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Is it valuable and safe to perform reoperation for recurrent thymoma?

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Abstract

A best evidence topic in thoracic surgery was written according to a structured protocol. The question addressed was whether it is valuable and safe to perform reoperation for recurrent thymoma. Altogether, more than 500 papers were found using the reported search, of which 15 represented the best evidence to answer the clinical question. The authors, journal, date and country of publication, patient group studied, study type, relevant outcomes and results of these papers are tabulated. This paper includes 1 level 1a study and 15 level 2b studies. The operative mortality was reported in six studies, ranging from 0 to 13.3%, and the operative morbidity in five studies, ranging from 0 to 32.1%. Most patients suffering from operative mortality (5/5) and morbidity (16/19) had myasthenia gravis. One meta-analysis demonstrated improved rates of long-term overall survival in patients with recurrent thymoma who were treated surgically compared with those treated non-surgically. Ten studies showed better survival after surgical treatment than after non-surgical treatment with the difference being statistically significant in 4 of them. Two studies reported that the prognosis in patients with complete reresection was comparable with that of patients without recurrence. One study found that patients with a thymus-related syndrome improved after re-resection. Another two studies revealed that debulking surgery for recurrent thymoma was associated with poorer survival and worse outcomes than both complete resection and non-surgical therapy. From the papers identified in our search, we can conclude that reoperation can be performed with acceptable morbidity and low mortality in appropriately selected patients with locally and/or regionally recurrent thymoma. Both survival and thymus-related syndromes are improved if the recurrence is surgically resected when compared with other medical treatments. Debulking surgery should be limited to those few selected patients in whom other treatment options are not available. In addition, morbidity and mortality most commonly occur in association with myasthenia gravis, and hence medical control of this should be optimized prior to reoperation.

Keywords: Review • Thymoma • Recurrence • Surgery

INTRODUCTION

A best evidence topic was constructed according to a structured protocol. This is fully described in the *ICVTS* [1].

THREE-PART QUESTION

In patients who [have recurrent thymoma], is [reoperation] safe in terms of [postoperative convalescence] and valuable in terms of [oncological outcome]?

CLINICAL SCENARIO

A 49-year old woman underwent a complete thymectomy for thymoma via a unilateral video-assisted thoracoscopic surgery approach 3 years ago and her postoperative course had been uneventful. Now, she presents with a new well-circumscribed 1.5-cm nodule which was incidentally found on the follow-up CT scan. It is located on the right costal pleura, and is suspected to be a pleural recurrence of the thymoma. Her therapeutic options include surgical resection, radiotherapy and/or chemotherapy. On discussion with the patient, she expresses concerns regarding whether surgical resection is a safe option and whether it is superior to other treatments. You resolve to check the literature yourself.

SEARCH STRATEGY

Search strategy from 1990 to 2014 using the PubMed interface for Medline [thymoma] AND [recurrence] AND [surgery].

SEARCH OUTCOME

A total of 502 papers were found using the above search strategy. From these, 18 papers were identified that were deemed most appropriate to address the set scenario. Because Marulli *et al*. [2] and Rea *et al*. [3] shared the same series, the results were collated and

