TREATMENT RESPONSE AFTER INDUCTION THERAPY IN ADVANCED THYMIC TUMORS: RESULTS FROM THE ITALIAN NATIONWIDE TYME DATABASE

Leuzzi Giovanni[1], Sabia Federica[1], Proto Claudia[2], Lo Russo Giuseppe[2], Ganzinelli Monica[2], Ferrari Michele[1], Perrino Matteo[3], Cordua Nadia[3], Checchi Luigi[3], De Vincenzo Fabio[4], Federico Antonio[3], Zucali Paolo[3,4], Lucchi Marco[5], Ambrogi Marcello Carlo[5], Aprile Vittorio[5], Mendogni Paolo[6], Rosso Lorenzo[6], Cecere Fabiana Letizia[7], Comacchio Giovanni[8], Bianco Roberto[9], Di Pietro Paolo Marzia[10], Fabbri Alessandra [11], Petrini Iacopo [12], Trama Annalisa [13], De Pas Tommaso Martino [14], Conforti Fabio [14], Galli Giulia [15], Ruffini Enrico [16], Garassino Marina Chiara [17], Franceschini Davide[18], Berardi Rossana [19], Pasello Giulia [20,21], Solli Piergiorgio[1], and *TYME GROUP* *

1. Division of Thoracic Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
2. Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale Dei Tumori, Milan, Italy
3. Department of Oncology, IRCCS Humanitas Research Hospital, Rozzano - Milan, Italy
4. Department of Biomedical Sciences, Humanitas University, Pieve Emanuele - Milan, Italy
5. Division of Thoracic Surgery, Cardiac, Thoracic, and Vascular Department, University Hospital of Pisa, Pisa, Italy
6. Thoracic Surgery and Lung Transplant Unit, Foundation IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy
7. Medical Oncology 2 IRCCS Regina Elena National Cancer Institute, Rome
8. Thoracic Surgery Unit, Division of Surgery, University - Hospital of Padua, Padua, Italy
9. Department of Clinical Medicine and Surgery, University Federico II, Naples, Italy, Naples, Italy

10. Medical Oncology Unit, Azienda Ospedaliero-Universitaria Ospedali Riuniti Umberto I, GM Lancisi, G Salesi Ancona, Italy
11. 2nd Pathology Division, Department of Pathology and Laboratory Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
12. Department of Translational Research & New Technologies in Surgery and Medicine, University of Pisa and Azienda Ospedaliero Universitaria Pisana, Pisa, Italy
13. Evaluative Epidemiology Unit, Fondazione IRCSS Istituto Nazionale dei Tumori, Milan, Italy
14. Division of Medical Oncology, Humanitas Gavazzeni, Bergamo, Italy
15. Department of Medical Oncology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
16. Department of Thoracic Surgery, University of Turin, San Giovanni Battista Hospital, Turin, Italy
17. Department of Medicine, Section of Hematology Oncology, The University of Chicago, Thoracic Oncology Program, Chicago, USA
18. Department of Radiotherapy and Radiosurgery, IRCCS Humanitas Research Hospital, 20089 Rozzano, Italy
19. Medical Oncology Unit, Università Politecnica delle Marche, 60126 Ancona, Italy
20. Oncologia Medica 2, Istituto Oncologico Veneto, Istituto di Ricovero e Cura a Carattere Scientifico, 35121 Padova, Italy.
21. Department of Surgery, Oncology and Gastroenterology, University of Padova, 35127 Padova, Italy

***TYME GROUP:** Proto Claudia, Lo Russo Giuseppe, Ganzinelli Monica, Leuzzi Giovanni, Solli Piergiorgio, Perrino Matteo, Cordua Nadia, Checchi Luigi, De Vincenzo Fabio, Federico Antonio, Zucali Paolo, Lucchi Marco, Ambrogi Marcello Carlo, Aprile Vittorio, Melfi Franca, Mendogni Paolo, Rosso Lorenzo, Vespro Valentina, Cecere Fabiana Letizia, Tortora Marianna, Del Vecchio Silvana, Comacchio Giovanni, Bianco Roberto, Di Pietro Paolo Marzia, Fabbri Alessandra, Petrini Iacopo, Trama Annalisa, Francesco Habetswallner, De Pas Tommaso Martino, Conforti Fabio, Galli Giulia, Ruffini Enrico, Garassino Marina Chiara, Franceschini Davide, Berardi Rossana, Pasello Giulia, Palmieri Giovannella, Marino Mirella, Lyberis Paraskevas, Calabrese Fiorella.

ABSTRACT

Background: Induction therapy (IT) prior to surgery is a key strategy to improve resectability in advanced thymic tumors (ATTs). This study aimed to assess prognostic factors and the impact of IT on clinical outcomes.

Material and methods We retrospectively analyzed 64 patients with TNM-stage II–IV ATTs treated with IT and surgery between January 2002 and December 2024, using data from the TYME multicenter Italian database. Radiological response (RR) was defined by RECIST v1.1. Statistical comparisons were performed using Chi-square, t-test, or Wilcoxon rank-sum test. Univariate and multivariate logistic models evaluated associations between variables and outcomes.

