The Role of Surgery in the Management of Thymoma: A Systematic Review

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The literature describing multimodal treatment of thymomas consists almost exclusively of retrospective case series. We have used a systematic review to investigate the role of surgery in the management of thymomas. The use of surgery as the sole therapeutic maneuver in thymoma depends on the stage considered. Subtotal resection followed by adjuvant treatment may prolong survival, but studies are equivocal. Some data supports re-resection of recurrent thymoma in the belief that survival will be prolonged. Approaches to thymectomy other than sternotomy in early stage thymoma are technically sound, but long-term outcome data are lacking.

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Thymomas are very rare tumors of the thymus gland. Recent reports have demonstrated incidence estimates of 0.15 per 100,000 person years in the United States [1]. Thymomas are typically slow-growing tumors that spread by local extension. Metastases are usually confined to the pleura, pericardium, or diaphragm, whereas extrathoracic metastases are uncommon [2, 3]. Thymomas are also known to have a propensity for late recurrence even after complete resection [4, 5].

Histopathologically, thymomas are primary tumors of thymic epithelial cells [6]. Thymic carcinoids and thymic carcinomas are also tumors of thymic epithelial cells. Thymic carcinoids are histopathologically and clinically quite different from thymomas [7–9]. On the other hand, the distinction between thymomas and thymic carcinomas has been somewhat controversial. Thymomas are for the most part considered cytologically benign. Thymic carcinoma is meant to describe that category of thymic epithelial cell tumors with malignant cytologic features [6, 10]. The World Health Organization histopathologic classification of thymomas is the most recent, and it has been validated in several studies [11–13]. It describes thymoma and thymic carcinoma along a continuum. Studies have demonstrated markedly decreased survival for thymic carcinoma compared with thymoma [14–19]. Thymic carcinoma may therefore be treated as a distinct pathologic and prognostic entity.

The most widely used staging system for thymomas is that published by Masaoka and colleagues [20] in 1981. Their publication describes thymomas in terms of local extension of the tumor (see Table 1). It has been shown to predict survival in several studies [11, 21–27]. Investigators have begun to describe the molecular changes that confer differing degrees of invasiveness and their relationship to the Masaoka staging system [28–30]. The Masaoka staging system is a particularly useful tool in studies of thymoma, given the rarity and histopathologic heterogeneity of this tumor.

Patients with thymomas present with symptoms related to involvement of local structures or as asymptomatic findings on imaging of the chest. The most common presenting symptoms for thymomas are dyspnea, chest pain, cough, and symptoms of myasthenia gravis [31–34]. Superior vena cava syndrome is not an unusual presentation for the patient with stage III or IV thymoma [35, 36]. Thymomas are frequently associated with paraneoplastic phenomena and as a consequence that can have quite varied presentations [37–39].

The incidence of thymomas is increased in patients with myasthenia gravis (MG). Approximately 10% of patients with MG will have a thymoma [40–42]. Some authors have proposed that MG is an adverse prognostic factor for patients undergoing resection of thymoma because of the increased perioperative mortality, typically secondary to myasthenic respiratory failure [34]. Other authors have argued that MG is a positive prognostic factor, possibly because of earlier diagnosis of thymoma [11, 16, 43]. Some case series have shown that the presence of MG has no effect on survival from thymoma, and the authors attribute this finding to improvements in the perioperative management of MG [3, 24, 44–47]. The perioperative care of the MG patient undergoing thymectomy has been the subject of a recent review [48].

The treatment of thymomas involves combinations of surgery, radiation, and chemotherapy. The determination of which combination is chosen is reflected mostly by the stage of the disease. In the case of invasive disease, radiation therapy is often used as adjuvant treatment. Chemotherapy has been used in the induction and adjuvant setting. The interested reader may refer to a systematic review on the role of radiation and chemotherapy in thymoma by Hejna and colleagues [49].

Numerous reviews on the surgical treatment of thymomas have been published [50–65]. The reviews present either a single-centre case series or provide opinions

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Table 1. Masoaka Staging System

Stage	Description
I	Macroscopically encapsulated and no microscopic capsular invasion
II	Macroscopic invasion into adjacent tissue (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

based on a nonsystematic analysis of the literature. We believe that an evidence-based recommendation on the role of surgery in thymoma has not yet been published. Any review of thymoma will be complicated by its rarity, confusion surrounding its histopathologic classification, and its propensity for late recurrence. We have developed an evidence-based recommendation on the role of surgery in thymoma using reproducible inclusion and exclusion criteria. It was not the aim of our study to address the evidence supporting the role of radiation therapy in the management of thymoma. However, we have included literature that purports to describe the adequacy of surgery alone in the management of thymoma, and this inevitably leads to outcome comparisons with patients who have received adjuvant radiation. We have not addressed the role of chemotherapy either in the induction or adjuvant setting.

