An Overview of Thymectomy Approaches among Myasthenia Graves Patients: Review Article

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ABSTRACT
Background: Myasthenia gravis (MG) is a syndrome characterized by fatigue- and activity-induced improvements in skeletal muscular weakening. There is a wide range of possible involvement, including but not limited to the muscles of the eyes, face, oropharynx, trunk, and limbs. Once the patient's level of weakness has been managed to the point that surgery is possible, thymectomy is recommended. Preoperatively, patients are typically treated with mild doses of intravenous immunoglobulins as well as glucocorticoids.
Objective: Review of the literature on thymectomy approaches among myasthenia graves' patients.
Methods: We scoured medical journals and databases including PubMed, Google Scholar, and Science Direct for information on thymectomy and myasthenia graves. Between September 2006 and August 2022, however, only the latest or most comprehensive study was considered. The authors also assessed the usefulness of references drawn from similar books. Documents written in languages other than English have been overlooked because of lack of funding to translate them. Unpublished articles, oral talks, conference abstracts, and dissertations were all generally agreed upon not to constitute valid scientific investigation.
Conclusion: It has been argued that a maximum thymectomy, in which both the transsternal and transcervical techniques are used on the same MG patient, yields superior results. After extensive transsternal thymectomy or video-assisted thoracoscopic thymectomy, half of patients with non-thymomatous MG had complete stable remissions at 6 years of follow-up.
Keywords: Thymectomy, Myasthenia graves.

INTRODUCTION

Myasthenia graves (MG) is a syndrome characterized by fatigue- and activity-induced improvements in skeletal muscular weakening. Variable involvement of ocular, facial, oropharyngeal, axial, and limb muscles is possible **[1]**.

The global population as a whole, and the MG population specifically, have both had longer life spans in recent decades. In spite of the decade-weighted mean MG prevalence of 60 per million, The prevalence of MG in the United States is estimated to be around 200 per million people, based on recent studies from a variety of European nations and the United States, with point prevalence rates ranging from 100 to 150 per million population **[2]**. In spite of the prevalence of complaints of weakness and fatigue, the diagnosis of MG is frequently missed in people whose weakness is modest or limited to a small number of muscles. It is important to verify a clinical diagnosis **[3]**.

Patients with MG should have their treatment tailored to their specific needs and disease severity. The pathogenesis of MG dictates one of two treatment modalities. Immunosuppressive drugs reduce antibody binding to cholinergic receptors, and acetylcholinesterase inhibitors increase the amount of acetylcholine available to engage with the postsynaptic receptor **[4]**. MG is treated with four primary approaches include: (i) acetylcholinesterase inhibitors for symptom relief, (ii) plasmapheresis and intravenous immunoglobulin for rapid short-term immunomodulating treatment, (iii) glucocorticoids and other immunosuppressive drugs for chronic long-term immunomodulating treatment, and (iv) surgical intervention **[1]**.

Surgical Management:
Thymectomy:

Once the patient's level of weakness has been managed to the point that surgery is possible, thymectomy is recommended. Low-dose glucocorticoids and intravenous immunoglobulin (IVIg) are common preoperative treatments for surgical patients. Because anti-MuSK antibody-positive patients' thyme lacks the germinal centres and infiltrates of lymphocytes that characterize thyme in patients who have anti-acetylcholine receptor (AchR) antibodies, thymectomy may not be a viable therapeutic option for these individuals. This provides evidence that MG with an anti-MuSK Ab but not an anti- Ab has a distinct pathogenic mechanism **[5]**.

Patients diagnosed with thymoma are highly encouraged to undergo surgical therapy. Thymectomy has been shown to be effective in some clinical settings, while its utility in others has been questioned due to insufficient evidence for its utility. Long-term thymectomy benefits become clearer as time passes **[6]**. Thymectomy is considered a treatment option for anti-AchR Ab-positive gMG in patients less than 50 years old **[7]**. Patients with AChR antibody-positive MG benefit clinically from thymectomy. Non-thymomatous and thymomatous MG patients may both benefit from minimally invasive thymectomy **[8]**.

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Surgical Management of Myasthenia Gravis:

Thymus anatomy:

The thymus gland is a two-lobed, soft, encased organ. It's located above the aortic arch and below the sternum in the anterior portion of the inferior mediastinum, not far from the pericardium. The thymus can be found beneath the sternum, far from the heart and its major arteries. Above the level of the inferior poles of the thyroid gland, it runs down to the fourth costal cartilage. The phrenic nerves run parallel to the gland on both sides (which go on to supply the diaphragm). An isthmus runs down the middle of the thymus and connects its two separate lobes (Figure 1) [9].

