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Role of radiotherapy in Masaoka stage II and III thymomas – single center experience

Masaoka evre II ve III timomada radyoterapinin rolü - tek merkez deneyimi

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Abstract

Aim: Thymomas are rare neoplasms. Complete surgical resection is the cornerstone of the treatment. The role of adjuvant radiotherapy (RT) in Masaoka stage II disease is controversial, but in more advanced stages and the role of radical RT in inoperable cases are clear. This study is conducted to evaluate local control, relapse free survival and overall survival rates in Masaoka stage II and III thymoma patients after adjuvant or radical RT.

Materials and Methods: The medical records of thymoma patients who were treated and completed their RT course between January 2010 and August 2016 in a single center were evaluated retrospectively.

Results: Twenty-two patients were available for analysis. Treatment planning was adjuvant in 18 patients and radical in 5 patients. Median age at diagnosis was 59 (50-62). Type of resection was R0 in all cases. The adjuvant RT dose was 50 Gy; radical RT dose was 60-66 Gy. The most common acute toxicity was grade 1 pneumonitis which was reported in 9 patients (39%). Grade 2 acute pneumonitis was experienced by 3 patients (13%), grade 2 acute esophagitis was experienced by 2 patients (9%). One patient had late grade 3 esophageal toxicity. Follow-up time ranged from 6 to 99 months, median 18 months, local control rate was 100%, relapse free survival (RFS) was 96%, cancer specific survival was 96%, 2 years overall survival (OS) was 83%.

Conclusion: Although our results seem to be in concordance with the literature, longer follow-up is needed to be able to make a conclusion in terms of LC, RFS and OS, since thymoma has an indolent course with low relapse rate and long RFS.

Keywords: Thymoma, radiotherapy, stage II, stage III.

Öz

Amaç: *Timomalar oldukça nadir tümörlerdir. Tam rezeksiyon tedavinin ana öğesidir. Adjuvan radyoterapinin (RT) rolü Masaoka evre II hastalıkta tartışmalıyken, daha ileri evrelerde ve inoperabl olgularda nettir. Bu çalışma, evre II-III timoma olgularında adjuvan veya radikal RT sonrası lokal kontrol, yinelemesiz sağ kalım ve genel sağ kalım (GS) sonuçlarını araştırmak için planlandı.*

Gereç ve Yöntem: *Ocak 2010-Ağustos 2016 arasında timoma tanısıyla RT uygulanan olguların medikal verileri geriye dönük olarak incelendi.*

Bulgular: *Adjuvan RT uygulanan 18 ve radikal RT uygulanan 5, toplam 23 evre II-III olgu analizlere dahil edildi. Ortanca yaş 59 (50-62) idi. Opere olguların tümünde rezeksiyon R0 şeklindeydi. Adjuvan RT dozu 50 Gy, radikal RT dozu 60-66 Gy idi. En sık izlenen toksisite 9 olguda (%39) gelişen derece 1 pnömoni idi. Derece 2 pnömoni 3 olguda (%13), derece 2 özofajit 2 olguda (%9) izlenirken, 1 olguda geç dönem özofajial toksisite izlendi. İzlem süresi ortanca 18 aydı (6-99 ay). Lokal kontrol oranı %100, yinelemesiz sağ kalım oranı %96, kansere özgü sağ kalım %96, 2 yıllık GS oranı %83'tü.*

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Sonuç: *Sonuçlarımız literatür ile uyumlu görünmesine rağmen, timomanın yineleme oranı düşük ve yinelemesiz sağ kalımı uzun bir hastalık olması nedeniyle lokal kontrol, yinelemesiz sağ kalım ve GS sonuçlarımızla ilgili yorum yapabilmemiz için daha uzun izlem süresine ihtiyaç duyulmaktadır.*
Anahtar Sözcükler: *Timoma, radyoterapi, evre II, evre III.*

Introduction

Thymic epithelial tumors are rare neoplasms of the anterior mediastinum, arising from epithelial cells within thymus (1). Thymoma represents the most common type and has the ability of local invasion with low metastatic potential (2). World Health Organization (WHO) histology, Masaoka stage and extent of resection are the main prognostic factors (2-4). Optimal management of this disease is controversial and treatment outcome has not evolved since last decades in spite of many advances in imaging, surgery, radiotherapy (RT) and chemotherapy (CT) (2).

