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Long-term Oncological Outcomes of Paratesticular Sarcoma Patients

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Abstract

Objectives:

To present long-term oncologic outcomes of patients with paratesticular sarcoma treated by a multidisciplinary team.

Materials and Methods:

Patients managed at the Princess Margaret Cancer Centre between 1990-2012, were analyzed. A sarcoma expert performed central pathology review. Kaplan-Meier graphs compared local-recurrence, metastasis and overall survival of patients treated with hemiscrotectomy vs. those not. Univariable Cox proportional hazards analysis, was performed to delineate predictors of local recurrence, metastasis, and overall survival.

Results:

Overall, 51 men with a median follow-up of 132 months (IQR 51.6-226.8) were analyzed. At presentation 92.2% (n=47) had localized disease. Only five patients (9.8%) had undergone initially planned hemiscrotectomy. Completion and salvage hemiscrotectomy was performed in 25 (54.3%) and 7 (15.2%) men, respectively. Recurrence and metastasis occurred in 12 (25.5%), and ten patients (19.6%), respectively. At last follow-up, 21.6% (n=11) had died, with (n=8) dying of their disease. Kaplan-Meyer graphs demonstrated that hemiscrotectomy entailed improved local-recurrence (median not reached vs.

62.4 months, log-rank p=0.008) and overall survival (median not reached vs. 168 months, log-rank p=0.081). Univariable analysis found hemiscrotectomy to be associated with lower local-recurrence rate (HR 0.21, p=0.02), while positive margins at initial surgery were associated with increased local recurrence (HR 4.81, p=0.047). No metastasis predictors were found, but age (HR =1.04, 95% C.I. 1.0-1.08, p=0.02) and non-localized disease at presentation (HR=5.17, 95% C.I. 1.33-20.06, p=0.017) were associated with worse overall survival.

Conclusion:
Paratesticular sarcoma is a rare tumor, predominantly manifesting as localized disease. Most patients receive an initial suboptimal oncological surgery. Improved long-term outcomes are demonstrated following early hemiscrotectomy.

Keywords: Hemiscrotectomy; Local recurrence; Paratesticular sarcoma; Positive surgical margins

Introduction:

Primary paratesticular tumors account for 7-10% of all intra-scrotal tumors[1], and include both neoplastic and non-neoplastic lesions with soft-tissue, mesothelial, epithelial and lymphoid origins, in addition to a variety of secondary malignancies.[2] The paratesticular area comprises several anatomic structures, including the tunica vaginalis, epididymis, ductus deferens, spermatic cord, vessels, lymphatic channels, and additional supportive tissues of the testis.[3, 4]

Sarcomas of the genitourinary tract account for less than 5% of all sarcomas and less than 2% of all urologic malignancies.[5] Paratesticular sarcomas (PTS) are rare mesenchymal, but clinically significant tumors. They are the most common urologic sarcomas, both in adults and children, accounting for 30% of all paratesticular tumors.[6] PTS occur in all age groups, most commonly presenting as slow-growing, painless, firm scrotal/groin lesions, ranging from small to extremely large masses.[7] The most common

histologic subtypes include liposarcoma, leiomyosarcoma, and rhabdomyosarcoma (RMS).[8]

Lack of awareness of these tumors may lead to delayed or misdiagnosis, since presentation may be mistaken for more common clinical entities, including inguinal hernia or other benign inguinoscrotal conditions.[8] Furthermore, the possibility of malignancy could be considered only mid-surgery.[9] Early hemiscrotectomy with wide clear margins is the most oncologically beneficial treatment. An inappropriate intervention with local excision and without wide margins, may compromise and increase the risk of subsequent local failure. Consequently, more surgery is required, resulting in a higher risk for a plausible fatal recurrence.[10]

Treatment necessitates complex multidisciplinary care and should be performed in centers with multidisciplinary sarcoma expertise. Furthermore, experienced pathologists and sophisticated molecular pathology techniques may be required for final diagnosis. Almost two decades ago, our group had presented their initial data on 14 patients with a relatively short median follow-up.[11] In this study, we present a description of a larger cohort with long-term oncological outcomes.

Patients and Methods:

Patient cohort and study endpoints

After receipt of approval by the institutional ethics committee, we performed a retrospective review of the Princess Margaret Cancer Centre (PMCC) institutional case records between 1990 and 2012. All PTS-diagnosed patients were analyzed, including those presenting with coexisting retroperitoneal disease. All patients were referred from outside hospitals and had undergone contemporary re-review of available specimens by a highly experienced sarcoma pathologist (B.D.). Study endpoints included local recurrence (LR) rates, recurrence-free survival (RFS), metastasis-free survival (MFS), and overall survival (OS).

Diagnosis, treatment and follow-up protocol

All patients underwent a full physical examination; staging imaging which included computed tomography (CT) scans of the thorax, abdomen, and

pelvis. Patients had either undergone planned initial surgery, defined as surgery with curative intent for a known or suspected sarcoma diagnosis; or those who underwent unplanned initial surgery, defined as a procedure done without a sarcoma diagnosis, and deemed insufficient for a cure. Unplanned surgeries included inguinal hernia repair, excisional mass biopsy, and radical orchiectomy for a testicular tumor. Men who originally underwent unplanned initial surgery were advised to undergo completion-hemiscrotectomy with wide local excision.

