2020

Investigating the effect of thyroid nodule location on the risk of thyroid cancer

Sina Jasim

Thomas J. Baranski

Sharlene A. Teefey

William D. Middleton

THYROID
Volume 30, Number 3, 2020

DOI: 10.1089/thy.2019.0478

Investigating the Effect of Thyroid Nodule Location on the Risk of Thyroid Cancer

Sina Jasim,[1] Thomas J. Baranski,[1] Sharlene A. Teefey,[2] and William D. Middleton[2]

Background: Thyroid nodules are routinely evaluated with ultrasound. Our aim was to determine if thyroid nodule location was a useful feature to predict thyroid cancer.
Materials and Methods: Retrospective review of patients with thyroid nodules from six referral centers from 2006 to 2010. A total of 3313 adult patients with thyroid nodules and confirmed benign or malignant thyroid diagnoses were included.
Results: Mean patient age was 54.2 (18–97) years, and the majority were women ($n = 2635$, 79.8%). A total of 3241 nodules were analyzed, 335 (10.3%) of which were malignant. Thyroid nodule location was an independent risk factor in predicting thyroid cancer ($p = 0.005$). Thyroid cancer odds were highest in the isthmus (odds ratio [OR] = 2.4, 95% confidence interval [CI] 1.6–3.6, $p < 0.0001$). In a multivariate regression model adjusting for age, sex, family history of thyroid cancer, radiation exposure, nodule size, and American College of Radiology (ACR) TI-RADS (Thyroid Imaging Reporting and Data System) score, the isthmus nodules had the highest risk of malignancy (OR = 2.4 [CI 1.5–3.9], $p = 0.0007$), followed by upper thyroid nodules (OR = 1.8 [CI 1.2–2.7], $p = 0.005$) and then middle thyroid nodules (OR = 1.5 [CI 1.1–2.0], $p = 0.01$) compared with lower thyroid nodules. Isthmus nodules were significantly smaller in size compared with middle ($p < 0.0001$) and lower ($p = 0.0004$), but not upper nodules ($p = 0.25$), with a mean size of 15.5 mm (±10.7).
Conclusions: Thyroid nodule location is an independent risk factor in predicting the risk of thyroid cancer. Isthmic nodules carry the highest risk of cancer diagnosis and lower lobe nodules carry the lowest risk.

Keywords: thyroid nodule, ACR TI-RADS, location, isthmus, thyroid cancer

Introduction

Thyroid nodules are common in clinical practice. The estimated prevalence of thyroid nodules detected using high-resolution ultrasound (US) can range from 19% to 68% with higher frequencies in older adults and women (1,2).

Thyroid nodule evaluation is particularly important to exclude thyroid cancer. Thyroid US is used to identify nodules for fine-needle aspiration (FNA) sampling. Cytological analysis of FNA samples is the safest and most cost-effective diagnostic tool available for the clinical evaluation of malignancy in thyroid nodules (3,4); However, it is an invasive procedure and may carry its own complication risks (5).

The incidence of thyroid nodules is dramatically increasing, in part, due to incidental detection of nodules on imaging studies for other indications. The reported thyroid malignancy prevalence can range from 7% to 15% (6), which means the majority of all biopsied thyroid nodules are nonmalignant. However, since the early 1990s, the thyroid cancer incidence has been increasing more than any other cancer type in the United States. In South Korea, screening for thyroid cancer led to a 15-fold increase in the rate of thyroid cancer diagnosis between 1993 and 2011 without a corresponding increase in mortality (7). This is consistent with overdiagnosis. While the dominant cause of the current ''epidemic'' of thyroid cancer is overdiagnosis, data from the Surveillance, Epidemiology, and End Results -9 cancer registry program showed that trends in thyroid cancer incidence from 1994 to 2013 were associated with an average relative annual increase in mortality of 1.1% per year, suggesting that a component of the epidemic is due to a small but real increase in papillary thyroid cancer incidence (8). Moreover, our understanding of the genetic mechanisms of thyroid carcinogenesis has dramatically evolved over the last 2 decades, leading to the clinical utility of molecular testing and the impact on the clinical management of patients with thyroid nodules (9).

In addition to the considerable patient anxiety that can occur because of the increasing incidence of thyroid nodules, the cost of thyroid cancer care in the United States is

[1]Division of Endocrinology, Metabolism and Lipid Research, Department of Internal Medicine; [2]Mallinckrodt Institute of Radiology; Washington University in St. Louis, School of Medicine, St. Louis, Missouri.

estimated to reach $18–$21 billion in 2019 based on historic incidence trends (10). This significant burden placed on patients and health care resources can be reduced by decreasing unnecessary FNAs and surgical resection of nonmalignant thyroid nodules.

Numerous guidelines have been developed within the last decade to assist physicians in deciding when it is appropriate to perform FNA versus observation of thyroid nodules in low-risk adult patients. A risk-stratifying approach is currently used by the American Thyroid Association (ATA) and American Association of Clinical Endocrinologist (AACE) to determine if FNA sampling should be pursued (6,11).

