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Outcome of primary neuroendocrine tumors of the thymus: A joint analysis of the International Thymic Malignancy Interest Group and the European Society of Thoracic Surgeons databases

Read at the 94th Annual Meeting of The American Association for Thoracic Surgery, Toronto, Ontario, Canada, April 26-30, 2014.

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Objective

Primary neuroendocrine tumors of the thymus (TNET) are exceedingly rare. We studied a large series of TNET identified through the International Thymic Malignancy Interest Group and the European Society of Thoracic Surgeons databases.

Methods

This was a retrospective multicenter study of patients undergoing operation for TNET between 1984 and 2012. Outcome measures were: overall survival (OS) and cumulative incidence of recurrences (CIR). OS was analyzed using the Kaplan-Meier method and CIR was analyzed using competing risk analysis. Associations with clinical and prognostic factors for OS and CIR were evaluated using the log rank test and Gray test.

Results

Two hundred five patients with TNET were treated: 25 patients received induction therapy (19 chemotherapy [CT] and 6 radiotherapy [RT]). Data about resection status were available in 47% of cases: complete resection was performed in 52 patients (54%). Masaoka-Koga stages I, II, III, and IV were observed in 12, 33, 56, and 47 patients, respectively. Atypical carcinoid was the commonest histologic subtype (71 cases; 40%). One hundred one patients with TNET received adjuvant treatment; 52 patients died and 36 experienced a recurrence. The median OS was 7.5 years; 5-year OS was 68%, and 5-year CIR was 39%. OS was significantly influenced by Masaoka-Koga stage (P = .02) and completeness of resection (P = .03). CIR significantly increased in high Masaoka-Koga stages (P = .04). Histologic subtype was not associated with either OS or CIR.

Conclusions

Our results confirm the high biologic aggressiveness of these rare neoplasms; pathologic stage and completeness of resection were demonstrated to be strong prognostic factors, whereas histology did not influence patients outcome.

CTSNet classification

- 13;
- 43

Abbreviations and Acronyms

- CIR, cumulative incidence of recurrences;
- ESTS, European Society of Thoracic Surgeons;
- ITMIG, International Thymic Malignancy Interest Group;
- OS, overall survival;
- R0, complete tumor resection;
- R1, microscopically residual disease;
- R2,macroscopically residual disease

See related commentary on pages 110-1.

Primary neuroendocrine tumors of the thymus (TNET) were described for the first time by Rosai and Higa1 in 1972. Since then, the number of cases reported in the literature is approximately 400. Moreover, the majority of these articles are case reports, and only a small number of articles contain modest single-center clinical series, and are therefore unable to provide uniform assessment and validated prognostic factors for these neoplasms.

TNET are exceedingly rare tumors, accounting for approximately 0.4% of all carcinoid tumors2 and <5% of all anterior mediastinal neoplasms3; an age-adjusted incidence rate of 0.18 per 1,000,000 US population4 has been observed. A male predominance, with a peak incidence in the fifth decade, has also been reported.4 and 5

According to the 2004 World Health Organization classification of tumors,6 TNET are included in the thymic carcinoma group, and are classified into 4 entities in 2 major histopathologic types: well-differentiated neuroendocrine carcinomas (also called typical carcinoid and atypical carcinoid) and poorly differentiated neuroendocrine carcinomas (small-cell carcinoma and large-cell neuroendocrine carcinoma).

Almost 50% of these tumors can be complicated by endocrine disease, either due to ectopic adrenocorticotropic hormone secretion (Cushing syndrome) or because of its association with other endocrine tumors, such as in multiple endocrine neoplasia type 1 syndrome.

The prognosis of patients with TNET is poor because of the high incidence of local recurrences and distant metastases, even after a radical tumor resection: the reported overall 5-year survival rate may vary from 30% to 70%.7, 8 and 9

Due to the fact that TNET are rare neoplasms that remain unfamiliar to the majority of practicing thoracic physicians and surgeons, the reported studies were unable to validate factors influencing long-term outcome, and there has been very limited improvement in management of these tumors, we used and analyzed the International Thymic Malignancy Interest Group (ITMIG) and the European Society of Thoracic Surgeons (ESTS) retrospective databases on thymic malignancies with the aim to evaluate factors influencing TNET patient outcomes. This article represents the first joint analysis of ITMIG and ESTS retrospective database for TNET cases.

