

Clinical Outcome of Rhabdomyosarcoma in Adolescent and Adult Patients: Single Center Experience from Turkey

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USTUNER, Z., BASARAN, M., DIZDAR, Y., AGAOGLU, F.Y., BILGIC, B., SAKAR, B., BASARAN, G.A., DARENDELILER, E., OZGER, H., ONAT, H. and BAVBEK, S. *Clinical Outcome of Rhabdomyosarcoma in Adolescent and Adult Patients: Single Center Experience from Turkey*. Tohoku J. Exp. Med., 2007, **213** (3), 221-229 — Rhabdomyosarcoma (RMS) is rare disease in adults (age ≥ 16 years). The data from randomized prospective trials are scarce; the clinical outcome of these patients seems poor with the currently available treatment strategies. In this study, we report a single institution's experience in the treatment of adult RMS. We reviewed the medical records of patients with RMS who were ≥ 16 years and have been treated in our institution between 1988 and 2003 retrospectively. We analyzed the survival outcome of these patients and the prognostic impact of clinical/pathological factors on their survival. In total, 23 patients with RMS were identified. Median age was 26 years (range, 16-72 years). Majority of patients were male (n : 17, 73.9%), and had large tumors (≥ 5 cm, n : 13, 56.5%), localized disease (N0, M0, n : 12, 52.2%), and embryonal histology (n : 10, 43.5%). Median overall survival was 31.3 months, and the 3-year progression-free survival and overall survival rates were 19.9% and 34.94%, respectively. Patients with smaller tumors (< 5 cm) ($p < 0.04$), local disease ($p < 0.01$), and normal lactic dehydrogenase (LDH) level ($p < 0.01$) at the time of diagnosis were found to have better survival outcome. The tumor size, serum LDH level, and metastatic disease at the time of diagnosis are potential predictors of outcome in patients with adult RMS. Adult RMS is an aggressive disease with poor survival despite treatment. The data from prospective, randomized multicenter trials are necessary in order to improve the clinical outcome of adult RMS patients. ——— rhabdomyosarcoma; adult; lactic dehydrogenase; survival; adolescent

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Received June 29, 2007; revision accepted for publication September 14, 2007.

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Rhabdomyosarcoma (RMS) is a malignant tumor of mesenchymal origin, believed to arise from cells committed to a skeletal muscle lineage (Dagher and Helman 1999). Although RMS makes up approximately 60% of all soft tissue sarcomas in the pediatric ages (Carli et al. 1997), it is less common in adults, and accounting for less than 3% of adult soft tissue sarcomas (Hawkins et al. 2001). The most common sites of presentation are; genitourinary and head and neck in pediatric ages but truncal and extremity in adult ages. The histological subtypes, embryonal, botryoid, and alveolar RMS occur predominantly in children and adolescents, and the relative proportion of pleomorphic RMS increases in adults (Dagher and Helman 1999).

RMS is an aggressive neoplasm with a propensity for early local infiltration and eventual metastatic dissemination. The overall survival rate for pediatric localized RMS is approximately 80% with adjuvant and neoadjuvant chemotherapy regimens based on the data from randomized controlled trials (Crist et al. 2001). Although multi-disciplinary and multimodality management, including chemotherapy, surgery, and radiation therapy has improved the prognosis in the pediatric population, the prognosis of RMS in adults poor in the literature (Kattan et al. 1993; La Quaglia et al. 1994). Adult RMS is very rare and clinical experience is limited. Often, the management of adult patients has been extrapolated from the experience with pediatric RMS patients (Hawkins et al. 2001). Esnaola et al. (2001) reported that patients with localized/locoregional disease had a 5-year survival rate of 44% which is much lower than the results observed in children. Of note, recently Ferrari et al. (2003) reported that adult and pediatric RMS patients had roughly similar outcome if the adult patients had received a treatment similar to that required for children and when series were stratified according to known prognostic factors (Esnaola et al. 2001). In the present retrospective study, we evaluated the clinical of adolescent and adult patients with RMS who have been treated in our institution.

