

The Role of Postoperative Radiotherapy in the Management of Patients with Thymic Tumors – A Retrospective Study

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Abstract. *Background:* Thymomas are the most common tumor arising in the anterior mediastinum. Surgery is the cornerstone for the management of these tumors. The role of postoperative radiotherapy in Masaoka stage II thymomas remains controversial, but it is well established in the advanced stages. The aim of this study was to investigate the role of postoperative radiotherapy in the overall management of thymomas, and the evaluation of potential prognostic factors. *Patients and Methods:* Between 1989 and 2007, 41 thymoma patients underwent surgery and 27 of them received radiotherapy with a curative intent. The Masaoka staging system was used. The histopathological records and specimens of patients were thoroughly reviewed. Clinical and radiological evaluations took place every 6 months. The mean patient follow-up was 69 months (range: 2-212). *Results:* DFS (disease free survival), TS (total survival) and DSS (disease specific survival) differed significantly between stages and histological types ($p < 0.04$). Stage I patients were managed only surgically, with none recurring or dying. Concerning stage II patients, TS was significantly longer in non-irradiated cases (10/21) ($p = 0.025$). Stage III ($n = 8$) and IV ($n = 8$) patients underwent postoperative radiotherapy, with 4/8 of stage IV disease also receiving induction chemotherapy. Six out of 8 stage III-IV patients recurred (1 distant and 5 intrathoracic failure), out of whom 4 died due to disease progression despite further treatment (all type C histology). The mean DFS and TS

for stage III patients were 49.2 and 50.3 months respectively, with the corresponding values for stage IV being 14.5 and 29.1 months. Patients with myasthenia had a favorable outcome and the ones with complete resection a significantly longer DFS ($p = 0.0003$) and DSS ($p = 0.039$). The Cox regression analysis showed that myasthenia and tumor size are important prognostic factors for DFS ($p < 0.05$). *Conclusion:* Myasthenic patients have a more favorable prognosis. Radiotherapy can be omitted in totally resected stage I-II patients, whereas it is beneficial in more advanced stages.

Thymomas typically occur in adults over 40 years and are the most common tumor arising in the anterior mediastinum (1). The symptomatology of patients with thymic malignancies varies widely and only one third of patients with localized disease are symptomatic. The majority of patients present with cough, dyspnea, upper respiratory complaints and chest discomfort or pain (2, 3). About 30% to 50% of patients with thymoma have myasthenia gravis (MG), whereas about 15% of patients with MG are diagnosed with thymomas (4).

The most commonly used staging system is the one proposed by Masaoka and co-workers, summarized in Table I (5). Similarly, the histological classification that is currently widely accepted is the one established by WHO (Table II) (6). WHO histology, completeness of resection, size of tumor and vessel invasion are prognostic factors identified through multivariate analysis in recent clinical trials (2, 7-9). It has also been reported that Masaoka stage and WHO histology stratify survival fairly well (5, 10, 11).

Surgery is the cornerstone for the management of thymomas and a successful treatment depends on the completeness of resection. The principles of surgical resection include a complete median sternotomy with a wide opening of pleural cavities and a thymectomy, which has to be as complete as possible (12).

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Table I. *Clinical staging by Masaoka and co-workers (10).*

Masaoka stage	Staging criteria
Stage I	Macroscopically and microscopically encapsulated tumor
Stage II	A: Microscopic transcapsular invasion B: Macroscopic invasion into surrounding fatty tissue or grossly adherent to but not through mediastinal pleura or pericardium
Stage III	Macroscopic invasion into neighboring organs (pericardium, great vessels and lung) A: without invasion of great vessels B: with invasion of great vessels
Stage IV	A: Pleural or pericardial dissemination B: Lymphogenous or hematogenous metastasis

Several investigators have reported that postoperative radiotherapy can reduce local recurrences in thymomas and prolong survival (13). Recurrence rates after complete resection of stage I thymomas are approximately about 1.5% and therefore it is generally accepted that no adjuvant radiotherapy should be administered (12). In such cases, surgery alone can achieve 5-year and 10-year survival rates of 100% (14). However, current therapeutic indications for stage II thymomas are controversial, since some authors have advocated postoperative radiotherapy (15-18) whereas others have argued against its usefulness (14, 19-21). The necessity of postoperative radiotherapy in stage III or IV thymoma patients is less debatable, since it has been shown that it can improve local control and TS (15, 22, 23). Furthermore, the administration of radiotherapy preoperatively in cases of locally advanced thymomas has shown to reduce the recurrence rates (24) and render unresectable tumors resectable (25). Multimodality treatment involving induction chemotherapy, surgery and radiotherapy has also been successfully employed in the management of stage III and IV thymomas (26-28) and often in thymic carcinomas due to their aggressive nature (29, 30).

In this retrospective study the therapeutic outcome of 41 patients with thymic tumors managed at two Institutions, between 1989 to 2007 is presented. The role of postoperative radiotherapy in the overall management of thymomas and potential prognostic factors are evaluated. Additionally, the natural history, clinical presentation, pathologo-anatomical and epidemiological aspects, and the current management strategies for thymomas are thoroughly discussed.

