Original Article

A single-center analysis of 71 patients with thymic carcinoma: the chronological changes in the surgical procedure and prognosis

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Background: Effective treatments for thymic carcinoma (TC) have not been established due to its rarity and the prognosis has not yet been improved. In the present study, data of patients who underwent treatment for TC at our single institution were retrospectively reviewed to investigate the chronological changes in the clinical characteristics, surgical procedure, and prognosis.

Methods: A total of 71 patients were included in this study. To investigate the chronological changes, the patients were divided into two groups at January 2009, when minimally invasive surgery (MIS) for thymic epithelial tumors (TETs) was introduced.

Results: Among the 71 TC patients, 24 patients underwent surgery through December 2008 (earlier period), and 21 underwent surgery from January 2009 (later period). The patients in the later group were more likely to be diagnosed by chest computed tomography (CT) scan without subjective symptom. The rates of MIS and complete resection were significantly higher and the number of the patients at the early stage were significantly greater in the later group. The 5-year overall survival (OS) rate of the patients who underwent surgery at earlier and later groups were 58.7% and 92.8% respectively (P<0.01).

Conclusions: The prognosis of TC has improved over time, thanks to early detection by CT screening and complete surgical resection.

Keywords: Thymic carcinoma (TC); single-center analysis; chronological change; minimally invasive surgery (MIS); sub-total thymectomy

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Introduction

Thymic carcinoma (TC) is a rare and aggressive mediastinal neoplasm with a poor prognosis. Although several studies have been reported concerning TC (1-8), the clinicopathologic characteristics and prognosis of TC remain unclear, due to its rarity.

Among thoracic malignant tumors, lung cancer, which is the leading cause of death worldwide, has an improved overall survival (OS) compared with several decades ago (9,10). However, there have been few reports concerning the changes in the prognosis over time for thymic epithelial tumors (TETs), especially TC, due to the small number of such cases. Therefore, whether or not the treatment or prognosis of TC has improved over the years remains unclear.

In recent years, small-sized TETs have been treated more frequently than before due to the spread of computed

tomography (CT) (11,12). Based on the background of widely spread CT, chest CT has become a tool for us in general physical examinations (13), and small-sized tumors in the lung field have been detected more frequently than before in recent years. In addition to small pulmonary nodules, small-sized anterior mediastinal tumors have also been detected and treated in the early stage. In addition, the application of minimally invasive surgery (MIS) for general thoracic surgery, including that for TET, has spread recently (11,14,15). Several studies have demonstrated that MIS for TET was equal in survival outcomes and reduced perioperative complications, compared to open surgery (16,17). In our institution, MIS for TETs, which includes video-assisted thoracoscopic surgery (VATS) and robot-assisted thoracoscopic surgery (RATS), has been available since January 2009, with the frequency of performance increasing in association with the increase in small-sized anterior mediastinal tumors.

While there are few large-scale reports of TC, some have indicated an improved prognosis due to the development of medical care over time. In the present study, we examined the results of continuous treatment of 71 TC cases, which is considered to be a relatively large number of cases reported by a single institution, and clarified the changes in the clinical characteristics, surgical procedures and prognosis of TC patients over time. We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-490/rc).

