Surgical indications and clinical management of benign and malignant follicular thyroid tumors: An algorithmic-based approach

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Abstract. The present study retrospectively reviewed the treatment courses and results of patients with follicular thyroid tumors, including carcinomas. In the 5 year study period from April 2015 to March 2020, 797 patients with differentiated thyroid carcinoma and 128 patients with follicular tumors (FTs) received surgery or treatment for distant metastases and recurrence at the Kanagawa Cancer Center (Japan). Of these patients, 73 that were diagnosed with follicular thyroid carcinoma (FTC) were included in the present study. An algorithm used for the application of treatment strategies was assessed. The aim of the present study was to examine patients with FT or FTC who were treated at the Kanagawa Cancer Center to devise appropriate treatment strategies and to evaluate the various treatment outcomes of FTC. Pre-diagnostic serum thyroglobulin and thyroid stimulating hormone levels, follow-up and overall survival (OS) were investigated in the present study. The results revealed that OS was significantly increased in patients with minimally invasive follicular thyroid cancer (MIFTC) compared with widely invasive follicular thyroid cancer (WIFTC) (log-rank test, P=0.017). Additionally, OS was significantly higher in patients without distant metastasis at the first consultation compared with those initially diagnosed with distant metastasis (log-rank test, P=0.023). Although all patients without distant metastasis at the first consultation and those with MIFTC are alive, the 10-year survival rates were 75.3% for patients with WIFTC and 75.6% for those with distant metastasis at the first consultation. The results of the present study suggested that the prognosis of WIFTC was the worst among patients with FTC and distant metastasis, and that total thyroidectomy surgery and radioactive iodine treatment are essential. Additionally, if the disease progresses, prompt inclusion of tyrosine kinase inhibitor therapy is necessary.

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Abbreviations: FTC, follicular thyroid carcinoma; DTC, differentiated thyroid cancer; FT, follicular tumor; Tg, thyroglobulin; TSH, thyroid stimulating hormone; OS, overall survival; MIFTC, minimally invasive FTC; WIFTC, widely invasive FTC; RAI, radioactive iodine; TKI, tyrosine kinase inhibitor

Key words: follicular thyroid carcinoma, lenvatinib, distant metastasis, retrospective study, prognosis

Introduction

Thyroid masses are common abnormalities, many of which are classified as benign diseases, such as cystic mass, adenomatous goiter, and follicular tumor, and are rarely subjected to surgical treatment. One of the still unsolved challenges for endocrine surgeons is the diagnosis of follicular thyroid carcinoma (FTC). Preoperative diagnosis of FTC without distant metastasis is impossible, and there is no indication of the types of follicular tumors (FTs) that should be operated on to obtain evidence of FTC. Various diagnostic tools have been reported in the past, but none have been applied clinically to date. If follicular cells without nuclear morphology are diagnosed as benign by cytology, fewer tumors are indicated for surgery and FTC cannot be diagnosed (1,2). Therefore, only a retrospective study has been conducted. The aim of this study was to examine patients with FT or FTC who were treated in our hospital to devise appropriate treatment strategies and to evaluate the various treatment outcomes of FTC.

Patients and methods

Patient selection. At our hospital, Kanagawa Cancer Center in Japan, several patients with advanced DTC and distant metastasis have been treated. During the 5 years from April 2015 to March 2020, 797 patients with DTC and 128 patients with FT were referred to our hospital for the treatment of distant metastases and their recurrence. Of these 925 patients, 73 patients were diagnosed with FTC and were retrospectively followed up. This study was approved by the Institutional Review Board of Kanagawa Cancer Center (IRB approval no. 27-61). All patients provided comprehensive

consent for using their samples from medical examination for medical investigation and clinical research. Table I presents a list of these 73 patients, including a comparison of MIFTC with WIFTC. The median follow-up period was 6.8 years (0.5-29.7 years). WIFTC had significant differences compared with MIFTC, with strong local invasion and high frequency of lymph node and pulmonary metastases, but no significant difference in the frequency of bone metastases.