Table 1: Best evidence papers

Author, date, Journal and country Study type (level of evidence	Patient group	Outcomes	Key results	Comments
Sandri *et al.* (2014), J Thorac Oncol, Italy [7] Retrospective cohort study (level 2b)	Study period: 2001–2013 From three hospital centres	OS from initial thymectomy	5-year survival rates (94.8%) and 10-year survival rates (71.7%); *P*-value is not available	The analysis failed to identify any significant differences in terms of outcomes between surgery and CT/RT, even if a positive trend was observed in patients with intrathoracic disease treated with surgery with respect to patients treated with CT/RT
	Locoregional recurrence (62); distant (19) Surgery (61) Non-surgery (20): [CT/RT (14), no treatment (2), missing (4)]	5-, 10-year survival	Surgery: 70.2 and 54.1%, non-surgery: 64.3 and 46.9%; (*P* = 0.19)	
		DFS from recurrence	5-year DFS (73.6%) and 10-year DFS (48.3%); *P*-value is not available	
		5-, 10-year DFS	Surgery: 100 and 80.0%, non-surgery: 60.5 and 46.4%; (*P* = 0.23)	
		OS from recurrence of patients with intrathoracic recurrence	5-year survival rates (70.6%) and 10-year survival rates (56.0%); *P*-value is not available	
		5-, 10-year survival of patients with intrathoracic recurrence	Surgery: 61.5 and 52.7%, non-surgery: 72.4 and 55.7%; (*P* = 0.12)	
Hamaji *et al.* (2014), Ann Thorac Surg, Japan [8] Meta-analysis (level 1a)	Eleven studies were identified between 1950 and 2013	5-year OS after initial thymectomy	The combined 5-year OS risk difference was 0.34 [0.21, 0.48]	This meta-analysis showed significant differences in the rates of 5- and 10-year OS after thymectomy and in 5-year OS after recurrence, favouring surgically managed patients. Surgical resection may be associated with improved long-term survival and should be considered for patients with recurrent thymoma
	5-year OS from the date of recurrence was calculated in 8 articles and from the date of initial thymectomy in 7 articles; 10-year OS from thymectomy was available in 6 articles	10-year OS after initial thymectomy	The combined 10-year OS risk difference was 0.47 [0.24, 0.71]	
		5-year OS after recurrence	The combined 5-year OS risk difference was 0.44 [0.26, 0.62]	
		Publication bias	Lack of significant publication bias	
Imai *et al.* (2013), Surg Pract, Japan [9] Retrospective cohort study (level 2b)	Study period: 1986–2006 Local recurrence (10); metastasis (10) Surgery (8) Non-surgery (12)	The median relapse-free survival	27.5 months (range: 5–136 months)	Reoperation for recurrent thymoma might give a moderate response rate and improve survival Including details about each patient; high reliability
		5-year survival	Surgery: 54.7%, non-surgery: 34.7%; *P*-value is not available	
Hamaji *et al.* (2012), Ann Thorac Surg, USA [10] Retrospective cohort study (level 2b)	Study period: 1956–2009 Locoregional recurrence (28); distant (2) Surgery (20) Non-surgery (10)	Progression-free survival and median survival after recurrence	Progression-free survival: 68 months (1–497 months); median survival: 53.5 months (0.2–497 months)	Surgical management was associated with prolonged survival and improved progression-free interval
		5-year survival	Surgery: 74.7%, non-surgery: 0; (*P* = 0.0002)	
		Therapeutic-specific survival	Multivariate analysis: only surgical management (*P* = 0.0038) associated with improved survival	
Bae *et al.* (2012), J Thorac Oncol, Korea [11]	Study period: 1986–2009	OS after recurrence	5-year survival rates (59.7%) and 10-year survival rates (33.2%)	The complete reresection group had better survival after recurrence than the

Continued

Table 1: (*Continued*)

