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Genitourinary Rhabdomyosarcoma in Adolescents and Adults–20 Year Experience from a Tertiary Cancer Centre

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Abstract **Original Research Article**

Rhabdomyosarcoma (RMS) accounts for <3% of soft tissue sarcoma in adults, but is the most frequent soft tissue sarcoma in children. We performed a retrospective analysis of adolescents and adult patients (≥15 years) with genitourinary RMS treated at our Institute during 1995 – 2015. Among a total of 126 patients with RMS (≥15 years), 26 (20.6%) had genitourinary primary. Twenty were males and 6 were females, with a median age of 17 years. Patients presented with swelling, pain, bleeding / discharge per vagina, urinary retention and renal failure. Among males, primary sites were testis/paratestis in 15, prostate in 3 and urinary bladder in 2. Among females, primary sites were vulva/vagina in 5 and cervix in 1. Eleven had embryonal RMS (ERMS), 7 had alveolar RMS (ARMS), 6 had RMS not otherwise specified (RMS-NOS) and 2 had pleomorphic RMS. Eleven patients were in group I, none in II, 10 in III, and 5 in group IV. Five patients presented with metastasis. All patients received systemic chemotherapy with vincristine, actinomycin and cyclophosphamide (VAC); 12 patients received an additional drug (doxorubicin, cisplatin and/or etoposide). Complete excision was done in 11 patients (orchidectomy in 10 and wide excision in 1), partial cystectomy in 1and biopsy in 14. Eleven patients received local radiotherapy (median dose 40Gy). Four patients progressed, at a median of 21.5 months; 2 each had locoregional and systemic sites of failure. Five year overall survival (OS) was 60%. The 5 year OS for patients with histological subtypes ERMS, RMS-NOS and ARMS was 75%, 50% and 40% respectively. Among the two patients with Pleomorphic RMS, one is still alive at 120 months follow up. Median OS of Group 1 was 70 months and that for combined group 3 and 4 was 25 months (p – 0.215).

Keywords: Rhabdomyosarcoma, Genito-urinary, Adolescents, Paratesticular RMS, VAC.

INTRODUCTION

Rhabdomyosarcoma (RMS) is an aggressive malignancy of mesenchymal origin. It accounts for less than 1% of solid tumour malignancies in adults, and <3% of soft tissue sarcoma in adults, but is the most frequent soft tissue sarcoma in children [1-4]. Large multinational collaborative studies on RMS in children have dramatically improved the results and currently the 5-year overall survival (OS) exceeds 70% for non-metastatic RMS [5-7]. In contrast, the outcome of adult patients remains poor and given the rarity of adult RMS, limited information is available in the literature on its optimal management. Although RMS can arise from anywhere in the body, 25% of paediatric RMS are genitourinary (GU-RMS), however GU-RMS is rare among adults [8]. We present our 20 year experience with GU-RMS in patients 15 years of age and above who were treated at our centre during 1995-2015. The primary aim of the present retrospective study is to describe the clinical characteristics, treatment, outcome, and prognostic factors for adult patients with GU-RMS.

MATERIALS AND METHODS

This is a 20 year retrospective audit carried out in the department of Medical Oncology at our Institute among patients 15 years of age and above who had histologically confirmed RMS of the genitourinary site. The medical records were studied in detail regarding the

baseline clinical characteristics, treatment, outcome and survival.

Statistical Analysis

Descriptive statistics for categorical variables and continuous variables is presented. Continuous variables were compared using Student's *t*-test and categorical variables were compared using the chi-square test or Fisher's exact test if necessary. Disease free survival (DFS) was calculated from the date of diagnosis to date of relapse and OS was calculated from date of diagnosis to date of death or last follow-up. OS was estimated using the Kaplan-Meier method and compared using log-rank test. A p- value of < 0.05 was taken as significant. Median follow-up was calculated using the reverse Kaplan–Meier method.

