Title

Paraneoplastic Syndromes and Thymic Malignancies: An Examination of the International Thymic Malignancy Interest Group Retrospective Database

Journal

Journal of Thoracic Oncology, 13(3)

ISSN

1556-0864

Authors

Padda, Sukhmani K
Yao, Xiaopan
Antonicelli, Alberto
et al.

Publication Date

2018-03-01

DOI

10.1016/j.jtho.2017.11.118

Peer reviewed

HHS Public Access

Author manuscript

J Thorac Oncol. Author manuscript; available in PMC 2019 March 01.

Published in final edited form as:

J Thorac Oncol. 2018 March ; 13(3): 436–446. doi:10.1016/j.jtho.2017.11.118.

Paraneoplastic Syndromes and Thymic Malignancies: An Examination of the International Thymic Malignancy Interest Group Retrospective Database

Sukhmani K. Padda, MD[a], **Xiaopan Yao, PhD**[b], **Alberto Antonicelli, MD**[c], **Jonathan W. Riess, MD/MS**[d], **Yue Shang, PhD**[e], **Joseph B. Shrager, MD**[f], **Robert Korst, MD**[g], **Frank Detterbeck, MD**[h], **James Huang, MD**[i], **Bryan M. Burt, MD**[j], **Heather A. Wakelee, MD**[k,*], and **Sunil S. Badve, MD**[l,*]

[a]Department of Medicine, Division of Oncology, Stanford Cancer Institute/Stanford University School of Medicine, Stanford, CA/USA; 875 Blake Wilbur Drive, Stanford, CA 94305

[b]Department of Surgery, Division of Thoracic Surgery, Yale University School of Medicine, New Haven, CT/USA; 333 Cedar Street, New Haven CT 06510

[c]Department of Surgery, Division of Thoracic Surgery, Yale University School of Medicine, New Haven, CT/USA; 333 Cedar Street, New Haven CT 06510

[d]Department of Medicine, Division of Oncology, University of California Davis Cancer Center, Sacramento, CA/USA; 4501 X Street, Suite 3016, Sacramento, CA 95817

[e]The MathWorks, Naticka, MA/USA; 1 Apple Hill Drive, Natick, MA 01760

[f]Department of Cardiothoracic Surgery, Stanford Cancer Institute/Stanford University School of Medicine, Stanford, CA/USA; 300 Pasteur Drive, Stanford, CA 94305

[g]Department of Thoracic Surgery, Icahn School of Medicine at Mount Sinai Health System, New York, NY/USA and Valley/Mount Sinai Comprehensive Cancer Center, Paramus, NJ/USA; 1468 Madison Avenue, New York, NY 10029

[h]Department of Surgery, Division of Thoracic Surgery, Yale University School of Medicine, New Haven, CT/USA; 333 Cedar Street, New Haven CT 06510

[i]Department of Surgery, Thoracic Service, Memorial Sloan Kettering Cancer Center, New York, NY/USA; 1275 York Avenue, New York, NY 10065

[j]Department of Surgery, Division of Thoracic Surgery, Baylor College of Medicine, Houston, TX/USA; One Baylor Plaza, MS390, Houston, TX 77030

(corresponding author) padda@stanford.edu.

*co-senior authors

Conflict of Interest Statement: No relevant COI for all authors for this submitted work.

Dr. Wakelee has the following disclosures but not relevant to this submitted work: Consultant/Honoraria: Peregrine, ACEA, Pfizer, Helsinn, Genentech (uncompensated) Grant/Research: Clovis, Exelixis, AstraZeneca/Medimmune, Genentech/Roche, BMS, Gilead, Novartis, Xcovery, Pfizer, Celgene, Pharmacyclics, Lilly

Dr. Padda has the following disclosures but not relevant to this submitted work: Consultant/Honoraria: G1 therapeutics, Janssen, AstraZeneca Research: EpicentRx, Forty Seven Inc.

[k]Department of Medicine, Division of Oncology, Stanford Cancer Institute/Stanford University School of Medicine, Stanford, CA/USA; 875 Blake Wilbur Drive, Stanford, CA 94305

[l]Department of Pathology, Indiana University, Indianapolis, IN/USA; 635 Barnhill Drive MS A-135, Indianapolis, IN 46202

Abstract

Introduction—Thymic epithelial tumors (TETs) are associated with paraneoplastic autoimmune (PN/AI) syndromes. Myasthenia gravis is the most common PN/AI syndrome associated with TETs.

Methods—The International Thymic Malignancy Interest Group (ITMIG) retrospective database was examined to determine (i) baseline and treatment characteristics associated with PN/AI syndromes and (ii) the prognostic role of PN/AI syndromes for patients with TETs. The competing risks model was used to estimate cumulative incidence of recurrence (CIR) and the Kaplan-Meier method was used to calculate overall survival (OS). A Cox proportional hazards model was used for multivariate analysis.

Results—6670 patients with known PN/AI syndrome status were identified from 1951-2012. PN/AI syndromes were associated with younger age, female sex, type B1 thymoma, earlier stage, and an increased rate of total thymectomy and complete resection status. There was a statistically significant lower CIR in the PN/AI (+) group compared to the PN/AI (−) group (10-year 17.3% vs. 21.2%, respectively, p=0.0003). The OS was improved in the PN/AI (+) group compared to the PN/AI (−) group (HR 0.63, 95% CI 0.54-0.74, P<0.0001, median OS 21.6 years versus 17.0 years, respectively). However, in the multivariate model for recurrence-free survival and OS, PN/AI syndrome was not an independent prognostic factor.

Discussion—Previously, there has been mixed data regarding the prognostic role of PN/AI syndromes for patients with TETs. Here, using the largest dataset in the world for TETs, PN/AI syndromes were associated with favorable features (i.e. earlier stage, complete resection status) but were not an independent prognostic factor for TETs.

Keywords

thymic epithelial tumor; thymoma; thymic carcinoma; paraneoplastic; myasthenia gravis

Introduction

Thymic epithelial tumors (TETs), including thymomas and thymic carcinomas, are rare tumors of the anterior mediastinum.[1] Thymomas have been associated with paraneoplastic autoimmune (PN/AI) syndromes more frequently than have thymic carcinomas.[2] Paraneoplastic syndromes can precede the diagnosis of a tumor and tend to improve with treatment of the tumor. Although myasthenia gravis (MG) is the most common PN/AI syndrome associated with TETs,[3] there are others related to hematopoietic cells, including pure red cell aplasia[4] and hypogammaglobulinemia.[5] There are many additional PN/AI syndromes reported as case reports such as systemic lupus erythematosus.[6]

With regards to MG, 10-20% of patients with MG have thymoma and 30% of patients with thymoma either present with or develop MG.[3, 7] Myasthenia gravis is a result of autoantibodies against the neuromuscular junction, with the most common being acetylcholine receptor (AChR) antibodies.[3] The hallmark MG symptoms of skeletal muscle weakness and fatigability can range from isolated ocular symptoms to more generalized symptoms.[7] There are specific antibodies associated with MG that co-exist with AChR antibodies[8] and increase the likelihood of a coexisting thymoma and may herald more severe disease, including antibodies against titin[9], a large intracellular protein important for muscle contractility, and against ryanodine receptor (RyR), a calcium channel in the sarcoplasmic reticulum.[10] Although autoantibodies play a critical role in the development of MG in patients with thymoma, there are seronegative cases reported, implicating alternative mechanisms of immune dysregulation.[11, 12]

Although the exact pathogenesis remains unknown, it is not surprising that TETs are associated with autoimmune disorders, given that the thymus is critical in building the T-cell repertoire (i) via positive selection in thymic cortical epithelial cells and (ii) in maintaining immune homeostasis and central self-tolerance via negative selection in the thymic medulla.[13]

Thymomas have a deranged tumor microenvironment, carry out abnormal intratumoral thymopoiesis, and thus disseminate an abnormal circulating T-cell repertoire that has been insufficiently tolerized to self-antigens.[14, 15] For example, one study showed that patients with thymoma-associated MG had increased circulating mature $CD4^+/CD45RA^+$ T-cells, and another study showed that they had decreased regulatory T-cells compared to patients with thymoma without MG.[16, 17] Also, autoimmune regulator (AIRE), a protein that regulates expression of self-antigens in the thymic medulla and plays a critical role in central tolerance,[18] is absent in the vast majority (>95%) of thymomas.[19] Finally, thymoma epithelial cells have decreased major histocompatibility class II (MHC II) expression, which in conjunction with decreased self-antigen expression results in a biased T-cell repertoire.[20]

In the current study, we examined patients with TETs, including thymomas, thymic carcinomas, and neuroendocrine tumors of the thymus (NETT), with PN/AI syndrome status recorded in the International Thymic Malignancy Interest Group (ITMIG) retrospective database.[21] Our objectives were two-fold: (i) to determine patient, tumor, and treatment characteristics associated with PN/AI syndromes and (ii) to determine whether the presence of PN/AI syndrome is an independent prognostic factor for patients with TETs.

