

Review

Narrative Review of Surgery for Myasthenia Gravis

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Received: June 25, 2021**Accepted:** October 03, 2021**Published:** October 15, 2021**Abstract**

Myasthenia Gravis (MG) is a rare autoimmune disorder characterized by antibody mediated blockade of neuromuscular transmission. Up until the last decade, evidence suggesting benefit of thymectomy for myasthenia gravis has been based on non-randomized control studies. Our paper serves as an expert narrative review of new literature pertaining to surgical management of myasthenia gravis based on review of articles from PubMed and Cochrane database from date of inception through June 14, 2021. We used the MeSH search terms: "myasthenia gravis"; "thymectomy"; "thymoma"; and "surgery" to identify any new relevant articles for inclusion in our review. The results of these studies are summarized below. We reviewed multiple articles including two randomized control trials. As a result of these studies over the past decade, the American Academy of Neurology's most recent practice advisory, published online March 25, 2020, gives a level 'B' recommendation for thymectomy for MG in patients with acetylcholine receptor antibody-positive generalized MG age 18-65 years old. They additionally noted the need for further discussion surrounding the benefits and risks of surgery and whether minimally invasive approaches to thymectomy would provide the same benefits as the traditional transsternal approach. Evidence recommending thymectomy during pregnancy remains limited due to lack of available data. Emerging evidence suggests



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that performance of video-assisted or robotic-assisted thymectomy is feasible, but further study is needed due to a lack of randomized control trials.

Keywords

Myasthenia gravis; thymectomy; antibody; surgery; minimally invasive; robotic

1. Introduction

Myasthenia gravis (MG) is a rare autoimmune disorder characterized by antibody mediated blockade of the neuromuscular transmission causing skeletal muscle weakness [1, 2]. The reported prevalence of MG ranges from 7.7 to 20 cases per 100,000 population and it affects twice as many females as males [3, 4]. MG has two forms: ocular where the eyelids and extraocular muscles are affected, and generalized where variable types of muscles are affected. It is further separated into subtypes by age, antibody involvement (anti-acetylcholine receptor (AChR) positive, anti-muscarinic (MuSK) positive, anti-lipoprotein receptor-related protein-4 (LRP4) positive, and seronegative) and presence of thymoma [5, 6].

The association between MG and thymic tumors was first described by Weigert in 1901 [7]. Thymomas are considered rare tumors accounting for only 1% of malignancies but 50% of anterior mediastinal masses [8]. It is now understood that 10-30% of patients with MG have thymomas [9-11]. Of note, a recent systematic review placed that number closer to a pooled estimate of 21% (95% Confidence Interval (CI): 20-22%) across population-, hospital- and surgery-based studies with considerable variation by region (13%; 95% CI 12-15% for Americas to 29%; 95% CI 26-31% for Asian cases) [12].

Initial reports of symptomatic MG improvement following thymectomy for thymoma and non-thymomatous disease were limited to case reports and large case series in the early 20th century starting with Blalock et al. in 1944 [13-15]. There were no well-designed prospective randomized trials examining surgical thymectomy until the 2016 New England Journal of Medicine MGTX study [16]. This led to disagreement about the role of thymectomy for MG due to lack of understanding of the underlying physiologic basis for remission, lack of randomized trials, and reports of spontaneous remission without surgery ranging from 10-20% [10].

Furthermore, indications for thymectomy are not uniform. An understanding of MG subtypes is important for surgical decision making, often in conjunction with a MG specialist. Current indications include non-pregnant adults aged 18-65 with MG and thymomas regardless of subtype and non-thymomatous MG (anti-AChR antibody positive) with generalized symptoms [17]. While thymectomy for double-seronegative MG (anti-AChR antibody negative and anti-MuSk antibody-negative) has been proposed [18], thymectomy is not typically recommended for patients with anti-MuSK antibodies due to differences in thymic pathology and lack of randomized trials) [19]. It is uncertain if thymectomy in patients with anti-LRP4 positive MG is beneficial due to lack of larger, randomized trials. Some small case studies, however, have demonstrated an improvement in symptoms after thymectomy in anti-LRP4 positive MG cases [20, 21].

Our paper serves as an expert narrative review of new literature over the last decade pertaining to the surgical management of myasthenia gravis including landmark trials, indications for surgery, advances in operative techniques, and post-operative outcomes associated with thymectomy.

2. Materials and Methods

Articles for inclusion were identified by two authors after search of PubMed, Medline and Cochrane library. Articles included were performed from date of inception through June 12th, 2021. Final incorporation into the review was decided by an independent senior author. We used the MeSH search terms: “myasthenia gravis”; “thymectomy”; “thymoma”; and “surgery” to identify any new relevant articles for our review. We excluded articles not written in English. The results of these studies are summarized below.

