

Childhood rhabdomyosarcoma. Anatomico-clinical and therapeutic study on 25 cases. Surgical implications

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Abstract

Rhabdomyosarcomas (RMS) are the most frequent soft tissue sarcomas of childhood. Despite advances in knowledge about biological pathways of tumorigenesis, risk stratification and multimodal treatment, the immediate and long-term prognosis of these lesions in many countries with limited resources is still poor. *Patients and Methods:* Twenty-five histologically confirmed pediatric RMS were recorded during the period of study. Demography, clinical presentation, diagnostic means, pretreatment staging and post-surgical grouping, histological type, therapy and outcome were evaluated. *Results:* The mean age was 6.7 years; the group included 12 boys and 13 girls. Twelve lesions were localized in the genitourinary tract, eight in the trunk and extremities, two cases each in head and neck and retroperitoneum and one case in biliary tract. Primary surgical attempt was performed in 15 patients but only in nine of them underwent complete resection (three with free margins) other six cases achieving removal with residual disease. In 10 cases, solely biopsy was possible. Twenty-four patients received chemotherapy but only four cases performed radiation therapy. Overall survival rate was only 36% (nine cases). *Conclusions:* As mean feature children from our series had late presentation with locally extended (bulky and node positive) lesions and unfavorable sites. Improved multimodal management of RMS in recent years will probably lead to better survival curves in an increasing number of cases and an outstanding outcome in children with locally advanced disease.

Keywords: pediatric rhabdomyosarcoma, taxonomy, multimodal treatment, surgery.

Introduction

Rhabdomyosarcomas (RMS) are the most common pediatric soft tissue sarcomas constituting 3–8% of all malignancies in childhood with an aged standardized annual incidence of rate between 4–5 per million in children less 18-year-old. These tumors are considered to be highly malignant neoplasms arising from existing skeletal muscle as well as from the pluripotential mesenchymal cells of connective tissue [1–4].

The first mention of RMS belongs to Weber (1854) who described a lingual location but a clear anatomico-histological definition was made by Stout (1946) who recognized the distinct morphologic features of these tumors [1, 5, 6].

Histologically, RMS are classified into embryonal tumors with botryoid and spindle cell variants, typically described in young children, alveolar RMS occurring in teenagers and young adults and undifferentiated (pleomorphic) RMS arising in adults. Cytogenetic abnormalities as embryonal loss of heterozygosity on the short arm of chromosome 11(11p,15,5) were identified suggesting inactivation of a tumor suppressor gene. Also, in alveolar RMS appeared translocations t(2;13)(q35;q14), t(1;13)(q36;q14) and gene fusions: PAX3-

FKHR, PAX7-FKHR. Both of these may have a prognosis importance [4, 7–10].

The childhood RMS may occur in any site the relative frequency is head and neck (42%), urogenitally tract (34%) and extremities (11%). Signs and symptoms vary of the anatomic site of the origin of the tumor and prognosis depends to the size, histology, localization, clinical variant and cytogenetic characteristics [2, 4, 10].

Constitution of the *Intergroup Rhabdomyosarcoma Study (IRS)* in 1972 enables elaboration of modern protocols of multimodal approach of these tumors [11–14]. Together with *UICC* traditionally *TNM* system, clinical grouping system based on therapeutic decision, risk stratification and identification of favorable or unfavorable appurtenance of the tumors, the RMS taxonomy contributed to an unitary and better supportive care and systematic application of increasing effective surgery, chemo- and radiotherapy and have dramatically improved five years survival rates over the last two decades from 10–20% exceeding 70% nowadays [4, 7, 15].

Patients and Methods

This is a retrospective study of 25 consecutive pediatric patients with positive histological diagnosis of RMS treated

in “St. Mary” Children Emergency Hospital Iassy, Romania, during the period between January 2000 to December 2011. The study population included patient age 0.1 to 17 years at time of diagnosis. The medical records were reviewed for following data: clinical onset symptoms and signs, primary tumor site, staging, post-surgical grouping and risk stratification of the lesions, imaging studies and therapeutic protocols.

The same experienced pathologist (D.M.) revised histological slides. The follow-up was realized in day hospital or as inpatient admission when necessary, minimum one year and maximum five years after the end of the therapeutically procedure.

