

Surgery for the treatment of myasthenia gravis

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The role of thymectomy

“It is of considerable interest to find a relationship between a mysterious disease, myasthenia gravis, and a mysterious gland, the thymus gland.”

O. Theron Clagett (1951)

The history of surgery for MG

1901 Thymic tumour found at post-mortem of MG patient (Weigert)

1917 Thymic abnormalities found in >50% of MG patients at post-mortem (Bell, Mayo Clinic)

1936 Resection of thymic mass in MG patient – complete symptom resolution (Blalock)

1941 First case series - 6 patients, 5 survivors, 3 complete remission, 2 partial remission (Blalock)

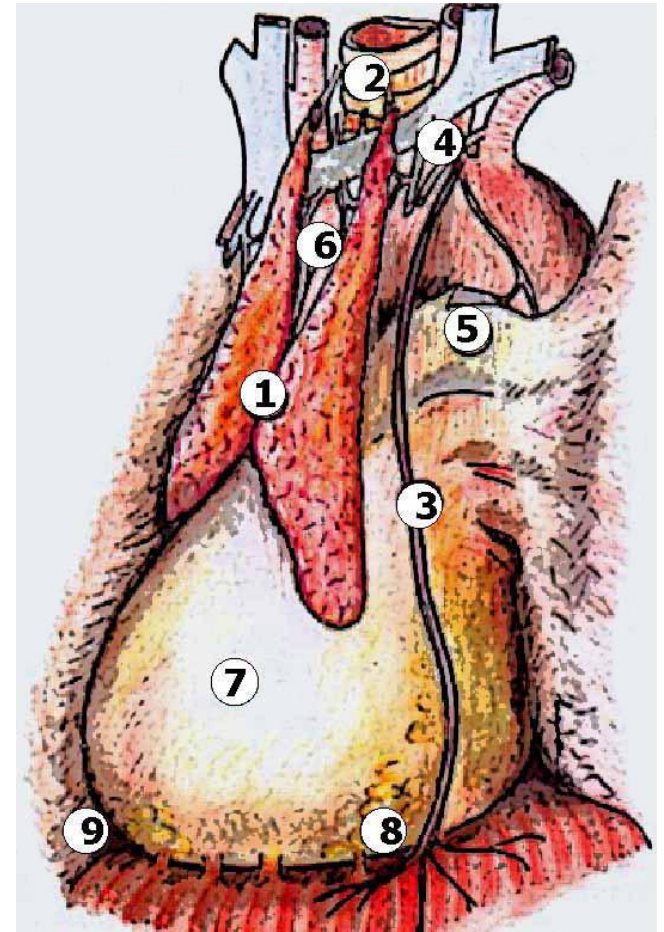
**The treatment of myasthenia gravis (by) removal of the thymus gland:
preliminary report.**

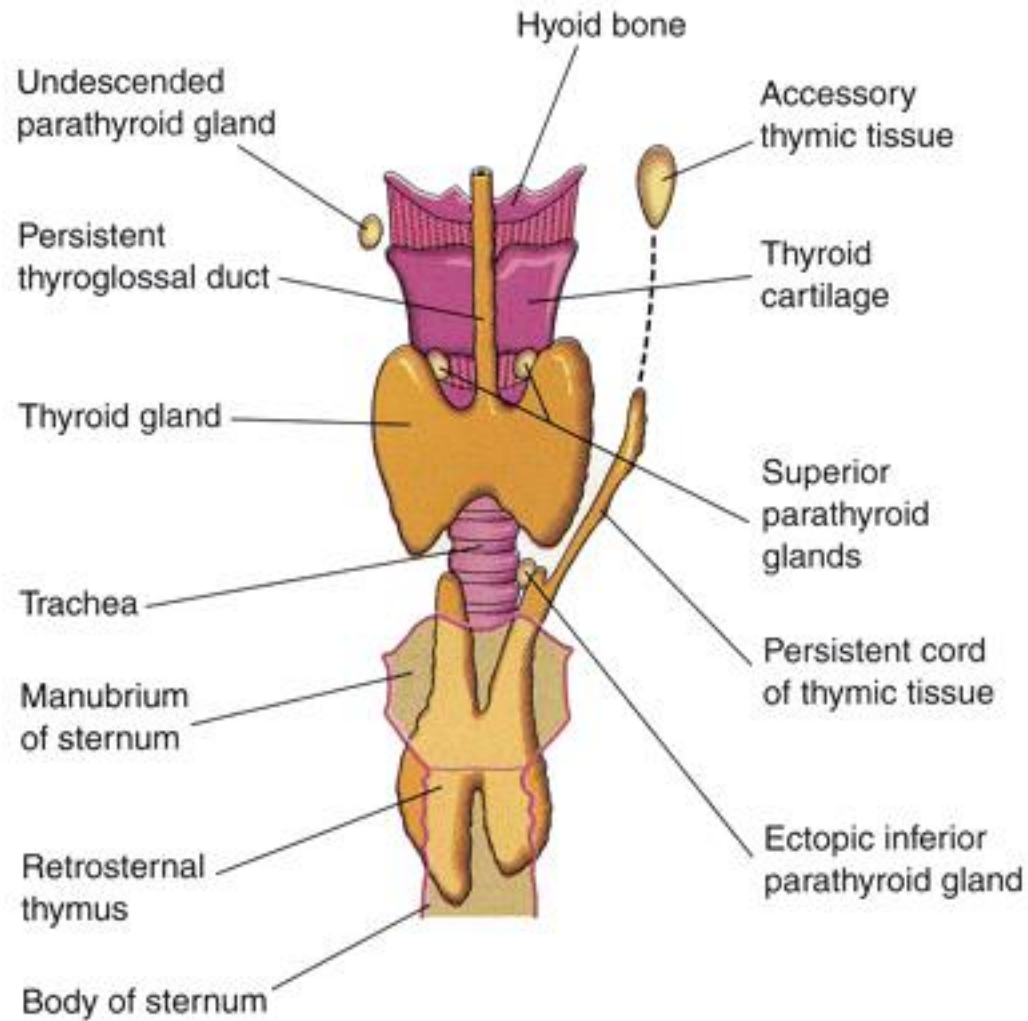
Blalock A, Harvey AM, Ford FR, Lilienthal JL Jr. *JAMA*. 1941;117:1529.

