Review of the literature about Thymic Carcinomas

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.

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 from 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.nlm.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).
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

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[33] Dee S-W, et al. 1 Chronic shoulder pain referred from thymic carcinoma: a case report and review of literature Neuropsychiatric Disease and Treatment 2012;8:399-403
[34] 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
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 170 mm. 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. An increase of \( \beta \)-HCG and \( \alpha \)-FP levels were reported normal in 5 cases. ACE level was assessed in 246 cases and showed cerebral metastases in 88 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%), mucopidermoid carcinoma in 32 cases (1.8%), sarcomatous carcinoma in 26 cases, basaloïd 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 I 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 210 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 tumor 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, histoprosoponosis 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, basaloïd carcinomas, lymphoepithelioma–like carcinomas, mucopidermoid carcinomas, adenosquamous carcinomas,
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 cyclophosphamid) 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 [10,12,21,45,47,50,52,56,59,63,6
8]. 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 Y535N, 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, mucopidermoid carcinoma and basaloïd 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 resectability 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
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.

References


87. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Thymomas and Thymic Carcinomas Version 1.2015