The study group is numerically limited but still relevant. Univariate analysis was performed using the

chi-square test considered to be significant when the *p*-value was <0.05.

Results

Twenty-five patients, 12 boys and 13 girls aging from three days to 17 years (median age 6.7 years) were considered in our study over a 12 years period. A quarter of cases were infants. The age distribution peaked between three and nine years. The most frequently affected site was genitourinary tract in 12 (48%) patients, followed by the trunk and extremities with eight (32%) patients and as less attended localizations must be noticed the head and neck and retroperitoneum two cases each and biliary tract one case (Figures 1 and 2).



Figure 1 – Vaginal botryoid RMS in a 10 months ♀.

The presenting features included swelling or painless mass in varying sites in 15 (60%) cases, local pain and features of organ compression in seven (28%) cases each and local bleeding in two (8%) cases. The biliary tract tumor developed early jaundice. The non-specific pattern of presentation in our group of subjects delayed the hospital admission from two to six months, especially for the four patients aged 12–17 years. Four cases between 1–5 years were brought to the hospital in maximum two weeks after onset. Seventy-five percent of children had been checked and eventually received different treatment for other common pediatric conditions. Pretreatment TNM staging system included four (16%) patients in stage I, also four in stage II, eight (16%) in stage III and nine (36%) cases in stage IV.

According to the IRS post-surgical-based grouping system, only three (12%) patients were group I (complete excision with “clear” margins) and 12 (48%) in group II (macroscopic excision) and III (residual disease). The remaining 10 patients with advanced or metastatic disease performed biopsy only.

The same overlapped proportions were found in risk groups:

- Low: embryonal RMS except those in favorable primary sites that have been completely resected – three (12%) patients;
- Intermediate: embryonal or non-embryonal RMS in unfavorable sites that have been completely or incompletely resected – 12 (48%) patients;



Figure 2 – Biliary tree botryoid RMS in a 4-year-old ♀.

- High: inoperable or metastatic RMS – 10 (40%) patients.

Tumor size was <5 cm in 11 cases and >5 cm in 14. Invasion of adjacent structures were present in six (24%) cases. The tumor metastasized in the regional lymph nodes in seven (28%) cases and in distant sites including lymph nodes, liver and lung in nine (36%) cases.

Embryonal RMS was the most common histological subtype in 20 (80%) cases (including five botryoid and three spindle cell tumors). At the same time, our study differs from many other papers by the presence of only one (4%) alveolar RMS but especially of three cases of pleomorphic RMS rarely reported in children [8, 16].

A diagnosis of probability was made on clinical grounds some difficulties appearing from the non-specific and indolent character of the initial features: fatigue, weight loss and low blood counts mimicking many others pediatric diseases.

Once RMS was suspected an insistent work-up was performed to get the diagnosis and to perform the correct staging of the tumors with extensions to adjacent tissues, regional lymph nodes or metastases. Standard radiological examinations, ultrasound and sometimes CT or IRM revealed important additional information, suggestive but not definitive for the diagnosis.

Traditional pathology completed by electron microscopy is still the most important diagnosis tool of RMS.

Embryonal RMS 20 (80%) cases showed round to spindle small, monotonous looking medium to poorly

undifferentiated cells with hyperchromatic nuclei having a known favorable outcome (Figure 3).

Between 20 embryonal RMS, we distinguished also five botryoid and three spindle cell RMS, all of them with the same better behavior and prognosis. Botryoid subtype account for 20% of all cases of RMS being particularized by the formation of polypoid masses demonstrating malignant cells in an abundant myxoid stroma with caveat that a cambian layer is essential for diagnosis (Figures 4–6).

Fusiform RMS account for 12% for all cases containing scattered or polygonal spindle cells with abundant brightly eosinophilic cytoplasm and collagen (Figures 5 and 6).

Alveolar RMS only one (4%) case typically presented fibrous septa separating clusters of small round cells in an alveolar growth pattern with eccentric, small nuclei and scant eosinophilic cytoplasm. Rare rhabdoid features were present (cytoplasmic bodies, eosinophilic nucleoli) (Figures 7 and 8).

