

Thymectomy for juvenile myasthenia gravis: a narrative review

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Background and Objective: Thymectomy as a management strategy for juvenile myasthenia gravis (JMG) has been increasingly adopted with the advent of minimally invasive surgical techniques. This review evaluates existing evidence regarding the surgical management of JMG, including the benefits of surgical compared to medical therapy, important considerations when evaluating surgical candidacy and determining optimal timing of intervention. In addition, we provide an overview of the open, thoracoscopic and robotic surgical approaches available for thymectomy and compare the existing data to characterize optimal surgical management.

Methods: A thorough literature review was conducted for full length research articles, including systematic reviews, retrospective cohort studies and case series, published between January 2000 and July 2023 regarding open, thoracoscopic or robotic thymectomy for management of JMG. Reference lists of the identified articles were manually searched for additional studies. Evidence was summarized in a narrative fashion with the incorporation of the authors' knowledge gained through clinical experience.

Key Content and Findings: Although data specific to JMG are limited to small retrospective cohort studies, available evidence supports equal to greater disease control following thymectomy versus pharmacologic management. Furthermore, outcomes may be optimized when surgery is performed earlier in the disease course, particularly for patients who are post-pubertal with generalized or severe disease and those necessitating high-dose steroid administration thereby limiting its metabolic and growth inhibitory effects. Open transsternal resection is the historic gold-standard; however, as surgeons become more comfortable with thoracoscopic and robotic-assisted thymectomy, an increasing proportion of patients are expected to undergo thymectomy. At present, the data available is unable to support conclusions regarding which surgical approach is superior; however, minimally invasive approaches may be non-inferior while offering superior cosmesis and decreased morbidity.

Conclusions: Higher-level investigation through the use of multi-institutional databases and randomized prospective trials is warranted in order to understand which child warrants thymectomy, at what point in their disease course and their development, and which surgical approach will optimize postoperative outcomes.

Keywords: Myasthenia gravis (MG); thymectomy; thoracoscopy; robotic surgical procedures; pediatrics

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Introduction

Myasthenia gravis (MG), an incumbering autoimmune disease with prevalence of 150–200 cases per million people, is a result of antibodies directed against antigens located at the postsynaptic endplate of the neuromuscular junction (1). When present, antibodies most commonly target the acetylcholine receptor; therefore, the neurotransmitter is out-competed impeding motor nerve to skeletal muscle impulse resulting in weakness and fatigability (1-3). Juvenile MG (JMG), defined as symptom onset prior to 18 years old, accounts for 15% of patients with MG (4). JMG is most often limited to oculomotor symptoms (e.g., ptosis, diplopia and ophthalmoplegia); however, this may be accompanied with or progress to generalized muscle weakness, involving the bulbar, facial, limb and respiratory muscles. While those with pure ocular-type JMG more often have pre-pubertal onset, those with post-pubertal onset are more likely to have generalized disease (5).

The thymus is rich with anti-acetylcholine receptor (anti-AChR) antibody-promoting antigens; therefore, making it the target of surgical management (6). While ocular JMG can often be controlled medically, through an astute combination of cholinesterase inhibitors, corticosteroids and/or immunomodulators, those with generalized or medically-refractory JMG may warrant thymectomy (2,7). However, much of the evidence directing the management of JMG is a result of the extrapolation of data from adult MG studies (8-18). Even still, the only prospective randomized evidence regarding the efficacy of surgical management in adults is limited to the Thymectomy Trial in Non-Thymomatous Myasthenia Gravis Patients Receiving Prednisone Therapy (MGTX) which demonstrated superior outcomes following open transsternal thymectomy when compared to pharmacotherapy for generalized non-thymomatous seropositive MG (19-21). However, caution should be taken when applying adult studies to JMG as there are significant differences in the demographics of and prognosis for these diseases (5,22). Despite this, thymectomy as a management strategy for JMG has become generally accepted, and attention is pivoting to attempt to understand which child warrants intervention, when surgery should take place and by which approach.

The objective of this review is to evaluate the existing evidence regarding the surgical management of JMG, including the benefits of surgical versus medical management and important considerations to make when determining surgical candidacy and timing of

intervention. In addition, we provide an overview of the approaches available to perform thymectomy for JMG and compare existing data to characterize its optimal surgical management. We present this article in accordance with the Narrative Review reporting checklist (available at <https://med.amegroups.com/article/view/10.21037/med-23-41/rc>).

Methods

The search strategy is outlined in *Table 1*. A thorough literature review was conducted using the PubMed database in July of 2023. A free text search was performed with the following search terms: (“thymectomy”) AND (“juvenile” OR “children” OR “pediatric”) AND (“myasthenia gravis”). Full length research articles in English, including systematic reviews, retrospective cohort studies and case series, published between January 2000 and July 2023 regarding open, thoracoscopic or robotic thymectomy for management of JMG were included. In addition, reference lists of the identified articles were manually searched for additional studies. Case studies, editorials and commentaries were excluded as well as those with content or study population extending beyond the surgical management of JMG. Article selection is visualized in *Figure 1*.