Author, date, Journal and country Study type (level of evidence	Patient group	Outcomes	Key results	Comments
Retrospective cohort study (level 2b)	Local recurrence (6); regional (24); distant (5)	5-year survival	Surgery: 77.0%, non-surgery: 49.1%; *P*-value is not available	non/incomplete reresection group and had comparable survival after initial resection of thymoma to the patients without recurrence
	Surgery (15) Non-surgery (26)	5-year survival after recurrence	Complete reresection: 90.9%, non/incomplete reresection: 44.7; ($P = 0.014$)	Including details about each patient; High reliability
		5-, 10- and 15-year survival after initial resection	Complete reresection: 91.7, 91.7 and 91.7%, without recurrence: 90.7, 86.5 and 82.7%; ($P = 0.618$)	
		Operative mortality	None in 30-day; during adjuvant CT, 2 patients died of pancytopenia	
		Operative morbidity	3/15, 20% [chylothorax (1) and prolonged drainage (2)]	
		CT adverse events[a]	25% (grade 4), 18.8% (grade 3), 31.2% (grade 2)	
Margaritora *et al.* (2011), Eur J Cardiothorac Surg, Italy [12]	Study period: 1972–2008	Long-term survival	Debulking: 25%; medical treatment: 35%; *P*-value is not available	Debulking surgery is not recommended for the treatment of recurrent thymoma
Retrospective cohort study (level 2b)	Locoregional recurrence (42); distant (1)	5-year survival	Complete resection: 91%, debulking: 31%; ($P < 0.001$)	
	Surgery (30) Non-surgery (13)	Operative mortality	None	
		Operative morbidity	8/30, 27% 7 patients had MG	
		RT/CT adverse events[a]	2 cases of toxicity: [oesophageal toxicity (grade 2) and haematological toxicity (grade 2)]	
			1 patient died of respiratory failure	
Marulli *et al.* (2011), Eur J Cardiothorac Surg, Italy [2]	Study period: 1980–2009	DFS	Overall 10-year DFS rate was 74%	The surgical treatment of recurrence led to a significantly better survival in comparison with medical treatments
Retrospective cohort study (level 2b)	From four Italian institutions	10-year survival rate from the first intervention	Surgery: 75%, medical treatment: 13%; ($P < 0.0001$)	
	Intrathoracic (27) Extrathoracic (13) Both (3)			
	Surgery (24) Non-surgery (19)			
Yano *et al.* (2011), Interact CardioVasc Thorac Surg, Japan [13]	Study period: 1994–2009	OS	5-year survival (73.3%) and 10-year survival (25.1%)	There was no difference in OS in those with or without resection
Retrospective cohort study (level 2b)	Pleura (21), pulmonary (1), retroperitoneal lymph node (1), local recurrence (1)	5-year survival	Surgery: 83.3%, non-surgery: 66.7%; ($P = 0.423$)	
	Surgery (12) Non-surgery (12)	RT/CT adverse events	1 patient died due to radiation pneumonitis and 1 patient died of acute	

Continued

Table 1: (*Continued*)

