



# Robotic thymectomy: current perspective in myasthenia gravis and thymoma

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**Abstract:** Thymectomy is an established therapeutic option both in the multidisciplinary approach of nonthymomatous myasthenia gravis and in the treatment of thymoma. Different surgical techniques have been described to perform thymectomy, but transsternal approach is still considered the gold standard. Anyway, in the last decades, minimally invasive techniques have gained attention and widely developed in this surgical field. Among these, robotic thymectomy represents the most modern surgical technique. Different authors have described their experience with robotic thymectomy and from published data it can be considered a safe and feasible operation. Anyway, different issues are still ongoing, both in terms of surgical indications and technique. Particularly, the role of robotic thymectomy in patients with thymoma is still matter of debate, although available results seem promising both from the surgical and oncological point of view.

**Keywords:** Thymectomy; thymoma; robot; myasthenia gravis (MG)

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## Introduction

Thymectomy is the most frequent surgical procedures involving the anterior mediastinum. Although it is an established operation both for benign and malignant diseases of the thymus, many issues are still ongoing or controversial, both in terms of procedural indications and of surgical technique.

Removal of the thymic gland is nowadays a well-established surgical approach in the management of myasthenia gravis (MG) and, at the same time, thymectomy represents the main treatment for thymic tumors, particularly in early stage disease (1,2).

From the surgical point of view, different surgical approaches have been described for thymectomy with median sternotomy still being considered the gold standard. However, the complications and the mortality related to

this technique led to the development of minimally invasive approaches in this surgical field, especially for benign diseases.

Robotic surgery has been developed as an evolution of standard video-assisted thoracoscopic surgery (VATS). Advantages of robotic technique over other minimally invasive approaches become clear particularly for procedures in a surgically challenging anatomical region, such as the anterior mediastinum (3).

After the first surgical applications of the robotic technique mainly in the cardiac surgery field, in 2001 Yoshino described the first robotic thymectomy for a thymoma (4-6). Since this first experience, various studies have been published describing the application authors of robotic thymectomy both for nonthymomatous MG and for thymic tumors (1,3,7-27).

## MG and robotic thymectomy

MG is an autoantibodies-mediated disease involving the neuromuscular junction, characterized by weakness and fatigability of skeletal muscles. The incidence of MG is 2.5–10 per 1,000,000 and it's more common in women between 20 and 40 years old and in people of both sex between 50 and 60 years old, showing a double peak prevalence. Moreover, MG is the most frequent paraneoplastic syndrome associated to thymomas, in about 30–40% of cases (28).

Approximately in 80–90% of the patients affected it is possible to find anti-acetylcholine receptor (AChR) antibodies. The link between AChR antibody and AChR results in an alteration of the neuromuscular transmission, which is responsible of the clinical picture (29). About 10–15% of MG patients are sero-negative for AChR antibodies: in this subgroup of patients it is possible to detect, in 40–70% of the cases, another type of antibody direct against the muscle-specific tyrosine kinase (MuSK) (30–33).

The treatment of MG is composed by several options that include pharmacological therapy, plasmapheresis and surgery. Within the pharmacological therapy, cholinesterase inhibitors and immunomodulating drugs represent the mainstay of treatment. Among the former the most used is pyridostigmine (Mestinon), which is frequently associated with corticosteroids. Intravenous immunoglobulin or plasmapheresis are used in order to treat myasthenic crisis or severe exacerbations of the disease (34).

Thymectomy represents the surgical therapeutic option. Since the first experiences described by Blalock, thymectomy has been considered part of the multidisciplinary treatment of MG, although only recently a prospective randomized clinical trial demonstrated the benefits of thymectomy in myasthenic patients (35). Currently, thymectomy is indicated in all myasthenic patients with thymoma or patients affected by non-thymomatous generalized MG. In case of non-thymomatous ocular MG, the surgical approach is still source of debates (9,36,37). Thymectomy should be performed in patients with stable disease, particularly with no recent crisis, and shows increased benefits when performed early after the onset of the symptoms (38). There is also evidence that thymectomy may have less effects in patients with presence of anti-MuSK antibodies (39).

