Radiology

ORIGINAL RESEARCH • HEAD AND NECK IMAGING

US Predictors of Papillary Thyroid Microcarcinoma Progression at Active Surveillance

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Conflicts of interest are listed at the end of this article.

See also the editorial by Reuter and the review "International Expert Consensus on US Lexicon for Thyroid Nodules" by Durante et al in this issue.

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Background: Active surveillance (AS) is an accepted strategy for patients with low-risk papillary thyroid microcarcinoma (PTMC). While previous studies have evaluated the prognostic value of US features, results have been inconsistent.

Purpose: To determine if US features can help predict tumor progression in patients with low-risk PTMC undergoing AS.

Materials and Methods: This prospective study enrolled 1177 participants with PTMC from three hospitals between June 2016 and January 2021. Participants were self-assigned to either immediate surgery or AS, and those with two or more US examinations in the absence of surgery were included in the analysis. A χ^2 test was used to compare estimated tumor progression rate at 4 years between participants stratified according to US features. Multivariable Cox regression analysis was used to assess the association of clinical and US features with overall tumor progression and specific progression criteria.

Results: Among 699 participants included in the analysis, 68 (mean age, 49 years ± 12 [SD]; 40 female participants) showed tumor progression (median follow-up, 41.4 months ± 16 [SD]). Tumor progression was associated with the US features of diffuse thyroid disease (DTD) (hazard ratio [HR], 2.3 [95% CI: 1.4, 3.7]; $P = .001$) and intratumoral vascularity (HR, 1.7 [95% CI: 1.0, 3.0]; $P = .04$) and the participant characteristics of male sex (HR, 2.8 [95% CI: 1.7, 4.6]; $P < .001$), age less than 30 years (HR, 2.9 [95% CI: 1.2, 6.8]; $P = .01$), and thyroid-stimulating hormone level of 7 μU/mL or higher (HR, 6.9 [95% CI: 2.7, 17.4]; $P < .001$). The risk of tumor progression was higher for participants with DTD (14%, $P = .001$) or intratumoral vascularity (14%, $P = .02$) than for participants without these features (6%). DTD and intratumoral vascularity were associated with tumor enlargement (HR, 2.7 [95% CI: 1.4, 5.1]; $P = .002$) and new lymph node metastasis (HR, 5.0 [95% CI: 1.3, 19.4]; $P = .02$), respectively.

Conclusion: DTD and intratumoral vascularity were associated with an increased risk of tumor progression in participants with PTMC undergoing AS.

Clinical trial registration no. NCT02938702

Supplemental material is available for this article.

Active surveillance (AS) is accepted as an alternative strategy to immediate surgery for low-risk papillary thyroid microcarcinoma (PTMC) (1–3) because mortality is very low in PTMC (4–6). Tumor enlargement and new lymph node metastasis (LNM) are regarded as important markers of disease progression during AS. Although most PTMCs tend to be indolent, some tumors may progress during AS (4–7). Thus, the appropriate selection of candidates for AS and the timely management of patients with disease progression during AS are important clinical issues.

Several patient and tumor characteristics have been associated with tumor progression (4,8–10). Young age at diagnosis is consistently associated with an increased risk of tumor progression (4,11). Elevated thyroid-stimulating hormone (TSH) levels have also been associated with tumor growth (12,13). Furthermore, in the recent Multicenter Prospective Cohort Study of Active Surveillance on Papillary Thyroid Microcarcinoma, age under 30 years, male sex, and tumor size of 6 mm or larger were indicated as predictors of tumor progression (10).

US features, which reflect intrinsic imaging phenotypes of tumor biology, have also been used as predictors of recurrence or LNM in PTMC in previous studies (14–16). However, the results of previous studies examining the importance of US characteristics in PTMC under AS are inconsistent (17–19).

Abbreviations

AS = active surveillance, DTD = diffuse thyroid disease, HR = hazard ratio, LNM = lymph node metastasis, PTMC = papillary thyroid microcarcinoma, TSH = thyroid-stimulating hormone

Summary

The presence of diffuse thyroid disease and intratumoral vascularity at US helped accurately predict tumor progression in participants with low-risk papillary thyroid microcarcinoma during active surveillance.

Key Results

- This prospective study found that the US features of diffuse thyroid disease (DTD) (hazard ratio [HR], 2.3; $P = .001$) and intratumoral vascularity (HR, 1.7; $P = .04$) were independently associated with an increased risk of tumor progression in 699 participants with low-risk papillary thyroid microcarcinoma undergoing active surveillance.
- The presence of DTD was associated with tumor size enlargement (HR, 2.7; $P = .002$), while the presence of intratumoral vascularity was associated with new lymph node metastasis (HR, 5.0; $P = .02$).

Given that participants with PTMC undergo serial US examinations as part of surveillance, it is of clinical relevance to know whether US features have prognostic value; however, evidence from a prospectively designed cohort is lacking. In this study, we assessed whether US features could help predict tumor progression in participants with low-risk PTMC undergoing AS.

Materials and Methods

Study Participants

This study was part of the Multicenter Prospective Cohort Study of Active Surveillance on Papillary Thyroid Microcarcinoma (ClinicalTrials.gov: NCT02938702), which was conducted at three referral hospitals in Korea (Seoul National University Hospital, Seoul National University Bundang Hospital, and National Cancer Center). The study was approved by the institutional review boards of the participating institutions (Seoul National University Hospital, 1603-044-747; Seoul National University Bundang Hospital, B-1605-348-402; and National Cancer Center, 2016-0183). Informed written consent was obtained from all participants.

Patients diagnosed with PTMC (diameter ≤ 1 cm) without involvement of adjacent structures or lymph nodes or distant metastases between June 2016 and January 2021 were considered for inclusion in this study. Biopsy was performed according to Korean Society of Thyroid Radiology guidelines (20) or at participant's request. Patients who met the inclusion criteria were given the option to choose between AS and immediate surgery. Informational materials were provided to all participants before they decided on their preferred management plan. A total of 1177 participants were consecutively enrolled, and 699 participants underwent two or more US examinations in the absence of surgery with a follow-up period of more than 6 months to observe the development of tumor progression. These 699 participants were included in the analysis, in accordance with the predefined study protocol. The enrollment criteria and study protocol have been described previously (21,22). The details of the study design and previously published articles on this cohort are provided in Appendixes S1 and S2, respectively.

Neck US Examination Procedure and Image Processing

At each visit, US of the thyroid and neck was performed by one expert radiologist at each institution (Seoul National University Hospital: J.H.K., with 22 years of experience in thyroid imaging; Seoul National University Bundang Hospital: Y.K.K., with 15 years of experience; National Cancer Center: C.Y.L., with 17 years of experience). Images were collected using high-resolution US units (iU22, Philips Medical Systems; Aixplorer, Supersonic Imagine; Aplio i800, Canon Medical Systems) with high-frequency linear transducers (12–15 MHz). Gray-scale static images and video clips of the thyroid gland and each nodule were obtained. All nodules were evaluated using the transverse and longitudinal planes for three-dimensional evaluation (Fig S1). Color Doppler imaging was performed for each nodule with standardized parameters set to obtain high sensitivity and a low wall filter to allow detection of weak flow. The gain was initially increased until color noise became visible in background tissue. Then, the gain was gradually decreased until all noise speckles were removed, ensuring proper setting adjustment (23). For the evaluation of LNM, US was performed with meticulous scans of bilateral cervical compartments, covering levels I to VI.

