Thymectomy in Myasthenic Patients With Thymoma: Killing Two Birds With One Stone

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Background. **Thymoma and myasthenia gravis share several pathogenetic aspects including the role of surgery as a therapeutic option. Extended thymectomy is associated with excellent survival and good local control, especially in early stages, and its role for the neurologic disease has been recently validated. The aim of this study is evaluating oncologic and neurologic outcomes of myasthenic patients with thymoma who underwent extended thymectomy.**

Methods. **We retrospectively collected surgical, oncologic, and neurologic data of all myasthenic patients with thymoma who underwent extended thymectomy at our department from January 1994 to December 2016. Clinical and pathologic data, neurologic remission rate, and overall survival and disease-free interval were analyzed.**

Results. **In all, 219 patients underwent extended thymectomy. The B2 histotype was the most represented thymoma (24.2%), and the most prevalent pathologic Masaoka stage was IIB (37.9%). The overall survival and disease-free survival were statistically different between early stage and advanced stage. During the surveillance, 33 patients (15.1%) had recurrences, treated in 21 cases with iterative surgery. Regarding neurologic outcomes, 75 patients (34.2%) reached a complete stable remission, 84 (38.4%) a pharmacologic remission, 51 (23.3%) had an improvement of their symptoms, and in 9 patients (4.1%) myasthenia was unchanged or worsened.**

Conclusions. **Surgery is a cornerstone in the treatment of patients with both thymoma and myasthenia gravis. Extended thymectomy, as proposed by Masaoka, offers considerable oncologic outcomes with an excellent survival and low recurrence rate of thymoma; moreover, surgery leads to remarkable neurologic results.**

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Thymoma is a rare neoplasia originating from thymic epithelial cells, accounting for nearly 20% of all cancers of the whole mediastinum.[1] Thymomas are frequently associated with paraneoplastic syndromes, which occur in nearly 40% of the patients, whereas 30% of thymomas are associated with myasthenia gravis (MG), a chronic and disabling neurologic pathology characterized by skeletal muscle weakness and fatigability. Conversely, 75% of myasthenic patients have thymic abnormalities, and according to literature, thymoma may be found in as many as 20% of cases.[2]

Surgery plays an unquestionable role in the treatment of thymoma, not only in the early stages but also in the advanced stages, usually as part of multimodal treatment protocol, thanks to the radio-chemo sensitive nature of this kind of tumors.[3] Owing to the natural behavior of thymoma, characterized by a propensity for local growth and involvement of the surrounding organs rather than developing distant metastases, the most used surgical approach is median sternotomy, which allows a wide surgical field to control all the eventually involved structures. Over the last decades, minimally invasive approaches (namely, video-assisted thoracoscopic and robotic surgery) emerged as valid alternatives in selected cases, allowing a lower perioperative morbidity and an improvement of postoperative quality of life, even if long-term oncologic outcomes are still lacking.[4]

Instead, the therapeutic role of thymectomy for MG has long been a matter of debate worldwide and, only recently, validated for a selected subset of MG patients.[5] Indeed, in 2016, a randomized controlled trial conducted

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by Wolfe and colleagues[6] provided data in favor of the surgery as a therapeutic alternative in nonthymomatous MG. Because the thymus plays a fundamental role in the development of both pathologies, one of most used approach both for thymoma and MG is the extended thymectomy, as described firstly by Masaoka and associates,[7] related to a lower risk of subsequent thymic-correlated syndromes guided by the residual thymic tissue, and to a reduced recurrence rate.

The aim of this study is reporting oncologic and neurologic results of all myasthenic patients affected by thymoma who underwent extended thymectomy, analyzing potential risk factors affecting outcomes and supporting the double role of surgery for this subset of patients.

Material and Methods

Patients and Methods

We have retrospectively collected demographic, clinical, surgical, oncologic, and neurologic data of all patients affected by both thymoma and MG who underwent extended thymectomy at our department from January 1994 to December 2016, with at least 2 years of follow-up. The study was approved by the Ethics Committee at the University of Pisa.

