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This is the author's manuscript

Original Citation:

Availability:
This version is available http://hdl.handle.net/2318/146356 since 2016-10-19T11:29:28Z

Published version:
DOI:10.1093/ejcts/ezt567

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(Article begins on next page)
This is the author's final version of the contribution published as:

Filosso PL; Venuta F; Oliaro A; Ruffini E; Rendina EA; Margaritora S; Casadio C; Terzi A; Rena O; Lococo F; Guerrera F.. Thymoma and inter-relationships between clinical variables: a multicentre study in 537 patients.. EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY. 45 (6) pp: 1020-1027. DOI: 10.1093/ejcts/ezt567

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http://hdl.handle.net/2318/146356
Thymoma and inter-relationships between clinical variables: a multicentre study in 537 patients†

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Abstract

OBJECTIVES In thymomas, the roles of Masaoka-Koga stage, histology and the presence of myasthenia gravis (MG) have been considered fundamental for patient management and outcomes. In this study, we retrospectively evaluated several clinical variables, with the aim of outlining their relationships and clinical/prognostic significance in resected thymoma patients.

METHODS A retrospective search of our surgical database for patients operated on for thymoma in six Italian high-volume thoracic surgery centres between 2000 and 2011 was conducted. The following clinical variables were evaluated: Masaoka-Koga Stage, tumour histology, the presence of MG, other autoimmune syndromes or second tumours, the completeness of tumour resection and the development of recurrences.

RESULTS Five hundred and thirty-seven (273 males—51%) were retrospectively included in this study. Our results indicate that: (i) MG correlates with early Masaoka-Koga stage and B-type thymoma; (ii) Stage III–IVa tumours correlate with B-type tumour; (iii) autoimmune paraneoplastic syndromes correlate with Stage I–II thymoma; (iv) second malignancies correlate with the absence of paraneoplastic disorders and weakly with B-type tumour and (v) overall survival was influenced by Masaoka-Koga stage and completeness of surgical resection.

CONCLUSIONS In thymomas, Masaoka-Koga stage, histology, MG, other autoimmune syndromes and second malignancies are inter-related, but only Masaoka-Koga tumour stage, amid these clinical variables, has been demonstrated to be a strong prognostic indicator of survival.

Key words: Thymoma, Surgery, World Health Organization, Pathology, Myasthenia gravis, Paraneoplastic disorders, Cancer
INTRODUCTION

Thymomas are rare neoplasms arising from the thymic epithelial cells and characterized by an extreme variability in histological appearance, as well as in clinical behaviour. Usually with an indolent growth, very often thymomas present with neighbouring organ/structure invasion, pleural dissemination and, although rare, distant metastases. From a histological point of view, they represent a mixture of neoplastic cells and non-neoplastic lymphocytes, and a number of classification systems have been proposed during the years, resulting in confused nomenclature. At present, the 2004 World Health Organization (WHO) classification [1] seems to provide the standard system. The rarity of the disease (with an overall incidence in the USA of 0.15 cases per 100.000 person-year [2]) might explain the fact that currently, no official staging system has been defined by the Union Internationale Contre le Cancer (UICC) and the American Joint Commission on Cancer (AJCC). The thymus plays a central role in the immune system, because it is the site of maturation for T cells from bone marrow progenitors. The autoimmune regulator (AIRE) system is fundamental to the autoreactivity screening [3]: in the normal thymus medulla, T-lymphocytes with potential autoaggressive characteristics were deleted. In a normal working condition, only self-tolerant and immunosurveillant against neoplastic cells T-lymphocytes are released systematically from the thymus. Most thymomas present a thymopoietic activity: autoreactive T-lymphocytes are exported from the neoplastic thymus and can persist for a long time in the periphery, accounting for the possible onset of autoimmune disorders, of which myasthenia gravis (MG) is by far the most common. In fact, while MG is known to affect ~45% of patients with thymoma [4], the frequency of other paraneoplastic diseases is reported to be between 2 and 15% [5]. Finally, a higher than expected incidence of second extrathymic malignancies in patients with thymoma (range 9–27%) have been reported [2, 6, 7]. Relatively few papers have investigated the possible inter-relationships between clinical variables in thymoma patients. We hereby report the results of a multicentre study from six high-volume Italian institutions for thymoma surgery, with the aim of evaluating how the most important variables may influence the others and which is their impact on thymoma outcomes.