US Image Evaluation

The presence of diffuse thyroid disease (DTD) at US was evaluated in all participants, and participants were followed up by the same radiologist who performed initial imaging to minimize interobserver variability. On gray-scale US images, the presence of DTD was determined based on the parenchymal echogenicity, echotexture, size, glandular margin, and vascularity (unilateral or bilateral) (24,25) of the thyroid gland. The details for determining the presence of DTD are summarized in Appendix S3, and examples of DTD are shown in Figure 1.

US findings, including nodule location, were evaluated (20). When a nodule abutted the thyroid capsule without any intervening thyroid parenchyma, it was identified as having a subcapsular location (20). The composition of the nodule was categorized as solid or partially cystic ("mixed cystic and solid" in the American College of Radiology Thyroid Imaging Reporting and Data System [TI-RADS] [26]). Using anterior neck muscles and normal thyroid parenchyma as a reference, nodule echogenicity was categorized as marked hypoechoic ("very hypoechoic" in TI-RADS), mild hypoechoic ("hypoechoic" in TI-RADS), isoechoic, or hyperechoic. Nodule margin was categorized as smooth or ill-defined versus irregular, and orientation (shape) was categorized as parallel (wider than tall) versus nonparallel (taller than wide) (20,26). Calcifications were categorized as punctate echogenic foci (diameter ≤ 1 mm), macrocalcifications (diameter > 1 mm), peripheral calcifications, or none observed. Intratumoral vascularity on Doppler images was recorded as either present or absent.

Follow-up Protocol and Outcome Measures

In participants who chose AS, PTMCs were monitored for tumor progression. Follow-up visits were scheduled twice a

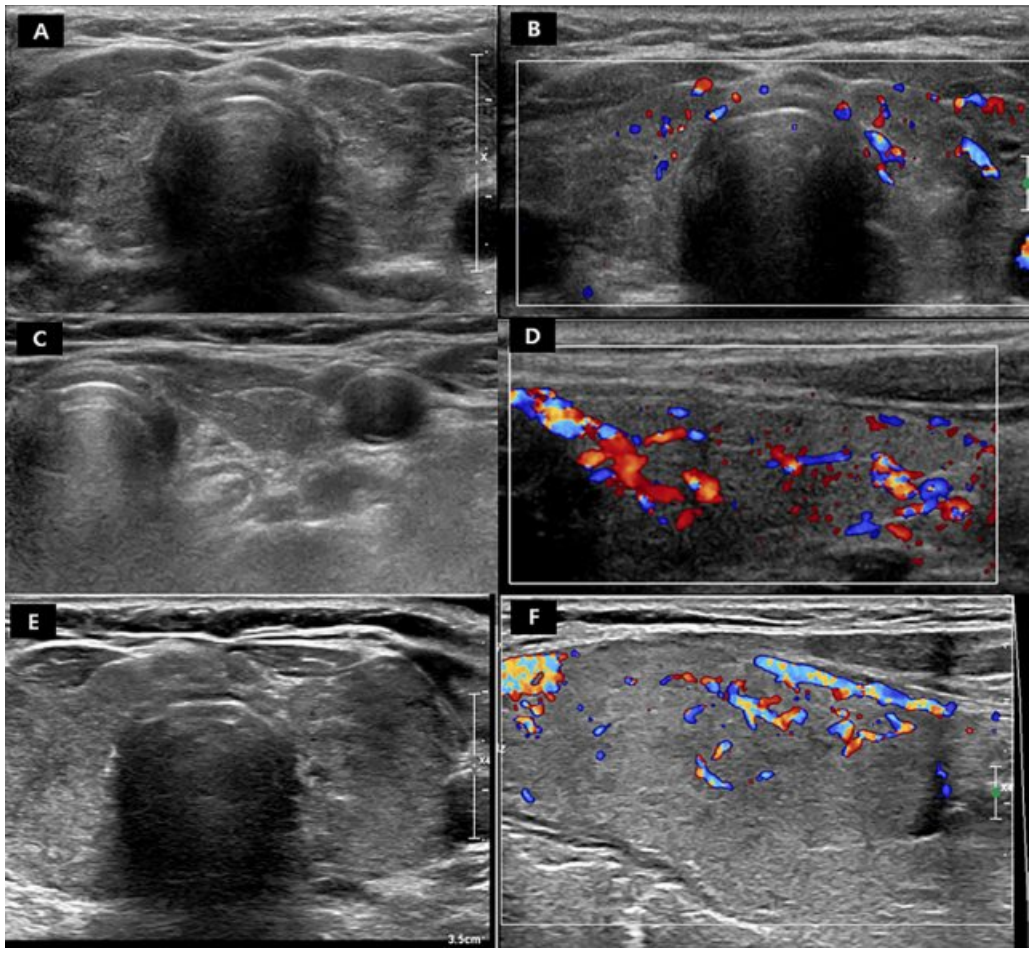

Figure 1: Examples of US features of diffuse thyroid disease (DTD) in three participants. **(A, B)** US images in a 42-year-old female participant with DTD. **(A)** Transverse gray-scale image shows heterogeneous coarse echotexture with decreased parenchymal echo and normal anteroposterior diameter. The glandular margin is lobulated. **(B)** Color Doppler image shows slightly increased vascularity. **(C, D)** US images in a 63-year-old female participant with DTD. **(C)** Transverse image shows diffusely decreased parenchymal echo with decreased glandular size. **(D)** Color Doppler image shows increased vascularity. **(E, F)** US images in a 35-year-old female participant with DTD. **(E)** Transverse image shows decreased parenchymal echo with coarse echotexture, increased anteroposterior diameter of the thyroid gland, and lobulated glandular margin. **(F)** Color Doppler image shows increased parenchymal vascularity.

year during the first 2 years after diagnosis and then annually. Comprehensive physical examinations, interviews, and thyroid function tests were performed at each visit (21). At every evaluation session, additional imaging or biopsy was performed as necessary. Participants underwent surgery if disease progression was detected. Some participants also elected to undergo surgery in the absence of progression. If a participant refused surgery despite progression, AS was continued. Tumor progression was defined as a size increase of 3 mm or more in at least one dimension or 2 mm or more in at least two dimensions, suspected extrathyroidal tumor extension (direct extension into perithyroidal structures including the trachea, esophagus, nerves, and vessels at imaging), pathologic diagnosis of LNM, or suspected distant metastasis (1,3,4,7,21). Any suspicious lymph nodes (with abnormal hyperechogenicity, cystic change, calcification, or abnormal vascularity) with shortest diameter more than 3 mm were biopsied according to current guidelines (20).

