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Risk Factors for Distant Metastasis in Patients with Follicular Thyroid Carcinoma

Min Kyu Sung, Yu-Mi Lee, Tae-Yon Sung, Jong Ho Yoon, Ki-Wook Chung, Suck Joon Hong

Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Purpose: The major issue of follicular thyroid carcinoma (FTC) diagnosed after hemithyroidectomy is whether to undergo further treatments. The aim of this study is to examine the clinico-pathological characteristics of FTC and to evaluate the risk factors for distant metastasis.

Methods: From 1993 to 2010, 274 patients underwent initial thyroid surgery and were subsequently diagnosed as FTC. After review of the histological sections by an experienced pathologist, 211 patients were confirmed as FTC and were enrolled in this study. Clinicopathological features were compared based on the presence or absence of distant metastases, and the risk factors for distant metastases and distant metastases-free survival (DMFS) rates were analyzed.

Results: The patients included 39 males (18.5%) and 172 females (81.5%), with a mean age of 44.0±14.5 years. The median follow-up period was 99.5 months (range, 13.0～222.0). Distant metastases were detected in 23 patients (10.9%), including 15 synchronous distant metastases and 8 metachronous distant metastases. In multivariate analysis, age ≥45 years, widely invasive FTC, tumor size ≥4.3 cm, and vascular invasion were independent risk factors for distant metastasis. DMFS rates in patients with these risk factors were significantly poorer than those in patients without these risk factors.

Conclusion: Older age, aggressive histological classification, larger tumor size, and vascular invasion were independent risk factors for distant metastasis. FTC patients with these risk factors may be candidates for further treatments after diagnostic thyroid hemithyroidectomy.

Key Words: Follicular thyroid carcinoma, Distant metastasis, Risk factor, Survival rates

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Correspondence: **Jong Ho Yoon**
Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea
Tel: +82-2-3010-3931
Fax: +82-2-3010-6701
E-mail: gsyoon@amc.seoul.kr

INTRODUCTION

Follicular thyroid carcinoma (FTC) can be histologically classified into two categories: minimally and widely invasive FTC. According to the World Health Organization (WHO) classification, minimally invasive FTC (MIFTC) is a grossly encapsulated solitary tumor with limited capsular and vascular invasion, whereas widely invasive FTC (WIFTC) is characterized by widespread infiltration of adjacent thyroid tissue and blood vessels.(*1*)

FTC can only be confirmed based on the pathological examination after diagnostic thyroid hemithyroidectomy because it is difficult to know the presence of capsular and/or vascular invasion through the pre-operative fine needle aspiration cytology. Since patients with WIFTC have a high rate of distant metastasis, there are no debates concerning whether WIFTC patients need further treatments such as completion thyroidectomy and radioactive iodine (RAI) remnant ablation.(*2,3*) However, further treatments for MIFTC are still controversial. Patients with MIFTC usually have an excellent prognosis; however, distant metastasis can be present during follow up

period.(*2,4-9*)

The aim of this study is to demonstrate the clinico-pathological characteristics of FTC and to evaluate the risk factors for distant metastasis in patients diagnosed with FTC after thyroid surgery.

METHODS

From February 1994 to December 2010, 274 patients were diagnosed with FTC after surgery. Hematoxylin and eosin stained sections of these patients were reviewed according to WHO criteria by a single experienced pathologist. After reviewing, 63 of these patients were reclassified as other diagnoses (Fig. 1). The remaining 211 patients were confirmed as FTC and included in this study (Fig. 1).

Through the retrospective review of medical records, clinico-pathological characteristics and outcome data were recorded. Written informed consent was not obtained from participants for their clinical records. Instead, anything that can be used to identify patients was all removed from the data prior to analysis by a researcher who was irrelevant to this study.