Methods

Study population

A total of 71 patients underwent treatment for TC from January 1983 to January 2020 at Nagoya City University Hospital. The clinical and pathological data of these patients were retrospectively reviewed. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board of Nagoya City University Graduate School of Medical Sciences (IRB No. 60-20-0136). Because of the retrospective nature of the study, patient informed consent was not required. Regarding the diagnosis of TC, imaging diagnosis was performed by chest CT. The biopsy of TC for pathological diagnosis was performed when it was thought to be difficult to perform an initial surgery due to the tumor progression. To investigate the chronological changes in the clinical characteristics, surgical procedure and prognosis, the patients were divided into two groups at January 2009, when MIS for TET was started at our institution. Regarding the treatment strategy for TC at our institution, the patients were considered inoperable as initial surgery if the following findings were noted on preoperative diagnostic images: (I) massive invasion of two or more great vessels, (II) cervical lymphogenous metastasis, (III) distant metastasis, or (IV) pleural or pericardial dissemination. Regarding the treatment of inoperable patients, chemotherapy was selected in the patients with distant metastasis, while chemo-radiotherapy was selected in the inoperable patients with locally advanced TC. When chemoradiotherapy was considered to be intolerable, radiotherapy was selected. Postoperative additional treatments including chemotherapy, radiotherapy, and chemo-radiotherapy, were considered for incomplete resection cases. As chemotherapy, ADOC regimen (50 mg/m^2 of cisplatin and 40 mg/m^2 of doxorubicin on day 1, 0.6 mg/m^2 of vincristine on day 3, and 700 mg/m^2 of cyclophosphamide on day 4, at 3 weeks interval) or CP regimen (AUC6 of carboplatin and 200 mg/m^2 of paclitaxel on day 1 at 3 weeks interval) was selected if tolerable (18,19). Adjuvant therapy was considered an option after complete resection, but the criteria for adjuvant therapy have not been stablished. Preoperative treatment was performed in some patients, whose radiotherapy was limited to 40 Gy, whereas radical radiation was fully performed at a dose of 60 Gy. Salvage surgery underwent for patients with good response to chemoradiotherapy and expected complete resection. Regarding the indication of MIS for TET, only small-sized TETs which were 3 cm or less were selected at first, however, MIS has been performed in the cases with the clinical Masaoka stage I–III tumors except for those needed great vessels resection followed by reconstruction nowadays. In the cases with invasion of the left brachiocephalic vein, MIS has been selected. Regarding the lymph node dissection for TET in MIS, lymphadenectomy for N1 lymph nodes were performed in the cases with total thymectomy. For small-sized anterior mediastinal tumors, limited thymectomy is selected in some cases at our institution. There is no clear indication of limited thymectomy, however, patients whose tumor is located in the relatively caudal part of the thymus and with a certain distance from left brachiocephalic vein are tend to be selected. In the present study, TC was diagnosed by the pathologist of the Department of Pathology at Nagoya City University. Clinical and pathological staging was performed in accordance with the Masaoka classification and the Masaoka-Koga classification respectively (20). OS

Table 1 The clinical characteristics of the 71 patients with TC

Factors	Value
Gender	
Male	44
Female	27
Mean age (years)	60.7 (range, 27–86)
Subjective symptom	
Yes	34
No	37
Modality of identification	
X-ray	22
CT	15
Clinical Masaoka stage	
I	4
II	8
III	13
IVa	6
IVb	20
Unknown	20
Treatment	
Surgery	45
In-operation	26
Resection	
R0	31
R1–2	14
Non-surgical treatment	
Chemotherapy	14
Radiotherapy	2
Chemo-radiotherapy	7
Best supportive care	1
Unknown	2
Histology	
Squamous cell carcinoma	48
Adenocarcinoma	4
Lymphoepithelioma-like carcinoma	3
Others	12
Unclassifiable	4

TC, thymic carcinoma; CT, computed tomography.

was calculated from the date of having a surgery to that announcing a death or the December 31, 2021.

Statistical analysis

Statistical analyses of the survival were performed using the Kaplan-Meier and univariable log-rank tests. Statistical significance was defined as $P<0.05$. All statistical analyses were performed with the JMP® 14 software program (SAS Institute Inc., Cary, NC, USA).

Results

The clinical characteristics of the 71 patients are shown in *Table 1*. There were 44 men and 27 women, with a mean age of 60.7 (range, 27–86) years old. Thirty-four of the 71 patients visited a hospital with subjective symptom and underwent treatment. The remaining 37 patients were found to have an abnormal shadow without any symptoms. The clinical Masaoka stage of the 71 patients was as follows: stage I in 4, stage II in 8, stage III in 13, stage IVa in 6, stage IVb in 20, and the stages of the remaining 20 patients were unknown. Among the 45 patients who underwent surgery, R0 resection was performed in 31. Regarding non-surgical treatment, 14 patients received chemotherapy, 2 radiotherapy, 7 chemo-radiotherapy, and 1 only best supportive care. As a pathological diagnosis, 48 patients were diagnosed with squamous cell carcinoma, 4 with adenocarcinoma, 3 with lymphoepithelioma-like carcinoma, and 12 with other types of carcinoma; the subtypes of 4 patients were not identified. Regarding the prognosis, the 5-year OS of the 71 patients was 65.1% (*Figure 1*).