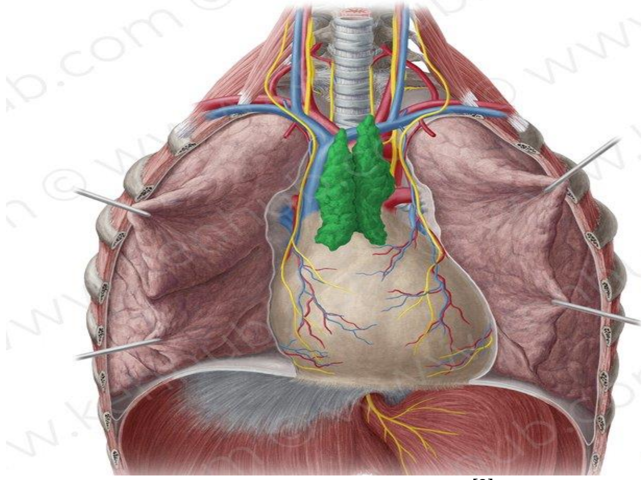

Figure (1): Thymus Gland [9].

The thymus receives blood flow from the superior thyroid artery, the inferior thyroid artery, and the internal thoracic artery. All three thyroid veins (superior, middle, and inferior) and the left innominate vein receive drainage. The interlobular septae provide a pathway for multiple thymic arteries to access the organ proper. The blood thymus barrier is composed of reticular endothelial cells, lymphocytes, and macrophages, as well as the arteries that create a series of complicated arcades in the thymic cortex. A lack of fenestrations in the endothelium and a substantial basal lamina in thymic capillaries render them protein-impermeable. After that, it goes into the medullary veins [10].

Lymphatics: There are no afferent lymphatics connecting the thymus with the rest of the body. In close proximity to the thymus gland are a number of lymph nodes, including the mediastinal-brachiocephalic. tracheobronchial-hilar, as well as internal mammary-parasternal [11].

Nerve supply: Tissue in the thymus receives its meagre neural supply from the vagus nerve and the sympathetic nervous system, both of which send postganglionic noradrenergic fibers deep into the thymus [12].

