Surgical treatment of thymoma

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Objective: To describe experience with the surgical treatment of thymoma. **Design:** A retrospective study. **Setting:** A teaching hospital at the University of Ottawa. **Patients:** Over 25 years, 42 consecutive patients (22 men, 20 women) who had a thymoma requiring operation. **Interventions:** Thymectomy. **Outcome measures:** Age, sex, association with myasthenia gravis, presence of a paraneoplastic syndrome, extent of surgical resection, tumour size, histologic features of the tumour, clinical staging of the thymoma and short- and long-term outcome after surgery. **Results:** The mean (and standard deviation) age of the patients was 52.8 (12.5) years. Thirteen patients had myasthenia gravis. With respect to tumour staging, 24 patients had stage I, 7 had stage II and 11 had stage III disease. Three patients were lost to follow-up. Radiotherapy was used as an adjunct to surgical treatment in 83% of patients with stages II and III disease. Fifty-one percent of patients available for follow-up survived 175.1 months, and the cumulative 5- and 10-year overall survival rates were 87.3% and 81.4% respectively. Only 1 patient died of metastatic thymoma. Complete or partial remission of myasthenia gravis was seen in 10 (77%) affected patients. Mixed cellular histologic features and a tumour size of less than 115 cm^3 were more commonly seen with stage I disease. **Conclusions:** Thymomas are characterized by slow growth and prolonged survival even in patients with invasive disease as long as the tumour is resected completely and treatment is accompanied by radiotherapy.

Objectif : Décrire l'expérience du traitement chirurgical du thymome. **Conception :** Étude rétrospective. **Contexte :** Hôpital d'enseignement de l'Université d'Ottawa. **Patients :** Sur une période de 25 ans, 42 patients consécutifs (22 hommes, 20 femmes) atteints d'un thymome nécessitant une intervention chirurgicale. **Interventions :** Thymectomie. **Mesures de résultats :** Âge, sexe, lien avec la myasthénie grave, présence d'un syndrome paranéoplasique, étendue de l'exérèse, taille et caractéristiques histologiques de la tumeur, stade clinique du thymome et résultat à court et à long termes après la chirurgie. **Résultats :** L'âge moyen (et l'écart type) des patients s'établissait à 52,8 (12,5) ans. Treize patients étaient atteints de myasthénie grave. En ce qui concerne les stades de la tumeur, 24 patients avaient une tumeur du stade I, sept, une tumeur du stade II et 11, une tumeur du stade III. On a perdu trois patients au suivi. On a utilisé la radiothérapie comme traitement adjuvant de la chirurgie chez 83 % des patients atteints d'une tumeur des stades II et III. Cinquante et un pour cent des patients disponibles pour le suivi ont survécu 175,1 mois et les taux de survie globaux cumulatifs à 5 et à 10 ans s'établissaient à 87,3 % et 81,4 % respectivement. Un seul patient est mort à cause d'un thymome à métastases. On a constaté une rémission complète ou partielle de la myasthénie grave chez 10 (77 %) des patients atteints. Les caractéristiques histologiques cellulaires mixtes et une tumeur de moins de 115 cm3 étaient les plus courantes dans le cas de la maladie au stade I. **Conclusions :** Les thymomes sont caractérisés par la lenteur de la croissance et la survie prolongée même chez les patients atteints d'une maladie envahissante à condition que la tumeur soit réséquée complètement et que l'on conjugue la radiothérapie au traitement.

Thymomas are rare epithelial neoplasms of the thymus gland and are the most common tumours of the anterior superior mediastinum, comprising 20% to 30% of mediastinal masses in adults.[1] Thymomas grow slowly but eventually progress by invading surrounding structures or by distant metastases. The best treatment for thymoma remains surgical resection. The survival rate of patients has improved when the results of old published series are compared with recent data.[2–4] This is owing probably to refinement in the

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classification of thymomas, which now exclude thymic carcinoma, and to the use of adjuvant treatment in most patients with invasive disease. However, there is still discrepancy when assessing the prognostic role of such factors as myasthenia gravis,[4] the extent of surgical resection,[5] the value of adjuvant radiotherapy[6] or chemotherapy,[7] the prognostic value of the Masaoka staging system[8] and the role of tumour size. This study reports our experience with 42 consecutive patients with thymoma who underwent thymectomy to assess the role of this procedure and the prognostic values of patients' demographic and clinical characteristics.

