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Review Article

Thymectomy by Video-Assisted Thoracic Surgery in Myasthenia Gravis

Timectomia por Cirurgia Torácica Vídeo-Assistida na Miastenia Gravis

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ABSTRACT

Laparoscopic surgery provides a minimally invasive alternative to open resection of the thymus in the control of Myasthenia Gravis. It is easy to see the increasing number of publications from groups of surgeons who are adopting this technique, bringing valuable information from their results. This article presents a summary of the different techniques of video-assisted thymectomy with their results and also describes the technique used by the authors of the work and case series.

Key words: Video-assisted thoracic surgery, thoracic surgery, *myasthenia gravis*, thymectomy.

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INTRODUCTION

The Myasthenia Gravis (MG) is an autoimmune disease resulting from changes in the neuromuscular junction, characterized clinically by abnormal and prolonged fatigability of striated muscles that is worsened by repetitive action or tension and regain strength with rest or with the use of cholinesterase inhibitors. Its relationship with the thymus is evident and current treatment of its generalized form includes thymectomy.

Videosurgery has brought us a new option with the possibility of performing a more radical resection with a less invasive technique and, that consequently causes less morbidity and mortality.

MYASTHENIA GRAVIS

The treatment is performed with the use of anticholinesterase drugs, corticosteroids, immuno-suppressants, plasmapheresis or immunoglobulin and/or by removing the thymus.

There is considerable controversy regarding the best treatment for the control of Myasthenia Gravis. Spontaneous remission occurs naturally, but unpredictably. Results after thymectomy are highly variable; some patients experience complete remission while others no improvement whatsoever. For some the post-thymectomy response occurs only after several years. And yet, there seems to be a consensus for surgical therapy, as this presents remission rates or rates of clinical improvement that are significantly higher than in the groups treated only with medications. [1,2,3,4,5]

There are different types of surgical access, such as transcervical, partial or total transsternal, combined cervical-sternal, or resection by video-assisted thoracic surgery (VATS). The Myasthenia Gravis Foundation of America (MGFA) classified the various forms of thymectomy which are performed in myasthenic patients and gives a percentage of thymic and perithymic tissue that each technique can remove.[6]

- T-1 Transcervical Thymectomy
  a. Basic (40% to50%)
  b. Extended (75% to 80%)
- T-2 Videoscopic Thymectomy
  a. Classic VATS (80% to 85%)
  b. VATET
- T-3 Trans-sternal Thymectomy
  a. Standard (70%to80%)
  b. Extended (85% to 95%)
- T-4 Transsternal and Transcervical Thymectomy (98% to 100%)

The MGFA also published a modified clinical classification of Myasthenia Gravis.[6] (Figure 1)

In adults with generalized disease, thymectomy is always indicated, once the diagnosis is established. This early indication for surgery seeks a more rapid and complete remission, or at least an increased chance of improvement. [2,3,5,7,8,9] Others only recommend surgery in cases in which clinical control has failed.[10,11] In the pure ocular form, many agree that when clinically controlled, surgery is not necessary,[10,12,13] except when they present evidence of generalized disease demonstrated by electromyography and not evident clinically, or when a thymoma is present.[5,14,15]

Class I	Any ocular muscle weakness May have weakness of eye closure All other muscle strength is normal
Class II	Mild weakness affecting other than ocular muscles May also have ocular muscle weakness of any severity
IIa	Predominantly affecting limb, axial muscles, or both May also have lesser involvement of oropharyngeal muscles
IIb	Predominantly affecting oropharyngeal, respiratory muscles, or both May also have lesser or equal involvement of limb, axial muscles, or both
Class III	Moderate weakness affecting other than ocular muscles May also have ocular muscle weakness of any severity
IIIa	Predominantly affecting limb, axial muscles, or both May also have lesser involvement of oropharyngeal muscles
IIIb	Predominantly affecting oropharyngeal, respiratory muscles, or both May also have lesser or equal involvement of limb, axial muscles, or both
Class IV	Severe weakness affecting other than ocular muscles May also have ocular muscle weakness of any severity
IVa	Predominantly affecting limb and/or axial muscles May also have lesser involvement of oropharyngeal muscles
IVb	Predominantly affecting oropharyngeal, respiratory muscles, or both May also have lesser or equal involvement of limb, axial muscles, or both
Class V	Defined by intubation, with or without mechanical ventilation, except when employed during routine postoperative management. The use of a feeding tube without intubation places the patient in class IVb.

