Original Article | Thyroid

eISSN 2005-8330
https://doi.org/10.3348/kjr.2023.0461
Korean J Radiol 2024;25(1):103-112

Korean Journal of Radiology
KJR

Association of Ultrasonography Features of Follicular Thyroid Carcinoma With Tumor Invasiveness and Prognosis Based on WHO Classification and TERT Promoter Mutation

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Objective: To investigate the association of ultrasound (US) features of follicular thyroid carcinoma (FTC) with tumor invasiveness and prognosis based on the World Health Organization (WHO) classification and telomerase reverse transcriptase (TERT) promoter mutations.

Materials and Methods: This retrospective study included 54 surgically confirmed FTC patients with US images and TERT promoter mutations (41 females and 13 males; median age [interquartile range], 40 years [30–51 years]). The WHO classification consisted of minimally invasive (MI), encapsulated angioinvasive (EA), and widely invasive (WI) FTCs. Alternative classifications included Group 1 (MI-FTC and EA-FTC with wild type TERT), Group 2 (WI-FTC with wild type TERT), and Group 3 (EA-FTC and WI-FTC with mutant TERT). Each nodule was categorized according to the US patterns of the Korean Thyroid Imaging Reporting and Data System (K-TIRADS) and American College of Radiology-TIRADS (ACR-TIRADS). The Jonckheere-Terpstra and Cochran-Armitage tests were used for statistical analysis.

Results: Among 54 patients, 29 (53.7%) had MI-FTC, 16 (29.6%) had EA-FTC, and nine (16.7%) had WI-FTC. In both the classifications, lobulation, irregular margins, and final assessment categories showed significant differences (all $Ps \leq 0.04$). Furthermore, the incidences of lobulation, irregular margin, and high suspicion category tended to increase with increasing tumor invasiveness and worse prognosis (all *Ps* for trend ≤ 0.006). In the WHO groups, hypoechogenicity differed significantly among the groups ($P = 0.01$) and tended to increase in proportion as tumor invasiveness increased (P for trend = 0.02). In the alternative group, punctate echogenic foci were associated with prognosis ($P = 0.03$, P for trend = 0.03).

Conclusion: Increasing tumor invasiveness and worsening prognosis in FTC based on the WHO classification and TERT promoter mutation results were positively correlated with US features that indicate malignant probability according to both K-TIRADS and ACR-TIRADS.

Keywords: Ultrasonography; Follicular thyroid carcinoma; TERT promoter mutation; WHO classification

Received: May 25, 2023 **Revised:** October 20, 2023 **Accepted:** November 2, 2023

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INTRODUCTION

Telomerase reverse transcriptase (TERT) promoter mutations are highly associated with tumor aggressiveness and are considered potential prognostic molecular markers [1-4]. Furthermore, previous studies have supported ultrasound (US) as the first-choice imaging method for thyroid cancer diagnosis. US imaging findings are closely correlated with clinical behavior, prognosis, and genetic mutation status of thyroid cancer, including TERT promoter mutations. However, previous studies have mainly focused on patients with papillary thyroid carcinoma (PTC) [5-7].

Follicular thyroid carcinoma (FTC) is the second most common type of thyroid cancer, accounting for approximately 10% of all thyroid cancer cases after PTC [8]. Although both FTC and PTC are derived from the follicular epithelium of the thyroid gland and are usually considered differentiated thyroid carcinomas (DTCs), the epidemiological, pathological, and clinical characteristics of FTC differ from those of PTC [9-14]. The previous World Health Organization (WHO) classification (WHO 2004), categorized FTC into minimally invasive and widely invasive types. Following the revision of the WHO classification in 2017, FTC is currently divided into the following three types based on the invasive pattern and angioinvasion: minimally invasive FTC (MI-FTC), encapsulated angioinvasive FTC (EA-FTC), and widely invasive FTC (WI-FTC), and the predictability of disease-free survival (DFS) has since improved [15]. This revision was adopted to improve the predictability of DFS in patients with FTC [16].

A recent study revealed that combining TERT promoter mutation status and WHO classification can predict cancer-specific survival and DFS in patients with FTC [17]. Based on the aforementioned results, we hypothesized that tumor invasiveness and prognosis of FTC would correlate with US findings, as observed in previous studies on PTC [1,18-20]. Therefore, we aimed to investigate the association of US features of FTC with tumor invasiveness and prognosis based on the WHO classification and TERT promoter mutations.

MATERIALS AND METHODS

This retrospective study was approved by the Institutional Review Board of Samsung Medical Center (IRB no. 2022-04-024). The need to obtain informed consent was waived and patient information was anonymized before analysis. The 54 patients included in this study were those previously reported in an earlier study [17], which focused on combining the WHO classification and TERT promoter mutations for improved tumor response prediction in patients with FTC. This study focused on the role of US in predicting tumor invasiveness and prognosis in patients with FTC.