The aim of surgery in myasthenic patients is the complete removal of the thymus, together with the surrounding mediastinal fat, frequently containing foci to

ectopic thymus, since the completeness of resection of as much as possible of thymic tissue is associated with higher improvement rate (40).

First thymectomies were performed through median sternotomy. Anyway, the increased risk of respiratory failure, myasthenic crisis and the concerns regarding the sternal healing impairment in myasthenic patients with chronic steroids use, led to the introduction of minimally invasive approach, such as cervicotomy and VATS thymectomy (41).

The first descriptions of robotic thymectomy for myasthenia were performed in 2003 by Ashton *et al.* and Rea *et al.* (42,43). Since these first experiences, different authors reported their experience with robotic approach for myasthenic patients showing results comparable with open approaches, both in terms of surgical and neurological outcomes, with an improvement rate of symptoms ranging between 77% and 90% and complete remission rate between 16.2% and more than 40% (Table 1).

## Thymoma and robotic thymectomy

Thymomas are generally considered rare tumors, representing less than 1% of all malignancies, but account for more than 50% of all anterior mediastinal neoplasms (44). Surgery is the main treatment of thymoma, particularly for Masaoka stages I and II, and completeness of resection is the most important factor for patients' prognosis (45,46). The established and most widespread surgical approach is represented by median sternotomy, which has the advantages of allowing in most cases a technically easy and oncologically safe operation (47).

As in other surgical fields, in recent years, minimally invasive techniques (in particular the thoracoscopic approach) have gained popularity in the surgical treatment of neoplastic diseases of the mediastinum, for their capability to assure a complete removal of the tumor, without the disadvantages of the open technique. Anyway, several surgeons have been hesitant to use thoracoscopic approach for thymic tumor resection, because it is considered a difficult operation requiring a long learning curve. Other additional issues that slowed the diffusion of VATS resection for thymomas are represented by the possible rupture of the capsule during endoscopic maneuvers, the supposed reduced safety margins with increased risk of recurrence and the lack of long-term oncologic results (26).

Different authors have published their experience with the robotic approach for thymic tumors (Table 1). Analysis of

**Table 1** Major series of robotic thymectomy

Author	Number of patients	Thymoma/non-thymoma (n)	MG (n)	OC (%)	OT (min)	Morbidity (%)	POS (days)	FU (months)	RR (%)	Thymoma 5-year survival (%)	MG remission (CRS, PR)
Rea <i>et al.</i> , 2006 (1)	33	2/31	33	0	–	6.0	2.6**	28.8*	0	–	16.6% CSR
Cakar <i>et al.</i> , 2007 (7)	9	4/5	9	0	154.0*	11.1	5.0*	13.0**	–	–	100% I
Augustin <i>et al.</i> , 2008 (8)	32	6/26	NA	3.1	–	6.2	6.0**	25.0*	0	–	–
Ruckert <i>et al.</i> , 2008 (9)	95	12/83	95	8.3	186.0*	2.1	–	29.1**	0	–	>40% CSR
Fleck <i>et al.</i> , 2009 (10)	18	0/18	18	5.5	175.0*	33.3	4.2*	18.0**	–	–	55.5%
Goldstein <i>et al.</i> , 2010 (11)	26	5/21	26	15.3	127.0*	15.3	2.0*	26.0*	–	–	38.0% PR
Balduyck <i>et al.</i> , 2011 (3)	14	5/9	5	7.1	224.2*	21.4	9.6*	34.2*	–	–	–
Freeman <i>et al.</i> , 2011 (12)	75	0/75	75	0	113.0*	6.6	2.2*	45.0*	–	–	53.3%
Ruckert <i>et al.</i> , 2011 (13)	74	11/63	74	1.4	198.0*	2.7	–	42.0*	–	–	39.3% CSR
Mussi <i>et al.</i> , 2012 (14)	14	14/0	1	7.7	139.0*	14.2	4.0*	14.5**	0	100	100% I
Melfi <i>et al.</i> , 2012 (15)	39	13/26	20	5.1	124.3*	12.8	4.3*	16.0**	0	–	90.0% I
Marulli <i>et al.</i> , 2012 (16)	79	79/0	45	1.3	165.0*	12.7	4.4*	51.7*	1.3	97	–
Weksler <i>et al.</i> , 2012 (17)	15	10/5	5	0	84.0*	6.6	1.0**	–	–	–	–
Marulli <i>et al.</i> , 2013 (18)	100	8/92	100	0	120.0**	6.0	3.0**	67.0**	0	100	28.5% CSR; 87.5% I
Schneiter <i>et al.</i> , 2013 (19)	20	20/0	12	0	–	10.0	5.0**	26.0**	11.1	100	–
Ye <i>et al.</i> , 2014 (20)	23	23/0	0	0	97.0*	4.3	3.7*	16.9*	0	100	–
Keijzers <i>et al.</i> , 2014 (21)	37	37/0	28	13.5	149.0*	16.2	3.0**	36.0**	2.7	100	21.4%
Seong <i>et al.</i> , 2014 (22)	34	11/23	2	–	157.2*	0	2.7*	13.3*	0	–	–
Jun <i>et al.</i> , 2014 (23)	55	21/34	NA	0	139.8*	10.9	7.2*	–	–	–	–
Huang <i>et al.</i> , 2014 (24)	23	23/0	1	0	85.2*	4.3	3.6*	24.8*	0	–	100% I

