-Original Article-

Limited Thymectomy for Stage I or II Thymomas

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Abstract

Background: Once an anterior mediastinal tumor has been diagnosed as a thymoma, complete excision including the thymic gland and perithymic fat is currently the procedure of choice. However, little is known about the clinical outcome of grossly encapsulated thymomas excised only with the surrounding tissue while leaving a part of the thymic gland. *Methods:* A retrospective historical comparative study was conducted on 79 patients who had received surgery for stage I (n=25) or stage II (n=54) thymomas. Total thymectomy was performed in 61 patients (Total Thymectomy Group), whereas resection of tumors with only the surrounding tissue was carried out in 18 (Limited Thymectomy Group). The follow-up interval was longer in the Limited Thymectomy Group because these patients were treated longer ago (104.2 ± 58.1 months vs 67.3±54.8 months, $p < 0.05$). *Results:* One case in the Limited Thymectomy Group showed postoperative myasthenia gravis (5.6%). Two patients with multiple thymomas (2.5%) were treated with total thymectomy. One case in the Limited Thymectomy Group, which had been diagnosed as Masaoka stage II and WHO type B3 at initial surgery, recurred. None died of tumor progression in this study. Disease free survival rates at 10 years did not differ between the Limited Thymectomy and Total Thymectomy Groups (85.7% and 82.0%, respectively). There were no statistical differences in the incidence of postoperative myasthenia gravis and disease free survival between the

two groups. *Conclusion:* Resection of thymomas with surrounding tissue instead of total thymectomy can be indicated for stage I or II thymomas in light of disease free and overall survival, post-operative onset of MG, and the incidence of multiple lesions.

Key Words

Thymoma

Limited surgery

Thymectomy

Masaoka staging

WHO histologic classification

Postoperative

Myasthenia gravis

Multiple thymoma

Introduction

Thymoma is indolent in growth but it is potentially malignant in its clinical course because of neighboring-organ invasion, pleural dissemination, and occasional systemic metastasis [1]. Therefore, surgical resection should be considered for this anterior mediastinal tumor, although the vast majority of these tumors are localized [2]. The World Health Organization's histologic classification (WHO classification) which was revised in 2004 [3,4] (Table 1) has proven to be a significant independent prognostic factor. However the Masaoka staging system [5] still plays an important role in deciding therapeutic strategy and estimating prognosis [2,3,6] (Table 2).

In patients with a grossly encapsulated, noninvasive or microinvasive lesion corresponding to Masaoka stage I or II, complete exicision including a total thymectomy, is currently considered to be the procedure of choice [6,7]. Although there has been some controversy [8,9], surgery alone, without adjuvant therapy, has become widely accepted for treating stage I or II thymomas [1,10,11]. The overall survival rates for these thymomas has been reported as 87 - 100% at 10 years [2,3,12,13]. Total thymectomy in addition to complete tumor resection has been supported widely because of the occurrence of postoperative myasthenia gravis (MG), and multi-focal or metastatic thymomas [7,14].

Nowadays, advanced imaging technologies such as computed tomography (CT) or magnetic

resonance imaging (MRI), enable us to incidentally detect relatively small tumors in the anterior mediastinum. When an anterior mediastinal mass cannot be distinguished readily from other malignant tumors, a biopsy is indicated to establish a diagnosis prior to making any decision regarding therapy. Depending on the size and anatomic location of the mass, percutaneous needle biopsy, surgical or video-assisted approaches may be required. For resectable anterior mediastinal tumors compatible with grossly encapsulated thymoma, the tumor should be resected with all surrounding tissues. The question is, however, should a total thymectomy be performed additionally for such small thymoma when a lesion is diagnosed as a thymoma intraoperatively?

We hypothesized that limited thymectomy is not inferior to total thymectomy for treating stage I or II thymomas in terms of surgical outcome and postoperative complications.

At our institutes, thymoma resection without total thymectomy has been performed historically, mainly before 1997, depending on the tumor location and extension to the hemi thorax cavity, or because of co-morbidity. We carried out a retrospective study in order to evaluate the surgical outcomes of tumor resection without total thymectomy for early stage thymoma in terms of disease control, postoperative MG, and the incidence of multiple or recurrent thymoma.

Material and Methods

Patients

This study involved 79 patients with stage I or II thymoma. Subjects were selected from 123 consecutive patients with thymomas treated at the Tsukuba University Hospital and Tsuchiura Kyodo General Hospital, between April 1982 and October 2007. Clinical records, CT scan images, resected materials, and follow-up data were reviewed retrospectively.

