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ORIGINAL ARTICLE

Prognosis Assessment in Thymic Tumors: A Single-center Experience

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OBJECTIVE

This study's objective is to assess the effectiveness of treatment and the prognostic factors that affect survival in 28 patients with epithelial thymic tumors who had adjuvant or definitive radiotherapy (RT) at our facility.

METHODS

The study comprised 28 patients who received RT at the Radiation Oncology Department of Eskişehir Osmangazi University Faculty of Medicine between 2010 and 2021. Each patient received RT (3DCRT/IMRT/VMAT).

RESULTS

The median overall survival (OS), disease-free survival (DFS), and progression-free survival (PFS) at a median follow-up of 74 months were 76 (3–201), 29, and 57 (0–198) months, respectively. The median RT dose was 50 Gy (44–66). While there was no statistically significant difference between DFS and RT doses (p=0.88), there was a statistically significant difference between PFS and OS and 50 Gy and higher doses (p=0.03 vs. p=0.02).

CONCLUSION

Post-operative RT has been proven to be beneficial in cases of incomplete resection, even if the role of adjuvant RT in patients with complete resection remains debatable. It is well established that primary unresectable thymic tumors can be treated safely and successfully with neoadjuvant or definitive chemoradiotherapy.

Keywords: prognosis; radiotherapy; thymic tumors.
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INTRODUCTION

Thymic tumors are rare mediastinal tumors with an annual incidence rate of 1.7/million in Europe.[1] Since they are uncommon, the ideal treatment strategy has not yet been established.[2]

The World Health Organization (WHO) classification is based on the ratios of lymphocytes to non-malignant thymic epithelial cells (A, AB, B1, B2, B3, and C), whereas the MASAOKA staging system is based on the localization of pertinent areas and the macroscopic and microscopic extension of the tumor (Stage I, II, III, and IV).[3] The evaluation of the tumor's radical resectability serves as the cornerstone of the treatment for thymic malignancies. After resection, its histological degree and capsular invasion status can be used to

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assess whether adjuvant therapy is necessary.[4] Patients are usually diagnosed while investigating myasthenia gravis or having a thorax computed tomography (CT) scan for another reason. Up to 70% of thymomas are associated with paraneoplastic syndromes. Depending on the size of the tumor and how it affects the surrounding organs, clinical symptoms may include cough, chest pain, dyspnea, hoarseness, superior vena cava syndrome, and tumor hemorrhage. Although less frequently, symptoms of anorexia, dysphagia, and weight loss can also be seen.[5,6]

The clinical diagnosis is made through CT and positron emission tomography-CT (PET-CT), despite the fact that it coincidentally presents on direct chest radiographs as anterior mediastinum enlargement. There are several techniques for histological diagnosis, including thoracoscopic biopsy, true-cut biopsy, anterior parasternal mediastinotomy, and fine-needle aspiration biopsy.[7]

There are surgical, chemotherapy (ChT), and radiotherapy (RT) alternatives for treatment (RT). The MASAOKA stage and resectability are the most significant variables influencing the prognosis (R0, R1, R2). Anemia, serum lactate dehydrogenase, serum leukocyte, performance status, weight loss, coexisting disorders, tumor size, involvement of the pericardium, and lymph node metastatic status are additional factors.[8,9] Yan et al.[10] found no evidence that adjuvant RT improved overall survival (OS) or progression-free survival (PFS) in 88 stage I–II thymoma patients; however, adjuvant RT improved OS and PFS in Stage III–IV.

In this study, we examined the disease-free survival (DFS), PFS, and OS rates of patients who received adjuvant or definitive RT at Radiation Oncology Department of the Faculty of Medicine, Eskişehir Osmangazi University.

MATERIALS AND METHODS

Patient Characteristics

The study involved 28 patients who received thymic tumor diagnosis between 2010 and 2021. The study included cases that were more than 18 years old, had been confirmed to have thymic tumors with pathological diagnosis, did not have any distant metastases, did not have multiple primary diagnoses, and was being closely followed up. In clinical staging, Masaoka staging was implemented. Histological grading was conducted using the WHO grading system.[11,12] For staging, thoracic and abdominal CT as well as FDG-PET CT imaging techniques were used. Our study was approved by Eskişehir Osmangazi University Clinical Research Ethics Committee with protocol number E-25403353-050.99-392767.