Table 1 (continued)

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Author	Number of patients	Thymoma/non-thymoma (n)	MG (n)	OC (%)	OT (min)	Morbidity (%)	POS (days)	FU (months)	RR (%)	Thymoma 5-year survival (%)	MG remission (CRS, PR)
Keijzers <i>et al.</i> , 2015 (25)	125	31/94	125	4	125**	7.2	3.0**	33.0**	6.5	–	77% I
Marulli <i>et al.</i> , 2016 (26)	134	134/0	70	8.9	140**	17.1	4.0**	48.0*	0.7	100	–
Kumar <i>et al.</i> , 2017 (27)	71	21/50	71	0	140**	7.0	–	33.0**	0	–	38% CSR

\*, mean; \*\*, median. MG, myasthenia gravis; OC, open conversion; OT, operative time; POS, post-operative stay; FU, follow-up; RR, recurrence rate; CSR, complete stable remission; PR, pharmacologic remission; I, improved; NA, not available.

current literature data shows that robotic thymectomy may be considered a technically sound and safe operation in the hands of trained surgeons: there are no major complications reported and no mortality occurred, whereas the mean rate of open conversion is 6.6%.

Recently, Friedant *et al.* addressed this issue performing a systematic review of the available literature regarding VATs and robotic thymectomy versus open approach for Masaoka stage I and II thymic tumors. Authors concluded that, based on current data, there are no significant differences in terms of R0 resection and locoregional recurrence between the two groups (48).

These data are promising regarding the robotic/thoracoscopic treatment of Masaoka stage I and II thymomas whereas for advanced stages, although technically feasible, no clear data or indications are available, at the moment. Therefore, extended resections should still be considered experimental and reserved to very selected cases (26).

Focusing on the oncologic outcome, these reports show a low recurrence rate (0–11.1%), comparable with open approaches. However, these series have several limitations based on their retrospective fashion, a relatively small sample size and a short oncologic follow-up. These issues make current data promising, but further studies with longer follow up are needed, particularly for tumors such as thymomas that show a relatively indolent nature and a long recurrence time.

