Robotic thymectomy in patients with myasthenia gravis: neurological and surgical outcomes

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Abstract

OBJECTIVES: Thymectomy is frequently used in the treatment of myasthenia gravis (MG). But indication, timing or surgical approach remain controversial. This study reports our experiences with robotic thymectomy and surgical and neurological outcomes in a large cohort of patients with MG.

METHODS: We retrospectively analysed the outcome of 125 patients with MG who underwent a robotic thymectomy using the da Vinci Surgical System (Intuitive Surgical, Inc., Sunnyvale, CA, USA) between 2004 and 2012. The Myasthenia Gravis Foundation of America (MGFA) Classification was used to determine preoperative and postintervention status.

RESULTS: Ninety-five women and 30 men underwent a robotic thymectomy. One hundred patients had a neurological follow-up of more than 12 months. Preoperative most severe MGFA classification was Stage I in 11 patients (8.8%), Stage IIA in 18 patients (14.4%), Stage IIB in 18 patients (14.4%), Stage IIIA in 7 patients (5.6%), Stage IIIB in 29 patients (23.2%), Stage IVA in 10 patients (8.0%), Stage IVB in 29 patients (23.2%) and Stage V in 3 patients (2.4%). Median surgical procedure time was 123 min (range 45–353 min). There were no major perioperative complications or deaths. The median postoperative hospital stay was 3 days (range 2–24 days). Histological analysis showed thymic remnant tissue in 41 patients (32.8%), follicular hyperplasia in 52 patients (41.6%), thymoma in 31 patients (24%), lipoma in 1 patient (0.8%) and a cyst in 1 patient (0.8%). Patients with thymic remnant tissue were significantly more preoperative steroid users compared with the follicular hyperplasia group (P = 0.02). With a median follow-up of 33 months (range 12–104 months), 77% of the patients showed neurological improvement. Three-year probability remission rate [complete stable remission (CSR) and pharmacological remission] is 28.2%. Patients who were not treated with prednisolone preoperatively showed a significant higher CSR than patients who did take prednisolone (P = 0.014). No significant difference was observed regarding timing of surgery (P = 0.37).

CONCLUSIONS: Robotic thymectomy in patients with MG is safe and feasible. A neurological benefit and decreased use of steroids can be obtained in the majority of patients. No significant difference in neurological outcome was observed as the result of timing of robot thymectomy after the onset of MG.

Keywords: Myasthenia gravis • Robotic thymectomy • Minimally invasive surgery
INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disorder that affects the neuromuscular junction and is characterized by weakness and fatigability of skeletal muscles worsening upon exertion. With an incidence of 30 per 1,000,000 person-years, MG is regarded as a rare disease [1]. The pathogenesis of MG has not yet been fully understood; however, the thymus plays a central role in the complex pathogenesis of MG [2]. Non-thymomatous MG can be distinguished based on the age of disease onset in early onset MG (EOMG) (<50 years) and late onset MG (LOMG) (>50 years). In LOMG, but not in EOMG, hyperplasia of the thymus is found. MG associated with thymoma is most often seen in older patients, supporting the varying roles of thymic pathology in the different forms of MG [3]. In 1911, Ferdinand Sauerbruch was the first to report improvement of myasthenic symptoms after thymectomy in a female with MG and hyperthyroidism [4]. Blalock was the first to report clinical improvement after therapeutic thymectomies in 20 patients with MG [5].

Extended thymectomy is currently recommended as a treatment option for patients younger than 60 years and with a combination of generalized MG and antibodies against acetylcholine receptor (AChR+) [6]. However, a Cochrane review showed that the level of evidence is low; hence, a randomized, controlled trial is missing [7]. A large multicenter randomized, controlled prospective Phase III study supported by the National Institutes of Health–National Institute of Neurological Disorders and Stroke and the Myasthenia Gravis Foundation of America (MGFA) comparing steroid treatment plus thymectomy by sternotomy versus steroid treatment in 150 patients is ongoing and results are expected in August 2015 [8].

Many different surgical approaches exist, ranging from an invasive maximum transcervical-transsternal thymectomy [9] to minimally invasive approaches such as conventional three-port thoracoscopic thymectomy and robotic thymectomy [10, 11]. In addition, the heterogeneity of MG and the various classification systems used to quantify the postintervention status makes it even more difficult to come to a consensus [12].