Treatment Protocol

In the supine position, the patients were immobilized hands above the head with the Wingboard. Using the Somatom Definition AS™ CT simulator device, planning CT was examined at 3–5 mm cross-sectional intervals. Image fusion was carried out using FDG/PET and thorax CT scans taken at the time of diagnosis. Surgery reports, post-operative thorax CT, PET-CT, and surgical clips were used for contouring in patients undergoing adjuvant RT. In patients receiving definitive RT, gross tumor volume was contoured using visible gross tumors and surgical clips, if present. In patients with PET-CT, planning CT and PET-CT fusion were carried out. In our study, the planned target volume (PTV) margin was determined as 3–5 mm, while the clinical target volume (CTV) margin was determined as 5–10 mm. In patients receiving adjuvant RT, the CTV was determined to comprise the whole thymus (in partially resected individuals), surgical clips, and possible residual disease areas. In patients scheduled for adjuvant RT, PTV was created by giving an 8–10 mm margin to the CTV, and RT was administered at a dose of 1.8–2 Gy/day, with a median dose of 50 Gy (44–60) using the 3DCRT/IMRT/VMAT technique with Varian Trilogy™/TrueBeam™ and Elekta Precise™ devices. When definitive RT was anticipated, concomitant ChT was scheduled while taking into account the Karnofsky Performance Status (KPS), comorbid conditions, and blood parameters.

Patient Follow-up

Patients were assessed for response to therapy through physical examination, anamnesis, and thorax CT during the 1st month following treatment. Patients underwent thoracic CT scans, physical examinations, and anamnesis as part of patient follow-up setting, and cases with suspected recurrence were discussed in a multidisciplinary council every 3 months for the first 2 years, every 6 months for up to 5 years, and every year after 5 years.

Statistical Methods

The data were analyzed using the Statistical Program for the Social Sciences version 26 package program (IBM Corp., Armonk, NY, USA), with summary values of qualitative variables displayed as frequency and percentage and quantitative variables shown as mean±standard deviation. Shapiro–Wilk test was used to assess the

Table 1 Patient, tumor, and treatment characteristics

Feature	n	%
Sex		
Female	15	53.6
Male	13	46.4
Marital status		
Married	23	82.1
Single	5	17.9
Age, median (min-max)	57 (33–77)	
Tumor size (cm), median (min-max)	7.1 (1.9–20)	
Capsule invasion		
Yes	27	96.4
No	1	3.6
RT dose (gy), median (min-max)	50 (44–66)	
ChT history		
Yes	13	46.4
No	15	53.6
Surgery		
Yes	23	82.1
No	5	17.9
Resection status		
R0	11	47.8
R1	9	39.1
R2	3	13.1
Time between surgery and RT (days), median (min-max)	58 (22–279)	
KPS, median (min-max)	100 (70–100)	

RT: Radiotherapy; ChT: Chemotherapy; KPS: Karnofsky performance score

compatibility of quantitative variables to normal distribution. Because there was no normal distribution in the comparisons of the two groups, Mann–Whitney U-test was performed. Because no normal distribution was seen in group comparisons of more than two groups, Kruskal–Wallis test was used. For survival analysis, Kaplan–Meier approach was utilized. Cases with $p<0.05$ as a result of the analysis were considered significant.

RESULTS

The study included 28 patients, with a median age of 57 (min:33-max:77), including 15 women and 13 men. The median KPS was 100 (min:70-max:100). The average tumor size is 7.1 (min:1.9-max:20) cm in diameter. Of the 28 cases, 23 (82.1%) underwent surgery and received adjuvant RT, while the other six (17.9%) received definitive RT. The median interval between surgery and RT was 58 days (range: 22–279). Capsule invasion was found in 29 (96.7%) of the patients included in the study. The median RT dose administered to patients is 50 Gy (min: 44-max: 66) and median RT doses according to R0, R1, and R2 resection status are 50 Gy (min: 44-max:50.4), 50 Gy (min: 45-max: 54), and 54 Gy (min: 46-max: 66), respectively. 13 (46,4%) of the patients received adjuvant ChT, while 15 (53.6%) did not. Table 1 summarizes patient, tumor, and treatment characteristics.

Table 2 The MASAOKA stage of the patients

MASAOKA stage	n	%
I	1	3.6
II	17	60.7
III	2	7.1
IV	8	28.6
Total	28	100

The MASAOKA stage of the patients is given in Table 2. When the stage and OS were evaluated, no statistically significant differences were detected ($p=0.48$). When the resection status of 23 patients undergoing adjuvant RT was evaluated, it was seen that 11 (47.8%) patients had R0, 9 (39.1%) patients had R1, and 3 (13.1%) patients had R2 resection. No statistically significant relationship between resection status and OS has been established ($p=0.84$). When evaluated in terms of OS, DFS, and PFS, it was observed that the median OS duration was 76 (3–201) months, the median DFS 29 months (0–195) months, and the median PFS duration was 57 (0–198) months. Statistically significant differences in OS were not observed between patients receiving adjuvant and definitive RT ($p=0.38$). In the RT dose and survival assessment of patients, the median PFS and OS periods were 28.5 months and 37 months, respectively, in the group with <50 Gy RT; and median PFS and OS periods with doses ≥50 Gy above were 95 and 99 months, respectively. Statistically significant differences in PFS and OS were observed between groups with <50 Gy and ≥50 Gy RT ($p=0.03$). No statistically significant differences were observed between DFS and RT dose ($p=0.88$). OS is indicated in the sequence of the DFS and PFS times with the delivered RT dose in Figure 1a-c. After treatment at the median follow-up of 74 months, complete response (71.4%) was monitored in 20 patients, partial response (14.3%) in 4 patients, stable response (10.7%) in 3 patients, and progression in 1 patient (3,6). During the median follow-up of 74 months, 17 cases were alive and 13 cases died. Of the 13 cases with ex, 6 died due to thymic tumor, and the remaining 7 died due to non-tumor causes.