Materials and Methods

The ITMIG retrospective database of thymic malignancies is the result of an international collaboration of 56 institutions, which has been described in detail elsewhere.[21] This study was conducted with use of a limited dataset with de-identified information and therefore, without requirement of authorization or documentation of waiver of the institutional review board. After execution of a data use agreement, a limited dataset from each institution was provided to ITMIG for the sole purpose of research. Only the ITMIG statistical core and

selected members of the database committee had full access to the data (X.Y., Y.S., A.A., F.D., J.H.).

Of 7795 patients in the ITMIG retrospective database from 1951-2012, we identified 6670 with known paraneoplastic/autoimmune (PN/AI) syndrome status at initial diagnosis and known pathologic diagnosis of thymoma, thymic carcinoma, and NETT. The final sample size was 6297 patients (Figure 1). The PN/AI syndrome data field terms included myasthenia gravis, pure red cell aplasia, hypogammaglobulinemia, and other. Only “other” PN/AI syndromes with further description were included in the analysis. The vast majority (97%) of patients in this cohort were from the time period 1991 onwards. Patient, tumor, and treatment characteristics were collected. Each contributing site to the database reported histology per 2004 World Health Organization (WHO) classification,[22] and there was no central pathology review. Patients with histology of metaplastic, micronodular, or “other” without further specification were excluded. There were only 90 cases of micronodular thymoma and 16 cases of metaplastic thymoma in the database. Of the cases with micronodular and metaplastic thymoma, 3 and 1 had a PN/AI syndrome, respectively, with missing information on PN/AI syndrome status in 58% and 50%, respectively.

Pathologic stage was described by Masaoka staging,[23] Masaoka-Koga staging,[24] or Masaoka-Koga staging with ITMIG clarifications.[25] The ITMIG/International Association for the Study of Lung Cancer (IASLC) staging project demonstrated no difference in outcomes between stage IIA and IIB patients or between Masaoka and Masaoka-Koga staging systems.[26] Therefore, stage IIA, IIB, and II were categorized as stage II for the purpose of analyses. Given the differences in outcomes observed between stage IVA and IVB patients,[26] cases with “stage IV” disease without further subset clarification were excluded.

Statistical Analyses

All analyses were performed with SAS 9.3 software (SAS Institute Inc., Cary, NC, USA) and R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics were used to summarize the baseline and treatment characteristics, including continuous variables as medians and ranges, and categorical variables as frequencies and relative percentages. The Chi-square test and t-test were used to compare categorical variables and continuous variables, respectively, between patients who had paraneoplastic/autoimmune syndromes [PN/AI (+)] and patients who did not [PN/AI (−)]. The competing risks model was used to estimate the thymic malignancy recurrence-free survival (RFS), which was measured from the date of intervention to the date of death or date of malignancy recurrence, whichever occurred first, and censored at the date patient last known to be alive without recurrence. In the competing risks model, death was included as the competing event, though curves of death are not shown in the cumulative incidence plots. The difference in RFS between PN/AI (+) patients and PN/AI (−) patients was assessed using Gray’s test.[27] The Kaplan-Meier method was used to calculate the overall survival (OS), which was measured from the date of intervention to the date of death, and censored at the date patient last known to be alive. The log rank test was used to compare OS of PN/AI (+) patients and PN/AI (−) patients. Outcomes were also examined stratified by PN/AI

syndrome status in subsets of thymoma and thymic carcinoma, stage subsets, and time periods.

A Cox proportional hazards model for multivariate analysis of RFS and OS included all factors detailed in Table 1 including age, sex, continent (North America, South America, Asia, Europe), pathology (thymoma, thymic carcinoma, NETT), WHO subtype (A, AB, B1, B2, B3), pathologic stage (I, II, III, IVA, IVB), extent of thymectomy (none, partial, total, extended), chemotherapy (curative, palliative/none), radiation (curative, palliative/none), and resection status (R0, R1, R2). Patients with missing data were excluded from this analysis; no imputations were performed. A two-sided P-value of <0.05 was considered statistically significant for any statistical test employed.

Results

Full Cohort Characteristics

A total of 6297 patients were included in the analysis (Figure 1). Cohort characteristics are reported in Table 1. The majority of patients were from Asia (42%) followed by Europe (33%) and North America (25%). As expected, thymoma pathology predominated (86%), with the most common histotypes being AB and B2. Thymic carcinoma was relatively well–represented (12%) in this cohort but NETT was rare (2%). Approximately one-third of patients had a PN/AI syndrome, with the vast majority being MG. However, there were also cases of pure red cell aplasia (n=47) and hypogammaglobulinemia (n=13). Pathologic stage was biased towards early stage I-II disease, representing two-thirds of the cohort. Almost all patients (99%) underwent surgery, with most patients undergoing a total thymectomy (81%) and achieving a complete R0 resection (84%).

Baseline and Treatment Characteristics associated with Paraneoplastic Autoimmune Syndromes

Patients with PN/AI syndrome [PN/AI (+)] were younger (median age 50 years-old) and predominantly female and European (Table 1). Patients without PN/AI syndrome [PN/AI (−)] were older (median age 55 years-old) and predominantly male and Asian. In both PN/AI (+) and PN/AI (−) groups, the most common pathology was thymoma. However, the most common thymoma WHO histotype was B2 for the PN/AI (+) group and AB for the PN/AI (−) group. In addition, the PN/AI (−) group also had a higher proportion of thymic carcinoma histology (17% vs. 2%, respectively). Pathologic stage was mostly early stage I-II in both PN/AI (+) and PN/AI (−) groups, however, the PN/AI (−) group had a higher proportion of advanced stage III-IVB disease. Both PN/AI (+) and PN/AI (−) groups most commonly underwent a total thymectomy, received no (or palliative) chemotherapy, no (or palliative) radiotherapy, and achieved a complete R0 resection. However, when comparing the PN/AI (+) group to the PN/AI (−) group, the rate of total thymectomy, no (or palliative) chemotherapy, and complete R0 resections was higher. There was no difference in radiation practices between the groups. The findings of this analysis were the same when only examining the PN/AI syndrome of MG (data not shown).

Cumulative Incidence of Recurrence (CIR) and Overall Survival (OS)

The median follow-up for the whole group was 3.7 years. The median follow-up for the PN/AI (+) group was 4.4 years and for the PN/AI (−) group was 3.3 years. Recurrence-free survival (RFS) information was available on 4375 patients. Overall, there was a statistically significant lower CIR in the PN/AI (+) group compared to PN/AI (−) group (p=0.0003; Figure 2): 10-year, 17.3% vs. 21.2%, respectively; 20-year, 27.2% vs. 28.1%, respectively; 30-year, 29.5% vs. 39.4%, respectively; and 40-year, N/A vs. 29.5%, respectively. There was no difference in CIR between PN/AI (+) and PN/AI (−) groups when examining the subgroups of thymoma (p=0.93), thymic carcinoma (p=0.76) (Supplementary Data Fig.1–2), and stage (Supplementary Data Fig.3–7).