Neurologic Evaluation

All patients were evaluated at the specialistic outpatient clinic for MG and staged according to both the Osserman and Myasthenia Gravis Foundation of America (MGFA) classifications (Supplemental Table 1). All patients of this series underwent surgery while receiving therapy with steroids (prednisolone) and cholinesterase inhibitors at various dosage, when not contraindicated by side effects. We reported neurologic data collected preoperatively, including the Osserman and MGFA class, MG composite score, and main dose of steroids or other immune-suppressive drugs; afterward, these values were compared with those collected during the last follow-up.[8,9] Neurologic results were classified according to the MGFA postintervention status and MG composite score, focusing on complete stable remission (CSR [Supplemental Table 2]), defined as no myasthenic symptoms or signs without any ongoing treatment for at least 1 year. The neurologic medical therapy was unchanged during the perioperative course to avoid worsening of MG symptoms, but then gradually decreased in dosage according to their improvement.

Surgical Evaluation and Technique

Before the operation, all patients were discussed in a multidisciplinary board and, therefore, addressed to surgery or in alternative to neoadjuvant or exclusive chemotherapy according to the clinical stage and resectability. In all cases we performed an extended thymectomy with radical intention through a partial median sternotomy, with cosmetic incision sparing 3 cm both from the jugulum and the xiphoid. In case of invasive thymoma deboarding in a hemithorax or in patients with pleural implants, we performed a hemiclamshell or a posterolateral thoracotomy incision. All thymic tissue including thymoma and mediastinal fat was removed, when possible, to achieve a radical resection (R0) except for selected cases of single phrenic nerve involvement, in

Table 1. Baseline Characteristics of Study Population

Variables	Values
Median age, years	53 (10-83)
Female	113 (51.6)
Male	106 (48.4)
Other paraneoplastic syndromes	
Hypogammaglobulinemia	12 (10.1)
Red cell aplasia	6 (5)
Neuromyotonia	2 (1.7)
Osserman class	
I	24 (11)
IIa	37 (16.9)
IIb	144 (65.8)
III	9 (4.1)
IV	5 (2.3
MGFA class	
I	24 (11)
IIa/IIb	31 (14.2)/6 (2.7)
IIIa/IIIb	91 (41.6)/14 (6.4)
IVa/IVb	32 (14.6)/19 (8.7)
V	2 (0.9)
Median hospital stay, days	6 (3-30)
Complications	
Total	48 (21.9)
Bleeding requiring transfusion	26 (12)
Phrenic nerve paralysis	4 (1.8)
Myasthenic crisis	6 (2.7)
Respiratory failure on awakening	6 (2.7)
Others	6 (2.7)
Pathologic Masaoka stage	
I	24 (11)
IIa	68 (31.1)
IIb	83 (37.9)
III	22 (10)
IVa	22 (10)
Pathologic WHO classification	
A	43 (19.6)
AB	41 (18.7)
B1	38 (17.4)
B2	54 (24.7)
B2-B3	8 (3.7)
B3	35 (16)
Surgical radicality	
R0	185 (84.5)
R1	27 (12.3)
R2	7 (3.2)

Values are n (%) or median (range).

MGFA, Myasthenia Gravis Foundation of America; WHO, World Health Organization.

which case we usually attempt a nerve-sparing surgery when there is no diaphragmatic paralysis.[10] Histology of thymomas was defined according to the World Health Organization classification, and the Masaoka-Koga staging system was used for thymomas pathologic staging. After surgery, all cases were reconsidered in a multidisciplinary setting and then directed to surveillance or adjuvant therapy according to histology and pathologic stage.