Material and Methods

ESTS and ITMIG Retrospective Databases

The ESTS database project was launched in 2011 among ESTS members (Appendix E1), collecting data of surgically treated primary thymic tumors from 1990 to 2011. The ITMIG database, with similar purpose, started in 2012 with 67 participating institutions (Appendix E2).
A central data handling team and database committee overlooked the process for each dataset; details of 2 patient populations were recently described elsewhere.10 Both datasets have similar data fields and variables, including gender, previous malignancy, TNET histology, lymph node involvement, distant metastases, clinical and pathologic Masaoka or Masaoka-Koga staging system, resection status, chemotherapy and/or radiotherapy treatment, and recurrence. Moreover, duplicate cases from ESTS centers that were already participating in ITMIG dataset have been removed for analyses.
For the purpose of our study, all TNET patients treated between 1984 and 2012 were considered, and 205 cases were identified.

Approval for this study was granted by the Yale University Institutional Review Board (No. 1307012419).

Management of Clinical Variables and Standard Outcome Measures

A dedicated staging system for TNET does not exist,11 and different institutions worldwide used either Masaoka or Masaoka-Koga systems. In fact, these 2 classifications only differ in how stages I and II are defined.
Furthermore, as recently observed,12 there is no difference in outcomes between stage I and II. Hence, for the purpose of our study, cases with stages I and II (II, IIa, and IIb) were joined and analyzed together, and cases staged using the Masaoka and Masaoka-Koga staging systems were combined together.
According to ITMIG standards,13 surgery was considered radical when a complete tumor resection (R0) with negative gross and microscopic margins was accomplished, and as incomplete when there was microscopically residual disease (R1) or macroscopically residual disease (R2). Debulking surgery was also considered an R2 resection. Time intervals were calculated.

Overall survival (OS)

Time interval between the date of surgery or last day of medical treatment (chemotherapy) and the date of death or the date of the last follow-up.

Cumulative incidence of recurrence (CIR)

Time interval between the date of R0 surgery and the date when recurrence was diagnosed or the date of the last follow-up without recurrence.

Statistical Analysis

A core statistical team of ITMIG performed all analyses with SAS version 9.3 (SAS Institute, Inc, Cary, NC) and R (R Foundation for Statistical Computing, Vienna, Austria). For patient characteristics, continuous data are presented as median (range) and categorical data as frequency with percentage.

OS and CIR were the primary outcomes. OS was analyzed using the Kaplan-Meier method. The association of overall survival with clinical and prognostic factors was tested using the log-rank test. Prognostic factors that were significantly associated with survival in univariate analysis ($P < .05$) were included in a Cox proportional-hazards model for multivariate analysis.
CIR was assessed using competing risk analysis, with death included as the competing event. The effect of clinical factors on freedom from recurrence was assessed using Gray test.

Results

Patient Characteristics

A total of 205 TNET cases were collected for analysis after joining ITMIG and ESTS databases. A male predominance (155 patients; 77%) was observed. Median age of patients was 54 years (range, 19-82 years). No geographic predominance was observed in patient distribution.

Previous malignancies were seen in 17 cases (8.3%), the most common of which were prostate (n = 5) and skin cancer (n = 2). No data concerning endocrine related disorders was available in either database.

Typical carcinoid histology was regarded as low grade (n = 49 out of 178 patients; 28%), atypical carcinoid histology as intermediate grade (n = 71 out of 178 patients; 40%) followed by poorly differentiated carcinoma (large-cell neuroendocrine carcinoma or small cell lung carcinoma) in 49 patients (28%). A generic diagnosis of carcinoid not otherwise specified was provided in 9 cases (4%). No data concerning tumor histology occurred in 13% of cases (27 out of 205 patients).

The median tumor size was 8 cm (range, 2.1-30 cm); the majority of TNET cases presented at an advanced stages (stage III-IV n = 103; 69%). Other patient clinical characteristics are summarized in Table 1.

Table 1.

