




Selection Criteria for Completion Thyroidectomy in Follicular Thyroid Carcinoma Using Primary Tumor Size and *TERT* Promoter Mutational Status

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ABSTRACT

Background. A stepwise surgical approach with hemithyroidectomy and completion thyroidectomy was used to achieve definite characterization of follicular thyroid carcinoma (FTC). Choosing appropriate candidates for completion thyroidectomy has been controversial.

Objective. The aim of this study was to clarify the selection criteria for completion thyroidectomy using telomerase reverse transcriptase (*TERT*) promoter mutation.

Methods. A total of 87 FTC patients who had information about *TERT* promoter mutation from August 1995 to November 2020 were investigated. The cumulative risk of

initial distant metastasis, disease recurrence, and cancer-specific death according to primary tumor size in each of the World Health Organization (WHO) 2017 classifications were calculated.

Results. Of the 87 patients, 8 (9.2%) had initial distant metastasis and 15 (17.2%) had persistent disease or developed structural recurrence. The threshold diameter for initial distant metastasis, disease recurrence, and cancer-specific death was 2 cm in minimally invasive FTC (MI-FTC) with mutant *TERT* (M-*TERT*) and in encapsulated angioinvasive FTC (EA-FTC) with M-*TERT*, while that in MI-FTC with wild-type *TERT* (WT-*TERT*) and EA-FTC with WT-*TERT* was 4 cm. The cumulative risk of initial distant metastasis, disease recurrence, and cancer-specific death according to primary tumor size in each WHO 2017 classification was significantly different only in patients with WT-*TERT* ($p = 0.001$, $p = 0.019$, and $p = 0.005$, respectively).

Conclusions. The data suggest 2 cm as a critical threshold diameter for performance of completion thyroidectomy in MI-FTC with M-*TERT* and EA-FTC with M-*TERT*. *TERT* promoter mutational status can help select candidates for completion thyroidectomy.

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Follicular thyroid carcinoma (FTC) is the second most common form of thyroid carcinoma, accounting for about 10% of all cases.¹ FTC is defined as a malignant epithelial tumor arising from the follicular cells and lacking the diagnostic nuclear features of papillary thyroid carcinoma (PTC).² Classic PTC demonstrates hallmark nuclear changes such as overlap, crowding, or palisading nuclei, and many cells show nuclear clefts and intranuclear cytoplasmic pseudo inclusions or vacuoles.³ However, those nuclear features are not found in FTC, making its diagnosis difficult by fine-needle aspiration. Furthermore, pathological examination of capsular and vascular invasion is important to distinguish FTC from benign follicular adenoma. Thereby, diagnosis of FTC based on cytological findings is limited.

For these reasons, a stepwise surgical approach with hemithyroidectomy and completion thyroidectomy has been used based on the definite histopathological diagnosis of follicular neoplasm.⁴ However, the subjects who should be chosen for completion thyroidectomy are controversial. In American Thyroid Association (ATA) guidelines, completion thyroidectomy is recommended when patients would have undergone initial total thyroidectomy if post-operative histopathological diagnosis had been available.⁵ Total thyroidectomy is recommended in patients with tumor size > 4 cm, gross extrathyroidal extension (ETE), presence of node metastasis, or presence of initial distant metastasis.^{6–11} In addition, ATA guidelines suggest that encapsulated angioinvasive FTC (EA-FTC) with invasion of four or more blood vessels should undergo completion thyroidectomy.

Traditionally, FTC has been classified into minimally invasive FTC (MI-FTC) and widely invasive follicular carcinoma (WI-FTC). However, an important change was made to the World Health Organization (WHO) 2017 classification based on the prognostic significance of vascular invasion in MI-FTC.^{12–14} Furthermore, the Armed Forces Institute of Pathology (AFIP) suggested four categories considering the prognostic significance of vascular invasion extent.^{15, 16} ATA guidelines also suggest consideration of extent of vascular invasion in the decision to perform completion thyroidectomy. Additional evidence is needed to reach consensus on this treatment.

Previous studies revealed that telomerase reverse transcriptase (*TERT*) promoter mutations are an important prognostic marker in thyroid cancer.^{17–21} In a recent study, the presence of *TERT* promoter mutations was significantly associated with poor survival in FTC patients.²² Of note, patients with mutant *TERT* (*M-TERT*) in EA-FTC or WI-FTC showed significantly worse prognoses than wild-type *TERT* (*WT-TERT*). Thus, *TERT* promoter mutations might be an important clue when deciding the completion

thyroidectomy. The aim of this study was to clarify which FTC patients will need completion thyroidectomy based on *TERT* promoter mutational status.