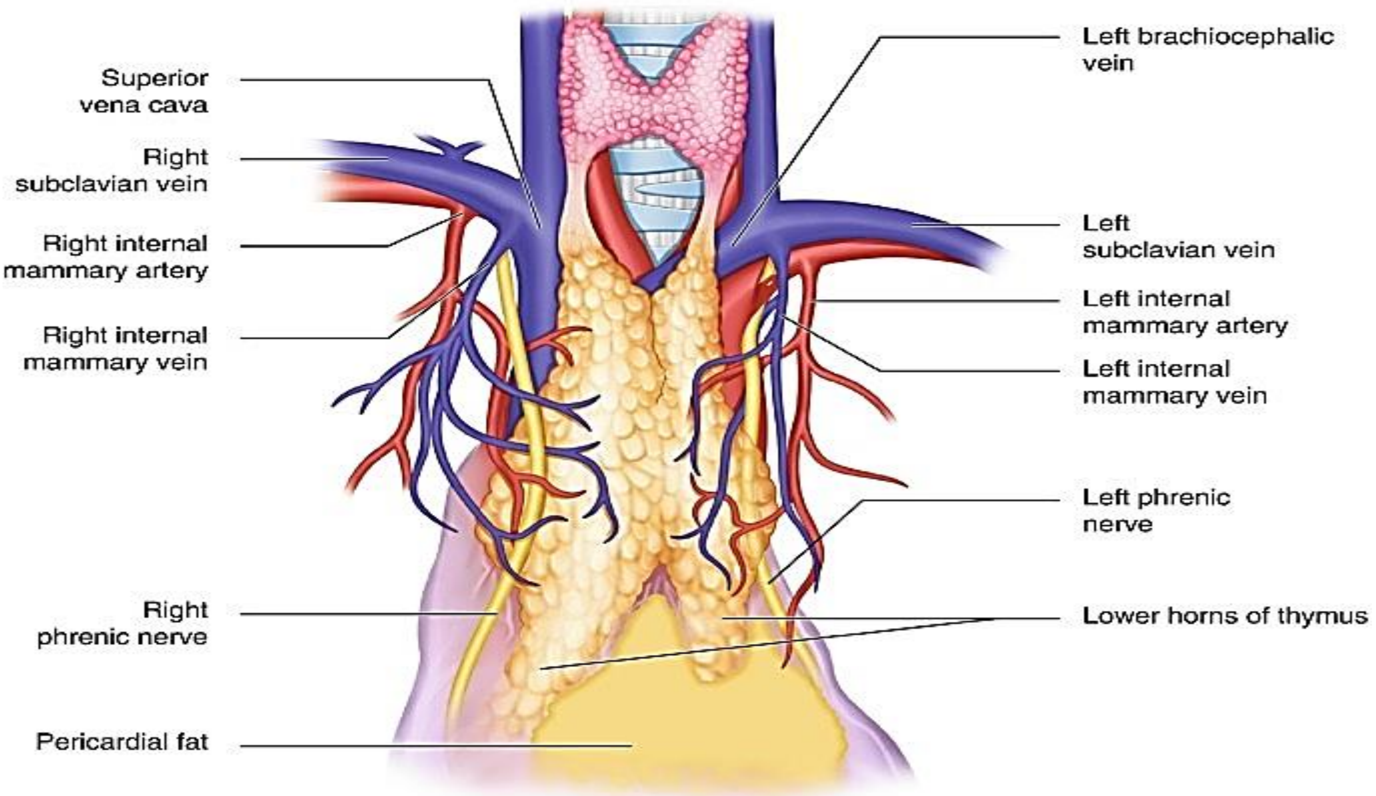

Figure (2): Blood and nerve supply of thymus gland [9].

Thymomatous Myasthenia Gravis:

The most common correlation between MG and another disease is the presence of a thymoma, an epithelial tumour of the thymus gland. Thymomas affect roughly 15% of adult MG patients and are usually harmless. Serum AChR antibodies were shown to be elevated in patients with MG who also had a thymoma. Antibodies in their serum against skeletal muscle increase cross-striational immunofluorescent staining in all of them, even up to a third of MG patients without a thymoma. Patients over the age of 50 years make up the majority of the second category, hence striational antibodies are highly predictive of a thymoma among those under 45–50 years [7].

Non-Thymomatous Myasthenia Gravis:

Thymectomy's significance in the treatment of MG is still being investigated. Cochrane issued an "empty review" in 2013 that concluded there was inadequate evidence to justify thymectomy for non-thymomatous MG and that more randomised and quasi-randomized studies were required [13].

Cataneo *et al.* [14] using data from 19 articles, performed a meta-analysis on 5841 patients (2911 surgical and 2930 non-surgical). Non-thymomatous MG was successfully treated by thymectomy, achieving a greater remission rate than with non-surgical treatment.

Thymectomy:

The variable natural history of MG, the vast range of severity across patients, and the different surgical techniques utilised to remove the thymus all contribute to the difficulty in predicting thymectomy outcomes. Through a prolonged transsternal thymectomy, the surgeon makes a cut in the chest bone to gain access to the thymus. Although some surgical groups advocate for a more invasive technique through the chest, known as a transsternal thymectomy, other groups advocate for a less invasive approach through the neck, known as an extended transcervical thymectomy, claiming equivalent results [15]. Maximal thymectomy, in which both the transsternal and transcervical techniques are used on the same MG patient, is said to have better outcomes [16].

Half of patients with non-thymomatous MG have complete stable remissions at 6-year follow-up after undergoing video-assisted thoracoscopic extended thymectomy, which is on par with the results of extended transsternal thymectomy [17].

Patients with MG who exhibited both AChR antibodies and thymic hyperplasia fared best after undergoing thymectomy [18]. However, it appears that the absence of serum antibodies does not rule out a positive response to thymectomy [19], Despite the fact that this is still up for debate.

The full effect of surgery, if any, may not be seen for several months or even years following the procedure. Those who have undergone a thymectomy report continued benefits for up to two decades after the operation [20].

Surgical Approaches:

There are a few different ways surgeons can go about performing a thymectomy on a patient with MG: transsternal, transcervical, a hybrid transsternal/transcervical technique, or a laparoscopic procedure. Help from a video or robot. Transsternal technique has been compared to medicinal care in randomised controlled trials, and open surgical procedures have been employed for quite some time. However, there has been considerable growth in the use of non-invasive methods. While the results of open techniques like transsternal and transcervical thymectomy are comparable, the minimally invasive approach has the benefits of less pain, faster recuperation, avoiding significant scars, early mobilization, and early departure from the hospital [21].

Video assisted thoracoscopic surgery (VATS):
Introduction:

Thoracoscopy was pioneered in 1910 by Professor of Medicine Hans Christian Jacobaeus. Therapeutic pneumothorax was achieved in a patient with pulmonary tuberculosis by means of lysis of pleural adhesions using a modified cystoscope [22].

