

# Non-specific malign stromal tumors of testis

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## Abstract

**Aim:** In this study, we aimed to share our experiences about patients with miscellaneous non-specific malign stromal tumors of testis. We report the demographic and clinical characteristics and the long-term results in patients with non-specific malign stromal tumors of testis.

**Material and Methods:** 234 patients with testicular cancer between June 1994 and January 2019 have been evaluated retrospectively. Eleven patients (Dedifferentiated liposarcoma, Diffuse large B-cell lymphoma, Embryonal rhabdomyosarcoma, Adenocarcinoma of the epididymis, Ewing's sarcoma of the testis, Testicular leiomyosarcoma, Well-differentiated liposarcoma, Paratesticular high grade sarcoma and Paratesticular malignant mesothelioma) whose data were reached, are taken into the study. Patients' age, scrotal localization of symptoms, clinical examination findings, serum tumor marker levels, pathology results and follow-up period were recorded.

**Results:** The mean age at diagnosis was 43.7 years (range, 18 to 79). 54.5% of the lesions were localized to the right hemiscrotal area and of 45.4% to the left hemiscrotal area. None of patients had a history of unilateral undescended testis in medical history or testicular cancer in familial history. Serum tumor markers were normal in all patients. The mean scrotal mass lesion at diagnosis was 59.9 mm<sup>3</sup> (range, 33 to 138 mm<sup>3</sup>). 3 or 4 cycles of chemotherapy protocols were administered in necessary cases. Mean follow-up period was 80.6 months (range, 12 to 297 months). Tumor recurrence was occurred in only two patients (Dedifferentiated liposarcoma and Adenocarcinoma of the epididymis) during the follow-up.

**Conclusion:** Miscellaneous non-specific malign stromal tumors of the testis should be kept in mind especially in middle age group patients presented with malign scrotal lesions. Surgical treatment should be aggressive and additional specific treatment according to pathology result should be planned without delay. Follow-up protocols are recommended to be tumor specific.

**Keywords:** Non-specific malign stromal tumors; testicular cancer; testis tumors.

## INTRODUCTION

Testicular tumors represent 5% of urological tumor (1).%90-95 of cases are germ cell tumors (GCT). Miscellaneous non-specific stromal tumors of the testis are uncommon lesions that accounts for about less than 1% of all testicular mass. These tumors may be benign or malignant. These tumors are divided into different titles according to The World Health Organization (WHO) 2016 classification of non-germ cell origin tumors of the testis (2). Ovarian epithelial-type tumors, Serous cystadenoma, Serous tumor of borderline malignancy, Serous cystadenocarcinoma, Mucinous cystadenoma, Mucinous borderline tumor, Mucinous cystadenocarcinoma, Endometrioid adenocarcinoma, Clear cell adenocarcinoma,

Brenner tumor, Juvenile xanthogranuloma, Haemangioma, Diffuse large B-cell lymphoma, Follicular lymphoma (Not otherwise specified), Extranodal Natural Killer/T-cell lymphoma (nasal-type), Plasmacytoma, Myeloid sarcoma and Rosai-Dorfman disease are included in this classification. Another classification is similar to WHO classification and made by EAU committee. It is also defined in current guideline of EAU in 2018. According to EAU guideline; Ovarian epithelial tumors, Tumors of the collecting ducts and rete testis (adenoma or carcinoma), Tumors of Paratesticular structures (Adenoid tumor, Mesothelioma, Epididymal tumors), Cystadenoma of the epididymis, Papiller cystadenoma, Adenocarcinoma of the epididymis and Mesenchymal tumors of the spermatic cord and Testicular adnexae are pathological classification

**Received:** 28.09.2019 **Accepted:** 10.10.2019 **Available online:**

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of miscellaneous non-specific malign stromal tumors of the testis. Tumors appear either from the testis or the paratesticular tissue. Clinical information of these rare tumors is usually reported in the literature as case reports.

We aim to discuss demographic and clinical characteristics and the long-term outcomes in patients with miscellaneous non-specific malign stromal tumors of the testis. We also wanted to emphasize different aspects from germ cell tumors.