Patients and Methods

Patient population and assessment methods. Between 1989 and 2007, 41 patients diagnosed with thymomas were treated at the University of Patras Medical School, Greece and at the Bank of Cyprus Oncology Centre in co-operation with the Nicosia General Hospital,

Table II. *Histological classification of thymomas by WHO (11).*

WHO type	
Type A	Medullary thymoma, spindle cell
Type AB	Mixed thymoma
Type	
B1	Predominantly cortical, lymphocyte predominant
B2	Cortical
B3	Well-differentiated thymic carcinoma; epithelial predominant
Type C	Thymic carcinoma

Cyprus. The clinical records of all patients were reviewed in detail to obtain all available data concerning clinical characteristics (age, gender), clinical presentation of disease (MG, local symptoms, incidental findings), preoperative and postoperative radiological assessments (Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) scans, or chest radiographs), surgical procedures and reports, postoperative complications, histopathological reports, radiotherapy or chemotherapy treatment and accompanied complications, and long term follow-up information. Apart from the review of the hospital's and offices' records, follow-up was completed (when necessary) through telephone interviews.

Clinical staging and pathological review. Operative notes were reviewed in order to evaluate intraoperative local invasion, gross tumor extension into neighboring structures, tumor size and completeness of resection. The histopathological specimens (slides) of all patients were retrospectively reviewed and staged by using the Masaoka criteria (Table I) (7). A complete agreement was found between initial histological examination and the review on the margin status and degree of transcapsular invasion. Similarly, the histological classification was performed by using the five histological classification subtypes set by WHO (Table II) (8).

Postoperative radiotherapy. Patient referral for adjuvant radiotherapy was based on the surgeon's evaluation of the risk of recurrence. The main factors that were taken into consideration for patient referral were a tumor diameter >4 cm, preceding open biopsies and close resection margins (phrenic nerve stripping). Radiotherapy regimens were reviewed and techniques, total doses, fractionation, treatment duration and acute and late complications were recorded in detail.

Patient follow-up. Patients underwent both clinical and radiological evaluations postoperatively every six months. Radiological assessments were carried out by CT and clinical examinations involved a detailed neurological assessment. Any missing information from the patients' record was acquired through telephone contact. Survival times were calculated from the date of operation. Deaths that were related to treatment (operative or postoperative) were considered as deaths due to thymoma. The disease free survival (DFS), time to death due to thymoma (disease specific survival, DSS) and time to death from any cause (total survival, TS) were recorded for all patients taking part in the study.

Analysis and statistical considerations. Results are expressed as range, mean±SD and median values. Intergroup comparisons, regarding correlation of several clinical with therapeutic and

Table III. Patient and disease characteristics.

	Total	Masaoka stage				p-value
		I	II	III	IV	
No. of patients	41	4	21	8	8	
Demographics						
Range of age	19-86	19-67	31-75	30-86	30-74	0.73
Median age	57	59	50	63	61.5	
Mean age \pm s.d.	54.9 \pm 15.6	51 \pm 21.7	53 \pm 14.3	58.8 \pm 18.9	58 \pm 14.4	
Males	18	0	10	4	4	0.32
Females	23	4	11	4	4	
Presenting symptoms						
Local symptoms	14 (34.1%)	-	4	5	5	
Myasthenia	18 (43.9%)	2	13	2	1	
Asymptomatic	9 (22%)	2	4	1	2	
Tumor diameter						
Mean (mm) \pm s.d.	70.9 \pm 24.8	52.8 \pm 15.8*	62.2 \pm 17.4*	86.8 \pm 30.1*	86.9 \pm 25.5*	*0.006

Table IV. WHO histological classification for each Masaoka stage.

	Masaoka stage (n)				Radiotherap, n (%)		Total (n)
	I	II	III	IV	YES	NO	
Type (WHO)							
A		2			1 (50%)	1 (50%)	2
AB	1	4		1	3 (50%)	3 (50%)	6
B1	1	1			0	2 (100%)	2
B2	1	6		1	1 (12.5%)	7 (87.5%)	8
B3	1	8	3	2	12 (85.7%)	2 (14.3%)	14
C	0	0	5	4	9 (100%)	0	9
Total (n)	4	21	8	8	26 (63.4%)	15 (36.6%)	41

$p=0.143$ (stage vs. type); $p=0.001$ (types vs. radiotherapy).

pathological features, were performed using one-way analysis of variants (ANOVA). Whenever the equal variance test or normality tests failed, the Kruskal-Wallis non-parametric test was applied. In order to address the problem of multiple comparisons, the ANOVA and Kruskal-Wallis tests were followed by a *post hoc* Bonferroni test. The Kaplan-Meier procedure was also used to compare the survival curves. More specifically disease free survival, disease specific survival and total survival curves were reported separately. Finally, the Cox proportional hazards model was employed to reveal the effects of clinicopathological and therapeutic factors that were studied on survival. Data were analyzed using the SPSS statistical package (SPSS, Release 10.0.1). Significance was defined as $p<0.05$.

Results

Patient and disease characteristics. The study population included 18 male and 23 female patients, with a mean age of 54.9 years (median 57, range 19-86). At the time of disease diagnosis, 14/41 (34.1%) patients suffered from local symptoms such as cough, dyspnea and hoarseness and 18/41 (43.9%) had myasthenia. The rest of the patients (9/41) (22%) were asymptomatic (Table III).

