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A Cohort Study of Adult Rhabdomyosarcoma: A Single Institution Experience

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Abstract: Rhabdomyosarcoma (RMS) is an uncommon neoplasm in adult population. Outcome for adult RMS is poorly documented due to its rarity. Published series have reported worse results for adults compared with children with RMS. Eighteen adult patients with RMS whose age were 17 years and older were treated between 1979 and 2004 and were analyzed retrospectively for treatment outcome. Univariate statistical methods were used to evaluate outcome. Patient ages ranged from 17 to 70 (median 21). Embryonal RMS was the most common subtype. Anatomic sites of origin were extremity (33.3%), genitourinary tract (33.3%), head and neck (22.2%) and trunk (11.2%). Tumor size was 5 cm or smaller in 39% of patients. Regional lymph node metastasis was present in 17% of patients at presentation. Treatment consisted of radiation therapy (RT) alone in 6%, RT and surgery in 11%, RT and chemotherapy in 44% and all three modalities in 39%. With a median follow-up of 61 months, the 4-year overall survival rate was 25%. The major determinant of survival was tumor size (p=0.0337). Adult RMS is a highly malignant tumor with a significant incidence of metastatic recurrence. The current series parallels other published series in that it confirms the relatively poor long-term outcome for adult RMS patients. Continuing investigations of new and potentially more effective chemotherapy is crucial.

Key words: Rhabdomyosarcoma · Radiation · Chemotherapy

INTRODUCTION

Rhabdomyosarcoma (RMS) is a common childhood cancer, constituting more than 50% of all soft tissue sarcomas, although it is infrequent in adults: soft tissue sarcomas make up less than 1% of all adult malignancies and RMS accounts for 3% of all soft tissue sarcomas [1]. RMS can occur within mesenchimal tissue at any site, although it has a predilection for the head and neck, genitourinary organs, retroperitoneum and extremities [2,3]. The embryonal subtype is the most common, representing up to 60-80% of tumors at above sites. Alveolar tumors are more common among adolescents, often arise in the extremities and carry a worse prognosis [4,5]. Based on the results of studies like Intergroup Rhabdomyosarcoma Study Group (IRSG), generally accepted treatment guidelines for childhood RMS include gross total resection with preservation of function, systemic chemotherapy (CT) and radiation therapy (RT) for all but completely resected tumors of embryonal subtype [6-10].

Experiences from childhood RMS are extrapolated widely to adults with this disease and despite the use of multimodal therapy, the prognosis in older patients appears to be worse than in children [11-13]. Even in the IRSG studies, an advers effect of increasing age on outcome has been documented [9]. RMS in adults is very rare and the literature regarding its management is limited. Detailed reports of multimodal treatment outcome, patterns of failure and prognostic factors in adult patients with RMS are few [14,15]. In this study, we reviewed our experience of adult patients with RMS treated with multimodal therapy.

MATERIALS AND METHODS

Between 1979 and 2004, 18 patients (17 years or older) with RMS were irradiated in Gulhane Military Faculty of Medicine. A retrospective review of medical records was performed.

In most cases, staging at diagnosis involved a full history, physical examination, routine blood tests, chest radiography and evaluation of local extent with computarized tomography and/or magnetic resonance imaging and abdominal ultrasound. Location of tumor was divided into head and neck, trunk, genitourinary tract and extremity. The trunk group included tumors of the thorax, abdominal and pelvic retroperitoneum. Histologic subtype

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was divided into embryonal, alveolar and pleomorphic subtype. Tumor size (=5 cm, >5 cm) was based on the largest dimension of the primary tumor as reported in pretreatment computed tomography and/or magnetic resonance scans or pathologic specimen. Nodal involvement was based on physical examination, imagining studies and/or lymph node sampling at the time of surgery.

We attempted to retrospectively define stage of disease according to both the clinical pretreatment TNM classification and IRSG postsurgical grouping system [16].

RT consisted of external beam radiotherapy. Systemic chemotherapy consisted of multiagent regimens. Following treatment, patients were followed at 3 month intervals for the first 2 years, 6 months intervals for the next 3 years and yearly thereafter. All deaths were due to progression of disease.