We also noted three pleomorphic RMS, very rare described in children, a high-grade sarcoma with “bizarre” polygonal, round or spindle cells with abundant cytoplasm, hyperchromatic nuclei and atypical mitosis but without embryonal or alveolar cellular elements (Figures 9 and 10).

Along from histology, electron microscopy showing features of microfilaments and sarcoma, immunohisto-

chemical (IMC) staining, were the most useful examinations in the diagnosis of RMS and was performed in most our cases. IMC staining for myogenin (extremely sensible and specific for rhabdomyoblastic differentiation), desmin, vincristin, CD45 in lymphocytes but no in tumor, CD34 in vessels but no in tumor (CD99 and NSE) contributed to a better diagnosis support and treatment stratification in these patients (Figures 11 and 12).

In our experience, the gradual introduction of the contemporary multidisciplinary approach utilizing complete surgical resection, prolonged courses of multiagent chemotherapy but sporadic radiation therapy somehow improved the therapeutic results in these little patients. Starting treatment with surgery depended in time on diagnosis accuracy, site, size and extent of the tumor and progressively taking into account its stage and grading and also the opportune-ties offered by the new-introduced cytostatic drugs.

From 15 patients operated on with curative intent only in nine was achieved macroscopic complete removal of the tumor in different peripheral sites, bladder or prostate, whilst other six cases located on the head and neck, retroperitoneal or biliary and genitourinary tract had some residual disease. All patients received chemotherapy, four of them also performing radiotherapy (Table 1).

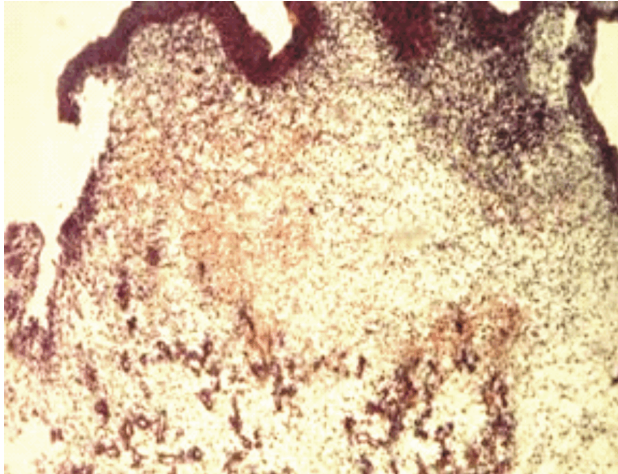


Figure 3 – Embryonal RMS (Goldner–Szekely staining, $\times 40$).

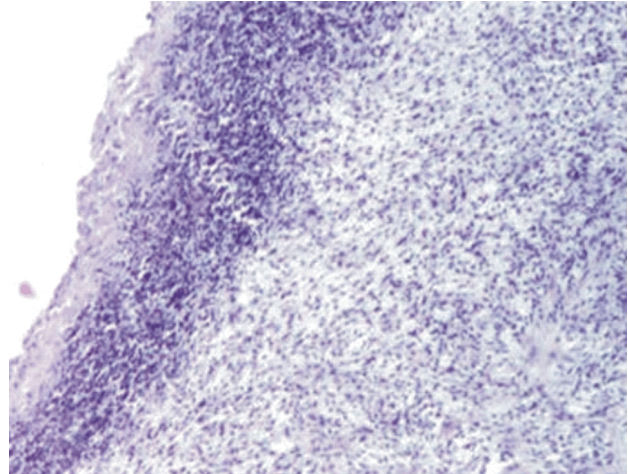


Figure 4 – Botryoid RMS; suburothelial cambian layer (HE staining, $\times 40$).

