# Effects of Thymectomy in Myasthenia Gravis

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**Factors influencing onset of remission in myasthenia gravis were evaluated in 2062 patients, of whom 962 had had thymectomy. Multivariate analysis showed that appearance of early remissions among all patients was significantly and independently influenced by thymectomy, by milder disease, and by absence of coexisting thymomas. Patients with mild generalized symptoms treated with thymectomy reached remission more frequently, even when compared with those with ocular myasthenia treated without surgery. Short duration of disease before thymectomy in mild cases was another factor associated with earlier remissions. Mortality for all patients was significantly and independently influenced by severity of symptoms, age, associated thymomas, and failure to remove the thymus. Patients without thymectomy and with thymomas had, in addition, earlier onset of extrathymic neoplasms. Morbidity after the transcervical approach was minimal. This study demonstrates that early thymectomy by the transcervical approach, when technically feasible, has significant clinical advantages over the transthoracic approach and should be advocated for all patients with myasthenia gravis, including those with ocular disease.**

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THE ROLE OF THYMECTOMY in myasthenia gravis has not been fully investigated beyond confirming early empirical observations[1] that it is frequently followed by remission of symptoms of the disease. Reports of delayed remissions after thymectomy,[2,3] of decreases in associated extrathymic neoplasms,[4] and of the low morbidity with the transcervical approach[5] have provided additional indications for early surgical intervention, even in patients with mild generalized symptoms. As a result, thymectomy, which was previously used in a selected subgroup of patients,[6] is now performed in all patients with generalized disease.

Indications for the various treatment modalities have changed in recent years. Age, sex, severity of symptoms, lack of control of symptoms with medication, duration of disease, and presence of thymoma were used in earlier years as indicators for surgery.[6] The effect of these factors on the clinical course of the disease has not been adequately studied, even though they should be considered potential confounders when evaluating the results of treatment. It seemed appropriate, therefore, to perform multivariate analysis to identify factors that significantly influence the time intervals either from diagnosis or from thymectomy, to the onset of remission, the development of extrathymic tumors, and death.

The long-term results of the transcervical and transthoracic approaches were compared to determine whether the latter offers any clinical advantage, since in the existing controversy proponents of the sternal approach have advocated a "complete thymectomy" rather than demonstrating a clinical advantage from "radical thymectomy."[7-10] The immediate postoperative course of transcervical and transthoracic approaches was also evaluated.

## Materials and Methods

The clinical course of 2062 patients with myasthenia gravis registered at our institution between 1951 and 1985, of whom 962 had had thymectomy, was evaluated to identify factors that influenced the onset of complete remission, the appearance of extrathymic neoplasms, and mortality.

The following factors were considered potential confounders in evaluating the interval from onset of disease, or from surgical treatment, to the end points of the study: age and sex of the patient, age at onset of symp-

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TABLE 1. *Patients in the Study*

| Treatment | No Thymectomy | Thymectomy | | |
|---|---|---|---|---|
| | | All | Cervical | Thoracic |
| No thymoma | 1048 | 788 | 651 | 137 |
| Ocular/Mild/Severe | (297/401/350) | (3/472/313) | (3/432/216) | (0/40/97) |
| Thymoma | 52 | 174 | 44 | 130 |
| Ocular/Mild/Severe | (4/11/37) | (9/57/108) | (0/22/22) | (9/35/86) |
| Total | 1100 | 962 | 695 | 267 |

toms, severity of disease at time of confirmation of diagnosis, presence of thymoma, age at thymectomy, time period and hospital where surgery was performed, surgical technique, operating surgeon, and duration of disease from onset to thymectomy. For the development of extrathymic tumors, only the first primary malignancy, occurring after the diagnosis of myasthenia gravis, was taken into consideration. Skin neoplasms other than melanomas were not included in the analysis.

In the multivariate analysis severity of disease was coded as: ocular; mild generalized, which included cases with Classes IA and IIA symptoms; or severe, which included cases with Classes IIB, III, and IV symptoms, using the Osserman classification.[11] Duration of disease before surgery was coded as either short, *i.e.,* less than 3 years, or long, which included patients operated on with a delay of 3 or more years after diagnosis. Surgical technique was coded as transcervical or transthoracic. The latter included median sternotomy (complete or partial), lateral intercostal thoracotomy, and parasternal mediastinotomy. One of us (AEP) performed 557 operations, of which 512 were for patients without associated thymoma, and results in this group were compared with those obtained by other surgeons. Patients followed at our institution but operated on in other hospitals were grouped in a separate category. Remissions and mortality were evaluated from the time of diagnosis in all patients and also from the time of surgery in those patients who had thymectomy. Since the proportion of patients in remission increases with time after thymectomy,[2] the analysis of patterns of remission was performed taking this factor into consideration.

Postoperative mortality, need for prolonged postoperative ventilatory assistance or for tracheostomy, and length of hospital stay were factors that were considered in evaluating the immediate postoperative course. The postoperative courses of patients operated on between 1973 and 1986 were evaluated separately from those of the preceding period, as the perioperative management of patients remains essentially unchanged since 1973. Adherence to a variety of postoperative treatment protocols in different years precluded an unbiased evaluation of the immediate postoperative course and complete information on the variables of interest was not available in all patients.

Follow-up information was obtained by patient examination or by questionnaire. Statistical analysis of onset of remission, mortality, and appearance of extrathymic neoplasms was performed using the Cox Proportional Hazards model[12] and the patterns of remissions and of mortality were plotted using the 1L program of the BMDP Statistical Software package (BMDP Statistical Software, Department of Biomathematics, University of California, Los Angeles, CA).[13] Associations between noncontinuous variables were evaluated using the chi-square test.

