A Recurrence Predictive Model for Thymic Tumors and Its Implication for Postoperative Management: a Chinese Alliance for Research in Thymomas Database Study

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ABSTRACT

Objective: Our aim was to investigate appropriate postoperative management based on the risk of disease recurrence in thymic epithelial tumors after complete resection.

Methods: The Chinese Alliance for Research in Thymomas retrospective database was reviewed. Patients having stage I to IIIa tumors without pretreatment and with complete resection were included. Clinicopathologic variables with statistical significance in the multivariate Cox regression were incorporated into a nomogram for building a recurrence predictive model.

Results: A total of 907 cases, including 802 thymomas, 88 thymic carcinomas, and 17 neuroendocrine tumors, were retrieved between 1994 and 2012. With a median follow-up of 52 months, the 10-year overall survival rate was 89.5%. Distant and/or locoregional recurrences were noted in 53 patients (5.8%). The nomogram model revealed histologic type and T stage as independent predictive factors for recurrence, with a bootstrap-corrected C-index of 0.86. On
the basis of this model, patients with T1 thymomas or T2 or T3 type A, AB, or B1 thymomas had a significantly lower incidence of recurrence (low-risk group) than those with T2 or T3 type B2 or B3 thymomas and all thymic carcinomas and neuroendocrine tumors (high-risk group) (2.7% versus 20.1% [p < 0.001]). In the high-risk group, more than half of the recurrences (55.2% [16 of 29]) were seen within the first 3 postoperative years, whereas all recurrences but one were recorded within 6 years after surgery. Recurrence occurred quite evenly over 10 postoperative years in the low-risk group.

Conclusions: A 6-year active surveillance should be considered in high-risk patients regardless of adjuvant therapy. For low-risk patients, annual follow-up may be sufficient. Studies examining postoperative adjuvant therapies would be plausible in high-risk patients.

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Keywords: Thymic epithelial tumors; Recurrence predictive model; Postoperative management; Postoperative surveillance

Introduction

Thymic epithelial tumors (TETs) are rare tumors that are mostly seen in the anterior mediastinum. Surgical resection remains the best chance of cure, and complete (R0) resection is one of the most important prognostic factors for disease-free survival and overall survival (OS). The Chinese Alliance for Research in Thymomas (ChART) retrospective database contains data on patients with TET treated at 18 tertiary referral centers in the People’s Republic of China from 1994 to 2012.

Despite a paucity of data regarding adjuvant chemotherapy for resected early-stage thymoma, recurrence may still occur even after R0 resection and have significant impact on patients’ survival and their quality of life. Although several organizations, including the National Comprehensive Cancer Network, issue guidelines for the surveillance of thymic malignancies survivors, the risk factors and patterns of recurrence remain unclear, mainly because of the rarity of the disease. Most surveillance recommendations are based on expert opinion instead of evidence from large cohort studies or clinical trials. Ultimately, the modalities and schedules for follow-up of patients with the aim of early detection of recurrence remain elusive.

For these reasons, we aimed to investigate the details of recurrent disease in TET after complete surgical resection so as to develop postoperative management strategies based on the risk of disease recurrence and predictive factors. Considering the low incidence of recurrence in the entire cohort, we hypothesized that it would be essential to identify the subgroup of patients with a higher risk of disease recurrence after R0 resection.

Acquisition of Clinical Data

The Chinese Alliance for Research in Thymomas (ChART) retrospective database contains data on patients with TET treated at 18 tertiary referral centers in the People’s Republic of China from 1994 to 2012. For the purpose of this study, patients were included if they had (1) histologically confirmed thymic tumors, including thymomas, thymic carcinomas, and neuroendocrine thymic tumors (NETTs); (2) complete surgical resection (R0, with no residual disease); (3) International Association for the Study of Lung Cancer/International Thymic Malignancy Interest Group (IASLC/ITMIG) stage I to IIIa disease; and (4) no pretreatment before surgery. Patients with previous malignancy were also excluded. All cases included in the study were restaged according to the IASLC/ITMIG stage classification. The recently published WHO criteria were used to classify histologic subtypes. Follow-up strategy was determined individually at each participating center, mostly involving chest computed tomography (CT) scan at 6- to 12-month intervals. Failure patterns were recorded as local relapse (disease appearing in the anterior mediastinum or locoregional lymph nodes), regional recurrence (pleural and/or pericardial dissemination), and distant failure (organ metastasis, including
both intrathoracic and extrathoracic). This was essentially what had been suggested by ITMIG, except that disease relapse in locoregional lymph nodes was included as local recurrence. 