MATERIALS AND METHODS

Patients

A total of 87 patients who were pathologically diagnosed with FTC and had information about *TERT* promoter mutation status from August 1995 to November 2020 were included in this study; however, patients with Hurthle cell carcinoma and poorly differentiated thyroid carcinoma (PDTC) were excluded. The study protocol was approved by the Institutional Review Board of Samsung Medical Center (IRB no. 2021-04-085). Patient consent was waived by the committee owing to the retrospective design of the study.

Treatment and Follow-up Protocol

In Korea, there were no significant changes in the treatment or follow-up strategy during the study period.^{23–25} The initial surgical extent was decided based on guidelines, and completion thyroidectomy was performed when needed. Patients underwent regular follow-up at 6–12 months with physical examination, neck ultrasonography, thyroid function test, serum thyroglobulin (Tg) test, and anti-Tg antibody test. Patients with total thyroidectomy were treated with levothyroxine to suppress thyrotropin to < 0.10mIU/L, and radioactive iodine ablation was considered when patients were at high risk for recurrence. Computed tomography (CT), magnetic resonance imaging (MRI), ¹⁸F-fluorodeoxyglucose positron emission tomography (¹⁸FDG-PET), diagnostic I-131, and ^{99m}Tc whole-body bone scintigraphy (^{99m}Tc WBS) were performed as needed. The frequency of follow-up visits and imaging tests was based on the clinical course.

Clinicopathological Data

Pathology reports and surgical records were reviewed to refine tumor categories based on the WHO 2017 classification and the 8th edition of the American Joint Committee on Cancer/Tumor-Node-Metastasis (AJCC/TNM) classification. For patients who were described as having multifocality or cervical lymph node metastasis in the initial pathology report, pathology slides were reviewed by a pathologist (YLO) to exclude the possibility of initial misdiagnoses, such as follicular variant PTC (FV-PTC). Clinical data were obtained from review of the electronic medical record (EMR) system.

Initial distant metastasis was defined as detection of distant metastasis within 6 months of initial surgery. Distant metastasis was detected by CT, MRI, ^{18}F FDG-PET, diagnostic I-131 scan, and/or $^{99\text{mTc}}$ WBS. Disease-free survival (DFS) was defined as the time from initial surgery to the date of the first structural recurrence, defined as persistent or recurrent disease. This was determined cytologically or pathologically and/or by the presence of highly suspicious metastatic lesions on imaging. Cancer-specific survival (CSS) was defined as the time from initial surgery to the date of thyroid cancer-specific death. Survival status and cause of death were obtained from the EMR or the Korean Statistical Information Service (KOSIS).

Detection of Telomerase Reverse Transcriptase (*TERT*) Promoter Mutation

TERT promoter mutations were identified using semi-nested polymerase chain reaction and direct Sanger sequencing of the hot spots (chr5:1,295,228C > T and chr5:1,295,250C > T, commonly termed C228T and C250T, respectively), as described in previous studies.^{20, 26}

Statistical Analysis

Continuous variables are presented as mean and standard deviation (SD) and categorical variables are presented as number and percentage. The Jonckheere–Terpstra test was used to analyze *P* for trend for continuous variables, and linear-by-linear association was used to analyze *P* for trend for categorical variables. The cumulative risks of initial distant metastasis, disease recurrence, and cancer-specific death were calculated using the Kaplan–Meier method and the results were compared using the log-rank test.²⁷ Statistical analysis was performed using SPSS version 25.0 for Windows (IBM Corporation, Armonk, NY, USA).

RESULTS

Baseline Characteristics

The baseline clinicopathological characteristics are described in Table 1. Of the total 87 patients, 67 (77.0%) were female and 20 (23.0%) were male. The mean (SD) primary tumor size was 3.7 (2.1) cm, and 15 (17.2%), 43 (49.4%), and 29 (33.3%) patients had tumors ≤ 2 cm, > 2.0 cm but ≤ 4.0 cm, and > 4 cm, respectively. Considering completion thyroidectomy as total thyroidectomy, 60 (69.0%) patients underwent initial total thyroidectomy or lobectomy followed by completion thyroidectomy. Initial distant metastases were present in 8 (9.2%) patients,