Survival curves were calculated according to the Kaplan-Meier method [17] and test of the significance were based on the log rank statistic [18]. Survival was evaluated from the date of histologic diagnosis. Median follow-up, as of December 2005, was 61 months. Univariate analyses of factors potentially correlated to all outcomes included sex, age, histologic subtype, primary site, dimension of primary tumor, lymph node status, stage and treatment were calculated by using SPSS. 10.0 computer program.

RESULTS

18 patients were considered for the current study. Clinical characteristics of the patients can be seen in Table 1.

Table 1: Patient characteristics

Study period	1979-2004
No.of patients	18
Gender	
Male	15
Female	3
Median age(Range)	21(17-70)
Disease spread	
Localized	15
Metastatic	3
Histology	
Embryonal	10
Pleomorphic	5
Alveolar	3
Site of origin	
Extremity	6
Genitourinary tract	6
Head and neck	4
Trunk	2
Size	
≤5 cm	7
>5 cm	11
Nodal involvement	
Negative	15
Positive	3

Patient and Tumor Characteristics: Most of the patients were male(n=15, 83%). Patient age ranged from 17 to 70 years with a median of 21 years. 12 patients were 21 years of age and younger. Embryonal subtype was present in 10 patients (55%) whereas pleomorphic in 5 (28%) and alveolar in 3 (17%). The primary tumor site was as follows: extremity, 6 (33.3%); genitaurinary truct, 6 (33.3%); head and neck, 4 (22.2%); and trunk, 2 (11.2%). Primary tumor size ranged from 2 to 15 cm (median 6.5 cm); 7 (39%) were 5 cm or smaller and 11 (61%) were larger than 5 cm in larger dimension. Tumor size was smaller for genitourinary tract lesions (median, 5 cm) compared with lesions of head and neck (median, 5.5 cm), trunk (median, 7.5cm) and extremity (median, 11 cm). 3 patients (17%) had clinical or pathologic evidence of regional lymph node metastases at presentation and all of these metastases arised from genitourinary tract tumors. Histopathology of the patients with lymph node metastases were alveolar (n=1), embryonal (n=1) and pleomorphic (n=1). There were differences in histopathologic tumor subtype according to patients' ages. Among 12 patients =21 years of age, 9 (75%) had embryonal RMS. Among 6 patient 22 years of age or older, only 1 (17%) had this histologic subtype. According to the clinical pretreatment TNM classification the disease was stage 1 in 4 patients (22%), stage 2 in 3 patients (17%), stage 3 in 8 patients (44%), stage 4 in 3 patients (17%). According to the IRSG postoperative staging the tumors were grouped as follows: Stage 1, 4 patients (22%); stage 2, 7 patients (39%); stage 3, 4 patients (22%); stage 4, 3 patients (17%).

Treatment: Patients were treated with a relatively consistent approach, which in most cases included surgery, CT and RT. The therapeutic goal for all patients was complete surgical resection with sparing of both function and cosmesis where possible. For the 10 patients undergoing resections, the resection margins were pathologically negative in 6 (60%) and positive or uncertain in 4 (40%).

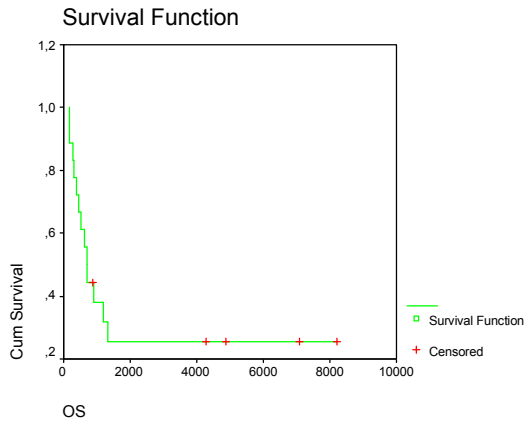

Fig. 1: Overall survival curve for all patients

RT was administered to all the patients. All the patients were irradiated by using photon or electron beam energies with conventional fractionation (1.8 - 2 Gy daily for 5 days per week) using techniques appropriate to each primary tumor site and regional lymph nodes where applicable. The total dose ranged from 36 to 68 Gy, with a median dose of 55 Gy. Median 6 cycle of systemic CT was delivered to 15 of 18 patients (83%). Most patients received a multidrug regimen that included cyclophosphamide or ifosfamide, vincristine and actinomycin. Some patients also received adriamycin, dacarbazine, epirubicin and cisplatin in various combinations or alternating regimens.

