Thoracic Cancer ISSN 1759-7706

ORIGINAL ARTICLE

Surgical management of locoregionally recurrent thymoma

Byungjoon Park*, Joon Suk Park*, Hong Kwan Kim, Yong Soo Choi, Kwhanmien Kim, Young Mog Shim & Jhingook Kim

Department of Thoracic and Cardiovascular Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Keywords
Extrapleural pneumonectomy; recurrent thymoma; surgery.

Correspondence
Jhingook Kim, Department of Thoracic and Cardiovascular Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Irwon-dong, Gangnam-gu, Seoul 135-710, Korea.
Tel: +82 2 3410 3483
Fax: +82 2 3410 6986
Email: jkimsmc@skku.edu

Received: 18 July 2011;
accepted: 17 August 2011.

doi: 10.1111/j.1759-7714.2011.00072.x

*These authors contributed equally in this manuscript.

Abstract

Objectives: There is no standard treatment for recurrent thymoma, but treatment is usually palliative therapy. For this article, we retrospectively reviewed our experiences to examine the efficacy of surgical treatment and the extent of adequate resection.

Methods: From 1997 to 2007, 15 patients underwent surgical resection for locoregional recurrence of thymoma in the Samsung Medical Center. The tumors at the initial resection were B1 in two patients, B2 in six, B3 in three and C in four according to the World Health Organization histological classification. Complete resection was achieved in 12 patients with pleurectomy (n = 11) or extrapleural pneumonectomy (n = 1).

Results: There was neither perioperative mortality nor significant immediate postoperative morbidity. After discharge, chest computed tomography scans were evaluated after a minimum of 6 months and the median follow-up duration was 45 months. At the time of writing, 10 patients had survived with (n = 5) or without (n = 5) rerecurrence (3-year survival = 84.0%). Survival was significantly superior in patients with complete resection compared with those with incomplete resection ($P = 0.008$).

Conclusions: Surgical resection could be considered in patients with locoregionally recurrent thymoma because it can be performed safely and offers a chance of long-term survival to some patients. To achieve complete resection, more extended surgery must be considered for multiple pleural metastases.

Introduction

Thymoma is one of the most common tumors in the mediastinum, especially in adults. Distant metastasis is relatively rare, but locoregional invasion or pleural dissemination often happens. Surgical resection is recommended as a standard treatment. However, even after complete resection, recurrence rates range from 30% to 50%.[1] In these patients with locoregional recurrence, there is no standard treatment, and they have been managed in a palliative manner.

However, a few recent studies have shown that surgical resection of recurrent tumors could be helpful for some patients.[2–5] In these studies the 5-year survival ranged from 30% to 50% and emphasized the achievement of complete resection.

Still, the benefit of surgery for recurrent thymoma is not clear, and the potential candidate of repeated resection has not been identified. Furthermore, because recurrence is often manifested as pleural dissemination, it is very difficult to determine the extent of re-resection.

In this article, we retrospectively review our overall experiences to discuss the efficacy of surgical treatment, in an attempt to discover the optimal surgical strategy, including the adequate extent of resection for patients with recurrent thymoma.

Methods

From January 1995 to December 2007, 249 patients underwent thymectomy for thymoma in the Samsung Medical Center (SMC).

Table 1 Patients' demographics

	Re-resection group	Non-surgical group	*P*
Number	15	13	
Mean age (range)	44 (23~63)	56 (35~78)	0.04
Sex ratio (M : F)	7:8	6:7	0.78
WHO class			0.14
B1	2 (13%)	0 (0%)	
B2	6 (40%)	2 (15%)	
B3	3 (20%)	2 (15%)	
C	4 (27%)	9 (70%)	
Masaoka stage			0.12
I & II	2 (13%)	2 (16%)	
III	10 (67%)	7 (54%)	
IV	0	4 (30%)	
Unidentified	3 (20%)	0	

WHO, World Health Organization

Twenty patients had locoregional recurrence after complete resection. Seven of them underwent subsequent repeated resection for recurrence, and the other 13 received non-surgical treatments. The reasons for deciding against re-resection were as follows: poor physical condition in two cases; refusal of treatment by the patient in four; patient reluctance to undergo repeated resection in seven cases led to non-surgical treatment such as chemotherapy and/or radiotherapy. These patients undergoing non-surgical treatment were older than those that underwent surgical treatment ($P = 0.04$) and were more likely to have a World Health Organization (WHO) type C tumor, yet statistically this was not significant ($P = 0.14$) (Table 1).

