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Full Length Article

Clinical significance of anaplasia in childhood rhabdomyosarcoma

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KEYWORDS

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Abstract *Background:* The presence of anaplastic features has been known to correlate with poor clinical outcome in various pediatric malignancies, including Wilms tumor and medulloblastoma but not in rhabdomyosarcoma.

Aim: Aim was to study the frequency of anaplasia at presentation in childhood rhabdomyosarcoma and its relationship to clinical and pathological characteristics as well as to outcome.

Patients and Methods: Anaplasia was retrospectively assessed in 105 consecutive pediatric rhabdomyosarcoma patients who were registered at the Children's Cancer Hospital in Egypt (CCHE) during the period from July 2007 till the end of May 2010.

Results: Anaplasia was diagnosed in 18 patients (17.1%), focal in 10 (9.5%) and diffuse in 8 (7.6%). The distribution of anaplasia was found to be more common in older patients having age $\geqslant$ 10 years. Also it was more likely to occur in the high risk group and in tumors with unfavorable histology (alveolar subtype), and stage IV. The 3-year failure free survival rates for patients with and without anaplasia were 27.8 ± 10.6% and 53.4 ± 5.8%, respectively (p = 0.014) and the 3-year overall survival rates were 35.3 ± 11.6% and 61 ± 6%, respectively (p = 0.019).

Conclusions: The frequency of anaplasia in pediatric patients with rhabdomyosarcoma in our study was 17.1%. The presence of anaplasia had statistically significant worse clinical outcome.

Introduction

Rhabdomyosarcoma (RMS) is the fourth most common pediatric solid tumor with increasing incidence, predominantly

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affecting young children. Multimodal treatment has improved survival significantly during the last decades to approximately 70% [1]. The intensity of treatment depends on the estimated relapse risk, thus treatment is risk adapted. Extent of disease, primary tumor site, clinical group and histology have been associated consistently with prognosis [2] and thus have proven useful for the development of risk-based therapy. Although the majority of patients achieve a complete remission (CR) with primary therapy, a substantial number still experience recurrences with poor prognosis [3,4]. More accurate estimation of prognosis is needed to improve patient stratification and permit further treatment tailoring according to relapse risk.

Rhabdomyosarcoma can be divided into several histologic subsets: embryonal rhabdomyosarcoma, which has embryonal, botryoid, and spindle cell subtypes; alveolar rhabdomyosarcoma; and pleomorphic rhabdomyosarcoma.

Pleomorphic rhabdomyosarcoma occurs predominantly in adults aged 30 to 50 years and is rarely seen in children [4]. In adults, pleomorphic rhabdomyosarcoma is associated with a worse prognosis. In children, the term *anaplasia* is preferred.

Anaplasia is rare in childhood rhabdomyosarcoma and has not been included in the International Classification of Rhabdomyosarcoma (ICR). A review of the Soft Tissue Sarcoma Committee of the Children's Oncology Group (COG) suggests that anaplasia might be more common than previously reported and may impact clinical outcome [5].

The degree of anaplasia was further defined not just by relative quantity but also apparent clonal expansion of the anaplastic nuclei in the tumor. Type I tumors as defined by Kodet included anaplastic cells loosely scattered among non-anaplastic cells (so called focal anaplasia), and type II tumors included those with anaplastic cells that were aggregated in clusters or formed continuous sheets. Despite the suggestion that anaplasia could significantly affect outcome, its relative rarity and lack of reproducibility on multi-reviewer studies precluded incorporation of this feature as a morphologic criteria for assessment in the International Classification of Rhabdomyosarcoma [5].

A better understanding of biologic differences and new, active agents is needed to improve outcome of patients with unfavorable features at presentation [10].

The aim of this work was to study the frequency of anaplasia at presentation in childhood rhabdomyosarcoma and its relationship to clinical and pathological characteristics as well as to outcome.

Patients and methods

One-hundred and five consecutive pediatric patients with newly diagnosed rhabdomyosarcoma who were registered at the Children's Cancer Hospital in Egypt (CCHE) during the period from July 2007 till end of May 2010 were included in this study. Their ages ranged from 2 months to 17.7 years. They included 70 males and 35 females.

