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Outcome of surgically resected thymic carcinoma: A multicenter experience☆

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ABSTRACT

Objective: Thymic carcinoma (TC) is a rare and invasive mediastinal tumor, with poor prognosis. Most of the previous published papers are single-institution based, reporting small series of patient, sometimes including palliative resection. This study collected patients with TC treated in 5 high-volume Italian Thoracic Surgery Institutions.
Methods: A multicenter retrospective study of patients operated for TC between 2000 and 2011 was conducted. Exclusion criteria were: Neuroendocrine thymic neoplasms, debulking/palliative resection and tumor biopsy. Cause specific survival (CSS) was the primary endpoint.
Results: Four hundred and seventy-eight patients underwent surgery for thymic malignancies: 40 of them (8.4%) had TC. Eleven (27.5%) received induction chemotherapy because of their radiological invasiveness. A complete resection (R0) was achieved in 36 (90%; 9/11 submitted to induction chemotherapy). Adjuvant radio/chemotherapy was offered to 37 patients, according to the type of surgical resection and tumor invasiveness. Three, 5 and 10-year survival rates were 79%, 75% and 58%. Recurrences developed in 10 patients. R0 resection ($p < 0.0003$) and absence of tumor recurrences ($p = 0.03$) resulted significant prognostic factors at univariate analysis. Independent CSS predictor was the achievement of a complete resection ($p < 0.05$).
Conclusions: TC is a rare and invasive mediastinal tumor. A multimodal approach is indicated especially in TC invasive forms. The achievement of a complete surgical resection is fundamental to improve survival.

1. Introduction

Thymic Epithelial Neoplasms (TENs) are rare: they account for 50% of all anterior mediastinal masses and are the most frequent mediastinal tumors in adults, with an incidence of 0.05 per 100.000 person/years [1,2]. A small TENs percentage (less than 10%) is represented by thymic carcinomas (TCs), characterized by cytologic atypia, margin invasion, loss of organo-typical aspects and usually, locally advanced disease or distant metastases. Their long-term survival is significantly lower if compared to Thymomas, with 5-year survival rates ranging from 28% to 60% [3,4].

The rarity of these tumors limited the disposal of studies concerning their outcome. These studies usually concern retrospective series, which cover very long-term periods, reporting a limited number of patients or including both resected and unresected tumors.

This is a retrospective multicentre study, conducted in a relative short period of observation amongst 5 high-volume Italian Thoracic

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Surgery Institutions, with the aim to delineate predictors of survival and tumor recurrence development.

2. Materials and methods

This is a multicentre retrospective study of patients operated for TC between 2000 and 2011 in 5 different high-volume Italian Thoracic Surgery Institutions. Data were obtained from hospital records, outpatient controls or telephone interviews.

In this period, 478 interventions for TENs were performed: 438 Thymomas and 40 (8.4%) TCs. Exclusion criteria were: (1) debulking/palliative surgery; (2) inoperable tumors or those submitted to biopsy, only; and (3) Thymic Neuroendocrine Tumors (4 cases).

Preoperative standard workup included routine preoperative blood tests, electrocardiography (EKG), ecocardiography if required (the case of invasive lesions, or high risk patients), pulmonary function tests with diffusion capacity (diffusion lung capacity for carbon monoxide, DLCO) and arterial blood gas analysis, total body computed tomography (CT). Magnetic resonance (MR) and Positron Emission Tomography (PET) scan were not routinely performed in every center.

Tumor histological diagnosis was achieved through surgical biopsy by an anterior mediastinotomy or thoracoscopy or, in selected cases, through transthoracic biopsy under ultrasound guidance.

Complete sternotomy was the standard surgical approach. Lateral thoracotomy or other combined incisions have seldom been performed when required by the clinical presentation of the tumor.

Outcome measures were analyzed according to the International Thymic Malignancy Interest Group (ITMIG) guidelines [5].

Surgery was considered radical if a complete tumor resection (R0) was achieved, whilst in case of micro-macroscopic residuals (R1–R2), the resection was considered incomplete.

Tumor recurrences were calculated only in case of R0 resection.

