Thymectomy in myasthenia gravis

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Purpose of review
Thymectomy has long been used in the treatment of patients with myasthenia gravis and antibodies against the acetylcholine receptor. However, its effectiveness has only been proven a few years ago in a randomized controlled trial in patients under the age of 65. Here, we review the current literature focusing on patient subgroups, potential biomarkers for outcome prediction and the choice of surgical approach.

Recent findings
Long-term follow-up studies after thymectomy confirmed that the benefits regarding clinical outcome parameters and a reduced need for immunosuppressive treatment persist. Nevertheless, a substantial proportion of patients in real-world cohorts do not reach complete stable remission after thymectomy indicating that the underlying autoimmune process is sustained in the periphery. Our understanding of the responsible mechanisms has improved with recent studies. Presently, outcome data after thymectomy in several patient subgroups, such as those aged over 50 years, those with juvenile onset or those with purely ocular symptoms are limited and have been the focus of recent research activities. Similarly, biomarkers guiding an appropriate patient selection for thymectomy are under investigation. A number of cohort studies demonstrated that minimal invasive surgical techniques such as extended robotic thymectomy lead to similar positive outcomes as a transsternal approach with potentially fewer short-term adverse effects.

Summary
Thymectomy is an effective treatment option in adult patients with early onset acetylcholine-receptor positive myasthenia gravis but uncertainty remains with regard to certain patient subgroups.

Keywords
myasthenia gravis, outcome, surgical approach, thymectomy, thymus

INTRODUCTION

After the pioneering work of thoracic surgeons in the last century, thymectomy has long been considered an option in the treatment of nonthymomatous myasthenia gravis. However, until a few years ago there have only been data from nonrandomized observational studies [1–3]. This issue was only settled with the completion of the international MGTX trial that clearly demonstrated that adult patients aged between 18 and 64 years with acetylcholine receptor-antibody (AchR-ab) positive nonthymomatous myasthenia gravis and generalized symptoms benefit from an extended transsternal open thymectomy done within 5 years of disease onset in terms of better strength (lower myasthenia gravis scores) and less need for steroids [4].

Initial worries that the positive effect of the thymectomy might only be transient were subsequently addressed by an extension study, which confirmed that the benefit persisted for at least 5 years [5]. In addition, in a post hoc analysis of the trial this long-term benefit also showed up in the much higher likelihood of patients in the thymectomy group in reaching a minimal manifestation status (MM) with complete withdrawal of prednisone as compared to the conservatively managed patients (64% vs. 38%) [6].

Based on these studies, thymectomy in nonthymomatous myasthenia gravis is generally recommended for patients fulfilling the criteria as set out in the MGTX trial [7,8].

However, given the complex nature of this topic, inevitably some questions were left unanswered by the MGTX trial. In particular, whether all patients within the broad inclusion criteria would benefit equally from a thymectomy and if its benefits would also apply to patient groups excluded from the trial.

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KEY POINTS

- Thymectomy is an effective treatment for early onset acetylcholine-receptor positive (AchR-ab+) myasthenia gravis.
- Whether thymectomy benefits patients with AchR-ab+ myasthenia gravis over the age of 50 as well as patients with purely ocular symptoms is still uncertain.
- Current date point to the effectiveness of thymectomy in patients under the age of 18 years but the potential long-term adverse effects warrant further investigation.
- Extended minimally invasive surgical approaches appear to be safe and equally effective in comparison with an extended open transsternal thymectomy.
- Future research should focus on biomarkers that help predict long-term outcome and patient selection.

Specifically, the following questions have been subject to ongoing research activities and are reviewed in this article: (1) Can the beneficial effects of thymectomy be transferred to the clinical practice in the real world, beyond the controlled conditions of a randomized trial? (2) What are the exact immunopathological mechanisms by which thymectomy works? Is there a role for the thymus histology or other parameters of the immune-system as biomarkers for the success of thymectomy? (3) What are the relevant cut-off ages for thymectomy with regards to juvenile myasthenia gravis and late-onset myasthenia gravis? (4) Will patients with a purely ocular form of myasthenia gravis also benefit from thymectomy? (5) Are newer less invasive surgical techniques such as robotic thymectomy equally beneficial as the extended transsternal procedure used in the MGTX trial.