**Ethics Statement**

This study was approved by ethics committee of Shanghai Chest Hospital. Because it was a retrospective study based on the ChART retrospective database, a waiver of informed consent was granted.

**Statistical Analysis**

Categorical variables were compared by using Fisher’s exact test for differences. Continuous data were compared by using Student’s t test. OS was plotted by the Kaplan-Meier method, and differences in survival were assessed by a log-rank analysis. Univariate analysis was first performed in Cox regression. All variables were entered into a multivariable Cox proportional hazards model according to Akaike information criterion minimization to estimate the hazard ratio and 95% confidence interval. All p values less than 0.05 were considered statistically significant. All statistical analyses were performed using R software (version 3.5.1, R Core Team, Vienna, Austria). We generated a predictive nomogram model to predict high risk of recurrence. On the basis of the results of the multivariable analysis, variables that achieved significance at p less than 0.05 were selected to formulate a nomogram by using R software (version 3.3.0, http://www.r-project.org) with the survival and root mean square (rms) package. Clinopathologic variables with statistical significance in the multivariable Cox regression were incorporated into the prediction models and the nomogram. Performance of the prediction models was assessed and compared by using the concordance index (C-index).15 The C-index estimates the probability of concordance between predicted and observed responses. A value of 1.0 indicates perfect separation of patients with different groups, and a value of 0.5 indicates no predictive discrimination. Internal validation was conducted by comparing the C-index of each model with the C-indexes of 1000 bootstrap replications that were averaged, and bootstrap-corrected performance was estimated.

**Results**

**Patient Characteristics**

A total of 907 patients with IASLC/ITMIG stage I to IIIa TET who underwent R0 resection between 1994 and 2012 were identified from the ChART database. There were 477 WHO type A, AB, and B1 thymomas (52.6%); 325 type B2 and B3 thymomas (35.8%); 88 thymic carcinomas (9.7%); and 17 NETTs (1.9%). Patients with T1 tumors accounted for 84.3% of the entire group (n = 765), followed by T3 lesions (n = 107 [11.8%]) and T2 lesions (n = 35 [3.9%]). In all, 373 patients (41.1%) were treated with adjuvant therapy after surgery (Table 1).

**Follow-up Results**

With a median follow-up time of 52 months (range 4–147 months), the 10-year OS rate for all patients was 89.5% and the median OS was not reached. Disease recurrence was noted in 53 patients (5.8%). Detailed data on first recurrence were available for 36 patients. The 10-year OS of patients without recurrence was significantly higher and the median OS significantly longer than those of patients with recurrent disease (95% versus 43.7% and 207 versus 100 months, respectively [p < 0.001]).

**Risk Factors and Predictive Nomogram For Recurrences**

Table 2 shows the results of univariate analysis for recurrence-free survival. Absence of myasthenia gravis (p = 0.015), higher-grade WHO histologic type (p < 0.001), higher IASLC/ITMIG T stage (p < 0.001), and adjuvant therapy (p < 0.001) were significantly associated with increased risk of recurrence. No significant correlation was found between recurrence status and age, sex, Eastern Cooperative Oncology Group (ECOG) score, tumor size, surgical approach, or extent of thymic resection.