In the absence of a leading directive, there also remains controversy regarding the surgical approach and the timing of thymectomy. The selected approach of our center is the robotic thymectomy when there was a suspicion for a thymoma. Occasional patients who improved according to the MGFA postintervention status. The clinical improvement rate was determined of all the patients who went a robotic thymectomy between April 2004 and December 2012 referred from all over the Netherlands (41 centers). The majorit of the thymectomized patients had generalized MG with AChR antibodies. Patients with LOMG were only eligible for thymectomy when there was a suspicion for a thymoma.

MATERIALS AND METHODS

We retrospectively analysed all consecutive patients who underwent a robotic thymectomy between April 2004 and December 2012 referred from all over the Netherlands (41 centers). The majority of the thymectomized patients had generalized MG with AChR antibodies. Patients with LOMG were only eligible for thymectomy when there was a suspicion for a thymoma. Occasional patients who improved according to the MGFA postintervention status. The clinical improvement rate was determined of all the patients who went a robotic thymectomy between April 2004 and December 2012 referred from all over the Netherlands (41 centers). The majority of the thymectomized patients had generalized MG with AChR antibodies. Patients with LOMG were only eligible for thymectomy when there was a suspicion for a thymoma.

Statistical analysis

Data were reported as median and range. Statistical analysis was performed with SPSS 20.0 statistical software (SPSS, Inc., Chicago, IL, USA). The 3-year probability of remission was determined by the Kaplan–Meier analysis. Differences between survival curves were tested with the log-rank test. A Cox proportional hazard regression analysis was performed as multivariety analysis. The chi-square test was used to test differences of proportions between the levels of categorical data. Statistical significance was considered with the probability value of P < 0.05.

SURGICAL TECHNIQUE

All procedures were performed by one or two surgeons who were trained in robotic surgery, with a specialized nursing team. The patient was placed supine with the middle part of the right thoracic cavity lifted up with an inflatable balloon to 30°, taking care...
that the right shoulder remained lying down as much as possible to prevent interference with the movement of the right robotic arm. Three trocars were introduced after single left-lung ventilation had been installed, and the intercostal nerves were blocked at each trocar position. The first trocar was located in the fifth intercostal space at the mid-clavicle line. CO2 insufflation was started and the camera was temporarily introduced through this port to allow introduction of the second and third trocars in the fifth and third intercostal space at the anterior axillary line. Thymomas were resected according to the ‘no touch’ approach recommended by the International Thymic Malignancy Interest Group (ITMIG) criteria, as described in our recent published series [13]. An extended resection according to Masaoka et al. [14] with resection of all the ectopic thymic tissue started from the right phrenic nerve upwards, focusing on the bodies and the hind parts of the thymus up to the left phrenic nerve. Dissection continued in the jugular direction until the brachiocephalic vein was reached. Thymic veins were cut with cautery or using clips. During this time, connection of the specimen with the sternum was left untouched, as it helps to lift the specimen up from the major vessels. The left lung could be temporarily hyperinflated to get a better view of the left phrenic nerve. To complete dissection, the upper lobes were pulled down towards the diaphragm and freed from the jugular structures. The specimen was removed en bloc in an endobag through the mid-clavicular incision. If resection of lung tissue was necessary, an endoscopic stapler was introduced through one of the trocars depending on the best angle for stapling. A small pleural catheter was introduced through a separate 2-mm puncture hole, allowing the trocar wounds to be closed completely. This drain was removed as soon as an X-ray confirmed the absence of a pneumothorax, usually on the day of surgery.

RESULTS

Ninety-five women (76%) and 30 men (24%) with MG underwent a robotic thymectomy between 2004 and 2012. Patient characteristics are given in Table 1. The median age was 33.5 years (range 12–82 years). Patients were equally distributed over MGFA Class I–IV. The median procedure time was 123 min (range 45–353 min). The median postoperative hospitalization was 3 days (range 2–24 days). There were no perioperative complications and no additional access ports or any conversions for surgical complications. In 5 patients (4.0%), all patients with a thymoma, a conversion to median sternotomy or thoracotomy was preferred because an invasive thymoma was suspected during operation. In one of the patients (procedure time 353 min), a conversion to a thoracotomy was needed because of invasion of the caval vein and brachiocephalic vein [13].

