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Non Metastatic Rhabdomyosarcoma in Children: Therapeutic Outcome and Prognostic Factors of a Single Institution Case Series

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Abstract

Background: Rhabdomyosarcoma (RMS) is the most common soft tissue tumor in childhood with a cure rate of 70% in localized disease. We aimed to study the prognostic factors of non-metastatic RMS in Tunisian paediatric patients.

Methods: We reviewed data of children aged <18 years, treated in the Salah Azaiez Institute for a localized RMS during 20 years. Prognostic factors were studied and survival data analysed.

Results: 75 patients were included. Mean follow up was 30 months. The 5-year OS and DFS were 50% and 26%, respectively. By univariate analysis, DFS was significantly correlated to chemotherapy, radiotherapy (RT) and post-surgical RT with p 0.02, 0.003 and 0.01, respectively. The surgery failed to be a significant factor. We didn`t find any factor with a significant relationship with DFS in multivariate analysis. By univariate analysis, 5-year OS was significantly and adversely influenced by 4 factors: tumour size>4 cm, non-alveolar RMS, positive regional nodes and para-meningeal location, with p: 0.050, 0.05, 0.04 and 0.04, respectively. RT and postsurgical RT were associated with a good prognosis in OS p=0.009 and 0.05, respectively. Age, histology, primary site and IRS group failed to be significant. By multivariate analysis, OS was strongly correlated to radiotherapy p=0.03, Odds Ratio (OR) 3.1, confidence interval (IC) 95% [1.05-9.3] and para-meningeal site p=0.04, (OR) 0.3, confidence interval (IC) 95% [0.1-0.9].

Conclusions: Compared to the literature, we noticed that the prognosis of our patients was worse so we should improve it by making the treatment more personalized and encouraging research.

Keywords: Rhabdomyosarcoma • Prognostic factors • Children • Surgery

Introduction

Rhabdomyosarcoma is the most common soft tissue tumor in childhood [1]. During the last 30 years, the introduction of multimodal therapy has resulted in a significant improvements in survival, with a create of approximately 70% for patients with localized disease [1-3].

Several trials from Collaborative pediatric groups such as the Intergroup Rhabdomyosarcoma Study Group (IRSG) have revolutionized the therapeutic methods for this sarcoma [3]. Based on the conclusions of these studies, multimodal treatment regimens, involving surgery, chemotherapy and/or radiation, are decided by tumor staging (based on tumor primary site, tumor size, the presence or not of regional lymph node involvement and of distant metastasis), grouping (defined by the amount of residual tumor after initial surgery), and the histologic subtype of the tumor [3].

Patients and Methods

The overall study population consisted of 75 children aged <or=18 years, with non-metastatic RMS treated between 1994 and 2016. Patients with isolated regional lymph node involvement were not considered to have metastatic disease. All patients had received histological confirmation of tumor. All patients received conventional multiage chemotherapy based on alkylating agents (cyclophosphamide or ifosfamide), vincristine, and dactinomycin. Some patients received other drugs, depending on the research group and specific protocol. Patient subsets with risk of treatment failure were identified on IRS post-surgical groups (Annex 1).

Pretreatment stratification IRSG (Intergroup rhabdomyosarcoma study group) before 2005 was detailed in the Annex 1.This classification was suitable for the patients treated between 1994-2004.The EPSSG (European Pediatric soft tissue sarcoma study group) had conducted new risk group stratification in the protocol RMS 2005. (Annex 2).So our patients diagnosed between 2005 and 2016 were classified by this protocol.

Prognostic factors

Prognostic factors assessed in relation to DFS and OS were age, sex, group, stage, tumor size, nodal status, primary site and histological subtype.

Statistical analysis

Statistic all analysis were performed at the Salah Azaiez Institute. The survival curves were calculated by Kaplan-Meier method. The OS was evaluated from the date of the start of treatment to the last follow-up or death. Disease-free survival (DFS) was calculated from the date of the start of treatment to the date of the first event, defined as tumor progression, relapse, or death as a result of any cause.

The pre-treatment patient characteristics considered as prognostic factors were evaluated with univariate analysis using the Kaplan-Meier method to calculate survival probabilities for DFS and OS at 5 years [4]. The log-rank test compared survival differences. Associations among variables were assessed with the chi2 test. Multivariate analysis was conducted using the Cox proportional hazards regression method. All calculations were performed with SPSS (statistical package for social sciences) version 20.

