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Mona Mlika[1,2]* and Faouzi Mezni[1,2]

[1]Department of Pathology, Abderrahman Mami Hospital, University Tunis El Manar, Tunisia
[2]12UR18 Research Unit, Tunis El Manar Faculty, Tunisia

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***Corresponding author:** Mona Mlika, Department of Pathology, Abderrahman Mami Hospital, 2037, Tunis, Tunisia, Tel: 00216 98 53 8862; E-mail: mlika.zorgati.mona@hotmail.com

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Review Article

Review of the literature about Thymic Carcinomas

Abstract

Background: Thymic carcinomas (TC) are rare tumors with challenging diagnosis and management. We aimed to describe the clinical and microscopic characteristics of TC through a literature review.

Results: 82 articles and abstracts were retained about 2913 TC. Our study contained 1760 men and 1153 women with a mean age of 55.32 years. The delay of diagnosis was specified in 10 cases and varied between 8 months and 2 years. Symptoms consisted mainly in chest pain and dyspnea. The Computed Tomography-scan (CT-scan) findings were specified in 63 cases. Microscopic findings were noticed in 1766 cases. They consisted mainly in squamous cell carcinoma in 1297 cases and undifferentiated carcinoma in 239 cases. The patients presented stage 1 tumors in 165 cases, stage II in 362 cases, stage III in 1011 cases and stage IV in 1166 cases. The treatment modalities were noticed in 2803 cases. There was no consensus of the regimen of chemotherapy or the place of the radiation therapy but all studies highlighted the key role of the complete surgical resection when possible.

Conclusion: Our results highlight the lack of consensual management of TC. The chemotherapy regimen, the second-line chemotherapy and the indications of radiation therapy seem non-consensual and need further studies. Many interrogations remain concerning the management of these tumors according to their histologic grade. The real place of targeted therapy remains to assess and the rare opinions published are based on rare and non-representative cases.

Abbreviations

TC: Thymic Carcinoma

Background

Thymic carcinomas are rare mediastinal tumors characterized by a challenging diagnosis and management [1,2]. These tumors are classified within thymic tumors according to the 2015 World Health Organization Classification. Clinical symptoms are nonspecific resulting in a delayed diagnosis [1,3-10]. Radiological findings are also nonspecific. In fact, they help to highlight the malignant nature of the tumor without presuming of its nature. Positive diagnosis is based on the microscopic exam which is performed in almost all cases on small samples with many crowding artifacts. This fact is due to the difficulty of complete resection of these tumors. The microscopic diagnosis of thymic carcinomas is a diagnosis of exclusion because these tumors present no particularity in comparison with other tumors observed in other organs. The only particularity of these tumors consists in their thymic localization.

Our aim was to describe the clinical, the radiological, the microscopic and the therapeutic characteristics of thymic carcinomas through a literature review.

Methods

A review of the literature was performed from 1976 to 2016.

- **Inclusion criteria:** articles and abstracts containing the clinical, microscopic, immunohistochemical and characteristics of the disease were included.
- **Non-inclusion criteria:** articles and abstracts in Spanish, Chinese or other foreign languages different form French or English weren't included
- **Withdrawal criteria:** all articles about mediastinal tumors different from thymic carcinomas weren't included. Bibliographic research: bibliographic research was performed in the sites pubmed (http://www.ncbi.nih.gov/pubmed), google and google scholar using the key-words: « thymic carcinoma, thymic tumour, mediastinal tumour ».
- **Statistical analysis:** the statistical analysis was performed using the SPSS software (version 12.0).

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Results

According to our criteria, 82 articles and abstracts were retained about 2913 thymic carcinomas. All the articles included are represented in table 1. Our study contained 1760 men and 1153 women with a sex-ratio (H/F) of 1.5. The mean age of the patients was 55.32 years. Habits were described in 94 cases and consisted in smoking in all cases. Four patients presented a particular past medical history consistent in diabetes mellitus in one case, b-viral hepatitis in 1 case, co-infection of hepatitis and HIV in one case, T-cell lymphoma in one case and urothelial carcinoma of the bladder in 3 cases, prostate cancer in 5 cases breast cancer in 2 cases, germ cell tumor of the testis in 1 case, colorectal cancer in 1 case. The delay of diagnosis was specified in 10 cases and varied between 8 months and 2 years. Symptoms were specified in 728 cases and consisted in chest pain (263 cases) and dyspnea (187 cases). The other symptoms consisted in cough (151 cases), superior vena cava syndrom (57 cases), dysphonia (30 cases), weight loss (11 cases), asthenia (10 cases), fever (11 cases), and para-neoplastic syndrome (28 cases). The tumor was asymptomatic in 107 cases. Physical exam findings were specified in 3 cases and revealed sub-clavicular lymph node in 1 case and right cervical tumefaction in 1 case. Chest-x-ray findings were specified in 2 cases and consisted in an anterior mediastinal mass situated in the left lung with pleural effusion and nodules in one case and a mediastinal