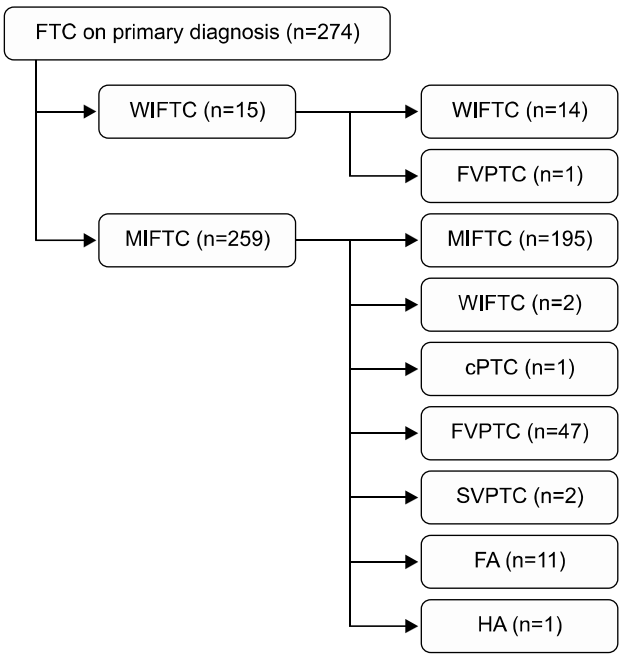

Fig. 1. The algorithm of selection for eligible patients in this study. All Hemotoxylin and eosin slides were reviewed by an experienced pathologist (DE Song). FA = follicular adenoma; cPTC = classical papillary thyroid carcinoma; FTC = follicular thyroid carcinoma; FVPTC = follicular variant papillary thyroid carcinoma; HA = Hurthle cell adenoma; SVPTC = solid variant papillary thyroid carcinoma; MIFTC = minimally thyroid carcinoma; WIFTC = widely invasive follicular thyroid carcinoma.

Diagnostic hemithyroidectomy is the standard initial surgical procedure used at our institution to treat patients diagnosed with follicular neoplasm on preoperative fine needle aspiration cytology. Whenever a patient has a concomitant thyroid disease, i.e., Graves' disease or a nodular goiter of the opposite lobe, total thyroidectomy is performed as the primary surgery. Central compartment node dissection (CCND) is not routinely performed. However, ipsilateral or bilateral CCND is performed if there were enlarged or suspicious lymph nodes.

All patient who were diagnosed as WIFTC underwent completion thyroidectomy following RAI ablation. In MIFTC, completion thyroidectomy is recommended to patients, whose their primary tumor size was ≥4.0 cm, or if they have lymph node metastasis or vascular invasion, especially. We recommend patients who refuse completion thyroidectomy receive sufficient information about the potential risks, and follow up without further treatments.

Patients were classified into two groups; one with distant metastasis and one without distant metastasis. Distant metastasis involved both synchronous and metachronous distant metastasis. Synchronous distant metastasis was defined when metastasis was detected at the point of initial diagnosis or within 12 months from the initial operation. Distant metastasis was diagnosed by using whole-body iodine scintigraphy, chest computed tomography (CT), or 18 F-fluorodeoxyglucosepositron emission tomography/CT and confirmed by serial imaging or biopsy.

Clinico-pathological features were investigated and compared between the two groups based on the presence or absence of distant metastases. Categorical variables were presented as numbers and percentages, and continuous variables as means±standard deviations. Risk factors for recurrence were evaluated using a univariate and multivariate Cox proportional hazards model. Multivariate analysis was performed after adjusting statistically significant risk factors from the univariate

analysis. To improve clinical utility, continuous variables from the independent risk factors proven by multivariable analysis were converted into categorical variables on the basis of the cut-off values calculated by receiver operation characteristic (ROC) curve. Kaplan-Meier method and log rank tests were used to evaluate differences in distant metastasis-free survival (DMFS) between the groups. All p values were two-sided. Data were considered statistically significant if $P<0.05$. All statistical analyses were performed using the SPSS program, version 21.0 (SPSS Inc, Chicago, IL).

