Thoracic Cancer

Open Access

Thoracic Cancer ISSN 1759-7706

ORIGINAL ARTICLE

# Is thymomectomy sufficient for non-myasthenic early stage thymoma patients? A retrospective, single center experience

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**Keywords**
Thymoma; thymectomy; thymomectomy.

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This manuscript was presented at the 24th European Conference on General Thoracic Surgery, May 31, 2016, Naples, Italy (Abstract Number: F126-Sicilia-31052016).

Received: 7 August 2017;
Accepted: 17 September 2017.

doi: 10.1111/1759-7714.12542

Thoracic Cancer **9** (2018) 88–93

## Abstract

**Background:** Thymic complete resection is considered the standard treatment for all thymic tumors; however, the ideal resection for non-myasthenic early stage thymic tumors has not yet been determined. We conducted a retrospective study to examine this unique scenario.

**Methods:** We retrospectively analyzed the data of 118 early stage thymoma patients who underwent thymectomy (TM) or thymomectomy (TMM) with curative intent between January 2003 and December 2013 at our institution. Patients with myasthenia, thymic carcinomas, tumors with undetermined histology, and more advanced stage thymoma patients were excluded. We compared overall survival (OS) and disease-free survival (DFS) according to the extent of thymic resection, tumor staging, and size.

**Results:** One hundred and eighteen patients were staged as early thymoma. TM was performed in 43 (35.6%) patients and TMM in 75 (64.4%). Forty-nine (65.3%) patients with a tumor ≤ 3 cm underwent TMM, and 9 (20.9%) TM. Twenty-six (34.7%) patients with a tumor > 3 cm underwent TMM, and 34 (79.1%) TM. Seventy-four patients were categorized as stage I: 57 (76%) underwent TMM and 17 (39.5%) TM. Forty-four patients were categorized as stage II: 18 (24%) underwent TMM and 26 (60.5%) TM. There was no statistically significant difference in recurrence between the groups ($P = 0.250$).

**Conclusion:** No difference in the rate of recurrence was observed in early stage non-myasthenic patients following thymic resection and Masaoka–Koga staging. However, TM is considered a better option for early stage thymoma patients with tumors > 3 cm.

## Introduction

Despite rare incidence, thymoma is the most common malignancy of the anterior mediastinum.[1,2] Typically, surgery has been considered the treatment of choice, with complete thymectomy (TM), defined as complete resection of the thymoma and entire thymus gland, recommended in much of the literature. Recent papers have strongly recommended that thymoma should be resected together with the surrounding thymus and fatty tissue rather than completely removing the tumor with the capsule, because they are all considered malignant and transcapsular invasion is difficult to detect intraoperatively.[3]

A minimally invasive approach has become the standard of care for early stage lung cancer patients over the last decade. However, the adoption of video-assisted thoracoscopic TM for thymic malignancies has slowly progressed,[4,5] mainly because of the limitations and concerns related to the disease and its anatomic location. Advances in minimally invasive surgery and improvements in the detection of small early-stage tumors has led to more opportunities for the use of less extensive resection, known as limited TM, which is defined as complete resection of the thymoma with the surrounding thymus and fatty tissue, but not the entire thymus gland; thus encompassing thymomectomy (TMM) (complete excision of the

thymoma only). Until now, there has been no consensus on the appropriate extent of resection for thymoma patients.[6,7] However, the International Thymic Malignancy Interest Group recommends TM for patients with early-stage thymoma, even in the absence of associated myasthenia gravis (MG).[3]

Most authors recommend TM even in the case of partial involvement of the gland; however, there is a lack of objective data to substantiate this assumption. Therefore, the purpose of this study was to compare TM and TMM with respect to survival, recurrence, and perioperative outcomes.

## Methods

### Patients

The records of 379 patients who underwent resection of a primary thymic tumor with curative intent at the First Affiliated Hospital of Zhejiang University from January 2003 to December 2013 were retrospectively reviewed. Exclusion criteria were: (i) thymic carcinoma, (ii) tumors with unknown origins, (iii) thymic hyperplasia or cysts, (iv) thymic non-epithelial tumors, (v) tumors only biopsied intraoperatively, and (vi) thymic tumors treated with neoadjuvant therapy. We also excluded patients with MG, and advanced stage patients (Masaoka–Koga stages III and IV). The patients were divided into two groups according to the treatment received: TM ($n$ = 43) and TMM ($n$ = 73). Clinical data of the remaining 118 patients, including age, gender, tumor size, surgical approach, extent of resection, World Health Organization (WHO) histologic type, completeness of resection, adjuvant therapy, perioperative outcomes, recurrence, and survival were retrospectively reviewed.