TABLE 1 Baseline characteristics of 87 patients

Characteristics	
Age, years (mean \pm SD)	42.4 \pm 15.4
Sex	
Female	67 (77.0)
Male	20 (23.0)
Size	
Mean, cm (mean \pm SD)	3.7 \pm 2.1
≤ 2 cm	15 (17.2)
> 2 cm and ≤ 4 cm	43 (49.4)
> 4 cm	29 (33.3)
Surgical extent	
Total or subtotal thyroidectomy	60 (69.0)
Lobectomy	27 (31.0)
Gross ETE	
Absent	84 (96.6)
Present	3 (3.4)
Initial distant metastasis	
Absent	79 (90.8)
Present	8 (9.2)
<i>TERT</i> promoter mutations	
Wild-type	71 (81.6)
Mutation	16 (18.4)
WHO classification	
Minimally invasive FTC	47 (54.0)
Encapsulated angioinvasive FTC	25 (28.7)
Widely invasive FTC	15 (17.2)
AJCC/TNM 8th stage	
I	74 (85.1)
II	10 (11.5)
III/IV	3 (3.4)

Data are expressed as *n* (%) unless otherwise specified

SD standard deviation, ETE extrathyroidal extension, *TERT* telomerase reverse transcriptase, WHO World Health Organization, FTC follicular thyroid carcinoma, AJCC/TNM American Joint Committee/Tumor-Node-Metastasis

and *TERT* promoter mutations were present in 16 (18.4) patients. When patients were classified by the WHO 2017 classification, 47 (54.0%), 25 (28.7%), and 15 (17.2) patients were classified as MI-FTC, EA-FTC, and WI-FTC, respectively.

The study population was divided into three groups according to primary tumor size (Table 2). There were no significant clinicopathological factors, such as age, WHO 2017 classification, surgical extent, gross ETE, initial distant metastasis, and *TERT* promoter mutational status, between the groups. On the other hand, age, surgical extent, gross ETE, initial distant metastasis, *TERT* promoter mutations, and AJCC/TNM stage were significantly

TABLE 2 Clinicopathological characteristics according to primary tumor size

	≤ 2 cm	> 2 cm and ≤ 4 cm	> 4 cm	<i>p</i> for trend
Age, years (mean ± SD)	44.3 ± 13.4	40.2 ± 15.4	44.7 ± 16.4	0.794*
Sex				
Female	14 (93.3)	35 (81.4)	18 (62.1)	0.016
Male	1 (6.7)	8 (18.6)	11 (37.9)	
WHO classification				
MI-FTC	9 (60.0)	25 (58.1)	13 (44.8)	0.663
EA-FTC	1 (6.7)	14 (32.6)	10 (34.5)	
WI-FTC	5 (33.3)	4 (9.3)	6 (20.7)	
Surgical extent				
Total or subtotal thyroidectomy	9 (60.0)	29 (67.4)	22 (75.9)	0.534
Lobectomy	6 (40.0)	14 (32.6)	7 (24.1)	
Gross ETE				
Absent	15 (1000)	42 (97.7)	27 (93.1)	0.201
Present	0 (0.0)	1 (2.3)	2 (6.9)	
Initial distant metastasis				
Absent	13 (86.7)	40 (93.0)	26 (89.7)	0.878
Present	2 (13.3)	3 (7.0)	3 (10.3)	
<i>TERT</i> promoter mutations				
Wild-type	11 (73.3)	38 (88.4)	22 (75.9)	0.866
Mutation	4 (26.7)	5 (11.6)	7 (24.1)	
AJCC/TNM 8th stage				
I	13 (86.7)	40 (93.0)	21 (72.4)	0.266
II	2 (13.3)	1 (2.3)	7 (24.1)	
III/IV	0 (0.0)	2 (4.7)	1 (3.4)	

Data are expressed as *n* (%) unless otherwise specified

SD standard deviation, *WHO* World Health Organization, *MI-FTC* minimally invasive FTC, *EA-FTC* encapsulated angioinvasive FTC, *WI-FTC* widely invasive FTC, *FTC* follicular thyroid carcinoma, *ETE* extrathyroidal extension, *TERT* telomerase reverse transcriptase, *AJCC/TNM* American Joint Committee/ Tumor-Node-Metastasis

**p* for trend for continuous variables was analyzed using the Jonckheere–Terpstra test

different between groups when patients were divided using the WHO 2017 classification (Table 3).

