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ORIGINAL ARTICLE

TREATMENT STRATEGIES FOR THYMIC CARCINOMA IN A REAL-LIFE SETTING. INSIGHTS FROM THE RYTHMIC NETWORK.

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ABSTRACT

BACKGROUND: Thymic carcinomas are an aggressive and difficult to treat subset of thymic epithelial tumors that represent a heterogeneous group of rare intrathoracic malignancies. Treatment strategy of thymic carcinomas is based on whether surgical resection may be achieved, what represents the most significant favorable prognostic factor on survival. For this study, we took advantage of the unique prospective RYTHMIC database to describe baseline characteristics, analyze treatment strategies in light of existing guidelines, and provide landmark patient outcomes data with regards to response and survival of patients in a real-life clinical practice setting.

METHODS: Inclusion criteria for this analysis were the following: 1) histologically-confirmed thymic carcinomas – excluding neuroendocrine tumors- after pathological review by the RYTHMIC pathology panel, 2) discussion of the case at the RYTHMIC multidisciplinary tumor board, 3) at least one active treatment modality.

RESULTS: A total of 213 patients were analyzed. Overall, 60 (28%) patients were considered as surgical candidates upfront, 91 (43%) received primary chemotherapy, and 62 (29%) received exclusive chemotherapy. Median OS was 49.2 months (IC95%: 34.8-63.6); OS was significantly longer in patients with a lower stage at diagnosis ($p<0.001$), who were operated on upfront, as opposed to patients who received primary or exclusive chemotherapy ($p<0.001$). Surgery, conducted upfront or after primary chemotherapy, was significantly associated with more prolonged OS ($p<0.001$); complete resection and postoperative radiotherapy were also predictors of better outcome ($p=0.018$ and $p=0.051$, respectively).

CONCLUSIONS: Our cohort is the first to analyze in depth outcomes and treatment strategies in a prospective cohort of consecutive patients with thymic carcinoma. While we confirm the

major prognostic impact of surgery, our data highlight the need for optimized multidisciplinary management and innovative therapies as the survival of patients remains limited.

KEY-WORDS

Thymic carcinoma

Chemotherapy

Surgery

Guidelines

Radiotherapy

INTRODUCTION

Thymic carcinomas are a subset of thymic epithelial tumors that represent a heterogeneous group of rare intrathoracic malignancies, which are aggressive and difficult to treat [1]. Contrary to thymomas, that usually present with local and regional disease progression, thymic carcinomas have a higher risk of advanced or metastatic presentation at diagnosis [2-6]. While the historical Masaoka-Koga staging system was primarily designed for thymomas [7], the recent implementation of TNM staging allows a better recognition of the actual invasiveness of thymic carcinomas [8].

Treatment strategy of thymic carcinomas is based on whether surgical resection may be achieved, what represents the most significant favorable prognostic factor on survival [2-5]. Meanwhile, most of the current knowledge on those tumors rely on the one hand on retrospective, surgically-oriented databases focusing on early-stage disease, that may not reflect the actual burden of non-resectable tumors [2-5]; on the other hand, small prospective, single-arm trials have been conducted in metastatic thymic carcinomas, mostly in a refractory, late-line setting [9-12]. In a routine practice setting, the management of patients with thymic carcinoma raises multiple questions, from the transposability of strategies established for thymomas, including primary/induction chemotherapy and surgery for advanced disease, to the actual value of recommendations such as postoperative chemotherapy and the treatment of recurrences [13].

“Réseau tumeurs THYMIques et Cancer” (RYTHMIC) is the nationwide network for TET in France, which was established in 2012 [13]. Within the network, the management of any patient diagnosed with thymic epithelial tumor has to be systematically discussed on a real-time basis at a national multidisciplinary tumor board; it is also recommended to discuss the patient at any

step of disease progression, allowing a prospective follow-up with multidisciplinary quality control. A database is hosted by the French Thoracic Cancer Intergroup (IFCT) and collects information for all consecutive patients. For this study, we took advantage of this unique prospective database to describe baseline characteristics, analyze treatment strategies in light of existing guidelines, and provide landmark patient outcomes data with regards to response and survival of patients in a real-life clinical practice setting.

METHODS

Study design

RYTHMIC is a nationwide network dedicated to the management of thymic malignancies in France. It was appointed in 2012 by the French Institut National du Cancer (INCA) as part of its rare cancer initiative [13, 14]. The network aims at a territorial coverage by 15 regional expert centres, the dissemination of the highest standards for diagnosis and treatment, and the promotion of collaborative research. The RYTHMIC multidisciplinary tumor board takes place twice a month using web-based conferencing system and characteristics of all patients, treatments, and follow-up are prospectively collected in the network database. Systematic pathological review of cases is conducted by an international panel of expert pathologists based on the standard WHO classification [15, 16]. Multidisciplinary tumor board decisions are based on RYTHMIC recommendations (downloadable at www.rythmic.org/01/images/RYTHMIC/Doc/Referentiel_RYTHMIC_2016.pdf), which are based on the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines [17].

