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Oncology

Thymic malignancies: Prognostic factors, multimodal management and the role of postoperative radiotherapy

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ABSTRACT

Purpose: Thymomas and thymic carcinomas are rare malignant neoplasms and behave variably in clinics. In this retrospective observational study, our primary study aim was to determine prognostic factors in thymomas and thymic carcinoma patients and the impact of postoperative radiotherapy (PORT).

Methods: All 121 patients with thymoma or thymic carcinoma in Sun Yat-sen University Cancer Center between 2001 and 2014 were performed a retrospective analysis.

Results: Five-year os for stages I, II, III, and IV was 94.4%, 90.0%, 60.0%, 43.5% and ten-year os was 83.3%, 81.8%, 41.6%, and 11.2%, respectively. Patients with thymoma had a better survival compared with thymic carcinoma (5-year os: 76.0% vs 42.3%). For patients with locally advanced disease (stages III and IVA), the 5-year os (77.1% vs. 60.0%) and 10-year os (56.9% vs 0%) were both significantly improved by adding PORT. While in Masaoka Stage II, no benefit was noted for PORT.

Conclusions: Masaoka–Koga stage and WHO type were both important prognostic factors. The ideal management for thymomas and thymic carcinomas requires a multidisciplinary regimen with postoperative radiotherapy in locally advanced disease. Radiation toxicity was mild in most patients and no severe toxicity was registered.

KEYWORDS : thymomas; thymic carcinomas; prognostic; multimodal management; postoperative radiotherapy; toxicity.

INTRODUCTION:

Thymomas and thymic carcinomas are rare intrathoracic tumors of thymic epithelial origin[1], with an overall incidence of 0.39 per 100,000 person-years in China (based on the Chinese Alliance of Research database, ChART, 2016) and 0.21 per 100,000 person-years in USA (based on Surveillance, Epidemiology and End Results database, SEER, 2016).

Although thymomas and thymic carcinomas are the most common tumors in the anterior mediastinum in adults[2], the rare incidence, the heterogeneity of subtypes and the different practices for diagnosis, therapy, and follow-up have made the treatment guidelines lack of strong evidence[3]. At present, the Masaoka–Koga Stage system widely used is based on the data of less than 100 cases from one single institution in 1981[4].The pathologic staging system proposed by the World Health Organization (WHO) in 1995 has since been widely accepted[5]. However, there still exists a considerable debate on the Masaoka–Koga Stage and WHO Histological Subtype system until now.

Surgical resection is the mainstay of treatment for thymoma[6]. Most treatment regimens should be based on retrospective results. Local control advantage of postoperative RT for thymoma have been shown in some studies[7, 8]. Postoperative RT has so far found no benefit in Masaoka Stage I [9, 10]. In stage II, there was no conclusive advantage of adjuvant RT[11, 12]. In stage III and IVA, postoperative RT has a well-established role in clinics, although the evidence so far is low. The most recent trials failed to show any significant advantage [9, 13, 14]

Since thymic malignancies are insert, and the survival of patients can be relatively long even after progression, a long follow-up time (more than 10 years) is recommended to retrieve patients' overall survival [15]. Although in the last few decades there has been an increased interest in thymic malignancies[16], a retrospective observational study with long follow-up time is infrequent.

Our study aims to detail the prognostic significance of tumor classification, stage, MG and mode of treatment. We have analyzed the treatment and outcome of 121 patients with thymoma or thymic carcinoma at a single department Sun Yat-sen University Cancer Center from 2001 to 2014.

PATIENTS AND METHODS:

Patient Selection:

In this retrospective observational study, we have analyzed 121 patients received treatment for thymoma or thymic carcinoma at Sun Yat-sen University Cancer Center from January 4, 2001 to May 23, 2014, and all of the patient history was complete and analyzed. Chart review was performed to obtain demographic and treatment data. This study was approved by the Ethics Committee of Cancer Center of Sun

Yat-sen University.