Surgical vs. medical management

There are no prospective studies which compare complete stable remission (CSR), disease improvement, or change in medication requirement for thymectomy relative to medical management for JMG, such as the MGTX trial did for MG; however, we identified four retrospective studies (*Table 2*) and two systematic reviews (*Table 3*) which evaluate thymectomy and compare it to medical management for JMG. Available data consist of small and heterogeneous populations limiting cohort comparisons; however, patients who undergo thymectomy have less postoperative corticosteroid and cholinesterase inhibitor use in addition to comparable if not higher rates of CSR (4,23,26). Furthermore, thymectomy has been shown to decrease the number of days spent intubated, in the intensive care unit and hospitalized (23). An analysis of the KID database demonstrated between 2003 and 2012 there was stability in the number of thymectomies performed in children for JMG (27). However, data estimating the number of pediatric thymectomies performed before and after the publication of the MGTX trial in 2016 is not available at present.

Table 1 The search strategy summary

Items	Specification
Date of search	July 24, 2023
Databases and other sources searched	PubMed
Search terms used	Free text search including the terms: (“thymectomy”) AND (“juvenile” OR “children” OR “pediatric”) AND (“myasthenia gravis”)
Timeframe	Jan 2000 to Jul 2023
Inclusion and exclusion criteria	<p>Inclusion: full length research articles written in the English language regarding open, thoracoscopic or robotic thymectomy for pediatric/juvenile myasthenia gravis</p> <p>Exclusion: case reports, commentaries/editorials, articles purposed to evaluate medical or anesthetic management of juvenile myasthenia gravis, cohort contained patients undergoing thymectomy for disease other than juvenile myasthenia gravis</p>
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	Article selection was collectively performed by M.C. and S.U.
Any additional considerations, if applicable	Reference lists for relevant articles were manually searched for additional studies