## Results

Thymectomy and/or the transcervical approach were treatment methods not evenly distributed among subgroups of patients. There were significant variations in the proportions of patients with thymomas and/or severe symptoms both among the groups treated with or without surgery and within the subgroups defined by surgical technique. Thymomas were observed in 226 of 2062 patients (11%) with myasthenia gravis. Among patients who had thymectomy, the proportion was significantly higher compared with that of patients who were not operated on as 174 of the 963 patients who were operated on (18%) were found to have thymomas, compared with 52 of 1100 (5%) patients who were not operated on ($p = 0.0001$). Significant differences in the percentage of thymomas were also noted in relation to severity of disease. Among mild cases, 81 of 1254 patients (6%) had thymomas, whereas among those with severe symptoms 145 of 808 patients (18%) had associated thymic tumors ($p = 0.0001$). Only one third of patients without thymomas had severe symptoms compared with two thirds of those with associated thymomas. The majority of patients who had thymectomy (72%) were operated on *via* the transcervical approach but there was a significant difference in this proportion in relation to the presence of thymoma. Of 788 patients without thymoma, 651 (83%) had transcervical thymectomy compared with 44 of 174 patients (25%) with thymoma ($p = 0.0001$). Most patients who had the transcervical approach had milder disease compared with those operated on by one of the transthoracic approaches (Table 1). The majority of patients with ocular disease were not

TABLE 2. *Clinical Outcome*

| Class | No Thymectomy All | Remission (%) | Mortality (%) | Extrathymic Neoplasm | | | Thymectomy All | Remission (%) | Mortality (%) | Extrathymic Neoplasm | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ocular I | 301 | 59 (20) | 39 (13) | (6)* | 22† | 8%§ | 12 | 2 (18) | 2 (18) | (1)* | 0† | (0)‡ | 0%§ |
| No thymoma | 297 | 58 (20) | 37 (12) | (6) | 21 | 7% | 3 | 1 (33) | 1 (33) | (1) | 0 | (0) | 0% |
| Thymoma | 4 | 1 (25) | 2 (50) | (0) | 1 | 25% | 9 | 1 (11) | 2 (22) | (0) | 0 | (0) | 0% |
| Mild IA, IIA | 412 | 64 (15) | 87 (21) | (10) | 41 | 10% | 529 | 125 (23) | 41 (7) | (9) | 22 | (13) | 4% |
| No thymoma | 401 | 63 (16) | 81 (20) | (10) | 40 | 10% | 472 | 120 (25) | 28 (6) | (8) | 17 | (8) | 4% |
| Thymoma | 11 | 1 (9) | 6 (55) | (0) | 1 | 10% | 57 | 5 (9) | 13 (23) | (1) | 5 | (5) | 9% |
| Severe IIB, III, IV | 387 | 25 (6) | 159 (41) | (9) | 26 | 8% | 421 | 71 (17) | 96 (23) | | 20 | (12) | 5% |
| No thymoma | 350 | 25 (7) | 129 (37) | (7) | 22 | 6% | 313 | 60 (19) | 45 (14) | (7) | 13% | (8) | 4% |
| Thymoma | 37 | 0 (0) | 30 (81) | (2) | 4 | 11% | 108 | 11 (10) | 51 (47) | (3) | 6 | (4) | 6% |
| Totals | 1100 | 148 (13) | 285 (26) | (25) | 89 | 8% | 963 | 198 (21) | 139 (14) | (20) | 42 | (25) | 4% |
| No thymoma | 1048 | 146 (14) | 247 (25) | (23) | 83 | 8% | 788 | 181 (23) | 73 (9) | (16) | 30 | (16) | 4% |
| Thymoma | 52 | 2 (4) | 38 (73) | (2) | 6 | 12% | 174 | 17 (10) | 66 (37) | (4) | 12 | (9) | 7% |

* Neoplasms diagnosed before onset of myasthenia gravis.
† Neoplasms diagnosed after onset of myasthenia gravis.
‡ Neoplasms diagnosed after thymectomy.
§ Percentage of patients in whom neoplasms developed after onset of symptoms.

treated by thymectomy. Remission and mortality varied significantly with severity of disease and presence of thymoma in both the operated and nonoperated groups of patients (Table 2). Overall, patients who had thymectomy had a higher proportion of remissions, lower mortality, and less frequent extrathymic neoplasms.

Severity of disease, presence of thymoma, and thymectomy were all factors that emerged from the multivariate analysis using the Cox Proportional Hazards model as significantly and independently influencing the interval from onset of disease to onset of remission. The most important factors contributing to an early onset of remission were milder forms of disease, thymectomy, and absence of thymoma with all three factors having a significant and independent influence (Table 3). Sex and age of the patient did not influence the results. The patterns of remission from time of diagnosis for patients with or without thymectomy and with or without thymoma are shown in Figure 1. The earliest remissions appear in patients without thymoma treated by thymectomy. Patients with thymomas who had operation, although they had considerable delay in onset of remissions, eventually had a higher proportion of remissions than patients without thymomas treated without surgery (Fig. 1).