- “We wish to emphasize again the absence of conclusive proof that the improvement noted in our patient is due to the removal of the tumor from the thymic region.”
- “The present attempt to influence the course of myasthenia gravis differs from those described in that the operation was performed with the deliberate purpose of removing all the thymic tissue by complete exploration.”

The thymus gland

- Anterior mediastinum
- Prominent in childhood, involutes (normally) in adulthood
- Site of T cell maturation



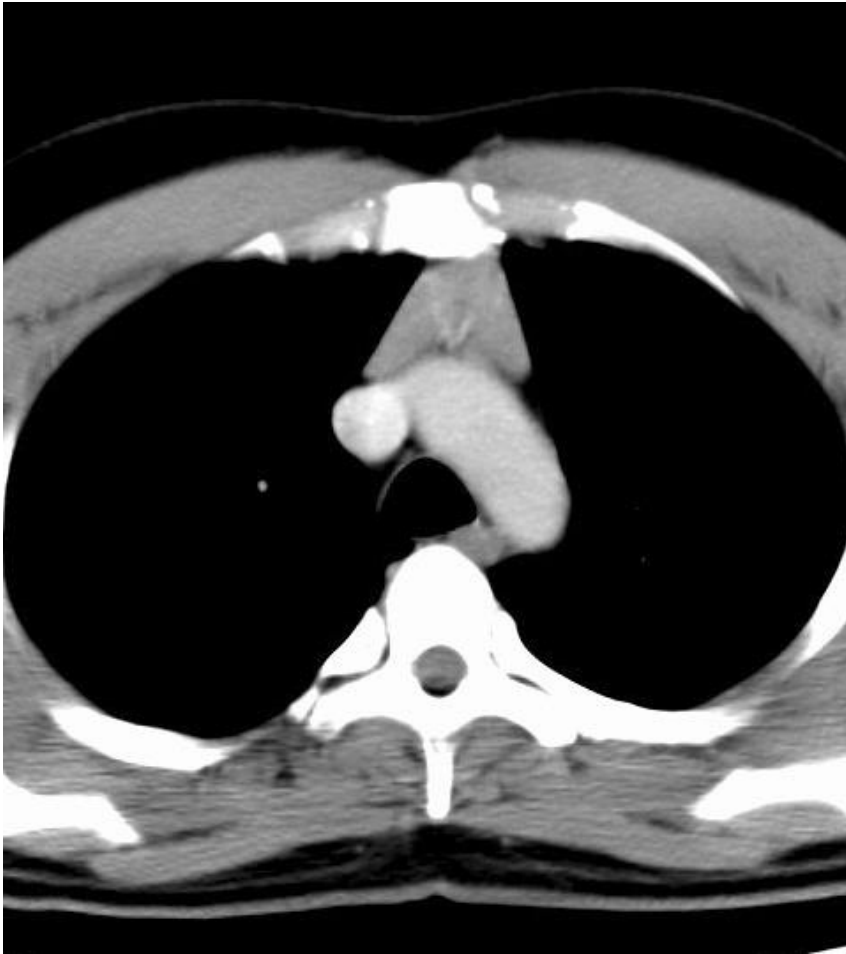




Myasthenia gravis

- Most common disorder of neuromuscular transmission
- Annual incidence 10-20 per million
- Weakness results from antibody-mediated, T-cell dependent attack on proteins in post-synaptic membrane of NMJ
- 12% have underlying thymoma