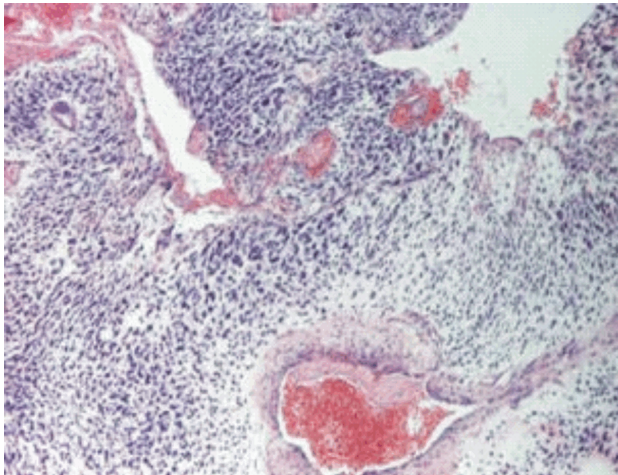


Figure 5 – Embryonal RMS proliferate by spindle cells (HE staining, $\times 40$).

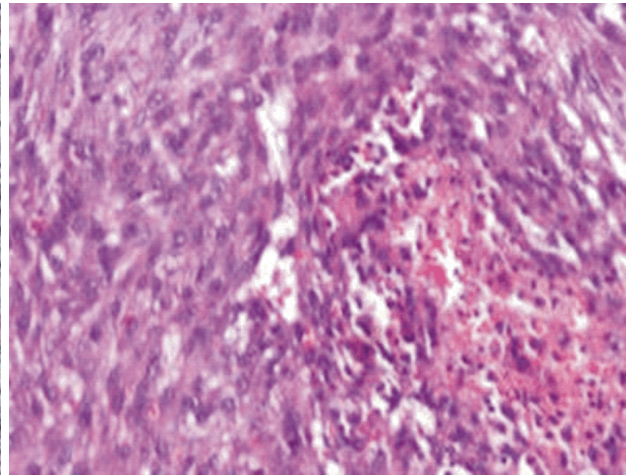


Figure 6 – Spindle cell RMS (HE staining, $\times 100$).

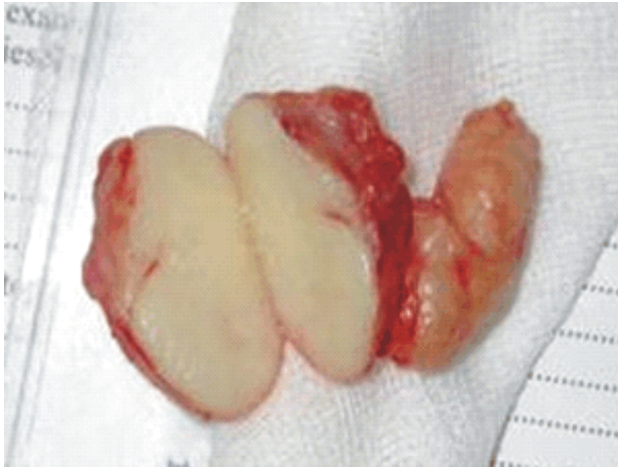


Figure 7 – Alveolar RMS; operative specimen with lymph node.

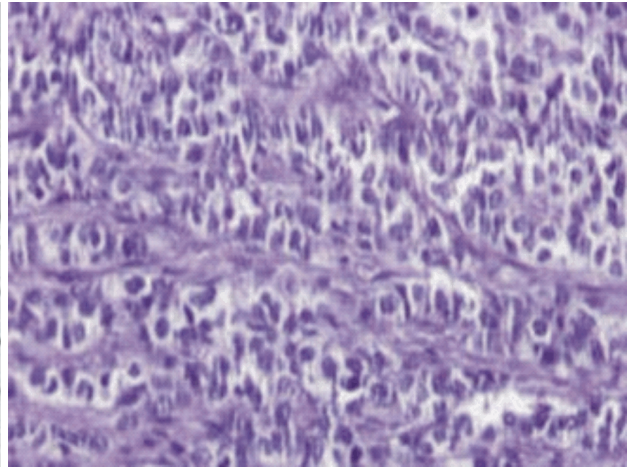


Figure 8 – The same case: microscopy (HE staining, $\times 100$).

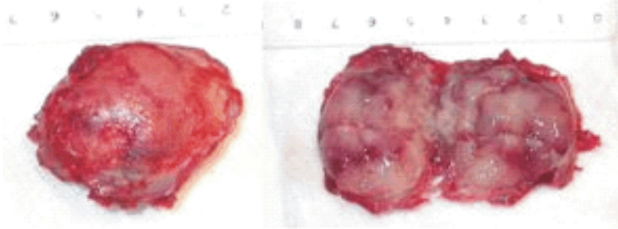


Figure 9 – Pleomorphic shank's RMS; operative specimen.

