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Original research article

Thymic tumors and results of radiotherapy☆

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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.

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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 ≤ 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).

Table 1 – Clinical features of cases.

Clinical features	N (range/%)
Age (median, year)	44 (19–83)
Sex	
Male	17 (55)
Female	14 (45)
Karnofsky performance status (median)	90 (70–100)
Smoking	
Present	12 (39)
Absent	19 (61)
Smoking pack/year (median)	15 (9–82.5)
Histology	
Thymoma	25 (81)
Thymic carcinoma	4 (13)
Thymic neuroendocrin carcinoma	2 (6)
Tumor size (median, cm)	8.5 (3.5–20)
Myasthenia Gravis at diagnosis	
Present	4 (13)
Absent	27 (87)
Autoimmune disorder	
Present	9 (29)
Absent	22 (71)
Masaoka stage	
I	4 (13)
II	12 (39)
III	12 (39)
IV	3 (9)
Resection type	
R0	18 (58)
R1	6 (19)
R2	4 (13)
Biopsy	3 (10)
Surgery-RT interval (median, days)	50 (29–99)
RT dose (median, cGy)	5400 (1620–6596)
Fraction dose (median, cGy)	180 (180–200)
RT duration (median, days)	46 (11–56)
Adjuvant chemotherapy (*n*: 23)	
Present	7 (30)
Absent	16 (70)
Adjuvant chemotherapy cycles (median)	6 (1–6)
Chemotherapy	
Present	15 (48)
Absent	16 (52)
Family cancer history	
Present	5 (16)
Absent	26 (84)
Comorbidity	
Present	17 (55)
Absent	14 (45)

A R0 resection was performed in 18 cases (58%). The median number of resected lymph nodes was 2 (range, 1–12) in 12 cases and lymph node metastasis was present in one case. Three cases had undergone biopsy (*n*: 3) and 10 cases underwent R+ resection with macroscopic (*n*: 4) and microscopic (*n*: 6) residual disease.

The median interval between surgery and RT was 50 (range, 29–99) days. A total median 5400 cGy (range, 1620–6596 cGy) RT was given to patients over a median 46 (range, 11–56) days. A case biopsied and given only 1620 cGy RT and 1 cycle of CHE died within 3 months. A R0 case with MG, who had been receiving pyridostigmine bromide and prednisolone, died due to pneumonitis during RT at 4140 cGy dose. The other R0 case was irradiated with only 2520 cGy because of atypical pneumonia that developed during RT. Postoperative RT was performed in four stage-I cases due to high mitosis/proliferation index or WHO type B2–3 tumor. A rate of acute total and ≥G2 esophagitis, radiation pneumonitis, and hematological toxicity was found at 71%, 32%, 13%, and 23%, respectively. No ≥G3 late toxicity was detected in any patient.

Cisplatin-doxorubicin-based adjuvant CHE was performed for a median of 6 cycles (range, 1–6) in seven stage I–IV cases. Two cases with R2 resection received adjuvant concurrent chemo-RT with weekly paclitaxel at a dose of 60–70 mg/m^2. The other two cases with biopsy (a thymoma and TC case) received concurrent chemo-RT with standard CHE regimen for 2 and 3 cycles. Complete or partial response was obtained and one of them underwent R1 resection. Partial response was achieved in a case with stage IV-A thymoma receiving 4 cycles of neoadjuvant CHE and this case also received adjuvant RT and CHE after R2 resection.

No recurrence was seen in favorable subgroups. A total of 29% recurrences (one TC case before RT and eight cases after RT) were seen at pericardium, anterior mediastinum, lung, bone and pleura in a median of 29.5 (range, 6.5–105) months. Recurrence via local and drop metastasis developed in four cases (13%), whereas lung, bone or distant pleural recurrence developed in five cases (16%). There were three in-field local recurrences for one case with R0 and the other two with R2 resection. No case of marginal recurrence was reported. The one TC case had stage IV at diagnosis that recurred repeatedly before RT. The patient died due to progressive disease 6 months after RT with 48 months follow-up period. Two cases with pericardial recurrence after RT (one of in-field and one of drop metastasis), received a second course of RT at a dose of 3960–6000 cGy after second surgery and one of the cases also received CHE. One of these cases is still on follow-up without disease after the third surgical procedure performed due to a second recurrence. Two cases with local recurrence at 14 and 32.5 months were lost to follow-up and we were informed by telephone that they had died with 20 and 33.5 months survival, respectively. One case with pleural and bone recurrences received 40 Gy RT to the left hemithorax but died two months later due to surgical complication for vertebral metastasis. Two cases with pleural recurrence are still alive with salvage CHE and/or re-surgery. An atypical NEC case achieved stable response with salvage CHE and is alive with 26 months of follow-up after distant recurrences. One thymoma case developed a second primary lung cancer after 10 years and died of surgical complication.