The analysis was repeated in patients without thymoma after stratification according to severity of symptoms. A higher proportion of remissions was noted in those with mild disease treated by thymectomy. Patients who had progressed to severe symptoms before thymectomy had a similar pattern of remission as patients treated without thymectomy who had ocular or mild generalized symptoms. The group with the fewest remissions was that of patients who had progressed to severe symptoms but had not had thymectomy (Fig. 2). The duration of preoperative symptoms for patients who had thymectomy is shown in Table 4. It was noted that 25% of patients without thymoma had a duration of symptoms of more than 3 years by the time of thymectomy. Although 87% of thymomas were diagnosed and treated within 3 years of onset of symptoms among patients operated on in each of the subsequent periods, 21 of 218 patients (10%) were found to have thymomas (Table 4). Thymomas were found with increasing frequency in the older age group, particularly among patients with severe symptoms. The highest proportion (42%) was noted in patients over 50 years of age at the time of surgery, who had severe symptoms.

When remissions were evaluated for patients who had thymectomy, it became evident that the time from thymectomy to remission was significantly and independently influenced by the presence of thymoma, severity of disease, the surgical approach, and by the duration of preoperative symptoms. Patients without thymoma, those with milder symptoms, those who had had transcervical thymectomy, and those with short duration of disease (less than 3 years) showed earlier onset of remis-

TABLE 3. *Factors Influencing Remission After Diagnosis in all Patients**

| | Univariate p | Stepwise p | Coefficient/SE |
|---|---|---|---|
| Severity of disease | 0.0000 | 0.0000 | −4.9393 |
| Thymectomy | 0.0002 | 0.0000 | 4.8537 |
| Thymoma | 0.0058 | 0.0130 | −2.7083 |

* Age of onset of symptoms and sex of patient had no independent significant effect. Number of patients = 2062; number of patients in remission = 346.

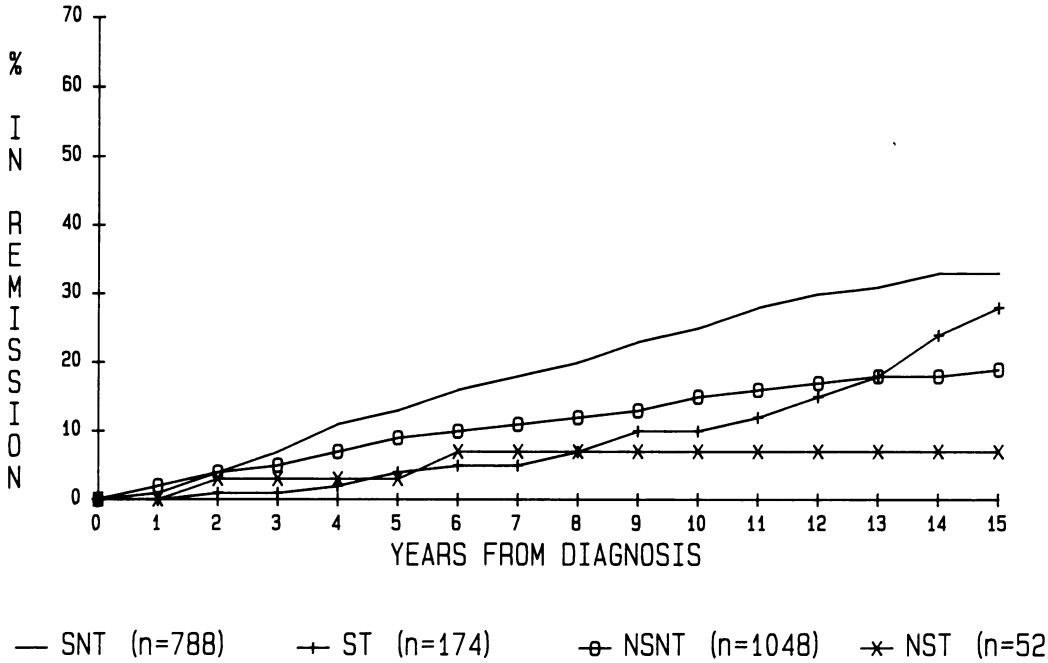


FIG. 1. Intervals from diagnosis to remission in relation to treatment and presence of thymoma. SNT: thymectomy, no thymoma; NSNT: no surgery, no thymoma; ST: thymectomy, thymoma; NST: no surgery, thymoma.

sion (Table 5). Comparison of the patterns of remission from the time of surgery in patients with and without thymoma revealed that patients without thymoma and who were operated on by the transcervical approach had earlier remissions, and the advantage was sustained in the entire follow-up period (Fig. 3). No significant difference in the remission rate of patients with thymomas was noted in relation to surgical technique.

The pattern of remissions was evaluated separately for patients operated on by one of us (AEP) because inclusion of the variable "surgeon" in the multivariate analysis showed that this factor significantly influenced the results. Within the homogeneous group of patients without thymomas who were operated on by AEP, those who presented a combination of mild disease with short duration of symptoms had the earliest onset of remissions, whereas the other three groups showed delayed patterns (Fig. 4). The analysis was limited to the first 10 postoperative years because there were no patients with mild symptoms who were operated on within 3 years from onset of myasthenia, with a follow-up longer than 12 years. At 10 years after thymectomy, 67% of patients with short duration of symptoms and mild disease were in remission compared with 28% of those who had progressed to severe symptoms.