RESULTS

Baseline characteristics (shown in Table-1):

During 1995 – 2015, a total of 126 patients with RMS (≥15 years of age) were treated at our centre and among them, 26 (20.6%) patients had genitourinary primary. Twenty one patients were between 15 – 20 years age group, 3 between 21 – 30 years and 1each was 40 years and 49 years of age. The median age was 17 years (range 15 – 49 years). There were 20 males and 6 females. The presenting symptoms were swelling in 19, pain in 5, bleeding / discharge per vagina in 4, urinary retention in 2 and renal failure in 1 (either alone or in combination). The median duration of symptoms was 5 weeks. Out of 20 males, the primary sites were testis / paratestis in 15, prostate in 3 and urinary bladder in 2. Among 6 females, the primary site was vulva / vagina in 5 and cervix in 1. Six patients had regional lymphadenopathy at initial presentation (primary sites were testis in 3, vulva / vagina in 2 and prostate in 1). Staging work up included complete hemogram, liver function test, renal function test, local imaging by Computed Tomography / Magnetic Resonance Imaging (CT/MRI), CT Chest, bone marrow study and bone scan. All patients had histopathological confirmation of the primary either from the excision specimen or biopsy. On microscopic detailing, the tumour was characterised by small round blue cells with high nucleo-cytoplasmic ratio. At our centre, immunohistochemistry (IHC) was available only from later half of the study period. Out of the 15 tested, all tested positive for desmin and 4 had myogenin positivity. Regarding the histological subtype, 11 (42.3%) had embryonal RMS (ERMS), 7 (27%) had alveolar RMS (ARMS), 6 (23%) had RMS – not otherwise specified (RMS-NOS) and 2 (7.7%) had pleomorphic RMS. The stage of the disease was determined by the Intergroup Rhabdomyosarcoma Study Group (IRSG) post-surgical grouping system. There were 11 (42.4%) patients in group 1, none in group 2, 10 (38.4%) in group 3 and 5 (19.2%) in group 4. At staging work up, 5 (19.3%) male patients had metastasis at presentation (lung metastasis in 3, bone metastasis in 1 and bone marrow metastasis in 1).

Table-1 (Baseline patient characteristics)

Baseline patient characteristics	n
Total no. of patients	26
Sex:	
Males	20 (77%)
Females	6 (23%)
Age	
15-20 years	21 (81%)
21-30 years	3 (11.5%)
>30 years	2 (7.5%)
Median age	17 years
Symptoms (either alone / in combination)	19
Swelling	5
Pain	4
Bleeding / discharge per vaginum	2
Urinary retention	1
Renal failure	
Median duration of symptoms	5 weeks (range 1-30)
Primary site	
Males (n-20)	
Testis / paratesticular	15
Prostate	3
Urinary bladder	2
Females (n-6)	
Vulva / vagina	5
Cervix	1
Histological subtype	
ERMS	11 (42.3%)
ARMS	7 (27%)
RMS-NOS	6 (23%)
Pleomorphic RMS	2 (7.7%)
IRSG post-surgical grouping	
Group 1	11 (42.3%)
Group 2	0 (0%)
Group 3	10 (38.5%)
Group 4	5 (19.2%)
Stage	
Non metastatic	21 (80.8%)
Metastatic	5 (19.2%)
Lung	3
Bone	1
Bone marrow	1

Treatment Characteristics

The treatment was multimodality. All patients received systemic chemotherapy with vincristine, doxorubicin and cyclophosphamide (VAC) regimen. Twelve patients received an additional drug namely doxorubicin, cisplatin and/or etoposide. Surgical management consisted of complete excision in 11 patients, ie, orchidectomy in 10 and wide excision in 1. One patient with bladder RMS underwent partial cystectomy. The remaining 14 patients underwent biopsy from the primary site. Eleven patients received

local radiotherapy (RT) and the median dose was 40Gy (range 35 – 50.4 Gy).