Diagnostic algorithm and treatment. An algorithm was created to completely follow the prognosis of FTC in the 73 patients with different diagnostic methods (Fig. 1). There are three different methods based on which FTCs can be diagnosed: Postoperative histological diagnosis, distant metastasis from FTC, and surgery to assess local invasion that is suspected to be a malignant tumor. When FTC is diagnosed based on biopsy of distant metastasis, it is natural to perform total thyroidectomy. Radioactive iodine (RAI) treatment is the gold standard, followed by metastatic lesion treatment, if necessary. Patients with thyroglobulin (Tg) levels that returned to a normal value after diagnostic thyroidectomy were followed up. Distant metastasis was suspected in patients with persistently high Tg and in those with increased Tg levels after surgery; consequently, completion thyroidectomy was performed, followed by RAI treatment. Moreover, when follicular cells without nuclear morphology are identified by local invasion, they may be diagnosed as FTC based on local findings, and total thyroidectomy may be selected at the initial surgery.

Parameters and statistical analysis. We retrospectively reviewed the preoperative serum Tg levels, treatment courses, and treatment results in 73 patients with FTC treated at our hospital. The median values between two groups were compared using Fisher's test for nominal variables and Student's t test for continuous variables. The statistically significant difference was set at $P<0.05$. All statistical data were analyzed using EZR software version 2.4 (3). We compared OS between MIFTC and WIFTC and between the initial M0 patients and initial M1 patients. OS and 10-year survival rates were calculated using the Kaplan-Meier method with SPSS software (version 24; IBM Corp.), and a log-rank test was applied. $P<0.05$ was considered statistically significant.

Results

Diagnostic process. Seventy-three patients with FTC were diagnosed using three routes of the algorithm (Fig. 1). Fifteen patients were preoperatively diagnosed with malignant lesions due to local invasion or tumor embolization to blood vessels, and total thyroidectomy was initially performed. Twenty-seven patients were diagnosed with FTC based on the presence of distant metastasis. Nine patients were diagnosed with FTC based on histological concordance between the thyroid nodule and distant metastasis without capsular or vascular invasion. There were eight patients with sychronicity, and only one patient was previously diagnosed with a benign nodule. Of the 31 patients who underwent diagnostic lobectomy, 15 patients underwent surgery for suspicious malignancy based on ultrasound findings and 16 of 128 patients underwent prophylactic surgery for an FT of ≥4 cm and a Tg level of ≥1,000 ng/dl.

Comparison of WIFTC and MIFTC. WIFTC showed a significantly higher degree of local invasion (T, N) than MIFTC; therefore, total thyroidectomy was more common at the initial surgery. Initial metastasis was noted in 14/25 (56.0%) patients with WIFTC, and postoperative metastasis was noted in 4 patients. Vascular invasion was observed in 34 patients and capsular invasion in 46 patients. Both invasions were not noted in 9 patients, and they were diagnosed with FTC based on the matching of the metastatic lesion and the thyroid mass. These results are summarized in Table I. There were 37 patients with distant metastases, 11 with pulmonary metastasis, 13 with bone metastasis, 13 with pulmonary and bone metastases, and 1 with renal metastasis. There were 5 deaths owing to both metastases. TKI treatment was applied in 40.0% patients with WIFTC; the prognosis was poor, and 5 (20.0%) patients died. Conversely, none of the patients with MIFTC died in the follow-up period (Table I). Fig. 2 depicts the clinical course of MIFTC and WIFTC with or without distant metastasis. In the 14 patients treated with TKI, OS was for a median of 3.1 (range, 0.2-4.6 years), and PFS was for a median of 1.6 (range, 0.2-3.3 years).