All patients received thoracotomy, followed either by incomplete resection (n =88) or biopsy only (n = 33). ⅢI(n=10), ⅣIa (n= 9) underwent several cycles(ranged from 1 to 7) postoperative chemotherapy, which included cisplatin (60mg/m^2 on day 1) adriamycin (30mg/m^2 on day 1), cyclophosphamide (500mg/m^2 on day 1) , repeated every 3 weeks and then received postoperative radiotherapy . Postoperative radiotherapy was administered with Megavoltage photon(6-8MVor cobalt-60) . The mediastinal irradiation fields were classified into two patterns: 18patients were treated with involved field irradiation that covered the primary tumor bed with margin of about 1–2 cm margin. Patients were treated with parallel opposed anteroposterior fields with the spinal cord dose limited to 40--44 Gy in all patients . Lateral or off-cord oblique fields were used to boost the mediastinum to higher doses. The total dose ranged from 48 to 68 Gy , administered in 1.8 to 2.0 Gy of daily dose fractions, 5 fractions a week . The 31 patients underwent computed tomography (CT) and a three-dimensional treatment plan simulation. In all patients, the clinical target volume encompassed the entire mediastinal space in which the tumor was located. Elective nodal irradiation was not performed. The planning target volume was calculated by adding a margin to the clinical target volume that ranged from 0.5 to 1 cm. The total dose delivered varied from a minimum of 44 Gy to a maximum of 68 Gy, according to stage and margin status. The dose fraction was either 2.0 or 1.8 Gy per day.

Statistical methods:
SPSS20.0 (SPSS Inc, Chicago, IL) was applied for all statistical analysis. Differences between variables were analyzed with the x^2 test. The overall Survival and disease-free survival(DFS) rates were determined by Kaplan-Meier method. Differences in categorical variables between the groups (sex, gender, pathology, margin status, stage of disease, performance of surgery, myasthenia gravis at presentation, dose of radiation and radiochemotherapy) were analyzed by Log-rank test. multivariate analysis was applied according to Cox regression hazards model. In this study, a *p* value less than 0.05 was considered significant in all comparisons.

Follow-up:
A CT scan was performed before and after surgery, and 60 days after completion of adjuvant radiotherapy. In addition, follow-up was performed with periodic clinical visits consisting of anamnesis, physical examination, and a CT scan. Follow-up visits were at 6-monthly intervals during the first 2 years following the end of radiotherapy. After 2 years, follow-up was yearly.

Disease-free survival was calculated starting from the end of radiotherapy through to recurrence or death. Overall survival was considered as the time elapsing from the end of radiotherapy to patient death. In the absence of either recurrence or death, patients were censored to the date of the last follow-up visit. Acute toxicity was determined by analyzing the side effects occurring within 3 months from the beginning of radiotherapy. Late toxicity was determined by evaluating the side effects occurring after 3 months from the beginning of radiotherapy.

Pathology and Staging Review:
Stage was identified according to the Masaoka–Koga system. The histological information was retrieved from the original pathology report done by World Health Organization (WHO): types A, AB, B1, B2, B3, and C (thymic carcinoma).

RESULTS:
WHO Histological Subtype and Masaoka–Koga Stage
The 121 Patients presented with WHO types: A(4.96%), AB (10.7%), B1 (11.6%), B2 (25.6%), B3 (16.5%), C(30.6%) .The Masaoka stages were found: stage I (17.4%), stage II (16.5%), stage III (50.5%), and stage IV (35.5%).

Majority of WHO type A thymomas showed stage III and IV(66.7%). Most AB thymomas were in stages I (53.8%) and II (23.1%), while only three AB thymoma cases were found in stage III and IV. The type B1 thymomas showed similar numbers in stage I (21.4%), II(21.4%), III(28.6%) and IV(35.7%). More than half cases were found in III and IV in WHO type B2 (64.5%) and B3(65%). Nearly all thymic carcinomas (WHO type C) were invasive, with only one case presenting in clinical stage I.

Myasthenia Gravis:
MG was presented in 17 patients (14.0%). Survival curve showed no significant difference in patients with MG and those without MG (Fig.1). Myasthenia gravis was observed more often in female patients (17.8%, 8 of 45) than in male (12%, 9 of 55). Most MG occurs in patients of WHO type B (15 of 17). The highest frequency was in WHO type B2 (32.3%), followed by WHO type B3 (14.3%) and WHO type B1 (21.4%). There was one case with MG in WHO type AB and C (thymic carcinoma), respectively. The frequency of MG in Masaoka–Koga stages were: stage II (26.7%) and stages III (26.0%), followed by stage IV (14.3%), and then in stage I (10%).