Statistical Analysis

Values are presented as mean ± SD or median with range. Student's *t* test or Wilcoxon's rank sum test was used to compare continuous variables. Overall survival (OS) analysis was estimated by the Kaplan-Meier method using the univariate log rank test and Cox regression model, calculated from the date of primary surgical treatment to death. Disease-free survival (DFS) was calculated from the date of surgery to the date of the first radiologic study demonstrating a recurrence. Factors potentially affecting OS, DFS, and CSR were analyzed by the Cox proportional hazards regression model, calculating the hazard ratio (HR) with 95% confidence interval (CI) in univariable and multivariable analysis. Variables with *P* values less than .05 at the univariate analysis were entered into the multivariable analysis.

Results

Surgical Results

In 23 years, 225 myasthenic patients with thymoma underwent surgery at our institution. Of them, 6 patients were lost to follow-up and excluded from this study. Results are summarized in Table 1. Nearly all patients reached good control of myasthenic symptoms just before surgery thanks to the administration of steroids and cholinesterase inhibitors, and only 5 patients who were not responsive to the medical therapy underwent surgery with uncompensated neurologic symptoms or immediately after a myasthenic crisis. Twenty-one patients required neoadjuvant therapy owing to the tumor's extension, in view of attempting a radical surgical resection.

Median sternotomy was the selected approach for extended thymectomy in 186 patients (84.9%), whereas other approaches (15.1%) were preferred in the remaining cases. No intraoperative adverse events occurred in this series, and 213 patients (97.3%) were extubated immediately after the operation. The median postoperative course was 6 days (range, 3 to 30) with a morbidity rate of 21.9% (48 patients): bleeding requiring a transfusion (26 patients, 12%) was the most reported complication, and 6 patients required prolonged mechanical ventilation after surgery. No 30-day mortality was reported; 2 patients died within 90 days from surgery owing to respiratory crisis. Adjuvant therapy was necessary in 143 patients in case of macroscopic extracapsular invasion or nonradical intervention (R1 in 27 patients and R2 in 7). Conventional radiotherapy was the most used treatment (132 patients), whereas chemotherapy and radiochemotherapy were required in 7 and 3 patients, respectively, in case of R2 resection or IVa stage.

Oncologic Results

After a mean follow-up of 100.4 ± 66.6 months, 22 patients were deceased, 13 of them due to causes other than MG and thymoma. The estimated OS was 260.8 months (95% CI, 242.4 to 279.3) with a statistical difference ($P < .001$) between early stages (270.3 months; 95% CI, 249.8 to 290.9) and advanced stages (169.8 months; 95% CI, 142.6 to 97). The OS rate was 97% (SE 0.015) at 5 years and 88.5% (SE 0.037) at 10 years for early stages, and 76.7% (SE 0.07) at 5 years and 69.7%SE 0.08) at 10 years for advanced stages (Figure 1).

