

Surgical and oncological outcomes of thoracoscopic thymectomy for thymoma

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Abstract: Thymoma remains the most common primary anterior mediastinal neoplasm. Surgical resection remains central to the treatment of thymoma, with thoracoscopic thymectomy (TT) being increasingly performed. This present review article aimed to summarize current studies comparing TT and open thymectomy (OT). Recently, most patients with Masaoka stage I–II thymoma have been receiving TT. This procedure is associated with a significantly shorter post-operative hospital stay, decreased intraoperative blood loss, and fewer complications compared with OT. Recurrence rates of thymoma after TT range from 0% to 6.7%, and the 5-year disease-free survival (DFS) ranges from 83.3% to 96%. The oncological outcomes of TT are comparable to that of OT. Masaoka stage and the World Health Organization (WHO) type classification are valuable predictors of the prognosis of thymoma; hence, the optimal treatment for thymoma should be performed according to these two. TT is less invasive, with equivalent oncological outcomes, when compared with the OT. Minimally invasive surgery including TT for stage I–II thymomas is becoming the mainstay of therapy.

Keywords: Thymoma; thoracoscopic thymectomy (TT); open thymectomy (OT); WHO type classification; Masaoka stage

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Introduction

Thymoma remains the most common primary anterior mediastinal neoplasm (1,2). Surgical resection remains central to the treatment, and multimodality therapy, including radiation and/or chemotherapy, is indicated as adjuvant therapy (3-5). Total thymectomy via standard median sternotomy is the standard treatment for early and advanced stage thymoma (6,7). With recent developments in thoracoscopic surgical instruments and practices, thoracoscopic procedure has been increasingly indicated for thymoma (7-9). Recent studies have shown that thoracoscopic thymectomy (TT) improves surgical

outcomes, including reduced postoperative pain, fewer postoperative complications, and shorter postoperative hospital stay, due to the decreased invasiveness of the procedure (10,11). Furthermore, equivalent oncological outcomes have been demonstrated for TT compared with open thymectomy (OT) (7,10,11). However, currently, several controversies exist over the applicable surgical approach, surgical criteria, operative indication of thoracoscopic procedure, and the resected extent of the thymus. Additionally, there are no critical guidelines of TT for thymoma. This present review article aimed to summarize current studies comparing TT and OT.

Table 1 Masaoka staging system

Stage	Description
I	Macroscopically encapsulated and no microscopic capsular invasion
II	Macroscopic invasion into adjacent tissues (fatty or mediastinal pleura) or microscopic capsular invasion
III	Macroscopic invasion into adjacent organ(s)
IVA	Pleural or pericardial dissemination
IVB	Lymphogenous or hematogenous metastasis

Thymoma

Thymoma is usually an indolent disease. Epithelial tumors of thymus generally involve thymoma, thymic carcinoma, and carcinoid. Thymomas are associated with autoimmune diseases, such as myasthenia gravis (MG), hypogammaglobinemia, and pure red cell aplasia. Thymic carcinoma and carcinoid are very rare neoplasms (2). Most patients with thymomas are asymptomatic; however, a few patients experience systemic symptoms including a cough, dyspnea, and autoimmune disease. Thymomas may cause local symptoms associated with compression of surrounding structures. Approximately 30% of patients with thymomas have MG (12), and around 20% of patients with MG have thymomas (13). Thymomas are generally considered cytological benign whereas thymic carcinomas have malignant cytological features. Thymic carcinomas have a significantly worse oncological prognosis (14–16).

Clinical stage

Bergh *et al.* (17) presented the initial clinical staging for thymoma in 1978, which was subsequently altered by Wilkins and Castleman (18). Masaoka *et al.* established an alternative clinical staging system (6) in 1981 and the Masaoka stage is widely accepted based on clinical treatments (Table 1). Recently, the Masaoka-Koga stage (19) was shown as a modified clinical staging system by the International Thymic Malignancy Interest Group (ITMIG). The Masaoka stage is recognized as an effective prognostic factor for thymoma (16). Several reports have shown that the oncological outcomes significantly correlated with Masaoka stages (16,20–23). In our previous study (24), Masaoka stage III–IV thymoma patients experienced more recurrences than those with stage I–II patients. The 5-year disease-free survival (DFS) for stage III–IV thymomas was

significantly poorer than those for stage I and II thymoma (47% *vs.* 97.5% and 94.1%, respectively). Hence, the Masaoka stage was a valuable predictor of the prognosis of thymoma.