Survival Outcome

Among non-metastatic patients, 4 patients progressed, at 14 months, 19 months, 24 months and 48 months respectively, 2 each had locoregional and systemic sites of failure. The 5 year overall survival (OS) was 60% (Fig-1). Non-metastatic patients had better 5 year OS when compared to metastatic patients (72% vs. 24%), the median being 70 months vs. 20 months, with a significant p value of 0.039 (Fig-2). When stratified for age, the median survival for 15-20 years and >20 years was 66 months and 20 months respectively, although not statistically significant (p – 0.07) (Fig 3). The median survival for both males and females was 60 months (Fig-4). The median survival of Group 1 patients was 70 months and that of combined group 3 and 4 patients was 25 months (p – 0.215) (Fig-5). The 5 year survival for patients with histological subtypes namely ERMS, RMS-NOS and ARMS was 75%, 50% and 40% respectively (Fig-6). We had 2 patients with Pleomorphic RMS, of which one patient had 6 month survival (lost follow up) and one is still alive with no evidence of disease at 120 months follow up.

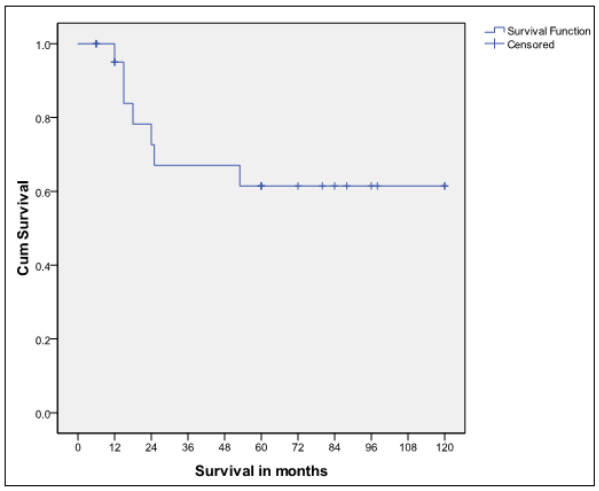

Fig-1: Overall survival

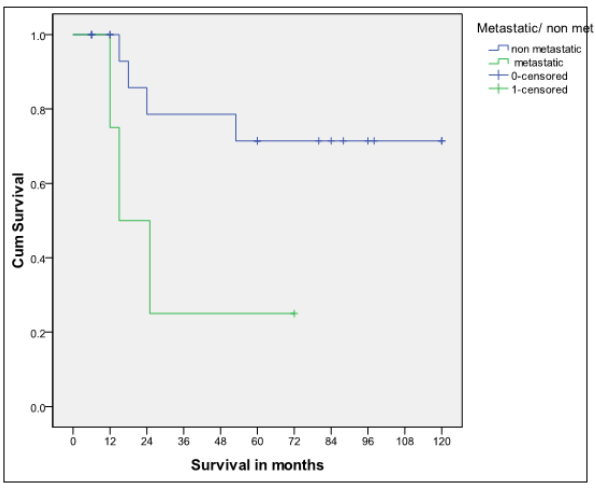

Fig-2: Overall survival (Non metastatic vs. metastatic)

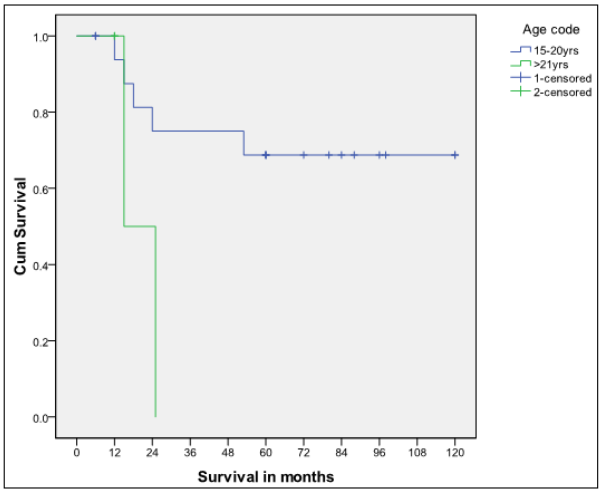

Fig-3: Overall survival (15-20 yrs vs. >21yrs)