We also checked references of relevant articles and review articles for inclusion. In addition, after consensus review between all authors, articles deemed relevant and not identified in above mentioned searches were added to the review.

3. Results

3.1 Major Studies Investigating Thymectomy for Myasthenia Gravis

In the last decade prior to the NEJM MGTX RCT [16], no randomized trials existed involving surgical treatment of MG. A systematic review in 2013 by Cea et al. [22] identified most studies as case series or retrospective cohorts with no properly designed analytical observational studies investigating the role of surgery for MG. The three retrospective cohort studies identified were ultimately excluded due to methodological flaws [23-25]. Reporting was heterogeneous with non-conventional outcomes in the report by Bedlack et al. [26] and there was insufficient patient data in the Kawaguchi et al report [25]. In the case of Buckingham et al. [24], despite an increased proportion of remission in MG patients undergoing thymectomy, the matched medical arm was considered too limited as compared to the surgical patients (n = 24 out of 104 patients).

In August 2016, the NEJM published the first prospective multicenter randomized controlled trial (MGTX) comparing extended transsternal thymectomy and alternate day prednisone versus alternate day prednisone alone [16]. A total of 126 patients ranging in age from 18 to 65 years were randomized over 6 years at 36 sites from 2006-2012. Patients were included if they had generalized non-thymomatous myasthenia gravis of 5 years or less duration with Myasthenia Gravis Foundation of America (MGFA) clinical class II to IV [27]. The primary end point was quantitative time-weighted MG score (range 0-39) over a 3- year period. The thymectomy arm was statistically superior for both improved symptoms (as evidenced by a time-weighted average Quantitative Myasthenia score; 6.15 vs. 8.99, $p < 0.001$), less hospitalizations for exacerbations (9% vs. 37%, $p < 0.001$) and lower dose requirement of both prednisone and azathioprine (17% vs. 48%, $p < 0.001$). A main point was that treatment related complications were similar, with lower rates of immunosuppressive side effects ($p < 0.001$) or distress related symptoms ($p = 0.003$) in the thymectomy cohort. However, this study failed to achieve their target goal of 200 patients and had to increase the age of their cohort and the duration of disease to increase accrual, while limiting their cohort to those with only mild to moderate disease, ocular MG or seronegative MG [28]. Furthermore, only limited studies in the elderly population have followed this study [29].

To date, the most recent systematic review and meta-analysis by Cataneo et al. [4] included 19 articles encompassing 5,841 patients (2,911 surgical, 2,930 non-surgical) and two RCTs (notably the MGTX study considered to be low risk of bias and a small Columbian study by Lorenzana et al. considered to be moderate risk of bias) [16, 30] with the remainder being case series or case-control studies. Cataneo et al. [4] found thymectomy, compared to medical therapy, led to increased remission (pooled odds ratio (OR) 2.34, 95% CI 1.79-3.05; $I^2 = 56\%$). When limited to 4 studies with matched cohorts, this number increased (OR 4.10, 95% CI 2.25-7.44; $I^2 = 20\%$). Unfortunately, due to heterogeneity (87%) pooled analysis of improvement was unable to be performed.

As a result of these studies over the past decade, the American Academy of Neurology's (ANN) most recent practice advisory published online March 25, 2020 [17] gives a level 'B' recommendation for thymectomy in patients with anti-AChR positive generalized MG age 18-65 years old. Their recommendation also notes the need for discussion surrounding the magnitude of the benefits and risks of surgery. There is also uncertainty whether the benefit obtained by transsternal thymectomy will also be obtained by minimally invasive approaches. Societal guidelines do not recommend thymectomy during pregnancy due to lack of available data at this time [31]. Details of technique and outcomes for surgical approach including open and MIS techniques will be described below in more detail.

3.2 Perioperative Management and Workup

3.2.1 Preoperative Care

In addition to typical elements of a preoperative assessment, certain things should be considered when evaluating a patient with myasthenia gravis. A patient's disease should be well controlled and stable before undergoing surgery [32-35]. Various studies have investigated potential predictors of postoperative myasthenic crisis. Leventhal et al. examined several patient factors in 24 patients with myasthenia gravis who underwent thymectomy via multivariate analysis and found that duration of disease greater than 6 years, presence of respiratory disease such as chronic obstructive pulmonary disease, pyridostigmine dosage greater than 750 mg/day, and vital capacity <2.9 L were significantly correlated with need for postoperative ventilation [36]. Other studies have found presence of bulbar symptoms, Osserman stage, previous myasthenic crisis, intraoperative blood loss >1000 mL, and anti-acetylcholine receptor antibodies >100 nmol/mL as risk factors of postoperative myasthenic crisis [37-42]. Thus, when collecting a history, clinicians should pay particular attention to the presence of any bulbar symptoms, history of myasthenic crisis, dyspnea, infection, current medications for myasthenia gravis, as well as other diseases as these may lead to negative outcomes. Other autoimmune disorders as well as endocrine disorders are often seen with myasthenia gravis and the presence of some, such as thyroid disorders, may affect symptoms [28, 31, 39, 40].