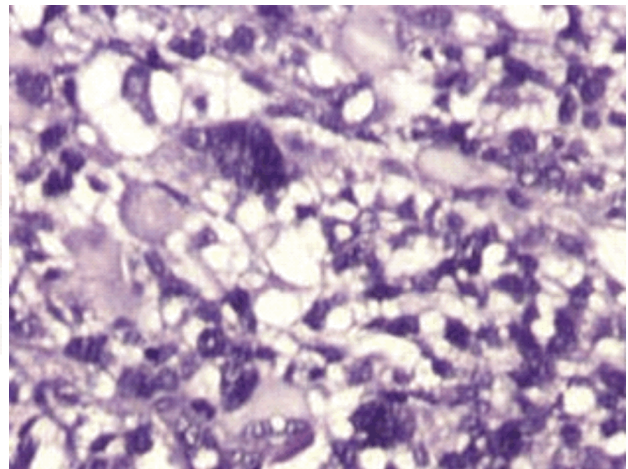


Figure 10 – The same case: microscopy (HE staining, $\times 200$).

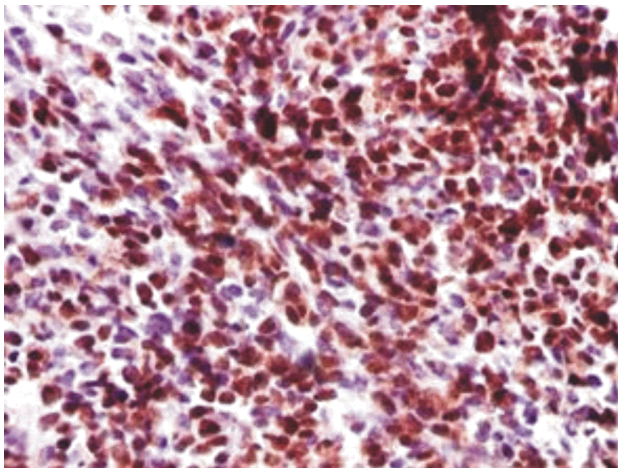


Figure 11 – Embryonal RMS; myogenin, $\times 100$.

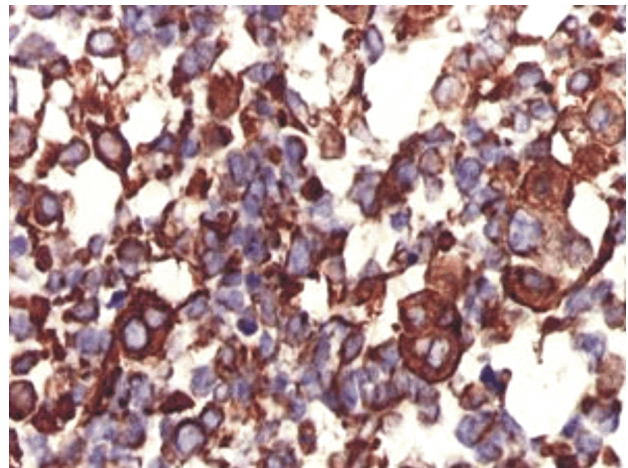


Figure 12 – Pleomorphic RMS; desmin, $\times 200$.

Table 1 – Pediatric RMS surgically removed

No.	Case	Sex/age	Site	T \approx 5 cm	Lymph node	Histological subtype	IRS group	CR	CT	RT	Result
1.	F.I.	♀/9 years	FI	<	-	E	I	-	+	-	alive
2.	Z.M.	♀/5 years	H&N	<	+	E	II	+	+	+	dead
3.	I.E.	♀/7 years	Extr	<	-	E	I	-	+	-	alive
4.	G.M.	♂/8 months	UG	<	-	B	I	-	+	-	alive
5.	U.A.	♀/17 years	HN	>	+	A	III	-	+	+	dead
6.	Z.S.	♂/1 year	UG	<	-	B	I	+	+	-	alive
7.	G.D.	♀/10 months	UG	>	-	E	II	-	+	-	alive