Patient characteristics

Variable	n	%
Continent	160	
Europe	66	41
Asia	57	36
North America	37	23
Age, y∗	54	19-82
Gender	202	
Male	155	77
Female	47	23
Previous malignancy/second primary	122	
None	105	86
Skin	2	1
Breast	1	1
Hematologic	1	1
Colorectal	1	1
Prostate	5	4
Other	7	6
Tumor size, cm∗	8	2.1-30
Neuroendocrine tumors of the thymus histology	178	
Carcinoid NOS	9	4
Well-differentiated (typical carcinoid)	49	28
Moderately differentiated (atypical carcinoid)	71	40
Poorly differentiated (large-cell or small-cell neuroendocrine carcinoma)	49	28
Clinical Masaoka-Koga stage	99	
I	13	13
II	11	11
III	55	56
IV A	9	9
IV B	11	11
Pathologic Masaoka stage	148	
I	12	8
II	33	22
III	56	38

Variable	n	%
IV-NOS	2	1
IV A	11	7
IV B	34	23

NOS, Not otherwise specified.

*
Values are presented as median and range.

Table options

Treatment and Outcomes

Data concerning surgical resection were available for 132 cases. Complete sternotomy was the most common surgical approach; lateral thoracotomy or other combined incisions have been adopted when required, according to anatomic features of the tumor. A minimally invasive approach (video-assisted thoracoscopic surgery or robotic) was performed in only 7 cases.

Seven patients did not undergo surgery; 5 patients received chemotherapy and 2 received radiotherapy.

Data concerning resection status were available in 96 patients (47%); a complete surgical resection (R0) was achieved in 52 patients (54%).

Radiotherapy was administered in 81 patients (39.5%), mostly in adjuvant settings (70 out of 81 patients; 87%); neoadjuvant radiotherapy was offered in 6 patients, and 5 received both induction and adjuvant radiotherapy. Additionally, 4 patients had palliative radiotherapy prescribed.

Sixty-six patients with TNET (32%) received chemotherapy, mostly as adjuvant treatment (31 out of 66 patients; 47%); induction chemotherapy was offered to 19 patients. Six patients underwent both induction and adjuvant chemotherapy, and in 10 patients palliative chemotherapy was administered.

Data concerning the vital status were available in 156 patients (76%). The median follow-up time was 4.06 years. Fifty-two patients died, mostly from tumor-related causes. Data concerning tumor recurrence were available in 94 patients (46%): relapses occurred in 36 patients (38%). Table 2 summarizes the patients' treatments and outcomes.

Table 2.

Treatment modalities and outcomes

Variable	n	%
Surgery	132	
Sternotomy	95	72
Thoracotomy	20	15
Sternotomy + thoracotomy	2	2
Hemiclamshell or clamshell	8	6
Video-assisted thoracoscopic surgery or robotic	7	5
Chemotherapy	134	
No chemotherapy	68	51
Neoadjuvant	19	14
Adjuvant	31	24
Both pre and post	6	4
Palliative	10	7
Radiation treatment	135	
No radiation treatment	50	37

Variable	n	%
Neoadjuvant	6	4
Adjuvant	70	52
Both pre and post	5	4
Palliative	4	3
Recurrence status	94	
Recurred	36	38
Not recurred	58	62
Vital status	156	
Dead	52	33
Alive	104	67

Table options

Survival Analysis and Prognostic Predictors

The median TNET OS was 7.5 years (95% confidence interval [CI], 6.79-not reached); actuarial 5- and 10-year OS rates were 68% and 39%, respectively (Figure 1, A).