In addition to a thorough history and physical, certain preoperative tests may be helpful in assessing a patient with myasthenia gravis. As discussed above, some studies have found that pulmonary function tests may indicate which patients are at higher risk of developing myasthenic crisis or respiratory problems postoperatively. One study examined 393 patients at multiple medical centers in Japan who underwent thymectomy and found that a vital capacity <80% was a risk factor for postoperative myasthenic crisis [43]. Additionally, a recent meta-analysis identified preoperative lung function as an independent risk factor for myasthenic crisis after thymectomy (MCAT) (OR = 5.71, 95% CI 3.11-10.48, $p < 0.00001$) [42]. Routine preoperative EKG on patients with MG is

additionally useful as some patients may have conduction disorders and arrhythmias. Any evidence of congestive heart failure in the preoperative workup should be further investigated with echocardiography [32, 35]. Additionally, myasthenia gravis antibodies, tumor markers, and thyroid functions tests may be useful labs in the workup of a patient for thymectomy.

Obtaining the previously mentioned tests not only informs surgeons and anesthesiologists of the level of care a patient will need postoperatively, but also identifies modifiable factors that can be addressed or optimized before surgery. The care of patients with MG should be performed in collaboration with multiple subspecialties. Neurologists work closely with the perioperative team and optimize the patient's immunotherapy regimen and medication doses [31]. For patients with severe or unstable disease, preoperative intravenous immunoglobulins (IVIG) or plasmapheresis may be helpful [31, 34, 44, 45]. Additionally, any concurrent autoimmune or endocrine disorders should be appropriately treated under the guidance of rheumatologists, endocrinologists, and the patient's primary care physician preoperatively. Conduction disorders or other cardiac dysfunctions detected on preoperative EKG should trigger involvement of cardiology for appropriate workup and treatment.

Imaging is also a vital tool in the preoperative evaluation of a patient for thymectomy. Cross-sectional imaging, specifically computed tomography (CT) with contrast, can inform the surgeon on the size of the lesion and whether it invades adjacent structures which determines the degree and method of resection. Specifically, if an enlarged lobe favors one side of the patient, it affects the operative approach in minimally invasive cases. Additionally, subtle relationships of the cervical horns of the thymus to the innominate vein can be helpful during dissection, thus it is useful to visualize this on preoperative imaging. Finally, these scans can identify any enlarged lymph nodes. Positron emission tomography (PET) scans can provide additional information about the metabolic activity of the lesion and magnetic resonance imaging (MRI) may also be a useful imaging study.

3.2.2 Intraoperative Care

There are various medications utilized intraoperatively that can either exacerbate MG symptoms or cause CNS depression and respiratory distress [46]. Thus, careful consideration should be taken in the intraoperative management of patients with MG.

Premedication with opioids or sedatives should be performed cautiously due to the potential for respiratory depression and upper airway obstruction in certain patients [46, 47]. When considering agents to induce and maintain general anesthesia, it is important to note that some may worsen symptoms. For example, studies have found a reduction in neuromuscular transmission with inhaled anesthetics in MG patients [48]. However, there have been cases of safe use of these anesthetics as well as total intravenous anesthesia with propofol or remifentanyl in patients with MG [49, 50].

Neuromuscular blocking agents (NMBAs) should be avoided given that these agents can cause myasthenic crisis and other unpredictable reactions in these patients. If a NMBA must be utilized intraoperatively, it is recommended to use a nondepolarizing NMBA at a dose reduced by one half to two thirds [35, 46, 51]. Sugammadex, a substance that deactivates nondepolarizing NMBAs by enveloping them, is the recommended choice for reversal given that it is not affected by anticholinesterase medication. Neostigmine, on the other hand, can be unpredictable in its reversal effects and could lead to myasthenic or cholinergic crisis. Many studies have supported the use of

Sugammadex including a retrospective review of a national inpatient database which found that patients reversed with Sugammadex had decreased instances of postoperative myasthenic crisis, decreased hospital costs, and decreased hospital length of stay [52].

3.2.3 Postoperative Care and Complications

Most patients after thymectomy are extubated in the operating room. While not always indicated, a low threshold for intensive care admission may be necessary. Need for sternal precautions post operatively is based on surgical approach. Most patients will receive a chest tube and daily chest x rays (CXRs) will be obtained, with removal of chest tubes when appropriate. While overall operative mortality is <1% [53], routine complications are possible including pneumonia, infection, or fluid changes, and close attention must be turned to a patient's respiratory status. Additionally, consultation with the neurology team is often crucial in the care of these patients. Monitoring for ocular symptoms or traditional methods of respiratory monitoring in myasthenia gravis patients may be utilized. The challenge in post-operative care unique to myasthenia patients is the fact that post-operative lung infection is an independent risk factor for myasthenic crisis after thymectomy (MCAT) [42].

