Clinical outcomes of follicular tumor of uncertain malignant potential of the thyroid: real-world data

Yasuhiro Ito\(^1\), Mitsuyoshi Hirokawa\(^2\), Toshitetsu Hayashi\(^3\), Minoru Kihara\(^1\), Naoyoshi Onoda\(^1\), Akihiro Miya\(^1\) and Akira Miyauchi\(^1\)

\(^1\)Departments of Surgery, Kuma Hospital, Kobe, Hyogo 650-0011, Japan
\(^2\)Departments of Diagnostic Pathology, Kuma Hospital, Kobe, Hyogo 650-0011, Japan

Abstract. Thyroid tumors arising from follicular cells can generally be divided into malignant and benign tumors. However, some cases are difficult to clearly diagnose whether they are benign or malignant. Therefore, in the most recent version of World Health Organization (WHO) classification, some borderline lesions such as follicular tumor of uncertain malignant potential (FT-UMP), well-differentiated tumor of uncertain malignant potential (WDF-UMP), and noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) were proposed. In this study, we investigated the clinical aspects, including the prognosis, of FT-UMP patients. We investigated the clinical features of 339 patients with FT-UMP. On ultrasound, 68% of the tumors were diagnosed as intermediate, and only 5% of those tumors were diagnosed as malignant. On cytology, 40% of the tumors were diagnosed as follicular neoplasm, and only 1% of these were suspected to be or diagnosed as malignancy. The diagnosis was based on questionable capsular invasion for 332 patients, questionable vascular invasion for 2 patients, and both for 5 patients. Eighty-six percent of the tumors showed low cell proliferation activity. To date, five patients (1%) have shown distant recurrence during postoperative follow-up and underwent various treatments such as radioactive iodine therapy, orthopedic surgery, and denosumab injection. None of these patients have died due to thyroid carcinoma. Our findings suggest that FT-UMP is generally an indolent disease, but some patients show distant recurrence. Physicians should carefully follow patients, although it remains unknown how long they should be observed after surgery.

Key words: Follicular tumor of uncertain malignant potential, Thyroid, Prognosis

THYROID TUMORS arising from follicular cells can generally be divided into malignant and benign tumors, but pathologists occasionally encounter borderline lesions. Follicular tumor of uncertain malignant potential (FT-UMP) is one of these borderline lesions; it was first proposed by Williams et al. in 2000 [1]. In the most recent World Health Organization (WHO) classification, FT-UMP is defined as “an encapsulated or well circumscribed tumour composed of well-differentiated follicular cells with no nuclear features of papillary thyroid carcinoma (PTC) with questionable capsular or vascular invasion [2].” The clinical aspects of FT-UMP have been unclear, and we thus conducted the present study to investigate the clinicopathological features and prognoses of patients with FT-UMP.

Patients and Methods

Patients with FT-UMP

Between August 2010 and December 2018, 13,089 patients with thyroid tumors underwent surgery at our institution (Kuma Hospital, Kobe). Of these, 8,873, 3,709, and 502 patients were pathologically diagnosed as having malignant, benign, and borderline tumors (i.e., FT-UMP and well-differentiated tumor of uncertain malignant potential), respectively. FT-UMP based on the WHO classification [2] was diagnosed in 339 patients (3%), and we enrolled these patients in the study. FT-UMP in our series was diagnosed after consultation by two pathologists (M.H., and T.H.) based on the findings of representative preparations, but cases having potential mimickers of invasion have been re-examined by deeper cut or additional preparations. We excluded cases in which a thyroid carcinoma (e.g., papillary, follicular and anaplastic carcinomas) detected on preoperative imaging studies coexisted with the FT-UMP, but we included 21 patients with incidentally detected PTC (diagnosed on pathology, but not detected by preoperative ultrasound).
Ultrasound (US) findings were subject to the US classification (USC) system established by Yokozawa and Miyauchi et al. [3]. Tumors with the USC scores ≥3.5, 3, and ≤2.5 were diagnosed as or suspected of malignancy, intermediate, and benign.

For cytology, we used the Bethesda classifications: unsatisfactory (UNS), cyst fluid (CF), benign (BN), undetermined significance (AUS), follicular neoplasm (FN), suspected of malignancy (SFM), and malignant (MT) [4]. Ki-67 immunostaining was often, although not always, performed for tissue sections using an antibody against Ki-67 (MIB1). The details of immunostaining and evaluation were as described [5]. We classified the Ki-67 labeling index (LI) into three categories: 1+, 0%–5%; 2+, >5% and ≤10%; and 3+, >10%.

