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ORIGINAL ARTICLE

Thymic carcinomas: clinicopathologic study of 37 cases from a single institution

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Abstract Thymic carcinomas represent the rarest and the more aggressive form of thymic epithelial tumors. We retrospectively reviewed a series of 37 consecutive cases seen in our hospital over a 15-year period. The patient group consisted of 14 female and 23 male patients, aged 31 to 80 years (mean=57). Nineteen patients were smokers (mean 29 PY). Two nonsmokers had undergone radiotherapy for breast cancer, respectively, 9 and 15 years earlier. Twenty-four cases were squamous cell carcinomas (SCCs) expressing CD5 (90 %) and CD117 (87 %) and displaying a c-Kit mutation (n=3). Ten cases were atypical carcinoids, including four associated with MEN1 and three others with Cushing syndrome. Three cases were undifferentiated large cell carcinomas including one associated with a type A thymoma. Twenty-seven patients had undergone a total (n=25) or subtotal (n=2), often extended resection. The overall survival (OS) rate was 66.6 % at 36 months, and median OS was 94 months. Carcinoid tumors (P=0.007), surgical resection (P=0.009), and Masaoka–Koga stage II (P=0.049) were significantly associated with better OS. The TNM and three-grade staging systems were also significantly associated with survival but were not superior to the Masaoka–Koga system. Mediastinal lymph node recurrences treatable by reoperation and pulmonary metastases were the most frequent events in carcinoid tumors and SCCs, respectively. In conclusion, our case series suggests that smoking and radiation might constitute previously unrecognized risk factors. It confirms that SCCs express both CD5 and CD117 and possibly a c-Kit mutation. Lymph node dissection should be systematic when resection is performed, especially for carcinoid tumors.

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Introduction

Thymic carcinomas represent a small group of thymic epithelial tumors [1–3]. They differ clinically from the more common thymomas because they are not associated with myasthenia gravis nor with other autoimmune diseases [2], and their behavior is more aggressive with local invasiveness and frequent lymph node or hematogenous metastases [3, 4]. They also differ (a) histologically, because they are devoid of organotypic (thymus-like) architectural features, they exhibit cytological atypia, and there are several types that are akin to those seen in other organs [1–3]; (b) immunohistologically, due to the expression of markers such as CD5, CD117, or Bcl2, in the most common squamous cell type [5]; and (c) genetically, because of more frequent tumor-related genetic and molecular epigenetic abnormalities [6], including p53, p16, and MGMT alterations [5, 7, 8].

Rather scant data concerning thymic carcinomas mostly come from Far East countries where these tumors are not so rare [6]. The staging system is controversial [9–11]. We decided to undertake a review of a large series of cases operated on in our surgical center, in order to report our experience and try to better define the clinical setting, pathological features, and the behavior of these infrequent tumors.

Materials and methods

All surgically treated cases of thymic carcinoma, at Marie Lannelongue Surgical Center between February 1997 and January 2012 (15 years), were reviewed. The past history, signs and symptoms, clinical or pathological staging, the type of surgery, and follow-up data were obtained by reviewing patient hospital files including surgical and pathology reports. The tumor size was assessed using the surgical specimen or imaging for biopsy samples and post-chemotherapy resection specimens. The initial stage was established according to the Masaoka–Koga system [9]. The statistical significances of the unofficial TNM classification [1, 10] and of a recently proposed three-grade staging system [11] were also assessed.

Overall survival (OS) was calculated from the date of the histological diagnosis to the date of death (obtained from the death registries at the patients' native town halls) or the last follow-up examination. The Kaplan–Meier estimate limit method was used to plot OS curves. A univariate Cox model analysis was performed to test the prognostic influence of the histological subtype, surgical procedure, and the Masaoka, TNM, and three-grade staging systems. We considered the following groups: carcinoid vs. squamous cell carcinoma/undifferentiated carcinoma, surgical resection vs. biopsy alone, Masaoka stage II vs. III–IV, TNM stage II vs. III–IV, and three-grade system stage I vs. II–III. Median survival time was reported for each subgroup. In a multivariate analysis, the Cox proportional hazard regression model was used to determine the interest of combining univariate significant variables for prognostic modeling. Correlation between categorical variables was assessed using Fisher's exact test. All analyses were performed using the statistical R software package (http://www.r-project.org). P values <0.05 were considered statistically significant.