## Robotic system

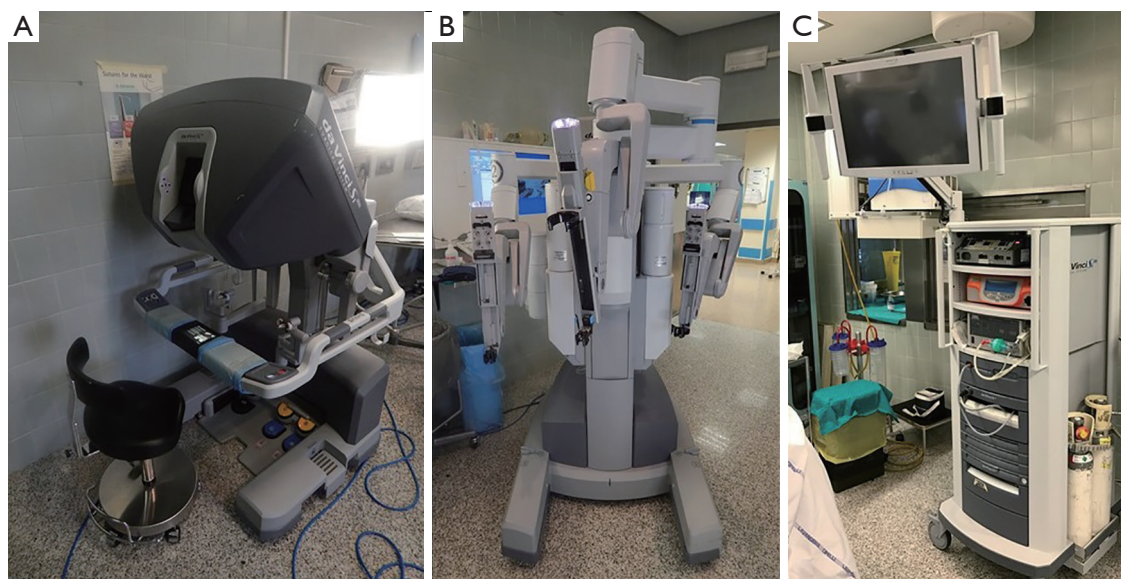
The da Vinci (Intuitive Surgical, Inc) is the most widespread robotic system nowadays.

The system includes a console where the surgeons sits

while operating, a cart that supports the interactive robotic arms and a magnified vision system. The surgeon operates at the console far from the operating table. The console is connected both to the video system, giving the surgeon, through a binocular localized in the upper part of the console, a high-definition, three-dimensional (3D) view inside the patient's body, and to the robotic cart. The system allows the surgeon's hand movements to be translated into identical, smaller and precise movements of the instruments inside the patient's chest (*Figure 1*).

## Surgical technique

The patient is under general anesthesia and has an endotracheal double-lumen tube for selective single lung ventilation during the time of operation. The patient is positioned supine at a 30-degree angle upon a bean bag. For the left side approach, the left arm is positioned on a support parallel to the bed, to allow an easier exposure of the axillary region, whereas for the right-side approach it is the opposite. Considering an eventual emergency conversion to an open approach (sternotomy or thoracotomy), the operative field is always draped including the entire hemithorax and the sternal region. Ports are introduced as follows: first the camera port through a 15-mm incision on the 5th intercostal space in the anterior portion of the midaxillary region. Then, aided by direct internal vision, the other two ports are inserted, one on the 3rd intercostal space on anterior portion of the midaxillary region and another on the 5th intercostal space on the midclavicular/parasternal line (*Figure 2*). Subsequently, the arms of the da Vinci system are attached to the ports, the middle one to the port-inserted endoscope and the other two to the remaining access points. The right arm is



