Turkish Journal of Clinics and Laboratory

To cite this article: Sezgin Y, Karhan O, Bicer A, Ileri S, Yerlikaya H, Tunc S, Aydin I, Urun M, Aldemir MN. Prognostıc factors in testicular cancer. Turk J Clin Lab 2024; 2: 176-181

Research Article

Prognostıc factors in testicular cancer

Testis kanserinde prognostik faktörler

Yasin Sezgin*[1], Ogur Karhan[2], Abdurrahman Bicer[3], Serdar Ileri[4], Halis Yerlikaya[4], Sezai Tunc[6], Ibrahim Aydin[3], Muslih Urun[1], Mehmet Naci Aldemir[1]

[1]Yüzüncü Yıl University Faculty of Medicine, Clinic of Mecical Oncology Van, Turkey,
[2]Gaziantep private Liv hospital medical oncology department Gaziantep, Turkey,
3Van training and research Hospital Internal Medicine Van, Turkey,
4Gazi Yaşargil training and research Hospital. Department of Medical Oncology, Diyarbakır, Turkey,
[5]Batı Private Hospital, Medical Oncology, Diyarbakır, Turkey,
[6]Dicle University Faculty of Medicine, Department of Medical Oncology, Diyarbakır, Turkey.

Abstract

Aim: Testicular cancer is the most common cancer in men aged 15-35 years and accounts for 1% of all lifetime male cancers. There are two histologic subtypes: seminoma and nonseminoma. In our study, we aimed to investigate the factors predicting recurrence in early stage testicular cancers.

Material and Methods: The present study is a retrospective analysis of early-stage testicular cancers admitted to the Medical Oncology Clinic of our hospital between 2006 and 2018. A total of 344 patient files were reviewed, and 130 patients who met the study criteria were included in the analysis. The primary objective of this study was to investigate the factors predicting recurrence in early-stage testicular cancer. The relationship between these factors and disease-free survival (DFS) was also analysed.

Results: In the evaluation of DFS in patients with nonseminoma with and without lymphovascular invasion, no median DFS value was reached in both groups. However, DFS was found to be worse in patients with LVI (p=0.037). In the comparison of stage 1 with stage 2 in seminoma patients, median DFS values could not be reached. However, there was a statistically significant difference between the two groups in terms of recurrence (p=0.019).

Conclusions: In our study, we found no correlation between tumour size, embryonal carcinoma predominance, tunica albuginea invasion, spermatic cord involvement and tumour marker values and recurrence in nonseminoma germ cell testicular tumours. Disease-free survival was shorter in patients with lymphovascular invasion (LVI) compared to those without LVI. In seminoma patients, lymphovascular invasion, spermatic cord involvement, tunica albuginea involvement and rete testis involvement were not associated with disease recurrence. However, higher disease stage predicted the risk of recurrence.

Keywords: testicular cancer, prognosis, disease-free survival

Corresponding author*: Yasin Sezgin, Yüzüncü Yıl University Faculty of Medicine, Clinic of Mecical Oncology Van, Turkey.
E-mail: dr.yasin1982@hotmail.com
Orcid: 0000-0003-4122-8389
Doi: 10.18663/tjcl.1445426
Recevied: 01.03. 2024 accepted: 27.05.2024

Öz

Amaç: testis kanserleri 15-35 yaş arası erkeklerde en sık görülen kanser olup tüm yaşam boyu erkek kanserlerinin %1'ini oluşturmaktadır. Seminom ve nonseminom olarak iki histolojik subtipi vardır. Çalışmamızda erken evre testis kanserlerinde nüksü predikte eden faktörleri araştırmayı amaçladık

Gereç ve Yöntemler: Çalışmamız, 2006-2018 yılları arasında hastanemiz Tıbbi onkoloji kliniğine başvuran erken evre testis kanserlerinin incelendiği retrospektif bir çalışmadır. Çalışma sırasında 344 hasta dosyası taranmış olup çalışma kriterlerine uyan 130 hasta çalışmaya dahil edildi. Bu çalışmada primer amacımız erken evre testis kanserlerinde nüksü predikte eden faktörleri araştırmaktı. Nüksü predikte eden faktörler ile hastalıksız sağ kalım (DFS) arasındaki ilişki analiz edildi.

