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Research Paper

Tumor size combined with staging systems for thymoma recurrence prediction: A 28-year experience

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ABSTRACT

Background: We evaluated a new thymoma prognosis prediction model by combining current staging systems with tumor size.
Methods: The clinical records of thymoma patients in a single center between January 1993 and December 2021 were collected, and data on tumor size and stage and recurrence-free survival (RFS) was obtained. The prediction model was designed by combining staging with tumor size.
Results: During 28 years, 219 thymoma patients were enrolled. Twenty-seven patients had a median RFS of 8.2 years. Further, 153 patients were categorized into limited stage and 66 patients into advanced stage. The RFS was statistically different between these two groups ($P = 0.022$). The largest area under the curve (AUC) of receiver operating characteristic (ROC) was the dividing group as 5 cm (AUC: 0.804).
Conclusions: Combining tumor staging and size improves thymoma recurrence prediction. Patients with advanced stage and tumor size >5 cm may show a poor prognosis.

Introduction

Thymoma is a common epithelial tumor with malignant potential. It is rare with an annual incidence is 1.5 cases per million worldwide [1]. Thymoma is a slow-growing tumor that occurs in all age groups. Large databases are available for other solid tumors such as lung, breast, renal, and colorectal; however, it is difficult to analyze the outcome of thymoma patients with existing data due to the small sample size in most studies.

Autoimmune paraneoplastic diseases linked with thymomas are myasthenia gravis (MG), pure red cell aplasia, and hypogammaglobulinemia (Good syndrome). MG symptoms are seen in about one-third of thymoma cases, being the most frequently reported autoimmune disease associated with thymoma [2–4]. The World Health Organization (WHO) histological classification system, the Masaoka-Koga (M-K) staging system, and the tumor-lymph node-metastasis (TNM) staging system serves as reliable predictors of thymoma outcome [5–9]. These systems provided good prognosis predictions for overall and recurrence-free survival previously [5–9]. The prediction was based on the tumor invasion range or tumor pathological status. The modified M-K staging system is widely used for thymoma outcome prediction and further treatment after operation. In 2015, Roden et al. showed that stage and tumor size are independent prognostic factors for thymoma [10]. Although their findings focused on overall survival (OS), they also showed that tumor size is associated with disease-free survival (DFS), or rather recurrence-free survival (RFS). Thereafter, an increasing number of studies have focused on tumor size to predict outcomes in thymoma [11–13]. Thymoma tumor size is a potential independent prognostic factor in thymoma recurrence rate or overall survival rate. Although a strong association between tumor size and the present thymoma staging system was not established, a relationship between the tumor size and staging has been observed. Furthermore, earlier studies have used tumor size as a secondary prognostic factor [10,14,15].

There are few studies that focus on thymoma tumor size combined

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with staging for thymoma prognosis prediction. Consequently, the purpose of this retrospective study is to evaluate whether combination of staging and tumor size is a better predictor of prognosis for thymoma recurrence than the tumor size or stage alone.

Materials and methods

Patient and data collection

The clinical records of patients who underwent medical treatment for thymic tumors between January 1993 and December 2021, were collected from the medical center of Shin Kong Wu Ho Su Memorial Hospital (SKH). During a 28-year period, 317 patients were diagnosed with thymoma before treatment in SKH. The exclusion criteria were 1) having not undergone a surgical procedure. The operative patients received neoadjuvant or adjuvant treatment were also excluded, 2) the final diagnosis was not thymoma, such as benign, carcinoid, carcinoma, or neuroendocrine tumors, and 3) massive medical records lost or not obtained (supplementary fig. E1). Most patients visited the SKH outpatient department (OPD) for follow up, and their medical records could be viewed in the SKH database. Patients who did not stay in SKH after treatment were telephone interviewed to collect information for the study. The Institutional Review Board of the SKH approved the protocol and granted an exemption from the requirement for informed consent (20220311R).

Following

Most thymoma patients with myasthenia gravis regularly visit neurologists' outpatient departments (OPD). During the initial three years, these patients undergo an annual chest CT scan. After this period, neurologists shift their focus to monitoring myasthenia gravis symptoms. If no new MG symptoms appear, it can be assumed that there is no thymoma recurrence.

