Original Article

Paratesticular rhabdomyosarcoma in young adults: A tertiary care institute experience

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ABSTRACT

Introduction: Paratesticular rhabdomyosarcoma (RMS) is a rare tumor arising from the mesenchymal tissues of the spermatic cord, epididymis, testis and testicular tunics. It represents only 7% of all patients entered in the Intergroup Rhabdomyosarcoma Study (IRS) and 17% of all malignant intrascrotal tumors in children less than 15 years old. We present our experience in combined modality management of 10 successive patients of paratesticular RMS.

Material and Methods: We retrospectively reviewed 10 patients of paratesticular RMS treated in our institute from July 2004 to December 2010. Clinical characteristics and treatment modality in form of surgery and chemotherapy (CCT) were noted. Statistical analysis was done with regards to progression-free survival (PFS) and overall survival (OS) using Kaplan-Meier survival analysis.

Results: The median age of the patients was 16.5 years. The median duration of symptoms was 5 months. Five patients had retroperitoneal lymphadenopathy (RPLAP) while three had lung metastases and one had orbital metastases. All patients underwent high inguinal orchidectomy followed by systemic chemotherapy (CCT). Retroperitoneal node dissection was not a required staging procedure. Four patients had partial response to treatment while six had complete response. Mean duration of PFS was 48 months and mean OS was 56 months.

Conclusions: Paratesticular RMS are rare neoplasms with aggressive growth patterns. Cure rates have dramatically improved and 60% of patients in our series had complete response. This success is due to development of multimodality and risk adapted treatment approaches.

Key words: Chemotherapy, paratesticular, rhabdomyosarcoma

INTRODUCTION

Rhabdomyosarcoma (RMS) is one of the most frequent soft tissue sarcomas. Paratesticular RMS is rare and consists 7% of all RMS.[1] Paratesticular RMS represents the most common non-germinal malignant tumor in this site.[2] Paratesticular RMS can develop from mesenchymal elements of the spermatic cord, the epididymis and the testicular envelopes, resulting in development of a painless scrotal mass. The clinical presentation includes a short history of painless swelling of the scrotum in a child or a young adult. Embryonal RMS is the predominant histological subtype and has a good prognosis.[3] RMS is regarded as a highly malignant tumor with frequent recurrence. Spread of the tumor is mostly by lymphatics to the iliac and para-aortic nodes, but hematogeneous spread does occur, most commonly to the lungs and liver.[2,4] The efficacy of chemotherapy has diminished the role of surgery and radiotherapy following radical excision in early stages. The combined modalities of surgery, chemotherapy and radiation therapy have greatly improved the survival rate in paratesticular RMS without significant long-term complications. We herein report our institutional experience of 10 successive patients of paratesticular RMS being treated from July 2004 to December 2010.

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MATERIAL AND METHODS

Patient population and initial evaluation

We retrospectively reviewed the patients of paratesticular RMS from July 2004 to December 2010 treated in our

institute. Total number of patients was 10. We reviewed the records of these patients to extract the following information: Age, sex, clinical symptoms, histology, testicular ultrasound, radiology [contrast-enhanced computed tomography (CECT)/ magnetic resonance imaging (MRI)], tumor extent, and extent of surgical resection, Intergroup Rhabdomyosarcoma Study Group (IRSG) clinical group,[5] TNM stage, chemotherapy (regimen, number of cycles), toxicity, response, recurrence, progression, metastases and death. Metastatic workup for distant metastases included CECT of the chest, abdomen and pelvis and bone scintigraphy. Laboratory studies included blood chemistry (electrolytes, liver and kidney function tests), and a complete blood count was performed.

Pathological review and staging

Operative notes were reviewed to determine intraoperative suspicion of invasion, gross tumor extension into adjoining structures, and completeness of resection. Pathology reports were obtained for all patients and the tumors were classified according to histopathological subtype. Surgical assessment of the retroperitoneal lymph nodes was not used as a staging procedure. Staging was based on the surgical, radiological and pathological criteria as per TNM and IRSG clinical group system.

Treatment

Surgery and CCT was used in the treatment. High inguinal orchidectomy was the primary surgical approach and systemic CCT was administered with VAC regimen comprising vincristine, adriamycin and cyclophosphamide 3 weekly for 4-6 cycles. All patients underwent primary surgery in form of high inguinal orchidectomy followed by systemic CCT with VAC regimen. The median number of CCT cycles was six.