All pathological materials were reviewed blindly by two pathologists for the presence of anaplasia. Cases were categorized according to the International classification of Childhood Sarcomas [6].

Anaplasia was defined as the presence of multipolar polyploid mitotic figures with marked nuclear enlargement and hyperchromasia (at least 3 times the size of neighboring nuclei). Anaplastic cells present in one or a few sharply localized regions within the primary tumor were categorized as focal anaplasia, while those that were aggregated in clusters or formed continuous sheets were considered as diffuse anaplasia [7].

The presence or absence of anaplasia (diffuse or focal) was correlated with clinical and pathological variables including age, sex, primary tumor site, histologic subtype, IRS clinical group, stage, tumor size, tumor invasiveness and nodal status as well as to clinical outcome.

Staging and classifications

Tumors were classified according to the Intergroup Rhabdomyosarcoma Study (IRS) pretreatment TNM staging [8] and grouping system [9]. Imaging and surgery determined the extent of disease for assignment of IRS Stage and Group, respectively. Tumors were categorized according to sites of origin into favorable sites (orbit, non-parameningeal head and neck, genitourinary other than bladder and prostate) or unfavorable (extremity, bladder, prostate, parameningeal sites, retroperitoneum, trunk, other). Histology was determined as embryonal (including spindle cell and botryoid subtypes), and non-embryonal histology that included alveolar subtype and undifferentiated.

Therapy

Patients were treated with risk adapted combined modality treatment including surgery, multiagent chemotherapy and/or radiotherapy.

Therapy was assigned based on the IRSG rhabdomyosarcoma risk group classification [10,11]. Patients were classified according to the stage, clinical group and histological subtype into:

a. **Low risk group**: Included patients with embryonal RMS or botryoid who had:
   - Non-metastatic tumors arising in favorable sites (stage1), clinical group I, II, or III.
   - Non-metastatic tumors in unfavorable sites (stage 2 or 3) that are grossly resected with or without microscopic residual (clinical group I or II).
b. **Intermediate risk group**: Included patients with:
   - Embryonal RMS or botryoid who had stage 2 or 3 and clinical group III.
   - Alveolar RMS who had stage 1, 2, or 3 and clinical group I, II, or III.
   - Non metastatic Parameningeal primary site regardless of the histology who had clinical group I, II, or III.
c. **High risk group**: Included all metastatic patients with stage 4.

Chemotherapy

Treatment protocol is summarized in Table 1.

Local therapy

A delayed surgery if possible was performed for patients with clinical group III disease on week 12. No radiotherapy was

Table 1 Chemotherapy protocol of the studied Rhabdomyosarcoma patients.

a. Low risk group

Weeks	1	2	3	4	5	6	7	8	9	10	11	12	13
	VAC	V	V	VAC	V	V	VAC	V	V	AC	**	**	VA
Weeks	14	15	16	17	18	19	20	21	22	23	24	25	26
	V	V	VA	V	V	VA	V	V	A	**	**	VA	V
Weeks	27	28	29	30	31	32	33	34	35	36	37	38	39
	V	VA	V	V	VA	V	V	A	**	**	VA	V	V
Weeks	40	41	42	43	44	45	46	47					
	VA	V	V	VA	V	V	VA	**					

Vincristine (V): 1.5 mg/m^2 (max. 2 mg) IV push.
Actinomycin (A): 0.045 mg/kg (max. 2.5 mg) IV push.
Cyclophosphamide (C): 1.2 gm/m^2 IV infusion over 60 min with hydration and MESNA.
**No chemotherapy and the time of re-evaluation (at weeks 12, 24, 36 and 47 end of therapy).

b. Intermediate and High risk group

Weeks	0	1	2	3	4	5	6	7	8	9	10	11	12
	VAC	V	V	VAC	V	V	VAC	V	V	VAC	V	V	VAC**
Weeks	13	14	15	16	17	18	19	20	21	22	23	24	25
	–	–	VC	–	–	VC	V	V	V	VAC	V	V**	VAC
Weeks	26	27	28	29	30	31	32	33	34	35	36	37	40
	V	V	VAC	–	–	VAC	V	V	VAC	V	V	VAC	**