Clinical course of patients with initial M0. No distant metastasis was noted, and FTC was postoperatively diagnosed (n=46). Among the 35 patients with MIFTC and 11 patients with WIFTC, total thyroidectomy was initially performed in 15 patients based on local findings; and lobectomies were performed in the remaining 31 patients. Fifteen patients underwent completion total thyroidectomy because of recurrent mass in the residual thyroid or elevated Tg after lobectomy; 10 patients exhibited distant metastases after surgery. Twelve patients who underwent total thyroidectomy, 16 who underwent lobectomies, and 8 who underwent completion total thyroidectomy for a total of 36 patients showed no recurrence during follow-up (Fig. 2). The Tg level was <1 ng/ml in 9 of the 19 patients who underwent total thyroidectomy, indicating no evidence of disease (NED). The distribution of Tg levels and TSH values after total thyroidectomy are shown in Fig. 3.

At our hospital, total thyroidectomy was initially performed in five of 11 patients; among these 11, distant metastasis was observed in 4 (36.4%) patients. Among the 35 patients with MIFTC at our hospital, 6 (18.2%) patients developed distant metastases after the initial surgery, and five of the six surgeries were lobectomies.

Clinical course of patients with initial M1. Distant metastasis was recognized at the first consultation, and FTC was diagnosed on the basis of the matching tissues (n=27). There were 13 patients with MIFTC, 14 with WIFTC, 9 with lung metastasis, 6 with bone metastasis, and 12 with both metastases. The prognosis of patients with WIFTC was poor, and 11 (78.6%) of the 14 patients showed disease progression. Nine patients were treated with TKI drugs, and 5 (35.7%) patients died of FTC. Conversely, because MIFTC progresses slowly even with distant metastasis, the treatment is considered successful with stable disease. Currently, TKI treatment for the progressive disease in 3 (23.1%) of 13 patients, and

Table I. Comparison of patients with MIFTC and WIFTC.

Pathology	MIFTC	WIFTC	P-value
N	48	25	
Age, years	66.5 [20, 84][b]	65.0 [11, 78][b]	0.770
Sex, n (%)			0.021[a]
Female	27 (56.2)	21 (84.0)	
Male	21 (43.8)	4 (16.0)	
Stage			0.009[a]
T1 (%)	9 (18.8)	0 (0.0)	
T2 (%)	18 (37.5)	7 (28.0)	
T3 (%)	21(43.8)	16 (64.0)	
T4 (%)	0 (0.0)	2 (8.0)	
Capsular invasion	27 (56.2)	19 (76.0)	0.128
Vascular invasion	19 (39.6)	15 (60.0)	0.138
Nodal metastasis (%)	2 (4.2)	8 (32.0)	0.002[a]
Total thyroidectomy (%)	23 (47.9)	19 (76.0)	0.026[a]
Nodal dissection (%)	5 (10.4)	10 (40.0)	0.005[a]
Initial metastasis (%)	13 (27.1)	14 (56.0)	0.022[a]
Pulmonary metastasis (%)	8 (16.7)	15 (60.0)	<0.001[a]
Bone metastasis (%)	13 (27.1)	12 (48.0)	0.118
TKI therapy (%)	4 (8.3)	10 (40.0)	0.003[a]
Death (%)	0 (0.0)	5 (20.0)	0.004[a]
Thyroglobulin (ng/ml)	494 [6.80, 93,000][b]	549 [5.00, 250,000][b]	0.206
TSH (μIU/ml)	0.26 [0.01, 4.55][b]	0.09 [0.01, 4.01][b]	0.035[a]

[a]P<0.05. [b]Continuous variables are indicated using median and range [minimum and maximum]. TNM staging was performed using the 8th edition of the AJCC staging system for thyroid cancer (AJCC-8). TKI therapy was often introduced with the progression of disease with high mortality. The thyroglobulin value was compared with the preoperative value and TSH was compared with the recent value. The median values between the two groups were compared using Fisher's test for nominal variables and Student's t-test for continuous variables. MIFTC, microinvasive follicular carcinoma; WIFTC, widespread invasive follicular carcinoma; TKI, tyrosine kinase inhibitor; TSH, thyroid stimulating hormone.

the disease has been kept under control to date in 10 of these 13 patients (Fig. 2).