### Histologic classification and staging

Thymomas were classified into histological types (A, AB, B1, B2, and B3) according to the WHO classification system.[8] Tumor stage was determined by review of surgical records and pathological reports and was classified according to the Masaoka–Koga staging system (I, II, III, IVa, IVb).[9] Patient characteristics are listed in Table 1.

**Table 1** Patient characteristics

| Variables | Thymomectomy ($n$ = 75) | Thymectomy ($n$ = 43) | $P$ |
|---|---|---|---|
| Gender | | | |
| Male | 39 (52.0) | 22 (51.2) | 1.000 |
| Female | 36 (48.0) | 21 (48.8) | |
| Age | | | |
| ≤ 40 years | 23 (30.7) | 11 (25.6) | 0.833 |
| 41–59 years | 31 (41.3) | 18 (41.9) | |
| ≥ 60 years | 21 (28.0) | 14 (32.6) | |
| WHO classification | | | |
| A | 26 (34.6) | 3 (7.0) | <0.001 |
| AB | 30 (40.0) | 13 (30.2) | |
| B1 | 11 (14.7) | 9 (20.9) | |
| B2 | 8 (10.7) | 13 (30.2) | |
| B3 | 0 (0.0) | 5 (11.6) | |
| Tumor size | | | |
| < 3 cm | 49 (65.3) | 9 (20.9) | < 0.001 |
| > 3 cm | 26 (34.7) | 34 (79.1) | |
| Masaoka–Koga staging | | | |
| Stage I | 57 (76.0) | 17 (39.5) | < 0.001 |
| Stage II | 18 (24.0) | 26 (60.5) | |
| Adjuvant therapy | | | |
| Not administered | 52 (70.3) | 11 (25.6) | < 0.001 |
| Administered | 22 (29.7) | 32 (74.4) | |
| Survival | | | |
| Survived | 74 (98.7) | 38 (88.4) | 0.024 |
| Died | 1 (1.3) | 5 (11.6) | |
| Recurrence | | | |
| Yes | 2 (2.7) | 3 (6.9) | 0.456 |
| No | 73 (97.3) | 40 (93.1) | |

WHO, World Health Organization.

### Treatment

Six surgeons performed all thymic resections during the study period, which included both video-assisted thoracoscopic surgery (VATS) and open procedures (transsternal approach and thoracotomy). The choice of procedure was determined by the tumor characteristics and the surgeon's preference. Open thymic resections were performed in all patients with large tumors and in earlier stages. In 2009, minimally invasive surgeries became the surgeon's preference at our center, thus VATS thymic resections became more widely used at this time. Adjuvant radiation, chemotherapy, or chemoradiotherapy were administered primarily to patients with WHO type B2 and B3, tumor size > 3 cm and Masaoka–Koga stage II. However, the decision was largely dependent on the surgeon's discretion because there are no clear, standardized indications. The Institutional Review Board of the First Affiliated Hospital of Zhejiang University approved this retrospective study, as did each participating institution's review board. Informed consent was waived because of the retrospective nature of the study.

### Statistical analysis

The general characteristics of the study group were analyzed using Student's $t$-tests for continuous variables and chi-squared or Fisher's exact tests for categorical variables. Continuous data are expressed as means and standard deviations, whereas categorical variables are expressed as

  

