13 Thymectomy for Non-thymomatous Myasthenia Gravis

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Introduction

Despite having been employed for over 75 years in the treatment of myasthenia gravis (MG), evidence for the effectiveness of thymectomy has until only recently been limited to observational data. The publication of the first randomized prospective study of thymectomy in non-thymomatous myasthenia gravis unequivocally demonstrates the benefit of surgical removal of thymic tissue in the treatment of this disease [1]. However, many critical issues remain, including patient selection, timing of surgery, perioperative management, appropriate surgical approach, and role of thymectomy in the various subtypes of MG. While many studies that address such issues exist in the current literature, current practice recommendations are drawn from retrospective data rather than controlled prospective studies.

In addition to reviewing the surgical anatomy of the thymus, various thymectomy techniques, and their outcomes, this chapter will attempt to summarize remaining controversies as well as make recommendations based on available evidence regarding surgical management of non-thymomatous MG.

Total Thymectomy Is Indicated

Even before the role of the thymus in MG was understood, "total" thymectomy was considered the goal of surgery. In 1941 Blalock wrote "complete removal of all thymic tissue offers the best chance of altering the course of the disease" [2], and this has been reiterated by most leaders in the field [3–16]. Pathologic and immunologic studies have since clearly demonstrated that the thymus plays a central role in the autoimmune pathogenesis of MG [17–19]. However, its pathologic function may vary between the different antibody subtypes (anti-AChR, anti-MuSK, or seronegative) [20, 21], with important clinical implications regarding which patients with MG benefit from thymectomy.

When thymectomy is undertaken in the treatment of non-thymomatous MG, the concept that the entire thymus should be removed is supported by animal models and by clinical experience. In an animal model of myasthenia gravis, complete neonatal thymectomy in rabbits

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prevents experimental autoimmune myasthenia gravis, whereas incomplete removal does not [22]. In humans, both incomplete transcervical and incomplete transsternal resections have been followed by persistent symptoms that were later relieved by a more extensive reoperation with the finding of residual thymus [23–29]. And removal of as little as 2 g of residual thymus has been therapeutic [27]. In addition, several studies comparing aggressive thymic resections with limited resections support the premise that the entire thymus should be removed [30, 31].

Surgical Anatomy of the Thymus

Since complete removal of the thymus appears indicated when a thymectomy is performed in the treatment of non-thymomatous MG, its anatomy should be understood by all those involved in the treatment of these patients and in the analysis of the results of the surgery. Importantly, the thymus is not "two well-defined lobes that appear almost as distinct as do the two lobes of the thyroid" as described by Blalock [2].

Detailed surgical-anatomical studies (Fig. 13.1) have demonstrated that the thymus

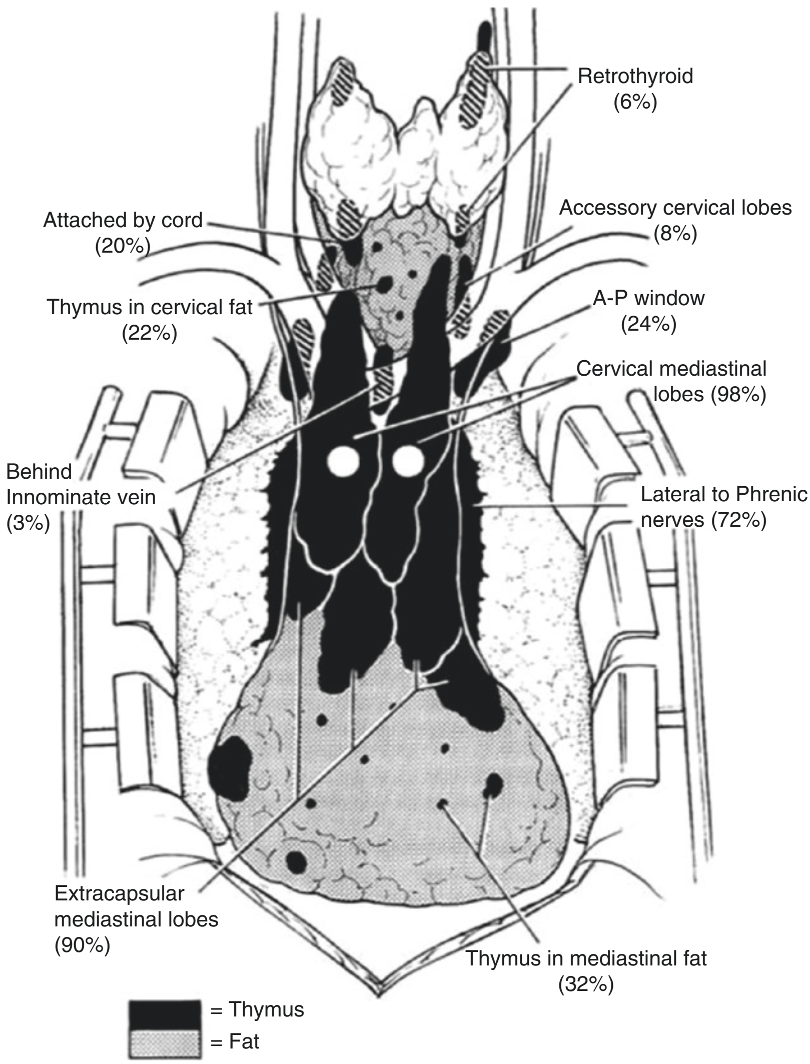

Fig. 13.1 Composite anatomy of the thymus. This illustration represents what is now accepted as the surgical anatomy of the thymus. The frequencies (percentages of occurrence) of the variations are noted. Thymus was found outside the confines of the two classical cervical-mediastinal lobes (A and B) in the neck in 32% of the specimens, in the mediastinum in 98% (black, thymus; gray, fat, which may contain islands of thymus and microscopic thymus) [37]. Reprinted with permission from Jaretzki A, Thymectomy for myasthenia gravis: Analysis of the controversies regarding technique and results, Neurology, 48, Suppl 5, S52–S63, http://www.neurology.org/content/48/Suppl_5/52S.extract

frequently consists of multiple lobes in the neck and mediastinum, often separately encapsulated, and these lobes may not be contiguous. In addition, unencapsulated lobules of thymus and microscopic foci of thymus may be widely and invisibly distributed in the pretracheal and anterior mediastinal fat from the level of the thyroid, and occasionally above, to the diaphragm and bilaterally from beyond each phrenic nerve [32, 33]. Occasionally, microscopic foci of thymic tissue have been found in the subcarinal fat [34].

Table 13.1 MGFA thymectomy classification (italics signifying modification from the original classification [35])

T-1 transcervical thymectomy	
(a)	Basic
(b)	Extended
(c)	*Extended with partial sternal split*
(d)	*Extended with videoscopic technology*
T-2 videoscopic thymectomy	
(a)	Classic VATS (unilateral)
(b)	VATET (bilateral with cervical incision)
(c)	*Bilateral VATS (no cervical incision)*
(d)	*Videoscopic with Robotic Technology (unilateral or bilateral)*
T-3 transsternal thymectomy	
(a)	Standard
(b)	Extended
T-4 Transcervical and transsternal thymectomy	
T-5 Infrasternal thymectomy	
(a)	*Combined transcervical-subxiphoid*
(b)	*Videoscopic subxiphoid (uni- or multiportal)*
(c)	*Videoscopic subxiphoid with robotic technology*

Surgical Techniques and Their Resectional Potential

The use of a standardized thymectomy classification system is necessary in order to compare outcomes between different techniques. Accordingly, we rely on the system developed by the Myasthenia Gravis Foundation of America (MGFA), with the understanding that the classification system will require continual modification as new more minimally invasive techniques are introduced, including novel approaches that are in essence a combination of those previously described (Table 13.1) [35, 36]. These hybrid operations, utilizing a combination of cervical, thoracoscopic, and infrasternal approaches with or without the use of robotic technology, are beginning to defy easy categorization as set out by the MGFA guidelines. Rather than becoming mired in the semantics of classification, the focus should remain on studies clearly describing operative techniques, so that as long-term, high-quality outcomes data become available, the various approaches can be accurately compared and the benefit of additional exposure or technology evaluated.

If total thymectomy should remain the goal in the surgical treatment of MG, an understanding of how much gross and microscopic thymus each resectional technique is capable of removing is necessary. The following presents a basic description of the resection technique and estimates of what each type of resection can accomplish. These estimates are based on published reports, drawings, photographs of resected specimens, videos of the procedures when available, and our personal experience. The videos taken at operation and photographs of the resected specimens are frequently the most revealing. A review of what appears to be the potential of each thymectomy technique strongly suggests that all resections are not equal in extent [37].

Regardless of the selected technique, however, when complete removal of all thymic tissue is the goal of the thymectomy technique employed, the actual extent of each individual resection is determined in part by the operating surgeon's conviction that as much thymus that can be removed safely should be removed, the surgeon's commitment to take the time to do so meticulously, and the surgeon's experience with the technique employed. In that respect, while a classification system is necessary in order to compare outcomes, the ultimate question is not which resectional technique is best, but whether or not a particular approach allows for total thymectomy *when properly performed*.

Combined Transcervical and Transsternal Thymectomy (T-4)

Combined transcervical–transsternal maximal thymectomy [33], also known as extended cervico-mediastinal thymectomy [38] or "maximal" thymectomy, is considered the benchmark operation against which other resectional procedures should be measured [11]. Its design is based on the surgical anatomy of the thymus and employs both a complete median sternotomy and a cervical incision to achieve wide exposure in the neck [39]. An en bloc resection is used, removing in a single specimen all gross thymus, suspected cervical-mediastinal thymus, and anterior cervical-mediastinal fat. Sharp dissection is utilized in the removal of the specimen with both sheets of mediastinal pleura and on the pericardium, as blunt dissection may leave microscopic foci of the thymus on these structures [40]. Extreme care is taken to protect the recurrent laryngeal, left vagus, and phrenic nerves.

These resections are exenteration in extent and are "performed as if it were an en bloc dissection for a malignant tumor" so as ensure that islands of thymus are not left behind and to guard against the potential of seeding of thymus in the wound [41]. It predictably removes all surgically available thymus in the neck and mediastinum, including the unencapsulated lobes and the lobules of the thymus and microscopic thymus in the pre-cervical and anterior mediastinal fat (an estimated 98–100% of thymic tissue).