Registration of all patients diagnosed with thymic malignancies is recommended as a part of good clinical practice for oncologists. From January 2012 to April 2019, a total of 2723 patients

were enrolled Based on national epidemiological data, the RYTHMIC network is estimated to cover 95% of newly diagnosed patients in France [12]. The current analysis was approved by the steering and ethics committee of the RYTHMIC network.

Identification of patients

Inclusion criteria for this analysis were the following: 1) histologically-confirmed thymic carcinomas – excluding neuroendocrine tumors- after pathological review by the RYTHMIC pathology panel, 2) discussion of the case at the RYTHMIC multidisciplinary tumor board, 3) at least one active treatment modality. Patient were identified using the RYTHMIC prospective database, hosted by the French Thoracic Cancer Intergroup (IFCT) according to ongoing legal requirements. The inclusion period was from January 2012 to April 2019. Follow-up was obtained in all cases and was censored on December 30th, 2020.

Data collection

The data (including patients baseline characteristics, histology, stage, chemotherapy regimen, dates of treatment initiation and discontinuation, dates of progression) were collected after a review of patient's medical records and multidisciplinary tumor board reports, especially for analyses of treatment sequences. Masaoka-Koga stage was assessed according to the International Thymic Malignancy Interest Group (ITMIG) recommendations, using clinical, imaging, and pathological findings [7]; given the period of this study, we did not prospectively use the 8th American Joint Committee on Cancer / Union for International Cancer Control TNM system [8]. Best response to systemic treatment was assessed by treating physicians, according to ITMIG recommendations adopted by the RYTHMIC/ESMO guidelines [17, 18].

Definitions for chemotherapy and radiotherapy treatments

According to definitions and policies of the ITMIG [19], chemotherapy for thymic malignancies includes: 1/ *primary chemotherapy*, delivered as induction treatment for unresectable locally-advanced tumors at time of diagnosis, with the intent of subsequent surgical resection or definitive radiotherapy; 2/ *postoperative chemotherapy*, delivered after surgery in the absence of macroscopic residual disease or tumor progression; 3/ *exclusive chemotherapy*, in advanced tumors with no plan for surgery or radiotherapy, e.g. in patients with metastatic disease; 4/ *chemotherapy for recurrence* after surgery or radiotherapy, or disease progression after exclusive chemotherapy; multiple lines of chemotherapy may be administered for second, third, and if possible subsequent recurrences. In this study, we analyse the modalities and outcomes of chemotherapy and other systemic treatments using the framework of those definitions.

Similarly, as for radiotherapy, ITMIG recommendations distinguish 1/ *postoperative radiotherapy* delivered after surgery, 2/ *definitive radiotherapy*, alone or combined with chemotherapy, in the setting of non-metastatic tumors non amenable to surgery, and 3/ *radiotherapy for recurrence* [20].

Statistical analyses

All patients were included in the statistical calculations. Categorical variables were compared using the Chi-square or Student 's test, and continuous variables by the Mann-Whitney non-parametric test. Survival was assessed using the Kaplan-Meier method. For patients who were operated on, disease-free survival (DFS) was calculated from the date of surgery. For patients who received primary chemotherapy, time-to-progression (TTP) was calculated from the date of initiation of chemotherapy to the date of relapse, with censoring at the date of last follow-up if the patient had not presented with disease progression. For patients who received exclusive chemotherapy or chemotherapy for recurrence, progression-free survival (PFS) was calculated

from the date of initiation of chemotherapy to the date of progression, with censoring at the date of last follow-up if the patient had not presented with disease progression. Overall survival (OS) was calculated from diagnosis to the date of death, censoring at the last follow-up date if the patient was alive. Relevant parameters were studied for influence on survival by univariate analysis using the Log Rank test. The differences were considered as statistically significant at the 0.05 level. All analyses were performed using the SPSS software program (Chicago, IL), version 25.0.