The American College of Radiology (ACR) developed a Thyroid Imaging Reporting and Data System (TI-RADS) (12), which uses a point-based classification system for risk stratification of thyroid nodules based on US features similar to those used in the ATA guidelines. Points are added to create an ACR TI-RADS scoring category (TR) ranging from TR1 (0 points) or least suspicious nodule with no indication for FNA or follow-up, to TR5 (≥7 points) being highly suspicious and requiring follow-up US if between 0.5 and 0.9 cm and FNA if ≥1.0 cm.

Recently, two small studies proposed integrating nodule location within the thyroid gland to risk stratification systems (13,14). However, the inconsistent results and small sample size of those studies called for validation in a larger study. The aim of our study was to test the risk of thyroid malignancy based on thyroid nodule location in a large multi-institutional cohort of patients with biopsy-proven nodules.

Materials and Methods

This is a retrospective data analysis of an existing thyroid nodule registry. The same database was previously used to evaluate the ACR TI-RADS, and full details of the study methods and original data collection are described in that prior report (15). Approval for this analysis was granted by the Washington University School of Medicine Institutional Review Board.

Patients/subjects

Adult patients, 18 years or older, from six tertiary academic institutions in the United States who underwent thyroid nodule FNA between 2006 and 2010 were analyzed. A total of 3313 patients with 3419 thyroid nodules were included in the database. At the time of their FNA, patients filled out a questionnaire that included information about race/ethnicity, family history of thyroid cancer, and radiation exposure. Patients with multiple thyroid nodules were approached similar to those with one nodule.

In patients who had more than one thyroid nodule, the decision to biopsy those nodules was similar to that in case of solitary nodules and was based primarily on the sonographic appearance of the nodule.

Image analysis

Analysis of sonographic images of all biopsied nodules was performed by two radiologists who were blinded to the pathologic results. Nodules were assessed for composition, echogenicity, margins, echogenic foci, size, location, and multiplicity. The presence of suspicious lymph nodes was also determined. For the purpose of this study, we analyzed the relationship of thyroid nodule location with the risk of thyroid cancer. Thyroid nodule location was categorized as isthmus, upper lobe, middle lobe, and lower lobe. The thyroid was subjectively divided into thirds to differentiate the upper, middle, and lower lobes. Thyroid nodules occupying both the middle and lower thyroid lobe were included in the lower thyroid nodule category. Thyroid nodules occupying the entire thyroid lobe were excluded from the analysis.

Pathology analysis

Cytology reports from the patients FNA and, when applicable, surgical pathology reports of resected specimens were collected from the six participating sites. Nodules with FNA results that were interpreted as malignant (Bethesda 6) or benign (Bethesda 2) were considered diagnostic and were included in the final analysis. Almost all malignant nodules were surgically removed, while most benign nodules were not.

Nodules with nondiagnostic (Bethesda 1) or indeterminate (Bethesda 3 and 4) FNA results were excluded unless subsequent definitive FNA results were available or the nodule was resected and histologic results were available. Nodules with suspicious FNA results (Bethesda category 5) were also excluded unless there was a subsequent definitive FNA or surgery to confirm the diagnosis. As such, there were 66 Bethesda category 5 lesions that were included in the final analysis. Forty of the included nodules were malignant and 26 were benign, which is compatible with the estimated risk of malignancy of 60–75% for category 5 in the Bethesda classification (16).

Statistical methods

We used descriptive statistics to summarize patient demographics and the general characteristics of biopsied thyroid nodules. Data are presented as frequencies (percentages) for categorical variables with means (standard deviations) or (range) as appropriate for continuous variables.

Differences between categorical variables were assessed using the chi-square test or Fisher exact test and between continuous variables using Student's *t*-test (parametric) or Wilcoxon/Kruskal–Wallis test (nonparametric) as appropriate. A p value <0.05 was considered statistically significant.

In Table 2, summarizing the thyroid nodule characteristics, we used a two-sample *t*-test for maximum nodule size to obtain the *p*-value. For all the other characteristics that involved frequencies, we used a chi-square test and the generated *p*-values were used for a simple two-group comparison.

Univariate and multivariate logistic regression analyses were performed to estimate the odds ratios (ORs) of malignancy and their 95% confidence intervals (95% CIs). $p = 0.05$ was considered statistically significant. We used contingency table chi-square tests and multivariate binary logistic regression to test the association of thyroid nodule location with the risk of thyroid cancer diagnosis. We adjusted for certain variables that may influence the risk of thyroid cancer such as patient age, sex, family history of thyroid cancer, radiological features of thyroid nodule (shape, composition, echogenicity, margin, and calcification), and scoring system. We also adjusted for the existing ACR TI-RADS score/category.

For all univariate (unadjusted) and multivariate (adjusted) models, thyroid nodule location differences were evaluated with the log OR of each location pair and corrected for false positivity with the Bonferroni adjustment. Statistical software (SAS, version 9.4, SAS Institute) was used to conduct data analyses.