The histological slides were reviewed. One to 28 (mean=8.5±6.5) paraffin blocks containing tumor were available for each case including the primary lesion and possible metastases or recurrences. Following the current WHO histological classification [1], well-differentiated neuroendocrine carcinomas (carcinoids) were included in this series, whereas the so-called well-differentiated thymic carcinomas (type B3 thymomas) were excluded.

An immunohistochemical analysis was performed after microwave antigen retrieval and with the HRP/AEC Kit (Microm, Francheville, France) and the AEC Permanent Kit (Diagomics, Blagnac, France). The primary antibodies were directed against the following antigens: CD117 (c-Kit, polyclonal, Microm), CD5 (SP3 clone, Clinisciences, Nanterre, France), cytokeratins 5–6 (D5/16B4 clone, Microm), p63 (4A4 clone, Clinisciences), pankeratin (AE1–AE3, Microm), chromogranin (SP12 clone, Microm), synaptophysin (SP11 clone, Microm), and TTF1 (8G7G3/1 clone, Diagomics).

For the molecular analysis, DNA was extracted from sections of formalin-fixed, paraffin-embedded tissues. In each case, the histological examination of a close section showed that more than 30 % of the cells were tumor cells. Ten cases tested, dating from before 2005, had undergone post-fixation in Bouin's fixative. A mutation study of the c-Kit gene was performed by gene amplification with PCR and direct sequencing of exons 8, 9, 11, 13, and 17 (GenBank NM000222.2).

Results

Cases were classified according to histological type: there were 24 squamous cell carcinomas (SCCs), ten carcinoid tumors, and three undifferentiated carcinomas.

Clinical data There were 14 female and 23 male patients. Ages ranged from 31 to 80 years (mean=57.2±13.0). Twelve patients with SCC, four patients with a carcinoid tumor, and three patients with undifferentiated carcinoma

were smokers. The smoking habit was quantified in 13 of these 19 smokers and ranged from 6 to 50 pack-years (mean 29±15). One smoker patient, with thymic SCC, had both a history of bladder cancer without evidence of tumor progression and a synchronous T1N0 pulmonary adenocarcinoma. In two nonsmoker patients, thymic SCC had developed 9 and 15 years, respectively, after a breast cancer treated with radiotherapy. Four of the ten carcinoid tumors had arisen in the setting of MEN1 syndrome with a parathyroid adenoma (four out of four), a pancreatic tumor (three out of four), and adrenocortical and pituitary adenomas (one out of four). In three cases, the diagnosis of MEN1 syndrome was known for 7, 7, and 5 years, respectively; in one case, it was concomitant. One patient with thymic SCC had been treated for a medullary thyroid carcinoma 2 years earlier.

Seven cases were asymptomatic. Three carcinoid tumors (without MEN1 syndrome) were associated with Cushing syndrome. Otherwise, tumors were revealed by superior vena cava syndrome (n = 5), substantial weight loss (n = 4), or pain, cough, or dyspnea (n = 11). No patient had suffered from myasthenia gravis. Serum β-HCG and α-fetoprotein levels were normal in all cases. The serum carcinoembryonic antigen level was only slightly elevated in 2 out of 26 cases (5.4 and 7.2 ng/ml, N<5). The serum lactate dehydrogenase level was normal (n = 9).

The seven cases evaluated by positron emission tomography (PET) were positive. Standardized uptake values were 6.15, 7.3, 14.5, and 36, respectively, in 4 SCCs and 6.6 in a carcinoid tumor.

