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Thirteen years follow-up after radical transsternal thymectomy for myasthenia gravis. Do short-term results predict long-term outcome?☆

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Abstract

Objective: Long-term evaluation of efficacy and quality of life after radical surgical approach for myasthenia gravis (MG). Comparison between short-term follow-up and long-term outcome. **Methods**: All patients ($n = 26$, 16 men and 10 women, mean age: 40.7 years) underwent total transsternal thymectomy for MG between 1986 and 1989. Prospective analysis of the patients for short-term follow-up (mean 22.4 months) was published in 1991. The same group of patients was reevaluated in 2001 (range of follow-up 11.4–15.2 years) and assessed according to the classification of Osserman and Oosterhuis. **Results**: Mean follow-up was 13.0 years (range 11.4–15.2 years). Two patients were lost from follow-up and one died 4 years after thymectomy for reasons unrelated to MG ($n = 23$). No early or late postoperative mortality was observed. One sternal osteomyelitis occurred. Late postoperative morbidity included sternal instabilities ($n = 2$), mild residual thoracic pain ($n = 6$), and hypertrophic scars ($n = 7$). Five patients were rehospitalized for aggravating MG and needed plasmapheresis ($n = 3$) and intubation ($n = 1$). Thirteen patients (56.5%) showed objective clinical improvement, including six patients (26.1%) with complete remission. Eleven patients (47.8%) do not take any medication at all. Because some late relapse may occur several years after operation, the rate of improvement decreased slightly, whereas the difference between short and long-term follow-up was not statistically significant ($P = 0.405$). Twenty patients (87%) returned to work, including part-time occupation ($n = 4$). Fourteen patients (61%) are performing sports regularly. **Conclusions**: Our data confirm that radical, transsternal thymectomy is an effective and safe therapeutic modality for MG. Short-term results seem to deteriorate over time, therefore long-term studies for minimally invasive approaches have to prove equal results before replacing the standard procedure.

Keywords: Myasthenia gravis; Thymectomy; Transsternal

1. Introduction

Myasthenia gravis (MG) is an acquired autoimmune disease, with an incidence of about 0.3 and prevalence of 5.3 patients per 100 000 [1] with predominant onset in females of the third decade without any ethnic, occupational or endemic area predilection.

Most common symptoms are ptosis and diplopia in 65% of all patients, but only 10% of them stay with the ocular form of MG [2]. Mostly the disease gradually spreads to the skeletal muscles with weakness of the proximal girdle and the bulbar muscles with dysarthria, dysphagia and poor mastication. Generalized weakness and involvement of respiratory muscles are the final stage, which may lead to death without treatment in more than 29% of these patients [1].

MG is a disorder of the neuromuscular transmission leading to fatigue and weakness after repetitive use of voluntary muscles. The underlying autoimmune mechanism is the production of specific antibodies directed against the acetylcholine receptor (AChR) complex of the motor end-plate with functional impairment and numeric decrease of these receptors. The thymus, as the site of T-lymphocyte education with resulting self-tolerance, is thought to be an integral part in the pathogenesis of MG.

Thymectomy has been used to remove the main source of antibody production since the first operation for MG by Sauerbruch in 1911 [3]. After decades of transcervical operation Blalock established the transsternal approach in 1936 and demonstrated the favourable effect of the operation on the course of MG, with only six cases published in 1941 [3]. In 1942 Keynes published 200 transsternal thymectomies with a mortality of 33.5% for his first 20

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patients. Since 1965 Akamura and Crile promoted the transcervical approach with certain advantages which were confirmed by Papatestas and Cooper. Masaoka developed the extended transsternal thymectomy in 1975 with good success.

Selection of patients and choice of ideal operation technique remains controversial, especially since introduction of minimally invasive approaches. Only few studies focus on long-term outcome after thymectomy for MG. The aim of the present study is to analyse long-term results with objective evaluation of efficacy and quality of life after a transsternal radical approach for MG patients and most importantly to compare short-term follow-up results with long-term outcome.