Bulgular: Nonseminoma hastalarında Lenfovasküler invazyonu olan ve olmayan hastaların DFS açısından yapılan değerlendirmede, her iki grupta da median DFS değerine ulaşılamadı. Ancak LVİ olan hastalarda DFS daha kötü olarak saptandı (p=0.037). Seminom hastalarında evre 1 ile evre 2'nin karşılaştırılmasında median DFS değerlerine ulaşılamadı, ancak iki grup arasında rekürrens açısından istatiksel farklılık vardı (p=0.019)

Sonuçlar: Çalışmamızda nonseminom germ hücreli testis tümörlerinde tümör boyutu, embriyonel karsinom predominans, tunika albuginea invazyonu, spermatik kord tutulumu ve tümör markır değerleri ile nüks arasında bir ilişki saptamadık. LVİ olan ve olmayanlar kıyaslandığında, LVİ olan hastalarda DFS daha kısa idi. Seminom hastalarında lenfovasküler invazyon, spermatik kord tutulumu, tunika albuginea tutulumu ve rete testis tutulumu ile hastalık rekürensi arasında ilişki izlenmezken, hastalığın evresinin yüksek olması rekürrens riskini predikte etmekte idi.

Anahtar Kelimeler: testis kanseri, prognoz, hastalıksız sağ kalım

Introduction

Testicular cancer is one of the most common cancers in men between the 2nd and 3rd decades of life, accounting for 1% of all lifetime cancers in men. Previously responsible for 11% of cancer deaths in men aged 25-34, it now accounts for only 0.1% of male deaths, according to 2019 data (1). Testicular cancers may contain single or multiple histological components. They are classified as pure seminomas and non-seminomas (2,3). Nonseminomas are less common but have a more aggressive course. Sometimes two components are present together. In this case, it should be treated as non-seminoma testicular cancer because of its more aggressive course (4).

Orchiectomy cures 85% of stage 1 seminomas and 75% of stage 1 non-seminomas (5,6). For patients with stage 1 seminoma, drug-free follow-up after orchiectomy is recommended in the absence of risk factors (7). While the bleomycin-etoposide-cisplatin (BEP) protocol is the standard of care for advanced seminoma and non-seminoma patients, single-dose carboplatin is also an option for stage I seminoma patients due to its low toxicity (8). Adjuvant treatment after surgery significantly reduces the risk of recurrence, but in many patients this approach leads to unnecessary treatments and short- and long-term complications associated with these treatments. To avoid unnecessary adjuvant treatment, it is important to identify factors that predict recurrence and to plan adjuvant treatment according to these factors (9,10). Although early-stage testicular cancer has a good prognosis, 10-15% of stage 1 seminomas and 25-30% of stage 1 non-seminomas have occult metastases (11). In early-stage testicular cancer, several risk factors have been identified as predictors of recurrence. For non-seminoma, these risk factors include T3-T4 tumour staging and lymphovascular invasion (12-15). For seminoma, increasing tumour size is a risk factor, but no cut-off value has been established (16-18). The same studies also reported rete testis involvement as a predictor of disease recurrence. With this literature information in mind, we analysed the factors that influence prognosis in early-stage seminoma and non-seminoma testicular cancer.

Material and Methods

Our study is an analysis of early stage testicular cancer admitted to our Medical Oncology Clinic of Dicle University Medical Faculty between 2006 and 2018. Patients aged 18-80 years who had at least two outpatient clinic visits after diagnosis were included in this study; patients aged 17 years and younger and patients aged 81 years and older were excluded, as were patients with a secondary malignancy and patients who did not attend regular follow-up visits. During the trial, 344 patient records were reviewed and 130 patients who met the study criteria were included in the study. Our primary objective in this study was to investigate the factors that predict recurrence

in early-stage testicular cancer. Clinical and demographic characteristics, treatment regimens, histopathological characteristics of the tumour and disease-free survival (DFS) of the patients were analysed. Histopathological features of the tumour were analysed for tumour size, lymphovascular invasion, rete testis involvement, spermatic cord involvement, embryonal carcinoma content, tunica albuginea involvement and their relationship with recurrence.