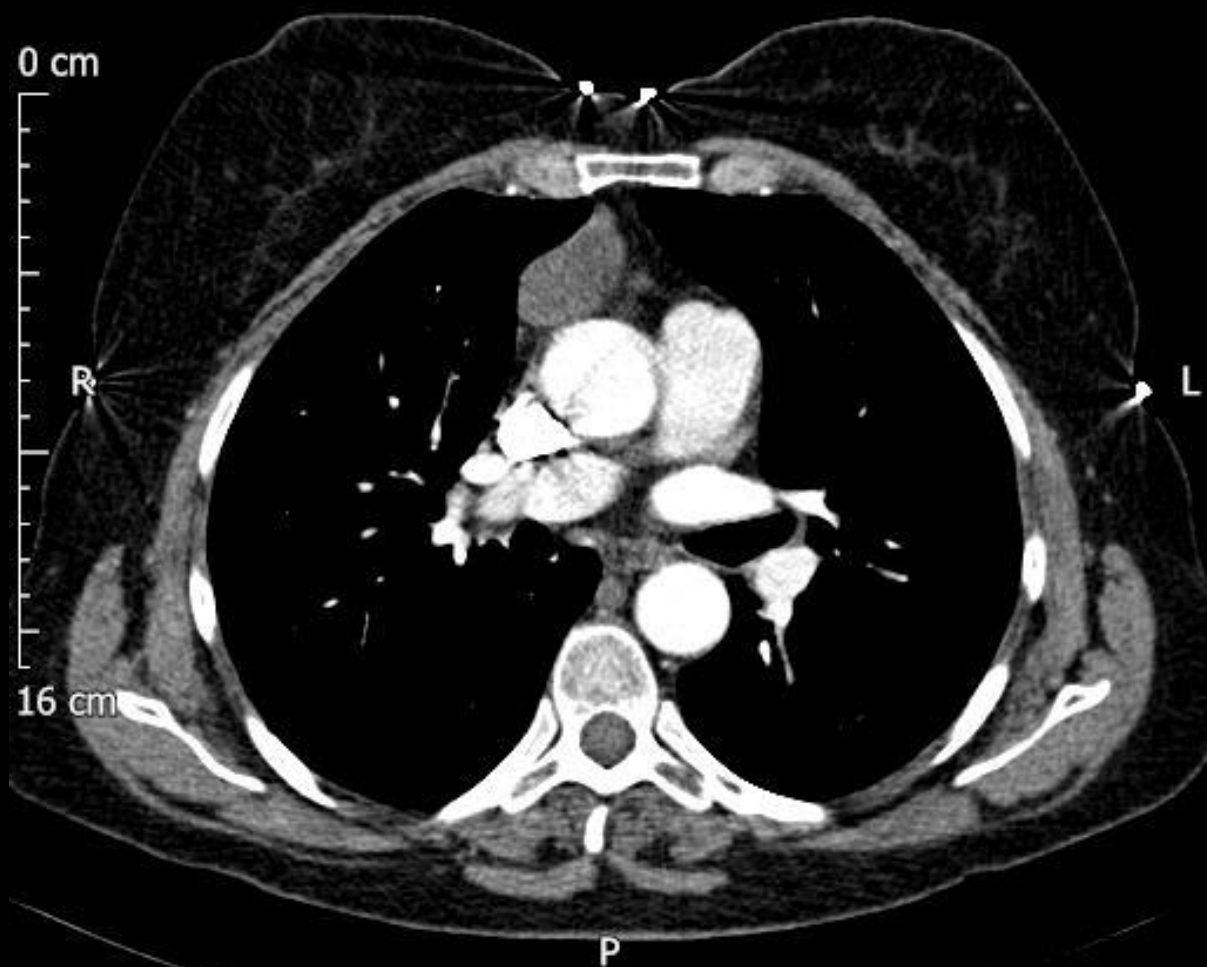
Role of the thymus gland in MG



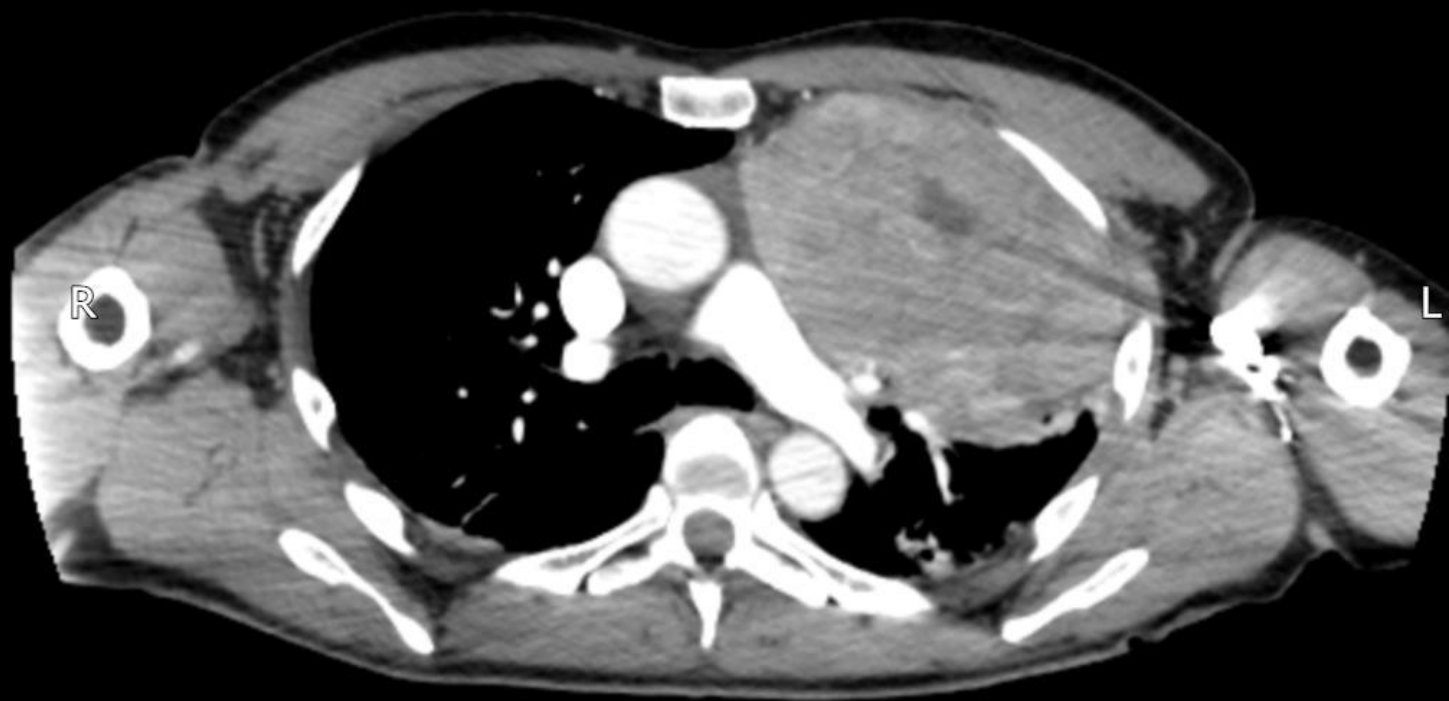
- Still unknown
- Thymic hyperplasia often seen in MG
- Antigens in thymic tissue stimulate antibodies against NMJ

A

ww:350 wl:50
1:1, All
Value [-1008]



A



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Modified Osseman classification

- 0 asymptomatic
- 1 ocular signs and symptoms
- 2 mild generalized weakness
- 3 moderate generalized weakness
- 4 severe generalized weakness, respiratory dysfunction or both

MGFA classification

- I Ocular symptoms
 - II Mild extra-ocular weakness \pm ocular symptoms
 - III Moderate weakness
 - IV Severe weakness
 - V Intubated
-
- a predominantly limb/axial muscles
 - b predominantly bulbar/respiratory muscles

Current treatment of MG

- Symptomatic treatment (anticholinesterases)
- Chronic immuno-modifying agents
- Acute immuno-modifying agents
- **Surgery**

Rationale for surgical treatment

- Initial results
- Thymus may have a role in the pathogenesis of MG
- Thymic abnormalities present in patients with MG:
 - Thymic hyperplasia 60-70%
 - Thymoma 12%