## **MATERIAL and METHODS**

### **Study Population**

234 patients with miscellaneous non-specific malign stromal tumors of the testis in Sultan Abdulhamid Han Education and Research Hospital between June 1994 and June 2018 were evaluated. The data were collected retrospectively. Eleven patients with non-specific malign stromal tumors of the testis treated in our clinic were enrolled in the study.

### **Inclusion and exclusion criteria**

The current cohort with available data includes 11 patients. Patients over 18 years of age with and non-specific malign stromal tumors of the testis available data were enrolled in the study. The exclusion criteria included age under 18 years, patients with germ cell tumors, germ cell tumors unrelated to germ cell neoplasia in situ or sex cord/stromal tumors and unavailability of data.

The patients' medical records were retrospectively reviewed. Patients' data including age, initial complaints (such as scrotal pain, swelling, mass or infertility), location of tumor (the right or left testis), smoking habit, medical or family history, preoperative lactate dehydrogenase (LDH), alpha-fetoprotein (AFP) and  $\beta$ -human chorionic gonadotrophin ( $\beta$ -HCG) levels, diagnostic imaging findings for staging, pathology results, follow-up time and tumor recurrence status were evaluated.

### **Clinical examination and biochemical measurements**

For all scrotal masses; each testicle was examined with both hands. All patients were routinely evaluated with scrotal grey scale ultrasonography. Testicular or paratesticular mass volume was measured using the following formula: length (L) x width (W) x height (H) x 0.52. Imaging methods and results were evaluated by specialized urologists. Routine radical inguinal orchiectomy with high dissection and ligation of the spermatic cord due to suspicion of testicular malignancy were performed for all scrotal masses in our clinic. Pathologic specimens were reviewed by one genitourinary pathologist. Minimal follow-up in the first two years were 6 times tumor markers  $\pm$  doctor visit, 2-3 times Chest X-ray, 2-3 times abdominopelvic computed tomography (CT)/magnetic resonance imaging and thorax CT when it is necessary. After the first two years, tumor markers  $\pm$  doctor visit and Chest X-ray/ abdominopelvic CT were 3 and 2 times for per year, respectively. After five years, check-up within one time for per year was recommended.

### **Histopathologic Examination**

All testicular materials were sampled macroscopically and the sections of each case were examined by uropathologist. Tissue samples were processed in the tissue processor price through the night. Tissues embedded in paraffin blocks and multiple recuts made from blocks. Then the staining process was done. Surgical specimen of testis tissue was examined histologically by routine hematoxylin&eosin (H&E) staining. Specific immunohistochemical evaluation for possible diagnoses was also made.

### **Study Design**

Demographic characteristics of the patients were recorded and descriptive factors were identified. Pathological differential diagnoses were evaluated. Treatment and follow-up protocols discussed. The reasons for possible recurrences or relapses that may occur in the follow-up period were planned to be investigated.

### **Statistical Analysis**

All data was analysed with Microsoft excel computer programs. In the analysis of the data, the descriptive statistics were presented as means (minimum-maximum) for continuous variables. Discontinuous variables were defined as present or absent.

## **RESULTS**

For the 11 patients who enrolled in analyses, the mean age at diagnosis was 43.7 years (range, 18 to 79 years). Lesions were located on the right side of the scrotum in 6 patients, while they were located on the left side in 5 patients. In 7 of 11 (63.6%) patients who admitted with testicular mass, 5 of 7 patient presented with scrotal pain and swelling (45.4%), 2 of 7 patients had only scrotal swelling (18.1%) and four patients with a testicular mass presented with a painless lump (36.3%). There were no risk factors such as undescended testis in the patients' medical history. None of the patients had a family history for testicular cancer. Of the patients, 36.3% were smokers or tobacco users. In all patients, the preoperative mean  $\beta$ -hCG, AFP and LDH isoenzyme levels were normal and 1.12 mIU/mL, 1.69 ng/mL, and 335.72 U/L, respectively. All patients underwent inguinal orchiectomy. The mean testicular or paratesticular mass volume was 59.9 mm<sup>3</sup> (range, 33 to 138 mm<sup>3</sup>). Mean follow-up period was 80.6 months (range, 12 to 297 months). Two patients with recurrence of tumor (Dedifferentiated liposarcoma and Adenocarcinoma of the epididymis) were observed in the follow-up (Table 1).