Survival information was available on 4962 patients. In the overall population, OS was improved in the PN/AI (+) group compared with the PN/AI (−) group (HR 0.63, 95% CI 0.54-0.74, P<0.0001, median OS 21.6 years vs. 17.0 years, respectively; Figure 3). In the thymoma subgroup, there was a statistically significant improvement in OS for the PN/AI (+) group versus the PN/AI (−) group (HR 0.82, 95% CI 0.70-0.97, p=0.02) (Figure 4A). In the thymic carcinoma subgroup, there was also a trend for improved OS in the PN/AI (+) group (HR 0.56, 95% CI 0.29-1.10, p=0.09), with the survival curves separating early (Figure 4B). When stratified by stage, the improved OS in the PN/AI (+) group compared to the PN/AI (−) group remained in the stage III and stage IVB subgroups (Supplementary Data Fig.8–12). The above analyses of CIR and OS were also repeated for patients who only had MG and the results were the same (data not shown).

Survival was also examined over three time periods, 1951-1970, 1971-1990, and 1991-2012, which included 50, 228, and 5678 patients, respectively, with a prevalence of PN/AI syndrome of 70.0%, 52.2%, and 32.0%, respectively. For the PN/AI (+) group, the OS was significantly improved in the most recent time period (p=0.001; Supplementary Data Fig. 13). However, for the PN/AI (−) group, there was no difference in OS among the different time periods (p=0.87).

Multivariate Model for Recurrence-Free Survival and Overall Survival

There was complete data available on 2193 patients and 2352 patients for the multivariate analysis of RFS and OS, respectively. In a multivariate model (Table 2), the following characteristics were independently associated with increased recurrence: older age, histology of thymic carcinoma and NETT, advanced stage III-IVB disease, larger tumor size, and R2 resection status. Characteristics independently associated with decreased recurrence included: Asia continent and receipt of curative radiation (i.e. neoadjuvant, adjuvant, and definitive setting). In a multivariate model, the following characteristics were independently associated with worse OS: older age, histology of thymic carcinoma and NETT, advanced stage III-IVB disease, receipt of curative chemotherapy (i.e. neoadjuvant, adjuvant, and in definitive setting with radiation), and R2 resection status. Characteristics independently associated with improved OS included: receipt of curative radiation and B1 histotype. The presence of PN/AI syndrome was not independently associated with clinical outcomes of RFS and OS.

Discussion

To our knowledge, this is the largest study and the first multi-continent study, examining PN/AI syndromes in patients with TETs. This was achieved using the International Thymic Malignancy Interest Group (ITMIG) retrospective database, which serves as a paradigm for performing research in rare malignancies. Previously, there has been conflicting data about the prognostic role of PN/AI syndromes for TETs.[28] Our main finding is that the presence of PN/AI syndromes [PN/AI(+)] was associated with favorable prognostic factors but was not an independent prognostic factor for recurrence-free survival (RFS) or overall survival (OS) for patients with TETs. Our results were identical when only examining the PN/AI syndrome of MG (data not shown), which as expected comprised the majority (96%) of PN/AI syndromes in this cohort. Given the small numbers of pure red cell aplasia and hypogammaglobulinemia, we were not able to independently assess the clinical impact of these syndromes and thus, they were analyzed in aggregate with MG. In the ITMIG cohort, approximately one-third of patients with TETs had a PN/AI syndrome.[29] This is similar to the prevalence of MG reported in national retrospective database studies[29], including Japanese Association for Research on the Thymus (JART)[30], European Society of Thoracic Surgeons (ESTS)[31], and Chinese Alliance for Research in Thymomas (ChART)[32]. There is overlap with these national databases and our ITMIG database cohort, including 31% cases from the ChART database and 14% cases from the ESTS database (Supplementary Data Fig. 14), while the JART database was not included.

PN/AI Syndrome and Patient, Tumor, and Treatment Factors

In our cohort, the PN/AI (+) group was associated with known favorable prognostic factors. In regards to demographic factors, the PN/AI (+) group was younger in age by a median of 5 years and had a higher proportion of female sex, confirming prior findings in the literature.[30, 32–34] In regards to pathology, the PN/AI (+) group had a higher proportion of favorable histology thymoma, and a lower proportion of thymic carcinoma. Type B2 was the most common thymoma histotype (37%) in the PN/AI (+) group, while type AB (30%) was the most common in the PN/AI (−) group. These thymoma histotypes have also been previously identified as the most common when stratified by PN/AI syndrome status[35] in the JART[30] and ChART databases.[32] The consistent association of PN/AI syndromes with type B2 thymoma across large database studies may be explained by B2 thymomas containing heavy lymphocyte regions, including $CD4^+CD8^+$ double-positive T-cells that are vulnerable to altered positive selection in the setting of thymic epithelial cells with low expression of HLA-DR.[36] Of note, 6% of patients in our cohort with thymic carcinoma had a PN/AI syndrome. An increasing number of thymic carcinomas with PN/AI syndromes are being reported,[30, 32, 34] including a 12% prevalence of MG in a single institution series of 49 patients.[37] It is possible since there was no central pathology review in the ITMIG retrospective database that a proportion of thymomas were misclassified as thymic carcinomas since poor inter-observer reproducibility has been demonstrated between B3 thymoma and thymic carcinoma.[38] We also reported that 4% of NETTs had MG, which has been rarely reported in the literature.[32, 39]

The PN/AI (+) group also had a higher rate of earlier stage disease and complete R0 resections, which has been described previously.[30–34] Innumerable studies have shown that stage and resection status are the strongest independent prognostic factors for patients with TETs.[30–32] The likelihood of a complete resection is also higher with earlier stage disease.[31, 32, 40] PN/AI (+) TETs may be caught at an earlier stage due to the presence of symptoms, and it is also possible that PN/AI (+) TETs are associated with better biology.[35]

In regards to treatment, a higher proportion of patients in the PN/AI (+) group underwent a total thymectomy [90% PN/AI (+) vs. 77% PN/AI (−)]. It has been hypothesized that to increase the chances of remission of MG, a total thymectomy is required. This was recently supported by the results of an international randomized trial demonstrating thymectomy, including en bloc resection of all mediastinal tissue containing either gross or microscopic thymic tissue, is more beneficial than prednisone therapy alone for the treatment of non-thymomatous MG.[41] Despite Myasthenia Gravis Foundation of America (MGFA) status at diagnosis[42] (i.e. describing severity of MG symptoms) and MGFA post intervention status (i.e. clinical state after treatment such as thymectomy) being collected for the ITMIG database, it was not done consistently. Therefore, we cannot comment on how surgical intervention affected the severity of MG symptoms in our cohort. Preoperative MGFA classification was examined in the JART database and showed no difference in recurrence or survival for thymomas when stratified by MGFA classification.[30] In a systematic review, MGFA status indicating mild disease preoperatively enhanced the chance of complete MG remission after thymectomy.[43] Partial thymectomy can be considered in patients with early stage tumors without MG since prior retrospective studies have shown similar recurrence rates for partial versus total thymectomy in this group.[44, 45] This could account for the higher proportion of partial thymectomies performed in the PN/AI (−) group of our cohort.