Patients and methods

We reviewed the chart of all 42 patients (20 women, 22 men) operated on for thymoma at the Ottawa Hospital, between 1975 and 1999. The mean age was 53 years (range from 25–73 yr). The clinical records of each patient were reviewed to define the demographic attributes of the group, including age, sex, association with myasthenia gravis, association with a paraneoplastic syndrome, extent of surgical resection, size and histologic features of the tumour, clinical staging of the thymoma, and short- and long-term outcomes. All tumours were approached through a median sternotomy. However, in 4 patients who had a small, well-circumscribed tumour localized in the anterior superior mediastinum, a cervical approach was used to completely resect the thymus. As an estimate of size, we used the tumour volume calculated from length, width and height of the tumour obtained after resection. Thymomas were classified according to descriptions of Lewis and associates[8] as follows: predominantly epithelial, where epithelial cells constituted more than 66% of the tumour; predominantly lymphocytic tumours, where less than 33% of the cells were epithelial in origin; mixed lymphoepithelial thymomas, which were found in a proportion of approximately 33% to 66% respectively; and spindle cell thymomas, consisting of prominent fusiform cells in an arrangement of fascicles and whorls. Tumour invasiveness and clinical behaviour were classified according to the system devised by Masaoka and colleagues[9] as follows: stage I, macroscopically completely encapsulated; stage II, tumour with invasion into surrounding fatty tissue and mediastinal pleura; stage III, macroscopic invasion into the neighbouring organs such as pericardium, great vessels or the lung; stage IVa, pleural or pericardial dissemination; and stage IVb, hematogenous or lymphogenous metastases. Patients with stage IV disease were usually treated with chemotherapy and radiotherapy only, and were therefore outside the scope of this study.

Survival curves were plotted according to the Kaplan–Meier method. Differences in means were tested with Student's *t*-test. A Cox–Wermuth multivariate dependency graph was used to guide the interpretation of multivariate analysis. The calculations were made using S-Plus 2000 (*Guide to Statistics*, vol. 1, Data Analysis Products Division, Math Soft, Seattle, Wash.). Differences were regarded significant at a p value of less than 0.05.

Results

Thirteen of the 42 patients had myasthenia gravis (6 men, 7 women). Based on the Osserman classification, 1 patient presented with grade I myasthenia having purely ocular symptoms, 5 had grade II with mild generalized weakness, and 7 patients had grade III myasthenia with moderate generalized weakness. The median duration of symptoms of myasthenia before resection was 5.0 months (range from 1–120 mo). Preoperative plasmapheresis was carried out in 7 patients to reduce myasthenic symptoms, and repeated postoperatively in 2. All patients had a visible tumour on chest radiography. The diagnosis was established preoperatively in 3 out of 8 patients who had fine-needle aspiration biopsy. The patients with a negative aspirate and the remainder of the group underwent open biopsy through a parasternal incision without contamination of the pleural space. Additional findings at the time of operation included non-thymic malignancies, myositis, thrombocytopenia, neutropenia, erythematous rash, Coombs' positive hemolytic anemia, chronic lymphocytic leukemia, nephrotic syndrome with hypoalbuminemia, gastrointestinal candidiasis and muscular dystrophy (Table 1).

The surgical approach used for resection of the thymoma was median sternotomy in 38 patients and a cervical approach or thoracotomy in 4 patients. The extent of resection is reported in Table 2. The entire thymus and surrounding fatty tissue or adherent mediastinal structures was resected in all patients. Thirty-two patients had a complete resection of

Table 1

Clinical Presentation of 42 Patients Who Underwent Thymectomy for Thymoma

Presentation	Patients, no. (and %)
Abnormal chest radiograph	42 (100)
Myasthenia gravis	13 (31)
Superior vena caval syndrome	3 (5)
Associated malignant disease	7 (17)
Malignant melanoma	3
Colon cancer	2
Breast cancer	1*
Hodgkin's lymphoma	1
Chronic lymphocytic leukemia	1
Bone-marrow aplasia	1
Hypogammaglobulinemia	1
Coombs' positive hemolytic anemia	1
Gastrointestinal candidiasis and diarrhea	1
Myositis	1
Muscular dystrophy	1

*This patient also had colon cancer.

the thymoma, and 10 patients had an incomplete resection (6 microscopically and 4 macroscopically). There were no operative deaths. Postoperative complications included unsustained arrhythmia in 8 patients (19%), respiratory failure requiring temporary mechanical ventilation in 4 patients (10%), minor wound infection in 2 patients (5%), pneumonia in 1 patient (2.4%) and operative blood loss requiring transfusion in 1 patient (2.4%). Two patients with respiratory failure after operation had myasthenia gravis, but only 1 with stage III disease required preoperative plasmapheresis. Four patients had phrenic nerve palsy after resection of the ipsilateral nerve, none contributing to respiratory insufficiency postoperatively.