The interval from the time of diagnosis to death of the disease was influenced significantly and independently by the factors shown in Table 6. Those patients who

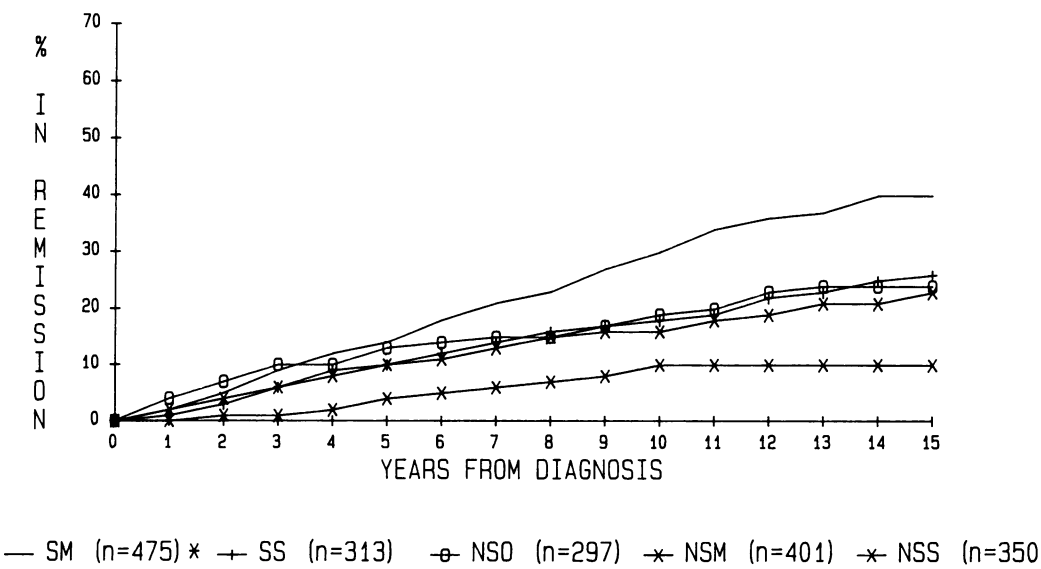


FIG. 2. Interval from diagnosis to remission in patients without thymomas in relation to treatment and severity of disease. SM: thymectomy, mild symptoms; SS: thymectomy, severe symptoms; NSO: no thymectomy, ocular symptoms; NSM: no thymectomy, mild symptoms; NSS: no thymectomy, severe symptoms. *Includes three patients with ocular disease.

TABLE 4. *Duration of Symptoms Before Thymectomy, Age, Severity of Disease, and Likelihood of Thymoma*

| Duration of Symptoms | 0–3 Years (%) | 3–5 Years (%) | 6–10 Years (%) | +10 Years (%) | Total (%) |
|---|---|---|---|---|---|
| No thymoma | 591 (75) | 56 (7) | 55 (7) | 86 (11) | 788 (100) |
| Thymoma | 153 (87) | 8 (5) | 5 (3) | 8 (5) | 174 (100) |
| Total | 754 | 64 | 60 | 94 | 962 |
| **Age at Thymectomy** | **20 Years (%)** | **20–29 Years (%)** | **30–49 Years (%)** | **+50 Years (%)** | **Total (%)** |
| No thymoma | 117 (96) | 215 (95) | 253 (78) | 203 (70) | 788 |
| Thymoma | 5 (4) | 11 (5) | 73 (22) | 85 (30) | 174 |
| Total | 122 (100) | 226 (100) | 326 (100) | 288 (100) | 962 |
| Severe Symptoms | | | | | |
| No thymoma | 72 (96) | 85 (91) | 92 (64) | 64 (58) | 313 |
| Thymoma | 3 (4) | 8 (9) | 51 (36) | 46 (42) | 108 |
| Total | 75 (100) | 93 (100) | 153 (100) | 110 (100) | 421 |

were older at diagnosis, with severe forms of the disease, and those with thymoma and without thymectomy had a shorter survival. The pattern of mortality in relation to presence of thymoma and surgical treatment is shown in Figure 5. Mortality after thymectomy was significantly influenced by four independent factors (Table 7). Those patients operated on *via* a transthoracic approach, those with more severe disease, with thymomas, and older at time of diagnosis had a higher mortality.

Evaluation of the development of extrathymic neoplasms revealed 131 patients in whom the first extrathymic neoplasms were diagnosed after the onset of myasthenia gravis, and 25 patients in whom neoplasms occurred after thymectomy. Of these, 89 occurred in patients who had not undergone thymectomy and 42 occurred among patients who were operated on (Table 2). Multivariate analysis showed that in addition to the age of the patient, there were three other significant and independent factors influencing the appearance of extrathymic tumors after the diagnosis of myasthenia gravis. Earlier appearance was noted in patients with thymoma, in those who did not have thymectomy, and those who had not reached remission (Table 8).

Comparison between the postoperative courses of patients who had transcervical and transthoracic thymectomy was made after stratification by the time in which the patients had thymectomy. The majority of operations in recent years were performed by the transcervical approach. Mortality was very low in patients without thymoma, and no postoperative deaths occurred after 1973. Patients who were operated on after 1973 also had a lower postoperative morbidity in that fewer patients required tracheostomy, prolonged intubation or ventilation, or extended hospital stay (Table 9). Approximately three of four patients without thymoma who had thymectomy required hospitalization for no longer than 5 days. Within the group of patients operated on after 1973, those who had transcervical thymectomy had a significantly higher proportion of short hospitalizations and fewer tracheostomies.

