



# Clinical-histopathological Features of Paratesticular Masses and Factors Affecting Survival: Single Center Experience

## Paratestiküler Kitlelerin Klinik-histopatolojik Özellikleri ve Sağkalıma Etki Eden Faktörler: Tek Merkez Deneyimi

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### ABSTRACT

**Objective:** As paratesticular masses constitute 2-3% of all scrotal and inguinal masses, published cases in the literature are limited. We aimed to present our experiences of nine cases which we have treated and followed up in our department.

**Methods:** Between January 2013 and February 2017, we retrospectively analyzed the data of nine patients with paratesticular mass in our department.

**Results:** Seven (77.8%) patients presented with scrotal mass or swelling, while two (22.2%) patients had swelling in the inguinal region. Histological types of malignant tumors were rhabdomyosarcoma [(RMS), 2 cases, 22.3%], liposarcoma [(LPS), 1 case, 11.1%], leiomyosarcoma [(LMS), 1 case, 11.1%]] and malignant fibrous histiocytoma [(MFH), 1 case, 11.1%]]. Benign tumors were fibroma (1 case, 11.1%), adenomatoid tumor (1 case, 11.1%), cystadenoma (1 case, 11.1%) and inflammatory myofibroblastic tumor (1 case, 11.1%). During median 23.5 (4-62) months of follow-up of paratesticular sarcomas, the rates of recurrence-free and progression-free survival were 60%, overall survival rate was 60%. LMS and MFH had poor prognosis. No recurrence or progression was observed in the follow-up of LPS and RMS. Among them, LPS had the best prognosis. The disease-free survival was 100% at the median 49 (36-64) months follow-up of four benign masses without any

### ÖZ

**Amaç:** Paratestiküler kitleler, tüm skrotal ve inguinal kitlelerin %2-3 gibi oldukça az bir kısmını oluşturduğundan, literatürde bildirilmiş olgular kısıtlıdır. Kliniğimizde paratestiküler kitle nedeniyle takip ve tedavisini gerçekleştirdiğimiz dokuz olguya ait deneyimlerimizi sunmayı amaçladık.

**Yöntemler:** Ocak 2013-Şubat 2017 arasında, kliniğimizde paratestiküler kitle nedeniyle takip ve tedavi ettiğimiz 3-72 yaş arasındaki dokuz olgunun verilerini, postoperatif takip sürecindeki bulgularını retrospektif olarak inceledik.

**Bulgular:** Yedi (%77,8) olgu skrotal kitle, şişlik yakınması ile başvururken, iki (%22,2) hasta inguinal bölgede şişlik nedeniyle başvurdu. Patolojik tanısı malign gelen tümörlerin histolojik tipleri rhabdomyosarkom [(RMS), 2 olgu, %22,3], liposarkom [(LPS), 1 olgu, %11,1], [leiomyosarkom (LMS), 1 olgu, %11,1]] ve malign fibröz histiyostom [(MFH), 1 olgu, %11,1]] idi. Benign patolojili tümörler ise, fibroma (1 olgu, %11,1), adenomatoid tümör (1 olgu, %11,1), kistadenom (1 olgu, %11,1) ve enflamatuvar miyofibroblastik tümör (1 olgu, %11,1) olarak saptandı. Beş sarkom olgusunun medyan 23,5 (4-62) aylık takibinde nüksüz ve progresyonsuz sağkalım oranı %60 iken, genel sağkalım oranı %60 idi. Bu beş olgudan en kötü prognozlu olanlar LMS ve MFH idi. LPS ile RMS olgularının takibinde nüks ve progresyon gözlenmezken, en iyi prognoz LPS'ye aitti. Adjuvan tedavi gereksinimi olmayan

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**Received:** 08.01.2019

**Accepted:** 12.02.2019

**Cite this article as:** Selvi İ, Başar H. Clinical-histopathological Features of Paratesticular Masses and Factors Affecting Survival: Single Center Experience. Bezmialem Science 2020;8(1):1-7.

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need for adjuvant treatment. According to FNCLCC Classification, times of local recurrence-free survival and overall survival in grade II sarcomas were significantly higher than those with grade III ( $p=0.039$ ).

**Conclusion:** It is difficult to differentiate clinically benign paratesticular masses from sarcomas. LPS has better prognosis and high-grade sarcomas have poor prognosis. If adjuvant treatments are not added, local recurrence or progression may be observed in a short time.