Figure 1

The cases best suited for resection include the generalized form of myasthenia that required progressive increases in medications for control of symptoms, or those that present a poor response to these medications with myasthenic crises and/or repetitive cholinergic crises, and those that do not experience a spontaneous remission after a long course of medication.[16]

The only situation in which, no doubt, all agree with the formal indication for surgery in Myasthenia Gravis, is when we see the presence of a thymoma. To prevent recurrence the resection should be as complete as possible, removing the entire thymus gland – a procedure called "thymothymomectomy" – and when necessary, resecting nearby invaded structures *em bloc* (lung, pleura, pericardium, great vessels) along with tumor implants and nodules when present (radical or extensive surgery).[17,18] The preferred path for this surgery is sternotomy, but there are reports of resection via a suprasternal approach[19] and even video-assisted thoracic surgery for those thymomas in stage I.[20,21,22] On the other hand, the main factors that are associated with longer survival were the presence of complete encapsulation, removing the entire tumor, small size and predominance of non-epithelial cell in the tumors, with 10 year survival ranging from 78% to 95% in Trastek and Payne stages I and II.[23]

The **MGFA** proposed a standardization of the assessment of the myasthenic state after thymectomy, defining every type of patient response quite well. [6] (Figure 2)

CHANGE IN STATUS

Improved (I) - A substantial decrease in pretreatment clinical manifestations or a sustained substantial reduction in MG medications as defined in the protocol. In prospective studies, this should be defined as a specific decrease in QMG score.

Unchanged (U) - No substantial change in pretreatment clinical manifestations or reduction in MG medications as defined in the protocol. In prospective studies, this should be defined in terms of a maximum change in QMG score.

Worse (W) - A substantial increase in pretreatment clinical manifestations or a substantial increase in
MG medications as defined in the protocol. In prospective studies, this should be defined as a specific increase in QMG score.

Exacerbation (E) - Patients who have fulfilled criteria of CSR, PR, or MM but subsequently developed clinical findings greater than permitted by these criteria.

Died of MG (D of MG) - Patients who died of MG, of complications of MG therapy, or within 30 days after thymectomy.

THYMECTOMY BY VIDEO-ASSISTED THORACIC SURGERY

Landreneau in 1992 published the first report of a thymectomy performed using videosurgery in the treatment of a patient with myasthenia gravis and a thymoma. [24]

Currently, there are a large number of surgeons performing thymectomy in myasthenic patients by video-assisted thoracic surgery, with removal only of the gland, without any concern for carrying out the removal of the pericardial fat and the perithymic tissue.[20,22,25,26,27]

Videothoracoscopy can be performed with access through the left hemithorax: with the patient in a supine position and the left side elevated approximately 30º to 45º, three to four incisions are made anteriorly between the midaxillary line and internal mammary artery.[29,36] Kaiser et al operated on 15 patients through the left hemithorax using this technique. Nine thymomas were encapsulated. A complementary left inframammary minithoracotomy was performed frequently. [25]

Those who use a complementary anterior cervical incision, with or without a sternal elevator, report that it is easier to free the superior poles and ligate the thymic veins.[28,29,30,31]

Those who perform thymectomy on the right side position the patient in left lateral decubitus, placing three to four incisions – for the introduction of instruments in right hemithorax – between the anterior axillary line and the scapula. They report that they can free the superior poles up to the neck without cervicotomy. [25,26,32,33,34,35,36]

Mack and Scruggs (1998) demonstrated the performance of type T2a thymectomy with the extension described and documented their technique with photos. Many who perform the type T2a thymectomy, however, performed a more limited resection according to the assessment by Jaretzki. [35]

According to Yim and cols. the use of this technique was associated with a reduced need for analgesics in the postoperative period ($p < 0.05$), a shorter hospitalization (five days on average) ($p < 0.05$) and an increase in operative time (107.8 + / -22.2

Complete Stable Remission (CSR)	The patient has had no symptoms or signs of MG for at least 1 year and has received no therapy for MG during that time. There is no weakness of any muscle on careful examination by someone skilled in the evaluation of neuromuscular disease. Isolated weakness of eyelid closure is accepted.
Pharmacologic Remission (PR)	The same criteria as for CSR except that the patient continues to take some form of therapy for MG. Patients taking cholinesterase inhibitors are excluded from this category because their use suggests the presence of weakness.
Minimal Manifestations (MM)	The patient has no symptoms of functional limitations from MG but has some weakness on examination of some muscles. This class recognizes that some patients who otherwise meet the definition of CSR or PR do have weakness that is only detectable by careful examination.
MM-0	The patient has received no MG treatment for at least 1 year.
MM-1	The patient continues to receive some form of immunosuppression but no cholinesterase inhibitors or other symptomatic therapy.
MM-2	The patient has received only low-dose cholinesterase inhibitors (< 120 mg pyridostigmine/day) for at least 1 year.
MM-3	The patient has received cholinesterase inhibitors or other symptomatic therapy and some form of immunosuppression during the past year.

