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Prognostic factors of minimally invasive follicular thyroid carcinoma: Extensive vascular invasion significantly affects patient prognosis

Yasuhiro Ito¹⁾, Mitsuyoshi Hirokawa²⁾, Hiroo Masuoka¹⁾, Tomonori Yabuta¹⁾, Minoru Kihara¹⁾, Takuya Higashiyama¹⁾, Yuuki Takamura¹⁾, Kaoru Kobayashi¹⁾, Akihiro Miya¹⁾ and Akira Miyauchi¹⁾

¹⁾Department of Surgery, Kuma Hospital, Kobe 650-0011, Japan

²⁾Department of Pathology, Kuma Hospital, Kobe 650-0011, Japan

Abstract. Follicular thyroid carcinoma (FTC) is divided into two categories: minimally and widely invasive FTC. Generally, the prognosis of minimally invasive FTC is excellent, but patients showing certain characteristics have a dire prognosis. In this study, we investigated the prognostic factors of minimally invasive FTC using a series of 292 patients. On multivariate analysis, extensive (4 or more) vascular invasion, age ≥ 45 years, and tumor size > 4 cm were independent prognostic factors of patient disease-free survival (DFS). Distant metastasis at diagnosis (M1) was the strongest prognostic factor of cause-specific survival (CSS). Extensive vascular invasion and tumor size > 4 cm also independently affected patient carcinoma death. Capsular invasion was not related to patient prognosis. The ten-year DFS rate of patients with extensive vascular invasion was 80%, which was poorer than that of those having tumor size > 4 cm (91%) and aged 45 years or older (90%). These findings suggest that 1) M1 most strongly affects the CSS of patients, and 2) M0 patients with extensive vascular invasion may be candidates for completion total thyroidectomy and radioactive iodine ablation.

Key words: Follicular carcinoma, Minimally invasive, Prognosis, Vascular invasion

FOLLICULAR THYROID CARCINOMA (FTC) is the second most common malignancy originating from thyroid follicular cells. It is generally difficult to diagnose by preoperative cytology and the diagnosis of FTC is usually confirmed on pathological examination [1]. Although lymph node metastasis is uncommon, FTC is likely to metastasize to distant organs such as the lungs and bone.

There are two types of FTC based on the degree of invasion, minimally and widely invasive FTC [2]. In WHO classification [2], it is described that “minimally invasive FTC have limited capsular and/or vascular invasion and widely invasive FTC have widespread infiltration of adjacent thyroid tissue and/or blood vessels,” but it provides no concrete numbers for vascular invasion to discriminate between minimally and widely invasive FTC. Both in WHO classification

[2] and General Rules for the Description of Thyroid Cancer edited by The Japanese Society of Thyroid Surgery [3], there are no descriptions indicating that preoperatively detectable distant metastasis is a diagnostic criterion of widely invasive FTC. Previous studies showed that widely invasive FTC displays a significantly poorer prognosis than minimally invasive FTC [4, 5]. To date, other conventional prognostic factors of FTC such as distant metastasis at diagnosis (M1), old age, and large tumor size have also been identified [5-22]. However, prognostic factors of minimally invasive FTC have not been intensively investigated and, to our knowledge, only one manuscript has been published for a large series of patients [23]. In this study, therefore, we investigated prognostic factors of minimally invasive FTC using a series of 292 patients.

