Clinicopathological features and outcomes of intrathyroidal thymic carcinoma: a single institution study

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Abstract. Intrathyroidal thymic carcinoma (ITTC) is a rare malignancy of the thyroid. It is thought to originate from ectopic thymic tissue or embryonic thymic rest, in, or adjacent to, the thyroid. We analyzed the backgrounds, clinicopathological features, and prognosis of 20 patients with ITTC, treated at our hospital. Thirteen of the 15 patients (86%) who underwent ultrasonography were diagnosed as malignant, based on imaging findings. 16 of the 17 patients (93%) who underwent cytology, were diagnosed or suspected to be malignant. Locally curative surgery (thyroidectomy and lymph node dissection) was performed for 19 patients. Large tumor size (>4 cm) was positively related to pathological node metastasis ($p = 0.0389$). Fourteen patients, including nine Ex-positive patients, underwent adjuvant external beam radiotherapy (EBRT) of the neck after surgery. Two patients showed recurrence of thyroid bed after and neither of them underwent adjuvant EBRT after surgery. Two patients who underwent EBRT showed recurrences of the lateral nodes (level V and level II), but they were easily dissected by re-operation. Ten- and 20-year local recurrence-free survival rates were 84.9% and 60.6%, respectively. To date, four patients showed distant recurrence, and 10- and 20-year distant recurrence-free survival rates were 75.0% and 75.0%, respectively. Our findings indicate that 1) the prognosis of ITTC is generally favorable, and 2) large tumor size is significantly related to lymph node metastasis. Two patients showing recurrence of the central region did not undergo EBRT; thus, further comparative studies are desirable to elucidate whether EBRT can prevent significant local recurrence.

Key words: Intrathyroid thymic carcinoma (ITTC), Extrathyroidal extension, Prognosis, Radiotherapy

INTRATHYROIDAL THYMIC CARCINOMA (ITTC) is a rare thyroid malignancy. Its histology resembles that of squamous cell carcinoma (SCC) of the thyroid. However, ITTC shows a much more favorable prognosis than SCC. Its origin is thought to be ectopic thymic tissue or embryonic thymic rest in or adjacent to the thyroid. This disease was first proposed by Miyauchi et al. in 1985, as intrathyroidal epithelial thymoma [1] and was accepted as a novel entity in the textbook by Rosai et al. [2].

However, it was denominated as carcinoma showing thymus-like differentiation in 1991 due to insufficient evidence of thymic cell origin [3]. In 2004, this neoplasm was renamed to the present ITTC, acknowledging its thymic cell origin by the World Health Organization classification of tumors of endocrine organs [4]. In 2013, Hirokawa et al. demonstrated that immunohistochemical findings in ITTC were essentially similar to those of thymic lymphoepithelioma-like carcinoma, indicating that ITTC is derived from ectopic thymus [5].

ITTC is usually located in the lower pole of the thyroid. Cytologic diagnosis is difficult, although previous studies revealed several typical cytologic and pathological features [1, 2, 6, 7]. For pathological diagnosis, immunohistochemistry of CD5 and PAX8 (by monoclonal antibody) is helpful [8, 9].

This is a rare disease, and our knowledge about its clinicopathological aspects remains inadequate. To date, one collaborative study, and one pooled analysis have been published [10, 11]. Herein, we conducted a
single-institution study to investigate the clinicopathological features and prognosis of ITTC patients.

**Materials and Methods**

In this study, 20 patients who underwent initial surgery for ITTC at Kuma Hospital between 1961 and 2021, were enrolled. Some patients were also enrolled in the collaborative study [10], but their follow-up time periods were much shorter than those in this study. Therefore, data of this study were independently established and not related to the collaborative study. This series includes two of the three patients from the original paper [1]. The remaining patient was operated on at another hospital and his clinicopathological features and prognosis were unclear; thus, this patient was not enrolled. The patients’ backgrounds are summarized in Table 1. There were four males and 16 females, and the median age was 54 years (25–74 years). All patients were diagnosed with ITTC based on the pathological examination of one pathologist (M.H.). Fourteen patients also underwent adjuvant external beam radiotherapy (EBRT) after initially curative surgery. The main purpose of EBRT was to prevent recurrence in the region where dissected tumor was located. The detail was unspecified in two patients, but the remaining 12 underwent EBRT to the tumor bed in the central region (area where the thyroid was located). The total radiation fields were based mainly on radiologists’ discretion and differed according to a case-by-case basis, e.g., the central region only, central region and upper mediastinum, central region and lateral compartment, and whole neck. Total radiation value ranged from 45 Gy to 70 Gy.