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Results

Patient characteristics

The characteristics of the 75 patients included in the analysis are listed in Table 1. Median age at diagnosis was 8 years, but most patients (71%) were younger than 10 years of age. Male patients outnumbered female patients (Sex ratio=1.27). Embryonal RMS was the most common histologic type (72%) followed by alveolar (21%) and pleomorphic (1%). The most frequently affected sites were head and neck (43%) and genito-urinary (28%). As per Intergroup Rhabdomyosarcoma Study Group (IRSG) site classification, just over half of tumors were located at favorable prognostic site (orbit; non parameningeallhead and neck; genitourinary tract except kidney, bladder, and prostate; biliary tract).

Survival

For the entire cohort, the mean follow-up of survivors was 300months, with a range of 1 month to 17.1 years. Estimated 5-year OS and DFS for all patients were550% and126%, respectively. There were no differences in survival by age or sex. Analysis by histology type revealed that alveolar had the best overall survival (5-year OS=90%, P=0.05) (Figure 1A). Patients with tumors<or=4 cm in size and without any lymph node involvement had better survival (5-year OS=65%, 60%, respectively) (Figure 1B).The tumor site failed to be significant but only unfavorable Para meningeal RMS was associated to a worst prognosis (Figure 1C).Surgical resection wasn't associated with improved survival (5-y OS: 53% versus 50% for no surgery, P=0.5). Overall, radiation therapy mainly post-surgical RT was associated with an overall 5-year survival improvement (P =0.009). (Figure 1D). However, chemotherapy

Characteristics		Number	% of total	5-year OS	log rank test(p)
SEXE	Male	42	56	42%	0.7
	Female	33	44	46.20%	
AGE, years	<5	31	42	47.50%	0.14
	05-Oct	22	29	27.60%	
	Nov-18	22	29	38.60%	
Primary site	Orbit	11	14.7		0.7
	Non-PM head and neck	14	18.7		
	PM	7	9.4	20%	0.041
	GU(bladder/prostate)	4	5.4		0.7
	GU(non-bladder/prostate)	17	22.6		
	Limbs	5	6.6		
	other	17	22.6		
	No primary	0	0		
Primary site	Favourable	42	56	48%	0.7
	Unfavourable	33	44	40%	
Regional nodal status	No	50	66.7	60%	0.041
	Yes	21	28	40%	
	Unknown	4	5.3	-	
size	< or =4cm	18	24	65%	0.05
	>4 cm	55	73.3	42%	
Pathology	Alveolar	16	78.6	90%	0.05
	non alveolar	59	21.4	38%	
Period of treatment	before 2005	29	38.6	40.50%	0.14
	after2005	46	61.4	53%	
chemotherapy	yes	70	93	45%	0.07
	no	5	7	28%	
Radiation	yes	36	48	71%	0.009
	no	39	52	31%	
Surgery	yes	37	49.3	53%	0.5
	no	38	50.7	50%	

Table 1. Patient characteristics.

Protocol	Number of patients
MMT89	6
MMT95	18
IVADO (RMS 2005)	12
IVA (rms 2005)	7
VAC-VAD	2
OTHERS	3

Table 2. Neoadjuvant chemotherapy protocols.

