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ORIGINAL ARTICLE

# Adult Rhabdomyosarcoma: Clinical Features and Radiotherapy Outcomes—The Turkish Oncology Group (TOG) Bone and Soft Tissue Sarcoma Study Group

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**OBJECTIVE**

Although rhabdomyosarcoma (RMS) is the most frequent soft tissue sarcoma diagnosed in childhood, it represents only 2%–5% of adult soft tissue sarcomas. The aim of the present study was to better understand the clinical characteristics, treatment approaches, and outcomes of patients with adult RMS who received radiotherapy (RT) as a component of their multidisciplinary management since there are scarce data on adult RMS due to its rarity.

**METHODS**

The medical records of patients with adult RMS who were ≥18 years old and treated with RT between January 1995 and August 2016 in four different radiation centers were evaluated in terms of clinical characteristics, treatment, and follow-up data retrospectively.

**RESULTS**

There were 28 patients. The median age at diagnosis was 28 (19–53) years. The most common site of involvement was the head and neck (25%), and parameningeal region involvement was prominent (92%) among them. In general, unfavorable site of involvement was markedly higher than favorable ones (82% vs. 18%). Alveolar and pleomorphic subtypes compromised 75% of the cases. Fifteen patients had surgery, 26 chemotherapy, 10 radical intent of RT, 9 adjuvant, 3 preoperative, and 6 palliative. The follow-up time was from 3 to 235 (median 18) months, disease-free survival was between 2 and 48 (median 12) months, and 5-year overall survival (OS) was 25% (median OS 20 (4–235) months). There were significant differences in terms of survival according to histopathological subtypes (p: 0.017), risk groups (p<0.001), Intergroup Rhabdomyosarcoma Study Group (IRSG) grouping and IRSG staging (p<0.001).

**CONCLUSION**

Adult RMS has unfavorable clinical presentation and worse outcome compared with pediatric RMS. Histopathological subtype and risk grouping to define the prognosis used in pediatric cases also might be valid in adult RMS.

**Keywords:** Adult rhabdomyosarcoma, Soft tissue sarcoma, Treatment, Outcomes.


*This study has been conducted on behalf of Turkish Oncology Group (TOG) Bone and Soft Tissue Sarcoma Study Group and was presented as an oral presentation in 13th National Radiation Oncology Congress at 30th April 2018.*

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## Introduction

Although rhabdomyosarcoma (RMS) is the most frequent soft tissue sarcoma diagnosed in childhood,[1] it represents only 2%–5% of adult soft tissue sarcomas.[2] Clinical behavior, distribution of histopathological subtypes, less sensitivity to chemotherapy (CT) and radiotherapy (RT), lower tolerance to intensive treatment protocols, and poor outcome make adult RMS a distinct entity compared with childhood RMS. In addition, there has been great controversy in treatment approaches between them. Childhood RMS is often managed by multidisciplinary approach, including surgery, intensive CT, and mostly RT, as conceived by the Intergroup Rhabdomyosarcoma Studies (IRS I–V) that achieved significant improvement in survival in the last four decades.[3–7] In contrast, treatment of adult RMS seeks standard treatment protocols; some authors use management based on pediatric RMS, whereas others use mainly surgery complemented often with RT, sparing adjuvant CT for selected cases because of the low level of benefit.[2, 8–11] However, owing to the rarity of adult RMS, there is no any prospective study testing childhood regimens in adults, yet.[12]

The main aim of the present study was to better understand the clinical characteristics, treatment approaches, and outcomes of patients with adult RMS who received RT as a component of their multidisciplinary management since there are scarce data on adult RMS. The secondary aim was to evaluate the reliability of risk grouping and prognostic significance of histopathological subtypes in adult RMS.

## Materials and Methods

The medical records of patients with adult RMS who were ≥18 years old and treated with RT between January 1995 and August 2016 in four different radiation centers were evaluated in terms of clinical characteristics, treatment, and follow-up data retrospectively. An age of 18 years is the cut-point age used in our clinics for pediatric patients.

History and physical examination were the first evaluations made for all patients. Local extent of lesions was mostly evaluated by computerized tomography (CT). Magnetic resonance imaging directed to the primary lesion was available in 67.8% of the patients. Bone marrow aspiration and/or biopsy were performed in 28.5% of the cases. Cerebrospinal fluid examination was done in 25% of the cases with head and neck involvement. Since 2010, positron-emission tomography/CT was performed in 42.8% of the patients.