Transsternal Thymectomies (T-3)

Standard Transsternal Thymectomy (T-3a)

The standard transsternal thymectomy used by the pioneers Blalock, Keynes, and Clagett [2, 3, 42, 43] was originally limited to removal of the well-defined cervical-mediastinal lobes that were thought to be the entire gland [44]. Currently, although a complete or partial [45–48] sternotomy may be performed, the resection is more extensive than originally described and includes removal of all visible mediastinal thymic lobes. Mediastinal fat, varying in extent, may or may not be removed. The cervical extensions of the thymus are removed from below, with or without some adjacent cervical fat.

This technique appears to fall short of total thymectomy as the residual thymus has been found in the neck and in the mediastinum at reoperation following a standard transsternal thymectomy [26–28]. Accordingly, many consider the standard transsternal thymectomy incomplete and no longer use it for the treatment of MG [49, 50].

Extended Transsternal Thymectomy (T-3b)

The extended transsternal thymectomy [51, 52] is also known as aggressive transsternal thymectomy [53] or transsternal radical thymectomy [54]. The extent of these resections varies in the mediastinum, but is more extensive than the standard transsternal thymectomy. Ideally, the extended technique is identical to the mediastinal dissection of the "maximal" T-4 procedure [51]. However, similar to the standard transsternal technique, cervical thymic extensions are removed from below, with or without some additional cervical tissue, but without a formal neck dissection.

While the extended transsternal technique may approximate the mediastinal resection achieved with a "maximal" T-4 approach, they remove less tissue in the neck (where a small amount of thymic tissue is present in approximately 30% of specimens) [33]. Mulder has expressed the view, however, that the risk to the recurrent laryngeal nerves in performing the extensive neck dissection of the combined transcervical–transsternal maximal thymectomy is not "justified by the small potential gain" [55].

Transcervical Thymectomies (T-1)

Basic Transcervical Thymectomy (T-1a)

The basic transcervical thymectomy employs an intracapsular extraction of the mediastinal thymus via a small cervical incision and is limited to the removal of the intracapsular portion of the central cervical-mediastinal lobes. No other tissue is removed in the neck or mediastinum [5, 56, 57]. Although originally considered to be a "total thymectomy" [5], the basic transcervical thymectomy is unequivocally an incomplete resection in both the neck and the mediastinum as evidenced by the findings of residual thymus during reoperations [23–29].

Extended Transcervical Thymectomy (T-1b)

The extended transcervical thymectomy [58–60] employs a special manubrial retractor for improved exposure of the mediastinum via a cervical incision. The mediastinal dissection is extracapsular and includes resection of the visible mediastinal thymus and mediastinal fat. Sharp dissection may or may not be performed on the pericardium. The mediastinal pleural sheets may be included in the resection but usually are not. The neck exploration and dissections vary in extent and may or may not be limited to exploration and removal of the cervical-mediastinal extensions of the thymus.

The extended transcervical thymectomy resection, as warned by Cooper [58], when performed by others may be less extensive than the procedure described by him.

Extended Transcervical Thymectomy Variations (T-1c-d)

The extended transcervical thymectomy has been modified to include a partial median sternotomy (T-1c) [61] and use of videoscopic technology (T-1d) to aid in visualization and dissection of the mediastinum. Video-assisted variations include addition of transcervical thoracoscopy [62, 63] or a subxiphoid videoscopic inferior approach (described below in Infrasternal Thymectomies) [64].

Videoscopic-Assisted Thymectomies (T-2)

Classic VATS (Unilateral) (T-2a)

The video-assisted thoracic surgery (VATS) thymectomy employs unilateral videoscopic exposure of the mediastinum (right or left) with removal of the grossly identifiable thymus and variable amounts of anterior mediastinal fat. Sharp dissection may or may not be used on the pericardium, and the mediastinal pleural sheets are not routinely removed with the specimen. Complete removal of the mediastinal and diaphragmatic fat on the operative side is routinely performed. The cervical extensions of the thymus are usually removed from below [16, 64–69].

The VATS resections, based on the published reports, vary in extent in the mediastinum. They appear to be more extensive than the standard transsternal resections. Since it is unilateral, left or right, the contralateral side of the mediastinum does not appear to be as well visualized as the operative side.

Video-Assisted Thoracoscopic Extended Thymectomy (Bilateral with Cervical Incision) (T-2b)

The video-assisted thoracoscopic extended thymectomy (VATET) uses bilateral thoracoscopic exposure for improved visualization of both sides of the mediastinum as well as a possible cervical incision for exposure of the recurrent laryngeal nerves and removal of the cervical thymic lobes and pretracheal fat under direct vision [70, 71]. Extensive removal of the mediastinal thymus and peri-thymic fat is described, the thymus and fat being removed separately. Sharp dissection may or may not be used on the pericardium. The mediastinal pleural sheets are usually not removed. Modifications to VATET include addition of an anterior chest wall-lifting method [72]. The VATET operation is conceptually more complete than the unilateral VATS since it offers excellent visualization of both sides of the mediastinum and includes a neck dissection as well.

Bilateral VATS (No Cervical Incision) (T-2c)

Bilateral VATS thymectomy without a cervical incision has also been described [73, 74], with reportedly similar resection capability to extended transsternal thymectomies (T-3b) [73]. Notably, bilateral VATS thymectomy without a cervical incision is occasionally referred to as VATET in the literature, though the two procedures may differ in their resectional extent.

A study designed to evaluate bilateral VATS thymectomy with and without transcervical neck dissection observed that between 2 and 3% of thymic tissue may be left in the absence of additional cervical approach [75]. As such, we believe bilateral VATS without cervical incision should be treated as a separate entity from VATET when comparing outcomes and deserves a distinct classification.

Videoscopic with Robotic Technology (Unilateral or Bilateral) (T-2d)

Robotic-aided video-assisted thoracoscopic thymectomy, unilateral or bilateral, is becoming increasingly common since its introduction in the early 2000s [76–80, 163]. The instrumentation offers enhanced optics with three-dimensional visualization and ×12 magnification; the surgical arms allow precise tissue dissection. Therefore the technique has the potential for extensive, yet safe, resection of the thymus and anterior mediastinal fat as well as exploration of the neck. However, robotic technology certainly adds significant cost and time to the procedure.

Infrasternal Thymectomies (T-5)

The infrasternal thymectomies make use of a subxiphoid incision that reportedly allows improved visualization and dissection of bilateral mediastinal spaces that would otherwise be difficult from a unilateral thoracoscopic approach [81]. The operation may be performed solely through a subxiphoid incision [82, 83] or supplemented with bilateral thoracoscopic ports [84] and may include a cervical incision to facilitate neck dissection [82]. A combined transcervical-subxiphoid thymectomy (T-5a) utilizes both an open cervical dissection and subxiphoid video-assisted inferior approach and has been reported to achieve comparable resection to the "maximal" T-4 approach [64]. While the single incision subxiphoid approaches may result in aesthetically more appealing results, decreased maneuverability may increase operative time or hamper adequate dissection needed to achieve total thymectomy.

Robotic technology has also been employed in subxiphoid thymectomy, through single or multiple ports [85, 86]. While robotic technology has the aforementioned benefits and may overcome the limitations in dexterity encountered in single port operations, such procedures are still in their infancy, and the benefits in terms of long-term clinical outcomes versus cost and time remain to be demonstrated.

The Results of Thymectomy

Introduction

The publication of the first randomized prospective trial investigating thymectomy versus medical management marks a great step forward in the evidence supporting the benefit of thymectomy in non-thymomatous MG [1]. The following review summarizes the evidence supporting thymectomy as a treatment modality in non-thymomatous MG, the problems in the analysis of thymectomy for MG, as well as best available information on the outcomes of different thymectomy techniques, relying on studies employing uniform definitions and reliable statistical methods of analysis and acknowledging when no such information exists.

We firmly support the clinical research standards set out by the MGFA in 2000 and revised in 2012, which have added much needed consistency and clarity to the design, implementation, and interpretation of MG clinical research [35, 87]. Adherence to a unified system of classification of MG clinical subtypes, disease severity, therapy status, morbidity and mortality information, and measure of response is essential for accurate assessment of treatment impact. Despite wide adoption, not all data included in this review adhere to this classification system (due in part to its relatively recent introduction).

Problems in the Analysis of Thymectomy for MG

Inappropriate statistical analysis, including the comparison of unrelated statistical techniques, has led in many instances to incorrect conclusions concerning the relative merits of the thymectomy techniques. The following is a brief review of material previously reviewed and analyzed in detail [37, 88].

Remission has been considered the measurement of choice in defining results following thymectomy and the most desirable outcome from the patient standpoint [89–91]. However, not all studies adhere to its strictest definition as delineated in the MGFA guidelines, arguing that it represents a relatively rare outcome. Additionally, other studies argue that outcomes such as minimal manifestation status (MMS) or pharmacologic remission are more attainable and equally acceptable post-intervention statuses compared to complete stable remission.

Life table analysis, using the Kaplan–Meier method, is considered the preferred statistical technique for the analysis of remissions following thymectomy [92]. It provides a comparative analysis using all follow-up information accumulated to the date of assessment, including information on patients subsequently lost to follow-up and on those who have not yet reached the date of assessment [93, 94]. This analysis should be supplemented by multivariable analysis to identify and correct for significant variables. Hazard rates (remissions per 1000 patient-months) correct for length of follow-up and censor patients lost to follow-up. However, these rates depend on the risk (remissions per unit of time) being constant [95], which may not be the case in MG.

Uncorrected crude rates, the number of remissions divided by the number of patients operated upon or sometimes divided by only the number of patients followed (potentially a very different denominator), have been the primary form of analysis in the comparative evaluation of remissions and improvement following thymectomy. This is unfortunate since this form of analysis does not include in the evaluation all the follow-up information accumulated to the date of assessment. In addition, patients evaluated many years after surgery may appear to do as well or better than patients with a shorter follow-up. And even the differing denominators in the two subsets (patients operated upon versus patients followed) are not comparable but have frequently been compared without comment. Accordingly, uncorrected crude data should have no place in the comparative analysis of results of thymectomy and for this reason has been omitted from this review. Although correcting crude data for mean length of follow-up enables a rough comparison of the uncorrected crude data remission rates and confirms the fallacy of comparing uncorrected crude data, it should not be used as a substitute for life table analysis and therefore is also not included in this presentation.

