Survival and Factors Predictive of Survival in Patients with Thymic Carcinoma

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ABSTRACT

Objective: Thymic carcinoma is a rare malignancy that has a poor prognosis and low 5-year survival. The rarity of this disease and the variety of histologic subtypes has limited the evidence needed to establish disease-specific staging and treatment guidelines. The aim of this study was to investigate overall survival, the factors that predict survival, and the treatment modalities that influence survival in patients with thymic carcinoma.

Methods: All thymic carcinoma cases diagnosed and treated at Siriraj Hospital (Bangkok, Thailand) during 1997-2013 were retrospectively reviewed. Univariate and multivariate analyses were performed to identify factors that predict survival, and overall survival was estimated by Kaplan-Meier method.

Results: Of the 45 patients diagnosed during the study period, 8 were lost to follow-up. The remaining 37 patients were included in our analysis. The median survival time was 2.5 years, with 5-year and 10-year survival of 40% and 16%, respectively. In univariate analysis, tumors >10 cm (p=0.017), high-grade histologic subtypes (p=0.014), and high Masaoka stage (p=0.011) were significant determinants of survival. Multivariate analysis revealed tumor size (HR: 3.594, 95% CI: 1.103-11.714; p=0.034) and high-grade histologic subtypes (HR: 8.175, 95% CI: 1.689-39.566; p=0.009) to be independent predictors of survival. Patients who underwent tumor removal had significantly longer median survival time than those who didn't (3.85 vs. 0.63 years; p=0.005).

Conclusion: Thymic carcinoma patients have low 5-year and 10-year survival. Tumor size and high-grade histologic subtype were identified as independent predictors of survival, and surgical therapy was found to be significantly associated with longer median survival time.

Keywords: Thymic carcinoma; malignant thymoma; invasive mediastinal tumor (Siriraj Med J 2019; 71: 472-479)

INTRODUCTION

Thymic tumors are the most common primary neoplasms located at the anterior mediastinum, with an incidence of less than 0.13 per 100,000 person-years in the USA. However, thymic carcinoma is a very rare malignancy that accounts for only 0.06% of all thymic neoplasms.[1-5] Thymic carcinoma is an invasive, aggressive, metastasis-prone malignancy that has a poor prognosis with an estimated 5-year survival of 30%.[7] The classification and clinical staging of thymic carcinomas has not been conclusively established due to the rarity of this condition and the variety of histologic subtypes and their dissimilar characteristics.[8,9,10] The clinical staging system that is currently most appropriate for the evaluation of thymic carcinomas is Masaoka staging due to its prognostic value.[3] The aim of this study was to investigate overall survival, the factors that predict survival, and the treatment modalities that influence survival in patients with thymic carcinoma.

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MATERIALS AND METHODS

This retrospective chart review included patients diagnosed with and treated for thymic carcinoma at the Division of Cardiothoracic Surgery, Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand during the January 1997 to December 2013 study period. The following patient data were collected and analyzed: patient demographics; clinical presentations; preoperative diagnosis; Masaoka stage; tumor size; surgical procedure, including no surgery, local therapy only, (including excisional biopsy), thymic excision (including debulking and/or simple, total, and radical excision); radiation therapy; histologic subtype; recurrence; and, survival data. Patients with missing treatment and/or follow-up data were excluded. In case of the patients were deceased, they or their families would be contacted by telephone to determine whether they were alive or not.

The protocol for this study was approved by the Siriraj Institutional Review Board (Si 609/2014(EC2)]. The customary requirement to obtain patient written informed consent was waived due to the retrospective nature of this study.

Statistical analysis

Continuous data variables were analyzed using Student's *t*-test. Nominal data were analyzed using crosstabs and Pearson's chi-square test. Data are reported as mean and range or frequency and percentage. Kaplan-Meier survival curves were generated, and they were compared using log-rank test. A Cox proportional hazard model was used to identify the variables that significantly impact overall survival. The proportionality of hazards was evaluated using Cox regression analysis with time-dependent covariates. The assumption of proportionality of hazards was tested, and was not to be broken in any of the Cox regression models. Statistical analysis was performed with SPSS statistical software package version 18.0 (SPSS, Inc., Chicago, IL, USA). Statistical significance was set at a probability value less than 0.05.