The study population consisted of 35 male and 44 female patients. The mean age was 65 years ranging from 22 to 80 years. MG, when symptomatically suspected, was diagnosed and confirmed by neurological examination and serological test for antiacetylcholine receptor-binding antibody (ARAb). Preoperative MG was defined as MG diagnosed before thymoma surgery, whereas postoperative MG was defined as MG appearing only after thymectomy. Preoperative MG was diagnosed in 28 of the 79 patients (35.4%). The mean tumor size measured in the resected materials was 5.2 cm in maximal diameter, ranging from 1.5 to 18.0 cm. All 123 of the thymoma cases were classified using the Masaoka staging system [5] (Table 2) and the application of the WHO classification [4] (Table 1). In each case, three pathologists evaluated postoperative pathological findings by reviewing hematoxylin-eosin stained sections from paraffin-embedded blocks without any knowledge of the patients' clinical features. In the end, there were 79 cases

which had 81 thymoma lesions, because 2 cases of multiple thymoma were included in the study according to the pathologic findings. The results of the Masaoka stagings were stage I in 25 patients, and stage II in 54. The WHO pathologic subtypes were type A in 6 patients, type AB in 16, type B1 in 16, type B2 in 29, and type B3 in 11. Others were lipofibroadenoma (one case), and undetermined because of sample deterioration (2 cases).

Although all the cases had undergone complete thymoma resection, macroscopically and microscopically, postoperative radiotherapy was performed in 24 patients (30.4%) in this study. All the patients who had received postoperative radiotherapy, were diagnosed as Masaoka stage II, pathologically. The indication criteria for postoperative radiotherapy were based on the surgeon's subjective assessment of the risk of recurrence. In radiotherapy, the tumor bed as the target volume and the portal arrangement were determined with CT scanning taking surgical and pathologic findings into consideration. Antero-posterior opposing portals or an anterior portal and 6 or 10 MV X-rays were used. The target dose was 1.8 or 2.0 Gy per fraction with five fractions per week, with a mean total dose of 48.0 Gy ranging from 40.0 to 50.4 Gy.

Subjects were divided into two groups depending on the operation modes. One was the Total Thymectomy Group of 61 patients, in which complete tumor resection, including total thymectomy, was performed through a median sternotomy (Fig 1a). Extended en bloc thymectomy including the surrounding tissue of the anterior mediastinum was performed in 27 cases of co-existing MG in this

group. There was one case of co-existing pure red cell aplasia (PRCA) and lung cancer with thymoma. This patient was treated with total thymecomy and right upper lobectomy of the lung through a median sternotomy, and categorized into the Total Thymectomy Group. The other group was the Limited Thymectomy Group of 18 patients, in which complete tumor resection including the surrounding thymic tissue was carried out in 15 cases and resection including involved ipsilateral thymic lobes in 3 patients (Fig 1b,1c). In this group, operation was performed through a median sternotomy in 7 cases, through an antero-lateral thoracotomy in 7, and through a parasternal mini-thoracotomy in 4. Limited thymectomy was indicated mainly before 1997 depending on tumor location and extension to the hemi thorax cavity. Additionally, it was indicated in the presence of co-morbidity in 2 cases, involving lung cancer and dilated cardiomyopathy respectively. Only one patient with preoperative MG was in this group. Although he had been diagnosed as MG 23 years before the limited surgery, no MG symptoms were observed at operation, and he had not been on any medication. The characteristics of individual cases in the Limited Thymectomy Group are shown in Table 3.

Postoperative follow-up was done with annual chest radiograph and CT scan when necessary. Overall survival and disease-free survival rates were estimated by the Kaplan-Meier method setting the date of surgical intervention as the starting point. The mean ± standard deviation (SD) follow-up interval was 76.6 ± 58.4 months in patients with stage I or II thymoma.

Statistical analysis

Data were shown as mean ± SD. The patients' characteristics and results were compared using the student *t* test and χ^2 test to determine the level of significant difference between the two groups. The log-rank test was used to compare Kaplan-Meier survival curves. The statistical data were processed using the statistical program SPSS version 16.0 (Chicago, GA: SPSS). Differences were considered significant at $p < 0.05$.

Results

The characteristics of the patients in each of the 2 groups are shown in Table 4. Gender, age, maximal diameter of the tumor, and the population of Masaoka staging and WHO subtypes did not differ between the two. Twenty seven patients were diagnosed MG preoperatively with high serum ARAb of 39.8 ± 36.1 (median 30.0) nmol/l in the Total Thymectomy Group, whereas only one, that is patient number 13 in Table 3, had preoperative MG in the Limited Thymectomy Group, as described in the material and methods. The values of serum ARAb were not available for the Limited Thymectomy Group. There were no significant differences in the ratio of the number patients who had undergone radiotherapy and in the radiation doses received between the two groups. Follow-up intervals were longer in the Limited Thymectomy Group than in the Total Thymetomy Group, because limited thymectomy had been performed either before 1997, or indicated for complicated cases. Table 5 summarizes the surgical outcomes with the two groups.