2. Patients and methods

2.1. Inclusion criteria

Twenty-six consecutive patients underwent transsternal radical thymectomy for MG at our institution between 1986 and 1989. Three patients (11.5%) presented with thymoma. Diagnosis of MG was confirmed by clinical assessment by a neurologist, and electromyographic studies, edrophonium chloride (Tensilon) test and circulating acetylcholine receptor (AChR) antibodies.

2.2. Indications for surgery

Indications for surgery included new onset of generalized MG, failure of long-term conservative therapy (inclusively ocular form of MG, which is usually associated with a positive clinical provocation tests) or myasthenic symptoms with associated thymoma.

2.3. Operative technique

Median sternotomy is followed by opening the pleural space. The mediastinum is thoroughly explored up to the cervical thymic extension and laterally down to the phrenic nerves. All thymic tissue and the entire pericardial and mediastinal fat from the diaphragm to the thyroid is removed en bloc.

2.4. Analysis of the group

Prospective analysis of short-term follow-up was published in 1991 [4]. One patient of the original group ($n = 27$) had a malignant thymoma without symptoms and was consequently excluded from further analysis. One patient with thymoma was initially classified into the wrong group. Except for these two changes the identical group of patients was re-evaluated with the same criteria by telephone interview and by written questionnaire in March 2001. Two patients were lost from follow-up (back in ex-Yugoslavia and in Libya, respectively) and one patient died 4 years after thymectomy of lung embolism.

Table 1
Osserman classification

I	Indicating ocular myasthenia characterized by ptosis and diplopia without involvement of other muscle groups
IIa	Indicating slow onset, frequently ocular, gradually spreading to the skeletal and bulbar musculature. Respiratory muscles are spared
IIb	Indicating gradual onset with dysarthria, dysphagia and poor mastication more prevalent than in group IIa. Respiratory muscles are spared
III	Indicating rapid onset of severe bulbar and skeletal muscle weakness with involvement of the respiratory muscles
IV	Indicating severe myasthenia gravis developing at least 2 years after onset of group I or II symptoms

Two patients with thymoma remained in the analysis and were not treated as a separate group.

One patient had already received a permanent tracheostoma 27 years before thymectomy and mediastinal irradiation.

2.5. Data analysis

Data were collected on actual symptoms, changes in health condition, hospitalizations, present medication and physician's care needed, local effect of surgery, effect of pregnancies, hormone treatments and other medication as well as capability to work and perform sports. Preoperative, postoperative, and short-term follow-up data were taken from the previous report.

For clinical assessment the actual severity of disease the classification of Osserman (Table 1) and Oosterhuis (Table 2) were applied by the same neurologist as in the study published 10 years ago.

2.6. Definitions

Patients without symptoms or medication for MG were considered to have 'complete remission'. 'Improvement' was defined as lower stage classification of Osserman or Oosterhuis compared to the previous stage with or without medical therapy, including patients with complete remission.

2.7. Statistical analysis

We applied the McNemar Chi-square test to compare different stages of the same group over time. Univariate analysis with Fisher's test for evaluation of predictive

Table 2
Oosterhuis classification

Class 0	Remission, no medication
Class 1	Minimal signs and symptoms
Class 2	Mildly disabled
Class 3	Moderately disabled
Class 4	Severely disabled
Class 5	Respiratory support needed

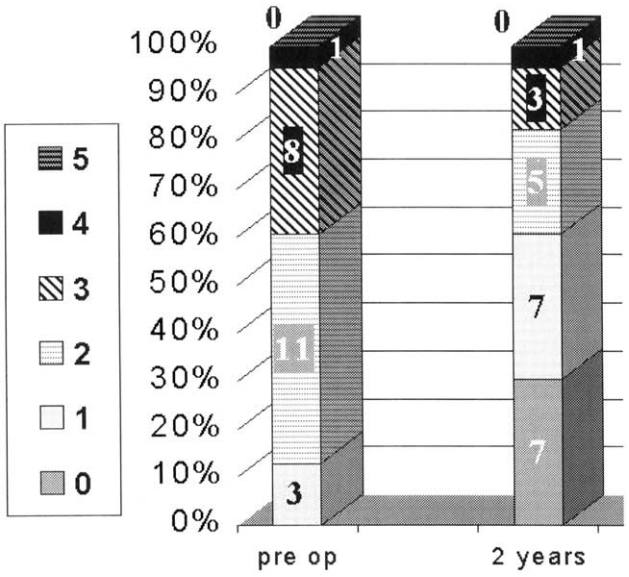

Fig. 1. Staging of patients preoperatively, at 2, and at 13 years according to Oosterhuis classification.

factors was used. A *P*-value of lass than 0.05 was considered significant.

