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Outcomes after robotic thymectomy in nonthymomatous versus thymomatous patients with acetylcholine-receptor-antibody-associated myasthenia gravis

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ABSTRACT

The aim of this study was to investigate the surgical and long-term neurological outcomes of patients with acetylcholine-receptor-antibody-associated myasthenia gravis (AChR-MG) who underwent robotic thymectomy (RATS). We retrospectively analyzed the clinical-pathological data of all patients with AChR-MG who underwent RATS using the DaVinci® Robotic System at the MUMC+ between April 2004 and December 2018. Follow-up data were collected from 60 referring Dutch hospitals. In total, 230 myasthenic patients including 76 patients with a thymoma (33.0%) were enrolled in this study. Mean follow-up time, procedure time and hospitalization were, respectively 65.7 ± 43.1 months, 111±52.5 min and 3.3 ± 2.2 days. Thymomatous patients had significantly more frequently and more severe complications than nonthymomatous patients (18.4% vs. 3.9%, $p<0.001$). Follow up data was available in 71.7% of the included patients. The Myasthenia Gravis Foundation of America postintervention score showed any kind of improvement of MG-symptoms after RATS in 82.4% of the patients. Complete stable remission (CSR) or pharmacological remission (PR) of MG was observed in 8.4% and 39.4% of the patients, respectively. Mean time till CSR/PR remission after thymectomy was 26.2 ± 29.2 months. No statistical difference was found in remission or improvement in MGFA scale between thymomatous and nonthymomatous patients. RATS is safe and feasible in patients with MG. The majority of the patients (82.4%) improved after thymectomy. CSR and PR were observed in 8.4% and 39.4% of the patients, respectively, with a mean of 26.2 months after thymectomy. Thymomatous patients had more frequently and more severe complications compared to nonthymomatous patients.

1. Introduction

Myasthenia Gravis (MG) is a rare autoimmune disorder of the neuromuscular junction. Depending on the geographic location, the prevalence of MG ranges between 2.2 to 36.7 per 100.000 persons [1]. MG is characterized by muscle weakness and fatigability.

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Serum antibodies against the acetylcholine receptor (anti-AChR-ab) are present in 90% of patients with generalized MG and in 50% of patients with ocular MG [2]. Although the exact primary cause of MG has not yet been discovered, previous research showed the beneficial effect of immunosuppressive drugs and thymectomy on clinical symptoms [3,4]. MG is found in 20–25% of the patients with a thymoma and, vice versa, thymomas occur in 10–20% of myasthenic patients [5]. A thymectomy for nonthymomatous patients with MG is increasingly performed, especially after the randomized control trial (MGTX-trial) of Wolfe et al. was published in 2016 [3]. Regardless of the surgical technique, an extended thymectomy is necessary for the removal of all the thymic tissue to favourable influence MG symptoms [6,7]. Previous studies showed beneficial surgical outcomes of minimal invasive approaches, such as robotic-assisted thoracoscopic surgery (RATS) and video-assisted thoracoscopic surgery (VATS), compared to more invasive techniques [8–11]. Since 2004, RATS is the standard approach of the Maastricht University Medical Center+ (MUMC+). The aim of this study is to investigate the surgical-, and long-term neurological outcomes of all patients with MG who underwent RATS at the MUMC+ between 2004 and 2018. Furthermore, we aimed to investigate if nonthymomatous MG patients have better outcomes after robotic thymectomy compared with thymomatous MG patients.

2. Materials and methods

2.1. Study population

All patients with AChR-associated MG who underwent robotic thymectomy between April 2004 and December 2018 were retrospectively included. The patients were referred to the MUMC+ from eight academic- and 52 non-academic Dutch hospitals. This study was approved by the ethics committee of the MUMC+ (METC number: 2018–0491 and amendment 2018–0491-A-9). Patients under 18 years old and patients with a (radiological) suspected thymic carcinoma were excluded from this study. Patients with anti-AChR-ab without the history of symptomatic MG before thymectomy ('subclinical MG') were excluded, because they were not comparable with the symptomatic patients [12]. Also patients with non-AChR mediated MG were excluded. Patients were excluded from robotic surgery if they had insufficient lung capacity for single-lung ventilation (forced vital capacity $<70\%$). All patients were initially operated by RATS, however, a planned conversion to thoracotomy could be part of the surgical strategy to accomplish a complete resection.