Results

The mean patient age was 54.2 (range: 18–97) years. The majority of patients were women ($n=2635$, 79.8%) and Caucasians ($n=2596$, 80.7%). There was a self-reported family history of thyroid cancer in 302 (9%), and radiation exposure to the head and neck region in 435 (13%). Eight hundred thirty-eight patients (25.8%) had a single nodule, the remainder had two or more nodules (Table 1).

One hundred seventy-eight nodules were excluded from the final analysis because data regarding nodule location were missing ($n=117$) or the nodule occupied the entire lobe of the thyroid ($n=61$). This left a total of 3241 nodules that were ultimately analyzed. Three hundred thirty-five of these nodules were malignant and 2906 were benign (Fig. 1).

Of the 335 cytologically proven malignant nodules in the database, a total of 289 were resected and histology was obtained. One hundred seventy-seven (52.8%) were papillary cancer, 82 (24.5%) were a follicular variant of papillary cancer, 15 (4.5%) were follicular cancer, 5 (1.5%) were medullary cancer, 1 (0.3%) was anaplastic cancer, and 9 (2.7%) were other types of malignancies (Table 2).

Table 1. Patient Characteristics

Characteristic	*Data,* n *(%)*
Total, *N*	3313
Male	667 (20.2)
Female	2635 (79.8)
Missing	11 (0.3)
Age in years, mean (range)	54.2 (18–97)
Race/Ethnicity	
African American	386 (12)
Asian	78 (2.4)
Caucasian	2596 (80.7)
Hispanic/Latino	53 (1.6)
Native American	38 (1.2)
Pacific Islander	4 (0.12)
Other	63 (1.9)
Missing	95 (2.9)
Family history of thyroid cancer	
Yes	302 (9.1)
No	2904 (87.6)
Unknown	107 (3.2)
History of head and neck radiation	
Yes	435 (13.1)
No	2757 (83.2)
Unknown	121 (3.6)
Number of nodules	
1	838 (25.8)
2	610 (18.8)
3	460 (14.2)
4	303 (9.3)
5–10	799 (24.6)
>10	218 (6.7)
Confluent (cannot determine)	19 (0.6)
Missing	66 (1.9)

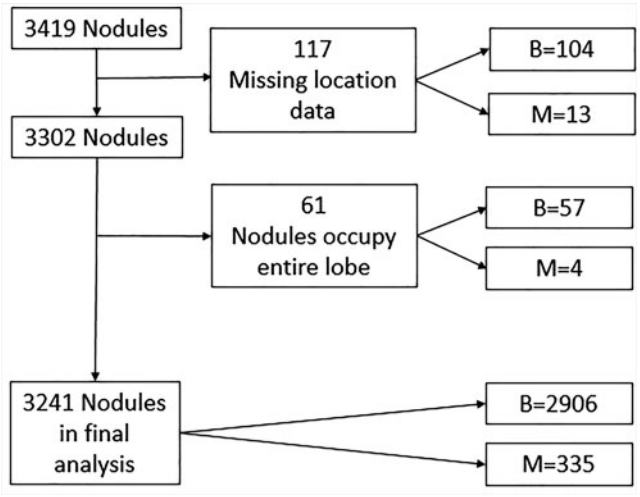

FIG. 1. Thyroid nodule exclusion flowchart. B, benign; M, malignant.

The nodules were almost evenly disturbed in the right ($n=1627$, 50.2%) and the left ($n=1419$, 43.8%) lobes, and less frequently in the isthmus in 195 (6%). Those nodules were located in the upper lobe in 355 (11%), middle lobe in 1481 (45.7%), lower lobe in 1210 (37.3%), and isthmus in 195 (6%). Nodule location was significantly different between benign and malignant nodules ($p<0.0001$). Malignant nodules accounted for 14.6% (52/355), 10.2% (151/1481), 8.1% (98/1210), and 17.4% (34/195) of nodules in the upper lobe, middle lobe, lower lobe, and isthmus, respectively. The mean maximum size of thyroid nodules was 23.8 mm (±13.3) with significant difference ($p<0.0001$) in size between benign and malignant nodules (Table 2).

The distribution of ACR TI-RADS score (TR) among all thyroid nodules was 8.9% TR1 ($n=288$), 15.8% TR2 ($n=513$), 22.9% TR3 ($n=742$), 36.4% TR4 ($n=1179$), and 16% TR5 ($n=519$), with the majority of thyroid malignancies classified as TR4 and 5 (Table 2).

A logistic regression model showed that location within the thyroid is an independent risk factor in predicting thyroid cancer ($p=0.005$). Other known significant associations with thyroid cancer included the following: composition ($p<0.0001$), echogenicity ($p<0.0001$), calcifications ($p<0.0001$), and margins ($p=0.0001$) (Supplementary Table S1). This model was not included in the final regression model as those features are included in the ACR TI-RADS points.