MATERIALS AND METHODS

Between January 2000 and December 2011, a total of 537 patients with thymoma were operated on at six different Italian institutions of thoracic surgery. Patients with thymic carcinoma and primary neuroendocrine tumours of the thymus were excluded from this study, as well as those with an inoperable lesion or those who received tumour biopsy only. Preoperative standard work-up included routine blood tests, electrocardiography (EKG), echocardiography if required (in case of invasive lesions or high-risk patients), pulmonary function tests with diffusion capacity (diffusion lung capacity for carbon monoxide) and arterial blood gas analysis, neurological consultation to rule out MG according to the clinical status, and total body computed tomography. Magnetic resonance was used in case of advanced lesions to check possible tumour invasion of great vessels, heart, trachea and other mediastinal organs/structures. Positron emission tomography scan was not routinely done: in fact, it was performed according to the particular oncological protocols of each institution. Complete sternotomy was the standard surgical approach; lateral thoracotomy or combined incisions have seldom been performed, according to the tumour clinical/radiological presentation. According to the International Thymic Malignancy Interest Group (ITMIG) standard outcome measures for thymic malignancies [8], surgery was considered radical if a complete tumour resection (R0) was achieved and, contrariwise, in case of incomplete micro–macroscopic residuals (R1–R2). Histology was assessed according to the 2004 World Health Organization (WHO) classification [1]. According to ITMIG standards, tumour staging was determined using the Masaoka-Koga classification system [9]. Preoperative chemotherapy (CT) (occasionally associated with radiotherapy (RT) according to the oncological standards of each institution) was administered in case of anticipated tumour unresectability. Postoperative RT and/or CT was offered to invasive thymomas (Stages II–III–IVa) according to the oncological policy of each centre. The follow-up protocol was quite similar at all institutions: it included CT scan every 6 months for the first 3 years, and afterwards on a yearly basis or on clinical demand. Patient clinical data were obtained from hospital records; outcome data were acquired by outpatient controls or telephone interviews. For the inter-relationship evaluations, the following clinical variables were assessed: WHO histology, Masaoka-Koga stage,
MG, other paraneoplastic syndromes, extrathymic second tumours, administration of induction or adjuvant therapy, completeness of surgical resection and development of tumour recurrence. For the statistical analysis, we dichotomized both WHO histology and Masaoka-Koga stages into two categories (WHO: 1, A + AB + B1; 2: B2 + B3; Masaoka-Koga: 1: Stages I and II; 2: Stages III and IVa), as we did in two previous articles [7,10].

STATISTICAL ANALYSIS

Study outcomes

The primary outcome was overall survival (OS) calculated from the date of intervention to the date of death from any cause. Patients alive were censored on the date of last follow-up. Then, we evaluated the inter-variable frequencies according to the WHO histology, thymoma Masaoka-Koga stage, presence of MG, other autoimmune paraneoplastic disorders and extrathymic second tumours.

Statistical analysis

Continuous data are presented as medians (interquartile range, IQR) and categorical ones as number (percentage, %). We report the number of non-missing observations. Probabilities of survival were estimated by the Kaplan–Meier method, using the date of surgical resection as the starting point and the date of death or the last follow-up date as the endpoint. Cox proportional hazards regression models were used to identify the association between individual factors and OS. Univariate and multivariate analyses were also performed. We considered the following variables: gender (male vs female), age at intervention (as continuous), MG status (yes vs no), paraneoplastic syndrome (yes vs no), previous malignancies (yes vs no), second malignancies (yes vs no), resection status (R0 vs R1–R2), histology (WHO A/AB/B1 vs B2/B3), Masaoka-Koga Stage (I–II vs III–IVA), induction therapy (yes vs no), adjuvant therapy (yes vs no) and tumour recurrence development (yes vs no). In all models fitted in this study, missing data in the evaluated factors were multiple-imputed. Combined estimates were obtained from 10 imputed datasets. The inter-relationship among variables of interest, WHO histology, Masaoka-Koga stage, MG, autoimmune paraneoplastic syndromes, second tumour and resection status, was assessed using a logistic regression (logit) model. Odds ratio (OR) and the corresponding 95% confidence intervals (95% CIs) were provided for each model. A P-value of <0.05 was considered significant. All statistical analyses were performed using STATA (version 12.1).