Patients and Methods

We enrolled 292 patients who underwent initial surgery for solitary or multiple nodules between 1983 and 2007. All available H & E sections of these

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Correspondence to: Yasuhiro Ito, M.D., Ph.D., Department of Surgery, Kuma Hospital, 8-2-35, Shimoyamate-Dori, Chuo-ku, Kobe 650-0011, Japan. E-mail: ito01@kuma-h.or.jp

patients were reviewed by a coauthor, who is a thyroid pathologist (M.H.), and they were diagnosed as minimally invasive FTC. Cases with poorly differentiated lesions and other thyroid malignancies were excluded from our series. They consisted of 44 males and 248 females and the average patient age was 46.7 years old (13-92 years). The diagnosis of FTC was based on the presence of capsular and/or vascular invasion and the absence of nuclear features of papillary thyroid carcinoma. Capsular invasion and vascular invasion were evaluated based on the categories in the textbook written by Chan [24], in which minimally invasive FTC was divided into three categories: with capsular invasion only, with limited (<4) vascular invasion, and with extensive (≥ 4) vascular invasion. The cutoff number of vascular invasion was set at 4 based on the findings of previous studies [25-27]. Widely invasive FTC was defined as tumor with widespread invasion of adjacent thyroid tissue and/or blood vessels and such cases were not enrolled in this study under the diagnosis of our coauthor (M.H.). Capsular invasion was diagnosed as positive when definite capsular invasion was detected or when duplication of the capsule and/or satellite nodule was observed [24]. We counted the total number of vascular invasion in all available H & E sections in each case. Then, the number of H & E sections that we examined depends on tumor size and varies according to case. We classified cases with 4 or more vascular invasion as having extensive vascular invasion. Seven patients had distant metastasis at diagnosis and they were classified as M1 (4 lung, 2 bone, and 1 lung, bone and liver metastases). The remaining 285 were classified as M0, because no distant metastasis was observed preoperatively. Two of these did not have capsular or vascular invasion, but we included them in our series as a previous study [23]. Table 1 summarizes the background and clinicopathological features of the 292 patients.

Seven M1 patients underwent total thyroidectomy. Of 285 M0 patients, 50 and 4 underwent total and subtotal thyroidectomy, respectively, because they had other pathological lesions in the contralateral lobe. The remaining 231 patients underwent more limited thyroidectomy such as lobectomy and isthmectomy. Eighteen patients also underwent lymph node dissection because physicians suspected papillary carcinoma at the time of surgery.

All patients were followed up once or twice per year by US, chest roentgenography, and/or computed

Table 1 Backgrounds and clinicopathological features of the 292 patients (%)

Gender (M/F)	44 (15)/248 (85)
Age (≥ 45 / < 45)	161 (55)/131 (45)
Tumor size (≥ 4 cm/ < 4 cm)	126 (43)/166 (57)
M factor (M1/M0)	7 (2)/285 (98)
Oxyphilic cell carcinoma (y/n)	50 (17)/242 (87)
Duplication of the capsule (y/n)	154 (53)/138 (47)
Satellite nodule (y/n)	58 (20)/234 (80)
Definite capsular invasion (y/n)	144 (49)/148 (51)
Extensive vascular invasion (y/n)	35 (12)/242 (88)

tomography (CT) to screen for recurrence in the lymph nodes and distant organs. For 7 M1 patients, we performed radioactive iodine (RAI) therapy after total thyroidectomy. Also, after the confirmation of distant recurrence during follow up, we performed completion total thyroidectomy and RAI therapy.

We repeatedly sent questionnaires to survey patients who were postoperatively referred to other hospitals near their residences to obtain data on disease-free and cause-specific survival. The mean follow-up time in our series was 117 months (6-329 months). To date, 19 patients (7%) showed FTC recurrence. Lung and bone recurrence were detected in 12 and 10 patients, respectively. Recurrence to lymph nodes and peritracheal tissue were detected in 3 and 1 patient, respectively. Six patients showed recurrence to two or more organs. Seven patients (2%) have died of FTC to date. Four of these were M1 patients.

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.

Results

We performed multivariate analysis of disease-free survival (DFS) of 285 M0 patients (Table 2). Extensive vascular invasion, together with age 45 years or older and tumor size larger than 4 cm, had an independent prognostic value. Although *p* values of duplication and/or satellite nodules and definite capsular invasion were less than 0.05, they did not have prognostic value because their odds ratios and 95% confidence intervals (CIs) were less than 1.0.

