DOI: 10.4274/anatoljmed.2025.09327
Anatol J Gen Med Res 2025;35(3):269-275

CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

ANATOLIAN JOURNAL of GENERAL MEDICAL RESEARCH

Long-term Outcomes in Stage I Seminoma Patients: A Single-center Retrospective Study

Evre I Seminom Hastalarının Uzun Dönem Takip Sonuçları: Tek Merkez Deneyimi

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Cite as: Ön S, Ayaz D, Altın Z, Keskin MZ. Long-term outcomes in stage I seminoma patients: a single-center retrospective study. Anatol J Gen Med Res. 2025;35(3):269-275

Abstract

Objective: This study aims to evaluate long-term outcomes and relapse rates in patients with stage I seminoma treated at our center and to assess the effectiveness and safety of active surveillance and adjuvant therapy in clinical practice.

Methods: This retrospective study included 63 patients diagnosed with stage I seminoma at our institution between 2007 and 2024. All patients underwent radical inguinal orchiectomy. Patient demographics, tumors' pathological features, relapse rates, treatment-related adverse events, and long-term oncological outcomes were analyzed.

Results: The median age was 36 years, and the median follow-up was 50.5 months. Tumor size was ≥4 cm in 52.4% of cases, and rete testis invasion was present in 33.3%. Postoperative management included surveillance (n=43), adjuvant carboplatin (n=18), and radiotherapy (n=2). Adjuvant therapy was more frequently administered in patients with higher-risk features. Two patients (3.2%) relapsed during surveillance, both achieved a complete response with salvage chemotherapy. No cancer-related deaths occurred, and treatment-related toxicity was minimal, with only one case of infertility reported.

Conclusion: Our findings confirm that stage I seminoma has an excellent prognosis regardless of the initial post-orchiectomy management approach. Carboplatin is a safe adjuvant treatment option. Surveillance may prevent unnecessary adjuvant treatment. Decisions regarding adjuvant therapy should be patient-centered, based on the individual risk of relapse and the potential toxicity of therapy.

Keywords: Seminoma, testicular neoplasm, human chorionic gonadotropin, beta subunit, adjuvant chemotherapy, surveillance

Öz

Amaç: Bu çalışma ile evre I seminom hastalarında cerrahi sonrası uzun dönem takip sonuçlarını ve nüks oranlarını değerlendirmeyi, bunun yanı sıra klinik pratikte aktif izlem ve adjuvan tedavinin etkinliğini ve güvenilirliğini incelemeyi amaçladık.

Yöntem: 2007-2024 yılları arasında kurumumuzda evre I seminom tanısı almış 63 hastanın verileri retrospektif olarak incelenmiş ve çalışmaya dahil edilmiştir. Tüm hastalara radikal inguinal orşiektomi uygulanmıştır. Hastaların demografik özellikleri, tümörlerin patolojik özellikleri, nüks oranları, tedaviye bağlı yan etkiler ve uzun dönem onkolojik sonuçlar istatistiksel olarak analiz edilmiştir.

Bulgular: Ortanca yaş 36, ortanca takip süresi 50,5 aydır. Tümörlerin %52,4'ü ≥4 cm, %33,3'ünde rete testis invazyonu vardır. Postoperatif dönemde 43 hastada aktif izlem, 18 hastada adjuvan karboplatin, 2 hastada ise adjuvan radyoterapi uygulanmıştır. Yüksek risk özellikleri olan hastalarda adjuvan tedavi

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Received/Geliş tarihi: 03.05.2025
Accepted/Kabul tarihi: 22.09.2025
Published date/Yayınlanma tarihi: 30.12.2025

Öz

daha sık tercih edilmiştir. İzlem grubunda iki hastada (%4,7) nüks gelişmiş ve her ikisi de salvage kemoterapi sonrası tam yanıt vermiştir. Testis kanserine bağlı ölüm görülmemiş, ciddi tedaviye bağlı toksisite sadece bir infertilite olgusu ile sınırlı kalmıştır.

Sonuç: Bulgularımız evre I seminonum cerrahi sonrası tedavi seçiminden bağımsız olarak mükemmel prognoza sahip olduğunu doğrulamaktadır. Karboplatin güvenli bir adjuvan tedavi seçeneğidir. Aktif izlem, gereksiz adjuvan tedavilerin önüne geçebilir ve güvenli görünmektedir. Adjuvan tedavi kararı, nüks riski ve tedaviye bağlı toksisite göz önünde bulundurularak hasta tercihleri de göz önüne alınarak verilmelidir.