Overall 4 patients (9.8%) had Masaoka stage I disease, 21 (51.2%) had stage II, 8 (19.5%) had stage III and 8 (19.5%) had stage IV. Table IV shows the WHO histological classification for each Masaoka stage, as well as the percentage of patients of each histological sub-type who underwent postoperative radiotherapy.

Surgery. All patients were operated with the intention of a complete tumor resection. After a full median sternotomy and ligation of the thymic vasculature, the thymoma was resected en block with the total thymus gland, the soft perithymic tissue and the mediastinal, pericardial and cervical adipose tissue. The surgical resection included any lung parenchyma and/or pericardium as well as the phrenic nerve and brachiocephalic vein if implicated. Prior to closing, two drains were placed to drain both pleural cavities and mediastinum (31).

All patients with Masaoka stage I and II thymomas underwent a complete thymectomy with clear surgical margins. From the 8 patients with stage III disease, 5 had a complete and 3 an incomplete tumor resection. Regarding

patients with stage IV disease, only 3 out of 8 had a complete tumor excision with clear surgical margins.

There were no perioperative mortalities and the morbidities that were recorded were two wound infections requiring re-exploration and drainage, two tachycardias and one atrial fibrillation that was managed conservatively (chemical cardioversion).

Radiotherapy. None of the patients with stage I thymoma was irradiated postoperatively, whereas from the patients with stage II disease only 11/21 (52.4%) were submitted to radiotherapy. On the contrary, all patients with stage III and IV thymomas underwent postoperative radiotherapy. Three-dimensional conformal radiotherapy was performed by using 6 MV and 18 MV photon energy and a combination of isocentric fields. Patients were treated daily, 5 times/week, with antero-posterior opposed fields or two oblique-wedge-off-cord portals. The anterior mediastinum (tumor bed) was boosted to higher doses by the application of two oblique-wedge-off-cord portals. The dose to spinal cord was limited to a maximum of 45 Gy and less than 40% of the lungs received 20 Gy.

The average treatment dose was 50.7 Gy (range 39-58 Gy) with a daily fractionation of 1.8-2.0 Gy. Three dimensional treatment planning was carried out to allow for minimization of toxicity of organs at risk such as the lung and spinal cord. The gross tumor volume (GTV) was defined as any visible tumor/or surgical clips on treatment planning CT transverse sections and the clinical target volume (CTV) included areas with potential microscopic disease. A small margin around the CTV was also added to compensate for positioning uncertainties or tumor motion due to breathing, yielding the planning target volume which is the volume that was to be irradiated (PTV). The supraclavicular fossa was not included in the irradiated field in any of the patients.

Seven patients who underwent postoperative radiotherapy had treatment related complications. A patient developed limited pulmonary fibrosis (in field), two grade II esophagitis (NCI common toxicity criteria) and four grade II dermatitis (WHO criteria).

Chemotherapy. Induction chemotherapy was performed in four stage IV patients with thymic carcinoma (WHO type C), consisting of 500 mg/m² cyclophosphamide on day 1, 20 mg/m² doxorubicin per day on days 1-3, 30 mg/m² cisplatin per day on days 1-3 and prednisone (100 mg/day) on days 1-5. Each cycle was repeated three times at 3-4 week intervals. Two patients developed grade III neutropenia (WHO criteria), followed by neutropenic fever in one patient. No other severe toxicities were recorded.

Survival. Patients were followed-up for 2-212 months post surgery (mean±SD: 69±58.9 and median 54 months). Three patients who died of causes not related to thymoma

were free of disease at the time of death. A total of 7 patients recurred, with one having a distant recurrence (bone metastases) and the rest local intrathoracic recurrences. From the patients who recurred, three had stage IV disease with Type C (WHO) histology (2 pleural and 1 mediastinal recurrence), one had stage IV disease with type B3 histology (mediastinal recurrence), two had stage III thymomas with type C histology (one had distant and the other pleural recurrence) and a patient with IIB disease with AB histology who developed disseminated pleural disease in spite of undergoing postoperative radiotherapy. A total of 5 patients with recurrence died due to disease progression despite re-operation and/or chemotherapy (2 had stage IV disease with type C histology, 2 had stage III thymomas with type C histology and 1 stage II disease with AB histology).

DFS, TS and DSS were analyzed with respect to surgical margins, myasthenia, histological type, stage and use of radiotherapy. Patients with negative surgical margins had a significantly longer DFS as compared to those with positive surgical margins ($p=0.0003$) (mean value in months: 75.3 versus 26.3, Figure 1A). The difference in TS between patients with free and involved surgical margins was not statistically significant ($p=0.08$, Figure 2A), whereas for DSS a significant difference was observed ($p=0.039$, Figure 3A). Interestingly, patients with MG had a significantly longer DFS ($p=0.018$), TS ($p=0.02$) and DSS ($p=0.006$) than non-myasthenic patients (Figures 1B-3B).