3. Results

3.1. Patients

The mean age of the 23 patients (14 men and nine women) evaluated for long-term results was 38.1 years (range 14.9–64.9) at the day of operation and 51.1 years (range 26.6–77.6) at the time of re-evaluation. The mean time of short-term follow-up was 22.4 months (range 6–53) and 13.0 years (range 11.4–15.2) for the long-term outcome. Mean duration of symptoms before operation was 6.2 years (range 2 weeks to 29 years).

3.2. Early morbidity and mortality

In the group of 23 patients no mortality was observed. All patients were extubated immediately after surgery; none needed tracheotomy.

Postoperative mean hospital stay including the period at the division of Neurology to stabilize MG was 9.4 days (range 7–23). One patient (4%) developed sternal osteomyelitis which needed intravenous antibiotic therapy and surgical debridement. We did not observe any other postoperative complications such as pneumonia or phrenic nerve palsy.

3.3. Late surgical complications

Two late reoperations were necessary: one for sternal wire removal after 1 year, and one re-exploration because of relapse of MG 9 years after the initial intervention for thymoma. Remnant thymic tissue was resected without clinical improvement (Osserman stage IIa).

Six patients (26%) had residual pain of the chest with only one needing medication. Two patients had minor sternal instability (9%) not requiring stabilization. Seven patients (30%) were noted to have hypertrophic scars but only one young woman was cosmetically disturbed. No patient considered correction of the scar.

3.4. Short-term results

At short-term follow-up (mean of 22.4 months, range 6–53) objective improvement in terms of Oosterhuis classification was observed in 17 patients (73.9%), including seven patients (30.4%) in complete remission. The accurate assessment was as follows: seven patients in stage 0 (30.4%), seven in stage 1 (30.4%), five in stage 2 (21.7%), three in stage 3 (13.2%) and one patient in stage 4 (4.3%); no patient was in stage 5 (Fig. 1) [4].

The evaluation according to Oosterhuis shows that the short-term follow-up was significantly better than preoperation (mean value improved from 2.70 to 1.48), $P = 0.00016$.

3.5. Late outcome

After 13.0 years of follow-up (range 11.4–15.2) six patients (26%) were in complete remission and objective improvements in terms of the Osserman classification was achieved in 13 patients (56.5%), $P = 0.0013$ (Fig. 2).

Five patients improved by one grade of Osserman classification (21.7%), seven by two grades (30.4%) and one by three grades (4.3%). Nine patients (39.1%) did not change the Osserman stage and one patient (4.3%) deteriorated by one grade (Fig. 3).

Improvement was assigned to different groups as follows: 25% of the patients with Osserman stage I, 62.5% with stage IIa and 62.5% stage IIb ,as well as 100% with stage IV improved.

Slight deterioration of the 2 years' result (mean value:

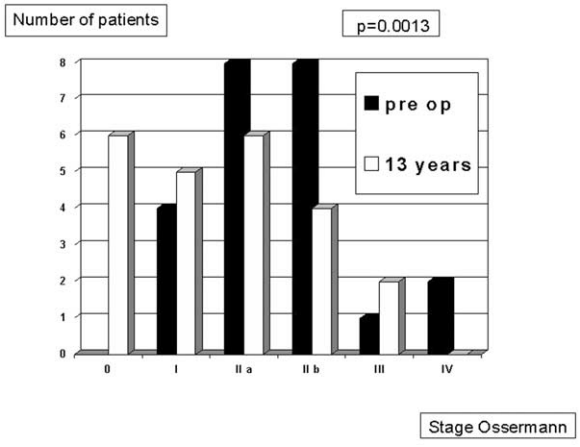

Fig. 2. Staging of patients preoperatively and at 13 years according to Osserman classification.