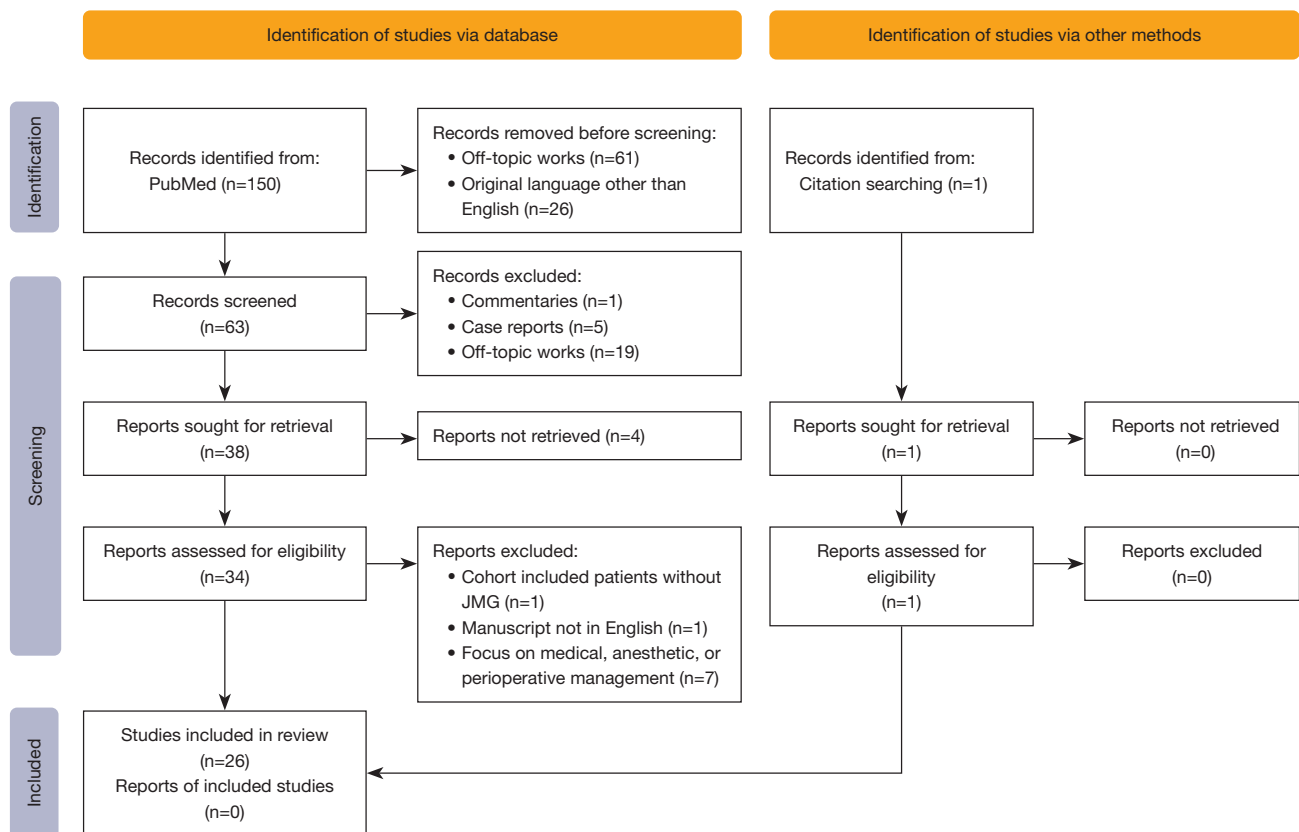


Figure 1 Flow chart demonstrating article selection for evaluating thymectomy for management of juvenile myasthenia gravis. JMG, juvenile myasthenia gravis.

Table 2 Retrospective studies comparing surgical and medical management for juvenile myasthenia gravis

Authors, year published	Surgical approach [n]	Mean [range] age at thymectomy	Mean [range] disease duration prior to thymectomy	Key findings
Tracy <i>et al.</i> (23), 2009	Thymectomy, unspecified [13] vs. non-surgical [32]	10 years 10 months [17 months–18 years 7 months]	9.2 months [17 days–2 years 9 months]	(I) 62% improvement, 31% CSR (II) Mean time from onset to surgery longer in those who did not improve (397 vs. 198 days) (III) Thymectomy resulted in a reduction in days intubated, in the intensive care unit, and in the hospital
Wang <i>et al.</i> (24), 2013	Thymectomy, unspecified [52] vs. non-surgical [24]	NR	NR	(I) No significant association between thymectomy and delayed bone age and height based on chronological age (II) Delayed bone age and height retardation in JMG thought to be related to past cumulative prednisone intake and age at disease onset might be a factor
Popperud <i>et al.</i> (25), 2021	Thymectomy, unspecified [32] vs. non-surgical [15]	17 [2–33] years	21 [9–31] months	(I) Patients who undergo thymectomy have evidence of premature immunosenescence not related to age at surgery (II) No clinical consequence of premature immunosenescence demonstrated at last follow-up {median [IQR] 12 [7–26] years}
Li <i>et al.</i> (4), 2022	Robotic [47] vs. non-surgical [20]	NR	16 [7–25] months	(I) Patients who underwent robotic thymectomy had a significantly shorter disease duration, greater preoperative steroid use and larger proportion were anti-AChR+ (II) Median [IQR] follow-up 47 [30–94] months (III) Robotic thymectomy cohort had higher proportion as well as significantly higher 5-year cumulative probability of CSR (IV) Robotic thymectomy cohort experienced a reduction in daily dose of cholinesterase inhibitors and corticosteroids while the non-surgical group did not (V) 19.1% postoperative complication rate

anti-AChR+, anti-acetylcholine receptor antibody positive; CSR, complete stable remission; IQR, interquartile range; JMG, juvenile myasthenia gravis; NR, not reported.

Surgical candidacy

While thymoma is rare in children, affecting just over 2% of children with JMG, thymomatous JMG is always surgical (22,28–30). As such, after diagnosis of JMG, either magnetic resonance imaging or computed tomography is performed to evaluate for the presence of thymic enlargement or thymoma (31). When imaging suggests non-thymomatous disease, there is lack of consensus regarding the indications for surgical management. This is perpetuated by a lack of standardized classification system between existing pediatric

studies. Likewise, available evidence regarding the role of thymectomy for patients with ocular *vs.* generalized disease, pre- *vs.* post-pubertal age at surgery, and seropositive *vs.* seronegative antibody status remain insufficient (26).

The first categorization system developed, the Osserman Score, was introduced in 1958 (32). Ranging from Class I to IV based on symptom severity and progression, Class I involves only the ocular muscles while Classes II–IV represent progressive and increasing severity of generalized muscle involvement (32). Hans Oosterhuis published his scoring system in the 1980s after observing more than

Table 3 Systematic reviews evaluating outcomes following thymectomy for juvenile myasthenia gravis