Table 1: The different studies included in our review of the literature

8	Author	Nber	Title	Journal
[1]	Xu J-P, et al.	37	Efficacy and safety of the combination of paclitaxel and platinum in advanced thymic carcinoma	Thoracic Cancer 2016;7:222-5
[3]	Macaron G, et al.	1	Morvan Syndrome Secondary to Thymic Carcinoma in a Patient with Systemic Lupus Erythematosus.	Case Rep Neurol Med. 2016;2016:9142486.
[4]	Shima H, et al	1	Response to chemotherapy with carboplatin plus albumin-bound paclitaxel in a patient with lymphoepithelioma-like thymic carcinoma: A case report.	Mol Clin Oncol. 2016;4(5):715-718.
[5]	Hirai F, et al.	1	C-kit mutation-positive advanced thymic carcinoma successfully treated as a mediastinal gastrointestinal stromal tumor: A case report.	Mol Clin Oncol. 2016;4(4):527-529.
[6]	Matsuoka K, et al.	1	Ectopic thymic carcinoma presenting as an intrathoracic mass.	Asian Cardiovasc Thorac Ann. 2016 ;24(5):480-3.
[7]	Nagamata M, et al.	1	Thymic Carcinoma With Endobronchial Metastasis: A Case Report.	J Bronchology Interv Pulmonol. 2016;11.
[8]	Xu JP, et al.	37	Efficacy and safety of the combination of paclitaxel and platinum in advanced thymic carcinoma.	Thorac Cancer. 2016;7(2):222-5.
[9]	Kashima J, et al.	1	Osseous oligometastases from thymic carcinoma: a case report suggesting the effectiveness of palliative-intent radiotherapy treatment.	Onco Targets Ther. 2016;29;9:1029-32.
[10]	Mlika M, et al.	11	About thymic carcinomas: challenges in diagnosis and management.	Asian Cardiovasc Thorac Ann. 2016;24(4):350-4.
[2]	Luo Y, et al.	13	Chemotherapy with gemcitabine plus cisplatin in patients with advanced thymic squamous cell carcinoma: Evaluation of efficacy and toxicity.	Thoracic Cancer 2016;7:167-72
[11]	Okuma Y, et al.	23	Response to Cytotoxic Chemotherapy in Patients Previously Treated With Palliative-Intent Chemotherapy for Advanced Thymic Carcinoma	Clinical Lung Cancer 2015;16(3):221-7
[12]	Song Z, et al.	86	Chemotherapy and prognosis in advanced thymic carcinoma patients	Clinics. 2015;70(12):775-80
[13]	Sun Y, et al.	32	Treatment and prognosis of Masaoka stage 3 thymic carcinoma: A retrospective study of 32cases	OncoTargets and Therapy 2015 ;8 :699-702
[14]	Mao Y, et al.	54	Treatment and survival analyses of completely resected thymic carcinoma patients	OncoTargets and Therapy 2015;8:2503–7
[15]	Watanabe N, et al.	13	Docetaxel for platinum-refractory advanced thymic carcinoma	Japanese Journal of Clinical Oncology 2015;45(7):665-9
[16]	Weksler B, et al.	229	Impact of Positive Nodal Metastases in Patients with Thymic Carcinoma and Thymic Neuroendocrine Tumors	J ThoracOncol. 2015;10:1642-7
[17]	Filosso P. L, et al	40	Outcome of surgically resected thymic carcinoma: A multicenter experience	Lung Cancer 2014;83:205-10
[18]	Okuma Y, et al.	68	The potency of curative-intent treatment for advanced thymic carcinoma	Lung Cancer 2014;84:175-81
[19]	Kawasaki H, et al.	17	Weekly chemotherapy with cisplatin, vincristine, doxorubicin, and etoposide followed by surgery for thymic carcinoma	EJSO 2014;40:1151-5
[20]	Litvak A. M, et al.	121	Clinical Characteristics and Outcomes for Patients With Thymic Carcinoma Evaluation of Masaoka Staging	J ThoracOncol. 2014;9:1810-5
[21]	Ruffini E, et al.	229	Thymic Carcinoma: A Cohort Study of Patients from the European Society of Thoracic Surgeons Database	J ThoracOncol. 2014;9:541-8