In the study presented here, nodules in the lower pole were least likely to be malignant. Compared with the lower lobe using a simple (univariate) logistic regression analysis, the odds of a nodule being malignant were highest in nodules located in the isthmus (OR = 2.4 [95% CI 1.6–3.6], $p<0.0001$), followed by upper lobe nodules (OR = 1.9 [CI 1.4–2.8], $p=0.0004$) and then middle lobe nodules (OR = 1.3 [CI 0.9–1.7], $p=0.06$) (Table 3).

This association held true after adjusting for each of the following variables: age, sex, family history of thyroid cancer, radiation exposure, maximum nodule size, and ACR TI-RADS score (Table 3). All of which, except radiation

Table 2. Thyroid Nodule Characteristics

Characteristic	*All data,* n	*Benign*	*Cancer*	p
Total, *N* (%)	3241 (100.0)	2906 (89.7)	335 (10.3)	<0.0001*
Laterality (%)				
Right	1627 (100.0)	1462 (89.9)	165 (10.1)	0.0031*
Left	1419 (100.0)	1283 (90.4)	136 (9.6)	
Isthmus	195 (100.0)	161 (82.6)	34 (17.4)	
Nodule location (%)				
Upper	355 (100.0)	303 (85.4)	52 (14.6)	<0.0001*
Middle	1481 (100.0)	1330 (89.8)	151 (10.2)	
Lower	1210 (100.0)	1112 (91.9)	98 (8.1)	
Isthmus	195 (100.0)	161 (82.6)	34 (17.4)	
ACR TI-RADS score (%)				
TR1	288 (100.0)	287 (99.7)	1 (0.3)	<0.0001*
TR2	513 (100.0)	505 (98.4)	8 (1.6)	
TR3	742 (100.0)	708 (95.4)	34 (4.6)	
TR4	1179 (100.0)	1076 (91.3)	103 (8.7)	
TR5	519 (100.0)	330 (63.6)	189 (36.4)	
Maximum size, mean (SD), mm	23.8 (13.3)	24.2 (13.1)	20.3 (14.16)	<0.0001
Upper	18.9 (9.2)	19.4 (9.3)	16.2 (7.9)	0.1058
Middle	25.4 (14.5)	25.8 (14.3)	22.2 (16.4)	0.0016
Lower	23.9 (12.6)	24.1 (12.5)	21.2 (13.4)	0.0362
Isthmus	20.3 (11.3)	21.3 (11.2)	15.6 (10.7)	0.0206

*p-Values refer to contingency analysis only of descriptive nature for the entire group (group characteristic vs. cancer diagnosis).
ACR, American College of Radiology; SD, standard deviation; TI-RADS, Thyroid Imaging Reporting and Data System.

exposure, were independently and significantly associated with the risk of thyroid cancer in the univariate logistic regression. Furthermore, all above variables, except maximum nodule size, were independently and significantly associated with the risk of thyroid cancer in the final multivariate logistic regression model. In particular, the odds of a nodule being malignant are higher in males than in females (OR = 1.8, [CI 1.4–2.5], $p < 0.0001$), lower as age progresses on a continuum (OR = 0.9 [CI 0.97–0.99], $p < 0.0001$), higher in patients with a positive family history of thyroid cancer (OR = 1.5 [CI 1.0–2.2], $p = 0.04$), and higher with higher ACR TI-RADS levels using TR1 as the reference TR2 (OR = 4.4 [CI 0.8–82.3], $p = 0.09$), TR3 (OR = 13.1 [CI 2.8–233], $p < 0.0001$), TR4 (OR = 25.8 [CI 5.7–455], $p < 0.0001$), and TR5 (OR = 155.6 [CI 34.5–999.9], $p < 0.0001$). In looking into the points contributing to the ACR TI-RADS, we confirmed that the risk of thyroid cancer increased by 73% with each increase in the score by one point (OR = 1.73 [CI 1.6–1.8], $p < 0.0001$).

Table 3. Thyroid Nodule Location and the Risk of Thyroid Malignancy Adjusted for Other Variables

	Univariate analysis		*Multivariate analysis*	
	Unadjusted model		*Adjusted model*	
Variables	*OR (95% CI)*	p	*aOR (95% CI)*[a]	p
Nodule location				
Isthmus	2.4 (1.6–3.6)	<0.0001	2.4 (1.5–3.9)	0.0007
Upper	1.9 (1.4–2.8)	0.0004	1.8 (1.2–2.7)	0.0055
Middle	1.3 (0.9–1.7)	0.0607	1.5 (1.1–2.0)	0.0107
Lower—ref	—	—	—	—
Age	0.98 (0.97–0.99)	<0.0001	0.98 (0.97–0.99)	<0.0001
Sex (ref = female)	1.7 (1.3–2.2)	<0.0001	1.8 (1.4–2.5)	<0.0001
Family history (ref = no)	1.6 (1.2–2.2)	0.0055	1.5 (1.0–2.2)	0.0409
Radiation exposure (ref = no)	1.1 (0.8–1.4)	0.7496	—	—
Maximum size	0.97 (0.96–0.98)	<0.0001	0.97 (0.96–0.98)	0.6951
TIRADS				
TR2	4.5 (0.8–84.6)	0.0871	4.4 (0.8–82.3)	0.0953
TR3	14.7 (3.2–261.5)	<0.0001	13.1 (2.8–233.5)	<0.0001
TR4	29.0 (6.4–510.9)	<0.0001	25.8 (5.7–455.4)	<0.0001
TR5	167.4 (37.3–999.9)	<0.0001	155.6 (34.5–999.9)	<0.0001
TR1–ref	—	—	—	—