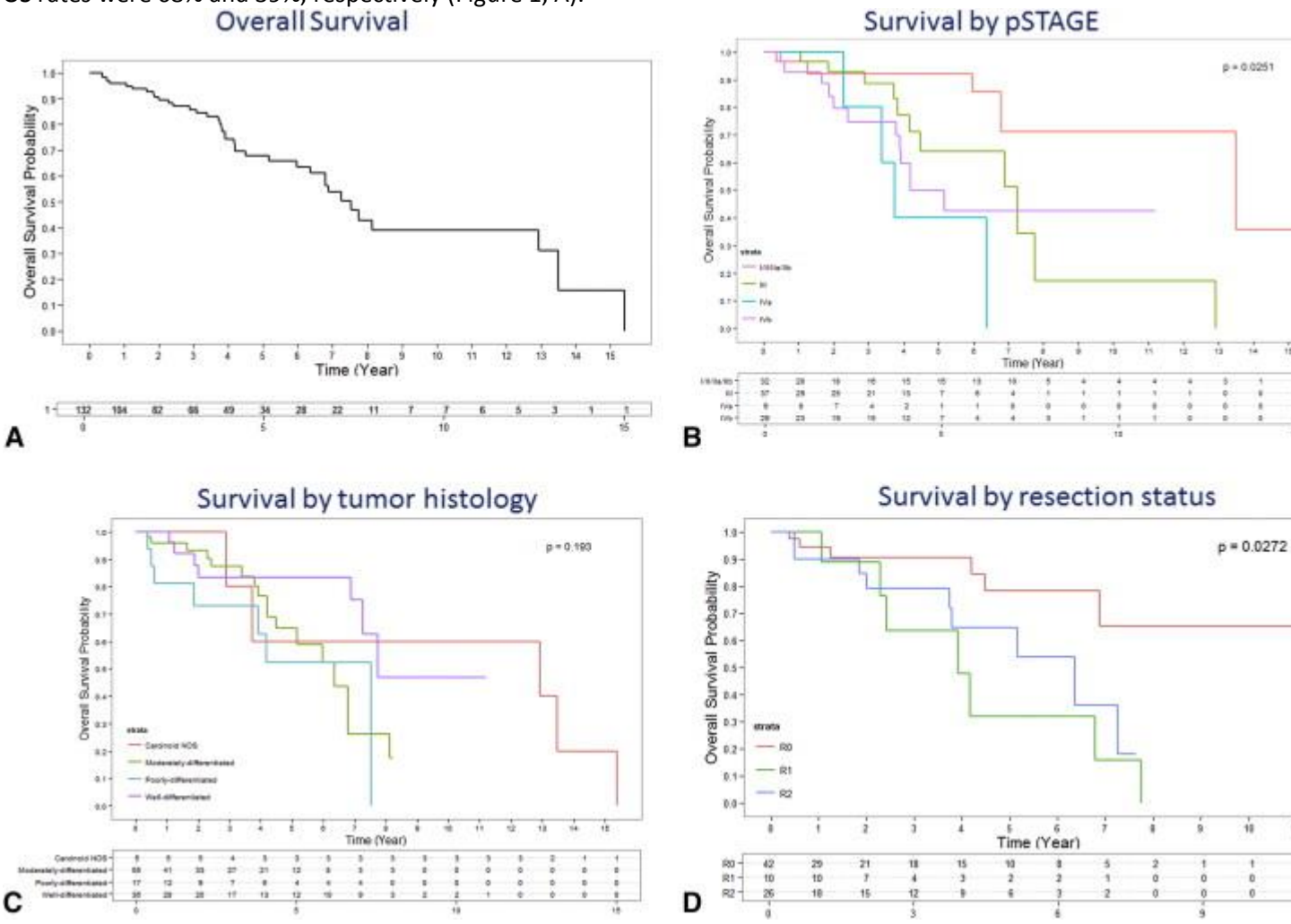

Figure 1.
Outcomes for a cohort of patients with neuroendocrine tumors of the thymus. A, Overall survival. B, Survival by pathologic stage (pSTAGE). C, Survival by tumor histology. D, Survival by resection status.

Figure options

Masaoka stage was a significant prognostic factor for overall survival (P = .02) (Figure 1,B): in particular, median survival was 13.5 years for stages I and II, 7.3 years for stage III, 3.8 years for stage IVa, and 4.2 years for stage IVb, respectively.

Histologic subtype did not show any significant effect on survival (P = .19). In fact, median overall survival times were quite similar in all 3 subtypes: 7.8 years in well-differentiated TNET, 6.4 years in moderately differentiated TNET, and 7.5 years in poorly differentiated TNET, respectively (Figure 1, C).

No difference in survival was also observed amongst patients with TNET without and with lymph node involvement (P = .48) as well as for those without and with distant metastases (P = .9).

R0 (P = .03) was associated with significantly increased overall survival (Figure 1, D). There was no difference detected between patients with R1 and R2 positive margins.