RESULTS

1. Clinico-pathological characteristics

The median follow-up period was 99.5 months (range, 13～222). Of the 211 patients, 23 patients (10.9%) developed distant metastases. 15 patients had synchronous distant metastases, whereas 8 patients developed metachronous distant metastases. Among these patients, 10 (4.7%) died during the follow-up period. The clinico-pathological characteristics of these patients are summarized in Table 1.

2. Risk factor analysis for distant metastasis

In univariate analysis, age ≥45 years, surgical extent (total thyroidectomy, including completion thyroidectomy), lymph node dissection, widely invasive FTC, primary tumor size >4.3 cm, and the presence of vascular invasion were potentially significant risk factors for distant metastasis (Table 2). In multivariate analysis after adjusting for statistically significant variables from the univariate analysis, age ≥45 years (Hazard ratio, HR [95% Confidence interval, CI]=3.50 [1.08～11.36], P=0.037), histological classification of widely invasive FTC (HR [95% CI]=3.11 [1.04～9.32], P=0.043), primary tumor size >4.3 cm (HR [95% CI]=3.56 [1.35～9.36], P=0.01), and the presence of vascular invasion (HR [95% CI]=2.45 [1.05～5.71], P=0.038) were recognized as independent risk factors for distant metastasis (Table 2). Adopted surgical extent did not influence the development of distant metastases in multivariate analysis (HR [95% CI]=2.74 [0.76～9.91], P=0.125) (Table 2).

3. Comparison of DMFS rates on the basis of each independent risk factor

DMFS rates in patients with each independent risk factor were significantly poorer than those in each counter one (Fig. 2).

Table 1. Clinico-pathological characteristics of patients with follicular thyroid carcinoma

N=211	N (%)
Sex	
Female	172 (81.5)
Male	39 (18.5)
Age (years)	
Mean±SD (range)	44.01±14.45 (13～78)
<45	112 (53.1)
≥45	99 (46.9)
Surgical extent	
Hemithyroidectomy	97 (46.0)
Total thyroidectomy	114 (54.0)
Lymph node dissection	
No	148 (70.1)
CCND	63 (29.9)
Diagnosis	
Minimally invasive	195 (92.4)
Widely invasive	16 (7.6)
Tumor size (cm)	
Mean±SD (range)	3.95±2.08 (0.5～15)
Thyroiditis	
No	195 (92.4)
Yes	16 (7.6)
Extrathyroidal extension	
No	154 (73.0)
Yes	57 (27.0)
Vascular invasion	
No	160 (75.8)
Yes	51 (24.2)
RAI ablation*	
No	6 (7.0)*
Yes	108 (93.0)*
Distant metastasis	
No	88 (89.1)
Yes	23 (10.9)
Synchronous	15
Metachronous	8
Final status	
No evidence of disease	188 (89.1)
Alive with disease	13 (6.2)
Death	10 (4.7)

CI = confidence interval; CCND = central compartment node dissection; RAI = radioactive iodine. *This calculation was performed in the patient who underwent total thyroidectomy.

Table 2. Univariate and multivariate analysis for distant metastasis in the patients with follicular thyroid carcinoma