In summary, 1 patient (6%) received single modality treatment with radiation; 10 (55%) received two modalities (RT and CT, 8; RT and surgery, 2); and 7 (39%) received all three modalities.

Disease Outcome and Patient Survival: Median follow-up was 61 months. At the time of analysis, 5 patients were alive. The 4-year overall survival (OS) rate in this series was 25% (Figure 1). Median survival time for all patients was 24 months. The effects of various demographic, histopathologic and clinical variables on survival are summarized in Table 2. In univariate analysis, the OS rates were approximately equal for patients =20 years old and >20 years old (25% vs 26%, P=0.78). Patients applied >55 Gy showed a higher survival rate than patients applied =55 Gy, but the difference was not statistically significant (33% vs. 22%, P=0.69). Chemotherapy appeared to have an adverse effect on survival in this series, the OS rate was inferior for patients treated with CT, but the difference was not also significant (27% vs 33%, P=0.51). The reason of the adverse effect of

Table 2: Analysis of prognostic factors for overall survival

Characteristic	4-overall survival(%)	*p* value
Age		
≤20 years	25	
>20 years	26	0.78
Histologic subtype		
Embryonal		
Pleomorphic		
Alveolar		
Tumor site		
Extremity		
Genitourinary tract		
Head&neck		
Trunk		
Tumor size		
≤5 cm		
>5 cm		
Lymph node status		
Negative		
Positive		
Stage		
Chemotherapy		
Yes	27	
No	33	0.51
Total RT dose		
≤55 Gy	22	
>55 Gy	33	0.69

CT is probably that CT was administered to patients with advanced disease. The median time to development of metastases was 3 months (1-7 months). The only significant factor for survival was tumor size (>5 cm vs = 5 cm; p= 0.0337)

DISCUSSION

Among 18 adult patients with RMS who were treated at a single institution during a 25-year period and retrospectively reviewed, 4-year OS was 25%. This rate is lower than rates reported in selected series from pediatric trials [9,19,20] and closely parallels the results of other studies of adults with RMS [15,21]. It remains to be understood why, in most published studies [13,21], survival of adults with RMS has been lower than that of children, falling in the range of 20-40%, just as in the current series.

Some authors express that adult RMS is inherently different from pediatric RMS [13,14]. The results of our study was comparable to those reported before for adult patients with RMS, i.e., disease outcome is considerably less favorable for adults than for children. Apart its poorer

response to treatment, RMS in adults also appears to differ from childhood RMS in several other features. Although head and neck sites are common in children, where they account for some 35% of cases, the 22% incidence in our study appear lower. There are few other studies on adult disease which to compare this incidence. In one report by Hawkins *et al*. [14], head and neck sites accounted for only 24% of sites in patients. However, most reports on adult disease agree that orbital presentations distinctly uncommon [14,22]. There was only one (6%) such case in our series. Orbital presentations are among the most favorable for childhood RMS, as demonstrated in all four IRSG studies [6-9] and relative paucity of these among adult patients might partly explain their worse overall prognosis.

Another significant difference between childhood adult RMS is the proportion of histopathologic subtype. In IRS-IV, the relative subtype proportions were embryonal, 70%; alveolar, 20%; and others, 10% [9]. In our series, as well as in other adult series, there was a high incidence of pleomorphic RMS than in childhood series. Pleomorphic RMS is an aggressive neoplasm that probably is closer to adult high-grade soft tissue sarcomas than to pediatric RMS. Recognizing the advantageous outcome associated with the embryonal subtype, it is classified in IRSG protocols as favorable in contrast to alveolar and other types [10]. The balance in distribution of favorable versus unfavorable histotype in children and adults may place adults at a disadvantage. These differences may explain in part the less favorable outcome of adult patients overall and they invite us to treat adults with intensive approaches.