Complete surgical resection is the cornerstone of the treatment but the knowledge about the role of radiotherapy (RT) in thymoma depends on retrospective series, except one small randomised data considering stage I disease (5). Due to its rarity, these retrospective series had patient enrollment over a long time period that witnessed major evolutions in imaging, staging, pathologic classification, RT indications and techniques. Besides, the results were controversial; some data suggested survival advantage of adjuvant RT (6-9), while others reported no advantage (5,10-13) and some found conflicting results (1). In stage I disease which has an excellent prognosis adjuvant RT is not recommended (14,15). In stage II, adjuvant RT has been considered as the standard treatment (16,17) but recently it has been questioned due to of lack of prospective trials (18,19). Additionally, in recent series it has been shown that the most common recurrence site is the pleura which cannot be prevented by adjuvant mediastinal RT (15). The role of adjuvant RT in stages III and IV and radical RT in inoperable cases are clear (20,21).

This study is conducted to better understand the optimal role of adjuvant and radical radiotherapy in Masaoka stage II and III disease as a component of multidisciplinary management. The primary aim of the study was to evaluate; local control, relapse free survival and overall survival. Secondary aims were to evaluate the clinical characteristics and treatment related toxicity,

Materials and Methods

The medical records of thymoma patients who were treated and completed their RT course between January 2010-August 2016 in a single center were evaluated in terms of clinical characteristics, treatment and follow-up data, retrospectively. All patients were available with confirmed histologic diagnosis.

Stage was defined using both the Masaoka System (22) and TNM staging proposed by the International Association for the Study of Lung Cancer (IASLC) staging process and International Thymic Malignancies Interest Group (ITMIG) (23). Histological classification was done according to WHO criteria (24).

Surgical approach was total thymectomy via median sternotomy or video-assisted thoracoscopy or thoracotomy. Extended thymectomy was carried out for larger tumors. Parietal pericardial resection was done if the lesion was in contact with the pericardium. Complete resection with negative surgical margins was defined as R0, incomplete resection with microscopic residue was defined as R1 and subtotal resection with gross residue was defined as R2. None of the patients received adjuvant CT.

The adjuvant RT dose was 50 Gy. In radical intent, a dose of 40-45 Gy was followed by 20 Gy boost. The fractionation dose was 2 Gy. In adjuvant setting clinical target volume (CTV) was delineated according to preoperative radiologic findings and surgical clips placed at the time of surgery describing the extent of resection. In radical setting, CTV encompassed the gross tumor volume (GTV) and the thymus, the planning target volume (PTV) covered CTV with a 1 to 2 cm. margin. The extended field RT had never been used.

Follow-up schedule was by 3-month intervals for first 2 years, 6-month intervals for the next 3 years, and annually thereafter. Radiation morbidity was graded according to RTOG/EORTC acute and late morbidity score (25).

Local control, relapse-free survival (RFS), overall survival (OS), acute and late side effects were defined as study end-points. Relapse was defined as any clinico-radiological evidence of tumor recurrence. RFS was calculated from the time of pathologic diagnosis to the relapse (locally or distantly) time, OS was calculated from the date of diagnosis to final follow-up or to date of death from any cause.

Statistical Analysis

Due to the skewed distribution of the data continuous variables were expressed as median (25th-75th percentiles). Normality was evaluated with Shapiro Wilk test. Categorical data were expressed as numbers (%). Time to event analysis was performed by Kaplan Meier method.

Results

There were 30 patients treated with RT as part of their management. There wasn't any preoperative RT indication. Seven patients who were treated with palliative intent were excluded. The remaining 23 patients were available for the final analysis. Median age at diagnosis was 59 (50-62) male to female ratio was 1.09. At the time of diagnosis 4 patients (17%) had myasthenia gravis (MG) and had symptoms related to it. Six patients were asymptomatic and had diagnosis of thymoma as a result of incidentally discovered mass on chest radiograph or CT screening. Chest pain was the most frequent symptom in the remaining patients (46%). One patient had additional T2 glottic and T1cN0 non-small cell lung cancer diagnosed synchronously with thymoma. One patient who presented with both Sjörgen syndrome and MG had myasthenia crisis after operation. RT was postponed until his crisis was settled down by medical intervention.