PN/AI Syndrome, Recurrence, and Survival

The PN/AI (+) group had statistically significant improved outcomes compared to the PN/AI (−) group for cumulative incidence of recurrence (CIR) and overall survival (OS) in the overall cohort. However, when performing the analysis in thymoma, thymic carcinoma, and stage subgroups, there was no difference in CIR between the PN/AI (+) and PN/AI (−) groups, indicating that these may be confounding factors. When performing the same subgroup analyses for OS, the improved OS for patients with PN/AI syndrome remained significant in the thymoma subgroup, trended in the thymic carcinoma subgroup, and remained significant in advanced stage III and IVB disease. The trend for improved OS in PN/AI (+) thymic carcinoma has been shown in other series probably due to the association with favorable prognostic factors including smaller tumors, earlier Masaoka stage, and higher rates of complete resection.[37] The improved OS in advanced stage disease suggests that the presence of PN/AI syndromes may indicate better biology or a type of selection bias among advanced stage tumors that is not readily identified in this retrospective cohort. In regards to time period, we found that the PN/AI (+) group had significantly improved OS in the most recent time period (1991-2012) but there was no difference in OS in the PN/AI (−) group over time. This observation is possibly due to improved treatment and supportive care of MG, as reports prior to the 1980s showed that MG negatively impacted OS for patients with TETs.[28]

The most important finding in our study is that PN/AI syndrome status was not an independent factor associated with RFS or OS in a multivariate model. Independent factors associated with RFS and OS in this study included age (older age worse), histology (non-thymoma histology worse), stage (advanced stage III-IVB worse), and resection status (incomplete R2 resection status worse). PN/AI syndrome status was likely not an independent prognostic factor because of its association with these strong prognostic factors. Additional unfavorable factors found in the multivariate analysis for RFS and OS was larger size[46] and receipt of chemotherapy, respectively. The latter could be because chemotherapy agents (i.e. anthracyclines) have long-term toxicities including cardiomyopathy and secondary malignancies. Curative intent radiation was an independent favorable factor for both RFS and OS, possibly because radiation is capable of destroying microscopic islands of thymus not surgically excised. Independent favorable features for RFS included Asian continent and for OS included type B1 thymoma.

There are limitations of the recurrence and survival analyses in our study. The recurrence analysis was limited by the likely variable frequency of follow-up imaging at each institution and thus, when a recurrence was first detected. The ITMIG standards recommend follow-up after surgical resection with a computed tomography (CT) chest each year for 5 years and thereafter, alternating chest x-ray and CT chest until year 11, at the minimum.[47] However, these follow-up standards were not likely applied given the cohort spanned multiple countries and was retrospective in nature. Limitations of the OS analysis for our study included (i) a significant proportion of missing data for cause of death (>90% missing), (ii) the relatively short median follow-up time of the group (< 4 years), and (iii) lead time bias since patients with PN/AI syndrome may be diagnosed earlier.

Here, we place our findings in the context of the existing literature. Similar to our study, the ChART database demonstrated a decreased rate of recurrence in patients with MG even in those with advanced Masaoka stage III/IV disease (15.7% vs. 31.7%, respectively), although there were significantly lower rates of thymic carcinoma and smaller tumor size in the MG cohort.[32] However, the JART database showed similar recurrence-free interval in patients with and without MG (5-year 93% vs. 92% and 10-year 89% vs. 87%, respectively), although only patients with thymoma were included in this analysis.[30] Of these databases, the ESTS database was the only one that examined recurrence in a multivariate model and unlike our study, showed that MG was an independent prognostic factor associated with lower CIR.[31] Similar to our study, the ChART authors observed OS was improved in patients with MG with advanced stage III/IV disease but unlike our study, they also found that OS was worse in patients with MG with stage I disease.[32] Across the ChART,[32] ESTS, [31] and JART[30] databases, the PN/AI syndrome of MG in TETs was not an independent prognostic factor for OS in multivariate analyses.

Conclusions

We have used the largest and only multi-continent database for TETs to clarify the controversial prognostic role of PN/AI syndromes.[28] Despite the strength in numbers of this study, it has the standard limitations of a retrospective database including missing information and selection bias. We found PN/AI syndromes to be associated with favorable

features such as younger age, type B1 thymoma, earlier stage, and increased rate of complete resection status. However, the presence of PN/AI syndrome was not an independent prognostic factor for TETs for either RFS or OS. Importantly, our study confirms prior national database studies that PN/AI syndrome status (represented by MG in these studies) is not an independent factor associated with OS.[30,32,30, 31]

Acknowledgments

Disclosure of Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Abbreviations

AChR	acetylcholine receptor
AIRE	autoimmune regulator
ChART	Chinese Alliance for Research in Thymomas
CIR	cumulative incidence of recurrence
ESTS	European Society of Thoracic Surgeons
IASLC	International Association for the Study of Lung Cancer
ITMIG	International Thymic Malignancy Interest Group
JART	Japanese Association for Research on the Thymus
KART	Korean Association for Research on the Thymus
MG	myasthenia gravis
MGFA	Myasthenia Gravis Foundation of America
MHC II	major histocompatibility class II
NETT	neuroendocrine tumors of the thymus
OS	overall survival
PN/AI	paraneoplastic autoimmune
PN/AI (+)	presence of paraneoplastic autoimmune syndrome
PN/AI (−)	absence of paraneoplastic autoimmune syndrome
RFS	recurrence-free survival
RyR	ryanodine receptor
TETs	thymic epithelial tumors
WHO	World Health Organization

References

1. Engels EA. Epidemiology of thymoma and associated malignancies. J Thorac Oncol. 2010; 5(10 Suppl 4):S260–265. [PubMed: 20859116]
2. Evoli A, Lancaster E. Paraneoplastic disorders in thymoma patients. J Thorac Oncol. 2014; 9(9 Suppl 2):S143–147. [PubMed: 25396312]
3. Marx A, Pfister F, Schalke B, Saruhan-Direskeneli G, Melms A, Strobel P. The different roles of the thymus in the pathogenesis of the various myasthenia gravis subtypes. Autoimmun Rev. 2013; 12(9):875–884. [PubMed: 23535159]
4. Hirokawa M, Sawada K, Fujishima N, Nakao S, Urabe A, Dan K, et al. Long-term response and outcome following immunosuppressive therapy in thymoma-associated pure red cell aplasia: a nationwide cohort study in Japan by the PRCA collaborative study group. Haematologica. 2008; 93(1):27–33. [PubMed: 18166782]
5. Montella L, Masci AM, Merkabaoui G, Perna F, Vitiello L, Racioppi L, et al. B-cell lymphopenia and hypogammaglobulinemia in thymoma patients. Ann Hematol. 2003; 82(6):343–347. [PubMed: 12715206]
6. Bernard C, Frih H, Pasquet F, Kerever S, Jamilloux Y, Tronc F, et al. Thymoma associated with autoimmune diseases: 85 cases and literature review. Autoimmun Rev. 2016; 15(1):82–92. [PubMed: 26408958]
7. Gilhus NE, Skeie GO, Romi F, Lazaridis K, Zisimopoulou P, Tzartos S. Myasthenia gravis - autoantibody characteristics and their implications for therapy. Nat Rev Neurol. 2016; 12(5):259–268. [PubMed: 27103470]
8. Sommer N, Willcox N, Harcourt GC, Newsom-Davis J. Myasthenic thymus and thymoma are selectively enriched in acetylcholine receptor-reactive T cells. Ann Neurol. 1990; 28(3):312–319. [PubMed: 2241114]
9. Szczudlik P, Szyluk B, Lipowska M, Ryniewicz B, Kubiszewska J, Dutkiewicz M, et al. Antititin antibody in early- and late-onset myasthenia gravis. Acta Neurol Scand. 2014; 130(4):229–233. [PubMed: 24947881]
10. Skeie GO, Mygland A, Treves S, Gilhus NE, Aarli JA, Zorzato F. Ryanodine receptor antibodies in myasthenia gravis: epitope mapping and effect on calcium release in vitro. Muscle Nerve. 2003; 27(1):81–89. [PubMed: 12508299]
11. Rigamonti A, Lauria G, Piamarta F, Fiumani A, Agostoni E. Thymoma-associated myasthenia gravis without acetylcholine receptor antibodies. J Neurol Sci. 2011; 302(1–2):112–113. [PubMed: 21236448]
12. Maggi L, Andreetta F, Antozzi C, Confalonieri P, Cornelio F, Scaioli V, et al. Two cases of thymoma-associated myasthenia gravis without antibodies to the acetylcholine receptor. Neuromuscul Disord. 2008; 18(8):678–680. [PubMed: 18657424]
13. Miller JF. The golden anniversary of the thymus. Nat Rev Immunol. 2011; 11(7):489–495. [PubMed: 21617694]
14. Hoffacker V, Schultz A, Tiesinga JJ, Gold R, Schalke B, Nix W, et al. Thymomas alter the T-cell subset composition in the blood: a potential mechanism for thymoma-associated autoimmune disease. Blood. 2000; 96(12):3872–3879. [PubMed: 11090072]
15. Hsieh CS, Lee HM, Lio CW. Selection of regulatory T cells in the thymus. Nat Rev Immunol. 2012; 12(3):157–167. [PubMed: 22322317]
16. Strobel P, Helmreich M, Menioudakis G, Lewin SR, Rudiger T, Bauer A, et al. Paraneoplastic myasthenia gravis correlates with generation of mature naive CD4(+) T cells in thymomas. Blood. 2002; 100(1):159–166. [PubMed: 12070022]
17. Strobel P, Rosenwald A, Beyersdorf N, Kerkau T, Elert O, Murumagi A, et al. Selective loss of regulatory T cells in thymomas. Ann Neurol. 2004; 56(6):901–904. [PubMed: 15562414]
18. Giraud M, Taubert R, Vandiedonck C, Ke X, Levi-Strauss M, Pagani F, et al. An IRF8-binding promoter variant and AIRE control CHRNA1 promiscuous expression in thymus. Nature. 2007; 448(7156):934–937. [PubMed: 17687331]