## Discussion

The current study clearly demonstrates that thymectomy significantly influences the clinical course in patients with myasthenia gravis. Compared with nonsurgical treatment, thymectomy is followed by an earlier onset of remissions, lower mortality, and a delay in the appearance of extrathymic neoplasms. The multivariate analysis demonstrates that the presence of a thymoma, the severity of disease, and the age of the patient are factors that significantly influence the clinical course of the disease regardless of treatment and represent independent prognostic indicators. No meaningful evaluation of treatment modalities in myasthenia gravis is possible without taking into consideration the effect of these factors. This study also confirms that thymectomy has an advantage over nonsurgical treatments[14] and that the effects of thymectomy are delayed.[2,3]

The findings indicate that even patients treated by thymectomy show an increasing percentage of remissions with increasing time intervals after diagnosis. This observation confirms previous reports[15] of delayed remissions among patients with generalized disease who

TABLE 5. *Factors Influencing Remission After Thymectomy**

| | Univariate p | Stepwise p | Coefficient/SE |
|---|---|---|---|
| Severity of disease | 0.0001 | 0.0023 | 2.9933 |
| Thymoma | 0.0001 | 0.0047 | 2.6193 |
| Duration of disease | 0.0846 | 0.0211 | 2.2593 |
| Surgical approach | 0.0001 | 0.0589 | 1.8396 |

* Number of patients = 962; number of patients in remission = 198.

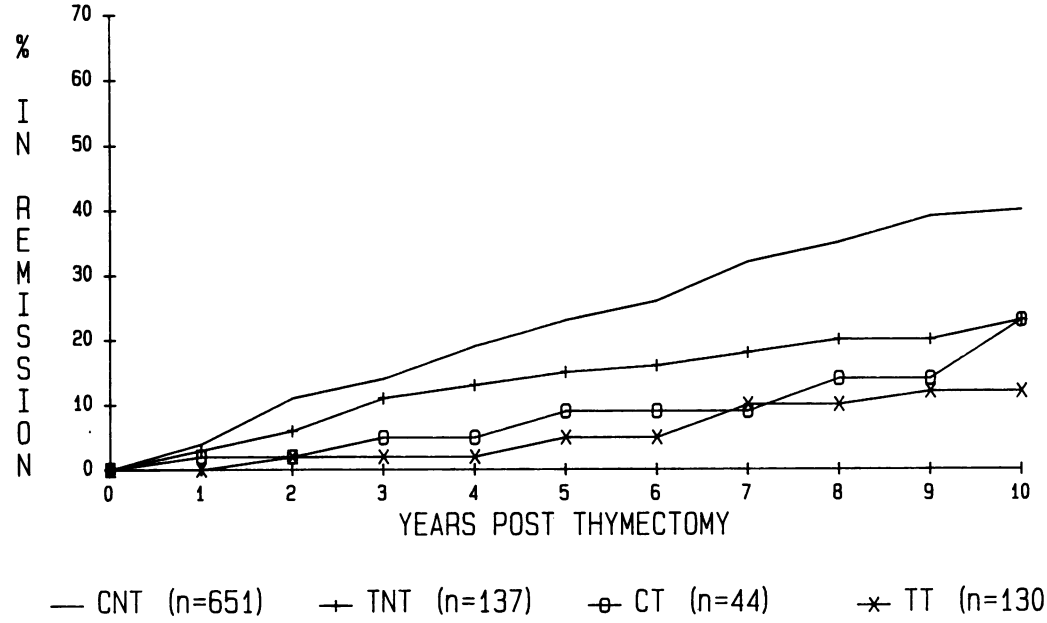


FIG. 3. Interval from thymectomy to remission in relation to thymomas and surgical approach. CNT: cervical approach, no thymoma; TNT: transthoracic approach, no thymoma; CT: cervical approach, thymoma; TT: transthoracic approach, thymoma.

were treated without surgery and does not support the previously held notion that spontaneous, or rather, nonsurgical remissions are limited to patients with ocular disease. It is obvious, therefore, that the pattern of delayed remissions, which had been demonstrated repeatedly in patients after thymectomy,[2,3,5,15] is evident in all subgroups. Results shown in Figure 2 seem to be similar to those of Oosterhuis[15] except for the ocular group, and his results suggest that overall the natural course of the disease is influenced by the same factors in both the Dutch series and ours. The difference noted in the ocular group between the two series may be associated with the less strict criteria used by Oosterhuis, who included patients with sporadic diplopia and ptosis when fatigued at the end of the day in the remission group.

From the observed differences in remission and/or in mortality, among patients treated with and without thymectomy, it appears that the role of thymectomy is to avert progression of the disease, decrease mortality, and accelerate the onset of remission.

