

# Myasthenia gravis as a prognostic marker in patients with thymoma

Bernardo Cacho-Díaz<sup>1</sup>, Karen Salmerón-Moreno<sup>1</sup>, Nydia A. Lorenzana-Mendoza<sup>1</sup>, Julia Texcocano<sup>1</sup>, Oscar Arrieta<sup>2</sup>

<sup>1</sup>Neuroscience Unit, Instituto Nacional de Cancerología, México City, México; <sup>2</sup>Thoracic Oncology Unit, Instituto Nacional de Cancerología, México City, México

*Contributions:* (I) Conception and design: B Cacho-Díaz, O Arrieta; (II) Administrative support: B Cacho-Díaz, O Arrieta; (III) Provision of study materials or patients: K Salmerón-Moreno, B Cacho-Díaz; (IV) Collection and assembly of data: NA Lorenzana-Mendoza, B Cacho-Díaz; (V) Data analysis and interpretation: J Texcocano, O Arrieta; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

*Correspondence to:* Bernardo Cacho-Díaz. Av. San Fernando 22, Sección XVI Tlalpan Z.C. 14080 México City, México.

Email: bernardocacho@doctor.com.

**Background:** Thymoma is the most common mediastinal tumor, representing <1% of all cancers. It is usually associated with paraneoplastic disorders, mainly myasthenia gravis (MG). The aim of the present study was to describe patients with thymoma and the differences between those with MG and those without it.

**Methods:** A retrospective 10-year database of the patients with thymoma treated at a single cancer referral hospital (National Institute of Cancer, Mexico City), was analyzed.

**Results:** Sixty-four files from patients with thymoma were analyzed, 18 of them had MG. The symptoms that occurred most frequently in patients with MG were ptosis, diplopia, appendicular weakness, dysphonia and dysphagia. The most frequent Myasthenia Gravis Foundation of America (MGFA) stage was IIIb followed by stage I. Almost all the patients with MG had positive Acetylcholine Receptor antibodies (P<0.001), with not specified antibodies in four patients. The median overall survival showed a trend to be higher among the patients with MG, but there were no significant differences.

**Conclusions:** In patients with thymoma MG manifests with different clinical and autoimmune traits, but not survival differences. A larger multi-centric study should be encouraged to evaluate the prognostic implications of having MG in patients with thymoma.

**Keywords:** Thymoma; myasthenia gravis (MG); acetylcholine receptor (AChR)

Submitted Dec 16, 2017. Accepted for publication Mar 29, 2018.

doi: 10.21037/jtd.2018.04.95

View this article at: <http://dx.doi.org/10.21037/jtd.2018.04.95>

## Introduction

Thymic epithelial tumors (TET) are mainly composed of thymomas (T) and thymic carcinomas; they are the most common primary neoplasms of the anterior mediastinum. Thymomas are the most frequent mediastinal neoplasm, their frequency is about 20% of cases (1,2). Thymic carcinomas are more aggressive neoplasms and their relation with autoimmune diseases is extremely rare, due to its cytological atypia and lack of thymus like features (2). Compared with all cancers, thymomas account for less than

0.5%, with an incidence of 0.15 per 100,000 person years (3). The mean age at the time of diagnosis is 52 years, without gender predominance. TET are usually asymptomatic and are found as an incidental mediastinal mass in chest X-ray. One-third of the patients with TET have chest pain, cough or dyspnea related to tumor compression or invasion (4).

Myasthenia gravis (MG) is a rare neuromuscular disease caused by antibodies against neuromuscular junction and represents the most common paraneoplastic disease associated with thymoma (5), however, a wide range of autoimmune diseases have been reported, i.e., Cushing

syndrome, pure red blood cell aplasia, rheumatoid arthritis, immunodeficiency (Good's syndrome) and thymoma-associated multiorgan autoimmunity (6,7). Most patients with MG associated thymoma have antibodies against the postsynaptic nicotinic acetylcholine receptor (AChR) (8). Nevertheless, non-AChR muscle antibodies could also be present in more than 95% of thymoma patients, targeted mainly against striated muscle titin and ryanodine receptor (strational antibodies), and are usually associated with a severe and late-onset form of MG (9,10).

MG is present in 30–50% of patients with thymoma, while 10–20% of patients with MG have thymoma (although some report an association as high as 80%) (2,5,8). Thymoma associated MG is considered to have a worse prognosis and poor outcome, being thymoma a negative prognostic factor between MG patients; paradoxically, some have postulated that patients with thymoma and MG have a survival advantage over patients without MG; thus a prognostic significance has not yet been established (11–13).