No.	Case	Sex/age	Site	T ≈ 5 cm	Lymph node	Histological subtype	IRS group	CR	CT	RT	Result
8.	B.B.	♀/4 years	BT	>	+	E	III	-	+	-	dead
9.	R.O.	♀/3 days	Extr	<	-	F	I	+	+	-	alive
10.	M.I.	♀/15 years	Extr	>	-	F	II	+	+	-	alive
11.	L.E.	♀/11 years	UG	>	-	F	III	+	+	+	dead
12.	C.C.	♂/8 years	UG	>	-	E	III	+	+	-	dead
13.	R.Y.	♂/4 months	UG	<	-	B	II	-	+	-	alive
14.	M.C.	♂/6 years	FI	<	-	F	I	+	+	-	alive
15.	M.D.	♂/1 year	UG(P)	<	-	B	II	+	+	-	alive

BT – Biliary tree; Extr – Extremities; FI – Flank; H&N – Head & neck; P – Prostate; UG – Urogenital; T – Tumor size; A – Alveolar; B – Botryoid; E – Embryonal; F – Fusiform; CR – Complete resection; CT – Chemotherapy; RT – Radiotherapy.

Surgical resection was not feasible in difficult located or extended and metastatic tumors, therefore in 10 (41.6%) cases only incisional or excisional biopsy (iterative in three cases) was achieved.

Quasi-majority (24) of our patients received chemotherapy, which started immediately after surgery or simple biopsy or as main treatment in inoperable or metastatic cases with role in primary cytoreduction as well as eradication of gross and micrometastatic disease. Because the drug treatment was closely completed in some cases by radiotherapy, the use of both methods is presented together.

We adopted the French *SIOP (International Society of Pediatric Oncology)* protocol *MMT 95-2001* depending upon the clinical stage TNM, *SIOP pTNM* and *IRS* group, histology and primary site stipulating the therapy decisions remaining unmodified over the years. Drug doses were reduced by 50% in infants under the age of six months and by 33% in infants between the ages of six and 12 months:

- Clinical stage I, post-surgical stage pT1, embryonal histology, site limb: one patient had nine weeks of V 1.5 mg/m² day 1, 8, 15, A 1.5 mg/m² day.

- Clinical stage II, post-surgical stage pT3, embryonal, urogenital tract: two patients received 27 weeks of chemotherapy IVA (I 3 mg/m² day 1, 2; V 1.5 mg/m² 1, 8, 15, A 1.5 mg/m², evaluation week 9 followed by 2×CEV: C 500 mg/m² day, E 75 mg/m² day 1–2, V 1.5 mg/m² day 1, and 1×IVE (I 3 mg/m² day 1, 2, 3, V 1.5 mg/m² day 1, E* 150 mg/m² day 1, 2, 3). Between weeks 18–23, one patient had radiotherapy of 35 Gy.

- Clinical stage II or III, any post-surgical stage with residual tumor, any local extension, alveolar or non-alveolar, any localization 13 patients had IVA–CEV–IVE nine weeks, followed by additional 18 weeks of IVA–CEV–IVE. Local radiation therapy was concurrently administered of 45 Gy, beginning by week 18 to three patients over seven years who have no achieved a complete remission by week 17. For these three patients radiotherapy was additionally followed by two protocol sequences of CVE and IVE.

- Clinical stage IV, any localization and any histology was treated with chemotherapy after biopsy. Ten patients delivered 14 weeks five courses of IVA, CEV, IVE, CEV, IVE than a evaluation was done.

Abbreviations: V – Vincristine; A – Actinomycin; I – Ifosfamide; C – Carboplatin; E – Epirubicin; E* – Etoposide.

Summarizing, the VA regimen was administered for limited intervals only in a single embryonal lesion in low disease stage and group but tumors in more advanced disease stages and groups imposed different, progressive and repeated chemotherapy schedules involving majority

of current drugs used in different combinations, even requiring radiotherapy in four cases.

Significant toxic effects was recorded only in few cases perhaps that drugs metabolism and treatment related toxicity might differ in younger patients. However, interruption and delay of scheduled chemotherapy deemed necessary.