2.2. Preoperative evaluation

Preoperative evaluation took place at the MUMC+. A neurological assessment was performed in all patients, including: patient history, medication history, current symptoms, medication and a standard neurological examination. Furthermore, tests with outstretching an arm (90° sitting) and leg (45° supine) were performed for testing generalized muscle weakness. Dysarthria was tested by asking the patient to count out loud [13]. The clinical severity of MG was classified using the criteria of the Myasthenia Gravis Foundation of America (MGFA); no symptoms (MGFA class 0), any ocular symptoms (MGFA class I), mild generalized weakness (MGFA class II), moderate generalized weakness (MGFA class III), severe generalized weakness (MGFA class IV) and intubation due to respiratory failure (MGFA class V). Class II-IV are divided in predominantly involvement of limb muscles (A) or bulbar/respiratory muscles (B) [14]. In all patients, the antibody status was analysed in case this was not performed in the referring center. Analysing anti acetylcholine receptor antibodies (anti-AChR-ab) using a quantitative radioimmunoassay technique (IBL International GmbH, Hamburg, Germany) is a standard procedure. Since the last decade, anti muscle-specific tyrosine kinase antibodies (anti-MuSK-ab) and anti-lipoprotein receptor-related protein 4 antibodies (anti-LRP4-ab) were determined as well in anti-AChR-ab negative patients. Single-fiber electromyography (SFEMG) was not routinely performed in referred patients who were already diagnosed with MG. Preoperative radiological evaluation was performed with at least one computed tomography (CT) scan or Magnetic Resonance Imaging (MRI) scan of the thorax. In case of a suspected thymoma, a pulmonologist (oncologist) was consulted as well. The medical team decided together if a patients' condition was satisfying for thymectomy. When the patients' condition worsened during the last months before thymectomy (especially when immunosuppressive drug treatment was increased or started acutely) and in case of a myasthenic crisis, the thymectomy was postponed. Preferably, patients who received prednisone were first tapered to a daily dose <30 mg without serious relapse of MG (MGFA $\geq$ IV) before the thymectomy was performed, unless the multidisciplinary medical team decided that surgery was a priority at that moment.

2.3. Surgical technique

All robotic thymectomies were performed with the DaVinci® Robotic Surgical System (Intuitive Surgical, Sunnyvale, CA, USA). The thymectomies were performed using a right-sided approach, except for (suspected) thymomas located on the left side. The robotic procedures were performed by surgeons trained in robotic surgery. The patients were operated under general anesthesia and intubated with a double lumen tube. The anaesthesiological team took into account the patients' history and the use of medication, and according adapted the anesthetic drug regimen. Then, patients were placed in the supine position and the middle part of the thorax was elevated to 30° at the incision site, taking care that the patient's shoulder remained lying flat on the table to prevent interference with the movement of the robotic arm. Three ports were placed in the anterior axillary line through the third, fourth and sixth intercostal space. The latter being used for removal of the specimen at the end of the procedure, using endobags with various sizes and strengths depending on the size of the thymic mass. In accordance with the guidelines of the International Thymic Malignancy Interest Group (ITMIG), the thymomas were resected using the 'no-touch' and 'en bloc' strategies [15,16]. Finally, a small pleural drainage catheter was introduced through a separate stab incision. The procedure time was defined as the time from the first incision until the closure of the skin.

2.4. Postoperative care

Patients were immediately weaned from the ventilator in the operation room and subsequently monitored in a postoperative care unit with special attention for the occurrence of respiratory failure, signs of a myasthenic crisis for two to three hours, after which the patient was brought to the general ward. The period of hospitalization was recorded in days, from the day of surgery until discharge from hospital. Operative mortality was defined as death within 30 days after surgery or during the same period of hospitalization. Complications were registered and classified in accordance with the Clavien-Dindo classification [17]. Worsening of MG symptoms or signs of a myasthenic crisis were reasons for consulting a neurologist. Within 30 days after discharge, patients had a phone appointment with the clinical team to discuss pathological outcomes and postoperative care.

2.5. Pathological evaluation

A specialized pathologist analysed all resected material. Resected specimens of thymomas were discussed by a multidisciplinary team including a pulmonologist, a pathologist, a radiologist, a surgeon and a radiation oncologist. Complete resection (R0) was defined as no evidence of residual tumor tissue. Incomplete resection was defined as microscopic (R1) or macroscopic (R2) evidence of residual tumor tissue. Thymomas were histologically classified by the WHO Histological Classification of Thymomas. Tumor invasion was classified by the Masaoka-Koga Staging System and TNM Classification of Malignant Tumors [18].

2.6. Follow-up

Because most patients were referred to the MUMC+ for robotic thymectomy, follow-up visits took place in the referring hospital. Improvement in MG status was quantified according to the MGFA post-intervention status classification [14]. According to this classification there is complete stable remission (CSR) if a patient has no symptoms of MG for at least 1 year and receives no therapy for MG during that time. Pharmacological remission (PR) is accomplished if the patient had no symptoms, but used some form of immunosuppressive therapy. Minimal manifestations (MM) were divided in four categories and not further discussed in this study. A myasthenic exacerbation was defined as an increase of MG symptoms of at least one of the following symptoms: difficult swallowing, acute respiratory failure and major functional disability, which required to change the therapeutic intervention [19,20]. In case of a thymoma, detailed oncological and follow-up advice was given by the MUMC+ to the referring hospital.