In comparing results of different thymectomy techniques, other confounding factors are also frequently ignored and may conceal the disadvantages of the procedure being touted [37]. These include (1) failure to assess or define the length of illness preoperatively, (2) failure to account for the length of postoperative follow-up, (3) inclusion of multiple surgical techniques and combining two or more series with differing definitions and standards, (4) combining patients with and without thymoma in a composite analysis, (5) including reoperations in the primary analysis when most patients at the time of the reoperation had severe symptoms of long duration and may have failed earlier thymectomy for undetermined reasons, (6) use of meta-analysis based on mixed and uncontrolled data, (7) failure to report relapses, and (8) failure to consider the rate of spontaneous remissions.

Additionally, when immunosuppression is included in the preoperative or postoperative thymectomy regimen, the patients are not always compared to a control group and do not follow a predefined schedule of medications and dose reduction that is required in assessing the additive benefit from thymectomy and immunosuppression. Thus, under these circumstances, it is not possible to infer retrospectively the effects of thymectomy itself [96].

Thymectomy Versus Medical Management

The results of the Thymectomy Trial in Non-thymomatous Myasthenia Gravis Patients

Receiving Prednisone Therapy (MGTX) provide the first class I evidence in support of thymectomy for non-thymomatous MG [1]. The study, published in 2016, was a multicenter, prospective, randomized, and rater-blinded trial designed to evaluate the effect of thymectomy plus prednisone versus treatment with prednisone alone on improvement of MG symptoms, MG exacerbations, total prednisone and alternative immunosuppression requirements, and treatment-related complications.

The trial enrolled 126 patients between the ages of 16 and 65 with acetylcholine receptor antibody-positive MG, not associated with a thymoma, with disease duration of less than 5 years. Patients with ocular symptoms only or severe disease requiring intubation (class I and class V, respectively) were excluded, as were those who had undergone immunotherapy with anything other than prednisone. MGFA classification guidelines were utilized with regard to disease severity (Quantitative Myasthenia Gravis score, QMG) and post-intervention status. Participants were randomized to either undergo extended transsternal thymectomy (T-3b) in addition to a standardized prednisone protocol or the prednisone protocol alone and were followed for three years. Surgeons were required to adhere to a prescribed approach and underwent mandatory training to eliminate potential variability introduced by different thymectomy techniques.

Participants undergoing thymectomy in comparison to those treated with prednisone alone were observed to have significantly lower QMG scores (6.15 vs. 8.99, $p < 0.001$) indicating a clinically significant reduction in disease severity. Additionally, patients undergoing thymectomy required lower doses of prednisone to achieve minimal manifestation status (MMS) (44 mg vs. 60 mg, $p < 0.001$). Alternative immunosuppression requirements and MG exacerbations were significantly lower in the thymectomy group. Patients who underwent thymectomy were hospitalized with MG exacerbations less frequently (9% vs. 37%, $p < 0.001$) than those treated with prednisone alone. Treatment-related complications were equivalent.

While the MGTX trial demonstrates the benefit of thymectomy for patients with non-thymomatous MG, it is limited to patients with generalized MG associated with AChR antibodies and of relatively recent disease onset. Additionally, subgroup analysis of the trial failed to demonstrate the benefit of thymectomy for patients who had not previously been taking prednisone on QMG score or prednisone requirement, or for men with regard to QMG score, though this may be related to a relative small number of patients in such groups. Additionally, the primary outcome studied was MMS, rather than remission. The authors stated that remission, when strictly defined, is a relatively rare occurrence and that MMS is considered a desirable and achievable outcome [97].

Additional data that lend support for thymectomy in the treatment of non-thymomatous MG is limited to nonrandomized observational studies. A 2014 best-practice review that included papers evaluating thymectomy in non-thymomatous MG summarized that patients undergoing thymectomy are “more likely to achieve medication-free remission, become asymptomatic and clinically improve, particularly [those] with severe and generalized symptoms” compared to those undergoing medical management only [98]. A 2016 review of such studies demonstrated an odds ratio of 2.44 for remission in patients undergoing thymectomy to those treated nonoperatively [99]. However, such systematic reviews are limited by high heterogeneity among studies with regard to how patients are selected to undergo surgical versus nonsurgical treatment, operative approaches, and definition of remission.

Of note, the benefit of thymectomy is not immediate; remission rates more than 30% are rarely reported at 2 to 3 years post-thymectomy, though they typically continue to increase over time, and benefit may be seen as late as 15 years after surgery (Table 13.2).

Table 13.2 Comparative Kaplan–Meier remission rates of thymectomy techniques

	n	Pre-op duration					Years post-thymectomy						
		Class/severity (%)[a]					Symptom (% of patients achieving CSR)						
		Ocular	Mild	Mod	Severe	(Med years)	2–3	5	6	7.5	9–10	15	
No thymectomy[b]													
	149	9	16	73	2	–	10	15	–	18	20	–	[118]
Transcervical thymectomy													
T-1a	651	0.46	–	–	–	–	14	23	–	33	40	–	[119]
T-1b	151	21	39	28	12	–	34	–	34	–	36	–	[120]
T-1c	215	16	52	22	10	0.75	–	29	–	–	36	40	[121]
T-1d	120	11	32	37	20	0.8	–	30	–	–	91	–	[62]
Videoscopic thymectomy													
T-2a	36	22	42	14	22	–	–	13	20	–	75	–	[122]
	240	0	49	35	16	1.17	–	60	–	–	88	–	[123]
	79	4	33	43	20	–	–	20	–	–	–	–	[127]
	59	5	30	33	32	–	15	28	–	–	–	–	[160]
T-2b	159	12	–	76	12	–	35	51	51	–	–	–	[124]
T-2c	31	29	32	39	–	–	–	52	–	–	–	–	[161]
T-2d	100	–	–	–	–	0.92	–	29	–	–	–	–	[79]
	74	5	34	47	14	–	–	39	–	–	–	–	[127]
Transsternal thymectomy													
T-3a	60	–	–	–	–	1.95	12	15	–	–	–	–	[126]
T-3b	47	0	0	89	11	–	19	45	49	–	–	–	[124]
	98	18	41	23	18	–	–	30	–	–	45	–	[125]
	75	–	–	–	–	2.9	39	49	–	–	–	–	[126]
Transsternal-transcervical thymectomy													
T-4	72	0	18	52	30	–	30	50	–	81	–	–	[27]
	51	18	43	12	27	–	–	8.4	–	–	51	87	[162]
Infrasternal thymectomy													
T-5	292	–	–	–	–	2.3	39	48	–	–	–	–	[126]

[a]Osserman Classification or MGFA Clinical Classification

[b]Since we did not find for comparison spontaneous life table analysis remission rates for adults, we included life table analysis remission rates in children [118]. However, not included in this table is a study of standard transsternal thymectomies limited to children under the age of 17 years. It had a Kaplan–Meier remission rate at 7.5 years of 44% [118]

Indications for Thymectomy

In light of the MGTX trial, thymectomy appears indicated for adults less than 65 years with generalized, AChR antibody-positive non-thymomatous MG [1]. Expert consensus guidelines recommend thymectomy for non-thymomatous MG patients in order to improve symptoms, increase the chance of remission, and decrease need for immunosuppressants, though with caveats regarding (1) MG subtype, (2) patient age, (3) timing during disease course, and 4) disease severity [100].

Thymectomy is recommended for patients with AChR antibodies and generalized MG [1, 100, 101]. However, the benefit of thymectomy for patients with ocular MG is controversial; though some studies have shown that ocular MG patients undergoing thymectomy were more likely to achieve remission and less likely to progress to generalized MG [102, 103], others argue against it and believe that the data in favor of it is still lacking [104]. Expert guidelines do not recommend thymectomy as a first line treatment for ocular MG, but it may be considered if medical management fails [105].

The role for thymectomy is again unclear in patients with generalized MG but who are AChR antibody negative. Some argue that a percentage of seronegative MG patients (no detectable AChR and MuSK antibodies) may represent “false negatives”: patients with undetectable but present anti-AChR antibody, as studies have shown similar benefit to thymectomy compared to AChR-antibody-positive patients [106, 107]. As such, thymectomy is generally recommended in seronegative patients [100, 101]. However, patients who are MuSK or LRP4 antibody positive have not consistently been demonstrated to benefit from thymectomy [108, 109]; consensus guidelines recommend against its use in these cases [100, 101].

It is suggested that thymectomy provides greater benefit when performed early during the course of the disease and should be performed within 3 to 5 years of onset [110, 111], the rationale being that early surgery provides the highest chance at achieving remission while minimizing the total exposure to immunosuppressives. Additionally, as the thymus naturally involutes over time, older patients with atrophic thymuses may derive less benefit from thymectomy [112, 113].

Furthermore, surgical risk increases with age. Given limited data in this age group, thymectomy is not routinely recommended in patients over 60 [113]. However, age has not been demonstrated to be an absolute contraindication to thymectomy (as evidenced by the inclusion of patients up to 65 years of age in the MGTX trial) and the decision to proceed with thymectomy in elderly patient should be decided on an individualized basis. The indication for thymectomy in children is a separate issue addressed by others [114–117].

Given that the benefits of thymectomy are not immediate and the increased risk of perioperative complications with poorly controlled symptoms, thymectomy should be performed on an elective basis when patients are as symptom-free as possible [118, 119]. While evidence indicates that patients with less severe illness who are operated upon early in their course do better, a thymectomy should be considered for most adult patients with more than very mild generalized non-thymomatous MG, regardless of the duration of symptoms or age of the patient, unless a specific contraindication exists.

Comparative Results Following Thymectomy

The available evidence continues to suggest that the less thymus left behind, including extra-lobar lobules of the thymus and microscopic thymus in the peri-thymic fat, the better the long-term results. However, while there are no well-designed prospective studies that conclusively indicate which resectional technique is the thymectomy of choice, as previously mentioned, there may be multiple approaches that allow for total thymectomy. The question then becomes which techniques allow for as total a resection as achieved by the T-4 “maximal” thymectomy. While certainly the size and weight of specimens may on average vary between the techniques, the most meaningful measure is clinical outcome or, more specifically, rates of complete sustained remission.