Local control (LC) was 86% for 29 cases, excluding two who could not be assessed. Local control was 100%, 100%, 70% and 67% for Masaoka stage I, II, III and IV ($p = 0.059$), and 100%, 89% and 70% for favorable, moderate and unfavorable risk groups ($p = 0.08$), respectively.

Twenty-two cases were alive in January 2016 with median 51.5 (2–170.5) months follow-up. Follow-up period did not exceed 48 months in four TC cases. The causes of death were

Table 2 – Masaoka staging related with WHO subclassification.

Masaoka stage	WHO classification (*n*)								
	A	AB	B1	B2	B3	Unclassified subtype of B	C	NEC	Total
I	1			2		1			4
IIA		1	1					1	3
IIB		2	2	1	2	1	1	1	9
IIIA		1			1	1			3
IIIB		1			3	3	2		9
IVA									1
IVB					1		1		2
Total	1	5	3	3	7	6	4	2	31

Table 3 – Univariate analysis: mean and 5 years overall (OS) and disease-free survival (DFS) rates according to prognostic factors.

Prognostic factors (*n*)	Mean survival, months (95% CI), 5 year survival	*p*
OS	119 (94–144), 78%	
DFS	116 (89–144), 73%	
Resection type		
R0 present (18) & absent (10)		
OS	135 (108–161), 81% & 74 (38–111), 43%	0.06
DFS	132 (103–162), 69% & 70 (31–110), 46%	0.05
Masaoka stage		
I–II (16) & III–IV (15)		
OS	160 (142–177), 75% & 72 (45–98), 52%	0.001
DFS	160 (142–177), 75% & 59 (31–88), 37%	<0.001
Prognostic groups		
Good (10) & moderate (9) & poor (12)		
OS	Not reached, 100% & 134 (102–166), 89% & 59 (33–85), 48%	0.003
DFS	Not reached, 100% & 131 (96–166), 87% & 43 (24–62), 27%	0.004

pneumonitis during RT in one (11%), postoperative complication following surgery in three (33%), disease progression in four patients (44%), whereas in one case (11%) the cause could not be identified.

The mean and 5-year OS were 119 (94–144) months and 78%, and the mean and 5-year DFS were 116 (89–144) months and 73%, respectively (Table 3, Figs. 1 and 2). The 5-year OS and DFS differed significantly for resection type of R0 and R+ resection (81% vs. 43%, $p = 0.06$, and 69% vs. 46%, $p = 0.05$), and Masaoka stage I–II and III–IV disease (75% vs. 52%, $p = 0.001$, and 75% vs. 37%, $p < 0.001$), respectively. Five-year OS was 100%, 89% and 48% ($p = 0.003$), and 5-year DFS was 100%, 87% and 27% ($p = 0.004$) for favorable, moderate and unfavorable risk groups, respectively. The presence of relapse led to a significant decrease in mean OS and DFS (139 vs. 79 months, $p = 0.03$, and 139 vs. 53 months, $p = 0.008$), respectively. Mean OS and DFS were shorter in the patients receiving CHE (147 vs. 86 months, $p = 0.008$ and 147 vs. 77 months, $p = 0.006$), respectively, due to these patients having poor PFs with R+ resection, advanced disease, a great tumor size or TC. No significant relationship was found between the other PFs and survival, and this result was attributed to the limited number of patients.

5. Discussion

Today, consensus on the treatment of TETs is lacking. The type of resection is the guide in deciding on adjuvant therapy.[1,2] Regnard et al. reported that the rates of R0, R+ and biopsy were 85%, 10% and 5%, respectively, and extracapsular spread and peritumoral adhesion to the surrounding tissues are poor PFs even with EI and R0 resection.[8] With adjuvant RT, it was reported that recurrence rate decreased from 20% to 0% in these patients and from 30% to 5% in R0 resected stage II–III tumors.[1,8–10] However, retrospective series reported that no difference in terms of 10-year local or distant recurrences.[11–13] On the other hand, studies including only RT series demonstrated that relapse rates increase with stage (stage II, 10–19%, and stage III, 44%) and it is emphasized that adjuvant RT is needed.[9,14]