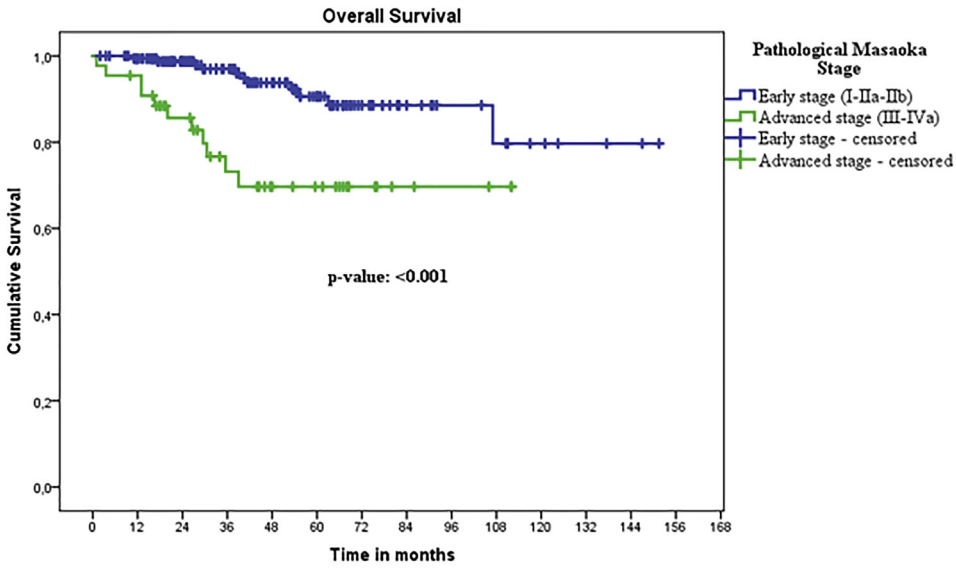

Figure 1. Overall survival according to thymoma pathologic Masaoka stage: early stage, I-IIa-IIb (blue); and advanced stage, III-IVa (green). Hatch marks indicate censored data.

Table 2. Oncologic Outcomes

Outcomes	Values
Months follow-up, mean ± SD	100.4 ± 66.6
Recurrence of thymoma	
No	186 (84.9)
Yes	33 (15.1)
Treated relapse	
Total	31 (14.2)
By surgery	21 (9.6)
Surgery alone	7 (3.2)
Surgery associated with HITHOC	10 (4.6)
Associated with radiotherapy	3 (1.4)
Associated with chemotherapy	1 (0.5)
By radiotherapy	7 (3.2)
By medical therapy	3 (1.4)
Dead at follow-up	
Total	22 (10)
Dead of disease	9 (4.1)
Dead of other causes	13 (5.9)

Values are n (%) unless otherwise indicated.

HITHOC, hyperthermic intrathoracic chemotherapy.

The estimated DFS was 243.1 months (95% CI, 221.8 to 264.4) with a clear distinction ($P < .001$) between early (278.6 months; 95% CI, 258.6 to 298.6) and advanced stage thymomas (82.6 months; 95% CI, 62.8 to 102.37). The disease-free interval rates for early stages were 96.6% (SE 0.015) and 93.2% (SE 0.029) at 5 and 10 years, respectively; and for advanced stages, 51.3% (SE 0.085) and 27.2% (SE 0.081) at 5 and 10 years, respectively (Figure 2).

During the follow-up, 33 patients had a recurrence (15.1%) as reported in Table 2, and were further discussed by a multidisciplinary board to decide the most appropriate treatment. Iterative surgery was the most used treatment (21 patients), frequently associated with hyperthermic intrathoracic chemotherapy (10 cases);[11] in the remaining patients, exclusive radiotherapy and somatostatin analogue therapy was used in 7 and 3 cases, respectively.

At the univariate analysis (Table 3), OS was significantly affected by preoperative and postoperative MGFA class ($P = .006$ and $P < .001$), age ($P = .026$), pathologic Masaoka stage ($P = .009$), surgical radicality ($P = .015$), and further recurrences ($P = .028$); DFS, instead, was influenced significantly by pathologic stage ($P < .001$), surgical radicality ($P < .001$), and by the World Health Organization histology with better results for A, B1, and B2 thymomas compared with B3 ($P < .001$). The multivariable analysis confirmed the significant role of postoperative MG severity in predicting the OS, and that advanced pathologic stage significantly affected DFS (Table 4).

Neurologic Results

The most common preoperative MG class was IIIa according to MGFA classification in 91 patients (41.6%), and IIb according to the Osserman in 144 cases (65.8%); 24 patients (11%) were affected by the ocular form. All but 4 patients had measurable serum acetylcholine receptor antibodies with a mean of 10.2 ± 7.3 nmol/L.

At last follow-up, 75 patients (34.2%) reached a CSR; 84 patients (38.4%) reached pharmacologic remission with the use of the lowest possible dose of corticosteroids (mean dose of prednisolone 10.5 ±10 mg per day). Other immunosuppressant agents were administered in 49 patients (22.4%). Fifty-one patients (23.3%) improved their neurologic symptoms control; only in 9 patients (4.1%) was surgery ineffective or detrimental to control the neurologic symptoms (Table 5).