Author, date, Journal and country Study type (level of evidence	Patient group	Outcomes	Key results	Comments
			leukaemia during chemotherapy	
Lucchi *et al.* (2009, J Thorac Cardiovasc Surg, Italy [14]	Study period: 1980–2006	Actuarial survival rates from the resection of pleural recurrence	5-year survival (43.1%) and 10-year survival (25.8%)	Repeat operation on patients with pleural thymoma recurrences is feasible and safe
Retrospective cohort study (level 2b)	Pleura (20)			
	Surgery (20)	Actuarial survival rates from the initial resection	10-year survival (66%) and 20-year survival (34.3%)	
		Operative mortality	None	
		Operative morbidity	3/20, 15% [bleeding (1) and prolonged air leaks (2)]	
		Thymus-related syndrome	Remission (5), improved (6), stable (3), worsened (1)	
Okumura *et al.* (2007), J Surg Oncol, Japan [15]	Study period: 1957–2002	10-year survival rates following initial resection	Surgery: 70%, non-surgery: 35%; (P = 0.002)	Reresection for recurrent thymoma is considered to be an effective and acceptable option of treatment
Retrospective cohort study (level 2b)	Mediastinum (7), pleura (16), lung (8), chest wall (1)	Operative mortality	None	
	Surgery (22) Non-surgery (45)			
Evoli *et al.* (2002), Neurology, Italy [16]	Study period: 1972–2001	5-year survival after thymectomy	Surgery: 100%, non-surgery: 75%; P-value is not available	Reoperation has proved effective in prolonging survival
Retrospective cohort study (level 2b)	Locoregional recurrence (17); distant (1)	5-year survival after recurrence	Surgery: 85.7%, non-surgery: 25%; P-value is not available	Including details about each patient; High reliability
	Surgery (10) Non-surgery (8)			
Haniuda *et al.* (2001), J Surg Oncol, Japan [17]	Study period: 1963–1999	OS from the time of recurrence	5-year survival (37.1%) and 10-year survival (15.9%)	Reoperation should not be attempted for all patients with recurrent thymoma, because the effect of subtotal resection for severe pleural recurrence is disappointing
Retrospective cohort study (level 2b)	Surgery (15) Non-surgery (9)	5-year survival	Surgery: 40%, non-surgery: 33%; (P = 0.08)	
		Operative mortality	2/15, 13% (bleeding and respiratory failure due to pneumonia) both patients had MG	
		Operative morbidity	None	
Regnard *et al.* (1997), Ann Thorac Surg, France [18]	Study period: 1956 –1995	OS	5-year survival (51%) and 10-year survival (43%)	Reresection can be recommended in selected patients
Retrospective cohort study (level 2b)	Local (7); regional (15); distant (5); thoracotomy scar (1)	5-year survival	Complete resection: 64%, incomplete resection: 25%; (P = 0.08)	Postoperative morbidity and mortality were quite high, especially in myasthenic patients
	Surgery (28)	Operative mortality	3/28, 11% (respiratory failure, pneumonia and haemoptysis due to bronchoarterial fistula all patients had MG	
		Operative morbidity	9/28, 33% [pneumonia (3), respiratory failure requiring a tracheal intubation (7), pulmonary embolism (1), myocardial infarction (1)] All patients had MG	
Ruffini *et al.* (1997), J Thorac Cardiovasc Surg, Italy [4]	Study period: 1974–1993	OS from the time of recurrence	5-year survival (48%) and 10-year survival (24%)	Total resection of the recurrent tumour offers the

Continued

Table 1: (*Continued*)

Author, date, Journal and country Study type (level of evidence	Patient group	Outcomes	Key results	Comments
Retrospective cohort study (level 2b)	Local (11); regional + distant (17) Surgery (16) Non-surgery (14)	Survival	Complete resection of the recurrent tumour ($B = 1.85$; $P = 0.03$) worse 5- and 10-year survival in debulking surgery than exclusive radiotherapy	best chance of long-term survival
Blumberg *et al.* (1995), Ann Thorac Surg, USA [19] Retrospective cohort study (level 2b)	Study period: 1949–1993 Local (17), distant (5), local + distant (3) Surgery (13) Non-surgery (12)	OS 5-year survival 5-year survival RT adverse events	5-year survival (65%) Surgery: 85%, non-surgery: 45%; ($P = 0.001$) Surgery + RT: 85%, non-surgery: 42% Some grade of lung fibrosis in all cases, no severe functional impairment	Resection of recurrence resulted in a favourable 5-year survival, which was similar to that of patients with complete resection who did not have recurrence

[a]According to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.
RT: radiotherapy; CT: chemotherapy; MG: myasthenia gravis; OS: overall survival; DFS: disease-free survival.

analysed as a single series. The cases in Ruffini *et al.* [4], Urgesi *et al.* [5] and Maggi *et al.* [6] were from the same institution, and therefore, the latter two studies were excluded to avoid duplication. This left a final selection of 15 papers which are presented in Table 1.

RESULTS

No randomized trial evidence was found, and all studies were retrospective case series, except for one meta-analysis. The operative mortality rate was reported in 6 studies, ranging from 0 to 13.3%, and the operative morbidity rate in 5 studies, ranging from 0 to 32.1%.

Sandri *et al.* [7] compared patients receiving surgery versus those receiving chemo/radiotherapy for recurrence, and found no difference between the groups in terms of rates of overall survival (OS) after initial thymectomy and disease-free survival after treatment for recurrence ($P = 0.19$ and $P = 0.23$, respectively). However, in patients with intrathoracic recurrence, a trend was observed for better survival in patients treated with surgery compared with patients treated with radio and/or chemotherapy alone, although the difference fell short of statistical significance ($P = 0.12$).