Masaoka staging and WHO classifications are reported to be the best and valid predictors that influence the decision for adjuvant therapy.[1,4,15–17] Five-year OS has been reported to be 85% and 65% for Masaoka stage I–III and IV thymoma, respectively.[3,18,19] The importance of histological types has also been demonstrated, and while 5-year survival was 93% in advanced-stage thymoma, the rate is lower (67%) for TC, even with R0 resection.[13] The WHO classification is reported to be an independent PF associated with clinical behavior of disease, however, it is emphasized that the concordance rates reach maximum 0.63 over two groups (A–AB–B1 vs. B2–B3–C) and are inadequate in decision making for treatment.[3,5,20–22]

Many centers have adopted individualized, risk-adjusted treatment approach according to low and high risk groups using Masaoka staging and WHO classification.[23,24] D'Angelillo et al. reported that 10-year survival difference was significant based on recommended treatment approach according to prognostic groups.[6] All of these studies suggest

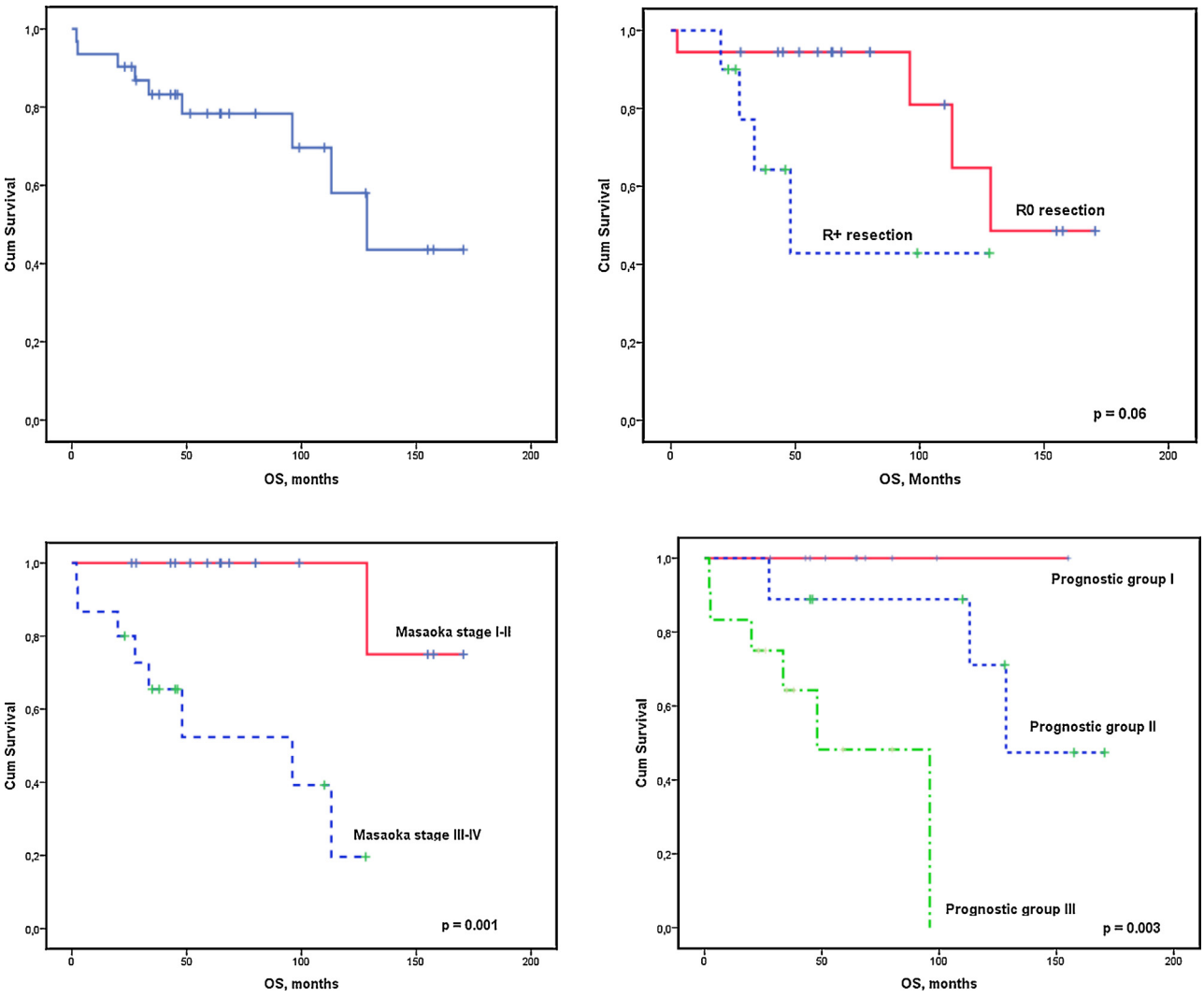

Fig. 1 – Overall survival (OS) and prognostic factors.

that there is a need to create new prognostic groups to decide on the optimal therapy.