Cumulative Risks of Initial Distant Metastasis, Disease Recurrence, and Distant Metastasis

The cumulative risks of initial distant metastasis according to primary tumor size in each WHO 2017 group are shown in Fig. 1. The cumulative risk was significantly higher in the aggressive categories (Fig. 1a). The cumulative risks increased linearly with increasing tumor size in EA-FTC and WI-FTC, but initial distant metastasis was not found in MI-FTC regardless of primary tumor size. Interestingly, when patients were stratified according to *TERT* promoter mutational status (WT-*TERT* vs. M-*TERT*), initial metastasis was not found in EA-FTC with WT-*TERT* patients regardless of primary tumor size (Fig. 2b). Furthermore, cumulative risk of initial distant metastasis according to primary tumor size was not significantly

different between EA-FTC with M-*TERT* and WI-FTC with M-*TERT* (Fig. 1c). The threshold diameter for initial distant metastasis in EA-FTC with M-*TERT* patients was 2 cm.

Figure 2 shows the cumulative risk of disease recurrence according to primary tumor size. The slope of the curve for disease recurrence was steeper in WI-FTC than in EA-FTC and MI-FTC, but the difference was not statistically different (Fig. 2a). However, when patients were stratified according to *TERT* promoter mutational status, cumulative risk was significantly different according to aggressiveness of the WHO 2017 classification in patients with WT-*TERT* (Fig. 2b). Hence, cumulative risk of disease recurrence was not different according to the WHO 2017 classification in patients with M-*TERT* (Fig. 2c). The threshold diameter for disease recurrence in MI-FTC and EA-FTC with M-*TERT* was 2 cm, while that in MI-FTC with WT-*TERT* and EA-FTC with WT-*TERT* was 4 cm. We further discuss this in the Discussion section using two

TABLE 3 Clinicopathological characteristics according to the WHO 2017 classification

	MI-FTC	EA-FTC	WI-FTC	<i>p</i> for trend
Age, years (mean ± SD)	39.7 ± 13.1	42.5 ± 18.4	50.8 ± 14.8	0.063*
Sex				
Female	38 (80.9)	17 (68.0)	12 (80.0)	0.651
Male	9 (19.9)	8 (32.0)	3 (20.0)	
Size				
Mean, cm (mean ± SD)	3.2 ± 1.5	4.0 ± 1.7	4.9 ± 3.4	0.063*
≤ 2 cm	9 (19.1)	1 (4.0)	5 (33.3)	0.688
> 2 cm and ≤ 4 cm	25 (53.2)	14 (56.0)	4 (26.7)	
> 4 cm	13 (27.7)	10 (40.0)	6 (40.0)	
Surgical extent				
Total or subtotal thyroidectomy	23 (48.9)	22 (88.0)	15 (100.0)	< 0.001
Lobectomy	24 (51.1)	3 (12.0)	0 (0.0)	
Gross ETE				
Absent	47 (100.0)	24 (96.0)	13 (86.7)	0.017
Present	0 (0.0)	1 (4.0)	2 (13.3)	
Initial distant metastasis				
Absent	47 (100.0)	23 (92.0)	9 (60.0)	< 0.001
Present	0 (0.0)	2 (8.0)	6 (40.0)	
<i>TERT</i> promoter mutations				
Wild-type	42 (89.4)	20 (80.0)	9 (60.0)	0.013
Mutation	5 (10.6)	5 (20.0)	6 (40.0)	
AJCC/TNM 8th stage				
I	47 (100.0)	19 (76.0)	8 (53.3)	< 0.001
II	0 (0.0)	4 (16.0)	6 (40.0)	
III/IV	0 (0.0)	2 (8.0)	1 (6.7)	

Data are expressed as *n* (%) unless otherwise specified

SD standard deviation, *WHO* World Health Organization, *MI-FTC* minimally invasive FTC, *EA-FTC* encapsulated angioinvasive FTC, *WI-FTC* widely invasive FTC, *FTC* follicular thyroid carcinoma, *ETE* extrathyroidal extension, *TERT* telomerase reverse transcriptase, *AJCC/TNM* American Joint Committee/Tumor-Node-Metastasis