Six of 7 patients with stage II who had fixation of the tumour to the surrounding structures and 9 of 11 patients with stage III disease who had an incomplete resection received radiotherapy postoperatively. One patient presented with superior vena caval obstruction and received both radiotherapy and chemotherapy before operation with the objective of increasing the resectability of the tumour. The daily fractions of radiotherapy ranged from 1.8 to 2 Gy with an average target dose of 45 Gy (range from 30–50 Gy). The complications of radiotherapy included pneumonitis (1), esophagitis (1) and pulmonary fibrosis (1). In 1 patient a midthoracic esophageal carcinoma developed 15 years after radiotherapy. None of the patients who received radiotherapy died of cardiovascular related diseases. Two patients with stage III disease who had residual tumour after operation received chemotherapy postoperatively.

Table 2

Type of Resection in 42 Patients Who Underwent Thymectomy for Thymoma

Resection	Patients, no. (and %)
Complete	32 (76)
Incomplete	10 (24)
Macroscopic	4
Microscopic	6
Associated resections	
Pericardium	20 (48)
Lung	16 (38)
Phrenic nerve	4 (10)
Pleurectomy	3 (7)
Recurrent laryngeal nerve	2 (5)
SVC repair	1 (2)
SVC resection	1 (2)

SVC = superior vena caval.

The median volume of the tumours was 110.0 cm^3 [range from 6–1000 cm^3]. As expected, larger tumours were associated with more invasive lesions ($p = 0.002$) and more incomplete resections ($p = 0.02$). Myasthenia gravis was more common in patients with small tumour volume (<100 cm^3). Sixty-seven percent of patients with myasthenia gravis had a tumour with mixed cell type. Two patients were worse postoperatively, requiring an increase in the dosage of their medication (Table 3). With the exception of myasthenia gravis, there was no association between the presence of the paraneoplastic syndromes present at the time of operation and tumour size or stage of the disease. All paraneoplastic syndromes except muscular dystrophy improved postoperatively.

Survival and risk factors assessments

Using the Kaplan–Meier estimate of survival, 51% of patients survived 175.1 months. Three patients were lost to follow-up shortly after operation. The mean follow-up for patients with stages I, II and III disease were 92.1, 65.6 and 85.8 months respectively. Nine patients were followed up for more than 10 years. Seven patients died. Three deaths were due to cardiovascular disease; 1 patient with stage III disease died of complications of aplastic anemia; 1 patient with stage III invasive thymoma died 2 years postoperatively of metastatic thymic carcinoma; 1 patient died 15 years postoperatively of midesophageal cancer; and 1 patient died of metastatic colon cancer. The overall survival at 5, 10 and 15 years was 87.3%, 81.4% and 51.1% respectively.

Table 3

Postoperative Outcome of Patients Having Myasthenia Gravis

Outcome	Patients, no. (and %)
Complete remission	2 (15)
Partial remission	8 (62)
No improvement	1 (8)
Worse	2 (15)

Table 4 presents the association of different risk factors with disease staging. Disease-free survival could not be studied because there was only 1 death directly attributable to thymoma. Instead, we used the distribution of variables within the stages of the disease as a surrogate outcome. The results of the multivariate analysis are reported in Fig. 1. Using the approach advocated by Cox and Wermuth, we determined that a mixed cell type ($p = 0.017$) and a tumour volume of less than 115 cm^3 ($p = 0.001$) were more common with stage I disease and that a smaller tumour was also more commonly seen in patients with myasthenia gravis ($p = 0.034$). Other statistically significant relationships such as the one between resectability and stage were not considered clinically significant.

Discussion

Thymomas are heterogeneous, rare tumours with several histologic appearances and clinical stages of invasiveness. These non-uniform characteristics are likely responsible for difficulties in attempting to identify definite prognostic factors with respect to patient outcome. This study is an attempt to identify the characteristics of a group of patients having thymoma and to evaluate the risk factors associated with a favourable outcome (early stage of disease) after surgical resection.