There also were eight more patients who had undergone an initial thymectomy at other hospitals, then had surgery for recurrent thymoma in our institution. Therefore, 15 patients underwent surgical resection of locoregionally recurred thymoma and were evaluated in this study (Fig 1).

After the second operation, we routinely performed chest computed tomography (CT) every 3 months for the first year and every 6 months thereafter. Recently, positron emission tomography (PET)/CT scan was added to the systemic assessment of patients. Collection of data was obtained by reviewing medical records and additional data was obtained by telephone contact with patients or their family members. All data were completely obtained without loss.

All statistical analyses were performed using PASW 17.0 (SPSS Inc., Chicago, IL, USA). The χ^2 test was used to assess differences of tumor characteristics between patients who had a relapse and those who had not. Survival curves were estimated by the Kaplan–Meier product limit method and were compared by the log–rank test.

Results

Of the 15 patients who underwent repeated resection, seven were male and eight were female. The mean age of patients at the time of recurrence was 43.7 years, ranging from 23 to 63. WHO histological classifications of the tumors were B1 in two patients, B2 in six, B3 in three and C in four. Ten patients had Masaoka stage III tumor, and two patients each had stage I and II. In three patients that underwent the initial operation in other hospitals, data for tumor stage could not be obtained (Table 1). After initial resection, one patient had adjuvant chemotherapy, six had radiotherapy, and one had both. The median interval between the initial resection of the thymoma and detection of recurrent disease was 26.4 months, ranging from 7 to 121.

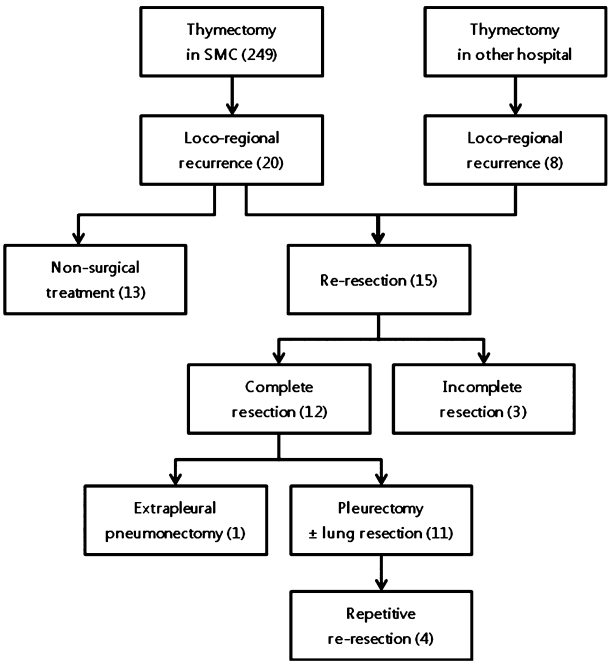

Figure 1 Patient enrollment and treatment. A total of 15 patients received re-resection; 12 patients underwent complete resection, including one extrapleural pneumonectomy, 11 pleurectomy with or without lung resection. Four patients received repetitive re-resection.

Repeated resections were carefully designed for each individual patient based on preoperative radiological examination, which included PET and CT. Sites of recurrence in patients with re-resection are shown in Table 2. Surgery was

Table 2 Sites of recur in re-resection group

Recurrence site	Number
Parietal pleura	6
Solitary	1
Multiple	5
Visceral pleura & lung	4
Solitary	2
Multiple	2
Pleura & diaphragm	5

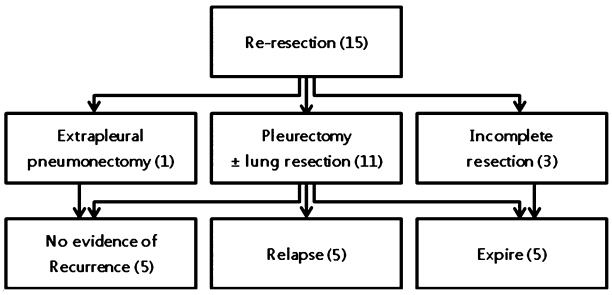

Figure 2 One patient who underwent extrapleural pneumonectomy and five patients who received pleurectomy with or without lung resection showed no evidence of recurrence. All three patients who had incomplete resection died during follow up.

performed only if all the recurrent lesions were considered to be resectable, and the extent of surgery was decided by the individual surgeon, considering patient's general condition and findings in the surgical field. Pleurectomy was generally selected for pleural nodules if a sufficient resection margin could be secured. In the case that the metastasis was disseminated through the entire pleura and the involved lung could not be saved, more extensive resections including extrapleural pneumonectomy (EPP) were also considered, depending on the physical condition of the patient and possibility of complete resection. If the lung, diaphragm or pericardium was also involved, combined resection and reconstruction was also performed.