RESULTS

Patients characteristics

A total of 213 patients with thymic carcinoma discussed at the RYTHMIC multidisciplinary tumor board during the study period, representing 11.7% of the 1814 patients enrolled in the RYTHMIC prospective database. With regards to patients' characteristics, 140 (66%) patients were men, and mean age at diagnosis was 63 (range: 32-84 years) (**Table 1**); 64% of patients with smoking status available were never smokers. Only 6 patients had autoimmune disorders at diagnosis. A majority of patients had Masaoka-Koga stage IVA (15%) or IVB (35%) disease at time of diagnosis. Most frequent metastatic sites were the following: lungs (24 patients), lymph nodes (21 patients), liver (19 patients), bones (15 patients); brain locations were infrequent (5 patients); 40 (53%) had only 1 site of metastasis. Histologic subtype was squamous cell carcinoma in 142 (67%) patients, and undifferentiated carcinoma in 53 (25%) patients; only 6 tumors were reported to harbour *KIT* activating mutations, and 1 *PI3KCA* mutation.

With regards to treatment strategies, 60 (28%) patients were considered as surgical candidates upfront, 91 (43%) received primary chemotherapy, and 62 (29%) received exclusive chemotherapy.

Treatment strategies

Upfront surgery was performed for 60 patients (**Figure 1**). A preoperative biopsy was available for 49 patients. ; surgical approach consisted of median sternotomy for 49 (82%) patients, thoracotomy for 6 (10%) patients, and thoracoscopy for 5 (8%) patients. Surgical resection included resection of mediastinal structures, including great vessels, lung, pericardium, in 50 (83%) patients. Resection status was R0 in 38 (63%) patients, R1 in 18 (30%) patients, and R2 in 4 (7%) patients. Incomplete resection occurred in patients with stage T2 (2 out of 18 patients), T3 (14 out of 34 patients) and T4 (6 out of 8 patients). Postoperative radiotherapy was delivered to 43 (72%) patients, and postoperative chemotherapy to 7 (12%) patients, consisting of platinum and etoposide in 4 patients, platinum and adriamycin and cyclophosphamide (PAC) in 3 patients.

Primary/induction chemotherapy with intent for subsequent local treatment – surgery or radiation therapy- was delivered to 91 patients. All patients had a preoperative biopsy. PAC regimen was the most frequently delivered, to 56 (62%) patients (**Figure 2A**); median number of cycles was 4 (range 2-6). Objective response was observed in 51 (56%) patients, stable disease in 29 (32%), and progression disease in 9 (10%) patients; 2 patients were not assessable for response. Surgery was ultimately performed for 40 patients (**Figure 2B**); surgery was more frequently performed in responders to primary chemotherapy ($p < 0.001$). Surgical approach consisted of median sternotomy for 36 (90%) patients, thoracotomy for 3 (8%) patients, and

thoracoscopy for 1 (3%) patients. Surgical resection included resection of mediastinal structures, including great vessels, lung, pericardium, in all patients. Resection status was R0 in 22 (55%) patients, R1 in 13 (33%) patients, and R2 in 5 (13%) patients. Incomplete resection mostly occurred in patients with stage T3 (10 out of 28 patients) or T4 (8 out of 12 patients). Postoperative radiotherapy was delivered to 27 (72%) patients, and postoperative chemoradiotherapy to 7 (12%) patients, consisting of platinum and etoposide in 5 patients, and platinum and docetaxel in 2 patients; all the 5 patients with a R2 resection received postoperative chemoradiotherapy. Overall, 51 patients who were deemed not to be surgical candidates, received definitive radiotherapy to a median dose of 60 Gy.

Exclusive chemotherapy was delivered to 62 patients, who all received platinum-based regimen as first-line treatment (**Figure 3**); PAC regimen was delivered to 66% of patients. Median number of cycles was 6 (range-2-9). Best objective response to first-line chemotherapy was partial response in 33 (53%) patients, stable disease in 15 (24%) patients, and progression in 14 (23%) of patients. Median PFS was 8.0 months (IC95%: 5.0-11.1); while regimen was not a predictor of PFS, histologic type (squamous vs. other) and response were significantly associated with longer PFS ($p < 0.001$ and $p = 0.001$, respectively).

Recurrences

After a median follow-up of 36 months, 17 (28%) of the 60 patients who were operated upfront, presented with disease recurrence. Sites of recurrences were the following: lung in 8 patients, pleura in 6 patients, mediastinum in 4 patients, liver in 2 patients, and bone in 1 patient. Median DFS was 52.0 months (IC95%: 39.0-65.0); none of the following factors were not significantly associated with OS: age, gender, smoking, histological subtype, stage, resection completeness, or delivery of postoperative treatment. Treatment consisted of surgical resection, mostly for

pleural recurrences, in 5 patients, chemotherapy – combination of platinum and etoposide or paclitaxel or adriamycin-cyclophosphamide- in 10 patients, and sunitinib in 2 patients. Best objective response to systemic treatment was partial response in 5 patients, stable disease in 5 patients, and 2 progression in 2 patients.