MATERIALS AND METHODS

We reviewed the medical records of adult (≥ 16 years) RMS patients who have been treated in the Istanbul University, Institute of Oncology between June 1988 and January 2003. We recorded patient and tumor characteristics including age at diagnosis (16-20 years or > 20 years), gender, extent of disease (primary site only, regional or distant metastatic), tumor size (≤ 5 cm or > 5 cm), histological subtype (embryonal, alveolar, or pleomorphic) and lactic dehydrogenase (LDH) level at the presentation (normal or elevated). The tumor size, regional lymph node involvement, and metastatic disease were determined by computed tomography (CT) or magnetic resonance imaging (MRI) scans. The histological diagnosis was based on a revised classification of childhood RMS that was proposed by Newton in 1995. Chromosomal analysis was not performed for the diagnosis of alveolar RMS.

The lesion sites were divided into 5 groups: 1. head and neck, including orbit; 2. parameningeal, including nasopharynx, nasal cavity, paranasal sinuses, middle ear-mastoid region, infratemporal fossa, or pterygoid-palatine fossa; 3. trunk, including intrathoracic, abdomen and retroperitoneum; 4. extremity and 5. genitourinary (Pedrick et al. 1986; Little et al. 2002). The prognosis of parameningeal RMS is poorer than head and neck RMS in the pediatric ages, therefore was not included in the head and neck site. Other sites with favorable prognosis include orbit, head and neck (excluding parameningeal sites) and non-bladder/non-prostate genitourinary region. The extent of disease was assessed as localized, regional, and metastatic based on TNM classification described by the International Society of Pediatric Oncology (SIOP) (Rodary et al. 1989). Stage I and II disease was described as localized disease, stage III disease (having regional nodal involvement) was described as regional disease. RMS was also classified into Group I, II, III, and IV by the Intergroup Rhabdomyosarcoma Study Group (IRSG) based on surgical resection (Pedrick et al. 1986). Patients with group I tumors were those with no residual tumor after surgery; group II represents patients with complete resection of the primary tumor with microscopic positive tumor margins or patients with completely removed positive regional lymph nodes. Group III is described as gross residual disease that remained after initial definitive surgery. Group IV patients had evidence of metastatic disease. There were six patients with stage IV, six patients with stage III, five patients with stage II and six patients with stage I disease

(IRS classification). Treatment of RMS was guided by the IRS studies based pediatric protocols. The study was approved by the Ethics Committee of the Institute of Oncology of Istanbul University.

Treatment

The patients were treated with multimodality approach including chemotherapy (CT), radiation therapy (RT), and surgery. Eleven patients underwent complete surgical resection (50.0%). Six out of eleven (55%) patients operation were done at our center. There were seven patients resected by negative margins and four patients with positive margins. Those who did not receive surgery as a primary therapy had unresectable or metastatic tumors. In total, 21 patients (95.5%) received chemotherapy, and 17 (77.3%) were treated with external beam radiation therapy. One patient who was 72 years old did not receive CT due to his performance status. His treatment consisted of radiotherapy after surgery.

Among 21 patients receiving CT, six patients were treated every three weeks with regimens containing two cytotoxic drugs : VA (actinomycin-D 1.2 mg/m² IV plus vincristine 1.4 mg/m² IV) or IA (doxorubicin 75 mg/m² IV plus ifosfamide 2 g/m²/d IV × 5 days with mesna); others received three or four drug-containing regimens every three weeks including VAdrC (vincristine 1.4 mg/m² IV, doxorubicin 75 mg/m² IV, cyclophosphamide 1,200 mg/m² IV) or VAC (vincristine 1.4 mg/m² IV, actinomycin-D 1.2mg/m² IV, cyclophosphamide 1,200 mg/m² IV), or VACAdr (vincristine 1.4 mg/m² IV, actinomycin-D 1.2 mg/m² IV, cyclophosphamide 1,200 mg/m² IV, doxorubicin 60 mg/m² IV). Eighteen patients received a CT regimen that contained either VAC or VACAdr. Primary drug resistance was observed in one patient who progressed under VAC treatment. Subsequently this patient was treated with IE (ifosfamide 1.8 g/m²/d IV × 5 days with mesna plus etoposide 100 mg/m²/d IV × 5 days every three weeks combination regimen. The patients received IE or vincristine plus cyclophosphamide regimen during radiotherapy.