**Keywords:** Benign paratesticular masses, FNCLCC grading system, local recurrence free survival, overall survival, paratesticular sarcomas

dört benign kitlenin median 49 (36-64) aylık takibinde hastalısız sağkalım %100'dü. FNCLCC sınıflandırması'na göre derece 2 sarkomlarda lokal nüksüz sağkalım ve genel sağkalım süreleri, derece 3'e göre anlamlı olarak daha fazla saptandı ( $p=0,039$ ).

**Sonuç:** Benign paratestiküler kitleleri, sarkomlardan klinik olarak ayırt etmek zordur. Paratestiküler sarkomlarda histolojik alt tipler içerisinde LPS daha iyi prognoza sahiptir. Yüksek dereceli sarkomların prognozu daha kötüdür. Adjuvan tedaviler eklenmezse, kısa sürede lokal nüks veya progresyon gözlenebilmektedir.

**Anahtar Sözcükler:** Benign paratestiküler kitleler, FNCLCC derecelendirme sistemi, genel sağkalım, lokal nüksüz sağkalım, paratestiküler sarkomlar

## Introduction

Paratesticular area consists of embryological remains such as epididymis, spermatic cord, tunica vaginalis, appendix testis, and inguinal canal and supporting tissues (1). Although tumors originating from this region are rare, they have a wide distribution in terms of pathological diversity due to the different anatomical structures they contain (2). Paratesticular masses account for 2-3% of all scrotal masses (1,3). Although the rate of malignancy is lower than intratesticular masses, it is difficult to distinguish precisely with clinical findings. When the suspicion of malignancy cannot be ruled out in benign masses, radical orchiectomy is often performed (3). On the other hand, malignant masses can be interpreted as benign inguinoscrotal masses such as hernia, lipoma, epididymal cyst, and incomplete resections of malignant masses which are thought to be benign, can lead to tumor recurrence in up to 50% of patients (4).

Paratesticular sarcomas are tumors with poor prognosis, originating from embryonic mesenchymal cells. The incidence of soft tissue sarcoma is 5 in 100.000 per year, of which less than 5% is due to the genitourinary system. It accounts for 1-2% of all genitourinary malignancies (4). Since paratesticular sarcoma is rare, studies with a large population of patients in the literature are very few (5,6). Therefore, our knowledge of its natural course and prognosis is limited, and no definitive follow-up and treatment protocols have been established. To our knowledge, the largest patient series belong to Ap Dafydd et al. (4) whose study was performed on 77 patients.

Tumor stage, degree, histopathological subtype and size are important in predicting resectability and survival in paratesticular sarcomas (5,6). Complete surgical resection, known to increase survival rates, is the recommended treatment to be done in the first stage. Adjuvant treatment protocols have not yet been standardized and their contribution to survival varies in different studies (6). Since our knowledge of paratesticular masses is limited, we aimed to examine the clinical-pathological characteristics of benign and malignant patients in our clinic and to evaluate the prognostic factors that may have an effect on oncological outcomes in cases with sarcoma.

## Methods

We examined the pathological data of patients who underwent radical orchiectomy due to intratesticular or extratesticular mass in our clinic between January 2013 and February 2017. Nine patients with ages of 3-72 years who were treated and followed up due to paratesticular masses were included in the study. The clinical and histopathological data of the patients and their findings in postoperative follow-up were evaluated retrospectively. Demographic data, presenting symptoms, side of the tumor, localization of the tumor in the paratesticular area, the status of metastasis at diagnosis, pathological tissue diagnosis, pathological tumor size, the performed surgical treatments, surgical resection status (complete/incomplete), surgical margin positivity, adjuvant therapy given during postoperative follow-up, postoperative follow-up period, local recurrence, progression and survival status were recorded.

The French Fédération Nationale des Centers de Lutte Contre le Cancer (FNCLCC) Grading system was used for the pathological examination of patients with sarcoma and the pathological rating of each patient was recorded according to this system. In this system, three parameters including tumor differentiation, mitotic activity and tumor necrosis degree are scored separately and according to the total score, patients are classified as grades I, II, III (low, medium, high grade) in terms of sarcoma grade (7,8).