LR was defined as the first clinical recurrence of loco-regional disease, including disease occurring in the scrotal, inguinal, penile, perineal or in an isolated pelvic area. All patients with LR were offered salvage surgery.

The follow-up protocol included clinic visits on a 3-6 monthly basis for the first three years, and then annually. Every clinic visit entailed a clinical examination and chest x-ray. Surveillance pelvic cross-sectional imaging was performed at the discretion of the physician.

Covariates and outcomes

Data collected included patient age at diagnosis, clinical presentation and stage, tumor laterality and location, and details of previous treatment. Additionally, treatment details, histologic data, grade, tumor size, and rate of positive surgical margins (PSM) were obtained. The median follow-up time, LR and metastasis rates, and survival data were compared between patients undergoing hemiscrotectomy vs. those who did not. Cause of death was obtained from the Provincial Cancer Registry. Lastly, the outcomes of patients with RMS tumors were analyzed specifically, as these are more aggressive and harder to treat. We also repeated the analyses for the entire cohort after excluding all RMS patients, to see whether this had any effect on the results.

Surgical Technique

This entailed wide local excision including a hemiscrotectomy (Figure 1a), and a radical orchiectomy if testis had remained in-situ. Furthermore, en-bloc resection of the soft tissues/lymph nodes of the superficial inguinal region and the scar from any previous radical orchiectomy was performed (Figure 1b). Lastly, excision of any residual soft tissues surrounding the spermatic cord to

the deep inguinal ring was performed as well. Primary closure of the incision was usually performed (Figure 1c), unless more complex reconstruction was needed, requiring assistance by plastic surgeons.

Radiotherapy and Chemotherapy

Preoperative radiotherapy was considered before salvage surgery in patients with locally-extensive disease, or postoperatively, for management of PSM in primary or recurrent patients. When employed, non-RMS patients received pre-operative radiotherapy with 50 Gray in 25 fractions to the inguinal area, and postoperatively to the surgical bed with 66Gy in 33 fractions.

Distant recurrence and retroperitoneal disease were managed with chemotherapy, radiotherapy, and metastasectomy as clinically indicated. In patients with non-RMS histology, chemotherapy was not routinely employed in the curative setting. In contrast, in the palliative setting, doxorubicin-based chemotherapy was always used. In patients with RMS histology, all underwent retroperitoneal lymph node dissection (RPLND) since positive retroperitoneal nodes are reported in 40%-50% of cases.[12] Patients received either preoperative chemotherapy in the form of vincristine, actinomycin and cyclophosphamide (VAC), when evidence of radiographic nodal disease was demonstrated, or postoperatively when viable tumor was discovered in primary RPLND.

Statistical Analyses

Descriptive analyses (mean with standard deviation and median with interquartile range) was used for continuous variables, and proportions for discrete variables. Kaplan-Meier (KM) graphs (log-rank test) were used to compare LR free survival, MFS, and OS. Univariable analysis was performed using Cox-proportional hazards regression to decipher LR, metastasis, and OS predictors among all patients. Due to the low number of events, the multivariable analysis could not be performed. Statistical tests were two-tailed and a p-value <0.05 was considered statistically significant. All analyses were conducted using SPSS software version 23.0 (SPSS Inc., Chicago, IL) and SAS 9.4 (SAS Institute, Cary, North Carolina).

Results:

A total of 51 patients were identified from the PMCC institutional database. Figure 2 demonstrates the consort diagram of the study. Contemporary re-review of available specimens was achievable in 36/51 (70.6%) patients. In 3/36 (8.3%) of these patients the diagnosis had changed from malignant fibrous histiocytoma to undifferentiated pleomorphic sarcoma; leiomyosarcoma to dedifferentiated liposarcoma; and sclerosing liposarcoma to cellular angiofibroma.

Clinical features at diagnosis of all patients are shown in Table 1. Median follow-up time was 132 months (IQR 51.6-226.8 months), with a median age at diagnosis of 52 years (range 15-89). At presentation, 47/51 (92.2%) patients demonstrated localized disease, while 3/51 (5.9%) presented with inguinal or retroperitoneal nodes, and only one patient (1.9%) presented initially with distant metastatic disease. In follow-up, 12/47 (25.5%) patients experienced LR, 7/47 (14.9%) patients developed metastasis, and 5/47 (10.6%) died of their disease.

The three most common histologic subtypes were liposarcoma (43.1%), leiomyosarcoma (17.6%), and RMS (11.9%). Surgery was performed without a preoperative diagnosis of sarcoma in 46/51 (90.2%) patients, and 7/51 patients (13.7%) had presumed benign lesions excised before eventual accurate diagnosis. Only 5/51 (9.8%) patients underwent upfront hemiscrotectomy. Completion-hemiscrotectomy was offered to all men who received prior surgery without a preoperative diagnosis of sarcoma, with 25/46 (54.3%) patients consenting to the procedure and 7/46 (15.2%) additional patients undergoing a salvage hemiscrotectomy after LR had occurred. The remaining 14/46 patients (30.5%) did not undergo a hemiscrotectomy procedure at any stage. Table 2 demonstrates the preoperative features stratified by the surgical treatment patients had received.

Usage of Radiotherapy and Chemotherapy

A total of 11/51 (21.5%) had received radiotherapy. Two of these patients (18.2%) had RMS and received it as a part of their curative therapy.