Surgical treatment Surgery had been performed after neoadjuvant chemotherapy in five cases. Twenty-four patients had undergone a resection of the primary mediastinal tumor in our institution. Tumors were Masaoka stage II (n = 6), stage III (n = 13), or stage IV (n = 5). Resections included the pericardium (n = 15), pulmonary tissue (n = 8), the vena cava (n = 4), phrenic nerve (n = 3), or sternal body (n = 1). The resection was complete (n=22) or subtotal because of invasion of both phrenic nerves (n = 1) or positive pericardial margins (n = 1). This resection was straightforward (n = 5), or after the histological diagnosis based on a needle biopsy specimen (n = 1), surgical biopsy specimen (n = 5), or frozen section analysis (n = 13). Two other cases (carcinoid tumors) had undergone a complete resection of a local recurrence after a prior resection performed in another center. The initial Masaoka stage was III in one case and had not been documented in the other. Eleven patients had only undergone a surgical biopsy of a stage III (n = 5) or stage IV (n = 4) unresectable tumor. Most patients had received adjuvant radiotherapy and chemotherapy. However, the effects of these treatments which had been performed in other centers and were not standardized could not be evaluated because of missing data.

Follow-up For the 35 patients with complete follow-up information, the OS rate was 85.2 % (95 % confidence interval, 74.0–98.1) at 12 months, 70.0 % (95 % confidence interval, 56.0–87.4) at 24 months, and 66.6 % (95 % confidence interval, 52.3–84.9) at 36 months. Median OS was 94 months.

The carcinoid subtype, a surgical resection, and Masaoka stage II were significantly correlated with better OS (Table 1). TNM stage II and stage I of the three-grade system were also significantly correlated with better OS (P = 0.049). However, the information provided by the TNM and three-grade systems were equivalent to that of the Masaoka staging system (kappa coefficient = 0.95). We considered a new variable (denoted in the following as "combined staging") that gathered the information on the Masaoka stage and the surgical procedure: group 1—Masaoka II and the surgical resection, group 2—Masaoka III–IV and the surgical resection, and group 3—Masaoka III–IV and the biopsy alone. This new variable was highly significantly associated with OS (P = 0.006). As expected, this variable was significantly correlated with the histological subtype (P = 0.013). In Fig. 1, we plotted the Kaplan–Meier curves according to the histological subtype, surgical procedure, Masaoka staging, and combined staging. For the multivariate analysis, we tested the prognostic impact of the histological subtype and combined staging. Combining the two variables did not increase the statistical significance of the model compared to the univariate models. In 11 patients with SCC, metastases to the lungs (n = 7), pleura (n = 2), extra-thoracic lymph nodes (n = 3), liver (n = 2) or bone (n=1),

Table 1 Univariate overall survival analysis

Histology	
Carcinoid: n=10	
Squamous cell carcinoma/undifferentiated: n=25	P=0.007
Surgery	
Surgical resection: n=26	
Biopsy only: n=9	P=0.009
Masaoka staging	
Stage II: n=6	
Stage III–IV: n=28	P=0.049
Surgery–Masaoka combined staging	
Group 1: n=6	
Group 2: n=19	
Group 3: n=9	P=0.005