Study Population and Clinicopathological Data

A total of 77 consecutive patients with FTC who underwent initial thyroid cancer surgery at our institution between August 1995 and April 2021 and had a confirmed TERT promoter mutation status, were enrolled in this study. Among them, 23 patients were excluded because preoperative US evaluations were not available. Finally, 54 patients with surgically confirmed FTC, who underwent preoperative US and TERT mutation analyses, were included (Fig 1). Among them, there were 41 females (median 43.0, interquartile range

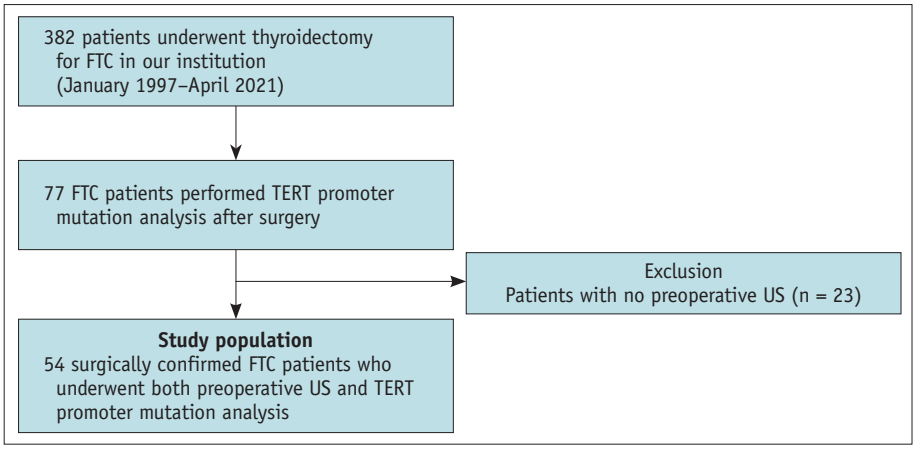

Fig. 1. Patient selection flow chart. A total of 54 patients with surgically confirmed FTC with TERT promoter mutation analysis were included in our study from 1997 to 2021. FTC = follicular thyroid carcinoma, TERT = telomerase reverse transcriptase, US = ultrasound

https://doi.org/10.3348/kjr.2023.0461

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[IQR], 30.5–54.0) and 13 males (median 43.0, IQR 26.5–50.0), with an overall median age of 40.0 (IQR, 30.0–51.0) years. The median tumor size was 3.2 (IQR, 2.4–5.0) cm.

Clinicopathological data including age, sex, tumor size, gross extrathyroidal extension, distant metastasis, pathologic stage based on the American Joint Committee on Cancer (AJCC)/tumor, node, metastasis (TNM) staging system, recurrence, and death were retrieved from medical records, operating records, and final pathologic reports. An experienced thyroid pathologist at the Department of Pathology reviewed the slides to confirm the status of vascular invasion, and all FTCs were classified according to the WHO classification as follows: MI-FTC, EA-FTC, and WI-FIC [15].

Detection of TERT Promoter Mutations

DNA samples for molecular analysis were extracted from postoperative surgical specimens using a Qiagen DNA FFPE Tissue Kit (Qiagen), according to the manufacturer's instructions. TERT promoter mutations were analyzed by polymerase chain reaction amplification and direct Sanger sequencing of hot spots as previously described (chr5:1,295,228C>T and chr5:1,295,250C>T, commonly termed C228T and C250T) [21,22].

Preoperative US Imaging Analyses

During the study period, all preoperative thyroid US examinations were performed with a 5–12 MHz linear array transducer using a Logiq 700 scanner (General Electric Healthcare), HDI 5000 scanner (Philips Ultrasound), or IU22 scanner (Philips Medical Systems) by one of the eight radiologists (four faculty members and four fellows) with 1–16 years of experience in thyroid imaging.

All US images were retrospectively reviewed and interpreted by two radiologists (M.K.K. and S.Y.H.) with 4 and 14 years of experience, respectively, who were blinded to the clinicopathological characteristics and TERT promoter mutation analysis results.