Results: Mean age was 52 years; 58% were male. Most tumors (83.4%) were stage III–IV, with thymoma as the predominant histology (79.7%). Radiological signs of mediastinal or vascular invasion and tumor diameter >5 cm were present in over 86% of cases. Platinum-based chemotherapy was administered in 96.9%, with CAP regimen used in 62.5%. Partial response was achieved in 69% (Responders, RE), while 31% had stable/progressive disease (Non-responders, NRE). Extended surgery was performed in 84.4%, with R0 resection in 76.3%. Relapse occurred in 78.6% (local) and 21.4% (distant). No significant differences were found between RE and NRE in clinical, radiological, or pathological features. Five-year OS (88% vs 93%) and RFS (45% vs 43%) were similar between groups. ECOG performance status was the strongest independent predictor of better RFS (OR 7.18), while ASA score was associated with RR (OR 0.20).

Conclusion: The TYME database analyses revealed no significant outcome differences between RE and NRE following IT in ATTs, underscoring the complexity of predicting long-term outcomes based on RR alone. This study also suggests the prognostic value of physical status via ASA score and ECOG PS. Further studies with varied chemo regimens are needed to improve response rates in multimodal ATT therapy.

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Abbreviations

TETS: thymic epithelial tumours

ATTS: advanced thymic tumors

IT: induction therapy

RR: radiological response

TYME: Italian collaborative group for ThYmic MalignanciEs

RECIST: Response Evaluation Criteria in Solid Tumours

RE: responders

NRE: non responders

OS: overall survival

RFS: recurrence-free survival

OR: odds ratio

CT: computed tomography

ITMIG: International Thymic Malignancy Interest Group

ECOG: Eastern Cooperative Oncology Group

PS: performance status

ASA: American Society of Anaesthesiologists

CAP: Cisplatin, Doxorubicin, and Cyclophosphamide

INTRODUCTION

Thymic epithelial tumors (TETs), encompassing thymomas and thymic carcinomas, are rare malignancies that usually require challenging treatments. While complete surgical resection remains the cornerstone of treatment for these tumors, the optimal management strategy for locally advanced thymic tumors (ATTs), particularly those classified in the past as Masaoka stage III-IV, remains a matter of ongoing debate and research [1, 2, 3, 4, 5, 6].

For patients with locally advanced or potentially unresectable TETs, induction therapy (IT) emerges as a crucial strategy. The primary goal of IT is to downstage the tumour, reduce its bulk

and improve the likelihood of achieving a complete (R0) surgical resection, which is reported as the major prognostic factor for long-term survival [7, 8, 9, 10, 11]. Multimodality treatment approaches, including induction chemotherapy, with or without radiotherapy, followed by surgery and often adjuvant therapy, have shown promising results in improving resectability and long-term outcomes [12, 13, 14, 15, 16, 17, 18, 19, 20].

Despite the growing evidence supporting the use of IT, several challenges persist. The heterogeneity of TETs, ranging from indolent thymomas to aggressive thymic carcinomas, complicates the clinician to perform adequate treatment stratification. Furthermore, the criteria for selecting patients who would most benefit from IT and the optimal regimens and duration of induction treatment, are not yet fully standardized. While radiological response (RR) after IT is commonly assessed using criteria like Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, its correlation with pathological response and, more importantly, with long-term survival outcomes, is not always straightforward [21, 22, 23].

This study aims to contribute to the understanding of IT in ATTs by analyzing data from the Italian collaborative group for ThYmic MalignanciEs (TYME) multicentric database. We sought to evaluate prognostic factors and the impact of IT on the outcomes of ATTs, with a particular focus on the correlation between RR and long-term survival.

METHODS

This study comprised a multicenter retrospective observational analysis of patients diagnosed with TETs who received treatment with IT followed by surgery. Data were systematically analysed from January 2002 to December 2024 through the Italian collaborative group for ThYmic MalignanciEs (TYME) multicentric database. The TYME network (IRB protocol n. 121/24) , established in Italy in 2014, is dedicated to fostering collaboration among specialized Italian centers with multidisciplinary expertise in TETs. At the time of this analysis (June 2025), the network

encompasses 33 member centers, with the initial 8 actively contributing to the Italian Registry on TETs and participating in this specific retrospective study.

Medical records for all eligible patients were thoroughly reviewed to extract comprehensive clinical, radiological, histopathological, surgical and oncological factors relevant to both induction and adjuvant therapies. Inclusion criteria specifically focused on patients with ATTs classified as clinical 8th TNM stage II to IV. To ensure diagnostic accuracy, all selected cases underwent rigorous review and confirmation by the referring pathologist and oncologist at each respective center. RR following IT was meticulously assessed and defined according to the internationally recognized RECIST version 1.1 guidelines [23,24]. Patients were categorized as Responders (RE) if they achieved a partial response and Non-Responders (NRE) if they had stable or progressive disease. Median follow-up time was 2.8 years.