Median tumor size ranged from 4 to 7cm (median 6.2cm). Type B2 was the most frequent histopathological subtype (30%). There was not any thymic carcinoma. CD45, CD1a and pancytokeratin were the most studied molecular markers besides others and they were positive in all cases. The clinical characteristics of patients are shown in Table-1.

Distribution of patients according to the Masaoka system and TNM staging is shown in Table-*2.* One patient refused surgery and received radical RT. Five Masaoka stage III patients were found to be unresectable at presentation. One of them received radical RT without induction CT. Four cases received induction CT (cyclophosphamide adriamycin and cisplatin-CAP) and had repeat CT imaging for re-evaluation; 1 of them underwent R0 resection, 3 of them was found to be unresectable again and received radical RT. Eighteen patients had surgery. The median sternotomy was the most common (61%) operative approach. VATS was used in 22% and thoracotomy in 11% of cases. Partial pericardial resection and wedge resection of lung were performed additionally if needed. The resection type was R0 in all patients.

Table-1. Clinical Characteristics of Patients.

No. of patients	23	
Age	59 (50-62)	
Male/female	12/11	
Tumor size (cm)	6.2 (4-7)	
	Patient numbers	
WHO histologic subtype	Masaoka stage II	Masaoka stage III
Type A	1	0
Type AB	3	0
Type B1	4	1
Type B2	6	1
Type B3	2	4
Type C	0	0
Unclassified	1	0
Type of resection	Patient number	
R0	18	
No operation/only biopsy	5	

Table-2. Distribution of Patients According to Modified Masaoka Staging System and TNM Staging.

Masaoka Staging System	n (patients)	TNM Staging	n (patients)
I	0	I	15
II	17	II	2
III	6	III	6

Three-dimensional conformal radiotherapy (3D-CRT) planning was used in all patients. RT was administered with radical intent in 5 and adjuvant in 18 patients. The distribution of patients who received adjuvant radiotherapy according to Masaoka staging system and TNM staging is shown in Table-3. The median time interval between surgery and the start of RT was 41 (33-103) days.

Table-3. Distribution of 18 Patients Who Received Adjuvant RT According To Masaoka Staging System and TNM Staging.

Masaoka Staging System	n (patients)	TNM Staging	n (patients)
I	0	I	14
II	16	II	2
III	2	III	2

All patients were able to complete their RT schedules. None of the patients received concurrent CT with RT. The most common acute toxicity was grade 1 pneumonitis which was reported in 9 patients (39%). Grade 2 acute pneumonitis was experienced by 3 patients (13%), grade 2 acute esophagitis was experienced by 2 patients (9%). One patient had late grade 3 esophageal toxicity at 4 years during follow-up. There wasn't any reported toxicity in 8 patients.

None of the patients developed local recurrence during follow-up. One patient developed regional-out-field recurrence at 32 months. Synchronously she developed multiple distant metastases and died due to disease at 37 months. At the time of analysis 19 patients were alive, 3 patients died of other reasons not related to cancer.

Follow-up time was median 18 months (minimum 6, maximum 99 months), local control rate was 100%, RFS was 96%, cancer specific survival was 96%, median survival was 18 months (95%CI:12-24), 2 years OS was 83% (Figure-1).

Since there was only one disease related event, prognostic factor analysis could not be established.

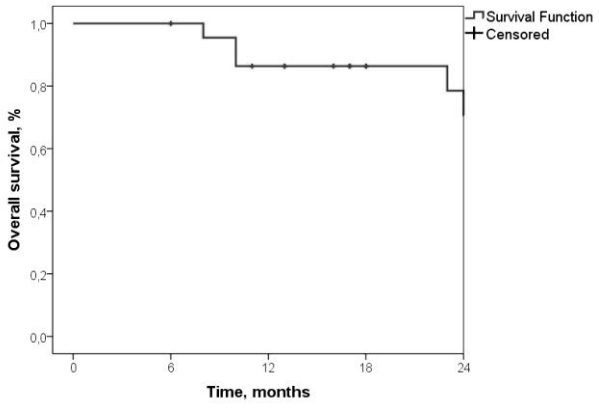

Figure-1. Kaplan-Meier two years overall survival curve of patients.