Histology was assessed according to the 2004 World Health Organization (WHO) classification [6] and staging was postoperatively determined according to the Masaoka-Koga classification system [7].

Tumor treatment was decided according to its clinical/radiological presentation:

1. When the lesion was judged resectable with a curative intent, upfront surgery was offered.
2. Preoperative platinum-based chemotherapy (CT) was uniformly administered in case of anticipated tumor unresectability.
3. Postoperative radiotherapy (RT) and/or CT were administered to patients presenting with invasive lesion, accordingly to the oncological policy of each institution.

The response to induction treatment was recorded as partial response (PR), stable disease (SD) or progression of disease (PD) according to the RECIST (Response Evaluation Criteria in Solid Tumors) criteria.

The follow-up protocol was quite similar in all the Institutions: CT scan every 6 months for the first 3 years, on a year basis or on clinical demand afterwards.

2.1. Pathological characterization

All histological specimens have been evaluated by high experience in thymic malignancies Pathologists. Histological diagnostic protocol contemplates a mean of 1 formalin-fixed paraffin-embedded (FFPE) block per cm/tumor size. FFPE blocks were stained with hematoxylin and eosin (H&E) for morphological evaluation.

2.2. Statistical analysis

ITMIG survival measures [5] were considered.

Primary endpoint was cause specific survival (CSS) calculated from date of intervention to the date specific TC death.

Secondary endpoint was freedom from recurrence (FFR).

The association between clinical/pathological variables and incomplete resections was also analyzed.

Continuous data are presented as mean (standard deviation, StD) and categorical data as number (percentage, %).

Cumulative survival rates were estimated by the Kaplan–Meier method. Cumulative incidence of recurrence (CIR) was calculated by the Nelson–Aalen estimator.

Competing-risks regression models (Fine and Gray method), taking into account death by any causes as competing event, were used to identify the association between individual factors and CSS or FFR. Univariate and multivariate analyses were performed.

We considered the following variables: age, gender, presence of Myasthenia Gravis, Masaoka-Koga stage (Stage II as reference), tumor size (expressed in cm), administration of induction therapy, microscopic vs. macroscopic tumor invasiveness, tumor resection status (R0 as reference) and presence of recurrences. For Multivariate analysis we considered variables with a p value equal or less than 0.1 at univariate models.

Logistic regression (logit) model was used to calculate odds ratio (OR) of having an incomplete resection, according to variables of interest.

Odds ratio (OR), hazard ratios (HR) and corresponding 95% confidence intervals (95%CI) were provided for each model. A p value less than 0.05 was considered significant.

All the statistical analyses were performed using STATA (version 12.1, StataCorp LP, Texas, USA).

3. Results

3.1. Patients

Four hundred and seventy-eight patients received a surgical resection for a TEN between January 2000 and December 2011 at the above-mentioned Italian Centers. TC patients' characteristics are summarized in Table 1.

Amongst TCs, Squamous Cell Carcinoma (SCC) was the commonest histologic subtype (31 cases, 77.5%), followed by Sarcomatoid Carcinoma [2], Lymphoepithelioma-like Carcinoma [1] and Mucoepidermoid Carcinoma [1]. In 5 cases (12.5%), a generic histological diagnosis of Carcinoma, without any other sub-classification was achieved.

Myasthenia Gravis (MG) was clinically observed in 13 cases (32.5%; 9 SCCs, 1 sarcomatoid carcinoma and 3 not otherwise specified carcinomas). In all these patients, a definitive TC diagnosis was confirmed on the basis of above mentioned immunohistochemical studies.

Data concerning MG grading, according to the Myasthenia Gravis Foundation of America (MGFA) system, were available in 11 cases (85%): 2 grade II and 9 grade III. A satisfactory clinical disease control was always achieved before surgery.

3.2. Treatment protocol

Induction platinum-based chemotherapy was administered in 11 patients (27.5%). The decision to administer preoperative chemotherapy was done accordingly to the clinical tumor presentation, its possible loco-regional invasiveness and to the oncologic policy of each Institution. Ten patients receiving induction therapy had a preoperative surgical biopsy (5 anterior mediastinotomies