Surgical techniques

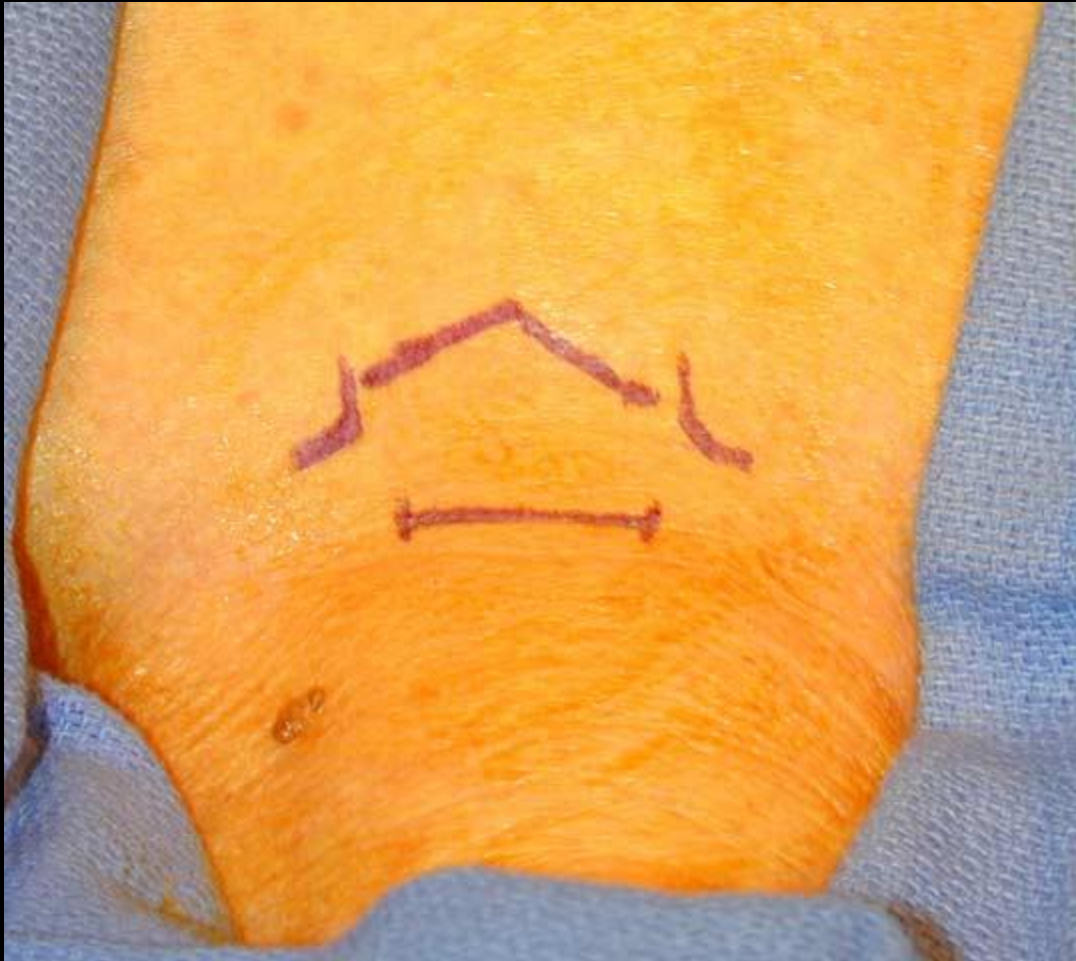
- “Maximal thymectomy” – combined trans-sternal and trans-cervical
- Classical trans-sternal
- Trans-cervical
- Video-assisted thoracic surgery (VATS)
- Sub-xiphoid
- Robotic

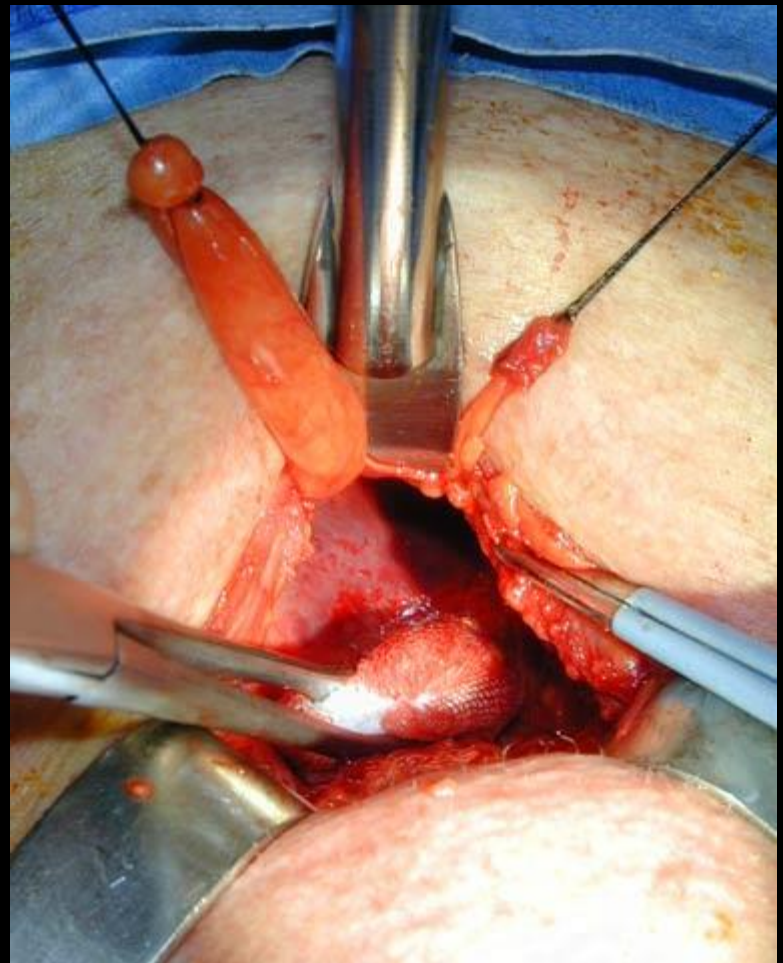
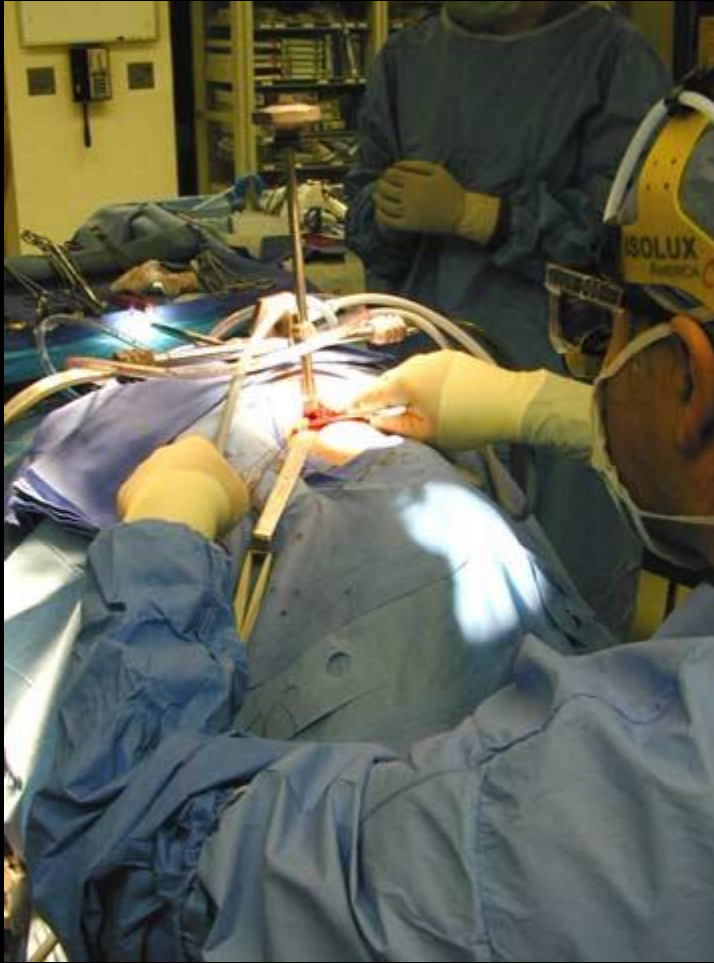
Maximal thymectomy