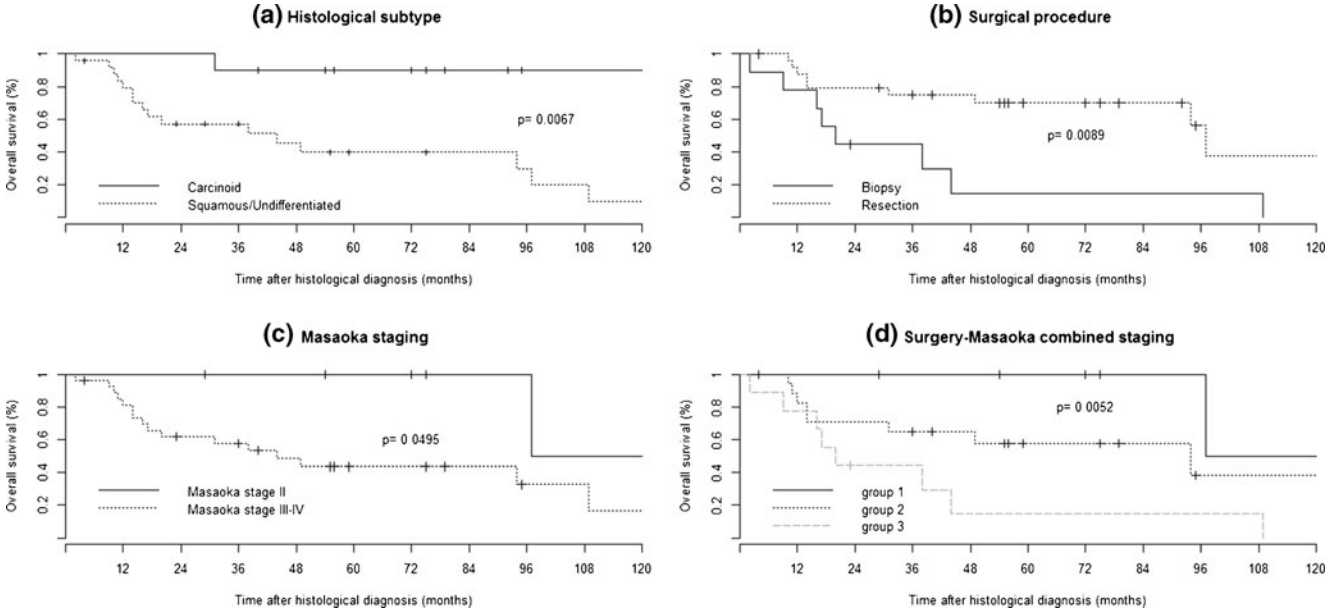

Fig. 1 Kaplan–Meier curves for thymic carcinomas, according to **a** the histological subtype, **b** the surgical procedure, **c** Masaoka staging, and **d** surgery–Masaoka combined staging (see text)

or local recurrences (n=4) had occurred at 0 to 48 (mean = 11) months after diagnosis.

All patients with carcinoid tumors had undergone a complete resection, two with initial lymph node metastases and one with a single pleural metastasis. Mediastinal lymph node recurrences, associated with pleural metastases (n = 2) or subclavian lymph node metastasis (n = 1), had developed in five patients at an interval of 1 to 7 year(s) (mean = 4). These recurrences had all been treated surgically with two reoperations in one case. Two other patients had an associated progressive pancreatic neuroendocrine tumor. The only patient who died at 31 months had initially presented with pleural metastasis and had developed pulmonary metastases at 10 months. The other nine patients were alive with a mean follow-up of 81.8±38.9 months.

The three patients with undifferentiated thymic carcinoma had died despite resection (n = 2), chemotherapy, and radiotherapy, with local progression (n = 1), pulmonary, liver and osseous metastases (n = 1), and pleural metastases (n = 1).

Pathology The largest tumor dimension ranged from 2.5 to 15 cm (mean = 7.5±3.4). On average, undifferentiated carcinomas were larger (mean size = 10.7 cm) than carcinoid tumors (mean = 7.3) and SCCs (mean = 7.1).

The 24 SCCs were subclassified into well- (n = 5), moderately (n = 9), or poorly (n = 10) differentiated lesions, which had no significant prognostic value. In two moderately differentiated cases, foci of squamous differentiation simulated Hassall's corpuscles (Fig. 2). The four post-chemotherapy cases were histologically progressive. Fibro-inflammatory stroma was a constant feature in all cases. Desmoplasia was present in two cases and myxoid transformation in one (Fig. 2). An immunohistochemical analysis showed that tumors expressed p63 (seven out of seven), keratins 5/6 (17/17 cases), CD5 (22/24 including four with only focal positivity), and CD117 (20/23). All tumors were positive for either CD5 or CD117 and the four focally positive cases with anti-CD5 were CD117 positive. Four out of nine cases were focally positive for synaptophysin but all were negative for chromogranin (11/11). Three cases showed deletions in exon 11 of the c-Kit gene. No mutation was observed in the 15 other cases in which DNA had been amplified.

The ten carcinoid tumors were all atypical carcinoids. Mitotic figures ranged from 4 to 8 per 10 HPF (mean 5.3± 1.4). Particular pathological features of the primary lesion were carcinomatous lymphangitis in the adjoining fat and thymus (four out of eight), subtotal encapsulation (three out of eight), a multi-nodular intrathymic tumor (three out of eight), necrosis over 50 % of the tumor volume (two out of eight), and a spindle cell tumor (one out of ten). All cases were positive for both chromogranin (ten out of ten) and synaptophysin (eight out of eight) and negative for both keratins 5/6 (four out of four) and CD5 (six out of six). Weak diffuse staining was observed with anti-CD117 antibody (five out of five).