2.7. Statistical analysis

Descriptive statistics are reported as mean, standard deviation (SD), median and range. Statistical analysis were performed with SPSS statistical software (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp). Chi-square test of independence and Student's *t*-test were performed to compare categorial and continuous variables. Statistical significance was considered to have the probability value of $p < 0.05$.

3. Results

3.1. Patient characteristics

Between 2004 and 2018, 398 thymectomies were performed in the MUMC+ and 230 patients were included in this study (Fig. 1). Of the 230 included patient, 76 thymomas were diagnosed (33.0%). Baseline characteristics are shown in Table 1. A higher prevalence of females was found in nonthymomatous patients, compared with thymomatous patients (79.2% vs. 48.7%, $p < 0.001$). Mean age was 40.9 ± 16.7 years and nonthymomatous patients were significantly younger than patients with a thymoma (mean: 33.6 ± 12.9 vs. 55.8 ± 13.6 years, $p < 0.001$). The mean time between diagnosis of AChR-MG and thymectomy was significantly less in patients with a thymoma compared with nonthymomatous patients (mean: 16.4 ± 27.4 vs. 28.7 ± 44.0 months, $p = 0.010$). Although severity of MG before thymectomy was equally distributed between both groups, thymomatous patients were more often diagnosed with mild MG (MGFA stages I-IIB) than severe MG (MGFA stages IIIA-V). Before thymectomy, 1.7% of all patient had no therapy, 47.4% had cholinesterase inhibitor monotherapy and 50.9% used immunosuppressive drugs. There was no significant difference in use of cholinesterase inhibitor monotherapy or immunosuppressive drugs before thymectomy between both groups. Before thymectomy, 43.5% of all patients used prednisone (monotherapy or combined with other drugs). Prednisone combined with azathioprine was used in 27.0% of all patients. There was no significant difference between both groups in use of prednisone or azathioprine before thymectomy. Intravenous immunoglobulin (IVIG) was used in 14 patients (6.1%) two till six months before thymectomy. There was no data available about the use of plasmapheresis (PLEX), a sporadically applied therapy that is only used in case of a crisis in The Netherlands.

3.2. Post-surgical results

No surgical mortality was reported. The procedure time ranged from 40 to 353 min, with a mean of 111±52.5 min. Mean hospitalization was 3.3 ± 2.2 days. Procedure time and hospitalization had no significant difference in outcome between thymomatous and nonthymomatous patients. A left-sided thymectomy was performed in thymomatous patients more often than in nonthymomatous patients (25.0% vs. 5.8%, $p < 0.001$). Conversions to thoracotomy (1.3%) and sternotomy (0.9%) were part of the planned surgical strategy and were only performed in patients with a thymoma. All nonthymomatous patients had a R0 (complete) resection, while this was the case in 86.8% of the thymomatous patients. Within the first 30 days after thymectomy, 20 complications occurred in 15 patients. After the first 30 days, eight complications in eight patients were registered. Patients with a thymoma had significant more severe complications than nonthymomatous patients (18.4% vs. 3.9%, $p < 0.001$) (Table 2). Also, 30 days after thymectomy, more complications were reported in patients with a thymoma, however, the numbers were too small for statistical analysis. Analysation of the severity of the complications, using the Clavien-Dindo classification, showed that the complications of thymomatous patients were significantly more severe compared with nonthymomatous patients ($p = 0.002$). Pain around the surgical areas, more than 30 days after thymectomy and treated with a nonsteroidal anti-inflammatory drug or opioids, was reported in nine patients (3.9%). A myasthenic crisis was reported in two patients. Patient 1 was a 43-years old female, who was treated only with pyridostigmine before thymectomy for a thymoma, and had a pre-operative MGFA of 3B Directly after the thymectomy she developed respiratory failure and she was intubated for six days. Patient 2 was a 82 years old female, who was treated with prednisone and azathioprine before thymectomy for a thymoma, and had a pre-operative MGFA of 3B After thymectomy she had a complicated hospitalization with a pneumonia and atrial fibrillation. One week after thymectomy she developed a myasthenic crisis and she was intubated. Both patients recovered after treatment with plasmapheresis and prednisone, and later intravenous immunoglobulin. During follow-up, seven patients with a thymoma and one nonthymomatous patient died, with a median time of 90 months (range: 29–155) between thymectomy and death. The median age at time of death was 83 years (range: 52–93). The cause of death was heart failure ($N = 1$), pneumonia ($N = 1$), pancreatic carcinoma ($N = 1$), progression of disease in thymoma ($N = 1$), unknown ($N = 4$).