**p* for trend for continuous variables was analyzed using the Jonckheere–Terpstra test

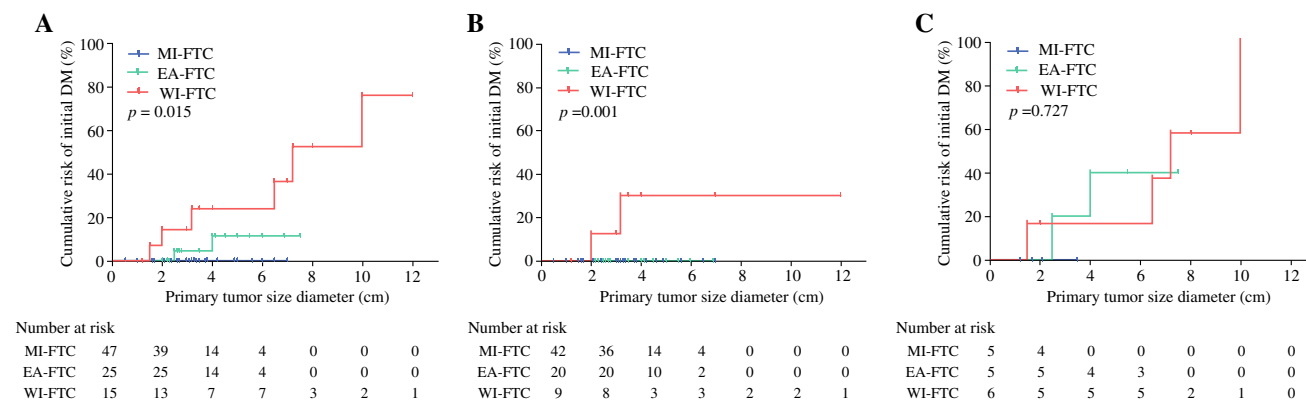


FIG. 1 Cumulative risk of initial distant metastasis according to primary tumor size in each WHO 2017 classification. **A** Overall patients; **B** patients with wild-type *TERT*; and **C** patients with

mutant *TERT*. *EA-FTC* encapsulated angioinvasive FTC, *FTC* follicular thyroid carcinoma, *MI-FTC* minimally invasive FTC, *TERT* telomerase reverse transcriptase, *WI-FTC* widely invasive FTC

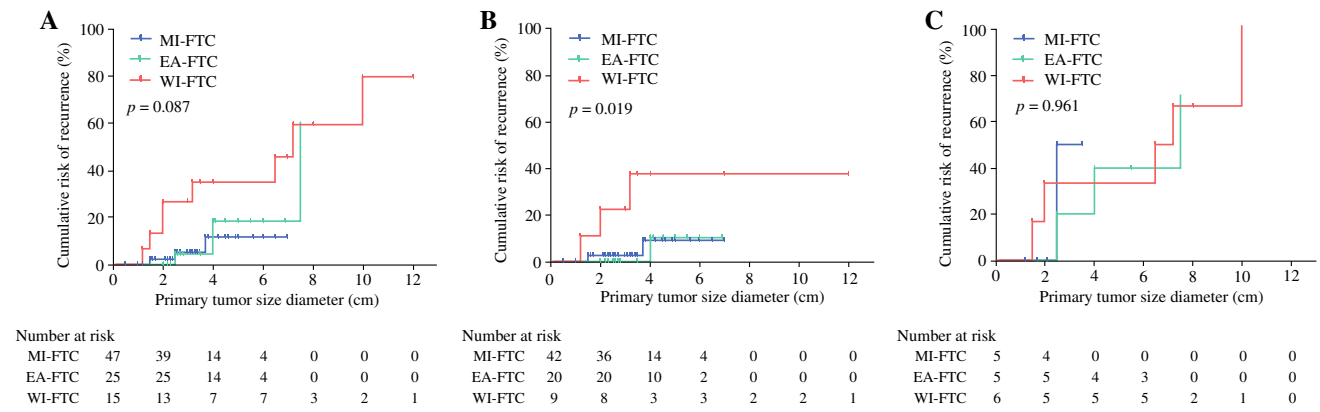


FIG. 2 Cumulative risk of disease recurrence according to primary tumor size in each WHO 2017 classification. **A** Overall patients; **B** patients with wild-type *TERT*; and **C** patients with mutant *TERT*.

EA-FTC encapsulated angioinvasive FTC, *FTC* follicular thyroid carcinoma, *MI-FTC* minimally invasive FTC, *TERT* telomerase reverse transcriptase, *WI-FTC* widely invasive FTC

MI-FTC patients with WT-*TERT* who experienced disease recurrence despite primary tumor size < 2 cm.