Upon multivariate analysis, only increasing WHO histologic type (NETT versus thymic carcinoma versus type B2 and B3 thymoma versus type A, AB, and B1 thymoma [p < 0.001]) and higher IASLC/ITMIG T stage (T2 and T3 versus T1 [p = 0.016]) were independent indicators of recurrence (see Table 2). Consequently, a final model including WHO histologic type and IASLC/ITMIG T stage was built as a nomogram (Fig. 1A). The nomogram illustrated that WHO histologic type has a greater contribution to risk of recurrence than the IASLC/ITMIG T category does. Each category within these variables was assigned a score on a point scale. By adding up the total score and locating it on the total point scale, probability of recurrence could easily be estimated. The nomogram had a high predictive performance with a bootstrap-corrected C-index of 0.86 (95% confidence interval: 0.793–0.927, [Fig. 1B]). On the basis of this model, patients were divided into a low-risk group consisting of those with all T1 thymomas or T2 and T3 type A, AB, and B1 thymomas (total points <60 on the nomogram) and a high-risk group with T2 and T3
type B2 and B3 thymomas and all thymic carcinomas and NETTs (total points \( \leq 60 \) on the nomogram). The incidence of recurrence was 2.7% in the low-risk group (20 of 743) but was 20.1% in the high-risk group (33 of 164) \( (p < 0.001) \). The low-risk group had significantly higher 10-year recurrence-free survival when compared with the high-risk group (96.8% versus 61.1% \( [p < 0.001] \) [Fig. 2]).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate Analyses</th>
<th>Multivariate analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td>HR (95% CI)</td>
<td>p Value</td>
</tr>
<tr>
<td>Sex (male vs. female)</td>
<td>1.013 (0.986-1.040)</td>
<td>0.354</td>
</tr>
<tr>
<td>ECOG (0-1 vs. 2-3)</td>
<td>1.278 (0.662-2.466)</td>
<td>0.465</td>
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<tr>
<td>Tumor size</td>
<td>0.301 (0.07-1.293)</td>
<td>0.107</td>
</tr>
<tr>
<td>Preoperative MG (none vs. yes)</td>
<td>1.095 (0.971-1.235)</td>
<td>0.14</td>
</tr>
<tr>
<td>WHO histologic type (reference A + AB + B1)</td>
<td>11.661 (1.597-85.143)</td>
<td>0.015</td>
</tr>
<tr>
<td>B2 + B3</td>
<td>10.266 (2.286-45.743)</td>
<td>0.002</td>
</tr>
<tr>
<td>TC</td>
<td>45.013 (10.285-197.001)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NETT</td>
<td>163.685 (33.540-798.827)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IASLC/ITMIG T2 + T3 (reference T1)</td>
<td>7.338 (3.792-14.198)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Surgical approach (open vs. VATS)</td>
<td>2.957 (0.698-12.523)</td>
<td>0.141</td>
</tr>
<tr>
<td>The extent of thymic resection (total vs. partial)</td>
<td>1.094 (0.498-2.402)</td>
<td>0.823</td>
</tr>
<tr>
<td>Adjuvant therapy (none vs. yes)</td>
<td>0.195 (0.085-0.447)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; MG, myasthenia gravis; NETT, neuroendocrine thymic tumor; IASLC/ITMIG, International Association for the Study of Lung Cancer/International Thymic Malignancy Interest Group; TC, thymic carcinoma; VATS, video-assisted thoracic surgery.
Failure Patterns

For the 53 patients who had recurrence during follow-up, the median time to recurrence was 23 months (range 1–108 months). The median time to recurrence was 33 months in the low-risk group and 19 months in the high-risk group ($p = 0.38$).

Detailed data on first recurrence were available for 36 patients (nine of 743 [1.2%] in the low-risk group and 27 of 164 [16.5%] in the high-risk group). The most common failure pattern was local recurrence (15 of 36 [41.7%]), followed by distant metastasis (12 of 36 [33.3%]) and pleural and/or pericardial dissemination (nine of 36 [25%]). In the low-risk group, local recurrence, pleural and/or pericardial dissemination, and distant metastasis accounted for 66.7% (six of nine), 22.2% (two of nine), and 11.1% (one of nine) of cases of disease relapse, respectively. In contrast, in the high-risk group, distant metastasis was the most common type of recurrence (11 of 27 [40.7%]), followed by local recurrence (nine of 27 [33.3%]) and pleural and/or pericardial dissemination (seven of 27 [25.9%]) (see Fig. 2). Detailed data on time to recurrence were available for 36

![Graph showing recurrence patterns](image-url)
patients (seven in the low-risk group and 29 in the high-risk group). More than half of the recurrences (55.2% [16 of 29]) in the high-risk group were seen within the first 3 postoperative years, whereas all recurrences but one were recorded within 6 years after surgery. In contrast, in the low-risk group, recurrence occurred quite evenly during the 10 years after surgery (Fig. 3).