We believe that the most reliable data for a comparative analysis of thymectomy techniques are reports that employ Kaplan–Meier life table analysis to report rates of remission. Table 13.2 represents a summary of such reports. We have omitted a presentation of crude data and adjusted crude data because, as previously discussed, the use of this form of analysis is not a valid statistical method to compare the results of the various thymectomy techniques. We recognize, however, that even though these studies have employed Kaplan–Meier analysis, they are not truly comparable because of significant variations in the severity and duration of the preoperative illness, variable use of pre- and postoperative corticosteroids and other immunosuppressive therapies, and various definitions of remission. However, this represents what we consider to be the best available evidence at this time.

Upon review of the table, it is immediately apparent that the patient populations widely vary between studies with regard to disease severity and preoperative duration, two factors with important implications for post-intervention outcomes. Additionally, while the MGFA defines complete stable remission as "no symptoms or signs of MG for at least 1 year and has received no therapy for MG during that time," a number of studies have defined remission as patients asymptomatic for at least 6 months off all medication or while only taking low-dose non-cholinesterase inhibitors [120, 121]. With this in mind, in addition to the variability in definitions of remission between studies, it is tempting to dismiss any attempt at comparison as futile.

However, a number of interesting observations can be made, the first being that the benefit of thymectomy is indeed not immediate and the superiority of one technique versus another may not be apparent until 5 or more years after surgery. Additionally, additional outcome data reported since our initial review continue to reinforce that all resections are not equal.

The transcervical resections appear to plateau at approximately 40% remission rate, with the exception of 91% remission rate at 10 years for the T-1d approach [62], which certainly deserves further consideration as a minimally invasive means to achieve good long-term results.

Of the videoscopic-assisted (T-2) techniques, the majority of data is limited to results within 6 years of operation. The most data exist on the unilateral VATS thymectomy (T-2a), with marked variability in rates of remission at 5 years between the studies, ranging from 13 to 60%. The 75% and 88% remission rates of the T-2a technique reported by Manulu et al. (2005) and Tomelescu et al. (2011) at 10 years are certainly intriguing and cannot be explained by more favorable patient populations or generous interpretations of "remission" [122, 123]. Long-term follow-up of the other videoscopic approaches is much needed.

Of the transsternal resections, while relatively few studies of short follow-up duration exist, the limited T-3 standard approach does not appear to achieve acceptably comparable results to other techniques. Notably, the T-3b extended transsternal thymectomy while demonstrating 30–49% remission rates at 5 years that are comparable to those of other approaches that demonstrate continued benefit at 10–15 years is lacking long-term data that it does similarly [124, 125].

The results of the two maximal T-4 thymectomy studies demonstrate its ability to achieve a relatively high rate of remission, but notably at a time point relatively remote from surgery. Of the one paper reporting life table analysis of an infrasternal–transcervical approach, while it appears to have relatively good 5-year remission rates, as with many of the other approaches, long-term prospective data is needed [126].

Selecting the Thymectomy Technique

While numerous studies utilizing MGFA research standards aimed at investigating both established and novel thymectomy techniques have been added to the literature since our initial review, in the absence of controlled prospective studies, it is still not possible to state with certainty which technique should be the procedure of choice. Accordingly, it is necessary for the referring neurologist to have an understanding of the debate herein presented in determining what procedure to recommend. However, regardless of the surgical approach, surgical expertise and experience are required. The surgeon should be convinced of the importance of complete removal of the thymus and be willing to commit the necessary time and care to achieve this goal safely. Since the need for complete removal of all gross and microscopic thymus has not been definitively confirmed, it is generally considered preferable to leave behind small amounts of suspected thymus, or even likely thymus, than injure the recurrent laryngeal, the left vagus, or the phrenic nerves. Injury to these nerves can be devastating to a patient with MG.

Based on an analysis of the available data, it appears that the more thorough the removal of all tissue that may contain the thymus, the better the long-term results. Therefore, historically and conceptually, the combined transcervical–transsternal thymectomy best fulfills these criteria. However it is now clear that varying minimally invasive thechniqes and approaches can encompass and replicate the resectional specimens that had been performed in open procedures.

We continue to support the extended transsternal thymectomy since in the hands of experienced surgeons, it predictably removes all but a possible small amount of the thymic variations in the neck, has less risk of injuring the recurrent laryngeal nerves, and has produced good 5-year results. However, it is now clear that minimally invasive approaches, again in experienced hands, can reliably remove the same tissue as a properly performed extended transsternal thymectomy. The most data exists for T-2a unilateral VATS thymectomy, and the two studies reporting outcomes at 10 years suggested it may provide an acceptable "minimally invasive" alternative to the T-4 approach. The VATET thymectomy (T-2b) is conceptually appealing based on the surgical anatomy and the 51% 6-year remission rate reported in the one available study is promising, though longer-term results are needed [124]. Bilateral approach overall appears to best afford maximal dissection with protection of the phrenic nerves, although the unilateral robotic technique described by Ruckert has been uniquely able to use the robotic approach to remove bilateral disease that others have not been able to achieve unilaterally [127]. The variability of 5-year remission rates of the video-assisted thymectomies underscores the need for well-designed, prospective trials comparing surgical techniques.

Increasing expertise and facility with minimally invasive techniques in combination with the conviction that total thymectomy is necessary may yield a number of surgical approaches to thymectomy that achieve comparable results to the "maximal" T-4 method. Thus, the debate is shifted from which thymectomy technique is best to whether a not a particular technique can allow for adequate exposure for safe removal of all thymic tissue. Based on the handful of studies that exist with long-term outcomes data, it appears likely that a number of approaches, including those relying solely on thoracoscopic or videoscopic techniques, may achieve outcomes comparable to the "maximal" thymectomy. If one of the minimally invasive techniques can consistently be demonstrated to be as effective in the treatment of MG as the procedures that employ a median sternotomy, it would be our choice for most patients.

Reoperation

A repeat thymectomy may be appropriate and highly desirable for patients who have had an unsatisfactory result after one of the more limited thymic resections [128]. This recommendation appears to be straightforward when applied to a patient who still has, or progresses to, an incapacitating and poorly controlled illness, especially if repeated hospitalizations and ICU stays have been required 3–5 or more years following a basic transcervical (T-1a) or a standard transsternal thymectomy (T-3a).

It is more difficult to recommend reoperation for less severe symptoms or after more extensive original operations, but it probably is appropriate in selected instances. Unfortunately at this time, it is not possible to determine the location, or even presence, of even moderate amounts of residual thymus prior to surgery or even by gross inspection at the time of surgery. Negative CT scans or MRI examinations do not exclude the presence of the residual thymus, and antibody studies are usually not helpful [29]. However, a review of the operative note and pathological report of the original surgery, which is mandatory in any case, usually makes it clear that an incomplete resection had been performed. Hopefully the day will come when techniques are developed that can determine the location of even small amounts of thymic tissue. The timing of reoperations is also a difficult decision. Although a 3- to 5-year wait frequently seems prudent, earlier reoperation may be more appropriate and many years later should not disqualify a patient from reoperation.

If reoperation is undertaken for persistent or recurrent symptoms, it should be as extensive as the combined transcervical–transsternal T-4 resections in both the neck and mediastinum, regardless of the thymectomy technique employed in the initial operation. This recommendation is supported by the findings following reoperations using the "maximal" technique [27]. Obviously, however, a reoperation is more difficult and time consuming than a primary resection, and the risk to the nerves and the thoracic duct is greater. Therefore, wide exposure in the neck and mediastinum, with the use of a "T" incision rather than separate neck and sternal incisions, appears highly desirable [33]. If the surgeon is not experienced in neck surgery, the assistance of a surgeon experienced in this area is suggested.

Reoperation thymectomies via extended transsternal [23, 28] and VATS [129] approaches have been described with reported improvement in the majority of patients, though studies are limited to retrospective examinations of relatively small, heterogeneous patient groups [130]. Incomplete resection and failure to remove residual thymus must account for at least some of those who fail to benefit from reoperation; we therefore cannot recommend any approach less extensive than the maximal T-4 approach without high-quality data that suggests otherwise.

Perioperative Patient Management

Patients undergoing thymectomy in the treatment of MG require the care of a team of neurologists, pulmonologists, respiratory therapists, intensive care specialists, anesthesiologists, and surgeons who have had experience in the care of these patients. Such teamwork has been demonstrated to improve outcome following thymectomy for MG [131], as has operative volume in other cardiothoracic operations [132–134]. And regardless of the surgical technique employed, the surgeons should be totally conversant with the special problems of patients with MG and committed to the frequently difficult postoperative care. To accomplish these goals, these operations should be performed at centers where such teams exist. It is, of course, important that the diagnosis of MG be unequivocally established prior to thymectomy and, as emphasized by Kaminski [135], the patient and the patient's family should have a thorough understanding of the illness, nonsurgical and surgical treatment options, anticipated postoperative course and morbidity, and, of course, the potential results, or lack thereof, of the surgery.

The special problems associated with the perioperative care of these patients are directly related to the severity of the MG manifestations at the time of surgery. The major risk is the presence of oropharyngeal and respiratory muscle weakness with the potential for aspiration of oral secretions, inability to cough effectively postoperatively, and respiratory failure. A number of variables are associated with increased risk of postoperative myasthenic crisis and respiratory failure, including a history of myasthenic crisis and longer duration of disease; some, however, such as preoperative bulbar symptoms and lower vital capacity, are potentially modifiable [136, 137].

Accordingly, the preoperative preparation of these patients is central to the success of surgery [138]. The patient should be as symptom-free as possible at the time of surgery, especially free of signs and symptoms of oropharyngeal and respiratory weakness. Cholinesterase inhibitors are the mainstay of symptomatic treatment of MG, though their use in the perioperative period is complicated by interactions with neuromuscular blocking agents (NMBAs), medications often essential in anesthesia and critical care (see below). Most recommend continuing anticholinesterase medications up to the day of surgery to prevent worsening of respiratory symptoms preoperatively [138, 139]. However, anticholinesterase medications should not be the sole means used to achieve adequate control of symptoms as these inhibitors only temporarily mask MG-related weakness, which may then flare up in the early postoperative period and result in a high rate of postoperative respiratory complications [140, 141]. Steroids are essential in the perioperative management of MG symptoms [142]. The concern about wound healing and infection associated with steroids is likely overemphasized and much less of a concern than performing an operation on an inadequately prepared patient [143]; clinicians should be cognizant of the potential for need for stress-dose steroids perioperatively. Plasmapheresis and/or IVIG administration is routinely used to improve the preoperative status of patients with history of severe respiratory compromise due to their MG [144–146].