Thymomas are classified based upon their histologic appearance in five subtypes according to the World Health Organization (WHO) system: A, AB, B1, B2, B3, and thymic carcinoma cases are classified as C. Most of the data supporting treatment decisions are based on the most widely used tool for staging thymic malignancies: the Masaoka-Koga staging system (14).

Thymectomy is the cornerstone treatment modality in patients with early stages of TET and is an approved treatment modality for patients with seropositive MG even without thymoma (15). Thymectomy in patients with T has a probability of complete remission of 28–48% (16), a complication rate of 20% (blood vessel damage, postoperative myasthenic crisis, pain, and infection) and a 2% mortality (17).

The present study describes the clinical features and prognosis of the patients with TET and MG and compares them to those without MG.

## Methods

At a cancer referral hospital (National Institute of Cancer, Mexico City), all the files of the patients with TET from 2006–2016 were analyzed. The database collected: demographic, clinical symptoms, oncologic history, comorbid paraneoplastic disorders, and outcome characteristics. Patients with TET and myasthenia gravis (TMG) were compared to those without myasthenia gravis (TnMG). The study was reviewed and approved by our

Institutional ethics and scientific committees (INCAN/CI/837/17). Variables were compared using the chi-square or Student T tests according to the case. Prognosis was analyzed using Kaplan-Meier curves with log-rank test to identify the differences between the groups,  $P < 0.05$  was considered to be statistically significant. SPSS Statistics v.18 software (IBM Corp., Armonk, NY, USA) was used to perform the analysis.

## Results

We report 64 patients with thymoma, 35 (54.7%) were men, 29 (45.3%) were women; the most common WHO stage was B (28%). Eighteen patients (28.1%) were diagnosed with MG as seen in *Table 1*. We classified MG patients according to the Myasthenia Gravis Foundation of America (MGFA), and the most common stage was IIIb followed by stage I (*Table 2*). The mean age at the time of thymoma diagnosis was 51.4 years (range, 16–81 years) and the mean age at the time of thymectomy was 52.5 years; the mean age at the time of MG diagnosis was 49.6 years (range, 27–65 years). The mean latency of time between the diagnosis of MG and thymectomy was 8 months. All patients had biopsy proven TET; according to the treatment, 34 (53.1%) patients underwent surgery, of which, 30 (88.2%) were treated with extended transsternal thymectomy; and 3 (8.8%) were treated with partial median sternotomy thymectomy, two of them due to non resectable tumor and the last one due to hemodynamic complications during surgery. The detailed first line therapy is described in *Table 3*.

After a mean of 3-year follow-up three TMG patients died, causes of death were due to postoperative cardiac arrest and Good's Syndrome. In the TnMG, ten patients died: five deaths were due to cardiac arrest, four due to cancer progression and one due to hypovolemic shock. *Figure 1* and *Table 4* shows the overall survival and the survival differences between both groups; no difference in overall survival was seen between patients with thymoma or thymic carcinoma. Clinical findings, metastases and acetylcholine receptor antibody (AChr-Ab) comparing TMG and TnMG groups, are described in *Table 5*. Most frequent symptoms in TMG were: diplopia 15 (83%), appendicular weakness 13 (72%), ptosis 13 (72%), dysphagia 11 (61%) and speech impairment 9 (50%), the rest of the symptoms were not statistically significant. Metastatic disease was found more frequent in TnMG (8 patients had lung, 7 bone, 4 hepatic and 1 CNS metastases). AChR-Ab was positive in 14 (78%) MG patients, and not specified in