Pathologic classification

The pathologic classification of thymoma has remained controversial for many years (25). The World Health Organization (WHO) has developed the most widely adopted pathologic classification for epithelial tumor of thymus by taking into consideration both histological and morphological features (26). There are two staging systems for epithelial tumor of thymus (27). Most widely used clinical stage was first described by Masaoka *et al.* in 1981, and it is a clinical staging system describing thymomas in terms of local extension or invasion of the tumor (6). The TNM staging follows the pattern of T for tumor descriptor, N for nodal spread, and M for distance metastasis. In 1999, the WHO Consensus Committee published a histologic typing system for neoplasms of the thymus (28). Thymomas are classified into types A, AB, B1, B2, B3, and C based on the morphology of epithelial cells and ratio of lymphocyte-to-epithelial cells. Recently, the WHO Consensus Committee recommended that epithelial tumors of thymus be classified as thymoma, including type A, AB, B1, B2, and B3 thymoma and thymic carcinoma (29). Most of the WHO type A, AB, B1, and B2 thymomas are benign; however, types B3 and C have malignant potential (30). Our study (24) demonstrated that 16 of 140 thymomas patients experienced recurrences. Of those 16 patients, 12 patients had WHO type B3 or C thymomas. Thus, pathological aggressiveness seems to strongly influence recurrence. Several reports have indicated the impact of the WHO type on the decision-making during clinical treatments (26).

Surgical treatment

Most patients having Masaoka stage I–II thymoma receive surgical treatment. Recently, TT has been attempted as a surgical treatment for thymoma. TT for thymoma consists of extended thymectomy (ET), total thymectomy, subtotal thymectomy (STT), and partial thymectomy according to the classification of the extent of the thymus resected. In this review, a few authors classified thymectomy by total and partial thymectomy, while some authors do not describe the resected extent of thymus clearly. Total thymectomy was defined as the resection of the entire thymus, and



Figure 1 Thoracoscopic subtotal thymectomy (STT) for thymoma. In this case, STT from left thoracic cavity for a large thymoma (32).

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ET was defined as the resection with the thymus and surrounding fat tissues together. ET was usually performed in patients who had MG. For these patients, thoracoscopic ET was performed using a bilateral thoracic approach in our institution. STT was defined as the resection of the thymus without the superior and inferior poles in a contralateral thymic lobe (31). Total thymectomy and STT using a unilateral thoracic approach are the main thoracoscopic procedures for thymoma in our institution (Figure 1). Resection is initiated in the pericardial fat and normal thymic tissues with careful handling of the tumor to evade disruptions into the capsule of thymoma. This thoracoscopic technique ensures a satisfactory view to the surgeon despite deep and narrow spaces. In addition, multiple thoracoscopic instruments support the technical difficulties.

Surgeons who favor the right-side thoracic approach state that the superior vena cava can be obviously recognized and used as a marker to dissect around the left innominate veins. Surgeons who use the bilateral thoracoscopic approach advocate that it improves the visualization of main anatomical structures and consequently enables complete resection. Hence, the laterality of approach depends on the surgeon or institution indications, which are influenced by their experience and training (33). Furthermore, some institutions use a sternal lifting (34) or carbon dioxide insufflation (35,36). Recently, most thymoma patients indicated TT in our institution. Most reports show that patients with Masaoka stage I–II thymomas underwent TT (37). The invasion to the innominate vein, phrenic nerve, or other major vessels should be a contraindication to

a TT (36). Patients with Masaoka stage III thymoma should be indicated for OT.

In agreement with previous reports (12,38,39), several authors demonstrated the decreased invasiveness of TT for thymoma. Most of the reports in this review revealed that TT showed a significantly shorter post-operative hospital stay, decreased intraoperative blood loss, and fewer complications compared to OT (Table 2).

Concern regarding the chance of thymoma capsule rupture and risk of pleural dissemination by the thoracoscopic approach has been raised. The thymoma should not be grasped directly with instruments because of these risks. Exact gentle handling should be recommended (36). However, this concern is not confirmed by published evidence (46). Kimura *et al.* (8) reported that three (6.7%) of 45 patients with thymoma >5 cm who underwent a thoracoscopic approach had disease recurrence with pleural dissemination. Lucchi *et al.* reported that pleural recurrence after TT was comparable to that after OT via sternotomy (47). The recurrence ranged from 0% to 6.7% with variable follow-up periods (30–66 months). Patients who experienced recurrence tended to have Masaoka stage III–IV or WHO type B3–C thymoma. The 5-year DFS ranged from 83.3% to 96% (Table 2). According to recent reports, surgical treatment for thymoma demonstrated that the overall 5-year survival rate of patients with Masaoka stage I and II thymoma ranged from 89% to 100% and 71% to 95%, respectively (48). Ye *et al.* (41) demonstrated that the oncological outcomes were comparable for TT and OT groups. Manoly *et al.* (42) concluded that the DFS was comparable between the groups. Several reports demonstrated that there was no significant difference in the DFS between the groups (43,49).