DFS was also found to differ considerably between patients with different histological types ($p=0.017$). Patients having thymomas with type B1 histology had the longest mean DFS with 134.5 months and the ones with type C the shortest with 25.8 months (Figure 1C). A statistically significant difference between patients with thymomas of different histological types was also observed for TS ($p=0.043$), with the patients of B1 histology having the longest mean TS with 134.5 months and patients with type C histology the shortest with 39.4 months (Figure 2C). Figure 3C presents the DSS among patients with different histological types ($p=0.041$).

The analysis of results also revealed a statistically significant difference in DFS between patients of different Masaoka stages (I-IV) ($p=0.002$). More specifically, patients with stage I disease had the longest mean DFS with 122 months (none recurred during follow-up), followed by stage II patients with 78.1 months, stage III patients with 41.2 and stage IV patients with 14.5 months (Figure 1D). Concerning TS, the statistical difference between the patients with different stages was also significant ($p=0.012$) and the corresponding mean values of TS for stage I-IV patients were 122, 78.5, 50.3 and 29.1 months respectively (Figure 2D). DSS also differed significantly between patients with different stages ($p=0.037$) (Figure 3D).

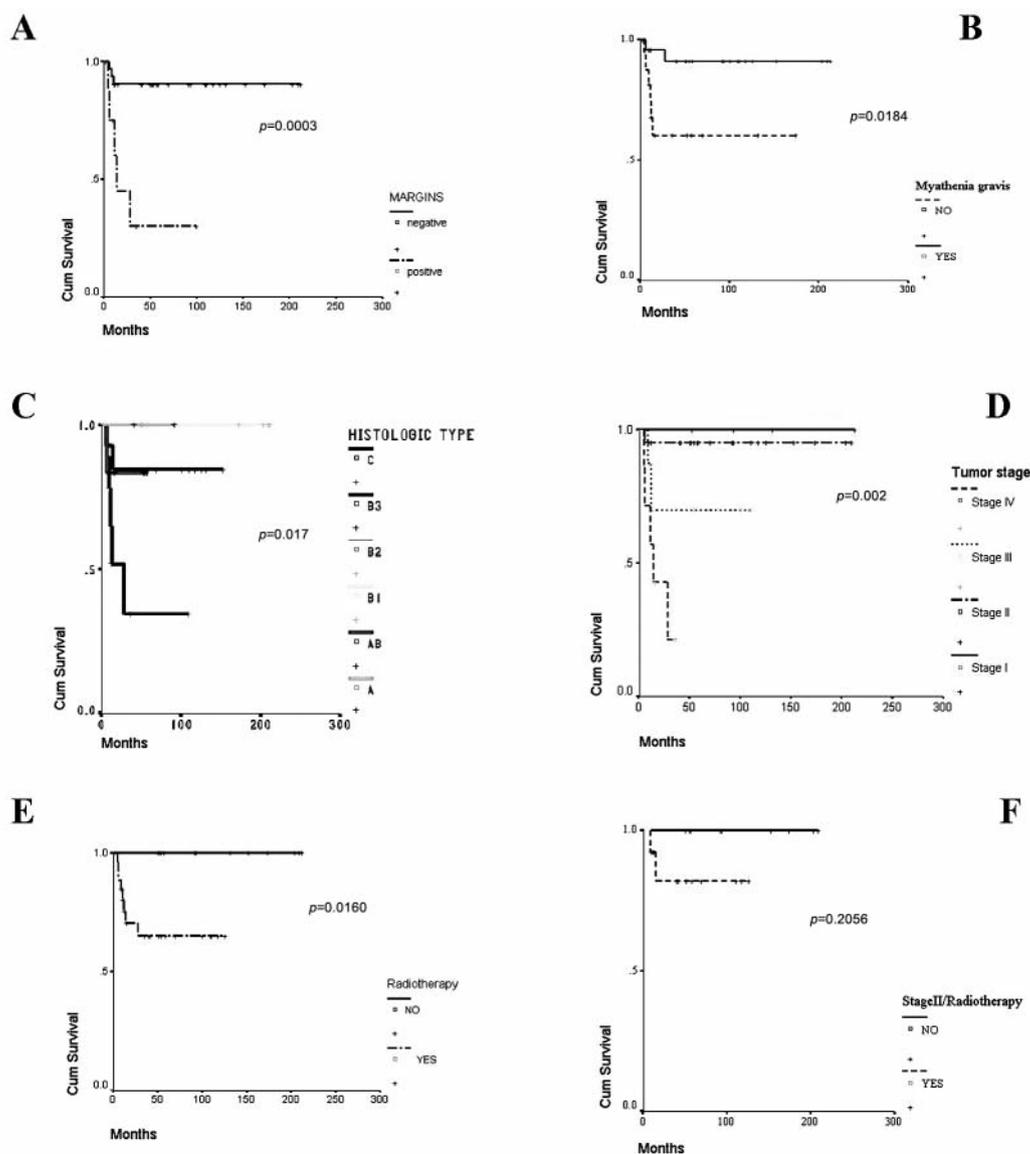


Figure 1. Kaplan Meier survival curves showing the relation between disease free survival and: A: status of margins, B: presence or absence of myasthenia gravis, C: tumor histological type, D: tumor stage, E: application or omission of radiotherapy and F: irradiated and non-irradiated stage II patients.