RESULTS

Of the 45 cases diagnosed with thymic carcinoma during the study period, 8 patients were excluded due to loss to follow-up after the first hospital visit (Fig 1). The remaining 37 patients were included. The gender proportion breakdown was 24 males and 13 females, with a mean age of onset of 47.59 years (range: 20-71). The mean tumor size was 8.41 cm, and 25 patients (67.57%) had tumor size less than 10 cm. The majority of patients were in Masaoka Stage III and had high-grade histologic subtypes. Half of all the patients (51.35%) had great vessel tumor invasion, and 7 patients (18.92%) had metastasis, which involved liver and/or bone in most cases (Table 1). The number of patients that underwent radiation therapy (RT) and chemotherapy (CMT) was 16 (43.24%) and 22 (59.46%), respectively. Eight patients (21.62%) had recurrent tumor. The major histologic subtypes were well-differentiated squamous cell carcinoma (32.43%) and undifferentiated carcinoma (16.21%) (Fig 2).

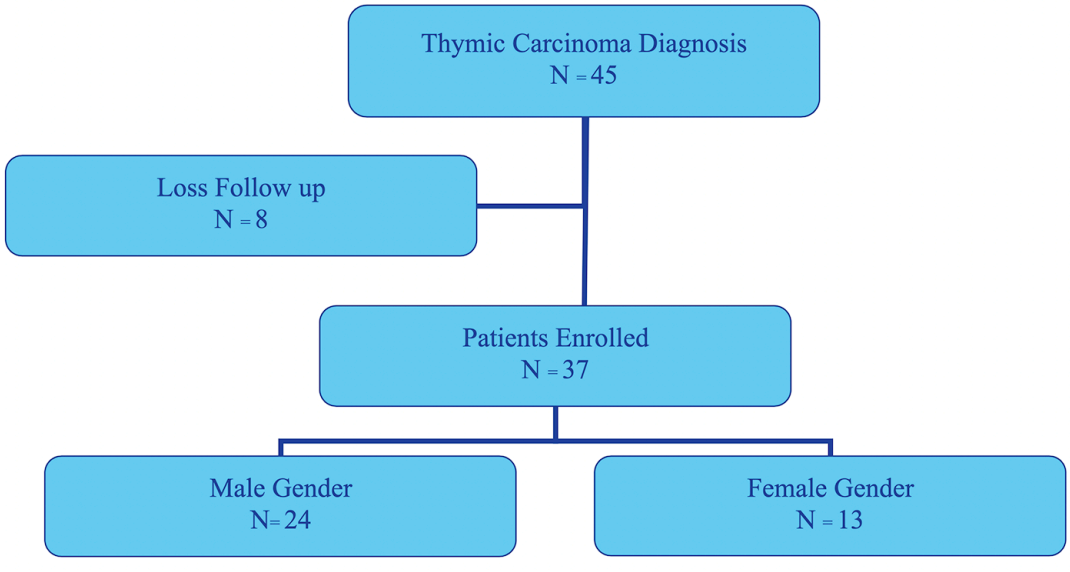


Fig 1. Flow diagram describing enrollment of thymic carcinoma patients and the gender proportions of the 37 enrolled patients.

TABLE 1. Demographic and clinical characteristics of 37 thymic carcinoma patients.

Characteristics	n (%)
Age of onset (years), mean (range)	47.59 (20-71)
Gender	
Male	24 (64.86%)
Female	13 (35.14%)
Tumor size (mean: 8.41 cm)	
≤10 cm	25 (67.57%)
>10 cm	12 (32.43%)
Masaoka Staging	
I and II	7 (8.10%)
III	15 (40.54%)
IV	12 (32.43%)
Tumor removal surgery performed	28 (75.68%)
Resection	
R0	8 (21.62%)
R1	10 (20.02%)
R2	10 (20.02%)
SVC invasion	19 (51.35%)
Histologic subtypes	
Low-grade	15 (40.54%)
High-grade	22 (59.46%)
Metastasis (liver and/or bone)	7 (18.92%)
CMT	22 (59.46%)
RT	16 (43.24%)
Recurrence	8 (21.62%)

Abbreviations: SVC = superior vena cava; CMT = chemotherapy; RT = radiation therapy