After surgery, the patients were followed-up once or twice per year using ultrasonography and blood examinations including thyroid stimulating hormone, free thyroxine, or free triiodothyroxine. Computed tomography and positron emission tomography were also performed at the attending physicians’ discretion. For patients referred to other hospitals, questionnaires were sent once a year to evaluate their conditions. The median follow-up period was 160 months (range: 2–385 months).

For statistical analysis, chi-square test was adopted for comparing variables. The Kaplan–Meier method was used for time series analysis. Statistical significance was set at $p < 0.05$. StatFlex software (Artec, Osaka, Japan) was used for all analyses.

This study was approved by the ethical committee at Kuma Hospital (No. 20200709-1).

| Sex          | Number (Percentage) |
|--------------|---------------------|
| Male         | 4 (20%)             |
| Female       | 16 (80%)            |

| Age at surgery, years | 25–74 (median 54) |
|-----------------------|-------------------|
| Tumor size, mm (two unknown) | 16–70 (median 42) |

| Ultrasound findings          | Number (Percentage) |
|------------------------------|---------------------|
| Malignant                    | 13 (86%)            |
| Intermediate                 | 2 (14%)             |
| Unknown                      | 5                   |

| Clinical node metastasis     | Number (Percentage) |
|------------------------------|---------------------|
| Present                      | 1 (5%)              |
| Absent                       | 19 (95%)            |

| Cytological findings        | Number (Percentage) |
|-----------------------------|---------------------|
| MT                          | 13* (76%)           |
| SFM                         | 3 (18%)             |
| AUS                         | 1 (6%)              |
| Not done                    | 3                   |

| Extent of thyroidectomy:    | Number (Percentage) |
|------------------------------|---------------------|
| Total thyroidectomy          | 6 (30%)             |
| Subtotal thyroidectomy       | 3 (15%)             |
| Hemithyroidectomy            | 11 (55%)            |

| Extent of lymph node dissection: | Number (Percentage) |
|---------------------------------|---------------------|
| Central and lateral node dissection | 12 (60%)           |
| Central node dissection only    | 5 (25%)             |
| Not done                        | 3 (15%)             |

| Locally curative surgery       | Number (Percentage) |
|------------------------------   |---------------------|
| Yes                          | 19 (95%)            |
| No                           | 1 (5%)              |

| Extrathyroidal extension to adjacent organs (Ex)* | Number (Percentage) |
|--------------------------------------------------|---------------------|
| Yes                                               | 10 (50%)            |
| No                                                | 10 (50%)            |

| Pathological node metastasis | Number (Percentage) |
|------------------------------|---------------------|
| Yes                          | 6 (35%)             |
| No                           | 11 (65%)            |
| Unknown                      | 3                   |

| EBRT after surgery          | Number (Percentage) |
|------------------------------|---------------------|
| After initial palliative surgery | 1 (5%)             |
| After initial curative surgery | 14** (70%)         |
| After second surgery         | 1 (5%)              |
| Not done                     | 4 (20%)             |

| Postoperative follow-up period, months | Number (Percentage) |
|---------------------------------------|---------------------|
| 2–385 (median 160)                    |                    |

| Structural recurrence               | Number (Percentage) |
|------------------------------------|---------------------|
| Yes                                | 7*** (35%)          |
| No                                 | 13 (65%)            |

* Based on intra-operative findings
** Nine of these were Ex-positive.
*** Three showed local recurrence, 3 showed distant recurrence, and 1 showed both.
AUS: undetermined significance, SFM: suspicious for malignancy, MT: malignant, EBRT: external beam radiotherapy
Results