Similar trends were shown in curves for cumulative risk of CSS. Cumulative risk of CSS was not significantly different between the WHO 2017 classifications (electronic supplementary Fig. 1a), but when patients were stratified using *TERT* promoter mutational status, the cumulative risk of CSS was significantly different between three WHO 2017 groups (electronic supplementary Fig. 1b). CSS was not different in patients with M-*TERT* (electronic supplementary Fig. 1c). The threshold diameter for CSS was 2 cm in EA-FTC with M-*TERT*, but 4 cm in MI-FTC with WT-*TERT* and EA-FTC with WT-*TERT*.

Similarly, CSS according to *TERT* promoter mutational status was significantly different when primary tumor size was larger than 2 cm (electronic supplementary Fig. 2). When primary tumor size was ≤ 2 cm, DFS and CSS were not different according to *TERT* promoter mutational status.

DISCUSSION

The purpose of this study was to assess whether *TERT* promoter mutation, an emerging molecular prognostic marker, can be useful to clarify proper candidates for completion thyroidectomy. During a mean follow-up period of 10.6 years, we found that the WHO 2017 classification was significantly associated with oncologic outcomes only in patients with WT-*TERT*. The thresholds of primary tumor diameter for initial distant metastasis, disease recurrence, and cancer-specific death were smaller according to tumor aggressiveness in the WHO 2017 classification. In patients with M-*TERT*, disease recurrence and cancer-specific death occurred at a much smaller tumor

Prognostic Outcomes According to Tumor Diameter and TERT Promoter Mutations

DFS according to *TERT* promoter mutational status in three primary tumor size categories is shown in Fig. 3. *TERT* promoter mutations were significantly associated with DFS when primary tumor size was larger than 2 cm.

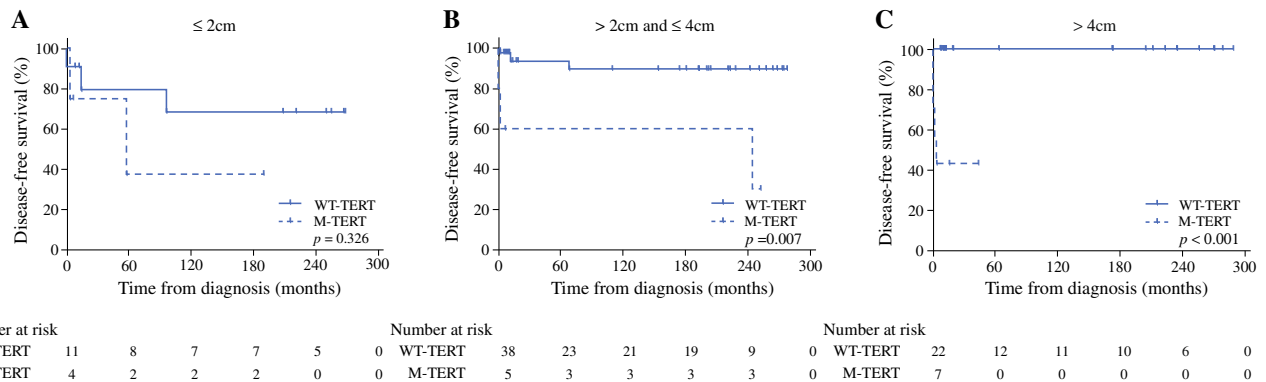


FIG. 3 Disease-free survival according to the presence of *TERT* promoter mutations in three primary tumor size categories. **A** ≤ 2 cm; **B** > 2.0 cm but ≤ 4.0 cm; and **C** > 4 cm. M-*TERT* mutant *TERT*, *TERT* telomerase reverse transcriptase, WT-*TERT* wild-type *TERT*

size and there was no significant difference between the WHO 2017 classifications. In addition, initial distant metastasis did not occur in EA-FTC with WT-*TERT* but did occur in EA-FTC with M-*TERT*. Based on these results, we suggest 2 cm as a critical threshold diameter for performance of completion thyroidectomy in MI-FTC with M-*TERT* and EA-FTC with M-*TERT*. In addition, 4 cm may be a critical threshold diameter in MI-FTC with WT-*TERT* and EA-FTC with WT-*TERT*. Patients with WI-FTC will need completion thyroidectomy regardless of primary tumor diameter and *TERT* promoter mutational status.