Regarding patients undergoing radiotherapy *versus* those who were only operated, a significant difference was noted in DFS ($p=0.016$), TS ($p=0.0022$) and DSS ($p=0.0028$) (Figures 1E-3E). Group II patients were also analyzed separately, with the results revealing that the mean DFS was longer for those not undergoing radiotherapy (90.5 *versus* 43 months) ($p=0.21$, Figure 1F). The difference in the TS between non-irradiated and irradiated stage II patients was statistically significant (mean value of 91.05 *versus* 43 months respectively) ($p=0.025$, Figure 2F). The difference in DSS however was not significant ($p=0.172$, Figure 3F).

Cox regression analysis for DFS, TS and DSS. The results of multivariate analysis for DFS are presented in Table V. MG and tumor size were found to be statistically significant prognostic factors for DFS ($p<0.05$).

Discussion

The current study presents the therapeutic outcome of 41 patients with thymic tumors. All histological specimens were re-evaluated so that both the Masaoka stage and the WHO histological classification were established. Apart from investigating the role of post operative radiotherapy, several

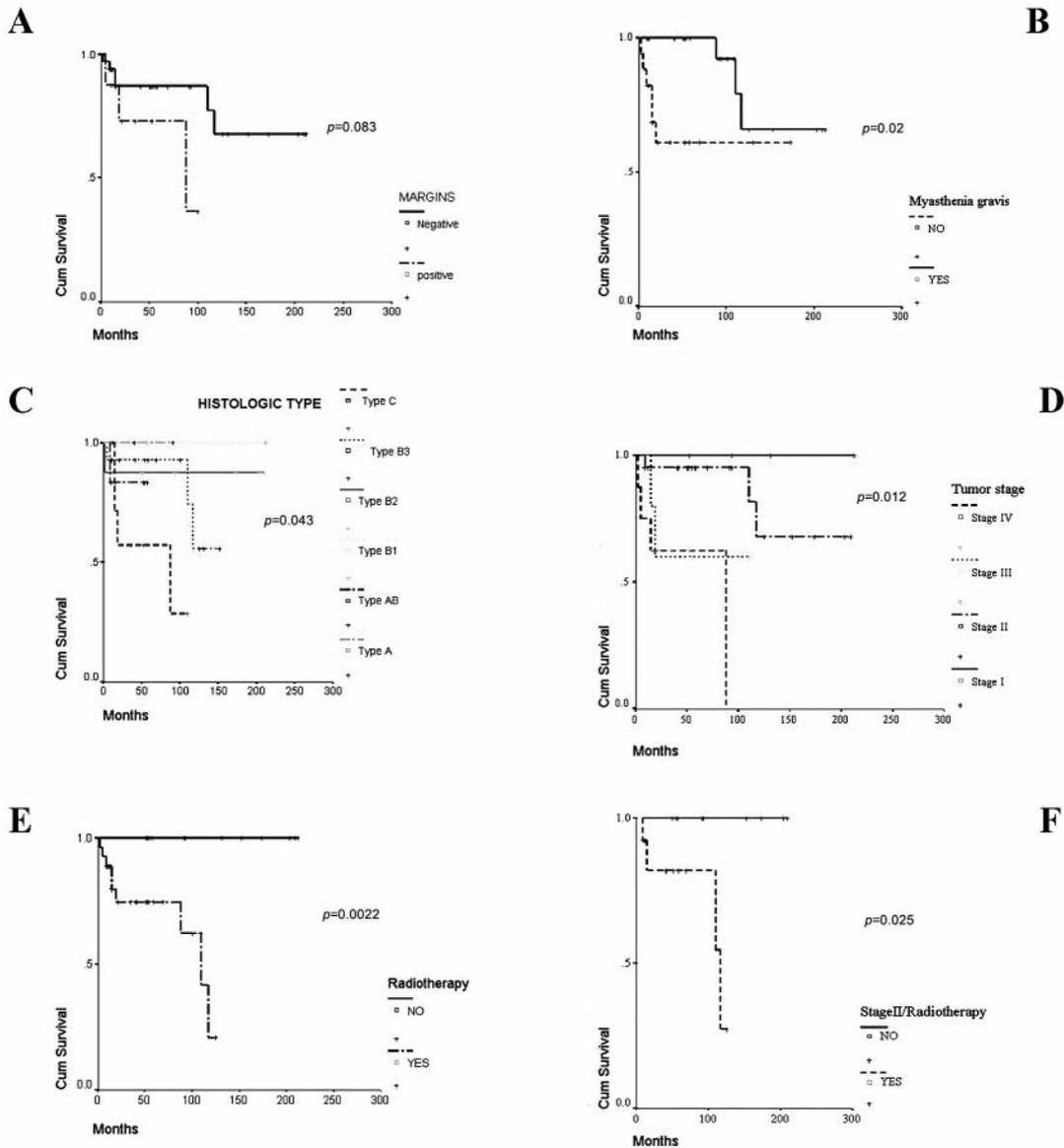


Figure 2. Kaplan Meier survival curves showing the relation between total survival and: A: status of margins, B: presence or absence of myasthenia gravis, C: tumor histological type, D: tumor stage, E: use or omission of radiotherapy and F: irradiated and non-irradiated stage II patients.

parameters were analyzed *via* multivariate analysis in an effort to reveal potential prognostic factors for DFS, TS and DSS.