Vincristine (V): 1.5 mg/m^2 IV push.
Actinomycin (A): 1.35 mg/m^2 IV push.
Cyclophosphamide (C): 1.5 mg/m^2 at weeks 0 and 3 to be increased to 1.8 gm/m^2 if tolerated, given IV infusion over 2 h with MESNA and fluids.
** Time of re-evaluation (at weeks 12, 24, and 40 end of therapy).

given in non-metastatic embryonal tumors with clinical group I. All other patients received radiotherapy following week 12 except in cases of parameningeal sites with criteria of meningeal extension, where radiotherapy was given on day 0.

The gross tumor volume (GTV) was defined as the pre-treatment visible and for palpable disease detected by physical examination, operative findings, CT or MRI including any involved lymph nodes. For all clinical groups, the clinical target volume (CTV) was defined by adding one cm safety margin to GTV. Those who have clinical group III disease who do not undergo a second look operation may have a second CTV defined for a core down boost. The planning tumor volume (PTV) is created by adding safety margins that deal with the setup position uncertainties. Clinical group II (stage I and II) without nodal involvement received 36 Gy, while those with nodal involvement (N1) received 41.4 Gy. Clinical group III received 45 Gy if in the orbit and 50.4 Gy in non-orbit sites. Patients received radiotherapy to metastatic sites which can be localized and imaged (i.e. excluding the bone marrow).

Clinical outcome

Based on previously published data correlating tridimensional measurements to bi-directional and unidirectional measurements the following response criteria for the primary tumor will be used:

Complete Response (CR): Complete disappearance of the tumor confirmed at >4 weeks.

Partial Response (PR): At least 64% decrease in volume compared to the baseline.

Progressive Disease (PD): At least 40% increase in tumor volume compared to the smallest measurement obtained since the beginning of therapy.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest disease measurement since the treatment started.

Statistical analysis

Patients' data were tabulated and processed using (SPSS) statistical package (16) for Windows [12]. Qualitative data were expressed as frequency and percentage, while quantitative data were expressed as mean $\pm$ SD and median. The chi-square test and Fisher Exact test were used for comparative analysis. Statistically significant level was considered at $p \leqslant 0.05$.

Survival estimates were calculated using the Kaplan–Meier method and the standard error of the life-table estimates was calculated with Greenwood formula. Patients without adverse events were censored on the date of the last reported contact. The differences between curves were tested for statistical significance using the log rank test [13].

Failure-free survival (FFS)

Failure-free survival (FFS) was defined as the time from the start of treatment to disease progression, recurrence, or death as a first event.

Overall survival (OS)

Overall survival (OS) was defined as the time from the start of treatment to death whatever the cause is.

Results

Patient characteristics

The study included 105 newly diagnosed consecutive RMS recruited from July 2007 till the end of May 2010. The median age of diagnosis was 3.6 years (range 2 months–17.7 years) mean 4.98 ± 4.1. The male to female ratio was 2:1. Fifteen patients (14.3%) presented with an age ⩽ 1 year, 72 (68.6%) between 1 and 10 years, and 18 (17.1%) ⩾ 10 years. The follow up period ranged 25–66 months with a median of 47.5 months.

Tumor characteristics

The primary site location was favorable in 34 (32.4%) and unfavorable in 71patients (67.6%). The histological subtype was embryonal in 88 (83.8%) [sarcoma botryoides in 9 (8.6%) and spindle cell in 20 (19%)], and alveolar in 17 (16.2%) of the tumors.

Anaplasia was diagnosed in 18 patients (17.1%), focal in 10 (9.5%) and diffuse in 8 (7.6%). Twelve patients had embryonal subtype and six patients were classified as alveolar. Fig. 1 shows an embryonal rhabdomyosarcoma with diffuse anaplasia (Hx and E stain).