Statistical Analysis

Univariable and multivariable Cox proportional hazards regression models were used to evaluate the effects of variables on tumor progression. Variables in this analysis included presence of DTD at US, tumor size, tumor location, US features of the tumor, and clinical features such as age, sex, serum TSH level, and body mass index at baseline (10). For calcifications, we dichotomized the categories according to the presence of macrocalcifications (17,18). The assumption of proportional hazards was tested by assessing Schoenfeld residuals. The variables used in the multivariable model were determined by backward variable selection, with a P value less than .2 indicating a statistically significant difference. Kaplan-Meier curves were plotted for statistically significant variables to compare hazard ratios (HRs) using the log-rank test. We compared participant- and tumor-related features according to statistically significant US findings.

Participants were also stratified into subgroups based on US features, and time-to-progression curves were plotted and

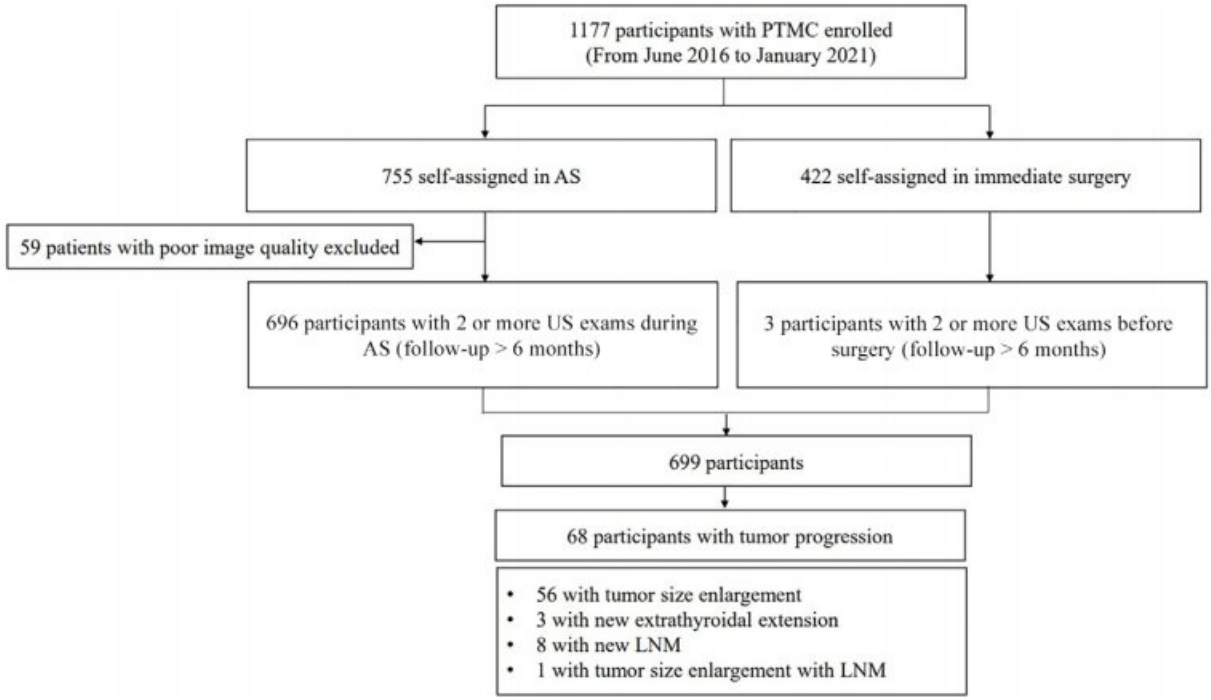

Figure 2: Flow diagram of study participants. AS = active surveillance, LNM = lymph node metastasis, PTMC = papillary thyroid microcarcinoma.

compared post hoc using the log-rank test. The time to progression was extrapolated to 4 years to estimate the potential progression rate beyond the available follow-up period. Tumor progression rate at 4 years was also compared between participants stratified according to US features using a χ^2 test. US features and participant characteristics were analyzed for their association with certain progression criteria using multivariable Cox proportional hazards regression analysis. All statistical analyses were performed by two authors (J.Y.L. and H.S.C., with 7 and 15 years of experience, respectively) using R software (v.4.0.2; R Foundation for Statistical Computing). $P < .05$ was considered to indicate a statistically significant difference or association.

Results

Participant Inclusion and Tumor Progression

A total of 1177 participants were enrolled: 755 of 1177 (64.1%) were self-assigned to AS, and 422 of 1177 (35.9%) were self-assigned to immediate surgery. Of the 755 participants undergoing AS, 59 (7.8%) were excluded due to poor image quality (Fig 2). Additionally, three of the 422 (0.7%) participants who underwent surgery underwent two or more US examinations before their operation. Thus, 699 participants were included in our analysis. The baseline clinical characteristics of participants and the US features of tumors are summarized in Table 1.

The median follow-up period was 41.4 months (range, 6–60.2 months), during which 68 of 699 (10%) participants (mean age, 49 years ± 12 [SD]; 40 female participants, 28 male participants) showed tumor progression. Among these 68 participants with tumor progression, 56 (82%) were classified as having tumor enlargement, with a 3-mm or larger increase observed in 18 of the 68 (26%) participants, a 2-mm or larger increase in at least two dimensions observed in 16 of the 68 (24%) participants, and both a 3-mm or larger increase and a 2-mm or larger increase in two dimensions observed in 22 of the 68 (32%) participants. Additionally, three of the 68 (4%) participants developed extrathyroidal extension, and eight of the 68 (12%) participants developed LNM. One of the 68 (2%) participants demonstrated an increase in tumor size (≥3 mm) simultaneously with LNM. None of the participants had distant metastasis or died during the AS period.

Baseline Clinical Characteristics and US Features Associated with PTMC Progression

Univariable analysis indicated that the US features of DTD (HR, 2.12 [95% CI: 1.32, 3.41]; $P = .002$) and presence of intratumoral vascularity (HR, 2.02 [95% CI: 1.19, 3.44]; $P = .009$) at baseline were associated with tumor progression in participants. The baseline participant characteristics associated with tumor progression were male sex (HR, 2.39 [95% CI: 1.47, 3.87]; $P < .001$); age less than 30 years (HR, 2.18 [95% CI: 1.04, 5.06]; $P = .04$); TSH level of 7 μU/mL or higher (HR, 7.36 [95% CI: 2.96, 18.34]; $P < .001$), and nodule size of 6 mm or more (HR, 1.16 [95% CI: 1.01, 1.34]; $P = .04$). In the multivariable analysis, DTD (HR, 2.27 [95% CI: 1.39, 3.69]; $P = .001$) and presence of intratumoral vascularity (HR, 1.74 [95% CI: 1.01, 2.99]; $P = .04$) were independently associated with tumor progression, along with male sex (HR, 2.82 [95% CI: 1.72, 4.62]; $P < .001$), age less