- Popularised by Jaretzki
- Cervical incision to mobilise superior thymic poles in neck
- Sternotomy and excision of all thymic tissue and mediastinal fat in anterior mediastinum (“phrenic to phrenic”)
- Standard against which others are compared

Trans-cervical thymectomy

- Popularised by Cooper
- Small neck incision (no sternotomy)
- Customised retractor beneath sternum
- Recent modifications include addition of thoracoscope to improve illumination and visualisation

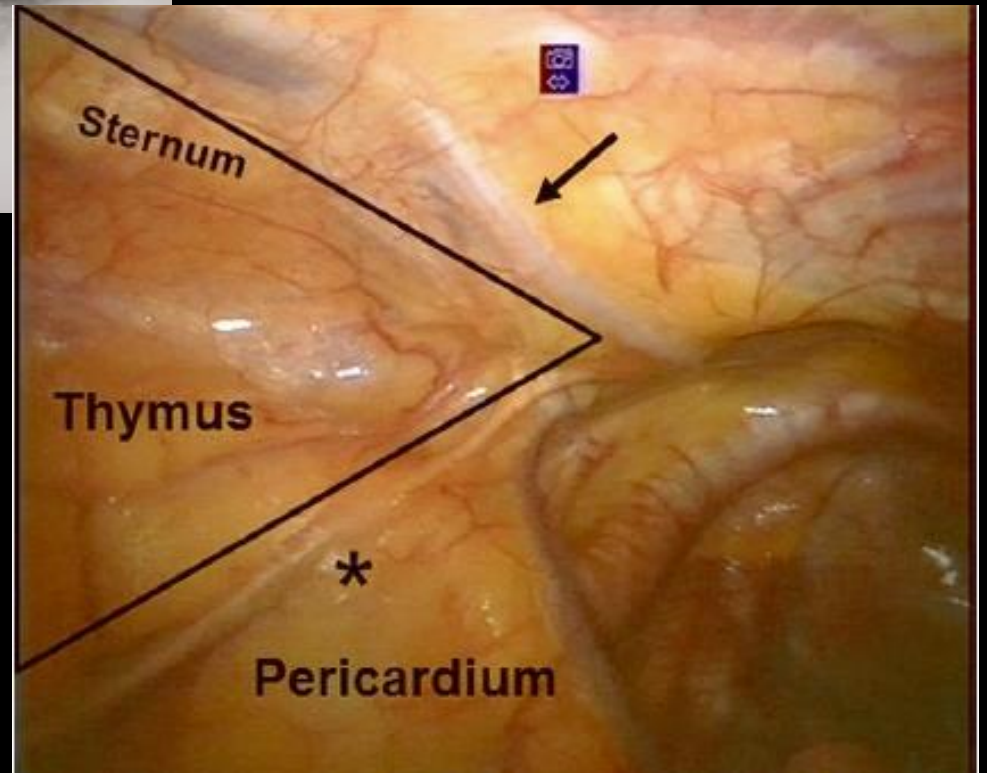


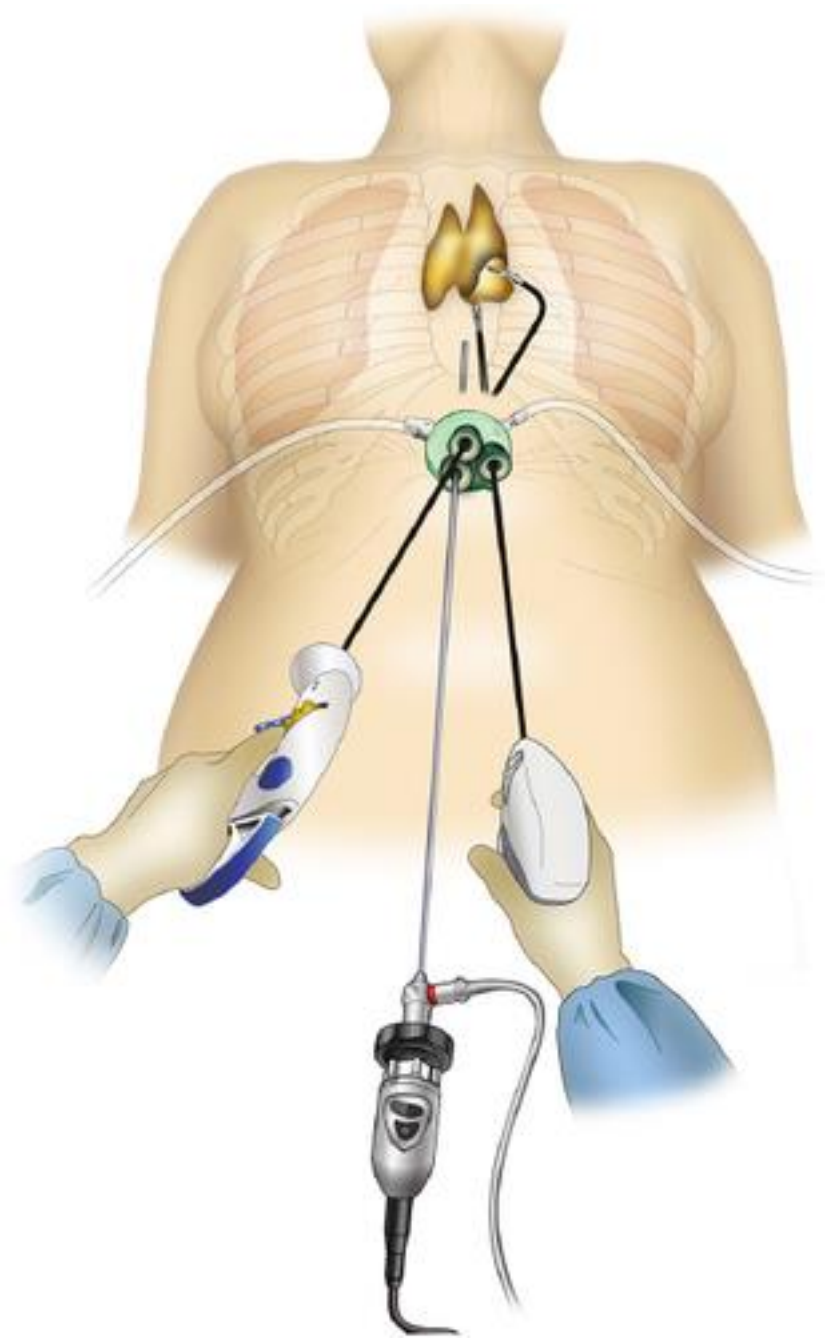




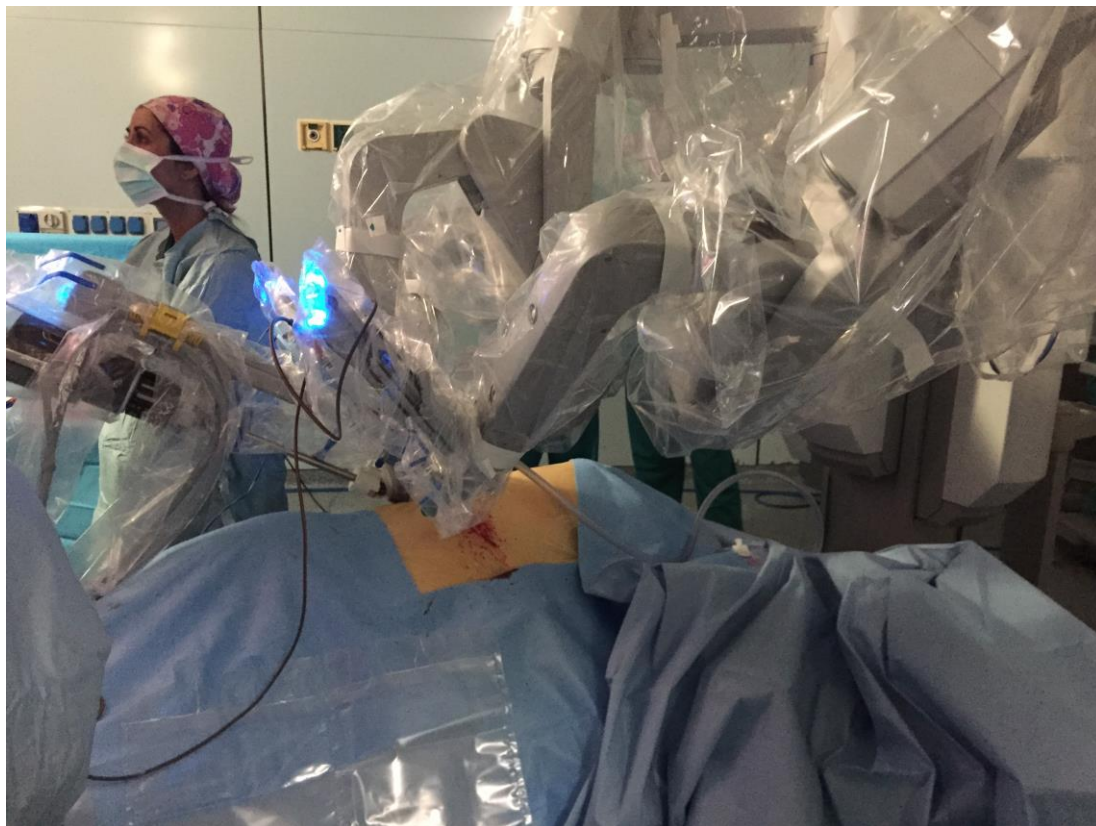
VATS thymectomy

- First described by Tony Yim
- Minimally invasive approach
- Requires single-lung ventilation as anterior mediastinum approached trans-pleurally
- Variety of approaches (left, right, subxiphoid, combination)