There is always the risk of missing or overinterpreting multivariate

analysis given small sample sizes, especially in retrospective nonrandomized studies. To help guard against this, we used an approach advocated by Cox and Wermuth (multivariate dependency graphs) by which variables are graphically laid out from right to left, where variables to the right can be causally related to variables on the left, but not vice versa. For instance, values of variables to the right are determined before variables to the left. The multivariate analysis then commences with the left-most variable and utilizes regression analysis on all variables to the right to determine which variables to its right are "independently" related to it. Arrows are then drawn from the statistically significant variables on the right to the left-most variable. Then this is repeated on the second left-most variable and then the third left and so on. In this way dependencies between the variables are shown on the graph. It is important not to take the lack of an arrow as evidence of no relationship but simply as a lack of evidence of a relationship (i.e., in this study inadequate sample size).

As shown in Fig. 1 for this study the left-most variable is disease-specific surviva,l but due to completely inadequate sample size (only 1 event) there are no arrows from any variables on its right (i.e., there is a lack of evidence in this study for any relationship). The next left-most variable is radiation, for which there are arrows from stage, tumour volume, gender and age, indicating evidence of independent relationships. The next left-most variable is resection, for which there is an arrow from stage. The next left-most variable is stage, which has arrows from histology and tumour volume. Of course, as this is a retrospective nonrandomized study, there is always the risk that some arrows do not represent real underlying relationships but are due to bias and confounding. Similarly, true relationships may not be represented because of cancellation by bias and confounding.

Table 4

Distribution of Patient and Tumour Variables According to the Stage of the Disease

Variable	Stage of disease 1 (n = 24)	2 (n = 7)	3 (n = 11)
Mean (and SD) age, yr	53.6 (11.8)	48.4 (12.4)	53.9 (14.7)
Male/female	10/14	5/2	7/4
Resection			
Complete	23	6	3
Incomplete macroscopically	0	0	4
Incomplete microscopically	1	1	4
Histologic features			
Predominant epithelial	2	0	3
Predominant lymphocytic	5	3	3
Mixed	11*	1	3
Spindle cell	5	3	3
Adjuvant radiotherapy	0	6	8
Paraneoplastic syndrome	7	5	4
Myasthenia gravis	10	1	2
Tumour volume			
≤115 cm^3	16†	4	2
>115.cm^3	7	3	9

*p = 0.017, multivariate analysis.
†p = 0.001, multivariate analysis.

Age and gender

We found no association between age, gender and stage of the disease. Myasthenia gravis, which is present in 30% to 73% of patients with thymo-

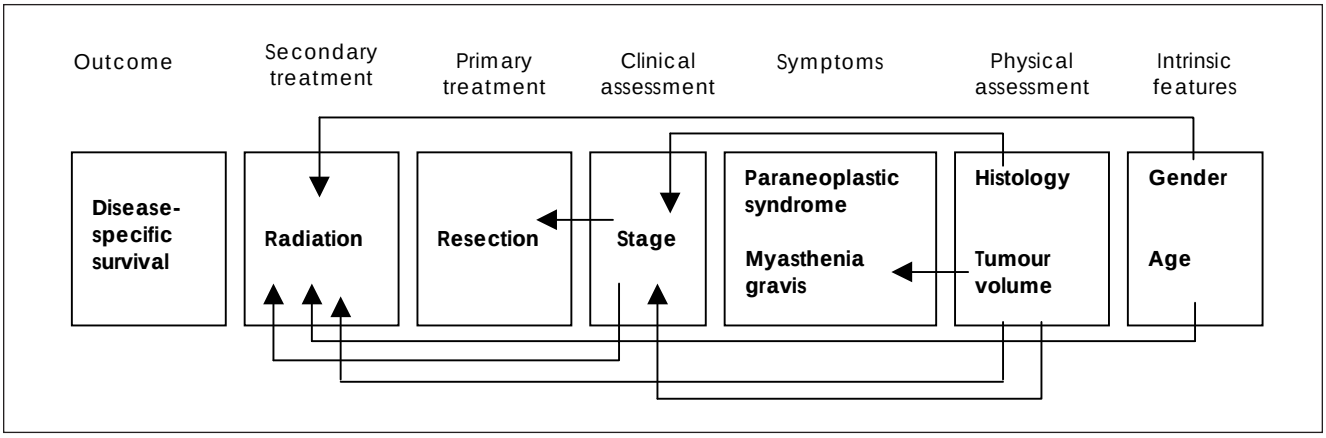

FIG. 1. Multivariate dependency graph. The multivariate analysis begins with the left-most variable and utilizes regression analysis on all variables to the right in order to determine the related variable to the right. Arrows indicate the significant relationship. Disease-specific survival — all arrows are missing, therefore there is no evidence of any relationship in this study. Radiation — 4 relationships as follows: stage (p = 0.001), tumour volume (p = 0.002), gender (p = 0.001), age (p = 0.044). Resection — stage s(p = 0.001). Stage — histology (p = 0.017), tumour volume (p = 0.001). Myasthenia gravis — tumour volume (p = 0.034).