19. Strobel P, Murumagi A, Klein R, Luster M, Lahti M, Krohn K, et al. Deficiency of the autoimmune regulator AIRE in thymomas is insufficient to elicit autoimmune polyendocrinopathy syndrome type 1 (APS-1). J Pathol. 2007; 211(5):563–571. [PubMed: 17334980]
20. Strobel P, Chuang WY, Chuvpilo S, Zettl A, Katzenberger T, Kalbacher H, et al. Common cellular and diverse genetic basis of thymoma-associated myasthenia gravis: role of MHC class II and AIRE genes and genetic polymorphisms. Ann N Y Acad Sci. 2008; 1132:143–156. [PubMed: 18567864]
21. Huang J, Ahmad U, Antonicelli A, Catlin AC, Fang W, Gomez D, et al. Development of the international thymic malignancy interest group international database: an unprecedented resource for the study of a rare group of tumors. J Thorac Oncol. 2014; 9(10):1573–1578. [PubMed: 25521402]
22. Travis WD, Brambilla E, Burke AP, Marx A, Nicholson AG. Pathology and Genetics: Tumours of the Lung, Pleura, Thymus and Heart. IARC, Lyon. 2004
23. Masaoka A, Monden Y, Nakahara K, Tanioka T. Follow-up study of thymomas with special reference to their clinical stages. Cancer. 1981; 48(11):2485–2492. [PubMed: 7296496]
24. Koga K, Matsuno Y, Noguchi M, Mukai K, Asamura H, Goya T, et al. A review of 79 thymomas: modification of staging system and reappraisal of conventional division into invasive and non-invasive thymoma. Pathol Int. 1994; 44(5):359–367. [PubMed: 8044305]
25. Detterbeck FC, Nicholson AG, Kondo K, Van Schil P, Moran C. The Masaoka-Koga stage classification for thymic malignancies: clarification and definition of terms. J Thorac Oncol. 2011; 6(7 Suppl 3):S1710–1716. [PubMed: 21847052]
26. Detterbeck F. MS16.2 - Towards a TNM-Based Prognostic Classification for Thymic Tumours. 15th World Conference on Lung Cancer. 2013
27. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Statist. 1988; 16:1141–1154.
28. Osserman KE, Genkins G. Studies in myasthenia gravis: review of a twenty-year experience in over 1200 patients. Mt Sinai J Med. 1971; 38(6):497–537. [PubMed: 4941403]
29. Kondo K, Monden Y. Therapy for thymic epithelial tumors: a clinical study of 1,320 patients from Japan. Ann Thorac Surg. 2003; 76(3):878–884. discussion 884-875. [PubMed: 12963221]
30. Nakajima J, Okumura M, Yano M, Date H, Onuki T, Haniuda M, et al. Myasthenia gravis with thymic epithelial tumour: a retrospective analysis of a Japanese database. Eur J Cardiothorac Surg. 2016; 49(5):1510–1515. [PubMed: 26537756]
31. Ruffini E, Detterbeck F, Van Raemdonck D, Rocco G, Thomas P, Weder W, et al. Tumours of the thymus: a cohort study of prognostic factors from the European Society of Thoracic Surgeons database. Eur J Cardiothorac Surg. 2014; doi: 10.1093/ejcts/ezt649
32. Wang F, Pang L, Fu J, Shen Y, Wei Y, Tan L, et al. Postoperative survival for patients with thymoma complicating myasthenia gravis-preliminary retrospective results of the ChART database. J Thorac Dis. 2016; 8(4):711–717. [PubMed: 27114839]
33. Kondo K, Monden Y. Thymoma and myasthenia gravis: a clinical study of 1,089 patients from Japan. Ann Thorac Surg. 2005; 79(1):219–224. [PubMed: 15620947]
34. Filosso PL, Evangelista A, Ruffini E, Rendina EA, Margaritora S, Novellis P, et al. Does myasthenia gravis influence overall survival and cumulative incidence of recurrence in thymoma patients? A Retrospective clinicopathological multicentre analysis on 797 patients. Lung Cancer. 2015; 88(3):338–343. [PubMed: 25819383]
35. Margaritora S, Cesario A, Cusumano G, Meacci E, D'Angelillo R, Bonassi S, et al. Thirty-five-year follow-up analysis of clinical and pathologic outcomes of thymoma surgery. Ann Thorac Surg. 2010; 89(1):245–252. discussion 252. [PubMed: 20103246]
36. Okumura M, Fujii Y, Shiono H, Inoue M, Minami M, Utsumi T, et al. Immunological function of thymoma and pathogenesis of paraneoplastic myasthenia gravis. Gen Thorac Cardiovasc Surg. 2008; 56(4):143–150. [PubMed: 18401674]
37. Li W, Miao Z, Liu X, Zhang Q, Sun L, Li P, et al. Thymic carcinoma patients with myasthenia gravis exhibit better prognoses. Int J Clin Oncol. 2016; 21(1):75–80. [PubMed: 26138264]

38. Wu J, Fang W, Chen G. The enlightenments from ITMIG Consensus on WHO histological classification of thymoma and thymic carcinoma: refined definitions, histological criteria, and reporting. J Thorac Dis. 2016; 8(4):738–743. [PubMed: 27114842]

39. Wu MH, Tseng YL, Cheng FF, Lin TS. Thymic carcinoid combined with myasthenia gravis. J Thorac Cardiovasc Surg. 2004; 127(2):584–585. [PubMed: 14762376]

40. Burt BM, Yao X, Shrager J, Antonicelli A, Padda S, Reiss J, et al. Determinants of Complete Resection of Thymoma by Minimally Invasive and Open Thymectomy: Analysis of an International Registry. J Thorac Oncol. 2017; 12(1):129–136. [PubMed: 27566187]

41. Wolfe GI, Kaminski HJ, Aban IB, Minisman G, Kuo HC, Marx A, et al. Randomized Trial of Thymectomy in Myasthenia Gravis. N Engl J Med. 2016; 375(6):511–522. [PubMed: 27509100]

42. Jaretzki A 3rd, Barohn RJ, Ernstoff RM, Kaminski HJ, Keesey JC, Penn AS, et al. Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. Ann Thorac Surg. 2000; 70(1): 327–334. [PubMed: 10921745]

43. Mao Z, Hu X, Lu Z, Hackett ML. Prognostic factors of remission in myasthenia gravis after thymectomy. Eur J Cardiothorac Surg. 2015; 48(1):18–24. [PubMed: 25108896]

44. Narm KS, Lee CY, Do YW, Jung HS, Byun GE, Lee JG, et al. Limited thymectomy as a potential alternative treatment option for early-stage thymoma: A multi-institutional propensity-matched study. Lung Cancer. 2016; 101:22–27. [PubMed: 27794404]