[a]OR adjusted for age, sex, family history, radiation exposure, maximum size, and ACR-TIRADS.
CI, confidence interval; OR, odds ratio.

Compared with lower lobe nodules, isthmus nodules continued to demonstrate the highest risk of malignancy in a multivariate regression model (OR = 2.4 [CI 1.5–3.9], $p = 0.0007$), followed by upper lobe nodules (OR = 1.8 [CI 1.2–2.7], $p = 0.005$) and then middle lobe nodules (OR 1.5 [CI 1.1–2.0], $p = 0.01$) (Table 3). The higher risk of cancer in nodules located in the upper lobe followed by the middle lobe compared with the lower lobe remained significant when we excluded the isthmus from this analysis.

Isthmus nodules were significantly smaller in size compared with middle ($p < 0.0001$) and lower ($p = 0.0004$), but not upper nodules ($p = 0.25$). When adjusted for thyroid cancer diagnosis, isthmus nodules remained significantly smaller in size compared with middle ($p = 0.007$) and lower ($p = 0.03$), but not upper nodules ($p = 0.82$), with a mean size of 15.5 mm (±10.7) (Supplementary Tables S2 and S3).

Discussion

This study shows that thyroid nodule location is an independent risk factor for thyroid cancer diagnosis even after adjusting for other significant sonographic predictors of thyroid cancer. While thyroid nodules located in the isthmus were the least frequent (6%), they had the highest risk of being malignant (OR = 2.4 [CI 1.4–3.8], $p = 0.001$). This risk remained significant after adjusting for patient age, sex, family history of thyroid cancer, radiation exposure, maximum nodule size, and ACR TI-RADS score. Furthermore, malignant thyroid nodules located in the isthmus were significantly smaller in size compared with other locations. Thyroid nodules located in the lower lobe were associated with the lowest risk of malignancy.

High-resolution neck US is widely used for evaluating thyroid nodules, stratifying the risk of malignancy, and guiding for FNA (6). Several sonographic features have been described to predict the risk of thyroid cancer (primarily papillary thyroid cancer) in a nodule, including solid composition, echogenicity (hypoechoic, in particular, markedly hypoechoic), the presence of microcalcifications, and irregular margins, with improved specificity when a combination of more than one feature is present (17–24).

Multiple professional societies use these US features to predict the risk of cancer and together with nodule size provide management guidelines for FNA. The ATA and AACE currently follow a pattern recognition approach to recommend FNA of thyroid nodules based on size thresholds and the level of clinical and sonographic suspicion (6,11). Using similar sonographic features, but a point-based approach with higher size thresholds, the ACR TI-RADS achieves a higher accuracy and specificity and reduces the unnecessary FNA rate. To maintain sensitivity, it substitutes US follow-up for FNA in some nodules (15,25,26).

Our study confirms that thyroid nodule composition, echogenicity, calcifications, and margins, but not vascularity on color Doppler, are significant independent risk factors for thyroid cancer in a multiple regression model. This is not surprising given those features are well described in the literature, and the fact that we performed a secondary analysis of data used in evaluating the ACR TI-RADS, which is based on those sonographic features (15). When we added location of the nodule within the thyroid to the above model, we found that it is an independent risk factor to predict thyroid cancer adjusting for other known sonographic features.

In many respects, our findings are in agreement with recent reports proposing the use of thyroid nodule location in stratifying the risk of thyroid cancer (13,14). Similar to our results, both of these studies showed that the risk of malignancy was lowest for lower lobe nodules and higher for upper and middle lobe nodules. The ORs for upper and middle lobe nodules were 4.7 and 9.7, respectively, in one study (11) and 5.8 and 3.7, respectively, in the other study (12). We also demonstrate that the risk is higher in the upper pole, and to a lesser extent in the middle lobe, but the ORs of 1.9 for the upper lobe and 1.3 for the middle lobe were much lower. The differences in the OR are likely due to the very small sample sizes used to analyze nodule location in the previous studies [189 total nodules with 14 malignancies (11), and 225 total nodules with 12 malignancies (12)]. Single cases of malignant nodules in the isthmus also precluded meaningful analysis of this location in the prior studies. In our study, 34/195 nodules in the isthmus were malignant, resulting in the highest OR of 2.4.

