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Robotic thymectomy for myasthenia gravis with or without thymoma—surgical and neurological outcomes

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Abstract:

Context (Background): We report our experience with robotic thymectomy in patients with myasthenia gravis (MG)and provide data on the surgical results and neurologic outcomes, as per the Myasthenia Gravis Foundation of America (MGFA) recommendations for MG clinical research standards.

Objective: The study aims at reporting the surgical and neurological outcomes of patients of Myasthenia gravis treated by robotic thymectomy.

Materials and Methods: Prospective data was collected from 71 patients with myasthenia gravis (in the age range 15-67 years) with or without thymoma, who had completed a minimum follow up of one year. All patients were treated with robotic radical thymectomy. The clinical classification, status of preoperative and postoperative therapy, evaluation of post-interventional clinical status, and descriptions of morbidity/mortality were done as per the MGFA recommendations. Univariate and multivariate analysis was done to assess the factors associated with achievement of complete stable remission(CSR).

Results: A total of 71 patients were included in this study. Twenty-one out of 71 patients (29.6%) with myasthenia gravis had thymoma. At the last follow up, 70 patients were alive. No evidence of tumour recurrence was found in patients with thymoma. The overall CSR rate was 38% with the median time to CSR of 17.5 months (range 11-48 months). The CSR rate for patient of MG with thymoma was 19 % (*n*=4/21). Factor found to be significantly predicting CSR were young age, lesser severity of MG and non-thymomatous histology.

Conclusions: Robotic thymectomy is a technically feasible and safe operation with a low morbidity and short hospitalization. It is associated with good neurological long-term results in terms of both CSR and clinical improvement.

Key Words:

Myasthenia gravis, outcome, robotic thymectomy, surgery, thymoma

Key Message:

Robotic thymectomy for myasthenia gravis is technically safe, cosmetic and provides good neurologic long-term results.

Thymectomy is a radical but effective treatment for generalized myasthenia gravis (MG).[1,2] One of the strongest evidences of its efficacy comes from a computer-matched series, which has shown a reduction in myasthenia-related mortality from 44% to 14% and an increase in the remission rate from 8% to 35%.[3]

There is an ongoing debate regarding the best surgical approach. A variety of approaches ranging from open (transsternal) to minimally invasive approaches, including the transcervical, video-assisted thoracoscopic thymectomy. and robot-assisted thymectomy, have been described. Each approach has its own benefits and drawbacks. The present literature comprises mainly nonrandomized retrospective case series for comparing the operative approaches. The heterogeneity of data and different methods applied for evaluating the results, along with many other confounding factors, have made a comparative analysis complicated, if not impossible.[4] All these factors are responsible for the difficulties that arise in achieving a consensus in treatment protocols.

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How to cite this article: Kumar A, Goyal V, Asaf BB, Trikha A, Sood J, Vijay CL. Robotic thymectomy for myasthenia gravis with or without thymoma–surgical and neurological outcomes. Neurol India 2017;65:58-63.

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Robotic thymectomy has been proposed as a valid alternative to open approaches. Robotic instruments with human wrist-like function enable the surgeons to perform the dissection with ease and safety as seen in open surgery but without the need for a sternotomy. We report our experience with robotic thymectomy in 71 consecutive patients with MG and provide data on the surgical results and neurological outcomes, as per the Myasthenia Gravis Foundation of America (MGFA) recommendations for MG clinical research standards.[5]