On the other hand, thymoma patients without myasthenia gravis are followed by thoracic surgeons in the outpatient department. In the thoracic surgeon's OPD, a similar protocol is followed. During the first three years, these patients also undergo an annual chest CT scan. If no signs of thymoma recurrence are detected, patients receive chest X-rays for an additional 3 to 5 years, depending on their preference. In this study, we referred to advanced stage patients without recurrence before December 31, 2021, to undergo an additional chest CT scan to assess their medical condition. This strategy was employed to minimize costs and address the higher risk of thymoma recurrence in advanced stage patients.

Definitions

The preoperative tumor size of most cases in this study was assessed using computed tomography (CT) scanning. Primary tumor size was measured in the maximum dimension. One team member measured CT tumor sizes in all the cases to reduce evaluator bias. The patients were grouped based on the M-K classification [16,17]. The details are listed in Supplementary Table E1. Tumors not invading the lymph nodes or adjacent organs were defined as limited-stage thymoma (M-K stage I to IIb). Other tumors were defined as advanced stage thymoma based on the Yun et al. study [13].

The primary endpoints were tumor recurrence, death, predictive value of tumor recurrence, and patient death by tumor size and limited/advanced staging. RFS was defined as the period between the date of operation of thymoma and the date of the last follow-up or diagnosis of recurrence.

Statistical analysis

The clinical data of the thymoma patients were retrieved from the medical records. Predictive Analytics SoftWare version 25.0 (PASW; International Business Machines Corporation, Chicago, IL, USA) was used for all of the statistical analyses.

The Shapiro–Wilk test was used for <50 samples and the Kolmogorov–Smirnov test was used for >50 samples to check the normal distribution of continuous data, such as operational age, median tumor size, recurrence-free and overall survival. Continuous data with normal distribution were presented as mean ± SD and performed with Student's t–test. Otherwise, continuous data without normal distribution were performed with the Mann–Whitney *U* test. Categorical variables were computed into frequency and percentage using the chi–squared test or Fisher's exact test for >20 % of the field <5 samples. The receiver operating characteristic (ROC) curve was used to find better prediction models. The area under the curve (AUC) was used to judge the discriminative power of the ROC curve. $0.7 \leqq AUC \leqq 0.8$ was defined as acceptable discrimination, and $0.8 \leqq AUC \leqq 0.9$ was defined as excellent discrimination. Two types of survival analyses were conducted: OS and RFS. Survival curves were estimated using the Kaplan–Meier method and were compared across categorical predictors using log-rank tests. The Kaplan–Meier curve were generated using R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria) using the KMggplot2 packages.

Results

Baseline patient characteristics

In total, 219 patients were diagnosed with thymoma as shown in

Table 1
Total patients' characteristics.

	Patients' s/p OP (N = 219)	Range or %
Gender, male (%)	109	49.8 %
OP age, year	49.4 ± 12.7	17.0–79.0
Pre-OP CT tumor size, cm (n = 212)	5.3 ± 2.3	1.0–12.0
Major comorbidity		
MG	175	79.9 %
CAD	6	2.7 %
Cancers other than thymoma	8	3.7 %
COPD	5	2.3 %
CKD	6	2.7 %
HBV/HCV	8	3.7 %
CVA	2	0.9 %
OP method		
Median sternotomy	123	56.2 %
Lateral thoracotomy	3	1.4 %
Transcervical	2	0.9 %
VATS	91	41.6 %
LN dissection numbers	32	14.6 %
M-K stage		
I	103	47.0 %
IIa	37	16.9 %
IIb	13	5.9 %
III	55	25.1 %
IVa	10	4.6 %
IVb	1	0.5 %
WHO histotype (n = 192)		
A	27	14.1 %
AB	44	22.9 %
B1	23	12.0 %
B2	70	36.5 %
B3	27	14.1 %
Metaplastic thymoma	1	0.5 %
Recurrence patient numbers	27	12.3 %
Recurrence-free period, year	8.2 ± 6.0	0.02–27.0
Survival period, year	8.9 ± 6.0	0.03–27.0

MG, myasthenia gravis; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; HBV, hepatitis B virus; HCV, hepatitis C virus, CVA, cerebrovascular accident; M-K, Masaoka-Koga; OP, operative; WHO, World Health Organization.