Anahtar kelimeler: Seminoma, testis neoplasm, insan koryonik gonodotropin, beta subunit, adjuvan kemotereapi, surveyans

Introduction

Germ cell testicular tumors are among the most common solid tumors in men under the age of 40. Globally, approximately 75.000 men are diagnosed with testicular cancer each year[1]. In our country, the annual incidence is around 1.700 cases. The disease is more prevalent among Caucasian populations, particularly in Scandinavian countries, and its incidence has been increasing over time[2]. Histologically, germ cell tumors are classified into two main groups: seminomas and non-seminomas. Distinguishing between these subtypes is critical, as they differ in clinical course and systemic treatment approaches. Approximately half of all germ cell testicular tumors are of pure seminoma histology[3].

Patients most commonly present with a painless testicular mass. Physical examination and scrotal ultrasonography constitute the first-line diagnostic steps. Three serum tumor markers have established roles in the diagnosis and management of testicular cancer: alpha-fetoprotein (AFP), the beta subunit of human chorionic gonadotropin (β-hCG), and lactate dehydrogenase (LDH). While elevated AFP levels are not typically observed in pure seminomas, mild elevations in β-hCG and LDH levels may be present. Radical inguinal orchiectomy provides both a definitive histological diagnosis and local tumor control. Staging after orchiectomy is performed using radiological imaging and postoperative tumor marker levels. According to the eighth edition of the American Joint Committee on Cancer (AJCC) staging system, disease confined to the testis is classified as stage I[4]. In the presence of persistently elevated postoperative LDH or β-hCG, the disease is classified as stage IS, which represents a distinct entity from stage I, it suggests residual disease, and is managed similarly to systemic disease. Approximately 80% of seminomas present as stage I at diagnosis[5].

The prognosis of stage I seminoma is excellent. Following orchiectomy, recurrence rates range between 13% and 20%[6-8]. In the presence of risk factors such as tumor size, rete testis invasion, and lymphovascular invasion (LVI), the risk of relapse can exceed 30%[9,10]. Without these risk factors, the recurrence rate may be as low as 4%[11]. Seminoma is a radiosensitive and chemosensitive disease. In the adjuvant setting, radiotherapy and single-agent carboplatin have reduced relapse rates to below 10%[12]. However, due to the increased long-term risk of secondary malignancies, radiotherapy is no longer recommended. Although adjuvant carboplatin is generally well tolerated, its efficacy diminishes in the presence of multiple risk factors, with relapse rates approaching 10%; the estimated number needed to treat to prevent one relapse ranges between 15 and 20 patients. Moreover, adjuvant carboplatin has not demonstrated a survival benefit. Salvage treatment administered at relapse achieves nearly 100% survival[13]. As a result, international guidelines recommend active surveillance as the preferred management strategy for stage I seminoma[14].

However, risk-adapted adjuvant treatment remains a common approach in clinical practice. Considering the potential for recurrence and the higher toxicity associated with salvage treatment in the event of relapse, some patients may prefer to receive adjuvant carboplatin. This complicates the process of making clinical decisions. There is a need for more definitive prognostic risk factors, to better guide therapy. Furthermore, the literature lacks sufficient long-term data regarding the toxicity of adjuvant carboplatin and its impact on late relapse. Therefore, in this study, we aimed to evaluate the clinical characteristics of patients with stage I seminoma managed with surveillance or adjuvant therapy in our institution to identify factors influencing the decision to administer adjuvant carboplatin and to assess long-term follow-up outcomes.

Materials and Methods

Data on patients diagnosed with stage I seminoma who underwent surgery at our hospital between 2007 and 2024 and had at least one year of follow-up were retrospectively collected from the hospital's medical record system. Since

approximately 80% of relapses occur within the first year, only patients aged 18 years or older with a minimum of one-year follow-up were included in the study[7]. Postoperative cross-sectional imaging had to confirm stage I disease according to the 8th edition of the AJCC staging system[4]. Patients were included only if postoperative tumor markers (AFP, β-hCG, and LDH) were within normal limits. Patients with non-seminomatous germ cell components (i.e., mixed histology) were excluded. Postoperative follow-up, including tumor markers and imaging, was performed following contemporary guideline recommendations. Patients with missing follow-up data were excluded from the analysis. Patients lost to follow-up were included up to the last available follow-up point.