The three undifferentiated carcinomas were large cell carcinomas without morphological signs of differentiation, in

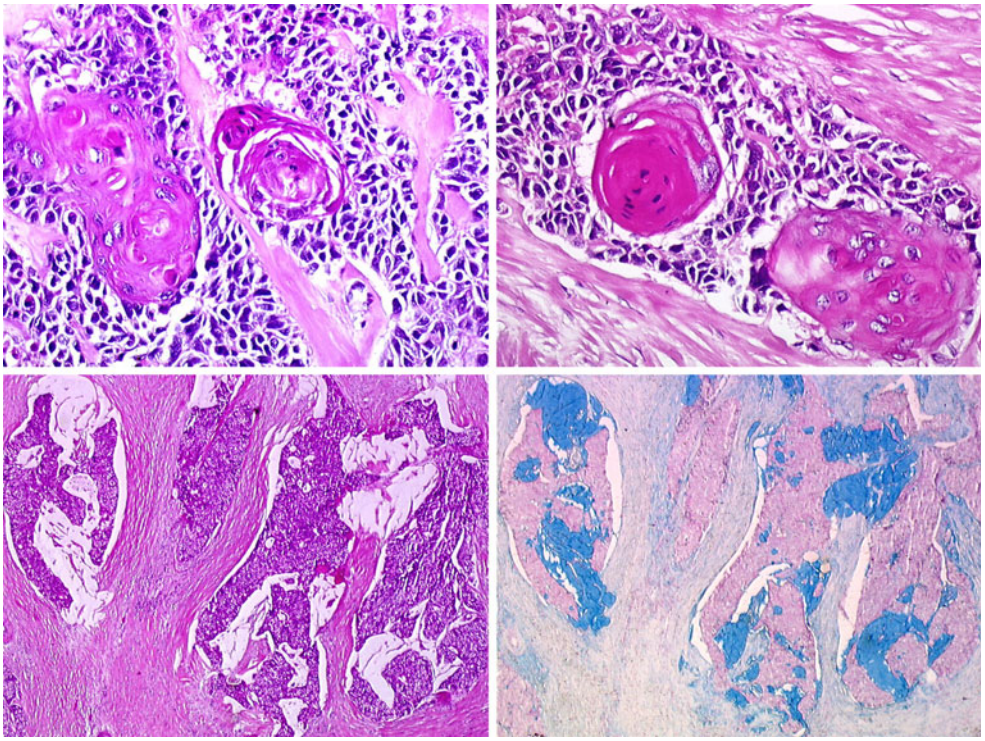

Fig. 2 Peculiar histological features in thymic SCC. *Top*: foci of keratinization resembling Hassal's corpuscles (hematein and eosin stain). *Bottom*: mucoid stromal transformation simulating glandular differentiation (*left*: hematein and eosin stain, *right*: alcian blue stain)

particular no neuroendocrine features. One case was associated with a type A (spindle cell) thymoma, without a transition area between the two components (Fig. 3). Undifferentiated carcinomas expressed pankeratin (three out of three), CD117 (one out of three), synaptophysin (one out of three), and the three lesions were negative for chromogranin, keratins 5–6, p63, TTF1 and CD5.