On univariate analysis, surgical treatment (P < .01), resection status (R0 vs R1-R2;P = .03) and pathologic stage (I-II vs III vs IV; P = .01) were statistically significant predictors of overall survival. Gender, TNET histology, chemotherapy, and radiotherapy did not exhibit any statistical significance (Table 3).

Table 3.

Overall survival results of univariate and multivariate analyses

Clinical variable	P value
Univariate analyses	
Gender	.4887
pStage (I/II vs III vs IVA vs IVB)	.0251
Histology	.1926
Resection status (R0 vs R1-R2)	.0142
Surgery (yes vs no)	.0082
Chemotherapy (yes vs no)	.1967
Radiotherapy (yes vs no)	.5339

Clinical variable	df	Wald χ2	P value
Multivariate analyses			
pStage (I/II vs III vs IVA vs IVB)	3	0.9452	.8145
Resection status (R0 vs R1-R2)	1	3.8999	.0483
Surgery (yes vs no)	1	0.0181	.0120
Chemotherapy (yes vs no)	1	0.0653	.8930
Radiotherapy (yes vs no)	1	6.3099	.7983

Boldface indicates P < .05. pStage, Pathologic stage; R0, complete resection; R1-R2, incomplete resection.

Table options

On multivariate analysis, surgical resection (hazard ratio, 0.024; 95% CI, 0.001-0.442;P = .012) and completeness of resection (R0 vs R1-R2) (hazard ratio, 0.343; 95% CI, 0.119-0.992; P = .048) were the only independent predictors associated with overall survival. Masaoka stage and chemotherapy or radiotherapy administration did not demonstrate any statistical significance at multivariate analysis (Table 3). CIR was 0.34 and 0.54 at 5 and 10 years, respectively (Figure 2, A).

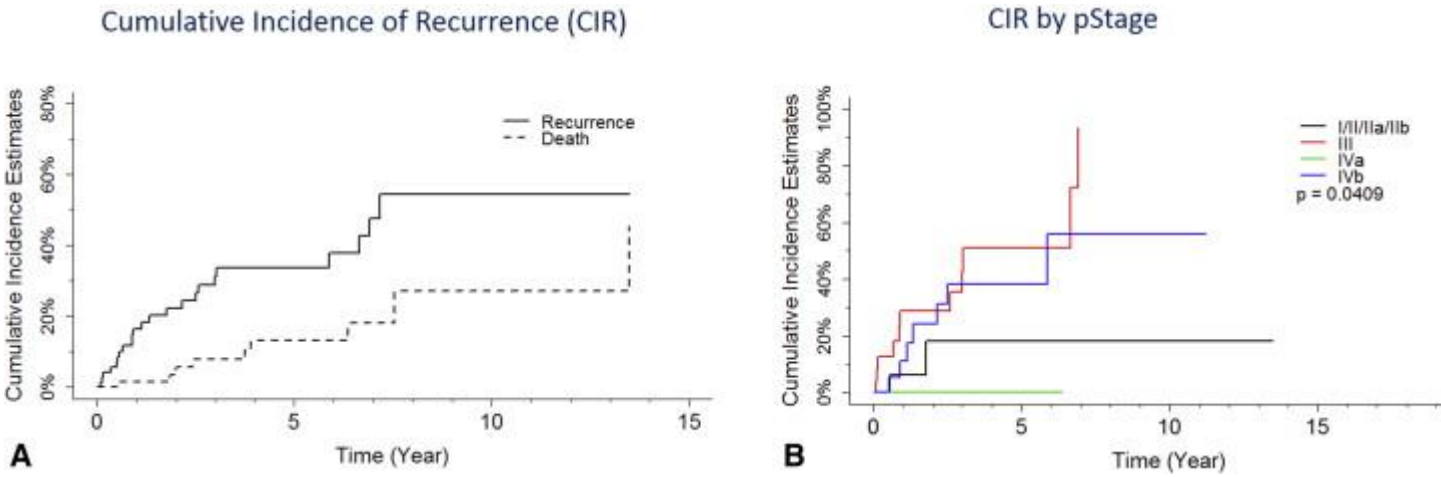

Figure 2.