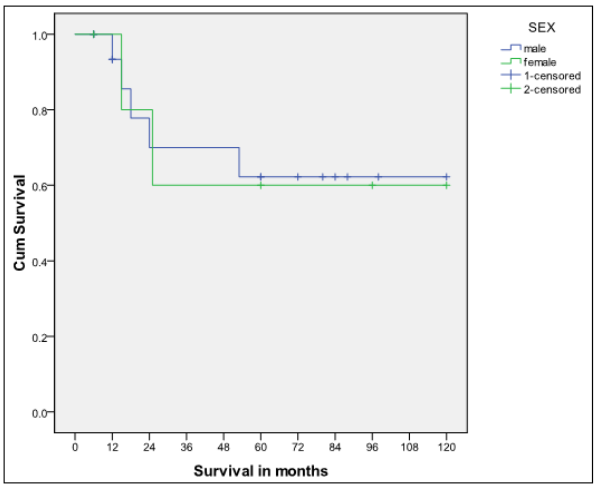

Fig-4: Overall survival (Male vs. Female)

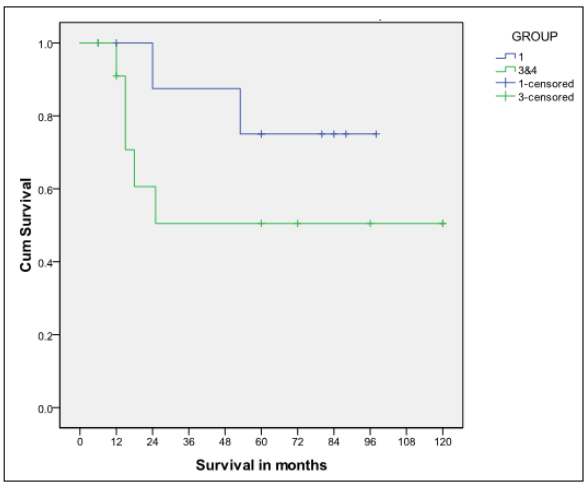

Fig-5: Overall survival (Group 1 vs. 3& 4)

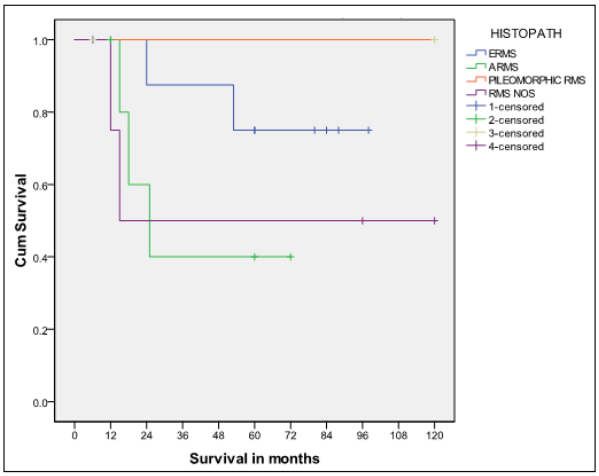

Fig-6: Overall survival (as per histological subtypes)

In our study, among testis /paratesticular RMS (n-15), the median OS was 53 months and 2 year and 5 year OS was 60% and 47% respectively. The longest survival with prostate RMS (n-3) was 12 months and that of bladder RMS was 120 months. Among patients with vulvovaginal RMS (n-5), median OS was 25 months (range 6-120 months) and the patient with cervix primary survived for 60 months.