The difficulty in evaluating the results of treatment

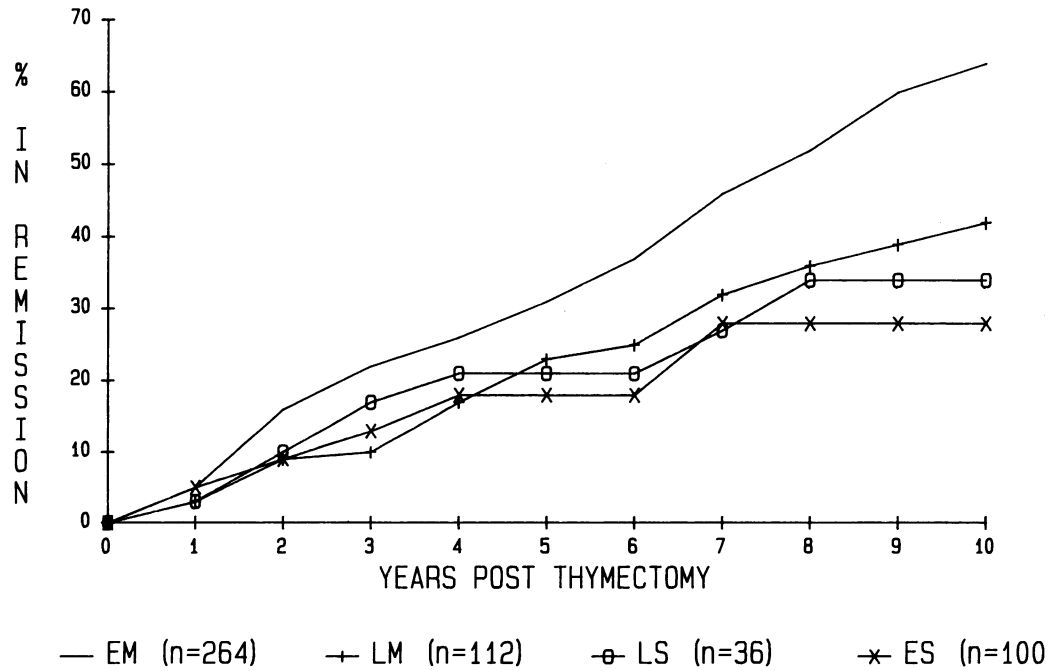


FIG. 4. Interval from thymectomy to remission in patients without thymoma operated on by AEP. EM: short duration and mild symptoms; LM: long duration and mild symptoms; LS: long duration and severe symptoms; TS: short duration and severe symptoms.

modalities without considering potential confounders is further complicated by the facts that thymomas occur more frequently in association with severe disease, are frequently undetected on routine roentgenograms, and may have been unrecognized in previous years when thymectomy was performed only in young patients in whom nonsurgical treatment had failed. The data in Table 4 indicate that approximately 10% of patients who had thymectomy more than 3 years after onset of myasthenia had thymomas and that these were more frequent than had been previously noted among older patients with severe symptoms. Although the adverse clinical course of patients with thymoma has been known for many years,[1,15] the independent impact of the severity of disease on the clinical course has not been previously appreciated.

The findings of our study (Fig. 2) lend support to Schumm's suggestion[16] that thymectomy is indicated in ocular cases. Since thymectomy stops progression of the disease, early intervention before the symptoms become generalized may be advisable. Thymectomy, particularly when performed *via* the transcervical approach, has minimal morbidity and is devoid of the risk of side effects from immunosuppressive drugs. The inability to determine the clinical course of the disease at the time of onset of symptoms[17] and the inability to exclude the presence of thymoma are additional indications for early intervention.

The current study also casts doubt on the validity of the earlier concepts that the sex of the patient influences therapeutic results and that patients over the age of 40 do not do well after thymectomy, as neither sex nor age entered the stepwise analysis when the interval to remission was analyzed (Tables 3 and 5). This confirms the results of our previous report that evaluated thymectomy in patients over the age of 40.[18]

TABLE 6. *Factors Influencing Mortality After Diagnosis in All Patients**

| Variable | Univariate p | Stepwise p | Coefficient/SE |
|---|---|---|---|
| Class at diagnosis | 0.0000 | 0.0000 | 8.6581 |
| Age at onset | 0.0000 | 0.0000 | 9.9893 |
| Thymoma | 0.0000 | 0.0000 | 8.4123 |
| Thymectomy | 0.0000 | 0.0000 | 5.2179 |

* Number of patients = 2062; number of patients who died = 391.

In recent years thymectomy has become recognized as an established therapeutic procedure,[14,19] and arguments as to whether thymectomy should be performed in myasthenia gravis have taken second place to the question of which is the appropriate surgical approach to the thymus. The focus of the controversy has been the feasibility of complete removal of the thymus *via* the transcervical approach rather than the advantage offered by the surgical approach in terms of superior long-term clinical results. Proponents of the transthoracic approaches and advocates of radical thymectomy, which includes removal of mediastinal fat through a combined transcervical and transthoracic approach, have failed to prove a relevant clinical advantage of these procedures over the transcervical approach.[10] Therefore, the argument that a more complete thymectomy can be achieved with the radical approach is a moot point if