OS curves. OS was significantly better for patients with MIFTC than for those with WIFTC (log-rank test, P=0.017), and OS for initial M0 patients was significantly better than for initial M1 patients (log-rank test, P=0.023), as shown in Fig. 4. Although all initial M0 patients and those with MIFTC are alive, the 10-year survival rates were 75.3% for patients with WIFTC and 75.6% for the initial M1 patients.

Discussion

Unfortunately, despite certain unique aspects of presentation and prognosis, there are currently no specific recommendations for the management of FTC in evidence-based guidelines (4). We used an algorithm to get a complete picture of FTs and FTCs in a single institution by examining the entire clinical course of the patients in detail. Using the algorithm, we were able to clearly show the approach used for the diagnosis and outcomes of all patients (Figs. 1 and 2). The major advantage of our approach was the ability to trace the course of similar cases with an algorithm. In our hospital, the presence of an FT of ≥4 cm (T3) or a serum Tg level of ≥1000 ng/ml indicated the need for surgery, and 16/128 (12.5%) of the FTs were FTCs based on the surgical results. The current American Thyroid Association guidelines recommend surgery for growing large nodules >4 cm that are considered benign based on repeat fine needle aspiration cytology (4). Based on reports showing that the growth rate of FTs is not different from that of adenomas (5), we recommend that T3 FTs and those accompanied with a serum Tg level of ≥1,000 ng/ml should be removed surgically, as followed in our hospital. One study reported mutational testing for *BRAF* or the seven-gene mutation marker panel (*BRAF*, *RAS*, *RET/PTV*, *PAX8/PPARγ*) for indeterminate thyroid lesions (6), a condition that is not covered by insurance in Japan. Even benign thyroid FTs without histological evidence of carcinoma can metastasize (7). Additionally, we followed-up patients with the FTs diagnosed as benign after surgery, and noted that none of the study patients with FTs developed distant metastasis at the final follow-up examination. Nine (18.8%) patients with MIFTC could not be operated upon without distant metastases were initially T1. We must then decide what kind of FT should be suspected as cancer and what type of surgery is needed.