According to the revised Korean Thyroid Imaging Reporting and Data System (K-TIRADS) and American College of Radiology-TIRADS (ACR-TIRADS) [23,24], all FTC lesions were described according to the following criteria: 1) composition (cystic with no obvious solid component, predominantly cystic with > 50% of cystic portion, predominantly solid with ≤ 50% of cystic portion, or solid with no cystic component), 2) echogenicity (hyperechoic, isoechoic, mild hypoechoic, or marked hypoechoic), 3) margin (smooth, ill defined, or irregular including spiculated and microlobulated), 4) echogenic foci (punctate echogenic foci, macrocalcification, rim or peripheral calcification, or intracystic echogenic foci with comet tail artifact), and 5) orientation (parallel or nonparallel). In addition, lobulation (defined as rounded projection areas where the base of the outward protrusion measures ≥ 2.5 mm) [25,26] and heterogeneity (defined as the presence of two different portions of echogenicity [iso or hyperechoic vs. mild or marked hypoechogenicity] within the solid portion) were also evaluated.

For the final K-TIRADS assessments [23], thyroid nodules were classified into five groups: category 1, no nodule; category 2, benign nodule (iso/hyperechoic spongiform, partially cystic nodule with intracystic echogenic foci and comet tail artifact, or pure cyst); category 3, low-suspicion nodule (partially cystic or iso/hyperechoic nodule without any of the three suspicious US features [punctate echogenic foci, nonparallel orientation, and irregular margin]); category 4, intermediate suspicion nodule (solid hypoechoic nodule without any of the three suspicious US features, partially cystic or iso/hyperechoic nodule with any of the three suspicious US features, or entirely calcified nodules); and category 5, high suspicion nodule (solid hypoechoic nodule with any of the three suspicious US features).

Based on the ACR-TIRADS [24], points were given for all US features in a nodule, with more suspicious features being awarded additional points, as follows: composition, 0 points for cystic or almost completely cystic and spongiform, 1 point for mixed cystic and solid, 2 points for solid or almost completely solid; echogenicity, 0 points for anechoic, 1 point for hyperechoic or isoechoic, 2 points for hypoechoic, 3 points for very hypoechoic; shape, 0 points for wider-than-tall, 3 points for taller-than-wide; margin, 0 points for smooth, 0 points for ill-defined, 2 points for lobulated or irregular, 3 points for extra-thyroidal extension; echogenic foci, 0 points for none or large, 1 point for macrocalcifications, 2 points for peripheral (rim) calcifications, 3 points for punctate echogenic foci. The total number of points determined the nodule's ACR-TIRADS level, and the US features were categorized as benign (0 point), not suspicious (2 points), mildly suspicious (3 points), moderately suspicious (4–6 points), or highly suspicious (7 points or more) for malignancy.

Statistical Analyses

For statistical analyses, all FTCs were categorized according to the WHO and alternative classifications. The

 https://doi.org/10.3348/kjr.2023.0461

WHO classification consists of MI-FTC, EA-FTC, and WI-FTC based on the degree of tumor invasiveness. An alternative classification was made by combining the WHO classification with TERT promoter mutation status for better prognostic prediction, with reference to a recent study [17]. This combined classification system comprises three groups: Group 1 (MI-FTC with wild type [WT]-TERT and mutant [M]-TERT; EA-FTC with WT-TERT), Group 2 (WI-FTC with WT-TERT), and Group 3 (EA-FTC with M-TERT; WI-FTC with M-TERT).

Clinicopathological features including US findings of the WHO classification groups were compared using the χ^2-test or Fisher's exact test for categorical variables and the Kruskal–Wallis test for continuous variables. The trends of variables across the WHO and alternative classifications were tested using the Jonckheere-Terpstra and Cochran-Armitage trend tests for continuous and categorical variables, respectively. Statistical significance was set at $P < 0.05$. All statistical analyses were performed using the SPSS software (PASW Statistics, version 27; IBM Corp.).

RESULTS

Clinicopathological Characteristics

The 54 FTCs comprised 29 MI-FTCs (53.7%), 16 EA-FTCs (29.6%), and nine WI-FTCs (16.7%) based on the WHO classification, and had 42 cases (77.8%) in Group 1, five cases (9.3%) in Group 2, and seven cases (13.0%) in Group 3 based on the alternative classification.

Table 1 presents the clinicopathological characteristics of the patients with FTC according to the WHO classification. The TERT promoter mutation status, AJCC/TNM stage, recurrence, and death were significantly associated with tumor invasiveness (all *Ps* ≤ 0.02 and *Ps* for trend ≤ 0.01). Furthermore, gross extrathyroidal extension, distant metastasis, and AJCC/TNM stage III/IV were only found in the WI-FTC group. There were no significant differences in sex, age, or primary tumor size among the WHO classification groups.