Authors, year published	Years included	Number of articles	Key findings
Madenci <i>et al.</i> (26), 2017	2000–2016	16	<p>(I) 488/1,131 (43%) underwent thymectomy</p> <p>(II) Preoperative severity: 50% Osserman stage I, 30% stage II, 14% stage III, 6% stage IV</p> <p>(III) Approach: 82% transsternal, 17% thoracoscopic, 1% transcervical</p> <p>(IV) 77% had post-operative improvement, 29% CSR</p> <p>(V) Postoperative complications were rare (range, 0–30%), most common pneumonia/atelectasis and mechanical ventilation</p> <p>(VI) 0.2% cause-specific mortalities</p> <p>(VII) 3 studies compared surgical and non-operative management, 1 reported trend toward higher CSR with thymectomy, 1 reported thymectomy to be protective against the development of generalized symptoms, 1 reported similar CSR rates</p> <p>(VIII) 4 studies compared open to thoracoscopic thymectomy, 3 concluded thoracoscopic to be non-inferior in terms of reduction in disease severity, 1 noted incomplete resection with thoracoscopic; thoracoscopic was associated with less blood loss, shorter length of stay, lower to similar complication rate</p> <p>(IX) Studies were entirely retrospective, power limited and with heterogeneous populations</p>
Ng and Hartley (22), 2021	1997–2020	17	<p>(I) 588 patients underwent thymectomy</p> <p>(II) 77% improvement, 40% CSR</p> <p>(III) Overall, surgical outcomes may be associated with early intervention, post-pubertal intervention, AChR+, more severe disease, presence of thymic hyperplasia</p> <p>(IV) 6 studies compared open and thoracoscopic thymectomy, overall report similar clinical outcomes with reduced length of stay and improved cosmesis with thoracoscopic</p> <p>(V) Pathology: 62% hyperplasia, 24% normal, 2% thymoma</p> <p>(VI) Mixed results regarding seropositivity, 1 found improved outcomes while 1 found no difference</p> <p>(VII) Studies limited by retrospective nature, variable follow-up times, lack of control groups and statistical power</p>

CSR, complete stable remission; AChR+, anti-acetylcholine receptor antibody positive.

400 patients with MG. Scores of 1–4 represent increasing degree of disability while 0 represents complete remission and 5 mechanical ventilatory dependence (33). In 2000, the Myasthenia Gravis Foundation of America (MGFA) published the Quantitative MG Score (QMG) intended as the first objective system based on a patient's strength when performing specified actions (34). This system was utilized in the MGTX trial; however, it has not been adopted widely by pediatric studies which continued to use the Osserman or Oosterhuis classifications for grading preoperative disease severity (22). However, the QMG was modified for pediatric patients by eliminating the grip strength test and incorporating a straw for bulbar strength evaluation to create the first JMG-specific scoring system that is both

more developmentally appropriate and less impacted by a child's cooperability (35).

Despite this heterogeneity, most JMG cohorts are described as to whether disease is pure ocular or with generalized involvement. Although pure ocular disease is more common, nearly two-thirds of children who undergo thymectomy have generalized JMG (30). In addition, there is a trend in some studies toward greater response to thymectomy for those with generalized and/or more severe disease than those with pure ocular type (22). However, this was not found across all studies (22,36,37).

Approximately 80% and 3.5% of JMG patients have anti-AChR and anti-muscle specific tyrosine kinase (anti-MuSK) antibodies, respectively (22,30). Overall, data regarding

the influence of seropositivity in response to surgery is insufficient (26). The presence of anti-AChR antibodies has been shown to correlate with greater surgical response; therefore, anti-AChR seropositivity often contributes to the determination to pursue thymectomy (22,38). However, some patients who are anti-AChR negative respond to thymectomy; therefore, the role of surgery remains ambiguous for those with anti-MuSK antibodies or who are seronegative (22,39).

Still, there remains significant controversy surrounding the appropriate age and timing from symptom onset to thymectomy. Delaying thymectomy affords a chance for spontaneous remission, an event which occurs as often as 20–29% of the time in children (40). Furthermore, the thymus is critical in the growth and development of a child's immune system; therefore, many argue that surgery should be postponed due to concern that removing the thymus while the immune system is still in development will have negative consequences later in life (22,41–43). As such, a study performed by Popperud *et al.* confirmed that thymectomy for JMG performed at median (range) age at thymectomy of 17 [2–33] years can lead to premature immunosenescence, including a reduced number of B cells, naive cytotoxic T cells and helper T cells and increased memory T cells at median (interquartile range) 12 [7–26] years after thymectomy was performed. However, these findings were not related to age at thymectomy nor with any discernible clinical consequence (25). However, it is necessary to mention a 2023 case-control study in adults with MG who are five years or more post-thymectomy found thymectomized patients have not only decreased production of CD4+ and CD8+ lymphocytes and higher levels of proinflammatory cytokines but also a higher incidence of cancer and all-cause mortality compared to their non-thymectomized counterparts (44).

There is also controversy regarding the impact of age and timing from symptom onset on the efficacy of thymectomy. A study with 31% CSR and 62% symptom improvement rates following thymectomy in 13 patients with mean (range) age at thymectomy of 10.8 (1.4–18.6) years and mean (range) time from disease onset of 9.2 (0.6–33.0) months found that time from onset to surgery was a mean 199 days longer in those who did not respond to thymectomy (23). In a study performed on 141 patients with JMG with median (range) age at onset of 6 [1–18] years who underwent open transsternal resection at median (range) age of 12 [3–18] years found improved CSR rates if surgery is performed when patients are at least 12 years old (37).