The present study only includes patients who were referred to our department and thus Masaoka stage I ratio was 13%. The rates of R0, R+, and biopsy were 58%, 32%, and 10%, respectively. The median age of our patients was 44 years indicating a younger study population as compared to the literature.[4,8,13,17] The unclassified WHO type B ratio was 31%, comparable to previous reports.[5,20] Five-year OS and DFS rates were 83% and 73%, respectively and was found statistically different according to prognostic groups. Therefore, our results highlight the importance of prognostic risk classification.

With preoperative treatment, it is aimed to increase resectability rates by reducing the tumor load and prevent tumor seeding during surgery, and prolong OS in unresectable cases.[1,3,10,11,25] In stage III cases, it is reported that R0 resection increased from 50% to 53–75% with neoadjuvant RT and 5-year OS of 86% was obtained in those with R0 resection.[1,11,25,26] Thymic tumors are also sensitive to CHE.[1–3,10] In unresectable cases, it is reported that objective clinical and complete pathological response rates to multi-drug neoadjuvant CHE were 77–100% and 4–31%, respectively, and R0 resection can be performed in 57–82% of the cases with 57–95% of 5-year survival rates.[1,3,27] In our study, complete or partial response was achieved in three out of four cases (75%) that underwent neoadjuvant or definitive concurrent chemo-RT and one of them underwent R1 resection. However, considering all patient, survival was shorter in patients that received CHE due to poor risk factors (147 vs. 86 months, $p = 0.008$).

Thymus gland where T cells mature, plays an important role in immunity. Thus, prevalence of MG is 30–50% and co-occurrence of TETs with autoimmune diseases other than MG is reported at the rate of 2–5%.[1,2] Thymic tumor-related autoimmune deficiency is associated with respiratory tract hypersensitivity and multiple organ injury, and opportunistic respiratory tract infections are frequently encountered.[28,29] In addition to radiation dose to organs at risk, female gender and CHE have also been reported as risk factors for acute and late lung toxicity in patients with thymoma.[30,31] In the present study, there was 16% autoimmune disorders including MG at

