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Original Article / Özgün Araştırma

Evaluation of Relapse Risk Factors and Treatment Outcomes in Stage 1 Germ Cell Testicular Tumors

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Abstract

Aim: This study aims to evaluate risk factors for relapse in stage 1 germ cell tumors (GCTs) and compare relapse and survival outcomes between treated and untreated patients.

Method: The study encompasses patients diagnosed with GCTs aged 18 and above, treated and monitored at our oncology clinic between 2012 and 2022. After excluding cases with secondary malignancies, 54 patients with confirmed histopathological stage 1 testicular tumors were analyzed. Patient data, treatment received, and follow-up information were recorded, and statistical analyses were performed using IBM SPSS Statistics version 22.0.

Results: In the seminoma subgroup, relapse was observed in 3 out of 24 (12.5%) patients. Although there was no statistically significant difference in terms of relapse between the groups with and without risk factors such as rete testis involvement and tumor diameter, it was observed that relapse occurred at a higher frequency in both risk groups. Among non-seminomatous tumors, 5 out of 30 (16.7%) patients experienced relapse. Although a notable numerical difference in lymphovascular invasion —a defined risk factor—was observed, statistical significance was lacking. A significant difference in relapse was observed between patients receiving adjuvant treatment and those who did not.

Conclusion: For both seminoma and non-seminomatous tumors at stage 1, surveillance is recommended for patients lacking identified risk factors. Nevertheless, patients with established risk factors warrant personalized consideration, weighing factors such as age, comorbidities, and preferences to guide treatment decisions.

Keywords: Testicular cancer, Seminoma, Germ cell tumors, Non seminomatous germ cell tumors, Adjuvant chemotherapy

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Evre 1 Germ Hücreli Testis Tümörlerinde Relaps Risk Faktörleri ve Tedavi Sonuçlarının Değerlendirilmesi

Öz

Amaç: Bu çalışma, evre 1 germ hücreli tümörlerde nüks risk faktörlerini değerlendirmeyi ve tedavi edilen ve edilmeyen hastalar arasında nüks ve sağ kalım sonuçlarını karşılaştırmayı amaçlamaktadır.

Yöntemler: Çalışma, 2012-2022 yılları arasında tanı konulan 18 yaş ve üstü germ hücreli tümör hastalarını kapsamaktadır ve hastanemiz onkoloji kliniğinde tedavi ve takip edilen hastaları içermektedir. İkincil maligniteleri olan hastalar hariç tutulduktan sonra, onaylanmış histopatolojik evre 1 testis tümörü tanısı konmuş 54 hasta analiz edildi. Hasta verileri, alınan tedaviler ve takip bilgileri kaydedildi ve istatistiksel analizler IBM SPSS Statistics sürüm 22.0 kullanılarak gerçekleştirildi.

Bulgular: Seminoma alt grubunda, 24 hastanın 3'ünde (%12,5) nüks görüldü. Nüks açısından rete testis tutulumu ve tümör çapı gibi risk faktörleri olan ve olmayan gruplar arasında istatistiksel olarak anlamlı bir fark bulunmasa da, her iki risk grubunda da nüksün daha yüksek sayıda olduğu gözlendi. Non-seminomatöz tümörler arasında, 30 hastanın 5'inde (%16,7) nüks yaşandı. Lymphovascular invazyon gibi bir risk faktöründe belirgin sayısal bir fark görülse de, istatistiksel anlamlılık bulunmamaktadır. Adjuvan tedavi alan ve almayan hastalar arasında anlamlı bir nüks farkı gözlemlenmiştir.

Sonuç: Hem seminoma hem de non-seminomatöz tümörlerde evre 1'de, risk faktörleri belirlenmeyen hastalar için takip önerilirken, risk faktörleri belirlenen hastalar özelleştirilmiş bir şekilde ele alınmalı, yaş, eşlik eden hastalıklar ve tercihler gibi faktörler göz önünde bulundurularak tedavi kararları yönlendirilmelidir.

Anahtar kelimeler: Testis kanseri, Seminoma, Non-seminomatöz germ hücreli tümörler, Germ hücreli tümörler, Adjuvan kemoterapi.