Statistical Analysis

Outcomes of the present analysis were (a) the RR to IT (complete or partial response vs. progressive or stable disease); (b) overall survival (OS) from the date of surgery to death, and (c) recurrence free survival (RFS) from the date of surgery to cancer recurrence or death.

Descriptive analyses of selected variables were reported as numbers and percentages for categorical data and as median with interquartile range (IQR) or mean with standard deviation (std) for continuous ones. Comparisons were made by Chi-square test of Fisher exact test for categorical data and by two sample t-test or the Wilcoxon rank-sum test for continuous data, as appropriate.

Univariate and multivariate logistic models were performed to test the association of selected variables and the principal outcomes of the present analysis as described above. Only statistically significant results at alpha level 0.05 were reported as odds ratio (OR) with 95% confidence interval (95%CI), with coefficient estimate and p-value. Only variables statistically significant in the univariate model were included in multivariate analysis.

OS and RFS were estimated by Kaplan-Meier curves and comparisons between selected variables were made by Log-Rank test.

All analyses were carried out by SAS® (Statistical Analysis Software, version 5.2.1, SAS Institute Inc., Cary, NC, USA).

RESULTS

Overall Population

The study population included 64 patients (Table 1). The mean age was 52 years (SD 12.5). Gender distribution showed 37 males (57.8%) and 27 females (42.2%). Myasthenia gravis was reported in 33 (54.1%) cases. Eastern Cooperative Oncology Group (ECOG) performance status (PS) and American Society of Anaesthesiologists (ASA) scores were predominantly 1 (74.1% and 44.8%, respectively).

86.3% and 56.9% of TETs presented with diameter greater than 5 cm and volume lower than 511.7 cm^3, respectively. A radiological mediastinal or vascular invasion was reported in 32 patients (86.5%). Tumour burden (according to radiological invasion, number of metastatic site and tumour volume) was categorized as low in 56 patients (93.3%) and high in 4 patients (6.7%).

Clinical Masaoka stages were distributed as follows: I (1.9%), II (20.8%), III (47.2%), and IV (30.2%). Clinical TNM stages were II (18.3%), III (46.7%), and IV (36.7%).

Regarding IT, platinum-based chemotherapy was administered to 96.9% of cases, with Cisplatin, Doxorubicin, and Cyclophosphamide (CAP) scheme the most administered regimen (62.5%). 54.7% of patients received more than 4 chemo cycles.

Histology revealed Thymoma in 51 patients (79.7%) and subtypes included A (5.9%), AB (9.8%), B1 (15.7%), B2 (45.1%), B3 (17.7%). Immuno-histological markers included CD5/CD1a/CD3/CD8 (14.3%), CK (AE1/AE3/PAN) (71.4%) and TTF1 (3.6%).

Extended surgical resection was performed in 54 patients (84.4%). Resection status was R0 in 45 patients (76.3%) and R+ in 14 patients (23.7%). Pathological T (according 8th TNM) were pT1 (15.3%), pT2 (8.5%), pT3 (59.3%) and pT4 (16.9%). Pathological TNM stage was categorized as stage I, II, IIIA, IIIB, IVa and IVB in 10%, 8.3%, 31.7%, 3.3%, 30% and 16.7% of patients, respectively. Adjuvant radiotherapy was performed in 42 (66.7%) of cases.

Responders vs. Non-Responders

There were 20 (31%) NRE and 44 (69%) RE. As reported in Table 1, no significant differences were observed between both groups, except for ECOG PS (p=0.0302) and ASA Score (p=0.0062).
The 5-year OS was 93% for NRE and 88% for RE (p-value 0.8011, Figure 1). Similarly, no difference was reported in terms of 10-year OS (p-value 0.5304).
The 5-year RFS was similar for both subgroups (43% and 45% for NRE and RE respectively, p-value 0.9296, Figure 1).

Outcome Analyses

Radiological Response

Univariate logistic regression analysis for RR (Table 2) identified two significant factors: ECOG PS and ASA Score. Concerning ECOG PS, an OR of 0.27 (95% CI: 0.08-0.91, p=0.0354) suggests that patients with higher ECOG PS (2 or 3) were less likely to achieve a RR. Similarly, a unit increase in ASA Score was associated with a decreased likelihood of RR, with an OR of 0.16 (95% CI: 0.04-0.71, p=0.0160).
In multivariate analysis for radiological response, ASA Score only remained the most significant predictor of RR (OR 0.20 [95% CI: 0.04-0.93], p=0.0406).

Overall Survival

The median OS time was 2.8 years with a global 5-year and 10-year OS of 93% and 80%, respectively.

Univariate logistic regression for OS showed that Myasthenia gravis had an OR of 0.11 (95% CI: 0.01-1.00, p=0.0503), suggesting that myasthenic patients had an 89% lower risk of overall mortality (Figure 2A); however, this evidence has not been corroborated by multivariate analysis (Table 3).

Outcome comparative analyses are reported in Supplementary Table1.

Recurrence-Free Survival

The median RFS time was 1.5 years with a global 5-year and 10-year OS of 36% and 12%, respectively. Relapse was local or regional in 22 patients (78.6%) and distant in 6 patients (21.4%).