US Imaging Findings

The main US findings on MI-FTC were solid composition (58.6%), iso/hyperechogenicity (55.2%), smooth margins

Table 1. Clinicopathological characteristics according to the WHO classification

	MI-FTC (n = 29)	EA-FTC (n = 16)	WI-FTC (n = 9)	*P*	*P* for trend
Sex				0.63	0.36
Female	21 (72.4)	12 (70.6)	8 (88.9)		
Male	8 (27.6)	4 (25.0)	1 (11.1)		
Age, yr, median (IQR)	48 (32.5, 57)	41 (31.3, 50.3)	35 (24, 48)	0.08	0.06
Age group				0.82	
< 55 yr	24 (82.8)	12 (75.0)	7 (77.8)		
≥ 55 yr	5 (17.2)	4 (25.0)	2 (22.2)		
Size, cm, median (IQR)	3.1 (2.2, 4.7)	4.1 (2.5, 5.9)	3.2 (2.0, 7.1)	0.35	0.24
Size group				0.55	0.77
≤ 4 cm	19 (65.5)	8 (50.0)	6 (66.7)		
> 4 cm	10 (34.5)	8 (50.0)	3 (33.3)		
TERT promoter mutation	2 (6.9)	3 (18.8)	4 (44.4)	0.02*	0.01†
Gross ETE	0	0	1 (11.1)	0.17	0.07
Distant metastasis	0	0	5 (55.6)	< 0.001*	< 0.001†
AJCC/TNM 8th stage				< 0.001*	< 0.001†
Stage I	29 (100.0)	12 (75.0)	4 (44.4)		
Stage II	0	4 (25.0)	4 (44.4)		
Stage III/IV	0	0	1 (11.1)		
Recurrence	2 (6.9)	0	6 (66.7)	< 0.001*	< 0.001†
Death	0	1 (6.3)	4 (44.4)	< 0.001*	< 0.001†

Data are number of patients with % in parentheses, unless specified otherwise.
*A *P*-value of < 0.05 was considered statistically significant, †A *P* for trend value of < 0.05 was considered statistically significant.
WHO = World Health Organization, MI-FTC = minimally invasive follicular thyroid carcinoma, EA-FTC = encapsulated angioinvasive follicular thyroid carcinoma, WI-FTC = widely invasive follicular thyroid carcinoma, IQR = interquartile range, TERT = telomerase reverse transcriptase, ETE = extrathyroidal extension, AJCC = American Joint Committee on Cancer, TNM = tumor, node, metastasis

https://doi.org/10.3348/kjr.2023.0461

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(93.1%), parallel orientation (100%), and no calcification (62.1%) (Fig. 2). In addition, the representative US findings in EA-FTC were solid composition (68.8%), hypoechogenicity (81.3%), heterogeneity (50.0%), lobulation (62.5%), smooth margins (93.8%), parallel orientation (100%), and no calcification (68.8%) (Fig. 3). Finally, US revealed a solid composition (100%), hypoechogenicity (88.9%), heterogeneity (66.7%), lobulation (88.9%), irregular margins (66.7%), parallel orientation (100%), and calcification, including punctate echogenic foci (66.6%) in WI-FTC (Fig. 4).

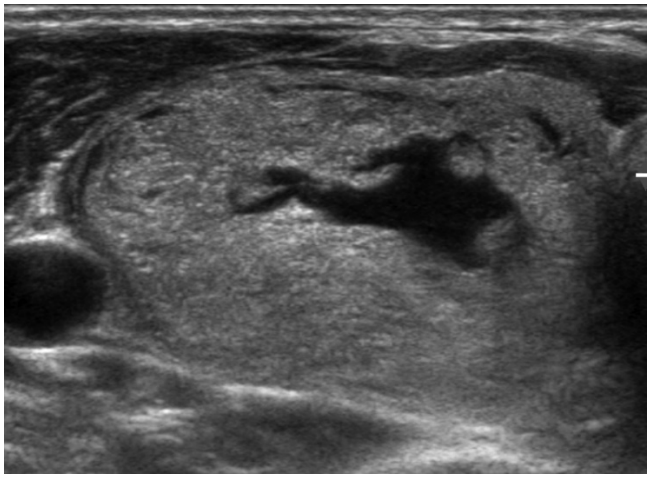

Fig. 2. Transverse US image of a 50-year-old male with minimally invasive follicular thyroid carcinoma with wild type TERT showing a 5.8 cm predominantly solid nodule with smooth margin, isoechogenicity, and parallel orientation. This nodule was classified as K-TIRADS category 3 and ACR-TIRADS category 2. After surgery, the TNM stage was confirmed as I (T3N0M0) and there was no recurrence during 5 years of follow-up. US = ultrasound, TERT = telomerase reverse transcriptase, K-TIRADS = Korean-Thyroid Imaging Reporting and Data System, ACR = American College of Radiology, TNM = tumor, node, metastasis