Figure 2

minutes) ($p < 0.05$) compared to thymectomy by sternotomy. They performed eight thymectomies in myasthenic patients by video-assisted thoracic surgery, with two thymomas in stage I. [33] Savcenko and cols. (2002) in 10 years of experience performed 47 T2a thymectomies in myasthenic patients by direct right videothoracoscopy. They had a 2% conversion rate (for bleeding) and had an average hospital stay of 1.64 days. With an average follow-up of 53 months the change in status according to the MSFA parameters was a CSR of 14%, PR of 8%, MM of 39%, I of 22% , U of 14%, and W of 3%. [58]

Locertales and cols. (2004) performed 25 type T2a thymectomies from the right side with no mortality and with three conversions (two for bleeding and one because of difficulty with the surgery). The mean hospital stay was 4.2 days. The cohort were followed for periods ranging from 14 to 68 months. Eleven patients were asymptomatic without medication, 10 patients were improved with medication, and four patients had no improvement in their myasthenic condition. This author reported that after surgery two patients were found on computed tomography imaging to have thymic remnants in the left hemothorax; both underwent a new left-sided videothoracoscopy.[36]

Ruckert and cols. (2000) in an anatomic and surgical study of cadavers demonstrated that resection was more incomplete when the surgical access was from the right rather than from the left.[37]

Chang and cols. (2005) conducted a prospective study comparing 15 patients who underwent thymectomy by bilateral videothoracoscopy and 16 patients who underwent post-sternotomy thymectomy (type T3b thymectomy). Their significant findings were that the video-assisted technique had a longer operative time, but less intraoperative bleeding. The two groups had a similar frequency of remission of myasthenia, but the patients who underwent type T3b thymectomy – as measured using a visual pain scale – had significantly greater pain complaints during the first three months post-operatively.[38]

The first report of the performance of an "extended" thymectomy with videothoracoscopic resection of the entire thymus and bilateral pericardial fat associated with a cervical exploration using a sternal elevator – known as as Video-Assisted Thoracoscopic Extended Thymectomy (VATET) or resection type T2b – was published by Novelino and cols. (1994). They reported performing 10 thymectomies in myasthenic patients, including two stage I thymomas, using a transverse cervical incision and bilateral videothoracoscopy with trocars entering the 1st intercostal space in anterior axillary line and two along the lateral inframammary line in the 2nd and 5th intercostal spaced, initially performed on the left, with the patient in a supine position.

The operative time ranged from 50 to 300 minutes; the mean hospital stay was five days.[28] Scelsi and cols. (1996), Saito and cols. (1998) and Mantegazza and cols (2003) also performed this same technique of extended thymectomy.[29,31,39]

Mantegazza and cols. (2003) compared 157 myasthenic patients who underwent VATET with 47 myasthenic patients who underwent extended transsternal thymectomy (type T3b resection) and concluded that the frequency of complete remission (Kaplan-Meyer curve) was similar, and thus is a valid alternative to T3b surgery in MG, with low morbidity, and better acceptance of the cosmetic result.[29]

In 2004 Bramis and cols. published a report of 10 patients who underwent Video-Assisted Transcervical Thymectomy (VATT). With a mean follow-up of 63.8 months there was 90% improvement rate.[40]

Another form of extended thymectomy by thoracoscopy in myasthenic patients was described by Zielinski et al who used a neck incision and a subxifoide incision, introducing the sternal elevator through these two incisions. The optic was introduced first through the right hemithorax and then through the left hemithorax. These authors reported that in 100 patients operated, 71% had ectopic thymic tissue, mainly in perithymic tissue (37%) and in the aortic-pulmonary window (33%). Of these, 48 patients were accompanied for one year; 83% improved while there was one death from Myasthenia Gravis. Twenty five patients were accompanied for two years; 32% had complete remission.[41]

The resection of thymomas in stage I, and of thymic cysts using thoracoscopy was also performed by other surgeons.[26,42]