While no randomized controlled trials exist which examine differences in surgical technique and approach, a recent meta-analysis found no difference in complications between limited and extended thymectomies [54]. Studies comparing minimally invasive methods to open techniques have shown reduction in hospital length of stay and overall adverse events. However, this has not always been demonstrated for pulmonary outcomes when compared to the transcervical approach [55, 56]. Furthermore, while VATS has been associated with less blood loss, it has been associated with higher phrenic nerve injury [57]. Further differences in outcomes by surgical method are discussed below.

3.3 Surgical Approach to Management

Since the first thymectomy performed in 1912 by Sauerbruch [14], countless new techniques have been developed over the years. Each technique varies not only in primary approach (transsternal, transcervical, or minimally invasive) but by the extent of resection. Additionally, each technique has many variations from the traditionally described procedure. For all of these techniques, surgeons should aim to completely resect thymic tissue, avoid injury to the phrenic, vagus, and recurrent laryngeal nerves, and avoid disruption of the capsule and dissemination in cases of thymoma [58]. The debate over which technique is superior has continued for years and still remains unanswered given the wide variability between studies and the lack of controlled studies. Table 1 demonstrates outcomes by thymectomy approach. In general, the tissue removed, and clinical outcomes as well as remission rates are nearly the same. Therefore, the correct surgical approach may be the one the individual surgeon prefers and is adept in.

Table 1 Outcomes by thymectomy approach.

Author (Ref.)	Year Published	No. of Patients	Approach	Remission*	Overall Complications	Myasthenic Crisis	Hospital LOS	30 Day Mortality
Masaoka et al. [59]	1996	375 (286 nonthymomatous, 89 thymomatous)	TS	Nonthymomatous: 45.8% at 5 yr, 55.7% at 10 yr, 50.0% at 20 yr Thymomatous: 23% at 5 yr, 30% at 10 yr, 37.5% at 20 yr	N/A	N/A	N/A	N/A
Mack et al. [60]	1996	33	VATS	18% mean follow up 23.39 mo.	1 (3%)	N/A	4.12 days	0
Calhoun et al. [61]	1999	100	TC	N/A	8 (8%)	1 (1%)	1.22 days	0
Mineo et al. [62]	2000	31	VATS	13% at 12 mo., 36% at 48 mo.	N/A	1 (3.2%)	5.2 days	0
de Perrot et al. [63]	2003	120	TC	91% at 10 yrs	4 (3.3%)	2 (2%)	2 days (before 1994), 1 day (after 1994)	0
Chang et al. [64]	2005	15	VATS	5 follow up 33 mo	1 (6.7%)	N/A	8.22 days	N/A
Kattach et al. [65]	2006	16	TS	6 follow up 29.38 mo	2 (12.5%)	N/A	11.76 days	N/A
Shrager et al. [66]	2006	85	TS	17% at 4.5 yrs	13 (15%)	N/A	8 days	0
		164	TC	33% at 3 yr, 35% at 6 yr	11 (7.3%)	N/A	1.10 days	0

Lin et al. [67]	2009	38	VATS	32% mean follow up 2 (5%) 38.5 mo	N/A	5.6 days	0	
		22	TS	36% mean follow up 1 (5%) 86.7 mo	N/A	8.1 days	0	
Rucket et al. [68]	2011	79	VATS	20.3% at 42 mo 2 (2.5%)	N/A	N/A	0	
		74	Robot	39.3% at 42 mo 2 (2.7%)	N/A	N/A	0	
Freeman et al. [69]	2011	75	Robot	28% mean follow up 45 5 (6.6%) mo	0	2.2 days	0	
Tomulescu et al. [70]	2011	240	VATS	61% median follow up 12 (5%) 67 mo	1 (0.4%)	2.1 days	0	
Marulli et al. [71]	2013	100	Robot	28.5% at 5 yrs 6 (6%)	1 (1%)	3 days	0	
Xie et al. [72]	2016	50	TS	42% at 5 yrs 20 (40%)	11 (22%)	11 days	N/A	
		31	VATS	52.1% at 5 yrs 2 (6.5%)	1 (3.2%)	9 days	N/A	
Imielski et al. [73]	2020	69	TS	*94.2% at 5 yr, 89.8% at 10 yr	N/A	4.3 days	N/A	
		97	VATS	*94.8% at 5 yr, 90.7% at 10 yr	N/A	0.7%	2.4 days	N/A
		54	Robot	*96.2% at 5 yr, 96.2% at 10 yr	N/A	1.3 days	N/A	
Luzzi et al. [74]	2021	57	Robot	N/A 31%	N/A	5.25 days	N/A	
		57	TS	N/A 33%	N/A	12.31 days	N/A	