Proposed mechanisms for an increased risk in the upper lobe include reactive oxygen species accumulation and induction of cancer-promoting mutations due to the tortuous route of the venous drainage of the upper lobes, as opposed to the more direct venous drainage of the lower pole because the inferior thyroid veins drain directly to the subclavian or brachiocephalic veins, located just posterior to the manubrium (14). Dental and diagnostic irradiation may also play a role in the increased risk of upper pole nodules (14).

It is not clear why thyroid nodules located in the isthmus are more likely to be cancerous. The findings support the concept that thyroid tissue should not be considered homogenous, and may determine not only the propensity to form nodules but also risk of malignant transformation.

The majority of thyroid cancer usually arises in the thyroid lobes with a small percentage arising from the thyroid isthmus. The reported rates of differentiated thyroid carcinoma (DTC) located in the isthmus range from 1% to 9.2% for all malignant thyroid nodules (27–33). In the present study, 1% of malignant nodules were seen in the isthmus, which is comparable with previous reports. The low incidence of DTC in the isthmus likely reflects the small volume of the isthmus relative to the lobes. Despite the low reported incidence, there are some data suggesting that DTC originating from the thyroid isthmus tends to behave more aggressively and carries poorer prognosis compared with that originating in thyroid lobe (34). Papillary thyroid carcinoma in the isthmus tends to be associated with more frequent lymph node metastases (35), multifocality (27,28), capsular invasion, and extrathyroidal extension (36), independent of tumor size (28). The aggressive behavior of isthmic thyroid cancer is likely related to the small size and thin shape of the isthmus, which may facilitate the invasion of adjacent tissues. In addition, compared with the lobes, the lymphatic drainage from the isthmus travels more frequently to the prelaryngeal and pretracheal nodes and then spreads to the paratracheal nodes (37–39).

The clinical risk factors for thyroid cancer such as age, sex (male more than females), family history of thyroid cancer, but not thyroid nodule size, are consistent with published data (40). Radiation exposure, a known risk factor for thyroid cancer (40), was not found to be a significant predictor of thyroid cancer in our cohort. This is probably due to the fact

that radiation exposure was self reported and not verified, subjecting it to recall bias. It is also likely that thyroid cancers that occur in the setting of prior radiation have similar sonographic features, and thus, similar ACR TI-RADS scores as those that occur without prior radiation.

The strength of our study relies on the large sample size that included comprehensive data points gathered from multiple academic institutions with sonographic expertise, allowing us to adjust for various confounding factors when studying the risk of thyroid nodule location in predicting thyroid cancer. The diagnosis of thyroid cancer was confirmed by cytology and/or surgical pathology. While the vast majority of our study population had DTC, we included all forms of thyroid malignancy in the data analysis. The limitation of the study is the retrospective nature, which introduces the risk of selection bias. We did not factor in the margin of error that might be associated with cytology results, or adjust for solitary versus multiple thyroid nodules in the analysis; the rationale is that thyroid nodules can carry a similar risk of malignancy regardless of whether the patient has a solitary nodule or multiple nodules (22).

In summary, thyroid nodule location appears to be an independent factor for the risk of thyroid cancer. Thyroid nodules located in the isthmus have the highest risk of cancer diagnosis, while nodules in the lower lobe have the lowest. Furthermore, thyroid nodules located in the isthmus are significantly smaller than nodules in the lobes mandating careful evaluation of the isthmus on a routine thyroid sonogram. It is also recommended that isthmus nodule location be factored in when estimating the risk of thyroid cancer using current guidelines, and future consideration be given to adding a point to the ACR TI-RADS guidelines for nodule location in the isthmus or using a lower size threshold for FNA or follow-up.

Acknowledgment

We thank Dean W. Coble, PhD, Senior Statistical Data Analyst in the Division of Biostatistics at Washington University in St. Louis for the statistical support.

Disclaimer

The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Author Disclosure Statement

No competing financial interests exist.

Funding Information

This project was supported by the Washington University Institute of Clinical and Translational Sciences, which is, in part, supported by the NIH/National Center for Advancing Translational Sciences (NCATS), CTSA grant UL1TR002345. Research reported in this publication was supported by the National Cancer Institute of the National Institutes of Health under Award No. R25 CA190190.