However, the same study, demonstrated improved postsurgical outcomes when thymectomy was performed within 12 months of onset of generalized symptoms (37). Conversely, a study by Kim *et al.* including 50 patients with JMG who underwent thoracoscopic thymectomy at mean (standard deviation, SD) age of 10.5 (0.8) years and mean (SD) time to thymectomy of 19.6 (4.2) months with 51.0% of patients with thymectomy within one year of disease onset found no difference in outcome when evaluating age or timing of thymectomy relative to symptom onset (45). A systematic review including 17 articles published between 1997 and 2020 encompassing 588 JMG patients who underwent thymectomy concluded that improved surgical outcomes may be associated with both early intervention and post-pubertal intervention (22). Moreover, by performing surgery early, children avoid growth failure, delay in bone aging and detrimental metabolic effects experienced by JMG patients who require prolonged corticosteroids (24). Overall, there may be benefit to performing surgery early relative to symptom onset, particularly for patients who are post-pubertal or with severe disease requiring prolonged use of high-dose steroids.

Surgical approach

Once the decision has been made to perform surgery, patients should be optimized medically and myasthenic symptoms well-controlled which may necessitate intravenous immunoglobulin administration or plasma exchange therapy (4). Traditionally performed through median sternotomy, the decision to pursue surgery required a careful consideration of the known risks of open thoracic surgery. The development of minimally invasive surgical (MIS) approaches, including both thoracoscopic and robotic thymectomy, was driven by the desire for decreased postoperative morbidity. However, as incomplete clearance of thymic tissue is associated with reduced remission rates, complete thymic resection in both thymomatous and non-thymomatous JMG is critical. As such, experts have voiced concern that MIS approaches provide inadequate visualization, and therefore, incomplete extirpation of mediastinal fat and ectopic foci of thymic tissue (46–49). Despite this controversy, there is paucity of high-level evidence to support an optimal approach to thymectomy in children (50). We identified twenty retrospective studies (*Table 4*) and two systematic reviews (*Table 3*) which evaluate and/or compare surgical approaches to thymectomy for JMG.

Table 4 Retrospective studies evaluating approach to thymectomy for juvenile myasthenia gravis

Authors, year published	Surgical approach [n]	Mean [range/± SD] age at thymectomy	Mean [range/± SD] disease duration prior to thymectomy	Key findings
Kolski, Vajsar and Kim (51), 2000	Thoracoscopic, right [6]	10.5 years	NR	(I) 0 postoperative complications (II) Mean follow-up 22 months (III) 100% with improvement, 50% in remission at mean follow-up 22 months
Kolski, Kim and Vajsar (52), 2001	Thoracoscopic, right [6] vs. open, transsternal [6]	11.3 [1.7–14.7] vs. 8.1 [1.9–15.8] years	0.8 [0.1–3.4] vs. 0.7 [0.1–1.4] years	(I) Thoracoscopic had shorter length of stay and less postoperative complications compared to open (II) 100% improved, 33% thoracoscopic were in CSR, 66% open CSR
Essa <i>et al.</i> (53), 2003	Open, transsternal-transcervical [30]	13.2 [4–16] years	19.3 [2–144] months	(I) Before surgery all patients underwent plasmapheresis and steroids weaned off (II) 90% effective, CSR 43.4% at mean follow-up 53.5 (range, 9–180) months (III) 33.3% ectopic thymic tissue which was found to be a significant poor prognostic factor for response to thymectomy
Seguier-Lipszyc <i>et al.</i> (54), 2005	Thoracoscopic, left [2]	10.75 years	4.5 years	(I) Ultrasound utilized intraoperatively to visualize the thymus (II) 0 complications (III) 100% improvement, 0% CSR
Wagner <i>et al.</i> (55), 2006	Thoracoscopic [6] vs. open, transsternal/transcervical [5/3]	9.8 [2–24] vs. 9.5 [7–15] years	0.8 [0.5–2] vs. 2.8 [0.5–8.0] years	(I) No difference in operative time (II) Thoracoscopic had significantly less blood loss and shorter length of stay than open (III) No difference in surgical effectiveness at mean follow-up of 43 (range, 4–111) months
Kanzaki <i>et al.</i> (56), 2008	Open [3]	13.3 [12–15] years	11.3 [5–20] months	(I) Extended thymectomy combined with postoperative high-dose steroid therapy (II) 100% improvement, 33% CSR
Yeh <i>et al.</i> (57), 2011	Thoracoscopic-assisted, subxiphoid [4]	NR	NR	(I) 100% improvement, 25% CSR
Ware, Ryan and Kornberg (58), 2012	Thoracoscopic [9] or open, transsternal [1]	11.3 [4–14] years	15.3 [3–38] months	(I) 70% effective (II) 30% refractory to thymectomy—2 underwent repeat surgery and 1 had residual thymus confirmed on path and subsequently improved
Parikh, Vaidya and Jain (59), 2011	Thoracoscopic, right [4]	9.25 [2.5–16.0] years	5 [3–8] months	(I) Operative time 55 min–2.5 hours (II) Chest drain removed within 24 hours (III) 75% effective (2 steroid free, 1 steroids at lower dose) at follow-up time of 6 to 46 months