Table 2 shows the US imaging findings of the WHO and alternative classification groups. In both, there were significant differences in lobulation and irregular margins (all *Ps* ≤ 0.005) and, at the same time, their incidences tended to increase with increasing tumor invasiveness in the WHO group (all *Ps* for trend ≤ 0.001) and worsening prognosis in the alternative group (all *Ps* for trend ≤ 0.002). In the WHO group, the incidence of heterogeneity had an increasing trend in the order of MI-FTC, EA-FTC, and WI-FTC (*P* for trend = 0.02). In addition, hypoechogenicity differed significantly among the WHO groups (*P* = 0.01) and tended to increase proportionately as tumor invasiveness increased (*P* for trend = 0.02). Calcification patterns differed significantly among the groups in both the classification systems (all *Ps* ≤ 0.03). The incidence of no calcification pattern in the alternative group showed a decreasing trend in the order of Groups 1, 2, and 3 (*P* for trend = 0.04). Meanwhile, punctate echogenic foci were observed in 57.1% of the patients in alternative Group 3 and were associated with a worse prognosis (*P* for trend = 0.03).

For the final assessment category based on K-TIRADS and ACR-TIRADS (Table 3), neither the low-suspicion K-TIRADS category nor the not suspicious and mildly suspicious ACR-TIRADS categories were assigned to WI-FTC or alternative Groups 2 and 3. In both the classification groups, final K-TIRADS and ACR-TIRADS assessment categories showed significant differences (all *Ps* ≤ 0.04), and the incidence of high suspicion categories tended to increase with

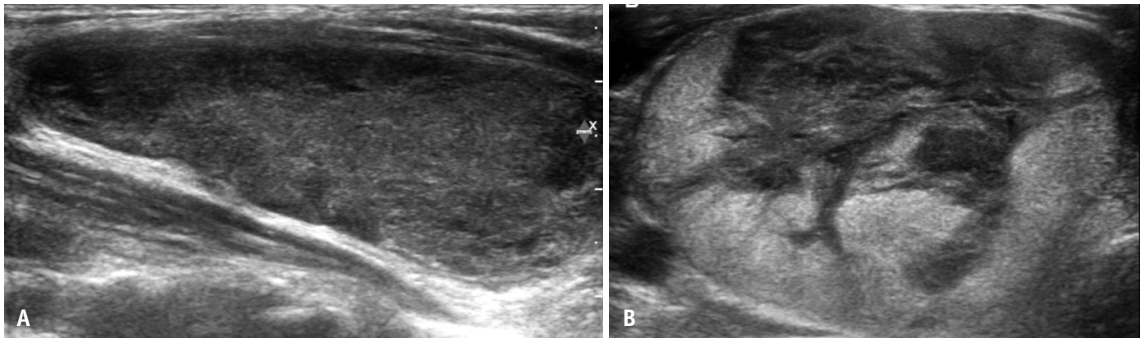

Fig. 3. US images in patients with encapsulated angioinvasive follicular thyroid carcinoma. **A:** Longitudinal US image of a 60-year-old female with wild type TERT showing a 4.7 cm solid nodule with a smooth margin, marked hypoechogenicity, heterogeneous echogenicity, and parallel orientation. This nodule was classified as K-TIRADS category 4 and ACR-TIRADS category 4. After surgery, the TNM stage was classified as II (T3aN0M0) and there was no recurrence during 7 years of follow-up. **B:** Transverse US image in a 64-year-old female with mutant TERT showing a 3.4 cm solid nodule with a smooth margin, marked hypoechogenicity, heterogeneous echogenicity, and parallel orientation. This nodule was classified as K-TIRADS category 4 and ACR-TIRADS category 4. After surgery, the TNM stage was categorized as II (T3aN0M0) and there was no recurrence during 3 years of follow-up. US = ultrasound, TERT = telomerase reverse transcriptase, K-TIRADS = Korean-Thyroid Imaging Reporting and Data System, ACR = American College of Radiology, TNM = tumor, node, metastasis