Table 1. The median age at the date of operation was 49.4 years, and the oldest age was 79 years. The median pre-operative CT tumor size was 5.3 cm. One hundred and seventy-five patients (79.9 %) had MG symptoms. Over half of the patients underwent a median sternotomy operation for thymoma resection. The other 41.6 % underwent video-assisted thoracoscopic surgery (VATS). One fifty-three patients were categorized into M-K limited stage, and 66 patients into advanced stage. Thymoma recurrence was observed in 27 patients (12.3 %). In the following 27 years, the median recurrence-free period was 8.2 years, and the survival period was 8.9 years.

Cutoff value for tumor size

The 219 thymoma patients were divided into different groups by 1 cm as 1 unit, ranging from 3 cm to 9 cm. Table 2 and Supplementary Fig. E2 show the RFS and OS rates of the different tumor size groups. For RFS, the 4 cm to 9 cm groups had statistical significance; however, the 3 cm group did not. For OS, although some groups had statistical significance, only 3 cases of death were directly associated with thymoma (Supplementary Table E2). The groups were divided by the boundary line of 5 cm as the sample is shown in Table 4. (See Table 3.)

Comparison between limited stage and advanced stage groups

Table 2 shows the comparison of characteristics between limited stage and advanced stage groups. The distribution in gender, pre-operative MG positive or negative, and operative age was similar. In the dividing group of 5 cm, in the limited stage group, about half of the patients had tumor size ≧5 cm. Contrarily, in the advanced stage group, about 70 % of the patients had size ≧5 cm. The rate of thymoma recurrence was 7 times higher in the advanced stage group than in limited stage. The median recurrence-free period in limited stage group was 8.8 years, and 6.9 years in the advanced stage group. There was a statistically significant difference in the RFS between these two groups (Supplementary fig. E3).

Assessment of staging plus tumor size as a prognostic factor

The ROC curve was used for evaluating prediction models for recurrence. The primary hypothesis was that the combination of limited/advanced stage plus tumor size will provide a better prediction model. We created a calculation formula of s x/10 * limited/advanced stage + (1-x)/10 * tumor size. A value of 0 was used for the limited stage, and a value of 1 for advanced stage. The algebra is a value we arbitrarily substitute, and its range is between 0 and 1. The value of 0 was used for tumor size below the dividing line, and 1 for tumor size above the dividing line. For example, one patient had a tumor size of 7 cm and was Masaoka Stage I. We randomly chose a value of x, such as 0.6, and then, we chose the divided group depending on tumor size (one group of tumor size ≧ 5 cm and another of tumor size <5 cm). For the tumor size of 7 cm, the value of tumor size in the formula was set as 1. The Masaoka Stage I in the value of limited/advanced stage was set as 0. These values were input into the formula as follows: 0.6 * 0 + (1–0.6) * 1 = 0.6 * 0 + 0.4 * 1 = 0.4. Different combinations were evaluated, and the result is shown in supplementary fig. E4. Fig. 1 shows that the best combination models (red line and green line), with limited/advanced stage and pre-operative CT tumor size as comparisons (blue line and orange line). Within these models, the best model was the combination of 0.6 * staging + 0.4 * tumor size (dividing group as 5 cm), and the AUC was 0.804. The second best was the combination of 0.6 * staging + 0.4 * tumor size (dividing group as 8 cm), and the AUC was 0.795. The AUC of limited/advanced stage was 0.771. Furthermore, all of the AUC of combinations depending on the formula were above the value of the AUC of limited/advanced stage.

Table 2
Cutoff value per 1 cm of tumor size.

Cutoff value	No. of patients	Recurrence-free survival P-value	Overall survival P-value
≧ 3.0 / < 3.0 cm	188 / 24	0.254	0.492
≧ 4.0 / < 4.0 cm	151 / 61	0.030	0.095
≧ 5.0 / < 5.0 cm	110 / 102	0.005	0.0352
≧ 6.0 / < 6.0 cm	80 / 132	0.013	0.002
≧ 7.0 / < 7.0 cm	56 / 156	0.025	0.067
≧ 8.0 / < 8.0 cm	32 / 180	< 0.001	0.021
≧ 9.0 / < 9.0 cm	17 / 195	0.004	< 0.001

Table 4
Patients' characteristics between groups with tumor size <5 cm and ≧ 5 cm.