Table 4 (continued)

Table 4 (continued)

Authors, year published	Surgical approach [n]	Mean [range/ \pm SD] age at thymectomy	Mean [range/ \pm SD] disease duration prior to thymectomy	Key findings
Cheng <i>et al.</i> (37), 2013	Open, transsternal [141]	12 [3–18] years	NR	(I) 6.4% perioperative complication rate (II) 7.1% with postoperative myasthenic crisis (III) 91.1% response rate (25.2% CSR, 20.7% in pharmacologic remission, 45.2% improved, 3.7% unchanged, 5.2% worsened) (IV) 43.2% cumulative remission rate at 10 years (V) Disease onset >6 years had higher CSR rates (VI) >12 years old at thymectomy had higher CSR rates (VII) Early thymectomy for generalized (within 12 months of onset) associated with better response to thymectomy (VIII) No corticosteroid use postoperatively associated with better response to thymectomy
Christison-Lagay <i>et al.</i> (60), 2013	Thoracoscopic, right [15]	11.3 [2.0–15.9] years	12.5 [3–40] months	(I) Mean operative time 145 min (decreased throughout study) (II) 0 postoperative complications (III) 47% in medical remission or CSR (IV) Postoperative symptom trend: 50% improved at 1 year, 86% at 2 years, 75% at 3 years
Castro <i>et al.</i> (3), 2013	Thoracoscopic [4] or open, transsternal [28]	NR	NR	(I) 75% improvement (II) Of 25% that didn't improve, half underwent repeat thymectomy as they had undergone primary thoracoscopic (III) Path: 21% thymic hyperplasia, 6% thymoma
Heng <i>et al.</i> (38), 2014	Open, transsternal [20]	Median 11 years 1 month	Median 9 months	(I) 10% required intensive care unit support postoperatively (5% required preoperatively) (II) 20% had surgical site infections which responded to antibiotics alone (all on steroids) (III) 95% improvement with 30% CSR postoperatively at median follow-up of 32 months
Özkan <i>et al.</i> (61), 2015	Thoracoscopic, right [40]	14.8 [\pm 2.2] years	15.9 [\pm 28.9] months	(I) Mean surgical time 48.9 (\pm 31.3) min (II) 7.5% postoperative complications (1 reintubation, 1 chest re-drainage, 1 atelectasis requiring bronchoscopy) (III) Mean chest tube duration 20.5 (\pm 12.1) hours (IV) Mean length of stay 1.8 (\pm 1.0) days

Table 4 (continued)

Table 4 (continued)

Authors, year published	Surgical approach [n]	Mean [range/ \pm SD] age at thymectomy	Mean [range/ \pm SD] disease duration prior to thymectomy	Key findings
Kitagawa <i>et al.</i> (36), 2015	Mediastinoscopic-assisted, subxiphoid [14]	9.4 [4–15] years	[3 months–7 years]	(I) Mean operative time 182 (\pm 44 min) (II) Mean blood loss 34 (\pm 43) cc (III) Chest tube removed postoperative day 1 (IV) Median length of stay 4.5 days (range, 4–6 days) (V) 2 patients with temporary incomplete paralysis of right recurrent laryngeal nerve (hoarseness resolved at 1 month and 3 months) (VI) 93% improved, 43% CSR at median follow-up of 27 months (range, 6–72 months)
Goldstein <i>et al.</i> (35), 2015	Thoracoscopic, right [12] vs. open, transsternal [16]	14 [\pm 5.8] vs. 13 [\pm 3.8] years	NR	(I) Utilized modified QMG score (II) Open had more severe disease preoperatively (mean MGFA 2.63 vs. 1.92) and lower pyridostigmine dose (III) Thoracoscopic had fewer complications, shorter postoperatively length of stay (IV) No difference in postoperative QMG score, steroid or pyridostigmine use between open and thoracoscopic approach at median follow-up of 23 months (thoracoscopic) and 44 months (open) (V) No difference in steroid dose pre- and postoperatively
Ashfaq <i>et al.</i> (62), 2016	Thoracoscopic, right [12]	Median 11 [3–17] years	Median 418 [75–1,756] days	(I) 0 postoperative complications (II) 100% improvement rate by DeFilippi classification
Kim <i>et al.</i> (45), 2019	Thoracoscopic, left [50]	10.5 [3–17] years	19.6 [0–168] months	(I) 0 postoperative complications (II) 45.5% Osserman I with no conversion to \geq II postoperatively (III) Mean follow-up duration 37.9 \pm 4.2 months (IV) 49.8% of patients showed improvement after surgery (V) Increasing cumulative probability of improved status on Kaplan-Meier analysis at 3.5 years follow-up (VI) Weight-adjusted total daily steroid intake (mg/kg/day) decreased significantly over 3.5 years of follow-up
Jastrzebska <i>et al.</i> (63), 2019	Thoracoscopic [23] or open, transsternal [16] or thymectomy, unspecified [34]	14.6 [6–22] years	1 [0–8] years	(I) Path: 2.2% thymoma, 2.2% thymic atrophy, 95.7% hyperplastic thymus (II) 90% improved, 11.9% in CSR, 11.9% in pharmacologic remission
Derderian <i>et al.</i> (64), 2020	Open [18] vs. thoracoscopic, left/right [15/1]	15.6 [\pm 4.4] vs. 11.9 [\pm 4.3] years	10.3 [\pm 8.8] vs. 10.7 [\pm 7.1] months	(I) Thoracoscopic had longer operative time, less blood loss, shorter length of stay, and shorter duration of intravenous narcotic use compared to open (II) No difference in clinical improvement or CSR (III) Surgical pathology not predictive of outcome