In total, seventeen patients received radiotherapy. Seven patients with unresectable tumors treated with radical radiotherapy (median dose = 54 Gy). Four patients with positive tumor margins were treated with radiotherapy (median dose = 50 Gy). Six patients with group III disease received preoperative radiotherapy (median dose = 45 Gy). Radiotherapy was started at 9th week except patients with primary parameningeal tumors. Patients with high-risk parameningeal features received radio-

therapy starting with the initiation of chemotherapy.

Radiotherapy fields covered primary tumor bed+2-3 cm margin ± involved lymph node area. For the parameningeal RMS, radiotherapy was delivered to the primary tumor bed with a 2-cm margin of the adjacent meninges or tumor bed plus craniospinal field according to IRS guidelines. Radiotherapy simulation and treatment planning were conventional. Treatment equipment was Co60 and 4MV LINAC treatment machines. External beam radiation therapy was delivered with conventional fractionation (1.8-2.0 Gy daily for 5 days per week) and total dose ranged from 45 to 64 Gy with median dose of 54 Gy.

Statistical analysis

Statistical calculations were performed by using the SPSS software (version 11.0). Survival was calculated using the Kaplan-Meier method and was determined from the date of surgery to the time of death. Multivariate analysis could not be performed due to small number of patients. Statistical significance was evaluated using the log-rank test for univariate influence. In all statistical analyses, *p* value < 0.05 (two-sided) was considered significant.

RESULTS

Clinical characteristics

Among 286 adult soft tissues sarcoma patients who were followed up in our institution between June 1988 and January 2003, we identified 23 adult RMS patients, accounting for 8.0% of all sarcoma cases. The patient characteristics of RMS patients are shown in Table 1. The median age of the study group was 26 years (range 16 to 72), and the distribution of patients with ages between 16-20 years old and > 20 years old were 34.8% and 65.2%, respectively. The majority of the patients were male (*n*: 17, 73.9%). Six patients had metastatic disease, 5 patients had regional lymph nodes involved and 12 patients had local disease at the time of presentation.

The median follow-up was 34 months (range, 2.7 - 79.3 months). Our patients received mean 5.5 cycles chemotherapy until progression. One patient was lost to follow up after first cycle of chemotherapy. Therefore this patient was not included in the survival analysis. The median overall survival was 31.3 months (CI: 95%, 16.4 -

TABLE 1. Distribution of clinical and pathologic characteristics in 23 patients with adult rhabdomyosarcoma.

Characteristics	<i>n</i>	%
Gender		
Male	17	73.9
Female	6	26.1
Age		
16-20	8	34.8
> 20	15	65.2
Primary tumor site		
Head and neck	6	26.1
Parameningeal	3	13.1
Truncal	5	21.7
Extremity	4	17.4
Genitourinary	5	21.7
Extent of disease		
Local only	12	52.2
Regional	5	21.7
Metastatic	6	26.1
Size		
≤ 5 cm	10	43.5
> 5 cm	13	56.5
Subgroups		
Embryonal	10	43.5
Alveolar	8	34.8
Pleomorphic	5	21.7
Treatment		
Surgery	11	50.0
Chemotherapy	21	95.5
Radiation	17	77.3

*Treatment was evaluated in 22 patients, other parameters were evaluated in 23 patient.
n, number of patients.

46.2 months). The 3-year disease free and overall survival rates were 19.9% and 34.94%, respectively (Fig. 1). The median survival of patients with metastatic, regional and localized disease was 10.3, 15.2 and 32.4 months, respectively (Table 2). In the univariate analysis, patients with negative surgical margins ($p < 0.01$), with tumor size ≤ 5 cm ($p = 0.04$) (Fig. 2A), with normal LDH level at presentation ($p < 0.01$), and local