No definitive guidelines have yet been established regarding the appropriate size of the thymoma that can be considered an indicator for thoracoscopic surgery. Minimal invasive surgery for a relatively large-sized thymoma remains controversial. There is presently no consensus on the appropriate size of the thymoma for which TT can be performed, and there are few reports that have examined the indications for TT based thymoma size. Most investigators accept that TT is technically safe and feasible for thymomas with a diameter <50 mm (37,50).

Concern regarding local recurrence or intrathymic relapse may limit the indications of limited resections including STT, partial thymectomy, and thymomectomy for Masaoka I–II stage thymoma without MG because the appropriate resected extent of the thymus is uncertain. No

Table 2 Review of published results on TT for thymoma

References	No. of patients	Masaoka stage	Tumor size, mm	Procedure	Duration (min)	Blood loss (mL)	Complication (%)	Convert (%)	POHS (days)	Survival (%)	F/U period (months)	Recurrence (%)
He <i>et al.</i> [2013] (40)	15	I:6, II:9	NA	Thymectomy	202*	98*	4 (26.7)	0	10.6*	ER 93.3	NA	0
Kimura <i>et al.</i> [2013] (8)	45	I:41, II:4	50 [†]	Thymectomy	180 [†]	50 [†]	NA	NA	11 [†]	NA	53	3 (6.7)
Liu <i>et al.</i> [2014] (38)	76	I:57, II:19	46*	Thymectomy	141*	105*	NA	1 (1.3)	7.1*	96.9	44	2 (2.6)
Ye <i>et al.</i> [2014] (41)	125	I:80, II:45	32.3*	Thymectomy	170 [†]	200 [†]	6 (4.8)	4 (3.2)	8 [†]	NA	41	1 (0.8)
Manoly <i>et al.</i> [2014] (42)	17	I:5, II:9, III:3	NA	ET	177*	NA	17.60	2 (11.8)	4.4*	83.3	30.5	1 (5.9)
Sakamaki <i>et al.</i> [2014] (43)	71	I:40, II:31	35 [†]	Thymectomy (partial: 42, total: 29)	NA	NA	NA	4 (5.6)	NA	RFS 92.4	48	2 (4.1)
Yuan <i>et al.</i> [2014] (44)	38	I:17, II:21	54 [†]	Thymectomy	127 [†]	114 [†]	NA	NA	5.2 [†]	NA	NA	NA
Odaka <i>et al.</i> [2015] (45)	67	I:33, II:34	40 [†]	Thymectomy (total: 19, subtotal: 40, partial: 8)	229 [†]	100 [†]	7 (10.4)	0	4 [†]	95.8	55	2 (2.9)
Chao <i>et al.</i> [2015] (39)	48	I:17, II:31	58*	Thymectomy (partial: 18, total: 30)	153*	40*	2 (4.1)	1 (2.0)	5.8*	NA	66	2 (4.1)

* , mean value; [†] , median value. Duration, duration of surgery; POHS, postoperative hospital stay; convert, convert to OT; survival, 5-year DFS; ER, effective rate; RFS, recurrence-free survival; NA, not applicable; TT, thoracoscopic thymectomy; OT, open thymectomy; DFS, disease-free survival; ET, extended thymectomy.

definitive guidelines have yet been established regarding the resected extent of the thymus for thymoma. Unnecessary, extensive resection of the thymus may increase the potential risk of the intra and post-operative complications. In our previous report, there was no significant difference in the DFS classified by the resected extent of the thymus (45). Thoracoscopic STT was the most frequently performed procedure in our department may have contributed to decreasing the potential risk with oncological equivalent. Sakamaki *et al.* (51) showed that partial thymectomy was feasible for the treatment of noninvasive thymoma without MG. There were no cases of marginal or mediastinal recurrence during the follow-up period. They also suggested that partial thymectomy with negative surgical margins does not carry a greater risk of recurrence than total thymectomy.

Post-thymectomy MG occurs in around 1–3% of the operated patients, and this disorder even progresses after ET (52), suggesting that extended total thymectomy is not beneficial in avoiding post-thymectomy MG over STT.

Tseng *et al.* (53) demonstrated that there was no significant difference in the recurrence rate between patients who received ET and those who received partial thymectomy. Singhal *et al.* (54) concluded that complete resection of thymoma was sufficient surgical treatment for Masaoka stage I–II thymoma. Several authors have reported that complete resection of thymoma is essential of the treatment for thymoma (51,55). Several studies demonstrated that complete resection is one of critical prognostic factor in the treatment of thymoma (4,22). Hence, complete resection is required for surgical treatment of thymoma. It will become necessary to determine an appropriate resection extent of the thymus.

Conclusions

TT is less invasive with oncological equivalent outcomes compared to OT. The Masaoka stage and WHO type classification were valuable predictors of the prognosis of thymoma. The optimal treatment for thymoma should be performed according to the Masaoka stage and WHO type classification. Minimally invasive surgery, including TT for stage I–II thymomas, is becoming the mainstay of therapy.

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Footnote

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