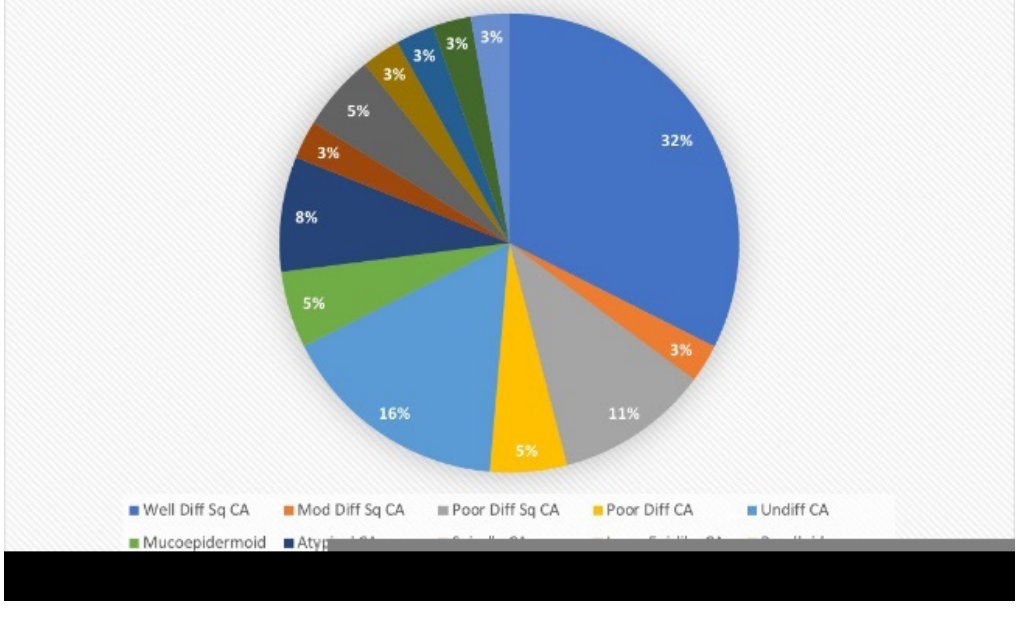
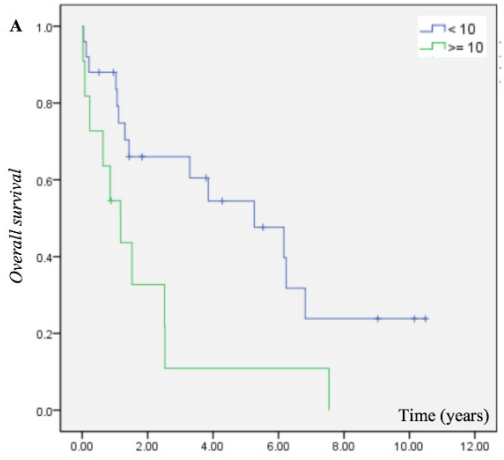
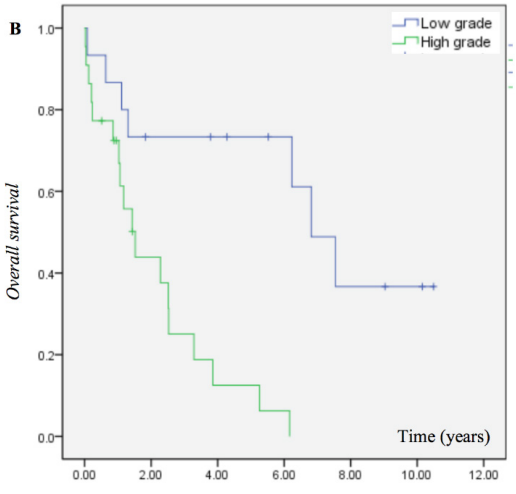


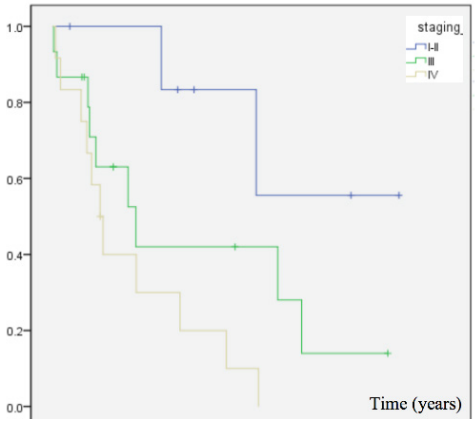
Fig 2. Histologic subtypes among thymic carcinoma patients.