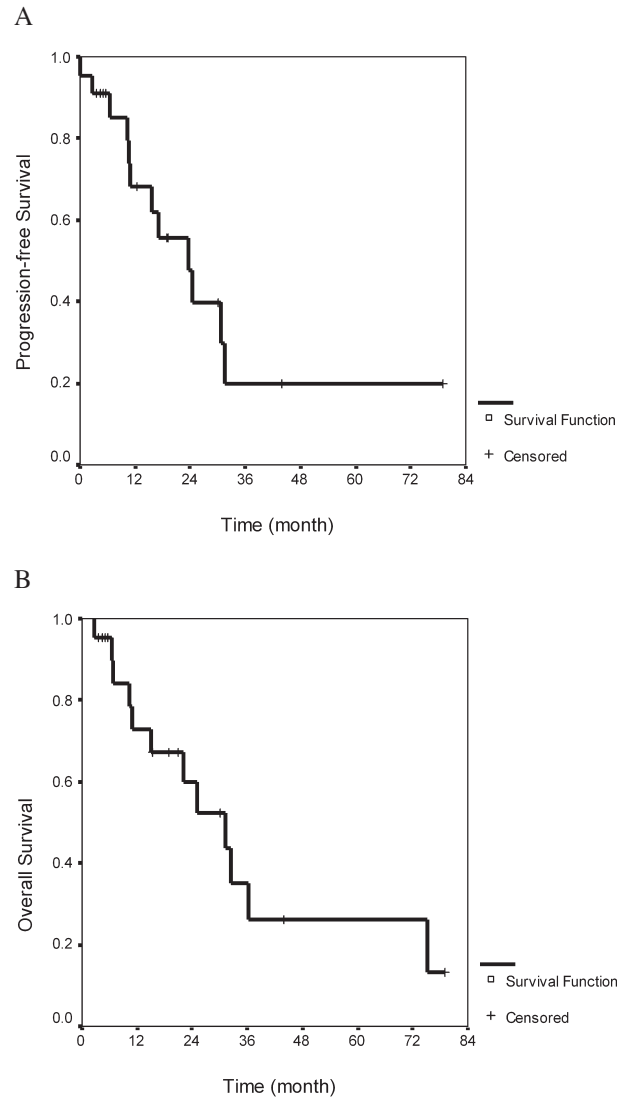


Fig. 1. Survival rates, progression-free survival (A) and overall survival (B) for patients in patients with adult rhabdomyosarcoma.

disease ($p < 0.01$) were shown to have better overall survival outcomes.

The prognosis of the younger patient sub-population (age between 16 - 20) was worse than older patients although it was statistically not significant. In this group, there was no extremity RMS and there was only one head and neck RMS. Thus, younger population had fewer favorable sites of disease. Among patients younger than 20 years old, 62.5% had regional and metastatic disease. In contrast, among patients older than 20

TABLE 2. Progression-free survival and overall survival in 22 patients with adult rhabdomyosarcoma.

Characteristics	<i>n</i>	PFS (Month)	<i>p</i> value	OS (Month)	<i>p</i> value
Gender					
Male	16	24.6	0.16	32.4	0.17
Female	6	15.6		10.2	
Age					
16-20	8	15.6	0.12	22	0.06
> 20	14	30.7		32.4	
Size					
≤ 5 cm	10	62.0	0.02	62.5	0.04*
> 5 cm	12	17.1		25.1	
Subtype					
Embryonal	9	30.7	0.17	31.3	0.22
Alveolar	8	15.6		22.0	
Pleomorphic	5	24.6		36.2	
Surgery					
Margin (-)	7	31.6	0.01	75.2	0.02*
Margin (+)	4	15.6		25.1	
LDH					
Normal	15	23.5	< 0.01	73.3	< 0.01*
High	5	6.6		7.0	
Extent of disease					
Local	12	30.7	< 0.01	32.4	< 0.01*
Regional	5	11.0		15.2	
Metastatic	6	10.3		10.3	

PFS, progression-free survival; OS, overall survival; CI, confidence interval; *n*, number of patients. * Statistically significant.

years, fewer patients (40%) had regional and metastatic disease.

The primary tumor sites in our patients were head and neck (26.1%), parameningeal (13.0%), trunk (21.7%), extremity (17.4%), and genitourinary (21.7%). The majority of tumors was large (> 5 cm, 56.5%), at localized stage (52.2%), and had embryonal histology 43.5%.

The patients with elevated LDH level (*n* = 5) had poorer progression-free survival and overall survival rates than patients with normal LDH levels (Fig. 2B).

Treatment failure

A total 12 treatment failures were observed. The sites of failure were local only in 4 patients

(33%), regional in 1 (8%), and distant in 7 patients (58%). A patient with distal recurrence has simultaneous local and distant recurrence. Six out of twelve patients with recurrences have alveolar histological subtype.