The tumor size was Ta in 34 (32.4%), Tb in 63 (60%), and unknown in 8 (7.6%), while the tumor extension was T1 in 38 (36.2%), T2 in 59 (56.2%) and unknown in 8 (7.6%). Regional nodal metastasis (N1) occurred in 36 (34.3%), while distant metastasis (M1) in 18 patients (17.1%). IRSG stage distribution was found to be: Stage 1 in 28 (26.7%), Stage 2 in 15 (14.3%), Stage 3 in 44 (41.9%) and Stage 4 in 18 (17.1%). Clinical group classification was I in 9 (8.6%), II in 4 (3.8%), III in 74 (70.5%) and IV in 18 (17.1%). Twenty patients (19%) were categorized as low risk, 67 (63.8%) as intermediate risk, and 18 (17.1%) as high risk. For the 18 patients who initially presented with distant metastasis, the sites of spread were pulmonary in six, bone in three, bone marrow combined with bone in two, pulmonary combined with bone, distant nodes or bone marrow in seven patients.

Outcome

Thirty-one patients had progressive disease, two were refractory and 17 patients died of toxicity. Seven patients lost follow up in CR and 48 patients were alive in continuous complete remission. The 3-year FFS was 48.6 ± 5.3%, while the 3-year OS was 56.1 ± 5.6% (Fig. 2).

Relation of anaplasia to outcome

Of the eighteen patients having tumors showing anaplasia, six (33.3%) were alive in CR, while 2 (11.1%) were refractory, 7 (38.9%) had progressive disease and 3 (16.7%) died of sepsis (Table 2).

There was a statistically significant association between the presence of anaplasia and clinical outcome ($p = 0.003$). The 3-year FFS rates for patients with and without anaplasia were 27.8 ± 10.6% and 53.4 ± 5.8%, respectively ($p = 0.014$) and the 3-year overall survival rates were 35.3 ± 11.6% and 61 ± 6%, respectively ($p = 0.019$) (Fig. 3).

Relation of anaplasia to clinical and pathological variables

The presence or absence of anaplasia was correlated to age, sex, primary tumor site, histologic subtype, IRS clinical group, stage, tumor size, tumor invasiveness, lymph node involvement and risk groups (Table 3).

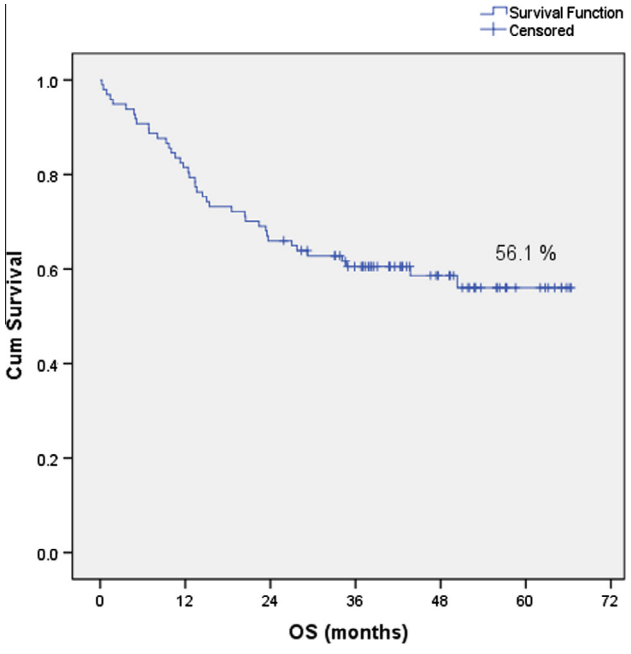

Figure 1 Embryonalrhabdomyosarcoma showing diffuse anaplasia: enlarged nuclei, prominent nucleoli and abnormal mitoses (arrows); Hx& E stain (100×).