Hamaji *et al.* [8] reviewed the literature available before the year 2013 and developed evidence-based recommendations. The authors demonstrated improved long-term survival in patients who were treated surgically compared with those treated non-surgically, including 5- and 10-year OS after initial thymectomy (risk ratio: 0.34 and 0.47) and 5-year OS after recurrence (risk ratio: 0.44).

In 2012 Bae *et al.* [11] reported that there was no postoperative 30-day mortality after reresection but 3 cases of minor morbidity, including 1 of chylothorax and 2 of prolonged chest drainage for more than 7 days. Regarding survival after initial resection, they found that in patients with complete reresection, their survival was comparable with that of patients without recurrence ($P = 0.618$). The same result was also found by Blumberg *et al.* [19].

Margaritora *et al.* [12], in a retrospective review of their 40-year experience, reported 5-, 10- and 15-year OS rates of 64, 51 and 43%, respectively, for patients with recurrence. In surgically managed patients, the postoperative mortality was nil, whereas postoperative complications occurred in 8 patients (27%), 7 of whom had myasthenia gravis (MG). The 5-year survival was significantly better when reoperation was performed for recurrence (91%, $P = 0.001$).

Marulli *et al.* [2] reviewed the survival outcomes of 43 patients treated at four different Italian institutions for recurrent thymoma. Surgical treatment of recurrence led to a significantly better 10-year survival rate from the first intervention in comparison with medical treatments alone (75 vs 13%, $P < 0.0001$).

Lucchi *et al.* [14] targeted patients with pleural thymoma recurrences and 15 of 20 patients had a thymus-related syndrome. After a median follow-up of 98 months after reresection, the majority of patients who had a thymus-related syndrome experienced symptomatic improvement and only 1 patient worsened. The authors reported no mortality and an acceptable percentage of morbidity ($n = 3$, 13.6%). Similarly, Evoli *et al.* [16] studied recurrent thymoma in patients with MG and their results proved that reoperation appeared effective in prolonging survival (87.5 vs 25%, *P*-value not provided).

Haniuda *et al.* [17] reported that of the 15 patients receiving reoperation, 2 died during the postoperative course. Both patients had developed severe MG paralleling the recurrence of thymoma, and 1 patient died of bleeding and the other of respiratory failure due to pneumonia. The authors reported no operative morbidity. On survival analysis, reoperation was found to have no beneficial effect on post-recurrence survival ($P = 0.08$).

Regnard *et al.* [18] investigated patients undergoing reoperation for recurrent thymoma and found that 3 (11%) patients died during the postoperative course. All 3 had MG. The overall

morbidity rate was 33%, but the morbidity rate among myasthenic patients was 60%. Survival seemed better after complete resection than after incomplete resection, but the difference fell just short of statistical significance ($P = 0.08$).

Two studies addressed the effectiveness of debulking surgery in recurrent thymoma. Margaritora *et al*. [12] revealed a worse long-term survival in patients who underwent debulking surgery than in those who received medical treatment (25 vs 35%). Ruffini *et al*. [4] showed that 5- and 10-year OS rates were better in patients receiving radiotherapy alone than in those receiving debulking surgery, although the absolute differences were not reported.

CLINICAL BOTTOM LINE

Although recurrent thymoma after initial thymectomy is rare, the evidence suggests that reoperation can be performed with acceptable morbidity and low mortality in appropriately selected patients with locally and/or regionally recurrent thymoma. Both survival and thymus-related syndromes are improved if the recurrence is surgically resected when compared with other medical treatments. Debulking surgery should be limited to those few selected patients where other treatment options (such as radiotherapy) are not available. In addition, most instances of morbidity and mortality during reoperation occur in association with MG, and hence medical control of this should be optimized prior to reoperation.

Conflict of interest: none declared.

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