mas,[10] is more commonly found among females, and the presence of myasthenia gravis is known to be associated with a better prognosis.[11] Despite this, there seems to be no survival advantage to female patients when gender is studied as an independent variable.[4] In the present study the absence of difference could be due to small sample size, for instance the 95% confidence interval for the odds ratio for sex was 0.60 to 5.94.

Tumour volume

From the overall dimensions of the resected thymoma, it was possible to calculate the tumour volume in cubic centimetres. Authors of several previous reports have examined the significance of tumour size and have not been able to find any relation to survival.[6] On the other hand, Lewis and associates[8] reported that survival decreased with increasing maximum diameter of the thymoma. Our findings concur with those of Lewis and associates. Calculating tumour volume is a more accurate way of judging tumour size as it correctly presents the proportions of irregularly shaped masses. We found increased tumour volume to be associated with more advanced stage of disease and therefore more invasiveness and decreased resectability.

Paraneoplastic syndromes

A number of paraneoplastic syndromes are associated with thymomas. In most cases, the paraneoplastic syndrome comprises autoimmune or hematologic disturbances.[10,12] Myasthenia gravis is the most common paraneoplastic syndrome associated with thymoma.[1,8] Several authors have reported myasthenic thymoma as being less malignant in nature, probably owing to an earlier presentation, thus leading to a better prognosis.[5,11,13] We support these findings by adding that myasthenia gravis is more commonly seen with tumours measuring less than 150 cm^3. However, in a number of other studies, similar rates of survival were found between patients with thymoma and myasthenia gravis and those with no autoimmune disease.[4,15]

We found no association between the presence of a paraneoplastic syndrome other than myasthenia gravis and tumour size or stage of the disease.

Clinical staging

The clinical staging system proposed by Masaoka and colleagues[9] is presently the standard classification for thymomas and reflects the degree of invasiveness of the tumour. Although this system appears to be a significant prognostic factor,[14] we were not able to show this due to the overall good survival of patients presented here. Recently, there has been an effort to improve the value of the staging by combining the Masaoka staging with other variables that were found to have significant prognostic factors individually. Pescarmona and colleagues[4] proposed a model of clinicopathological staging based on clinical stage and histologic type. They found this staging system had a much higher prognostic value than each factor considered individually. Others have suggested including the completeness of resection in the clinicopathologic staging.[15]

Pathological classification

All patients had a preoperative diagnosis obtained by an invasive fine-needle aspiration or open biopsy. In all cases, this was done via an extrapleural route, and we did not see any cases of pleural seeding in the long-term follow-up. Tumours with mixed histologic cell type were the most common variety and were mainly seen in stage I disease. Epithelial tumours were more common in stage III disease, probably indicating the more aggressive nature of the latter group. Similar findings have been reported in a number of reviews,[6,15,16] whereas another series, using similar histologic criteria, reported opposite results.[10] These differences may simply be due to lack of rigour in reporting and variability in the pathological description from institution to institution. The difficulty in establishing a precise histologic diagnosis is also exemplified by the 1 case of thymic carcinoma which erroneously was diagnosed as a grade III invasive thymoma at the time of resection. This stresses the importance of establishing a preoperative diagnosis and long-term follow-up in patients with invasive disease at onset.

Radiotherapy and completeness of resection

The treatment of thymoma has usually been surgical resection accompanied by radiotherapy when the tumour cannot be resected completely. There is a higher relapse rate when the resection is incomplete, and there is a significant reduction in relapse rate with the administration of radiotherapy.[6,15] Gripp and associates[6] observed the efficacy of postoperative radiotherapy for incompletely resected thymomas in studying the pattern of relapse of tumours. In 80% of cases this occurred outside the irradiated field.