As reported in Table 4, in univariate logistic regression analysis, administration of CAP scheme (Figure 2B), pathological TNM stage (Figure 2C) and ECOG PS were statistically significant.

In multivariate analysis for RFS, good ECOG PS only continued to be a strong independent predictor for better RFS, with an OR of 7.18 (95% CI: 1.15-44.96, p=0.0351, Figure 2D).

Further comparative analyses are reported in Supplementary Table1.

DISCUSSION

Our study, utilizing data from the Italian nationwide TYME database, offers valuable insights into the contemporary management and outcomes of ATTs treated with IT. The results are highly encouraging, demonstrating 5-year OS and RFS rates of 93% and 36% respectively. These figures

are remarkably similar to those reported in other substantial series and multi-institutional studies focusing on multimodal treatment strategies for ATTs [12, 13, 14, 15, 16, 17, 18, 19, 20]. This consistent demonstration of robust long-term outcomes strongly reinforces the paradigm that a meticulously planned multidisciplinary approach, integrating IT, aggressive surgical resection and often tailored adjuvant treatments, represents the cornerstone for optimizing prognosis in these rare and challenging cases [12,16]. The substantial rate of extended surgical resection achieved in our cohort (84.4%) is a testament to the efficacy of IT in transforming potentially unresectable tumours into surgically manageable entities, thereby maximizing the chances of achieving a R0 resection (76.3% in our series), in order to obtain a superior long-term survival in TETs [1, 5, 11].

However, a pivotal and thought-provoking finding of our study is the observed absence of a statistically significant difference in OS and RFS between RE and NRE patients, despite a substantial proportion (69%) of patients being classified as partial responders according to RECIST criteria. This outcome underscores a fundamental and extensively debated challenge within the oncology community, particularly pertinent to TETs: the inherent complexities in accurately interpreting RR and the acknowledged limitations of conventional RECIST criteria in this specific tumour type [21, 22]. While computed tomography (CT) imaging remains the primary modality for initial staging and monitoring treatment response [23, 25], the unique pathological characteristics of TETs can lead to discrepancies. Post-treatment morphological changes, such as the development of extensive fibrosis, hyalinization, or necrosis, may not always manifest as significant volumetric reduction on imaging [26]. Consequently, a tumour mass might contain a substantial proportion of non-viable fibrotic tissue, indicative of an excellent pathological response, but its overall dimensions might not sufficiently shrink to meet RECIST criteria for partial RR, leading to its categorization as stable disease or even progressive disease radiologically. This phenomenon contributes to the decoupling of radiological appearance from true pathological regression, which is often a more accurate reflection of treatment efficacy and a stronger predictor of long-term outcomes [21, 22]. Modifications to RECIST, such as those proposed by the International Thymic

Malignancy Interest Group (ITMIG) [27], have attempted to account for these specificities, acknowledging the unique growth patterns and post-treatment changes in TETs. Yet, even with these refinements, the perfect translation of imaging findings into precise prognostic indicators remains an ongoing area of research.

As well, the potential explanations for this apparent disconnect between RR and long-term survival outcomes are multifaceted. Firstly, as previously noted, the biological effects of IT on thymic epithelial tumours often involve a significant degree of tumour cell necrosis and subsequent replacement by fibrotic tissue [26]. This fibrotic scar, while representing effective tumour control, may retain its original volume, or even slightly increase, making it challenging for RECIST criteria (which primarily rely on unidimensional or bidimensional measurements of lesion size) to accurately reflect the true extent of tumour kill. For example, a patient could harbour extensive pathological regression, with only microscopic viable tumour cells remaining, yet fail to meet the strict RECIST criteria for response if the fibrotic tissue does not shrink sufficiently. Conversely, some tumours might show early shrinkage due to oedema resolution or mild cellular necrosis, but still retain aggressive viable tumour components that drive subsequent recurrence. Secondly, TETs encompass a spectrum of histological subtypes, from indolent thymomas (WHO Type A, AB, B1) to more aggressive thymomas (WHO Type B2, B3) and highly aggressive thymic carcinomas [20, 21]. The inherent biological aggressiveness, proliferative capacity and metastatic potential vary significantly across these subtypes. It is plausible that, in more aggressive histologies, even a seemingly good RR might mask microscopic residual disease with high intrinsic resistance or metastatic potential, leading to eventual recurrence despite initial shrinkage. For less aggressive thymomas, even a "stable disease" on imaging might indicate effective containment of an indolent tumour, leading to prolonged survival. Therefore, RR alone, without correlation to tumour biology and pathological findings, may not fully capture the prognostic implications. This underscores the need for integrating a more comprehensive understanding of tumour biology into RR assessment methods.