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[22]	Shitara M, et al.	12	Genetic profiling of thymic carcinoma using targeted next-generation sequencing	Lung Cancer 2014;86:174-9
[23]	Song Z, et al.	76	Outcomes after surgical resection of thymic carcinoma: A study from a single tertiary referral centre	EJSO 2014;40:1523-7
[24]	Yen Y-T, et al.	82	Factors Predicting Recurrence and Postrecurrence Survival in Completely Resected Thymic Carcinoma	Ann ThoracSurg 2014;97:1169-75
[25]	Song Z, et al.	15	Docetaxel-based chemotherapy as second-line regimen for advanced thymic carcinoma	Thoracic Cancer 2014;5:169-73
[26]	Okuma Y, et al.	40	Clinical outcomes with chemotherapy for thymic carcinoma	Lung Cancer 2013;80:75-80
[27]	Zhao Y, et al	105	Surgical Treatment and Prognosis of Thymic Squamous Cell Carcinoma: A Retrospective Analysis of 105 Cases	Ann ThoracSurg 2013;96:1019-24
[28]	Roden A. C, et al.	29	Clinicopathological features of thymic carcinomas and the impact of histopathological agreement on prognostical studies	European Journal of Cardio-Thoracic Surgery 2013;43:1131-9
[29]	Eom K-Y, et al.	40	Invasion of the great vessels or atrium predicts worse prognosis in thymic carcinoma	RadiatOncol J 2013;31(3):131-7
[30]	weksler B, et al.	290	Thymic Carcinoma: A Multivariate Analysis of Factors Predective of Servival in 290 Patients	Ann Thoracic Surg 2013;95:299-304
[31]	Park I. K, et al	37	Importance of Lymph Node Dissection in Thymic Carcinoma	Ann ThoracSurg 2013;96:1025-32
[32]	Sakai M, et al.	4	Early-stage thymic carcinoma: is adjuvant therapy required?	J Thorac Dis 2013;5(2):161-4
[33]	Ose N, et al	1	Multimodality Therapy for Large Cell Neuroendocrine Carcinoma of the Thymus	Ann ThoracSurg 2013;96:85–7
[34]	Weissferdt A, et al.	65	Thymic Carcinoma, Part 1 A Clinicopathologic and Immunohistochemical Study of 65 Cases	Am J Clin Pathol 2012;138:103-14
[35]	Weissferdt A, et al.	6	Anaplastic thymic carcinoma: a clinicopathologic and immunohistochemical study of 6 cases	Human Pathology 2012;43:874-7
[36]	Okereke I. C, et al	16	Thymic Carcinoma: Outcomes After Surgical Resection	Ann ThoracSurg 2012;93:1668-73
[37]	Weissferdt A, et al.	24	HER family receptor and ligand status in thymic carcinoma	Lung Cancer 2012;77:515-21
[38]	Weissferdt A, et al.	33	Thymic Carcinoma, Part 2A Clinicopathologic Correlation of 33 Cases With a Proposed Staging System	Am J Clin Pathol2012;138:115-21
[39]	Cardillo G, et al.	35	Primary Neuroendocrine Tumors of the Thymus: A Multicenter Experience of 35 Patients	Ann ThoracSurg 2012;94:241-6
[40]	Dee S-W, et al.	1	Chronic shoulder pain referred from thymic carcinoma: a case report and review of literature	Neuropsychiatric Disease and Teatement 2012;8:399-403
[41]	Okuma Y, et al.	9	Cisplatin and irinotecan combination chemotherapy for advanced thymic carcinoma: Evaluation of efficacy and toxicity	Lung Cancer 2011;74:492-6
[42]	Liu T, et al.	1	Thymic carcinoma with primary spine metastasis	Journal of Clinical Neuroscience 2011;18:840-2
[43]	Agatsuma T, et al.	34	Combination Chemotherapy with Doxorubicin, Vincristine,Cyclophosphamide, and Platinum Compounds for Advanced Thymic Carcinoma	J ThoracOncol. 2011;6:2130-4
[44]	Yassuda M, et al.	22	Results of surgical resction for patients with thymic carcinoma	Scandinavian Journal of Surgery 2011;100:159-63
[45]	Bott M J, et al.	10	Management and Outcomes of Relapse After Treatement for Thymoma and Thymic Carcinoma	Ann ThoracSurg 2011;92:1984-92
[46]	Shim H. S, et al.	32	Prognostic effect of stromal lymphocyte infiltration in thrymic carcinoma	Lung Cancer 2011;74:338-43
[47]	Disel U, et al.	1	Promising efficacy of sorafenib in a relapsed thymic carcinoma with C-KIT exon 11 deletion mutation	Lung Cancer 2011;71:109-12
[48]	Saint-Blancard P, et al.	1	Métastase ganglionnaire sus-claviculaire d'un carcinome thymique : présentation inaugurale inhabituelle d'une pathologie rare	Revue de Pneumologie Clinique 2010;66:330-4
[49]	Igawaa S, et al	11	Efficacy of chemotherapy with carboplatin and paclitaxel for unresectablethymic carcinoma	Lung Cancer 2010;67:194-7
[50]	Hosaka Y , et al.	21	Masaoka Stage and Histologic Grade Predict Prognosis in Patients With Thymic Carcinoma	Ann ThoracSurg 2010;89:912-7
[51]	Okuma Y, et al.	4	S-1 is an active anticancer agent for advanced thymic carcinoma	Lung Cancer 2010;70:357-63
[52]	Huang J, et al.	23	Comparison of patterns of relapse in thymic carcinoma and thymoma	J ThoracCardiovascSurg 2009;138:26-31
[53]	Lee C. Y, et al.	60	Early Masaoka stage and complete resection is important for prognosis of thymic carcinoma: a 20-year experience at a single institution	European Journal of Cardio-thoracic Surgery 2009;36:159-63
[54]	Magois E, et al.	9	Multimodal treatment of thymiccarinoma: Report of nine cases	Lung Cancer 2008;59:126-32