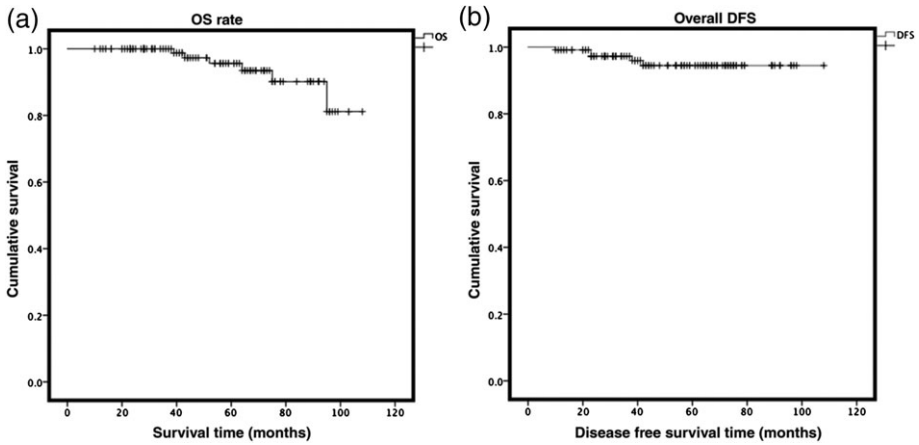


**Figure 1** Postoperative (**a**) overall survival (OS) and (**b**) disease-free survival (DFS) rates. The 10-year OS and DFS rates were 81.3 and 90.5%, respectively.

counts and percentages. Perioperative outcomes were analyzed using the Mann–Whitney *U* test, with values expressed as medians with interquartile ranges. Overall survival (OS) was calculated from the date of resection to the date of death from any cause. Disease-free survival (DFS) was calculated from the date of resection to the date of first recurrence. OS and DFS were estimated using the Kaplan–Meier method, and statistical differences were determined using the log-rank test. Multivariate Cox regression analysis was performed to adjust for confounding factors. Age, gender, approach, tumor size, stage, histologic type, extent of resection, tumor size, and adjuvant therapy were set as covariates. All statistical analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA).

## Results

The study group consisted of 118 early stage non-myasthenic thymoma patients (61 men and 57 women) with a median age of 56 years (range 32–73). Forty-three patients underwent TM and 75 patients underwent TMM. Gender distribution was similar between the groups: TM group 22 men (51.2%), TMM group 39 men (52.0%). Most of the patients were aged 40–60: TM 18 (41.9%), TMM 31 (41.3%). Patient characteristics are shown in Table 1. No significant differences were observed in gender or age between the two groups.

The patients were classified according to WHO classification: the numbers of A, AB, B1, and B2 patients in TMM group were 26 (34.7%), 30 (40.0%), 11 (14.7%), and 8 (10.7%) respectively. The numbers of type A, AB, B1, B2, and B3 thymoma patients in the TM group were: 3 (7.0%), 13 (30.2%), 9 (20.9%), 13 (30.2%), and 5 (11.6%), respectively. Type AB was the most common subtype in the TMM group, whereas both type AB and B2 were the most common subtypes in the TM group. There were no type B3 patients in the TMM group ($P < 0.001$).

Tumor size was calculated using computed tomography scans and pathologic findings. The tumor was < 3 cm in 49 (65.3%) patients in the TMM group, and > 3 cm in 34 (79.1%) patients in the TM group. Thus, most of the patients in the TMM group had smaller tumors, while larger tumors were more common in the TM group ($P < 0.001$).

The Masaoka–Koga staging system was used. Seventy-four (62.7%) patients were in stage I and 44 (37.3%) in stage II. In the TMM group, 57 patients were in stage I (76.0%) and 18 stage II (24.0%), while in the TM group, 17 patients (39.5%) were in stage I and 26 (60.5%) were in stage II.

In terms of the surgical approach, sternotomy was commonly used in the TM group, while thoracotomy was more frequently chosen in the TMM group, with a significant difference ($P < 0.001$). There was no significant difference in minimally invasive approach. A higher proportion of patients received adjuvant therapy after TM than after TMM (74.4% vs. 29.7%; $P < 0.001$) because of larger and more advanced staged tumors.

The 10-year OS and DFS rates were 81.3% and 90.5%, respectively (Fig 1). The TMM group experienced better survival (98.7% vs. 88.4%; $P = 0.022$); however, there was no significant difference in DFS between the groups (97.3% vs. 93.0%; $P = 0.250$) (Fig 2). The recurrence rate was 2.67% after TMM and 6.98% after TM, with no significant difference between the groups ($P = 0.456$). There was no statistically significant difference in survival between the groups according to tumor size, but we observed better DFS in patients with tumors < 3 cm (100% vs. 91.7%; $P = 0.023$) (Fig 3).