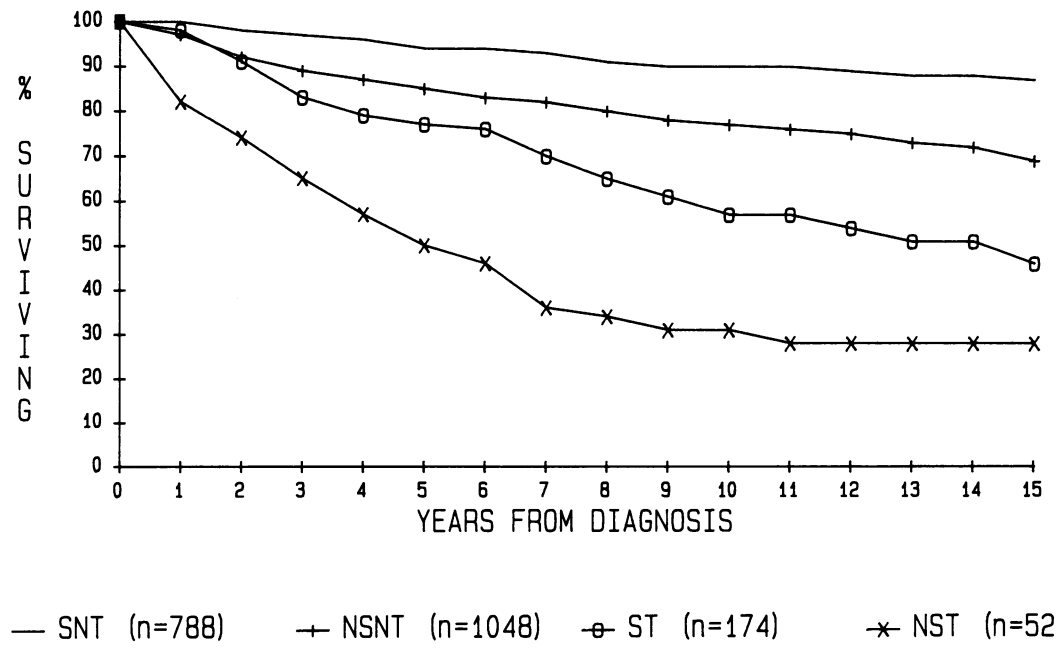


FIG. 5. Interval from diagnosis to death. SNT: thymectomy, no thymoma; NSNT: no thymectomy, no thymoma; ST: thymectomy, thymoma; NST: no thymectomy, thymoma.

TABLE 7. *Factors Influencing Mortality After Thymectomy**

| Variable | Univariate p | Stepwise p | Coefficient/SE |
|---|---|---|---|
| Age at onset | 0.0000 | 0.0001 | 3.9520 |
| Severity of disease | 0.0000 | 0.0011 | 3.8421 |
| Thymoma | 0.0000 | 0.0006 | 3.4280 |
| Surgical approach | 0.0000 | 0.0029 | 2.9265 |

* Number of patients = 962; number of patients who died = 139.

superior clinical results cannot be demonstrated after the use of this technique.

The current study, which addresses the question of whether surgical approach influences the clinical results, does not provide any evidence for advocating a transthoracic removal of the thymus. Indeed, even after considering the effect of independent confounders, a slight advantage of the transcervical approach persisted in terms of long-term results (Table 5). The highly significant advantage of the transcervical approach noted in the univariate analysis was not as significant in the stepwise analysis, indicating that most of it could be explained by the fact that the transcervical technique was used more frequently in patients without thymomas, in those with milder disease, and in those having a shorter duration of symptoms. It is clear that severity of disease and timing of operation affect the results more significantly than the approach, and that the best results were obtained in the group of patients who were treated with early intervention, before clinical progression of the disease. Two additional reports, from surgeons having a large experience with the transcervical approach, substantiate the advantage for early intervention.[8,20] Patients operated on by AEP had earlier onset of remission but this may also reflect a more complete follow-up as similar advantages were noted in patients operated on at our institution after 1973. In earlier years, asymptomatic patients were discharged from follow-up studies. Further analysis would be necessary to determine the cause for this advantage in these patients.

The experimental findings indicating that the protective effect of thymectomy against neoplasms is superior in mice operated on by a technique that results in retention of thymic remnants, compared with a technique that is associated with a complete removal of the thymus,[21] add additional doubts as to the validity of advocating a radical approach to thymectomy. The thymus, which is considered to have an endocrine function, is embryologically derived from the same brachial pouches as the parathyroid, whereas abnormalities of thyroid function are frequent in myasthenic patients.[11] The endocrine mechanism in myasthenia was pointed out by Simpson.[22] If we extrapolate from the experience obtained with thyroid and parathyroid surgery, complete excision of the endocrine gland for hyperthyroidism or primary hyperparathyroidism is rarely indicated and sufficient control is obtained in the majority (approximately 90%) of cases even with a subtotal removal. It is therefore difficult to justify the persistent calls for radical thymectomy since there is neither clinical evidence of, nor scientific basis for, advocating such an approach. Most surgeons who have had experience with the transcervical approach[7-9] prefer it over the transsternal approach, and they agree that the long-term results are comparable to those obtained with the transthoracic approach. In addition, the immediate postoperative course is smoother as a result of the minimal operative trauma. Some of the proponents of the transcervical approach do not recommend it in patients with thymomas,[7] but those who have become familiar with the technique and have used it extensively[5,8,23] report removal of small thymomas, when technically feasible, through the neck incision. The results in Figure 3 indicate that there is no clinical disadvantage when thymomas are removed by the transcervical approach and therefore the alleged disadvantage of the transcervical approach in terms of exposure does not appear to have any clinical relevance.

Residual thymus, or regeneration of the gland after thymectomy, has been implicated in the failure of the procedure to result in remission in all cases. Because of the delayed clinical response after thymectomy, which is influenced by factors unrelated to treatment and surgical technique, it is difficult to identify patients who might benefit from re-exploration to remove residual thymic tissue. Indications for re-exploration in the 10–15% of patients who fail to respond to thymectomy should be based on clinical course or computerized tomographic (CT scan) findings. Re-exploration for residual or ectopic thymus may be indicated, regardless of the original approach, if a patient shows signs of progressive deterioration of symptoms after a prolonged and sustained improvement. Additional thymic tissue has been found in patients operated on originally by both transcervical and transsternal approaches.[24-26] In our series one of the six patients who had reached remission after thymectomy had a relapse of symptoms 5 years later,

TABLE 8. *Factors Influencing Development of Extrathymic Neoplasms After Diagnosis**

| Variable | Univariate p | Stepwise p | Coefficient/SE |
|---|---|---|---|
| Age of patient | 0.0000 | 0.0000 | 5.5203 |
| Thymoma | 0.0109 | 0.0000 | 4.7650 |
| Thymectomy† | 0.0000 | 0.0000 | −4.4702 |
| Remission | 0.0001 | 0.0039 | −2.5917 |

* Number of patients = 2062; number of neoplasms = 131.
† Neoplasms occurring in operated patients before thymectomy listed as occurring in patients without thymectomy.