Materials and Methods

Between 2008 and 2014, a total of 124 robotic thymectomies were performed for various indications including MG with or without thymoma, thymoma without MG, and multiple endocrine neoplasia type I with thymic nodules. Prospective data was collected from 71 patients with myasthenia gravis (15–67 years) with or without thymoma, who had completed a minimum follow-up of 1 year. All patients were treated with robotic radical thymectomy. All the patients were diagnosed with myasthenia gravis on the basis of clinical features, repetitive nerve stimulation test, edrophonium chloride test, and acetylcholinesterase antibody (AbAchR) level. Patients with negative AbAchR results were also evaluated for anti- muscle-specific kinase (MuSK) antibodies and were excluded from surgery when these were found to be positive. Patients with radiologic evidence of an invasive thymoma and an inability to achieve single lung ventilation were also excluded. All the patients were evaluated for their ability to attain adequate control of their clinical manifestations with drugs, and in particular, for the absence of bulbar symptoms. Patients needing steroids were taken up for surgery when their daily dose requirement was reduced to at least 20 mg of prednisolone per day. The clinical classification, preoperative, and postoperative therapy status, post-intervention clinical status evaluation, and morbidity/mortality descriptions were done as per the MGFA recommendations for clinical research standards classification.[5]

Patients were defined as having complete stable remission (CSR—patients without symptoms or signs of MG for at least 1 year and no therapy); pharmacologic remission (PR—same as CSR except that the patient continued to take some form of medication, excluding cholinesterase inhibitors); and, minimal manifestations (MM—no symptoms or functional limitations but some weakness detectable by careful examination). The change in status was recorded as (improved = I, unchanged = U, worsened = W, exacerbation occurred = E, and died of MG = D). A minimum of 12-months follow-up was done to calculate CSR and PR. The hospital stay, type, and severity of MG, and any untoward intraoperative and postoperative events (e.g., conversion, complications, and operative time) were recorded.

Technique

The procedure was performed under general anesthesia. All procedures were performed using the da Vinci S Robotic System and later with the da Vinci Si System (Intuitive Surgical, Sunnyvale, California, USA). The patient was placed in a supine position at the left edge of the operating table with the left chest elevated by 30° [Figure 1]. We preferred the left-sided approach because it provided excellent exposure of the left phrenic nerve and because of the fact that a larger part of the thymus gland is located on the left side.[6] We used a three-port technique for the majority of our cases [Figure 2]. The entire thymus gland along with all anterior mediastinal and pericardial fat between the two phrenic nerves and from bilateral thyrothymic ligaments to bilateral pericardiophrenic recesses was resected *en bloc* in all patients. The specimen was placed in an endobag and removed through the 12-mm camera port site. The ports were closed with a single 24 Fr chest tube inserted through one of the ports.

Histologic types of the thymus were described as a normal, hyperplastic or involuted gland, and a thymoma. Outcome assessment was done using the MGFA recommendation for patients followed up for at least 12 months.

Statistical analysis

This paper investigates the univariate analysis using the generalised likelihood ratio (GLR) and multivariate analysis using the Cox regression model to potentially evaluate the CSR and improvement.

Results

A total of 71 patients were included in this study, including 34 male patients (48%) and 37 female patients (52%), with a mean age of 37.12 ± 15.69 years (range 23–50 years). The mean duration of symptoms before surgery was 25.18 ± 22.12 months (range of 2–96 months); all patients were AbAchR-positive except 1 (also anti-MUSK antibody negative). As per the MGFA classification, our group included 4 patients in class I, 28 patients in class IIa, 8 patients in class IIb, 19 patients in class IIIa, 6 patients in class IIIb, 1 patient in class IVa, 5 patients in class IVb, and 1 patient in Class V.

Twenty-one out of 71 patients (29.6%) with MG had thymoma (confirmed on histology). Majority of the patients (81%)