The effectiveness of this type of surgery is still unknown due to lack of follow-up time, but some report a response similar to that obtained with other thymectomy techniques.[26,29,34,35] As it is still a novel operation performed in few patients to date, there are advances in the instrumentation and surgical technique that are ongoing. With regard to the selection of patients, there is a tendency to recommend surgery in cases of Myasthenia Gravis of recent onset and milder

symptoms and in younger patients.[22] Those who perform video-assisted thymectomy report the advantages of performing a complete resection of the gland, with less pain, less morbidity, shorter hospital stays, and better cosmetic results.[20,25,26,33] These same advantages were also found in several other procedures performed by thoracoscopy.[43,44,45]

As this technique requires appropriate and expensive equipment, and training of the surgeon, it really has a higher initial cost, but this is offset with a shorter hospital stay, with lower morbidity, and a faster return to work.[20,25]

Because it is still a new technique, there are disadvantages such as a substantial increase in time under anesthesia with bronchial blockade, operating using a flat screen with only two-dimensional vision, and the loss of the sense of palpation.[46]

Special attention was given by some surgeons to the issue of trauma to the intercostal neurovascular bundle from the trocars with the onset of acute or chronic pain.[11,47] Landreneau and col. found no significant difference in the onset of chronic pain in patients undergoing pulmonary resection by thoracotomy or video-assisted thoracic surgery. [47]

In order to reduce the trauma of the intercostal nerves some surgeons advocate a partial resection of the rib[11] and the others do not use trocars, threading entry of instruments directly through the incision.[48] This can be achieved by flexion of the operating table in order to increase the intercostal spaces of the patient in lateral decubitus position, avoiding the exaggerated inclination of the thoracoscope during the procedure.[33]

It has been clearly observed that as more operations are performed, there is a decrease in operative time.[49] With the presence of a magnification camera, there is a better view of the tissue to be dissected with excellent illumination and the additional advantage of being able to demonstrate the procedure to assistants and students, and record all the steps of the operation on video.[49]

Certainly there is a promising future for videothoracoscopy with the technologic advances improving the optics, the staplers, and the instruments in general.

With advances in robotic surgery, some centers have performed thymectomy reporting advantages due to the precison in the dissection due to the three dimensional image and the instruments developed with much greater mobility when compared with those of video-assisted surgery. [50,51]

OUR SERIES

Our study cohort is composed of 48 patients with Myasthenia Gravis who underwent thymectomy by video-assisted thoracic surgery from May 1995 to February 2011. Of these, 42 were by the extended technique with cervical access and right and left videothoracoscopy, with type T2b (VATET) resection. In four patients thymectomy was performed by right-sided videothoracoscopy, and in two the thymectomy was performed by right neck incision and right-sided videothoracoscopy (Figure 3) .

Of the 42 patients who underwent extended thymectomy, 37 (88.0%) were women and five (12.0%) were men; their ages ranged from 17 to 70 years. Two patients had thymomas, both about 3 cm in size. The classification of the myasthenia gravis of these patients was based on MGFA. (Table 1)

As preoperative preparation, all patients – except for patients in Classes IIa and IIIa – underwent two to three sessions plasmapheresis (with an interval of 24 hours between them), the last plasmapheresis

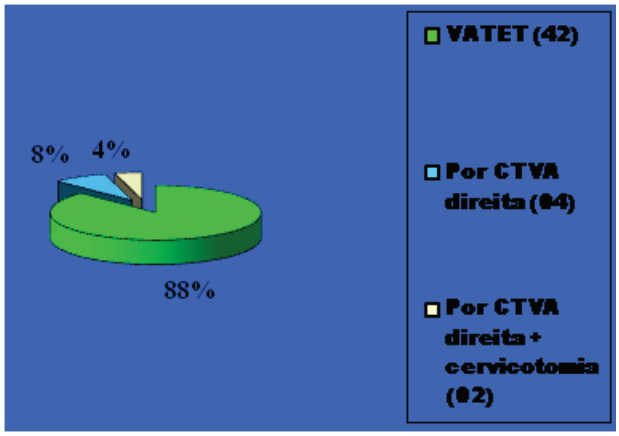

Figure 3 *- Gráfico das cirurgias realizadas.*

Table 1

	# of Patients	
Female	37	(88.0%)
Male	5	(12.0%)
Age	17-70	years
IIIb	38	(91.2%)
IIIa	2	(4.8%)
IIa	1	(2.4%)
IVb	1	(2.4%)

performed on the eve of the surgery. The period of preoperative preparation ranged from two to five days.