Patients were monitored on a monthly basis for the initial six-month period, with follow-up assessments conducted every three months between six and 24 months, and then every six months.

The therapeutic regimens prescribed for patients; Standard BEP consisted of cisplatin 20 mg/m2 days 1 through 5 and etoposide 100 mg/m2 administered days 1 through 5 for four cycles. Bleomycin was administered at a dose of 30 mg weekly for 12 weeks (total dose of bleomycin, 360 mg). A single dose of carboplatin was administered, with the area under the curve (AUC) calculated at 7.

Ethical approval: Prior to the start of this study, ethical approval dated 16.07.2020 and numbered 270 was obtained from the Clinical Research Ethics Committee of Dicle University Faculty of Medicine. Written informed consent was obtained from all patients enrolled in our study in accordance with the Declaration of Helsinki.

Statistical analysis

Categorical variables are presented as numbers (percentages) and continuous variables as means ± SD. Histograms and the Kolmogorov-Sminov test were used to determine whether numerical values followed a normal distribution. As quantitative variables were normally distributed, Student's t-test was used to compare two independent groups. Survival times were calculated using the Kaplan-Meier method and compared using the log-rank test. Prognostic factors for survival were assessed by Cox regression analysis. An overall p-value of less than 0.05 was considered statistically significant. The statistical software package SPSS (IBM, version 25) was used for the analysis of our study.

Results

In this study of 130 patients, the median age of the patients was 34.9 (26.2-38.9) years. The mean follow-up period of the patients was 67.8 months (2.6-106.3). There were 60 non-seminoma and 70 seminoma histological subtypes. The general characteristics of the patients are shown in Table 1.

In patients with nonseminoma type: When we examined the risk factors for recurrence in no- seminomatous patients; 21 (35%) had lymphovascular invasion, 11 (18.3%) had spermatic cord involvement, 17 (28.3%) had tunica albuginea involvement and 15 (25%) had rete testis involvement. Embryonal carcinoma predominance was present in 35 patients (58.3%). The mean tumour diameter was 4.4 cm. 38 (63.3%) patients had stage I disease and 22 (36.7%) patients had stage II disease. Chemotherapy regimen was bleomycin-etoposide-cisplatin (BEP) protocol in 47 (78.3%) patients and active surveillance in 13 (21.7%) patients. A total of 12 patients relapsed, including 10 patients with LVI. Lactate dehydrogenase (LDH) was 201 U/L in stage I patients and 229 U/L in stage II patients (p=0.006). When patients with and without lymphovascular invasion (LVI) were evaluated for DFS, DFS was worse in patients with LVI (p=0.037) (Figure 1). The relationship between tumour diameter, rete testis involvement, embryonal carcinoma predominance, spermatic cord involvement, tunica albuginea involvement and tumour marker levels and recurrence was evaluated. No significant correlation was found between these parameters and recurrence.

Table 1. General Characteristics Of Patients

Non seminoma	N	%	Semi-noma	N	%
Stage			Stage		
Stage I	38	63.3	Stage I	61	87.1
Stage II	22	36.7	Stage II	9	12.9
Lymphovascular invasion			Lymphovascular invasion		
Yes	21	35	Yes	29	41.4
No	39	65	No	41	58.6
The invasion of the spermatic cord			The invasion of the sper-matic cord		
Yes	11	18,3	Yes	10	14.3
No	49	81,7	No	60	85.7
Tunica albuginea involvement			Tunica albuginea in-volvement		
Yes	17	28.3	Yes	23	32.9
No	43	71.7	No	47	67.1
Rete testicular invasion			Rete testicular invasion		
Yes	15	25	Yes	20	28.6
No	45	75	No	50	71.4
Tumour diameter			Tumour diameter		
<4cm	25	41.7	<3cm	22	31.4
>4cm	35	58.3	>3cm	48	68.6
Beta HCG*			Beta HCG*		
Normal	49	81.7	Normal	66	94.3
High	11	18.3	High	4	5.7
Lactate dehydrogenase			Lactate dehydrogenase		
Normal	46	76.7	Normal	60	85.7
High	14	23.3	High	10	14.3
Treatment received			Treatment received		
Observation	13	21.7	Observ	20	28.6
Carboplatin	-	-	Carbo-platin	31	44.3
BEP**	47	78.3	BEP**	19	27.1
Relapse status			Relapse status		
Yes	12	20	Yes	10	14.3
No	48	80	No	60	85.7