As a basis for this review the authors performed a PubMed literature search to identify all studies of the years 2020 up to March 2023 containing the terms ''myasthenia gravis'' (as MeSH term) and either ''thymectomy'', ''thymus'' or ''thymoma'' (all fields) which yielded 371 papers. The publications were then manually reviewed and prioritized by the authors. The literature list was complemented for relevant older publication from the authors' personal library and citations from the above search results.

REAL-WORLD DATA ON THE EFFECTIVENESS OF THYMECTOMY IN NON-THYMOMATOUS MYASTHENIA GRAVIS

Although randomized control trials (RCTs) provide the highest evidence of medical knowledge it is nevertheless important to ensure that any benefits seen in RCT are not lost when translated into real-world settings. In turn, data from nonrandomized, observational studies, can reinforce evidence gathered from controlled trials. Regarding thymectomy in myasthenia gravis, the first systematic review and meta-analysis compiled after the MGTX-trial, supported the trial results [9]. This review compared surgical therapies against a conservative therapy in 5686 patients mainly with nonthymomatous myasthenia gravis from 17 observational studies and confirmed the superiority of the surgical treatment with thymectomy patients having a 2.34-fold higher odds ratio for achieving a remission in comparison to controls. [9].

Another recent indirect evidence of the beneficial effect of thymectomy was provided by a single center analysis of 141 acute myasthenic exacerbations necessitating hospitalizations. One of the key factors associated with a shorter length of hospital stay was a previous thymectomy (5.8 days versus 9.5 days in patients without thymectomy). The observation that thymectomy can have an unexpected impact on this clearly measurable parameter argues for a robust benefit conferred to patients by thymectomy [10▪].

Myasthenia gravis is a known for its unpredictable, fluctuating disease course over the years [11]. A recent single center retrospective review of 94 patients focused on the continued fluctuating nature of myasthenia gravis even after successful thymectomy [12▪]. Although 72% of patients initially achieved a good clinical response (defined as minimal manifestation or better) this response was sustained in only half of the patients over the long-term median follow-up of 90 months, which emphasizes that thymectomy, though beneficial, is certainly no cure for myasthenia gravis (Table 1).

Comorbidities are yet another factor complicating the treatment of patients with myasthenia gravis encountered in the real world. The negative effect of comorbidities on the outcome of generalized myasthenia gravis after thymectomy was shown in a cohort of 154 postoperative myasthenia gravis patients. In this long-term follow-up-study, complete stable remission (CSR) was significantly less likely in patients with comorbidities and also correlated with the Charlson comorbidity index scores [13].

WHAT DO WE KNOW ABOUT THE UNDERLYING PATHOPHYSIOLOGICAL MECHANISMS THAT DETERMINE THE SUCCESS OF THYMECTOMY - BIOMARKERS FOR POSTOPERATIVE OUTCOME

The response to thymectomy can be very heterogeneous, not all patients achieve CSR and some of

Table 1. Listing of recent papers analyzing different surgical methods of thymectomy in cohorts which included nonthymomatous myasthenia gravis patients