All patients were intubated with a double lumen endotracheal tube.

The position of the patient for the operation was the supine position with open arms. First the right hemithorax was approached, then the left. A metal arch was used to support the sternal elevator at the level of the sternal notch, raised to a height of 40 cm (Figure 4).

Two teams, one positioned at the head and the other on the right side of the surgical table, start the procedure (Figure 5).

The neck dissection was performed with an anterior transverse incision of about 5 to 8 cm, 2 cm above the sternal notch. Videothoracoscopy, first on the right and then on the left, was performed with three 10 cm trocars, two located between the midclavicular line and anterior axillary line in the 3rd and 6th intercostal spaces, and the other in the 5th intercostal space, in the anterior axillary line, with the removal not only of the thymus, but also of the pericardial fat and all of the perithymic tissue, bilaterally, as described in the surgical technique.[31] All the ressected tissues were removed through the cervical incision. During the operation, the right and left phrenic nerves were visualized and carefully preserved.

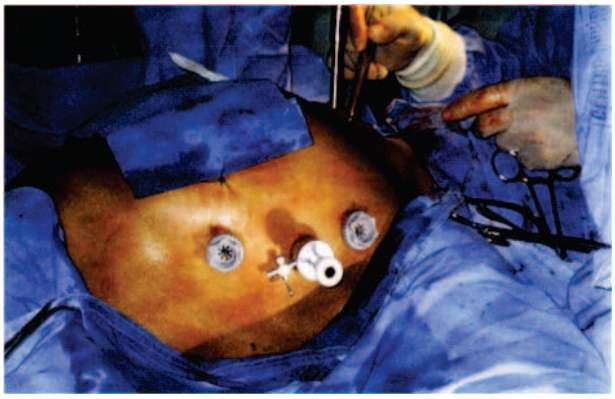

Figure 4 - *Location of sternum lifter (cervicotomy) and trocars in the left hemithorax for thoracoscopy.*

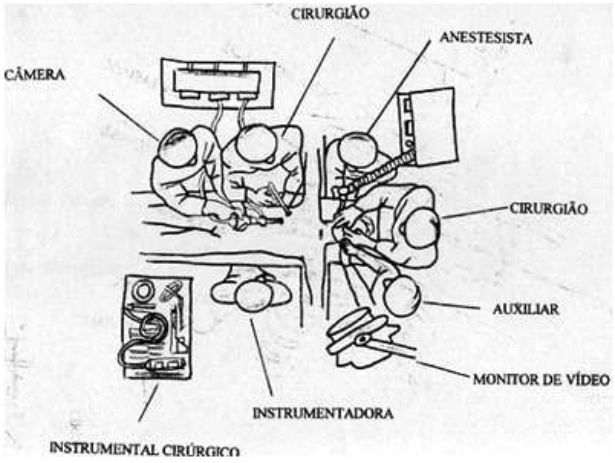

Figure 5 - *Positioning of the two teams.*

There was no operative mortality. One (2.4%) conversion to a partial sternotomy was necessary due to the presence of considerable fat around the thymic tissue. This sternotomy was performed out of concern about leaving thymic remnants after videothoracoscopy. In this case with the open approach the left and right pericardial fat were easily resected.

Mean operative time was 210 minutes. Three (7.2%) patients required ventilatory support postoperatively and had extended (60, 30, and 15 day) stays in the intensive care unit (ICU), two complicated by pneumonia.

All other cases were extubated in the operating room, with the patient under observance for about 24 hours in the ICU or intermediate care unit. On average drains were removed two days after surgery. The mean number of postoperative days hospitalized was 7.6 days; the mean length-of-stay for the entire hospitalization was 12.6 days.

Pain was readily controlled with analgesics (acetaminophen or dipyrone) and non-steroidal anti-inflammatory drugs (NSAIDs), which were administered regularly during the first two days of the postoperative period. This analgesia regimen was provided to all patients, associated with blockage of the intercostal nerves with Bupivacaine 0.5% adjacent to the trocar orifices.

Seven patients experienced dysphonia the first few days postoperatively, which gradually improved in five and persisted in two patients (4.8%). In these two patients laryngoscopy showed left vocal cord paralysis with partial improvement of dysphonia after speech therapy sessions. In those who experienced only transient dysphonia laryngoscopy was not performed.