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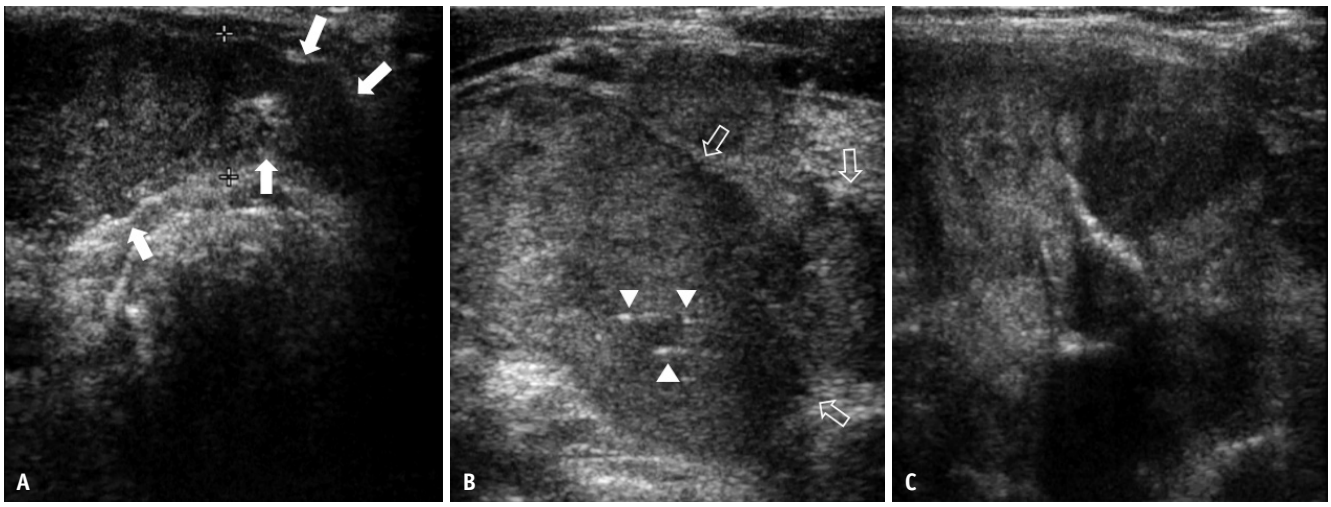

Fig. 4. A 72-year-old female with widely invasive follicular thyroid carcinoma with mutant TERT. **A-C:** Transverse US images show a huge solid nodule with irregular margin (open arrows), hypoechogenicity, heterogenous echogenicity, parallel orientation, lobulation (solid arrows), and punctate echogenic foci (arrowheads). This nodule was classified as K-TIRADS category 5 and ACR-TIRADS category 5. After surgery, the TNM stage was categorized as IV (T4aN0M1). Bilateral lung metastases were detected at the time of diagnosis and operative bed recurrences were diagnosed at 3 years after surgery. This patient expired 7 years after the surgery. US = ultrasound, TERT = telomerase reverse transcriptase, K-TIRADS = Korean-Thyroid Imaging Reporting and Data System, ACR = American College of Radiology, TNM = tumor, node, metastasis

Table 2. US characteristics according to the WHO and alternative classifications

	WHO groups					Alternative groups				
	MI-FTC (n = 29)	EA-FTC (n = 16)	WI-FTC (n = 9)	*P*	*P* for trend	Group 1 (n = 42)	Group 2 (n = 5)	Group 3 (n = 7)	*P*	*P* for trend
Composition				0.16					0.52	
Predominantly cystic	2 (6.9)	0	0		0.23	2 (4.8)	0	0		0.47
Predominantly solid	10 (34.5)	5 (29.4)	0		0.07	14 (33.3)	0	1 (14.3)		0.15
Solid	17 (58.6)	11 (68.8)	9 (100.0)		0.03†	26 (61.9)	5 (100.0)	6 (85.7)		0.10
Echogenecity				0.01*	0.02†				0.22	0.68
Iso/Hyperechogenicity	16 (55.2)	3 (18.8)	1 (11.1)			17 (40.5)	0	3 (42.9)		
Mild/Marked hypoechogenicity	13 (44.8)	13 (81.3)	8 (88.9)			25 (59.5)	5 (100.0)	4 (57.1)		
Heterogeneity	8 (27.6)	8 (50.0)	6 (66.7)	0.08	0.02†	15 (35.7)	2 (40.0)	5 (71.4)	0.26	0.09
Lobulation	9 (31.0)	10 (62.5)	8 (88.9)	0.005*	0.001†	16 (38.1)	4 (80.0)	7 (100.0)	0.002*	0.001†
Margin				< 0.001*	< 0.001†				0.003*	0.002†
Smooth	27 (93.1)	15 (93.8)	3 (33.3)			39 (92.9)	2 (40.0)	4 (57.1)		
Irregular (microlobulated/spiculated)	2 (6.9)	1 (6.3)	6 (66.7)			3 (7.1)	3 (60.0)	3 (42.9)		
Parallel orientation	29 (100.0)	16 (100.0)	9 (100.0)			42 (100.0)	5 (100.0)	7 (100.0)		
Echogenic foci				0.02*					0.03*	
No	18 (62.1)	11 (68.8)	3 (33.3)		0.25	28 (66.7)	2 (40.0)	2 (28.6)		0.04†
Punctate echogenic foci	3 (10.3)	5 (31.3)	2 (22.2)		0.21	6 (14.3)	0	4 (57.1)		0.03†
Other	8 (27.6)	0	4 (44.4)		0.85	8 (19.0)	3 (60.0)	1 (14.3)		0.72