Figure 1: Position for robotic thymectomy from the left side

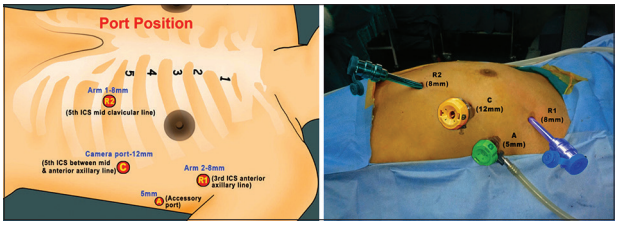

Figure 2: Port position for robotic thymectomy

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required multiple drugs (acetylcholinesterase inhibitors, steroids, and immunosupressants) preoperatively. In patients without a thymoma, all patients were connected directly to the robotic arm and the procedures were completed robotically with no conversion to a median sternotomy or thoracotomy. There were no deaths or intraoperative complications. In the patients with a thymoma, at first, a diagnostic thoracoscopy was performed and 3 patients were converted electively to an open procedure based on the findings of an invasive thymoma before robot docking. These patients were not included in the study. None of the robotic thymectomy procedures were converted to an open one. All patients were extubated in the operating room within 1 hour after surgery. The median operative time was 140 min (range, 120–210 min) in patients without a thymoma and approximately 30% longer (180 min) in patients with a thymoma. The median time to chest tube removal was 1 day and the median hospitalization time was 3 days (2–23 days) in patients without a thymoma and 7 days (3–30 days) in those with a thymoma. Postoperative complications occurred in two patients (3%) without a thymoma; one patient had a myasthenic crisis on postoperative day 2 (requiring mechanical ventilator support for 48 h) and another patient developed brachial plexus neuroapraxia possibly due to positioning, which completely recovered in 3 weeks time with conservative management. His brachial plexus MRI scan revealed the preservation of anatomical continuity that was suggestive of neuroapraxia.

In the patients of MG with thymoma, there were 3 complications. Two patients had a myasthenic crisis requiring mechanical ventilation and prolonged intensive care unit stay (7 and 30 days). One patient had hoarseness of voice, which resolved spontaneously in 6 weeks, and indirect laryngoscopy showed a normal vocal cord function.

Histology of the 71 cases revealed 37 thymic hyperplasias, 21 thymomas, 7 involuted thymic tissues, and 6 normal thymuses. In patients with a thymoma, histopathological analysis revealed 24% thymoma type A (5/21), 19% type AB (4/21), 10% type B1 (2/21), 24% type B2 (5/21), and 19 type B3 (4/21). No recurrence was reported in patients with a thymoma over a median follow-up of 33 months.

All patients were neurologically evaluated at 12, 24, 36, and 48 months. At the last follow-up (March 2013), 70 patients were alive. One patient had died 48 months after surgery (having a thymoma type B2) because of myasthenic crisis requiring prolonged mechanical ventilation leading to severe lower respiratory tract infection. No evidence of tumor recurrence was found in patients with thymoma. The overall CSR rate was 38% (27/71) with the median time to CSR being 17.5 months (11–48 months).

The CSR rate for patients of MG with a thymoma was 19% (4/21). The PR/MM status was seen in 39% (28/71) patients. Overall, 77% (55) patients showed improvement in their status and benefited from the robotic thymectomy.

In this study, more patients below the age of 36.5 years (19/27) achieved CSR than those above the age of 36.5 years (8/27). The difference was statistically significant both on uni- and multivariate analysis. Patients with less severe disease (MGFA class I and II) achieved CSR with a higher frequency as compared to those with more severe disease (class III and IV); however, this difference was not significant ($P = 0.051$) on univariate analysis. However, on multivariate analysis, significance was noted ($P = 0.029$). Moreover, relatively higher CSR rates were noted in patients of MG without thymoma compared with those who had thymoma; the difference was significant only on univariate analysis [Tables 1 and 2].

Discussion

There is significant controversy regarding the best surgical approach, the optimal extent of resection and the selection criteria for patients with MG. Various techniques ranging from open surgery (by sternotomy) to minimally invasive procedures (including transcervical, thoracoscopic, and robotic procedures) have been described. Most reports suggest similar results.[7-17] These reports suffer from a lack of uniform reporting with respect to the severity of MG, extent of resection, response to thymectomy, specimen histology, and follow-up duration, as well as in the application of nonstandard statistical methods.[1]

Minimally invasive techniques (i.e., thoracoscopic and robotic) have become increasingly popular when compared with the conventional transsternal techniques because of their lower morbidity and mortality, shorter hospital stay, better cosmetic results, minimal trauma during the gaining of surgical access, and reduced postoperative pain, which translates into better pulmonary function.[10,11,13,14,18]