Paper	Patients/methods	Question	Findings
Solis-Pazmino, P. *et al.* [42]	Meta-analysis (1598 patients, 13 studies) comparing at least two thymectomy techniques with at least 3 years of follow up and reporting of CSR-rates	CSR rates after various open and minimally invasive thymectomy techniques at 3 years postsurgery or later	CSR rates similar in VATS extended procedures and extended transsternal surgery from 3 year to 9 years postsurgery. CSR rates were lower in basic transcervical approach compared to extended transsternal thymectomy at 10 years
Lee, Y. *et al.* [43▪]	Meta-analysis of 26 studies, 3588 patients. Comparing open versus minimally invasive surgery (MIS) thymectomy. Subgroup-analysis in nonthymomatous myasthenia gravis.	MG-outcome (CSR rates and improvement) at 1, 3, and 5 years post thymectomy. Perioperative parameters in MIS and open thymectomy groups.	No statistical difference in CSR-rates between open and MIS thymectomies. CSR at 1 year better in the nonthymomatous MG subgroup (RR 1.38, 95% CI 1.04 to 1.83). Shorter hospital stay in minimally invasive group (2.58 days). MIS-thymectomy showed 36% decrease in overall complications compared to open thymectomy
Wilshire, C. L. *et al.* [44]	Multicenter review of 123 patients who underwent a minimally invasive thymectomy	Comparison of good outcome (CSR, PR or minimal manifestations (MM)) in left versus right sided unilateral minimally invasive thymectomy.	Left-sided approach had a shorter median operating time and achieved more often a good outcome (46%) than the right-sided (22%) approach.
Gao, J. *et al.* [45]	Retrospective review of 68 patients with myasthenia gravis who underwent VATS thymectomy using a propensity score matching.	Comparison of surgical and neurological outcomes (CSR) in modified subxiphoid approach vs. bilateral approach	Modified subxiphoid VATS resulted in shorter operative time and postoperative hospital stay. No difference in 2-year CSR rates (21.1% and 26.3%)
Luzzi, L. *et al.* [46]	114 patients who underwent thymectomy for various thymus diseases including 52 with MG (nonthymomatous and thymoma-associated MG (TAMG)	Safety and surgical outcome in robotic vs. open thymectomy	No statistical differences in operative time and complications rate. Lower postoperative pain and shorter hospital stay with robotic thymectomy
Romano, G. *et al.* [47]	34 patients with TAMG who were treated with robotic surgery.	Neurological outcome in 26 patients	MG-improvement in 76.5%, CSR in 14.7%, PR in 29.4%, MM in 32.3%.
Castillo-Larios, R. *et al.* [48]	148 patients from Florida Inpatient Discharge Dataset with nonthymomatous MG. 108 patients treated with open thymectomy, 40 with minimally invasive approach	Comparison of length of in-hospital stay and costs between minimally invasive and open approach	Significantly shorter length of stay and overall lower costs for minimally invasive thymectomy
Zhang, S. *et al.* [49]	155 patients with nonthymomatous myasthenia gravis undergoing extended thymectomy either with transsternal or thoracoscopic right unilateral thoracoscopy or thoracoscopic subxiphoid thymectomy	Detection rate of ectopic thymic tissue and postoperative recovery in the three surgical approaches	Highest detection rate of ectopic thymic tissue with transsternal thymectomy but longest short-term postoperative recovery
Raja, S. M. *et al.* [41▪]	1725 nonthymomatous thymectomies from an international surgical database. Analysis of different surgical approaches: VATS, robotic assisted VATS (RVATS), transcervical thymectomy (TC) and transthoracic thymectomy (TT)	Comparison of perioperative complication rates between different approaches (VATS, RVATS, TC, TT)	VATS, RVATS and TC had lower odds of perioperative complications than TT-thymectomies Higher odds of complications for VATS and RVATS than for TC. RVATS usage increased from 6% in 2009 to 44% in 2019
Rath, J. *et al.* [12▪]	Single center study of 94 patients with myasthenia gravis undergoing extended thymectomies (transsternal, transcervical or VATS/RVATS)	Comparison of good clinical response (CSR, PR or MM) between transsternal, transcervical or VATS/RVATS thymectomies	No significant difference regarding good clinical outcome between transsternal, transcervical or VATS/RVATS approaches
Scheriau, G. *et al.* [50]	Single center retrospective cohort study of 72 patients with myasthenia gravis undergoing RVATS. Monitoring of perioperative complications	Incidence of postoperative respiratory failure and optimal anesthetic management of patients after RVATS	5.6% of patients developed postoperative respiratory failure. 90.3% could be extubated in the operating room, 48.6% were transferred to ICU