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[55]	Yano M, et al.	30	Thymic Carcinoma: 30 Cases at a Single Institution	J ThoracOncol. 2008;3:265-9
[56]	Maruyama R, et al.	25	Persistent and aggressive treatment for thymic carcinoma - Results of a single-institute experience with 25 patients	Oncology 2006;70:325-9
[57]	Yamaguchi H, et al.	1	Thymic carcinoma with epidermal growth factor receptor gene mutations	Lung Cancer 2006;52:261-2
[58]	Lin J-T, et al.	20	Stage IV Thymic Carcinoma: A Study of20 Patients	Am J Med Sci 2005;330(4):172-5
[59]	Chalabreysse L, et al.	6	Les tumeurs neuroendocrinesdu thymus À propos de 6 cas	Ann Pathol 2005;25;205-10
[60]	Chen Y-Y, et al.	16	Concurrent Chemoradiotherapy forUnresectableThymicCarcinoma	Chang Gung Med J 2004;27:515-22
[61]	Nonaka T, et al.	12	The Role of Radiotherapy for Thymic Carcinoma	Jpn J Clin Oncol 2004;34(12)722-6
[62]	Takeda S-I, et al.	15	Thymiccarcinoma. Clinicalinstitutionalexperiencewith 15 patients	European Journal of Cardio-thoracic Surgery 2004;26:401-6
[63]	Kondo K, et al.	227	Therapy for Thymic Epithelial Tumors: A Clinical Study of 1320 Patients From Japan	Ann ThoracSurg 2003;76:878-5
[64]	Tseng Y-L, et al.	38	Thymic Carcinoma: Involvement of Great Vessels Indicates Poor Prognosis	Ann ThoracSurg 2003;76:1041-5
[65]	Yoh K, et al.	12	Weekly Chemotherapy with Cisplatin, Vincristine, Doxorubicin, and Etoposide Is an Effective Treatment for Advanced ThymicCarcinoma	Cancer 2003;98:926-31
[66]	Liu H-C, et al.	38	Primary Thymic Carcinoma	Ann ThoracSurg 2002;73:1076-81
[67]	Saint-Blancard P, et al.	1	Une tumeur maligne rare du médiastin : le carcinome thymique	Ann Pathol 2002;22:127-9
[68]	Hsu H-C, et al.	26	Post-operative Radiotherapy in Thymic Carcinoma : Treatement Results and Prognostic factors	Int. J. Radiation Oncologie Biol. Phys. 2002;52(3):801-5
[69]	Ogawa K, et al.	40	Treatement and Prognosis of Thymic Carcinoma A retrospective analysis of 40 cases	Cancer 2002;94:3115-9
[70]	Tomita M, et al.	8	Clinical and immunohistochemical study of eight cases with thymic carcinoma	BMC Surgery 2002, 2:3 http://www.biomedcentral.com/1471-2482/2/3
[71]	Lucchi M, et al.	7	The multimodality treatment of thymic carcinoma	European Journal of Cardio-thoracic Surgery 2001;19:566-9
[72]	Kitami A, et al.	7	Chemotherapy of Thymic Carcinoma : Analysis of Seven Cases and Review of the Literature	Jpn J ClinOncol 2001;31(12):601-4
[73]	Lucchi M, et al.	13	Thymic carcinoma: a report of 13 cases	European Journal of Surgical Oncology 2001; 27: 636-40
[74]	Gal A. A, et al.	10	Neuroendocrine Tumors of the Thymus: A Clinicopathological and Prognostic Study	Ann ThoracSurg 2001;72:1179-82
[75]	Nakamura Y, et al.	10	Platinum-based chemotherapy with or without thoracic radiation threrapy in patients with unresectablethymic carcinoma	Jpn J ClinOncol 2000;30(9):385-8
[76]	Blumberg D, et al.	43	Thymic carcinoma: current staging does not predict prognosis	J ThoracCardiovascSurg 1998;115:303-9
[77]	Mizukami Y, et al.	2	Thymic carcinoma involving the thyroid gland	Human Pathology 1995;26(5):576-9
[78]	Hsu CP, et al.	20	Thymic carcinomaTen years' experience in twenty patients	ThoracCardiovascSurg 1994;107:615-20
[79]	Weide L. G, et al.	5	Thymic Carcinoma: A Distinct Clinical Entity Responsive to Chemotherapy	Cancer 1993;71:1219-23
[80]	Suster S, et al.	60	Thymic Carcinoma : A Clinicopathologic Study of 60 cases	Cancer 1991 ;67 :1025-32
[81]	Arriagada R, et al.	56	Invasive Carcinoma of the Thymus. A Multicenter Retrospective Review of 56 Cases	Eur J Cancer Clin Oncol. 1984;20(1):69-74