Discussion

The role of adjuvant RT after complete resection in Masaoka stage II disease is controversial (26). Recently, well powered large sized studies showed increase in OS in Masaoka stage II and III thymoma with adjuvant RT (9,26,27). Radiotherapy planning should be established cautiously in adjuvant setting in terms of benefit versus toxicity, since thymomas grow in close proximity to critical organs (28). The recent analyses, showing benefit of adjuvant RT may rely on the advantage of RT planning and treatment techniques. High conformality in dose distribution and decreased dose to nearby critical tissues by modern RT techniques might decrease normal tissue complications and might improve the therapeutic ratio of RT. In our study, longer follow-up is needed to be able to make a conclusion if our RFS and OS rates are in concordance with the literature (15,29).

In relevant literature; R0 resection, Masaoka stage and WHO classification are stated as the most important prognostic factors for survival (2,30). In our cohort, all operable patients had R0 resection which reflected on results as excellent local control and high survival rates. We couldn't show any effect of stage and WHO classification on local control and survival possibly because of small number of patients. Moreover, 63% of our patients had follow-up time less than 3 years which is relatively short for thymoma, since the relapses are rare (10-30%) and may occur many years later. In the report on recurrent thymomas by Sandri et al. (31), mean disease free interval for relapse was 7 years. Possibly, because of this reason, we couldn't be able to predict any prognostic factor for local control or survival.

In terms of symptoms at presentation, we reiterate the literature findings. MG was present in 17% of our patient cohort which is in concordance with 15-60% depicted rate in the literature (32,33). Rate of asymptomatic patients and cough as being the most frequent symptom at presentation were similar to findings by Sperling et al (33).

When we classified the patients both by using TNM-based staging system that has been proposed by the IASLC-ITMIG and Masaoka staging system, there was a stage migration from Masaoka stage II to TNM stage I. If TNM staging were used for adjuvant RT indication, 77% of patients would not have RT indication (Table-3). This observation is in concordance with the

recommendation of European Society for Medical Oncology (ESMO) on maintaining the definition of staging according to Masaoka for adjuvant RT indication (34).

In the present study, although the number of patients is low, it was shown that, stage III patients had higher proportion of Type B3 disease, while stage II patients had mostly Type B1 and B2 disease. This finding is in line with the literature stating that stage increases in correlation with the histologic subtype from A to B3 (15).

For thymoma, definition of dose-response relationship is not possible because of the retrospective nature of the data. In one study, there was a dose-response relationship, but in two others there wasn't any (35,36). Our prescribed RT doses are in concordance with the suggested RT doses in literature (36).

In literature, the extent of RT fields has been controversial; while some authors favor extended field RT encompassing whole mediastinum or hemithorax (7), others favor localized RT fields (2). Similarly, in our cohort, localized RT portal was preferred in all cases.

RT technique is important both in terms of normal tissue toxicity and disease control in literature; 3D-CRT is found to be superior to conventional RT (37,38). Similarly, in our cohort, 3D-CRT treatment and planning was used in all patients. Our toxicity profile was tolerable although there might be underestimation because of the retrospective nature of the study. Also, with longer follow-up, we would be able to see the results of 3D-CRT in terms of local control.

In advanced stage thymomas, multimodality treatment provides improved survival (15,39). Invasive thymoma has been defines as sensitive to cisplatin-based CT (15). Cisplatin based induction CT was administered in 4 of 5 inoperable Masaoka stage III patients in our report. After induction R0 resection rate was 25%. The small number of patients makes it hard to conclude the effect of induction CT on operability in our cohort. Similarly in literature, though the patient numbers are relatively low, R0 resection rates after neoadjuvant CT, differ between 12-82% (13,39).

Our study has the usual limitations of studies on rare diseases**.** Retrospective nature of the study, relatively small number of patients and relatively shorter follow-up are the major limitations of our study**.** Besides, we do not have a comparator group (surgery alone) which represents a further significant limitation. Absence of data regarding CT schemes, duration and dosing is also lacking, because of the retrospective nature of the study.

On the other hand, homogenous patient cohort, R0 resection in all operable cases, uniform 3DCRT planning and treatment approach in all patients and short span of time for patient inclusion are thought to be the strengths of our study.

Conclusion

Although our results seem to be in concordance with the literature longer follow-up is needed to be able to make a conclusion in terms of LC, RFS and OS in thymoma which is a disease with low relapse rate and relatively long relapse-free interval. Since it's unfeasible for thymomas to proceed controlled, prospective trials because of its rarity and indolent nature, we should rely on these retrospective series. The next step for us might be to facilitate national collaboration of such a rare disease.

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