**Table 1** Characteristics of thymoma patients with and without myasthenia gravis

Characteristic	All (n=64), % (n/N)	Thymoma		P
		With MG (n=18), % (n/N)	Without MG (n=46), % (n/N)	
Gender				0.930
Female	45.3 (29/64)	44.4 (8/18)	45.7 (21/46)	
Male	54.7 (35/64)	55.6 (10/18)	54.3 (25/46)	
Age, years				
Mean ( $\pm$ SD)	51.4 (13.0)	50.8 (10.7)	51.7 (13.8)	0.966
<50	43.7 (28/64)	38.9 (7/18)	45.7 (21/46)	
>50	56.3 (36/64)	61.1 (11/18)	54.3 (25/46)	0.624
Histology				0.091
Thymic carcinoma	21.8 (14/64)	0 (0/18)	30.4 (14/46)	
Thymoma A	7.8 (5/64)	11.1 (2/18)	6.5 (3/46)	
Thymoma AB	15.6 (10/64)	22.2 (4/18)	13.0 (6/46)	
Thymoma B	28.1 (18/64)	55.6 (10/41)	17.4 (8/46)	
Fusocellular/mixed	14.0 (9/64)	5.6 (1/18)	17.4 (8/46)	
Other	12.5 (8/64)	5.6 (1/18)	15.2 (7/46)	
WHO stage				0.012
A	9.4 (6/64)	11.1 (2/18)	8.7 (4/46)	
AB	20.3 (13/64)	22.2 (4/18)	19.6 (9/46)	
B	28.1 (18/64)	55.6 (10/18)	17.4 (8/46)	
C	14.1 (9/64)	0 (0/18)	19.6 (9/46)	
Not specified	28.1 (18/64)	11.1 (2/18)	34.8 (16/46)	
Masaoka stage				0.300
I	11 (7/64)	11.1 (2/18)	10.9 (5/46)	
II	12.5 (8/64)	22.2 (4/18)	8.7 (4/46)	
III	6.2 (4/64)	5.6 (1/18)	6.5 (3/46)	
IV	31.2 (20/64)	33.3 (6/18)	30.4 (14/46)	
NE	39.0 (25/64)	27.8 (5/18)	43.5 (20/46)	
Tumor size				0.993
Mean ( $\pm$ SD)	67.05 (40.0)	65.7 (40.9)	67.6 (40.1)	

SD, standard deviation.

4 (22%) patients in whom the diagnosis was made by other institutions before National Institute of Cancer admission.

## Discussion

We studied 64 patients with thymoma and compared

those with MG with those without MG, although clinical symptoms and autoimmune presentations were different, no difference was found in overall survival.

In our study, the age of onset, the frequency of the patients with TMG and the stage of diagnosis was consistent with the previous reports (3,4,11,18). None of

**Table 2** MGFA classification of the 18 patients with thymoma associated myasthenia gravis

MGFA	n [%]	P
I	5 [28]	
Ila	-	
Ilb	1 [6]	
IIla	3 [17]	
IIlb	7 [39]	
IV	-	
Not specified	2 [11]	<0.001

MGFA, Myasthenia Gravis Foundation of America.

**Table 3** First-line treatment in patients with thymoma among patients with TMG and TnMG

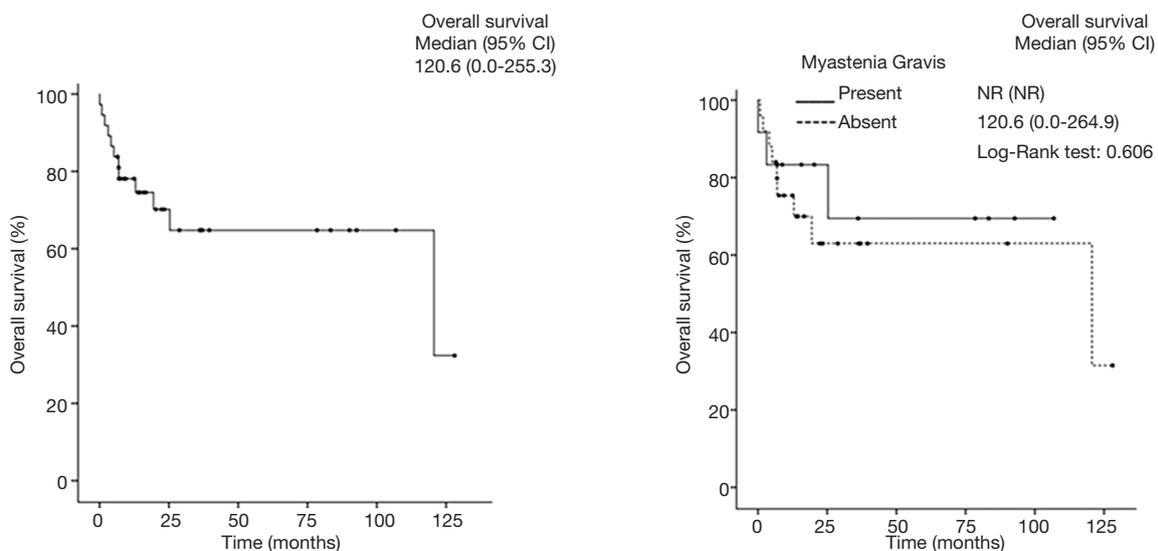
Treatment modality	Thymoma	
	With MG (n=18), % (n/N)	Without MG (n=46), % (n/N)
Qx	38.9 (7/18)	17.4 (8/46)
RT	0 (0)	10.9 (5/46)
Ch	0 (0)	8.7 (4/46)
Qx + Rt	11.1 (2/18)	15.2 (7/46)
Qx + Ch	11.1 (2/18)	0 (0)
Ch + RT	5.6 (1/18)	34.8 (16/46)
Qx + RT + Ch	27.8 (5/18)	6.5 (3/46)
Other	5.6 (1/18)	4.3 (2/46)