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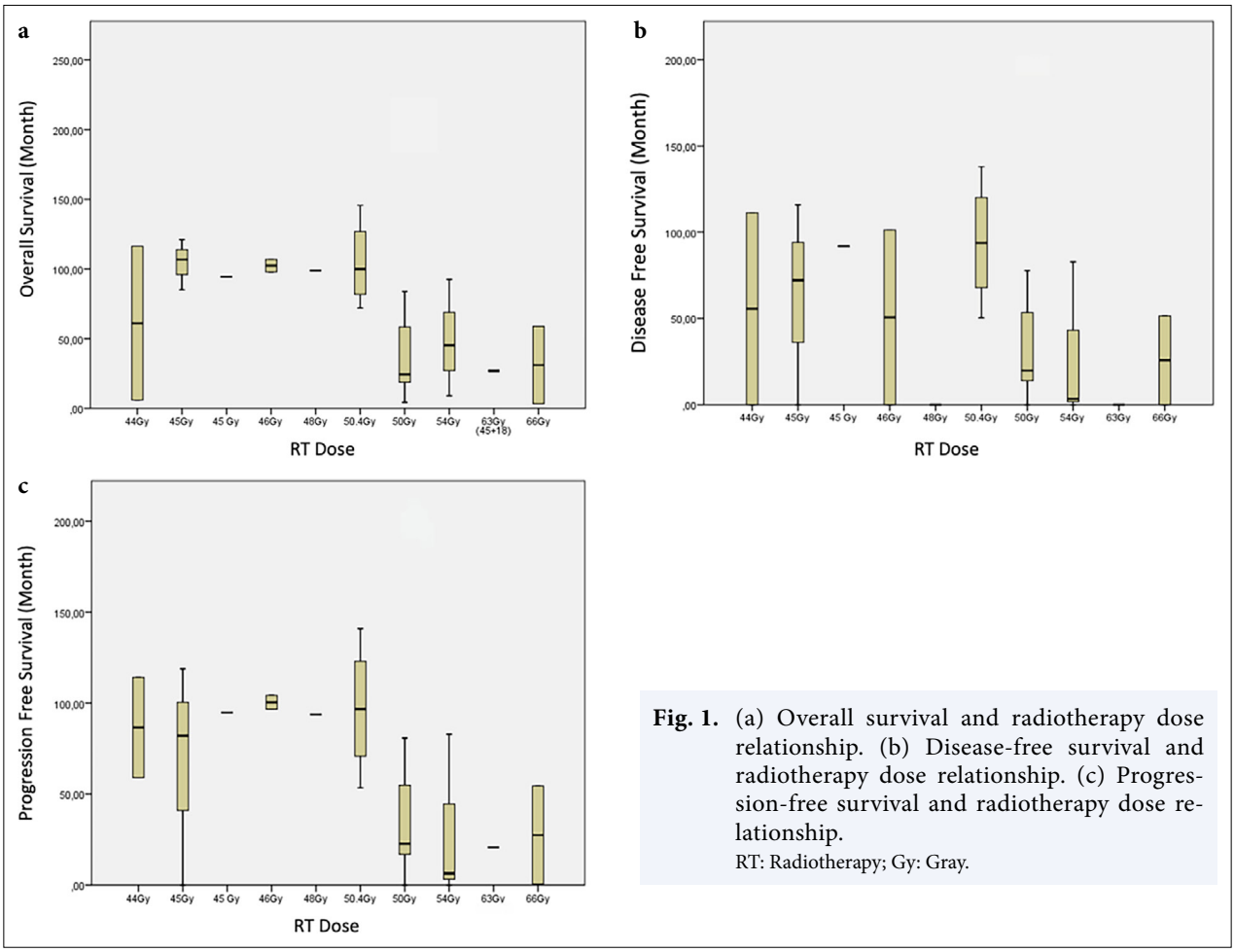

Fig. 1. (a) Overall survival and radiotherapy dose relationship. (b) Disease-free survival and radiotherapy dose relationship. (c) Progression-free survival and radiotherapy dose relationship.
RT: Radiotherapy; Gy: Gray.