As a result, complete resection was achieved in 12 patients, including one patient with EPP. Among these 12, only three had single or a few nodules which could be removed by simple pleurectomy or wedge resection of the lung. The others had multiple lesions in the pleural space or lung. Combined lung resections included seven wedge resections and two lobectomies. The patient who underwent EPP had type B3 tumor initially, and recurrence was manifested as miliary tumor dissemination through the entire pleura. However, this patient was a young man, 35 years old, with a good preoperative condition, and we decided to perform EPP.

Of the three patients with incomplete resection, two had unexpected diffuse multiple pleural metastases and it was impossible to remove all the disseminated nodules. However EPP could not be performed considering their old age and relatively poor physical condition. These two patients received adjuvant chemotherapy after re-resection. The other patient had mediastinal tumor extension, and heart invasion was found during tumor dissection; adjuvant radiotherapy was performed after the operation.

There were one case of chylothorax related to pleurectomy and one case of prolonged air leak over 2 weeks related to combined lobectomy. However, there were neither serious complications nor early mortalities after the operations.

Median follow-up was 45 months, ranging from 15 to 96. At the end of follow up, five patients, including the one that underwent EPP, were radiologically disease free, and another five were alive but had disease relapse. The other five patients, including all the three with incomplete resection, had another recurrence and died of tumor-related causes (Fig 2). The 3-year overall survival and disease-free survival were 84.0% and 46.7%, respectively, after repeated resection in the patients with surgical treatment of recurrent thymoma.

The patients with complete resections had statistically better survival rates compared to the patients who had incomplete resections ($P = 0.008$, Fig 3).The types of adjuvant therapy after the second surgery and tumor histology by WHO classification had no significant influence on survival.

Chemotherapy was recommended as a second line therapy for all the patients with unresectable relapse. Among the 13 patients undergoing non-surgical treatment for recurrent thymoma, six patients had chemotherapy, and another one patient had both chemotherapy and radiotherapy. The last six refused any further treatment. During the follow up, 10 eventually had multiple tumor metastases to other organs, such as bone, liver, brain, and spine. In the other three, the disease progressed despite radiation or chemotherapy. There was a statistically significant difference in survival between the patients undergoing non-surgical treatment and those undergoing surgical treatment (P = 0.007, Fig 4).

Discussion

There are certain difficulties in carrying out research on the treatment of recurrent thymoma: i) the patient population of recurrent thymoma is too small to have enough statistical power; ii) thymoma usually shows indolent progression and it is very difficult to manage patients for long-term follow up; iii) patients undergoing surgical treatment for recurrent thymoma usually have a better general condition and more limited disease compared to those having non-surgical treatment; iv) the indication for repeated resection is ambiguous. Therefore the role of surgery in recurrent thymoma largely

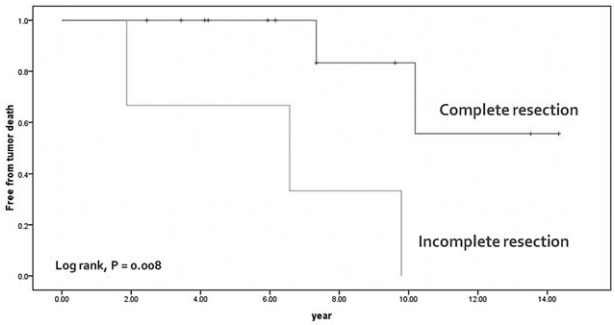

Figure 3 Overall survival differences associated with complete resection.