We have sought to answer several questions related to surgical intervention. First, is there evidence to support the use of surgery as the sole therapeutic maneuver in the management of thymoma? Second, does incomplete resection for thymomas (so-called debulking surgery) increase overall survival? Third, is surgery a useful modality in the treatment of recurrent thymoma? We have also reviewed the various surgical approaches used to achieve resection of thymoma. We articulated our treatment recommendations using the framework put forth by Guyatt and colleagues [66]. These are shown in Table 2.

Material and Methods

Literature Search Strategy

A search of the MEDLINE database was performed with the keywords "thymoma" and "surgery" using the following limits: English language only, humans only, and published after 1981 (the year in which the Masaoka staging system was published). The Cochrane database, the National Guideline Clearinghouse (http://www.guideline.gov/index.asp) and abstracts from the 2004 and 2007 American Association of Thoracic Surgery meetings were also searched for English language abstracts or manuscripts related to thymomas. The final literature search was performed on June 26, 2007.

Inclusion Criteria

We included any prospective, randomized trial dealing with thymoma regardless of language publication. We included any English language retrospective series describing surgical intervention in patients with thymoma, including those describing patients undergoing re-resection for thymoma recurrence. We included articles in which the focus of the article was a description of one or more operative approaches to thymectomy in thymoma.

Exclusion Criteria

The following were excluded from analysis:

- Case series of fewer than 40 patients (unless the article dealt specifically with minimally invasive surgical approaches to thymectomy).
- Articles in which the focus was basic science, pathology, biochemistry, or radiology.
- Articles describing chemotherapy protocols or the response to radiation (if no description of the effects of surgery on survival was given).
- Articles with no 5-year survival data and those in which the Masaoka stage was not used.
- Articles dealing solely with thymic carcinoids or thymic carcinoma and those in which thymoma, thymic carcinoma, or other mediastinal tumors were pooled in outcome determinations, or a combination thereof.
- Articles in which myasthenia gravis was the focus of the study. This led to exclusion of articles in which thymomas were present in the series of myasthenic patients, but in which the outcome measures focused on myasthenic phenomena.
- Letters and editorials reporting trial data.

Results

Literature Search Results

Our search strategy yielded 616 abstracts. Using our selection criteria we recovered a single prospective, randomized controlled trial and 23 retrospective series with between 40 and 1,093 patients. The patients in these studies were subjected to various combinations of surgery, radiotherapy, and chemotherapy. Patients within

Table 2. Levels of Treatment Recommendations

Level A: Methods strong, results consistent—multiple randomized clinical trials, no heterogeneity
A1: Effect clear—clear that benefits do (or do not) outweigh risks
A2: Effect equivocal—uncertainty whether benefits outweigh risks
Level B: Methods strong, results inconsistent—randomized clinical trials, heterogeneity present
B1: Effect clear—clear that benefits do (or do not) outweigh risks
B2: Effect equivocal—uncertainty whether benefits outweigh risks
Level C: Methods weak—observational studies
C1: Effect clear—clear that benefits do (or do not) outweigh risks
C2: Effect equivocal—uncertainty whether benefits outweigh risks

Table 3. Overall Survival Effects of Complete Resection in Thymoma, Retrospective Case Series Evidence