Supplementary Material

Supplementary Table S1
Supplementary Table S2
Supplementary Table S3

References

1. Guth S, Theune U, Aberle J, Galach A, Bamberger CM 2009 Very high prevalence of thyroid nodules detected by high frequency (13 MHz) ultrasound examination. Eur J Clin Invest **39:**699–706.
2. Tan GH, Gharib H 1997 Thyroid incidentalomas: management approaches to nonpalpable nodules discovered incidentally on thyroid imaging. Ann Intern Med **126:**226–231.
3. Castro MR, Gharib H 2003 Thyroid fine-needle aspiration biopsy: progress, practice, and pitfalls. Endocr Pract **9:**128–136.
4. Gharib H, Goellner JR 1993 Fine-needle aspiration biopsy of the thyroid: an appraisal. Ann Intern Med **118:**282–289.
5. Polyzos SA, Anastasilakis AD 2009 Clinical complications following thyroid fine-needle biopsy: a systematic review. Clin Endocrinol (Oxf) **71:**157–165.
6. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L 2016 2015 American Thyroid Association Management Guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines Task Force on thyroid nodules and differentiated thyroid cancer. Thyroid **26:**1–133.
7. Ahn HS, Kim HJ, Welch HG 2014 Korea's thyroid-cancer ''epidemic''—screening and overdiagnosis. N Engl J Med **371:**1765–1767.
8. Lim H, Devesa SS, Sosa JA, Check D, Kitahara CM 2017 Trends in thyroid cancer incidence and mortality in the United States, 1974–2013. JAMA **317:**1338–1348.
9. Nikiforov YE 2017 Role of molecular markers in thyroid nodule management: then and now. Endocr Pract **23:**979–988.
10. Aschebrook-Kilfoy B, Schechter RB, Shih YC, Kaplan EL, Chiu BC, Angelos P, Grogan RH 2013 The clinical and economic burden of a sustained increase in thyroid cancer incidence. Cancer Epidemiol Biomarkers Prev **22:**1252–1259.
11. Gharib H, Papini E, Garber JR, Duick DS, Harrell RM, Hegedus L, Paschke R, Valcavi R, Vitti P; AACE/ACE/-AME Task Force on Thyroid Nodules 2016 American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi Medical Guidelines for clinical practice for the diagnosis and management of thyroid nodules—2016 update. Endocr Pract **22:**622–639.
12. Tessler FN, Middleton WD, Grant EG, Hoang JK, Berland LL, Teefey SA, Cronan JJ, Beland MD, Desser TS, Frates MC, Hammers LW, Hamper UM, Langer JE, Reading CC, Scoutt LM, Stavros AT 2017 ACR Thyroid Imaging, Reporting and Data System (TI-RADS): white paper of the ACR TI-RADS Committee. J Am Coll Radiol **14:**587–595.
13. Ramundo V, Lamartina L, Falcone R, Ciotti L, Lomonaco C, Biffoni M, Giacomelli L, Maranghi M, Durante C, Grani G 2019 Is thyroid nodule location associated with malignancy risk? Ultrasonography **38:**231–235.
14. Zhang F, Oluwo O, Castillo FB, Gangula P, Castillo M, Farag F, Zakaria S, Zahedi T 2019 Thyroid nodule location on ultrasonography as a predictor of malignancy. Endocr Pract **25:**131–137.
15. Middleton WD, Teefey SA, Reading CC, Langer JE, Beland MD, Szabunio MM, Desser TS 2017 Multiinstitutional