The preoperative evaluation should include a detailed evaluation of the pulmonary function status. Vital capacity (VC) and respiratory muscle force measurements are recommended, both before and after cholinergic inhibitors, if the patient is receiving this medication and can tolerate its withdrawal for the 6–8 h interval necessary for this type of testing. The dual before and after measurements gives an indication of the deficits that may be masked by the cholinesterase inhibitors and the potential need for preoperative plasmapheresis or immunosuppression. Some studies suggest that vital capacity <2.0–2.9 L is predictive of increased risk of postoperative respiratory failure [147, 148]. The measurement of maximum expiratory force (MEF) is easy to perform, is an excellent measure of cough effectiveness (an important determination), and is more sensitive and reliable than the VC in the evaluation of these patients, both preoperatively and in the early postoperative period [149]. An MEF of less than 40–50 cm H_2O indicates a potential for postoperative respiratory complications and respiratory failure. These determinations are also helpful in assessing the timing of extubation in those patients that require postoperative ventilatory support [138, 149].

Due to the effects of antibodies directed toward acetylcholine receptors, patients with MG have a variable response to NMBAs. They may be resistant to depolarizing NMBAs while demonstrating acute sensitive to the effects of nondepolarizing NMBAs. The concomitant use of anticholinesterase medications (often used to reverse such medications during anesthesia) may exacerbate this effect and place the patient at risk for a cholinergic crisis [150]. Therefore, many believe that NMBAs should be avoided if possible. However, it is preferable to face the potential need for prolonged postoperative ventilation than have the patient suffer the consequences of hypoxia. Accordingly, should intubation be difficult, whether during anesthesia induction or at anytime intubation is required, immediate muscle paralysis may be mandatory to achieve intubation rapidly and successfully.

If the patient is well-prepared preoperatively and the preoperative MEF off cholinergic medication is satisfactory, regardless of the surgical technique employed and including transsternal incisions, extubation may be acceptable immediately postoperatively. However, emergency reintubation and respiratory support should be instituted immediately at any time for early signs of fatigue, progressive weakness, or impending respiratory failure. The use of cholinergic medication at such a time is usually ineffective and may delay needed intubation.

Postoperatively, these patients should be closely monitored in an intensive care setting by experienced personnel [151, 152]. The use of epidural anesthesia for control of pain following a median sternotomy is extremely helpful. An institutional protocol for the management of the postoperative MG patient is helpful and can include details of the ventilatory support management, defining the role of MEF measurements in deciding when to extubate, the role of physical therapy and bronchoscopy in maintaining a clear airway, pain control techniques, immunosuppression if indicated, the role of cholinergic medication, and timing and technique of a tracheostomy if necessary.

Surgical Management of Thymoma

Because approximately 10% of patients with MG will have a thymoma [153], a chest CT scan is indicated prior to thymectomy in all these patients. It should identify thymomas in most instances [154]. The presence of antibodies to striated muscle antigens also predicts the existence of a thymoma [15]. However, small thymomas may first be discovered at surgery. To avoid tumor seeding and late recurrences, the well-encapsulated and invasive tumors require wide local resection with as good tumor margins as practical, including the removal of adherent pericardium or wedges of adherent lung if necessary. Although a phrenic nerve may also appear to be involved, although always a difficult and individual decision, in most instances it can and perhaps should be preserved in patients with MG. In addition, a total thymectomy should be performed unless a specific contraindication exists.

Median sternotomy is the current standard of care approach [155]. While more minimally invasive techniques are becoming increasingly common in the resection of smaller tumors [156], they are not currently recommended by expert consensus guidelines [155] and should only be considered at centers with significant experience.

Outcomes Research

Well-designed and well-controlled prospective studies are required to begin to resolve the many conflicting statements and unanswered questions that exist concerning thymectomy in the treatment of MG. This goal must be achieved if patient protocols and operative techniques are to be properly evaluated. In this era of evidenced-based therapy, these steps are not only desirable but mandatory.

The ideal method of such evaluation is to undertake a prospective randomized clinical trial, class I evidence in the American Academy of Neurology (AAN) nomenclature [157]. However, since the development of such a study comparing thymectomy techniques is not only unlikely but probably unnecessary, a prospective risk-adjusted outcome analysis of nonrandomly assigned treatment [158], class II evidence in the AAN nomenclature, is an acceptable and achievable method of study that if properly controlled and carefully monitored should resolve many of the unresolved issues. To eliminate bias, the use of two or more surgical centers, comparing their respective preferences, is preferable to a single team performing and comparing two types of thymectomies. We strongly recommended that one or more such class II studies be undertaken.

In addition to a prospective study, the use of clinical research standards, which include definitions of clinical classification, quantitative assessment of disease severity, grading systems of post-intervention status, and approved methods of analysis are required. The "data bank" concept, appropriately developed and rigorously monitored [35], should be particularly useful and practical for multiple institutions to compare the relative value of the various thymectomy techniques. The primary focus of comparative analysis of thymectomy for MG should remain complete stable remission. Complete stable remission, while rare, is not only the most reliable measure of success but the most desirable result from the patient standpoint. "Survival" instruments, which are used in the analysis of remissions, are the most reliable determinant.

The Kaplan–Meier life table analysis is the technique of choice. The use of uncorrected crude data has no place in these analyses. Quality of life instruments, such as the Myasthenia Gravis Composite (MGC) score, should also be employed because therapy for MG is usually not innocuous and frequently does not produce a completely stable remission [87, 159]. They should not, however, replace "survival" instrument evaluation. Experts in the field of biostatistics and outcomes analysis should be included in the design of all studies, in the collection of the information, and in the evaluation of the data.

Conclusions

The results of the MGTX trial provide the first class I evidence validating the use of thymectomy in the treatment of non-thymomatous MG. But rather than marking the end of a decade-long debate, it should herald the beginning of a new era of high-quality research, utilizing standardized definitions, appropriate statistical methods, and prospective studies to address lingering questions.

Although arguments can undoubtedly be submitted to refute some of the statements herein, we hope that this presentation will lead to a better understanding of the thymectomy controversies and improved results following thymic resection for MG. We also hope, and expect, the day will come when some form of targeted immunosuppression or other nonsurgical therapy, with no significant side effects, produces long-term remissions in patients with autoimmune non-thymomatous myasthenia gravis. At that time, thymectomy in any form, especially the transsternal procedures, will be considered barbaric. Until such time, however, a thymectomy, properly performed, should be considered an integral part of the therapy of MG.

References

1. Wolfe GI, Kaminski HJ, Aban IB, Minisman G, Kuo H-C, Marx A, et al. Randomized trial of thymectomy in myasthenia gravis. N Engl J Med. 2016;375:511–22.
2. Blalock A, Harvey AM, Ford FF, Lilienthal J Jr. The treatment of myasthenia gravis by removal of the thymus gland. JAMA. 1941;117:1529–33.
3. Keynes G. The surgery of the thymus gland. Br J Surg. 1946;32:201–14.
4. Kirschner PA, Osserman KE, Kark AE. Studies in myasthenia gravis: transcervical total thymectomy. JAMA. 1969;209:906–10.
5. Kark AE, Kirschner PA. Total thymectomy by the transcervical approach. Br J Surg. 1971;56:321–6.
6. Faulkner SL, Ehyai AS, Fisher RD, Fenichel GM, Bender HW. Contemporary management of myasthenia gravis: the clinical role of thymectomy. Ann Thorac Surg. 1977;23:348–52.
7. Olanow CW, Wechsler AS, Roses AD. A prospective study of thymectomy and serum acetylcholine receptor antibodies in myasthenia gravis. Ann Surg. 1982;196:113–21.
8. Vincent A, Newsom-Davis J, Newton P, Beck N. Acetylcholine receptor antibody and clinical response to thymectomy in myasthenia gravis. Neurology. 1983;33:1276–82.
9. Hankins JR, Mayer RF, Satterfield JR, Turney SZ, Attar A, Sequeira AJ, et al. Thymectomy for myasthenia gravis: 14 year experience. Ann Surg. 1985;201:618–25.
10. Otto TJ, Strugalska H. Surgical treatment for myasthenia gravis. Thorax. 1987;42:199–204.
11. Cooper J, Jaretzki A III, Mulder DG, Papatestas AS. Symposium: thymectomy for myasthenia gravis. Contemp Surg. 1989;34:65–86.
12. Papatestas AE, Cooper J, Jaretzki A III, Mulder DG. Symposium: thymectomy for myasthenia gravis. Contemp Surg. 1989;34:65–85.
13. Verma P, Oger J. Treatment of acquired autoimmune myasthenia gravis: a topic review. Can J Neurol Sci. 1992;19:360–75.
14. Drachman DB. Myasthenia gravis. N Engl J Med. 1994;330:1797–810.
15. Penn AS. Thymectomy for myasthenia gravis. In: Lisak RP, editor. Handbook of myasthenia gravis and myasthenic syndromes. New York: Marcel Dekker, Inc; 1994. p. 21–339.
16. Mack MJ, Landreneau RD, Yim AP, Hazelrigg SR, Scruggs GR. Results of video-assisted thymectomy in patients with myasthenia gravis. J Thor Cardiovasc Surg. 1996;112:1352–60.
17. Penn AS, Jaretzki A III, Wolff M, Chang HW, Tennyson V. Thymic abnormalities: antigen or antibody? Response to thymectomy in myasthenia gravis. Ann NY Acad Sci. 1981;377:786–803.
18. Wekerle H, Muller-Hermelink HK. The thymus in myasthenia gravis. Curr Top Pathol. 1986;75:179–206.
19. Younger DS, Worrall BB, Penn AS. Myasthenia gravis: historical perspective and overview. Neurology. 1997;48(Suppl 5):1–7.
20. Hohlfeld R, Wekerle H. Reflections on the "intrathymic pathogenesis" of myasthenia gravis. J Neuroimmunol. 2008;201–202:21–7.