enlargement in the second case. The CT-scan findings were specified in 63 cases. The tumor was situated in the anterior mediastinum in all cases. The mean size of the tumor was 79,7 mm with average between 20 mm and 170mm. Secondary pulmonary localizations were noticed in 307 cases (10,58%). Pleural localizations were observed in 112 cases (3.86%). Mediastinal lymph nodes were observed in 68 cases (2.34%). Compression of the adjacent structures was observed in 1 case, a vascular invasion in 81 cases, a pleural effusion in 6 cases, pericardiac localizations in 210 cases, pericardiac effusion in 8 cases and invasion of the phrenic nerve in 61 cases. Bronchial endoscopy findings were mentioned in 35 cases and showed an external bronchial compression in 1 case. It was normal in 8 cases. The findings weren't specified in the other cases.

Abdominal CT-scan was described in 495 cases and showed hepatic lesions in 88 cases, sub renal masses in 4 cases and mesenteric lymph nodes in 23 cases. Cerebral CT-scan was performed in 246 cases and showed cerebral metastases in 16 cases (0.55%). Bone Pet-scan was performed in 356 cases and showed bone metastases in 161 cases. An increase of the LDL level was reported in 23 cases. βHCG and αFP levels were reported normal in 5 cases. ACE level was assessed in 8 cases and was increased in 2 cases. Based on the clinical and radiological findings, some diagnoses were suspected in 9 cases and consisted in pulmonary emboli in 1 case, germ cell tumor in 5 cases, thymoma in 16 cases and teratoma in 2 cases. Extemporaneous exam was performed in only one study. Surgical biopsy was performed in 422 cases through an antero-