Parameningeal site was described as middle ear, nasopharynx, paranasal sinuses, infratemporal and pterygopalatine fossa, and parapharyngeal region.[13]

Favorable sites of involvement were defined as orbit/eyelid, head and neck (excluding parameningeal), genitourinary (excluding prostate and bladder), and biliary tract. Unfavorable sites were defined as parameningeal, bladder, prostate, trunk, extremity, retroperitoneal, pelvis, and others.[7]

Compartment surgery was defined as resection of the entire tumor with its original compartment,[14] and all other types of surgery were accepted as noncompartment. We defined the extent of disease according to Intergroup Rhabdomyosarcoma Study Group (IRSG) postsurgical grouping system, IRSG staging system, and COG risk group, retrospectively.[3,7]

Following completion of their treatments, patients were followed up by 3-month intervals for the first 2 years, 6-month intervals for the next 3 years and then annually afterwards.

Local control, disease-free survival (DFS), overall survival (OS), and acute and late side effects were defined as study end-points. Relapse was defined as any clinicoradiological evidence of tumor recurrence. DFS was calculated from the time of pathological diagnosis to the relapse (locally or distantly) time. OS was calculated from the date of diagnosis to the event-free final follow-up or to the date of death of any cause.

### Statistical Analysis

Continuous data were expressed as mean (SD) when normally distributed and compared with Student's t-test and median (25th–75th percentiles) when skewed distributed and compared with Mann–Whitney U test. Normality was evaluated by the Shapiro–Wilk test. Categorical data were expressed as numbers (%) and compared with Fisher's exact test. Time to event analysis was performed by the Kaplan–Meier method, and comparisons were done by log rank test. A two-sided p value $<0.05$ was considered as significant.

## Results

There were 28 patients with adult RMS treated with RT as a part of their management. The median age at diagnosis was 28 (19–53) years, and the male-to-female ratio was 1.15. None of the patients had a diagnosis of any genetic syndrome. Pain and mass at the site of lesion were the most frequent symptoms (82%). The me-

**Table 1** Clinical characteristics of the patients

| | |
|---|---|
| No. of patients | 28 |
| Age (years) | 28 (19–53) |
| Male/female | 15/13 |
| Symptom | Pain and mass |
| Tumor size (cm) | 6 (4–11) |
| Site of origin | Head–neck 12 (paranasal 7/12) |
| Paratesticular | 4 |
| Genitourinary | 4 |
| Extremity | 4 |
| Trunk | 2 |
| Perianal/anal | 2 |
| Histology | Alveolar 16 (%57) |
| | Embryonal 7 (25%) |
| | Pleomorphic 5 (%18) |

**Table 2** Distribution of patients according to IRSG group, IRSG stage, and COG risk group

| IRSG group | IRSG stage | COG risk group |
|---|---|---|
| Group I : 7 | Stage 1: 6 | Low-risk 8 |
| Group II : 4 | Stage 2: 4 | Intermediate-risk 10 |
| Group III: 8 | Stage 3: 9 | High-risk 10 |
| Group IV: 9 | Stage 4: 9 | |

IRSG: Intergroup Rhabdomyosarcoma Study Group; COG: Children's Oncology Group.

dian tumor size ranged from 4 to 11 (median 6) cm. The most common site of involvement was the head and neck region (25%), and parameningeal region involvement was prominent (92%) among them. In general, unfavorable site of involvement was markedly higher than favorable ones (82% vs. 18%). Alveolar was the most frequent histopathological subtype. Desmin was the most studied molecular marker in addition to others, and it was positive in all cases. Table 1 shows the clinical characteristics of the patients.

Table 2 shows the distribution of patients according to IRSG postoperative staging, IRSG staging, and TOG risk grouping. At diagnosis, 32% of the patients had clinical nodal involvement (N1), and 32% had distant metastasis (M1). The bone and lung were the most frequent distant metastatic sites.

Fifteen patients had surgery, four of them being non-compartment. Among six patients who had positive surgical margins initially, re-resection was performed in one patient, and negative surgical margin was achieved. As a result, final surgical margin was positive in five patients.