45. Nakagawa K, Yokoi K, Nakajima J, Tanaka F, Maniwa Y, Suzuki M, et al. Is Thymomectomy Alone Appropriate for Stage I (T1N0M0) Thymoma? Results of a Propensity-Score Analysis. Ann Thorac Surg. 2016; 101(2):520–526. [PubMed: 26482784]

46. Fukui T, Fukumoto K, Okasaka T, Kawaguchi K, Nakamura S, Hakiri S, et al. Prognostic impact of tumour size in completely resected thymic epithelial tumours. Eur J Cardiothorac Surg. 2016; 50(6):1068–1074. [PubMed: 27999073]

47. Huang J, Detterbeck FC, Wang Z, Loehrer PJ Sr. Standard outcome measures for thymic malignancies. J Thorac Oncol. 2011; 6(7 Suppl 3):S1691–1697. [PubMed: 21847049]

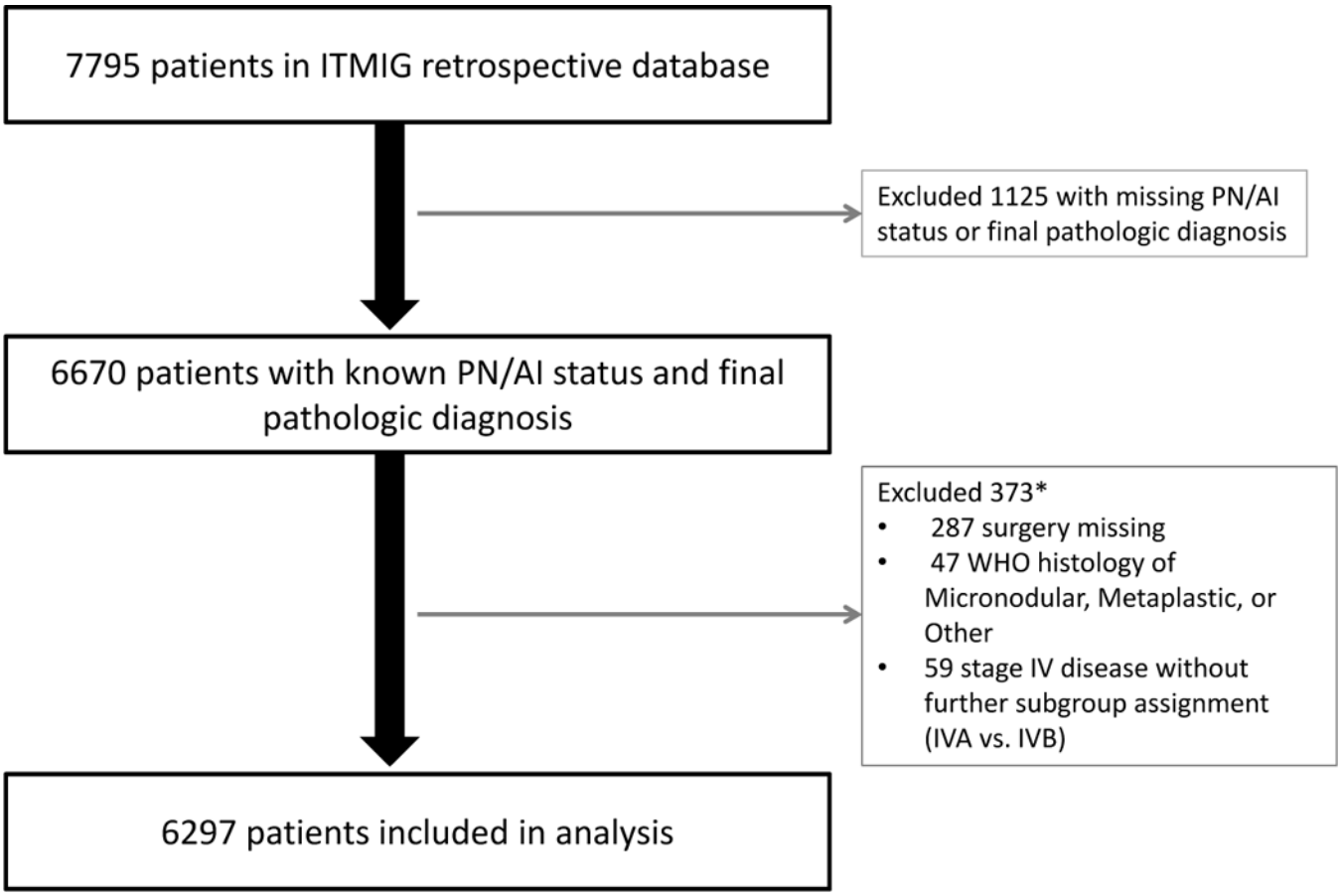
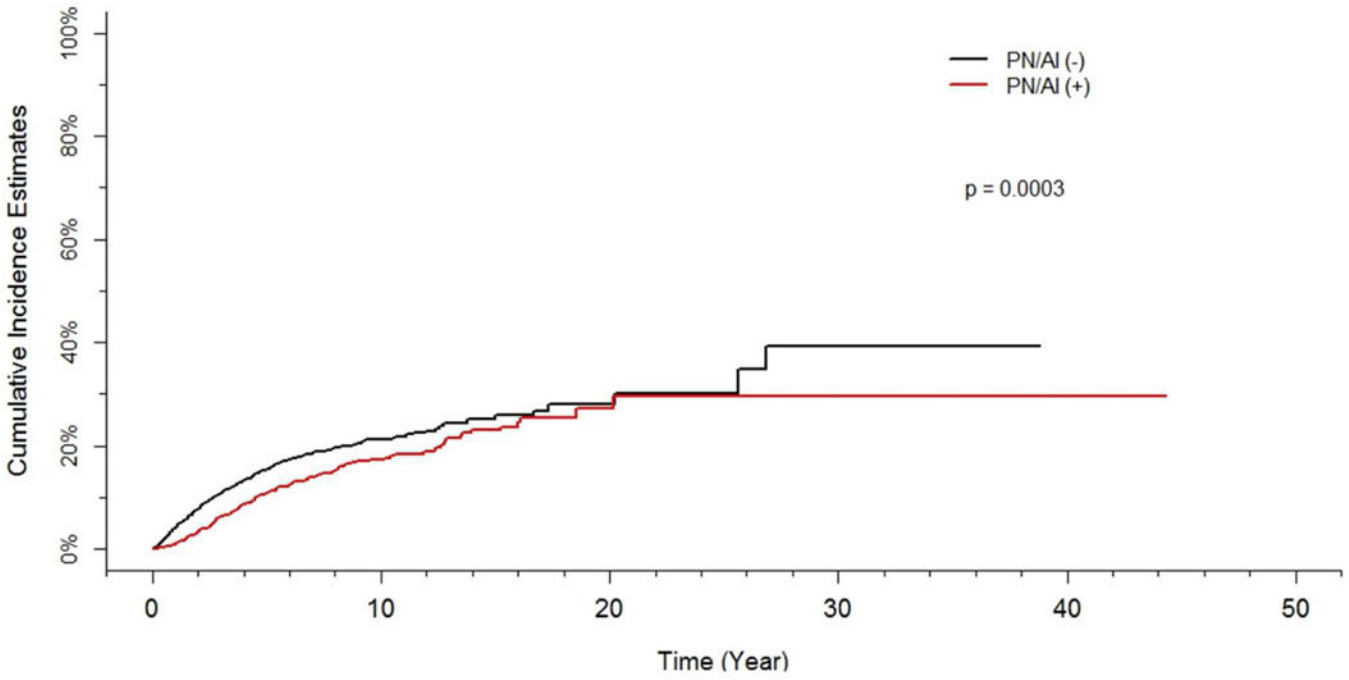


Figure 1.

Flow Diagram. *Numbers do not add up to 373 because there is overlap among patients with missing information for each variable. (*PN/AI=paraneoplastic/autoimmune syndrome*)



Cumulative incidence of recurrence (95% CI)	10-year	20-year	30-year	40-year
PN/AI (-)	0.21 (0.19-0.23)	0.28 (0.24-0.33)	0.39 (0.27-0.52)	N/A
PN/AI (+)	0.17 (0.15-0.20)	0.27 (0.22-0.33)	0.30 (0.23-0.37)	0.30 (0.28-0.37)

Figure 2.