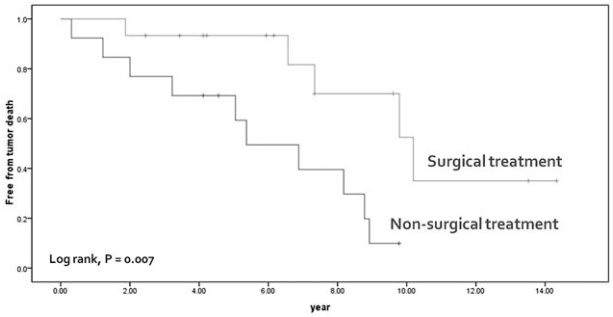

Figure 4 Overall survival differences between surgical group and non-surgical group.

depends on the surgeon's experiences and patient's positive consent to surgery. In the current study, four patients refused to receive any kind of treatment and seven chose to have non-surgical treatment.

There are several reports regarding surgical treatment of recurrent thymoma (Table 3).[1–8] Some authors agree on the surgical treatment of a repeated resection, reporting favorable outcomes after repeated resection with 5-year overall survival of 48% to 77%. However, the recurrence rate has been as high as 80% in some groups. Authors have also emphasized the importance of complete resection for favorable results. On the other hand, there is some opinion against surgery for recurrent thymoma. Haniuda *et al*. studied 15 patients who underwent re-resection, and the complete resection rate was 27%. Five-year and 10-year survival were 47% and 35%, and it was proposed that reoperation should not be attempted.

Our recent reports regarding the prognosis of surgically-treated thymoma suggested the importance of complete resection; prognosis was also closely related to the Masaoka stage of the thymoma, and a carefully designed treatment strategy for each patient.[9,10] In the current study, we observed encouraging results after repeated resection of locoregionally recurrent thymoma with 3-year survival of 84% using various surgical approaches, with no serious morbidity or mortality. On the other hand, most patients with locoregional recurrence who did not have surgical treatment, for various reasons, eventually experienced tumor progression or distant metastasis. We also observed that achievement of complete resection is crucial for a good outcome. This study included re-resection for four patients with thymic carcinoma (WHO type C), which has a very poor prognosis compared to other types of tumor. We tried re-resection because all of these patients had confined locoregional recurrence without evidence of distant metastasis, and it seemed that complete resection would be achieved. Even though two patients eventually had another recurrence after the re-resection, all of these patients survived more than 3 years. We therefore think that re-resection could be indicated for type C disease just as it is for other types, if complete resection seems possible.

To achieve complete resection, it is important to control pleural dissemination, which is the most common form of recurrence after surgery, accounting for 75% of all recurrences. In a recent review on surgical treatment for recurrent thymomas by Lucchi *et al*. re-resection for recurrent thymoma was feasible even for patients with multiple pleural metastases.[11]

Considering the results of previous reports and our study, it can be said that surgery plays a significant role in the treatment, not only in initial thymoma, but also in recurrent thymoma; and complete resection is most important for the best prognosis. Therefore the most important concern in the surgery of recurrent thymoma is deciding the extent and method of resection. The major issue in the role of surgery for recurrent thymoma would be pleural metastasis. Gross tumors can be removed by pleurectomy only, but that may not be sufficient as there is always the possibility of leaving a residual microscopic tumor behind. Therefore in the case of pleural metastasis, surgeons have to choose whether they will do a pleurectomy only and closely follow up the patient with or without adjuvant treatment, or do a more extensive resection, including pleuropneumonectomy or extrapleural pneumonectomy. In selecting the scope of surgery, the results reported by Wright *et al*. in 2006 on pleuropneumonectomy and Ishikawa *et al*. in 2009 on extrapleural pneumonectomy in stage IVa patients, were encouraging.[12,13] They observed

Table 3 Studies on surgical treatment of recurrent thymoma

Author (year)	Surgery	Complete resection (%)	5 years/10 years survival (%)	Conclusion
Blumberg *et al*. (1995)[1]	13	n/s	65/–	Surgery recommended
Ruffini *et al*. (1997)[2]	16	62	48/24	Surgery recommended
Regnard *et al*. (1997)[3]	28	68	51/43	Surgery recommended
Haniuda *et al*. (2001)[6]	15	27	47/35	Surgery not recommended
Ciccone and Rendina (2005)[4]	16	n/s	64/44	Surgery recommended
Okumura *et al*. (2007)[5]	22	82	–/70	Surgery recommended
Lucchi *et al*. (2009)[7]	20	n/s	43/26	Surgery recommended
Margaritora *et al*. (2011)[8]	30	73	77%/–	Surgery recommended

n/s, not stated.