After a median follow-up of 25 months, 53 (58%) patients who receive primary chemotherapy presented with recurrence; sites of first recurrence were the mediastinal pleura in 12 patients, mediastinal lymph nodes in 12 patients, the liver in 14 patients, the bone in 10 patients, the lung in 7 patients, and the brain in 2 patients. Median DFS was 21.0 months (IC95%: 5.9-36.1); surgical resection ($p=0.023$) and delivery of postoperative radiotherapy ($p=0.026$) were significant predictors of more prolonged DFS. Gender, age, smoking, histological type, stage, response to primary chemotherapy, resection completeness did not significantly predict DFS. Treatment for recurrence consisted of chemotherapy in 36 patients and radiotherapy or other local ablative therapy in 4 patients (**Figure 2**); 7 patients did not receive treatment for recurrence, and treatment was unknown in 6 patients.

After a median follow-up of 27 months, 41 (66%) patients who received a first-line of exclusive chemotherapy did received second-line treatment, mostly consisting of carboplatin and paclitaxel (61% of patients) (**Figure 3**). Best objective response was partial response in 9 (22%) patients, stable disease in 14 (34%) patients, and progression in 18 (44%) of patients. Median PFS was 8.1 months (IC95%: 5.2-11.1). Predictors of more prolonged PFS were squamous histologic subtype ($p=0.048$) and response ($p<0.001$). A total of 30 (48%) patients did receive third-line treatment, consisting of sunitinib or other multikinase, VEGFR inhibitors, in 17 (57%) patients. Best objective response was partial response in 6 (20%) patients, stable disease in 11 (37%) patients, and progression in 13 (43%) of patients. Median PFS was 3.0 months (IC95%: 2.2-3.8).

Overall survival

Median OS in the whole cohort of 213 patients was 49.2 months (IC95%: 34.8-63.6) (**Figure 4**); OS was significantly longer in patients with a lower stage at diagnosis ($p<0.001$), who were operated on upfront, as opposed to patients who received primary or exclusive chemotherapy ($p<0.001$). Surgery, conducted upfront or after primary chemotherapy, was significantly associated with more prolonged OS ($p<0.001$); complete resection and postoperative radiotherapy were also predictors of better outcome ($p=0.018$ and $p=0.051$, respectively).

In the 60 patients who were operated on upfront, median OS was 79.1 months (IC95%: 60.1-98.0). Only Masaoka-Koga stage was a significant predictor of OS in our cohort ($p=0.039$). The following factors were not significantly associated with OS: age, gender, smoking, histological subtype, resection completeness, or delivery of postoperative treatment.

In the 91 patients who received induction chemotherapy, median OS was 36.9 months (IC95%: 28.8-45.1); significant predictors of more prolonged OS were lower Masaoka-Koga stage ($p=0.027$), response to primary chemotherapy ($p=0.007$), and delivery of postoperative radiotherapy ($p=0.017$). Interestingly, the following factors were not significantly associated with OS: age, gender, smoking, histological subtype, chemotherapy regimen, surgery of the primary tumor, or resection completeness.

In patients who had exclusive chemotherapy, median OS was 32.9 months (IC95%: 20.6-45.1). Response to first-line chemotherapy and squamous histology were the only significant predictors of OS ($p=0.002$ and $p=0.040$, respectively); chemotherapy regimens were not associated with OS.

DISCUSSION

Taking advantage of the RYTHMIC network infrastructure, our analysis is the first to our knowledge, to analyse the treatment strategies for thymic carcinoma in a real-life setting, with no selection based on the actual recruitment of patients as we used a prospective nationwide cohort of consecutive patients, in the unique setting of systematic discussion at an expert MTB at each step of the management of patients, based on established clinical practice guidelines.

First, this unique process allows the analysis of data based on the actual intent of the treatment, what had not been made possible in the majority of previously reported retrospective or prospective studies which combined patients receiving surgery or systemic treatment in a curative and in a palliative intent, or patients treated in various lines of treatment [2-5]. While we confirm the major prognostic impact of surgery, our data highlight the need for optimized multidisciplinary management and innovative therapies as the survival of patients remains limited.

Our results clearly indicate the peculiar characteristics of patients with thymic carcinoma, that are mostly never smokers; this is a major point to consider as misdiagnosis with primary lung carcinoma may be frequent in the setting of a tumor arising in the mediastinum, and as in our study, is associated with lung lesions and lymph nodes. Immunohistochemistry using CD5 and CD117 helps to distinguish both entities, and should be systematically assessed in such clinical situations. This is even more relevant now that immunotherapy using anti-PD-1 checkpoint inhibitors are routinely used in lung carcinoma, while it may be associated with higher risk of autoimmune adverse events in thymic carcinomas [10, 11].