In terms of surgical outcome, we observed shorter surgical duration (113.4 ± 51.9 vs. 189.4 ± 49.3 minutes; $P < 0.001$), less blood loss (105.7 ± 49.3 vs. 201.5 ± 156.9 mL; $P = 0.034$), fewer postoperative drainage days (5.1 ± 1.3 vs. 6.3 ± 1.7 days; $P = 0.001$), and a shorter hospital stay (6.1 ± 1.5 vs. 7.8 ± 1.4 days; $P = 0.010$) in the TMM compared to the TM group. No difference in the rate of recurrence was observed between the groups ($P = 0.456$) (Table 2).

 

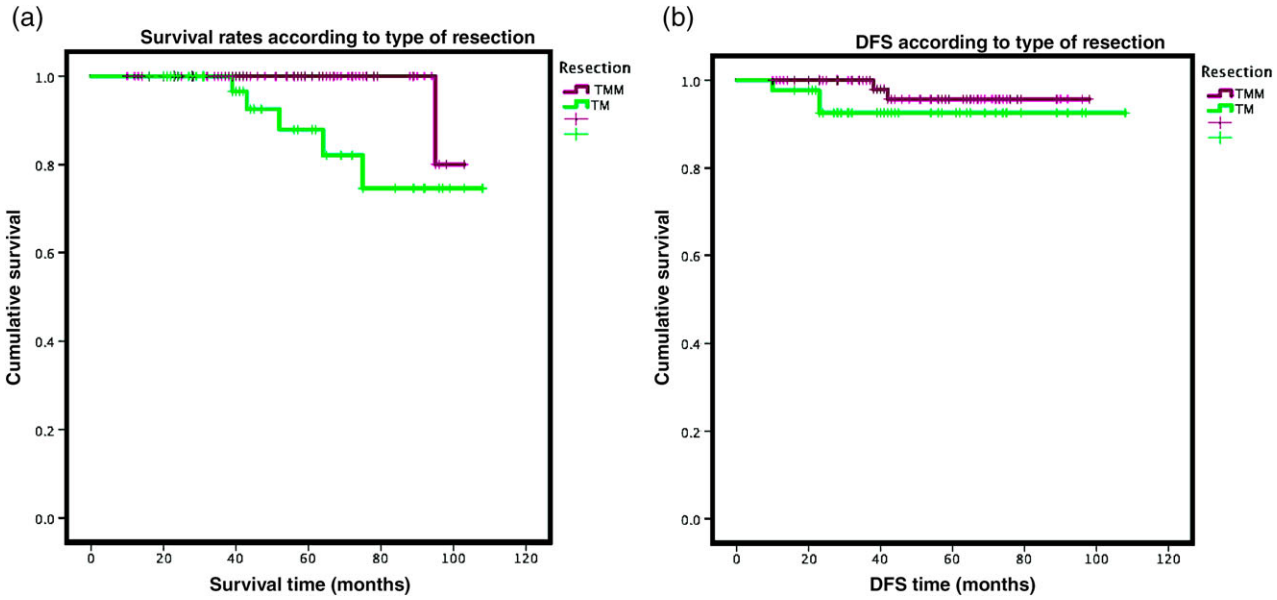


**Figure 2** A comparison of survival rates in the thymomectomy (TMM) and thymectomy (TM) groups. (**a**) We observed better survival in the TMM group (98.7% vs. 88.4%; $P = 0.022$); (**b**) however, there was no significant difference in disease-free survival (DFS) between the groups (97.3% vs. 93.0%; $P = 0.250$).