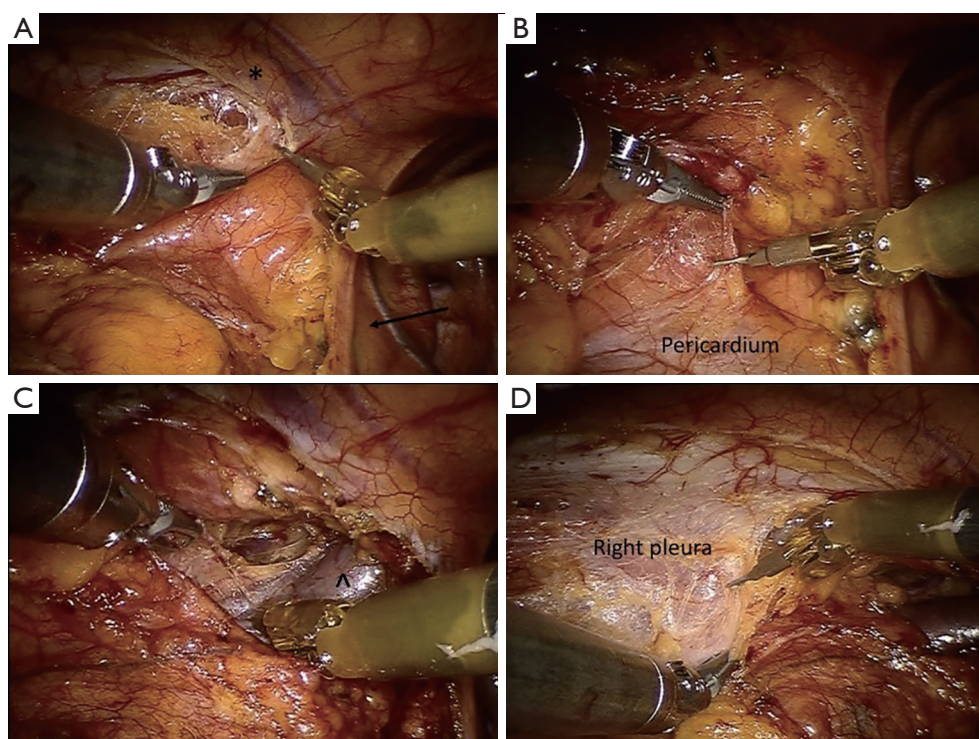
**Figure 1** Components of the robotic system. (A) Surgeon's operative console; (B) patient-side cart with interactive robotic arms; (C) vision system.



**Figure 2** Patient positioned left-side up, with ports' entrance sites marked on the skin.

generally connected to a dissector device (electric cautery or an ultrasound dissector) while the arm has an atraumatic grasper. Through the camera port, the hemithorax is inflated with CO<sub>2</sub> (pressure range 6–10 mmHg) to allow an easier dissection in the mediastinal region. Before beginning the dissection, the pleura is carefully explored to exclude any unexpected pleural lesion in case of thymic tumor. When a left-sided approach is performed, the dissection starts from the fat tissue at the left cardiophrenic angle and moves upwards along the anterior border of the phrenic nerve, isolating all mediastinal tissue from the nerve. Subsequently, the thymic gland is separated from the retrosternal area

(*Figure 3A*). The left inferior horn of the thymus is then located and dissected from the pericardium (*Figure 3B*), allowing the lower part of the gland to be mobilized upwards and the thymic tissue is dissected from the aortopulmonary window. The dissection continues on the right side with the visualization of right mediastinal pleura and the right inferior horn is found and dissected. The left innominate vein is then identified, and the dissection proceeds along the antero-superior border of the vein from the left to the right side. Keynes veins are identified, clipped, and divided. Concurrently, dissection continues upward to the neck until the left superior horn and then the right one are also identified and divided from the thyroid gland thus completing the dissection (*Figure 3C,D*). The resected specimen is placed in an Endobag, so that it can be entirely removed through the parasternal trocar incision. In case of predominantly right side thymoma, a right-side approach may be considered. In this case, as for the left side, the dissection of the thymus begins inferiorly from the cardiophrenic angle and moves upwards anteriorly following right phrenic nerve, separating all anterior mediastinal tissue from the nerve. Then, the pleura is divided all along the mammary vessels, from their origin to the diaphragm, thus dissecting the mediastinal tissue from the sternum. In the next step, the inferior horns of the thymus are dissected from the pericardium and then all the gland is elevated from the pericardium until the left innominate vein is



**Figure 3** Intraoperative pictures. (A) Dissection of the thymic tissue from the retrosternal area (\*, mammary vessels) and from the left phrenic nerve (arrow); (B) dissection of the thymus from the pericardium; (C) dissection of the right upper horn from the neck superiorly and from the left innominate vein inferiorly (^); (D) dissection of the right aspect of the thymus from the right pleura.

encountered. The dissection moves along the anterior-superior border of the vein and the Keynes veins are identified, clipped, and divided. Concurrently, dissection continues upward to the neck until the left superior horns are also identified and divided from the thyroid gland. The most delicate step is the dissection of the thymus on the left side, identifying the left phrenic nerve by opening the left pleura. After hemostasis, a 28-Fr drain tube is placed through the port in the fifth intercostal space. Generally, 24 hours after operation it is possible to remove the chest drain if the postoperative chest X-ray shows normal findings and the amount of pleural fluid is permissive.