3.3. Neurological follow-up

Follow-up data was complete in 165 patients (71.7%), of which 60.6% of the patients had nonthymomatous MG and 39.4% had thymomatous MG. The following neurological follow-up results are based on these two groups (Table 3). Incomplete follow-up was caused by lost to follow-up ($N = 47$), patients who gave no informed consent for collecting follow-up data ($N = 10$) and patients who died ($N = 8$). Mean follow-up time was 65.7 ± 43.1

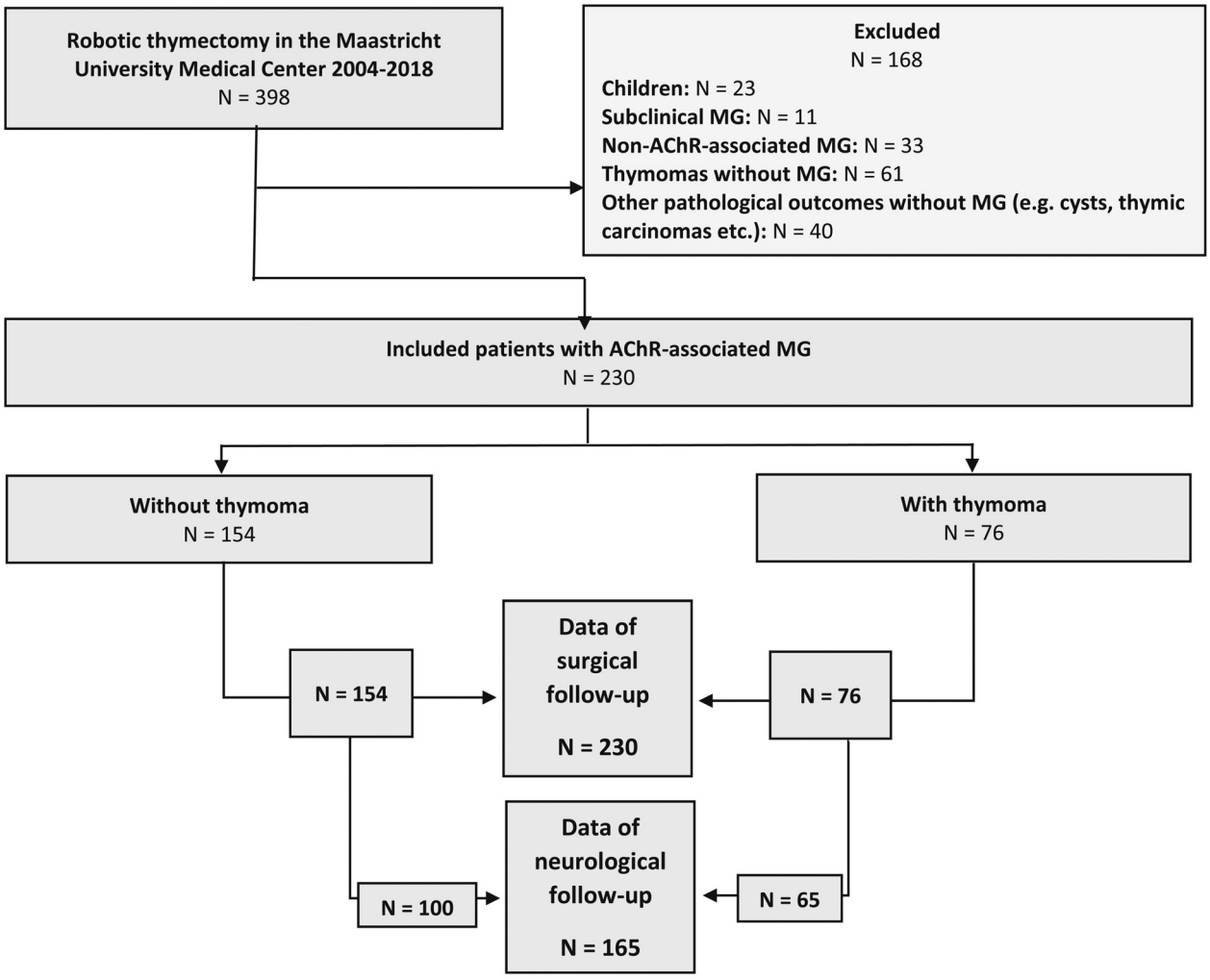

Fig. 1. Flow chart of the study.
MG: Myasthenia gravis, AChR: acetylcholine receptor, WHO: World Health Organization

months. CSR and PR were accomplished in 8.5% and 39.4% of the patients, respectively. There was no significant difference in accomplishing CSR or PR in nonthymomatous patients versus thymomatous patients. Mean time between thymectomy and CSR or PR was 26.2 ± 29.2 months. Of the 84 patients without CSR or PR, the majority were females (74.7%), diagnosed with MG less than 24 months before thymectomy (69.9%), without a diagnosis of thymoma (61.4%) and without the use of immunosuppressive drugs upfront surgery (51.8%). The MGFA postoperative change score at the end of the follow-up, showed that 82.4% of patients improved in MGFA scale after thymectomy. No statistical difference was found in improvement in MGFA scale between nonthymomatous patients and thymomatous patients.