## **DISCUSSION**

Testicular tumors are more common 3rd (non-seminoma) or 4nd (pure seminoma) decade of life at time of diagnosis. Miscellaneous non-specific malign stromal tumors of the testis are rare phenomenon and diagnosis age of the disease which is a wide scale between childhood and advanced age change according to pathology of tumor. In our cohort, mean age at diagnosis was 43.72 years (range,

**Table 1. Evaluation of descriptive characteristics in patients with miscellaneous non-specific malign stromal tumours of testis were managed by inguinal orchiectomy.**

Variable	Number of Patients (n)	Age (years)	Tumour Volume (mm <sup>3</sup> )	Lymph Node (+/-)	Follow-up month)	Recurrence (+/-)
Liposarcoma	3	55.66*	47*	-	75*	+
Diffuse Large B-cell Lymphoma	1	62	89	-	36	-
Embryonal Rhabdomyosarcoma	2	18.5*	85.5*	-	97*	-
Adenocarcinoma of the Epididymis	1	29	39	-	297	+
Ewing's Sarcoma	1	37	65	+	18	-
Leiomyosarcoma	1	56	45	-	12	-
High Grade Sarcoma	1	19	65	+	89	-
Malign Mesothelioma	1	74	45	-	20	-
All of Patients	11	43.72*	59.9*	2/11	80.63*	2/11

**\*: Mean value in groups with more than one patient**

18 to 79 years) and results were older than literature. Unlike seminoma or non-seminoma, the patients were diagnosed in the middle age group.

No etiologic factor such as undescended testis or family history for testicular cancer was observed in our cases. Of the patients, 36.3% were smokers or tobacco users, but it was not enough finding to assessment. In our country, in general, the presence of individuals with relatively weak economic status increases the likelihood of exposure to chemicals. However, it would not be right to argue that all tumors are due to this factor. Since we cannot find a genetic factor in the etiology, we think that the effect of environmental factors should be investigated better in these patients. Therefore it should be advised not to smoke, and if there is exposure to chemical, change of profession should be recommended.

Liposarcoma; It consists of soft tissue and originated from mesodermal tissues. Approximately 200 cases have been reported in the literature (3). Well differentiated, dedifferentiated, myxoid and pleomorphic type are four histological subtypes of liposarcoma (4). Liposarcoma of paratesticular area is usually diagnosed at sixth decade (5). Multimodality therapy was suggested a few article in the literature (6,7). Retroperitoneal lymph node dissection is not recommended except for metastasis (8). The

evidence of radiotherapy and chemotherapy is limited for treatment. In our cohort three cases was evaluated and mean age at diagnosis of the cases was 55.6 years (20-79 years) and was conformed the literature. Mean tumor volume was 47 mm<sup>3</sup> (39-57 mm<sup>3</sup>). No metastasis was found postoperatively. For all of cases, 3 cycle of cisplatin based chemotherapy was performed. Mean follow-up period was 75 months (24-129 months). In one patient, recurrence was obtained and retroperitoneal lymph node dissection (RPLND) was performed. The pathology result of RPLND was reported as liposarcoma. Liposarcomas can be treated more generously with RPLND since they are usually detected in the retroperitoneal area(9) and are likely to recurrence quickly.

Diffuse Large B-cell Lymphoma; chronic lymphoproliferative disorders affect usually digestive tract. In men older than 60 years of age, the most common malignant testicular tumor is lymphoma (10). Primary testicular involvement is extremely rare. Diffuse large B-cell lymphoma takes part in PET-avid lymphomas (11). The process of the disease is progressively aggressive (12). But it can now be cured in more than 50% of patients. APLES (Age >60 y, Performance status ≤ECOG grade 2, Lactate dehydrogenase >maximum normal, Extranodal sites ≥2, Stage III or IV) risk score of Diffuse Large B-cell Lymphoma from International

Prognostic Index is predicting treatment outcome (13). For 21 days, CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) plus the monoclonal antibody rituximab (Rituxan) is excellent treatment approach for this patients (14). In our case was 62 years old. Tumor volume was 89 mm<sup>3</sup> and APLES score was 2. There was a concern due to tumor size for micrometastasis. For three weekly CHOP-R treatments was performed. After the treatments, no recurrence was found during follow-up period for 36 months. We did not perform, but central nervous system (CNS) prophylaxis and scrotal irradiation are recommended for frequent CNS metastasis and recurrence in the opposite testicle necessitate.