Table 1: Participant and Tumor Characteristics at Baseline

Characteristic	Value
Patient characteristics	
Sex	
Female	534/699 (76.4)
Male	165/699 (23.6)
Age (y)*	50 ± 12
<30 years	29/699 (4.1)
Baseline TSH level (μU/mL)*	2.2 ± 3.6
≥7 μU/mL	13/699 (1.9)
Baseline BMI*†	23.8 ± 3.1
≥30.0	24/699 (3.4)
Baseline tumor size (mm)*	6.2 ± 1.6
≥6 mm	392/699 (56.1)
Baseline tumor volume (mL)*	97.6 ± 76.0
US features	
DTD	217/699 (31.0)
Tumor location	
Upper craniocaudal	551/699 (78.8)
Mid or lower craniocaudal	148/699 (21.2)
Isthmic	52/699 (7.4)
Subcapsular	313/699 (44.8)
ACR TI-RADS classification	
Highly suspicious (≥7 points)	312/699 (44.6)
Moderately suspicious (4–6 points)	387/699 (55.4)
K-TIRADS classification	
High suspicion	347/699 (49.6)
Intermediate suspicion	352/699 (50.4)
Composition	
Partially cystic (predominantly solid or mixed cystic and solid)	6/699 (0.9)
Solid	693/699 (99.1)
Echogenicity	
Marked hypoechoic (very hypoechoic)	240/699 (34.3)
Mild hypoechoic (hypoechoic)	459/699 (65.7)
Orientation (shape)	
Parallel (wider than tall)	347/699 (49.6)
Nonparallel (taller than wide)	352/699 (50.4)
Margin	
Smooth or ill-defined	123/699 (17.6)
Irregular	576/699 (82.4)
Macrocalcifications	
Absent	630/699 (90.1)
Present	69/699 (9.9)
Intratumoral vascularity	
Absent	587/699 (84.0)
Present	112/699 (16.0)

Note.—Except where indicated, data are numbers of participants, with percentages in parentheses. Sonographic descriptors in parentheses indicate terms in the ACR TI-RADS lexicon. ACR = American College of Radiology, BMI = body mass index, DTD = diffuse thyroid disease, K-TIRADS = Korean Thyroid Imaging Reporting and Data System, TI-RADS = Thyroid Imaging Reporting and Data System, TSH = thyroid stimulating hormone.

* Data are means ± SDs.

† Body mass index calculated as weight in kilograms divided by height in meters.

than 30 years (HR, 2.90 [95% CI: 1.24, 6.81]; $P = .01$), and TSH level of 7 μU/mL or higher (HR, 6.88 [95% CI: 2.72, 17.4]; $P < .001$) (Table 2). The assumption of proportional hazards was found to be not violated (Table S1, Fig S2).

Furthermore, age less than 30 years (log-rank test, $P = .045$), male sex (log-rank test, $P < .001$), TSH level of 7 μU/mL or higher (log-rank test, $P < .001$), and the presence of DTD (log-rank test, $P = .002$) and intratumoral vascularity (log-rank test, $P = .008$) at US accurately stratified tumor progression risk (Fig 3).

Characteristics of Participants with Tumors Showing US Features of DTD or Intratumoral Vascularity

Among all the participants included in the analysis, DTD was observed at US in 217 of 699 (31%) participants, and of those 217 participants, 34 (16%) exhibited tumor progression at US. These participants had higher baseline serum TSH levels than those with DTD but without progression (mean TSH level, 4.4 μU/mL ± 3.9 vs 2.1 μU/mL ± 1.6, respectively; $P = .046$). In participants without DTD, no difference was observed in serum TSH levels between those with and without tumor progression (mean TSH level, 1.6 μU/mL ± 3.7 vs 2.2 μU/mL ± 3.9, respectively; $P = .08$) (Table S2).

Of the participants in this study with intratumoral vascularity (112 of 699 [16%]), 19 of 112 (17%) exhibited tumor progression at US. These participants had larger tumors at baseline compared with those with intratumoral vascularity but without tumor progression (mean diameter, 7.9 mm ± 1.1 vs 6.1 mm ± 1.6, respectively, $P < .001$; mean volume, 164.9 mL ± 68.1 vs 93.0 mL ± 78.3, respectively, $P < .001$) (Table S3).

Progression Rates in Subgroups Stratified according to US Features

Using participants without DTD and intratumoral vascularity at US as the reference, the tumor progression HR was 3.5 for participants with DTD and intratumoral vascularity (95% CI: 1.32, 9.23), 2.2 for participants with intratumoral vascularity without DTD (95% CI: 0.97, 5.14), and 2.2 for participants with DTD without intratumoral vascularity (95% CI: 1.26, 3.89). These US-feature–based subgroups accurately stratified risk of tumor progression (log-rank test, $P = .001$) (Fig 4).

Table 3 shows the progression rates and time to progression in subgroups stratified according to US features. The progression rate at 4 years was higher for participants with intratumoral vascularity (14% [nine of 64]; $P = .02$), DTD (14% [24 of 169]; $P = .001$), or both intratumoral vascularity and DTD (21% [10 of 48]; $P < .001$) than for participants without DTD and intratumoral vascularity (6% [25 of 418]). No differences in progression rates were observed for participants with both intratumoral vascularity and DTD compared with participants with only intratumoral vascularity ($P = .35$) or only DTD ($P = .25$). The median time to progression was 16.4 months (IQR, 9.1–26.5 months) in participants with both DTD and intratumoral vascularity, 20.4 months (IQR, 9.1–23.3 months) in participants with only intratumoral vascularity, 21.6 months (IQR, 13.8–36.5 months) in participants with only DTD, and 27.8 months (IQR, 13.7–39.4 months) in participants with neither intratumoral vascularity nor DTD.

Table 2: Univariable and Multivariable Cox Proportional Hazards Analysis to Assess Variables Associated with Tumor Progression

	Univariable Analysis		Multivariable Analysis	
Variable	Hazard Ratio*	*P* Value	Hazard Ratio*	*P* Value
Patient characteristics				
Male sex	2.39 (1.47, 3.87)	<.001	2.81 (1.72, 4.62)	<.001
Age < 30 y	2.18 (1.04, 5.06)	.04	2.90 (1.24, 6.81)	.01
TSH level ≥ 7 μU/mL	7.36 (2.96, 18.34)	<.001	6.88 (2.72, 17.4)	<.001
BMI ≥ 30†	2.34 (0.94, 5.83)	.07	2.69 (0.98, 6.79)	.06
US features				
DTD	2.12 (1.32, 3.41)	.002	2.27 (1.39, 3.69)	.001
Maximal tumor diameter ≥ 6 mm	1.16 (1.01, 1.34)	.04		
Upper lobe location	0.59 (0.31, 1.17)	.13		
Isthmic location	0.79 (0.29, 2.17)	.65		
Subcapsular location	1.28 (0.80, 2.06)	.31		
Solid composition	0.40 (0.06, 2.87)	.36		
Mild hypoechoic (hypoechoic)	0.99 (0.61, 1.62)	.97		
Irregular margin	0.96 (0.58, 1.60)	.87		
Parallel (wider than tall) orientation	0.85 (0.53, 1.37)	.51		
Macrocalcifications	0.84 (0.36, 1.95)	.69		
Intratumoral vascularity	2.02 (1.19, 3.44)	.009	1.74 (1.01, 2.99)	.042

Note.—Sonographic descriptors in parentheses indicate terms in the lexicon of the American College of Radiology Thyroid Imaging Reporting and Data System. BMI = body mass index, DTD = diffuse thyroid disease, TSH = thyroid-stimulating hormone.