21. Lauriola L, Ranelletti F, Maggiano N, Guerriero M, Punzi C, Marsili F, et al. Thymus changes in anti-MuSK-positive and -negative myasthenia gravis. Neurology. 2005;64:536–8.
22. Penn AS, Lovelace RE, Lange DJ, Toufexis G, Brockbank K. Experimental myasthenia gravis in neonatally thymectomized rabbits. Neurology. 1977;27:365.
23. Masaoka A, Monden Y, Seike Y, Tanioka T, Kagotani K. Reoperation after transcervical thymectomy for myasthenia gravis. Neurology. 1982;32:83–5.
24. Rosenberg M, Jauregui WO, Vega MED, Herrera MR, Roncoroni AJ. Recurrence of thymic hyperplasia after thymectomy in myasthenia gravis: its importance as a cause of failure of surgical treatment. Am J Med. 1983;74:78–82.
25. Henze A, Biberfeld P, Christensson B, Matell G, Pirskanen R. Failing transcervical thymectomy in myasthenia gravis: an evaluation of transsternal re-exploration. Scand J Thor Cardiovasc Surg. 1984;18:235–8.
26. Rosenberg M, Jauregui WO, Herrera MR, Roncoroni A, Rojas OR, Olmedo GSM. Recurrence of thymic hyperplasia after trans-sternal thymectomy in myasthenia gravis. Chest. 1986;89:888–91.
27. Jaretzki A III, Penn AS, Younger DS, Wolff M, Olarte MR, Lovelace RE, et al. "Maximal" thymectomy for myasthenia gravis: results. J Thorac Cardiovasc Surg. 1988;95:747–57.
28. Miller RG, Filler-Katz A, Kiprov D, Roan R. Repeat thymectomy in chronic refractory myasthenia gravis. Neurology. 1991;41:923–4.
29. Kornfeld P, Merav A, Fox S, Maier K. How reliable are imaging procedures in detecting residual thymus after previous thymectomy. Ann NY Acad Sci. 1993;681:575–6.
30. Monden MAY. Comparison of the results of transsternal simple, transcervical simple and extended thymectomy. Ann NY Acad Sci. 1981;377:755–64.
31. Matell G, Lebram G, Osterman PO, Pirskanen R. Follow up comparison of suprasternal vs transsternal method for thymectomy in myasthenia gravis. Ann NY Acad Sci. 1981;377:844–5.
32. Masaoka A, Nagaoka Y, Kotake Y. Distribution of thymic tissue at the anterior mediastinum: current procedures in thymectomy. J Thorac Cardiovasc Surg. 1975;70:747–54.
33. Jaretzki A III, Wolff M. "Maximal" thymectomy for myasthenia gravis: surgical anatomy and operative technique. J Thorac Cardiovasc Surg. 1988;96:711–6.
34. Fukai I, Funato Y, Mizuno Y, Hashimoto T, Masaoka A. Distribution of thymic tissue in the mediastinal adipose tissue. J Thorac Cardiovasc Surg. 1991;101:1099–102.
35. Jaretzki A III, Barohn RJ, Ernstoff RM, Kaminski HJ, Keesey JC, Penn AS, et al. Myasthenia gravis: recommendations for clinical research standards. Neurology. 2000;55:16–23.
36. Sonett JR, Jaretzki A III. Thymectomy for nonthymomatous myasthenia gravis: a critical analysis. Ann N Y Acad Sci. 2008;1132:315–28.
37. Jaretzki A III. Thymectomy for myasthenia gravis: an analysis of the controversies regarding technique and results. Neurology. 1997;48:52–63.
38. Bulkley GB, Bass KN, Stephenson R, Diener-West M, George S, Reilly PA, et al. Extended cervicomediastinal thymectomy in the integrated management of myasthenia gravis. Ann Surg. 1997;226:324–35.
39. Anastasiadis K, Ratnatunga C. Thymectomy. In: Anastasiadis K, Ratnatunga C, editors. The thymus gland: diagnosis and surgical management. Berlin: Springer; 2007. p. 63–83.
40. Sonett JR, Jaretzki A III. Transcervical-transsternal maximal thymectomy for myasthenia gravis. In: Shields TW, LoCicero III J, Reed CE, Feins RH, editors. General thoracic surgery. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2009. p. 2306–11.
41. Clark RE, Marbarger JP, West PN, Sprat JA, Florence JM, Roper CL, Ferguson TB, et al. Thymectomy for myasthenia gravis in the young adult. Long-term results. J Thorac Cardiovasc Surg. 1980;80:696–701.
42. Blalock A, Mason MF, Morgan HJ, Riven SS. Myasthenia gravis and tumors of the thymus region: report of a case in which the tumor was removed. Am Surg. 1939;110:544–61.
43. Clagett OT, Eaton LM. Surgical treatment of myasthenia gravis. J Thorac Surg. 1947;16:62–80.
44. Blalock A. Thymectomy in the treatment of myasthenia gravis: report of 20 cases. J Thorac Surg. 1944;13:1291–308.
45. Nichols FC, Trastek VF. Standard thymectomy. In: Shields TW, LoCicero III J, Reed CE, Feins RH, editors. General thoracic surgery. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2009. p. 2278–82.
46. LoCicero J III. The combined cervical and partial sternotomy approach for thymectomy. Chest Surg Clin N Am. 1996;6:85–93.
47. Trastek VF. Thymectomy. In: Kaiser LR, Krin IL, Spray TL, editors. Mastery of cardiothoracic surgery. Philadelphia: Lippincott-Raven; 1998. p. 105–11.
48. deCampos JRM, Filomeno LTB, Marchiori PE, Jatene FB. Partial sternotomy approach to the thymus. In: Yim AP, Hazelrigg SR, Izzat B, Landreneau RJ, Mack MJ, Naunheim KS, editors. Minimally access cardiothoracic surgery. Philadelphia: WB Saunders; 1999. p. 205–8.
49. Masaoka A, Yamakawa Y, Niwa H, Fukai I, Condo S, Kobayashi M, et al. Extended thymectomy for myasthenia gravis: a 20 year review. Ann Thor Surg. 1996;62:853–9.
50. Zieliński M, Kuzdzal J, Szlubowski A, Soja J. Comparison of late results of basic transsternal and extended transsternal thymectomies in the treatment of myasthenia gravis. Ann Thorac Surg. 2004;78:253–8.
51. Mulder DG. Extended transsternal thymectomy. Chest Surg Clin N Am. 1996;6:95–105.

52. Masaoka A. Extended transsternal thymectomy. In: Shields TW, LoCicero III J, Reed CE, Feins RH, editors. General thoracic surgery. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2009. p. 2298–304.
53. Fischer JE, Grinvalski HT, Nussbaum MS, Sayers HK, Cole RE, Samaha FJ. Aggressive surgical approach for drug-free remission from myasthenia gravis. Ann Surg. 1987;205:496–503.
54. Hatton P, Diehl J, Daly BDT, Rheinlander HF, Johnson H, Shrader JB, et al. Transternal radical thymectomy for myasthenia gravis: a 15-year review. Ann Thorac Surg. 1989;47:838–40.
55. Mulder DM. Extended transsternal thymectomy. In: Shields TW, LoCicero III J, Reed CE, Feins RH, editors. General thoracic surgery. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2009. p. 2233–7.
56. Kark AE, Papatestas AE. Some anatomic features of the transcervical approach for thymectomy. Mt Sinai J Med. 1971;38:580–4.
57. Papatestas AE, Genkins G, Kornfeld P, Horowitz S, Kark AE. Transcervical thymectomy in myasthenia gravis. Surg Gynecol Obst. 1975;140:535–40.
58. Cooper J, Al-Jilaihawa A, Pearson F, Humphrey J, Humphrey HE. An improved technique to facilitate transcervical thymectomy for myasthenia gravis. Ann Thorac Surg. 1988;45:242–7.
59. Bril V, Kojic S, Ilse W, Cooper J. Long-term clinical outcome after transcervical thymectomy for myasthenia gravis. Ann Thorac Surg. 1998;65:1520–2.
60. Shrager JB, Deeb ME, Mick R, Brinster CJ, Childers HE, Marshall MB, et al. Transcervical thymectomy for myasthenia gravis achieves results comparable to thymectomy by sternotomy. Ann Thorac Surg. 2002;74:320–7.
61. Maggi G, Cristofori RC, Marzio PD, Pernazza F, Turello D, Ruffini E. Transcervical thymectomy with partial sternal split. Osp Ital Chir. 2004;10:53–60.
62. dePerrot M, Bril V, McRae K, Keshavjee S. Impact of minimally invasive trans-cervical thymectomy on outcome in patients with myasthenia gravis. Eur J Cardiothoracic Surg. 2003;24:677–83.
63. Bramis J, Diamantis T, Tsigris C, Pikoulis E, Papaconstaninou I, Nikolaou A, et al. Video-assisted transcervical thymectomy. Surg Endosc. 2004;18:1535–8.
64. Zielinski M, Kuzdzal J, Szlubowski A, Soja J. Transcervical-subxiphoid-video thoracoscopic "maximal" thymectomy—operative technique and early results. Ann Thorac Surg. 2004;78:399–403.
65. Sugarbaker DJ. Thoracoscopy in the management of anterior mediastinal masses. Ann Thor Surg. 1993;56:653–6.
66. Roviaro G, Rebuffat C, Varoli F, Vergani C, Maciocco M, Scalambra SM. Videothoracoscopic excision of mediastinal masses: indications and technique. Ann Thorac Surg. 1994;58:1679–84.
67. Sabbagh MN, Garza JJS, Patten B. Thoracoscopic thymectomy in patients with myasthenia gravis. Muscle Nerve. 1995;18:1475–7.
68. Yim APC, Kay RLC, Ho JKS. Video-assisted thoracoscopic thymectomy for myasthenia gravis. Chest. 1995;108:1440–3.
69. Magee MJ, Mack MJ. Video-assisted thymectomy. In: Shields TW, LoCicero III J, Reed CE, Feins RH, editors. General thoracic surgery. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2009. p. 2294–5.
70. Novellino L, Longoni M, Spinelli L, Andretta M, Cozzi M, Faillace G, et al. "Extended" thymectomy, without sternotomy, performed by cervicotomy and thoracoscopic technique in the treatment of myasthenia gravis. Int Surg. 1994;79:378–81.
71. Scelsi R, Ferro MT, Scelsi L, Novellino L, Mantegazza R, Cornelio F, et al. Detection and morphology of thymic remnants after video-assisted thoracoscopic thymectomy (VATET) in patients with myasthenia gravis. Int Surg. 1996;81:14–7.
72. Shiono H, Ohta M, Okumura M. Open video-assisted techniques: thoracoscopic extended thymectomy with bilateral approach and anterior chest wall lifting. In: Lavini C, Moran CA, Morandi U, Schoenhuber R, editors. Thymus gland pathology. Milan: Springer; 2008. p. 187–94.
73. Chang PC, Chou SH, Kao EL, Cheng YJ, Chuang HY, Liu CK, et al. Bilateral video-assisted thoracoscopic thymectomy vs. extended transsternal thymectomy in myasthenia gravis: a prospective study. Eur Surg Res. 2005;37:199–203.
74. Lee CY, Kim DJ, Lee JG, Park IK, Bae MK, Chung KY. Bilateral video-assisted thoracoscopic thymectomy has a surgical extent similar to that of transsternal extended thymectomy with more favorable early surgical outcomes for myasthenia gravis patients. Surg Endosc. 2011;25:849–54.
75. Shigemura N, Shiono H, Inour M, Minami M, Ochta M, Okumura M, et al. Inclusion of the transcervical approach in video-assisted thoracoscopic extended thymectomy (VATET) for myasthenia gravis: a prospective trial. Surg Endosc. 2006;20:1614–8.
76. Morgan JA, Ginsburg ME, Sonett JR, Morales DLS, Kohmoto T, Gorenstein LA, et al. Advanced thoracoscopic procedures are facilitated by computer aided robotic technology. Eur J Cardiothoracic Surg. 2003;23:883–7.
77. Ashton RC, McGinnis KM, Connery CP, Swistel DS, Ewing DR, DeRose JJ. Total endoscopic robotic thymectomy for myasthenia gravis (case report). Ann Thorac Surg. 2003;75:569–71.
78. Rea F, Marulli G, Bortolotti L, Feltracco P, Zuin A, Sartori F. Experience with the "Da Vinci" robotic system for thymectomy in patients with myasthenia gravis: report of 33 cases. Ann Thorac Surg. 2006;81:455–9.
79. Marulli G, Schiavon M, Perissinotto E, Bugana A, Di Chiara F, Rebusso A, et al. Surgical and neurologic outcomes after robotic thymectomy in 100 consecutive patients with myasthenia gravis. J Thorac Cardiovasc Surg. 2013;145:730–5.