To investigate the chronological changes in the surgical procedure and prognosis, the 45 patients who underwent surgical resection were divided into 2 groups based on the surgical timing: before or after January 2009, when MIS for TC was started at our institution. The clinical characteristics of the two groups are compared in *Table 2*. There were 24 patients who underwent surgery for TC through December 2008 (earlier group), and 21 patients underwent surgery from January 2009 (later group). The earlier group was more likely to have subjective symptoms than the later group. Regarding the 27 patients without subjective symptoms, those in the later group were more likely to be diagnosed by chest CT, whereas those in the earlier group were more likely to be diagnosed by chest X-ray. The rate of complete resection was significantly higher in the later

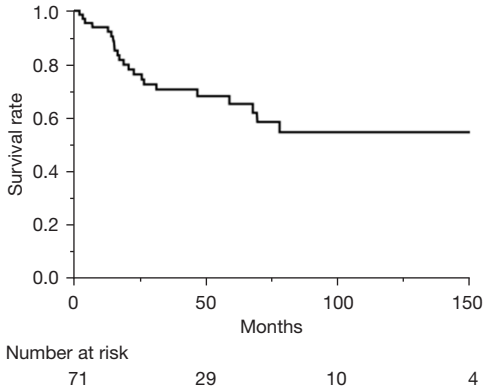

Figure 1 The OS of the 71 patients. The 5-year OS rate was 65.1%. OS, overall survival.

group (19/21, 90.5%) than in the earlier group (12/24, 50%), and the tumor size was larger in the earlier group rather than in the later group. To investigate the change in the screening modality, the total 71 patients were divided into the two groups and analyzed about the presence of symptom and the modality of identification. The breakdown of them is in *Table 3*. In summary, there was no significant difference but a tendency that the more patients who had no subjective symptom were diagnosed as TC by CT scan in the later group. There are 37 patients who had no subjective symptom and imaging diagnosis. The 5-year OS rate of these 45 patients who underwent surgical resection was 71.8% (*Figure 2A*), and the rates in the earlier and later groups were 58.7% and 92.8% respectively (*Figure 2B*) (P<0.01). Regarding the comparison of postoperative prognosis between the complete resection group and the incomplete resection group, the 5-year OS rate of the patients who underwent complete resection and incomplete resection were 81.3% and 53.6% respectively (P=0.02).

The surgical indication for TC at our institution showed no marked changes throughout the present study. The patients who underwent non-surgical treatment for TC were divided into two groups, similar to the patients who underwent surgical treatment. The data of the two non-surgical groups are compared in *Table 4*. The clinical Masaoka stage was more likely to be higher in the later group than in the earlier group (P=0.01). The 5-year OS rates of the groups were 66.3% in the later period and 38.9% in the earlier period, respectively, showing no significant difference (*Figure 3*) (P=0.89).

Among the 31 patients who underwent complete resection, 9 underwent sub-total thymectomy without lymph node dissection. The details of these nine patients are summarized in *Table 5*. All nine patients were in the later group and lacked subjective symptoms. The mean tumor size on CT was 2.1 (range, 1.3–3.2) cm. None of them had been diagnosed with TC preoperatively and all underwent MIS. Regarding the pathological Masaoka stage, 2 patients had stage I disease, 6 stage II, and 1 stage III. Although additional resection was considered and proposed in all cases, only 1 patient underwent a second operation, followed by radiation therapy. The remaining 8 cases received follow-up due to be performed R0 operation and patients' desire. The mean observation period of these 9 patients was 859 days, and all 9 were alive at the latest observation. Postoperative recurrence was seen in one patient with distant metastasis.

Discussion

The present study was a retrospective analysis of TC in 71 patients, which was a relatively large number for a single-center analysis. To investigate the chronological changes in the surgical procedure and prognosis for TC, two groups divided based on whether or not surgery was performed before January 2009, when MIS for TETs was started at our institution, were established in the present study. The results of a comparison between the two groups suggest that the ease of conducting a survey using CT, which has spread widely over the past few decades, leads to the early detection of TC before patients complain of subjective symptoms. Regarding surgical treatment, complete resection was reportedly associated with a better prognosis (4,21). In the present study, R0 resection surgery was performed in 31 patients (68.9%) among the 45 who underwent surgical treatment, which was almost the same as in a previous report (1). In the comparison analysis of the present study, R0 resection surgery was performed significantly more frequently in the later group than in the earlier group, with the later group also showing a better 5-year OS (92.8% *vs.* 58.7%, P<0.01). Detection of TCs at the earlier stage was thought to lead to the greater number of R0 resection in the later group compared to the earlier group. In summary, the prognosis of TC has improved over time thanks to early detection by CT screening and complete surgical resection.