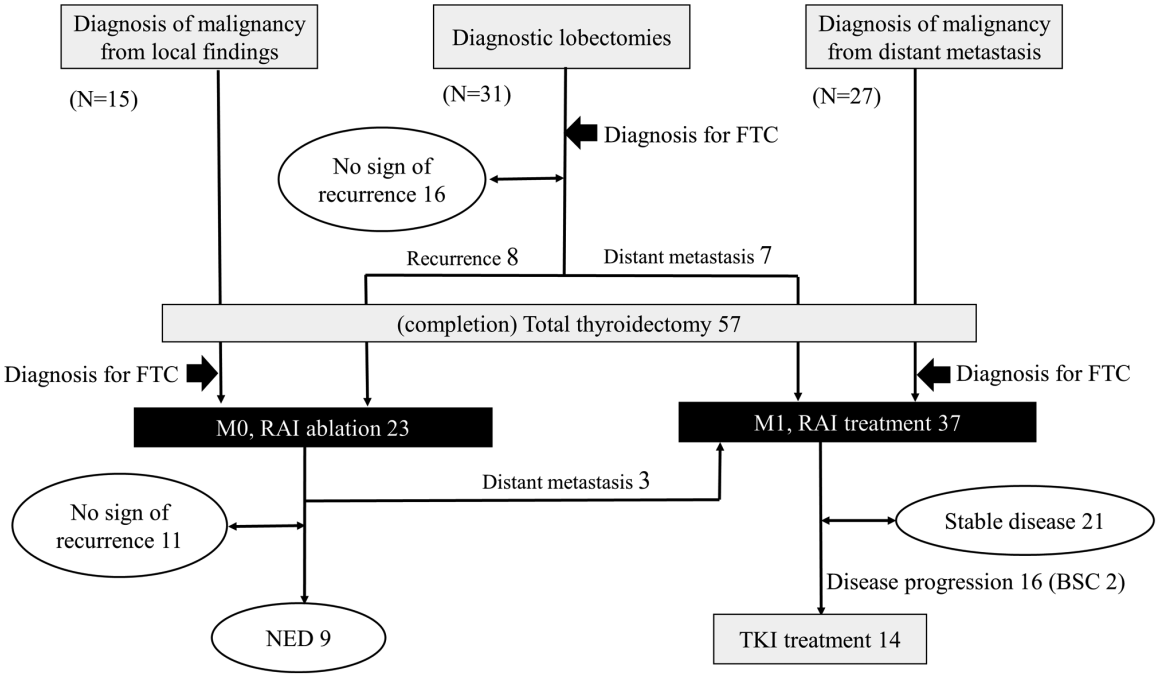

Figure 1. Treatment algorithm for 73 patients with follicular thyroid cancer. During postoperative surveillance, thyroglobulin levels were regularly measured and diagnostic imaging was performed to check for recurrences and distant metastases. Black arrows demonstrate definitive diagnosis of follicular thyroid carcinoma. The numbers listed in the algorithm represent the number of patients in each category. FTC, follicular thyroid carcinoma; M0, without distant metastasis; M1, with distant metastasis; RAI, radioactive iodine; NED, no evidence of disease; TKI, tyrosine kinase inhibitor; BSC, best supportive care; Tg, thyroglobulin.

