Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.elsevier.com/locate/rpor

Original research article

# Thymic tumors and results of radiotherapy☆

Sureyya Sarıhan[a,*], Ahmet Sami Bayram[b], Cengiz Gebitekin[b], Omer Yerci[c], Deniz Sıgırlı[d]

[a] Department of Radiation Oncology, Uludag University, Faculty of Medicine, Bursa, Turkey
[b] Department of Thoracic Surgery, Uludag University, Faculty of Medicine, Bursa, Turkey
[c] Department of Pathology, Uludag University, Faculty of Medicine, Bursa, Turkey
[d] Department of Biostatistics, Uludag University, Faculty of Medicine, Bursa, Turkey

ARTICLE INFO

*Article history:*
Received 23 April 2017
Received in revised form
4 October 2017
Accepted 11 December 2017
Available online 12 February 2018

ABSTRACT

*Aim:* The aim of this study was to evaluate thymic epithelial tumors (TETs) for treatment outcomes and prognostic factors on survival.

*Background:* TETs are very rare neoplasms and multidisciplinary approach is recommended according to prognostic factors.

*Materials and methods:* Between 1995 and 2013, 31 patients were treated with median 5400 cGy (range: 1620–6596 cGy) radiotherapy (RT). Eleven patients received adjuvant or concurrent chemotherapy. There were 25 thymomas, 4 thymic carcinomas and 2 thymic neuroendocrin carcinomas. According to Masaoka, staging and WHO classification, cases were divided to good (*n*: 10), moderate (*n*: 9) and poor (*n*: 12) prognostic risk groups. Survival was calculated from diagnosis.

*Results:* In January 2016, 22 cases were alive with median 51.5 months (range: 2–170.5) follow-up. Recurrences were observed in 29% of patients in median 29.5 months (range: 6.5–105). Local control, mean overall (OS) and disease-free survival (DFS) rates were 86%, 119 and 116 months, respectively. There was a significant difference for R0 vs. R+ resection (81% vs. 43%, $p = 0.06$, and 69% vs. 46%, $p = 0.05$), Masaoka stage I–II vs. III–IV (75% vs. 52%, $p = 0.001$, and 75% vs. 37%, $p < 0.001$), and also prognostic risk groups (100% vs. 89% vs. 48%, $p = 0.003$, and 100% vs. 87% vs. 27%, $p = 0.004$) in terms of 5-year OS and DFS, respectively.

*Conclusion:* In our study, prognostic risk stratification was shown to be a significant predictor of survival. There is a need to investigate subgroups that may or may not benefit from adjuvant RT.



☆ This study has been accepted for Poster Presentation at the IASLC 17th World Conference on Lung Cancer from December 4 to 7, 2016, in Vienna, Austria.

* *Corresponding author at*: Department of Radiation Oncology, Uludag University, Faculty of Medicine, 16059, Bursa, Turkey.
E-mail address: ssarihan@uludag.edu.tr (S. Sarıhan).

https://doi.org/10.1016/j.rpor.2017.12.002

## 1. Background

Thymic epithelial tumors (TETs) are very rare neoplasms accounting for 20% of mediastinal tumors in adults over the age of 40 years.[1] The histological type is thymoma in majority of cases, and surgery remains the main treatment strategy. Ten-year overall survival (OS) is reported to be 88% and 25% in cases undergoing complete (R0) and incomplete (R+) resection.[1–3] Relapse occurs at a rate <5% and 10–47% for Masaoka stage I and II–III in 3–7 years after complete resection, respectively. Adjuvant radiotherapy (RT) is recommended in patients who have invasion into neighboring organs or R+ cases, whereas definitive RT is recommended for unresectable cases. Adjuvant RT is category 2B recommendation in high-risk R0 patients.[3] Chemotherapy (CHE) is beneficial in metastatic, unresectable or recurrent disease, and high response rates are achieved with cisplatin-doxorubicin-based regimens.

Thymic carcinoma (TC) behaves more aggressively, invades the surrounding organs, and causes more regional lymph node and distant organ metastases.[1,3] Postoperative RT with or without CHE is recommended depending on the type of resection, while CHE with or without RT is recommended in those with unresectable or metastatic carcinoma. Neuroendocrine carcinoma (NEC) of the thymus is quite rare with high rates of distant metastasis and 5-year OS ranging between 30% and 85%.[1] Masaoka staging system and "World Health Organization (WHO)" classification (well, moderate and poor differentiation) are used in staging, and multidisciplinary approach is recommended for treatment.