In the present study, the chronological changes in the patients who underwent non-surgical treatment for TC were also investigated. The prognosis of these patients was found to not have improved significantly. One reason for this result is that effective systemic therapy, such as

Table 2 Comparison of the 45 patients who underwent surgical treatment

Factors	Early period (n=24)	Later period (n=21)	P value
Mean age (years)	57.3	61.2	0.27
Gender			0.23
Male	13	15	
Female	11	6	
Subjective symptom			0.03
Yes	13	5	
No	11	16	
Modality of identification			0.02
X-ray	9	6	
CT	2	10	
Tumor size (cm)			
Mean	6.8	4.4	<0.01
Median	6.2	4.1	<0.01
Surgical procedure			<0.01
Median sternotomy	24	11	
MIS	0	10	
Complete resection			<0.01
Yes	12	19	
No	12	2	
Pathological Masaoka stage			<0.01
0	0	1	
I	0	3	
II	5	11	
III	7	2	
IVa	6	0	
IVb	6	4	

CT, computed tomography; MIS, minimally invasive surgery.

Table 3 Comparison of the 71 patients with TC

Factors	Early period	Later period	P value
Subjective symptom (n=71)			0.05
Yes (n=34)	22	12	
No (n=37)	14	23	
Modality of identification (n=37)			0.06
X-ray (n=22)	11	11	
CT (n=15)	3	12	

TC, thymic carcinoma; CT, computed tomography.

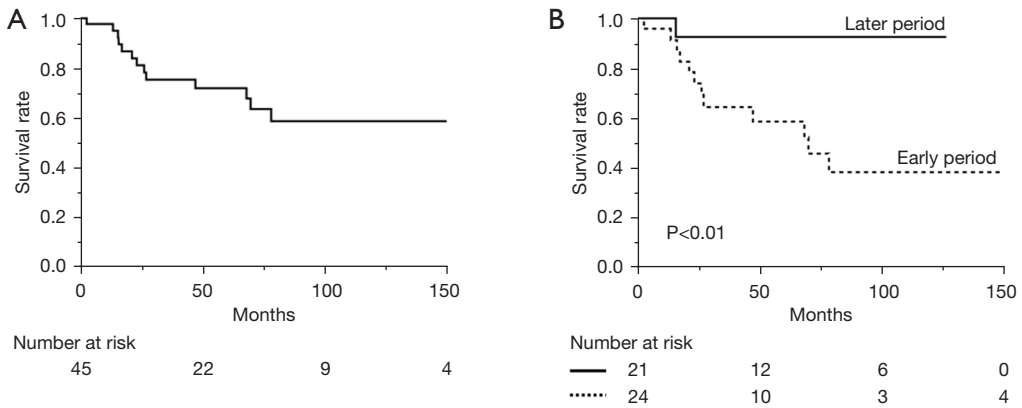

Figure 2 The OS of the 45 patients who underwent surgical treatment for TC. (A) The 5-year OS rate of the 45 patients was 71.8% and (B) the values in the earlier and later groups were 58.7% and 92.8% respectively (P<0.01). OS, overall survival; TC, thymic carcinoma.

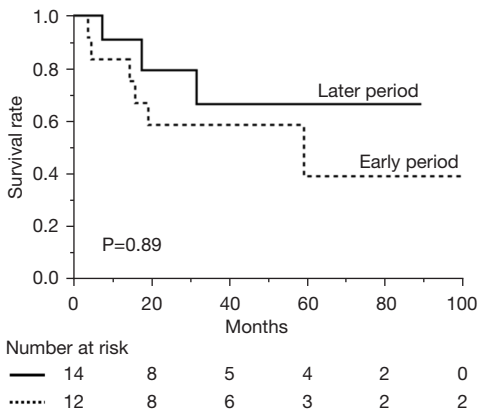

Figure 3 The OS of the 26 patients who underwent non-surgical treatment for TC. The 5-year OS rates in the earlier and later groups were 38.9% and 66.3%, respectively, showing no significant difference (P=0.89). OS, overall survival; TC, thymic carcinoma.

chemotherapy or immunotherapy for TC, has not yet been established. The efficacy of immune checkpoint inhibitors in various carcinomas has been demonstrated (22-30). In recent years, there have been several reports on immune checkpoint inhibitors that have been administered to treat TC (31-33), but no promising data on the efficacy or safety of immunotherapy in TC have yet been obtained. Regarding tyrosine kinase inhibitors (TKIs), lenvatinib which is a novel orally administered multi-targeted kinase inhibitor for VEGFR, FGFR, c-Kit, and other kinases, was recently approved for the treatment of advanced TC. In the single-arm phase 2 trial, the objective response rate of the patients with pathologically confirmed unresectable advanced or metastatic TC that progressed following at least 1 session of platinum-based chemotherapy was 38% (16 of 42 patients). This TKI may become a standard option for patients with advanced or metastatic TC (34).