Discussion

The risk factors for thymic carcinoma are not well established. Thymic carcinoid tumors occurring in a MEN1 setting, as in 40 % of our cases, are well recognized [12]. The fact that some thymic carcinomas, as in one of our cases, exhibit histological features of both thymoma and thymic

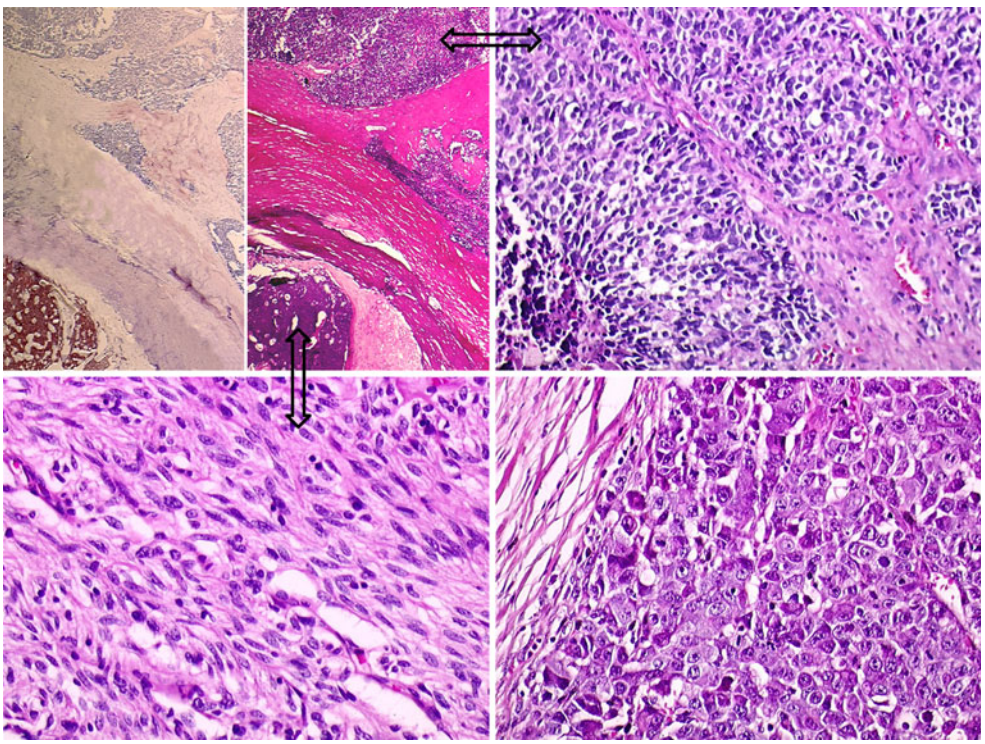

Fig. 3 Histological appearance of thymic undifferentiated large cell carcinomas. Case associated with a type A thymoma. *Top left*: low magnification with hematein and eosin (HE) staining showing a thymoma component separated from carcinoma by a calcified fibrous septa, and immunostaining of keratins 5 and 6 restricted to the thymoma component, on adjoining sections. *Top right* and *bottom left*: high magnification of carcinoma and thymoma components, respectively (HE). *Bottom right*: appearance of another case, a progressive lesion after neoadjuvant chemotherapy (HE)

carcinoma [13] suggest that thymic carcinomas might arise at least in part through transformation of an existing less aggressive and more differentiated tumor. Increased p53 expression and a change in CD5 expression were associated with such malignant transformation [13]. Thymic lymphoepithelioma-like carcinoma may be related to Epstein–Barr virus infection [1]. At least 19 of our 37 patients (51.4 %) were smokers, whereas the prevalence of smokers was 33.7 % in the 15–75-year-old French population in 2010 [14]. Radiotherapy (in two of our cases) and smoking might be risk factors not identified previously.

SCC is by far the most frequent type of thymic carcinoma, especially in a series with no referral bias for rare subtypes [15–17]. Well-differentiated neuroendocrine carcinomas (carcinoids) also represent a major subgroup in most series [17–20]. Thymic carcinoid tumors are far more aggressive than their pulmonary or intestinal counterparts [12], possibly because most of them are atypical, as in our series. They often occur in a MEN1 setting or produce adrenocoticotropic hormone leading to Cushing syndrome [12]. The carcinoid syndrome has only been reported in two cases [19]. Multiple intrathymic carcinoid tumors, as in three of our cases, have only been rarely reported [21]. However, such lesions highlight the need for a thymectomy with complete removal of the thymus.

Histological grading of thymic carcinomas according to differentiation may have prognostic value [17]. In a series of 40 cases, patients with low-grade histology had a median survival time of 25 to 49 months, compared to 11 to 18 months in patients with high-grade types [22].