Our data indicate that only a limited number of patients with thymic carcinoma are actually eligible to upfront surgical resection, 28% of patients in our cohort. Pre-operative biopsy was available for a majority of patients, even in the setting of a decision of upfront surgery, given

the tumor invasion at imaging. Meanwhile, complete resection was not achieved in 37% of patients. As per ESMO clinical practice guidelines recommendation, a majority of patients received postoperative radiotherapy [17]. As in previously reported surgical cohorts of patients, postoperative radiotherapy was associated with a more prolonged overall survival, what may be related to the high rate of R1 or R2 status. Interestingly, our data show that the recommendation of postoperative chemotherapy was actually applied to only 7 patients, mostly in the setting of incomplete resection and stage IV disease. More detailed studies on the location of R1 or R2 would be of interest to understand the pre- and per-operative decision making of the surgical teams. A high rate of incomplete resection has to be expected for patients with T4 disease, while debulking may be valuable to facilitate subsequent therapies and decrease the symptom burden. Accurate preoperative imaging may help to better assess the tumor invasion.

While our previous results reported in thymoma highlighted the need for distinguishing primary - induction before surgical resection of definitive radiotherapy - vs. exclusive - first-line for disease ineligible to focal treatment – chemotherapy, as clinicians' expectations may differ regarding response rates, ranging from 79% to 35%, respectively, data from this larger cohort of patients with thymic carcinoma indicate similar response rates in those situations, 56% and 53%, respectively. Those figures are still in line with historical studies [9]. Thymomas are known to be more sensitive to chemotherapy, what may partly be related to a “lympholytic effect” of cytotoxic agents and steroids in type B thymomas. PFS was actually limited – 8.1 months - in the setting of advanced thymic carcinoma, receiving chemotherapy alone. Besides histologic type, metastatic thymic tumors may present with more aggressive biological features leading to a lower sensitivity to first-intent systemic treatment, as compared with locally-advanced tumors; virtually no data regarding the molecular features of advanced TETs have

been made available so far, as the majority of comprehensive genomic studies were conducted in treatment-naïve, surgically resected tumors.

Meanwhile, distinguishing first-intent - primary or exclusive - treatment from recurrences provides with an insight in treatment sequences along with the management of patients; while PAC regimen is used upfront for the majority of patients - 62% to 66% of patients -, carboplatin and paclitaxel, sunitinib, and single agent chemotherapies are preferred regimens for recurrences, based phase II studies that provided the evidence for the development of the ESMO clinical practice guidelines, which have then been applied in our cohort [17].

Still, our results indicate that multiple lines of systemic therapy may be delivered beyond first-intent treatment, providing patients with an opportunity of clinically relevant median PFS, around 8 months in the setting of recurrent disease; indeed, patients presenting with thymic carcinomas are usually young, in a good medical condition with no co-morbidities. The impact of potential cumulative side effects of systemic treatments was not assessed in our study, as toxicities are not captured in the prospective RYTHMIC database; the increased use of non-cytotoxic agents in late lines of treatment suggests those aspects, especially performance status and history of hematological toxicities, were taken into account during discussions at the MTB.

One limitation of our study is the absence of blinded radiological review of imaging to assess objective response; still, the RYTHMIC MTB includes the review of available imaging that is shared to the multi-disciplinary panel - that includes a thoracic radiologist - through a using web-based conferencing system. Despite such a unique, nation-wide multidisciplinary approach, that includes a discussion of each case with a minimum of 3 experienced surgical teams together with medical oncologists and radiation oncologists, our results highlight the major challenges in defining and predicting the resectability of thymic carcinoma tumors, and

the need for clarifying the actual role for primary/induction chemotherapy to increase the chance of complete resection. Ultimately, the assessment of objective response and tumor invasion remains challenging in TETs given the frequent occurrence of pleural and mediastinal tumor targets for which standardization of measurements is debated.

Overall, our data indicate a median OS in the whole cohort of 213 patients as long as 49.2 months (IC95%: 34.8-63.6); while this is more prolonged than in patients with other thoracic malignancies, this is mainly driven by patients who are operated on, either upfront or after induction chemotherapy. Multimodal treatment is actually key, as shown by the significant prognostic value of postoperative radiotherapy and also the opportunity to achieve complete surgical resection after induction chemotherapy.

Ultimately, as no randomized or even prospective comparative study has ever been conducted to assess chemotherapy or other systemic agents in those clinical situations, there is paucity of prospective data regarding the outcome of patients; our real-life data provide with landmark OS, PFS and response rates that are needed when designing clinical trials assessing innovative agents, especially in the setting of single-arm phase II studies, that have been available for immune checkpoint inhibitors [23], or new targeted agents, such as lenvatinib [24]. Ultimately, the RYTHMIC nation-wide MTB offers the opportunity of systematically identifying patients who are potentially eligible for such clinical trials.