* Numbers in parentheses are 95% CIs.

† Body mass index calculated as weight in kilograms divided by height in meters.

Clinical Characteristics and US Features Associated with Tumor Progression

Tumor enlargement of 3 mm or more was associated with male sex (HR, 3.25 [95% CI: 1.72, 6.15]; $P < .001$), age less than 30 years (HR, 3.48 [95% CI: 1.21, 10.0]; $P = .02$), DTD at US (HR, 2.69 [95% CI: 1.43, 5.07]; $P = .002$), and TSH level of 7 μU/mL or higher (HR, 10.66 [95% CI: 3.72, 30.55]; $P < .001$) (Table 4). DTD (HR, 2.0 [95% CI: 1.05, 3.8]; $P = .04$) and TSH level of 7 μU/mL or higher (HR, 9.16 [95% CI: 2.79, 30.07]; $P < .001$) also showed an association with tumor enlargement of 2 mm or more in at least two dimensions. For new LNM, only intratumoral vascularity showed an independent association (HR, 5.01 [95% CI, 1.29, 19.43]; $P = .02$). Representative US images at baseline and follow-up from a participant who developed LNM and a participant with tumor enlargement are shown in Figures 5 and 6, respectively.

Discussion

The prognostic relevance of US features for tumor progression in participants with low-risk papillary thyroid microcarcinoma (PTMC) undergoing active surveillance is under debate. In this multicenter prospective cohort study, we investigated the predictive value of US features in terms of tumor progression with 4-year follow-up data. The US features of diffuse thyroid disease (DTD) (hazard ratio [HR], 2.3; $P = .001$) and intratumoral vascularity (HR, 1.7; $P = .04$) and the participant characteristics of age less than 30 years old (HR, 2.9; $P = .01$), male sex (HR, 2.8; $P < .001$), and serum thyroid-stimulating hormone (TSH) level of 7 μU/mL or higher (HR, 6.9; $P < .001$) were predictors of tumor progression in low-risk PTMC. Participants with DTD and/or intratumoral vascularity showed higher progression rates than participants without these features. While DTD (HR, 2.7; $P = .002$), age, sex, and TSH level were associated with tumor size enlargement, the presence of intratumoral vascularity was associated with the development of lymph node metastasis (HR, 5.0; $P = .02$).

Tumors with intratumoral vascularity and DTD observed on baseline US images more frequently demonstrated tumor progression compared with tumors without vascularity and DTD (10 of 48 [21%] vs 25 of 418 [6%]; $P < .001$). A previous study also reported that vascularized tumors showed a significantly higher progression rate than poorly vascularized PTMCs (17). This could indicate that angiogenesis is a prerequisite for tumor growth and metastasis, as occurs in many solid tumors (eg, breast, prostate, and kidney) (25,26). The role of TSH in the initiation or progression of papillary thyroid cancer has been previously demonstrated (27). A recent study showed an association between TSH level and tumor progression during AS (12); however, this association was not observed in another study (28). Several previous studies have reported on the relationship between the degree of sonographic thyroiditis and the severity of thyroid dysfunction (25,29). Given that our study found that participants with DTD and tumor progression showed high serum TSH levels, we hypothesize that parenchymal changes observed at US may be an early sign of thyroid dysfunction, manifesting as high serum TSH levels.

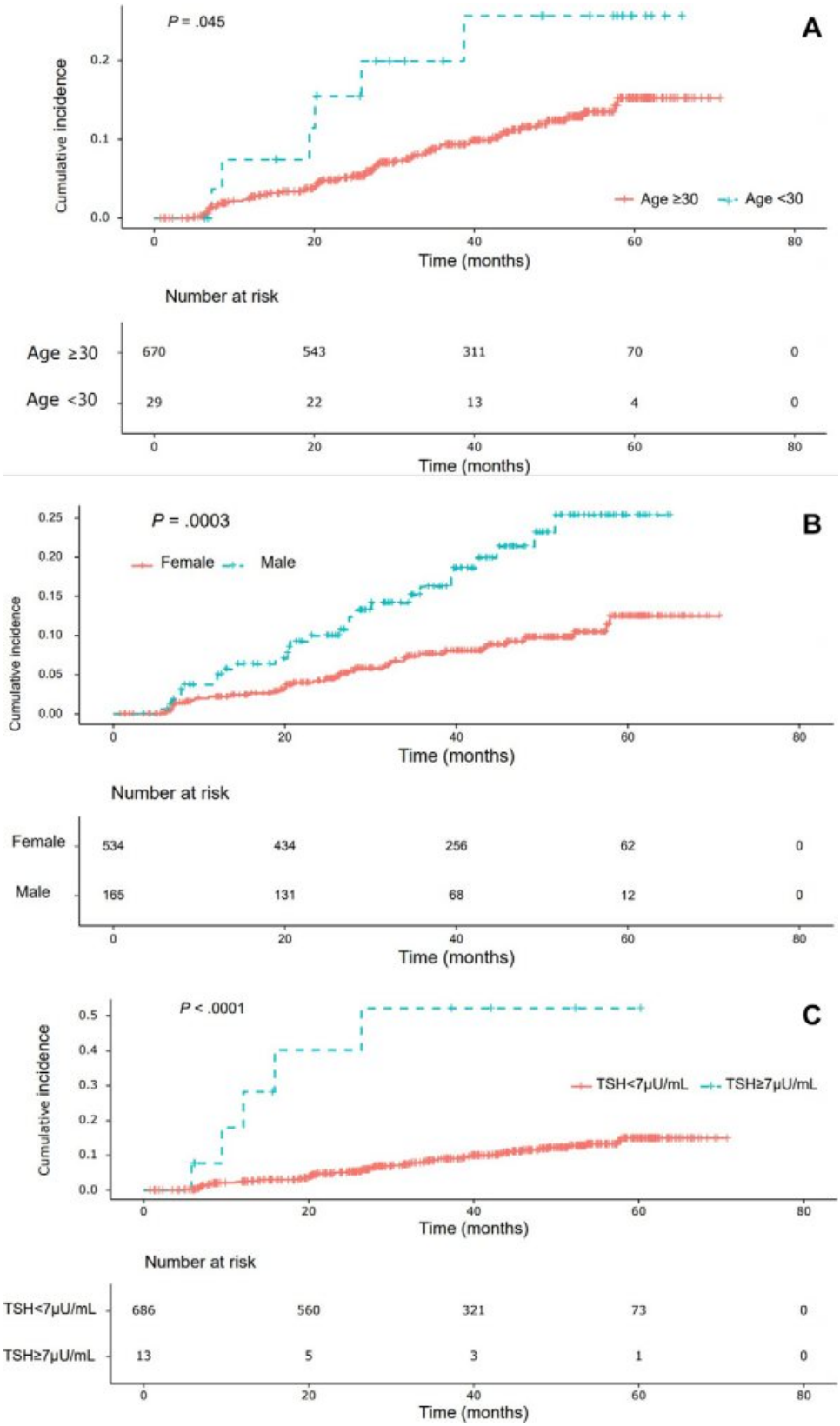

Figure 3: Kaplan-Meier curves show time-dependent cumulative incidence of tumor progression in participants with papillary thyroid microcarcinoma stratified according to participant characteristics or US features. **(A)** Participants less than 30 years of age showed a higher risk of tumor progression than participants 30 years of age or older (log-rank test, $P = .045$). **(B)** Male participants showed a higher risk of tumor progression than female participants (log-rank test, $P < .001$). **(C)** Participants with baseline serum thyroid-stimulating hormone (TSH) level of 7 μU/mL or higher showed a higher risk of tumor progression than those with baseline level less than 7 μU/mL (log-rank test, $P < .001$) *(Fig 3 continues)*.