Qx, thymectomy; RT, radiotherapy; Ch, chemotherapy; TMG, thymoma with myasthenia gravis; TnMG, thymoma without myasthenia gravis.

**Table 4** Univariate analysis of the clinical factors associated with OS among patients

Variable	Median, months (95% CI)	P
Overall	120.6 (0.0–255.3)	-
Gender		0.017
Female	NR (NR)	
Male	25.3 (0.0–70.3)	
Age, years		0.464
<50	120.6 (25.3–NR)	
>50	NR (NR)	
Histology		0.746
Thymoma	NR (NR)	
Thymic carcinoma	120.6 (0.0–272.1)	
WHO stage		0.247
A, AB	NR (NR)	
B, C	120.6 (0.0–266.7)	
Tumor size		0.245
<5	NR (NR)	
>5	120.6 (NR)	
Myasthenia gravis		0.606
Absent	120.6 (0.0–264.9)	
Present	NR (NR)	

NR, not reached.



**Figure 1** Kaplan-Meier curves for the OS of patients among all patients and according to the diagnosis or not of myasthenia gravis.

**Table 5** Clinical findings, metastases and AChR-Ab among patients with or without MG

Clinical finding	All (n=64), % (n/N)	Thymoma		P
		With MG (n=18), % (n/N)	Without MG (n=46), % (n/N)	
Diplopia				<0.001
Present	25 (16/64)	83.3 (15/18)	2.2 (1/46)	
Absent	75 (48/64)	16.7 (3/18)	97.8 (45/46)	
Appendicular weakness				<0.001
Present	26.6 (17/64)	72.2 (13/18)	8.7 (4/46)	
Absent	73.4 (47/64)	27.8 (5/18)	91.3 (42/46)	
Ptosis				<0.001
Present	20.3 (13/64)	72.2 (13/18)	0 (0/46)	
Absent	79.7 (51/64)	27.8 (5/18)	100.0 (46/46)	
Dysphagia				<0.001
Present	20.3 (13/64)	61.1 (11/18)	4.3 (2/46)	
Absent	79.7 (51/64)	38.9 (7/18)	95.7 (44/46)	
Speech impairment				<0.001
Present	18.7 (12/64)	50.0 (9/18)	6.5 (3/46)	
Absent	81.2 (52/64)	50.0 (9/18)	93.5 (43/46)	
Dyspnea				0.528
Present	56.2 (36/64)	50.0 (9/18)	58.7 (27/46)	
Absent	43.7 (28/64)	50.0 (9/18)	41.3 (19/46)	
Cough				0.084
Present	39.1 (25/64)	22.2 (4/18)	45.7 (21/46)	
Absent	60.9 (39/64)	77.8 (14/18)	54.3 (25/46)	
Pleural effusion				0.221
Present	14.1 (9/64)	5.6 (1/18)	17.4 (8/46)	
Absent	85.9 (55/64)	94.4 (17/18)	82.6 (38/46)	
Red series aplasia				0.837
Present	4.7 (3/64)	5.6 (1/18)	4.3 (2/46)	
Absent	95.3 (61/64)	94.4 (17/18)	95.7 (44/46)	
Metastases				0.062
Present	40.6 (26/64)	33.3 (6/18)	43.5 (20/46)	
Absent	59.4 (38/64)	66.7 (12/18)	56.5 (26/46)	
AChR-Ab positive				<0.001
Present	21.9 (14/64)	77.8 (14/18)	0 (0)	
Absent	4.7 (3/64)	0 (0)	6.5 (3/46)	
NA/NS	73.4 (47/64)	22.2 (4/18)	93.5 (43/46)	

NA, not applicable; NS, not specified; AChR-Ab, acetylcholine receptor antibody.