## Statistical Analysis

Before comparing the differences between benign and malignant pathologies, normality status was evaluated with Kolmogorov-Smirnov and Shapiro-Wilk tests. When there was normal distribution, Independent Sample t-test was used to compare age and tumor size, which are independent continuous variables. While Kaplan-Meier method was used for survival analysis in malignant patients, differences between patient subgroups were evaluated by the log rank test. This study was not suitable for the multivariate model, due to the small size of the sample. The analyses were done using IBM SPSS Statistics 21 (IBM, Armonk, NY USA) software.  $P<0.05$  was considered statistically significant.

## Results

The mean age at diagnosis of the nine male patients included in the study was 38.67±22.18 years. Seven patients (77.8%) were admitted with scrotal mass or swelling, while two patients (22.%) were admitted with swelling in the inguinal area. Histological types of malignant tumors were rhabdomyosarcoma [(RMS), 2 cases, 22.3%], liposarcoma [(LPS), 1 case, 11.1%], leiomyosarcoma [(LMS), 1 case, 11.1%] and malignant fibrous histiostoma [(MFH), 1 case, 11.1%]. Benign tumors were fibroma (1 case, 11.1%), adenomatoid tumor (1 case, 11.1%), cystadenoma (1 case, 11.1%) and inflammatory myofibroblastic tumor (1 case, 11.1%). Since the suspicion of malignancy could

not be ruled out clinically, surgical excision was applied in all patients. Surgical boundary positivity was observed in only one (11.1%) of all patients undergoing complete resection. Preoperative serum tumor markers (alpha fetoprotein, beta human chorionic gonadotropin, lactate dehydrogenase) were normal in all patients.

No metastasis was detected at the time of diagnosis in any of the five patients with sarcoma. Neoadjuvant therapy was not applied to the patients; adjuvant chemotherapy (CT) was administered in three patients, adjuvant radiotherapy (RT) was administered in one case, and one case was followed up. The recurrence-free and progression-free survival rate was 60%, while the overall

**Table 1.** Demographic, clinical, pathological data and oncological results of patients gender

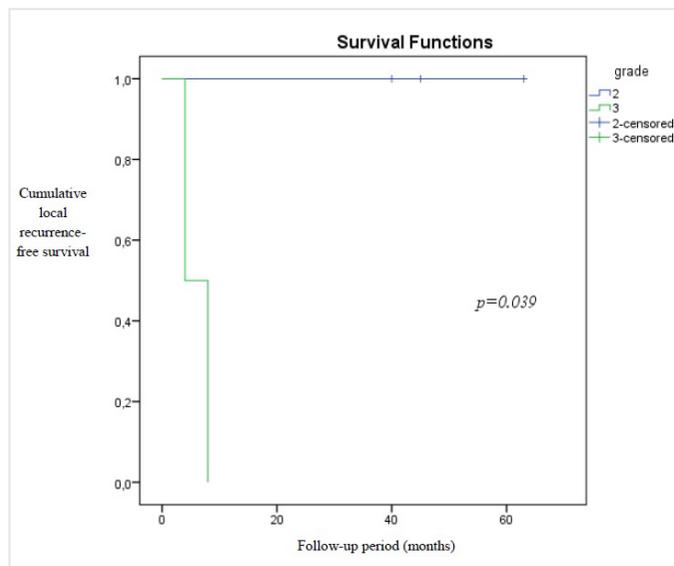
1	19	Male	Right scrotal swelling	Testis-epididymis	Spindle cell variant RMS grade 2	55x45x45	Right inguinal orchiectomy + 7 cycles of CT for left paraaortic 10x8 mm-diameter lymph node (vincristine, actinomycin D, cyclophosphamide)	63 months	No relapse, Alive
2	59	Male	Right scrotal swelling	Spermatic cord-epididymis	LPS grade 2	45x40x27	Right inguinal orchiectomy + follow up	49 months	No relapse, Alive
3	72	Male	Swelling in the left inguinal region	Spermatic cord	LMS grade 3	50x40x30	Left inguinal orchiectomy + inguinal mass excision + adjuvant RT due to surgical boundary positivity	4 months	Relapse in the 4 <sup>th</sup> month, The patient voluntarily left the follow-up, It was learnt that he died in the 28 <sup>th</sup> month
4	3	Male	Right scrotal swelling	Testis-epididymis	Embryonal RMS grade 2	11x10x5	Right inguinal orchiectomy + 12 cycles of CT (vincristin)	40 months	No relapse, Alive
5	60	Male	Left scrotal swelling	Spermatic cord-epididymis	Malignant fibrous histiocyoma grade 3	50x49x45	Left inguinal orchiectomy + 4 cycles of CT (ifosphamide, mesna, Adriamycin)	8 months	Relapse in the 8 <sup>th</sup> month, The patient voluntarily left the follow-up, It was learnt that he died in the 33 <sup>rd</sup> month
6	45	Male	Swelling in the right inguinal region	Spermatic cord	Fibroma	32x23x10		47 months	No relapse, Alive
7	26	Male	Left scrotal mass	Epididymis	Adenomatoid tumor	19x18x16		51 months	No relapse, Alive
8	30	Male	Left scrotal mass	Epididymis	Cystadenoma	16x14x12		36 months	No relapse, Alive
9	24	Male	Left scrotal mass	Epididymis	Inflammatory myofibroblastic tumor	15x12x11		64 months	No relapse, Alive