80. Melfi FM, Fanucchi O, Mussi A. Minimally invasive mediastinal surgery. Ann Cardiothorac Surg. 2016;5:10–7.
81. Hsu CP, Chuang CY, Hsu NY, Chen CY. Comparison between the right side and subxiphoid bilateral approaches in performing video-assisted thoracoscopic extended thymectomy for myasthenia gravis. Surg Endosc. 2004;18:821–4.
82. Uchiyama A, Shimizu S, Murai H, Kuroki S, Okido M, Tanaka M. Infrasternal mediastinoscopy thymectomy in myasthenia gravis: surgical results in 23 patients. Ann Thor Surg. 2001;72:1902–5.
83. Suda T, Sugimura H, Tochii D, Kihara M, Hattori Y. Single-port thymectomy through an infrasternal approach. Ann Thor Surg. 2012;93:334–6.
84. Hsu CP, Chuang CY, Hsu NY, Shia SE. Subxiphoid approach for video-assisted thoracoscopic extended thymectomy in treating myasthenia gravis. Interact Cardiovasc Thorac Surg. 2002;1:4–8.
85. Suda T, Tochii D, Tochii S, Takagi Y. Trans-subxiphoid robotic thymectomy. Interact Cardiovasc Thorac Surg. 2015;20:669–71.
86. Suda T, Kaneda S, Hachimaru A, Tochii D, Maeda R, Tochii S, et al. Thymectomy via a subxiphoid approach: single-port and robot-assisted. J Thorac Dis. 2016;8(Suppl 3):265–71.
87. Benatar M, Sanders DB, Burns TM, Cutter GR, Guptill JT, Baggi F, et al.; Task Force on MG Study Design of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. Recommendations for myasthenia gravis clinical trials. Muscle Nerve. 2012;45:909–17.
88. Weinberg A, Gelijns A, Moskowitz A, Jaretzki A III. Myasthenia gravis: outcomes analysis. 2000. www.neurology.org/content/suppl/2001/04/…/Myasth_Gravis-Outcomes_Analysis.doc.
89. McQuillen MP, Leone MG. A treatment carol: thymectomy revisited. Neurology. 1977;1277:1103–6.
90. Viet HR, Schwab RS. Thymectomy for myasthenia gravis. In: Veit HR, editor. Records of experience of Mass Gen Hosp. Springfield: Charles C Thomas; 1960. p. 597–607.
91. Oosterhuis HJ. Observations of the natural history of myasthenia gravis and the effect of thymectomy. Ann NY Acad Sci. 1981;377:678–90.
92. Lawless JF. Life tables, graphs, and related procedures. In: Lawless JF, editor. Statistical models and methods for life table data. New York: Wiley; 1982. p. 52–94.
93. Durelli L, Maggi G, Casadio C, Ferri R, Rendine S, Bergamini L. Actuarial analysis of the occurrence of remission following thymectomy for myasthenia gravis in 400 patients. J Neurol Neurosurg Psychiatry. 1991;54:406–11.
94. Olak J, Chiu RCJ. A surgeon's guide to biostatistical inferences. Part II. ACS Bull. 1993;78:27–31.
95. Blackstone EH. Outcome analysis using hazard function methodology. Ann Thorac Surg. 1996;61(Suppl 2):2–7.
96. Sanders DB, Kaminski HJ, Jaretzki A III, Phillips LH II. Thymectomy for myasthenia gravis in older patients. J Am Coll Surg. 2001;193:340–1.
97. Wolfe GI, Kaminski HJ, Sonett JR, Aban IB, Kuo H, Cutter GR. Randomized trial of thymectomy in myasthenia gravis. J Thorac Dis. 2016;8:1782–3.
98. Diaz A, Black E, Dunning J. Is thymectomy in non-thymomatous myasthenia gravis of any benefit? Interact Cardiovasc Thorac Surg. 2014;18:381–9.
99. Taioli E, Paschal PK, Liu B, Kaufman AJ, Flores RM. Comparison of conservative treatment and thymectomy on myasthenia gravis outcome. Ann Thorac Surg. 2016;102:1805–13.
100. Sanders DB, Wolfe GI, Benatar M, Evoli A, Gilhus NE, Illa I, et al. International consensus guidance for management of myasthenia gravis: executive summary. Neurology. 2016;87:419–25.
101. Skeie GO, Apostolski S, Evoli A, Gilhus NE, Illa I, Harms L, et al.; European Federation of Neurological Societies. Guidelines for treatment of autoimmune neuromuscular transmission disorders. Eur J Neurol. 2010;17:893–902.
102. Mineo TC, Ambrogi V. Outcomes after thymectomy in class I myasthenia gravis. J Thorac Cardiovasc Surg. 2013;145:1319–24.
103. Roberts PF, Venuta F, Rendina E, De Giacomo T, Coloni GF, Follette DM, et al. Thymectomy in the treatment of ocular myasthenia gravis. J Thorac Cardiovasc Surg. 2001;122:562–8.
104. Gilbert ME, De Sousa EA, Savino PJ. Ocular Myasthenia Gravis treatment: the case against prednisone therapy and thymectomy. Arch Neurol. 2007;64:1790–2.
105. Kerty E, Elsais A, Argov Z, Evoli A, Gilhus NE. EFNS/ENS Guidelines for the treatment of ocular myasthenia. Eur J Neurol. 2014;21:687–93.
106. Guillermo GR, Téllez-Zenteno JF, Weder-Cisneros N, Mimenza A, Estañol B, Remes-Troche JM, et al. Response of thymectomy: clinical and pathological characteristics among seronegative and seropositive myasthenia gravis patients. Acta Neurol Scand. 2004;109:217–21.
107. Yuan HK, Huang BS, Kung SY, Kao KP. The effectiveness of thymectomy on seronegative generalized myasthenia gravis: comparing with seropositive cases. Acta Neurol Scand. 2007;115:181–4.
108. Evoli A, Tonali PA, Padua L, Monaco ML, Scuderi F, Batocchi AP, et al. Clinical correlates with anti-MuSK antibodies in generalized seronegative myasthenia gravis. Brain. 2003;126:2304–11.
109. Gilhus NE, Verschuuren JJ. Myasthenia gravis: subgroup classification and therapeutic strategies. Lancet Neurol. 2015;14:1023–36.
110. Monden Y, Nakahara K, Kagotani K, Fujii Y, Nanjo S, Masaoka A, et al. Effects of preoperative duration of symptoms on patients with myasthenia gravis. Ann Thorac Surg. 1984;38:287–91.
111. Kumar V, Kaminski HJ. Treatment of myasthenia gravis. Curr Neurol Neurosci Rep. 2011;11:89–96.