Beyond the nuances of RR, our study highlights the critical importance of the patient's physical status, commonly assessed through validated PS scales like ECOG PS as well as ASA score, which takes into account patient's fitness prior surgery. As a rule, it is a well-established principle in oncology that a robust baseline physical status is a fundamental determinant of a patient's ability to tolerate intensive multimodality treatments, including IT and extensive surgery [1, 5, 12, 13, 14, 16]. Patients who are in good physical condition are generally more resilient to the side effects of treatment. This allows patients to complete their planned therapies and recover better after surgery, both of which are crucial for improving long-term outcomes. As cancer care evolves, the idea of personalized medicine is becoming increasingly important. For ATTs, this future approach should extend beyond analyzing tumour molecular profiles and imaging changes only. It should evaluate TETs patient's physical status comprehensively along with any existing health conditions and their overall functional status. This integrated evaluation could pave the way for truly individualized treatment plans. This would allow clinicians to optimize induction chemo schemes, tailor therapy regimens and duration and to refine surgical strategies in order to maximize treatment benefits while minimizing side effects, thus improving both survival and quality of life.

Our findings further confirm the CAP regimen as a valuable and frequently employed IT for ATTs, with 62.5% of our cohort receiving this combination. This is consistent with the established efficacy of platinum-based chemotherapy regimens in TETs, dating back to past trials reported in the Literature that demonstrated significant objective response rates [28, 29, 30, 31]. While CAP and other platinum-etoposide combinations have been confirmed to achieve tumour down-staging and facilitating resections, the persistent challenge of suboptimal RR, as observed in our study, underscores the urgent need for innovation in pharmacotherapy. Future efforts should be directed towards the identification and development of novel pharmacological agents or synergistic drug combinations capable of inducing a more profound and consistent radiological regression. This could involve exploring targeted therapies that interfere with specific oncogenic pathways identified in TETs, or leveraging immunotherapeutic approaches, such as immune checkpoint inhibitors,

which have revolutionized treatment across various thoracic malignancies and are actually under investigation, with promising results also for TETs [8]. Specifically, improved RR would offer several advantages for both surgeons and oncologists: it can help in predicting the need for more complex surgical resections as well as for less extensive resections, thereby mitigating surgical morbidity and accelerating patient recovery. Ultimately, superior RR holds the promise of translating into higher rates of complete pathological response and, consequently, further improvements in long-term survival and quality of life for patients.

Our study is subject to several limitations inherent to its retrospective and multicentric design. Data collection over an extended period (2002-2024) across multiple Institutions may introduce variability in diagnostic practices, treatment protocols and imaging techniques. The reliance on RECIST v1.1 for RR assessment, as extensively discussed, may not fully capture the pathological extent of tumour regression, which is a known challenge in TETs. While the cohort size of 64 patients is significant for a such rare disease, it still limits the statistical power for detecting subtle associations or conducting adequate subgroup analyses based on specific histological subtypes, complex treatment variations or the presence of paraneoplastic syndromes. Furthermore, due to the limited patient numbers, a correlation between RR and pathological downstaging after surgery could not be established; this issue warrants further investigation in larger-scale studies. Finally, the detailed assessment of patient physical status at baseline and its dynamic changes during treatment were not primary objectives of this study and thus were not comprehensively analysed.

Our study provides interesting evidences that IT followed by surgical resection represents a safe and highly effective strategy for patients with ATTs, contributing to acceptable OS and RFS rates. However, our results define a mismatch between RR and long-term outcomes in TETs. This issue strongly underlines the limitations of conventional radiology imaging in reflecting the biological and pathological impact of IT. As well, novel biomarkers and advanced imaging modalities should be tested in order to more accurately predict both pathological response and long-term prognosis. This integrated approach, combined with a comprehensive assessment of the patient's physical

status, will be instrumental in developing more personalized treatment strategies. While the established CAP regimen remains a valuable component of IT, there is critical need for the discovery and development of innovative pharmacological agents that can induce more profound and consistent radiological and pathological responses in ATTs.

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Conflict of Interests:

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Figure Legend

Figure 1. Kaplan–Meier curves of overall survival (A) and recurrence-free survival (B) in responders (RE) vs. non-responders (NRE) after induction therapy.

Figure 2. Kaplan–Meier curves of survival outcomes according to different prognostic factors. (A) anti-AChR status. (B) CAP regimen. (C) Pathological TNM stage. (D) ECOG performance status.