Size of tumors	0 year	2 years	5 years	10 years
< 10 cm	25	17	15	11
≥ 10 cm	11	4	1	1



	0 year	2 years	5 years	10 years
Low-grade	15	11	11	8
High-grade	22	11	6	4



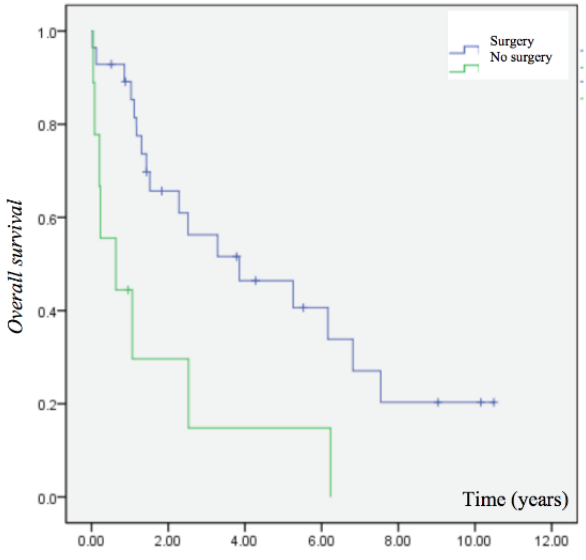
	0 year	2 years	5 years	10 years
Stage I-II	7	7	6	5
Stage III	15	10	8	6
Stage IV	12	5	2	1

Fig 4. Overall survival curve according to (A) size of tumor >10 cm [p=0.013], (B) high-grade histologic subtype [p<0.001], and (C) Masaoka Stage IV [p=0.014].

TABLE 3. Multivariate analysis for factors that significantly influence survival of patients with thymic carcinoma.

Factors	*P*-value	HR	95% CI
Size >10 cm	***0.034***	3.594	1.103-11.714
High-grade histology	***0.009***	8.175	1.689-39.566
Surgery	0.957	1.033	0.319-3.344
Recurrence	0.963	0.974	0.329-2.887

A *p*-value<0.05 indicates statistical significance
Abbreviations: HR= hazard ratio; CI= confidence interval



	0 year	2 years	5 years	10 years
Surgery	28	19	15	11
No surgery	9	3	2	1

Fig 5. Overall survival compared between patients who were and were not treated with surgical tumor removal (p=0.005).

DISCUSSION

Thymic carcinoma is a rare disease with variety in classification and treatment modality. We analyzed data to identify factors that impact prognosis and to determine the treatment modality that confers the most survival benefit. The main findings of our study were, as follows: (1) tumor size, high-grade histologic subtype, and Masaoka Stage IV were found to be significant predictors of survival in univariate analysis; (2) tumor size and high-grade histologic subtype were identified as independent predictors of survival in multivariate analysis; and, (3) patients who underwent surgical intervention for tumor removal had a median survival time significantly greater than that of patients who did not receive surgery for tumor removal. The largest cohort study in thymic carcinoma that included 290 patients also found surgical tumor removal to be significantly associated with longer median survival time.[7]

From previous studies – resectability, histology, tumor stage, and tumor size were identified as prognostic factors for survival in patients with thymic carcinoma.[7] In this study, size of the tumor, Masaoka staging, histologic subtype, SVC invasion, metastatic behavior, surgical intervention, and other modalities, such as CMT and RT, were investigated.

The 5-year cumulative survival rates reported in the literature vary widely (14.5%[21], 27.5%[7], 30.0%[22], 38.8%[23], and 61.1%[19]). In our study, the 5-year survival rate was 40%, and the 10-year survival rate was 16%, which is higher than the previously reported rate of 12.1%.[24]

The median survival times reported in the literature also vary widely (15.6 months[21], 35.6 months[23], 48.0 months[22], 53.0 months[7], and 66.7 months.[19] The median survival time in our study was 30 months. The observed differences among studies may be due to differences in patient selection, treatment modalities, and the number of cases that were included in the study (some studies had a very small study population).[24]

Previous studies found Masaoka stage to be a factor that significantly predicts survival thymic carcinoma.[7,23,19] In the present study, Masaoka stage was not only a prognostic factor, but it was also the strongest independent predictor of survival in multivariate analysis.[18] The Tumor-Nodes-Metastasis (TNM) staging system[25] was recently proposed; however, that system has not yet been widely accepted for general use in routine clinical practice. To date, Masaoka staging is the system that is most commonly used to stage patients with thymic carcinoma.