Discussion

We used a large cohort from the ChART multi-institutional retrospective database to study postoperative management strategy based on the risk of recurrence in patients with R0 resected TET. The 10-year OS of the entire group was 89.5%, which was consistent with previous reports.3,16 Only 5.8% of patients in the current study experienced recurrence. Patients with recurrent diseases had worse survival than did those without recurrence (median OS 100 versus 207 months [p < 0.001]). Upon multivariate analysis, higher-grade WHO histologic type and higher IASLC/ITMIG T stage were found to be independent risk factors of recurrence after complete resection. As TETs are generally indolent in nature, disease recurrence may be more appropriate for evaluating potential roles of postoperative management than OS is. The low incidence of recurrence in the current cohort implies that trial design for adjuvant therapies in patients with R0 TET resected and their follow-up strategies need to be assessed carefully and individually.

Several studies7-21 found that histologic type could be an indicator for recurrence in thymic malignancies. When the ChART database was used, WHO histologic type was again demonstrated as a strong independent predictor for recurrent diseases (p < 0.001). There was a great disparity in recurrence rates among different tumor histologic subtypes, being only 3.7% for thymoma but 18.2% for thymic carcinoma and 41.2% for NETT. This suggests that thymic carcinoma and NETT are more aggressive histologic subtypes that are associated with greater risk of recurrence, especially systemic metastasis. It has been suggested that patients with thymic carcinoma and NETT may need more intensive multimodality therapies so as to reduce the risk of treatment failure.5,6 Tumor histologic type should be carefully incorporated into postoperative management, including both adjuvant therapy trial design and definition of follow-up strategy.

IASLC/ITMIG T stage (p = 0.016) was another independent risk factor revealed in this study. Our results show that patients with invasive tumors (higher than IASLC/ITMIG T2 stage) were more likely to experience recurrence. Tseng et al.22 specifically analyzed patients with Masaoka stage III tumors by dividing them into six groups according to different sites of invasion. They claimed that innominate vein or superior vena cava invasion was associated with higher risk of recurrent disease compared with the lung, pericardium, or other structures. However, Masaoka stage III comprises a rather heterogeneous group of diseases, whereas in the IASLC/ITMIG staging system pericardial invasion is defined as T2, other readily resectable lesions are defined as T3, and those tumors that are unresectable are categorized as T4. In the IASLC/ITMIG analysis, no clear difference was found relative to the T3 structures invaded.23 In the current study, IASLC/ITMIG staging instead of Masaoka staging was used and only T1 to T3 tumors were included, as complete resection is usually hard to achieve in patients with T4 disease. Recurrence was found in 16.8% of patients with T3 disease and in 17.1% of patients with T2 disease. However, of the patients with T1 tumors not invading neighboring structures, only 3.8% experienced disease relapse. These results imply that patients with T2 or T3 tumors are more likely to benefit from adjuvant therapies. Future trials examining adjuvant therapies should be carried out only in this subgroup of patients.

The association of adjuvant chemotherapy or radiotherapy with increased recurrence might be related to confounding biases, as patients with thymic carcinomas and NETTs and those with tumors in higher T categories were more likely to be administered adjuvant treatment. As shown in the multivariate analysis, adjuvant therapy was not independently related to recurrence. In a

Figure 3. Failure pattern across time in patients with completely resected thymic tumor.
previous ChART retrospective study, adjuvant radiation after surgery was not found to be beneficial for completely resected Masaoka stage I to III TETs. A Japanese multicenter retrospective study also reported that the value of adjuvant radiation in Masaoka stage II to III completely resected tumors was unclear. However, a meta-analysis by Zhou et al. reached a contradictory conclusion, suggesting that patients with Masaoka stage II to III tumors after complete resection might benefit from adjuvant radiotherapy. The predictive model proposed by the current study may serve a useful tool for optimal design of future trials examining postoperative treatment to elucidate the issue. The low recurrence rate in the current study suggests that it is both unreasonable and inefficient to carry out clinical studies on adjuvant therapies in all patients with completely resected TETs. Specifically, the low-risk patients identified in this series were unlikely to benefit from adjuvant therapies, as their recurrence rate was merely 2.7%. Potential benefit from adjuvant therapies should be studied only in high-risk patients.