The role of radiotherapy for patients with thymic tumors remains unclear. Postoperative radiotherapy has been routinely used in the past, even in completely resected stage I cases. But the recognition of early and late radiation induced complications has led several investigators to narrow the use of this treatment modality to carefully selected patient subpopulations and to address the issue of novel radiotherapy techniques in the management of these patients (32, 33).

Stage I thymomas have an excellent prognosis after complete resection and it is currently accepted that the use

of adjuvant radiotherapy is not essential (14, 19). In a study of the Memorial Sloan Kettering Hospital, out of the 25 patients with stage I thymomas managed with surgery alone, only one recurrence was noted and the overall 5 year survival rate was 95% (20). In a different study by Fujimura *et al.*, no recurrences were reported in a total of 31 stage I patients treated by surgery alone, with the 10 year survival rate being 74.3% (34). Similarly, no relapses were recorded in 52 stage I patients in a study from the Massachusetts General Hospital, with none of the patients dying from thymoma (35). In the present study all stage I patients were managed only surgically, with none relapsing or dying due to

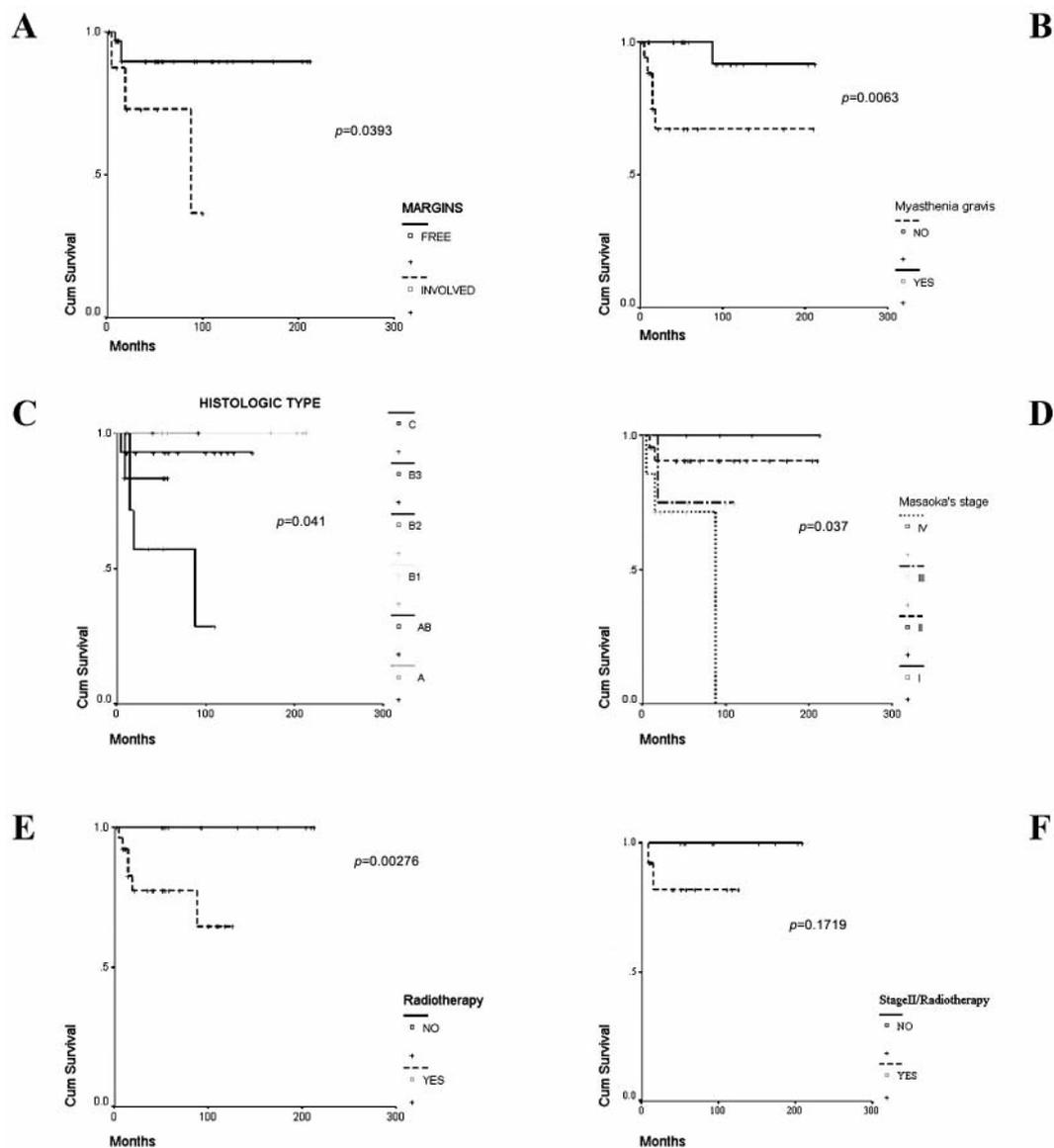


Figure 3. Kaplan Meier survival curves showing the relation between disease specific survival and: A: status of margins, B: presence or absence of myasthenia gravis, C: tumor histological type, D: tumor stage, E: irradiated and non-irradiated patients and F: application or omission of radiotherapy in stage II patients.

thymoma. These results support the omission of radiotherapy after surgery in totally resected stage I patients.