However, the prognostic significance of RMS subtype in adults is controversial. In one adult RMS series [21], patients with alveolar tumors experienced significantly poorer metastases-free rates than those with embryonal and pleomorphic tumors but this difference did not translate into significant disease-free or survival differences. In another study Hawkins *et al*. [14] histologic subtype was not predictive of outcome. The prognostic significance of RMS subtype in adults remains uncertain, but is unlikely to be a mojor factor.

The most common pattern of disease recurrence in adults with RMS is distant metastases [14,15], most often to the lungs. In our and other adult series[14,15], the major determinant of metastatic propensity was tumor size as specified by the AJCC TNM system (=5 cm vs. >5 cm). Moreover, tumors exceeding 10 cm had a particularly high metastatic rate. In two studies Esnaola *et al* [15] and Little *et al* [21], all patients with primary lesions in this size range were predicted to develop metastases. This may be the reason of the survival difference of our series.

Treatment results even have raised doubts as to whether CT should be used at all to treat adults with RMS. Hawkins *et al* showed that there was no evidence that CT provided any survival benefit for adults with RMS [14]. On the other hand Esnaola *et al* [15] and Ferrari *et al*. [23] revealed that CT has the same activity in adult and pediatric RMS and when CT was included in a regimen similar to those used for pediatric patients, the outcomes for adults and children were similar to each other. IRSG reported favorable results in children with metastatic disease treated with a combination of standart vincristine, actinomycin-D, cyclophosphamide combined with ifosfamide and etoposide, whose long-term outcome is also poor [24]. Also, there are data from the International Society of Pediatric Oncology that children with incompletely resected or inoperable RMS achieve complete remission of disease with CT [25].The high metastatic rate and chemoresponsiveness of this sarcoma mandate the continuing investigation of multiagent CT in adults with RMS.

Adult RMS is somewhat more radiosensitive than most adult sarcomas. However, the disease in adults is not as radiosensitive as in children where doses in the range 40-55 Gy result in local control in approximately 80% of patients treated for gross disease (IRS-III) [26]. We believe that optimal local control is achieved with a combination of gross total resection and local irradiation. For completely resected disease with negative margins, a dose of 50-56 Gy; and for margin-positive disease, a higher dose of 60 Gy is suggested by Little *et al* [21]. If gross tumor cannot be resected completely, then radiation to a dose of 66-70 Gy should be employed utilizing modern field-defining technologies. The two randomized trials on adult sarcoma in general,Pisters *et al* [27] and Yang *et al* [28] found that the addition of RT resulted in significant improvements in local control over surgery alone.

RMS is one of the few soft tissue sarcomas with a known propensity for regional lymph node metastases [29]. In children lymph node status is an important determinant of outcome [16,30,31]. In adults, unexpectedly, it has not been shown to be a significant prognostic factor[15]. The reasons for this discrepancy are not apparent, but may result from the overall poor disease outcome in adults. However, the high incidence of lymph node disease suggests that regional treatment should be a component of the overall treatment strategy. In our series, 3 patients (17%) had clinical evidence of

lymph node disease at presentation. Another adult series reported a 46% incidence of lymph node involvement [15]. The frequencies of lymph node disease in children with RMS are reported as 15-20% and lymph node metastases is uncommon in head and neck sites in childhood RMS [9,16,30]. In our data there was no significant correlation between primary site and lymph node metastases at presentation ($p>0.05$).

In conclusion, the current study confirms that, the outcome of RMS in adults appears to be worse than that of children. This is likely due in part to a higher proportion of adults presenting with poor prognosis as compared with children. Metastatic recurrence is major finding and the development of effective multiagnet chemotherapy is an urgent priority. The optimal treatment remains undefined, but multimodality approaches combining surgical resection, radiation and systemic chemotherapy need further investigation.

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