RMS: Rhabdomyosarcoma, LPS: Liposarcoma, LMS: Leiomyosarcoma, CT: Chemotherapy

survival rate was 60% in 5 patients with sarcoma during a median 23.5-month follow-up (4-62 months). Among these cases, those with the worst prognosis were LMS and MFH. In the case with LMS, after radical orchiectomy, adjuvant RT was applied due to surgical boundary positivity, but in the early stage (in the 4<sup>th</sup> month) there was local recurrence. In our case with MFH, local recurrence was detected in the 8<sup>th</sup> month. We do not know about the state of progression in these patients due to lack of follow up. However, the overall survival times of these patients were 28 and 33 months, respectively. In the follow-up of patients with LPS and RMS, recurrence and progression were not observed. We determined LPS as the histopathological type with better prognosis, because that patient with LPS did not show recurrence and progression during 49 months of follow-up, even though we did not administer adjuvant therapy.

The disease-free survival rate was 100% during the median 49-month follow-up (36-64 months) of four patients with benign masses without need of adjuvant therapy. While the mean tumor size was 43.00±18.04 mm in patients with sarcoma, the tumor size in benign masses was significantly smaller (20.25±8.09 mm) (p=0.047). No significant difference was observed between benign and malignant patients in terms of mean age at diagnosis (33.75±8.18 and 42.60±29.83, respectively) (p=0.555). The characteristics of the cases are seen in Table 1.

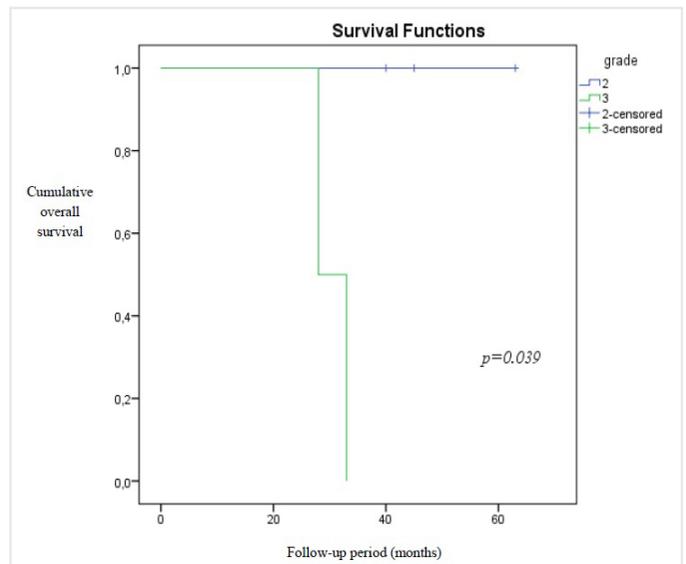
The oncological results of five patients with sarcoma were evaluated in terms of patient age, histopathological subtype of tumor, FNCLCC rating system and tumor size (>5 or <5 cm). In Kaplan-Meier analysis, local survival time without recurrence and overall survival time were significantly higher in grade II sarcomas than in grade III sarcomas according to FNCLCC classification (p=0.039, Figure 1, 2). No significant effects of other parameters were observed on survival without local recurrence and overall survival (Figure 3, 4, 5).