*Complete stable remission

LOS = length of stay

TS = Transsternal

TC = Transcervical

VATS = Video-assisted thoracoscopic surgery

Thymectomies can be generally grouped into: transcervical thymectomy (T1), thoracoscopic thymectomy (T2) (VATS and robotic), transsternal thymectomy (T3) (with either a partial or full sternotomy), and transcervical and transsternal thymectomy (T4) via the Myasthenia Gravis Foundation of America (MGFA) thymectomy classification [27]. Additionally, each of these categories have subtypes which vary in degree of resection. These subtypes can be broadly summarized as either basic or extended. Only the thymus is removed in a basic resection. The entire thymus and surrounding fat tissue are removed in an extended resection. Transsternal thymectomy can either be completed with a full or partial sternotomy. Additionally, it can be further subdivided into the “standard” (T3a) and the “extended” techniques (T3b). The transcervical thymectomy can be further divided into the “basic” (T1a) or “extended” (T1b) resections. An extended transcervical thymectomy utilizes a specialized sternal retractor to improve visualization and achieve a greater degree of resection. The combined transcervical and transsternal thymectomy (T4), as its name implies, utilizes a neck and sternal incision to resect all possible thymic tissue in the neck and mediastinum. Finally, the thoracoscopic thymectomy can be subdivided into “classic” video-assisted thoracic surgery (VATS) (T2a) and thoracoscopic extended thymectomy (VATET) (T2b). While a classic video-assisted thymectomy is performed unilaterally, the extended version uses bilateral incisions as well as a cervical incision [27]. Of note, Sonett and Jaretzki listed a modified MGFA classification to include variations such as extended with partial sternal split and extended with videoscopic technology for transcervical thymectomy, unilateral and bilateral robotic thymectomy, and added infra-sternal thymectomy (T5) as a category [75].

Even though the thymectomy performed by Sauerbruch [14] was completed via a transcervical approach, the transsternal approach was initially popular amongst surgeons for thymectomy in MG and was considered standard. The first thymectomy specifically for myasthenia gravis was performed by Alfred Blalock in 1939 via a transsternal approach with improvement in symptoms [13]. He later reported the results of thymectomy in 6 patients with MG and later 20 patients with mostly positive results [76, 77]. Various other surgeons followed suit and reported on their experiences with transsternal thymectomy. However, given the invasiveness of the transsternal approach, attention turned back to the original transcervical thymectomy. Kirschner and colleagues reported the course of 21 patients who underwent thymectomy via the transcervical approach (T1a) and noted that patients had less pain postoperatively and ambulated early. Additionally, at one year follow up, nine patients had almost complete remission or improvement in symptoms and three had no change in symptoms (eight couldn't be evaluated due to recent thymectomy) [78]. Others supported the transcervical approach as a less invasive and more accepted procedure by patients [78, 79]. However, there was significant concern that inadequate visualization would lead to incomplete resection and recurrence. Masaoka et al. noted that there was often additional thymic tissue within the mediastinal fat and advocated for the extended transsternal thymectomy [80]. They additionally published 20-year results with this method and noted favorable remission rates in patients with and without thymoma [59]. Jaretzki et al found multiple accessory lobes of the thymus throughout the mediastinum and advocated for a more aggressive and complete resection via a combined transcervical and transsternal thymectomy [81, 82]. Various studies have supported the transsternal and combined transcervical and transsternal approaches including the MGTX study which utilized an extended transsternal approach [16].

A major development to the transcervical approach was in 1988 where Cooper et al reported a modified transcervical thymectomy (T1b) utilizing a novel sternal retractor and followed the

outcomes of 65 patients over 8 years. Comparing the outcomes of these patients with those who had undergone transsternal thymectomy, they concluded that this new technique could have similar results [83]. They later published a retrospective review of 100 patients who had undergone transcervical thymectomy and found a mean operative time of 104 minutes, mean length of stay of 1.22 days, no significant postoperative complications, and significant reduction of Osseman grade in follow up (3 preoperatively to 1 postoperatively, $p < 0.001$). They concluded that the transcervical approach was comparable to the transsternal approach and carried with it fewer complications and decreased length of stay [61]. With the previous recurrence and reoperation rates and the success of the extended approach, the basic transcervical approach was largely abandoned. Various other retrospective reviews throughout the years have supported the transcervical approach (along with some variations) and demonstrated similar outcomes to more invasive approaches [63, 66, 84]. The new extended transcervical approach additionally yielded similar complete remission rates to those of the sternotomy approach. A retrospective chart review by Shrager et al. [85] utilizing life table analysis found a 43% complete remission rate at 5 years compared to a 50% complete remission rate at 5 years in median sternotomy cases reported by Jaretski et al. [82]. It is important to note, however, that for consideration of transcervical thymectomy, a patient must be able to extend their neck adequately. Additionally, morbid obesity, prior mediastinal surgery, and thymoma whether present or suspected are contraindications to the transcervical approach. Conversely, some have argued that resection of well contained small thymomas or lesions (<4 cm) could be adequately resected via the transcervical approach [86].