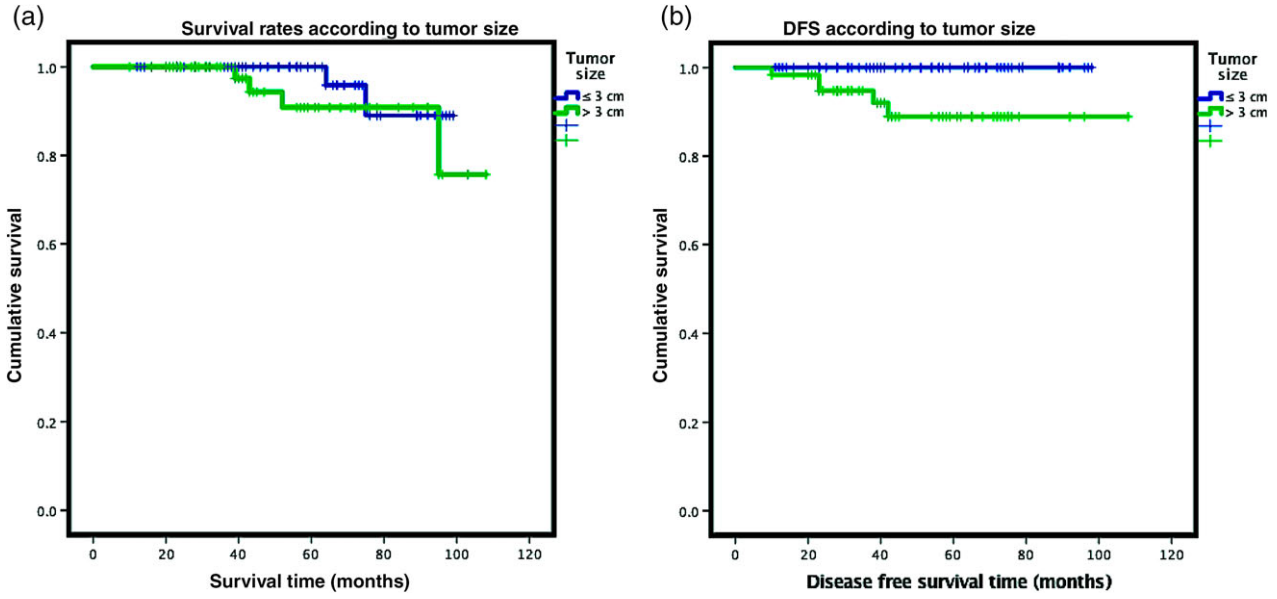


**Figure 3** A comparison of survival according to tumor size. (**a**) There was no statistically significant difference between the thymomectomy (TMM) and thymectomy (TM) groups; (**b**) however, we observed better disease-free survival (DFS) in patients with tumors < 3 cm (100% vs. 91.7%; $P = 0.023$).

## Discussion

Early stage thymomas are rare, indolent tumors of the thymus gland. Thymomas may develop at any age, but are most common between the ages of 35 and 70. Distribution between genders tends to be fairly equal, with a slight female predominance in older age groups.[10] Complete resection is the cornerstone of treatment, and has been shown to be effective in achieving high cure rates. For this reason, en bloc resection of the entire thymus gland and surrounding mediastinal areolar tissue is the standard of care in most centers today.[11,12] Complete thymic resection (TM) is considered the standard treatment for all

  

**Table 2** Perioperative outcomes

| Variables | TMM ($n$ = 75) | TM ($n$ = 43) | $P$ |
|---|---|---|---|
| Duration of surgery (min) | 113.4 ± 51.9 | 189.4 ± 49.3 | < 0.001 |
| Blood loss (mL) | 105.7 ± 49.3 | 201.5 ± 156.9 | 0.034 |
| Postoperative drainage (day) | 5.1 ± 1.3 | 6.3 ± 1.7 | 0.001 |
| Postoperative hospital stay (day) | 6.1 ± 1.5 | 7.8 ± 1.4 | 0.010 |
| Tumor recurrence | 2 | 3 | 0.456 |

TM, thymectomy; TMM, thymomectomy.

thymic tumors; however, the ideal resection for non-myasthenic early stage thymic tumors has not yet been determined. Complete surgical resection is commonly successful for early stage thymomas, and prognosis is favorable. A standardized surgical treatment does not exist.[13] Most authors recommend complete TM even in the case of partial involvement of the gland; however, there is a lack of objective data to substantiate this assumption.[14] Controversy persists over the optimal surgical approach for patients with thymoma.[15]