More than 50% of patients with an ocular form or MGFA class IIa reached CSR, whereas for the more severe myasthenic form, this rate was significantly lower ($P < .001$). The MG composite score evaluated both before surgery and at last follow-up showed a significant decrease for MGFA classes from I to IVb ($P < .001$), but not for MGFA class V, which included only 2 patients.

Table 3. Univariable and Multivariable Analysis of Factors Affecting Overall Survival

	Univariable		Multivariable	
Variables	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Preoperative MGFA	1.4 (1.1-1.8)	.006	...	...
Age[a]	1.0 (1.0-1.1)	.026	...	...
Pathologic stage	1.6 (1.1-2.3)	.009	1.1 (0.7-1.7)	.551
Radicality	2.9 (1.2-7.0)	.015	2.9 (0.9-9.2)	.062
WHO histology	1.1 (0.8-1.4)	.519	...	...
Adjuvant therapy	1.1 (0.4-2.8)	.813	...	...
Recurrence	1.6 (1.1-2.5)	.028	...	...
Postoperative MGFA	2.7 (1.7-4.3)	<.001	2.9 (1.8-4.8)	<.001

[a]Continuous variable.

CI, confidence interval; HR, hazard ratio; MGFA, Myasthenia Gravis Foundation of America; WHO, World Health Organization.

Table 4. Univariable and Multivariable Analysis of Factors Affecting Disease-Free Survival

	Univariable		Multivariable	
Variables	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Preoperative MGFA	1.1 (0.9-1.4)	.193	...	...
Age[a]	0.9 (0.9-1.0)	.064	...	...
Pathologic stage	3.9 (2.8-5.7)	<.001	2.7 (1.7-4.4)	<.001
WHO histology	1.5 (1.2-1.9)	<.001	1.1 (0.8-1.3)	.379
Radicality	11.8 (5.8-24.3)	<.001	2.1 (0.8-5.2)	.130
Adjuvant therapy	0.45 (0.1-1.1)	.080	...	...
Postoperative MGFA	1.2 (0.8-1.7)	.352	...	...

[a]Continuous variable.

CI, confidence interval; HR, hazard ratio; MGFA, Myasthenia Gravis Foundation of America; WHO, World Health Organization.

Table 5. Neurologic Outcomes

Outcomes	Postoperative Patients Reached CSR	Postoperative Patients Symptom free[a]	Preoperative MGCS	Postoperative MGCS	*P* Value
Preoperative MGFA					
I	15 (62.5)	21(87.5)	5.83 ± 1.1	0.5 ± 1.3	<.001
II	IIa 16 (51.6)-IIb 0 (0)	IIa 28 (90.3)-IIb 3 (42.9)	12.43 ± 1.9	1.25 ± 3.1	<.001
III	IIIa 37 (42)-IIIb 1 (6.7)	IIIa 80 (90.9)-IIIb 8 (53.3)	20.16 ± 2.5	1.37 ± 3.6	<.001
IV	IVa 2 (6.7)-IVb 4 (18.2)	IVa 4 (13.3)-IVb 15 (68.2)	31.12 ± 2.5	10.02 ± 8.9	<.001
V	0 (0)	0 (0)	43.5 ± 2.12	45 ± 0	.5
Postintervention MGFA	Number of Patients	Preoperative Steroid (mg)	Postoperative Steroid (mg)		
CSR	75 (34.2)	27.4 ± 16	0 ± 0		<.001
PR	84 (38.4)	32.3 ± 21	10.5 ± 10		<.001
Improved	51 (23.3)	40.5 ± 18	14.2 ± 8		<.001
Unchanged/worse	9 (4.1)	45.8 ± 19	47.5 ± 28		.655

[a]Complete stable remission (CSR) and pharmacologic remission (PR).

Values are n (%) or mean ± SD.

MGCS, myasthenia gravis composite score; MGFA, Myasthenia Gravis Foundation of America.