INTRODUCTION

Germ cell tumours (GCTs) are the most common solid malignant tumours in men aged 25-34 years. GCTs constitute approximately 95% of all malignant testicular tumours[1,2]. Histopathologically, GCTs are divided into two groups: seminomas and non-seminomas. Non-seminomatous tumours have a higher risk of relapse and a worse prognosis compared to seminomas of the same stage. In both groups, stage 1 disease is the most common presentation[3,4]. Stage 1 disease in GCTs is defined as being confined to the testis, with no radiological, biochemical, or clinical evidence of distant metastasis[5].

There are differing opinions regarding the management of stage 1 disease. While guidelines do not recommend adjuvant therapy as a standard, it has been highlighted as an option for stage 1 seminomas with tumour diameter >4 cm or rete testis involvement, and for non-seminomas with lymphovascular invasion (LVI), all of which have been identified as risk factors for relapse in the 2000s[6]. However, prospective studies conducted by Spanish researchers have reported similar outcomes in terms of overall survival (OS), despite differences in relapse-free survival (RFS) between patients who received adjuvant treatment and those who were managed with surveillance[7,8].

Alongside the limited contribution of adjuvant therapy to RFS, treatment-related side effects are also observed. Myelosuppression, gastrointestinal toxicity, impaired spermatogenesis, and most notably, the development of secondary malignancies, predominantly occurring more than 10 years after treatment, are the significant adverse effects associated with this approach[9].

Despite evolving management strategies for Stage 1 testicular tumors, uncertainties persist. Current practice recognizes active surveillance as an option for Stage 1 GCTs, but relapse risks

vary widely. While certain factors like rete testis involvement and tumor size correlate with relapse in seminomas, LVI independently predicts relapse in non-seminomatous cases. Thus, this study aims to comprehensively assess these risk factors and explore relapse and survival outcomes in treated and untreated Stage 1 patients.

METHODS

This study encompasses patients aged 18 and above who were diagnosed with germ cell testicular tumours and were under follow-up and treatment in our oncology clinic between the years 2012 and 2022. A total of 102 patients with a diagnosis of testicular tumours were identified from the hospital database, and patients with secondary malignancies were excluded from the study. Among them, 60 patients were diagnosed with stage 1 disease at the time of diagnosis. Six patients with incomplete follow-up data were excluded. Complete data were available for 54 patients diagnosed with stage 1 testicular tumours, all of whom had their diagnosis confirmed histopathologically. Patients' age, laboratory and pathological data, treatments received, follow-up durations, last follow-up dates, and current statuses were recorded. Pelvic-abdominal-thoracic computed tomography was employed for staging in all patients. The data for relapse-free survival (RFS) were calculated from the date of the operation to the date of relapse. Ethics committee approval for the study was obtained from the local ethics committee (number: AEŞH-EK1-2023-410, date: 26.07.2023). The study protocol adhered to the principles outlined in the 1964 Declaration of Helsinki.

Statistical analyses were performed using IBM SPSS Statistical Software (IBM SPSS Statistics version 22.0, IBM SPSS, USA). Descriptive analysis was utilized to analyze the clinical and demographic characteristics of the patients. Categorical and numerical variables were presented as numbers and percentages (n,%). Continuous data were expressed as means ± standard deviation if normally distributed; otherwise, they were presented as medians and ranges. Survival outcomes were compared using the Kaplan-Meier method with the log-rank test for univariate analysis or the Cox proportional hazards regression model for multivariate analysis. Only parameters demonstrating statistical significance in univariate analysis were included in the multivariate analysis. A significance level of $P < 0.05$ was considered for all analyses.

RESULTS

A total of 54 patients were included in the study, with a median age of 30 (18-50) years. The majority of patients had no significant comorbidities (96.4%), and 29 (53.7%) had a history of smoking. Among the patients, 30 (55.6%) were diagnosed with non-seminomatous tumours, while 24 (44.4%) had a diagnosis of seminoma. In the non-seminomatous subgroup, pathological subtypes revealed that 27 (50%) had mixed GCTs , and 3 (5.6%) had isolated embryonal carcinoma. Tumours were located in the right and left testes in 29 (53.7%) and 24 (44.4%) patients, respectively, and bilateral involvement was observed in 1 (1.9%) patient. The mean tumour diameter for the entire cohort, seminomas, and non-seminomas were 4.7 cm (SD ± 1.91), 3.92 cm (SD ± 1.38), and 5.1 cm (SD ± 2.12), respectively. The distribution of T stages was T1 in 33 (61.1%) patients, T2 in 20 (37%), and T3 in 1 (1.9%). Among the patients, 28 (51.9%) received adjuvant treatment during a median follow-up duration of 71 months (range: 7-163), while 8 (14.8%) developed relapse. In patients with relapse, the mean RFS was 14.14 months (SD ± 8.09). The clinical, pathological, and laboratory characteristics of the patients are presented in Table I.