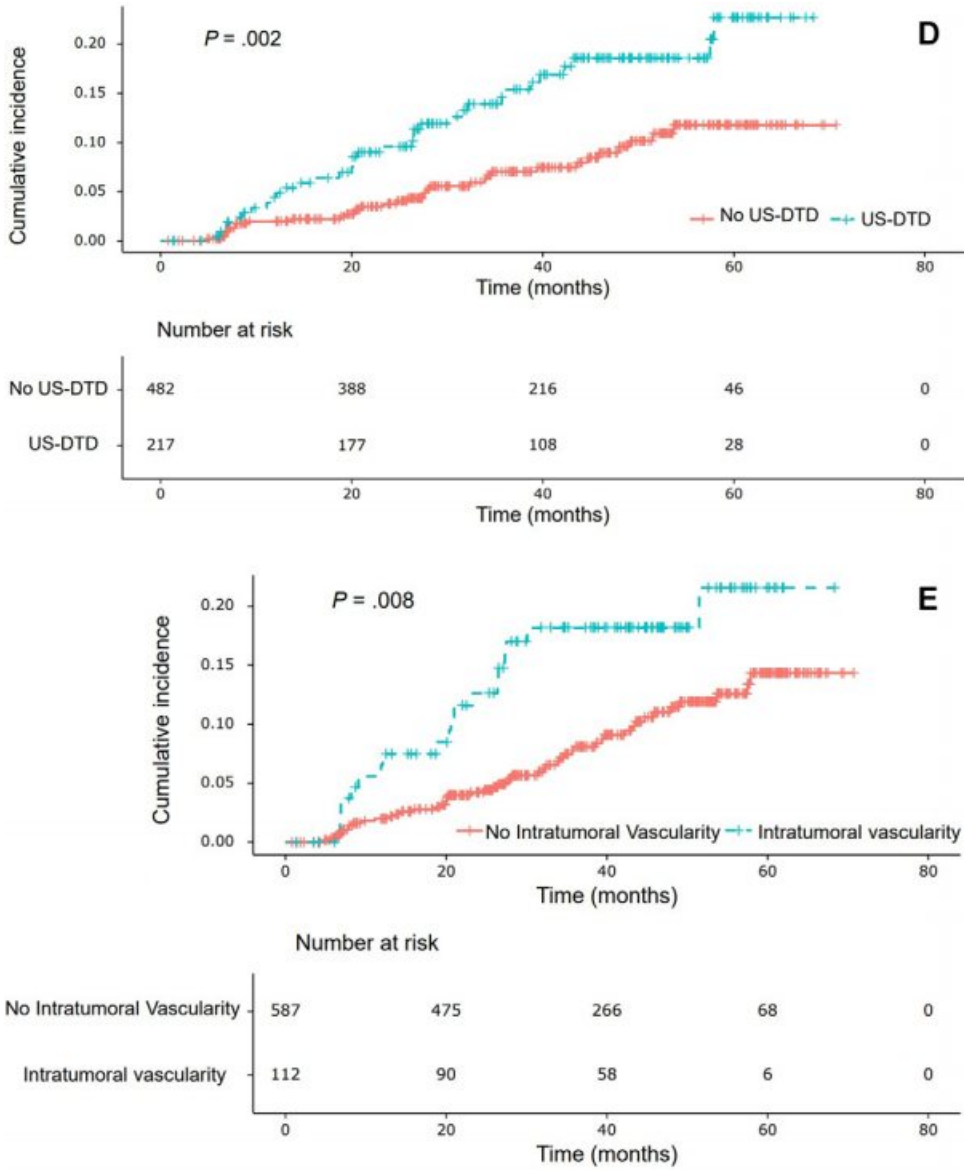

Figure 3 ***(continued)*****: (D)** Participants with diffuse thyroid disease at US (US-DTD) showed a higher risk of tumor progression than those without DTD at US (log-rank test, *P* = .002). **(E)** Participants with intratumoral vascularity on Doppler US scans showed a higher risk of tumor progression than those with no intratumoral vascularity (log-rank test, *P* = .008).

This study is the first to our knowledge to investigate the prognostic value of US features for predicting tumor progression in PTMC with a prospective and multicenter study design. Moreover, this study has clinical relevance as Doppler characteristics are thought to have little importance for risk stratification of thyroid nodules. Our results suggest that DTD and tumor vascularity should be evaluated on US scans in participants undergoing AS, along with tumor size changes, extrathyroidal extensions, and LNM. A robust model that accurately predicts progression could be used to help stratify surveillance protocols, and could reduce patient anxiety, enhance cost-effectiveness, and potentially allow for wider adoption of AS.

Younger age at diagnosis has been consistently reported as predictive of early tumor progression (4,30). Our results confirmed these findings as the risk of PTMC growth during AS in participants less than 30 years of age was more than double that of participants 30 years of age or older (HR, 2.9; *P* = .01). Male sex was also associated with a higher risk of tumor progression, which is in line with previous studies (8,16,31).

Our study has several limitations. First, the effects of thyroxine administration and changes in TSH levels and US features over time were not analyzed in this study. Since TSH suppression could potentially affect tumor progression (12,13), the effects of temporal changes in these variables should be validated in future studies. Second, DTD at US is heterogeneous and includes several etiologies. In practice, operators often perform US without any knowledge of autoantibody status. We believe that an intuitive evaluation of DTD at US has the potential