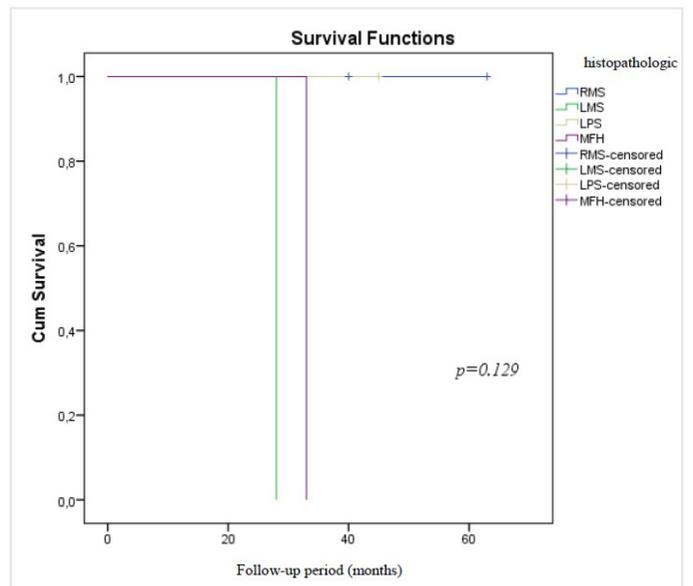
**Figure 1.** Kaplan-Meier graph of local recurrence-free survival curves according to histopathological grade

## Discussion

It is known that there is a lower rate of malignancy in paratesticular masses than intratesticular masses (3). When we examined our patient data, we detected germ cell tumors in 75 (87.2%) of 86 cases who underwent radical orchiectomy due to testicular mass in our clinic, while we observed malignancy in five (55.5%) of nine paratesticular masses. The incidence of paratesticular sarcoma was reported as 6.7% in radical orchiectomies performed with suspicion of testicular tumor (9), whereas in our radical orchiectomy series, this rate was 5.2%. Paratesticular benign tumors are more common in the third and fourth decades, while malignant tumors occur in the sixth and



**Figure 2.** Kaplan-Meier graph of overall survival curves according to histopathological grade



**Kaplan-Meier survival graph according to histopathological tumor type**

RMS: Rhabdomyosarcoma, LMS: Leiomyosarcoma, LPS: Liposarcoma, MFH: Malignant fibrous histiocytoma

seventh decades (10). Similarly, the mean age at diagnosis was 33.75±8.18 years in benign patients and 42.60±29.83 years in malignant patients in our study.

Paratesticular masses constitute 2-3% of all scrotal masses, 30% of these masses are sarcomas, more than half are benign tumors (11). Adenomatoid tumors, the most common benign mesothelial tumors of the paratesticular region, constitute 30% of all paratesticular neoplasms and 60% of all benign neoplasms (12). The second most common benign tumor is cystadenoma. Both tumors originate mostly from the epididymis (13). Synonym names such as inflammatory pseudotumor, atypical myofibroblastic tumor, and pseudosarcomatous myofibroblastic proliferation are also used for inflammatory myofibroblastic tumors (IMT), which account for about 6% of paratesticular masses (14). While there were no reported relapses in follow-

up, distant metastasis was observed in less than 5% of non-epididymic IMT cases (15). Fibromas, which constitute 6% of paratesticular tumors, originate from tunica vaginalis in 75% of cases and from epididymis in 10% of cases, and spermatic cord involvement is much rarer (16).

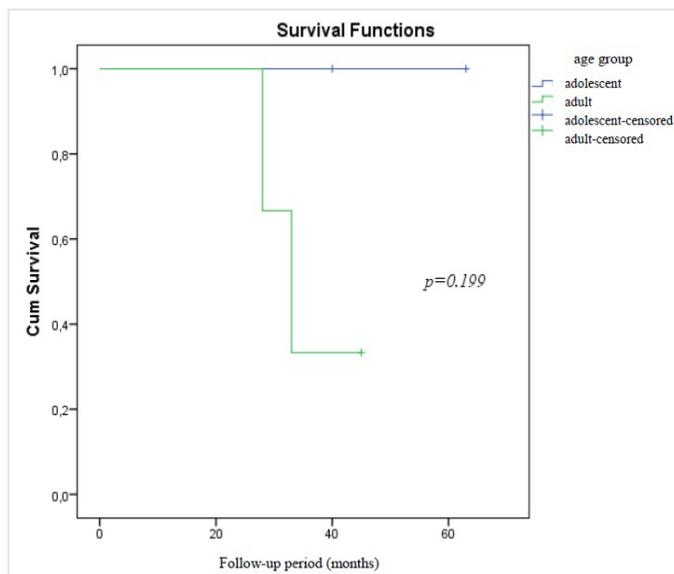
Since benign tumors with paratesticular placement do not show recurrence and progression, total mass excision with using a testicular protective approach is sufficient treatment method (2). However, it is often difficult to distinguish malignancy with clinical examination and radiological methods. Radical orchiectomy may be preferred especially in patients with involvement of tunica albuginea, rete testis and spermatic cord (2).