In the complete group with neurological follow-up ($N = 165$), immunosuppressive drugs were used in 52.0% of the nonthymomatous patients and in 49.2% of the thymomatous patients before thymectomy. After thymectomy, the use of immunosuppressive drugs was corrected for the amount of patients that had a complete follow-up in the specific year of follow-up. In the years after thymectomy, a trend in increase of use of immunosuppressive drugs use was observed, especially in thymomatous patients. After five years follow-up, 63.3% of the nonthymomatous patients and 93.1% of the thymomatous patients were using immunosuppressive drugs (Fig. 2). The use of prednisone decreased over time in the nonthymomatous group (44.0% before thymectomy vs. 28.6% five years after thymectomy) (Fig. 3). The use of combined therapy with prednisone and azathioprine also decreased over time in the nonthymomatous group (31.0% before thymectomy vs. 8.2% five years after thymectomy) (Fig. 4). On the contrary, patients with a thymoma showed a trend with light increase in use of prednisone (47.8% before thymectomy vs. 55.2% five years after thymectomy) and therapy of prednisone combined with azathioprine (30.8% before thymectomy vs. 41.4% five years after thymectomy). No specific data of cumulative doses of used immunosuppressive drugs was available.

Table 1
Baseline characteristics.

	Total patients with AChR-associated myasthenia gravis $N = 230$		
	Without thymoma	With thymoma	p-value
Patients, n	154	76	
Female, n (%)	122 (79.2)	37 (48.7)	<0.001
Age at surgery, mean years (SD)	33.6 (±12.9)	55.8 (±13.6)	<0.001
Therapy for MG (at time of surgery), n (%)			
No therapy	1 (0.6)	3 (3.9)	NS
Cholinesterase inhibitor monotherapy	78 (50.7)	31 (40.8)	NS
Immunosuppressive drugs	75 (48.7)	42 (55.3)	
Use of IVIG (2–6 months prior to surgery), n (%)	13 (8.4%)	1 (1.3%)	–
Duration of MG before thymectomy, n (%)			–
<12 months	52 (33.8)	51 (67.1)	
12–24 months	44 (28.6)	14 (18.4)	
25–36 months	25 (16.2)	4 (5.3)	
37–48 months	12 (7.8)	2 (2.6)	
48–60 months	2 (1.3)	0 (0.0)	
>60 months	19 (12.3)	5 (6.6)	
Duration of MG before thymectomy, mean months (SD)	28.7 (±44.0)	16.4 (±27.4)	0.010
Presurgical MGFA classification (at the latest two months before thymectomy), n (%)			–
0	3 (1.9)	2 (2.6)	
I	9 (5.8)	16 (21.1)	
IIA	28 (18.2)	9 (11.8)	
IIB	62 (40.4)	34 (44.8)	
IIIA	9 (5.8)	0 (0.0)	
IIIB	40 (26.0)	13 (17.1)	
IVA	0 (0.0)	0 (0.0)	
IVB	3 (1.9)	2 (2.6)	
V	0 (0.0)	0 (0.0)	
Severity of MG, n (%)			NS
Mild*	99 (64.3)	59 (77.6)	
Severe**	55 (35.7)	17 (22.4)	

AChR: acetylcholine receptor; MG: myasthenia gravis; NS: not significant: IVIG: intravenous immunoglobulin.
* Mild: MGFA stages I, IIA, IIB;.
** Severe: MGFA stages IIIA, IIIB, IVA, IVB, V.

Table 2
Post-surgical outcomes.