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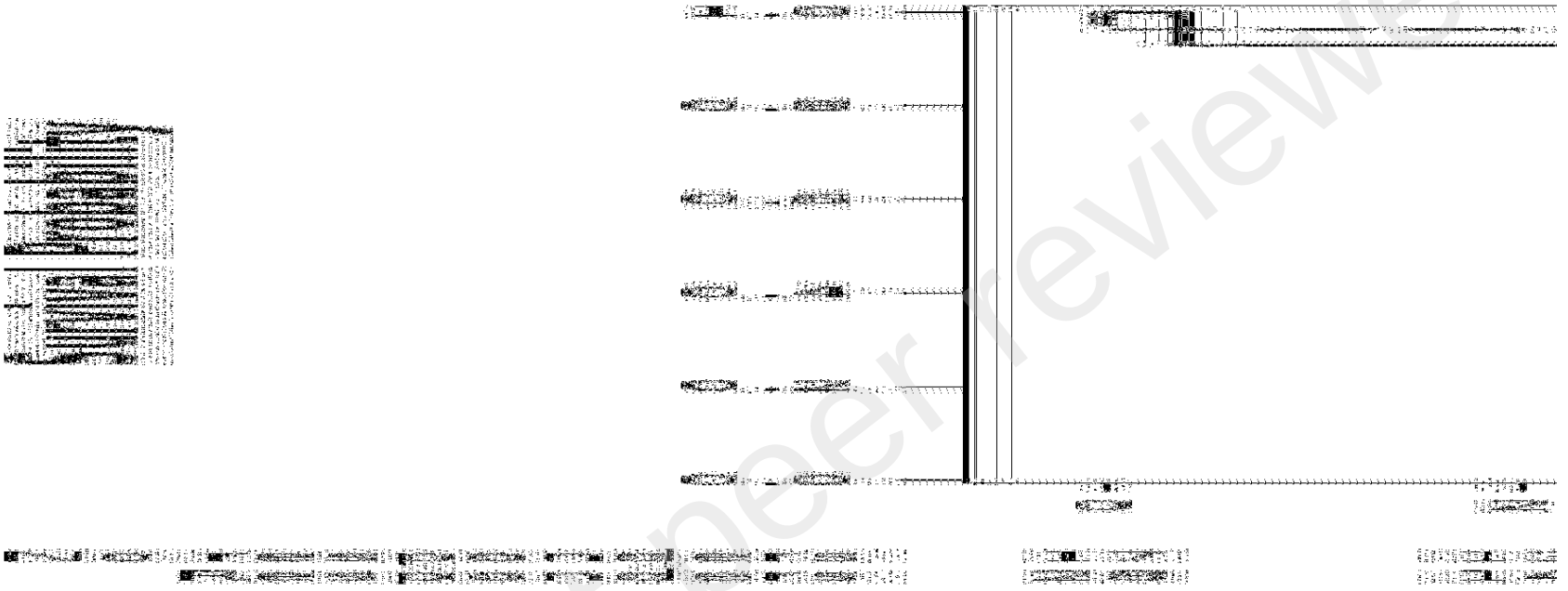