The mean prednisolone dose was significantly reduced after surgery in patients who reached CSR, pharmacologic remission, and improved MG ($P < .001$); patients in whom surgery was ineffective to control myasthenic symptoms, instead, showed a not statistical difference in the steroid dosage ($P = .655$).

The achievement of complete stable remission was significantly influenced, at both univariate and multivariate analysis, only by preoperative myasthenia severity according to the MGFA. Moreover, univariate analysis showed a correlation between CSR and the pathologic stage ($P = .049$), even if these data were not confirmed at multivariate analysis (Table 6).

Comment

In the past, MG was an indicator of poor prognosis in the management of thymoma because of high surgical risk and perioperative mortality. Recently, improved perioperative neurologic care as well as postoperative medical and respiratory support for MG patients reversed this trend.[12,13] The role of surgery in thymoma management has never been in dispute, either as exclusive treatment for early stage thymomas or as part of multimodality treatment in the advanced stage thymomas, although different surgical techniques were described, from the resection of the sole tumor (thymomectomy), to the thymectomy (or thymothymectomy) to the "extended" and the "maximal" thymectomy.[14-16]

The role of thymectomy in the treatment of MG, however, has been controversial for more than 60 years, mainly owing to lack of prospective studies.[5] Gilhus and colleagues[17] in 2015 conducted a systematic review on this issue, concluding that thymectomy is strongly recommended for early onset MG and thymomatous MG; and Wolfe and associates[6] published results of a randomized trial proving that surgery plays a fundamental role in the treatment of MG and improves clinical outcomes in nonthymomatous myasthenic patients. Because the thymus plays a fundamental role in the development of both pathologies, removing all thymic tissue, included ectopic tissue, should be considered the main goal of surgery.[18]

From the beginning, we performed an extended thymectomy in myasthenic patients (with or without thymoma), by removing the entire thymic gland en bloc with all the mediastinal fat through a median sternotomy; that allowed a safe and effective resection of the tumor and the potentially involved structures and the resection of most ectopic foci of thymic tissue. During this timeframe, no radical changes occurred in our surgical management in terms of approach and surgical extension, except for the routine use of minimally invasive techniques (video-assisted thoracic surgery/robotic) for thymic hyperplasia and selected small thymomas since 2015. However, no patients in this study underwent minimally invasive thymectomy. Also, the neurologic treatment remained basically unchanged, despite the introduction of new therapeutic regimens as the combination of steroids and cholinesterase inhibitors in our experience has proved to

Table 6. Univariable and Multivariable Analysis of Factors Affecting Complete Stable Remission

	Univariable		Multivariable	
Variables	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Preoperative MGFA	0.6 (0.5-0.7)	<.001	0.6 (0.5-0.7)	<.001
Age[a]	1.1 (0.9-1.1)	.111	...	...
Male	0.6 (0.3-1.1)	.139	...	...
Pathologic stage	0.7 (0.6-0.9)	.049	0.8 (0.6-1.1)	.167
Radicality	0.6 (0.3-1.4)	.255	...	...
WHO histology	0.9 (0.8-1.1)	.580	...	...

[a]Continuous variable.

CI, confidence interval; HR, hazard ratio; MGFA, Myasthenia Gravis Foundation of America; WHO, World Health Organization.

Table 7. Comparison of Neurologic Outcomes in Recently Reported Series

First Author	Patients (n)	Surgical Technique	CSR (%)	PR (%)	Follow-up (years)
Jaretzki[16]	15	Maximal	13.3	53.3	3.3
Masaoka[15]	89	Extended	37.5	50	20
Venuta[24]	62	Extended	14.5	46	9.9
Maggi[19]	197	Extended	9.6	NR	7.6
López-Cano[27]	108	Simple and extended	15.7	50.9	10
Evoli[22]	207	Extended	9.2	21.6	10.1
Park[25]	49	Extended	27.7	NR	7.4
Current study	219	Extended	34.2	38.4	8.4

CSR, complete stable remission; NR, not reported; PR, pharmacologic remission.

be the most effective and safe therapy in this subset of patients. All patients with unresectable thymoma at the preoperative computed tomography scan are referred to neoadjuvant chemotherapy to achieve a reduction of the bulky mass; and regarding the adjuvant therapy, indications are provided by a dedicated multidisciplinary team once in possession of histology analysis. However, all patients with a locally advanced thymoma (stage IIb or higher) or R1/R2 resections underwent adjuvant therapy when not contraindicated.

