

NOTE

## Distant metastasis at diagnosis and large tumor size are significant prognostic factors of widely invasive follicular thyroid carcinoma

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**Abstract.** In contrast to minimally invasive follicular thyroid carcinoma (FTC), widely invasive FTC is aggressive and is associated with a dire prognosis. However, prognostic factors of widely invasive FTC have not been intensively investigated. In this study, we investigated this issue in a series of 79 widely invasive FTC patients. In the subset of 70 patients who did not show distant metastasis at diagnosis (M0), only a tumor size larger than 4 cm had a prognostic impact on disease-free survival (DFS) both on uni- and multivariate analyses. Regarding the cause-specific survival (CSS) of 79 patients, only distant metastasis at diagnosis (M1) had a significant prognostic value on uni- and multivariate analyses. None of the 70 M0 patients with a tumor measuring 4 cm or less died of FTC. Other clinicopathological features such as age, gender, and oxyphilic carcinoma were of no prognostic value. These findings suggest that 1) M1 is the strongest prognostic factor for CSS of widely invasive FTC patients, and 2) a tumor size larger than 4 cm significantly affects the DFS and CSS of M0 patients. Aggressive therapies with careful follow-up are recommended, especially for these patients.

**Key words:** Follicular carcinoma, Widely invasive, Prognosis, Distant metastasis, Tumor size

**FOLLICULAR THYROID CARCINOMA** (FTC), which is the second most common malignancy originating from thyroid follicular cells, is usually diagnosed on pathological examination after hemithyroidectomy under the diagnosis of follicular tumor and adenomatous nodule [1]. FTC is more likely to metastasize to distant organs than regional lymph nodes and is classified into two categories based on the degree of invasion, minimally and widely invasive FTC [2], and widely invasive FTC is more aggressive and displays a poorer prognosis than minimally invasive FTC [3, 4].

Prognostic factors of FTC have been intensively investigated [4-22], but our knowledge about those of the subset of widely invasive FTC remains poor, possibly because it accounts for a low portion of FTC. In this study, therefore, we investigated the prognosis and

prognostic factors associated with widely invasive FTC in a series of 79 patients.

### Patients and Methods

Seventy-nine patients, who underwent initial surgery in Kuma Hospital between 1983 and 2007, were enrolled in this study. All available H & E sections of these patients were reviewed by a coauthor (M.H.), who is a thyroid pathologist, and they were diagnosed with widely invasive FTC based on widespread capsular and/or vascular invasion (more than 10 in H & E sections in total or grossly detectable tumor emboli to perithyroidal major blood vessels). Of 79 patients, 73, 2, and 4 were diagnosed based on capsular invasion, vascular invasion, and both, respectively. Cases diagnosed as poorly differentiated carcinoma on the WHO classification [2] and those including anaplastic components were excluded from our series. We also excluded cases with nuclei suspected of being papillary carcinoma. They consisted of 14 males and 65

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females, and the average patient age was 55 years old (14-87 years). Backgrounds and characteristics of 79 patients are summarized in Table 1.

Nine patients had distant metastases (lung in 4, bone in 2, lung and bone in 2, and lung and liver in 1 patient, respectively) at surgery and were classified as M1. Distant metastases were detected on preoperative imaging studies in 8 patients and on a postoperative whole body scan (WBS) using 10 mCi of radioactive iodine (RAI) in the remaining one.

Thirty patients, including 9 M1 patients, underwent total or near total thyroidectomy, and more limited thyroidectomy was performed in the remaining 49 (subtotal thyroidectomy in 2 and lobectomy in 47). Sixteen patients underwent central node dissection and 8 of these also underwent modified radical neck dissection because physicians suspected papillary or poorly differentiated carcinoma based on pre- and/or intraoperative findings. Twenty-two of 49 patients who underwent limited thyroidectomy received completion total thyroidectomy thereafter. Eleven of these underwent prophylactic completion total thyroidectomy in readiness for distant recurrence that might appear in the future and the remaining 11 underwent second surgery after the detection of recurrence.

We performed RAI therapy for M1 patients after total thyroidectomy. All patients were followed once or twice per year by US, chest roentgenography, and/or computed tomography (CT) to screen for recurrence in the lymph nodes and distant organs.

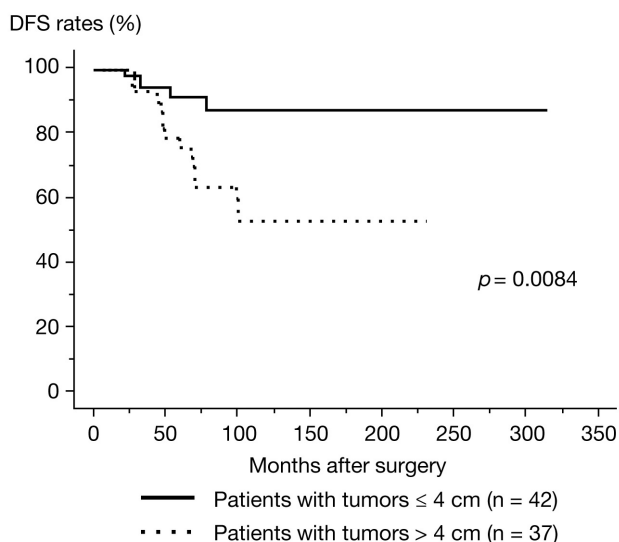
We repeatedly sent questionnaires to survey patients who were postoperatively referred to other hospitals near their residences to obtain data on disease-free (DFS) and cause-specific (CSS) survival. The mean follow-up time in our series was 117 months (3-315 months).