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lateral thoracotomy in 392 cases and a trans-thoracic approach in 57 cases. Lymph node biopsy was performed in 2 cases. A surgical excision of the tumor was possible in 1163 cases. Gross findings were described in one study. The tumor excised was reported necrotic and hemorrhagic. Microscopic findings were noticed in 1766 cases. They consisted in squamous cell carcinoma in 1297 cases (73%), undifferentiated carcinoma in 239 cases (13%), lympho-epithelioma-like carcinoma in 107 cases (6%), mucoepidermoid carcinoma in 32 cases (1.8%), sarcomatous carcinoma in 26 cases, basaloid carcinoma in 21 cases, adenocarcinoma in 18 cases, clear cell carcinoma in 17 cases and adenosquamous carcinoma in 9 cases. The immunohistochemical study was performed in 44 cases using the following antibodies CD4, CD5, CD8, CD20, CD99, CD117, EMA, CK7, CK8, CK18, CK19, CK, EMA, Bcl2. Lymphoid antibodies were negative in all cases and epithelial markers were positive in all cases. The patients presented stage 1 tumors in 165 cases, stage II in 362 cases, stage III in 1011 cases and stage IV in 1166 cases. The tumor stage wasn't mentioned in the other cases. The treatment modalities were noticed in 2803 cases. The first-line chemotherapy was used alone in 320 cases (11.41% of the cases) and was followed by a surgical resection in 365 cases (13% of the cases). It was associated to a radiation therapy in 201 cases (7.17% of the cases). A second-line chemotherapy was prescribed in 206 cases. Radiation therapy was used initially in 375 cases (13.37% of the cases), alone in 96 cases and in association with a chemotherapy in 201 cases. It was indicated before the surgical resection in 78 cases with a total dose varying between 40 and 70 Gy. Complete surgical resection was achieved in 1365 cases. A reduction of the tumor mass was performed in 474 cases. The follow -up period varied between 1 and 193 months. The mean follow-up period was noticed in 248 cases and reached 51 months. The mean survival period was noticed in 1305 cases and reached 60 years with average between 1 and 193 months. The 1-year survival was noticed in 309 cases and was estimated to 69.43%. The three-year survival was noticed in 526 cases and reached 61.75%. The 5-year survival was noticed in 1824 cases and reached 54.36%. The 10-year survival was noticed in 716 cases and reached 35.15%. The 5-year survival without tumoral progression was noticed in 602 cases and reached 56.30%. The mean survival of patients with complete surgical resection was noticed in 439 cases and reached 95.8 months. The five-year survival reached 84.35% in stage I and II and 46.43% in stages III and IV.

Discussion and Conclusion

Our study is about thymic carcinomas and present the advantage of studying an important number of series and cases. This study allowed a complete analysis of this pathology with the different aspects (epidemiology, symptoms, biology, microscopy, therapeutic management and prognosis). Our limits consist in the lack of clinical and microscopic findings. This study highlights the rarity of thymic carcinomas that account for 1 to 4% of all malignant tumors of the thymus and between 10 to 20% of thymic epithelial tumors [11,12,13-26]. They were differentiated from thymomas by Rosai and Levine in 1978 and were considered as a distinct entity in the WHO classification (1999), which distinguished the group of thymomas (TET de type A et B) and thymic carcinomas (TET de type C) [27- 39]. Thymic carcinomas are observed at any age with a mean age varying between 50 and 60 years [40-60]. The mean age in our review of the literature achieved 55.32 years with extremes varying between 10 and 89 years. A male predominance was observed in almost all cases [50-86]. Symptoms related to the extension of the tumor to the adjacent structures are mainly represented by chest pain, cough and superior vena cava syndrom. In opposition to other thymic epithelial tumors, the association to paraneoplastic syndrom has been rarely described. Fortuitous diagnosis has also been reported. It was described in 3 cases of our literature review [73]. Chest-x-ray findings have been rarely described. This exam seems neglected, according to our literature review, but it is useful to indicate a rapid thoracic CT-scan facing a compressive mediastinal mass [84]. The chest-x-ray findings have been described in only 2 cases of our literature review [32,60]. A mediastinal mass has been described in both cases with pulmonary localizations in one case. CT-scan findings may be suggestive of the diagnosis of thymic carcinoma when showing a mediastinal mass with irregular margins, necrotic or cystic foci, mediastinal lymph nodes with a size superior to 10 mm and criteria of invasion of the vessels or the adipose tissue [80,84]. The accurate role of the thoracic MRI hasn't been assessed in the literature but according to the 2015 NCCN guidelines, the MRI should be indicated [80]. The pet-scan has been performed in 316 cases and was abnormal in 84 cases. Biologic investigations were described in 17 cases and consisted in the dosage of ACE levels and showed normal levels [72]. Our findings aren't concordant with the NCCN recommendations. In fact, Serum beta-chorio-gonadotrophin Hormone (B-HCG) and alpha fetoprotein (AFP) levels should be assessed when dealing with a mediastinal mass. Microscopic exam plays a key role in the diagnosis, histoprognosis and the realization of a molecular tissue bank. It is usually performed on small samples because of the invasive and large size of these tumors. Open biopsies or fine needle biopsies are recommended in advanced tumors. In the literature, 392 cases were biopsied and the mass was totally excised in 501 cases [81]. Microscopic exam may also be performed on lymph node biopsies in 2 cases or on metastases in 2 cases of thyroid localizations [40,43,73]. Gross findings weren't accurately described in the literature despite of the important number of tumors totally excised. These tumors are usually non-encapsulated with cystic, hemorrhagic or necrotic foci [60]. Microscopic findings of thymic carcinomas aren't specific. This diagnosis is a diagnosis of exclusion. Facing an anterior mediastinal mass with malignant features, the pathologist has to rule out the diagnosis of invasive thymoma. This may be done when the diagnostic features of thymoma, including lobulation and the coexistence of epithelial cells and immature lymphocytes are absent. In a second time, when the diagnosis of thymoma is excluded, the diagnosis of a mediastinal metastasis has to be ruled out. This can be reached when a multidisciplinary approach including clinicians, radiologists and pathologists is done. Thymic carcinomas are diverse and include squamous cell carcinomas, basaloid carcinomas, lymphoepithelioma-like carcinomas, mucoepidermoid carcinomas, adenosquamous carcinomas,