Rückert *et al.*,[12] retrospectively compared the results of nonrobotic thoracoscopic procedures and robotic thymectomy in patients with MG. A significantly increased rate of CSR (39.2 vs. 20.3%; $P = 0.01$) was observed in the robotic group, which presumably could be related to the more radical resection. Most experiences in robotic thymectomy have reported a low conversion (<5%) and morbidity (<10%) rate and a short hospital stay (<4 days).[13-17] Our findings are in agreement with these results because we had no open conversion, a 7% incidence of complications, no permanent nervous or major vascular injuries, and a median hospital stay of 3 days. Our clinical long-term results are in line with the recent studies adopting the MGFA recommendations and reporting CSR rates ranging from 28[18] to 42.8%[11] for the conventional thoracoscopic thymectomy, and from 27[17] to 57%[19] for the robotic thymectomy. Likewise, a wide range of CSR rates have been reported for the open transsternal and transcervical approaches (17–34%).[10,20,21] This variability may depend on several factors such as different follow-up durations (18–45 months) and heterogeneous patient characteristics (thymomatous and nonthymomatous, ocular and generalized MG with different classes of severity, variable length of preoperative symptoms). The clinical evaluations were usually not performed by a single neurology team, and lack of standardized practices among neurologists with regard to the prescriptions and management strategy for weaning off drugs after the thymectomy existed. Our series suffered from similar limitations because we had a heterogeneous population of patients with both ocular and generalized MG as well as nonthymomatous and thymomatous (29.6%) MG.

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Our series also had a relatively higher proportion of patients with a thymoma. This reflects a referral bias because more patients with a thymoma are referred to tertiary centres. In general, it is accepted that thymectomy should be advised in young patients with generalized MG. However, for patients with purely ocular symptoms, seronegative disease and late-onset disease, the role of a thymectomy is still at the best, uncertain. Between 30 and 70% of patients with initial ocular symptoms will eventually develop generalized myasthenia. Gronseth and Barohn,[22] therefore, have advocated surgery even for patients with purely ocular MG. Patients with ocular myasthenia operated in this series were few and were seen at the beginning of our experience only.

Table 1: Comparison of various factors as predictors for CSR

	CSR rate (%)	*P**	*P***
Preoperative MGFA		0.051	0.029**
Class I-II (*n*=39)	48.72		
Class III-IV (*n*=31)	25.81		
Gender		0.352	0.468
Male (*n*=34)	43.24		
Female (*n*=37)	32.35		
Histology		0.031*	0.154
Benign thymus (*n*=53)	45.28		
Thymoma (*n*=18)	16.67		
Age		0.005*	0.027**
36.5 years or less (*n*=39)	48.72		
36.5 years or above (*n*=32)	25		
Preoperative duration of symptoms		0.935	0.675
12 months or less (*n*=39)	38.46		
12 months above (*n*=32)	37.50		

*Unadjusted *P* values performed by log-rank test. **Adjusted *P* values performed by Cox multivariate regression

In our study, a statistically significant correlation was found between MGFA class I–II and achievement of CSR, thereby suggesting that patients with less severe disease may be more likely to achieve CSR after a thymectomy. Similar results were reported by Rea *et al*.,[7] and Jaretzki[4] in their study wherein significantly higher rates of CSR and improvement for patients with ocular and mildly severe MG were reported. In contrast, the American Academy of Neurology review reported better clinical improvement after a thymectomy in cases with more severe MG.[22]

Our series also had better outcomes in younger patients similar to a couple of other studies.[11,23] However, no significant difference in the achievement of CSR was noted based on the preoperative duration of symptoms. A few of the other prominent studies reporting factors associated with better remission rates have been listed in Table 2.