Outcomes for a cohort of patients with neuroendocrine tumors of the thymus. A, Cumulative incidence of recurrence. B, Cumulative incidence of recurrence by pathologic stage (pStage). CIR, Cumulative incidence of recurrences.

Figure options

CIR at 5 years was lower in Masaoka stages I, II, IIa, and IIb (0.18; P = .04) than in stages III (0.51) and IVb (0.38). No recurrence was observed in stage IVa patients (Figure 2, B).

CIR did not differ significantly between patients with tumors of different histologic subtypes (P = .32): 5-years CIR was 0.34, 0.25, and 0.33 in well-differentiated, moderately differentiated, and in poorly differentiated TNET, respectively.

Discussion

We report the largest clinical TNET series ever described; this article represents the collaborative effort of 2 international scientific societies (ITMIG and ESTS), whose members currently include the vast majority of clinicians active in this field and involved in advancing thymic neoplasms research. Table 4 summarizes the patients' characteristics and results of all published series with >10 patients since 1990, compared with ours. ITMIG and ESTS designed, more or less at the same time, databases on thymic tumors, and the combined analyses concerning TNET are reported here. It is important to note that both datasets are mostly surgical, although multispecialty physicians compose the ITMIG membership. This may constitute a potential study limitation.

Table 4.

Patients characteristics and results in the recent (since 1990) published series with >10 patients

Author (y)	N	R0 (%)	Associated diseases	Histology	Postoperative treatment	Recurrences (%)	5-y survival (%)	10-y survival (%)
de Montpreville (1996)7	14	28	1 MEN-1	14 AC	NA	71	31	0
Fukai (1999)13	15	87	2 CS; 1 MG	1 TC; 9 AC; 5 SCC	5 RT; 1 CT + RT; 1 CT	67	33	7
Moran and Suster (2000)14	80	NA	4 CS	29 TC; 36 AC; 15 SCC	NA	47	28	10
Tiffet (2003)8	12	75	2 MEN-1; 1 CS	3 TC; 6 AC; 2 LCNC; 1 SCC	3 RT; 1 CT; 1 RT + CT	83	50	NA

Author (y)	N	R0 (%)	Associated diseases	Histology	Postoperative treatment	Recurrences (%)	5-y survival (%)	10-y survival (%)
Cardillo (2012)15	35	97	10 CS	17 TC; 13 AC; 5 LCNC	20 RT	26	84	61
Ahn (2012)16	21	81	3 CS	18 AC; 3 LCNC	9 RT; 3 CT; 9 RT + CT	33	NA	NA
Present study (2014)	205	52 *	NA	49 TC; 71 AC; 49 LCNC-SCLC; 9 carcinoid §	70 RT; 31 CT†	38‡	68	39

R0, Complete resection; MEN, multiple endocrine neoplasia; AC, atypical carcinoid; NA, not available;CS, Cushing syndrome; MG, myasthenia gravis; TC, typical carcinoid; SCC, small-cell carcinoma; RT, radiotherapy; CT, chemotherapy; LCNC, large cell neuroendocrine carcinoma; SCLC, small cell lung carcinoma.

*
Data available in 96 patients.

†
Data available in 135 patients.

‡
Data available in 94 patients.

§
Data available in 178 patients.

Table options

There was a quite similar distribution of patients between Europe, Asia, and America, and this may guarantee a satisfactory uniformity in our results. TNET have an age-adjusted incidence of 0.18 per 1,000,000 per year, far less than the annual incidence of lung neuroendocrine tumors, which has been reported to be 13.5 per 1,000,000 per year.9 Nevertheless the incidence has risen, likely as consequence of awareness and improvements in diagnostic techniques.2

Consistent with previous reports3, 4, 5, 7 and 8 a male predominance was seen, which is in sharp contrast to other neuroendocrine tumors, where the incidence between male and female is about equal. The mean age of patients at the time of surgery was 54 years, which is very similar to that reported in recent clinical experiences.4 and 5

Only a very limited percentage of patients with TNET (8.3%) had a synchronous/metachronous second malignancy; this is in contrast to thymomas, in which up to 24% of patients were recently reported having a second cancer history.17Unfortunately, we were unable to analyze the prognostic significance of endocrinopathies in patients with TNET, due to the lack of details about this topic in both datasets.