Author (yr) (n = No. of patients)	Stage: n	Interventions (n)	Mt	Mb	5-yr	10-yr	Effects of Complete Resection on Survival	Comments
Kondo [18] (2003) (n = 1,093)	I: 522 II: 247 III: 204 IVA: 73 IVB: 35	Stage I, II: all completely resected. Stage III, IV: total resections (196), subtotal resection (50), biopsies (24). Various radiation &/or chemotherapy regimens.	NR	NR	I, 100% II, 95% III, 89% IVA, 71% IVB, 53%	NR	For stages III and IV thymoma: 5-yr survival for total resection 92.9% vs 64.4% for subtotal resection ($p < 0.00001$)	Study data from a questionnaire sent to 185 institutes and replies from 115 (62%). Thus, potential for reporting bias is large and survival results should be interpreted accordingly.
Mehran [68] (2002) (n = 42)	I: 24 II: 7 III: 11	Complete resection (32), subtotal resection (10), Radiation (16).	0	16	87.3%	81.4%	Degree of resection was not associated with overall survival.	Stages pooled for survival data. Of the 42 patients, 3 lost to follow-up, and only 1 death attributed to spread of thymoma.
Matsushima [27] (2002) (n = 47)	I: 2 II: 11 III: 18 IVA: 6	Complete resections (39), 8 subtotal resections (8), radiation (21), chemotherapy (2), chemoradiotherapy (7).	NR	NR	1, 100% II, 85% III, 68% IVA, 34%	NR	5-yr survival for Complete resection 81% vs 0% for subtotal resection ($p < 0.02$)	Invasion of the great vessels ($p < 0.0004$). Great vessels: aorta, vena cava, brachiocephalic vein.
Gawrychowski [22] (2000) (n = 40)	I: 7 II: 9 III: 17 IV: 7	Complete resection (21), subtotal resection (5), biopsy only (14), radiation (31), chemotherapy (0).	1	NR	I, 100% II, NR III, NR IV, 0%	I,100% II, NR III, NR IV, NR	5-yr survival for complete resection 100%, vs 40% for subtotal resection ($p < 0.0016$)	Single operative death from myocardial infection.
Moore [21] (2001) (n = 71)	I: 33 II: 16 III: 13 IV: 9	Complete resections (60) Subtotal resection (11) Radiation (20) Chemotherapy (2) Chemoradiotherapy (1)	1	20	88%	76%	5-yr survival for complete resection 95% vs 50% for subtotal resection ($p < 0.0001$)	Stages pooled for survival data. Single operative death from myasthenic respiratory failure.
Sonobe [88] (2000) (n = 72)	I: 32 II: 9 III: 15 IV: 16	Complete resections (56) Subtotal resections (7) Biopsies (9) Various combination of radiation and chemotherapy for stages II, III, and IV	0	NR	I: 97% II: 89% III: 88% IV: 65%	I: 83% II: 89% III: 78% IV: 32%	5-yr survival for complete resection 84% vs 64% for incomplete resection ($p = 0.0464$)	Survival effect of complete resection marginal. No statistically significant difference between incomplete resection and biopsy only on 5-yr survival.
Whooley [89] (2000) (n = 38)	I: 9 II: 6 III: 15 IVA: 4 IVB: 4	Complete resection (21) Subtotal resection (4) Biopsy (13) Chemotherapy (15) Radiation (27)	1		I: 75% II: 50% III/IV: 23%	18%	NR	1 perioperative mortality due to respiratory failure.

Table 3. (Continued)

Author (yr) (n = No. of patients)	Stage: n	Interventions (n)	Mt	Mb	5-yr	10-yr	Effects of Complete Resection on Survival	Comments
Sugiura [45] (1999) (n = 40)	II: 6 III: 17 IV: 7	Complete resections (27) Subtotal resections (4) Biopsies (9) Radiation (30) Chemotherapy (4)	0	6	II: 72% III: 75% IV: 69%	II: 72% III: 47% IV: 0%	10-year survival 70% for complete resection vs 20% for subtotal resection (p = 0.019)	In this series of 40 patients, pleura resected in 22 cases, lung in 12 cases, pericardium in 8 cases, SVC, or innominate vein in 5, phrenic nerve in 1, and chest wall in 1.
Okumura [25] (1999) (n = 194)	I: 78 II: 94 III: 56 IVA: 10 IVB: 6	Complete resections (172) Subtotal resections (22) Various combination of radiation and chemotherapy for stages II, III, and IV	NR	NR	NR	I: 99 II: 94 III: 88 IVa: 30 IVb: 0	Extent of resection not significant in multivariate analysis.	By multivariate analysis involvement of great vessels (brachiocephalic veins, SVC, aorta) was significant predictor of survival (p = 0.02).
Murakawa [90] (2000) (n = 140)	I: 64 II: 32 III: 28 IV: 16	Not described.	NR	NR	I: 91% II: 97% III: 68% IV: 69%	I: 80% II: 92% III: 54% IV: 60%	Not described	Authors excluded operative mortalities and did not report incidence.
Gripp [91] (1998) (n = 70)	I: 15 II: 18 III: 30 IVA: 5 IVB: 2	Complete resection (48) Subtotal resection (18) Biopsy (4) Radiation (25) Chemotherapy (3)			71%	58%	NR	Stage survival data pooled. Authors do not comment on survival effects of complete vs incomplete resection.
Regnard [3] (1996) (n = 370)	I: 135 II: 70 III: 83 IV: 19	Complete resections (260) Subtotal resections (30) Biopsies (17) Various combinations of radiation &/or chemotherapy in stages I, II, III and IV	5	21	NR	67%	10-yr survival with complete resection 76% vs 28% with subtotal resection ($p <$ 0.0001)	5 operative mortalities from cardiorespiratory and embolic causes. Resection of pleura &/or pericardium (139), lung (27) resections, 14 single phrenic nerve (14), innominate vein (17) SVC (3).
Yagi [70] (1996) (n = 41)	III: 34 IVA: 5 IVB: 2	Complete resection (22) Subtotal resections (16) Exploratory (3) Radiation, induction (11) Radiation, adjuvant (38) Chemotherapy, induction (1) Chemotherapy, adjuvant (2)	0	NR	III: 82% IVA: 67% IVB: 0	III: 66% IVA: 33% IVB: 0	Complete resection 5 year survival 94% vs incomplete resection 5 yr 35% ($p <$ 0.01)	In 41 patients, pericardium resected 21 times, lung 17, SVC or innominate vein in 12 and chest wall in 2.
Etienne [47] (1993) (n = 53)	I: 13 II: 13 III: 9 IV: 18	Complete resection (28) Subtotal resection (25) Biopsy (5)	1	NR	I: 100% II: 66% III: 33% IV: 17%	I: 75% II: 66% III: 33% IV: 11%	Complete resection 10-yr survial 69% vs incomplete resection 10-yr 20%	1 operative mortality in patient with myasthenia gravis. No analysis of subtotal resection versus biopsy only.