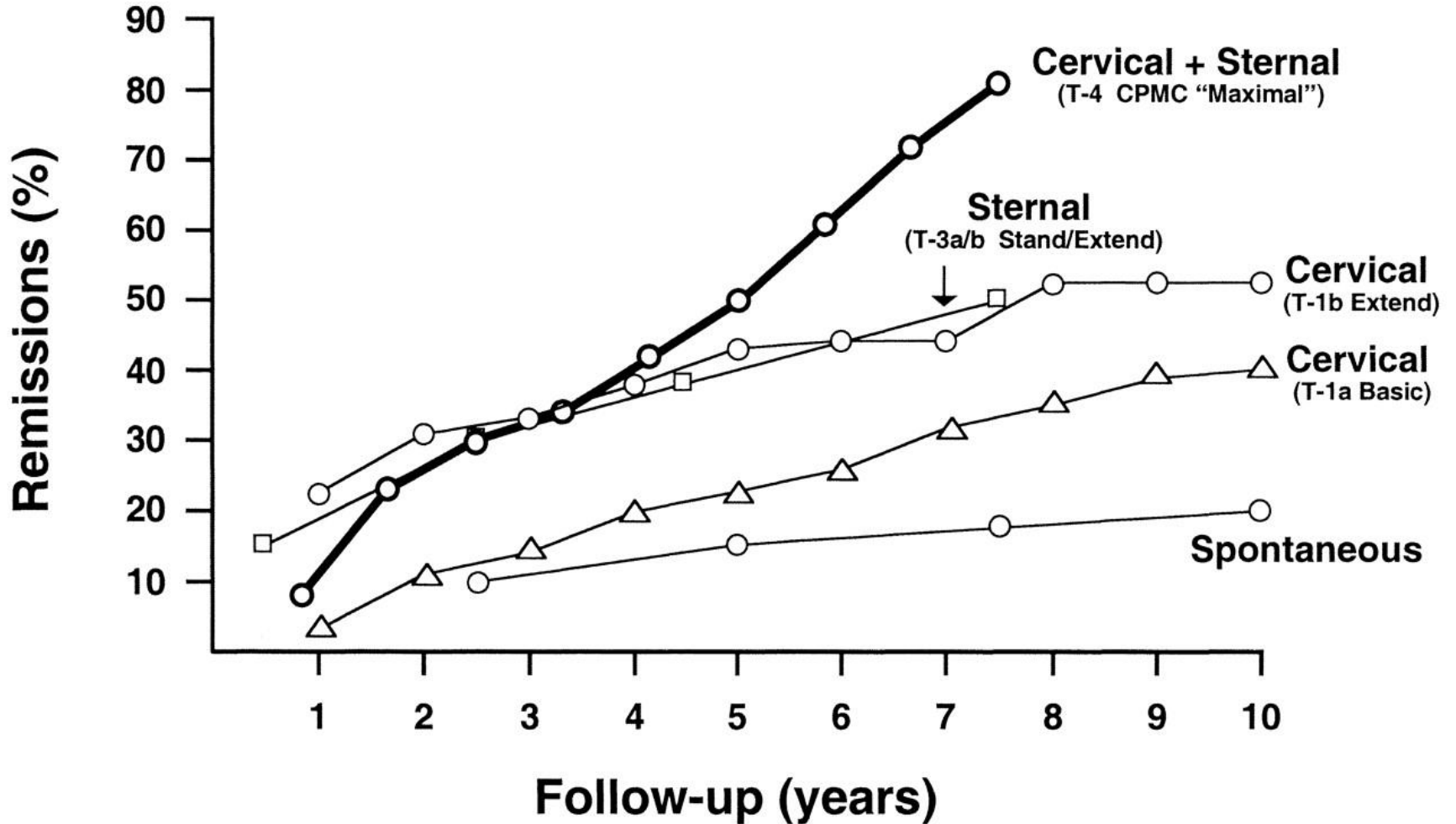




Robotic thymectomy



Results



Maximal thymectomy results

- Good
- Pain and respiratory compromise
- Length of stay around 7 days
- Mortality 1%

Trans-cervical thymectomy

- Good results
- Little pain, respiratory compromise or blood loss

Outcomes After 151 Extended Transcervical Thymectomies for Myasthenia Gravis

Joseph B. Shrager, MD, Derek Nathan, BS, Clayton J. Brinster, MD, Omair Yousuf, BS, Abraham Spence, BS, Zhen Chen, PhD, and Larry R. Kaiser, MD

Department of Surgery, Division of Thoracic Surgery, and Department of Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

- Median length of stay: 1 day
- Mortality 0%
- Morbidity 8% (inc. 1 myasthenic crisis)

Does surgery actually work?

- Many patients have only partial response
- Significant number of spontaneous remissions
- Long latent period between surgery and symptom relief

American Academy of Neurology (2000)

- “For patients with non-thymomatous autoimmune MG, **thymectomy is recommended as an *option*** to increase the probability of remission or improvement.”
- Practice parameter: thymectomy for autoimmune myasthenia gravis (an evidence-based review): report of the Quality Standards of the American Academy of Neurology. *Neurology*. 2000;55:7-15.

Practice parameter: thymectomy for autoimmune myasthenia gravis (an evidence-based review): report of the Quality Standards of the American Academy of Neurology.

Gronseth GS, Barohn RJ. *Neurology*. 2000;55:7-15.

- “We cannot determine from the available studies whether the observed association between thymectomy and improved MG outcome was a result of a thymectomy benefit or was merely a result of the multiple differences in baseline characteristics between surgical and non-surgical groups.”
- “Based on these findings, we conclude that the benefit of thymectomy in non-thymomatous MG has not been established conclusively.”

- There is no randomized controlled trial literature that allows meaningful conclusions about the efficacy of thymectomy on MG.
- Data from several class III observational studies suggest that thymectomy could be beneficial in MG.
- An RCT is needed

Myasthenia gravis: Association of British Neurologists' management guidelines

Jon Sussman,¹ Maria E Farrugia,² Paul Maddison,³ Marguerite Hill,⁴
M Isabel Leite,⁵ David Hilton-Jones⁵

- “Ocular & generalised MG: If the serum ACh-R antibody is positive and the patient is aged under 45 years, **consider thymectomy at presentation**”
- “Thymectomy may induce remission, may prevent generalisation of ocular myasthenia and may reduce corticosteroid requirements”

International consensus guidance for management of myasthenia gravis – Myasthenia Gravis Foundation of America

Sanders DB et al. *Neurology* 2016;87:1-7

- In non-thymomatous MG, thymectomy is performed:
 - to avoid or minimize the dose or duration of immunotherapy
 - if patients fail to respond to an initial trial of immunotherapy or have intolerable side-effects
- “It should be performed when the patient is stable and deemed safe to undergo a procedure where postoperative pain and mechanical factors can limit respiratory function.”

At last – a trial...

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Randomized Trial of Thymectomy in Myasthenia Gravis

G.I. Wolfe, H.J. Kaminski, I.B. Aban, G. Minisman, H.-C. Kuo, A. Marx, P. Ströbel, C. Mazia, J. Oger, J.G. Cea, J.M. Heckmann, A. Evoli, W. Nix, E. Ciafaloni, G. Antonini, R. Witoonpanich, J.O. King, S.R. Beydoun, C.H. Chalk, A.C. Barboi, A.A. Amato, A.I. Shaibani, B. Katirji, B.R.F. Lecky, C. Buckley, A. Vincent, E. Dias-Tosta, H. Yoshikawa, M. Waddington-Cruz, M.T. Pulley, M.H. Rivner, A. Kostera-Pruszczyk, R.M. Pascuzzi, C.E. Jackson, G.S. Garcia Ramos, J.J.G.M. Verschuuren, J.M. Massey, J.T. Kissel, L.C. Werneck, M. Benatar, R.J. Barohn, R. Tandan, T. Mozaffar, R. Conwit, J. Odenkirchen, J.R. Sonett, A. Jaretzki, III, J. Newsom-Davis, and G.R. Cutter, for the MGTX Study Group*

MGTX

- Funded by National Institute of Neurological Disorders and Stroke
- Prospective multi-centre single-blind RCT
- **Best medical treatment (including steroids) vs. maximal thymectomy** in non-thymomatous myasthenia gravis
- Blind evaluation of patients: prednisolone prescribed to maintain “minimal manifestation status”