2D RT planning was used in 3, 3D conformal RT in 8, and IMRT in 17 patients. RT was administered to the primary site with radical intent in 10, adjuvant in 9, preoperative in 3, and palliative in 6 patients. The median RT dose was 50 (16–70) Gy (95% confidence interval (CI): 45–54), and fractionation dose was from 180 to 800 (median 180) cGy (95% CI: 180–200). In 46.8% of the patients, excluding palliative ones, RT was started in the first 12 weeks (early RT) of the initial treatment. All patients were able to complete their RT schedules. Concurrent CT was administered in 46.8% of the cases. All patients received systemic multiagent CT except two. The most frequently used agents were vincristine (V), actinomycin D (A), ifosfamide (I), and cyclophosphamide (C). The most commonly used combinations were VAI, VAC, and VA (64.2%). Other agents used were doxorubicin, etoposide, mitomycin C, and cisplatin.

Locoregional recurrence was detected during their course of the disease in 17 (60.7%) cases, 5 were infield, and 2 were marginal. Local recurrences were significantly higher in patients receiving <41.4 Gy (p: 0.041). There was local recurrence in all of the five cases who had positive final surgical margins. During follow-up, 9 patients out of 19 (47%) who were M0 at the time of diagnosis developed distant metastasis, mainly to the lung. In all cases except one, the reason of death was related to cancer. At the time of analysis, there were five patients who were alive.

Follow-up time ranged from 3 to 235 months, with a median of 18 months (95% CI: 15–20). DFS was between 2 and 48 months, with a median of 12 months (95% CI: 7–16). The 5-year OS was 25%, with a median OS of 20 months (95% CI: 16–23) ranging from 4 to 235 months. By the end of the study, there were five patients who were alive.

There were significant differences in terms of survival according to histopathological subtypes (p: 0.017), risk groups (p<0.001), IRSG grouping (p<0.001), and IRSG staging (p<0.001). Figs. 1, 2, and 3 show the Kaplan–Meier OS curves according to histopathological subtypes, risk groups, and IRSG grouping, respectively.

Age, tumor size, invasiveness of tumor, site of involvement, and presence of N1 disease at the time of diagnosis were not prognostic for outcome. M1 disease at presentation was significantly lower survival than M0 disease (13 vs. 23 months, log rank p<0.001).

## Discussion

The present study showed that stratifying patients with adult RMS according to risk grouping used in pediatric

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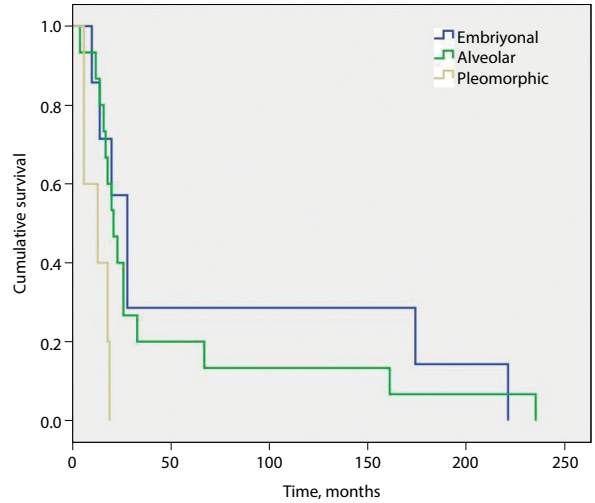