Since our information on paratesticular sarcomas belongs to series with a limited number of patients published in the literature; there is still no consensus on optimal treatment regimens and follow-up protocols (17,18). The most common type among all soft tissue sarcomas is LPS, while the most common types among genitourinary-derived sarcomas are LMS (29%), LPS (26%) and RMS (18%) (6), respectively. The most common types among paratesticular sarcomas are LPS (20-32%), LMS (19-32%) and RMS (11-24%) (19). We observed RMS in two cases (40%), LPS in one case (20%), LMS in one case (20%) and MFH in one case (20%) in patients with paratesticular sarcomas. However, because we have few cases, our rates do not match the literature. Embryonal type RMS is the most common paratesticular sarcoma in children and adolescents (19) and our 3-year and 19-year-old patients with RMS are compatible with the literature in this respect.

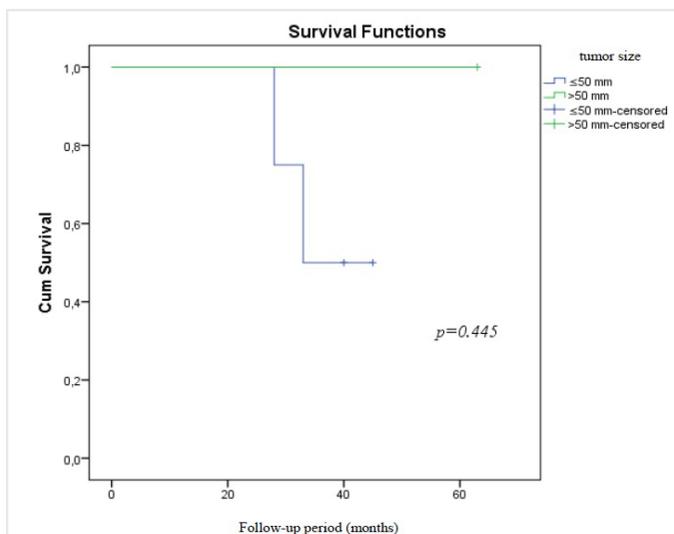
The admission complaint in paratesticular sarcomas is mostly painless scrotal mass and they develop from the mesenchymal elements of the spermatic cord, epididymis and testicular sheath. About 70% of them settle on spermatic cord (10). Of the five patients with sarcoma in our study, three (60%) originated from the spermatic cord.

When all genitourinary sarcomas are examined in the literature, survival rates of paratesticular sarcomas and sarcomas originating from bladder are reported to be higher than those originating from other organs (6). This was attributed to early admission of patients due to scrotal swelling in paratesticular sarcoma and hematuria in bladder sarcoma and to diagnosis in earlier stages (5). All nine cases in our study were admitted with noticeable swelling in the scrotal or inguinal region, and none of the five patients diagnosed as having sarcoma had metastasis at the time of diagnosis.

RMS is the most common primary paratesticular malignant neoplasia between 7 and 36 years of age (average age at diagnosis is 10 years) (20). It accounts for 80% of paratesticular tumors seen under the age of 21 and 24% of those detected in adults (21). The histopathological types; “embryonal type” and “spindle cell variant”, found in two cases with paratesticular RMS in our study had a better prognosis than the other RMS subtypes (22). In fact, no recurrence and progression were observed in the mean 50.5-month (39-62 months) follow-up of both cases.



**Figure 4.** Kaplan-Meier survival graph according to patient age groups



**Figure 5.** Kaplan-Meier survival graph according to tumor size

There are fewer reported cases with paratesticular LMS and LPS in the literature (23,24). Fisher et al. (23) showed that development of recurrence and metastasis can be prevented with radical orchiectomy in patients with low-grade paratesticular LMS. In our case, surgical boundary positivity was observed after complete excision and he received adjuvant RT. Despite multimodal treatment, development of local recurrence in the 4<sup>th</sup> month could not be prevented. Paratesticular LPS is mostly well differentiated and expected survival is longer in patients with paratesticular LPS (24,25). In our case with grade II paratesticular LPS, no recurrence or progression were observed during 48-month follow-up without adjuvant treatment.