Table 3. (Continued)

Author (yr) (n = No. of patients)	Stage: n	Interventions (n)	Mt	Mb	5-yr	10-yr	Effects of Complete Resection on Survival	Comments
McCart [92] (1993) (n = 41)	I: 19 II: 2 III: 12 IVA: 2 IVB: 5	Complete resections (34) Subtotal resections (3) Biopsies (4) Radiation (13) Chemotherapy (1) Chemoradiotherapy (4)	2	10	I: 98% II: NR III: 59% IVA: NR IVB: NR	NR	5-yr survival for complete & subtotal groups combined 90% vs 50% for biopsy. ($p < 0.0002$)	2 operative mortalities: pneumonia (1), ischemic gut (1). Number of incomplete resections (3) to small for comparison with complete resection or biopsy only.
Maggi [11] (1991) (n = 241)	I: 133 II: 34 III: 53 IVA: 21	Complete resection (211) Subtotal resector (21) Biopsy (9) Radiation (18) Chemotherapy (6) Chemoradiotherapy (10)	7	NR	I: 89% II: 71% III: 72% IVA: 59%	I: 87% II: 60% III: 64% IVA: 40%	5-yr survival for complete resection 83.8% vs 71.7% for subtotal resection. ($p < 0.001$)	5 of the post operative mortalities were due to myasthenic crisis.
Nakahara [26] (1988) (n = 141)	I: 45 II: 33 III: 48 IV: 15	Complete resection (113) Subtotal resection (16) Biopsy only (12) Radiation (103) Chemotherapy (?)	NR	NR	I: 100% II: 92% III: 88% IV: 47%	I: 100% II: 84% III: 77% IV: 47%	5-yr survival for complete resection 97.6% vs 68.2% for subtotal resection ($p < 0.001$)	

Mb = number of operative morbidities; Mt = number of operative mortalities; n = number of patients; NR = not reported; 5-yr and 10-yr = 5-yr and 10-yr overall survival, respectively.

Table 4. Surgery as the Sole Modality in Thymoma, Retrospective Case Series Evidence

Author (yr) (n = No. of patients)	Stage: n	Interventions (n)	Mt	Mb	5-yr	10-yr	Analysis of Adequacy of Surgery Alone	Comments
Mangi [93] (2005) (n = 45)	III: 45	Complete resection (36) Incomplete resection (9) Radiation (38)			NR	43% 54%	No difference in survival with addition of radiation ($p = 0.41$)	10-yr survival 54% in surgery + radiation group vs 43% in surgery only group ($p = 0.41$). Seven patients did not receive radiation. No protocol to determined need for radiation.
Singhal [71] (2003) (n = 70)	I: 30 II: 40	Complete resection (70) Adjuvant radiation (23) Chemotherapy (0)	0	7	I: 94% II: 90%	NR	No difference in survival for surgery only vs surgery with radiation ($p = 0.32$)	No significant survival difference if stage II patients treated separately ($p = 0.72$) Authors conclude that complete margin-negative resection is sufficient treatment for both stage I and II thymoma.
Mangi [72] (2002) (n = 49)	II: 49	Complete resection (49) Radiation (14) Chemotherapy (0)	NR	NR	II: NR	II: 100%	No difference in 10-yr survival for surgery only vs surgery with radiation ($p = 0.87$)	Authors state that most stage II patients do not require adjuvant radiation therapy.