Of 70 M0 patients, 20 showed FTC recurrence. Recurrence to the lung, bone, lymph node, brain, remnant thyroid, adrenal gland, and subcutaneous tissue was detected in 6, 8, 6, 1, 1, 1, and 1 patient, respectively. Five patients showed recurrence to two or more organs. To date, 8 patients, including 4 M1 patients, died of FTC.

The Kaplan-Meier method and log rank test were adopted to analyze time-dependent variables. The Cox-regression model was also adopted for multivariate analysis. A *p*-value less than 0.05 was regarded as significant. We employed Stat View 5.0 for these analyses.

**Table 1** Backgrounds and characteristics of 79 patients

Variables		Number of patients
Gender	Male/Female	14/65
Age	≥55 yrs/<55yrs	43/36
M factor	M1/M0	9/70
Tumor size	≥4cm/<4cm	34/45
Oxyphilic carcinoma	Yes/No	12/67
A basis for the diagnosis of widely invasive FTC Capsular inv./vascular inv./both		73/2/4



**Fig. 1** Kaplan-Meier curves of DFS of M0 patients with tumors larger than 4 cm and those with tumors 4 cm or smaller

**Table 2** Multivariate analysis of DFS in 70 M0 patients

Variables	<i>p</i> -values	Odds ratio (95% *CI)
Tumor > 4 cm	0.0185	3.831 (1.253-11.63)
Male gender	0.5833	1.400 (0.449-4.348)
Oxyphilic carcinoma	0.7108	1.163 (0.396-3.891)
Age 55 or older	0.9216	0.956 (0.387-2.361)

\* Confidence interval

## Results

Five-year and 10-year DFS rates of 70 M0 widely invasive FTC patients were 82 and 67%, respectively. On univariate analysis, a tumor larger than 4 cm was associated with a significantly poorer DFS than that 4 cm or smaller (*p* = 0.0084) (Fig. 1). A tumor size larger

than 4 cm independently affected the DFS of patients also on multivariate analysis (Table 2).

Five-year and 10-year CSS rates of 79 patients were 98 and 89%, respectively. M1 patients showed a significantly poorer CSS than M0 patients on univariate analysis (Fig. 2), and survival of the M1 patients for 10 years after the initial surgery could not be confirmed in our series. Four of 9 M1 patients died of FTC between 36 and 107 months after surgery. We followed 3 patients between 15 and 51 months after surgery, but failed to follow thereafter. Two are still alive and followed in our department 67 and 68 months after surgery. The M factor was also an independent prognostic factor for CSS on multivariate analysis (Table 3). In the subset of 70 M0 patients, none of the patients with tumors measuring 4 cm or smaller died of FTC (Fig. 3).

In our series, other clinicopathological features such as patient age, gender, and oxyphilic carcinoma had no prognostic impact on DFS and CSS on uni- and multivariate analyses (data not shown).

## Discussion

In this study, we demonstrated that, in the series of widely invasive FTC patients: 1) M1 patients have a very dire prognosis, and 2) a tumor size larger than 4 cm significantly affects the DFS and CSS of M0 patients.

In our previous study using an entire series of FTC, M1 was the strongest prognostic factor [3]. Even in the subset of minimally invasive FTC, the 10-year CSS rate of M1 patients in the series of Sugino *et al.* [22] and us [23] was 55 and 21%, respectively. In our series of widely invasive FTC, 4 of the 9 M1 patients died of FTC and, although follow-up periods are comparably short, none of M1 patients have survived for 10 years after the initial surgery. This indicates that widely invasive is more aggressive than minimally invasive FTC.

Using an entire series of FTC, we previously showed that a tumor size larger than 4 cm had a significant or marginal prognostic impact on DFS and CSS on univariate analysis [3]. However, the previous study also enrolled patients with poorly differentiated carcinoma based on the WHO classification [2], which very strongly reflected the prognosis. Therefore, the tumor size was not recognized as an independent prognostic factor. In the subset of minimally invasive FTC, a large tumor size had a prognostic value in the series of Sugino *et al.* [22] and ours [23]. Also, in this series, a tumor size larger than 4 cm was independently related to DFS