In the 1990s, video thoracoscopy was introduced as a method of thymectomy [87-89]. Variations on laterality as well as the overall procedure have emerged over time. Additionally, in the early 2000s, the use of the robotic platform for thymectomy was introduced [90-92]. These approaches, much like the transcervical approach, were appealing due to their minimally invasive nature. However, much like the other approaches to thymectomy, it has been debated whether video-assisted thoracoscopic (VATS or robotic) thymectomy provides adequate resection and remission. Initial studies as well as studies detailing laterality and remission rates will be described in further detail in subsequent sections.

3.4 Video-Assisted Thoracoscopic Thymectomy

As previously discussed, the open (transsternal) approach was considered the gold standard for thymectomy for years. While the maximal approaches provided excellent excision of all thymic tissue, they also came with higher morbidity and were a large physiologic strain on patients, especially those with MG. With the development of minimally invasive procedures such as the transcervical thymectomy, came significant concerns over whether these approaches could provide extended thymectomy. Indeed, these concerns appeared correct for the original “standard” transcervical thymectomy which was abandoned with time. In the 1990s, several single center retrospective studies reported on the use of videoscopic approaches for thymectomy the first by Sugarbaker [63, 66, 84]. Similar to its minimally invasive predecessor, there were several concerns with this new approach, namely whether it could offer as adequate resection as the open approaches.

3.4.1 Laterality

VATS thymectomy can be performed either unilaterally or bilaterally. Additionally, if approached unilaterally, a VATS thymectomy can be performed on either the left or right side of the patient. Those who prefer left sided thymectomy favor it for the extensive excision of perithymic tissue [62]. However, the left sided approach carries the potential for injury of the innominate vein and SVC junction. Those who prefer the right sided approach like the additional space provided and improved view of the superior vena cava as a landmark [60, 72, 93]. The right sided approach, however, has the potential for injury to the left phrenic nerve at the level of the left sided innominate vein. Currently, there is little data on bilateral vs unilateral VATS thymectomy, however, it is generally accepted that similar results can be achieved with either approach [94, 95]. Similarly, single center retrospective reviews haven't found significant differences in outcomes between laterality of VATS thymectomy [70, 72]. Thus, the decision between unilateral or bilateral VATS as well as left vs right sided approach depends largely on lesion (if present) location and surgeon experience and preference.

3.4.2 VATS vs Open Approaches

Various single center retrospective reviews have demonstrated that some of the clear advantages of VATS over open thymectomy are shorter hospital stay [55, 93, 96-98], fewer postoperative complications [99], and decreased intraoperative blood loss [64, 100, 101]. The former is a particularly appealing benefit to minimally invasive options considering the ongoing COVID epidemic and the need to minimize exposure in a healthcare setting. There have been mixed results regarding operative time for VATS and transsternal thymectomy. Some retrospective studies have demonstrated no significant differences in operative time [55, 67]. Conversely, other retrospective and prospective studies have found significantly longer operative times with VATS thymectomy (197 ± 35 min VATS vs 113 ± 43 min transsternal, $p < 0.001$) [102] (4.2 hours VATS vs 1.8 hours transsternal, $p < 0.05$) [64]. Intuitively, a minimally invasive approach would cause less pain and splinting and, thus, improved respiratory functioning postoperatively. A small prospective trial compared postoperative pulmonary function (via vital capacity, forced vital capacity, forced expiratory volume per second, and peak expiratory flow) between transsternal and VATS thymectomy in 20 patients and found that VATS patients had less impairment of their respiratory function immediately postoperatively and returned to their baseline functioning faster than those who underwent transsternal thymectomy [103].