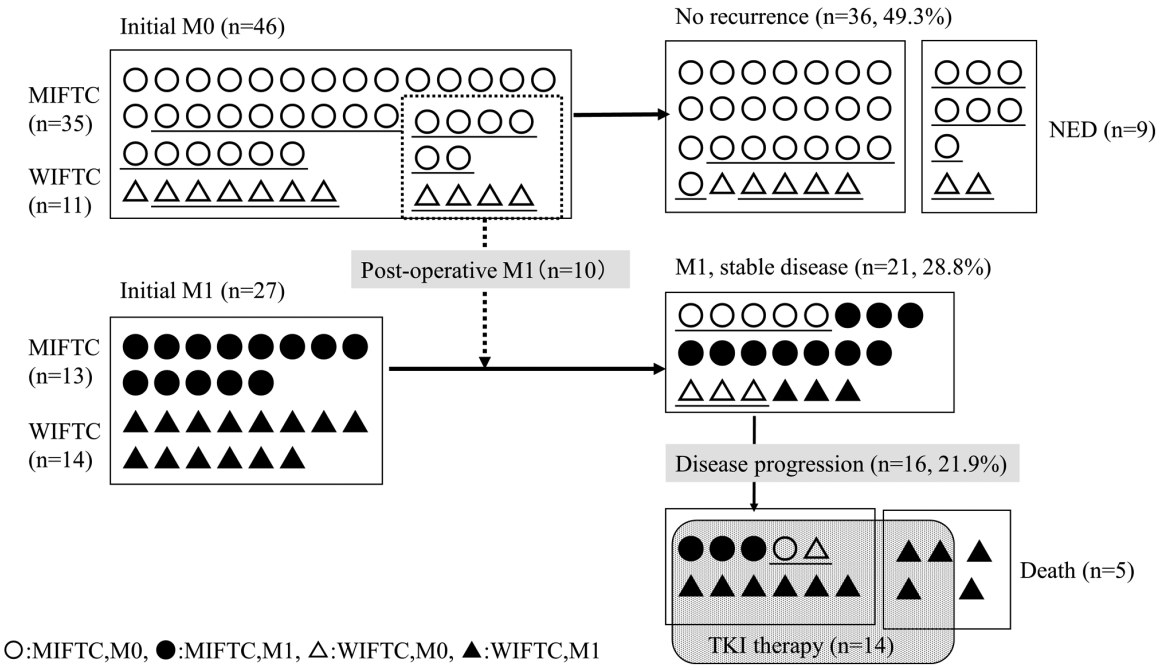

Figure 2. Initial diagnosis and treatment course of 73 patients with follicular thyroid carcinoma. Of the 46 patients without distant metastasis at the first consultation, the prognosis was good for both MIFTC and WIFTC; 10 (21.7%) patients had postoperative distant metastasis and 36 (78.2%) had neither recurrence nor distant metastasis. Conversely, among 27 patients with distant metastasis at the first consultation, WIFTC had a poor prognosis, with disease progression in 11 (78.6%) of 14 patients, 5 (45.5%) of which died. Only 3 (23.1%) of the 13 patients with MIFTC exhibited disease progression, none of whom died. MIFTC, minimally invasive follicular thyroid carcinoma; WIFTC, widely invasive follicular thyroid carcinoma; M0, no distant metastasis; M, distant metastasis; NED, no evidence of disease, biological complete status; TKI, tyrosine kinase inhibitor.

The effect of surgical choice on FTC outcomes has been analyzed only by retrospective observational studies. Goffredo *et al* (8) reported that MIFC is associated with survival that is comparable to that of the normative US general population. Thyroid lobectomy alone may be considered adequate treatment in these patients.

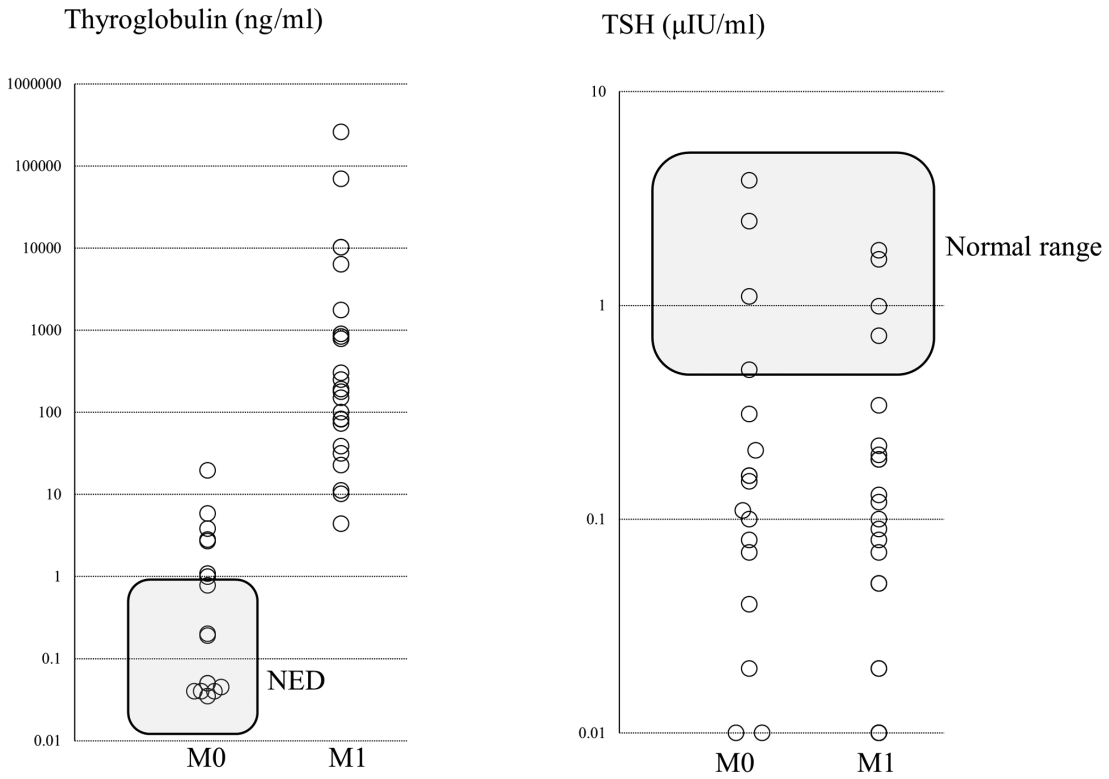

Figure 3. Distribution of Tg and TSH levels in 41 patients with total thyroidectomy. Among the 57 patients who underwent total thyroidectomy, recent Tg and TSH levels were recorded in 41 patients. Thyroglobulin antibody was assessed in the remaining 16 patients. Eight cases with normal TSH are surrounded by a square. The remaining 33 cases demonstrated TSH suppression. Nine cases surrounded by squares are patients diagnosed with no evidence of disease. Tg, thyroglobulin; TSH, thyroid stimulating hormone; M1, distant metastases. M0, cases without distant metastases; NED, no evidence of disease.