MGTX

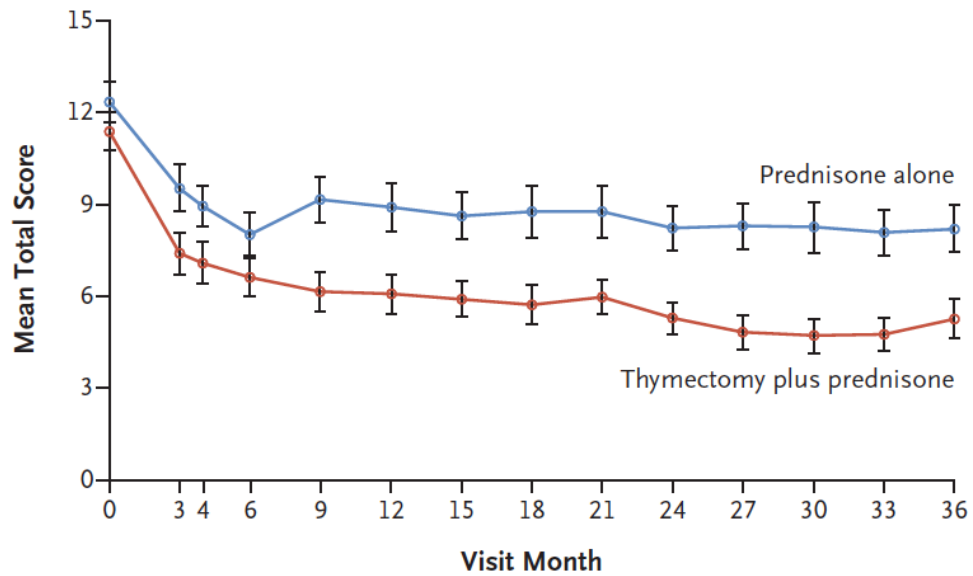
Inclusion/exclusion criteria:

- 18-65 years old
- Generalised non-thymomatous MG (MGFA class 2-4)
- ACh-R antibody positive
- Disease duration <5 years
- No immunosuppressants except prednisolone

MGTX

- Primary endpoints:
 - Muscle weakness (QMG score)
 - Time-weighted average dose of prednisolone over 3 years
- Secondary endpoints included:
 - Serious adverse events
 - Days of hospitalisation over 3 years
 - QoL
- Powered to measure 30% difference in outcomes

A Quantitative Myasthenia Gravis Score



B Prednisone Dose

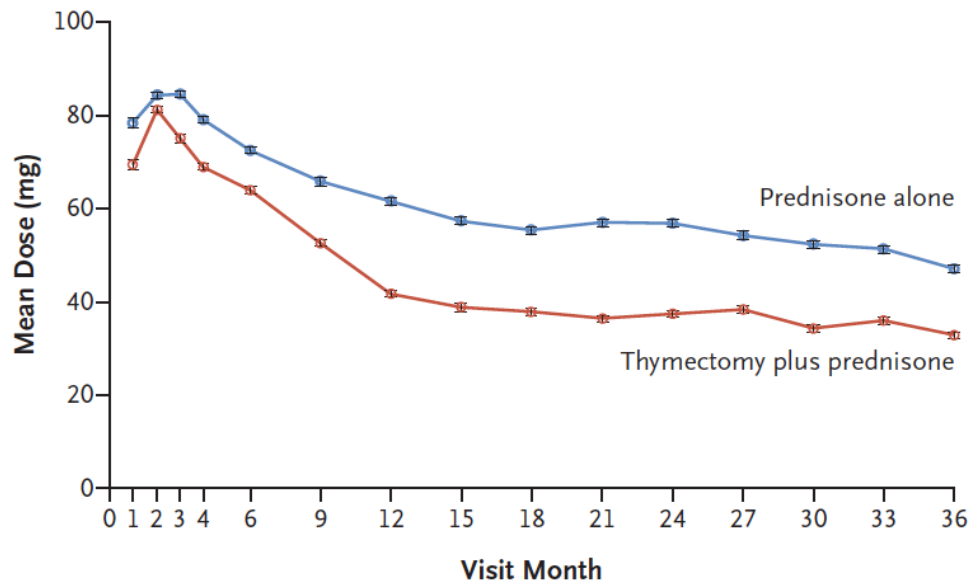


Figure 1. Quantitative Myasthenia Gravis Score and Prednisone Dose, According to Treatment Group.

Table 3. Adverse Events.*

Variable	Prednisone Alone (N = 60)	Thymectomy plus Prednisone (N = 66)	P Value
No. of events	93	48	<0.001†
≥1 event — no. of patients (%)	33 (55)	25 (38)	0.05‡
Event			
Life-threatening event — no. of patients (%)	7 (12)	1 (2)	0.03§
Disability or incapacity — no. of patients (%)¶	2 (3)	8 (12)	0.10
Event requiring medical or surgical intervention — no. of patients (%)	5 (8)	9 (14)	0.40
Death — no. of patients (%)	1 (2)	0	0.48
Complication due to thymectomy — no. of patients (%)	NA	1 (2)	—
Hospitalization — no. of patients (%)	31 (52)	15 (23)	<0.001‡
Hospitalization for exacerbation of myasthenia gravis — no. of patients (%)	22 (37)	6 (9)	<0.001‡
Cumulative no. of hospital days	19.2±24.5	8.4±8.6	0.09

MGTX – other results

- Myasthenia Gravis Activities of Daily Living scale (2.24 vs 3.41, $p=0.008$)
- Azathioprine use (17% vs 48% of participants, $p < 0.001$)
- Patients who had minimal-manifestation status at month 36 (67% vs 47% , $p=0.03$)
- No difference in QoL

MGTX –subgroup analysis

- Age at disease onset – no difference
- Sex – women had greater benefit
- Steroid use – prednisolone naïve patients had no benefit from thymectomy

Problems with MGTX

- 3 year follow-up
- Patient/neurologist/surgeon reluctance when other less invasive surgical options are available
- Withdrawal from trial if randomised to non-surgical treatment
- 126 patients randomised, >6000 screened

What about the other patients?

- Seronegative MG
- Ocular MG
- Elderly patients

What about the future?

- MGTX has demonstrated benefit of thymectomy over steroids
- How does thymectomy compare to:
 - Azathioprine
 - Mycophenolate
 - Rituximab
 - Stem-cell transplant?

Who do we want to operate on?

- Ocular or generalised MG
- ACh-R positive
- Young
- Recent diagnosis
- On steroids
- No other major comorbidities

What to tell the patient?

Left VATS thymectomy

- GA
- 3 small cuts
- 1-2 night stay, no ICU
- Few operative side effects

Outcomes often better than standard medical therapy:

- Prednisolone dose
- Symptoms
- Exacerbations/hospitalisations