Selection of candidates for completion thyroidectomy has been controversial over time. Recent recommendations from the British Thyroid Association (BTA), European Society of Endocrine Surgeons (ESES), and German Association of Endocrine Surgeons (CAEK) are total thyroidectomy for patients diagnosed with EA-FTC and WI-FTC. However, ATA guidelines suggest completion thyroidectomy when EA-FTC patients had high risk (> 4 vessels with angioinvasion) of structural disease recurrence. The ATA does not recommend completion thyroidectomy in low-risk patients compared with other guidelines.^{5, 28–30}

In the present study, initial distant metastasis, disease recurrence, and cancer-specific death occurred regardless of *TERT* promoter mutational status when the primary tumor diameter was < 2 cm in WI-FTC. Furthermore, disease recurrence and cancer-specific death occurred when the primary tumor diameter was > 4 cm even though the pathological diagnosis was EA-FTC or MI-FTC. These findings support current guidelines that completion thyroidectomy will be needed when the primary tumor diameter is > 4 cm or in patients with WI-FTC. Moreover, in real-world practice, entire histological examination of all specimens is practically impossible. Thus, the possibility of a small poorly differentiated component in a large tumor cannot be completely eliminated.³¹ Considering the cost of a labor-intensive evaluation to completely exclude any tiny poorly differentiated component in a large tumor, a size criterion of 4 cm is acceptable.

The 8th AJCC/TNM staging suggests that primary tumor size ≤ 2 cm be classified as T1 and that primary tumor size > 2 cm and ≤ 4 cm be classified as T2.³² Furthermore, Machens et al. reported that the critical threshold for distant metastasis is > 2 cm in differentiated thyroid carcinoma patients.³³ This study showed that initial distant metastasis, disease recurrence, and death occurred at 2–4 cm in MI-FTC and EA-FTC when a *TERT* promoter mutation was present. Based on these results, completion thyroidectomy followed by radioiodine remnant ablation or adjuvant therapy might be needed when a *TERT* promoter mutation is found at 2–4 cm in size in MI-FTC and EA-FTC patients. However, disease recurrence and death

occurred in only one patient in 2–4 cm-sized MI-FTC and EA-FTC when *TERT* promoter mutations were not present. Although a 3.7 cm MI-FTC with WT-*TERT* patient died of FTC according to KOSIS information, detailed information about the clinical course was not available because this patient transferred out during follow-up. Current guidelines recommend completion thyroidectomy in EA-FTC,^{28–30} however, EA-FTC with WT-*TERT* seems to be low risk. Poor prognosis was seen only in EA-FTC with M-*TERT*, while prognosis of EA-FTC with WT-*TERT* was similar to that of MI-FTC.²² Thus, lobectomy might be sufficient in 2–4 cm-sized MI-FTC and EA-FTC when *TERT* promoter mutations are not present.

Additionally, *TERT* promoter mutations tend to be found in larger tumors,³⁴ while the clinical implication of *TERT* promoter mutations in small tumors (T1 tumor) is unclear. In this study, DFS and CSS according to the presence of *TERT* promoter mutation were significantly different when the primary tumor diameter was > 2 cm. When the primary tumor diameter is < 2 cm, lobectomy might be sufficient for MI-FTC and EA-FTC regardless of *TERT* promoter mutational status. Among the MI-FTC and EA-FTC patients with primary tumor diameter < 2 cm, only one experienced disease recurrence. In this patient, the primary tumor diameter was 1.5 cm and initial diagnosis was MI-FTC with WT-*TERT*. Pathological diagnosis at the recurrent metastatic site was FTC with poorly differentiated components. Thus, it seems that FTC transformed into PDTC during follow-up. Thus, with no transformation into PDTC, lobectomy might be sufficient in patients with MI-FTC and EA-FTC with primary tumor ≤ 2 cm. However, as relatively small numbers of MI-FTC and EA-FTC patients were classified into primary tumor size ≤ 2 cm with M-*TERT*, external validation of this result is needed. Considering the poor prognostic outcome when a *TERT* promoter mutation is present, we recommend close monitoring in such patients after lobectomy.

A prognostic role of vascular invasion has been emphasized in patients with FTC.^{12, 13, 15, 16, 35} Furthermore, previous studies reported that patients with limited invasion of vessels have a better prognosis than those with extensive vascular invasion.^{15, 16} Thus, ATA 2015 guidelines suggest that more than four foci of vascular invasion be considered high risk and fewer than four foci of vascular invasion be considered low risk; however, this proposal has not been sufficiently validated.⁵ Furthermore, the role of an experienced endocrine pathologist is important to correctly evaluate the extent of vessel invasion, however it is difficult to retain an experienced specialist in every hospital. Thus, the clinical implication of vascular invasion extent is limited.