Keijzers *et al*.,[31] with a median follow-up of 33 months (range 12–104 months), reported a 77% clinical improvement in patients who underwent a robotic thymectomy for MG. Ismail *et al*.,[32] described the largest series, containing 317 thymectomies between 2003 and 2012 and reported a cumulative complete stable remission rate of 57% after robotic thymectomy for MG with no recurrences in patients with a thymoma.

The da Vinci robotic surgical system offers greater freedom of movement and intuitive dexterity than the conventional

Table 2: Prognostic factors associated with better remission rates after a thymectomy as reported by various studies

Authors/year	*n*	Surgical approach	Factors associated with better remission and improvement rates
Huang CS, 2005[24]	168	Transsternal	Univariate: Age <35 years old; Symptom duration before operation <24 months; Absence of preoperative steroid treatment Multivariate Cox regression analysis: Age <35 years; Symptom duration before operation <24 months
Park IK, 2006[26]	147	Transsternal	Early onset
Tomulescu V, 2006[11]	107	Thoracoscopic Thymectomy	An earlier onset age and early operation
Aghajanzadeh M *et al*., 2007[26]	70	Transsternal	Less than 1 year duration of disease; mild disease (Osserman stages I, IIa, and IIb); Female sex; Younger patient
Takanami I, 2009[27]	54	Transsternal	Duration of illness before operation was equal to or less than 24 months Patients in the advanced Myasthenia Gravis Foundation of America (MGFA) stage
Pompeo E, 2009[23]	32	Thoracoscopic Thymectomy	Shorter duration of symptoms (<12 months) and absence of oropharyngeal involvement
Prokakis C, 2009[28]	78	Transsternal	Absence of steroids in the preoperative medical treatment and World Health Organization (WHO) histologic classification
Lin MW *et al*., 2010[29]	60	Transsternal + thoracoscopic thymectomy	Age <40, hyperthyroidism, presence of thymic hyperplasia
Keating CP, 2011[18]	78	Thoracoscopic thymectomy	No prognostic factors for remission could be found
Liu CW, 2013[30]	187	Transsternal + thoracoscopic thymectomy	Two good prognostic factors were identified; preoperative prescription of anticholinesterase alone (*P*=0.035) and non-thymomatous MG (*P*=0.003)
Marulli G, 2013[7]	100	Robotic thymectomy	Preoperative MGFA class I to II AbAchR-positive patients
Keijzers *et al*., 2014[31]	125	Robotic thymectomy	Absence of prednisolone therapy preoperatively

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thoracoscopic instruments and has a superior stereoscopic three-dimensional vision, and therefore, allows for improved manoeuvrability, making dissection along vascular (innominate vein) and neural (phrenic nerve) structures safer and more precise. This translates into minimal morbidity, a shorter hospital stay, quicker return to work, and excellent cosmetic outcomes. In our experience of over 150 robotic thymectomies for various indications, the surgical robot has helped us in performing a more radical thymectomy when compared with the conventional thoracoscopic techniques by enhancing the dissection, particularly for difficult-to-access areas.

The only disadvantage that we can perceive at this moment, taking into consideration the available experience in the literature, is the higher cost involved in robotic-assisted procedures when compared with the thoracoscopic thymectomy. The need of the hour is to promote research and develop ways to reduce the cost, rather than to use the high cost as a reason to criticize the new technology.

Conclusion

This study presents a long-term follow up of 71 patients who underwent a robotic thymectomy for MG. It demonstrates that robotic thymectomy is a technically feasible and safe procedure. Good neurologic long-term results were noted for both CSR and clinical improvement in 77% of patients with MG. This state-of-the-art surgical method has minimal morbidity, a very short hospital stay, a quicker return to work, and excellent cosmetic outcomes in comparison to the conventional transsternal techniques, which are still practiced across the country. These results suggest that robotic thymectomy for MG should be more acceptable to patients as well as clinicians and should prompt an early referral for the procedure.

Acknowledgement
The authors recognize the role of Miss Neha Bhatnagar in carrying out statistical analysis of the data.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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