No official TNET stage classification has been provided by the Union Internationale Contre le Cancer and/or by the American Joint Commission on Cancer and no consensus exists concerning the different systems actually used. ITMIG recommends the Masaoka-Koga staging system also for the thymic carcinoma group, including TNETs, because it is the system in most common use worldwide, until a new formal Union Internationale Contre le Cancer and/or by the American Joint Commission on Cancer scientific validated system is developed.19 Moreover, Gaur and colleagues5 and Cardillo and colleagues16 adopted the SEER staging system for their analysis, which recognizes localized, locally, and distant invasive tumors. For our purposes, Masaoka and Masaoka-Koga systems were combined together, because they were adopted by almost all institutions involved in both databases and the analyses of the Staging and Prognostic Factors Committee has found no significant differences in outcomes between these. The majority of patients with

TNET (69%) in our database presented at an advanced stage, confirming the highly aggressive biological behavior of these neoplasms. Our data are consistent with those previously reported in other recent clinical series.5, 16 and 17

The 5- and 10-year survival rates reported in our study are better than those described in several recent series, probably due to the high complete resection rate and lower number of recurrences observed (Table 4). CIR was 0.34 and 0.54 at 5 and 10 years, respectively, which is significantly higher than that reported for thymoma, confirming once again TNETs high aggressive biological behavior.

Given the rarity of TNET, a clear consensus concerning the optimal treatment actually does not exist: data are necessary limited and guided by the small clinical series published and the lack of prospective clinical trials. Surgery remains the mainstay of therapy for resectable lesions, whereas induction/adjuvant chemotherapy/radiotherapy play a role in case of incomplete resections or unresectable tumors. The reported resectability rate may vary from 28% to 100% (mean 86%), strongly depending on the single center experience.16

Consistent with the recent literature4, 5 and 16 our report confirms that patients who underwent surgery and those who experienced an R0 resection had improved OS compared with those who did not; furthermore the ability to undergo surgery and the completeness of resection were found to be the strongest prognostic factors both in univariate and multivariate models. A complete surgical resection should be attempted whenever possible, even in advanced lesions, and incomplete resections mostly result from a highly locally aggressive neoplasm.

As for thymomas, our results highlight the importance of TNET stage for OS and CIR: early stage tumors survived longer and less commonly developed recurrence (Figure 1 and Figure 2, B), similar to what was reported in some recent clinical series. 5, 7,8, 16, 17 and 18 Even if TNET stage did not reach statistical significance in our multivariate model, this result could be explained by the confounding effects of both surgical tumor resectability and completeness of resection. Similar interrelationships have been recently described for thymomas. 12 and 19

Tumor histology was not found to be a prognostic indicator for either OS or CIR; this is in contrast with what Suster and Moran14 previously reported. Contrasting results were described by other authors.5, 16, 20 and 21 In our study, a central pathologic review was not available, although the number of patients and involved institutions make our results valuable.

Unlike that in advanced thymomas,10, 22, 23 and 24 the role of chemotherapy and radiotherapy in patients with TNET has not yet been outlined. In some of the most recent clinical experiences, a neoadjuvant approach (usually chemotherapy) was advocated with the aim to achieve tumor shrinkage making a R0 resection possible.7 and 16Concerning adjuvant treatment, only Tiffet and colleagues8 reported a better outcome (no recurrences) for those patients in which postoperative radiotherapy was administered after a complete tumor resection, whereas Gaur and colleagues5 and Cardillo and colleagues,16 on the contrary, reported a detrimental effect of radiotherapy for those patients who received it, compared with those who did not, and in a multivariate model there was no survival benefit for radiotherapy as a part of the treatment strategy. We did not find any statistical advantage in OS for adjuvant chemotherapy/radiotherapy, both in univariate and in multivariate models. Moreover, CIR was not statistically influenced by preoperative or adjuvant chemotherapy/radiotherapy regimens.

Instead, our results highlighted a trend to administer radiotherapy as induction therapy and chemotherapy/radiotherapy in an adjuvant setting, according to the tumor invasiveness, resection status, and possible presence of lymph node involvement. Nevertheless, we believe that definitive role of chemotherapy/radiotherapy should be evaluated in future prospective studies.