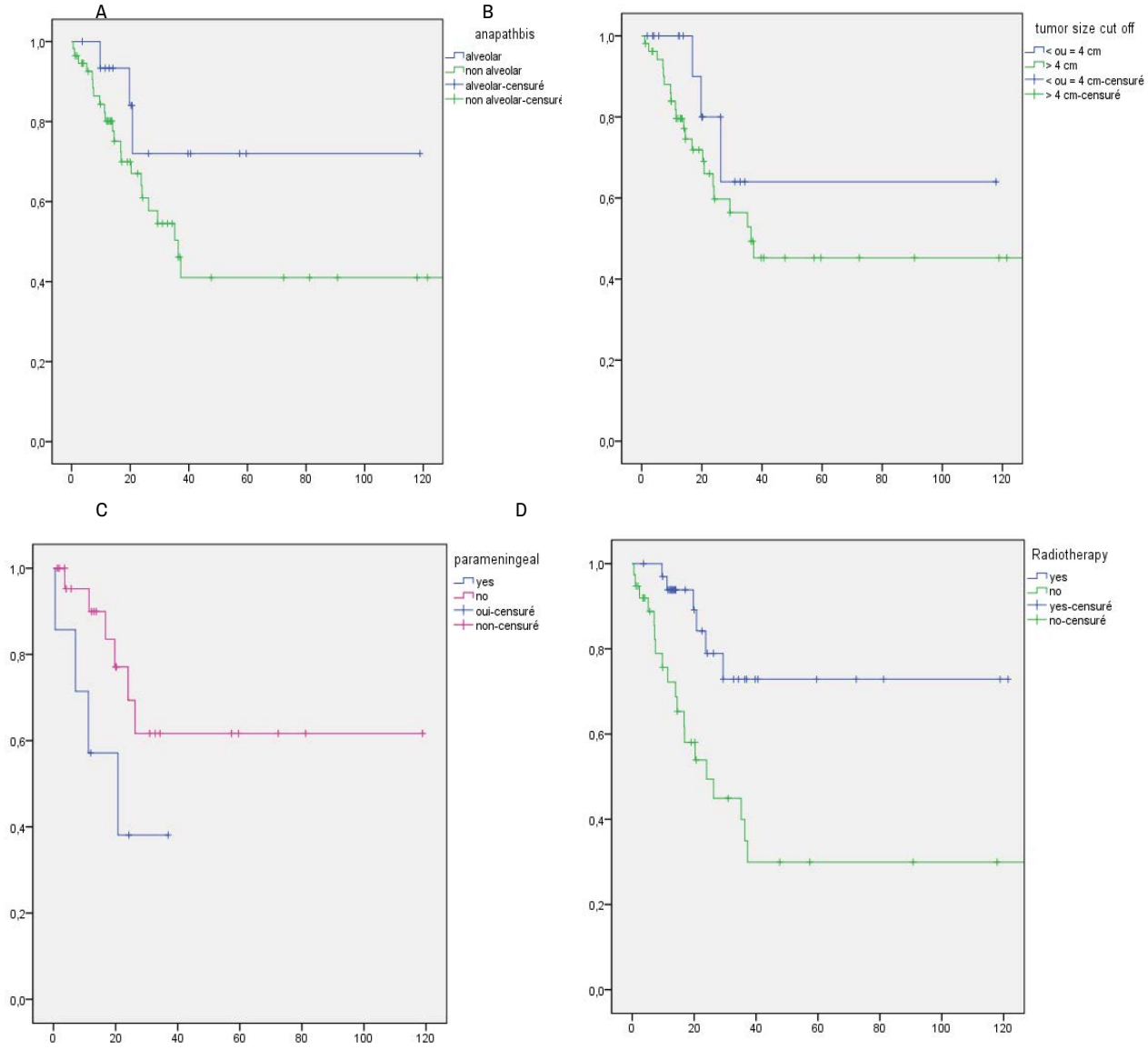

Figure 1. Kaplan-Meier survival curves to histologic type (1A and 1B): size, (1C): parameningeal site, (1D): radiotherapy.

(CT) didn't improve the overall 5 year survival (45% versus 28% without CT, p=0.07). The Table 2 shows the different protocols of neoadjuvant CT.

The predictive factors in DFS by univariate analysis were: chemotherapy, radiotherapy and post-surgical RT with p 0.02, 0.003 and 0.01, respectively.

Multivariate analysis

Results of multivariate analysis using the Cox regression model revealed that OS was strongly correlated to radiotherapy p=0.03, Odds Ratio (OR) 3.1, confidence interval (IC) 95% [1.05-9.3] and Para meningeal site p=0.04, Odds Ratio (OR) 0.3, confidence interval (IC) 95% [0.1-0.9]. We didn`t found any factor significantly correlated to the DFS.

Discussion

The treatment results in rhabdomyosarcoma have improved in the last 3 decades thanks to IRS studies as well as SIOP (International society of pediatric oncology) studies. The overall long-term survival rate for such patients with non-metastatic disease is expected to exceed 80% [5]. The two major histological subtypes of RMS (alveolar and embryonal) have different clinical outcomes and prognostic factors [6].