relatively good survival and excellent local control of tumors with acceptable risk after these extensive resections. In our study, we performed extrapleural pneumonectomy in a young male patient with good physical performance who had miliary pleural dissemination. He is still alive without any evidence of recurrence 38 months later. On the other hand, seven out of eight patients who had multiple nodules in the pleural space and were treated with pleurectomy had another recurrence despite complete resection being achieved. Additionally, in our hospital, extrapleural pneumonectomy was successfully performed in six patients with stage IV thymoma, without surgical mortality and 16.7% of recurrence (1 out of 6) after a median follow up of 30.6 months. Considering these facts, we should take a more aggressive approach to patients who have unconfined pleural dissemination keeping in mind that extrapleural pneumonectomy is one of the most effective therapeutic options for patients with sufficient functional ability to undergo extensive surgery.

Our study has obvious limitations. First, as mentioned above, the patient population was small. We had only 28 cases of locoregional recurrence of thymoma for a 12-year period. So it was very difficult to compare the results of repeated surgery with those of non-surgical treatment, and to compare the efficacy of various surgical approaches. Second, indications of adjuvant therapy were not consistent during the study period. Generally, adjuvant chemotherapy was administered for patients with type B2 or more aggressive disease, and radiation was done for patients with Masaoka stage III or more. Cisplatin plus paclitaxel or etoposide were usual combination regimens. However, these indications often were not followed. Finally, patients in the non-surgery group were older and had more type C tumors, although there was no statistical difference. This could somewhat influence the result. A case–control study with sufficient patient population might be needed to resolve these problems.

In conclusion, surgical resection could be considered preferentially for patients with locoregionally recurrent thymoma, because it can be performed with acceptable safety and can offer a chance of long-term survival for some patients. To achieve complete resection, more extended surgery must be considered in patients with multiple pleural metastases.

Disclosure

No authors report any conflict of interest.

References

1 Blumberg D, Port JL, Weksler B *et al*. Thymoma: a multivariate analysis of factors predicting survival. *Ann Thorac Surg* 1995; **60**: 908–13; discussion 914.

2 Ruffini E, Mancuso M, Oliaro A *et al*. Recurrence of thymoma: analysis of clinicopathologic features, treatment, and outcome. *J Thorac Cardiovasc Surg* 1997; **113**: 55–63.

3 Regnard JF, Zinzindohoue F, Magdeleinat P *et al*. Results of re-resection for recurrent thymomas. *Ann Thorac Surg* 1997; **64**: 1593–8.

4 Ciccone AM, Rendina EA. Treatment of recurrent thymic tumors. *Semin Thorac Cardiovasc Surg* 2005; **17**: 27–31.

5 Okumura M, Shiono H, Inoue M *et al*. Outcome of surgical treatment for recurrent thymic epithelial tumors with reference to world health organization histologic classification system. *J Surg Oncol* 2007; **95**: 40–4.

6 Haniuda M, Kondo R, Numanami H *et al*. Recurrence of thymoma: clinicopathological features, re-operation, and outcome. *J Surg Oncol* 2001; **78**: 183–8.

7 Lucchi M, Davini F, Ricciardi R *et al*. Management of pleural recurrence after curative resection of thymoma. *J Thorac Cardiovasc Surg* 2009; **137**: 1185–9.

8 Margaritora S, Cesario A, Cusumano G *et al*. Single-centre 40-year results of redo operation for recurrent thymomas. *Eur J Cardiothorac Surg* 2011; [Epub ahead of print].

9 Kang MW, Lee ES, Jo J *et al*. Stage III thymic epithelial neoplasms are not homogeneous with regard to clinical, pathological, and prognostic features. *J Thorac Oncol* 2009; **4**: 1561–7.

10 Kim HK, Choi YS, Kim J *et al*. Type B thymoma: is prognosis predicted only by World Health Organization classification? *J Thorac Cardiovasc Surg* 2010; **139**: 1431–5 e1.

11 Lucchi M, Mussi A. Surgical treatment of recurrent thymomas. *J Thorac Oncol* 2010; **5**: S348–51.

12 Wright CD. Pleuropneumonectomy for the treatment of Masaoka stage IVA thymoma. *Ann Thorac Surg* 2006; **82**: 1234–9.

13 Ishikawa Y, Matsuguma H, Nakahara R *et al*. Multimodality therapy for patients with invasive thymoma disseminated into the pleural cavity: the potential role of extrapleural pneumonectomy. *Ann Thorac Surg* 2009; **88**: 952–7.