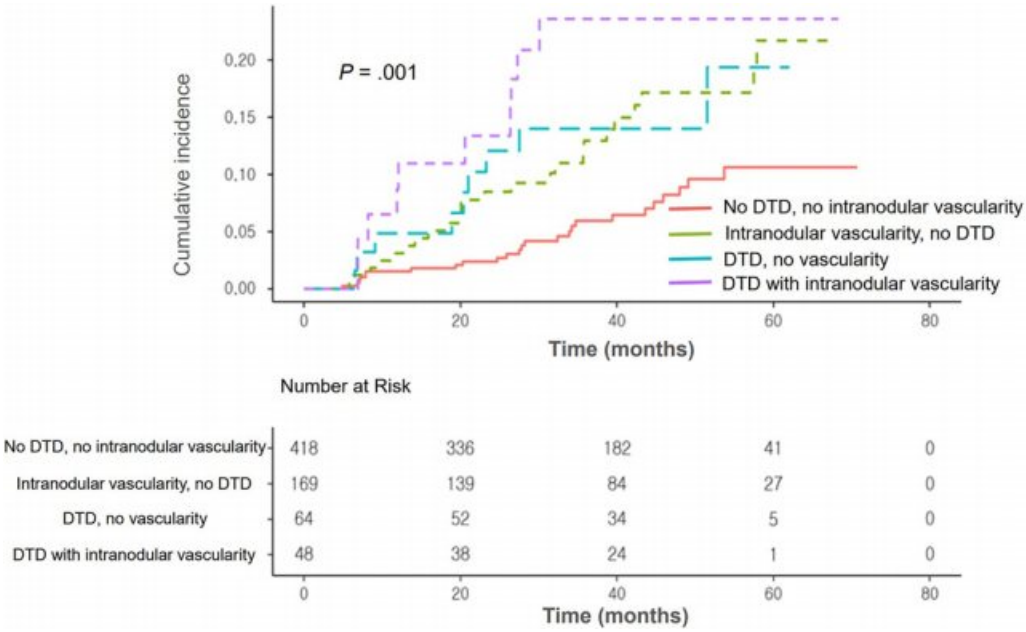

Figure 4: Kaplan-Meier curve shows time-dependent cumulative incidence of tumor progression in participants with papillary thyroid microcarcinoma stratified according to US features. The red line depicts participants with no diffuse thyroid disease (DTD) and no intratumoral (intranodular) vascularity at US; the green line depicts participants with intratumoral vascularity but no DTD; the blue line depicts participants with DTD but no intratumoral vascularity; and the purple line depicts participants with both DTD and intratumoral vascularity. These US-feature-based subgroups accurately stratified risk of tumor progression (log-rank test, *P* = .001).

Table 3: Progression Rates and Time to Progression in Subgroups Stratified according to US Features

Variable	Subgroup			
	Neither DTD nor IV (*n* = 418)	IV Only (*n* = 64)	DTD Only (*n* = 169)	IV and DTD (*n* = 48)
Follow-up duration (mo)*	36.9 ± 17.9	36.3 ± 17.9	36.5 ± 17.9	36.6 ± 18.1
Estimated tumor progression rate at 4 years†	25/418 (6)	9/64 (14)	24/169 (14)	10/48 (21)
Comparison of 4-year progression rate (*P* value)				
Neither DTD nor IV	Reference	.02	.001	<.001
IV only	.02	Reference	.98	.35
DTD only	.001	.98	Reference	.25
2-year estimated progression rate (%)‡	2.2 (1.0, 4.1)	10.9 (4.5, 21.2)	7.7 (4.2, 12.8)	12.5 (4.7, 25.3)
5-year estimated progression rate (%)‡	10.7 (6.4, 15.0)	19.4 (6.1, 32.6)	21.7 (12.6, 30.4)	23.5 (10.8, 36.5)
Median time to progression (mo)§	27.8 (13.7–39.4)	20.4 (9.1–23.3)	21.6 (13.8–36.5)	16.4 (9.1–26.5)

Note.—*P* values were calculated using χ^2 test. DTD = diffuse thyroid disease, IV = intratumoral vascularity.

* Data are means ± SDs.

† Data are numbers of participants, with percentages in parentheses.

‡ Data in parentheses are 95% CIs.

§ Data in parentheses are IQRs.

to overcome this lack of information. Third, tumor volume enlargement of more than 50% was not adopted as a marker of tumor progression in this study (9). We chose to use the conventional 3-mm criterion and a two-dimensional criterion, as we considered that a 50% volume increase could potentially fall within measurement error for US measurement, leading to unnecessary early surgery (32). Optimal criteria should be validated in future studies. Fourth, it should be noted that advanced techniques such as microvascular US were not employed at the outset of this study. Because this study was conducted using conventional Doppler US techniques, the results might have been different if microvascular imaging had been performed. To validate the relationship between microvascular imaging patterns and tumor progression, future studies will be necessary. Last, randomization was not performed in this trial. It is uncertain how regional and family characteristics as well as

Table 4: Multivariable Cox Proportional Hazards Analysis to Assess Participant and Tumor Characteristics Associated with Specific Tumor Progression Criteria

	Increase ≥ 3 mm and New LNM		Increase ≥ 3 mm in One Dimension		Increase ≥ 2 mm in Two Dimensions		New LNM	
Characteristic	Hazard Ratio	*P* Value	Hazard Ratio	*P* Value	Hazard Ratio	*P* Value	Hazard Ratio	*P* Value
Male sex	3.37 (1.8, 6.3)	<.001	3.25 (1.72, 6.15)	<.001	1.95 (0.99, 3.84)	.05	2.59 (0.68, 9.81)	.16
Age < 30 years	3.42 (1.2, 9.8)	.02	3.48 (1.21, 10.0)	.02				
DTD	2.54 (1.36, 4.73)	.004	2.69 (1.43, 5.07)	.002	2.00 (1.05, 3.80)	.04	2.24 (0.57, 8.75)	.25
TSH level ≥ 7 μU/mL	10.09 (3.52, 28.86)	<.001	10.66 (3.72, 30.55)	<.001	9.16 (2.79, 30.07)	<.001	6.75 (0.79, 57.72)	.08
Intratumoral vascularity	1.17 (0.87, 3.45)	.12	1.58 (0.78, 3.21)	.21			5.01 (1.29, 19.43)	.02

Note.—Data in parentheses are 95% CIs. DTD = diffuse thyroid disease, LNM = lymph node metastasis, TSH = thyroid-stimulating hormone.