When effective drugs became available to treat tuberculosis, pneumothorax therapy was phased out and thoracoscopy became less common. However, respiratory doctors in a number of European locations continued to utilise it as a diagnostic tool. Two international thoracoscopy symposiums, the first in Marseille in 1980 and the second in Berlin in 1987, sparked a renaissance in the field [23].

Because of the positive outcomes of laparoscopic cholecystectomy and other abdominal procedures in the late 1980s and early 1990s. The practice was first used by thoracic surgeons. Specialized tools for thoracoscopic procedures have been created. Video-assisted thoracoscopic surgery (VATS) is becoming increasingly common due to developments in endoscopic video systems, fiberoptic light transmission, and endoscopic surgical staplers. Pleurodesis, pleural biopsies, pulmonary wedge resections, and pleural effusion drainage were the first diagnostic procedures to employ VATS [24].

All major thoracic resections are now done by VATS due to the decreased conversion rates and better outcomes it provides as a result of improved surgical experience and technological developments in the tools used. As surgical techniques have advanced, many thoracic surgeons now routinely use VATS. Patients with myasthenia gravis who need a thymectomy now have a minimally invasive option thanks to the introduction of video-assisted thoracic surgery (VATS) in 1992. There are some debates and worries about partial resections in the literature, despite the growing popularity of VATS thymectomy [25].

VATS thymectomy approaches:

Soft tissue in the pre-vascular plane between the two phrenic nerves is excised in a radical thymectomy. Patients with myasthenia often have ectopic thymic tissue outside of the thymus. Resection and clearing of all thymic tissue is crucial for successful surgical management of myasthenia and long-term survival in individuals with thymomas. Both unilateral and bilateral VATS methods exist (either left or right). Whether the thymus should be approached from the left, the right, or both sides is a contentious topic of discussion. Since the superior vena cava is located outside of the operating field, it was recommended that dissection operations are safer when performed from the left side. According to the authors, it is easier to access the peri-thymic fatty tissue around the left peri-cardiophrenic angle if you start on the left [26].

Surgeons favouring the right-sided technique, on the other hand, argue that the superior vena cava is more easily identifiable when viewed from the right, making it easier to dissect around the innominate veins. Also, in patients with cardiomegaly, starting at the inferior pole is more convenient for right-handed surgeons since the right pleural cavity is larger and more forgiving of instrument misalignment [27].

Surgeons who favour the bilateral VATS method state that it improves visibility of critical anatomical components, which in turn allows for more thorough removal. Surgeons' personal preferences, which are informed by their background and training, continue to have a significant impact on the decision of which side to approach from. Case series evidence in general supports the validity and efficacy of all approaches, but large prospective studies are needed to determine whether VATS thymectomy approach is preferable [28].

All thymic tissue, including ectopic thymic tissue, which may be disseminated throughout the anterior mediastinum and cervical fat, can be removed using video-assisted thoracic surgery (VATS), which is beneficial for the patient since it causes less trauma [28].

Advantages:

VATS is now the gold standard in surgical imaging thanks to the development of high-definition cameras with the ability to tilt and pan to catch every detail. The advent of 3D operative imaging has also altered VATS's appearance. Minimizing access stress and removing all thymic tissue that may have extended over the anterior mediastinum and cervical fat, VATS thymectomy is an excellent and radical procedure [29].

There is less need for blood products, less of an inflammatory cytokine response, less time spent in the hospital, and a better cosmetic outcome when using VATS. Compared to the open (sternotomy) method, this one has a lower risk of respiratory and cardiac problems. In addition, there has been no discernible difference in long-term complications or survival rate between VATS and open methods. The trend toward widespread use of VATS by surgeons suggests that support for this minimally invasive technique is warranted [24].

Disadvantages:

Disease recurred with pleural spread in 3 (6.7%) of Kimura's VATS approach cases. All three patients had tumours larger than 5 cm, and of those three, two had capsular damage after VATS excision. The two studies looked back at data from the past and used the same group of people for analysis rather than randomly selecting new participants. When looking at thymectomy complication and recurrence rates, however, sternotomy does not seem to offer any advantages over VATS [30].