Postoperative complications occurred in 9 patients (7.2%). In our early experience, a myasthenic crisis requiring prolonged mechanical ventilation occurred in 2 patients (1.6%). Both patients were treated with plasmapheresis. One patient (0.8%) was readmitted 1 week after discharge after resection of thymic remnant tissue with a lung embolism and treated with anticoagulants for 6 months. Four patients (3.2%) were treated with antibiotics because of fever, and pneumonia was treated with antibiotics in 1 patient (0.8%). Pleural effusion necessitated pleural drainage in 1 patient (0.8%).

Histological analysis showed thymic remnant tissue in 41 patients (32.8%), follicular hyperplasia in 52 patients (41.6%), thymoma in 32 patients (25.6%), lipoma in 1 patient (0.8%) and a cyst in 1 patient (0.8%) as described in Table 2. In patients with thymic remnant tissue, there were significantly more patients on steroids preoperatively compared with the follicular hyperplasia group (P = 0.02), which is concordant with the fact that steroids are toxic for lymphocytes.

Follow-up

At the last follow-up in December 2012, all 125 patients were alive. Recurrence of thymoma was observed in 2 patients (6.5%). In 1 patient, a recurrence was seen 2 years postoperatively (thymoma type B2, Masaoka-Koga Stage Ia, conversion to thoracotomy, R1) and in the other patient a recurrence occurred 5 years postoperatively (thymoma type B2, Masaoka-Koga Stage I, R0).

Median follow-up was 33 months (range 12–104 months). Follow-up of more than 12 months was available for 105 patients. Five patients were lost to follow-up, none of them had a thymoma.

Table 1: Patient characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, no. (%)</td>
<td>125</td>
</tr>
<tr>
<td>Female</td>
<td>95 (76)</td>
</tr>
<tr>
<td>Age (years) Median</td>
<td>(range) 33.5 (12–82)</td>
</tr>
<tr>
<td>Antibodies, no. (%)</td>
<td></td>
</tr>
<tr>
<td>Anti-AChR positive</td>
<td>110 (88)</td>
</tr>
<tr>
<td>Seronegative</td>
<td>15 (12)</td>
</tr>
<tr>
<td>MGFA Classification</td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>11 (8.8)</td>
</tr>
<tr>
<td>Class II A</td>
<td>18 (14.4)</td>
</tr>
<tr>
<td>Class III A</td>
<td>18 (14.4)</td>
</tr>
<tr>
<td>Class III B</td>
<td>7 (5.6)</td>
</tr>
<tr>
<td>Class III B</td>
<td>29 (23.2)</td>
</tr>
<tr>
<td>Class IV A</td>
<td>10 (8.0)</td>
</tr>
<tr>
<td>Class IV B</td>
<td>29 (23.2)</td>
</tr>
<tr>
<td>Class V</td>
<td>3 (2.4)</td>
</tr>
</tbody>
</table>

AChR: acetylcholine receptor; MGFA: Myasthenia Gravis Foundation of America.

Table 2: Histological characteristics after thymectomy

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Data, no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histological analysis</td>
<td></td>
</tr>
<tr>
<td>Thymic remnant tissue</td>
<td>41 (32.8)</td>
</tr>
<tr>
<td>Follicular hyperplasia</td>
<td>52 (41.6)</td>
</tr>
<tr>
<td>Thymoma type A</td>
<td>5 (4.0)</td>
</tr>
<tr>
<td>Thymoma type A B</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td>Thymoma type B1</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td>Thymoma type B2</td>
<td>14 (11.2)</td>
</tr>
<tr>
<td>Thymoma type B3</td>
<td>5 (4.0)</td>
</tr>
<tr>
<td>Lipoma</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Cyst</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Masaoka-Koga staging</td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>13 (43.3)</td>
</tr>
<tr>
<td>Stage II A</td>
<td>8 (26.7)</td>
</tr>
<tr>
<td>Stage II B</td>
<td>6 (20)</td>
</tr>
<tr>
<td>Stage III</td>
<td>2 (6.7)</td>
</tr>
<tr>
<td>Stage IV A</td>
<td>1 (3.3)</td>
</tr>
</tbody>
</table>
The prednisolone dose after surgery was reduced to a median of 10 mg (range 2–60 mg). Patients who were not treated with prednisolone preoperatively showed a significant higher probability rate for 3-year CSR compared with patients who were treated with prednisolone ($P=0.014$) (Fig. 3). Cox proportional hazard regression analysis was performed for age, preoperative MGFA classification, histology, type of MG and preoperative prednisolone. This analysis showed no significant statistical difference.