**Fig. 1.** Kaplan-Meier overall survival curves of patients according to histopathological subtypes.

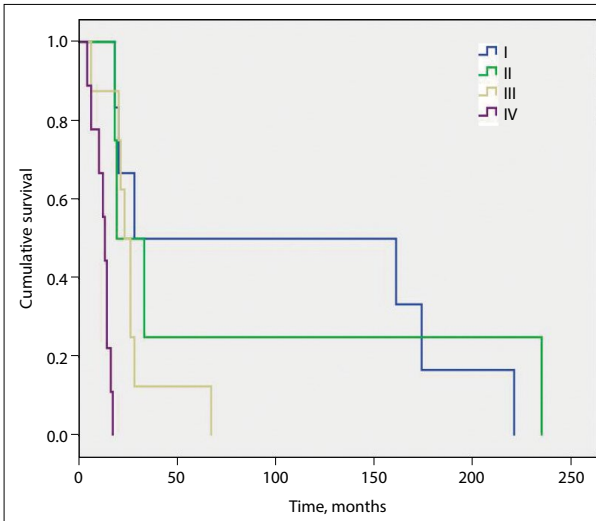


**Fig. 3.** Kaplan-Meier overall survival curves of patients according to IRSG postsurgical grouping.

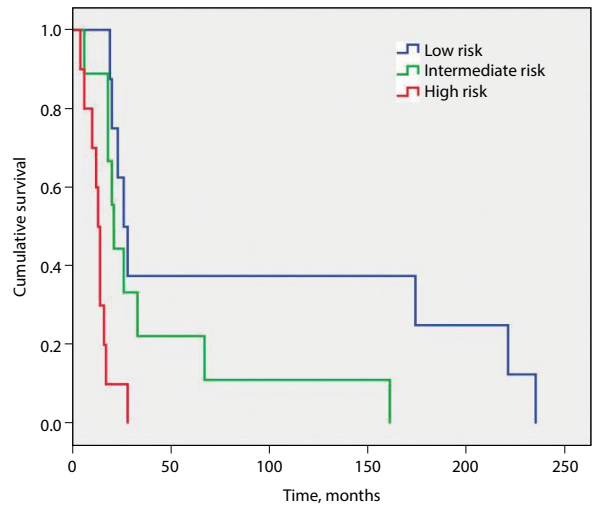


**Fig. 2.** Kaplan-Meier overall survival curves of patients according to risk groups.

RMS may be predictive for survival, although there has been uncertainty in the literature about the use of risk grouping in adults.[12] In addition, pathological subtype may have prognostic significance in adult RMS, which is a controversial issue.[9,11,15–17]

In our study, the 5-year OS was 25% and is in line with previously published data, which changes between 20% and 40%.[9,16–23] Inferior treatment outcomes in adults are obviously compared with 70%–80% 5-year OS in pediatric cases.[6,24] Many factors may play a role on these different outcomes between pediatric and adult RMS, such as (1) the lack of standard management, (2) decreased tolerance to intensive CT protocols because of change in pharmacokinetics and pharmacodynamics, (3) advanced presentation, and (4) different biology in adults.[17] Related to these factors, there are two opposite views on treatment approaches; some authors suggest that adult RMS is an inherently different entity even if there is no evidence of benefit of CT in terms of survival,[16] and others claim that if adult RMS would be treated with the same principles as in pediatrics, the outcomes would be similar.[2,9,22] In a retrospective study by Ferrari et al., it is established that patients with adult RMS who were treated with similar treatment guidelines in pediatric RMS have treatment outcomes very similar to pediatric cases.[2] In concordance with this view, there has been a change in the management of adult RMS separately from other adult soft tissue sarcomas in recent years. The treatment regimens have become more consistent with current pediatric RMS protocols, even IRSG has started to include patients up to age 50 in their protocols.[2,12,15] Similar to this approach, in our patient cohort, 92.8% of the cases received multiagent systemic CT, mainly composed of agents used in pediatric RMS.

The clinical presentation of our patient cohort was relatively unfavorable compared with pediatric cases that closely parallel with the literature in adult RMS.[2,17,25] The ratio of invasive tumor was 60%, 67.8% of tumors was >5 cm, patients with alveolar and pleomorphic types composed 75% of the cohort, unfavorable site of involvement was 82%, there was no any orbital

presentation, clinical lymph node involvement rate was 32%, and patients were mostly in IRSG postsurgical group III–IV, IRSG stage 3–4, and intermediate- and high-risk group.

A very high rate (82%) of unfavorable site involvement was defined in our study, which is in line with 67% and 79% reported by Gerber et al. and SEER data, respectively.[15,23] The first presentation with head and neck involvement represents 35% of pediatric cases. In the present study, it was 42.8%, which seems relatively higher than some adult RMS series,[2,16,26] but in concordance with the findings by Khosla et al. and Little et al.[9,11] Furthermore, in our series, there was no any orbital involvement that is known as the most favorable site[3–6] similar to the findings with other adult RMS studies.[16,27] In addition, 92% of our head and neck patients with RMS have their lesions in parameningeal site that is very unfavorable.[7,28] In general, parameningeal site involvement represents 39.2% of our patient cohort that is higher than IRSG reports (14%–18%).[3,4] However, in the literature, there have been at least two studies with such high proportion of parameningeal site involvement in adults.[9,29]