Data recorded included patient age, tumor size, histopathological features (rete testis invasion, LVI), preoperative serum β-hCG and LDH levels, adjuvant treatment status, presence of recurrence, and survival status. Acute and chronic toxicities related to adjuvant treatment, as well as any development of secondary malignancies, were recorded from patient files and national health system records. In the event of recurrence, the site of recurrence, salvage treatment administered, and treatment response were evaluated. Recurrence was defined as retroperitoneal lymph node involvement and/or distant lymph node or visceral organ metastasis. Development of a germ cell tumor in the contralateral testis was considered a second primary malignancy. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Non-Interventional Research Ethics Committee of University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital (approval no: 2025/02-01, date: 10.03.2025).

Statistical Analysis

Statistical analyses were performed using SPSS version 27.0. Means and standard deviations (SD) were calculated for normally distributed numerical variables, medians and interquartile ranges (IQR) were reported for non-normally distributed variables. Frequencies and percentages were used for categorical variables. The chi-square test evaluated the differences in clinical and pathological characteristics between patients who did and did not receive adjuvant therapy. A p-value <0.05 was considered statistically significant. Disease-free survival (DFS) was estimated using the Kaplan-Meier method. DFS was defined as the time from diagnosis to the date of relapse, death, or last follow-up, whichever occurred first.

Results

Data from 82 patients diagnosed with seminoma at our hospital were reviewed. Four patients (4.8%) were excluded from the study due to unavailable follow-up data. Among the remaining patients, one (1.2%) had stage IS disease, 12 (14.6%) had stage II, and two (2.4%) had stage III disease. A total of 63 patients (76.8%) were diagnosed with stage I seminoma and included in the data analysis. The median age of these patients was 34 years (IQR: 30-41), and five patients (8%) were 50 years or older. All patients underwent radical inguinal orchiectomy. According to pathological findings, the mean tumor size was 4.4 cm (SD±2.3), and in 52.4% of cases, the tumor measured greater than 4 cm. Testicular hilar soft tissue invasion was reported in only 11 patients, with five of them (7.9%) having confirmed invasion. Rete testis invasion was identified in 21 patients (33.3%), and LVI was present in 17 patients (27%).

Every patient underwent thorough blood count and biochemical testing before and after surgery. In the preoperative period, 20 patients (31.7%) had elevated β-hCG levels. Among these patients, the median β-hCG value was 12.5 U/L (IQR: 5-79), indicating mild elevations in most cases. Preoperative LDH levels were elevated in 19 patients (30.2%), with a median LDH level of 338 U/L (IQR: 264-449). Patients with tumors larger than 4 cm exhibited significantly elevated levels of β-hCG and LDH (p=0.045 and p=0.003, respectively). Postoperatively, β-HCG and LDH levels normalized in all patients.

All clinical stage I seminoma patients were assessed in the oncology clinic. Surveillance was recommended for 43 patients (68.3%), while 20 (31.7%) received adjuvant therapy. Among those receiving adjuvant treatment, two patients (10%) received radiotherapy, 17 (85%) received a single cycle of carboplatin at a dose of 7 area under the curve, and one patient (5%) received two cycles of carboplatin. The characteristics of patients who received adjuvant therapy are shown in Table 1. In summary, adjuvant treatment was more frequently administered in patients with tumor size >4 cm (p<0.001), rete testis invasion (p=0.009), elevated preoperative β-hCG (p=0.039), and elevated LDH levels (p=0.040). The presence of LVI did not significantly differ between patients who received adjuvant therapy and those who did not (p=0.28).

During a median follow-up period of 50.5 months (IQR: 31.3 to 80.9 months), two patients (3.2%) experienced a relapse. Both incidents occurred in the surveillance group, resulting

Table 1. Patients' characteristics				
	All patients	**Active surveillance**	**Adjuvant treatment**	**p-value**
Age	36.2 (SD±9.9)	36.1 (SD±10.2)	35.7 (SD±9.6)	
Tumor size				
≤4 cm	30 (47.6%)	27 (62.8%)	3 (15%)	p<0.001
>4 cm	33 (52.4%)	16 (37.2%)	17 (85%)	
Rete testis invasion				
Absent	35 (55.6%)	28 (65.1%)	7 (35%)	
Present	21 (33.3%)	9 (20.9%)	12 (60%)	p=0.009
Unknown	7 (11.1%)	6 (14%)	1 (5%)	
LVI				
Absent	31 (49.2%)	23 (53.5%)	8 (40%)	
Present	17 (27%)	9 (20.9%)	8 (40%)	p=0.2
Unknown	15 (23.8%)	11 (25.6%)	4 (20%)	
Preoperative β-hCG				
Normal	37 (58.7%)	28 (65.1%)	9 (45%)	
Elevated	20 (31.7%)	10 (23.3%)	10 (50%)	p=0.039
Unknown	6 (9.5%)	5 (11.6%)	1 (5%)	
Preoperative LDH				
Normal	34 (54%)	25 (58.1%)	9 (45%)	
Elevated	19 (30.2%)	9 (20.9%)	10 (50%)	p=0.04
Unknown	10 (15.9%)	9 (20.9%)	1 (%5)	
Relaps				
No	61 (96.8%)	41 (95.3%)	20 (100%)	p=0.46
Yes	2 (3.2%)	2 (4.7%)	0	