CSR, complete stable remission; MGFA, Myasthenia Gravis Foundation of America; NR, not reported; QMG, quantitative myasthenia gravis score; SD, standard deviation.

Open thymectomy

First performed by Alfred Blalock in the 1940s, today's proponents for open thymectomy believe transsternal open thymectomy is the most reproducible method to achieve maximal dissection (65). As such, as of 2016 greater than 80% of thymectomies for JMG were performed by an open approach (26). When performed in children, disease improvement rates as high as 90–100% have been reported alongside CSR rates of 25–66% (37,38,52,56).

Earliest reports of thymectomy are described in the 19th century when it was performed through a cervical incision in infants and young children due to a belief that thymic enlargement caused respiratory obstruction and sudden death (66). Transcervical thymectomy was first reported for JMG in 1912 by Ferdinand Sauerbach to be replaced with the transsternal approach with advances in thoracic surgery (66,67). However, attempts at reducing morbidity and simplifying recovery after thymectomy lead to the reintroduction of the transcervical approach in the 1960s in young adults (66). A transverse incision is made just above the suprasternal notch through the platysma. The sternohyoid and sternothyroid muscles are retracted laterally and the cervical aspect of the thymus identified enabling traction upward and dissection and deliverance of the mediastinal portion of the thymus up above the manubrium (66). However, many find the inferior and lateral thymus to be poorly visualized in this technique making it susceptible to residual thymus end procedure (68,69). In a study using a hybrid transcervical-transsternal approach, as many as 33.3% of patients had ectopic thymic tissue which was associated with poor response to thymectomy (53). Today, transcervical thymectomy accounts for as few as 1% of thymectomies for JMG (26).

Hybrid approaches incorporating a subxiphoid incision assisted by either mediastinoscopy or thoracoscopy have aimed to improve visualization while still avoiding median sternotomy (36,57). Although data boast impressive improvement rates of 93–100% and CSR rates of 25–43%, little is published on these approaches. Perhaps for good reason in the case of subxiphoid-mediastinoscopy, as 14% of patients experienced incomplete right recurrent laryngeal nerve paralysis which resolved between 1 and 3 months postoperatively (36).

Thoracoscopic thymectomy

As the thymus resembles the anterior mediastinal and

cervical fat it lies within and is laterally bounded by the phrenic nerves, adequate visualization is imperative to a safe and complete resection. However, the postoperative morbidity and cosmetic appearance following open thoracic surgery are suboptimal; therefore, the thoracoscopic approach to thymectomy was developed with the goal of achieving equivalent visualization, thymic resection and disease control as is achieved with the transsternal approach while decreasing postoperative recovery time and improving cosmesis.

Patients are positioned in a semi-lateral position at a 30° to 45° angle. Often, tracheal intubation affords superior exposure over selective endobronchial intubation as sufficient working space and visualization of the mediastinum are provided by capnopenothorax with insufflation pressures of 4–8 mmHg while selective intubation results in a collapse of the chest wall (59). A 30° thoracoscope and three 5–10 mm ports are utilized, including at the anterior axillary line, the inframammary midclavicular line and in the posterior axillary line at the 3rd or 4th intercostal space.