* B HCG: Human chorionic gonadotropin
** BEP: Bleomycin – Etoposide - Cisplatin

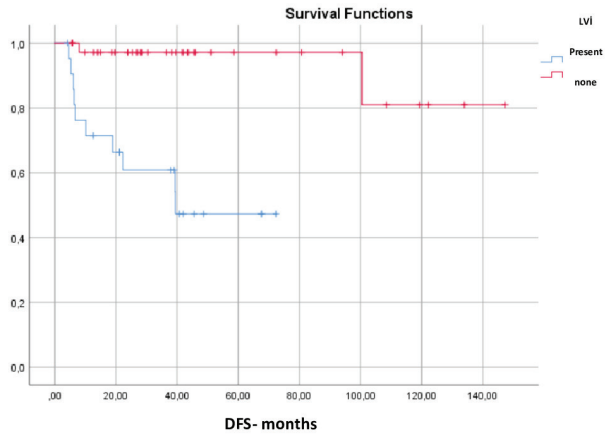

Figure 1: Disease-free survival according to lonfovascular invasion status

DFS: Disease-free survival

LVİ: lonfovascular invasion

In patients with seminoma type: İn terms of risk factors for recurrence in seminomatous patients: 29 (41.4%) had lymphovascular invasion, 10 (14.3%) had spermatic cord involvement, 23 (32.9%) had tunica albuginea involvement and 20 (28.6%) had rete testis involvement. Sixty-one (87.1%) patients had stage I disease and 9 (12.9%) patients had stage II disease. Chemotherapy regimens included BEP protocol in 19 (27.1%) patients, single-agent carboplatin in 31 (44.3%) patients, and observation in 20 (28.6%) patients. On statistical analysis, there was a statistical difference between stage 1 and stage 2 in terms of recurrence (p=0.019) (Figure 2). No significant correlation was observed between other parameters and recurrence.

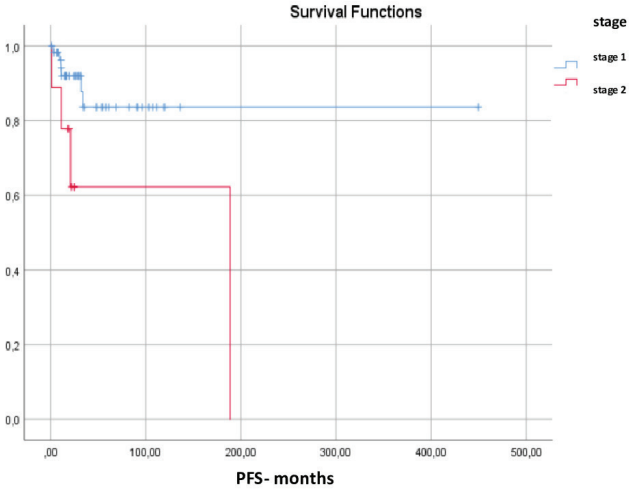

Figure 2: Disease-free survival according to stage

DFS: Disease-free survival

Discussion

The follow-up and treatment algorithm for testicular tumours varies according to tumour pathology and stage. The most important risk factors for recurrence in patients with nonseminoma tumours who have undergone orchiectomy are LVI, embryonal carcinoma predominance, and T3-T4 tumour. In the absence of any of these risk factors, the disease is considered low risk. The risk of recurrence in the low-risk group varies between 10 and 14%. In the presence of any risk factor, the risk of disease increases from 40 to 55%. Consequently, absolute adjuvant treatment should be recommended for these patients (12-15). We evaluated these risk factors and the relationship between tumour diameter, rete testis involvement, spermatic cord involvement, tunica albuginea involvement, and tumour marker levels and the risk of recurrence. Our findings indicate that patients with LVI exhibited a shorter DFS time and a higher LDH rate than those without LVI. Additionally, the LDH rate was higher in stage II tumours than in stage I tumours.