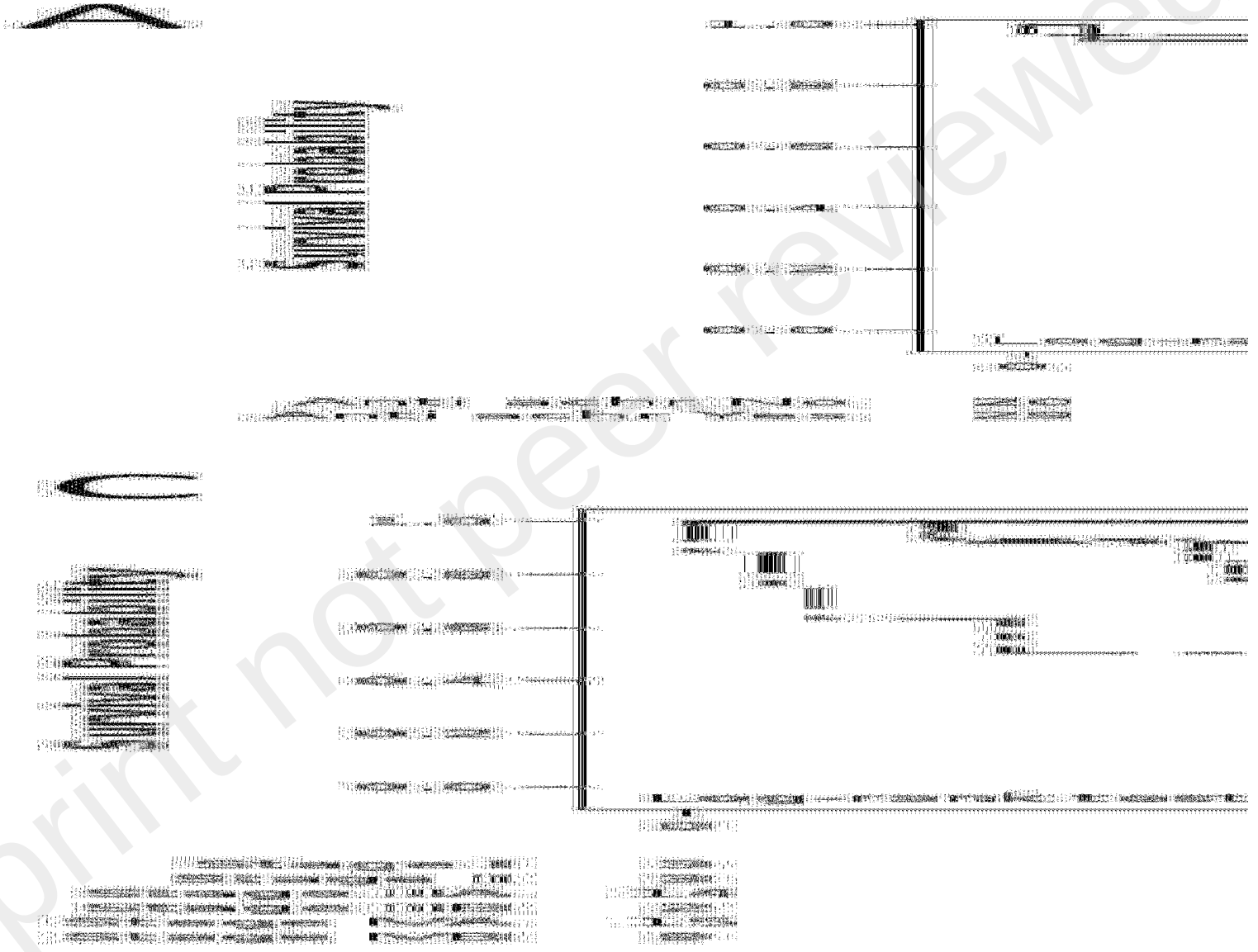

Figure Legend

Figure 1. Kaplan–Meier curves of overall survival (A) and recurrence-free survival (B) in responders (RE) vs. non-responders (NRE) after induction therapy.

Figure 2. Kaplan–Meier curves of survival outcomes according to different prognostic factors. (A) anti-AChR status. (B) CAP regimen. (C) Pathological TNM stage. (D) ECOG performance status.

Table1. Comparative analysis on Responders vs Non-Responders

	Non-Responders (%)	Responders (%)	Total (%)	p-value*
	20	44	64	
Age				
mean (std)	54 (13.3)	51 (13.0)	52 (12.5)	0.3206**
Gender				
Male	10 (50)	27 (61,4)	37 (57,8)	0.3935
Female	10 (50)	17 (38,6)	27 (42,2)	
BMI				
median (IQR)	23.2 (19.5-24.6)	27.3 (23.2-29.0)	24.9 (22.7-27.8)	0.1355***
Myasthenia gravis				
No	10 (55,6%)	18 (41,9%)	28 (45,9%)	0.3276
Yes	8 (44,4%)	25 (58,1%)	33 (54,1%)	
PS ECOG				
1	10 (55,6%)	33 (82,5%)	43 (74,1%)	0.0302
2 + 3	8 (44.4%)	7 (17,5%)	15 (25.9%)	
ASA Score				
1	0 (0%)	11 (57,9%)	11 (37,9%)	0.0062
2	7 (70%)	6 (31,6%)	13 (44,8%)	
3	3 (30%)	2 (10,5%)	5 (17,2%)	
4	0 (0%)	0 (0%)	0 (0%)	
Tumour diameter (cm)				
<5	2 (13,3%)	5 (13,9%)	7 (13,7%)	1
≥5	13 (86,7%)	31 (86,1%)	44 (86,3%)	
Tumour volume (cm^3)				
<511,7	10 (66.7%)	19 (52.8%)	29 (56.9%)	0.5361
≥511,7	5 (33.3%)	17 (47.2%)	22 (43.1%)	
Radiological mediastinal/vascular invasion				
No	2 (25.0%)	3 (10.3%)	5 (13.5%)	0.2917

yes	6 (75.0%)	26 (89.7%)	32 (86.5%)	
Pleural effusion				
No	4 (57.1%)	21 (70.0%)	25 (67.6%)	
Yes	3 (42.9%)	9 (30.0%)	12 (32.4%)	0.6594
Number of metastatic sites				
≤1	1 (16.7%)	5 (50.0%)	6 (37.5%)	
>1	5 (83.3%)	5 (50.0%)	10 (62.5%)	0.3069
Tumour Burden				
LOW (tumour volume < 511,7 or Number of metastatic sites ≤ 1 or radiological mediastinal invasion = no)	16 (94.1%)	40 (93.0%)	56 (93.3%)	1
HIGH (tumour volume ≥511,7 and Number of metastatic sites > 1 and radiological mediastinal invasion = yes)	1 (5.9%)	3 (7.0%)	4 (6.7%)	
SUVmax				
≤6	7 (70%)	6 (50%)	13 (59,1%)	0.4149
6	3 (30%)	6 (50%)	9 (40,9%)	
Clinical Masaoka stage				
I	0 (0%)	1 (2,7%)	1 (1,9%)	0.5762
II	3 (18,8%)	8 (21,6%)	11 (20,8%)	
III	6 (37,5%)	19 (51,4%)	25 (47,2%)	
IV	7 (43,8%)	9 (24,3%)	16 (30,2%)	
Clinical T				
T2	6 (30%)	6 (15%)	12 (20%)	0.3428
T3	10 (50%)	21 (52,5%)	31 (51,7%)	
T4	4 (20%)	13 (32,5%)	17 (28,3%)	
Clinical TNM				
II	5 (26,3%)	6 (15%)	11 (18,3%)	0.1063
III	5 (26,3%)	23 (57,5%)	28 (46,7%)	
IV	9 (47,4%)	13 (32,5%)	22 (36,7%)	
Cortison therapy				
no	4 (80%)	12 (85,7%)	16 (84,2%)	1