The current therapeutic indications concerning stage II thymomas are controversial, since some authors are in favor of the application of radiotherapy after surgery (15-18), whereas others are against its use (14, 19-21). In a study by Nakahara and co-workers it was reported that the recurrence rate in patients with stage II thymoma managed by surgery alone was 29% (2/7 patients recurred), as compared to only 8% (2/25 patients recurred) when radiotherapy was applied after surgery (15). In a different study involving 19 patients

with stage II thymoma, the majority of patients (18/19) were managed only surgically, with one receiving adjuvant radiotherapy. During the follow-up period 6/18 patients who were treated only surgically developed local recurrence. The authors concluded that surgical resection without adjuvant radiotherapy is inadequate (17). Similarly, in a series with 61 stage II patients, all patients received postoperative radiotherapy, with 4 developing pleural and 2 mediastinal recurrences. The authors reported that radiotherapy is useful in preventing mediastinal but not pleural disease failure (18).

Table V. Cox regression analysis for patients with thymoma, regarding DFS.

Factors	B	SE	Wald	df	Sig. (p)*	Exp(B)	95% CI for Exp (B)	
							Lower	Upper
Myasthenia gravis	-6.0	3.22	3.49	1	0.045	0.002	0	1.35
Gender	-0.762	1.39	0.3	1	0.58	0.47	0.031	7.09
Margins	5.14	3.44	2.24	1	0.14	171.4	0.202	145,402.8
Histological type (ref. category: Type C)			1.31	5	0.93			
Histological type A	-12.16	627.1	0	1	0.98	0	0	.
Histological type AB	-2.22	2.74	0.65	1	0.42	0.11	0.001	23.4
Histological type B1	-2.52	579.74	0	1	0.99	0.08	0	.
Histological type B2	-1.83	271.54	0	1	0.99	0.16	0	2.2+230
Histological type B3	1.93	1.93	1.0	1	0.32	6.88	0.16	299.42
Stage (ref. category: Stage IV)			4.18	3	0.24			
Stage I	-0.22	491.84	0	1	1.0	0.80	0	.
Stage II	2.69	2.73	0.96	1	0.33	14.69	0.07	3,102.58
Stage III	-7.04	3.68	3.65	1	0.06	0.001	0	1.2
Radiotherapy	7.56	259.84	0.001	1	0.97	1,912.6	0	2.88+224
Age	0.10	0.1	0.88	1	0.35	1.1	0.9	1.34
Tumor size	0.16	0.08	3.78	1	0.048	1.18	0.99	1.38

*p-values with statistical significance are in bold.

Other studies have, however, shown that the administration of adjuvant radiotherapy is not necessary for local tumor control and that its use may even negatively affect patient survival. In a study by Blumberg *et al.*, 17 out of the 26 patients with stage II thymoma received post-operative radiotherapy. No statistically significant differences were noted between irradiated and non-irradiated patients in the recurrence and survival rates (20). In a different study involving 32 stage II patients, 7/32 patients received adjuvant radiotherapy. The results analysis showed that the recurrence rate was 28.3 % for patients managed with both surgery and adjuvant radiotherapy, as compared to 8% for patients for whom radiotherapy was omitted (difference was not statistically significant) (35). Mangi *et al.* reported the results of a 27-year experience presenting the therapeutic outcome of 49 stage II thymoma patients. From these patients 35 underwent surgery alone and 14 also received postoperative radiotherapy. The addition of irradiation did not influence the long term local disease control and the DSS of both groups was 100% (21). Similarly, in a well balanced study involving 40 patients with stage II thymoma, half of the patients were treated by both surgery and postoperative radiotherapy and the rest were only operated. The recurrence rate was 5% in the group managed with both treatment modalities, as compared to no recurrences for those only undergoing surgery. No differences were recorded in the long term DFS ($p=0.72$). Finally, in a more recent paper, by Rena and colleagues, 32 patients were treated only surgically whereas 26 were also submitted to radiotherapy. Overall, 5 intrathoracic recurrences were reported, three in irradiated patients and two in non-irradiated patients. The long term analysis showed no

difference in survival between the two groups ($p=0.432$), with the authors noting that surgical resection alone is sufficient for the management of stage II thymoma patients (14).

In the present study, from the 21 patients with stage II disease, 11 were also submitted to adjuvant radiotherapy. Overall, one patient from the irradiated group recurred locally (disseminated pleural recurrence) and finally died due to disease progression in spite of further treatment. Notably DFS and DSS were longer for patients not undergoing radiotherapy (difference not statistically significant), whereas TS was significantly longer for the same group of patients ($p=0.025$). These results suggest that adjuvant radiotherapy may be omitted in totally resected stage II thymoma patients.