N=211	NED 188 (89.1%)	Distant metastasis 23 (10.9%)	Univariate		Multivariate	
			Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Sex						
Female	156 (83.0)	16 (69.6)	Ref.			
Male	32 (17.0)	7 (30.4)	2.4 (0.97~5.93)	0.075		
Age (years)						
<45	108 (57.4)	4 (17.4)	Ref.		Ref.	
≥45	80 (42.6)	19 (82.6)	5.79 (1.97~17.02)	0.001	3.5 (1.08~11.36)	0.037
Surgical extent						
Hemithyroidectomy	94 (50.0)	3 (13.0)	Ref.		Ref.	
Total thyroidectomy	94 (50.0)	20 (87.0)	5.61 (1.66~18.9)	0.005	2.74 (0.76~9.91)	0.125
Lymph node dissection						
No	137 (72.9)	11 (47.8)	Ref.		Ref.	
CCND	51 (27.1)	12 (52.2)	2.72 (1.2~6.2)	0.017	2.35 (0.83~5.57)	0.082
Final pathologic diagnosis						
Minimally invasive	180 (95.7)	15 (65.2)	Ref.		Ref.	
Widely invasive	8 (4.3)	8 (34.8)	11.27 (4.5~28.19)	<0.001	3.11 (1.04~9.32)	0.043
Tumor size (cm)						
≤4.3*	126 (67.0)	7 (30.4)	Ref.		Ref.	
>4.3*	62 (33.0)	16 (69.6)	4.31 (1.77~10.5)	0.001	3.56 (1.35~9.36)	0.01
Thyroiditis						
No	172 (91.5)	23 (100.0)	Ref.			
Yes	16 (8.5)	0 (0)	0.044 (0~45.07)	0.38		
Extrathyroidal extension						
No	137 (72.9)	17 (73.9)	Ref.			
Yes	51 (27.1)	6 (26.1)	1.02 (0.4~2.59)	0.97		
Vascular invasion						
No	149 (79.3)	11 (47.8)	Ref.		Ref.	
Yes	39 (20.7)	12 (52.2)	3.32 (1.46~7.53)	0.004	2.45 (1.05~5.71)	0.038
RAI ablation						
No	98 (52.1)	5 (21.7)	Ref.		Ref.	
Yes	90 (47.9)	23 (78.3)	3.43 (1.27~9.27)	0.015	2.56 (0.80~8.94)	0.088

CI = confidence interval; NED = no evidence of disease; CCND = central compartment node dissection; RAI = radioactive iodine; Ref. = reference. *This cut-off value was calculated by receiver operation characteristic curve.

DISCUSSION

In our current analysis, age ≥45 years, histological classification of widely invasive FTC, tumor size >4.3 cm, and the presence of vascular invasion were found to be significant risk factors for distant metastasis in FTC patients. In addition, these factors were significantly associated with poorer DMFS rates. With special consideration of the impact of surgical extent on the development of distant metastasis, adopted surgical extent did not affect the development of distant metastasis during the follow-up period.

Recent studies have focused on identifying risk factors for distant metastasis, prognosis of DMFS, and cause-specific survival rates of FTC patients. Male gender, age≥ 45 years, primary tumor size >4.0 cm, and vascular invasion have been associated with poor prognosis.(*2-14*) These results were consistent with the results of the present study except for gender. Several studies have reported that male sex is related to the development of distant metastasis(*9,12,13*); however, in this present study, male gender was not a significant risk factor for distant metastasis in both univariate and multivariate analysis.

Previous studies have reported that the cut-off value for primary tumor size is 4.0 cm to be a risk factor for distant metastasis. In our analysis, the cut-off value calculated by ROC curve was 4.3 cm. Furthermore, surgical extent of total thyroidectomy, including completion thyroidectomy, was a significant risk factor for the development of distant metastasis in univariate analysis, but the result did not conform in multivariate analysis. This can be due to the definition used for distant metastasis, which included both