In our institution, indication of MIS for TET had been 3 centimeters or less in maximum tumor diameter at first, which has been extended to clinical Masaoka stage III except for the invasion of great vessels needed reconstruction. To judge whether our indication of MIS for TC is feasible, further studies is needed (35). Regarding the lesion resected in thymectomy for TC in the present study, sub-total thymectomy without lymph node dissection was performed in nine patients. All 9 of these patients were in the later group, and none had a preoperative diagnosis. Regarding the surgical approach, all 9 patients underwent MIS, and 4 of them underwent robotic surgery. The mean observation period of the 9 patients was 859 (81–2,227) days, which was not enough to analyze the long-term prognosis. However, they were all alive at the latest observation and postoperative recurrence was seen in only one patient who was confirmed distant metastasis. Regarding small-sized anterior mediastinal tumors, surgical treatment, including limited thymectomy, is selected without a preoperative diagnosis in most cases (21,36,37). Regarding lymph node dissection for TC, the 8th edition of the TNM classification for TETs defines N1 as the anterior (perithymic) nodes and N2 as the deep intrathoracic or cervical nodes (38,39). However, the optimal extent of lymph node dissection for TC has not been defined. Based on our study, even sub-total thymectomy without lymph node dissection may be acceptable for patients with small-sized TC if it is completely resected with no lymphadenopathy on the

Table 4 Comparison of the 26 patients who underwent non-surgical treatment

Factors	Early period (n=12)	Later period (n=14)	P value
Gender			0.26
Male	6	10	
Female	6	4	
Mean age (years)	65.7	61.5	0.47
Subjective symptom			0.25
Yes	9	7	
No	3	7	
Clinical Masaoka stage			0.01
III	4	0	
IVa	4	2	
IVb	4	12	
Treatment			0.57
Chemo-radiotherapy	4	3	
Chemotherapy	5	9	
Radiotherapy	1	1	
Best supportive care	2	1	

Table 5 The clinical characteristics of the 9 patients who underwent sub-total thymectomy without lymph node dissection by video-assisted thoracic surgery

Factors	Value
Gender	
Male	8
Female	1
Mean age (years)	67.3
Subjective symptom	
No	9
Mean CT size (cm)	2.1 (range, 1.3–3.2)
Preoperative pathological diagnosis	
No	9
Surgical procedure	
MIS	9
Adjuvant therapy	
Radiation	1
Surgery + radiation	1
Pathological Masaoka stage	
I	2
II	6
III	1

CT, computed tomography; MIS, minimally invasive surgery.

preoperative diagnostic images or intraoperative findings. Further large-scale investigations are warranted.

Several limitations associated with the present study warrant mention. First, this was a retrospective study conducted over a long period. Therefore, the clinicopathological data were imperfect in some patients, especially in the early period. Second, length time bias should be taken into consideration in the present study, which may cause an overestimation of the survival outcome in the patients who were diagnosed by imaging modality without subjective symptom. Third, the present study included the 71 patients who underwent treatment for TC

from 1983 to 2020 at our institution, which is a relatively long duration. Therefore, the long time period may induce potential bias. Despite these drawbacks, the present study of 71 cases is considered a relatively large-scale study for a single center and may also be quite meaningful as well.

In conclusion, the prognosis of TCs has been improved over time by early detection used CT screening and complete surgical resection. However, the prognosis of advanced patients who cannot undergo surgical treatment has not changed, and the further improvement of systemic therapy is desired. Regarding the extent of resection in thymectomy for TC, even sub-total thymectomy without lymph node dissection may be acceptable for patients with small-sized TC. Further large-scale investigations concerning TC treatment are warranted.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-490/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-490/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-490/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-490/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board of Nagoya City University Graduate School of Medical Sciences (IRB No. 60-20-0136). Because of the retrospective nature of the study, patient informed consent was not required.

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