**DISCUSSION**

We report the results of robotic thymectomy in 125 patients with MG. We encountered no perioperative complications and a low rate of postoperative complications [9 patients (7.2%)]. With a median follow-up of 33 months, our 3-year probability of remission was 28.2%. MG improvement was seen in 77% of the patients. In patients using steroids, we observed a significantly increased incidence of thymic remnant tissue compared with follicular hyperplasia in patients who did not ($P=0.01$).

No perioperative complications occurred probably as a result of superior 3D quality of visualization of the thymus. This visualization also facilitated an easy, safe and precise dissection of thymic tissue from the phrenic nerve and vascular structures. No additional access ports were necessary to facilitate a radical extended resection. Robotic resection is also associated with disadvantages, such as high costs and lack of tactile feedback. The latter, however, is compensated by experience with the information the brain gets from the visualization with the 3D camera. Centralization of robotic surgery in specialized hospitals and multidisciplinary usage of the robotic system as in the Netherlands where Maastricht is a national referral centre, may result in lower costs in the future. Centralization probably also accounts for our low peri- and postoperative complications. At the start of our robotic programme, two patients experienced a myasthenic crisis requiring prolonged mechanical ventilation. The use of preoperative immunosuppression in severe MG patients possibly prevented a crisis occurring later on in our thymectomy programme.

The role of thymectomy in the treatment of non-thymomatous MG remains controversial because of the lack of a randomized, controlled trial. Therefore, results of an ongoing prospective randomized, controlled trial are awaited. The different classifications systems used to report remission rates make it difficult to compare the results of the published series. Recommendations for a uniform follow-up classification system in clinical research were published in 2000 by the MGFA [15]. We adapted these classifications and used the Kaplan–Meier analysis for remission rates.

Since the introduction of robotic thymectomy, around 500 robotic thymectomies have been published [16]. The largest series reported by Marulli et al. showed the surgical and neurological outcome after robotic thymectomy in 100 patients. The 5-year probability of CSR was 28.5% [10]. Other robotic series adopting the MGFA recommendations showed CSR rates between 28 and 42% [11, 17]. Remission rates for open trans-sternal thymectomy have been reported between 17 and 34% [18, 19]. Our 3-year probability of CSR is 16.9% and the 3-year probability of remission rate 28.2%. The relatively low remission rates might be caused by two components. First, patients prefer to continue pyridostigmine and are therefore not defined as CSR or PR. Moreover, neurologists in the Netherlands do not stop azathioprine treatment in patients who are free of symptoms because of the possibility of a relapse. Michels et al. [20] showed that discontinuation of azathioprine treatment led...
to a relapse in 60% of patients. For that reason, we continue medical treatment for at least 2 years in remission patients. Second, our short median follow-up of 33 months may therefore have led to a bias. The clinical improvement rate after surgery of 77% is in line with results following conventional surgery.

A significantly higher CSR rate was observed in patients without preoperative treatment of prednisolone ($P = 0.014$). Fifty-four percent of these patients had MGFA Class I and II. This is in contrast to the idea that steroid treatment combined with extended thymectomy will result in a more favourable outcome due to a more stable MG status [21]. We observed a trend in patients with early stage MG for higher CSR rates ($P = 0.08$). This is in line with the literature describing reluctant thymectomy for late-onset non-thymomatous MG. LOMG patients only underwent a thymectomy when a thymoma was suspected.

The median duration of preoperative symptoms was 12 months. Despite not seeing a significant difference in the duration of symptoms before surgery, we tend to perform thymectomy early after diagnosis as a delay does not result in a higher CSR rate. Earlier published series showed that patients with a thymoma have a worse CSR after thymectomy [22]. In our series, however, the CSR rate in thymoma patients did not differ from the non-thymomatous group.