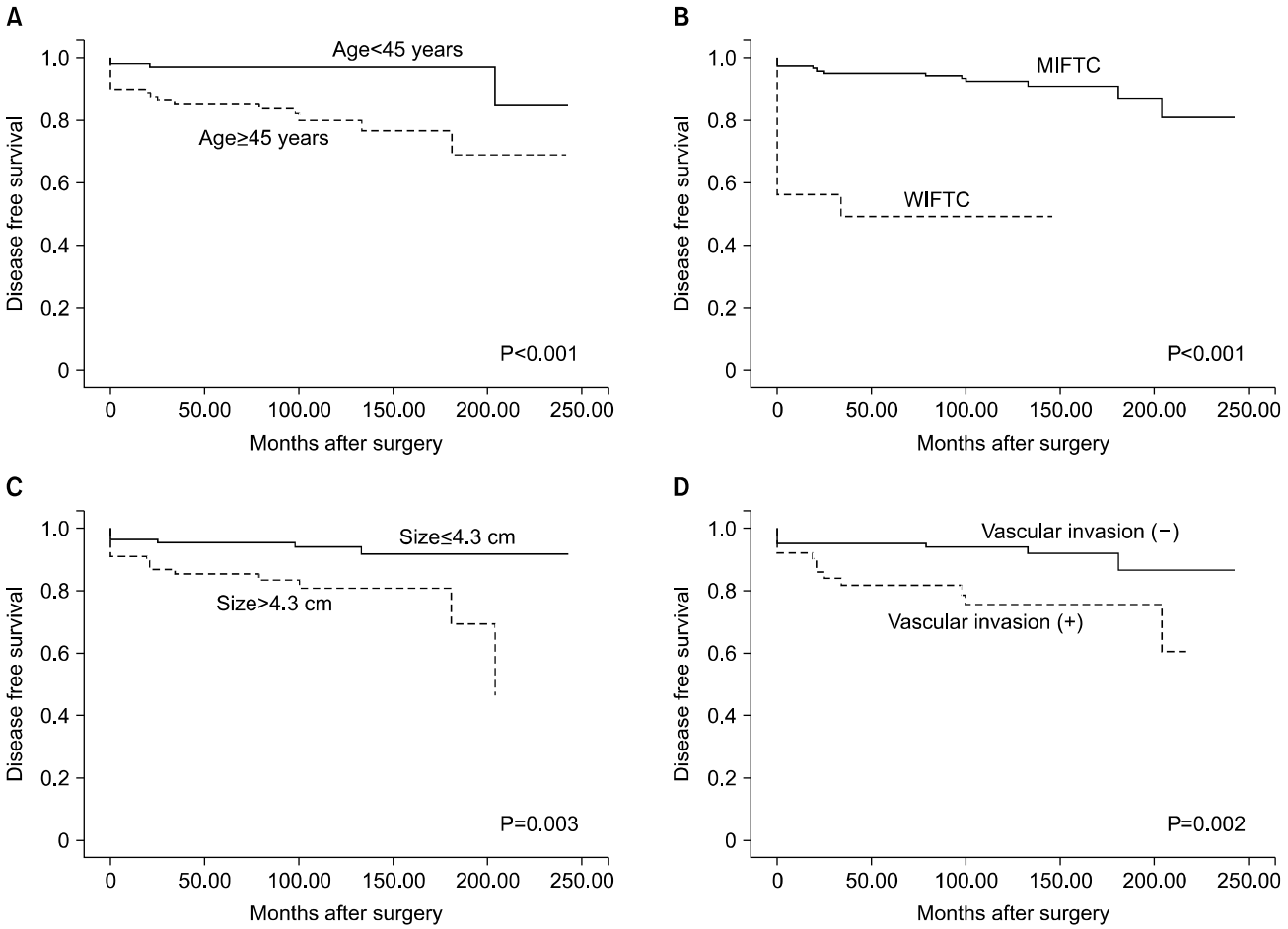

Fig. 2. Distant metastasis free survival rates according to the independent risk factors. (A) Age, (B) histological classification, (C) primary tumor size, (D) the presence of vascular invasion.

synchronous and metachronous metastases. Synchronous distant metastases were the majority of events (15/23), and all patients with synchronous distant metastases underwent total thyroidectomy. When we analyzed the patients with metachronous distant metastasis alone, the surgical extent was not significantly associated with distant metastasis (data not shown).

There are several limitations in this study. Since it is a retrospective study, there are various confounding selection biases. Therefore, future studies should focus on analyzing a larger number of patients with a longer follow-up period.

CONCLUSION

Older age, aggressive histological classification, larger tumor size, and the presence of vascular invasion were the independent risk factors for distant metastasis in patients with FTC. Therefore, further treatment such as completion thyroidectomy and/or RAI remnant ablation should be carefully suggested to the patients with these risk factors, considering the balance of the risks and benefits.

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