Survival Analysis:
The median follow-up time for overall survival was 100 months. Five-year overall survival was 65.4% and ten-year overall survival was 45.3%. About 90% of all patients were alive at 30 months, 80% of patients alive at 47 months, and 70% of patients alive at 54 months (Fig.2A).

Survival by Masaoka–Koga Stage:
Survival by Masaoka–Koga Stage was showed in Fig.2B, Five-year survival for stages I, II,III, and IV was 94.4%, 90.0%, 60.0%, and 43.5%, respectively. Ten-year survival for stages I, II, III, and IV was 83.3%, 81.8%, 41.6%, and 11.2%, respectively. About 90% of patients in stages I were alive at 96 months. In stage II, 90% of patients were alive at 88 months. In stage III, there was 90% survival at 28months and in stage IV, there was 90% survival at 20 months.

Survival by WHO type:
Survival varied significantly among patients with thymoma (WHO class A, B1, B2, B3, and AB) compared with thymic carcinoma as illustrated in Fig.2C. The median follow-up time in patients with thymoma was 130 months compared with 55 months for thymic carcinoma, five-year os was 76.0% vs 42.3% and 10-year os was 55.5% vs 24.5%.Survival data according to WHO type was also calculated (Fig.2D and Table 1). Patients with higher histological type have shorter five-year survival and ten-year survival.

Multimodal Therapy:
About 38.0% patients received multimodal therapy, consisting of surgery with neoadjuvant or adjuvant chemotherapy and/or postoperative radiotherapy. The rest (62.0%) were treated with surgery alone. Fig.3 shows the frequency of multimodal therapy used by Masaoka–Koga stage. Multimodal therapy was more frequently used in higher Masaoka–Koga stages by the Pearson $\chi 2$ test ($p < 0.001$).

With surgical therapy alone, the five-year-survival was 77.0% and ten-year-survival was 0%. Patient survival with multimodal therapy was 81.4% at five years and 22.0% at ten years. However, the overall survival of patients with multimodal therapy failed to show significant difference compared with patients received lone surgical therapy (Fig.4).

Postoperative Radiation of Early-Stage Disease:
Our study included 21 patients with stage I and 20 patients with stage II disease. Most patients of stage I (n=15) were treated with surgery alone, five patients had postoperative radiation and one had neoadjuvant chemotherapy.

In patients with stage II disease, 50% of patients received postoperative radiation therapy (n=10). The dose of PORT were 40 Gy to 64Gy, in 1.8 to 2 Gy fractions. There was no difference in the overall survival of stage II patients receiving and not receiving postoperative radiotherapy(Fig.5).

Postoperative Radiation of Locally Advanced-Stage Disease:
In this study, we specifically analyzed management in locally advanced-stage disease, included 37 patients of stage III and 10 patients of stage IVA. More than half of the patients (68.1%, n=32) received upfront surgery, and most received adjuvant therapy consist of postoperative radiation, chemotherapy or trimodality treatment (including surgery, chemotherapy, and thoracic irradiation). In this multimodal therapy group, 19 patients (76.0%) received PORT. The other non-opearable patients(n=15) received neoadjuvant therapy, 3 patients underwent surgery followed by postoperative radiation. The dose of PORT were 40 Gy to 64Gy, in 1.8 to 2 Gy fractions.

To analysis the role of postoperative radiation therapy in the treatment

of locally advanced-stage disease, we compared the difference in the overall survival, and found a significant difference in patients receiving and not receiving postoperative radiotherapy(P<0.05,Fig.6). The median survival, five-year survival and ten-year survival for patients receiving postoperative radiotherapy are respectively 130 months,77.1% and 56.9%, while the median survival, five-year survival and ten-year survival for others not receiving postoperative radiotherapy are 100 months, 60.0 % and 0%, respectively.