DISCUSSION

Adult RMS is a difficult to treat malignancy because of its rarity and heterogeneity. The childhood RMS and adult RMS differ in terms of their natural history, sensitivity to treatment and outcome. As age advances, there is higher likelihood of unfavourable primary sites, lymph node involvement and metastatic disease. The available data on GU-RMS from the literature is limited. In a review on 171 adult RMS patients by Andrea Ferrari et al, 36 had genitourinary primary [9]. In an Indian study by Divya Khosla etal, out of 25 patients (≥16 years of age), 5 patients had genitourinary primary [10]. The French Sarcoma Group reported one of the largest recent studies performed in a multicentre setting for adult RMS on 449 adult patients with RMS, among which 14 were GU-RMS [11]. In our series, among 126 cases of RMS above 15 years of age, there were 26 (20.6%) cases of GU-RMS over a 20 year period and it occurred predominantly in males (77%).

RMS is traditionally believed to originate from the pluripotent mesenchyme, which is committed to skeletal muscle lineage and hence can arise from any tissue in the body. According to Shapiro *et al*., GU-RMS occurs at 2 age peaks, one at 2-6 years and second during 15-19 years [12]. The median age at diagnosis for GU-RMS was 22 years in the FSG study [11], whereas in our study it was 17 years.

RMS of the testicular structures predominantly arises from paratesticular tissues, the majority being embryonal in variety [13]. Para testicular RMS (PT-RMS) comprises 7-10% of all GU-RMS [13]. In our study, out of 15 PT-RMS, 8 were ERMS, 4 were ARMS, 2 were RMS-NOS and 1 was Pleomorphic RMS. The histogenesis of ERMS from prostate and urinary bladder which lacks skeletal muscle is a matter of debate. It is postulated that they arise from undifferentiated mesenchymal cells in the distal urogenital tract which gets incorporated into bladder and prostate during embryonic evolution [14]. In our series, among 3 prostate RMS, 2 were RMS – NOS and 1 was ERMS. Bladder RMS has a male predisposition and in our study, both were males and one each was RMS-NOS and ARMS.

Nasioudis etal reported 144 cases of lower female genital tract RMS where 76% were ERMS, <10% were metastatic at presentation and the 5 year OS was 68% [15]. In our study, all females (n-6) had non-metastatic disease; 2 were of ERMS subgroup, 2 were ARMS, 1was Pleomorphic RMS and 1 was RMS-NOS and the 5 year OS was 60%.

The common symptomatologies are swelling, pain, bleeding and other symptoms related to obstruction. Histological confirmation was either by tumour excision or biopsy. Immunohistochemically, desmin was positive in all the samples tested for it. The most common metastatic sites are lymph nodes, lungs, bone, bone marrow and liver. In our series, 5 (19.2%) male patients presented with metastasis (3 - lung metastasis, 1 – bone metastasis, 1 - bone marrow metastasis).

As this disease is rare in adults, evidences and principles of treatment are extrapolated from paediatric protocols and upon retrospective analysis, responses and outcomes are found to be similar in paediatric and adult RMS [1]. The current multimodality treatment for RMS has evolved through the constant effort of researchers across the world. Presently, chemotherapy, surgery with or without RT is the standard of care for RMS patients. Exenteration / radical surgery are now being replaced by organ conservation surgery, without compromising the patient outcome and survival.

Micrometastatic nature of RMS has brought the concept of chemotherapy to the forefront in its management, over and above the local treatment modalities (surgery and RT) which were practiced earlier either alone or in combination. The optimum chemotherapy schedule for this disease has evolved from the landmark Intergroup Rhabdomyosarcoma Studies (IRS I-IV) [4, 7]. IRS – IV concludes that VAC + surgery + conventional RT is the gold standard for non-metastatic ERMS. In IRS – IV study, group 1 PT-RMS (n=112) patients were treated with surgery + VA only and the treatment outcome was inferior when compared to IRS – 3, both in terms of event free survival and locoregional failures. This was attributed to the lack of draining lymph node sampling criteria for the study and the imaging qualities at that time. For

patients with group 2 PT-RMS with positive retroperitoneal lymph nodes, VAC for 1 year and RT to retroperitoneum is advocated [7].