	Total patients with AChR myasthenia gravis $N = 230$		
	Without thymoma	With thymoma	p-value
Patients, n	154	76	
Hospitalization from day of thymectomy, mean days (SD)	3.30 (±0.8)	3.37 (±3.6)	NS
Procedure time, mean minutes (SD)	106.4 (±51.3)	121.9 (±54.2)	NS
Complications, number of patients (%)	8 (5.2)	15 (19.7)	<0.001
Type of complications <30 days after RATS, n (%)	6 (3.9)	14 (18.4)	<0.001
Myasthenic crisis (intensive care unit)	0	2	
Atrial fibrillation	0	5	
Pleural effusion with drainage	1	2	
Pulmonary embolism	0	2	
Pneumonia	1	1	
Pneumothorax with drain	1	2	
Heart failure (diuretics needed)	2	0	
Respiratory failure due to sputum	1	0	
Type of complications in 30–120 days after RATS, n (%)	2 (1.3)	6 (7.9)	–
Pulmonary embolism	2	1	
Chylothorax	0	2	
Phlebitis	0	1	
Pneumonia	0	1	
Increase in myasthenic symptoms	0	1	

AChR: acetylcholine receptor; RATS: robotic-assisted thoracoscopic surgery.
NS: not significant.

In the 84 patients who experienced no CSR or PR remission of MG during follow-up, immunosuppressive drugs were used in 47.6% before thymectomy. In patients who accomplished PR, the use of immunosuppressive drugs was lower, but not significant, compared with patients who accomplished no PR (1 year follow-up: 63.3% vs. 65.8%; 2 years follow-up 65.7% vs. 70.6%; 3 years follow-up 64.4% vs. 69.1%; 4 years follow-up 66.7% vs. 74.4%; 5 years follow-up 70.5% vs. 78.8%). There was no significant difference in time of follow-up between patients who accomplished CSR or PR (mean: 69.7 ± 42.5 months), compared to patients who experienced no CSR or PR (mean: 63.6 ± 43.6 months).

4. Discussion

This study focused on patients with AChR-MG who underwent robotic thymectomy. The results showed that RATS is safe and feasible in MG. Furthermore, this study showed that the MGFA

Table 3
Neurological follow-up.

	Total patients with AChR myasthenia gravis and follow-up $N = 165$		
	Without thymoma	With thymoma	p-value
Total patients with complete follow-up, n	100	65	
Length of follow-up, mean months (SD)	71.6 (±47.0)	60.3 (±36.9)	NS
Remission of MG after thymectomy, n (%)			–
CSR	11 (11.0)	3 (4.6)	
PR	37 (37.0)	28 (43.1)	
Minimal manifestations	20 (20.0)	14 (21.5)	
No remission	32 (32.0)	20 (30.8)	
Accomplished remission (CSR/PR), n (%)	48 (48.0)	33 (50.8)	NS
Accomplished remission after thymectomy, mean months (SD)	29.6 (±32.1)	20.9 (±23.5)	NS
MGFA postoperative change score, n (%)			–
Improved	64 (64.0)	36 (55.4)	
Improved with history of exacerbations after RATS	22 (22.0)	14 (21.5)	
Unchanged	14 (14.0)	13 (20.0)	
Worsened	0 (0.0)	2 (3.1)	
Died	0 (0.0)	0 (0.0)	
Improved after thymectomy, n (%)	86 (86.0)	50 (76.9)	NS

AChR: acetylcholine receptor; MG: Myasthenia gravis; MGFA: Myasthenia Gravis Foundation of America; CSR: Complete stable remission; PR: Complete stable pharmacological remission.

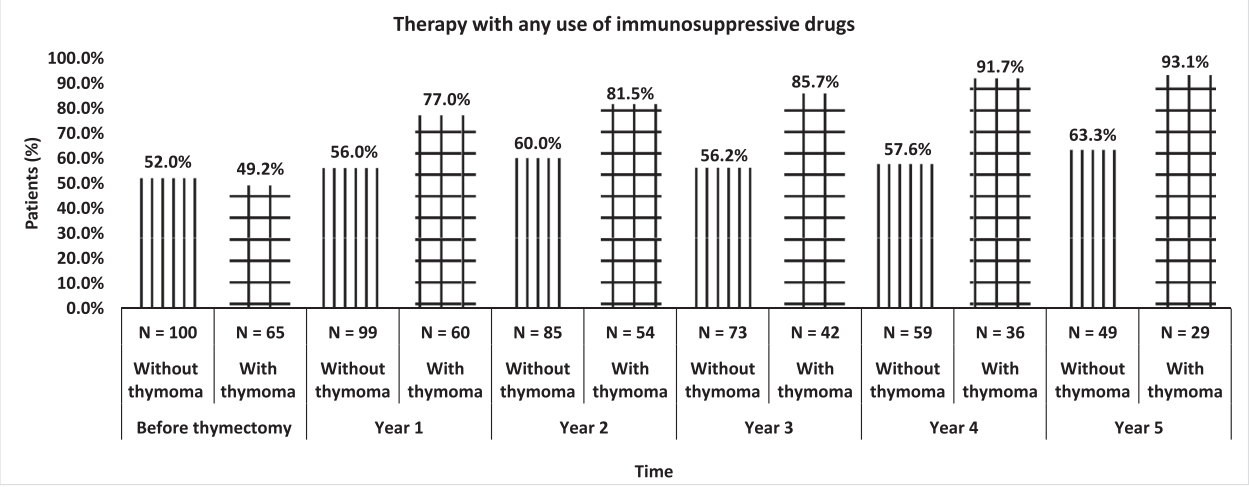

Fig. 2. Treatment with any use of immunosuppressive drugs.

postoperative change score improved in 82.4% of the patients after thymectomy.