Additionally, 5/11 (45.5%) received radiotherapy at LR, and the remaining 4/11 (36.3%) received it as part of the salvage therapy administered for metastatic disease. Importantly, patients treated with radiotherapy endured significant complications, including acute grade 3 moist desquamation and urethritis; late infected groin mesh, vesicocutaneous fistula, partial dehiscence, flap necrosis, and chylous ascites. Lastly, chemotherapy was given to all 10/51 (19.6%) patients who had metastatic disease, of which 4 of them (40%) had RMS.

Local Recurrence

LR had occurred in 12/47 (25.5%) patients initially presenting with localized disease, after a median time of 14.5 months from diagnosis (range 3-77 months). Median RFS was 62.4 months in those who did not undergo hemiscrotectomy, and it was not reached in those who underwent hemiscrotectomy, p=0.008 (Figure 3a). Five and 10-year RFS were 57.9% and 52.6% respectively for those who did not undergo hemiscrotectomy compared to 92.3% and 88.4% for those who did. All patients with LR were managed with aggressive surgical resection, and 5/12 (41.7%) patients received preoperative radiotherapy. Patients who underwent primary or completion hemiscrotectomy were less likely to endure LR compared to those who did not undergo a hemiscrotectomy (11.1% vs. 45%, p=0.008). No statistically significant difference was seen in the LR rates between patients who underwent primary hemiscrotectomy and those who underwent completion hemiscrotectomy (0% vs. 12%, p=0.525), but only five patients underwent primary hemiscrotectomy, limiting the robustness of this comparison. Overall 7/12 (58.3%) patients with LR remained disease-free at last follow-up. However, 4/12 (33.3%) patients developed distant metastasis and 1 (8.3%) patient had LR at the time of death from other causes. Two of the four patients (50%) developing metastasis had died of their disease. Univariable analysis (Table 3) demonstrated that undergoing hemiscrotectomy was protective of LR (HR 0.21, 95% C.I. 0.06-0.79, p=0.02), and PSM at initial surgery was associated with increased LR (HR 4.81, 95% C.I. 1.02-22.68, p=0.047).

Metastasis

In total, 10/51 (19.6%) patients developed metastases after a median time of 18 months from diagnosis (range 0-117 months). Five- and ten-year MFS was 89.4% and 84.2% respective for those who did not undergo hemiscrotectomy compared to 88.4% and 84.6% among those who did. Most common metastatic sites included: pulmonary (60%), retroperitoneum (40%) and mediastinum (40%). The median time from metastasis to death was 11.4 months (range 2.0-65.6). Univariable analysis (Table 3b) did not demonstrate any statistically significant predictors of metastases.

Overall Survival

Median OS was 168 months [IQR 50.3 months – not reached)] in those who did not undergo hemiscrotectomy, while it was not reached in those who underwent hemiscrotectomy, p=0.081(Figure 3c). Five- and ten-year OS was 73.7% and 68.4% respectively for those who did not undergo hemiscrotectomy as compared to 92.3% and 92.3% for those who did. At last follow-up, 11/51(21.6%) patients had died with 8/51 (15.7%) patients dying of deaths attributable to PTS, one patient died of an unrelated renal pelvis urothelial carcinoma, and 2/11 deaths were due to unknown causes. However, these two patients did have metastatic PTS. Significant predictors of worse OS (Table 3) included; age (HR 1.04, 1.00-1.08, p=0.02), and non-localized disease at presentation (HR 5.17, CI 1.33-20.06, p=0.017).

Rhabdomyosarcoma patients

Six patients (11.7%) with RMS were included in the cohort. Their median age was significantly younger (20, range 15-27). Three of the six patients (50%) had undergone completion-hemiscrotectomy. Two RMS patients (33%) also received radiotherapy as part of their curative treatment. All six patients also underwent RPLND; three with no radiographic nodal disease underwent primary RPLND; while three with nodal disease were administered chemotherapy and then underwent post-chemotherapy RPLND. Only one of the primary RPLND patients (33%) had positive nodes on pathology and received postoperative chemotherapy. Of the three patients undergoing postchemotherapy RPLND, viable tumor was discovered in 2/3 patients (67%).

At last follow-up, after a median follow-up of 83.9 months, 4/6 RMS patients (67%) were disease-free, 1 (16.7%) was lost to follow-up, and 1 (16.7%) had died. When analyzing the entire cohort after excluding these six patients, no significant differences in the univariate predictors of LR, metastases, and OS could be discerned, and KM curves remained similar.

Discussion:

Our study demonstrated that over 90% of the patients had localized disease at presentation. During a median follow-up of 132 months, approximately 25% had LR, 20% had developed metastasis, and 15% died of their disease. Importantly, only 10% of the patients had an initially-planned hemiscrotectomy. More than 50% of the remaining patients underwent completion-hemiscrotectomy, and 15% had a salvage-hemiscrotectomy when LR had occurred, leaving 27% of the patients not undergoing hemiscrotectomy at any stage. Patients who did not undergo hemiscrotectomy had almost a 34% higher LR rate than those who did. LR rate was also shown to be higher among those with PSM in the initial surgery. OS rate was improved among those who underwent hemiscrotectomy and was shown to be worse in older men, and patients presenting with non-localized disease.