Mb = number of operative morbidities; Mt = number of operative mortalities; n = number of patients; NR = not reported; 5-yr and 10-yr = 5-yr and 10-yr overall survival, respectively.

Table 5. Effects of Subtotal Resection for Thymoma, Retrospective Case Series

Author (year) (n = No. of patients)	Stage: n	Interventions (n)	Mt	Mb	5-yr	10-yr	Effect of Subtotal Resection on Survival	Comments
Liu [94] (2006) (n = 43)	III: 22 IVA: 21	Subtotal resection (15) Biopsy (28)	0	NR	40%	NR	Subtotal resection survival 106 months vs 57.2 months for biopsy (p = 0.03)	Stage-specific survival not provided.
Kondo [18] (2003) (n = 1,093)	I: 522 II: 247 III: 204 IVA: 73 IVB: 35	Stage I/II: 100% had complete resection. Stage III, IV: total resections (196), subtotal resection (50), biopsies (24). Various regimens of radiation &/or chemotherapy.	NR	NR	I: 100% II: 95% III: 89% IVA: 71% IVB: 53%	NR	For stages III & IV: 5-yr survival for subtotal resection was 64.4% vs 35.6% for biopsy (p = 0.0028).	Study data from a questionnaire sent to 185 institutes and replies from 115 (62%). Potential for reporting bias is large and survival results should be interpreted accordingly.
Sugiura [45] (1999) (n = 40)	II: 16 III: 17 IV: 7	Complete resections (27) Subtotal resections (4) Biopsies (9) Radiation (30) Chemotherapy (4)	0	6	II: 72% III: 75% IV: 69%	II: 72% III: 47% IV: 0%	No significant difference between incomplete resection & biopsy only (p = 0.65)	
Regnard [3] (1996) (n = 307)	I: 135 II: 70 III: 83 IV: 19	Complete resections (260) Subtotal resections (30) Biopsies (17) Various regimens of radiation &/or chemotherapyin stages I, II, III, and IV	5	21	NR	67%	For stage III patients 10-yr survival with subtotal resection 29% vs 35% with biopsy only. (p = 0.85)	5 operative mortalities from cardiac, respiratory and embolic causes.
Maggi [11] (1991) (n = 241)	I: 133 II: 34 III: 53 IVA: 21	Complete resection (211) Subtotal resection (21) Biopsy (9) Radiation (18) Chemotherapy (6) Chemoradiotherapy (10)	7	NR	I: 89% II: 71% III: 72% IVA: 59%	I: 87% II: 60% III: 64% IVA: 40%	5-yr survival for subtotal resection 72% vs 40% for biopsy only ($p < 0.001$)	5 of the post operative mortalities were due to myasthenic crisis.
Nakahara [26] (1988) (n = 141)	I: 45 II: 33 III: 48 IV: 15	Complete resection (113). Subtotal resection (16). Biopsy only (12). Radiation (103). Chemotherapy (?)	NR	NR	I: 100% II: 92% III: 88% IV: 47%	I: 100% II: 84% III: 77% IV: 47%	5-yr survival for subtotal resection 68.2% vs. 25% for biopsy only ($p < 0.01$)	

Mb = number of operative morbidities; Mt = number of operative mortalities; n = number of patients; NR = not reported; 5-yr and 10-yr = 5-yr and 10-yr overall survival, respectively.