Data are number of patients with % in parentheses. 'Group 1' is 'MI-FTC with wild type-TERT and mutant-TERT and EA-FTC with wild type-TERT', 'Group 2' is 'WI-FTC with wild type-TERT', and 'Group 3' is 'EA-FTC with mutant-TERT and WI-FTC with mutant-TERT'.
*A *P*-value of < 0.05 was considered statistically significant, †A *P* for trend value of < 0.05 was considered statistically significant.
US = ultrasound, WHO = World Health Organization, MI-FTC = minimally invasive follicular thyroid carcinoma, EA-FTC = encapsulated angioinvasive follicular thyroid carcinoma, WI-FTC = widely invasive follicular thyroid carcinoma, TERT = telomerase reverse transcriptase

https://doi.org/10.3348/kjr.2023.0461

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Table 3. Final assessment category on US according to the WHO and alternative classifications

	WHO groups					Alternative groups				
	MI-FTC (n = 29)	EA-FTC (n = 16)	WI-FTC (n = 9)	*P*	*P* for trend	Group 1 (n = 42)	Group 2 (n = 5)	Group 3 (n = 7)	*P*	*P* for trend
K-TIRADS				< 0.001*					0.004*	
3 (Low suspicion)	15 (51.7)	2 (12.5)	0		< 0.001†	17 (40.5)	0	0		0.01†
4 (Intermediate suspicion)	12 (41.4)	12 (75.0)	3 (33.3)		0.72	21 (50.0)	2 (40.0)	4 (57.1)		0.85
5 (High suspicion)	2 (6.9)	2 (12.5)	6 (66.7)		< 0.001†	4 (9.5)	3 (60.0)	3 (42.9)		0.006†
ACR-TIRADS				0.003*					0.04*	
2 (Not suspicious)	7 (24.1)	1 (6.3)	0		0.04†	8 (19.0)	0	0		0.12
3 (Mildly suspicious)	6 (20.7)	1 (6.3)	0		0.07	7 (16.7)	0	0		0.15
4 (Moderately suspicious)	15 (51.7)	13 (81.3)	4 (44.4)		0.75	25 (59.5)	3 (60.0)	4 (57.1)		0.92
5 (Highly suspicious)	1 (3.4)	1 (6.3)	5 (55.6)		< 0.001†	2 (4.8)	2 (40.0)	3 (42.9)		0.001†

Data are number of patients with % in parentheses. 'Group 1' is 'MI-FTC with wild type-TERT and mutant-TERT and EA-FTC with wild type-TERT', 'Group 2' is 'WI-FTC with wild type-TERT', and 'Group 3' is 'EA-FTC with mutant-TERT and WI-FTC with mutant-TERT'.
*A *P*-value of < 0.05 was considered statistically significant, †A *P* for trend value of < 0.05 was considered statistically significant.
US = ultrasound, WHO = World Health Organization, MI-FTC = minimally invasive follicular thyroid carcinoma, EA-FTC = encapsulated angioinvasive follicular thyroid carcinoma, WI-FTC = widely invasive follicular thyroid carcinoma, K-TIRADS = Korean-Thyroid Imaging Reporting and Data System, ACR = American College of Radiology, TERT = telomerase reverse transcriptase

increasing tumor invasiveness in the WHO group (all *Ps* for trend < 0.001) and worsening prognosis in the alternative group (all *Ps* ≤ 0.006).

DISCUSSION

To date, no studies have addressed the US findings of FTC based on TERT promoter mutation status and the updated WHO classification. According to our analysis, neither the low suspicion category nor the not suspicious/mildly suspicious categories were assigned to the WI-FTC group of the WHO classification or to Groups 2 and 3 of the alternative classification. According to WHO classification, hypoechogenicity, irregular margins, lobulation, and high suspicion categories differed significantly among the groups (all *Ps* ≤ 0.01), with an increasing trend with increasing tumor invasiveness (all *Ps* for trend ≤ 0.02). Contrarily, in the alternative classification, punctate echogenic foci, irregular margin, lobulation, and high suspicion category significantly differed among the groups (all *Ps* ≤ 0.04), and their incidences tended to increase with worsening prognosis (all *Ps* for trend ≤ 0.03).