To conclude, our data provide with a unique insight into systemic treatment strategies for thymic carcinomas, highlighting the value of the ITMIG definitions and policies to distinguish primary, exclusive, and recurrence settings, the relevance of ESMO clinical practice guidelines, and the benefit of multimodal treatment in the setting of multidisciplinary discussion.

Meanwhile, in the setting of a rare cancer with limited opportunities for the development of randomized clinical trials, systematic discussion at an expert MTB coupled with a prospective database offers the opportunity to ensure equal access to high quality care to all patients, with the opportunity of continuous assessment of treatment options.

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REFERENCES

1. Girard N, Mornex F, Van Houtte P, et al: Thymoma: a focus on current therapeutic management. *J Thorac Oncol* 2009;4:119-26.
2. Ruffini E, Detterbeck F, Van Raemdonck D, Rocco G, Thomas P, Weder W, et al. Thymic carcinoma: a cohort study of patients from the European society of thoracic surgeons database. *J Thorac Oncol*. 2014; 9:541-548.
3. Hishida T, Nomura S, Yano M, Asamura H, Yamashita M, Ohde Y, et al. Long-term outcome and prognostic factors of surgically treated thymic carcinoma: results of 306 cases from a Japanese Nationwide Database Study. *Eur J Cardiothorac Surg*. 2016;49:835-41.
4. Wei Y, Gu Z, Shen Y, Fu J, Tan L, Zhang P, et al. Preoperative induction therapy for locally advanced thymic tumors: a retrospective analysis using the ChART database. *J Thorac Dis*. 2016;8:665-72.
5. Ahmad U, Yao X, Detterbeck F, Huang J, Antonicelli A, Filosso PL, et al. Thymic carcinoma outcomes and prognosis: results of an international analysis. *J Thorac Cardiovasc Surg*. 2015;149:95-100.
6. Meurgey A, Girard N, Merveilleux du Vignaux C, et al: Assessment of the ITMIG Statement on the WHO Histological Classification and of the Eighth TNM Staging of Thymic Epithelial Tumors of a Series of 188 Thymic Epithelial Tumors. *J Thorac Oncol* 2017;12:1571-1581.
7. Detterbeck FC, Nicholson AG, Kondo K, et al: The Masaoka-Koga stage classification for thymic malignancies: clarification and definition of terms. *J Thorac Oncol* 2011;6:S1710-6.
8. Brierly JD, Gospodarowicz MK, Wittekind C. Thymic Tumors. In: *TNM classification of malignant tumors*. 8th Edition. Oxford, UK. John Wiley & Sons, 2017. p.74.

9. Ko R, Shukuya T, Okuma Y, Tateishi K, Imai H, Iwasawa S, et al. Prognostic Factors and Efficacy of First-Line Chemotherapy in Patients with Advanced Thymic Carcinoma: A Retrospective Analysis of 286 Patients from NEJ023 Study. *Oncologist*. 2018;23:1210-1217.
10. Giaccone G, Kim C, Thompson J, McGuire C, Kallakury B, Chahine JJ, et al. Pembrolizumab in patients with thymic carcinoma: a single-arm, single-centre, phase 2 study. *Lancet Oncol*. 2018;19:347-355.
11. Cho J, Kim HS, Ku BM, Choi YL, Cristescu R, Han J, et al. Pembrolizumab for Patients With Refractory or Relapsed Thymic Epithelial Tumor: An Open-Label Phase II Trial. *J Clin Oncol*. 2019;37:2162-2170.
12. Thomas A, Rajan A, Berman A, et al: Sunitinib in patients with chemotherapy-refractory thymoma and thymic carcinoma: an open-label phase 2 trial. *Lancet Oncol* 2015;16:177-86.
13. Girard N, Dansin E, Léna H, Pichon E, Thomas PA, Mazières J, et al. Systemic Treatment in Advanced Thymic Epithelial Tumors. Insights From a Prospective Cohort of 1000 Patients enrolled in RYTHMIC. International Association for the Study of Lung Cancer. World Conference on Lung Cancer 2015; Denver, USA. Citation: *J Thorac Oncol*. 2015; 10 : 353 .
14. Bluthgen M, Dansin E, Kerjouan M, et al. Updated incidence of thymic epithelial tumors (TET) in France and clinical presentation at diagnosis. *J Thorac Oncol* 2016;12:S524.
15. Travis WB, Brambilla A, Burke AP, Marx A, Nicholson A. WHO histological classification of tumours of the thymus. In: World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart. Lyon : IARC Press; 2015. p183