Table 6. Reoperation for Recurrent Thymoma, Retrospective Case Series Evidence

Author	Site of Recurrence (n)	Treatment for Recurrence (n)	Mt	Mb	Effect of Reoperation on Survival	Comments
Okumura [95] (2007) (n = 67)	NR	Complete resection (16) Subtotal resection (6) Nonoperative (45)	1	NR	10-yr survival for re-resection (n = 22) 70% vs 35% for no re-resection (n = 45) ($p = 0.002$)	1 mortality from myasthenic crisis. Recurrence site and treatment for non-operative group not specified.
Haniuda [76] (2001) (n = 24)	Pleural dissemination (22) Local (6) Distant metastases (5)	Complete resection (4) Subtotal resection (11) Radiation (14) Chemotherapy (0)	2	0	No survival difference between surgical treatment (n=15) and non-surgical treatment (n=9) of recurrence ($p = 0.08$)	2 operative mortalities in patients with severe myasthenia gravis
Regnard [75] (1997) (n = 28)	Pleural, pulmonary &/or pericardial dissemination (15) Surgical scar (1) Local (7) Distant metastases (2)	Induction chemotherapy (1) Complete resections (19) Subtotal resections (9) Radiation (16) Chemotherapy (2) Chemoradiation (1)	3	9	5-yr survival for complete resection 64% vs 25% subtotal resection not statistically significant. ($p = 0.08$)	3 operative mortalities had myasthenia gravis
Ruffini [4] (1997) (n = 30)	Local (11) Intrathoracic or extrathoracic dissemination (17)	Complete resection (10) Subtotal resection (6) Radiation (11)	NR	NR	5-yr survival for complete resection 72% vs 15% for subtotal resection. ($p = 0.008$)	8/10 completely resected patients had local recurrence.
Blumberg [33] (1995) (n = 25)	Local (17) Distant metastases (5) Local & distant (3)	Re-resections (13) Radiation (3) Chemotherapy (5) Chemoradiation (4)	NR	NR	85% 5-yr survival for surgery vs 45% for nonsurgical ($p < 0.001$)	12 of 13 patients treated surgically had local recurrence
Urgesi [96] (1992) (n = 21)	Local (7) Pleural dissemination (9) Local and pleural dissemination (5)	Complete resection (5) Subtotal resection (6) All 21 received radiation (adjuvant or only treatment)	NR	NR	Non-significant difference in 7-yr survival for surgical (74%) and nonoperative groups (65%)	

Mb = number of operative morbidities; Mt = number of operative mortalities; n = number of patients with recurrent thymoma; NR = not reported; 5-yr and 10-yr = 5-yr and 10-yr overall survival, respectively.

and between studies were very heterogeneous with respect to treatment protocols. Several small case series of between 1 and 22 patients were used in our discussion of surgical approaches to thymectomy.

Influence of Surgical Resection on Survival

The stage-specific survival, operative mortality and morbidity, and overall survival effects of surgical resection for thymomas from several retrospective studies [3, 11, 18, 21, 22, 25–27, 45, 47, 68, 70, 88–92] are shown in Table 3.

The studies described in Table 3 involved a wide range of treatment approaches, making it prohibitively difficult to correlate specific multimodality treatment regimens with survival. The types of treatment received by the patients in each study are nonetheless listed. Operative mortality was reported in 7 studies. In 3 studies (with a total of 151 patients) there were no operative mortalities. Operative mortality in the other studies was mostly due to myasthenic crisis and cardiac causes. For stage I, the 5-year survival ranged from 89% to 100% and the 10-year survival ranged from 87% to 100%. For stage II, the 5-year survival ranged from 71% to 95% and the 10-year survival ranged from 60% to 100%. For stage III, the 5-year survival ranged from 59% to 75% and the 10-year survival ranged from 47% to 88%. In the case of stage IVA disease, the 5-year survival ranged from 34% to 71% and the 10-year survival ranged from 30% to 40%. For stage IVB disease, only two studies reported the 5-year survival, and this ranged from 0% to 53%. The latter value of 53% was obtained from the study by Kondo and colleagues [18], which was in fact a questionnaire with a 62% response rate making it quite possible that substantial reporting bias is present.

Data on Surgery as the Sole Therapeutic Maneuver

The only prospective randomized trial was a study of 29 patients with completely resected stage I thymomas who were randomized to a group receiving no adjuvant treatment (n = 13) and a group receiving adjuvant radiation (n = 16). All patients underwent resection through a median sternotomy. The authors found no difference in 5-year and 10-year survival between the two groups. In addition, there was no recurrence or metastasis in either group [67].

The studies [71, 72, 93] summarized in Table 4 reveal that complete resection of thymoma is a statistically significant predictor of 5-year survival. This was seen to apply to stages I, II, and III. In several studies authors described resection of the pleura, lung, pericardium, and venous structures to achieve complete resection. In only two studies, the extent of resection was not a predictor of overall survival [25, 68]. In one of these, the authors found that invasion of the great vessels (ie, the aorta, vena cava, brachiocephalic vein) was the factor that predicted overall survival [25].

Only three retrospective series specifically focused on the role of surgery with or without adjuvant radiation; these are summarized in Table 4. They reveal that mortality in completely resected stage I and II thymoma is the same whether or not adjuvant radiation is added. In neither study was adjuvant chemotherapy used. A single study of stage III patients did not demonstrate a survival benefit to the addition of radiation therapy.

The Role of De-Bulking Surgery

Table 5 summarizes six retrospective series [3, 11, 18, 26, 45, 94] that have addressed the role of de-bulking surgery in thymoma. Four of the studies reveal improvement in overall 5-year survival of approximately 30% for the patient who undergoes subtotal resection. Two other studies demonstrate no survival difference when de-bulking was used.