Follow-up

The period between the first complaint and diagnosis was registered as symptom duration. Survival, recurrence and progression information were collected through chart review, patient or relative contact. Response evaluation was noted both clinically and radiologically and response evaluation criteria in solid tumors (RECIST) was applied.[6]

Statistical analysis

SPSS v 15 was used for statistical analysis. The Kaplan-Meier survival analysis was done for analyzing progression-free survival (PFS) and overall survival (OS).[7]

RESULTS

Patient characteristics

Patient characteristics are summarized in Table 1. Between July 2004 and December 2010, 10 patients of paratesticular RMS were registered in our department. The median age of the patients was 16.5 years and ranges from 13 to 38 years. The median duration of symptoms was 5 months. On histopathological analysis, seven patients had embryonal RMS histology tumors and 3 patients had alveolar RMS histology tumors. On metastatic workup, retroperitoneal lymphadenopathy (RPLAP) was present in five patients, lung metastases in three patients and one patient had orbital metastases. Overall, four patients were in clinical group I, two patients in clinical group II and four patients in clinical group IV. On TNM staging, six patients were in Stage I and four patients were in Stage IV.

Clinical outcomes

After treatment completion, patients were assessed for response both clinically and radiologically. Six patients were asymptomatic and four patients had significant improvement in symptoms. As per the RECIST criteria, six patients had complete response (CR) and four patients had partial response (PR). Mean duration of follow-up was 34 months, while median duration of follow-up was 20 months. Twenty month actuarial PFS of all patients was 53.0% [Figure 1] and mean PFS was 48 months. Twenty-month actuarial overall survival (OS) was 55.0% and mean OS was 56 months with median OS not reached [Figure 2].

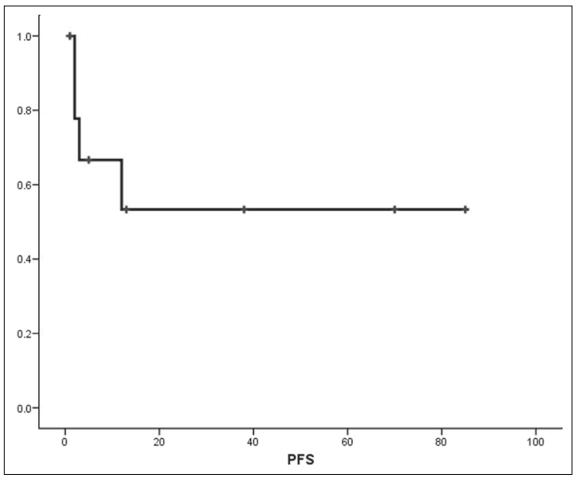

Figure 1: Kaplan-Meier curve showing progression-free survival

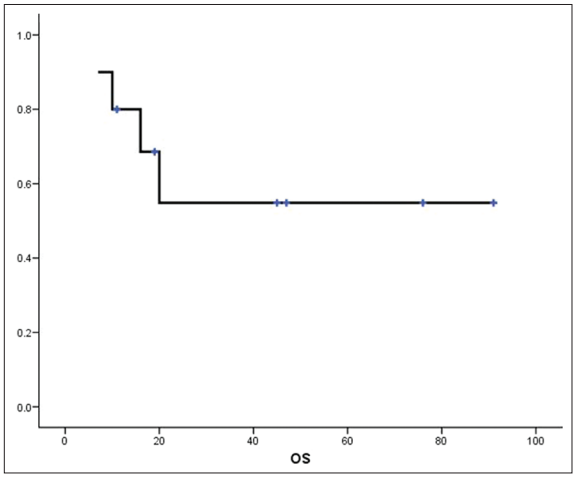

Figure 2: Kaplan-Meier curve showing overall survival

Table 1: Patient characteristics, treatment details and outcome

Age	Sex	Site	Metastatic site	Histology	Clinical group	Stage (TNM)	Treatment	Response	PFS	OS
13	M	Left	No	Embryonal	1	1	Sx+CCT	CR	91	91
20	M	Left	Lung	Alveolar	4	4	Sx+CCT	PR	7	16
15	M	Right	Retroperitoneum	Embryonal	2	1	Sx+CCT	CR	76	76
17	M	Right	Retroperitoneum, Lung	Embryonal	4	4	Sx+CCT	PR	15	20
14	M	Left	Retroperitoneum, Orbit	Embryonal	4	4	Sx+CCT	PR	7	10
18	M	Left	Lung	Embryonal	4	4	Sx+CCT	PR	5	7
21	F	Right	No	Alveolar	1	1	Sx+CCT	CR	47	47
16	M	Left	Retroperitoneum	Embryonal	1	1	Sx+CCT	CR	45	45
16	M	Right	No	Alveolar	1	1	Sx+CCT	CR	23	23
38	F	Right	Retroperitoneum	Embryonal	2	1	Sx+CCT	CR	15	15

PFS = Progression-free survival, TNM = Tumor Node Metastases, OS=Overall survival

Treatment toxicity and compliance

There were no surgical complications in form of postoperative deaths or wound complications. CCT toxicity was seen in seven patients in form of grade 1-2 hematological toxicity. All patients completed treatment with no significant toxicity or treatment interruption.