DISCUSSION

Adult RMS is an aggressive disease with poor survival despite treatment. Median overall survival was found 31.3 months and 3 - year progression - free survival (PFS) and overall survival were detected 19.9% and 34.9%, respectively in our study. Patients with smaller tumors (< 5 cm), local disease, and normal LDH level at the time of diagnosis were found to have better survival outcome.

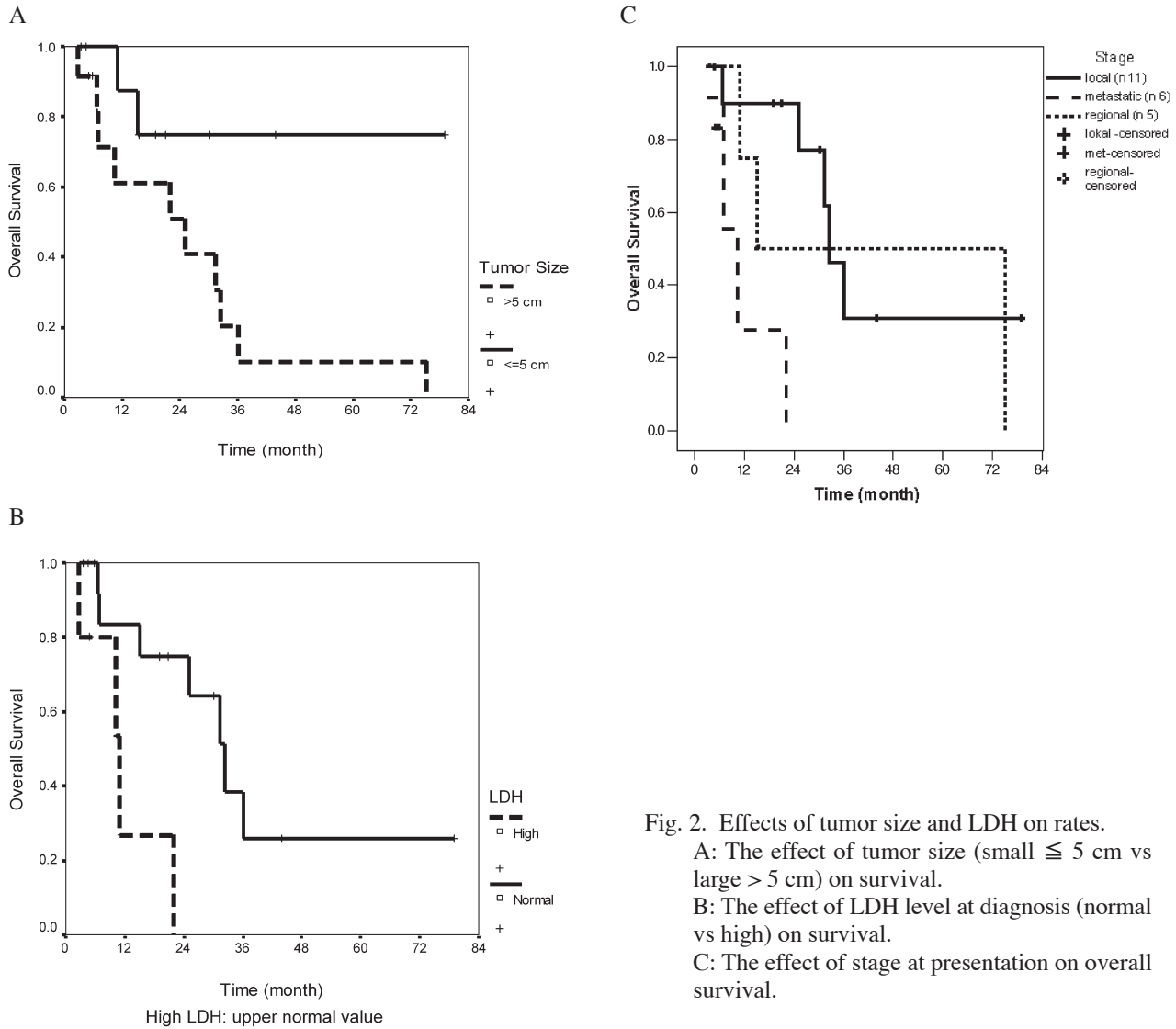


Fig. 2. Effects of tumor size and LDH on rates.
 A: The effect of tumor size (small ≤ 5 cm vs large > 5 cm) on survival.
 B: The effect of LDH level at diagnosis (normal vs high) on survival.
 C: The effect of stage at presentation on overall survival.