Over 90% of the patients in our cohort had undergone surgery without a preoperative diagnosis of sarcoma when the true diagnosis had not been originally suspected preoperatively. This extremely high percentage is similar to that reported in other series.[8] Our data demonstrate that PTS patients of all grades are at high risk for LR when not treated with wide margins hemiscrotectomy. Furthermore, PSM at initial surgery was noted to be associated with higher LR rates, similar to other series.[13] Our five-year LR rate was also similar to that previously published.[6, 13] Aggressive treatment with wide repeat excision resulted in a better local-control rate and improved OS.

Unfortunately, there are currently no clear guidelines or consensus on the optimal management strategy of PTS, and the natural history of the disease is not well-known. This emanates from the rarity of these tumors and the fact that most published data is derived from case reports and short series.[1, 6, 8, 9,

[11, 13-15] In an attempt to improve this, raising physician awareness of these tumors is an important first step. As always, history and clinical examination are fundamental in deciding which investigations are appropriate. On clinical examination, distinguishing between a cord lipoma or an inguinal hernia from PTS can be quite challenging.[8] However, a finding of an irreducible inguinal hernia should prompt physicians to use imaging, which is a critical tool in the assessment of paratesticular lesions.[16] Furthermore, if any suspicious intraoperative findings are witnessed during surgery for a presumed benign etiology, it is advisable to consider an incisional biopsy to determine the diagnosis, rather than perform a suboptimal oncologic resection.[13]

As mentioned earlier, imaging is critical and is most probably an underutilized tool in the assessment of paratesticular lesions. Ultrasound imaging is the most common modality used for paratesticular lesions, demonstrating a sensitivity of almost a 100% and specificity of approximately 70%.[4] However, if ultrasound provides questionable results, magnetic resonance imaging (MRI) should be used.[17] These modalities can be performed separately or in combination to differentiate benign from malignant lesions.[18] PTSs have atypical image appearance that could aid us in deciphering whether a lesion is a PTS.[19] RMS typically manifests as a large heterogeneous tumor with cystic/necrotic components.[8] Leiomyosarcomas appear as well-defined lesions with variable echogenicity, demonstrating a myriad of patterns, including necrosis, hemorrhage, or cystic degeneration.[18] Importantly, the solid parts of the lesion enhance, which should immediately trigger cross-sectional imaging.[8] Lastly, Liposarcoma has a distinct and exclusive feature of abnormal fat, which can be demonstrated on CT or MRI, concomitantly with the enhancement of existing solid parts. Seldom, calcification can also be seen. Although sonography can commonly demonstrate calcifications and increased vascularity within the lesion, it is suboptimal in differentiating between herniated and an abnormal fatty mass[8], making this commonly used modality at times insufficient.

Hemiscrotectomy was demonstrated to be critical in our analyses, providing lower LR rates and improved OS. In our opinion, this surgical treatment should be performed as early as possible. Following unplanned local excision, the option of surveillance with salvage hemiscrotectomy, only

when LR is evident, is a moot point due to the risk that the window for a cure may be missed. While our data demonstrated that salvage surgery achieved good local control, 4/12 (33%) patients with LR had developed metastases.

There has been a case report[20] and a case series of 8 patients[21] suggesting that hemiscrotectomy with wide surgical margins is not mandatory and orchiectomy could be sufficient. There has not been any large series supporting this approach, and in the mentioned case series, all eight patients received chemotherapy as well, in an attempt to sterilize scrotal dissemination[21]. Most series consisting of considerably larger cohorts support our recommendation that these patients should undergo hemiscrotectomy with wide surgical margins to decrease local recurrence rates and improve overall outcomes[6, 8, 13, 22]. Supplemental Table 1 summarizes some of the key points in our approach to the management of PTS.

When analyzing the data after excluding the RMS patients, the KM survival curves and the univariate analyses predicting LR, metastases, and OS remained similar, despite the more aggressive biology of the RMS tumors. Although only 6/51 (11.8%) of the patients had RMS, these similar results demonstrate that it is possible to include RMS together with the other subtypes of PTS when examining predictors of important outcomes in this rare tumor.

The fact that our cohort demonstrated a long median OS of 168 months (14 years), similar to a large Surveillance, Epidemiology, and End Results (SEER) population-based study[23], reflects a disease with indolent natural history and predominantly local pattern of recurrence. Some of the other published PTS reports, summarized in supplemental table 2, also demonstrate similar long median OS periods. However, due to the high risk of recurrence occurring even after five and ten years from surgery, long-term clinical and imaging follow-up for at least 120 months (ten years) is mandatory.[9]

Our study has several limitations; including its relatively small number of patients, retrospective design, and the fact that it has encompassed a long-time frame of accrual, with evolving changes occurring in the diagnosis and management policies. We attempted to address this by ensuring that all patients were managed by a small multidisciplinary team of sarcoma

specialists, using a consistent management strategy over time. Additionally, this study encompasses a heterogeneous group of cancers with different biology, with the majority being liposarcomas. Formulating generalizable conclusions on all various PTS subtypes is not realistic nor appropriate. Lastly, there were no pre-defined criteria for which patients should receive preoperative or postoperative radiotherapy, and this was decided on a case-by-case basis.

Our experience demonstrates that PTS is a rare disease with most patients undergoing an inappropriate oncological procedure as their initial treatment. This probably results from a lack of physician awareness and underutilization of helpful imaging tools. Importantly, most patients present with clinically localized disease and are potentially curable, if given the correct treatment. Early hemiscrotectomy with wide clear margins results in favorable oncologic outcomes. Due to the rarity of this disease, and to ensure the best possible outcomes, patients must be treated in centers of excellence by a highly-experienced multidisciplinary team of sarcoma specialists.