RESULTS

Five hundred and thirty-seven (273 males—51%) patients were retrospectively included in this study. The characteristics of these patients are reported in Table 1. In 29 cases, a different neoplasm was observed before thymoma diagnosis; in 41, a second malignancy developed after thymoma treatment (Table 2). The median age at surgery was 54 (±22 years, range 8–87) years. MG was observed in 271 (51%) cases, and other paraneoplastic syndromes in 50 (13%). Of the latter, the most common were: pure red cell aplasia [4], Good’s syndrome [1], thyroiditis [9], systemic lupus erythematosus [4], ulcerative colitis [6], glomerulonephritis [5], neuromyotonia [3] and rheumatoid arthritis [8]. Table 1 also reports the incidence of Masaoka-Koga stages and WHO histological subtypes; in particular, we had Stages III–IVA in 203 (38%), and high-grade WHO tumours (B2–B3) in 263 (49%) patients, respectively. Neoadjuvant therapy was administered in 53 (10%) cases. A complete resection (R0) was achieved in 401 (92%) patients. Adjuvant therapy was administered in 275 (51%) cases. The follow-up was completed in 523 (97%) patients. Our median follow-up was 70 (range 2–273) months; at the end of it, 92 (17%) patients were dead, 14 of whom from thymoma. Recurrences after R0 resection developed in 47 (12%) patients. Figure 1 shows the distribution of clinical variables (MG, other autoimmune paraneoplastic disorders, presence of second tumours, R1–R2 resection and tumour recurrences) according to thymoma, WHO and Masaoka-Koga stages.

Table 1: Patient characteristics
Table 2:
Number of previous and second malignancies by site

Figure 1:
Patient characteristics and distribution of clinical variables according to thymoma WHO and stage.

REGRESSION ANALYSIS

Regression analyses were performed to evaluate the inter-relationships between the clinical variables of interest; the results of these analyses are reported in Table 3.

Table 3:
Logistic regression analysis with four variables of interest (MG, other paraneoplastic syndromes, WHO histology and Masaoka-Koga stages)

WHO histology

When WHO histology is considered as the outcome variable, B2–B3 subtypes are associated with MG (OR: 2.72; 95% CI: 1.83–4.03, P < 0.00). B2–B3 thymomas are also associated with Masaoka-Koga Stage III–IVa (OR: 4.77; 95% CI: 3.07–7.41, P < 0.00).

Masaoka-Koga stage

Masaoka-Koga Stages I–II are likely associated with MG (OR: 0.59; 95% CI: 0.38–0.90, P = 0.02). When a thymoma is at Stages III–IVa, it is more frequently a B3–B3 WHO subtype (OR: 4.64; 95% CI: 3.00–7.16, P < 0.00). Stage III–IVa tumours are statistically associated with R1–R2 resections (OR: 19.84; 95% CI: 5.79–67.98, P < 0.00).

Myasthenia gravis

When considering MG as the outcome variable, it is associated with an early Masaoka-Koga stage (OR: 0.60, 95% CI: 0.39–0.92, P = 0.02) and B2–B3 WHO types (OR: 2.77; 95% CI: 1.87–4.10, P < 0.00), only.

Other paraneoplastic diseases

Paraneoplastic syndromes are statistically associated with an early Masaoka-Koga stage (OR: 0.45; 95% CI: 0.29–0.71, P < 0.00), only.

Extrathymic second malignancies

Second tumours are statistically associated with the absence of paraneoplastic syndromes (OR: 0.18; 95% CI: 0.09–0.35, P < 0.00); the association with B-type thymoma reached a weak statistical significance (OR: 1.50; 95% CI: 0.93–2.44, P = 0.09).