**Patients with minimally invasive follicular thyroid carcinoma**

In 2016, we published the manuscript regarding prognostic factors of minimally invasive FTC (FTC-min) [5]. The patient series in this study included 108 patients without distant metastasis at presentation who met the diagnostic criteria of FTC-min in the present version of WHO classification [2] and General Rules for the Description of Thyroid Cancer [6]. We enrolled this subset for the analysis.

**Statistical analyses**

We used the Kaplan-Meier method to analyze time-dependent variables. All statistical analyses were performed with the software StatFlex (Artec, Osaka, Japan).

**Results**

**Backgrounds, clinicopathological features, and prognosis of FT-UMP patients**

We enrolled 339 patients with FT-UMP. The diagnosis was based on questionable capsular invasion for 332 patients, questionable vascular invasion for 2 patients, and both for 5 patients.

The background and clinicopathological findings of the 339 patients with FT-UMPs are summarized in Table 1. Sixty-eight percent of the FT-UMPs were diagnosed as intermediate on US, while only 5% were diagnosed as malignant. Similarly, based on cytology, 60% of the tumors were diagnosed as follicular neoplasm, but only 1% were diagnosed as or suspected of malignancy. Only 14% of the tumors had high cell-proliferation activity; the remaining 86% showed low activity.

Postoperative follow-up period ranged from 12–131 months (median 55 months). Five patients (1%) have shown structural recurrences to distant organs as of this writing. Fig. 1 shows a Kaplan-Meier curve of the recurrence-free survival (RFS) rate; the 5-year RFS rate was 98%. Table 2 provides the profiles of these five patients. All patients had questionable capsular invasion, but questionable vascular invasion could be detected in none of these cases. The Ki-67 LI was low in four of the patients. All patients showed recurrence to the bone, and lung metastasis was also detected in one patient. Metastatic lesions were radioactive iodine I-131 (RAI)-avid in all five patients; these patients underwent treatment with RAI at 400–713 mCi. Orthopedic surgery was performed for two patients, and one underwent denosumab injection 1×/month.

Table 3 showed the change in thyroglobulin (Tg) levels (Electrochemiluminescence immunoassay, Roche Diagnostics K.K. [Tokyo, Japan]) before and after surgery until the detection of recurred lesions. All patients were negative for anti-Tg antibody. Cases no. 1, 3 and 4 underwent hemithyroidectomy and benign nodules were remained in contralateral lobe. These nodules were stable after surgery until the detection of recurred lesions. The Tg levels once decreased after surgery, but elevated again thereafter. Case 1 underwent chest CT scan 3 years after surgery but no abnormal findings were detected. Forty-four months after surgery, patients suffered bone fracture and then, bone metastasis was detected. Cases 2 and 5 underwent total thyroidectomy at initial surgery because of the coexisted multinodular goiter. However, Tg levels of both patients did not decrease completely and elevated again. Distant metastases were then detected by RAI administration in comparably early time. To date, none of these patients died due to the thyroid carcinoma.

**Prognosis of FTC-min patients without distant metastasis at presentation**

Of 108 patients, 17 were males and 91 were females (median age, 44 years). Median postoperative follow-up period was 131 months. Three patients (3%) showed recurrence to the lung 61, 80, and 155 months after surgery. Five-year and 10-year RFS rates were 100 and 98%, respectively, and none of the patients in this series died of thyroid carcinoma at a point of 2016.

**Discussion**

We investigated the clinicopathological features and prognosis of patients diagnosed with an FT-UMP. On ultrasound, 68% of the tumors were diagnosed as intermediate, and 60% of those were cytologically diagnosed as a follicular neoplasm. Only 1% of these tumors were suspected of or diagnosed as being malignant on cytology, which is reasonable because they have no nuclear features of PTC [2]. Our earlier investigation revealed
### Table 1  Background and clinicopathological findings of the FT-UMP patients (N = 339)