Author Contributions:

Design and conception: HG, LMW, BD, AE, TVDK, MASJ, RJH

Data collection: LMW, SY, TA

Writing of manuscript: HG, LMW

Editing and reviewing of the manuscript: BD, CC, SY, TA, AE, TVDK, MASJ, RJH

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Figure legends:

Figure 1 a)- Hemiscrotectomy borders of the incision. This includes the scar from previous surgery and the ipsilateral hemiscrotum. **b)** En bloc excision of superficial inguinal tissues. The median scrotal raphe provides an intact fascial plane and serves as the median margin. Additional important borders include buck's fascia at the base of the penis, the inguinal ligament, and the fascia lata overlying the femoral vessels. **c)** The mobility of the contralateral scrotum most commonly enables primary closure of the incision.

Figure 2 – Study consort diagram

Figure 3 – Kaplan Meier graphs demonstrating the effect of hemiscrotectomy on **a)** Recurrence-free survival (median of 5.2 years for no hemiscrotectomy vs. not reached for hemiscrotectomy, log-rank p= 0.008). **b)** Metastasis-free survival (median not reached in both groups, log-rank p=0.69). **c)** Overall

survival (median of 14 years for no hemiscrotectomy vs. not reached for hemiscrotectomy, log-rank p= 0.081)

Table 1: Clinical features at diagnosis

Total number of patients, n	51
Age at diagnosis (years)	
- median (IQR)	52.0 (36.0-65.0)
- mean (range)	50.4 (15-89)
Laterality, n (%)	
- left	30 (58.8)
- right	21 (41.2)
Clinical presentation, n (%)	
- painless scrotal mass	28 (54.9)
- painless inguinal mass	15 (29.4)
- other	4 (8)
- unknown	4 (7.7)
Clinical stage at diagnosis, n,%	
- localized	47 (92.2%)
- + inguinal disease	1(1.95%)
- + retroperitoneal disease	2 (3.9%)
- + metastatic disease	1 (1.95%)
Clinical status at presentation, n (%)	
- new diagnosis	6 (11.8)
- previous unplanned surgery	32 (62.8)
- loco-regional recurrence	9 (17.6)
- retroperitoneal/distant metastases	4 (7.8)
Tumor location, n (%)	
- paratesticular	20 (39.2)
- spermatic cord	19 (37.3)
- other: adipose tissue adjacent to cord (4), scrotal skin (4)	8 (15.6)
- unknown	4 (7.9)
Percutaneous (transcrotal) needle biopsy performed , n (%)	
- Yes	5 (9.8)

- No	46 (90.2)
Previous non-diagnostic surgery (i.e. “benign lipoma”), n (%) - Yes - No	 7 (13.7) 44 (86.3)
Initial/Diagnostic surgery performed, n (%) Planned definitive sarcoma surgery with inguinal orchiectomy + hemiscrotectomy Unplanned surgery - radical/inguinal orchiectomy - transcrotal orchiectomy, excision biopsy, hydrocelectomy - hernia repair Median follow up time (months) (IQR)	 5 (9.8) 33 (60.8%) 11(21.6%) 4 (7.8%) 132.0 (51.6-226.8)

Table 2: Pre-operative features of men by treatment

Original tumor characteristics	Primary hemiscrotectomy (n=5)	Completion hemiscrotectomy (n=25)	Salvage hemiscrotectomy (n=7)	No hemiscrotectomy (n=14)	All patients (n=51)
Mean age (years) (range)	43 (18-79)	48 (20-72)	57 (27-77)	52.1 (15-89)	50.4 (15-89)
Location of tumor, n (%)					
- Paratesticular	3 (60%)	8 (32%)	2 (29%)	8 (57.1%)	20 (39.2%)
- Spermatic cord	0	12 (48%)	4 (57%)	3 (21.45%)	19 (37.2%)
- Other	2 (40%)	5 (25%)	1 (14%)	3 (21.45%)	12 (23.5%)
Mean size of tumor (cm) (range)	12.7 (9-15)	7.0 (1.5-18)	7.5 (4.0-12.5)	7.2 (2.0-20)	7.45 (1.5-20)
Histology of initial tumor, n (%)					
- Liposarcoma	3 (60%)	12 (48%)	4 (58%)	4 (28.6%)	22 (43.1%)
- Leiomyosarcoma	0	7 (28%)	0 (0%)	2 (14.3%)	9 (17.6%)
- Rhabdomyosarcoma	0	2 (8%)	1 (14%)	3 (21.4%)	6 (11.9%)
- Other	2 (40%)	4 (16%)	2 (28%)	5 (35.7%)	14 (27.4%)
Histologic grade at initial surgery, n (%)					
- Grade 1	1 (20%)	9 (36%)	0 (0%)	3 (21.4%)	13 (25.5%)
- Grade 2	1 (20%)	4 (16%)	2 (29%)	2 (14.3%)	9 (17.6%)