Regarding histologic subtypes, we found 12 different subtypes in our study, all of which were previously defined as being part of a subgroup of thymic carcinoma according to a previous literature review6 and previous clinico-pathological studies.[10-14] Hosaka, *et al.*[19] reported that the prognostic values of histologic subtypes were different for different combinations of histologic subtypes. Due to the limited number of cases included in our study, we divided the histology into low-grade and high-grade histologic subtype as a definition of classification.[3,6,9-14] Levine and Rosai[26] defined the histologic features of thymic tumors, and the subsequent revisions culminated in the widely accepted classification system that was proposed by the World Health Organization (WHO) in 1999.[15] In our study, univariate analysis showed histologic subtype to be a prognostic factor for survival (p<0.001, Fig 4b). Subsequent multivariate analysis revealed histologic subtype to be an independent significant prognostic factor for overall survival (p=0.009, HR: 8.175, 95% CI: 1.689-39.566), which is consistent with previous reports.[13,15,19,21,27]

Multivariate analysis also revealed tumor size to be an independent predictor of survival (p=0.034, HR: 3.594, 95% CI: 1.103-11.714), which is consistent with the findings of two previous studies.[7,27] Specifically, tumor size less than or equal to 10 cm was associated with significantly longer overall survival when compared to tumor size greater than 10 cm (Fig 4a). A previously published review of the literature[6] suggested a cut point of 8 cm for determining patient prognosis, but that value applied to thymomas. Since not cut point currently exists for thymic carcinoma, we included 8 cm, 9 cm, and 10 cm tumor size values in our statistical analysis, and we found 10 cm to be the cut point that was associated with a significant difference in survival. However and given our small study population, additional study is needed to confirm the tumor size cut point threshold for determining patient prognosis.

All of the studies in thymic carcinoma that have been reported to date found surgical treatment to be significantly associated with improved survival, which explains why surgical therapy is the preferred treatment in thymic carcinoma.[2,28] Consistent with previous studies, we found the same survival benefit of surgical intervention. Patients who underwent tumor removal had a significantly longer median survival time than those who did not receive surgical therapy (3.85 *vs.* 0.63 years; p=0.005) (Fig 5). In comparison, an analysis of survival in 154 patients with thymic carcinoma by Kondo and Monden[16] revealed 5-year survival rates of 67% after total resection, 30% after subtotal resection, and 24% with no operation. Complete resection was analyzed in our study; however, no significant differences were observed among the in the R0, R1, and R2 subgroups. This may be explained by the small number of cases enrolled in our study. However, our data support the widely adopted opinion that surgery is the preferred modality of treatment for patients with thymic carcinoma.

Limitations

This study has some mentionable limitations. First, the retrospective nature of this study makes it vulnerable to missing or incomplete data. Second, all of the data included in this study was collected from a single center. Third, we included a small number of patients due to the relative rarity of thymic carcinoma. This small sample size may have limited the strength of our study to identify all significant differences and associations. Fourth, our center is a national tertiary referral center, which means that we are often referred cases that are too complicated to be treated in other care settings. This suggests that our findings may not be immediately generalizable to thymic cancer cases in other care settings. The strength of this study is that we included patients that were diagnosed, treated, and followed at our center during a 17-year study period. Moreover, the data from our study broaden our understanding of this rare disorder, and will contribute to the development of thymic carcinoma-specific staging and treatment guidelines in the future.

CONCLUSION

Thymic carcinoma is a rare and invasive mediastinal tumor with low 5-year and 10-year survival. Univariate analysis revealed size of tumor, high-grade histologic

subtype, and Masoaka Stage IV as factors that significantly influence survival. Of those, tumor size and high-grade histologic subtype were identified as independent predictors of survival in multivariate analysis. Patients who underwent surgical therapy had a significantly longer median survival time.

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Conflict of interest declaration: Both authors declare no personal or professional conflicts of interest relating to any aspect of this study.

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