DISCUSSION

Paratesticular RMS is rare and consists 7% of all RMS cases in adults.[1] Embryonal RMS is the predominant histological subtype in 90% of paratesticular RMS and has a good prognosis.[3] RMS is regarded as a highly malignant tumor with frequent recurrence. Spread of the tumor is mostly by lymphatics to the iliac and para-aortic nodes, but hematogenous spread does occur, most commonly to the lungs and liver.[2,4] The optimal management of paratesticular RMS remains unclear because of the rarity of the disease in adults. Treatment strategies reviewed in the literature include radical high inguinal orchidectomy, chemotherapy (CCT), radiotherapy (RT) and retroperitoneal lymph node dissection (RPLND).[8-10]

Ferrari *et al.* reviewed 216 patients of paratesticular RMS.[3] The histological subtype was embryonal RMS in 181 (84%), alveolar RMS in 18 (8%), spindle cells in 10 (5%), and "not otherwise specified" in seven (3%) of cases. In our series, seven patients (70%) of patients were diagnosed with embryonal RMS, whereas three patients (30%) had alveolar RMS.

Complete resection of the primary tumor was the treatment of choice in all patients; no patient underwent RPLND. The role of RPLND still remains controversial.[11] Hermans and colleagues described 19 paratesticular RMS patients treated with RPLND, and claimed that a combination of RPLND and systemic CCT afforded a high cure rate.[12] Ferrari and colleagues reported on 44 patients with paratesticular RMS who did not underwent RPLND.[4] The authors considered that RPLND was unnecessary for localized disease because of the sensitivity afforded by computed tomography, the potential RPLND-associated morbidity, the low rate of retroperitoneal recurrence, and the presumed efficacy of CCT in controlling of microscopic disease. An alternative approach toward the treatment of clinically enlarged retroperitoneal lymph nodes involves the use of a more intensive adjuvant chemotherapy regimen. Such an approach is based on results obtained in the IRS-III trial, which showed that patients experienced poor outcomes if treated with RPLND followed by CCT.[13] The 5-year survival rates were 69% and 96% in patients with clinically negative nodes treated with and without RPLND, respectively. CCT can control micrometastases into retroperitoneal nodes when a primary tumor has been completely resected. In our present series, no patient was treated with RPLND.

The role for adjuvant CCT in adults remains poorly understood.[11,14] Ferrari and colleagues reported that CCT was effective to treat childhood RMS, in adjuvant setting.[3] Vincristine, dactinomycin, cyclophosphamide, adriamycin, epirubicin, ifosfamide, carboplatin and etoposide were used in different combinations, and with varying dose schedules, in the cited study. A metaanalysis of genitourinary sarcoma of 14 randomized trials showed that doxorubicin-based adjuvant CCT prolonged the time to local recurrence and distant failure, but the data was not statistically significant.[15] Also, such treatment was associated with a considerable degree of toxicity. About a third of patients with paratesticular sarcomas die from metastatic disease. In our series five patients had RPLAP with four having systemic metastases. All patients received systemic CCT with VAC regimen in our study. The mean PFS and OS in our series was 48 months and 56 months, respectively. We believe CCT should be offered as a component of multimodal therapy in patients with paratesticular RMS to control retroperitoneal dissemination and to minimize such dissemination.

The OS rates of patients with pediatric RMS approached 70% with the combined therapy.[5,10] In a study evaluating RMS at all sites in 2600 patients, adults with RMS experienced

significantly worse prognosis than the children.[16] In another study, in which adult RMS patients also fared more poorly than children, the 5-year adult PFS and OS rates were 28% and 40%, respectively.[17] Survival rate depends, with statistical significance, on tumor histology, diameter, stage and location, patient age, response to CCT and metastases status.[17,18]

CONCLUSIONS

Paratesticular RMS is rare and aggressive neoplasm in young adults. The management is a paradigm of cooperation between clinicians, surgeons and pathologists from establishing diagnosis to organizing the therapeutic strategy. Radical high inguinal orchidectomy is the primary treatment. Systemic CCT is essential in both early and advanced disease and has resulted in improved survival outcomes. The improved response and survival in our series is attributed to multimodality and risk-adapted treatment approaches. With new techniques and drugs, there is a significant improvement of therapeutic standard and paratesticular RMS represent a model of therapeutic implementation and achievement in oncology.

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