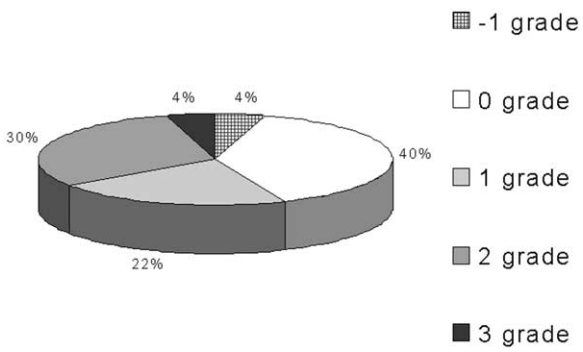

Fig. 3. Grade of improvement at 13 years according to Osserman classification.

1.48) was observed 13 years after thymectomy (mean value: 1.56), but the difference did not reach significance, $P = 0.405$ (Fig. 1). This tendency was due to worsening of MG in eight patients (35%).

Twenty-two hospital admissions including five injuries were necessary for 15 patients in the course of a mean 13 years: five times due to aggravation of MG of which two with myasthenic crisis, three needing plasmapheresis and one intubation. No cholinergic crisis nor brittle myasthenia was observed. Two patients (8.7%) developed a malignant disease: lymphoma and cancer of the uterus, respectively.

At the time of assessment 11 patients (47.8%) do not take any myasthenic medication and two (9%) need reduced therapy. Eleven patients (48%) still require prostigmine and six (26%) immunosuppressive therapy alone or in combination (Fig. 4).

3.6. Predictive factors

Classic predictive factors such as gender, age, severity of MG, AChR antibody and duration of symptoms were tested for complete remission and clinical improvement. In our study only female gender (nine of 23 patients) is a predictive factor for postoperative improvement (89% success versus 36% in males), $P = 0.029$.

In the univariate analysis factors such as age < 40 years

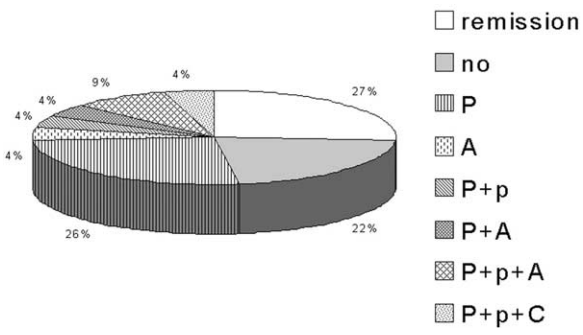

Fig. 4. Actual medication: P, prostigmine; A, azathioprine; p, prednisone; C, cyclosporine.

($n = 12$), duration of preoperative symptoms < 1 year ($n = 10$) and severe stage Osserman $>$ IIb ($n = 11$) did not significantly influence the outcome.

For complete remission no predictive factor could be detected. In contrast to other studies less severe initial disease (Osserman stage I–IIa) resulted in better remission rates (42 vs. 9%).

All patients had an AChR antibody serology preoperatively done, of which only four (17%) were negative (three with Osserman stage I and one with stage IV). Preoperative presence of AChR antibody did not predict better outcome (50 vs. 58%).

3.7. Subjective evaluation and patients' quality of life

Subjectively, 19 patients (82.6%) consider themselves to be in either very good condition ($n = 6$), good condition ($n = 4$) or better than before surgery ($n = 9$). Three patients did not observe any change (13.1%) and one feels worse than before surgery (4.3%).

Fifteen patients (65.2%) are working full-time, of which four women are housekeeping. One patient (4.3%) worked full-time until his retirement. Three patients (13.1%) experienced progressive incapability to work and are actually retired. One patient (4.3%) is working at a reduced level because of MG and three (13.1%) are not able to work. Fourteen patients (61%) perform some kind of sport regularly.