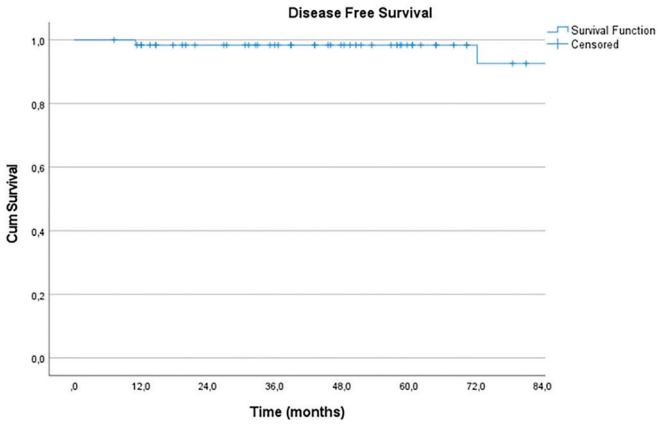
SD: Standard deviation, LVI: Lymphovascular invasion, β-hCG: Beta subunit of human chorionic gonadotropin, LDH: Lactate dehydrogenase

in a relapse rate of 4.7% within that group. One relapse took place at 12 months, while the other occurred at 74 months, with both relapses located in the retroperitoneal region (Graphic 1). Both patients were classified as good-risk and achieved remission following three cycles of bleomycin, etoposide, and cisplatin chemotherapy. Additionally, one patient who had undergone partial orchiectomy due to contralateral testicular atrophy, developed local recurrence and subsequently underwent radical orchiectomy. One patient was diagnosed with seminoma in the contralateral testis and subsequently received two cycles of adjuvant carboplatin following orchiectomy. There were no recorded deaths related to testicular cancer; however, one patient (1.6%) in the surveillance group died due to interstitial lung disease associated with scleroderma.

No secondary malignancies were identified as a result of adjuvant radiotherapy or chemotherapy. One patient who received a single cycle of carboplatin was diagnosed with infertility. Acute kidney injury was not observed in any patients treated with carboplatin. Grade 1-2 thrombocytopenia was reported in four patients, representing 22.2% of the cohort. All patients administered carboplatin also received granulocyte colony-stimulating factor support, and there were no hospitalizations due to febrile neutropenia. Furthermore, clinical side effects such as nausea, fatigue, or diarrhea were not documented in the patient records.

Discussion

In our tertiary referral center, where uro-oncological surgeries are commonly performed, 82 patients were diagnosed with seminoma over 17 years. Although seminomas are the most common testicular tumors in young men, they account for only about 1% of all solid tumors, making them relatively rare[1]. In comparison to non-seminomas, seminomas are typically diagnosed at a slightly older age, with peak incidence occurring between 35 and 39 years, whereas non-seminomas peak between 25 and



Grahpic 1. Disease-free survival

29 years. Notably, a second peak incidence for seminomas has been reported in individuals aged 50 to 55, particularly for the spermatocytic subtype[15]. The median age of our study population was consistent with the literature, and 8% of patients were over 50. However, we did not identify any cases of spermatocytic seminoma in the pathology records. Consistent with prior studies, approximately three-quarters of our patients presented with stage I disease.

Numerous studies have examined clinical and pathological factors that may predict relapse in stage I seminoma. Warde et al.[9] in a pooled analysis, identified two independent risk factors for relapse: tumor size greater than 4 cm and invasion of the rete testis. The prospective Swedish and Norwegian Testicular Cancer Group trial incorporated these factors and reported a relapse rate of 6.2% following a single cycle of adjuvant carboplatin. In that study, the relapse rate was 2% for patients without risk factors, compared to 9.2% for those with one or more risk factors[16]. Since that time, risk-adapted adjuvant therapy has been recognized as an option in clinical guidelines. In our study, we similarly demonstrated that considerations of tumor size and rete testis invasion were integral to the decision-making process regarding adjuvant treatment.