Cumulative Incidence of Recurrence in All Patients, PN/AI (+) vs. PN/AI (−) (*PN/AI=paraneoplastic/autoimmune syndrome*)

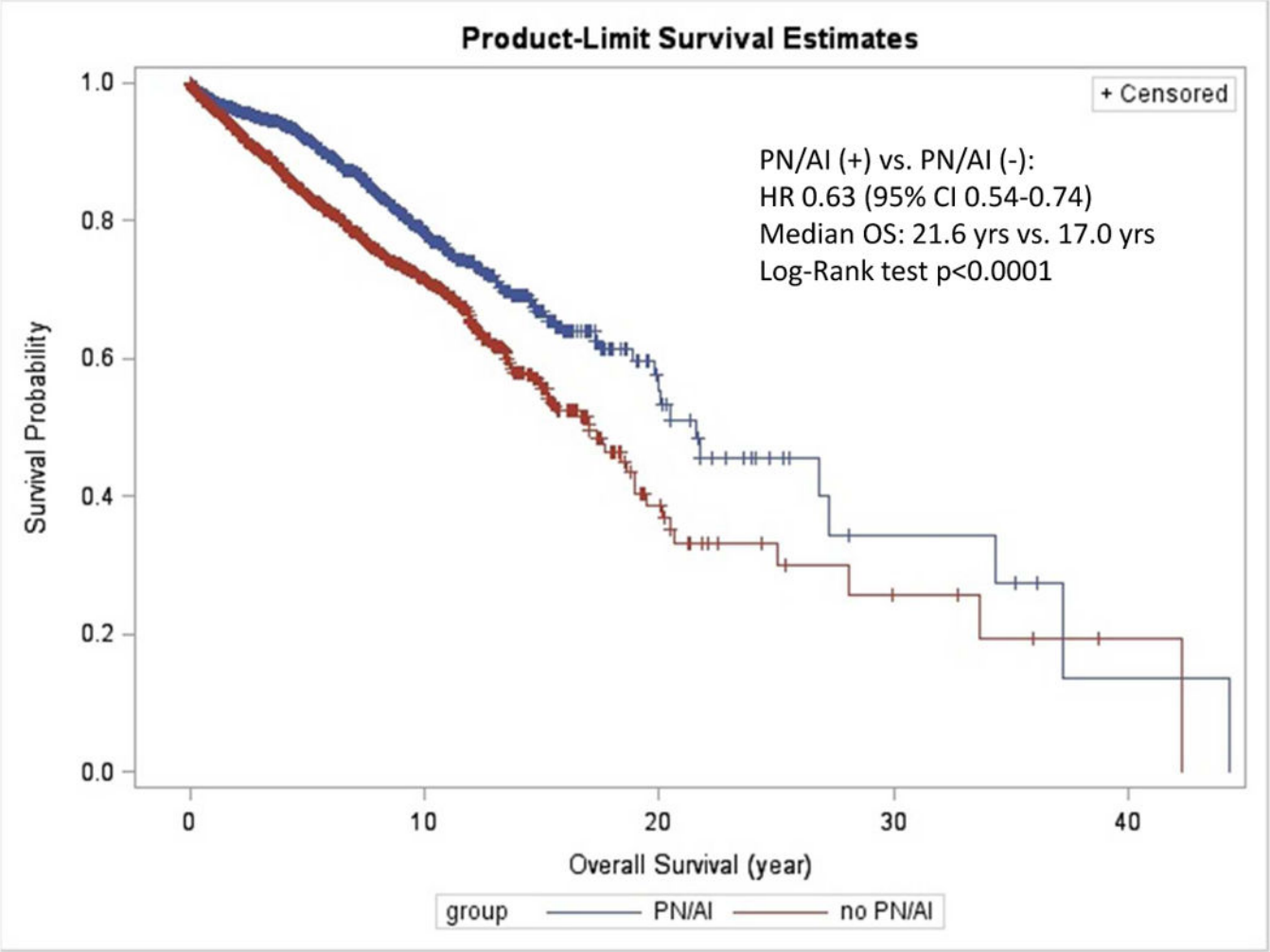


Figure 3.
Overall Survival in All Patients, PN/AI (+) vs. PN/AI (−) (*PN/AI=paraneoplastic/autoimmune syndrome*)

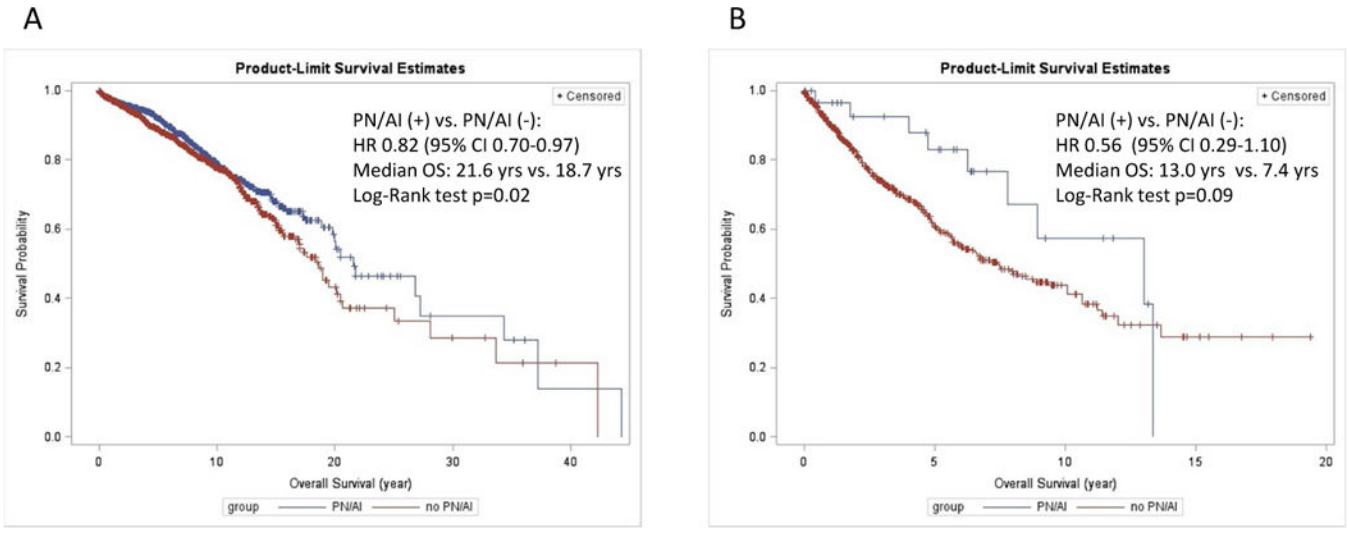


Figure 4.