Table I: Clinicopathological Characteristics and Laboratory Values of Patients

Features	Total (n)	Seminoma (n)	Non-seminoma (n)	P value (Seminoma vs non-seminoma)
Age (mean ±SD)	31.2 (±7.55)	33.5 (±7.2)	29.4 (±7.5)	0.051
Comorbidity				
Yes	2 (3.7%)	1 (4.2%)	1 (3.3%)	1
No	52 (96.3%)	23 (95.8%)	29 (96.7%)	
Smoker				
Yes	29 (53.7%)	11 (45.8%)	18 (60%)	0.300
No	25 (46.3%)	13 (54.2%)	12 (40%)	
Side				
Right	29 (53.7%)	15 (62.5%)	14 (46.7%)	
Left	24 (44.4%)	9 (37.5%)	15 (50%)	0.388
Bilateral	1 (1.9%)	0	1 (3.3%)	
pT(n,%)				
T1	33 (61.1%)	16 (66.7%)	17 (56.7%)	
T2	20 (37%)	8 (33.3%)	12 (40%)	0.555
T3	1 (1.9%)	0	1 (3.3%)	
Tumor size (mean ±SD)	4.57(±1.91)	3.91 (±1.38)	5.1 (±2.12)	0.220
Preop LDH (mean ±SD)	272.9(±92.2)	243.5(±60.9)	306.4(±111.3)	0.075
Preop hCG (mean ±SD)	86.9(±217.9)	57.1(±192.2)	86.5 (±234.5)	0.062
Preop AFP (mean ±SD)	329 (±1244)	3.13 (±1.92)	554.6 (±1592)	**<0.001**

AFP: Alfa Feto Protein, hCG: Human Chorionic Gonadotropin, LDH: Lactat Dehydrogenase, SD: Standard Deviation

Within the seminoma subgroup, 3 (12.5%) patients experienced relapse during a median follow-up duration of 73 months (range: 7-163). Median time to relapse is 26(12-85) months. In this group, 6 patients had rete testis involvement, while 18 did not. Among those with relapse, 1 out of 6 (16.7%) had rete testis involvement, while 2 out of 18 (11.1%) did not. The difference was not statistically significant (p=0.597). Regarding tumour size, 15 had tumours with a diameter below 4 cm, and 9 had tumours with a diameter of ≥ 4 cm. Among patients with tumours below 4 cm, only 1 out of 15 (6.7%) experienced relapse, while among those with tumours of ≥ 4 cm, 2 out of 9 (22.2%) experienced relapse. The difference was not statistically significant (p=0.308).

Within the non-seminoma subgroup, 5 (16.7%) patients experienced relapse during a median follow-up duration of 53 months (range: 11-142). The median time to relapse is 10(4-22) months. In this group, 10 (33.3%) had LVI, while 20 (66.7%) did not. No relapse occurred among those with LVI, while among those without LVI, 5 out of 20 (25%) experienced relapse. The difference was not statistically significant (p=0.109). However, when analyzing the rates of adjuvant treatment, among those with LVI, 8 (80%) received adjuvant therapy, while among those without LVI, 8 (40%) received adjuvant therapy. Information regarding risk factors in patients with and without relapse is presented in Table II.