CSR, completed stable remission; MG, myasthenia gravis; MIS, minimally invasive surgery; MM, minimal manifestation; PR, pharmacological remission; RVATS, robotic assisted video assisted thoracoscopic surgery; TAMG, thymoma-associated myasthenia gravis; TC, transcervical thymectomy; TT, transthoracic thymectomy; VATS, video assisted thoracoscopic surgery.

those who do can relapse later on [12▪]. To predict the success of thymectomy on an individual level it is obviously crucial to understand the mechanisms by which the removal of the thymus affects the disease course.

From a theoretical point of view, the removal of the ''surgical thymus'' [14] can only be curative or disease modifying for MG patients in two scenarios: (i) the cause of disease is limited to the thymectomy specimen (intra-thymic hypothesis of MG [15] or (ii) an imperative cross-talk between the thymus and extrathymic pathogenic mechanisms is interrupted by thymectomy.

The currently favored immunopathological concept sees the thymus as the primary immunological target in acetylcholine-receptor positive (AChR-ab+) early onset myasthenia gravis (EOMG) and at least initially as the site of priming and activation of AChR directed B-cells in concert with specific Th cells that provide the environment of B-cell maturation. A multistep cascade has been proposed whereby Th cells are activated after being exposed to folded AChR-antigen (originating from myoid, dendritic or medullary thymic epithelial cells). They then recruit and activate AChR-specific B-cells that eventually develop into antibody producing plasma-cells in germinal centers (CG) in the thymus, tertiary lymphoid structures that are physiologically not present in this organ. The timely removal of the thymus can consequently be seen as the appropriate intervention to interrupt this process [16–18].

Recently, substantial progress has been made in closer identifying the responsible dysregulated immune cells in AChR-ab+ myasthenia gravis [19]. In this study, peripheral and thymic immune cells from myasthenia gravis patients and controls were profiled in great detail and then subjected to a machine learning analysis to identify functional subsets of immune cells. In contrast to controls the inflamed thymi of myasthenia gravis patients were found to be highly infiltrated by B cells and Th cells. The study then identified two T-cell types, Th-CD103 and Th-GM cells that are highly enriched in the thymus but at the same time reduced in the circulation of patients before thymectomy or therapy. The Th-GM were mainly from the Th effector memory population (producing granulocyte-macrophage colony-stimulating factor) and the CD103 cells from a memory T-cell population that has been ascribed a shuttle function in transferring disease pathology to secondary (extrathymic) sites of chronic pathogenic antibody production. Interestingly, both T-cell types were inversely correlated with disease severity in the serum and rebounded after thymectomy. Also, both cell types were reduced by azathioprine treatment coinciding with immunosuppression. If confirmed, the potential of these specific Th-cells as biomarkers is highly promising [19].

Another recent key paper from a Finnish biobank highlighted the pathological relevance of thymic GC in EOMG. In this most thorough digital pathological analysis of thymi from patients with myasthenia gravis to date, the authors found a clear correlation between the numbers of GC and AChR-ab seropositivity in EOMG but, interestingly, not in late-onset MG (LOMG) [20▪▪]. A similar correlation between the number GC and AChR-ab-titers had previously been reported from the histological analysis of 1035 thymi of a French database [21]. Both studies thus provide evidence for a central role of thymic GC in the production of AChR-ab in EOMG. Supporting this notion, the numbers of germinal centers (GC) in the Finish study correlated well with a better postoperative outcome after thymectomy in EOMG. Further evidence for the role of thymic B-cell maturation as a driver of the disease has been provided by a recent report showing an increase of plasmablasts within the thymus of patients with nonthymomatous myasthenia gravis in comparison to controls and a correlation of their numbers with the preoperative disease activity [22▪▪] An assessment of GC in thorough histological analyses of postoperative thymi could thus have a potential in the outcome prediction after thymectomy [20▪▪].