This study analyzed one of the largest cohorts of patients with thymoma and MG who underwent surgery with radical intent in one single center to evaluate the double result, oncologic and neurologic, avoiding any comparison with nonmyasthenic or nonthymomatous patients to reduce, as much as possible, any confounding bias.

In this retrospective analysis we observed overall survival rates as 97% and 88.35% at 5 years and 10 years respectively, for early stages, and 76.7% and 69.7% at 5 and 10 years for advanced stages. These encouraging results appear in line with outcomes of different authors who advocate the use of extended thymectomy as the best approach to thymomas. Maggi and colleagues[19] reported 5-year and 10-year survival rates of 85% and 82%, respectively, in myasthenic patients affected by thymoma; Regnard and colleagues[20] had 10-year survival rate of 70% for surgical MG patients; and Kondo and associates[21] described a 5-year OS rate for myasthenic patients with stage III and IV thymomas of 85.7% and 85.1%, respectively.

Regarding the oncologic disease control, in our series the 5-year DFS rates were 96.6% for early stages and 51.3% for advanced stages thymomas; moreover, in more than 85% of cases, we achieved a radical resection and only 33 patients (15.1%) had a recurrence. These outcomes are also in accordance with the literature: Evoli and associates[22] described a 15.65% recurrence rate after surgery in patients affected by thymoma in stages II, III and IVa; and Margaritora and colleagues[23] described 5-year DFS rates of 99.1%, 97.1%, 80.8%, and 51.5% for stages I to IV, respectively.

In this study, older age, advanced stage, not radical surgery, and recurrences emerged as independent prognostic factors affecting OS. Nevertheless, only severe forms of MG or those not responsive to the surgical

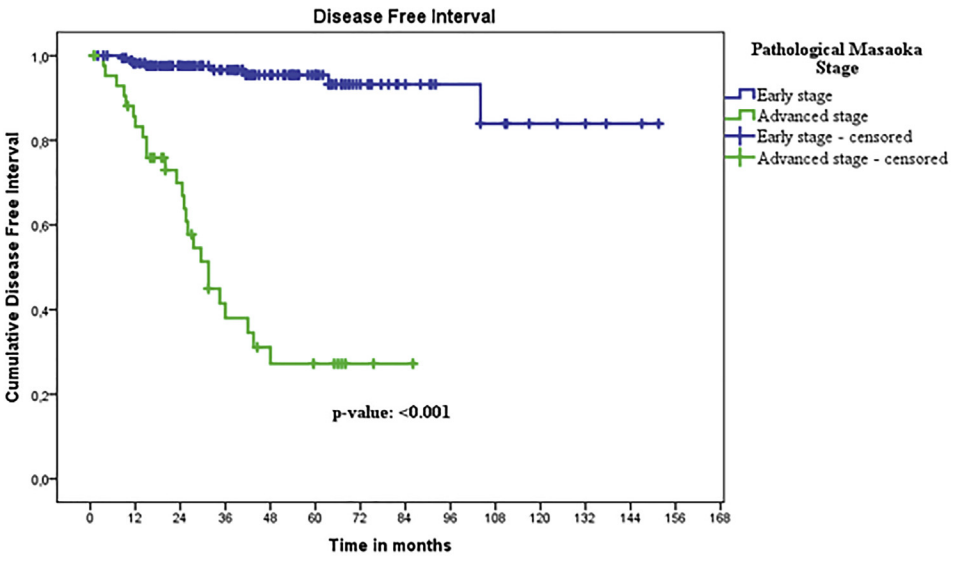

Figure 2. Disease-free survival according to thymoma pathologic Masaoka stage: early stage (blue); and advanced stage (green). Hatch marks indicate censored data.