| Category                                                                 | Count   | Percentage |
|-------------------------------------------------------------------------|---------|------------|
| **Male**                                                                | 68      | 20%        |
| **Female**                                                              | 271     | 80%        |
| **Age at surgery, yrs**                                                 | 12–82 (median 51) |         |
| **Ultrasound findings:**                                                |         |            |
| Calc only                                                               | 2       | 1%         |
| Benign                                                                  | 89      | 26%        |
| Intermediate                                                            | 232     | 68%        |
| Malignant                                                               | 16      | 5%         |
| **Tumor size, mm**                                                      | 9–101 (median 39) |         |
| **Cytological findings:**                                              |         |            |
| Not done                                                                | 2       |            |
| UNS                                                                     | 1       |            |
| BN or CF                                                                | 150     | 45%        |
| AUS                                                                     | 48      | 14%        |
| FN                                                                      | 135     | 40%        |
| SFM or MT                                                               | 3       | 1%         |
| **Coexisted thyroid or parathyroid diseases affecting surgical design:**|         |            |
| Adenomatous nodule or multinodular goiter                               | 35      | 10%        |
| Graves' disease                                                         | 7       | 2%         |
| Primary hyperparathyroidism                                             | 3       | 1%         |
| **Extent of thyroidectomy:**                                           |         |            |
| Total thyroidectomy                                                     | 52      | 15%        |
| Subtotal thyroidectomy or hemithyroidectomy                             | 287     | 85%        |
| **Extent of lymph node dissection:**                                   |         |            |
| Not done                                                                | 312     | 92%        |
| Central node dissection<sup>1</sup>                                      | 27      | 8%         |
| **Multiple FT-UMP:**                                                    |         |            |
| Yes                                                                     | 9       | 3%         |
| No                                                                      | 330     | 97%        |
| **Ki-67 labeling index:**                                              |         |            |
| Unknown                                                                 | 53      |            |
| 1+: 0%–5%                                                               | 247     | 86%        |
| 2+: >5%, ≤10%                                                           | 35      | 12%        |
| 3+: >10%                                                                | 4       | 2%         |
| **Oxophilic:**                                                          |         |            |
| Yes                                                                     | 21      | 6%         |
| No                                                                      | 318     | 94%        |
| **Postoperative follow-up period, months**                              | 12–131 (median 55) |         |
| **Structural recurrence:**                                             |         |            |
| Yes                                                                     | 5       | 1%         |
| No                                                                      | 334     | 99%        |
| **Five-year recurrence-free survival rate**                             | 99%     |            |
| **Death due to thyroid carcinoma:**                                     |         |            |
| Yes                                                                     | 0       |            |
| No                                                                      | 339     | 100%       |

<sup>1</sup> One patient also underwent lateral node dissection.

AUS, undetermined significance; BN, benign; CF, cyst fluid; FN, follicular neoplasm; MT, malignant; SFM, suspicious for malignancy; UNS, unsatisfactory.
that a high Ki-67 LI predicted a poorer prognosis of FTC-min [5]. In our series, the Ki-67 LI was 0%–5% in 86% of the tumors, indicating that FT-UMP is generally an indolent disease. However, to date, five (1%) of the present patients with FT-UMP showed distant recurrence. All recurred lesions were RAI-avid and, to date, none of the five patients died of thyroid carcinoma. A long period of survival can thus be expected even for FT-UMP patients with distant recurrence, if they undergo appropriate treatments such as RAI therapy, surgery, and denosumab. However, long-term post-surgery active surveillance should be conducted, even when these tumors are not pathologically diagnosed as malignant.

In our series, although portion of cases having potential mimickers of invasion have been re-examined by deeper cut or additional preparations, many were diagnosed as FT-UMP based on the findings of representative preparations. Most cases, including the five showing recurrence, were diagnosed as FT-UMP based

![Kaplan-Meier curve of FT-UMP patients for recurrence-free survival (RFS).](image)

**Fig. 1** Kaplan-Meier curve of FT-UMP patients for recurrence-free survival (RFS).

**Table 2** Profiles of the six patients with FT-UMP in whom recurrences were detected

| Case no. | Age at initial surgery, yrs | Gender | Tumor size, mm | Surgical design | Ki-67 LI | Opportunity of discovery | Time from surgery to discovery of metastasis, months | Organs to which tumor metastasized | Treatment | Patient outcomes: time from initial surgery, months |
|----------|---------------------------|--------|----------------|----------------|----------|--------------------------|--------------------------------|---------------------------------|-----------|--------------------------------------------------|
| 1        | 62, F                     | 31     | Hemi           | 1+ Bone fracture | 44       | Bone                     |                                          | RAI *400 mCi, Surg            | 104, alive |
| 2        | 64, F                     | 23     | Total          | 1+ Persistent disease | 14       | Bone                     |                                          | *713 mCi Surg, Deno        | 87, alive |
| 3        | 58, F                     | 27     | Hemi           | 1+ Tg elevation | 45       | Lung, bone               |                                          | RAI +700 mCi,                | 96, alive |
| 4        | 36, M                     | 58     | Hemi           | 2+ **Biopsy of bone lesion | 63       | Bone                     |                                          | RAI +500 mCi,                | 120, alive |
| 5        | 51, F                     | 65     | Total          | 1+ Persistent disease | 26       | Bone                     |                                          | RAI 413 mCi, Deno           | 62, alive |