There is still debate about the role of retroperitoneal lymphadenectomy (RPLND) in paratesticular sarcomas (25-27). At the time of diagnosis, only CT was applied instead of RPLND as adjuvant treatment for our RMS patient with a 10x8 mm diameter lymph node with a 10x8 mm diameter lymph node in the left paraaortic area. No recurrence or progression was observed during 62 months of follow-up.

The frequency of MFH, which is very rare and fast progressive, is 4.5% in all genitourinary sarcomas and 11.1% in paratesticular sarcomas (5). The size and histopathological characteristics of the tumor are important factors for development of metastasis. Despite multimodal treatment, 3-year survival is approximately 40% (28). The overall survival was 33 months in our patient with grade III paratesticular MFH. Despite adjuvant CT, he developed local recurrence in the 8<sup>th</sup> month.

There are very few reported studies regarding long-term follow-up results of paratesticular sarcomas. Since there is a greater incidence of RMS in the pediatric age group, most of the survival results were obtained from multicenter publications of RMS cases (9). Korkes et al. (9) indicated that overall survival was 27.8±6.2 months and overall survival rate was 50% after a median 31.4 (6-60) months of follow-up. In the same study, lung metastasis was observed in 50% of cases with LMS, while recurrence or progression was not detected in cases with LPS, and metastasis rate in RMS was found to be 50%. They found no difference between sarcoma types in terms of disease-free survival (9). In another study with a median 32.18 months (1-142) of follow-up, overall survival rate was 12.5% (29). Dotan et al. (6) showed that increased tumor size, incomplete surgical resection, positive surgical boundary and metastasis at the time of diagnosis in all genitourinary sarcomas were identified as negative factors that reduce disease-specific survival. Although the 5-year local recurrence rate was reported as 32%, metastasis-free survival rate as 60% and disease-specific survival rate as 69%; no subgroup analysis was performed for paratesticular sarcomas in this study (6).

Having the largest known series of patients (188 patients) with all kinds of genitourinary sarcomas, Dotan et al. (6) showed that 5-year disease-free survival rate was 12.5% and cancer-specific survival was 25%. In subgroup analyses of 56 patients with paratesticular sarcoma. The negative factors that affect recurrence-free survival are renal placement, female gender,

presence of metastases at diagnosis, and positive surgical margin and the negative factors that affect metastasis-free survival are the presence of incomplete surgical resection and positive surgical margin. During a median 23.5 (4-62) months of follow-up, we observed recurrence-free and progression-free survival as 60% and overall survival as 60% in five patients with sarcoma. In addition, we found local recurrence-free survival time and overall survival time were significantly higher in grade II sarcomas than in grade III sarcomas according to FNCLCC classification, while we were unable to show any significant effect of other parameters on oncological outcomes.

While complete surgical excision is the recommended treatment in the first step, the location of adjuvant CT and RT is still unclear. Although adjuvant treatments have been reported to reduce local recurrence and extend overall survival (9,30), in two cases with grade III tumor in our study, recurrence and progression were observed in a short period of time despite adjuvant CT and/or RT.

### Study Limitations

The retrospective design of our study, the inability to create randomization, the limited statistical analysis due to the small number of patients, short follow-up times and the follow-up results belonging to one center are the main limitations of our study.

### Conclusion

As a result, paratesticular masses are rare and low malignant pathologies, but it is often difficult to distinguish them with clinical findings. In cases where the suspicion of malignancy cannot be ruled out, radical orchiectomy is inevitable. In sarcomas of this region, complete surgical excision is often not sufficient for disease-free survival. Adjuvant treatments, on the other hand, do not increase overall survival in every case. According to our findings, tumor grade is the most important prognostic factor determining relapse and overall survival. It is necessary to better identify the prognostic factors that have effect on survival and to establish specific adjuvant treatment protocols according to the tumor subtype with other prospective, randomized, controlled, multicenter with large patient numbers and long follow-up.

### Ethics

**Ethics Committee Approval:** Association Declaration of Helsinki “Ethical Principles for Medical Research Involving Human Subjects”, (amended in October 2013).

**Informed Consent:** A consent form was completed by all participants.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Concept: İ.S., Design: İ.S., Data Collection or Processing: İ.S., Analysis or Interpretation: İ.S., H.B., Literature Search: İ.S., Writing: İ.S.

**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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