Of six children born by three women, none showed any neonatal form of transmitted MG. Only one caesarean section was needed. Five women used oral contraceptives and never experienced any change of myasthenic symptoms.

No patient ever sensed any worsening of MG after taking different medication.

3.8. Histology

Histological examination of the thymus showed atrophy ($n = 7$), normal thymus ($n = 6$), lymphoid follicles ($n = 6$), germinal centres ($n = 7$), hyperplasia ($n = 2$), and two thymoma stage I of Masaoka. Five times (22%) aberrant ectopic thymic tissue was found: four times in pericardial fat and once in the aorto-pulmonary window.

4. Discussion

This paper reports the longest mean follow-up after thymectomy for MG (Table 3). There is a growing interest in these long-term results as new operative techniques such as minimally invasive approaches have been developed. These techniques have to prove equal long-term outcome compared to the gold standard which still is the radical transsternal thymectomy. With this study we confirm the results of previous series which demonstrated a rate of complete remissions of about 30%. We cannot demonstrate

Table 3
Literature overview[a]

First author [Ref.]	Year	Approach	*n*	Remission (%)	Improvement (%)	Follow-up (years)
Mack [11]	1996	VATS	33	18	70	1.9
Yim [9]	1995	VATS	113	11	72	2.1
Mineo [10]	2000	VATS	31	36	60	3.3
Jaretzki [20]	1988	EXT	95	38	56	3.3
Hatton [21]	1989	TS	52	27	35	3.8
Klein [22]	1999	TS	51	40	47	3.9
Budde [19]	2001	TSt	113	21	54	4.3
Calhoun [14]	1999	TC	100	35	50	5.0
Bush [8]	1996	TS	86	19	52	7.7
Masaoka [7]	1996	TS	375	47	42	7.9
Bril [13]	1998	TC	52	44	46	8.0
Papatestas [6]	1987	TC/TS	962	32	–	10.0
Roth (this study)	2001	TS	26	26	31	13.0

[a] TS, transsternal thymectomy; TC, transcervical thymectomy; EXT, extended thymectomy; TSt, transsternal transverse thymectomy; VATS, video-assisted thoracic thymectomy.

a statistically significant difference between the results after 2 and 13 years. More late deteriorations (35%) than late improvements (22%) have been observed which stands in contrast to previously published series.

It is known that analysis of outcome of chronic and rare diseases with unpredictable and fluctuating courses is difficult. In addition a number of different classifications for MG are used throughout the literature: Osserman, Osserman modified, Oosterhuis, Myasthenia Gravis Foundation of America, Besinger score and de Filippini, which all try to integrate the Neurologist's assessment and the patient's perception of disease-related symptoms and limitations. Definitions as for 'complete remission' or 'improvement rate' are inconsistent in the literature. Furthermore, the groups in published studies are very heterogeneous. They contain mixed pathologies (invasive thymoma), do not differentiate between operative techniques, and vary in patient selection and indications for thymectomy. Even this presented group is small in comparison with previous publications; the observation period is very long, the group of patients is homogeneous, and only two patients were lost from follow-up.

To our knowledge no randomized study has ever been performed, neither between medical and surgical approach nor between different surgical procedures. The beneficial effect of thymectomy for MG is generally accepted and can be confirmed with the present study. The remission and improvement rate after surgery cannot be reached with conservative therapy, despite the fact that spontaneous remission may occur in 11–14% [5]. It is often forgotten that the mortality rate of non-operated patients with MG was as high as 26% and has decreased dramatically after the introduction of early thymectomy [6]. Our series also confirms the safety of this operative procedure, with no postoperative mortality and a minimal number of early and late complications, and therefore underlines the importance of thymectomy as a cornerstone of the treatment of MG.

We can demonstrate that 57% of the patients have a significant objective improvement including 26% of the patients with complete remission (no symptoms nor medication for MG) after 13 years of follow-up.