It is estimated that 90% of early-stage seminomas are in the low-risk group and have a favourable prognosis with orchiectomy alone. Their five-year survival rate is approximately 92%. Conversely, 10% of patients are in the intermediate-risk group, with a five-year survival rate of approximately 72% (19). In patients with advanced-stage seminoma, risk stratification includes lymph node and extrapulmonary involvement and elevated alpha-fetoprotein, which are considered to be known prognostic indicators (19). In our study, we investigated the prognostic significance of factors such as lymphovascular invasion, spermatic cord involvement, tunica albuginea involvement, and rete testis involvement. Our findings did not indicate a significant correlation between these factors and recurrence in patients with stage I-II seminoma. While orchiectomy or one or two cycles of carboplatin regimens are employed in early-stage seminoma patients (8), combination chemotherapies including cisplatin, etoposide and bleomycin (BEP) are utilised in advanced-stage patients (20). In our patient population, patients who had undergone orchiectomy and were undergoing active follow-up were administered a single course of carboplatin and BEP. At the time of initial presentation, 80% of patients had stage I disease, while 15% had stage II disease. However, the prognosis of stage I disease is superior to that of stage II disease (21). In our study, 61 (87.1%) patients had stage I disease and 9 (12.9%) patients had stage II disease, in accordance with the literature. There was a statistically significant difference between the two groups in terms of DFS between stage 1 and 2 (p=0.019). As with many cancers, the stage of seminoma affects the prognosis of the disease and thus the risk of recurrence. An increased tumour size has been identified as a

risk factor for recurrence in seminoma. While there is no established cut-off value for tumour size, the American Joint Committee on Cancer (AJCC) 8th edition states that tumours larger than 3 cm have a high risk of recurrence (22). In our study, there was no difference in recurrence between patients with tumours above and below 3 cm.

In the non-seminomatous group, patients with lymphovascular invasion (LVI) should be monitored more closely, as they have a higher risk of recurrence even if they receive treatment. The same is true for seminoma stage 2 patients. Stage 2 seminoma patients should be monitored more closely, as they have a higher risk of recurrence than stage 1 patients despite receiving adjuvant treatment.

Testicular cancer is a disease with low recurrence rates and long overall survival. However, in our study, there were limitations, including the small number of patients with recurrence and the follow-up periods being insufficient for a disease with long survival such as testicular cancer. Furthermore, the fact that recurrence was calculated according to histopathological evaluations in treated patients was a confounding factor. In addition to this, the fact that our study was single-centre and retrospective was another limitation of our study. Nevertheless, we believe that our study is of value because it reflects real-world data.

Conclusion

When we examined the factors that might predict the risk of recurrence in non-seminoma germ cell testicular tumors, we did not find a significant relationship between tumor diameter, rete testis involvement, embryonal carcinoma predominance, spermatic cord involvement, tunica albuginea involvement, and tumor marker level and recurrence. The DFS time of patients with lymphovascular invasion was found to be shorter than that of patients without lymphovascular invasion. In patients with seminoma, there was no correlation between potential predictors such as lymphovascular invasion, spermatic cord involvement, tunica albuginea involvement, and rete testis involvement and disease recurrence. However, higher disease stage predicted the risk of recurrence. As the survival time in testicular cancer is long, further studies with longer follow-up periods are required to confirm these findings.

Ethical approval

Prior to the start of this study, ethical approval dated 16.07.2020 and numbered 270 was obtained from the Clinical Research Ethics Committee of Dicle University Faculty of Medicine. Written informed consent was obtained from all patients enrolled in our study in accordance with the Declaration of Helsinki.