Table II: Risk Factors in patients with and without relapse

	Relapse Cases	Non-Relapse Cases	p value
Seminoma			
Median time to relaps(months)	26(12-85)		
Rete Testis invasion			
Yes	1(16.7%)	5(83.3%)	0.597
No	2(11.1%)	16(88.9%)	
Tumor diameter			
<4 cm	1(6.7%)	14(93.3%)	0.308
≥ 4 cm	2(22.2%)	7(77.8%)	
Adjuvant Treatment			
Yes	2(16.7%)	10(83.3%)	0.500
No	1(8.3%)	11(91.7%)	
Non-Seminoma			
Median time to relaps(months)	10 (4-22)		
Lenfovaskular invasion (LVİ)			
Yes	0(0%)	10(100%)	0.109
No	5(25%)	15(75%)	
Adjuvant Treatment			
Yes	0(0%)	16(100%)	**0.090**
No	5(35.7%)	9(64.3%)	

DISCUSSION

The management of stage 1 testicular tumors continues to evolve over time. In the early stages, retroperitoneal lymph node dissection (RPLND) was performed alongside orchiectomy. However, with studies showing that radiotherapy yields similar effectiveness to RPLND, post-orchiectomy radiotherapy (RT) has become a widely used approach in seminomas[10,11]. Considering the toxicities associated with alternative treatment strategies, active surveillance has emerged as a viable option for stage 1 GCTs, particularly given the availability of successful salvage therapies in the present day[12]. Nevertheless, the risk of relapse remains noteworthy, ranging from 20% in stage 1 seminomas to 50% in high-risk stage 1 non-seminomatous tumors[13]. For seminomas, risk factors for relapse include rete testis involvement and tumor diameter <4 cm, while in non-seminomas, LVI is recognized as an independent risk factor[6,14,15]. Given the elevated risk of relapse, the significance of accurately identifying these risk factors becomes evident.

In our study, within the seminoma subgroup, relapse occurred in 12.5% patients. No statistically significant relationship was observed between relapse and risk factors such as rete testis involvement and tumor diameter. However, proportionally, it is noticeable that there was a higher numerical incidence of relapse in both risk groups—those with rete testis involvement and those with larger tumor diameters. Due to the limited number of patients and variations in the receipt of adjuvant treatment among the risk groups, a direct interpretation is challenging. Looking at previous studies, relapse rates have ranged between 1.5% and 13.6%[16,17]. In this study, the median time to relapse was found to be 26 months (range: 12-85). Other seminoma studies have similarly reported median times to relapse ranging from 7 to 16 months[1,17].

Looking at non-seminomatous tumors, relapse occurred in 16.7% patients. Although there was a notable numerical difference in LVI —a defined risk factor between patients with and without relapse—this difference was not statistically significant. Regarding adjuvant treatment, among those who received adjuvant therapy, no relapses were observed, whereas 35.7% of patients who did not receive adjuvant therapy experienced relapse. There was a statistically significant difference in relapse between patients who received adjuvant treatment and those who did not. In a study by Kobayashi et al., no relationship was found between relapse and LVI. Among patients with non-seminomatous stage 1 testicular tumors, 9 out of 40 (22.5%) experienced relapse. All relapses were observed in the group of patients who did not receive adjuvant treatment (9 out of 36, 22.5%). The mean time to relapse was reported as 6 months (range: 2-13) in their study1. In a study by Kollmannsberger et al., relapse was observed in 221 out of 1139 (19%) patients. The median time to relapse was 6 months (range: 1-75) in their study[17]. Similarly, other studies conducted in a similar manner have reported relapse rates in the range of 25-30% for stage 1 non-seminomatous tumors[18].

Our study has certain limitations. Firstly, it should be noted that the retrospective design and single-center nature of the study may introduce potential biases. Additionally, the limited number of patients and the inadequate number of patients receiving treatment and being followed up reduce the statistical power. Another limitation of our study is the inability to assess the factor of embryonal carcinoma, which is recognized as a risk factor, due to the retrospective design, as access to this data was not available for all patients. When interpreting the results of the study, it is important to consider these limitations.

CONCLUSION

For patients with established risk factors, while recommendations for adjuvant treatment exist, a universally accepted standardized approach has yet to be established. In such scenarios, the most fitting approach would involve considering factors such as the patient's adherence and collaboration with follow-up and treatment, age, fertility expectations, comorbidities, and preferences when arriving at decisions.

Ethics Committee Approval: Ethics committee approval for the study was obtained from the local ethics committee (number: AEŞH-EK1-2023-410, date: 26.07.2023). The study protocol adhered to the principles outlined in the 1964 Declaration of Helsinki.

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