The Role of Re-Resection for Recurrent Thymoma

Six retrospective case series [4, 33, 75, 76, 95, 96] dealing with the role of re-resection in recurrent thymoma are summarized in Table 6. These studies were heterogeneous with respects to the sight of recurrence. At one extreme, the series reported by Haniuda and colleagues [23] revealed that 92% of recurrences consisted of pleural dissemination, whereas the other the series reported by Blumberg and colleagues [33] had 68% of recurrences occurring locally. In three of the six series there is no survival advantage conferred by debulking. In the two series that do show a 5-year survival of advantage of approximately 40% to 50%, the patients who underwent resection were almost exclusively patients with local recurrence.

The Surgical Approaches to Thymectomy in Thymoma

No abstracts or articles describing approaches to thymectomy other than sternotomy were found, which had greater than 40 patients or provided 5-year survival data. No formal analysis of these articles was undertaken.

Comment

A significant limitation to generation of evidenced-based recommendations in the management of rare diseases is the paucity of prospective data on which to soundly base those recommendations. In the case of thymomas (with a single exception) all of the English language literature consists of retrospective case series with inconsistently applied treatment regimens. Notwithstanding the fact that surgeons may rarely encounter such diseases, treatment should be based on the best available evidence.

The role of thymectomy in nonthymomatous myasthenia gravis was the subject of a recent systematic review, but there are no other English language guidelines dealing with diseases of the thymus or thymectomy [69].

Completeness of resection is the most commonly cited statistically significant prognostic factor in thymoma. In the case of stage III disease, combinations of partial pleurectomy, pericardial resection, wedge resections of lung, lobectomy, pneumonectomy, resection of a single phrenic nerve, superior vena cava, and innominate vein surgeries have all been performed in series that have demonstrated improved survival for locally invading stage III disease treated with complete resection [21, 45, 70]. In a small number of cases, the survival benefit of

complete resection also extended to stage IV thymomas [3, 26, 70].

The effect of complete resection in most of the series we reviewed was approximately a 50% increase in survival at 5 years. However, it must be emphasized that while this increase in survival is impressive, it is derived entirely from unblinded, uncontrolled retrospective case series. In the framework put forth by Guyatt and colleagues [66], the recommendation to pursue maximally aggressive resection in thymoma would be one with a clear effect (of enhancing survival), but backed by methodological, weak evidence.

The Role of Surgery as a Sole Therapeutic Maneuver

Four studies specifically addressed the role of surgery as the sole therapeutic modality in the management of thymomas. Prospective evidence from a single, small randomized trial exists for uniquely surgical treatment of stage I thymoma with no need for adjuvant treatment [67]. Further retrospective case series support the use of surgery only in the management of completely resected stage I and II disease [71, 72]. A single study showed no survival benefit to adjuvant radiation in stage III thymoma [73]. In none of these series were decisions to radiate driven by protocol, and thus significant selection bias is likely present. This was not an analysis of the role of radiotherapy in thymoma and many have recommended radiotherapy for thymomas of stage II and higher [11, 24, 26]. A prospective, randomized multicenter trial on the use of adjuvant radiation in stage I and II thymoma would be worthwhile, but it would be hindered by slow patient accrual and the need for long-term follow-up [4, 5].

The Role of Debulking Surgery

The literature we have reviewed does not convincingly demonstrate that incomplete resection (ie, debulking) increases survival in cases of invasive thymoma. Some authors report no survival advantage to debulking [18, 34, 45]. Others series have demonstrated approximately 30% increased 5-year survival with subtotal resection [11, 18, 26, 74]. Unfortunately, one of these studies is a questionnaire with a 62% response rate [18]. In addition, there is tremendous variability in the use of adjuvant treatments both within and between individual studies, making it impossible to draw sound conclusions on the role of debulking in thymoma. Debulking in thymoma is a surgical strategy for which the results are globally equivocal and the underlying data is very methodologically weak.

The Role of Re-Resection

Recurrence of thymoma after thymectomy is quite common. The largest reported series of 1,093 thymomas found recurrence rates for stages I, II, III, and IV were 0.9%, 4.1%, 28.4%, and 34.3%, respectively [18]. Series in which as much as 90% of the operative cases were because of local recurrence have shown that wherever possible re-resection improves survival [4, 33, 75]. Others surgeons have found that reoperation had no effect on survival or was no better than debulking [75, 76]. It is important to draw a distinction between local recurrences, to which virtually all of the survival benefit from re-resection applies, and intrathoracic pleural dissemination. Widely disseminated pleural disease is associated with a poor response to surgery.