our patients from the TMG group were diagnosed with thymic carcinoma, although it has been described (19,20). Nearly 90% of the patients with TMG had positive AChR-Ab, data that agrees with previous works and reports of the literature (8,12,20). In two patients with TnMG, MG was suspected and was tested for AChR-Ab: one with diplopia and appendicular weakness and the second with dysphonia; both were negative and had thymic carcinoma. To our knowledge, just a small number of authors have reported TMG without AChR-Ab (19,21). Pure red cell aplasia was found in 5% of all cases, similar to previous reports (2,4). The Good's syndrome in patients with T has an estimated incidence of 5% (4,6), we found it in one patient with TMG and in one patient with TnMG. It has been described that patients with thymoma associated MG have a worse prognosis, and hence were likely to have a worse outcome (12,22). As expected, our patients had several clinical manifestations of MG that had statistically significant differences, these manifestations were not remitted after thymoma treatment.

The prognostic value of MG associated thymoma remains controversial in the different reports of the literature, some established the presence of MG as a good survival prognostic factor related to the onset of MG symptoms that leads a prompt approach and treatment (23-25); others reported that having MG or not, didn't show any statistical significance, same as our results (11,26-28); and finally, some studies reported even a worse prognosis in patients with MG (17,29). This discrepancies are probably due to the wide range of clinical and pathogenic variants in MG patients, the present study has several limitations: the information was retrospectively acquired at a single institution, it includes only 64 patients and a referral bias should be considered, nevertheless, this report is valuable because in the best of our knowledge there is scarce information about MG and thymoma from Hispanic referral cancer centers; a study from 1991 had one of the largest population with MG and thymoma, and they reported a better overall survival in patients with MG compared with TnMG group (30). Since our database included patients that were detected years ago when the approach were less clearly and the patients were delayed in being referred to the appropriate specialist, most of our patients were in Masaoka stage IV, therefore, they had poor prognosis and high recurrence (13). According to the treatment 16 of TMG underwent thymectomy, one of them with partial resection; although there was a trend towards improved overall survival, this was not statistically

significant in contrast to the reported by others (31).

Thymomas usually have no gender predilection (22), in our population we found an increased frequency in males, actually, after the univariate analysis we found that being male represents a prognostic factor associated with better overall survival ( $P=0.017$ ).

Despite the low frequency of this disease, and given that there is still a lack of consensus on the impact of MG on overall survival, we encourage future studies to establish the optimal management and prognosis of thymoma patients and to find the best evidence.

## Conclusions

In a group of Hispanic patients with thymoma, MG had a prevalence of 28%, although we did not find statistically significant differences in overall survival; a larger multicentric study should be encouraged to have a better understanding of the prognostic implications of having MG in patients with thymoma. Moreover, it is recommended that all patients should be managed by a multidisciplinary team with experience in the management of TETs and with specific knowledge of the ongoing clinical trials.

## Acknowledgements

None.

## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* The study was reviewed and approved by our Institutional ethics and scientific committees (INCAN/CI/837/17).

## References

1. Ettinger DS, Riely GJ, Akerley W, et al. Thymomas and thymic carcinomas: Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2013;11:562-76.
2. Scorsetti M, Leo F, Trama A, D'angelillo R, et al. Thymoma and thymic carcinomas. *Crit Rev Oncol Hematol* 2016;99:332-50.
3. Kumar R. Myasthenia gravis and thymic neoplasms: A brief review. *World J Clin Cases* 2015;3:980-3.
4. Duwe BV, Sterman DH, Musani AI. Tumors of the