* Total dose of RAI administration. ** Detected by Positron-Emission Tomography. Deno, denosumab; F, female; Hemi, hemithyroidectomy; LI, labeling index; M, male; RAI, radioactive iodine; Surg, surgery; Tg, thyroglobulin; Total, total thyroidectomy; TSH, thyroid stimulating hormone.

**Table 3** Change in thyroglobulin levels before and after surgery in the five cases showing recurrence

| Case no. | Extent of thyroidectomy | Tg levels (ng/mL) (All cases were negative for anti-Tg antibody) |
|----------|-------------------------|---------------------------------------------------------------|
|          | Before surgery | 1 mo. later | 1 yr. later | 2 yr. later | 3 yr. later | 4 yr. later | At the time of detection of recurrence |
| 1        | *Hemi         | 38.6        | 7.7         | 20.1        | 77.8        | 479.1       | N/A | 479.1 |
| 2        | Total         | 1,658.0     | 9.0         | 37.7        | N/A         | N/A         | N/A | 37.7 |
| 3        | *Hemi         | 3,215.0     | 44.1        | 90.6        | 97.26       | 157.4       | N/A | 477.3 |
| 4        | *Hemi         | 360.8       | 20.5        | 9.4         | 13.9        | 13.6        | 44.4 | 170.8 |
| 5        | Total         | 1,004.0     | 19.7        | 1.12        | 7.18        | N/A         | N/A | 7.18 |

* Benign nodules were located in the remnant thyroid, but were stable after surgery. Tg, thyroglobulin; Hemi, hemithyroidectomy; Total, total thyroidectomy; N/A, not available.
on questionable capsular invasion, but not on vascular invasion. Thus, there is a possibility that vascular invasion not located in the representative preparations was overlooked for them. When questionable findings of capsular and/or vascular invasion are detected, it could be better to routinely perform re-examination by deep cut or additional preparations. The RFS rate of FT-UMP in the present series was similar to that of FTC-min in our previous series, although it is not appropriate to compare these two different series directly. If re-examination by deep cut or additional preparations were routinely performed for questionable cases, the incidence of FTC would become higher and prognoses of these patients would be more accurately predicted.

This study has some limitations. It was a retrospective analysis, and we used diagnoses of FT-UMP established in August 2010. The postoperative follow-up period was not long. Studies enrolling larger numbers of patients with long-term follow-up are needed to draw more certain conclusions. All five patients with FT-UMP in our series showed bone metastasis, while all three patients with FTC-min in the previous series showed lung metastasis. Further extensive study might solve this discrepancy in future.

In summary, FT-UMP is generally an indolent disease, but some cases show distant recurrence. Physicians should carefully follow patients, although it remains unknown how long they should be observed after surgery.

References

1. Williams ED (2000) Guest editorial: two proposals regarding the terminology of thyroid tumors. Int J Surg Pathol 8: 181–183.
2. Tumours of the thyroid gland. In: Lloyd RV, Osamura RY, Kloppel G, Rosai J (ed) (2017) WHO classification of tumours of endocrine organs (4th). IARC Publications, Lyon, France: 65–143.
3. Yokozawa T, Fukata S, Kuma K, Matsuzuka F, Kobayashi A, et al. (1996) Thyroid cancer detected by ultrasound-guided fine-needle aspiration biopsy. World J Surg 20: 848–853.
4. Ali SZ, Cibas ES (ed) (2018) The Bethesda System for reporting thyroid cytopathology: Definitions, criteria and explanatory notes (2nd) Springer New York, USA.
5. Ito Y, Hirokawa M, Miyauuchi A, Masuoka H, Yabuta T, et al. (2016) Prognostic impact of Ki-67 labeling index in minimally invasive follicular thyroid carcinoma. Endocr J 63: 913–917.
6. Japan Association of Endocrine Surgery and The Japanese Society of Thyroid Pathology (2019) General Rules for the Description of Thyroid Cancer (8th). Kanehara & Co., LTD., Tokyo (In Japanese).