Other much larger studies demonstrated this fact, but no study so far has such a long mean follow-up. The loss of 8% (2/26) of the patients after 13 years is very acceptable. In contrast to other series with long-term evaluation [7,8] we did not observe as many postoperative late remissions as expected from the literature, but a number of late relapses resulting in an overall slight decrease of improvement rate over the entire observation period. This finding indicates that every new technique has to be evaluated carefully and honestly for long-term results despite the advantages of the minimal invasive approach by either thoracoscopy [9–12] or transcervical procedure [13–15] with better acceptance by patients and neurologists.

We still favour the transsternal radical approach at our centre, as we have detected extrathymic fat tissue in 22% of the patients. In the literature this rate is even as high as 39.5% [16]. It is known that only 4.5 g of remnant thymic tissue may lead to symptoms [17] and therefore radical thymectomy has been chosen to obtain maximal therapeutic benefit [18]. The transverse sternotomy advocated by some authors does not seem to ameliorate the results of the standard procedure [19]. The extended thymectomy does not result in a better remission rate (38%), perhaps because of ectopic thymic tissue (like thyroid or tonsil) [20].

Almost half of the patients in the present study (48%) currently do not need any myasthenic medication and in 9% the medication could be strongly reduced postoperatively. We did not observe clinically relevant complications due to immunosuppressive therapy, particularly conditions after long-term steroid therapy such as diabetes, hypertension, gastric ulcer, osteoporosis or infection.

Additionally it has been reported that, due to a reduced immunosuppressive regimen, the risk of developing malig-

nant diseases can be reduced by 50% after thymectomy from 8 to 4% after 10 years' observation [6]. In our series we observed two malignancies in 13 years. Surprisingly we did not observe associated immunological diseases such as, for example, Hashimoto thyroiditis which is reported to occur in 10% of patients with MG.

Indeed, 70% of the patients did not consult a specialist such as a neurologist or ophthalmologist for their disease, and 39% of all patients did not consult any physician at the time of the assessment.

In summary, the quality of life of the group of patients in this study is very good with nearly 90% of the patients back to work after surgery (including partial work) and two-thirds (65.2%) actually working full-time (including 17% at home). Regular sports such as walking, hiking, horse riding, cycling, swimming, skiing or shooting are performed by 61%. To improve cosmetic results we use a transverse curved skin incision for young women which will be completely covered under a bra. The relatively long postoperative stay at hospital in the 1980s cannot be compared with patient management nowadays.

Only female gender has been identified as a predictive factor in our study. Other often mentioned prognostic factors [19] such as age (<40 years), duration of preoperative symptoms (<1 year) and severity (stage Osserman > IIb) did not influence the outcome in a statistically significant way. This might be because of the small number of patients, as for example 75% of the patients under 40 years improved in contrast to 36% over 40 years ($P = 0.10$).

Compared to previously published series [6–8,10–14,19–22], our results after 13 years of follow-up show similar results for complete remission with a rate of 26% (11–47%). The improvement rate of 31% was lower than in published studies, ranging from 34 to 70% (Table 3). These results may be influenced by an unfavourable inverted gender distribution (male/female ratio 7:4) in combination with long preoperative duration of symptoms up to 29 years, as it is known that MG becomes fixed after more than 15 years in the course of disease (burn-out stage) [23].

Analyzing the improvement rates of different studies (Table 3) in correlation to observation time we note that improvement was becoming worse with duration of observation, although most individual studies paradoxically indicate improvement of outcome over time. In this respect a careful meta-analysis of these studies is needed.

We also noted that the complete remission rate of patients operated on by a video-assisted thoracoscopic approach was low [10–12]. If the improvement rate is indeed declining over time, long-term studies after minimally invasive thymectomy might show surprising results.

In conclusion, the transsternal radical thymectomy remains the gold standard for thymectomy in MG patients. Two-thirds of the patients with a mean follow-up of 13 years lead a normal life with normal everyday activity including regular sports. Short-term results seem to predict long-term outcome, but careful review of the literature seems to indicate a deterioration of the initial results over time. Therefore, long-term studies for minimally invasive thymectomy are warranted to establish equal long-term results.

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