RMS is the most frequent soft tissue sarcoma in the pediatric patient population (Carli et al. 1997). Adult RMS is a rare disease, and constitutes a small fraction (2% - 5%) of soft tissue sarcoma (Hawkins et al. 2001). The present report analyzed the clinical outcome of 23 patients treated in our institution since 1988. The reason why the percentage of RMS (8.0% of all adult soft tissue sarcoma) cases was high in our retrospective analysis is probably due to the fact that our institution is a tertiary referral center for RMS patients.

Optimal therapeutic management of RMS

requires a combination of different treatment modalities such as surgery, chemotherapy, and irradiation (Crist and Kun 1991). Surgery remains an important treatment modality for RMS. Complete surgical resection that has been shown to improve outcome for most anatomic sites is currently recommended if it will not be mutilating or cosmetically damaging (Breitfeld and Meyer 2005). Overall survival of adult RMS patients was reported to be poor when compared to pediatric patients (Nayar et al. 1993). It was suggested that adult RMS is a different entity than pediatric RMS and its prognosis remains poor

despite aggressive therapy. This has been attributed to higher rate of unfavorable histopathologic subtypes, anatomic localization and an advanced stage of disease at presentation along with poor tolerance to treatment leading to reduced dose intensity. Esnaola et al. (2001) detected much lower 5-year survival rate in adult patients than the results observed in children, they reported that metastatic disease at presentation and poor response to chemotherapy are associated with poor prognosis. Importantly, Ferrari et al reported the largest adult RMS series, has recently reported that the outcome of adult RMS (who were treated according to current guidelines for pediatric RMS) might be roughly similar to the outcome of pediatric patients (Ferrari et al. 2003).

Median survival was 31.3 months in our series. Hawkins et al. (2001) were reported that among patients > 20 year-old, disease-specific median survival was 35 months for those without regional or distant spread and 15 months for those with regional or distant spread. Little et al. (2002) reported that median survival was 38 months for adult patients ($n = 82$) with a median age of 27 years (range: 17 - 84 years). The authors found that larger tumor size (> 5 cm) was associated with poor survival on uni- and multivariate analysis (Little et al. 2002), a finding consistent with the results of our analysis.

Four consecutive Intergroup Rhabdomyosarcoma Studies (IRS) have demonstrated increasingly higher five-year failure free survival (FFS) and overall survival rates for pediatric localized RMS (low risk), reaching up to 88% and 95%, respectively (Maurer et al. 1988, 1993; Crist et al. 1995; Baker et al. 2000). Adult RMS patients present with widely disseminated disease and die from their disease despite they achieve good responses to initial chemotherapy (Esnaola et al. 2001). The EURO CARE study demonstrated that adolescent RMS patients over 10 years had worse prognosis at diagnosis. In addition, female group had a lower survival in this series as observed in our study. The adverse impact of older age was explained by the fact that it is associated with less favorable tumor site and unfavorable (alveolar) histology (Stiller et al. 2001).

The most common location of RMS is head and neck region, followed by the genitourinary tract in adult patients. Our patients have the similar pattern for disease localization. It was reported in pediatric patients that the tumors of the orbit had the best prognosis (92% 5 years survival) and the other sites with better prognosis are head and neck and genitourinary tumors (non bladder and prostate) (about 80% 5 years survival). In adults with head and neck RMS were reported, poorer results as a 5 years survival rate of 7.6% for 26 patients (Nayar et al. 1993). The orbital presentation was uncommon in adult patients. Parameningeal, prostate, bladder, and extremity sites had the poorest prognosis (70% 5 years survival) in children (Maurer et al. 1993). Genitourinary RMS may occur in the paratesticular tissues, bladder, prostate, uterus, or vagina. In the Intergroup Rhabdomyosarcoma Study-I (IRS-I), IRS-II the rate of genitourinary RMS in pediatric patients was 21% and 23%, respectively (Maurer et al. 1988, 1993). In the adult patients, the rate of genitourinary RMS was reported as 18% - 20% (Esnaola et al. 2001; Ferrari et al. 2003). Twenty-two percent of patients in our study had genitourinary RMS. While the 5 - year survival rate of pediatric patients with genitourinary RMS was reported to be between 74 - 80% in IRS studies. In adult series it was reported to be 0% in one study and 60% in another (Pedrick et al. 1986; Maurer et al. 1993; Esnaola et al. 2001; Ferrari et al. 2003). Although paratesticular form of pediatric RMS represents one of the most favorable prognostic groups, this site in adult patients was shown to have poor prognosis and unfavorable survival outcome compared to children (Kattan et al. 1993).