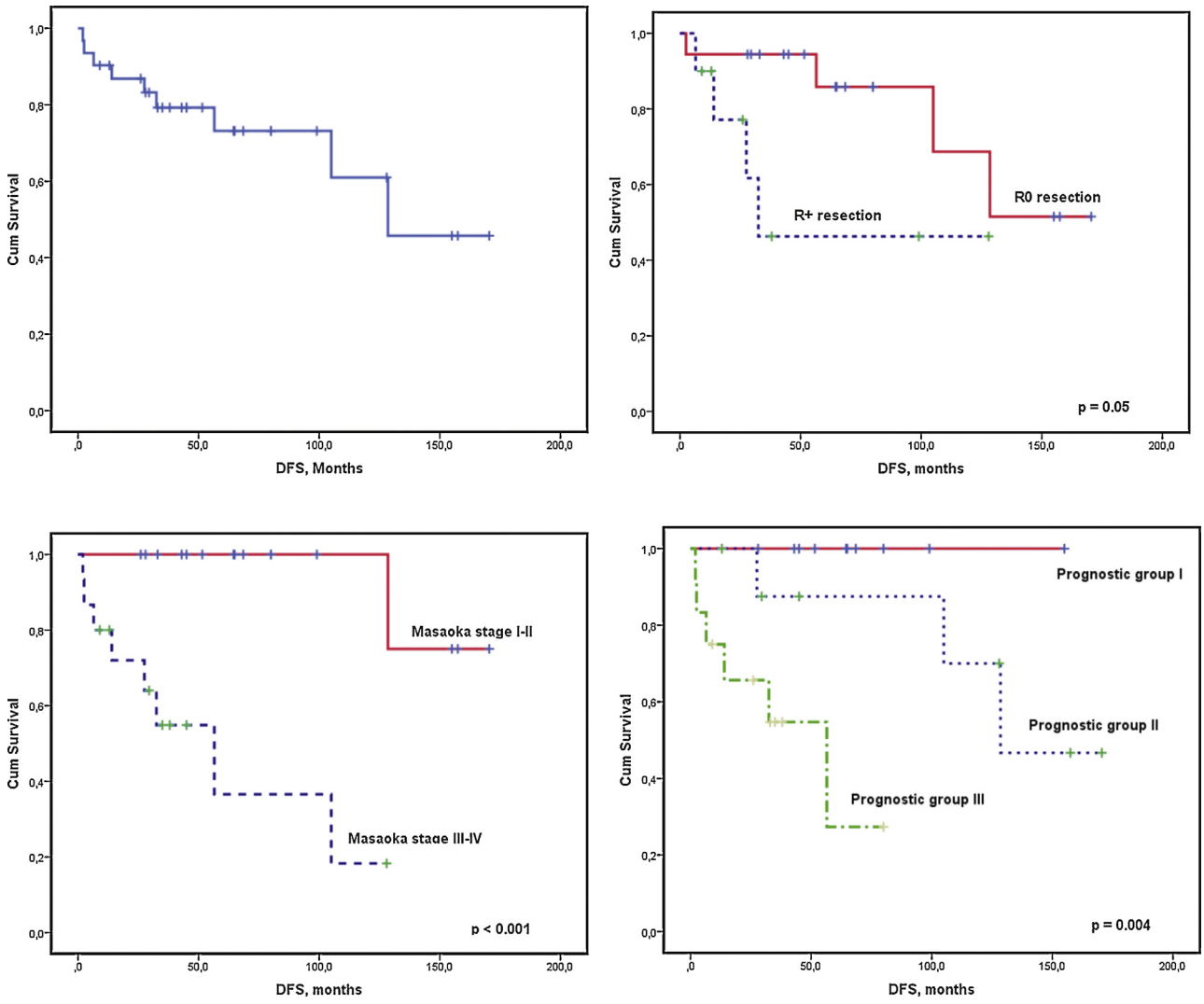

Fig. 2 – Disease-free survival (DFS) and prognostic factors.

diagnosis. However, adjuvant RT showed an acceptable toxicity profile (acute pneumonitis rate was 13%) in our patients. No ≥G3 late toxicity was seen.

Nowadays, thymic tumors are treated with involved-field RT like lung cancer due to the incidence of lymph node involvement is 3% in thymoma patients.[1,32] Although treatment toxicity is a limiting factor, advanced RT techniques and CT-based treatment planning has improved normal tissue protection and allow a safe delivery of RT with increasing survival.[17,33,34] Liao et al. demonstrated that a more advanced technique (four-dimensional (4D) CT simulation with IMRT) led to lower rates of high grade pneumonitis and better survival compared with 3D-CRT in patients with lung cancer.[35]

Advanced stage, large tumor size, non-thymoma histology and R+ resection are reported as predictive factors for recurrence.[2,4,9,26] In a recent study of 25 patients who experienced recurrent disease after initial resection, 82% experienced a second recurrence, although many of these patients had undergone re-surgery.[36] In that case, we should aim to increase LC by preventing recurrence with adjuvant RT in these sensitive tumors. In our study, LC was 86% when all patients are taken into consideration and there is a significant relationship between LC and Masaoka stage, and also an increasing trend in favorable and moderate risk groups.

The limitation of the present study is that 4D-CT simulation was not used, the number of patients was limited and not all have been evaluated with PET/CT. It is reported that standardized uptake values on PET/CT may differentiate WHO type B3, advanced stage and TC with ≥90% sensitivity, evaluate prognosis and allow a neoadjuvant treatment decision.[37]

6. Conclusion

In conclusion, type of resection, Masaoka stage, and prognostic risk classification were significant factors for survival in our study. It was observed that patients with TC generally had stage III–IV disease at diagnosis, were indirectly classified in unfavorable risk group, and had a lower survival rate. However, it is not understood whether there was no recurrence in the favorable group due to the effect of RT or if it can be followed without RT due to indolent behavior of these patients.

Our results emphasize the necessity of discussing the indication for adjuvant RT in the favorable risk group. We suggest that the results of prognostic risk groups should be confirmed in a multicenter study.

Conflict of interest

None declared.

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None declared.

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Contents are solely the responsibility of the authors.

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