There is consensus that total thyroidectomy is necessary for high-risk patients, such as WI-FTC or primary tumor size ≥ 4 cm. However, consideration should be given to the need for completion thyroidectomy among low- to intermediate-risk patients. Based on previous reports, patients with the presence of ETE and/or presence of regional lymph node metastasis are considered candidates for completion thyroidectomy. However, the suggestions for candidates for completion thyroidectomy were mainly based on PTC patients.^{7, 9–11} Unlike PTC, FTC is a unifocal disease and is less likely to have direct tumor extension or regional lymph node metastasis.³⁶ Based on this study, we suggest primary tumor size and *TERT* promoter mutational status are important criteria for completion thyroidectomy (Fig. 4). Furthermore, assays for *TERT* promoter mutations on preoperative fine-needle aspiration biopsies are currently available. Combining the findings of this study with preoperative *TERT* promoter mutation results can assist in the decision regarding surgical extent preoperatively. For instance, if *TERT* promoter mutational status is available preoperatively, total thyroidectomy should be offered to patients for whom completion thyroidectomy would have been recommended.

This study has several limitations. First, the study had a retrospective nature and involved a relatively small number of FTC patients due to its low prevalence in Korea, which is an iodine-sufficient area. Of 87 patients, 16 had *TERT* promoter mutations. Thus, further studies are required using a larger cohort to obtain more solid evidence to corroborate the results of this study. Second, we could not investigate other promising genetic markers³⁷ that *TERT* promoter mutational status because they could not be

obtained in this cohort. Third, this study was conducted in a single tertiary referral hospital, thus there is a possibility of selection bias.

CONCLUSION

In summary, primary tumor size and *TERT* promoter mutational status can be important criteria for selecting candidates for completion thyroidectomy. In 2–4 cm MI-FTC and EA-FTC patients, completion thyroidectomy should be considered when a *TERT* promoter mutation is present. Hence, lobectomy might be sufficient in 2–4 cm MI-FTC and EA-FTC when no *TERT* promoter mutation is present.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1245/s10434-022-13089-5>.

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AUTHOR CONTRIBUTIONS HP: Conceptualization (equal); writing – original draft preparation (lead); writing – review and editing (equal); formal analysis (lead). JH: Data curation (equal); methodology (supporting). C-SK: Data curation (supporting); resources (equal). JHS: Investigation (supporting); resources (equal). YLO: Investigation (supporting); resources (equal). YIS: Investigation (supporting); resources (equal). JSK: Investigation (supporting); resources (equal). SWK: Conceptualization (supporting); supervision (supporting). JHC: Conceptualization (supporting); supervision (supporting). TYK: Conceptualization (supporting); supervision (supporting). THK: Conceptualization (lead); supervision (lead); writing – review and editing (lead). J-HK: Conceptualization (lead); supervision (lead).

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DATA AVAILABILITY The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

DISCLOSURES Hyunju Park, Jung Heo, Chang-Seok Ki, Jung Hee Shin, Young Lyun Oh, Young Ik Son, Jee Soo Kim, Sun Wook Kim, Jae Hoon Chung, Tae Yong Kim, Tae Hyuk Kim, and Jung-Han Kim declare that there are no conflicts of interest to disclose.

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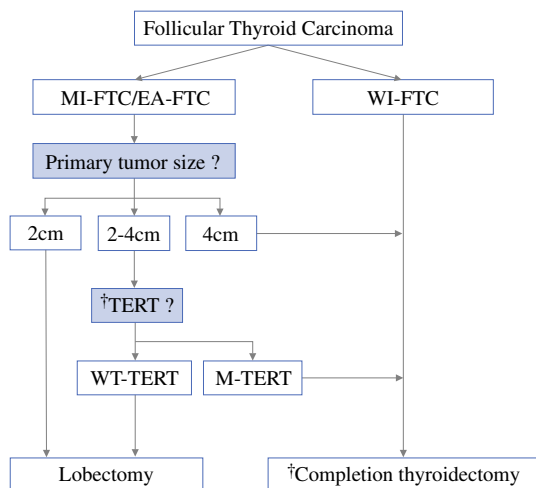


FIG. 4 Proposal of a candidate for completion thyroidectomy. EA-FTC encapsulated angioinvasive FTC, FTC follicular thyroid carcinoma, M-TERT mutant TERT, MI-FTC minimally invasive FTC, TERT telomerase reverse transcriptase, WI-FTC widely invasive FTC, WT TERT wild-type TERT

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