Radiotherapy after surgery (resection or biopsy) to control local microscopic or gross residual disease was prescribed in only four patients (one in stage/group II and three in more advances cases) with unfavorable sites (two of them in head and neck), alveolar histology and huge lesions incompletely resected, the low number being also due to the reticence of radiation oncologist to perform this medical attendance in young children.

Radiotherapy generally begun at eight to 12 weeks after initiation of chemotherapy and continued for five to six weeks. The dose per fraction ranged from 150 to 200 cGy according to tumor localization, extent and nodes involving. The microscopic residual tumoral clusters had to receive at least 4000 rad but up to 5000 rad must be administered for macroscopic residual lesions or recurrences. However, the advanced tumor stages hindered a lasting beneficial effect, three of patients dying in less than one year.

Our treatment results were inferior compared to most international studies, the overall survival rate being 37.5% (nine cases alive at the time of this audit without evidence of disease and mean survival of 65.5 months). Significant favorable prognostic factors as estimated by univariate analysis were age less nine years = 0.005, histological type = 0.001, primary site = 0.02, tumor size <5 cm = 0.04, IRS stage = 0.003, complete surgery = 0.002, suitable chemotherapy = 0.003. We recorded 16 deaths (one immediately postoperatively, others at 1–10 years after surgery with tumor recurrences and/or dissemination).

Mortality in our setting is still unacceptably high, late presentation, huge volume and advanced stage of the lesion and withholding from radiotherapy being the main contributing elements.

Discussion

RMS is a complex childhood malignancy with ubiquitous anatomic sites of presentation and varying histological types, each presenting with peculiar patterns of growth, clinical behavior and prognosis. The large pediatric trials have revolutioned the care of this neoplasm, more than 70% of children with non-metastatic disease being cured using multimodality treatment [12, 17–20].

Contrasting with extensive number of publications and international scientific societies dedicated to the RMS study in USA and western Europe, there is a paucity of

reports on the pattern of these tumors occurrence, diagnosis and therapy in countries with limited resources and even in Romania [21–28].

Our study aims precisely to present the clinical and pathologic features in a random series of cases gradually better managed according to contemporary guidelines and to evaluate whether the therapeutic standards achieved in RMS in developed countries can be reproduced in our activity.

Therefore, demographic analysis show an almost equal distribution between the sexes contrasting with most studies, which generally indicates a prominent male presence. Majority of our patients were under the age of nine years (two within one month of birth), age which appeared to be a clear boundary between two phases in biologic behavior of childhood RMS. The age distribution showed two peaks at 0.1–1 year and between 4–6 years. RMS prognosis was far worse in children under one year and over nine years.

Clinical characteristics were dominated by delayed presentation with advanced stage of disease and large asymptomatic masses, numerous observations having tumor diameter larger than 5 cm. In our series, genitourinary tract was the most common affected primary site followed by extremities and head and neck. These results are different from many statistics where the most common location is the head and neck. The clinical course and prognosis was noteworthy better in localized lesions situated in favorable sites. Seven cases presented regional lymph node but nine patients have distant metastases at the initial consultation.

The embryonal RMS was the most common pathological subtype described in related series having the better clinical behavior, but together with the alveolar subtype declined with age. Pleomorphic tumors rarely described in childhood was however present in three patients all of them marked by a fast poor course with reduced survival.

Management of childhood RMS tended to a multidisciplinary risk adapted approach including surgery, chemotherapy but in much lesser extent radiation therapy, each of them having its own specific role. The indications and order that these treatments were applied depended on site, size, histological diagnosis and subtype, extent of disease (stage) and risk stratification, which relied on tumor characteristics before use and results of surgery. All tumors should be subclassified based on the histology into favorable embryonal/botryoid/spindle cell subtypes and unfavorable alveolar/pleomorphic forms.