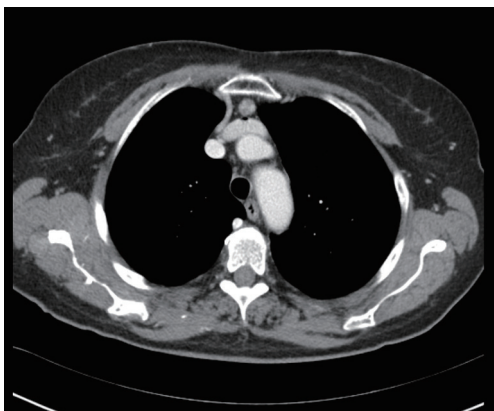
Recently, Suda and colleagues described a novel procedure by combining the subxyphoid approach performed through a midline camera port with the use of the robotic system. According to the authors, this approach would provide a good operative view in the neck region and enables an easy verification of both phrenic nerves (49).

Anyway, the main debate is whether it is better to perform thymectomy from the right or the left side. Surgeons supporting the left-sided approach point out

that usually the left lobe of the thymus gland is larger than the right one and that the most frequent sites of ectopic thymic tissue may be found the aortopulmonary window and below the left brachiocephalic vein are frequent sites of ectopic thymic tissue. In some cases, the thymus may show some anatomical variations, spreading lateral to or under the left phrenic nerve, or descending posteriorly to the left brachiocephalic vein. Moreover, when dissecting the thymus from the left side, the right phrenic nerve is hardly damaged, being protected by the superior vena cava (13,50).

On the contrary, surgeons supporting the right-side approach describe the advantages of a larger operative field and a safer entry of the instruments because of the absence of the heart, allows the improved visualization of the aortocaval groove and of the venous confluence. However, the left phrenic nerve cannot be always completely visualized. Anyway, according to these authors, this approach is safer especially at the beginning of the learning curve (50-52).

Another issue regards the extent of surgical resection, particularly thymectomy versus thymo-thymomectomy.



**Figure 4** Chest CT-scan showing small centrally-located thymic tumor.

According to the recent International Thymic Malignancy Interest Group (ITMIG) guidelines, thymomas should be removed together with the surrounding thymus and fatty tissue, particularly in case of myasthenic patients, to gain safety margins and reduce the risk of incomplete resection and local recurrence also for apparently capsulated thymomas (53). Indeed, clinical stage I thymomas are frequently found to be upstaged at final pathological examination, with subtle microscopically or macroscopically invasion of the surrounding tissue that may not be detected by the surgeon (53,54).

Moreover, surgeons should resect the thymoma using a “no-touch” technique, avoiding to grasp or squeeze the tumor with the endoscopic instruments because of the increased risk of capsule’s rupture and of consequent pleural dissemination of tumor cells (53). This “no-touch” technique requires obviously a more precise and complicated dissection, thus longer operative time and learning curve for the surgeon.

To better select candidates, Cheng and colleagues suggested some ideal radiological criteria supporting a robotic/VATS approach for resection of thymic tumors: the evidence of a tumor capsule, a distinct fat plane separating the tumor from the thoracic organs with no mass compression effect, the presence of residual normal thymic tissue surrounding the lesion, and the unilateral tumor predominance, particularly for lesions greater than 3 cm (Figure 4) (55).

Anyway, the right dimension of thymic tumors for robotic/thoracoscopic approach, it is still matter of debate, but generally an upper cut-off of 5 cm is considered acceptable (16,56). A large dimension of the thymoma is

not an absolute contraindication, however, it could make the endoscopic manipulation more difficult, increase the possibility of an open conversion or prolonged the operative time (16). This eventuality should be considered also in case of myasthenic patients with a small lesion but rather abundant mediastinal fat.