Conflict of interest

The authors declared no potential conflicts of interest for his study.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019; 69:7.
2. Groll RJ, Warde P, Jewett MA. A comprehensive systematic review of testicular germ cell tumor surveillance. Crit Rev Oncol Hematol 2007; 64:182.
3. Warde P, Gospodarowicz M. Evolving concepts in stage I seminoma. BJU Int 2009; 104:1357.
4. Vasdev N, Moon A, Thorpe AC. Classification, epidemiology and therapies for testicular germ cell tumours. Int J Dev Biol 2013;57:133–139.
5. Van de Wetering RAW, Sleijfer S, Feldman DR, Funt SA, Bosl GJ, de Wit R. Controversies in the management of clinical stage I seminoma: carboplatin a decade in-time to start backing out. J Clin Oncol. 2018; 36(9): 837-840.
6. Sturgeon JF, Moore MJ, Kakiashvili DM, Duran I, Anson LC, Berthold DR, et al. Non-risk-adapted surveillance in clinical stage I nonseminomatous germ cell tumors: the Princess Margaret Hospital's experience. Eur Urol 2011; 59:556.
7. Stenning S, Oliver T, Mead B, Gabe R. Carboplatin in clinical stage I seminoma: a valuable option for patient management. J Clin Oncol 2011; 29:4210.
8. Oliver RT, Mead GM, Rustin GJ, Joffe JK, Aass N, Coleman R, et al. Randomized trial of carboplatin versus radiotherapy for stage I seminoma: mature results on relapse and contralateral testis cancer rates in MRC TE19/EORTC 30982 study (ISRCTN27163214). J Clin Oncol 2011; 29:957.
9. Stephenson AJ, Sheinfeld J. Management of patients with low-stage nonseminomatous germ cell testicular cancer. Curr Treat Options Oncol 2005; 6:367.
10. Pectasides D, Pectasides E, Constantinidou A, Aravantinos G. Current management of stage I testicular non-seminomatous germ cell tumours. Crit Rev Oncol Hematol 2009; 70:114.
11. P. Albers (Chair), W. Albrecht, F. Algaba, C. Bokemeyer, G. CohnCedermark, K. Fizazi, et al. Guidelines Associates: J.L. Boormans,, J. Mayor de Castro EAU Guidelines 2018 http://uroweb.org/ guideline/testicular-cancer/
12. Lashley DB, Lowe BA. A rational approach to managing stage I nonseminomatous germ cell cancer. Urol Clin North Am 1998;25:405–23.
13. Spiess PE, Tannir NM, Brown GA, Liu P, Tu SM, Evans JG, et al. Recurrence in nonseminomatous germ cell testis tumor patients with no viable tumor at postchemotherapy retroperitoneal lymph node dissection. Urology. 2007 Dec;70(6):1173-8.

14. Donohue JP, Thornhill JA, Foster RS, Rowland RG, Bihrle R. Primary retroperitoneal lymph node dissection in clinical stage A nonseminomatous germ cell testis cancer. Review of the Indiana University experience 1965–1989. Br J Urol 1993;71:326
15. Krege S, Souchon R, Schmoll HJ; German Testicular Cancer Study Group. Interdisciplinary consensus on diagnosis and treatment of testicular germ cell tumours: result of an update conference on evidence-based medicine (EBM). Eur Urol 2001;40(4):372-391
16. Tandstad T, Stahl O, Dahl O, Haugnes HS, Hakansson U, Karlsdottir A, et al. Treatment of stage I seminoma, with one course of adjuvant carboplatin or surveillance, risk-adapted recommendations implementing patient autonomy: a report from the Swedish and Norwegian Testicular Cancer Group (SWENOTECA). Ann Oncol 2016;27:1299-1304.
17. Warde P, Specht L, Horwich A, Oliver T, Panzarella T, Gospodarowicz M, et al. Prognostic factors for relapse in stage I seminoma managed by surveillance: a pooled analysis. J Clin Oncol 2002;20:4448-4452.
18. Aparicio J, Maroto P, Garcia del Muro X, Munoz AS, Guma J, Margeli M, et al. Prognostic factors for relapse in stage I seminoma: a new nomogram derived from three consecutive, risk-adapted studies from the Spanish Germ Cell Cancer Group (SGCCG). Ann Oncol 2014;25:2173-2178.
19. International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group. J Clin Oncol 1997; 15:594
20. Feldman DR, Bosl GJ, Sheinfeld J, Motzer RJ. Medical treatment of advanced testicular cancer. JAMA 2008; 299:672.
21. Birch R, Williams S, Cone A, Einhorn L, Roark P, Turner S, et al. Prognostic factors for favorable outcome in disseminated germ cell tumors. J Clin Oncol 1986; 4:400.
22. Amin MB, Edge SB, Greene F, Compton CC, Gershenwald JE, Brookland RK, et al., eds. AJCC Cancer Staging Manual, 8th ed. New York: Springer International Publishing; 2017.