SURVIVAL ANALYSIS
OS, as outcome measures, was analysed in both univariate and multivariate models. Table 4 summarizes these results. Five and 10-year overall survival rates were 88 and 75%, respectively (Fig. 2A). OS survival curves for WHO histology (A + AB + B1 vs B2 + B3) and Masaoka-Koga stages (I–II vs III–IVa) are shown in Fig. 2B, respectively. Five- and 10-year OS for each Masaoka-Koga stage and WHO histological tumour type are also shown in Fig. 2A. At the univariate model, strong indicators of poor survival were: high Masaoka-Koga stages (OR: 2.37; 95% CI: 1.55–4.00, P< 0.00), R1–R2 resections (OR: 4.09; 95% CI: 2.39–7.01, P< 0.00) and the presence of tumour recurrences (OR: 1.94; 95% CI: 1.21–3.11, P = 0.01). At the multivariate model, Masaoka-Koga Stages III–IVa (OR: 2.36; 95% CI: 1.30–4.28, P = 0.01) and incomplete resections (OR: 3.11; 95% CI: 1.60–6.06, P< 0.00) were statistically negative prognostic factors. Contrariwise, the presence of MG (P = 0.68), other paraneoplastic syndromes (P = 0.66), second malignancies (P = 0.66) and WHO histology (P = 0.94) did not confer a significant survival advantage.

### Table 4:
Results of univariate and multivariate analyses

![Figure 2:](image)

(A) OS curve and survival table. (B) Survival curves according to WHO tumour histology and Masaoka-Koga tumour stages.

### DISCUSSION

The main purpose of our study was to assess, in a cohort study model, possible inter-relationships between the most important clinical variables in thymoma patients. Our study has the intrinsic bias due to its retrospective design, but also some strengths in the high number of patients collected in a relative short period of observation among six high-volume Italian thoracic surgery institutions, a quite similar protocol for pre-, intra- and postoperative management of patients and a similar oncological strategy for induction/adjuvant treatments. Our results indicate that: (i) MG correlates with early Masaoka-Koga stage and B-type tumour; (ii) Stage III–IVa tumours correlate with B-type thymoma; (iii) autoimmune paraneoplastic syndromes correlate with Stage I–II thymoma; (iv) second malignancies correlate with the absence of paraneoplastic disorders and weakly with B-type tumour and (v) OS was influenced by Masaoka-Koga stage and completeness of surgical resection.

Myasthenia gravis

Our results match those previously reported in the literature concerning the clinical correlation between MG and WHO/Masaoka-Koga stage [11–14]. Epidemiological data demonstrate that 10–20% of patients with MG have a thymoma, and on the other hand, 25–45% of patients with thymoma present with MG [15, 16]. Moreover, 4–7% of myasthenic thymoma patients have more than one paraneoplastic syndrome [5]. The association of thymoma and autoimmune disorders is related to the intratumoural development and maturation of autoaggressive T-lymphocytes. According to the WHO histological classification, B-type tumours consist of plump epithelioid neoplastic cells with a component of T-lymphocytes at different stages of maturation [1], while A and AB-type tumours present with no/low degree of lymphocytes. Okumura et al. [13] observed that a thymic cortical epithelial cell function was well represented in B1, AB and B2 tumours. Moreover, Evoli et al. [11] and Okumura et al. [13] first demonstrated that MG slightly correlates with A–AB tumours, and among B-type ones, it was most frequently observed in B1–B2-type. Therefore, the authors correlated this association with MG, to the functional aspects of thymomas. They, in fact, speculated that
MG pathogenesis might result from the epithelial function to induce T-lymphocyte development, which further strengthens the association between MG and B-type neoplasms. Our results seem to confirm the hypothesis that WHO classification might reflect thymoma immunological behaviour [17]. The high percentage of B3 thymomas associated with MG described in some series (as ours) might be explained by the tumour histopathological modifications induced by preoperative steroid medical treatment. In fact, the thymoma lymphoid component is known to be highly sensitive to steroid administration, and therefore, this therapy might have transformed the morphology of some B2 tumour into that comparable with that of B3 type. As previously reported in the literature [4, 11, 12, 18], we confirm a strict correlation between MG and early Masaoka-Koga tumour stage. This might be explained with an earlier diagnosis of thymoma in patients with MG, due to their strict follow-up. Other authors [19, 20], observing that (i) invasive thymomas are more frequently diagnosed in non-MG patients and (ii) Intratumoural T-cell maturation occurs in MG-associated tumour, with the formation of T cells autoantigen-specific to MG-related antigens. They postulated that thymoma with and without MG might be considered as two distinct entities, and a more aggressive biological pattern of growth of non-MG ones might be responsible of the different outcomes and recurrence rate of the two diseases. Our results did not show any survival benefit of MG on OS, which is in contrast with some previously published series [10, 14], but in line with Kondo’s large series results [12].