The distribution of the histological RMS subtypes in our series is similar to that was reported by Hawkins et al. (2001) (embryonal 51%, alveolar 30%, pleomorphic 17%, respectively). The incidence of pleomorphic tumors was reported to be increased by age (Esnaola et al. 2001). In our series all of the patients who had pleomorphic RMS (21.7%) were older than 20 years. The alveolar subtype is reported to have worse prognosis in adults (Crist and Kun 1991;

Ferrari et al. 2003). Histologic subtype was not shown to have any impact on survival outcome in our analysis. The shortest survival time was detected in alveolar histology in this study, but it should be noted that our small sample size might be the reason for the lack of any potential survival difference based on histologic subtype. Similar results have been reported in a study of adult RMS with small number of cases (Nayar et al. 1993). Adult patients with embryonal RMS were reported have an overall 5-year survival rate of 21% in one retrospective study. Of note, majority of patients (79%) were dead after an average time of 17 months after diagnosis (Llyod et al. 1983). Joshi et al. also were reported that adolescent RMS patients had worse prognosis. The alveolar (33%) and embryonal histology (44%) in adolescents were found in this study similar in our study (34.8%, 43.5%, respectively). Most alveolar tumors (~70%) have chromosomal translocations (t [1, 13] and t [2, 13]). The alveolar histology with t (2, 13) that has poorer prognosis and is more common in adolescents patients. Joshi explained that the relation between older age (over 10 years) and worse prognosis was most probably due to biological differences (Joshi et al. 2004).

Seventeen patients had localized (52.2%) and regional disease (21.7%) at presentation in our study. The survival of patients with metastatic disease at presentation was shorter than that of those with regional or localized disease (median 10.3, 15.2 and 32.4 months, respectively) (Fig. 2c). The data from other pediatric or adult series also confirm that metastatic disease at presentation is associated with poor outcome (Esnaola et al. 2001; Ferrari et al. 2003).

LDH is known to have prognostic value in several tumors such as lymphoma, germ cell tumors and melanoma. The prognostic significance of LDH has not been reported in other series of adult RMS. We analysed the relationship between LDH level at presentation and survival outcome with univariate analysis and found a significant association between high LDH levels and poor survival outcome. This finding needs to be confirmed in prospective studies with larger sample size.

Ferrari et al. (2003) suggests that adult RMS is fundamentally similar to pediatric RMS and probably may be treated according to protocols in large pediatric trials. Our series has very limited number of patients and they were treated by different treatment protocols that were similar to the IRS studies based on pediatric protocols. However, duration of treatment is generally shorter than pediatric series.

High-dose chemotherapy as a salvage treatment for recurrent and metastatic RMS in pediatric group was not shown to improve survival (Pappo et al. 1999; Mackall and Helman 2001; Weigel et al. 2001). We did not use high dose chemotherapy. Therapies with new agents have led to progressive increase in the survival of children with RMS. The poor survival outcome of adult RMS patients can be improved by proper identification of good versus poor prognostic groups and by finding specific molecular therapeutic targets. Prospective clinical studies are difficult to conduct for this uncommon type of sarcoma in adult patients. Therefore multicenter international studies are needed to be designed. The results of studies investigating the role of therapies with new agents are awaited with interest (Breitfeld and Meyer 2005).

In conclusion our study has shown that surgical resection with negative margins, tumor size, and metastatic disease at presentation are the most important predictors of survival outcome in patients with adult RMS. Additionally serum LDH level was also detected as one predictor of survival, but to evaluate this result, the patient numbers were not sufficient in our study. The prognosis was poor in adult patients with RMS. Conduction of prospective randomized studies for pediatric RMS should be a priority in this field in order to find out more effective therapeutic strategies for adult RMS.

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