The beneficial role of post-operative radiotherapy in resected stage III patients is less debatable. In a series by Nakahara *et al.* 35 patients with stage III disease who received postoperative radiotherapy had a 95% 15-year survival rate (15). In a different study by Urgesi and colleagues involving 33 totally resected stage III thymoma patients who received adjuvant radiotherapy, 3 out-of-field recurrences were noted during the follow-up period (22). Furthermore, in a study investigating the role of mediastinal radiotherapy in patients with invasive stage II and III thymomas, it was shown that 8/21 (38.1%) patients who did not receive radiotherapy after surgery had a mediastinal recurrence as the first site of failure, whereas the relapse rate for patients receiving radiotherapy was 0% (17). In another study of Ogawa *et al.*, which included 21 patients with Masaoka stage II or III thymomas, the 5- and 10-year actuarial overall survival was 77% and the authors concluded that in patients with pleural invasion, mediastinal irradiation alone might be insufficient to avoid pleural-based relapse (36).

Similarly, in a report with 15 patients with stage III and IV disease, all patients were submitted to adjuvant radiotherapy. Only 2 local recurrences were noted, with all patients being alive at the last follow-up (23).

The current study included 8 patients with stage III disease out of whom only 2 recurred (one had a local and one a distant recurrence). It should be noted that 5/8 patients with stage III disease had a type C histology, as was the case for the two patients who recurred. Unfortunately in spite of further treatment, both of these patients died during follow-up due to disease progression.

Even though post-operative radiotherapy can benefit patients with resectable stage IV thymomas or thymic carcinomas (13, 23, 37), such cases may also be successfully managed by the application of a multimodality treatment approach (11, 26-28). Multimodality treatment approaches typically include induction chemotherapy, surgery and radiotherapy. In a study by Yokoi and co-workers 17 patients with advanced thymomas (stage III and IV) were managed with the application of a multidisciplinary approach, achieving 5 and 10-year TS rates of 80.7%. Tumor progression after multimodality therapy occurred in 10 patients (26). Similar results were also reported by Kim *et al.* (27) and Lucchi *et al.* (28). In the present study, 4/8 patients with stage IV disease underwent induction chemotherapy that was followed by surgery and radiotherapy. The rest of stage IV cases were managed by surgery, followed by radiotherapy. Out of 8 patients with stage IV disease, 4 developed intrathoracic recurrence, with 2 dying due to further disease progression in spite of chemotherapy (both of type C histology). The mean DFS, TS and DSS for stage IV patients were 14.5, 29.1 and 29.1 months respectively (Figures 1D-3D).

The results on survival (DFS, TS and DSS) in this study stratified fairly well with the patients' stage as has been reported in other studies (5, 10, 11). As expected, patients with type C histology had the shortest mean DFS, TS and DSS from all histological types, confirming the aggressive nature of such tumors. It has been previously reported that the 5 year survival of patients with thymic carcinoma ranges between 38-50% (29). Notably, in the present series 5/7 patients who recurred had locally advanced tumors of type C histology, with 4/5 dying due to disease progression.

Interestingly, patients with myasthenia included in this study had a significantly longer mean DFS, TS and DSS, showing that such patients have a better prognosis. Another point that needs to be discussed is the fact that patients who underwent radiotherapy had a statistically significantly shorter DFS, TS and DSS than non-irradiated patients. This can be explained by the fact that the majority of patients who underwent radiotherapy were stage III and IV patients.

Patients with negative surgical margins had a significantly longer DFS as compared to those with positive surgical margins ($p=0.0003$). Regarding TS, no statistical difference was noted between patients with totally and incompletely

resected tumors, whereas the difference for DSS was statistically significant ($p=0.039$) (Figures 1A-3A).

The Cox regression analysis investigating the potential prognostic parameters for DFS, TS and DSS showed that myasthenia was an important prognostic factor for DFS ($p=0.045$). The same was true for tumor size ($p=0.048$) (Table V). The fact that no other prognostic parameters were revealed may be attributed to the relatively small number of patients, contrary to the study by Yano *et al.* who reported, in 30 patients with thymic carcinoma, that resectability was the only prognostic factor (38).

A few limitations of the current study need to be acknowledged. The first drawback is that the mean follow-up time is 69 months, a time period that may be inadequate since thymomas may recur beyond 10 years. The follow-up time of this study is nevertheless comparable to that of other recently published papers (19, 36). A second potential concern is the selection of patients of stage II disease referred for postoperative radiotherapy. This bias is a problem met in all retrospective studies since surgeons may select patients with more aggressive disease. In this series the proportion of patients with IIA and IIB disease in irradiated and non-irradiated patients was almost equal and tumor size and histological types were similar between the two groups ($p=0.229$ and $p=0.06$ respectively). Finally, the relatively small number of patients studied is a consequence of the rarity of thymic tumors and is common in relevant published studies.

In the current series the role of radiotherapy in managing patients with thymomas was investigated. It was found that postoperative radiotherapy is not essential in totally resected stage I and II patients, whereas it is beneficial for more advanced stages. Statistically significant differences in DFS, TS and DSS were noted between the four thymoma stages and histological types, with patients' stage stratifying well with survival. Interestingly, patients with myasthenia had a more favorable outcome in terms of DFS, TS and DSS, whereas patients with negative surgical margins had a significantly longer mean DFS and DSS. Myasthenia and tumor size were found to be significant prognostic factors for DFS.

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