We currently do not take out lymph nodes routinely during thymectomy. However, this may change in the near future, as the ITMIG will shortly publish a lymph node map for thymic malignancy.

Early adopters of robotic-assisted lung cancer surgery have pointed out that one of the major advantages of the robotic approach in comparison to the conventional VATS procedure is the quality and enhancements of the lymph node dissection [23]. If the thymectomy procedure has to be extended with a lymph node resection, the procedure is likely to benefit from the robotic approach in a similar way.

Meraouna et al. demonstrated that corticosteroid treatment can modulate thymic pathology. B-cell infiltration that leads to thymic hyperplasia might play a role in the development of MG. Steroid treatment has a biological effect on B cells. Numerous B-cell

| Table 3: Kaplan–Meier statistical analysis of 100 patients with a follow-up >12 months predicting remission |
|--------------------------------------------------------|-------------------------------|-------------------------------|-------------------------------|
| Factor | Three-year CSR rate (%) | $P$-value* | Three-year remission rate (%) | $P$-valuea |
| Age (12–82 years) | | | | |
| <33 ($n = 50$) | 20.9 | 0.06b | 28.0 | 0.99 |
| >33 ($n = 50$) | 7.7 | | 28.6 | |
| Gender | | | | |
| Female ($n = 73$) | 18.2 | | 26.3 | |
| Male ($n = 27$) | 4.5 | | 34.9 | |
| AChR antibodies | | | | |
| Positive ($n = 91$) | 14.5 | | 28.1 | |
| Seronegative ($n = 9$) | 11.1 | | 22.2 | |
| Preoperative MGFA | | | | |
| Class I–II ($n = 37$) | 20.2 | 0.10b | 33.5 | 0.28 |
| Class III–IV ($n = 63$) | 11.2 | | 24.2 | |
| Histology | | | | |
| Benign thymic tissue ($n = 73$) | 17.7 | 0.13b | 26.5 | 0.46 |
| Thymoma ($n = 27$) | 5.6 | | 34.1 | |
| Preoperative duration symptoms | | | | |
| <12 months ($n = 43$), range (0–12 months) | 12.2 | 0.37 | 30.8 | 0.98 |
| >12 months ($n = 57$), range (12–144 months) | 16.0 | | 26.8 | |
| Type of MG | | | | |
| Early onset ($n = 81$) | 20.4 | 0.08b | 28.7 | 0.71 |
| Late onset ($n = 19$) | 0.0 | | 25.8 | |
| Preoperative prednisolone | | | | |
| No ($n = 50$) | 25.9 | 0.014b | 36.1 | 0.20 |
| Yes ($n = 50$) | 6.2 | | 19.0 | |

Remission rate: CSR + PR; AChR: acetylcholine receptor; MGFA: Myasthenia Gravis Foundation of America; MG: myasthenia gravis.

*Unadjusted $P$-value performed by log rank.

bCox proportional hazard regression analysis showed no significant hazard ratio.
markers that are overexpressed in hyperplastic MG thymi are nor-
malized in the thymus of MG patients treated with corticosteroids [24]. The reduction in B-cell numbers was also observed in our
series; patients using steroids had significantly more often a thymic
remnant tissue compared with follicular hyperplasia (P = 0.02).

Limitations

This study has several limitations; it is a single-centre retrospective
analysis, which could have led to a selection bias. The patient
population is heterogeneous, including ocular, mild, generalized
and seronegative MG patients. Many patients were referred to our
hospital only for the surgery and follow-up was performed at the
referral centre, which may have resulted in different clinical eval-
uations and decisions regarding the medical treatment of MG.

CONCLUSIONS

In this article, we described robotic thymectomy in 125 patients
with MG. No surgical mortality occurred and morbidity rates were
low, demonstrating a feasible and safe surgical procedure. The
myasthenic symptoms improved in more than three quarters of
the patients after this minimally invasive procedure. No significant
difference in neurological outcome was observed as a result of dif-
fences in timing of robotic thymectomy.

Conflict of interest: Jos Maessen is a proctor for da Vinci, robotic
lung resections.

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