In addition, this predictive model may also be helpful in deciding surveillance strategies to detect tumor recurrence after surgery. ITMIG suggested a minimum of yearly CT scans of the thorax for 5 years after surgical resection and then alternating annually with a chest radiograph until year 11, followed by annual chest radiographs alone. Additional CT imaging every 6 months for 3 years was recommended for Masaoka-Koga stage III and IVa thymomas and thymic carcinomas. However, these were consensus-based proposals with little support from available evidence. Furthermore, a chest radiograph may not be an efficient tool to detect local recurrences in anterior mediastinum or pleural and/or pericardial dissemination, which were the most common types of disease relapse in the low-risk group in this study. For R0 resected thymic tumors, the current National Comprehensive Cancer Network guideline suggests surveillance for recurrences with chest CT scans every 6 to 12 months for 2 years, then annually for 5 years for thymic carcinoma and 10 years for thymoma. But this is merely expert opinion and there is no mention of systemic checkup for distant metastasis. In our study, we found that the low-risk group (patients with T1 thymomas or T2 or T3 type A, AB, and B1 thymomas) had a rather low incidence of recurrence (2.7%), whereas those with T2 or T3 type B2 and B3 thymomas had a significantly higher recurrence rate (16.9% [p < 0.001]) after surgery. Overall, the recurrence rate was much higher (20.1%) in the high-risk group identified with the nomogram, suggesting that a closer follow-up may be warranted in these patients.

We also analyzed the failure patterns across time in the current study. According to risk stratification by the nomogram, recurrence in the low-risk group was exclusively locoregional, and distant metastasis was seen only in the high-risk patients. In addition, almost half of the events in the high-risk group were seen within the first 3 postoperative years, whereas all recurrences but one were recorded within 6 years after surgery (see Fig. 3). Therefore, active surveillance should be considered for the high-risk group (patients with T2 or T3 type B2 and B3 and all thymic carcinomas/NETTs), as early detection of disease recurrence may allow timely intervention such as salvage surgery or radiotherapy. On the basis of the finding that recurrence was a low-probability event but scattered quite evenly throughout the 10 years after surgery in patients with completely resected low-risk tumors (see Fig. 3), surveillance for recurrence annually for 10 years may be sufficient. Furthermore, given that most recurrences in this low-risk group were locoregional, follow-up with chest CT scan only may be warranted. In contrast, recurrence was not uncommon in those high-risk patients. Closer follow-up every 6 months for 3 years and then annually for another 3 years seems warranted. Because distant metastasis was found to be the major failure pattern in this high-risk group, active surveillance with more thorough checkup methods such as imaging of the abdomen and pelvis in addition to chest CT may be necessary.

Although the ChART database provided us with an exceptionally large number of cases, limitations still existed in this study, especially those inherent to retrospective data collection. No standard follow-up policies were in place at these institutions, which would likely bias the results toward no difference. The ChART database also had a relatively high number of censored cases. The reasons could be (1) low incidence of disease recurrence and (2) long OS time even in the high-risk group of patients. These have made long-term follow-up after R0 resection rather difficult.

In conclusion, combining high-grade histologic types with advanced T stages helps identify risks of recurrence in patients with thymic tumors after complete resection. Potential benefit of adjuvant therapies may be expected only in those high-risk patients who should be considered as candidates in future studies of postoperative treatment. On the basis of the recurrence predictive nomogram model, a 6-year active surveillance with a thorough whole body checkup should be considered in patients with T2- or T3-staged type B2 and B3 thymoma and in all patients with thymic carcinoma or neuroendocrine tumor regardless of adjuvant therapy. For the low-risk group of patients with T1 thymomas or T2 or T3 type A, AB, and B1 thymomas, annual follow-up with chest CT alone may be sufficient.
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