An interesting explanation for the disease persistence after thymectomy was recently provided by an analysis of the B-cell repertoire in patients of the MGTX trial before and after thymectomy [23]. It was demonstrated that disease associated B-cells originate in the thymus before emigrating into the circulation. The persistence of such thymus derived B-cell clones after thymectomy was subsequently correlated with a worse clinical outcome (in terms of QMG-scores and steroid requirements). A lesson drawn from this analysis would clearly be that a thymectomy should ideally be attempted before an expansion of the immune-pathology to the periphery has taken place.

Although AChR-ab are clearly central to mediating the pathology on the neuromuscular junction in MG, absolute titers in the serum have not been reproducibly associated with disease activity possibly due to the polyclonal nature of AChR-Ab with not all antibody clones being equally pathogenic. Recent studies have focused instead on the potential of the relative decline of AChR-ab based on a report that showed that the rate of change of AChR-Ab levels correlated with clinical improvement [24]. This predictive potential of a stronger relative AChR-Abs decline might also predict a better postoperative outcome has now been shown in two different cohorts [12▪,25]

While the above discussed pathophysiological thymus-related considerations mainly apply to AChR-ab+ myasthenia gravis, the mechanisms in patients without AChR-ab might or do not involve the thymus to the same extent.

Thymectomy is unanimously not recommend for patients with antibodies against the muscle-specific kinase (MuSK) [26]. The evidence for patients with LRP4 ab is currently limited to case studies [27] and robust data on the benefit of thymectomy in patients with triple seronegative myasthenia gravis (including low-affinity AChR-ab) are lacking. It is therefore generally recommended that thymectomy in these patients should only be considered on a case-by-case basis.

THYMECTOMY IN LATE ONSET MYASTHENIA GRAVIS

There is an ongoing debate on the appropriate upper cut-off age for thymectomy as the MGTX trial had only included 17 patients at or above the age of 50 (up to the age of 64). An (underpowered) posthoc sub-analysis of these patients has not shown a significant benefit of thymectomy neither regarding the time-weighted average QMG-score nor in the prednisone usage though a trend was still visible [4]. The rationale for doubting the benefit of thymectomy in LOMG (usually defined by a disease onset after the age of 50 years) is that the thymus might not be as relevant as in EOMG. Underpinning this notion, hardly any GC can be found in patients above the age of 45, as recently demonstrated in the Finish pathology study in contrast to thymi of EOMG patients where GC are the hallmark of the disease [20▪▪]

A recent meta-analysis of observational studies addressed the question of the relative benefits of thymectomy for nonthymomatous LOMG patients. The authors analyzed 896 patients across nine studies and compared the likelihood of achieving CSR after thymectomy in EOMG versus LOMG (with an age cut-off between 40 and 50 years). EOMG patients were 1.95 more likely to achieve CSR (though there was no significant difference when the outcome ''improvement'' was added to this endpoint) [28]. Moreover, when analyzed in LOMG patients alone (3 studies, 216 patients) no significant difference was seen in the outcome (CSR or pharmacological remission) between thymectomy or conservative treatment [28]. In conclusion, as there are still no firm evidence-based data available on this topic, the decision to operate must be made with caution and on an individual case-by-case basis.

JUVENILE ONSET MYASTHENIA GRAVIS AND THYMECTOMY

Patients below the age of 18 (i.e., those with juvenile myasthenia gravis (JMG)) were not included in the MGTX trial [4]. The underlying pathomechanisms regarding AChR-ab+ generalized myasthenia gravis patients are thought to be similar to adult EOMG, however, the risk-benefit analysis both in terms of juvenile patients' capacity to benefit as well the potential long-term side effects in this patient group remain underexplored.