There has been a controversy on the prognostic significance of histopathological subtype in adult RMS. In three retrospective studies, there was no any association between histological subtype and survival; in the study by Little et al., there was lower metastasis-free survival in embryonal subtype that did not translate to DFS.[9,11,15,16] However, in our study, there was a significant survival difference according to histopathological subtypes (p: 0.017) similar to the findings by La Quaglia.[17] In addition, the proportion of embryonal subtype, which is proven to be favorable compared with other types,[7] composed only 25% of the patients in our study, similar to other adult RMS series.[9,11,23] It was reported as 70% in IRS IV.[6] Moreover, it should be kept in mind that pleomorphic RMS that is more often seen in adults may not have benefit from multiagent regimens used in pediatric protocols. All of these factors might pose additional disadvantages to adult RMS outcomes.[30]

Furthermore, we have shown that survival was significantly different according to risk group stratification used in pediatric RMS. As a result, risk stratification used in pediatric cases also might be valid in adult RMS. However, there is controversy in the literature about the use of childhood risk grouping in adults.[12]

Although risk-specific approach to staging has been used in pediatric cases,[30] there is no uniform staging algorithm for adults.[12] Similarly, in our cohort, we have seen that meticulous staging procedures were not the case. It might be better to standardize the current staging procedures for accurate diagnosis and evaluation to better define the risk groups, staging, and optimal treatment in adults because nodal and distant metastasis rates are higher in adults.[9,22,25]

RMS has the higher propensity for lymph node metastases among other soft tissue sarcomas. The rate of clinical presentation with lymph node metastases was 32% in our patient cohort. This rate is in concordance with other adult RMS series[9,22] but higher than those for pediatric cases (15%–20%).[6] Lymph node metastasis was higher in alveolar subtype, but the difference was not significant probably because of the small number of patients. Outcome of N+ patients was not inferior compared with N0 cases, which was a similar finding with two other studies that address this issue.[9,22] Overall poor outcome might have overcome this effect.

Adult RMS has higher distant metastasis rate than pediatric RMS (15%).[31] At presentation, it was 32% in our cohort, which is in line with adult RMS literature.[15,23] The lungs and bone were the most frequent metastatic sites; in the literature, they were lung and bone marrow.[31] A lower incidence of bone marrow studies in our cohort might explain this difference. In addition, patients with M1 disease at diagnosis had significantly lower survival, which is a similar finding with the literature.[23]

Although adult RMS is more radiosensitive than most adult sarcomas, it is probably less sensitive than pediatric RMS.[9,26,28] In our series, locoregional recurrence rate was 60.7%, almost half of them were in-field or marginal. After complete resection, Little et al. reported 50–56 Gy for negative margins, 60 Gy for positive margins, and 66–70 Gy after incomplete resections in patients with adult RMS.[9] In concordance with this, we have found that local control was significantly inferior with RT doses <41.4 Gy. Furthermore, in the subgroup analysis, there were local recurrences in all of the five patients who had positive final surgical margins, showing the importance of complete surgical resection.[9] In addition, all of these findings might inform us about the revision of RT dose and fields. Parameningeal predilection of lesions might be another reason for unsatisfactory locoregional control in our study, which has also poor local control rates in the literature.[9,32] Moreover, the ratios of early RT and concurrent CT that are preferable in pediatric protocols were low, which might contribute to lower local control and decreased survival rates.[12] Our RT

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schedule appears tolerable in terms of acute and late toxicity.

Limitations of the study: The retrospective nature of the study and relatively small number of patients treated over a long period are the major limitations of our study. The absence of central histological re-review of archived materials is another limitation since there has been improvement in immunohistochemistry recently. Furthermore, we could not analyze the details of CT schemes, duration, and dose intensity because of the retrospective nature of the study.

## Conclusion

Our results confirm that adult RMS has unfavorable clinical presentation and worse outcome compared with pediatric RMS. We think that our findings about the prognostic significance of histopathological subtype and risk grouping used in pediatric cases also might be valid and are very important in adult RMS. Nevertheless, optimal treatment approach needs to be defined. In addition, it is reasonable to employ RT early in the course of treatment concomitantly with CT similar to IRSG protocols to decrease the probability of locoregional recurrence since there is low chance of cure after relapse. Furthermore, doses and fields of RT need to be revised with the availability of today's sophisticated imaging, RT planning, and delivering modalities.

Since it is unfeasible for adult RMS to proceed controlled, prospective trials because of its rarity, we should rely on these retrospective series and information from pediatric series except those with pleomorphic RMS.

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