Paraneoplastic syndromes

The thymus’ primary functional role concerning the immunological system is to process T-lymphocyte selection and maturation (the so-called ‘negative selection process’). Although the most productive thymic activity takes place during foetal life, immune-pathological studies provide the evidence that thymic function may continue also during adulthood [21], which may explain why thymic neoplasms are associated with immunodeficiency and autoimmune disorders. Excluding MG, a wide variety of other autoimmune conditions are associated with Thy, of which the most common are: haematological (aplastic anaemia, pure red cell aplasia and Good’s syndrome), neurological (palsy, neuromyotonia, limbic encephalitis and psychosis/sleep disorders), cutaneous (pemphigus, vitiligo, alopecia and lichen) and generic ones (systemic lupus erythematosus, thyroiditis, ulcerative colitis and glomerulonephritis). This leads to the conclusion that, among human neoplasms, thymomas are associated with the highest frequency with paraneoplastic autoimmune disorders. A clear explanation for this phenomenon is still debated, but the possible mechanisms might be: (i) an inversion of CD4:CD8 cell ratios; (ii) B-cell lymphopenia and (iii) hypogammaglobulinemia [22]. Evoli et al. [5] hypothesized that the relationship between thymoma and paraneoplastic diseases might be based on the potential capability of the tumour to produce and export in periphery abnormal T-lymphocytes (increase in CD4+ and reduction in CD4CD25+ cells). The role of AIRE system and its expression in normal and neoplastic thymic tissue was already debated [3]. Histological models demonstrated that, in thymoma, AIRE-positive cells are extremely rare and could be detected only in B1-type tumours. Contrariwise, AIRE high expression was found to be 8.5-fold in non-tumoural thymus and equivalent in those with and those without MG [23]. CD25+Foxp3+ (Treg) cells levels are significantly higher in non-neoplastic thymus, suggesting that the tissue microenvironment is defensive in the process of negative selection of autoreactive T-lymphocytes. In fact, Tregcells show inhibitory effects on antigen-specific activation of naive autologous T-cells, and furthermore, they are key controllers of self-reactive cells and contribute to the maintenance of immunological tolerance. The fact that AIRE is poorly expressed in thymoma epithelial cells and that thymomas contain low Treg cell numbers indicate that the tumoural tissue of thymoma represents a poorly organized microenvironment in which the development of self-reactive T-cells is probably facilitated. Our results confirm that: (i) thymoma-associated autoimmune syndromes present with a relative high frequency (13%) and (ii) they appear to be very different involving several organs. To our knowledge, it is the first time a correlation between autoimmune paraneoplastic disorders and Masaoka-Koga early tumour stages has been described. Further multicentre cohort studies are required to confirm this evidence.