Postoperative MG

Only one case in the limited Thymectomy Group, number 14 in table 3, in which there had been no preoperative MG, showed ptosis, 9 years after the limited surgery. This symptom lasted for a year and remitted spontaneously without any medication.

Multiple lesions of thymoma

Two patients (3.3%) in the Total Thymectomy Group presented synchronous multiple lesions (Table 5). Each patient had two thymoma lesions without preoperative MG which were recognized by chest CT scan preoperatively. One case had two thymoma lesions of WHO type B2 measuring 8.0 cm and 5.0 cm in diameter. The other case had type A and type B2 WHO subtypes, measuring 1.8 cm and 3.0 cm in diameter respectively.

New lesions in the remnant thymus

There was one case in the Limited Thymectomy Group showing a metachronous lesion after surgery (case number 18 in Table 3), while there were none in the Total Thymectomy Group (Table 5). The first surgery for this case was complete tumor resection, including the surrounding thymic tissue, via a right antero-lateral thoracotomy. The lesion, measuring 3.5 cm in maximal diameter, had a capsule infiltrated by tumor cells microscopically, and was diagnosed as Masaoka stage II and type B3 of the WHO subtype. The surgical margin was evaluated as tumor free by pathologists, and postoperative radiotherapy was not performed. A new mediastinal tumor appeared near the surgical margin 84 months after the first surgical intervention. Tumor resection was completed with total thymectomy and partial resection of the right upper lobe of the lung and the pericardium

through a median sternotomy. The histologic findings were very similar to those of the previous surgery, type B3 WHO subtype, and therefore it was suspected to be local recurrence. Postoperative radiotherapy of 40 Gy was performed after the second surgery. This patient is now alive without recurrent thymoma 117 months after the second surgery.

Survival

None of the patients involved in this study died of thymoma progression, though three cases did die in the Total Thymectomy Group. The causes of death were lung cancer, cerebrovascular disorder, and head injury, respectively.

Overall survival rates at 10 years for the Limited Thymectomy Group, the Total Thymectomy Group, and all patients were calculated as 100%, 82.0%, and 88.7%, respectively. Disease free survival rates at 10 years for the Limited Thymectomy Group, the Total Thymectomy Group, and all patients were calculated as, 85.7%, 82.0%, and 84.0%, respectively. Overall survival of the limited Thymectomy Group was not statistically different from that of the Total Thymectomy Group (p = 0.17, hazard ratio = 0.022; 95% confidence interval = 0.00 – 345). And disease free survival of the Limited Thymectomy Group was not statistically different from that of the Total Thymectomy Group (p = 0.64, hazard ratio = 0.569; 95% confidence interval 0.059-5.498).

Discussion

MG appears at a rate of 1.5-28％ after thymoma resection without preoperative MG [14]. Ito et al. demonstrated that the incidence of postoperative MG cases in the Total Thymectomy Group (5.0 %) was equivalent to that after tumor resection without total thymectomy (4.2%). Their data and ours indicate that limited thymectomy did not lead to more postoperative MG [14,15]. Although it is unclear whether or not re-operation to remove remnant thymus for treating postoperative MG is always valid, completion thymectomy has been shown to be effective in solving this rare complication in selected cases [16]. Therefore, it would be worthwhile performing extended completion thymectomy to treat postoperative MG through median sternotomy if the early stage thymoma were initially resected by limited thymectomy which was not through median sternotomy [16].

When MG is complicated with thymomas, extended total thymectomy should be performed in order to treat both the MG and thymoma. On the other hand, a high value of serum ARAb may imply the autoimmunization against self-antiacetylcholine receptors even though MG was not apparent symptomatically and this may result in the occurrence of postoperative MG. Additionally, Nakajima et al have suggested that a positive preoperative ARAb might be a predictor for postoperative MG [17]. Therefore every patient with thymoma should have their ARAb measured

before surgery, and total or extended thymectomy would be better for resecting thymomas with high values of serum ARAb even for the patients without MG symptoms. Finally the appearance of postoperative MG may depend on the serum ARAb rather than on the mode of thymectomy [14,17].

As for the co-morbidity of thymoma, Kondo et al reported that PRCA were associated with 2.6% of thymoma patients [18]. A case of stage II thymoma complicated with PRCA and lung cancer was treated by total thymectomy in this study. The efficacy of total thymectomy for PRCA is controversial whether thymoma exists or not [19], thus it is unclear whether limited thymectomy should be avoided for thymoma cases with PRCA or not.