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clear cell carcinomas, sarcomatous carcinomas, adenocarcinomas, NUT carcinomas, hepatic carcinomas, rhabdoid carcinomas and micro-nodular carcinomas with lymphoid hyperplasia. All these tumors could be observed in other organs than the thymus. The primary thymic localization may be assessed using the CD5 and CD117 antibodies which are usually expressed by thymic carcinomas. In negative cases, the pathologist is unable to make the diagnosis of thymic carcinoma without assessing the clinical, radiological and biologic findings [23,87,88]. Surgical resection is the mainstay treatment of thymic carcinomas [4-6,8,10,12,16,21-24,26,28,30,31,36,37,42,44-48,52,54,56-59,62,63,66-68,72,74]. It should be as complete as possible. A resection of the tumor with the thymus and the peri-thymic adipose tissue is necessary. Lymph node curettage is also mandatory, especially in locally advanced tumors [23]. In case of extension to the adjacent structures, a monobloc thymectomy is suitable [80,89-95]. A surgical decrease of the volume of the mass was performed in 225 cases. This procedure is still discussed by some authors who reported that the 5-year-survival of incomplete surgical resection is similar to the tumors treated by radiation therapy and chemotherapy [59]. Neo-adjuvant chemotherapy is necessary in locally advanced disseminated tumors inducing in some cases the decrease in the tumoral volume and the possibility of surgical resection. Many protocols of chemotherapy have been used based on platinum [80,92]. Data suggest that the ADOC (cisplatin, doxorubicin, vincristine, and cyclophosphamide) regimen is effective. The role of the adjuvant chemotherapy hasn't been clearly assessed. Kondo K et al. and Weksler B et al., didn't report an improvement of the prognosis of the patients with completely resected tumors [19,22,56]. On the other hand, Weissferdt A et al., reported the important role of adjuvant chemotherapy in the control of completely resected tumors especially in low grade ones [29]. The advantage of this treatment is reflected by the improvement of the global survival, the survival without recurrence and without metastases [29,36]. A second line chemotherapy was used in 2 studies according to the protocols ABVD (Adriamycin + Delicum + Bleomycin + Velbemycin). This association was used in non resectable tumors [10,12,21,45,47,50,52,56,59,63,68]. The results of this association remain non-consensual because of the few number of patients included in this association. No prospective study has been described in the literature. Adjuvant radiation therapy has been discussed in the literature without a real consensus [91]. It was used in 19% of the cases. After a complete surgical resection, the utility of radiation therapy has been debated in the literature and was reported to have no effect on the global survival or the survival without progression [5,22,56,58]. For low grade tumors, some authors reported the role of radiation therapy following surgical resection in the decrease of loco regional recurrences and secondary localizations [6,9,28,36,54,61,62,66,80,92]. The place of targeted therapy has been assessed in the literature. A high expression of the Epidermal Growth Factor (EGFR) and HER has been reported especially in advanced tumors [29,89]. Moreover, the expression of Kit, assessed by immunohistochemistry, is characteristic of thymic carcinomas. It has been reported in 2 % of thymomas and 80 % of thymic carcinomas. The expression of Kit was also used as a diagnostic tool of these tumors [39,93]. Some mutations detected in thymic carcinomas have been reported in the gastrointestinal tumors (mutations V560del, L576P). Other mutations seems specific to thymic carcinomas (mutations Y553N, H697Y, D820E). The sensitivity of these tumors to KIT inhibitors is variable. These inhibitors have been used in refractory tumors and could be, based on rare cases, used to stabilize the tumors. The sunitinib, imatinib, dasatinib and sorafenib have been reported in isolated cases as efficient in terms of stabilization and tumoral response not only in mutated thymic carcinomas but also in wild type tumors [14,29,39,49,85,92-94]. Prognostic factors are variable. Some authors reported that the male sex was a good prognostic factor [22]. This finding wasn't shared by other authors. In a study about 229 cases, Ruffini E et al. concluded to a bad prognosis in young patients [13]. 