Previous studies on the US imaging findings of follicular neoplasms have mainly focused on the differentiation between follicular adenoma and carcinoma. According to previous studies [27-32], solid/predominantly solid compositions, irregular margins, mild/marked hypoechogenicity, heterogeneous echogenicity, tumor protrusion/lobulation, calcification, and a higher TIRADS category were significantly associated with FTC compared to follicular adenoma. Meanwhile, several other studies [29,33,34] that compared the US imaging findings between MI-FTC and WI-FTC based on a previous version of the WHO classification system showed that WI-FTC had irregular margins, mild/marked hypoechogenicity, microcalcification, lobulation, and heterogeneous echogenicity more frequently than MI-FTC. Hypoechogenicity, irregular margins, nonparallel orientation, and microcalcification (punctate echogenic foci) are widely known as suspicious malignant US characteristics of thyroid nodules. In this study, although we did not compare the US findings between FTC and follicular adenoma, our results were consistent with those of previous studies [27-34] and suggest that the more suspicious the US findings, the more likely the follicular neoplasm is associated with tumor invasiveness and poor prognosis.

A recent meta-analysis and other studies on TERT promoter mutations in thyroid carcinoma [35-37] revealed that TERT promoter mutations are strongly associated with poor prognosis and are important prognostic markers in PTC and FTC. These findings are consistent with our results, which showed that TERT promoter mutations correlate with increased tumor invasiveness and poor prognosis, including distant metastasis, AJCC/TNM stage, recurrence, and death. Therefore, TERT promoter mutations can provide important clues for determining the course of treatment for surgery and postoperative care.

To date, several studies have investigated the association between US imaging findings and gene mutation status in

 https://doi.org/10.3348/kjr.2023.0461

thyroid cancer [1,18-20,38]. Their study showed a strong relationship between malignant US findings in thyroid cancer and the presence of genetic mutations. While previous studies included patients with PTC, our study focused on patients with FTC and obtained similar results. In addition, this study is meaningful because both tumor invasiveness and prognosis showed a strong correlation with US findings in the analysis of the final category using ACR-TIRADS, a quantitative scoring method, and K-TIRADS, a pattern-based qualitative system.

According to a meta-analysis [35] related to TERT promoter mutations, the incidence of TERT promoter mutations in FTC is 15.1%–17.5%, which is in agreement with our result of 16.7% (9/54). Therefore, routine TERT promoter mutation analyses may be inefficient in terms of time and cost. However, preoperative US findings can predict tumor invasiveness and can help predict the prognosis when combined with TERT promoter mutation status. Therefore, if TERT promoter mutation analysis is performed before surgery, at least in patients with FTC with suspicious findings related to TERT promoter mutations on preoperative US, it can enable the establishment of a treatment plan. This could alert clinicians to perform total thyroidectomy instead of staged surgery, evaluate unexpected metastases more carefully, and provide these patients with closer follow-up, which may lead to a better prognosis.

This study had several limitations. First, this was a retrospective study conducted in a single tertiary institution, and we analyzed the TERT promoter mutation status in surgical specimens. Because the samples were collected before the era of widespread screening for TERT mutations, this study included a small number of tumors. Therefore, there is a possibility of selection bias associated with our data collection method. Second, our study sample size was relatively small because the prevalence of FTC is relatively low in iodine-sufficient areas of South Korea. Therefore, further prospective studies with larger sample sizes are required to validate our results.

In conclusion, increasing tumor invasiveness from MI-FTC to EA-FTC to WI-FTC, according to the WHO classification, was positively correlated with US features indicating malignancy. In addition, when both the WHO classification and TERT promoter mutation status were applied to the FTC classification, a worsening prognosis was positively associated with US features that indicate malignant probability according to both K-TIRADS and ACR-TIRADS.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

Jung Hee Shin, the editor board member of the *Korean Journal of Radiology*, was not involved in the editorial evaluation or decision to publish this article. All authors have declared no conflicts of interest.

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Conceptualization: Soo Yeon Hahn, Tae Hyuk Kim. Data curation: Myoung Kyoung Kim, Hyunju Park. Formal analysis: Myoung Kyoung Kim, Hyunju Park. Investigation: Myoung Kyoung Kim, Hyunju Park. Methodology: Soo Yeon Hahn, Tae Hyuk Kim. Project administration: Myoung Kyoung Kim, Hyunju Park, Soo Yeon Hahn, Tae Hyuk Kim. Resources: Young Lyun Oh, Jung Hee Shin, Soo Yeon Hahn, Tae Hyuk Kim. Software: Young Lyun Oh, Jung Hee Shin, Soo Yeon Hahn, Tae Hyuk Kim. Supervision: Young Lyun Oh, Jung Hee Shin, Soo Yeon Hahn, Tae Hyuk Kim. Validation: Young Lyun Oh, Jung Hee Shin, Soo Yeon Hahn, Tae Hyuk Kim. Visualization: Myoung Kyoung Kim, Hyunju Park. Writing—original draft: Myoung Kyoung Kim, Hyunju Park. Writing—review & editing: Soo Yeon Hahn, Tae Hyuk Kim.

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Funding Statement

None

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https://doi.org/10.3348/kjr.2023.0461