16. Marx A, Chan JK, Coindre JM, Detterbeck F, Girard N, Harris NL, et al. The 2015 World Health Organization Classification of Tumors of the Thymus: Continuity and Changes. *J Thorac Oncol* 2015;10:1383-95.
17. Girard N, Ruffini E, Marx A, et al: Thymic epithelial tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2015;26 Suppl 5:v40-55.
18. Huang J, Detterbeck FC, Wang Z, Loehrer PJ Sr. Standard outcome measures for thymic malignancies. *J Thorac Oncol* 2011;6:S1691-7.
19. Girard N, Lal R, Wakelee H, Riely GJ, Loehrer PJ. Chemotherapy definitions and policies for thymic malignancies. *J Thorac Oncol* 2011;6:S1749-55.
20. Gomez D, Komaki R, Yu J, Ikushima H, Bezjak A. Radiation therapy definitions and reporting guidelines for thymic malignancies. *J Thorac Oncol.* 2011;6: S1743-1748.
21. Basse C, Thureau S, Bota S, Dansin E, Thomas PA, Pichon E, et al. Multidisciplinary Tumor Board Decision Making for Postoperative Radiotherapy in Thymic Epithelial Tumors: Insights from the RYTHMIC Prospective Cohort. *J Thorac Oncol.* 2017;12:1715-1722.
22. Mervilleux du Vignaux C, Dansin E, Mhanna L, Greillier L, Pichon E, Kerjouan M, et al. Systemic Therapy in Advanced Thymic Epithelial Tumors: Insights from the RYTHMIC Prospective Cohort. *J Thorac Oncol.* 2018;13:1762-1770.
23. Giaccone G, Kim C. Durable Response in Patients With Thymic Carcinoma Treated With Pembrolizumab After Prolonged Follow-Up. *J Thorac Oncol.* 2021;16:483-485.
24. Sato J, Satouchi M, Itoh S, Okuma Y, Niho S, Mizugaki H, et al. Lenvatinib in patients with advanced or metastatic thymic carcinoma (REMORA): a multicentre, phase 2 trial. *Lancet Oncol.* 2020;21:843-850.

TABLE 1: Patients characteristics

	n	%
Total	213	100%
Gender		
Men	140	66%
Women	73	34%
8th TNM stage		
I	18	8%
II	0	0%
IIIA	50	23%
IIIB	12	6%
IVA	33	15%
IVB	75	35%
Unknown	25	12%
Histological subtype		
Squamous	142	67%
Undifferentiated	53	25%
Basaloid	7	3%
Sarcomatoid	2	1%
Adenocarcinoma	6	3%
Lympho-epithelioma-like	3	1%

FIGURE LEGENDS

Figure 1: Treatment strategies in 60 patients with upfront surgical resection of the tumor, possibly followed by postoperative radiotherapy (PORT) or postoperative chemotherapy (POCT).

Figure 2: Treatment strategies in 91 patients who received preoperative chemotherapy (A), and subsequently possibly were treated for recurrence (40 patients) (B). Legend: PAC: cyclophosphamide, adriamycin, and cisplatin

Figure 3: Systemic treatment regimens in 62 patients who received first-line exclusive chemotherapy (A), possibly followed by second-line (B) and third-line (C) systemic treatment. Legend: PAC: cyclophosphamide, adriamycin, and cisplatin; VEGFR: Vascular Endothelial Growth Factor Receptor

Figure 4: Overall survival (OS) in the whole cohort of 213 patients (A). OS according to treatment strategy: surgery upfront (blue), primary chemotherapy upfront (green), exclusive chemotherapy (red) (B). OS according to Masaoka-Koga stage: I (blue), IIA (red), IIB (green), III (orange), IVA (yellow), IVB (light green) (C). OS according to surgery, upfront or after primary chemotherapy: surgery (red) or no surgery (blue) (D).

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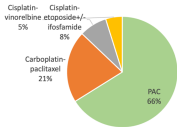
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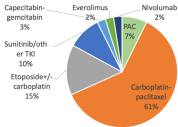
Resectable disease
Upfront surgery
n=60

Stage I n=1 R0=1	Stage IIA n=11 R0= 10; R1=1	Stage IIB n=9 R0=6; R1=3	Stage III n=22 R0=10; R1=8; R2=4	Stage IVA n=5 R0=1; R1=4	Stage IVB n=12 R0=10; R1=2
POCT n=0	POCT n=0	POCT n=0	POCT n=3	POCT n=3	POCT n=1
PORT n=0	PORT n=7	PORT n=9	PORT n=17	PORT n=3	PORT n=7
No adjuvant treatment n=1	No adjuvant treatment n=4	No adjuvant treatment n=0	No adjuvant treatment n=5	No adjuvant treatment n=2	No adjuvant treatment n=4