In IRS – III study, standard chemotherapy for RMS of bladder and prostate (RMS-B/P) included doxorubicin, cisplatin and etoposide and the overall survival was 83% [16]. In the IRS– IV study, 88 patients had RMS-B/P, 50% of patients were treated with chemotherapy after biopsy, partial cystectomy was done in 30%, 13 % had cysto prostatectomy and none in the rest [17]. RT was given in 84% of patients and 70% of patients who underwent bladder preservation approach had adequate bladder function, eventhough properly conducted urodynamic studies are lacking in this regard [17]. The 6 year survival was 82% among RMS – B/P in IRS-IV study [16]. In our study, among the 5 patients with bladder/prostate RMS, the longest survival with prostate RMS (n-3) was 12 months and that of bladder RMS (n-2) was 120 months.

RMS of the female genital tract is scarcely reviewed in the literature. In an analysis of 144 cases of lower female genital tract RMS, patients were treated with combination of chemotherapy, radiotherapy and localised surgery and 68% of patients had 5-year OS [15]. In IRS trials, 21% of female patients were completely cured with biopsy and chemotherapy, 42% received chemotherapy and re-excision, 19% patients needed RT after a 2nd excision and 12% received chemotherapy and RT [17]. According to Martelli etal, females with non-metastatic RMS of genital tract have excellent OS and the outcome was similar between vulvovaginal and uterine RMS [18]. In our study, among patients with vulvovaginal RMS (n-5), median OS was 25 months (range 6-120 months) and the patient with cervix primary had 60 months survival.

In our study, testis/paratesticular RMS (n-15) was treated with VAC regimen in all, orchidectomy in 14 and local RT in 4 patients. The median OS was 53 months and 2 year and 5 year OS was 60% and 47% respectively. Among 2 patients with bladder RMS, one was treated with partial cystectomy, followed by chemotherapy with VAC + Cisplatin + Etoposide and local conventional RT. The second one was treated with biopsy, VAC and local RT. Out of 6 female patients, primary sites were vulva/vagina in 5 and cervix in 1. Among vulvo/vaginal primary RMS, biopsy was done in 4 and wide excision was done in 1. All were treated with VAC regimen and 3 received RT. The patient with cervix primary was treated with biopsy, VAC regimen and local RT.

The bad prognostic factors in RMS are age<1yr and >10yrs, unfavourable sites of primary, alveolar histology, stage, regional node involvement and metastatic disease at presentation [1]. Patients with metastatic GU-RMS (non-bladder / non-prostate) fare better when compared to metastatic disease from other primary sites [2]. It is also known that lung only metastasis portend a good prognosis than other sites of metastasis. In the IRS – IV study, the 3-yr failure-free survival for ERMS, ARMS, Undifferentiated sarcoma and sarcoma – NOS was 83%, 66%, 55% and 66% respectively (p <0.001) [7].

In our study, the 5 year overall survival was 60%. The non-metastatic patients had statistically significant better 5 year OS than metastatic patients (72% vs. 24%, p – 0.039). Group 1 patients had longer median survival when compared to group 3 and 4 patients (70m vs. 25m, p – 0.215). Age and sex were not found to be statistically significant prognostic factor in our study. The 5 year survival for histologic subtypes ERMS, RMS–NOS and ARMS was 75%, 50% and 40% respectively. One of the 2 patients with pleomorphic RMS survived more than 10 years.

To conclude, GU-RMS is a rare disease with curative potential. Risk stratified treatment is the cornerstone in managing patients with GU-RMS. The standard of care is multimodal with the aim of improving survival with organ preservation.

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