From these data it would seem reasonable to consider re-resection of locally recurrent thymoma, but once again the data on which such a recommendation is based are methodologically weak. Recurrence of thymoma has been associated with very severe myasthenia gravis, and thus increased risk of operative mortality [75, 76].

Surgical Approaches to Thymectomy in Thymoma

In our literature review, there was not any 5-year survival outcomes reported for various surgical approaches to thymectomy for thymoma. Nonetheless, we chose to comment on this topic, as it is especially germane to the thrust of this article (ie, the role of surgery in the management of thymoma). The aim of surgery in thymoma is complete thymectomy as opposed to complete tumor excision, and this is supported by data demonstrating improved survival after complete thymectomy [34]. In all of the case series we have described thus far, median sternotomy was the most common surgical approach used.

Case reports attest to the possibility of performing thymectomy for stage I and II thymoma by video-assisted thoracoscopy [77–81]. The use of robotic surgery to resect stage I thymoma has recently been described [82]. Some authors have raised concerns about minimally invasive approaches to thymomectomy for thymoma, in particular capsular rupture with its risk of pleural spread [83]. In one series of 22 patients who underwent thymectomy for stage I thymoma, a patient (who may have been incorrectly assigned stage I disease) was reoperated on 3 years later for pulmonary thymoma metastases and was found to have recurrence along the pleural aspect of the utility thoracotomy scar [79].

Deeb and colleagues [84] have published articles on the role of transcervical thymectomy, which was studied in a select group of patients with suspected thymoma. Results in stage I and II were promising, but the authors did extend their incision to a sternotomy in 36% of the pathologic-proven thymomas.

Icard and colleagues [85] have recently demonstrated the technical feasibility of using a mini-sternotomy for complete excision of stage I and II thymomas. All patients had complete resection and the three stage II thymomas received adjuvant treatment. No data regarding regional recurrence or survival were provided.

Ohta and colleagues [86] have described resection of two stage I thymomas using an endoscopic approach in which the view of the mediastinum is maximized by elevating the thoracic wall using bilateral rib hooks. The authors claim that this approach has the advantage that dissection begins along the deep surface of the thymus and as a consequence early recognition of unexpected pericardial or great vessel involvement is facilitated. According to the authors, any such involvement would

Table 7. Evidence-Based Treatment Recommendations

Stage I
Complete surgical resection is sufficient treatment and should be followed by long-term follow-up.
C1: Methods weak, effect clear.
The VATS and transcervical approaches to thymectomy in stage I thymoma are technically sound and may be pursued by appropriately trained physicians. Long-term outcome data are lacking.
C2: Methods weak, effect equivocal
Stage II
Complete surgical resection is sufficient treatment for stage II thymoma and should be followed by long-term follow-up.
C2: Methods weak, effect equivocal
Minimally invasive techniques to thymectomy in stage II thymomas are experimental.
C2: Methods weak, effect equivocal
Stage III
The surgeon should strive to completely resect stage III thymomas as complete resection will increase survival.
C1: Methods weak, effect clear.
Subtotal resection followed by adjuvant treatment may be undertaken in the belief that it will prolong survival.
C2: Methods weak, effect equivocal
Stage III thymomas should be resected by a median sternotomy to achieve maximal exposure and maximally enable intraoperative macroscopic staging.
C2: Methods weak, effect clear.
Stage IV
Complete resection may be possible in rare and select cases and it may prolong survival.
C2: Methods weak, effect equivocal
Subtotal resection followed by adjuvant treatment may be undertaken in the belief that it will prolong survival.
C2: Methods weak, effect equivocal

precipitate conversion to sternotomy. A different endoscopic approach to extended thymectomy for thymoma has also been described using elevation of the sternum itself [87]. At the time of writing of this article, there exists insufficient data in the literature to make comments regarding the appropriateness of approaches to thymectomy in thymoma other than sternotomy, because objective assessments of outcome are lacking.

Although we have treated the topics addressed so far (ie, the extent of resection, adequacy of surgery alone, de-bulking, re-resection and minimally invasive thymectomy) as stand-alone questions, they are best evaluated within each of the thymoma stages. Table 7 lists the stage-specific treatment recommendations on the role of surgery in thymoma.

The evidence on which we based our recommendations is level V evidence (ie, retrospective uncontrolled case series). The sole exception is a small randomized, controlled trial of adjuvant radiotherapy in stage I thymomas. Nonetheless, this systematic review suggests that whenever possible, a complete resection of thymoma affords maximal survival advantage.

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