide valuable information regarding the tumor differentiation, aggressiveness, and nodal status.

Limitations of the current study include its small cohort size, single-center design, and the limited types of malignant nodules. Future refinement of the MRI technique by determining the best MRI coils (general neurovascular coil vs surface coil vs carotid surface coil), MRI sequence (multi-shot vs. single-shot, parallel imaging, etc., optimal b-values, and the added value of contrast material for risk stratification of thyroid nodules with indeterminate cytology needs to be performed. Validation of the data presented in this study by larger cohort multicenter studies needs to be conducted.

Conclusion

Despite the small cohort of this study, a dedicated thyroid protocol MRI with DWI and T2-weighted sequences may be a very sensitive tool for the discrimination of malignant from benign thyroid nodules in patients with indeterminate FNA cytology. Hence, thyroid MRI has the potential to solve a management dilemma and spare patients from unnecessary surgery.

Ethics Committee Approval: The study was approved by the medical ethics committee of İstanbul University Cerrahpaşa Hospital (No: 2019/02164).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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