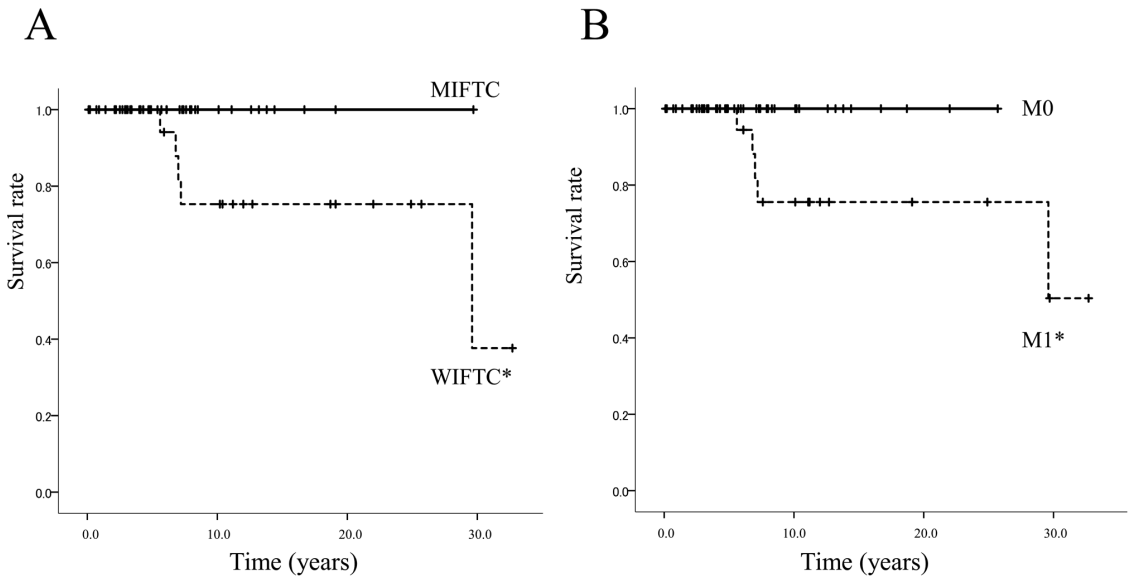

Figure 4. Overall survival curves. (A) Survival curves for MIFTC and WIFTC. Overall survival was significantly increased in MIFTC patients compared with WIFTC patients (log-rank test, P=0.017). (B) Survival curves for initial M0 and M1 patients. Overall survival was significantly increased in initial M0 patients compared with initial M1 patients (log-rank test, P=0.023). Kaplan-Meier survival curves indicated that the 10-year survival rates were 75.3% for patients with WIFTC and 75.6% for the initial M1 patients. All initial M0 and MIFTC patients are alive. *P<0.05. MIFTC, minimally invasive follicular thyroid carcinoma; WIFTC, widely invasive follicular thyroid carcinoma; M0, no distant metastasis; M, distant metastasis.

Lin *et al* (9) reported that total thyroidectomy and postoperative RAI therapy are mandatory in moderate- and high-risk groups. More than one-fourth of the patients with follicular thyroid cancer in the high-risk group died due to thyroid cancer despite aggressive treatment. Although various studies have reported risks, the prognosis of FTC appears to be broadly affected by two factors: i) The histological type of MIFTC or WIFTC and ii) the presence or absence

of distant metastasis. However, various methods were used in these studies, hindering the assessment of true prognostic factors. Clearly, WIFTC has a poor prognosis (10). Our analyses revealed that the prognosis of WIFTC was worse than that of MIFTC. Our results also demonstrated that the prognosis of patients with initial M1 was worse than that of the patients with initial M0 (Fig. 4). In other words, distant metastasis and WIFTC were risk factors. Even in MIFTCs, age at diagnosis and the existence of combined capsular and vascular invasion have been identified as important prognostic factors (11). Naturally, age is a risk factor for survival in statistical analyses along with vascular invasion and distant metastasis (10,12,13). Other prognostic factors include capsular and vascular invasion (14), distant metastasis, tumor size (15,16), and *TERT* promoter mutations; however (17), *RAS* mutations have also reportedly been associated with distant metastasis (18).