Table 2 Multivariate analysis of DFS in 285 M0 patients

Variables	<i>p</i> values	Odds ratio (95% *CI)
Age ≥ 45 yrs	0.0029	9.763 (2.177-43.780)
Male gender	0.5599	1.403 (0.449-4.545)
Oxyphilic	0.1181	0.194 (0.025-1.517)
Size > 4 cm	0.0352	3.509 (1.092-11.364)
Duplication and/or satellite nodule	0.0145	0.155 (0.035-0.691)
Definite capsular invasion	0.0053	0.118 (0.026-0.530)
Extensive vascular invasion	0.0040	5.405 (1.715-16.95)

* Confidence interval

Table 3 Multivariate analysis of CSS in 292 patients

Variables	<i>p</i> values	Odds ratio (95% *CI)
M1	< 0.0001	456.900 (47.619-1007.500)
Age ≥ 45 yrs	0.4637	2.555 (0.208-31.416)
Male gender	0.4707	0.413 (0.037-4.566)
Size > 4 cm	0.0474	25.641 (1.037-50.000)
Duplication and/or satellite nodule	0.8719	1.213 (0.116-12.658)
Definite capsular invasion	0.5222	2.915 (0.110-76.923)
Extensive vascular invasion	0.0430	13.699 (1.085-166.667)

None of the oxyphilic cell carcinoma patients died of FTC.

* Confidence interval

Table 4 Multivariate analysis of CSS in 285 M0 patients

Variables	<i>p</i> values	Odds ratio (95% *CI)
Male gender	0.4507	2.618 (0.215-32.258)
Duplication and/or satellite nodule	0.9936	1.022 (0.004-200.000)
Definite capsular invasion	0.8425	0.575 (0.003-142.857)
Extensive vascular invasion	0.0448	16.949 (1.672-250.000)

None of the oxyphilic cell carcinoma patients died of FTC.

All patients who died of FTC had tumors > 4 cm and were aged 45 or older.

* Confidence interval

Results of multivariate analysis of cause-specific survival (CSS) of 292 FTC patients are summarized in Table 3. None of the oxyphilic carcinoma patients died of FTC and so it was deleted from the analysis. M1 was the strongest predictor of carcinoma death. Extensive vascular invasion and tumor size larger than 4 cm also independently affected the CSS of patients.

We then performed multivariate analysis of CSS on M0 patients (Table 4). All patients who died of FTC had tumors larger than 4 cm and were aged 45 years or older and so these two factors were deleted from the analysis. Extensive vascular invasion was also regarded

as an independent predictor of carcinoma death.

We also performed these three multivariate analyses by including the presence of vascular invasion regardless of its number, instead of extensive vascular invasion, but it did not have an independent prognostic value (data not shown).

Table 5 shows 10-year DFS rates of M0 FTC patients with and without independent prognostic factors. The ten-year DFS rate of patients with extensive vascular invasion was 80%, which was lower than that of those aged 45 or older (90%) and having tumor size larger than 4 cm (91%). As shown in Table 6, the 10-year

Table 5 Ten-year DFS rates of M0 FTC patients with and without independent prognostic factors

Age \geq 45 yrs/ < 45 yrs	90% / 98%
Size > 4 cm/ \leq 4 cm	91% / 96%
Extensive vascular invasion Yes / No	80% / 95%

Table 6 Ten-year CSS rates of FTC patients with and without independent prognostic factors

M factor M1 / M0	21% / 99%
Age \geq 45 yrs/ < 45 yrs	96% *(99%) / 98% (100%)
Size > 4 cm/ \leq 4 cm	96% (97%) / 98% (100%)
Extensive vascular invasion Yes / No	96% (96%) / 97% (99%)

*(): CSS of M0 patients

CSS rate of M1 patients was very low, at 21%. In the subset of M0 patients, the 10-year CSS rate of patients with extensive vascular invasion (96%) was lower than that of those with tumors larger than 4 cm (97%) and aged 45 year or older (99%).