Onuki *et al.* reviewed 79 patients with stage I and II thymomas (18 cases underwent TMM, 61 TM) and found that the 10-year DFS rate was not significantly different between the groups (85.7% for the TMM vs. 82.0% for the TM group) and no thymoma-related death occurred.[16] Tseng *et al.* reviewed 95 patients with stage I and II thymomas and reported an OS of 100% in both groups, with recurrence in 1 out of 53 patients (1.9%) who underwent TMM and 2 of 42 patients (4.5%) who underwent extended TM.[6] Most recently, Nakagawa *et al.* performed a multi-institutional study using the Japanese Association for Research on Thymus database. They analyzed 1286 patients with Masaoka–Koga stage I and II thymomas (289 underwent thymomectomy, 997 underwent thymothymomectomy).[17] By definition, thymomectomy and thymothymomectomy are comparable to TMM and TM. They reported that five-year OS and DFS rates did not significantly differ (97.3% and 93.8% for the thymomectomy group vs. 96.9% and 94.7% for the thymothymomectomy group). Zhitao *et al.* evaluated the surgical outcomes of tumor resection with or without total TM for thymic epithelial tumors using the Chinese Alliance for Research in Thymomas database. They found that TM, instead of tumor resection alone, should be recommended as the surgical standard for thymic malignancies, especially for stage II tumors and those with concomitant MG.[18] However, for stage I and non-myasthenic thymomas, the optimal surgical option is still unclear.

In our series, 74 (62.7%) patients were in stage I and 44 (37.3%) in stage II: TMM group, 56 patients in stage I, 18 in stage II; TM group, 17 patients (39.5%) in stage I, 26 (60.5%) in stage II. The 10-year OS and DFS rates were 81.3% and 90.5%, respectively. We observed better survival in the TMM group (98.7 vs. 88.4%; $P$ = 0.022); however, there was no significant difference in DFS between the groups (97.3 vs. 93.0%; $P$ = 0.250). The recurrence rates were 2.67% after TMM and 6.98% after TM, but these results were not statistically significant ($P$ = 0.456). There was also no statistically significant difference in survival according to tumor size between the TMM and TM groups, but we observed better DFS in patients with tumor size < 3 cm (100% vs. 91.7%; $P$ = 0.023).

It is not clear whether tumor size is an independent prognostic factor for outcome in thymoma patients, although this has been suggested by various studies. Nakagawa *et al.* evaluated the factors limiting the prognosis of thymomas, and rated tumor size as a significant predictor of outcome ($P$ = 0.001).[19] These results were supported by a single-center study of 179 patients by Wright *et al.*, who found that a critical tumor size of ≥ 8 cm was an independent predictor for recurrence.[20] However, for early stage non-myasthenic thymomas, the prognostic value of tumor size has not yet been determined. In our study, tumor size was calculated using computed tomography scans and pathologic findings. The tumor size was < 3 cm in 49 (65.3%) patients in the TMM group and > 3 cm in 34 (79.1%) patients in the TM group ($P$ < 0.001).

Perioperative outcomes are also important for deciding the extent of resection. Tseng *et al.* reported that a TMM treatment group exhibited shorter surgical duration, less blood loss, fewer days until extubation, lower admission rates to the intensive care unit, fewer days requiring a chest tube, and a shorter length of hospital stay.[6] Further, the Japanese Association for Research on Thymus database showed lower complication rates in patients who underwent TMM compared to TM (4.3% vs. 8.3%).[17] We observed shorter surgical duration, less blood loss, shorter postoperative drainage days, and shorter hospital stays in the TMM group compared to the TM group. However, there was no difference in the rate of recurrence between the groups ($P$ = 0.456).

Several limitations exist in this study. First, this was a single center, retrospective study. Second, the extent of resection was decided by individual surgeons, potentially introducing selection bias. Finally, the follow-up period was relatively short considering the average time to recurrence in thymoma cases. Therefore, these results should be interpreted with caution. Future studies should include a longer follow-up period to confirm these results.

In conclusion, our study suggests that TMM is a safe option for small early stage non-myasthenic thymomas. The surgery was less invasive in the TMM group; however, in early stage thymoma patients with tumors > 3 cm, TM

 

is considered a better option. Further study is required to determine whether TMM can replace TM.

## Disclosure

No authors report any conflict of interest.

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