The guiding principle of RMS surgery was complete tumor removal providing that it do not cause mutilating or cosmetic damages. The role of extensive surgery however has become less important with advances of chemo- and radiotherapy. Surgery was done in noninvasive even bulky lesions, which can be largely extirpated initially or after clinical response with chemotherapy. Operation included an en block complete resection of the primary tumor with surrounding margins of uninvolved tissue during initial procedure. In three cases an adjacent lymph node dissection was done. Also, in two embryonal RMS, re-resection of cure was indicated since neoadjuvant therapy obtained a notable lesion shrinkage allowing a second-look operations. We avoided debulking surgery, excisions of residual or recurrent disease founded after first operation or chemotherapy and amputations in extremity

RMS. In many sites biopsy was the only feasible surgical procedure, and visceral exenterations, radical cystectomies, hysterectomies/vaginectomies were considered already historical procedures.

Therefore, surgery conserved a capital prime line importance in local control and also in establishing risk stratification in order of subsequent RMS therapy.

RMS are chemosensitive lesions and most our cases received combination chemotherapy as there were ample evidence that adjuvant and neoadjuvant therapy significantly improved remissions and even survival. Its main indication was to strength the healing in conveyable operated or even those not completely resected cases but also as upfront treatment in inoperable or metastatic cases [17–21].

We started chemotherapy as soon as possible after diagnostic studies are completed and primary excision or biopsy done, as its main role was the eradication of residual local or distant tumoral foci, improving disease control and prognosis.

Our current standard frontline chemotherapy consist of vincristine and actinomycin in combination with an alkylating agent namely ifosfamide or another regimen associating IVA with carboplatin, epirubicin and vincristine and two courses of IVE, both recommended to initially I–II stages/groups, sites, embryonal and low risk lesions. In advanced cases from any site, any stage/group, any non-embryonal type, local invasion, incomplete resection or recurrences (stages II–III) as in metastatic disseminations (stage IV), repeated courses of IVA+CEV+IV Etoposide completed by radiotherapy in few cases were used. Even if few patients initially had mixed response or apparently stabilized condition, after 4–6 months irreversible progressive disease was noticed for all this cases. The possibilities of chemotherapy are actually repositioned by several new-identified target specific compounds including inhibitors for receptor tyrosine kinases intracellular signaling molecules and angiogenic factors [19–21, 28, 29].

Although radiotherapy is an indispensable component of the current therapeutic “gold” triad in childhood RMS, the method was used only in few cases from our series. Beside anatomo-clinical characteristics, this was due mainly to reluctance of our external collaborators to apply radiotherapy in children under seven years, fearful of acute toxicity spectrum or long-term effects as myelosuppression, neutropenia, hepatopathy or even a second malignancy but also to some technical difficulties.

However, radiotherapy is an essential modality of treatment for local control of RMS eradicating residual tumoral cells and excepting first-grade embryonal lesions all histological subtypes should receive it to achieve long-time disease remissions. Newer methods of delivering radiation therapy included intensity modulated and proton-beam radiotherapy and also brachytherapy maintaining efficacy but reducing long-term sequelae of this method [17, 20, 21, 25, 30, 31].

Even if most our patients achieved substantial remissions for 1–10 years, the current series registered a 5-year survival overall and 5-year event free survival of 37.5% and 33.3% respectively constituting a modest long-term outcome comparing with the results in countries entirely applying verified therapeutic guidelines.

The multiple causes of this reality are clumsy recognition of early warning features and late presentation of our patients in advanced stages associated with probably

imperfect appreciation of risk categories, together with impossibility of complete removal in many cases and inappropriate use of radiotherapy.

☒ Conclusions

RMS remains one of the most common soft tissue sarcoma in childhood characterized by a significant morphological, clinical and prognostic heterogeneity with great differences between their genetic make-up, clinical features and behavior, response to initial therapy and long-term follow-up. Over the past years delimitations of genetic and molecular changes, cellular mechanisms and pathways involved in RMS pathogenesis opened opportunities for the modern concept of multimodal treatment of these tumors including surgery, chemo- and radiotherapy. Future goals of all those who treat childhood RMS consists in continuous improvement of current therapeutic measures for reducing morbidity and increasing long-term survival together with identification of new effective approaches for advanced and metastatic cases.

Contribution of authors

DS: Conceived and drafted the study; BM: Critical review and corrections; MI: Guarantor of the entire study; ASG: Performed the surgery, corresponding author; MD: Pathology expertise, essentially involved in drafting; OC: Manuscript preparation; ML: Definition of the intellectual content.

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