In a systematic literature review published in 2017 of 16 retrospective studies which included 1131 JMG patients of whom 488 had a thymectomy, a postoperative improvement was reported for 77% (with 29% achieving CSR) and the procedure appeared overall safe [29]. In a more recent review of 17 studies (involving 588 JMG patients after thymectomy) similar numbers were obtained (77% improved and 40% had CSR) [30].

A recent single center study in a German cohort of 47 JMG patients (aged between 10 to 15 years of age) studied the outcome after robotic thymectomy in comparison to conservatively managed patients of a similar age [31▪]. JMG patients in the surgical group were 3.8 times more likely to achieve CSR with a reduced dependency on steroids. However, the significance of these results was somewhat limited as the surgical group had a shorter disease duration before study entry and a higher usage of steroids which might have affected the results. This last point was recently underlined by a case series from China with 32 JMG patients who tended to have a better postoperative outcome when the disease duration before thymectomy was shorter [32].

The concern with a thymectomy in a child or juvenile patient with a still developing immune system is that the absence of a thymus could have negative long-term consequences for the immune responses later-on in life. Popperud *et al.* followed up on this question by analyzing T-cell subsets in thymectomized JMG patients (median age of 17 at thymectomy) [33]. Seven to 26 years after thymectomy they found a lower number of naive $CD4^+$ helper T-cells and CD8 cytotoxic T-cell subsets and an increase in memory T-cells indicating a premature ageing of the immune system, However, negative clinical consequences could not be discerned. In that context it is reassuring to note the observation of a recent study, that a thymectomy in adult patients without immunosuppression did not impair the proliferative T-cell response upon re-vaccination with tetanus toxoid [34▪].

OCULAR MYASTHENIA GRAVIS AND THYMECTOMY

In comparison to generalized myasthenia gravis, fewer studies have investigated thymectomy in purely ocular myasthenia gravis, who were also excluded from the MGTX trial. A meta-analysis on this topic was performed by Zhu *et al.* [35]. The authors analyzed 640 patients with ocular myasthenia gravis from 26 studies and obtained a pooled rate of CSR after thymectomy of 50% albeit with a considerable heterogeneity between different studies. A comparison with control groups was not possible but the randomized Epitome-trial may serve as an orientating reference-point, with a remission rate of 83% in the cortisone treated arm versus 0% in the placebo group [36]. Based on the limited evidence from retrospective data international guidelines advise that thymectomy can be offered to ocular patients only if conservative management has failed [7].

Recent studies have also explored the role of thymectomy in reducing the risk for generalization in ocular myasthenia gravis. A multicenter study from China retrospectively reviewed 519 patients with purely ocular symptoms for at least 3 months and no prior exposure to immunotherapy. The risk of generalization in the 131 patients who underwent thymectomy was reduced in comparison to those without thymectomy (23.7% vs. 31.4%, hazard ratio of 0.4) [37]. This reduction applied to patients with thymomatous and even more so to nonthymomatous myasthenia gravis. Another recent single center case series of 58 thymectomized patients with ocular myasthenia gravis from China found similar generalization rates of 22.4% after thymectomy, with a higher rate of conversions for thymomatous myasthenia gravis [38].

SURGICAL TECHNIQUE AND PERIOPERATIVE COMPLICATIONS

Based on pathophysiological considerations and clinical experience it is the generally accepted aim of a thymectomy in nonthymomatous myasthenia gravis to resect as much thymic tissue as possible. The ''surgical'', in contrast to the ''anatomic'', thymus may be made up of multiple (not only two) contiguous or separated lobes in the lower neck and anterior mediastinum as well as microscopically identifiable thymic tissue roughly distributed between the bilateral phrenic nerves from the lower level of the thyroid down to the diaphragm [14]. One problem to consider is that ectopic thymic tissue can be distributed across the mediastinum, which might not be equally accessible by the many different techniques [8,39,40], or not at all routinely covered by current surgical techniques (e.g. microscopic foci of thymus were found in pretracheal fat, behind the thyroid to as high as the hyoid cartilage, and bilaterally beyond each phrenic nerve, and in subcarinal fat) [14]. To date the response to thymectomy cannot be predicted preoperatively. There are neither preoperative imaging modalities that can distinguish between follicular and true thymic hyperplasia, nor is it possible to distinguish patients with myasthenia gravis disease activity confined to the thymus from those where the antibody-production has spread beyond the thymus. Such imaging would certainly be helpful in the preoperative planning of the radicality of thymectomy.