treatment were associated with a worse prognosis also at multivariable analysis; that may be explained by MG-related morbidity and mortality. Possible reasons for the nonsignificance of pathologic stage and surgical radicality at the multivariable analysis may be found in the indolent behavior of thymomas and in their high chemotherapy and radiotherapy sensibility, which make these tumors susceptible to multimodal treatments especially in case of nonradical surgery. Moreover, the close surveillance allowed early detection and treatment of recurrences that preserve the same attitude of the primary tumor and may benefit from iterative surgery, highly effective in local disease control.

As expected, DFS turned out to be significantly influenced at univariable analysis by advanced pathologic stage B2 and B3 forms of thymomas and not radical surgery, but only the pathologic stage was confirmed as a prognostic factor at multivariable analysis, probably because of the close correlation of the variables and the small number of events observed.[24-26] Adjuvant therapy (mainly radiation) was related, even if not in a significant way, to a trend toward better DFS at univariate analysis ($P = .08$); this result suggests that performing consolidation therapy in case of extracapsular invasion is a valid option to achieve better disease control.[3] Regarding neurologic outcomes, in this series, we observed a CSR rate and a pharmacologic remission rate of 34.2% and 38.4%, respectively. Compared with results of other researchers (Table 7), our results emphasize the role of the extended thymectomy.

Jaretzki and colleagues[16] conducted pioneering work on the transcervical-transternal maximal thymectomy and reported a 46% CSR rate and a 33% pharmacologic remission rate in nonthymomatous patients, whereas thymomatous patients showed 13.3% CSR and 53.3% pharmacologic remission.

Masaoka and associates[15] found a 50% of remission rate in nonthymomatous patients compared with 37.5% of the thymomatous group. Lopez-Cano and associates[26] reported their experience in 108 thymomatous and myasthenic patients operated on with two different techniques, total thymectomy (until the 1980s) and extended thymectomy, observing a CSR rate of 15.7% and a pharmacologic remission rate of 50.9% after 10 years of follow-up. Only Maggi and colleagues[19] and Evoli and coworkers[22] described a CSR rate reasonably lower (9.64% and 9.2%, respectively), probably owing to the methodologic approach to the analysis.

Regarding factors affecting CSR rate, we investigated the role of age, sex, preoperative MGFA classification, pathologic stage, resection radicality, and World Health Organization classification. Of them, only the preoperative MGFA classification ($P < .001$) and the pathologic stage showed a strong correlation with the CSR in the univariate analysis, but multivariate analysis confirmed only the prognostic effect of the preoperative MG severity. Indeed, we found a higher CSR rate in cases of less severe MG, even in stage I MG, the treatment of which is still under debate. This result was previously described by Masaoka and associates,[15] Maggi and colleagues,[19] Venuta and colleagues,[24] and Na and coworkers,[27] whereas other investigators such as Park and coworkers[25] and López-Cano and colleagues[26] have not found any correlations between CSR and MG severity.

An interesting result, moreover, is the relevant reduction of steroid dosage after surgery. Long-term use and high dose of steroids are associated with many side effects, including cushingoid features, infections, hypertension, diabetes mellitus, and osteoporosis. Patients who reached a CSR have suspended any treatment at last follow-up, whereas among patients who reached pharmacologic remission or had symptom improvement, we observed a significant reduction of the mean dosage of steroids ($P < .001$).

According to these results, we may conclude that surgery is considered a mainstay in the treatment of patients with association of both thymoma and MG. Extended thymectomy offers considerable oncologic outcomes with an excellent survival and a low recurrence rate of thymoma; moreover, it leads to satisfactory neurologic results. Cooperation between thoracic surgeon, anesthesiologist, and neurologist plays a fundamental role to optimize the treatment of such delicate patients through a synergistic effect.

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