Trans-sternal thymectomy:

The trans-sternal technique has been the standard for performing thymectomy for thymomas. Infections of the deep sternal wound are rare (0.4% to 5%), but when they do occur, they can cause serious complications that can shorten lives and even prove fatal. This occurs more frequently in people who are elderly, overweight, diabetic, smokers, those with chronic obstructive pulmonary disease (COPD), and those on steroids. Steroid use is common among those with myasthenia gravis, which increases the likelihood of infection and dehiscence in sternal wounds. A sternotomy increases the likelihood of postoperative discomfort and respiratory complications, which can require specialized postoperative care, lengthen hospital stays, and postpone the patient's return to normalcy and return to work. The heart must be constantly monitored and controlled because sympathetic activation from a sternotomy might produce arrhythmias and hemodynamic instability. Other major risks associated with sternotomy include harm to the brachial plexus due to retraction of the sternum, pseudoarthrosis, persistent neuropathic pain, and the creation of keloid scar tissue or hypertrophy, both of which can have an impact on the patient's appearance. Major morbidity, patient anguish, and prolonged recovery are all possible outcomes of the aforementioned problems [24].

Trans-sternal thymectomy vs. video assisted thoracoscopic surgery outcomes.

Despite some doubts, video-assisted thoracoscopic surgery (VATS) is replacing the more invasive sternotomy method, and it is becoming the standard. Smaller incision improves cosmesis, faster healing, shorter post-operative stay, lower cytokines, complete remission, and no difference in outcome. Adjuvant chemoradiation can be given to more advanced instances sooner due to reduced trauma and quicker recovery times. The open (median sternotomy) method is thought to provide superior visualisation, but it is more invasive and has a higher risk of morbidity. Less tissue is removed during the trans-cervical technique since it only requires a thin horizontal incision across the back of the patient's neck. In a systematic analysis of the long-term clinical result following trans-cervical thymectomy supports a shorter recovery time [26].

The review's scant follow-up data hampered meaningful conclusions. Access to uncommon thymic extensions behind the left brachiocephalic vein and limited neck extension in the elderly are two technical difficulties with the transcervical approach. There's no denying the benefits of this unique method, but it could be challenging to perfect [24].

In contrast, VATS allows for better exposure and lighting of the operation field because to the availability of modern cameras with changeable angles. While early VATS procedures relied on two-dimensional (2D) images, the introduction of 3D-operating imaging has helped to eliminate this limitation [31].

Surgery with VATS may take longer at the beginning of a surgeon's "learning curve," but it speeds up as the surgeon gains experience. Mortality rates after thymectomy performed with VATS and sternotomy are comparable, and there is no evidence to suggest that the two surgical approaches have different mid- to long-term complication or survival rates. Although open surgery has long-term benefits, the VATS method has clear advantages in the short-term aftermath of the procedure. Less intra-operative blood loss, earlier removal of chest drains, and a reduced need for blood products are all characteristics that make VATS the preferred method [32].

In comparison to the open (sternotomy) method, the risk of respiratory and cardiac problems (such as pneumonia, pleural effusion, or arrhythmias) is lower with the VATS approach. These difficulties necessitate individualized care, which in turn causes recuperation delays and extended hospital stays [15].

The patient and the medical facility both gain from the shorter recovery time that follows a VATS procedure. Faster recovery time is good for the patient, and shorter hospital stays are good for business since they allow more people to be helped. With the current state of the economy, a sternotomy is a costly procedure that can be avoided with the VATS method. While the setup costs for VATS may seem high at first, it has quickly become indispensable in the operating room. Due to shorter recovery times, fewer post-operative problems, and faster patient turnover, VATS ultimately saves money in the long run. As a result of its impact on the immune system, VATS has demonstrated promise as a leading oncological technique. Inflammatory cytokines such as interleukin (IL)-1, IL-6, and tumour necrosis factor-alpha (TNF-alpha) are known to surge in the bloodstream after a traumatic operation. Studies have shown decreased immune-chemokine disturbance with VATS procedures, but no studies have studied systemic inflammatory response [33].

Surgical tissue damage triggers a complicated cascade of inflammatory signals and the activation of a wide variety of cells, including epithelial cells, endothelial cells, inflammatory cells, platelets, and fibroblasts. Wound-healing proteins, such as growth factors, chemokines, and cytokines, have recently been shown to promote both local and distant tumor progression. Some evidence suggests that operating on cancer patients may increase their risk of developing metastases. Minimally invasive thoracic surgery has been associated with reduced postoperative levels of C-reactive protein, IL-6, and IL-8 compared to traditional open thoracic surgery. These features, taken together, promote rapid healing and recovery and pave the way for early post-operative multi-modality management [34].

CONCLUSION

It has been argued that a maximum thymectomy, in which both transsternal and transcervical methods are used on the same MG patient, yields superior results. Half of patients with non-thymomatous MG showed complete stable remissions at 6-year follow-up after undergoing video-assisted thoracoscopic extended thymectomy, with results comparable to those of extended transsternal thymectomy.

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