Although invasiveness, type of resection, tumor size and advanced age have been reported as prognostic factors (PF), prognosis is primarily associated with Masaoka stage and WHO histopathological classification.[1,2] The incidence of Masaoka stage I, II, III and IV is 40%, 19.5%, 21% and 19.5% and 5-year OS is reported to be 70% and 50% for stage I–III and IV for TETs, respectively.[4] The incidence of WHO subtype A, AB, B and C is 5%, 19%, 60% and 16%, respectively; however, their prognostic significance is less clear as compared to the type of resection.[3–5] Current approach is to treat patients according to risk groups. D'Angelillo et al. developed a classification system including favorable, moderate and unfavorable risk groups on the basis of the Masaoka stage and WHO classification and demonstrated differences between the groups in terms of survival (10-year OS: 95%, 90% and 50%, respectively; $p = 0.001$).[6]

## 2. Aim

In the light of the above information, we aimed to evaluate the TET cases in terms of treatment outcomes and PFs on survival.

## 3. Materials and methods

Thirty-one patients with TET were treated in our department according to a decision of the multidisciplinary committee between October 1995 and December 2013. Written informed consent was obtained from all patients. The clinical and treatment characteristics of them were evaluated retrospectively.

Staging had been performed by chest "computed tomography (CT)" in all cases and by "positron emission tomography (PET/CT)" after 2006 (*n*: 9). Postoperative RT was performed with a LINAC at a dose of 45–50 Gy in the case of negative or close surgical margin, 54 Gy in the case of microscopic residual disease (R1), and at least 60 Gy in the case of macroscopic residual disease (R2) or unresectable tumor. The planning target volume was defined as the entire thymus or tumor bed and any known sites of disease with margins of at least 1–1.5 cm and were treated with AP-PA fields to 45 Gy, followed by boost to angled fields with two-dimensional planning before June 2008. Whereas after that "three-dimensional conformal RT/intensity modulated RT (3D-CRT/IMRT)" was used to involved field with limited margin for minimizing dose to the non-involved critical structures according to current guidelines.[1,3] Adjuvant cisplatin-doxorubicin-based CHE regimens were used in the TC cases with R1–2 resection, and in thymomas with large size or R2 resection. Toxicity was assessed according to the RTOG criteria.[7] The patients were monitored by chest CT every six months in the first two years and every year thereafter.

The patients were assigned to prognostic groups using the D'Angelillo classification; favorable (*n*: 10; stage I, A–B2 or stage II, A–B1), moderate (*n*: 9; stage II, B2–B3 or stage III, A–B2) and unfavorable (*n*: 12; stage III, B3 or stage IV, any histology or TC) groups, respectively.[6] Patients with thymic NEC were classified in the unfavorable risk group.

The cases were analyzed in January 2016 using SPSS version 21. Overall and disease-free survival (DFS) were calculated from the date of diagnosis using the Kaplan–Meier test, and the difference between the groups was analyzed by log-rank test. A $p$ value $\leq 0.05$ was considered significant. Multivariable analysis could not be performed due to a limited number of patients.

## 4. Results

The median age was 44 (range, 19–83) years (Table 1). Nine (29%) patients had immune system disorders; four cases (13%) had Myasthenia Gravis (MG) and 1 case had autoimmune hepatitis at diagnosis, and four cases developed MG/systemic lupus erythematosus/vitiligo at median 7 (range, 2–7) years after diagnosis. Histopathological diagnosis were thymoma (*n*: 25), TC (*n*: 4) and thymic NEC (*n*: 2). Masaoka stages were as follows: 13% (stage I), 39% (stage II), 39% (stage III) and 9% (stage IV). According to the WHO subtype classification (*n*: 29), there were 3.5% of type A, 17% of type AB, 65.5% of type B and 14% type of C tumors. The median tumor size was 8.5 cm (range, 3.5–20 cm).

Distribution of the cases according to Masaoka staging and WHO classification is presented in Table 2. Following re-evaluation in nine cases, of which the diagnosis had been reported as TC, it was revealed that 5 had WHO type B3 and 4 had WHO type C tumors. Differential diagnosis between type B2 and B3 could not be made in 6 cases (31%, 6/19).