While the MGTX trial employed an invasive extended transsternal approach, the field of thymic surgery has moved on to better tolerable minimally invasive procedures over the last years [4,41▪]. Under this aspect, it has been a topic of intense research which surgical thymectomy procedure is best suited in clinical practice to achieve the goal of an optimal neurological outcome with minimal adverse effects.

An informative comparison of surgical techniques with regards to achieving clinical remission was provided in 2021 by an extensive meta-analysis of various open and minimally invasive thymectomy procedures [42]. The authors analyzed CSR rates at different postoperative timepoints with at least 3 years of follow up involving 1598 patients from 12 cohort studies and one RCT. Minimally invasive extended video assisted thoracoscopic surgery (VATS) techniques performed just as well as the traditional extended transsternal approach in terms of achieving CSR at all analyzed time-points from 3 to 9 years after thymectomy. Only the least aggressive approach of basic transcervical thymectomy appeared inferior to the extended transsternal approach. Among minimally invasive techniques, robotic VATS thymectomy resulted in lower CSR rates in comparison to nonrobotic VATS approaches at 3 years (with a relative risk of 1.99) but not at 5 years postsurgery.

A second recent large meta-analysis with somewhat broader entry criteria and only partly overlapping studies included 3588 patients from 26 mainly nonrandomized cohort studies [43▪]. It also compared open thymectomies with minimally invasive surgery in patients with myasthenia gravis regarding CSR rates or improvement as well as perioperative parameters. There was no statistical difference in the CSR-rates between open and minimally invasive thymectomies in the whole group which also included patients with thymomatous myasthenia gravis. In the subgroup-analysis of patients with nonthymomatous myasthenia gravis (1317 patients) significantly higher CSR rates were

observed in the minimally invasive group at 1 year after surgery, though the significance was lost at 3 and 5 years. Length of hospital stay was lower in the minimally invasive group and the overall complication rate was also lower.

Both analyses thus provided reassurance that extended minimally invasive procedures, which are associated with lower complication rates and shorter recovery times, are at least equally effective as open extended transsternal approaches, as employed in the MGTX trial. Various other reports comparing surgical techniques in cohorts consisting of nonthymomatous myasthenia gravis patients are listed in table 1. The overall picture that emerges is that the extended minimally invasive procedures such as (robotic) VATS are not inferior to the MGTX-tested extended transsternal approach in terms of neurological outcome but are superior in terms of perioperative complications and other parameters.

CONCLUSION

The seminal randomized controlled MGTX trial has settled the question whether thymectomy in Ach-R-ab positive early onset myasthenia gravis is an effective treatment clearly showing a positive effect on clinical outcomes up to 5 years after surgery. However, because of the narrow inclusion criteria of the trial uncertainties remain regarding patients with juvenile-onset myasthenia gravis, LOMG or purely ocular symptoms. Since another randomized controlled trial answering these questions will not be easily feasible, further high-quality cohort studies are necessary to investigate whether the benefit of thymectomy translate to these subpopulations. With a view to the optimal surgical approach, a number of retrospective cohort studies have shown the safety and effectiveness of extended minimal-invasive techniques such as robotic thymectomy with less short-term side effects compared to the open transsternal method used in the MGTX trail. Finally, there is a need for biomarkers, which predict long-term outcome after thymectomy and could consequently guide patient selection.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

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