This study observed no relapses in patients who received adjuvant therapy, even with long-term follow-up. Although this rate is better than that commonly reported in the literature, it may be attributed to the small sample size of patients (n=20), who underwent adjuvant therapy. In stage I seminoma, adjuvant carboplatin may delay rather than prevent contralateral testicular tumors. A long-term observational study reported a higher incidence of such tumors in patients receiving carboplatin compared to the general population[17]. We did not find any evidence that adjuvant carboplatin increases the risk of late relapse in our data. However, consistent with the literature, the relapse rate among patients under active surveillance was 4.7%[16]. Notably, there were no deaths related to testicular cancer. Two patients who relapsed were successfully treated with salvage therapy. These findings align with existing literature and reinforce the value of a risk-adapted management approach[18].

Nevertheless, growing evidence suggests that current prognostic factors may not be entirely reliable. Earlier studies have been limited by selective cohorts, inconsistent pathological reporting, missing data, and lack of statistical power. Furthermore, few analyses have evaluated all possible risk factors simultaneously[19,20]. Since adjuvant therapy does not improve overall survival, surveillance remains the preferred approach. However, there is a compelling need for more reliable predictive markers of relapse. A recent large cohort study identified that testicular hilum invasion, LVI, and elevated preoperative levels of β-hCG and LDH can, either individually or in combination, serve as predictors of relapse. In this study, the relapse rate was recorded at 6% for patients without risk factors, escalating to 60% for those presenting all four indicators. Testicular hilum invasion emerged as the most significant prognostic factor[21]. In our study, testicular hilum invasion was reported in only a few cases and did not influence adjuvant therapy decisions. However, elevated preoperative tumor markers appeared to influence treatment decisions. Preoperative marker levels were also correlated with tumor size. Due to the small number of relapses and a limited number of patients receiving adjuvant therapy, statistical analysis of prognostic factors was not feasible in our study. Further prospective data are needed to assess whether testicular hilum invasion and preoperative marker elevation can guide adjuvant treatment decisions.

Before the 2000s, adjuvant radiotherapy targeting the retroperitoneal field was widely used in stage I seminoma. As research increasingly linked radiotherapy to secondary malignancies[22], the utilization of this treatment modality experienced a decline. In our cohort, only two patients received radiotherapy, both before 2005. No secondary malignancies were detected during long-term follow-up. Among patients treated with single-cycle carboplatin, no severe adverse effects were noted. Grade 1-2 thrombocytopenia was observed in four patients (22.2%), and no patient experienced neutropenic fever or required hospitalization. According to the literature, severe toxicity from adjuvant carboplatin is rare, with nausea, vomiting, fatigue, and hematologic toxicity being the most common side effects in approximately half of

the patients[12]. Due to the retrospective nature of our study, clinical toxicities were not systematically recorded and post-treatment blood counts were not routinely monitored, which may explain the lower reported rate of hematologic toxicity. During a median follow-up of 50 months, one patient developed infertility potentially related to carboplatin. Consistent with the literature, no association has been found between carboplatin and secondary malignancies[23]. Our findings support the short- and long-term safety of adjuvant carboplatin. Given the young age and future fertility expectations of most patients, sperm cryopreservation before chemotherapy remains essential.

Conclusion

In conclusion, our study provides evidence that risk-adapted adjuvant treatment is effective and safe. However, it is essential to note that some patients undergoing adjuvant therapy may have experienced overtreatment, as they might not have relapsed in the absence of such interventions. Conversely, although salvage therapy can yield high remission rates in patients who have relapsed, it typically involves more prolonged and toxic treatment regimens. These facts should be clearly communicated to patients, and adjuvant treatment decisions should be patient-centered. Our study had a long follow-up period, ensuring reliable long-term data, but the main limitation was underreporting of acute toxicity. Another limitation of this study includes the small sample size and potential for selection bias inherent to its retrospective, single-center design. Given the lack of national data on this subject in our country, multicenter studies with larger patient populations are needed.

Ethics

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki and was approved by the Non-Interventional Research Ethics Committee of University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital (approval no: 2025/02-01, date: 10.03.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: S.Ö., D.A., Z.A., M.Z.K., Design: S.Ö., D.A., Z.A., M.Z.K., Data Collection or Processing: S.Ö., D.A., Analysis or Interpretation: S.Ö., D.A., Z.A., M.Z.K., Literature Search: S.Ö., Z.A., M.Z.K., Writing: S.Ö., D.A., Z.A., M.Z.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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