There were two (4.8%) vascular lesions, which occurred during neck dissection. One injury was to the innominate artery at the end of the operation that required sternotomy for the repair. This patient had undergone previous suprasternal thymectomy and

there were many adhesions in the tissues as well as the presence of residual thymus; there was no clinical improvement. After this case, we no longer recommeded videothorascopic surgery for the resection of residual thymic tissue. The other injury was of the left internal thoracic vein, which was repaired via neck incision.

Two (4.8%) patients presented alterations in coagulation after plasmapheresis with the presence of a large left intrapleural clot and another with hemothorax requiring bilateral drainage. The patient with the large clot was treated with 1,500,000 U intrapleural streptokinase administered through the chest tube, with significant reduction of the clot, no additional surgery was required. The other patient with hemothorax had to be re-operated. Diffuse bleeding from the resection area was encountered, requiring transfusion of clotting factors to treat the coagulopathy, with a satisfactory evolution. In these two patients plasmapheresis has been performed without replacement of plasma. Replacement of plasma was performed in the remaining patients who underwent preoperative plasmapheresis with part of the replacement after removal of the plasma filtrate. This fact makes us emphasize the need for fluid resuscitation in the plasmapheresis, not only albumin, but also with plasma.

The first day after surgery all patients resumed the medication previously used for the control of Myasthenia Gravis.

The postoperative care – which in our cohort ranged from 1 to 190 months – followed MGFA guidelines. There was one (2.4%) death attributed to the MG (D of MG), while the other 97.6% enjoyed better control of myasthenia gravis disease – (I) improved (CSR, PR, or MM). The patient who died had a myasthenic crisis triggered by urinary tract infection and died during the fourth postoperative month. This patient had undergone VATET *after* transcervical thymectomy with the finding of thymic tissue remnants.

Surgical specimens were sent to pathology separated: thymus, right pericardial fat, left pericardial fat, and other perithymic tissue when present. The thymus was so rigorously separated from the pericardial fat with the capsule intact that no cases were observed with fragmentation of the gland with the pericardial or perithymic tissues.

The histopathological results of the 42 patients who underwent VATET were: thymic hyperplasia (55.2%), thymic involution (24.0%), normal thymus (16.8%), and two (4.8%) thymomas (one encapsulated and the other with microscopic invasion of the capsule). A finding of great interest in histopathology was the presence of ectopic thymic tissue (not being a fragmentation of the gland) in seven (16.8%) patients. Six had it in the left pericardial fat, and one in the right and left pericardial fat and in the cervical region (Figure 6).

FINAL CONSIDERATION/THOUGHTS

Thymectomy by VATS has been performed increasingly, as the results presented by various authors demonstrate similar efficacy to those performed by conventional surgery, with the advantages associated with minimally invasive surgery. The technique of extended thymectomy by VATS described offers a triple view – cervical, and right and left intra-thoracic – and the confidence that resection not only of the entire thymus but also of the perithymic tissues can be performed without the need for total sternotomy. Similar to other procedures performed by video-surgery, the standardization of the technique is very important, and as one performs more procedures the safety and the efficacy are consolidated.

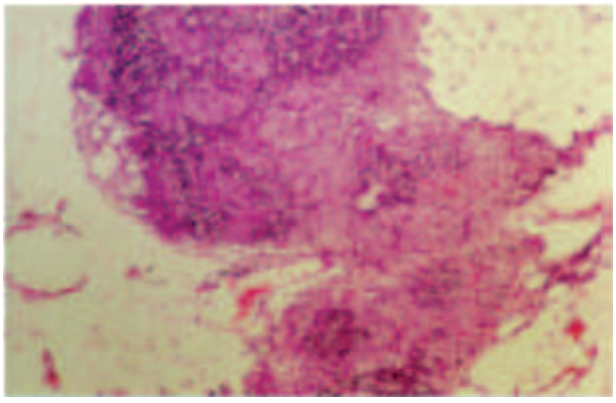

Figure 6 *- In the midst of pericardial fat, presence of thymic tissue (40x).*

RESUMO

A vídeocirurgia veio proporcionar mais uma alternativa de se realizar a ressecção do timo no controle da Miastenia Gravis com uma cirurgia minimamente invasiva. É nítido observar um crescente número de publicações de grupos de cirurgiões que aderiram a esta técnica, trazendo informações valiosas de seus resultados. O presente artigo traz um resumo das diferentes técnicas da timectomia video-assistida com seus resultados e também descreve a técnica utilizada pelos autores do trabalho e casuística.

Descritores: Cirurgia torácica vídeo-assistida, cirurgia torácica, *miastenia gravis*, timectomia.

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