Additionally, various studies have compared VATS thymectomy with more invasive approaches and have found similar rates of symptom reduction and remission [52, 60, 99, 101]. One single center retrospective study examined complete stable remission (CSR) rates. CSR is defined by the MGFA as no MG signs or symptoms for 1 year without therapy [27]. In patients who underwent extended unilateral VATS thymectomy, CSR occurred in 61% of patients with a median time of 18 months to achieving CSR. The probability of achieving CSR was 60% at 5 years and 88% at 10 years [89]. A recent meta-analysis compared CSR rates amongst various thymectomy approaches and found no significant differences in CSR at 3 years (RR 0.96, 95% CI 0.72-1.27, $p = 0.74$) and 9 years (RR 1.51, 95% CI 0.99-2.30, $p = 0.05$) between extended transsternal and extended VATS [104]. With regards to symptom relief, a retrospective cohort study compared VATS to transsternal thymectomy in MG patients and found similar rates of medication cessation after surgery between the two

groups (77.8% VATS vs 65.4% transsternal stopped prednisone, $p = 0.38$; 65.2% VATS vs 42.5% transsternal stopped pyridostigmine, $p = 0.08$; 100% VATS vs 54.6% transsternal stopped immunosuppressives, $p = 0.46$) [55].

3.5 Robotic Thymectomy

In 2001, Yoshino et al reported on the first use of the da Vinci® Surgical System (Intuitive Surgical Inc., Sunnyvale, CA) in thoracic surgery for excision of a thymoma [90]. Others began publishing case studies of their experiences with robotic thymectomy including the first thymectomies performed for patients with MG in 2003 [91, 92]. As mentioned previously, minimally invasive approaches to thymectomy had gained favor due to less postoperative complications, shorter hospital length of stay, and improved cosmesis [55, 66, 99, 103]. Robotic-assisted thymectomy, specifically, was seen as an approach that could yield better visualization given the 3D high-definition camera as well as potentially improved dissection within the mediastinum given the 360 degrees of motion and articulating wrists [105].

3.5.1 Laterality

Much like the previous approaches, there are many variations to robotic thymectomy. Robotic thymectomy can be performed from either the left or right side of the patient. Those who prefer left sided thymectomy favor it due to its easier access to the mediastinal tissue and thymus as well as good visualization of both phrenic nerves. Conversely, the right sided approach provides more space but sacrifices adequate view of the left phrenic nerve. Regardless of the approach, the surgeon should not hesitate to add ports to the contralateral side if they encounter difficulty or convert to open. Additionally, the goal of robotic thymectomy, regardless of laterality or variation, is complete resection of all thymic tissue.

3.5.2 Robotic vs Open Thymectomy

Various studies have compared robotic thymectomy to open approaches. The advantages of the robotic system become very apparent when comparing robotic thymectomy to transsternal thymectomy. A meta-analysis of 18 studies examined various perioperative variables between robot and open groups and found no difference in operative times, mortality rates, or intraoperative complications but significantly lower blood loss, postoperative complications, and positive margins [106]. Like other minimally invasive approaches, robotic thymectomy has been associated with fewer postoperative complications and shorter length of stay when compared to transsternal.

One prospective study examined differences in patient quality of life after robotic and transsternal thymectomy. It found that those who underwent robotic thymectomy returned to baseline physical functioning sooner than their counterparts who underwent transsternal thymectomy, who had significantly decreased physical functioning (baseline 81.5 vs 66.3, $p = 0.001$) and role functioning (baseline 71.9 vs 40.8, $p = 0.001$) scores a month after surgery. Additionally, those who underwent transsternal thymectomy had increased pain (baseline 15.2 vs 26.7, $p = 0.017$) up to 3 months after surgery and significantly increased fatigue (baseline 34.3 vs 50.5, $p = 0.003$) 1 month after surgery whereas the robotic thymectomy group had returned to baseline at these timepoints [107]. A propensity matched retrospective cohort study comparing open vs robotic

thymectomies found shorter hospital stays (5.25 ± 2.27 days vs 12.31 ± 13.62 days, $p=0.003$ for robot and open respectively) and no differences in operative time or postoperative complications (208.19 ± 99.69 min vs 195.69 ± 51.45 min robot and open respectively). Similar to the previous study, patients in the open group had higher postoperative pain scores as measured by a visual analog scale (VAS) compared to robot cases ($p<0.001$) however, this was not supported by a significant reduction in analgesic medication use [74]. Additionally, when discussing myasthenia gravis, it is important to consider complete remission rates. Previous studies have demonstrated similar CSR rates between the two approaches with probabilities of CSR in robotic cases 28-42% [71, 68, 69, 108] and rates for transsternal thymectomies from 17-34% [65, 109].

3.5.3 Robotic vs VATS Thymectomy

There have been a few studies which have aimed to compare VATS and robotic thymectomies in terms of operative time, complication rates, and remission rates. Overall, robotic thymectomy appears to have similar perioperative outcomes and remission rates to VATS. With regards to operative time, there have been mixed results between studies. A single center retrospective study found significantly longer operative times with the robot (139.80 vs 121.07 min, $p<0.05$) [110] while others found no difference [68, 73]. A retrospective cohort study comparing VATS and robotic thymectomies found similar conversion rates of 1.4% in the robotic group compared to a rate of 1.3% in the thoracoscopic group. Additionally, there were no 30-day mortalities in either group and overall postoperative morbidity rates were low in both groups (2.7% and 2.5% for robot and VATS, respectively) [68]. Another retrospective study found no significant differences in postoperative complications or morbidity between VATS and robotic cases but did note shorter hospital stays in the robot group (1.3 ± 0.82 vs 2.4 ± 3.2 days, $p = 0.01$ for robot and VATS respectively) [73].