	Tumor size <5 cm (n = 102)	Tumor size ≧5 cm (n = 110)	P-value
Sex, male (%)	45 (44.1 %)	61 (55.5 %)	0.099
MG positive (%)	86 (84.3 %)	83 (75.4 %)	0.109
OP age, year	51.0 ± 12.6	47.8 ± 12.8	0.076
Masaoka stage			0.005
I	59	40	
IIa	18	19	
IIb	7	6	
III	16	37	
IVa	2	7	
IVb	0	1	
Thymoma recurrence patient numbers, No. (%)	6 (5.9 %)	20 (18.2 %)	0.006
Recurrence-free period, year	8.5 ± 6.1	7.5 ± 5.9	0.203
Survival period, year	8.9 ± 6.1	8.4 ± 5.7	0.648

Table 3
Patients' characteristics between limited and advanced stage thymoma.

	Limited stage (n = 153)	Advanced stage (n = 66)	P-value
Gender, male (%)	76 (49.7 %)	33 (50.0 %)	0.965
MG positive (%)	122 (79.7 %)	53 (80.3 %)	0.924
OP age, year	49.7 ± 12.2	48.5 ± 13.9	0.505
Pre-OP CT tumor size, cm	4.7 ± 2.1	6.5 ± 2.3	<0.001
Tumor size <5 cm	84 (54.9 %)	18 (27.3 %)	<0.001
Tumor size ≧5 cm	65 (42.4 %)	45 (68.2 %)	
Thymoma recurrence patient numbers, No. (%)	7 (4.6 %)	20 (30.3 %)	<0.001
Recurrence-free period, year	8.8 ± 6.1	6.9 ± 5.8	0.022

Discussion

This study suggested that combination of stage and tumor size could be used for the prediction of thymoma recurrence, using the SKH database. This finding was inspired by the results of previous studies [10–13].

Since 1980, the first version of the Masaoka staging and then the modified M-K staging has been widely used [17]. Most patients' medical data recording depended on this guideline. Recently, TNM staging system gained attention because its classification is similar to that of other cancers [18]. However, neither M–K staging nor TNM staging, take