analysis of thyroid nodule risk stratification using the American College of Radiology Thyroid Imaging Reporting and Data System. AJR Am J Roentgenol **208:**1331–1341.
16. Cibas ES, Ali SZ; NCI Thyroid FNA State of the Science Conference 2009 The Bethesda System For Reporting Thyroid Cytopathology. Am J Clin Pathol **132:**658–665.
17. Cappelli C, Castellano M, Pirola I, Cumetti D, Agosti B, Gandossi E, Agabiti Rosei E 2007 The predictive value of ultrasound findings in the management of thyroid nodules. QJM **100:**29–35.
18. Horvath E, Majlis S, Rossi R, Franco C, Niedmann JP, Castro A, Dominguez M 2009 An ultrasonogram reporting system for thyroid nodules stratifying cancer risk for clinical management. J Clin Endocrinol Metab **94:**1748–1751.
19. Kwak JY, Han KH, Yoon JH, Moon HJ, Son EJ, Park SH, Jung HK, Choi JS, Kim BM, Kim EK 2011 Thyroid imaging reporting and data system for US features of nodules: a step in establishing better stratification of cancer risk. Radiology **260:**892–899.
20. Moon HJ, Kwak JY, Kim MJ, Son EJ, Kim EK 2010 Can vascularity at power Doppler US help predict thyroid malignancy? Radiology **255:**260–269.
21. Moon WJ, Jung SL, Lee JH, Na DG, Baek JH, Lee YH, Kim J, Kim HS, Byun JS, Lee DH; Thyroid Study Group, Korean Society of Neuro- and Head and Neck Radiology 2008 Benign and malignant thyroid nodules: US differentiation—multicenter retrospective study. Radiology **247:**762–770.
22. Papini E, Guglielmi R, Bianchini A, Crescenzi A, Taccogna S, Nardi F, Panunzi C, Rinaldi R, Toscano V, Pacella CM 2002 Risk of malignancy in nonpalpable thyroid nodules: predictive value of ultrasound and color-Doppler features. J Clin Endocrinol Metab **87:**1941–1946.
23. Remonti LR, Kramer CK, Leitao CB, Pinto LC, Gross JL 2015 Thyroid ultrasound features and risk of carcinoma: a systematic review and meta-analysis of observational studies. Thyroid **25:**538–550.
24. Salmaslioglu A, Erbil Y, Dural C, Issever H, Kapran Y, Ozarmagan S, Tezelman S 2008 Predictive value of sonographic features in preoperative evaluation of malignant thyroid nodules in a multinodular goiter. World J Surg **32:**1948–1954.
25. Grani G, Lamartina L, Ascoli V, Bosco D, Biffoni M, Giacomelli L, Maranghi M, Falcone R, Ramundo V, Cantisani V, Filetti S, Durante C 2019 Reducing the number of unnecessary thyroid biopsies while improving diagnostic accuracy: toward the ''Right'' TIRADS. J Clin Endocrinol Metab **104:**95–102.
26. Middleton WD, Teefey SA, Reading CC, Langer JE, Beland MD, Szabunio MM, Desser TS 2018 Comparison of performance characteristics of American College of Radiology TI-RADS, Korean Society of Thyroid Radiology TIRADS, and American Thyroid Association Guidelines. AJR Am J Roentgenol **210:**1148–1154.
27. Goldfarb M, Rodgers SS, Lew JI 2012 Appropriate surgical procedure for dominant thyroid nodules of the isthmus 1 cm or larger. Arch Surg **147:**881–884.
28. Karatzas T, Charitoudis G, Vasileiadis D, Kapetanakis S, Vasileiadis I 2015 Surgical treatment for dominant malignant nodules of the isthmus of the thyroid gland: a case control study. Int J Surg **18:**64–68.
29. Lee YS, Jeong JJ, Nam KH, Chung WY, Chang HS, Park CS 2010 Papillary carcinoma located in the thyroid isthmus. World J Surg **34:**36–39.
30. Mai KT, Gulavita P, Lai C, Swift J, Levac J, Olberg B, Purgina B 2014 Topographic distribution of papillary thyroid carcinoma by mapping in coronal sections of 125 consecutive thyroidectomy specimens. Int J Surg Pathol **22:**303–315.
31. Nixon IJ, Palmer FL, Whitcher MM, Shaha AR, Shah JP, Patel SG, Ganly I 2011 Thyroid isthmusectomy for well-differentiated thyroid cancer. Ann Surg Oncol **18:**767–770.
32. Roh JL, Park JY, Park CI 2007 Total thyroidectomy plus neck dissection in differentiated papillary thyroid carcinoma patients: pattern of nodal metastasis, morbidity, recurrence, and postoperative levels of serum parathyroid hormone. Ann Surg **245:**604–610.
33. Sugenoya A, Shingu K, Kobayashi S, Masuda H, Takahashi S, Shimizu T, Onuma H, Asanuma K, Ito N, Iida F 1993 Surgical strategies for differentiated carcinoma of the thyroid isthmus. Head Neck **15:**158–160.
34. Vasileiadis I, Boutzios G, Karalaki M, Misiakos E, Karatzas T 2018 Papillary thyroid carcinoma of the isthmus: total thyroidectomy or isthmusectomy? Am J Surg **216:**135–139.
35. Song CM, Lee DW, Ji YB, Jeong JH, Park JH, Tae K 2016 Frequency and pattern of central lymph node metastasis in papillary carcinoma of the thyroid isthmus. Head Neck **38 Suppl 1:**E412–E416.
36. Hahn SY, Han BK, Ko EY, Shin JH, Ko ES 2014 Ultrasound findings of papillary thyroid carcinoma originating in the isthmus: comparison with lobe-originating papillary thyroid carcinoma. AJR Am J Roentgenol **203:**637–642.
37. Chai YJ, Kim SJ, Choi JY, Koo do H, Lee KE, Youn YK 2014 Papillary thyroid carcinoma located in the isthmus or upper third is associated with Delphian lymph node metastasis. World J Surg **38:**1306–1311.
38. Lee YC, Na SY, Chung H, Kim SI, Eun YG 2016 Clinicopathologic characteristics and pattern of central lymph node metastasis in papillary thyroid cancer located in the isthmus. Laryngoscope **126:**2419–2421.
39. Santrac N, Besic N, Buta M, Oruci M, Djurisic I, Pupic G, Petrovic L, Ito Y, Dzodic R 2014 Lymphatic drainage, regional metastases and surgical management of papillary thyroid carcinoma arising in pyramidal lobe—a single institution experience. Endocr J **61:**55–59.
40. Grubbs EG, Rich TA, Li G, Sturgis EM, Younes MN, Myers JN, Edeiken-Monroe B, Fornage BD, Monroe DP, Staerkel GA, Williams MD, Waguespack SG, Hu MI, Cote G, Gagel RF, Cohen J, Weber RS, Anaya DA, Holsinger FC, Perrier ND, Clayman GL, Evans DB 2008 Recent advances in thyroid cancer. Curr Probl Surg **45:**156–250.

Address correspondence to:
Sina Jasim, MD, MPH
Division of Endocrinology, Metabolism and Lipid Research
Department of Internal Medicine
Washington University in St. Louis School of Medicine
660 South Euclid Avenue
St. Louis, MO 63110

E-mail: s.jasim@wustl.edu