A potential intrinsic limitation of our study is its retrospective and multicenter nature. Nevertheless, the use of ITMIG/ESTS databases allowed us to collect a large cohort of patients from high-volume international thoracic surgery institutions. Furthermore, a centralized histologic review process was not available; however, all the histologic specimens were reviewed by local and experienced pathologists and the definitive TNET diagnosis was achieved according to uniform histologic guidelines.

Conclusions

This study describes the largest clinical series of patients with TNET ever reported; our results confirm that these are rare and very aggressive tumors with a poor prognosis due to the high incidence of recurrent/metastatic disease after surgery. Surgical tumor resection, along with the involved neighboring organs, remains the treatment of choice because a complete resection has been demonstrated to be an independent prognostic factor. Advanced tumor stage and unresectable tumors, but not tumor histology, are predictors of negative outcome. Chemotherapy/radiotherapy both in induction and in adjuvant settings were not found to influence OS in this series.

Acknowledgements

The European Society of Thoracic Surgeons Thymic Group Steering Committee also includes Dirk Van Raemdonck, MD; Gaetano Rocco, MD; Pascal Thomas, MD; and Walter Weder, MD.

Appendix E1. List of Participating European Society of Thoracic Surgery Centers

1. King Faisal Specialist Hospital, Alfaisal University, Riyadh, Saudi Arabia
2. University of Eastern Piedmont, Novara, Italy
3. Ospedali Riuniti, Ancona, Italy
4. University of Alabama at Birmingham, Birmingham, Alabama
5. University of Parma, Italy
6. General Regional Hospital, Aosta, Italy
7. Aristotle University of Thessaloniki, A.H.E.P.A. University Hospital, Thessaloniki, Greece
8. Uludag University School of Medicine, Bursa, Turkey
9. Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain
10. University of Texas, Southwestern Medical Center and School of Medicine, Dallas, Texas
11. Medical University of Vienna, Vienna, Austria
12. IRCCS-CROB Centro Riferimento Oncologico della Basilicata, Rionero in Vulture, Italy
13. Royal Brompton and Harefield NHS Foundation Trust and National Heart and Lung Division, Imperial College, London, United Kingdom
14. Centre Hospitalier de l'Universitè de Montreal, University of Montreal, Montreal, Canada
15. Guy's Hospital, London, United Kingdom

16. SS Antonio e Biagio e Cesare Arrigo Hospital, Alessandria, Italy

17. IRCCS Fondazione Cà Granda Ospedale Maggiore Policlinico, Milano, Italy

18. University Hospital of Salamanca. IBSAL. Salamanca, Spain

19. Hospital Nord-Aix-Marseille University, Marseille, France

20. University of Torino and AO Città della Salute e della Scienza di Torino, Italy

21. Vittorio Emanuele Hospital, Catania, Italy

22. Thoracic Surgery, Sacred Heart Hospital Negrar, Verona, Italy

23. Papworth Hospital NHS Foundation Trust, Papworth Everard, Cambridge, United Kingdom

24. University of Rome SAPIENZA; Policlinico Umberto I; Fondazione Eleonora Lorilard Spencer Cenci, Rome, Italy

University Hospitals Leuven, Belgium

Cenci; Rome, Italy

University Hospital of Siena, Italy

Medical University of Gdansk, Poland

Appendix E2. List of Participating International Thymic Malignancy Interest Group Centers

1. University of Padua, Padua, Italy

2. Shanghai Chest Hospital, Shanghai, China

3.
Sichuan Cancer Hospital, Chengdu, China

4.
Tianjin Cancer Hospital, Tianjin, China

5.
Shanghai Pulmonary Disease Hospital, Shanghai, China

6.
Beijing Cancer Hospital, Beijing, China

7.
Henan Cancer Hospital, Zhengzhou, China

8.
Regina Elena National Cancer Institute, Rome, Italy

9.
University of Chicago, Chicago, Illinois

10.
Universitat Degli Studi di Napoli Federico II, Napoli, Italy

11.
Maastricht University Medical Centre, Maastricht, The Netherlands

12.
University Hospitals Leuven, Belgium

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