Several studies had shown the un-favorable prognosis of alveolar RMS (RMSA) versus embryonal RMS (RMSE). Raney and al found a DFS 88% for RMSE versus 66% for RMSA. This substantial difference in prognosis between RMS types may be due to well-known distinct genetic alterations that putatively play a role in the pathogenesis of these tumors and their response to treatment. For example, RMSA presents a genetic alteration which generates protein fusions. So, we distinguish two types: FNRMS (Fusion Negative Rms) and FPRMS (Fusion Positive Rms).FNRMS has the same well prognosis as RMSE [6] .In Tunisia, we haven't yet molecular study, this can explain our results that alveolar RMS had a better overall survival may be almost of them were FNRMS.

Age at presentation is also an important prognostic indicator for survival of patients with RMS. Joshi and al classified patients into three failure-risk categories based on age (<1 y; 1–9 y; >10 y) finding that infants and adolescents had significantly worse outcomes, and thereby identifying patient age as an independent risk factor for treatment failure in RMS [7]. Our analysis failed to be significant.

Long-term outcome and treatment recommendations for RMS are based on multiple factors. Pretreatment staging is based on a site (favorable versus unfavorable) modified TNM system. Clinical group assignment is used following the initial surgical procedure and is primarily based on the

surgical respectability of the tumor, extent of residual tumor, and presence of metastasis. Current COG protocols stratify patients into one of three risks treatment protocols according to tumor site, size, histology, TNM stage, clinical group, and patient age [8]. Our analysis confirms only that that Para meningeal site and tumor size have significant impact on survival for patients with RMS with a cut off 4 cm. However, in the literature data, the cut off is 5 cm.

Lymph node status is an important part of pre-treatment staging, clinical group and impacts risk-based treatment strategies in RMS. Nodal disease is also incorporated into Clinical Group as determined by pathology. Lymph node involvement is present in 23% of all RMS patients, predominantly in primary sites such as retroperitoneum, perineum, extremity, bladder/prostate, pretesticular and Para meningeal. Positive lymph nodes status is an independent poor prognostic factor for overall and disease free survival in patients with fusion positive ARMS but is not as important for fusion negative ERMS patients provided the nodal disease is treated appropriately with RT [9]. For our patients, lymph node positive RMS had a worse prognosis with an OS 40% versus 60% for N-. But, it failed to be significant in multivariate analysis and for the DFS.

Surgery is the backbone of the treatment of RMS. Alone, it achieved a cure in >20% of patients with RMS, which supposes that microscopic residual tumor invariably is remaining or disseminated in the majority of patients despite a total resection [8]. Survival has improved considerably, largely due to cooperative group trials (IRSG) and SIOP protocols employing multidisciplinary treatment protocols, which include multiage chemotherapy and radiotherapy in addition to surgery. Surgical resection remains the standard treatment for localized disease as long as functional and/or cosmetic results are acceptable [9].

By univariate and multivariate analysis, our patients undergoing surgery hadn't significantly higher OS or DFS.

Radiotherapy is used in all patients with RMS except for those with localized embryonal tumors that are completely excised without residual disease. In advanced cases, radiation therapy plays a critical role in achieving local tumor control [10]. Overall, we found that radiation therapy was associated with an important survival benefit. Furthermore, adjuvant radiotherapy following surgery was associated with improved survival.

Currently, multi agent chemotherapy is indicated for all patients with RMS. Following surgical resection, combination therapy consisting of vincristine, dactinomycin and cyclophosphamide (VAC) or vincristine, dactinomycin and Ifosfamide (IVA) is administered to achieve eradication of microscopic residual disease [11, 12]. Neoadjuvant chemotherapy can be indicated in case of un-respectable tumors or to obtain cyto reduction and facilitate subsequent surgical excision. However, chemotherapy failed to improve survival in this study.

Conclusion

This analysis showed Tunisian pediatric patients with non-metastatic rhabdomyosarcoma with different outcomes to current therapy. Clinical trials which are focused on the oncogenic mechanisms of these tumors proposed new therapies. Unfortunately, these molecules are emerging slowly in low income countries such as Tunisia.

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