Multiple thymoma is very rare, but is well-known and there are many case reports [7,20,21]. Its occurrence rate was reported as 2.2% [7]. In this study, there were 2 cases with multiple thymomas diagnosed preoperatively in the Total Thymectomy Group. Out of our 123 thymoma cases of all stages, there were only these 2 cases（1.6％）. It is controversial whether cases of multiple thymomas represent multi-centric origin or intra thymic metastasis [7], and therefore the cases with multiple thymic tumors should be selected for total thymectomy because of their undefined nature. All multiple tumors in these cases could be detected by CT scan preoperatively. Multiple thymoma lesions may appear in the remnant thymus after limited thymectomy, so that long time follow-up is mandatory. If a tumor appears after limited surgery, completion of total thymectomy should be carried out. It is the same strategy of postoperative MG as mentioned above [16].

Regarding the case of ours which showed a secondary lesion, patient number 18 in Table 4, the surgical margin at the first intervention was evaluated as tumor free microscopically. It is possible that there were micro satellite lesions near the main tumor, so this could have been a case of so-called intra-thymic metastasis [7]. Generally, WHO type B2 and B3 tumors display aggressive behavior compared with type A, AB, and B1 tumors in terms of invasiveness, postoperative survival, and tumor recurrence [3]. The histologic subtype of this secondary lesion was evaluated as WHO type B3, which is the most invasive subtype in thymoma [2,3] and resistant to radiotherapy [1]. Accordingly, it would be better to avoid limited thymectomy for WHO type B3 tumors. However, it is unlikely for this to be diagnosed preoperatively by needle biopsy in every small lesion or for diagnosis to be made intraoperatively by frozen section. Therefore, it would be better to complete total thymectomy afterwards in cases where in the end there is a pathological diagnosis of WHO type B3 tumor.

Because no one involved in this study died of thymomas, the long-term results were evaluated by the 10-year disease free survival rate (recurrence rate) by comparison with previous reports. The postoperative recurrence rate for early thymomas, treated with total thymectomy, has been reported as 0-30% [5,8,10-12,22-26]. In these cases, the majority of recurrences were local, and distant metastasis was rare, particularly following the resection of non-invasive or microscopically invasive thymoma [26]. We had a case that showed a secondary lesion in the Limited Thymectomy Group

(number 18 in Table 4), at 84 months after the first treatment. In this study, the 10-year disease free survival rate and the recurrence rate of the Limited Thymectomy Group were 85.7% and 5.6% respectively, and were equivalent to the rates shown in previous reports [5,8,10-12,22-26]. Total thymectomy is not statistically superior to limited thymectomy in terms of disease free survival at 10 years.

Postoperative radiotherapy after total thymectomy as a means of preventing local recurrence of early stage thymomas has not been recommended [10,11,27], except for in a few reports [23]. While there were 55 cases who had not received postoperative radiotherapy in this study (Table 6), there was only one recurrent case (number 18 in Table 4). The recurrence rate was 1.8% of all the cases and it made no statistical difference whether postoperative radiotherapy was performed or not. Moreover, 12 patients, who had not received postoperative radiotherapy in the Limited Thymectomy Group, showed the same or lower recurrence rate (8.3%) when compared with other reports in which resection was accomplished by means of total thymectomy [5,8,10-12,22-26]. These facts suggest that postoperative radiotherapy may not be necessary even after limited thymectomy cases of an early stage.

This study has several limitations. First, it involved a limited number of consecutive cases at two institutions. Second, because of its retrospective nature, treatment was not carried out according to the protocol. Third, there may have been case selection bias. Whether or not

patients received limited thymectomy or total thymectomy was based at least partly upon surgeon preference.

This study focused on the mode of thymectomy used in order to perform complete resection of stage I or II thymoma by analyzing surgical outcome in terms of disease free and overall survival, post-operative onset of MG, and the incidences of the multiple lesions. To conclude, limited thymectomy avoiding total thymectomy can be indicated for stage I or II thymomas. Recently, an increasing number of relatively tiny lesions in the anterior mediastinum have been detected by means of computed tomography of the chest. For these lesions, complete resection can be done by thoracoscopic surgery or through a mini-thoracotmy. Moreover, the problems of postoperative MG or a second tumor in the remnant thymus can be resolved by completion (extended) of total thymectomy via a median sternotomy.

Further investigation by means of a randomized controlled prospective study should be carried out to determine whether or not limited thymectomy or total thymectomy will be appropriate for early stage thymomas. To answer this question, a clinical trial entitled “Phase II Study of Thymomectomy for Thymoma Localized in the Thymus” is ongoing by the Japanese Association for Research on the Thymus. It may take more than 10 years to obtain satisfactory answers.

Conflict of interest statement

None declared.

Figure legends

Fig 1. Schemas showing resection modes for thymomas in this study as indicated by dotted lines. (a) total thymectomy, (b) complete tumor resection including the surrounding thymic tissue, and (c) resection of ipsilateral thymic lobe. (b) and (c) are put into Limited Thymectomy Group. T: thymoma.

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