Discussion

Similar to our previous study using an entire series of FTC, we showed that M1 had the strongest prognostic impact among minimally invasive FTC patients. Furthermore, we demonstrated that extensive vascular invasion, together with age 45 years or older and tumor size larger than 4 cm had a significant prognostic value not only of DFS, but also the CSS of patients.

Sugino *et al.* demonstrated that, in a series of 251 minimally invasive FTC patients, M1, tumor size larger than 4 cm and age 45 years or older had significant prognostic value [22, 23], which do not disagree with our findings. They also showed that neither capsular nor vascular invasion affected patient prognosis. In our series, we subdivided capsular invasion into three categories: duplication of the capsule, satellite nodules, and definite capsular invasion. Although *p* values of these factors were lower than 0.05 on multivariate analysis for DFS, their odd ratios and 95% CIs were also lower than 1.0. Furthermore, their *p* values were larger than 0.05 on multivariate analysis for CSS of patients. We can therefore conclude that capsular invasion does not have any prognostic significance, as demonstrated by Sugino *et al.* [23].

Similar to the findings of Sugino *et al.* [23], the presence of vascular invasion was not an independent prognostic factor in our series. However, extensive (4 or more) vascular invasion significantly affected the DFS and CSS of patients on multivariate analysis. Furthermore, as shown in Table 5, 10-year DFS rate of patients with extensive vascular invasion was 80%, which was poorer than that of those aged 45 years or older (90%) and having tumors larger than 4 cm (91%). It is therefore suggested that extensive capsular invasion has a significant prognostic value for minimally invasive FTC patients.

How to treat FTC patients remains an open question. Most FTC patients first undergo hemithyroidectomy under a diagnosis of follicular tumor and adenomatous nodules. Since FTC is likely to show distant metastasis, completion total thyroidectomy is preferable as a second surgery for patients with clinicopathological features predicting recurrence at a high incidence. Then, if recurrence is noted in the early phase by thyroglobulin monitoring. RAI therapy can be immediately performed. In our institution, we perform completion total thyroidectomy with RAI ablation for patients with widely invasive FTC, because its 10-year recurrence rate was high, at 35% [4], but not for minimally invasive FTC. In this study, however, we demonstrated that the 10-year recurrence rate of minimally invasive FTC patients with extensive vascular invasion was also high, at 20%. The acceptable recurrence rate varies according to physicians and patients, but this incidence is considered high for us, and so we regard these patients as possible candidates for completion total thyroidectomy with RAI ablation.

Differential diagnosis of minimally and widely invasive FTC varies according to pathologists, and there may be those who would say that patients with extensive vascular invasion in our series should be diagnosed as widely invasive FTC. However, to date, no concrete criteria to discriminate between minimally and widely invasive FTC regarding the degree of vascular invasion are available. Further studies are necessary to more clearly divide FTC into minimally and widely invasive FTC.

One limitation to this study is we did not produce H & E sections of all cut surfaces in each case. The cut-off number of extensive vascular invasion may require revision if sections of all cut surfaces are examined. Further study is needed to decide on accurate definition of extensive vascular invasion of minimally in-

sive FTC.

In our series, similar to our previous results in an entire series [3], the prognosis of oxyphilic cell carcinoma did not differ from non-oxyphilic cell carcinoma. Some studies from foreign countries showed higher mortality with oxyphilic cell carcinoma [15, 28-30]. The reason for the discrepancy remains unclear, but at least from our data, the therapeutic strategy for oxyphilic cell carcinoma can be the same as that for non-

oxyphilic carcinoma.

In summary, we demonstrated that extensive vascular invasion, together with distant metastasis at diagnosis, old age, and large tumor size, significantly affected DFS and CSS of minimally invasive FTC patients. Since the 10-year recurrence rate of patients with extensive vascular invasion was rather high, at 20%, these patients should be considered candidates for completion total thyroidectomy with RAI ablation.

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