Extrathymic second malignancies
An increased risk of developing second malignancies in thymoma patients has been reported in the literature [6, 7, 24]. In a recent paper [7], we described the results of a multicentre study in 302 patients, and we found that patients with thymoma have ~2-fold higher risk of developing a second cancer, compared with the normal population. We recorded 50 extrathymic tumours: 28 metachronous, 4 synchronous and 18 diagnosed before the intervention; besides, 8 patients developed two primary extrathymic tumours. An ‘intrinsic immune abnormality’, of which the tumour itself may be a marker, was suggested as a possible biological explanation for this phenomenon [6, 11, 24] by the finding of an increased risk of extrathymic tumours before the diagnosis of thymoma, along with a high incidence of autoimmune disorders, as mentioned above. As Welshet al. suggested [6], these tumours are true second cancers rather than cancers related to thymoma treatment. Our previous report also supported MG protective effect against second cancers, possibly due to a sort of anti-tumoural autoimmunity. A correlation between second tumours and B2–B3 thymomas, which was also described by us [7], was now confirmed in this study. The belief that aggressive tumours might be at higher risk of developing second cancer seems to be reinforced by the fact that a strong correlation exists between these and thymomas without autoimmune paraneoplastic disorders, which contrariwise we saw to be the preserve of early tumour stages. Death in thymoma patients, even in high stages, is not always tumour-related and might be due to other causes as, for example, to the associate MG. Many patients may experience a prolonged survival, even after a tumour recurrence. Our results concerning OS confirm that the risk of mortality increases with the increase of tumour stage and incomplete resections have been demonstrated to be a very strong indicator of poor survival. Neither WHO histology nor MG conversely conferred a significant advantage in survival. Our analyses are in line with the most important observational studies published in the literature [4, 10, 12, 14, 18, 25]. In conclusion, our study demonstrates the consistent role of relationships between clinical variables in Thy patients. Masaoka-Koga stage and WHO histological classification have been confirmed to possess a key role in identifying biologically more aggressive tumours and should guide a possible multimodal approach to such rare neoplasms.

Previous Section

Conflict of interest: none declared.

Footnotes

- ‡Filippo Lococo has taken part in the present study during his stay at the Catholic University of Rome.

REFERENCES

1. Marx A,
2. Strobel P,
3. Zettl A,
4. Chan JKC,
5. Harris NL,
6. Kuo TT
7. Engels EA,
8. Pfeiffer RM


7. Engels EA,
8. Pfeiffer RM


2. "

REFERENCES
1. Marx A,
2. Hohenberger P,
3. Hoffmann H,
4. Pfannschmidt J,
5. Schnabel P,
6. Hofmann HS,
7. et al

3. Detterbeck FC,
2. Parsons AM
3. Evoli A,
4. Minicucci GM,
5. Battaglia A,
6. Della Marca G,
7. Lauriola L,
8. Fattorossi A

9. Welsh JS,
10. Wilkins KB,
11. Green R,
12. Bulkley G,
13. Askin F,
14. Diener-West M,
15. et al
16. Filosso PL,
17. Galassi C,
18. Ruffini E,
19. Margaritora S,
20. Bertolaccini L,
21. Casadio C,
22. et al

23. Huang J,
24. Detterbeck FC,
25. Wang Z,
26. Loehrer PJ

27. Koga K,
28. Matsuno Y,
29. Noguchi M,
30. Mukai K,
31. Asamura H,
32. Goya T,
33. et al

34. Ruffini E,
35. Filosso PL,
36. Mossetti C,
37. Bruna MC,
38. Novero D,
39. Lista P,
40. et al


41. Evoli A,
42. Minisci C,
43. Di Schino C,
44. Marsili F,
45. Punzi C,
46. Batocchi AP,
47. et al


48. Kondo K,
49. Monden Y


50. Okumura M,
51. Shiono H,
52. Minami M,
53. Inoue M,
54. Utsumi T,
55. Kadota Y,
56. et al


57. Margaritora S,
58. Cesario A,
59. Cusumano G,
60. Meacci E,
61. D'Angelillo R,
62. Bonassi S,
63. et al


64. Phillips LH II.


65. Tormoehlen LM,
66. Pascuzzi RM


108. Scarpino S,
109. Di Napoli A,
110. Stoppacciaro A,
111. Antonelli M,
112. Pilozzi E,
113. Chiarle R,

4.

1. Weksler B,
2. Nason KS,
3. Mackey D,
4. Gallagher A,
5. Pennathur A

6. Detterbeck F,
7. Youssef S,
8. Ruffini E,
9. Okumura M