112. Keesey JC. A treatment algorithm for autoimmune myasthenia in adults. Ann NY Acad Sci. 1998;841:753–68.
113. Saperstein DS, Barohn RJ. Management of myasthenia gravis. Semin Neurol. 2004;24:41–8.
114. Adams C, Theodorescu D, Murphy E, Shandling B. Thymectomy in juvenile myasthenia gravis. J Child Neurol. 1990;5:215–8.
115. Andrews PIA. treatment algorithm for autoimmune myasthenia gravis in children. Ann NY Acad Sci. 1998;841:789–802.
116. Seybold ME. Thymectomy in childhood myasthenia gravis. Ann NY Acad Sci. 1998;841:731–41.
117. Della Marina A, Trippe H, Lutz S, Schara U. Juvenile myasthenia gravis: recommendations for diagnostic approaches and treatment. Neuropediatrics. 2014;45:75–83.
118. Rodriguez M, Gomez MR, Howard F, Taylor WF. Myasthenia gravis in children: long-term follow-up. Ann Neurol. 1983;13:504–10.
119. Papatestas AE, Genkins G, Kornfeld P, Eisenkraft JB, Fagerstrom RP, Pozner J, et al. Effects of thymectomy in myasthenia gravis. Ann Surg. 1987;206:79–88.
120. Shrager JB, Nathan D, Brinster CJ, Yousuf O, Spence A, Chen Z, et al. Outcomes after 151 extended transcervical thymectomies for myasthenia gravis. Ann Thorac Surg. 2006;82:1863–9.
121. Ruffini E, Guerrera F, Filosso PL, Bora G, Nex G, Gusmano S, et al. Extended transcervical thymectomy with partial upper sternotomy: results in non-thymomatous patients with myasthenia gravis. Eur J Cardiothorac Surg. 2015;48:448–54.
122. Manlulu A, Lee TW, Wan I, Law CY, Chang C, Garzon JC, et al. Video-assisted thoracic surgery thymectomy for nonthymomatous myasthenia gravis. Chest. 2005;128:3454–60.
123. Tomulescu V, Sgarbura O, Stanescu C, Valciu C, Campeanu A, Herlea V, et al. Ten-year results of thoracoscopic unilateral extended thymectomy performed in nonthymomatous myasthenia gravis. Ann Surg. 2011;254(5):761.
124. Mantegazza R, Baggi F, Bernasconi P, Antozzi C, Confalonieri P, Novellino L, et al. Video-assisted thoracoscopic extended thymectomy and extended transsternal thymectomy (T-3b) in non-thymomatous myasthenia gravis patients: remission after 6 years of follow-up. J Neurol Sci. 2003;212:31–6.
125. Park IK, Choi SS, Lee JG, Kim DJ, Chung KY. Complete stable remission after extended transsternal thymectomy in myasthenia gravis. Eur J Cardiothorac Surg. 2006;30:525–8.
126. Zielinski M, Hauer L, Hauer J, Pankowski J, Nabialek T, Szlubowski A. Comparison of complete remission rates after 5 year follow-up of three different techniques of thymectomy for myasthenia gravis. Eur J Cardiothorac Surg. 2010;37:1137–43.
127. Rückert JC, Swierzy M, Ismail M. Comparison of robotic and nonrobotic thoracoscopic thymectomy: a cohort study. J Thorac Cardiovasc Surg. 2011;141:673–7.
128. Kirschner PA. Reoperation on the thymus. A critique. Chest Surg Clin N Am. 2001;11:439–45.
129. Pompeo E, Nofroni I, Iavicoli N, Mineo TC. Thoracoscopic completion thymectomy in refractory nonthymomatous myasthenia. Ann Thorac Surg. 2000;70:918–23.
130. Ng JK, Ng CS, Underwood MJ, Lau KK. Does repeat thymectomy improve symptoms in patients with refractory myasthenia gravis? Interact Cardiovasc Thorac Surg. 2014;18:376–80.
131. Mussi A, Lucchi M, Murri L, Ricciardi R, Luchini L, Angeletti CA. Extended thymectomy in myasthenia gravis: a team-work of neurologist, thoracic surgeon, and anaesthetist may improve the outcome. Eur J Cardiothorac Surg. 2001;19(5):570.
132. Houghton A. Variation in outcome of surgical procedures. Br J Surg. 1994;81:653–60.
133. Crawford FA, Anderson RP, Clark RE, Grover FL, Kouchoukos NT, Waldhausen JA, et al. Volume requirements for cardiac surgery credentialing: a critical examination. Ann Thorac Surg. 1996;61:12–6.
134. Silvestri GA, Handy J, Lackland D, Corley E, Reed CE. Specialists achieve better outcomes than generalists for lung cancer surgery. Chest. 1998;114:675–80.
135. Kaminski HJ. Treatment of myasthenia gravis. In: Kaminski HJ, editor. Myasthenia gravis and related disorders. Totowa: Humana Press; 2003. p. 197–221.
136. Watanabe A, Watanabe T, Obama T, Mawatari T, Ohsawa H, Ichimiya Y, et al. Prognostic factors for myasthenic crisis after transsternal thymectomy in patients with myasthenia gravis. J Thorac Cardiovasc Surg. 2004;127(3):868–76.
137. Leventhal SR, Orkin FK, Hirsh RA. Prediction of the need for postoperative mechanical ventilation in myasthenia gravis. Anesthesiology. 1980;53:26–30.
138. Krucylak PE, Naunheim KS. Preoperative preparation and anesthetic management of patients with myasthenia gravis. Semin Thorac Cardiovasc Surg. 1999;11:47–53.
139. Tripathi M, Kaushik S, Dubey P. The effect of use of pyridostigmine and requirement of vecuronium in patients with myasthenia gravis. J Postgrad Med. 2003;49:311–4.
140. Kas J, Kiss D, Simon V, Svastics E, Major L, Szobor A. Decade-long experience with surgical therapy of myasthenia gravis: early complications of 324 transsternal thymectomies. Ann Thorac Surg. 2001;72:1691–7.
141. Jaretzki A III, Phillips L II, Aarli J, Kaminski HJ, Sanders DB. Preoperative preparation of patients with myasthenia gravis for stalls postoperative respiratory complications following thymectomy. Ann Thor Surg. 2003;75:1068–9.
142. Kadota Y, Horio H, Mori T, Sawabata N, Goto T, Yamashita S, et al. Perioperative management in myasthenia gravis: republication of a systematic

review and a proposal by the guideline committee of the Japanese Association for Chest Surgery 2014. Gen Thorac Cardiovasc Surg. 2015;63:201–15.
143. Zieliński M, Kuzdzał J, Staniec B, Harazda M, Nabiałek T, Pankowski J, et al. Safety for preoperative use of steroids for transsternal thymectomy in myasthenia gravis. Eur J Cardiothorac Surg. 2004;26:407–11.
144. d'Empaire G, Hoaglin DC, Perlo VP, Pontoppidan H. Effect of prethymectomy plasma exchange on postoperative respiratory function in myasthenia gravis. J Thorac Cardiovasc Surg. 1985;89:592–6.
145. Cumming WJK, Hudgson P. The role of plasmapheresis in preparing patients with myasthenia for thymectomy. Muscle Nerve. 1986;9:155–8.
146. Gotti P, Spinelli A, Marconi G, Duranti R, Gigliotti F, Pizzi A, et al. Comparative effects of plasma exchange and pyridostigmine on expiratory muscle strength and breathing pattern in patients with myasthenia gravis. Thorax. 1995;50:1080–6.
147. Loach AB, Young AC, Spalding JM, Smith AC. Postoperative management after thymectomy. Br Med J. 1975;1:309–12.
148. Lee HS, Lee HS, Lee HE, Bae MK, Chung KY, Shin HY, et al. Predictive factors for myasthenic crisis after videoscopic thymectomy in patients with myasthenia gravis. Muscle Nerve. 2015;52:216–20.
149. Younger DS, Braun NMT, Jaretzki A III, Penn AS, Lovelace AE. Myasthenia gravis: determinants for independent ventilation after transsternal thymectomy. Neurology. 1984;34:336–40.
150. Abel M, Eisenkraft JB. Anesthetic implications of myasthenia gravis. Mt Sinai J Med. 2002;69:31–7.
151. Mayer SA. Intensive care of the myasthenic patient. Neurology. 1997;48(Suppl 5):70–81.
152. Juel VC. Myasthenia gravis: management of myasthenic crisis and perioperative care. Semin Neurol. 2004;24:75–81.
153. Wekerle H, Muller-Hermelink HK. The thymus in myasthenia gravis. In: Muller-Hermelink HK, editor. Current topics in pathology. The human thymus. Histophysiology and pathology. New York: Springer; 1986. p. 179–206.
154. Ellis K, Austin JHM, Jaretzki A III. Radiologic detection of thymoma in patients with myasthenia gravis. Am J Radiol. 1988;151:873–81.
155. Falkson CB, Bezjak A, Darling G, Gregg R, Malthaner R, Maziak DE, et al.; Lung Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-Based Care. The management of thymoma: a systematic review and practice guideline. J Thorac Oncol. 2009;4:911–9.
156. Shields TW. Thymic tumors. In: Shields TW, LoCicero III J, Reed CE, Feins RH, editors. General thoracic surgery. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2009. p. 2323–62.
157. Miller RG, Rosenberg JA, Gelinas DF, Mitsumoto H, Newman D, Sufit R, et al. Practice parameter: the care of the patient with amyotrophic lateral sclerosis (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology: ALS Practice Parameters Task Force. Neurology. 1999;52:1311–23.
158. Kirklin JW, Blackstone EH. Clinical studies with non-randomly assigned treatment. In: Kirklin JW, Barrett-Boyes BG, editors. Cardiac surgery. 2nd ed. New York: Churchill-Livingstone; 1993. p. 269–70.
159. Burns TM, Conaway M, Sanders DB, MG Composite and MG-QOL15 Study Group. The MG composite: a valid and reliable outcome measure for myasthenia gravis. Neurology. 2010;74:1434–40.
160. Keating CP, Kong YX, Tay V, Knight SR, Clarke CP, Wright GM. VATS thymectomy for nonthymomatous myasthenia gravis: standardized outcome assessment using the myasthenia gravis foundation of America clinical classification. Innovations (Phila). 2011;6:104–9.
161. Liu Z, Yang J, Lin L, Huang J, Jiang G. Unilateral video-assisted thoracoscopic extended thymectomy offers long-term outcomes equivalent to that of the bilateral approach in the treatment of non-thymomatous myasthenia gravis. Interact Cardiovasc Thorac Surg. 2015;21(5):610.
162. Prokakis C, Koletsis E, Salakou S, Apostolakis E, Baltayiannis N, Chatzimichalis A, et al. Modified maximal thymectomy for myasthenia gravis: effect of maximal resection on late neurologic outcome and predictors of disease remission. Ann Thorac Surg. 2009;88:1638–45.
163. Yoshino I, Hashizume M, Shimada M, Tomikawa M, Tomiyasu M, Suemitsu R, et al. Thoracoscopic thymomectomy with the da Vinci computer-enhanced surgical system. J Thorac Cardiovasc Surg. 2001;122:783–5.