In this study, there was no significant difference in the frequency of distant metastasis between MIFTC and WIFTC, and it was necessary to carefully examine the levels of serum Tg and thyroglobulin antibody (TgAb) and to perform various imaging (e.g., radioiodine whole-body scans, CT scans, chest radiography, cervical ultrasound, and ^{18}F-fluorodeoxyglucose positron emission tomography) studies after surgery. In other words, the frequency of distant metastasis in M0 diagnosed as postoperative FTC is not very high at 10/46 (21.7%), and 36/46 (78.3%) of these patients had a favorable prognosis. Even if WIFTC is diagnosed, we believe that it is acceptable to follow-up carefully and to perform completion total thyroidectomy if necessary. In summary, the prognosis of WIFTC is the worst among FTCs with distant metastasis; surgery (total thyroidectomy) and RAI treatment are essential; and metastatic lesions should be treated simultaneously with the primary tumor. If the disease progresses, it is necessary to promptly include TKI therapy.

TSH suppression therapy has been recommended in many articles (19,20), but others have found that it had no significant effect (11). Clinicians should be aware of the potential adverse effects of TSH suppression therapy, which include increased risks for atrial fibrillation, osteoporosis, and ischemic heart disease (21,22). As shown in Table I, postoperative TSH levels were significantly higher for MIFTC than for WIFTC. TSH suppression therapy is strictly applied to patients with high levels of Tg or those with distant metastasis (Fig. 3).

RAI treatment was considered refractory if there is a lesion without uptake of I-131 or if a new lesion appears after treatment or if the disease progresses. Unless otherwise noted, we considered it to be effective and continued with the treatment every 6-12 months till a total treatment dose of 600 mci.

In most FTC patients, local invasion is rare, and resection of the primary lesion is almost possible without any complications. Thus, the primary prognostic factor is distant metastasis. Details of TKI treatment are provided in other reports, but the therapeutic effect varies depending on the target lesion (23). The best response to TKI treatment is noted for pulmonary metastases with poor local involvement. Bone metastases can be expected to prolong survival if pathological fractures or paralysis are avoided.

To better understand the current treatment of FTCs, we reviewed our experience by presenting an algorithm of the treatment strategies. In conclusion, the prognosis of WIFTC is the worst among patients with FTCs having distant metastasis, and surgery (total thyroidectomy) and RAI treatment are essential. If the disease progresses, prompt addition of TKI is necessary.

This retrospective study had certain limitations. The median follow-up period was relatively short. Due to the low frequency of FTCs, the variation of the period was large. However, the prognosis could be predicted to a certain extent by using an algorithm to follow the clinical course of similar cases.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

HI and ST designed the study. HI, ST, SK and DM designed the study and were involved in data analysis/investigation. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The chemotherapy committee of Kanagawa Cancer Center Hospital approved the regimen of lenvatinib for use in patients with ATC. The cancer board of the same hospital also approved lenvatinib treatment, including surgery, in patients with ATC. The present study was approved by the Institutional Review Board of Kanagawa Cancer Center.

Patient consent for publication

All patients provided a comprehensive signed consent form before receiving the treatment, stating that personal data could be used for academic purpose or paper presentation while ensuring complete anonymity.

Competing interests

The authors declare that they have no competing interests.

Authors' information

HI is an endocrine surgeon working at the Kanagawa Cancer Center and has extensive experience of various surgeries for advanced DTC, as well as TKI treatment.

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