Embryonal rhabdomyosarcoma; It is more common in children and young adult/teens (younger than 30 years) (15) and presented with painless palpable scrotum mass. But it may rarely diagnosed as painful edema of the scrotum mimicking epididymitis (16) or giant hydrocele (17). Three different types of rhabdomyosarcoma have been categorized as embryonal, alveolar and undifferentiated/pleomorphic type. For staging, retroperitoneal lymph node dissection can be performed. In the treatment, multimodality approach with surgery, chemotherapy and radiation is suitable for the patients. In our cohort, two cases diagnosed with embryonal rhabdomyosarcoma. Age at diagnosis of the cases were 18 and 19 years old. Tumor volumes were 33 and 138 mm<sup>3</sup>. One of them presented initially by scrotal pain and the other was admitted with painless scrotal mass. Retroperitoneal lymph node dissection for staging was performed in one case and not detected metastasis. The other patient received 4 cycles of cisplatin-based chemotherapy protocol. Mean follow-up period was 97 months. No recurrence was observed in both of patients. In cases with embryonal rhabdomyosarcoma, complete surgical resection is important. For the scanning of metastasis MRI is the first and best imaging modality. Age of patient, tumor size, morphology, residual tumor left after surgery and spread to other parts of body are risk factors for poor prognosis. We think that these patients should be followed up more frequently because of the possibility of metastasis.

Adenocarcinoma of the epididymis; primary epididymal masses are usually benign lesions. Malignant tumors are approximately 25% of all epididymal lesions (18). Nearly 70% of the patients with adenocarcinoma of the epididymis in the literature are older than 50 years (19). Mean tumor size in the 17 cases of literature was 33 mm (19). A significant number of cases cannot be diagnosed at the local stage. Retroperitoneal and pelvic lymph nodes are main drainage links for metastasis. Standardized treatment for adenocarcinoma of the epididymis is lacking. RPLND and pelvic lymph node dissection are recommended to contribute the treatment. The evidence of radiotherapy and chemotherapy is limited for the advanced disease. Our case was 29 years old boy who admitted with scrotal pain and palpable mass. Tumor volume was 39 mm<sup>3</sup> and consisted with the literature. In the abdomen tomography for staging after the surgery, there was found a 15 mm

lymph node in retroperitoneal area. 3 cycle of cisplatin based chemotherapy was performed. One year later the chemotherapy, abdomen tomography was repeated and found a 17 mm lymph node in same retroperitoneal area. Then RPLND was performed and pathology result was reported as metastasis of adenocarcinoma. 4 cycle of cisplatin based chemotherapy was performed. The any recurrence was not observed during 297 months in follow-up period. So, in cases with adenocarcinoma of the epididymis is aggressive tumors. Prognostic factors of these tumors are uncertain. Distant metastasis is the main cause of poor prognosis. No retroperitoneal LN metastasis found after RPLND may indicate good prognosis(19). Therefore RPLND can be routinely recommended for these patients.

Ewing's sarcoma of the testis; It is originated from primitive neuroectodermal cells. This malignancy can be occurred primary or secondary. Age at diagnosis of the Ewing's sarcoma of the testis is similar germ cell tumors. Prognosis of primary or secondary tumors is still poor. In primary tumors were associated with genetic factors. Foell, Hesse, Volkmer, Schmiedel, Neumann, Staeger (20) was reported phospholipase A1 beta as a gene with high expression in Ewing family tumors and Mahlendorf, Staeger (21) was reported that was characterized by chromosomal rearrangements involving members of the some RNA binding proteins. Secondary tumor may develop from BEP (bleomycin, etoposide, and cisplatin) chemotherapy (22). Vincristine, actinomycin D, cyclophosphamide, and doxorubicin (VACD) plus etoposide and ifosphamide (IE) is the standard chemotherapy (VACD-IE) of Ewing's sarcoma. In our case was 37 years old boy who admitted with painless scrotal mass. The age at diagnosis and was conformed with the literature(23). Tumor volume was 65 mm<sup>3</sup>. Computed tomography of abdomen and thorax in staging was used and not found any metastasis. Standart chemotherapy was performed and obtained no recurrence during the 18 months of follow-up period. All primitive neuroectodermal tumors show a 5-year survival rate of 58–61% with a median survival of 120 months(24). Therefore this follow-up period is a short time to evaluate of recurrence.