Backgrounds and Clinicopathological Features of 15 Patients with ITTC

Table 1 shows the backgrounds and clinicopathological features of 20 patients with ITTC. Of the 15 tumors evaluated using ultrasonography, 13 (86%) were considered malignant, based on our classification system [12]. Of the 17 tumors that were cytologically examined, 13 and three (76% and 18%) were diagnosed or suspected to be malignant. Of these 16, two (13%) were diagnosed as ITTC; for six (38%), there was a possibility of ITTC together with other malignancies such as poorly differentiated carcinoma, medullary carcinoma, and metastatic carcinoma from other organs. Eleven patients (55%) underwent hemithyroidectomy while total thyroidectomy was performed only for six patients (30%). Central node dissection was performed for 17 patients (85%) and 13 (65%) also underwent lateral node dissection (12 prophylactic and one therapeutic). One patient underwent palliative surgery (hemithyroidectomy only), but the other 19 received locally curative surgery. Regarding intra-surgical findings, 10 patients (50%) showed extrathyroidal carcinoma extension (Ex) to the adjacent organs such as recurrent laryngeal nerve, trachea, esophagus, and sternohyoid muscle corresponding to T3b or T4a in AJCC TNM classification [13]. Six patients (35%) were positive for node metastasis on pathological examination. Table 2 shows the relationship between Ex, tumor size, and pathological node metastasis on pathological examination. Large tumor size (>4 cm) was significantly related to pathological node metastasis (p = 0.0389), while Ex was not (p = 0.0637). One patient (5%) underwent EBRT after initial palliative surgery, and 14 (70%) underwent EBRT (including eight Ex-positive patients) after initial curative surgery as an adjuvant therapy. The remaining five did not undergo EBRT after initial surgery. One patient refused EBRT, although her tumor was Ex-positive. She underwent EBRT after second surgery for recurrence of the central region. Two patients did not undergo EBRT based on physicians’ discretion mainly because the tumors were Ex-negative. The remaining two were not originally diagnosed with ITTC and were not recommended EBRT.

Outcomes of 20 ITTC Patients

We analyzed the prognosis of patients in our series. One patient was excluded from further analysis because he underwent a palliative surgery and was lost to follow-up only 2 months after the surgery. Local recurrence was detected in four patients 31, 115, 205, and 209 months after the initial surgery. Fig. 1 indicates the Kaplan–Meier curve for local recurrence-free survival. Ten- and 20-year local recurrence-free survival rates were 84.9% and 60.6%, respectively. The lesions of recurrence were the central region for two patients, and regional lymph nodes for two patients (ipsilateral level V in one patient and contralateral level II in one patient). The former two (one Ex-positive and one Ex-negative) did not undergo adjuvant EBRT after the initial surgery. One patient underwent a second round of surgery for recurrence of the central region, but invasive lesions of the carotid artery and the esophagus remained undissected. The remaining patient with recurrence of the central region could not undergo surgery because of her poor condition, and coexisting dementia. Regarding the two patients showing recurrence of the regional lymph nodes, one with recurrence of ipsilateral level V underwent only central node dissection and another with recurrence of contralateral level II underwent only ipsilateral lateral

| Pathological lymph node metastasis | Present | Absent | Total* | p-values |
|-----------------------------------|---------|--------|--------|----------|
| Tumor size**                      |         |        |        |          |
| >4 cm                             | 5 (63%) | 3 (37%)| 8 (100%)| 0.0389   |
| ≤4 cm                             | 1 (13%) | 7 (87%)| 8 (100%)|          |
| Unknown                           | 4        |        |        |          |
| Extrathyroidal extension          |         |        |        |          |
| Present                           | 5 (56%) | 4 (44%)| 9 (100%)| 0.0637   |
| Absent                            | 1 (13%) | 7 (87%)| 8 (100%)|          |
| Unknown                           | 3        |        |        |          |

* Three patients who did not undergo lymph node dissection were excluded.
** Size of two cases was unknown.
node dissection at initial surgery, indicating that the recurred lesions were not dissected at the initial surgery. Both patients were re-operated and no further recurrences were observed.

Distant recurrence was observed in four patients, i.e., in the lung for three patients and in the bone and brain for one patient. Among these patients, distant recurrence was observed 14, 25, 49, and 53 months after the initial surgery. As shown in Fig. 2, 10- and 20-year distant recurrence-free survival rates were 75.0% and 75.0%, respectively. Radiation therapies such as EBRT, radiofrequency ablation, and gamma knife therapy were performed for recurred lesions.

To date, one patient who showed recurrence of the
central region (209 months after initial surgery) and underwent second surgery (but palliative) followed by EBRT died of ITTC 270 months after the initial surgery. Another patient who showed recurrence to the central region (205 months after the initial surgery) but could not undergo second surgery, died of natural causes 228 months after the initial surgery. One patient who showed recurrence to the bone and brain, was referred to another hospital for best supportive care 26 months after the surgery and was lost to follow-up. Three other patients were lost to follow-up 159, 306, and 355 months after the initial surgery. These patients did not show recurrence during the follow-up at our clinic. The remaining 13 still regularly visit our outpatient clinic for postoperative follow-up.