yes	1 (20%)	2 (14,3%)	3 (15,8%)	
Platinum-based chemotherapy				
no	1 (5%)	1 (2,3%)	2 (3,1%)	0.5308
yes	19 (95%)	43 (97,7%)	62 (96,9%)	
CAP scheme				
no	10 (50%)	14 (31,8%)	24 (37,5%)	0.1637
yes	10 (50%)	30 (68,2%)	40 (62,5%)	
Number of chemo cycles				
<4	10 (50%)	19 (43,2%)	29 (45,3%)	0.6115
≥4	10 (50%)	25 (56,8%)	35 (54,7%)	
Histology				
Thymoma	17 (85%)	34 (77,3%)	51 (79,7%)	0.7385
Thymic Carcinoma/Neuroendocrine	3 (15%)	10 (22,7%)	13 (20,3%)	
Thymoma subtypes				
A	2 (11.8%)	1 (2.9%)	3 (5.9%)	0.1457
AB	1 (5.9%)	4 (11.8%)	5 (9.8%)	
B1	2 (11.8%)	6 (17.7%)	8 (15.7%)	
B2	5 (29.4%)	18 (52.9%)	23 (45.1%)	
B3	6 (35.3%)	3 (8.2%)	9 (17.7%)	
Other	1 (5.95)	2 (5.9%)	3 (5.9%)	
C-KIT expression				
no	0 (0%)	2 (66,7%)	2 (33,3%)	0.4000
yes	3 (100%)	1 (33,3%)	4 (66,7%)	
Immuno-histological Markers				
CD5/CD1a/CD3/CD8	1 (12,5%)	3 (15%)	4 (14,3%)	1
CK (AE1/AE3/PAN)	6 (75%)	14 (70%)	20 (71,4%)	
TTF1	0 (0%)	1 (5%)	1 (3,6%)	
OTHERS	1 (12,5%)	2 (10%)	3 (10,7%)	
Extended resection				
No	4 (20%)	6 (13,6%)	10 (15,6%)	0.7116
Yes	16 (80%)	38 (86,4%)	54 (84,4%)	
Radicality				

R0	13 (72,2%)	32 (78,1%)	45 (76,3%)	0.6281
R+	5 (27,8%)	9 (22,0%)	14 (23,7%)	
pT				
1	2 (10%)	7 (17.9%)	9 (15.3%)	0.0657
2	4 (20%)	1 (2.6%)	5 (8.5%)	
3	9 (45%)	26 (66.7%)	35 (59.3%)	
4	5 (25%)	5 (12.8%)	10 (16.9%)	
pTNM stage				
I	2 (10.5%)	4 (9.8%)	6 (10.0%)	0.1106
II	4 (21.1%)	1 (2.4%)	5 (8.3%)	
IIIA	3 (15.8%)	16 (39.0%)	19 (31.7%)	
IIIB	1 (5.3%)	2 (2.4%)	2 (3.3%)	
IVA	5 (26.3%)	13 (31.7%)	18 (30.0%)	
IVB	4 (21.1%)	6 814.6%)	10 (16.7%)	
Adjuvant radiotherapy				
No	7 (35.0%)	14 (32.6%)	21 (33.3%)	0.8472
Yes	13 (65.0%)	29 (67.4%)	42 (66.7%)	
Relapse				
Local/Regional	9 (81,8%)	13 (76,5%)	22 (78,6%)	1
Distant	2 (18,2%)	4 (23,5%)	6 (21,4%)	

*Chi-square test or Fisher exact test as appropriate

** T-test

*** Wilcoxon test

Table 2. Logistic models for radiological response

RR	Logistic models					
	Univariate			Multivariate		
	estimate	OR (95% CI)	p-value	estimate	OR (95% CI)	p-value
ECOG PS (OR for 2+3 VS.1)	-0.6637	0.27 (0.08-0.91)	0.0354	-0.4734	0.39 (0.06-2.73)	0.3412
ASA Score (OR for unit increase)	-1.8444	0.16 (0.04-0.71)	0.0160	-1.6245	0.20 (0.04-0.93)	0.0406

Table 3. Logistic models for Overall Survival

OS	Logistic models				
	univariate			multivariate	
	estimate	OR (95% CI)	p-value	estimate	p-value
Myastenia gravis (OR yes vs no)	-2.2336	0.11 (0.01-1.00)	0.0503	-	-

4. Logisic model for Recurrence-Free Survival

RFS	Logistic models					
	univariate			multivariate		
	estimate	OR (95%CI)	p-value	estimate	OR (95%CI)	p-value
CAP (OR yes vs. no)	-1.8098	0.16 (0.05-0.57)	0.0043	-0.9717	0.38 (0.07-1.98)	0.2497
ECOG PS (OR 2+3 vs. 1)	1.1077	9.17 (1.72-48.84)	0.0095	0.9860	7.18 (1.15-44.96)	0.0351
p-TNM stage (OR for unit increase)	0.4378	1.55 (1.02-2.35)	0.0399	0.3652	1.44 (0.85-2.44)	0.1742