Mean time till remission was 26.2 months, suggesting that in most patients it took some time before remission was accomplished. Only 8.5% of all patients experienced CSR and 39.4% had PR. Previous literature showed higher CSR and lower PR rates [10,21]. Hypothetically, due to the long length of follow-up in our study (mean: 65.7 months), patients had more change to develop an exacerbation with a temporary need of immunosuppressive drugs resulting in a PR instead of CSR. Previous research showed that favorable variables associated with higher CSR rate are: sex (females), younger age at onset of MG (<40 years old), lower severity of symptoms, non-thymomas and a shorter disease duration from diagnosis [22–25].

Patients with a thymoma had more complications, compared with nonthymomatous patients. The most commonly complication in thymomatous patients was atrial fibrillation, caused by triggering of the pericardium during the resection [26]. Because no pericardial invasion and resection took place in nonthymomatous patients, it is realistic to assume that this complication is linked to patients with a thymoma.

Although our study had a different methodological design compared with the MGTX-trial, the use of prednisone decreased over the years in patients with nonthymomatous MG in our study as well [3]. It is unclear if this decrease is the effect of the thymectomy itself, the natural course of the disease, or a combination of both. The national guideline recommends to taper prednisone and switch to steroid sparing therapy, which could affect the prescription and use of prednisone as well [27]. Also, the combination of therapy with prednisone and azathioprine decreased over time in nonthymomatous patients. On the other hand, the total use of immunosuppressive drugs increased over time, suggesting that azathioprine is possibly switched to other drugs like mycophenolate mofetil, cyclosporine or tacrolimus. Besides that, a bias could be caused by patients who were not in need of immunosuppressive drugs and did not participate in the follow-up. A trend in the increase of the use of immunosuppressive drugs during follow-up in thymomatous patients was observed. Although most thymomatous patients should have years of oncological follow-up, the number of patients in our follow-up decreased drastically over the years. It is possible that patients were seen by the oncologist without need of neurological follow-up, suggesting that the thymomatous patients in our group were harder to treat, leading to a possible bias. Glucocorticoids are known for their impact on lymphocyte cells in thymomas and could have a beneficial impact [28,29].

Due to the retrospective set-up, it was not possible to analyze cumulative doses of drugs during follow-up. The mean time

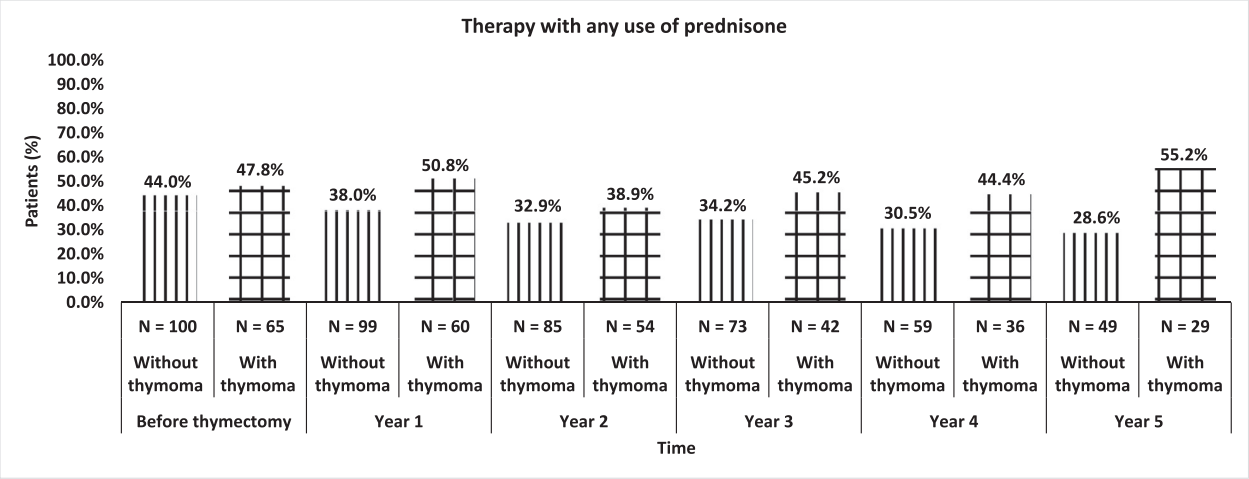

Fig. 3. Treatment with any use of prednisone.