Toxicity Related to Radiotherapy:

All toxicities related to radiotherapy for thymic malignancies were reported according to the guideline (CTCV4.0). The rate of grade 1 toxicity for radiation esophagitis, pneumonitis, and cardiac toxicities were 49.0%, 27.3% and 10.9%, respectively. The rate of grade 2 toxicities were 21.8%, 16.4% and 1.8%, respectively. No severer toxicity was registered.

Chemotherapy:

Chemotherapy was used in 57% (n=69) of the patients. CAP regimen (Cyclophosphamide-cisplatin-doxorubacin) was used in 87% of patients（n=60）. TP (Paclitaxel-cisplatin) and DDP regimens were used occasionally.

Discussion:

This series sought to investigate the clinical behavior and management of thymomas and thymic carcinoma patients at our department from 2001 to 2014. Our outcomes for thymic malignancies according to stage were similar to that of some previous large, reported, institutional studies[, ,] .and have highlighted the significance of postoperative radiation therapy in multimodal therapy for advanced-stage disease.

All patients' data were analyzed for this study and outcome measures used in this literature are suggested by global efforts, such as the ChART and the ITMIG [,]. In addition to median survival, five-year survival and ten-year survival are also shown.

Masaoka–Koga stage and WHO histological type are most widely accepted for thymomas and thymic carcinomas []. In our study, higher clinlical stage and higher histological type both show poorer survival. These findings corroborates prognostic significance of Masaoka–Koga stage and WHO histological type.

A unique feature of thymic malignancies is that they often have autoimmune complications, especially myasthenia gravis (MG) with a incidence of 22.8% (based on ChART). More than 90% of the MG happen in patients with type B disease. MG has been found not to be a significant predictor for either survival or recurrence[]. Consistent with previous studies, our study dosen't show corresponding between MG and overval survival.

Surgical resection is the principal treatment of thymic malignancies and the completeness of resection have been validated to be the prognostic factor for both survival and recurrence[]. Thymic malignancies have a tendency to local recurrence, thus a multidisciplinary team approach for management is recommended. Our data supports a multimodal therapy, similar to previously published studies [,]. Thymic malignancies show moderate-high radiosensitivity profiles. This has always been considered a prerequisite for the adoption of RT in the whole treatment strategy. RT may be delivered before surgery, after surgery, and as exclusive treatment in patients not eligible to surgical intervention or for treatment of recurrent tumors[,].

In this series, we found that postoperative RT with surgery in stage III and IVA thymic malignancies resulted in significantly better survival(log-rank test: $p < 0.05$) than those without postoperative RT, which have vertified that postoperative RT be a significant prognostic factor for management of locally advanced-stage patients(stage III and IVA). Postoperative RT should have a well-established role in the whole treatment strategy. Further researches are needed for the adoption of PORT in thymic malignancies to produce evidence-based guideline.

In a word, we conduct a retrospective observational study that underlines many controversial issues in treating thymic malignancies, where evidence-based information is still limited. Although advances in surgical techniques, radiation planning and multimodal treatment have been put into use in clinicians for thymic malignancies, global efforts and and collaborative are needed and are underway to further produce evidence-based guidelines. The earlier-mentioned ITMIG and ChART database provide platforms to promote researches that will undoubtedly help fulfiled understanding of diagnosis and therapy for thymic malignancies, and ultimately lead to better prognosis for these patients.

LEGENDS:

Table 1: Overall Survival according to WHO Type.
Figure 1: Survival of patients with MG and without MG.
Figure 2: Survival in patients with thymoma and thymic carcinoma**.**
A) Overall survival. Kaplan–Meier curve.
B)Survival according to Masaoka–Koga stage.
C) Comparison of patients with thymoma and thymic carcinoma.
D) Survival according to WHO type.
Figure 3: The application of multimodal therapy in different Masaoka–Koga stages.
Figure 4: Survival of multimodal therapy and surgical treatment alone.
Figure 5: Survival of stage II patients receiving and not receiving postoperative radiotherapy.
Figure 6: Comparison of survival of Locally advanced patients receiced postoperative radiation therapy or not.