Considering the greater degrees of motion with the robotic arms, one could argue that thymectomies performed via this approach may be able to achieve improved resection and thus have increased rates of symptom reduction and remission. Overall, long term follow up data for robotic cases are lacking but similar symptom reduction and remission rates to VATS cases have been demonstrated. Solis-Pazmino et al performed a meta-analysis of 13 studies comparing the various approaches to thymectomy. When comparing VATS thymectomy to its robotic counterpart in terms of complete stable remission, robotic extended thymectomy appeared to have higher CSR rates at 3 years (RR 1.99, 95% CI 1.16-3.42, $p = 0.01$). However, this advantage was not observed at 5 years (RR 1.10, 95% CI 0.76-1.6, $p = 0.62$). It is important to note that the quality of evidence in this analysis was low due partially to the small cohort sizes of the studies included. Thus, prospective randomized trials are required to draw definitive conclusions on remission rates between approaches [104]. Wei and D'Amico detail the literature on robotic vs VATS thymectomy [95]. With regards to symptom reduction, they note that studies have found reduction in symptoms similar to VATS resections in 87% of patients at 45 months [69], 82% at 26 months [111], and 90% at 17-24 months [92, 112].

3.5.4 Arguments Against the Robot

The robotic platform is not without its potential disadvantages. One of the larger arguments against the robot is its increased cost. When comparing costs of VATS vs robotic thymectomies, the robotic approach was found to be much more expensive in initial costs for the platform as well as

fixed and material costs [97]. Conversely, another study compared the total costs of VATS and robotic thymectomies and found no significant differences ($\$14,743 \pm \$13,113$ vs $\$14,075 \pm \$4,439$, $p = 0.71$ for VATS and robot respectively) [73]. Another argument against the robotic approach is the learning curve associated with the platform. Studies, however, have demonstrated a steep learning curve for robotic thymectomies. Power et al. [113] performed a systematic review on robotic thymectomies and lung resections and found that operative time was significantly reduced after 15-20 robotic thymectomies. There were mixed results regarding changes in length of stay and complications after the learning curve. However, this significant reduction in operating time after completing 15-20 cases was demonstrated in another single center retrospective study which utilized a propensity match. There were additionally no significant differences in blood loss, complications, conversion rate, and length of stay between early and late cases [114].

Another argument against the robot includes concerns regarding the lack of tactile feedback as opposed to VATS. However, as described in previous sections, studies comparing VATS and robotic thymectomies have demonstrated largely similar perioperative outcomes. Thus, this doesn't appear to significantly impact outcomes of patients when compared to other minimally invasive approaches.

4. Discussion

While thymectomy has been performed for more than 100 years, technique and approach have shifted with time to minimally invasive approaches. In the last century, usefulness of thymectomy for myasthenia gravis was debated due to spontaneous remission and lack of randomized trials. However, the MGTX trial [16] was the first major randomized trial that found surgery to be superior to medical therapy in patients with non-thymomatous myasthenia gravis. This study has led to the professional societal recommendation of thymectomy in appropriate surgical candidates with anti-AchR positive disease [17]. In those with thymomas, thymectomy has been less debated and considered an appropriate surgical indication. To date, thymectomy use in certain patient subsets (elderly or pregnant patients) has been less studied and is not currently recommended as standard of care.

Myasthenia patients themselves must undergo careful workup and often require unique intraoperative management including consideration of anesthesia choice. They also must be monitored closely in the post-operative setting for development of myasthenic crises.

Current literature now supports the use of minimally invasive thymectomy as it has been associated with reduced complication rates and improved patient outcomes as well as shorter hospital length of stay. These advantages are particularly important now during the COVID pandemic. However, differences in outcomes do appear to vary when compared to either the transcervical vs transsternal approaches and there remains a need for prospective randomized trials comparing open vs minimally invasive approaches.

5. Conclusion

Based on our review, thymectomy for thymoma or anti-AchR positive non-thymomatous disease is indicated in appropriate surgical candidates with the latter now validated in a randomized clinical trial. Use of minimally invasive techniques appears to be safe and associated with improved post-

operative outcomes overall and is routinely used now in our practice. However, prospective randomized trials are needed in the future to validate these findings.

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Author Contributions

ARD, ALD, MTJ all contributed to data accumulation, analysis, interpretation of results, and drafting of the manuscript.

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Competing Interest

The authors have declared that no competing interests exist.

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