Some surgeons prefer a right sided thoracoscopic approach due to a larger working space afforded by the right thoracic cavity as well as the superior ability to visualize the superior vena cava and trace it to the left brachiocephalic vein (35). However, those in favor of the left sided approach feel the left portion of the thymus is easier to approach from this side as it is oftentimes larger and can extend under the left phrenic nerve and up to the aortopulmonary window, a frequent location of ectopic thymus (70,71). Due to unique benefits afforded by both the right and left approaches, some support a bilateral thoracoscopic approach (52). Irrespective, a thoracostomy drain is typically left end-procedure and removed within the first 24 hours postoperatively, and the consequence of two thoracostomy drains should be considered if debating between a unilateral and bilateral approach.

Small noncomparative studies evaluating outcomes following right and left thoracoscopic approaches demonstrate 50–100% disease improvement rates with minimal to no postoperative complications (45,51,54,59-62). As mentioned, critics have argued that thoracoscopic thymectomy results in incomplete clearance of thymic tissue and is associated with lower remission rates compared to open thymectomy (3,48,49,72-75). However, retrospective studies comparing thoracoscopic and open thymectomy for JMG have found thoracoscopic thymectomy to have less operative blood loss, shorter postoperative length

of stay, improved cosmesis and either a comparable or lower postoperative complication rate with no difference in postoperative disease control (22,26,35,52,55,64,76). However, and notably, one study has identified incomplete resection with thoracoscopy (3,26).

Thoracoscopy's non-inferiority of resection extent and post-operative disease control has not been prospectively evaluated in adults or children to date (46,47,68). Despite this, it is suspected that as familiarity with thoracoscopic thymectomy continues to increase, not only will the proportion of thymectomies performed thoracoscopically increase, but as patients evade the morbidity of thoracotomy, the risk benefit ratio of surgical management will shift and thymectomy will be offered to an increasing proportion of JMG patients.

Robotic-assisted thymectomy

The first robotic-assisted thymectomy was performed for MG in 2003 (77), and since multiple approaches have been developed including left- and right-sided, bilateral and subxiphoid (71,77-80). However, the adoption of robotic-assisted surgery in children has been slow compared to adult surgery (24,25). We identified one study meeting our inclusion criteria which utilized robotic-assisted thymectomy for JMG (4). Employing the same procedural principles and considerations regarding sidedness as the thoracoscopic approach, the robotic approach delivers several technical advantages compared to traditional thoracoscopy. The robot camera affords a three-dimensional and magnified view of the operative field as well as operator control improving visuospatial orientation. In addition, the robotic articulating instruments provide a more natural dexterity than thoracoscopic instruments. This improves dissection capabilities, particularly for difficult to reach tissue planes, while eliminating instability secondary to tremor.

When compared to non-operative management, patients who underwent robotic thymectomy for JMG had a higher 5-year cumulative CSR rate as well as reduced daily dose of cholinesterase inhibitors and corticosteroids; however, with a 19.1% postoperative complication rate. Although studies have not yet compared robotic-assisted thymectomy to other surgical approaches for JMG, studies completed in adults, including comparisons between robotic-assisted and thoracoscopic thymectomy, have demonstrated its safety alongside comparable clinical outcomes relative to sternotomy and superior outcomes compared to

thoracoscopy (14,78,81). However, increased cost and infrastructure requirements in addition to time required for docking or conversion to open in the event of emergent bleeding are significant barriers to the use of robotic-assisted thymectomy in JMG (71).

Limitations

As mentioned, data evaluating surgical management of JMG is restricted to small retrospective analyses leaving them limited by both power and selection bias. When comparisons are able to be made between cohorts, they are reduced by heterogenous populations often differing in one or more important confounding variables such as preoperative disease severity, patient age, symptom duration, antibody status and follow-up duration—all factors which contribute to a patient's response to thymectomy. Multicenter retrospective studies are a first and necessary step to enable corrected comparisons to be made. Furthermore, randomized prospective evaluation comparing optimal surgical to optimal medical management is necessary in order to appropriately understand the role of thymectomy in the management of JMG.

Conclusions

This review evaluated the role of surgical management for patients with thymectomy including important considerations when determining candidacy, timing and surgical approach. Although data specific to JMG are limited, available evidence supports equal if not improved disease control following thymectomy relative to medical management. Furthermore, data do not suggest any degree of immunodeficiency following thymectomy regardless of patient age at surgery, and outcomes may be optimized when surgery is performed earlier in the disease course, particularly for patients who are post-pubertal with generalized or severe disease and those necessitating high-dose steroid administration. Open transsternal resection was the historic gold-standard; however, as surgeons become more comfortable with thoracoscopic and robotic-assisted thymectomy, we anticipate increasing proportion of patients with JMG will undergo thymectomy and in a minimally invasive manner. As such, higher-level data, through the use of multi-institutional databases and randomized prospective evaluation, which compares surgical to medical therapy is warranted to understand which child warrants thymectomy, at what point in their disease course and their

development, and which surgical approach will optimize their postoperative outcomes.

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Footnote

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