TABLE 9. *Postoperative Course*

| | Before 1973 | | | | 1973–1986 | | | |
|---|---|---|---|---|---|---|---|---|
| | Thoracic | | Cervical | | Thoracic | | Cervical | |
| Thymoma | − | + | − | + | − | + | − | + |
| All patients | 108 | 88 | 103 | 4 | 28 | 44 | 548 | 40 |
| Mortality | | | | | | | | |
| Number of patients | 33 | 7 | 1 | 0 | 0 | 0 | 0 | 0 |
| Percentage | 3% | 8% | 0.9% | 0 | 0 | 0 | 0 | 0 |
| With tracheostomy | | | | | | | | |
| Number of patients | 73 | 51 | 72 | 3 | 3 | 3 | 24 | 2 |
| Percentage | 68% | 58% | 69% | 75% | 11% | 7% | 4% | 5% |
| Length of stay* | | | | | | | | |
| 3–5 days | | | | | | | | |
| Number of patients | 1 | 0 | 7 | 0 | 4 | 6 | 325 | 21 |
| Percentage | 4% | 0% | 13% | 0% | 40% | 16% | 78% | 64% |
| 6–9 days | | | | | | | | |
| Number of patients | 2 | 1 | 5 | 1 | 2 | 8 | 36 | 5 |
| Percentage | 8% | 5% | 9% | 33% | 20% | 42% | 9% | 15% |
| 10+ days | | | | | | | | |
| Number of patients | 21 | 17 | 42 | 2 | 4 | 10 | 58 | 7 |
| Percentage | 88% | 85% | 78% | 67% | 40% | 42% | 14% | 21% |
| TOTAL | 24 | 18 | 54 | 3 | 10 | 24 | 419 | 33 |
| | Delay in Extubation over 30 Minutes† | | | | | | | |
| Number of patients with delay | | | | | 0 | 1 | 11 | 0 |
| Percentage | | | | | 0% | 25% | 11% | 0% |
| Total | | | | | 2 | 4 | 93 | 6 |
| Percentage | | | | | 100% | 100% | 100% | 100% |

* Data available in 585 patients.

† Data available in 105 consecutive patients operated on in 1983–1986.

had re-exploration, and residual thymus was removed. Relapse of symptoms after remission seems to be rare both in our experience and in other reports.[27] Whether the removal of residual tissue will benefit the patient is not clear as long-term follow-up information in these patients is not yet available. Blalock's original technique, as pointed out in the report of Mulder et al.,[27] was not a complete thymectomy, yet the patient derived a definite benefit.

The current study did not address the issue of specific mortality from myasthenia gravis because the cause of death was not always readily available from the records. It would be of interest to address this issue in future analyses, taking into consideration the possibility of increased mortality from associated extrathymic neoplasms in patients who had not had thymectomy.

Previous studies have suggested that there is an increased incidence of extrathymic neoplasia among myasthenic patients and that thymectomy is not followed by this increased incidence of extrathymic tumors.[4,28,29] The current study confirms that development of extrathymic neoplasms after the diagnosis of myasthenia gravis is significantly less frequent among those patients who had had thymectomy.

Thymectomy, particularly when performed by the transcervical approach, is evidently a safe procedure associated with minimal morbidity. Complete information on the immediate postoperative course was not available in all our patients. The available results (Table 9) indicate that in recent years (1983–1986), need for postoperative ventilation and frequency of tracheostomy have been decreasing.

Of 92 consecutive patients who had thymectomy from 1983 to 1985 and who were monitored in the postoperative period, only eight (8.7%) who had transcervical thymectomy required postoperative mechanical ventilation for more than 3 hours as we previously reported.[30] Other centers report that patients who have transsternal thymectomy require prolonged mechanical respiratory assistance far more frequently.[31–33] Routine tracheostomy used to be commonplace in previous years when the transsternal approach was used, and this accounts for the high proportion of tracheostomies shown in Figure 9 for the period preceding 1973. Even

in more recent series of transsternal thymectomies, 30% of patients required mechanical ventilation for more than 3 days and 7% required tracheostomy.[33] In our series only 26 of the 588 patients (4%) who had transcervical thymectomy after 1973 required tracheostomy, whereas intubation beyond 0.5 hour after completion of surgery was required in only 10% (Table 9). Early extubation was also noted in other centers using the transcervical approach.[34] Although thymectomy through the neck was described as a procedure taking 15–20 minutes,[35] in our experience the operating time is rarely less than 20 minutes and is more frequently 60–90 minutes. The difference may be due to the fact that thymic hyperplasia is encountered in most myasthenic patients and this necessitates additional blunt dissection to achieve good visualization of the lower attachments of the thymic lobes. Longer operative time is also necessary when parasternal mediastinoscopy[36] is required for removal of small thymomas.

In today's budget-conscious environment it is difficult to justify the added cost of technical procedures that have disadvantages in terms of immediate morbidity and no advantage in terms of long-term clinical results. Considering both long- and short-term advantages as well as efficient use of health resources, it would seem that early surgical intervention, *via* the transcervical approach when technically feasible, represents the treatment of choice for patients with myasthenia gravis.

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