Testicular leiomyosarcoma; It is mean age of presentation of fifth decade. Anabolic steroid use, chronic inflammation of testis and testicular field radiation for treatment of leukemia are known risk factors for testicular leiomyosarcoma (25). In our case, age at diagnosis was 56 years. No predisposing factor was found past medical history. The tumor volume was 45 mm<sup>3</sup>. In retroperitoneal area, lymphadenopathy was found and diameter of this lesion was 18 mm. 3 cycle of cisplatin based chemotherapy was performed. Mean follow-up was 12 months and not observed any recurrence.

Paratesticular high grade sarcoma; Paratesticular soft tissue tumors are rare entities and may develop from mesenchymal, epithelial and mesothelial cells. It is usually diagnosed at sixth decade. The patients are admitted with

painful or painless scrotal mass or swelling (26). Radical resection of the tumor with removal of surrounding tissue is the most important phase of treatment (27). Doxorubicin-based chemotherapeutic agents may be used for the treatment of metastasis or local and distant disease recurrence (28). There is not accurate indications for radiation therapy in testicular sarcoma. But it may be useful for the control of local disease. In our case was 19 years unlike the literature. Tumor volume was 65 mm<sup>3</sup>. There was no metastasis in scanning of thorax or abdomen by computed tomography. 4 cycle of doxorubicin-based chemotherapy was performed. Follow-up period was 89 months and obtained no recurrence during this time.

Paratesticular malignant mesothelioma; It is a rare pathology and generally diagnosed sixth decade. Exposure to asbestos is a known risk factor. Poor prognosis is associated with delay diagnosis and insufficient surgical treatment. Metastasis at initial clinical manifestation is about 15% of cases. The prognosis for patients is usually poor, with a lethal outcome in 30% over a 24-month period (29). In our case, age at diagnosis was 74 years, mass volume which presented with scrotal pain and swelling was 45 mm<sup>3</sup>, lymphadenopathy in thorax was detected at diagnosis and follow-up period was 20 months. After the surgical resection, we planned chemotherapy for lymphadenopathy, but could not be continued due to clinical deterioration. Patient died within 1 year of diagnosis.

Uncommon testicular tumors occur at an older age than germ cell tumors. The clinical condition of the patient in admission may rarely be confused with epididymitis, orchitis or hydrocele. However, most patients present with a painless mass. Tumor markers are often normal in these patients. In our study, a statistical evaluation was not presented because of limited number of patients. However, in our analysis, the tumor size and age factor had no effect on recurrence. Lymph node positivity leads to poor prognosis. Our clinical experience shows that, instead of cisplatin-based routine treatment, pathology-specific chemotherapy applications are more significant. You need to plan a follow-up protocol that is specific to tumor pathology. It is recommended that postoperative lymph node positive patients should be followed up more frequently.

One of the limitations of the study is the limited number of patients. It is difficult to reach a higher number of patients with extremely rare cases. Another point is the imaging methods. In our clinic, scrotal imaging methods are used for differentiating of benign or malignant tissue. Therefore, scrotal ultrasonography is adequate for this differentiation and magnetic resonance imaging is not performed routinely. Thus, the tumor-specific imaging modality findings were not discussed in this study.

## CONCLUSION

Miscellaneous non-specific malign stromal tumors of testis are rare lesions and in the literature that do not contain enough information about recurrence and follow-

up. The majority of studies in the literature are in the form of a case report and the number of studies related to long-term follow-up results are rare.

This type of tumors should be kept in mind especially when patients are over 40 years of age are admitted with a painless scrotal mass accompanied by negative tumor markers. It is recommended that the surgical treatment should be aggressively performed, after the surgery, the tumor-specific chemotherapy protocol should be started promptly in the presence of lymph node. The tumor specific follow-up protocols will lead to an early diagnosis of recurrence, thus increasing tumor free survival.

*Acknowledgements: I would like to thank Asso. Prof. Ömer Yılmaz and all the staff of Sultan Abdulhamid Han Training and Research Hospital for their contributions and support.*

*Competing interests: The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.*

*Financial Disclosure: There are no financial supports.*

*Ethical approval: Retrospective study*

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