Discussion

In this study, we investigated the clinicopathological features, including the prognosis of ITTC patients treated at our hospital; to our knowledge, this is the first single institution study for this disease. On ultrasonography, 13 tumors (86%) were diagnosed as malignant. On cytology, 16 tumors (94%) were diagnosed or suspected to be malignant. Of these, however, only two (13%) were diagnosed as ITTC and six (38%) had the possibility of ITTC diagnosis along with other malignancies such as poorly differentiated carcinoma, medullary carcinoma, and metastatic carcinoma. Thus, accurate diagnosis of ITTC before surgery is difficult.

In our series, 36% patients showed pathological node metastasis (one patient was also positive for clinical metastasis), which was similar to the results (44% patients) of the collaborative study [10]. Prophylactic lymph node dissection in the central and lateral compartment is actively performed in ITTC surgery. To date, two patients showed recurrent lymph node, but recurred lesions of both patients remained undissected at the initial surgery. Therefore, prophylactic node dissection might contribute to reduce local recurrence to some extent especially for large tumors, but comparative studies with patients that underwent and did not undergo prophylactic node dissection are necessary for more confirmative conclusions.

Postoperative EBRT is performed empirically after surgery for thymic carcinoma. Regarding its efficacy, previous studies showed discrepant results [14, 15], but a meta-analysis concluded that postoperative EBRT is associated with improved overall and progression-free survival [16]. Regarding ITTC, a collaborative study with member institutes of the Japanese Society of Thyroid Surgery demonstrated that none of the 10 patients who underwent adjuvant EBRT after curative surgery showed local recurrence, while among the 11 who did not receive EBRT, three (27%) had locoregional recurrence [10]. In contrast, in a pooled analysis, Gurizzan et al. analyzed 133 cases extracted from 50 studies, and showed that on multivariate analysis, lymph node involvement and presence of major symptoms independently predicted poor disease-free survival and overall survival, respectively; however, adjuvant EBRT did not have prognostic values for them [11]. In our series, two patients (one Ex-positive and one -negative) showed recurrence in the central region, although both patients underwent locally curative surgery. None of these patients underwent EBRT after the initial surgery. Of the 14 patients who underwent EBRT, no patient showed recurrence in the central region. Two showed node recurrence (one in level II and another in level V), but as indicated above, these lesions remained undissected at the initial surgery. Further, EBRT mainly targets tumor bed in the central region after thyroidectomy for local control and the total range of EBRT varied according to radiologists’ discretion. There is inadequate evidence regarding the efficacy of postoperative EBRT, but the incidence of recurrence in the central region, including the tumor bed, could be reduced. Further comparative studies are necessary to understand this better.

For distant recurrence, various kinds of radiation therapy were performed, partly because no evidence was available regarding the effectiveness of any medication therapy. In 2021, lenvatinib, a multi-target kinase inhibitor, was first adopted as a treatment option for patients with advanced or metastatic thymic carcinoma [17]. Subsequently, further improvement in the prognosis of patients with advanced/metastatic ITTC could be expected.

The collaborative study did not show local or distant recurrence-free survival rates [10]. However, it showed that three patients died of ITTC and the 5- and 10-year CSS rates were 90% and 82%, respectively. None of the patients negative for node metastasis or Ex died of this disease [10]. In our series, two patients positive for Ex and with N1b died of ITTC or underwent best supportive care, which was consistent with the results of collaborative study.

This study was performed at a single institution, which might be one of its strengths. However, it was retrospective in nature and enrolled a small number of patients; thus, further detailed analysis is required enrolling larger number of patients. The therapeutic strategy was not unified in advance; thus, it is difficult to show any practice guidelines for this disease, which is a significant limitation.

In summary, the prognosis of ITTC is generally favorable, and large tumor size is significantly related to lymph node metastasis. Two patients showing recurrence
in the central region did not undergo EBRT. Therefore, further comparative studies are desirable to elucidate whether EBRT can prevent recurrence to local lesions, including the tumor bed.

Conflicts of Interest

The authors have declared that there are no competing interests.

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