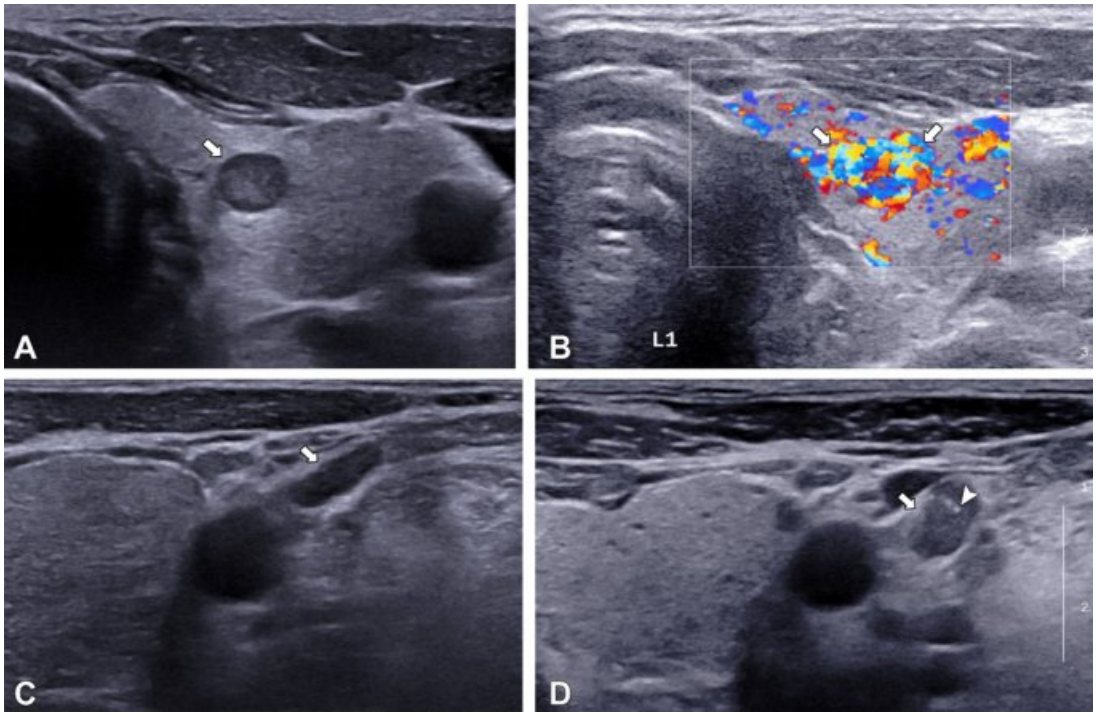

Figure 5: Progression of hypervascular tumor with lymph node metastasis in a 64-year-old male participant with papillary thyroid microcarcinoma. **(A–C)** Baseline US images. **(A)** Transverse gray-scale image shows a solid hypoechoic thyroid nodule (arrow) with a maximal diameter of 7 mm. **(B)** Color Doppler image shows hypervascularity, represented by increased vascularity above that of normal thyroid parenchyma (arrows). **(C)** Transverse gray-scale image shows a small, probably benign, lymph node at left level IV (arrow). **(D)** Transverse US image at 12-month follow-up demonstrates a suspicious lymph node (arrow) with increased shortest diameter and punctate echogenic foci (arrowhead). Subsequent fine-needle aspiration for this level IV lymph node revealed a metastatic thyroid papillary carcinoma.

the economic capacity of the participants influenced treatment decisions. However, the proportion of participants who chose surgery in this study was small, so it is believed that the influence of these factors would be minimal.

In summary, we demonstrated that two US features, diffuse thyroid disease and intratumoral vascularity, along with the participant characteristics of young age, male sex, and elevated baseline thyroid-stimulating hormone level, were associated with tumor progression in papillary thyroid microcarcinoma. Prediction incorporating US features may help personalize surveillance strategies in the future. Longer-term follow-up data are required to validate our results.

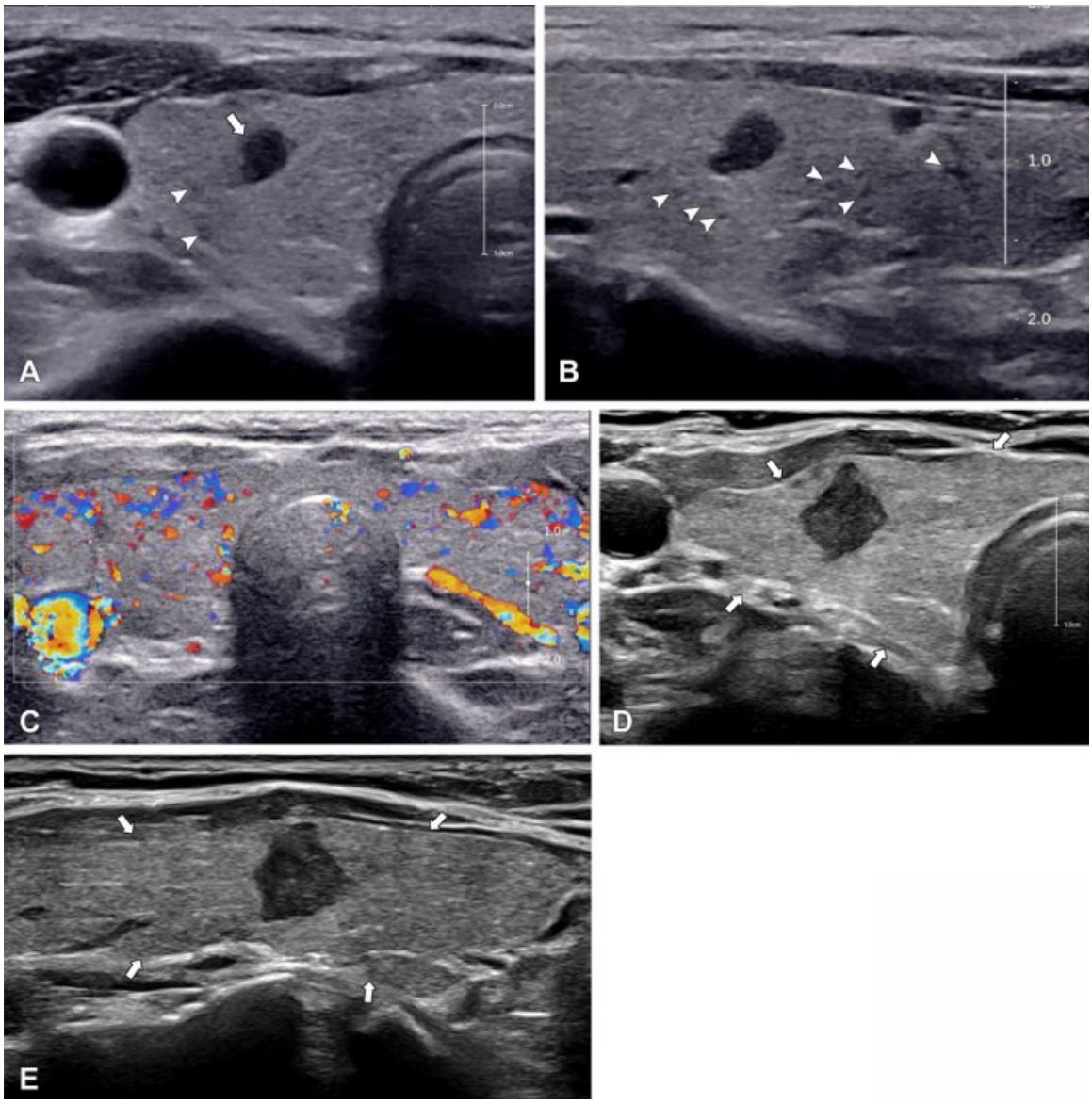

Figure 6: Enlargement of a tumor in the presence of diffuse thyroid disease in a 47-year-old female participant with papillary thyroid microcarcinoma (PTMC). **(A–C)** Baseline US images. **(A)** Transverse and **(B)** longitudinal images of the right thyroid gland show a solid hypoechoic nodule (arrow in **A**) with a maximal diameter of 4 mm. Thyroid parenchyma shows a coarse micronodular echotexture pattern (arrowheads) and was classified as positive for diffuse thyroid disease. **(C)** Color Doppler image shows diffuse increased vascularity in the thyroid gland. **(D, E)** US images at 18-month follow-up. **(D)** Transverse and **(E)** longitudinal US images demonstrate tumor enlargement to 8 mm. Background thyroid parenchyma shows mild diffuse hypoechogenicity involving whole thyroid gland, with lobulated contour (arrows). No suspicious lymph nodes were observed at US or CT. Subsequent lobectomy and ipsilateral central neck dissection showed PTMC with lymphocytic thyroiditis. Two metastatic lymph nodes were diagnosed out of five dissected lymph nodes.

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Data sharing: Data generated or analyzed during the study are available from the corresponding author by request.

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