Table 1: Overall Survival according to WHO Type

WHO type	N	%	5-y os	10-y os
A	6	5.0	100	100
AB	13	10.7	92.3	76.9
B1	14	11.6	69.8	59.9
B2	31	25.6	77.1	67.5
B3	20	16.5	69.6	26.1
C	37	30.6	42.3	24.5

5-y os: five-year overall survival; 10-y os: ten-year overall survival.

Figure 1:

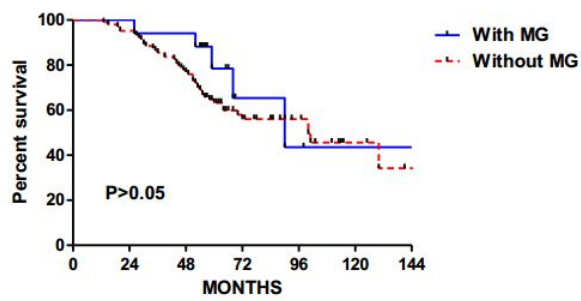


Figure 2:

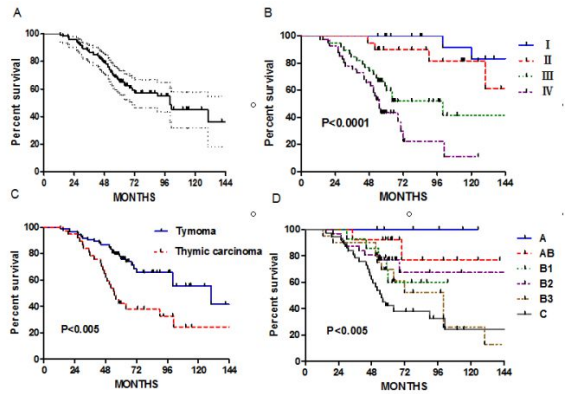


Figure 3:

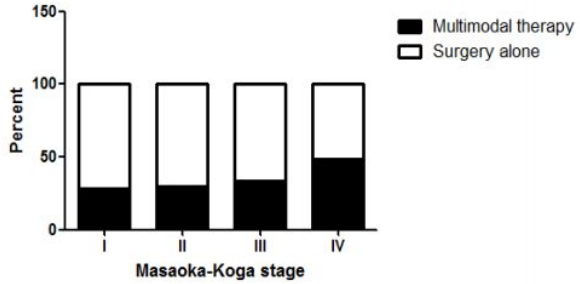
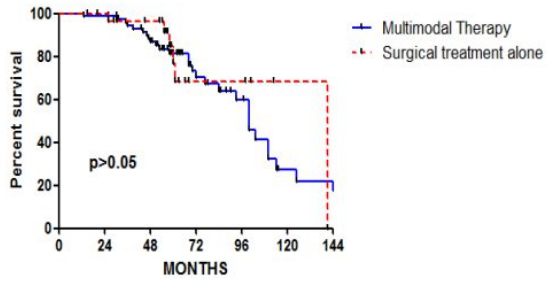


Figure 4:



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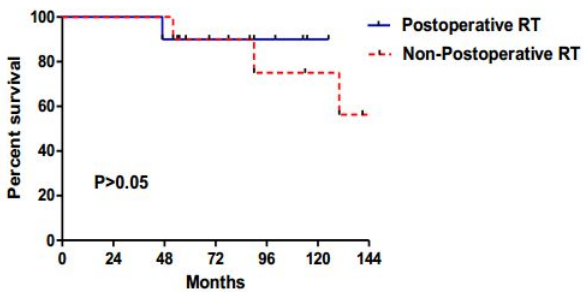
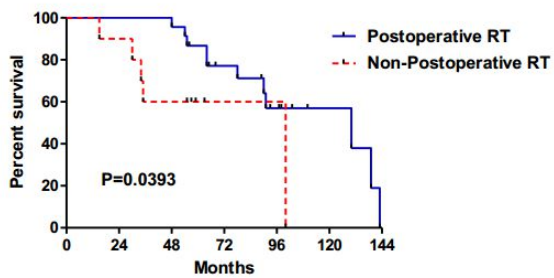


Figure 6:



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