The histological differential diagnosis between thymic SCC and thymoma, especially B3 thymoma, may prove to be difficult. Although B3 thymomas are more aggressive than other thymomas, they differ from SCC because they are frequently associated with myasthenia gravis and have a propensity for pleural dissemination rather than lymphatic or hematogenous metastases [1, 2]. In our experience, the recognition of a fibro-inflammatory stroma, which is different from the fibrous lobulation of thymomas, is very helpful for the diagnosis of SCC. Immunohistochemical staining of TdT-positive immature T lymphocytes, which are present in B3 thymomas and absent in SCC, is useful [1, 3]. CD5 and CD117 expressions are also useful for differentiating thymic carcinomas from both thymomas and pulmonary SCCs: 80 % [23], 86 % [24], 87 % (current series), or 100 % [25] of thymic carcinomas are CD117 (c-Kit) positive, whereas thymomas are negative [23–25] and only 9 % of pulmonary SCCs are focally positive for CD117 [26]. Our series confirms that in spite of frequent CD117 expression, c-Kit mutations are rare in thymic SCCs [24, 25, 27]. However, such mutations may have therapeutic implications [6, 28]. In our study, the three c-Kit mutations were diagnosed retrospectively, and our patients did not benefit from specific targeted therapy. Seventy percent of thymic carcinomas are CD5 positive [23], whereas pulmonary carcinomas are usually negative [23]. CD5 expression has been reported in two cases of lymphoepithelioma-like thymic carcinoma [18]. In a series of 37 thymic carcinomas, CD5 and CD117 expression was strictly restricted to the 11 tumors of the squamous cell type [25]. MUC1 expression, reported in thymic carcinoma and not in type B3 thymoma, may also be useful [29]. Stronger expression of glucose transporter 1 in thymic carcinomas has been correlated with the ^{18}fluoro-desoxy-glusose PET signal [30]. The mucoid stromal transformation that we observed in one SCC should not be confused with glandular differentiation. Such a lesion has previously been described in thymic carcinoids [31].

Thymic carcinomas carry a rather poor prognosis, but the range of reported OS rates at 5 years in the largest series is wide: 14.5 % [18], 27.5 % [19], 38 % [22], 38.8 % [20], 47.5 % [16], 53 % [4], and 61.5 % [17]. Surgical resection remains the treatment of choice [15]. Tumor resectability was identified as the only prognostic factor in a series of 30 patients [16]. In another series of 38 cases, median survival times after complete resection, debulking, or biopsy were 35, 25 and 17.4 months, respectively [19]. In the same report, neither radiotherapy nor chemotherapy benefited the patients. In our series, the effects of adjuvant therapies could not be evaluated. In a series of 40 cases, 12 of 16 patients who underwent complete resection were alive and free of disease with a follow-up of 44–193 months, compared with only 1 of the 24 patients treated with incomplete resection [22]. In a series of 60 patients, the 5-year survival rate was 85.1 % after a complete resection and was significantly better than after an incomplete resection (29.0 %) or with nonsurgical treatment (16.7 %) [20]. Our series confirms the importance of complete resection, which often has to be extended to adjacent structures. The Masaoka stage has also been established as a prognostic factor [17, 20]. In our series, we could not confirm better statistical significance neither for the TNM classification [1] nor for the recently proposed three-stage system [11]. This might be related to the small number of patients in our series. The value of these classifications has been assessed in a large series of thymic epithelial tumors with only a low proportion of carcinomas [10] or in a series of carcinomas excluding both carcinoid tumors and only biopsied cases [11]. We observed frequent peri-tumor carcinomatous lymphangitis in carcinoid tumors and frequent mediastinal lymph node metastases, either initially or occurring after resection. This suggests that mediastinal lymph node dissection should as a rule be performed in the surgical treatment of these carcinoid tumors.

In conclusion, our case series suggests that smoking and radiation might constitute previously unrecognized risk factors. It confirms that SCCs express both CD5 and CD117

and possibly a c-Kit mutation. Lymph node dissection should be systematic when resection is performed, especially for carcinoid tumors.

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