- **Grade 3**	1 (20%)	10 (40%)	4 (57%)	5 (35.7%)	20 (39.3%)
- **Unknown**	2 (40%)	2 (8%)	1 (14%)	4 (28.6%)	9 (17.6%)
Positive margin status in initial surgery(n, %)					
- **Yes**	0	13 (52%)	6 (86%)	4 (28.6%)	23 (45.1%)
- **No**	5 (100%)	9 (36%)	1 (14%)	9 (64.3%)	22 (43.1%)
- **Unknown**	0	3 (12%)	0	1 (7.1%)	6 (11.9%)

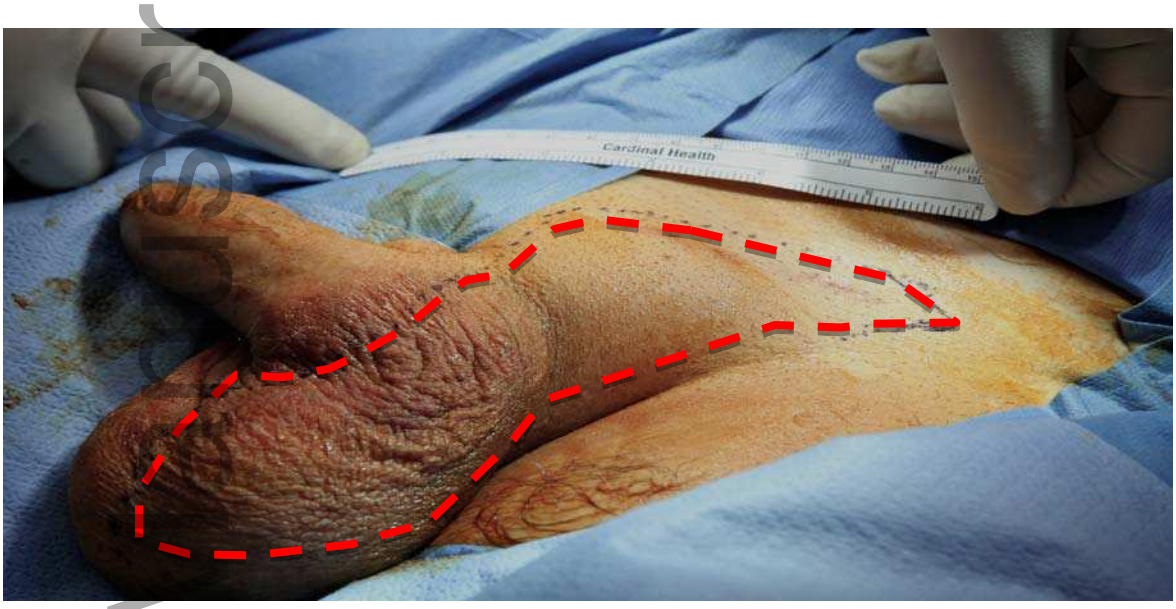
Table 3: Cox proportional hazards univariable analysis of predictors of local recurrence, metastasis and overall survival

	Local Recurrence		Metastasis		Overall Survival	
	HR (95% C.I.)	**p-value**	**HR (95% C.I.)**	**p-value**	**HR (95% C.I.)**	**p-value**
Age	1.02 (0.98-1.05)	0.33	1.002 (0.969-1.03)	0.906	***1.04 (1.00-1.08)***	***0.02***
Histology						
• **Liposarcoma**	Reference					
• **Leiomyosarcoma**	0.81 (0.16-4.02)	0.79	3.75 (0.618-22.79)	0.151	2.17 (0.47-9.91)	0.32
• **Rhabdomyosarcoma**	0.54 (0.07-4.53)	0.57	1.91 (0.173-21.19)	0.596	0.76 (0.08-7.01)	0.81
• **Other**	0.86 (0.21-3.45)	0.83	3.2 (0.581-17.66)	0.182	1.61 (0.40-6.49)	0.50
Histopathological grade						
• **Grade 1**	Reference					
• **Grade 2/3**	2.5 (0.529-11.8)	0.247	44.6 (0.11-17500)	0.213	5.73 (0.722-45.46)	0.099
Positive margin						
• **no**	Reference					
• **yes**	***4.81 (1.02-22.68)***	***0.047***	1.006 (0.251-4.03)	0.993	1.57 (0.45-5.45)	0.47
Hemiscrotectomy						
• **no**	Reference					
• **yes: (primary or completion)**	***0.21 (0.06-0.79)***	***0.02***	1.031 (0.295-3.6)	0.962	0.49 (0.16-1.54)	0.22