Clearly complete resection of invasive thymoma followed by postoperative radiation therapy results in an outcome similar to patients with stage I disease regardless of the stage or histologic type.[16,17] The results reported here support this. However, radiotherapy to the anterior mediastinum is not innocuous, especially in a group of patients in whom long-term survival is expected. Coronary insufficiency is an important potential complication but was not noted in our study. One of the patients included in this series suffered from a midesophageal carcinoma 15 years after radiotherapy. The diseased esophagus was included in the radiotherapy field.

Conclusions

Mixed cell type and a tumour less than 115 cm^3 in volume appear to be important factors associated with early stage thymoma. The use of radiotherapy after resection of stages II and III disease, irrespective of the status of resection, seems to be associated with as good a prognosis as that for patients with stage I disease.

References

1. Levine GD, Rosai J. Thymic hyperplasia and neoplasia: a review of current concepts. *Hum Pathol* 1978;9:495-515.

2. Weissberg D, Goldberg M, Pearson FG. Thymoma. *Ann Thorac Surg* 1973;16: 141-7.

3. Batata MA, Martini N, Huvos AG, Aguilar RI, Beattie EJ. Thymomas: clinicopathology features, therapy, and prognosis. *Cancer* 1974;34:389-96.

4. Pescarmona E, Rendina E, Venuta F, D'Arcangelo E, Pagani M, Ricci C, et al. Analysis of prognostic factors and clinicopathological staging of thymoma. *Ann Thorac Surg* 1990;50:534-8.

5. Masaoka A, Yamakawa Y, Niwa H, Fukai I, Kondo S, Kobayashi M, et al. Extended thymectomy for myasthenia gravis: a 20 year review. *Ann Thorac Surg* 1996;62:853-9.

6. Gripp S, Hilgers K, Wurm R, Schmitt G. Thymoma: prognostic factors and treatment outcomes. *Cancer* 1998;83:1495-503.

7. Fornasiero A, Daniele O, Ghiotto C, Piazza M, Fiore-Donati L, Calabro F, et al. Chemotherapy for invasive thymoma: a 13-year experience. *Cancer* 1991;68:30-3.

8. Lewis JE, Wick MR, Scheithauer BW, Bernatz PE, Taylor WF. Thymoma, a clinicopathologic review. *Cancer* 1987;60: 2727-43.

9. Masaoka A, Monden Y, Nakahar K, Tanioka T. Follow-up study of thymomas with special reference to their clinical stage. *Cancer* 1981;48:2485-92.

10. Maggi G, Giaccone G, Donaldo M, Ciuffreda L, Dalesio O, Leria G, et al. Thymomas: a review of 169 cases with particular reference to results of surgical treatment. *Cancer* 1986;58:765-76.

11. Shamji F, Pearson FG, Todd TR, Ginsberg RI, Ilves R, Cooper JD. Results of surgical treatment for thymoma. *J Thorac Cardiovasc Surg* 1984;87:43-7.

12. Kobayashi M, Hasegawa T, Iwabuchi S, Fukushima M, Koie H, Kannari K. The effect of thymectomy on myasthenia gravis, thrombocytopenia and granulocytopenia associated with thymoma: report of a case. *Jpn J Surg* 1995;25:1061-5.

13. Monden Y, Nakahara K, Iioka S, Nanjo S, Ohno K, Fujii Y, et al. Recurrence of thymoma: clinicopathological features, therapy, and prognosis. *Ann Thorac Surg* 1985;39:165-9.

14. Lardinois D, Rechsteiner R, Läng H, Gugger M, Betticher D, van Briel C, et al. Prognostic relevance of Masaoka and Müller–Hermelink classification in patients with thymic tumors. *Ann Thorac Surg* 2000;69:1550-5.

15. Regnard JF, Magdeleinat P, Dromer C, Dulmet E, de Montpreville V, Levi JF, et al. Prognostic factors and long-term results after thymoma resection: a series of 307 patients. *J Thorac Cardiovasc Surg* 1996;112:376-84.

16. Nakahara K, Ohno K, Hashimoto J, Maeda H, Miyoshi S, Sakurai M, et al. Thymoma: results with complete resection and adjuvant postoperative irradiation in 141 consecutive patients. *J Thorac Cardiovasc Surg* 1988;95:1041-7.

17. Maggi G, Casadio C, Cavallo, A, Cianci R, Molinatti M, Ruffini R. Thymoma: results of 241 operated cases. *Ann Thorac Surg* 1991;51:152-6.