Overall Survival, PN/AI (+) vs. PN/AI (−), in (A) Thymoma Patients and (B) Thymic Carcinoma Patients (*PN/AI=paraneoplastic/autoimmune syndrome*)

Table 1

Cohort Characteristics of 6297 Patients from ITMIG Retrospective Database

Characteristic	Total Cohort n=6297	PN/AI (+) n=2143	PN/AI (–) n=4154	p–value
Age median-years (range)	53 (5–89)	50 (5–89)	55 (7–88)	p<0.0001
Size median centimeters (range)	6.0 (0.1–30)	5.0 (0.1–22)	6.5 (0.3–30)	p<0.0001
Sex				
Male	3258 (51.8)	1010 (47.2)	2248 (54.1)	p<0.0001
Female	3035 (48.2)	1131 (52.8)	1904 (45.9)	
Missing	4	–	–	
Continent				
North America	1555 (24.7)	425 (19.8)	1130 (27.2)	p<0.0001
South America	54 (0.9)	33 (1.5)	21 (0.5)	
Asia	2635 (41.9)	683 (31.9)	1952 (47.0)	
Europe	2053 (32.6)	1002 (46.8)	1051 (25.3)	
PN/AI		–	–	–
Yes	2143 (34.0)			
Myasthenia Gravis	2068 (32.8)			
Pure Red Cell Aplasia	47 (0.7)			
Hypogammaglobulinemia	13 (0.2)			
Other	15 (0.3) [c]			
No	4154 (65.4)			
Pathology				
Thymoma	5306 (86.1)	2061 (97.7)	3245 (80.0)	p<0.0001
Thymic Carcinoma	717 (11.6)	42 (2.0) [d]	675 (16.7)	
NETT	139 (2.3) [d]	5 (0.2) [d]	134 (3.3)	
Missing	135	–	–	
WHO Histology				
A	525 (10.7)	145 (7.6)	380 (12.7)	p<0.0001
AB	1211 (24.7)	325 (17.0)	886 (29.6)	
B1	897 (18.3)	343 (17.9)	554 (18.5)	
B2	1329 (27.1)	708 (37.0)	621 (20.8)	
B3	943 (19.2)	394 (26.0)	549 (18.4)	
Missing	1392	–	–	
Pathologic Stage				
I	1986 (36.5)	682 (36.9)	1304 (36.2)	p<0.0001
II	1672 (30.7)	695 (37.6)	977 (27.1)	
III	1201 (22.0)	342 (18.5)	859 (23.9)	
IVA	355 (6.5)	103 (5.6)	252 (7.0)	

Characteristic	Total Cohort n=6297	PN/AI (+) n=2143	PN/AI (–) n=4154	p–value
IVB	234 (4.3)	25 (1.4)	209 (5.8)	
Missing	849	–	–	
Surgery[a]				
Yes	6188 (98.2)	2125 (99.2)	4063 (97.8)	p<0.0001
No	109 (1.7)	18 (0.8)	91 (2.2)	
Extent of Thymectomy				
None	140 (2.9)	21 (1.4)	119 (3.5)	p<0.0001
Partial	660 (13.4)	78 (5.1)	582 (17.3)	
Total	3983 (81.1)	1393 (90.4)	2590 (76.8)	
Extended	130 (2.7)	49 (3.2)	81 (2.4)	
Missing	1384	–	–	
Chemotherapy				
Curative [b]	1066 (20.3)	233 (13.3)	833 (23.8)	p<0.0001
Palliative/None	4190 (79.7)	1525 (86.8)	2665 (76.2)	
Missing	1041	–	–	
Radiation				
Curative [b]	2134 (41.9)	700 (42.9)	1434 (41.5)	p=0.35
Palliative/None	2955 (58.1)	933 (57.1)	2022 (58.5)	
Missing	1208	–	–	
Resection Status				
R0	4768 (83.5)	1729 (87.2)	3039 (81.5)	p<0.0001
R1	465 (8.1)	165 (8.3)	300 (8.1)	
R2	480 (8.4)	90 (4.5)	390 (10.5)	
Missing	584	–	–	

Abbreviations: PN/AI (+) = presence of paraneoplastic autoimmune syndrome; PN/AI (−) = absence of paraneoplastic autoimmune syndrome; NETT = neuroendocrine tumors of the thymus

Percentages calculated with exclusion of missing values and column percentages reported.

[a]=Surgery field (Yes/No) was derived from many separate surgical fields from the database for completeness and accuracy.

[b]=Curative includes neoadjuvant, adjuvant, and definitive (for chemotherapy, when given definitively with radiation).

[c]=Other included 2 Cushing's syndrome, 4 rheumatoid arthritis, and one each of anemia not otherwise specified, hemolytic anemia, erythrocytosis, thrombocytosis, neutropenia, polymyositis, Goodpasture syndrome, Grave's disease, polymyalgia rheumatica.

[d]=Of 42 PN/AI (+) thymic carcinoma, 38 had myasthenia gravis and 1 each of pure red cell aplasia, hypogammaglobulinemia, Cushing's syndrome, and rheumatoid arthritis. NETTs included 37 typical carcinoids, 55 atypical carcinoids, and 28 large cell or small cell neuroendocrine carcinoma, 9 carcinoid NOS, and 10 others not further classified. All PN/AI (+) NETTs had myasthenia gravis and included 1 each of typical and atypical carcinoid and 3 poorly differentiated neuroendocrine carcinomas.

Table 2

Multivariate Analysis

Characteristic	Recurrence–Free Survival HR (95% CI)	p-value	Overall Survival HR (95% CI)	p-value
PN/AI				
Present	1.05 (0.82–1.34)	0.70	1.10 (0.81–1.49)	0.54
Absent (ref)	1		1	
Age years	**1.00 (1.00–1.02)**[b]	**0.02** *	**1.04 (1.03–1.05)**	**0.02** *
Sex				
Female	0.96 (0.79–1.17)	0.68	0.91 (0.71–1.17)	0.46
Male (ref)	1		1	
Continent				
North/South America	0.94 (0.73–1.20)	0.59	0.82 (0.61–1.12)	0.21
Asia	**0.75 (0.57–0.97)**	**0.03** *	0.74 (0.54–1.02)	0.07
Europe (ref)	1		1	
WHO Histology				
A (ref)	1		1	
AB	0.74 (0.47–1.16)	0.19	0.82 (0.49–1.35)	0.43
B1	0.77 (0.49–1.23)	0.28	**0.54 (0.31–0.95)**	**0.03** *
B2	1.18 (0.78–1.80)	0.45	0.89 (0.54–1.45)	0.63
B3	1.17 (0.75–1.83)	0.50	1.10 (0.66–1.86)	0.71
Thymic Carcinoma	**1.98 (1.27–3.07)**	**0.003** *	**1.99 (1.21–3.27)**	**0.007** *
NETT	**2.19 (1.19–4.03)**	**0.01** *	**2.54 (1.26–5.12)**	**0.009** *
Pathologic Stage				
I (ref)	1		1	
II	1.18 (0.85–1.64)	0.33	0.94 (0.53–1.40)	0.75
III	**3.28 (2.35–4.59)**	**<0.0001** *	**2.47 (1.67–3.67)**	**<0.0001** *
IVA	**4.42 (2.94–6.65)**	**<0.0001** *	**2.63 (1.61–4.31)**	**0.0001** *
IVB	**4.34 (2.66–7.06)**	**<0.0001** *	**3.33 (1.86–5.98)**	**<0.0001** *
Tumor Size (centimeters)	**1.03 (1.00–1.06)**	**0.03** *	1.02 (0.99–1.06)	0.19
Extent of Thymectomy				
None (ref)	1		1	
Partial	0.96 (0.40–2.33)	0.94	0.98 (0.37–2.60)	0.97
Total	1.13 (0.49–2.58)	0.78	0.99 (0.40–2.48)	0.98
Extended	1.96 (0.53–7.26)	0.32	2.28 (0.52–9.99)	0.28
Chemotherapy				
Curative[a]	1.30 (1.00–1.68)	0.05	**1.44 (1.05–1.97)**	**0.02** *

Characteristic	Recurrence–Free Survival HR (95% CI)	p-value	Overall Survival HR (95% CI)	p-value
Palliative/None (ref)	1		1	
Radiation				
Curative[a]	**0.66 (0.52–0.83)**	**0.0003** *	**0.61 (0.46–0.90)**	**0.0004** *
Palliative/None (ref)	1		1	
Resection Status				
R0 (ref)	1		1	
R1	1.15 (0.85–1.56)	0.36	1.03 (0.69–1.52)	0.90
R2	**1.50 (1.08–2.09)**	**0.02** *	**1.59 (1.06–2.38)**	**0.02** *

Abbreviations: CI= confidence interval; HR = hazard ratio; PN/AI = paraneoplastic autoimmune syndrome; NETT = neuroendocrine tumors of the thymus

* statistically significant ($p<0.05$)

[a] = Curative includes neoadjuvant, adjuvant, and definitive (for chemotherapy, when given definitively with radiation).

[b] = 95% CI does not include 1 (1.001-1.016)