- mediastinum. *Chest* 2005;128:2893-909.
5. Marx A, Porubsky S, Belharazem D, et al. Thymoma related myasthenia gravis in humans and potential animal models. *Exp Neurol* 2015;270:55-65.
  6. Kelleher P, Misbah SA. What is Good's syndrome? Immunological abnormalities in patients with thymoma. *J Clin Pathol* 2003;56:12-6.
  7. Cufi P, Soussan P, Truffault F, et al. Thymoma-associated myasthenia gravis: On the search for a pathogen signature. *J Autoimmun* 2014;52:29-35.
  8. Romi F, Hong Y, Gilhus NE. Pathophysiology and immunological profile of myasthenia gravis and its subgroups. *Curr Opin Immunol* 2017;49:9-13.
  9. Fujii Y. The thymus, thymoma and myasthenia gravis. *Surg Today* 2013;43:461-6.
  10. Berrih-Aknin S. Myasthenia Gravis: Paradox versus paradigm in autoimmunity. *J Autoimmun* 2014;52:1-28.
  11. Aydemir B. The effect of myasthenia gravis as a prognostic factor in thymoma treatment. *North Clin Istanbul* 2017;3:194-200.
  12. Cacho Diaz B, Flores-Gavilán P, García-Ramos G, et al. Myasthenia gravis and its comorbidities. *J Neurol Neurophysiol* 2015;6:1-5.
  13. Filosso PL, Evangelista A, Ruffini E, et al. Does myasthenia gravis influence overall survival and cumulative incidence of recurrence in thymoma patients? A Retrospective clinicopathological multicentre analysis on 797 patients. *Lung Cancer* 2015;88:338-43.
  14. Masaoka A. Staging system of thymoma. *J Thorac Oncol* 2010;5:S304-12.
  15. Wolfe GI, Kaminski HJ, Aban IB, et al. Randomized trial of thymectomy in myasthenia gravis. *N Engl J Med* 2016;375:511-22.
  16. Marulli G, Rea F. Myasthenia gravis and thymectomy: many doubts and few certainties. *Eur J Cardiothorac Surg* 2015;48:46-7.
  17. Zhang Z, Cui Y, Jia R, et al. Myasthenia gravis in patients with thymoma affects survival rate following extended thymectomy. *Oncol Lett* 2016;11:4177-82.
  18. Safieddine N, Liu G, Cuningham K, et al. Prognostic factors for cure, recurrence and long-term survival after surgical resection of thymoma. *J Thorac Oncol* 2014;9:1018-22.
  19. Maggi L, Andreetta F, Antozzi C, et al. Two cases of thymoma-associated myasthenia gravis without antibodies to the acetylcholine receptor. *Neuromuscul Disord* 2008;18:678-80.
  20. Vincent A, Bowen J, Newsom-Davis J, et al. Seronegative generalised myasthenia gravis: clinical features, antibodies, and their targets. *Lancet Neurol* 2003;2:99-106.
  21. Richards J, Howard JF. Seronegative myasthenia gravis associated with malignant thymoma. *Neuromuscul Disord* 2017;27:417-8.
  22. Gadalla SM, Rajan A, Pfeiffer R, et al. A population-based assessment of mortality and morbidity patterns among patients with thymoma. *Int J Cancer* 2011;128:2688-94.
  23. Wang F, Pang L, Fu J, et al. Postoperative survival for patients with thymoma complicating myasthenia gravis-preliminary retrospective results of the ChART database. *J Thorac Dis* 2016;8:711-7.
  24. Akaishi T, Suzuki Y, Imai T, et al. Response to treatment of myasthenia gravis according to clinical subtype. *BMC Neurol* 2016;16:225.
  25. Li W, Miao Z, Liu X, et al. Thymic carcinoma patients with myasthenia gravis exhibit better prognoses. *Int J Clin Oncol* 2016;21:75-80.
  26. Kondo K, Monden Y. Thymoma and myasthenia gravis: a clinical study of 1,089 patients from Japan. *Ann Thorac Surg* 2005;79:219-24.
  27. Lee WS, Heo DS, Bang YJ, et al. Prognostic factors of patients with thymoma. *Korean J Intern Med* 1996;11:40-9.
  28. Yu L, Zhang XJ, Ma S, et al. Different characteristics of thymomas with and without myasthenia gravis. *Ann Surg Oncol* 2012;19:94-8.
  29. Li L, Wang Y, Peng T, et al. Metformin restores crizotinib sensitivity in crizotinib-resistant human lung cancer cells through inhibition of IGF1-R signaling pathway. *Oncotarget* 2016;7:34442-52.
  30. Maggi G, Casadio C, Cavallo A, et al. Thymoma: results of 241 operated cases. *Ann Thorac Surg* 1991;51:152-6.
  31. Mussi A, Lucchi M, Murri L, et al. Extended thymectomy in myasthenia gravis: a team-work of neurologist, thoracic surgeon and anaesthetist may improve the outcome. *Eur J Cardiothorac Surg* 2001;19:570-5.

**Cite this article as:** Cacho-Díaz B, Salmerón-Moreno K, Lorenzana-Mendoza NA, Texcocano J, Arrieta O. Myasthenia gravis as a prognostic marker in patients with thymoma. *J Thorac Dis* 2018;10(5):2842-2848. doi: 10.21037/jtd.2018.04.95