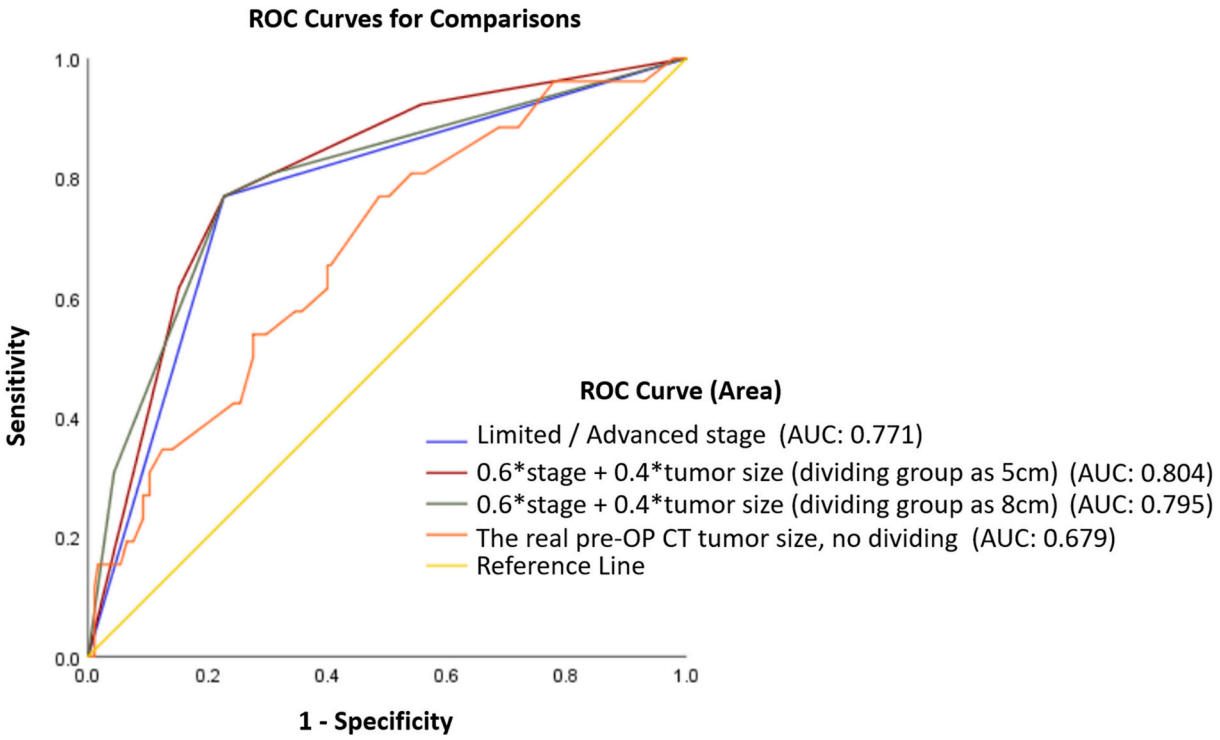

Fig. 1. ROC curve for evaluating better recurrence prediction models. The calculation formula is x/10 * limited/advanced stage + (1-x)/10 * tumor size. The combination of 0.6 * staging + 0.4 * tumor size (dividing group as 5 cm) has the best discriminative power in this study.

tumor size into consideration. Although this staging could provide prediction of disease prognosis, there must be factors other than tumor invasion, which affect thymoma recurrence. According to previous studies, tumor size was an independent factor for thymoma recurrence [10–13]. This study found 5 cm to be the better cutoff value to predict thymoma recurrence. This finding is similar to that of large-scale studies by Okumura et al. and Yun et al. [12,13] Furthermore, in our model, the best AUC discriminative power on the ROC curves is staging plus tumor size divided as 5 cm. Staging alone, could provide acceptable discrimination for evaluation. Combination of staging with tumor size could provide excellent discrimination to predict the thymoma recurrence rate. Although this prediction model may not be superior, it could provide statistical information for disease evaluation.

This study has some limitations. First, the small sample size in our database. Since only one middle volume hospital was used to document the rare disease, it was hard to collect data on sufficient thymoma patients for detailed statistical analysis. Therefore, we used limited and advanced stages to avoid some subgroups having too little samples, and their statistical power too low for accurate individual analysis. Although based on a small database, the study's statistical analysis outcome is similar to Japan and Korea's large-scale research [11–13], potentially indicating that this study's statistical power could be trusted. Second, for a long follow-up period, there would be some bias because of different treatment plans chosen by individual surgeons, even though majority of surgeons undergo the same training. The main difference was the surgical approach. In the early period, even with small tumor size, thoracotomy was mainly used. Experienced surgeons preferred resection of small tumors using Video-Assisted Thoracoscopic Surgery. The operation procedures could affect the outcome of the thymoma less. Contrarily, there were a few studies with a long follow-up. Thymoma progresses slowly and needs a longer time for observation. This study provides the experience for thymoma patients with longer prediction times. Third, being an MG-specific center, about one-third of patients in Taiwan are treated or have follow-ups in SKH. The patient distribution differed from other published studies focusing on thymoma. Our study findings indicated that MG symptoms did not affect thymoma recurrence, and a better survival outcome could be obtained as a result of close follow-up (Supplementary Discussion, Table E3, and Fig. E5). More studies are needed to verify this outcome.

Conclusion

Our study verifies the hypothesis that staging combined with tumor size can provide a better thymoma recurrence prediction. The calculation formula (x/10 * limited/advanced stage + (1-x)/10 * tumor size) may be one tool for the prediction of thymoma recurrence. However, the utility of this formula may be affected by the small simple size in this study; more data is needed to improve the utility of this formula in predicting thymoma recurrence. However, we believe that these findings may help clinicians to provide more accurate information to patients before planning treatment and to devise follow-up treatment plans.

Ethics approval

The experimental protocol was established, according to the ethical guidelines of the Helsinki Declaration and was approved by the Human Ethics Committee of Shin Kong Wu Huo-Shih Memorial Hospital. Written informed consent was obtained from individual or guardian participants.

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CRediT authorship contribution statement

Hao-Yun Liu: Data curation, Methodology, Writing- Original draft preparation.

Ya-Fang Liu: Formal analysis.
Yi-Chen Chang: Data Curation, Software.
Hou-Chang Chiu: Supervision.
Jiann-Horng Yeh: Supervision: Project administration.

Declaration of Generative AI and AI-assisted technologies in the writing process

This article did not use any AI or AI-assisted technologies.

Declaration of competing interest

All authors declare that no support, financial or otherwise, has been received from any organization that may have an interest in the submitted work; and there are no other relationships or activities that could appear to have influenced the submitted work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sopen.2023.10.005.

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