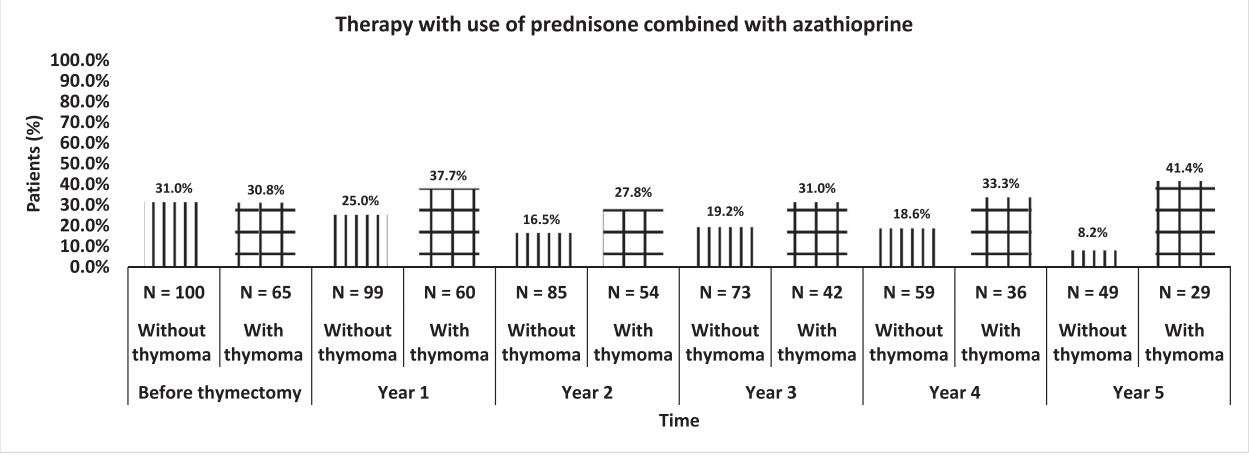

Fig. 4. Treatment with use of prednisone combined with azathioprine.

between diagnosis of MG and thymectomy was significantly less in thymomatous patients compared with nonthymomatous patients (16.4 vs. 28.7 months) These results suggest that patients with a thymoma were referred earlier for thymectomy. Besides preventing a delay in tumor treatment, a possible explanation is that neurologists preferred to optimize the MG in nonthymomatous patients first, before referring for thymectomy. Worsening of muscle weakness in MG occurs mostly during the first one to two years of the disease [30]. Therefore, the earlier thymic resection in thymomas could possibly lead to a lower progression to more severe MG. Follow-up data showed no significant difference in neurological outcomes during follow-up between nonthymomatous and thymomatous patients. Although the MUMC+ was already performing RATS a decade before the MGTX-trial, more patients with MG were referred for thymectomy after the trial. The time between diagnosis and thymectomy in nonthymomatous patients became shorter since the publication of the MGTX-trial. Because follow-up was performed in the referring hospitals and it is no national standard to analyze anti-AChR-ab in the years after thymectomy, it is unclear if the thymectomy had an effect on the levels of anti-AChR-ab.

This study has limitations. First, a referral bias was unavoidable due to the surgical role of the MUMC+ in the Netherlands. Second, patients had to give written permission to use their follow-up data and this could lead to a selection bias. Especially young adult nonthymomatous patients were lost to follow-up (58% < 30 years old), probably due to the natural movement of leaving the parental home. Theoretically, this could influence the neurological follow-up outcomes. At last, due to the retrospective set-up, it was not possible to use more specific neurological examination tests such as the quantitative myasthenia gravis score (QMG) and myasthenia gravis activities of daily living (MG-ADL).

A prospective analysis of cumulative doses of drugs with exact information about data and reason of switching to other drugs could be very helpful in the development of more personalized medicine. Further prospective research about the effect of a thymectomy on anti-AChR-ab is also recommended. At last, it would be interesting to analyze if there are differences in outcomes between AChR-MG patients with follicular hyperplasia versus thymic remnants.

5. Conclusions

This retrospective follow-up study showed that robotic thymectomy is safe and feasible in patients with AChR-MG. The majority of the patients (82.4%) improved their clinical manifestations after thymectomy. CSR or PR was accomplished in 47.9% of the patients, mostly within 26 months after thymectomy. Patients with a thymoma had more complications and planned conversions compared to nonthymomatous patients. No differences in remission and improvement of MG were observed between thymomatous and nonthymomatous patients. Prospective research

is required to analyze clinical improvement and (drug) treatment strategies more specifically.

Disclosures

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Declaration of Competing Interest

None.

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