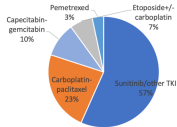
First-line
n=62



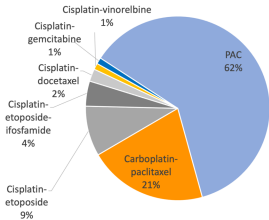
Second-line
n=41



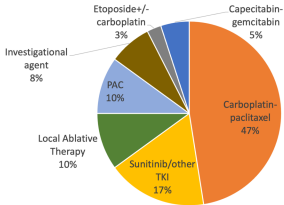
Third-line
n=30



Primary chemotherapy n=91



First recurrence n=40



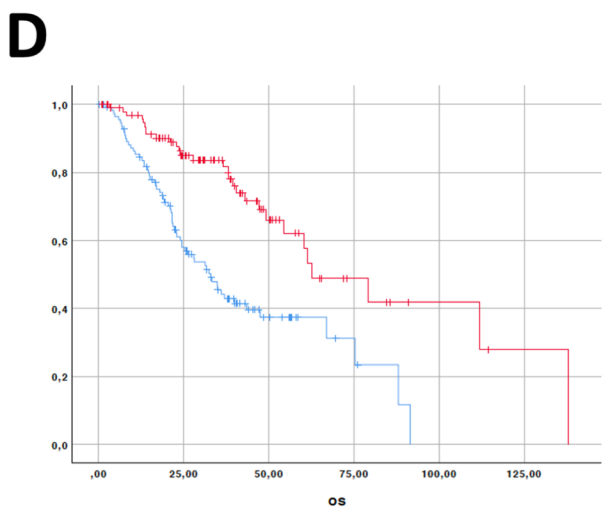
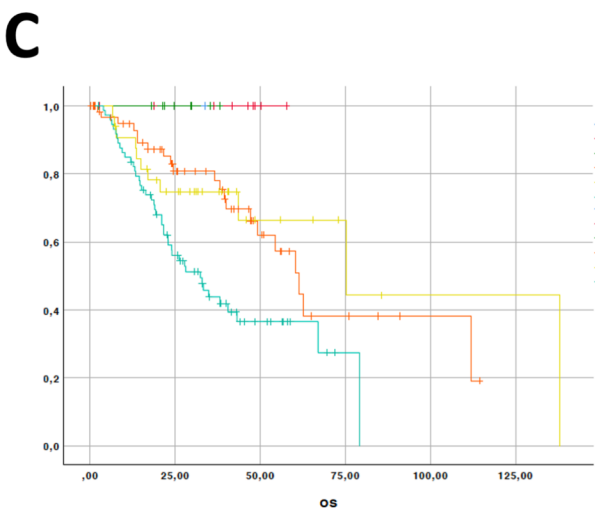
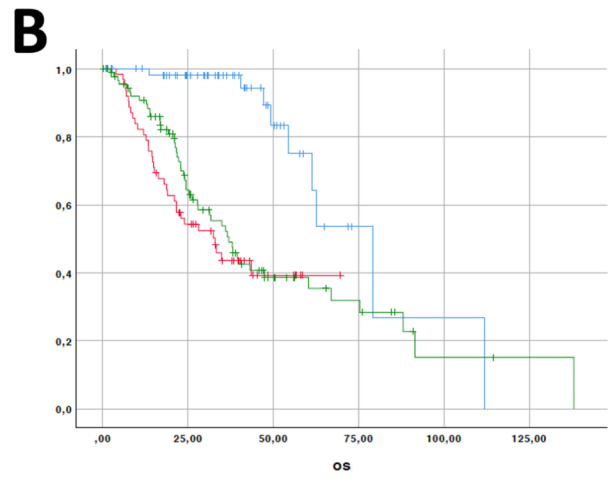
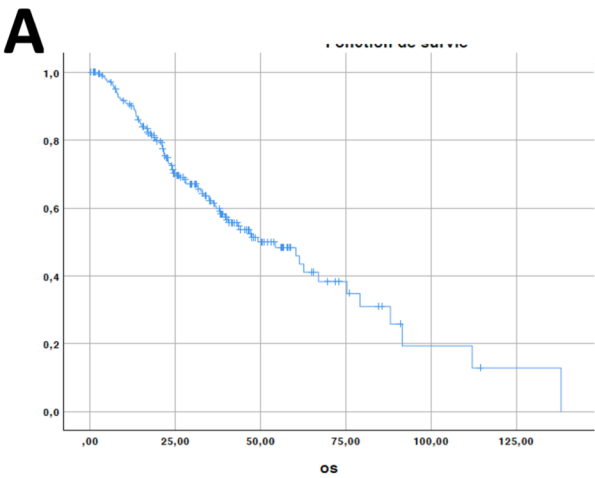


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