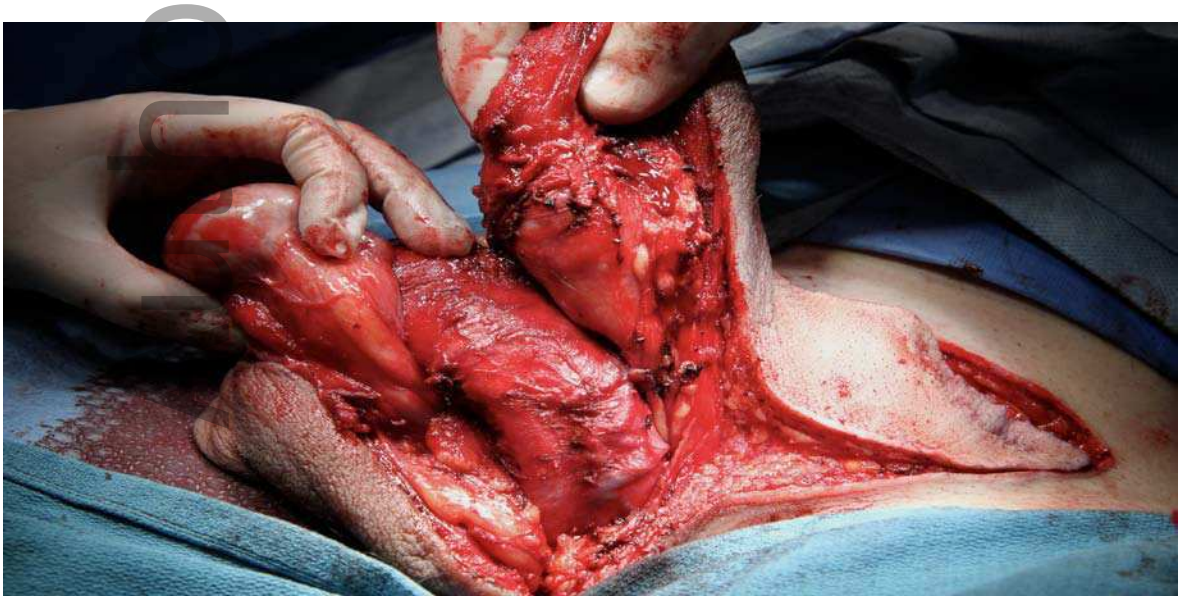
Clinical stage at diagnosis						
• **localized (n=47)**	Reference					
• **non-localized (n=4)**	**-**	**-**	**-**	**-**	***5.17 (1.33-20.06)***	***0.017***
Developed local recurrence						
• **no**	Reference					
• **yes**	-	-	1.5 (0.4-5.53)	0.539	0.987 (0.28-3.478)	0.984

Figure 1 a) Hemiscrotectomy borders of incision. This includes the scar from previous surgery and the ipsilateral hemiscrotum. b) Enbloc excision of superficial inguinal tissues. The median scrotal raphe provides an intact fascial plane and serves as the median margin. Additional important borders include buck's fascia at the base of the penis, the inguinal ligament, and the fascia lata overlying the femoral vessels. c) The mobility of the contralateral scrotum most commonly enables primary closure of the incision.

a.



b.



c.

Figure 2 – Study consort diagram:

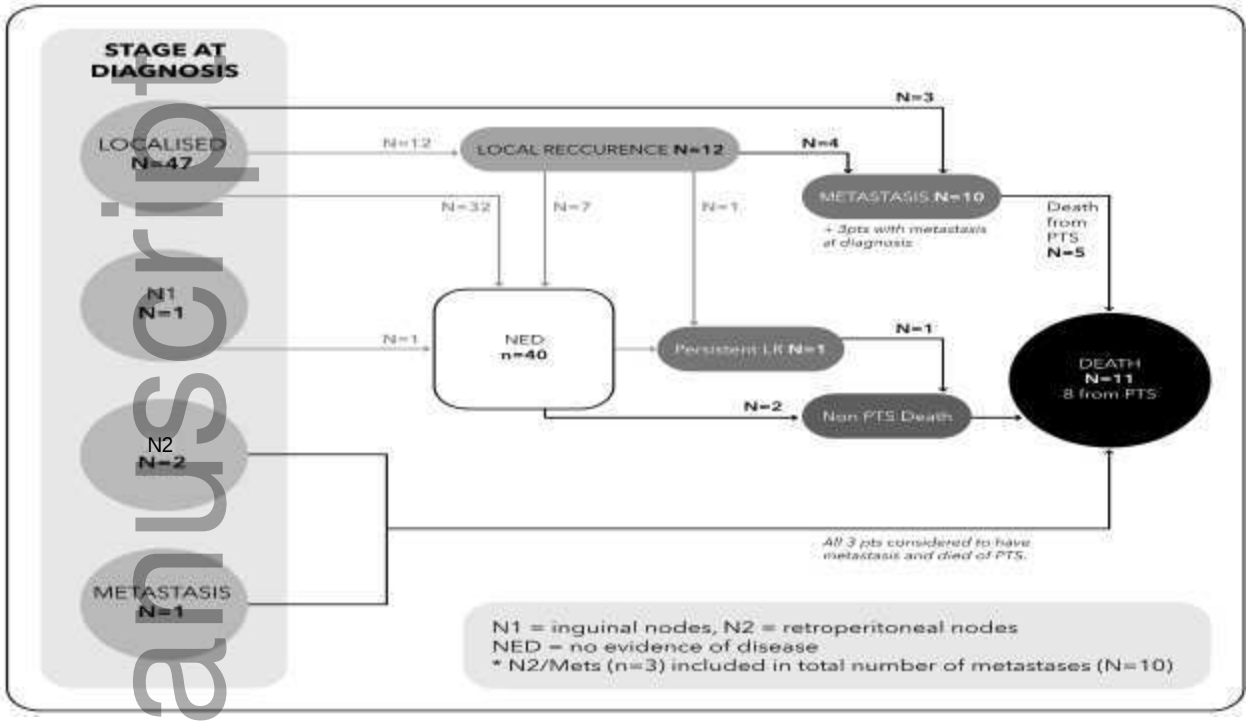
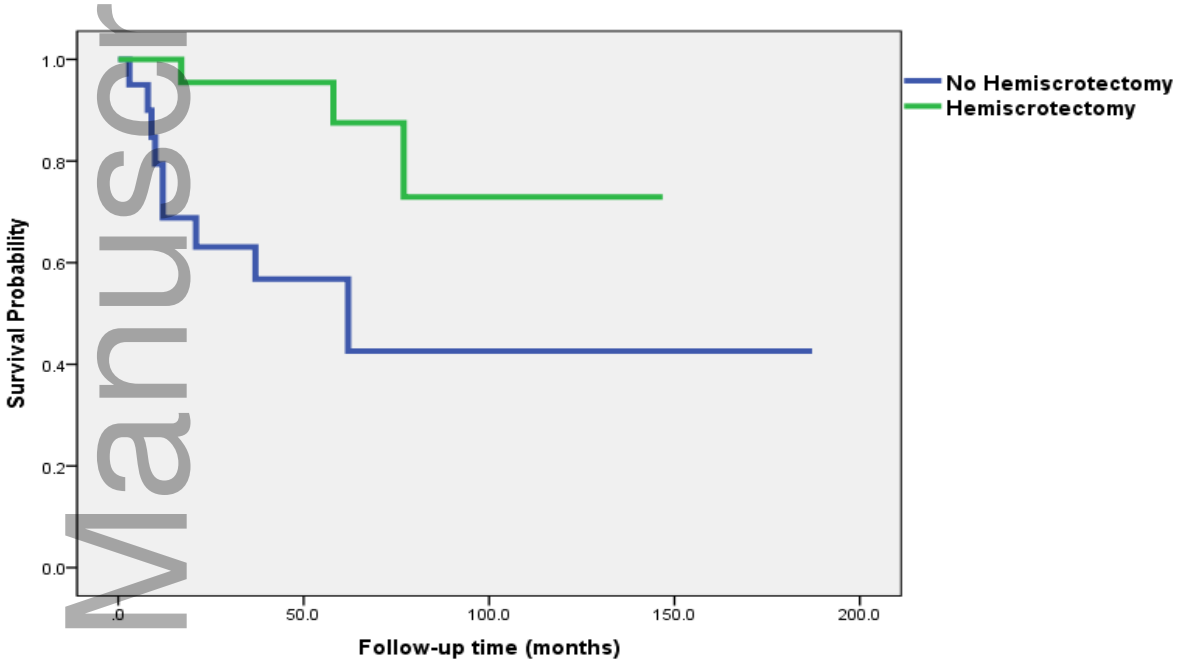
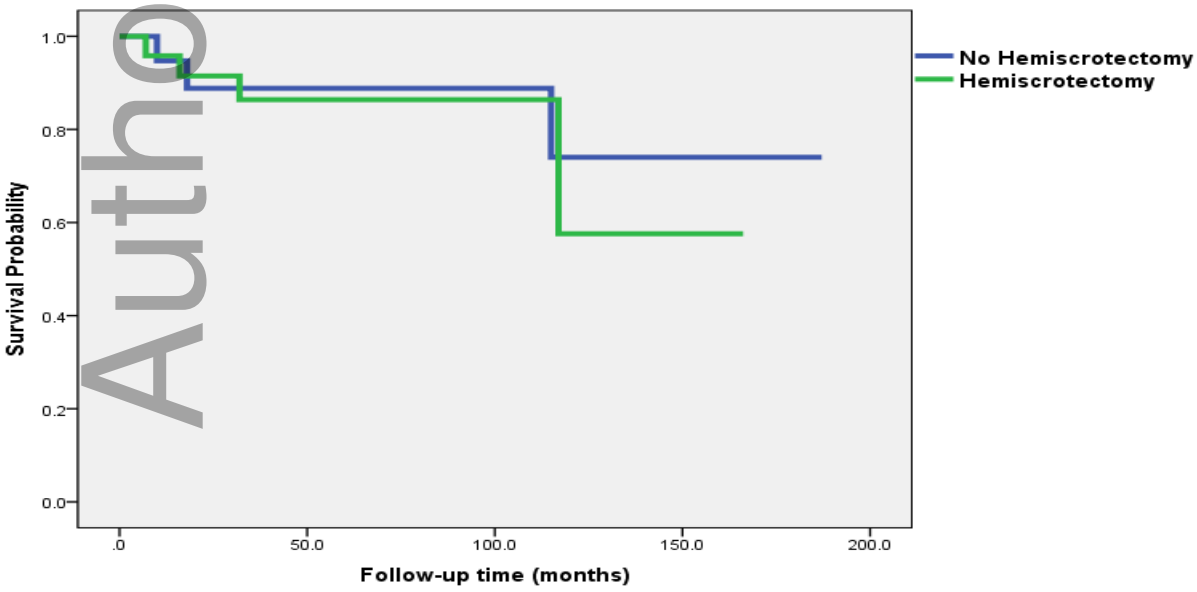


Figure 3 – Kaplan Meier graphs demonstrating the effect of hemiscrotectomy on a) Recurrence free survival (median of 62.4 months [IQR 23.3 – not reached] for no hemiscrotectomy vs. not reached for hemiscrotectomy, log rank p= 0.008). b) Metastasis free survival (median not reached in both groups, log rank p=0.69). c) Overall survival (median of 168 months [IQR 50.3 months – not reached)] for no hemiscrotectomy vs. not reached for hemiscrotectomy, log rank p= 0.081)

a.



b.



c.