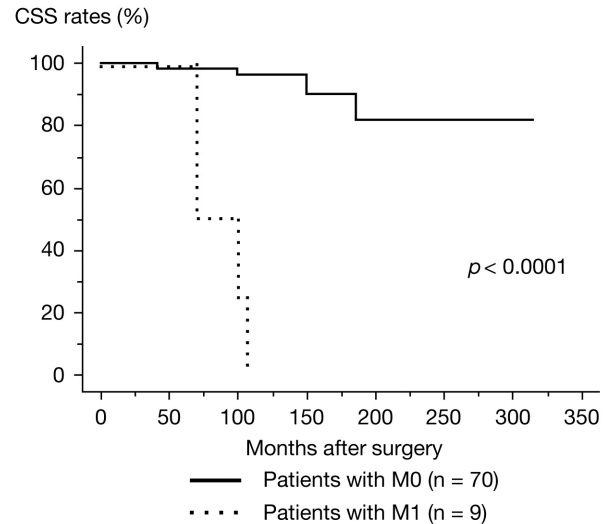


Fig. 2 Kaplan-Meier curves of CSS of M1 and M0 patients

Table 3 Multivariate analysis of CSS in 79 patients

Variables	p-values	Odds ratio (95% *CI)
M1	0.0007	83.333 (6.369-100.000)
Tumor > 4 cm	0.2613	3.597 (0.385-33.333)
Male gender	0.3612	0.248 (0.012-4.950)
Oxyphilic carcinoma	0.2628	0.164 (0.007-3.876)
Age 55 or older	0.9397	1.069 (0.189-6.062)

\* Confidence interval

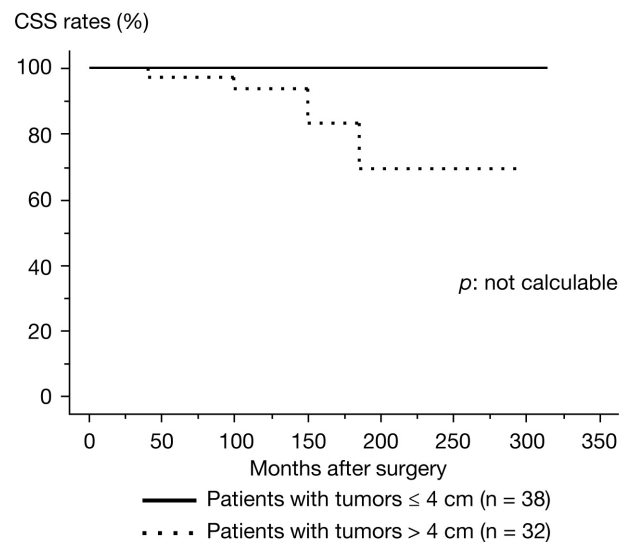


Fig. 3 Kaplan-Meier curves of CSS of M0 patients with tumors larger than 4 cm and those with tumors 4 cm or smaller

of widely invasive FTC patients. Furthermore, none of the M0 patients with tumors measuring 4 cm or smaller died of FTC, indicating that the tumor size significantly affected not only DFS but also CSS of M0 patients.

Age had a prognostic impact both on our entire series [3] and on the subset of minimally invasive FTC [22, 23]. However, it did not show any prognostic value in widely invasive FTC patients, which was in sharp contrast to minimally invasive FTC. We set the cutoff age not only at 55, but also at 45 and 60, but similar results were obtained (data not shown). The reason why age was not related to the prognosis of widely invasive FTC patients remains unclear, and further studies using a larger number of patients could be necessary to draw any firm conclusions.

In our series, prognosis of widely invasive FTC seems better than that in foreign countries. D'Avanzo *et al.* demonstrated that overall death rate of patients with widely invasive FTC was 62% [24]. Haigh *et al.* analyzed SEER database and showed that 10-year CSS rates of oxyphilic cell carcinoma and non-oxyphilic cell carcinoma were poor, at 73 and 83%, respectively, although their series included both minimally and widely invasive FTC. One explanation of the discrepancy is that our diagnostic criteria of widely invasive FTC may differ from that of D'Avanzo *et al.* In addition, dietary factor might also be a reason. Japanese

normally consume large amount of iodine, which can explain, at least in part, the difference in prognosis of FTC, including widely invasive FTC, between foreign countries and Japan.

In contrast to studies from foreign countries [25-27] oxyphilic cell carcinoma did not show a poorer prognosis than non-oxyphilic cell carcinoma in our study. Previous Japanese studies also showed a negative relationship between oxyphilic cell carcinoma and patients' prognosis [3, 22, 23]. The reason for such a discrepancy remains unknown, but there are some endemic reasons.

Immediate RAI therapy after total thyroidectomy is strongly recommended for M1 FTC patients. However, the prognosis of M1 widely invasive FTC patients in our series remains very poor, and the appearance of new therapies such as molecular-targeted agents is expected. Also, in the subset of M0 patients, the 10-year recurrence rate was high, at 33%. Therefore, even for M0 patients, completion total thyroidectomy as a second surgery in preparation for RAI therapy in the future is preferable if a patient has undergone hemithyroidectomy only in the initial surgery. Aggressive therapies, including total thyroidectomy, RAI ablation, and thyroid-stimulating hormone suppression, and careful follow-up are recommended for patients with tumors larger than 4 cm.

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