When compared to other surgical approaches, robotic thymectomy shows particular advantages compared to both sternotomy and standard VATS.

In literature, the comparison between robotic and transsternal thymectomy has been made only by few authors (3,7,17,20,22). The first series comparing the two approaches was made by Cakar and colleagues and showed a better clinical outcome, particularly a lower complications’ rate and a reduction in the post-operative stay, in patients who underwent robotic surgery (7). Balduyck and colleagues also compared the two techniques focusing on quality of life assessment, by means of specific questionnaires, and showed a better post-operative recovery in the robotic group (3). Seong *et al.* and, more recently, Kang *et al.* compared sternotomy and robotic thymectomy using a propensity score matching (22,57). Both studies showed a superiority of robotic approach over sternotomy in terms of surgical outcome and promising results in the intermediate follow up from the oncological point of view. It is clear that median sternotomy, although assuring a complete and safe removal of the thymic gland, shows concurrently some specific complications, as wound healing impairment and infections, sternal instability, hematomas, that are avoided or very rare with the robotic approach. The lower morbidity associated with the robotic approach has led to a greater acceptance of this operation, particularly in myasthenic patients, where the use of steroids and the respiratory impairment related to myasthenia, make higher the risk of complications.

In the field of minimally invasive techniques, the robotic approach is considered as a development of VATS. Anyway, to date only few studies were focused on a real comparison between these techniques. Published results showed similar surgical results, except for the operative, time hospitalization costs (increased for robotic approach) and length of hospital stay and (longer for VATS approach) (13,23,58,59). Only Rückert *et al.* showed also a better outcome for myasthenic patients after robotic thymectomy (13). Qian and colleagues recently performed a comparison between VATS, robotic approach and sternotomy in the treatment of early stage thymomas. This study showed better post-operative outcome, particularly in terms of duration of hospital stay and post-operative pleural

drainage volume, in patients treated through the robotic approach compared to median sternotomy and also to VATS group (59).

Anyway, no prospective randomized trials comparing outcomes based on different surgical approach are available and it is unlikely that they will be performed in the future. Therefore, preference between one or the other technique is based mainly on impressions and personal feeling than on scientific data. It is doubtless that the robotic approach, while displaying all the advantages of minimally invasive approaches, concurrently seems to overcome the disadvantages of standard VATS as the bidimensional vision, the less than ideal range of motion of the long thoracoscopic instrument placed through fixed entry points, thus creating a fulcrum effect, and the transfer of the surgeon's tremor. On the contrary, the 3D view, the articulated instruments with 360-degrees of rotation, the 7 degrees of freedom and the tremor filtering system seem to minimize difficulties in cases of challenging thymectomies (60). Apart from technical advantages, the robotic approach seems to have a shorter learning curve than that of standard VATS thymectomy, that, on the contrary, has always been considered a technically demanding operation (13,15,23,56,60).

Some financial concerns have been raised regarding the robotic surgery: as evaluated by Augustin and colleagues, conventional thoracoscopy is significantly cheaper compared to the robotic approach, with additional cost of about 91% for the robotic technique, mainly related to the initial capital costs of the robotic system, the need of annual maintenance and the disposable surgical materials (8). High cost may be partially compensated by the multidisciplinary use of the system, by fewer complications rates and a reduced post-operative stay, but to date no specific analysis on this issue has yet been performed (17).

Other disadvantages seem the lack of tactile feedback, that anyway seems to be widely compensated by the superior 3D view of the operating field, and the placement of the surgeon, away from the patient and operating at a non-sterile console (9,17).

## Conclusions

Nowadays, the robotic approach for thymectomy may be considered a safe and well-established surgical technique. Results in patients with MG are encouraging and comparable with other techniques, either open or minimally invasive ones. For patient with thymic tumors, the role of

robotic thymectomy is still under evaluation but available data confirm the promising results in terms of oncologic outcomes.

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