DISCUSSION

Due to the rarity of thymic tumors, a definite decision has not yet been reached on what the optimal treatment is. While surgery is the primary treatment option in early-stage tumors, definitive chemoradiotherapy (CRT) plays the role of primary treatment in advanced-stage tumors.[13]

In a study conducted between 2001 and 2016, Fukui et al.[14] evaluated the clinicopathological features and prognosis of 153 patients with stage I thymic epithelial tumors and underwent complete resection, and the 5-year OS and recurrence-free survival rates were found to be 94% and 80%, respectively. In multivariate analysis, patients with tumor size >5 cm were associated with a higher risk of recurrence (p=0.027). In our study, however, no statistically significant relationship was found between tumor size and OS, DFS, and PFS (p=0.20, p=0.54, p=0.33).

Jackson et al.[15] investigated the contribution of adjuvant RT to survival in 4056 patients with thymic tumors between 2004 and 2012 using National Cancer Database data. In multivariate analysis, parameters such as patient age, WHO histological subtype, Masaoka Stage, surgical margins, and ChT application were used in the evaluation of OS. Improvement in OS was observed in patients who received adjuvant RT in the early stage (p=0.001). In our study, regardless of the stage of the disease, the median DFS was 51 months in patients receiving adjuvant RT, and the median DFS was 0 months in patients receiving definitive RT, and a statistically significant relationship was found by using Kaplan Meier method (p=0.01), but no significant relationship was found in terms of OS and PFS (p=0.30, p=0.50). Similarly, Tateishi et al.[16] in a meta-analysis consisting of five separate studies, 4746 patients with thymoma with Masaoka Stage II-III were included in the study, and 2408 of these patients received adjuvant RT and their survival rates were evaluated. OS rates were observed to be better with adjuvant RT (p<0.001), but no statistically significant relationship was found with DFS (p=0.83).

Although the adjuvant RT dose in thymic tumors is known as 45–55 Gy, the surgical resection status is important in making this decision. For adjuvant treatment, the radiation dose consists of 45–50 Gy for clear/close margins and 54 Gy for microscopically positive resection margins. A total dose of 60–70 Gy should be given to patients with gross residual disease (similar to patients with unresectable disease).[17–19] While adjuvant RT is not recommended after complete resection in Stage I cases, RT can be applied to Stage II cases with R1 and R2 resections or capsule invasion. In patients with stage III-IV thymic tumors, the contribution of adjuvant RT to survival is evident. In some selected cases, definitive CRT can be tried in cases where surgery cannot be performed due to proximity or invasion of vascular structures. In a study by Urgesi et al.[20] on 77 patients with Stage III-IV thymic tumors between 1970 and 1987, the adjuvant RT dose was 1.8–2 Gy/day, a total of 39.6–46 Gy was administered, and the 10-year OS was found to be 58.3%. Ogawa et al.[21] administered adjuvant RT dose <40 Gy to 19 patients, 40 Gy to 45 patients, and >40 Gy to 39 patients in 103 patients with complete resection of thymoma, and no dose-response correlation was observed. Again, between 1981 and 1995, in a study conducted by Latz et al.,[22] local control analysis was performed with adjuvant RT in 43 (23 total, 20 subtotal resection) patients with thymic tumor after surgery. In this study, a local control rate of 74% (32 patients) was obtained.

In our study, 44–60 Gy (median 50 Gy) RT was applied to the patients, and the 5 and 10-year OS rates were found to be 50% and 10%, respectively. In this study, improvement in PFS and OS was observed at doses of 50 Gy and above (p=0.03 vs. p=0.02). We recommend that dosing 50 Gy and above because of thymic tumors are radiosensitive tumors and complete response with surgery alone is difficult. Dose applications under 50 Gy can be considered palliative.

The limitations of our study are that this study is single-centered, retrospective, limited number of patients, evaluation of surgical and non-surgical cases, and ex cases due to comorbid disease and COVID pneumonia.

Due to the fact that thymic tumors are very rare tumors and difficulties in calculating real survival rates during the COVID-19 pandemic period, multicenter studies with more patients are needed.

CONCLUSION

Adjuvant RT has a significant contribution to survival in these tumors. In this study, while a statistically significant difference was observed between 50 Gy and higher doses and PFS and OS (p=0.03 vs. p=0.02), no statistically significant difference was observed between DFS and RT doses (p=0.88). At the same time, DFS duration was longer in patients receiving adjuvant RT than in patients receiving definitive RT (p=0.01). Because thymic tumors are rare tumor and lack of studies on survival and prognosis, multicenter prospective studies with larger numbers of patients are needed for ideal treatment and prognostic factors.

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Ethics Committee Approval: The study was approved by the Eskişehir Osmangazi University Non-Interventional Clinical Research Ethics Committee (no: E-25403353-050.99-392767, date: 04/10/2022).

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