16 studies considered the histologic subtype as a prognostic factor with a better prognosis for low grade tumors including squamous cell carcinoma, mucoepidermoid carcinoma and basaloid carcinoma [4,6,9,10,18,27,41,42,46,48,50,57,59,62,75,76]. These tumors are characterized by a low tendency to recur and to metastasize [80]. Moreover, low grade tumors are more sensitive to chemotherapy and radiation therapy. These results were confirmed by Ogawa K et al. In a study containing 29 low grade tumors and 11 high grade tumors, they reported that the mean survival of low grade tumors was 29 months versus 11 months for high grade tumors [46]. Shim HS et al., reported in a study about 32 thymic carcinomas, that the prognosis was better in tumors with numerous CD4+, CD8+ and CD20+ stromal lymphocytes[38]. Other prognostic studies didn't prove the influence of the histologic subtype on the global survival, 5-year-survival or survival without progression [5,13,68]. The results concerning the prognostic impact of the tumoral stage are heterogeneous. 22 series considered that the localized tumors (stages I et II) present a favorable prognosis in comparison with advanced ones [8,10,12,13,15,16,18,21,22,28,31,36,40,42,43,45,56,59,61,62,67,76]. Lymph node metastases are considered as poor prognostic factors [8,31,67]. Nine studies reported that the staging wasn't a relevant prognostic factor [6,9,19,20,30,46,57,71,74]. These studies reported that the vascular invasion was a bad prognosis factor and that it needs to be integrated in the staging system [46,57,71]. The surgical resecability of thymic carcinomas has been reported in many studies [4-6,8,10,12,16,21- 24,26,28,30,31,36,37,42,44-48,52,54,56-59,62,63,66-68,72,74]. In a study about 290 patients, Weksler B, et al., reported that the surgical resection was correlated to a prolonged survival (105 months) in comparison with patients with unresectable tumors (29 months) [22]. The extension of the surgical resection has also been considered as a prognostic factor especially when associated to a lymph node curettage [8,23]. Adjuvant chemotherapy or radiation therapy have been also reported as a good prognostic factor related to the global survival and the survival without progression. [6,9,28,36,54,61,62,66,80].

Based on our literature review, the diagnosis of thymic carcinoma necessitates a multidisciplinary approach including clinicians, radiologists, pathologists and biologists. This is due to the absence of specific microscopic findings despite

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of the utility of some antibodies, especially CD5 and CD117 antibodies in the diagnosis of these tumors. We noticed that the information concerning the diagnostic delay between the biopsy and the issue of the pathology report weren't assessed so we can't have an idea about the diagnostic delay. Even if, the complete surgical resection represents the mainstay treatment, the advantages of the incomplete surgical resection still have to be proved. We noticed the variety of chemotherapy protocols used but noticed that in almost all cases, a platinum-based chemotherapy was used. The impact of targeted therapies wasn't assessed because of the rarity of the reported cases.

Conflict of Interest

The authors declare that they have no financial interest or conflict of interest exists.

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