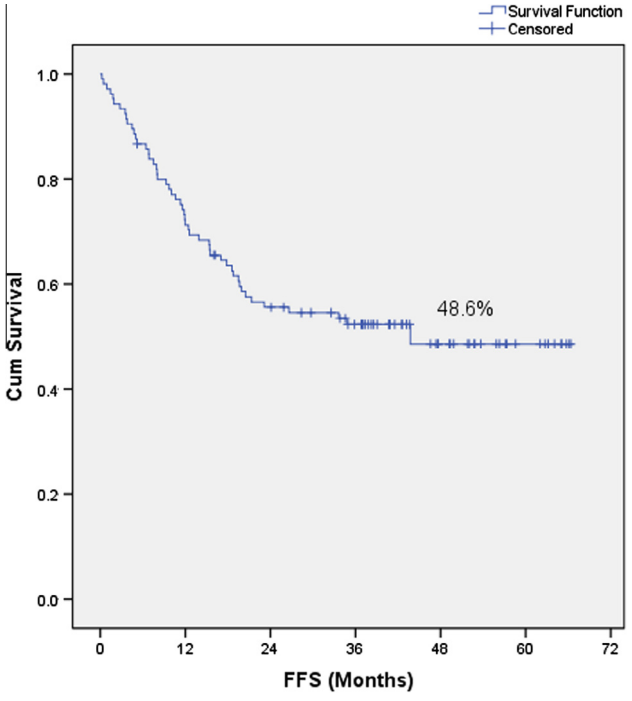

Figure 2 Failure free survival and overall survival of the studied rhabdomyosarcoma patients.

Table 2 Relation of anaplasia to outcome.

Anaplasia status	Alive in CR	NR	PD	Died of sepsis	*p*-value
Anaplasia ($n = 18$)	6 (33.3%)	2 (11.1%)	7 (38.9%)	3 (16.7%)	0.003
No anaplasia ($n = 87$)	60 (69%)	0	24 (27.6%)	3 (3.4%)	

Anaplasia was more likely to occur in older patients having age $\geqslant$ 10 years, in high risk group and in tumors with unfavorable histology (non-embryonal), and stage IV. However, these differences were statistically not significant.

Relation of anaplasia to surgical respectability

Of the eighteen patients with anaplasia, 3 (16.6%) patients had upfront surgery but with gross residual (R2) and 3 (16.6%) patients had delayed surgery at the time of local control (one complete resection R0, one microscopic residual R1 & one gross residual R2).

On the other hand, 20/87 (23%) patients without anaplasia had upfront surgery (9 R0, 5 R1, 6 R2), while 15 (17%) patients had delayed surgery at time of local control (10 R0, 3 R1 and 2 R2). Surgical resection with gross or microscopic residual was followed by radiotherapy.

Discussion

The presence of anaplastic features such as increased nuclear size, marked cytological pleomorphism, numerous mitoses, and apoptotic bodies has been known to correlate with poor clinical outcome in various pediatric malignancies, including Wilms tumor [14,15] and medulloblastoma [16,17].

Palmer first noted that the anaplastic cellular pattern he originally described with Beckwith in Wilms tumor was also present in rhabdomyosarcoma and that this subtype carried a similarly poor prognosis [5]. Few studies suggested that anaplasia in RMS could significantly affect outcome, however, it has not been included in the International Classification of Rhabdomyosarcoma (ICR) due to its apparent relative rarity.

Kodet et al. identified anaplastic cells in 3% among cases of rhabdomyosarcoma patients registered in the first 3 Intergroup Rhabdomyosarcoma Studies (IRS I-III) [18]. In a study by Qualman et al. (2008) [5], the soft tissue sarcoma committee of the Children's Oncology Group reported a significantly higher prevalence of focal or diffuse anaplasia in childhood rhabdomyosarcoma than previously reported in other studies. Anaplasia was noted in 13% of pathologic specimens of childhood rhabdomyosarcoma, focal in 7% and diffuse in 6%. In our study, anaplasia was diagnosed in 17.1% of the patients, focal in 9.5% and diffuse in 7.6%.

Furthermore, Qualman et al. observed that patients with anaplasia were more likely to have tumors in favorable sites, group IV disease, and tumor size of >5 cm. Anaplasia was less commonly observed in younger patients and in those with stage II, III, or clinical group III disease [5]. Similarly in this study, the distribution of anaplasia was found to be more common in older patients having age $\geqslant$ 10 years. Also it was more likely to occur in the high risk group and in tumors with unfavorable histology (alveolar subtype), and stage IV.

Anaplastic histology is the single most important histologic predictor of response and survival in patients with Wilms tumor. It is most consistently associated with poor prognosis

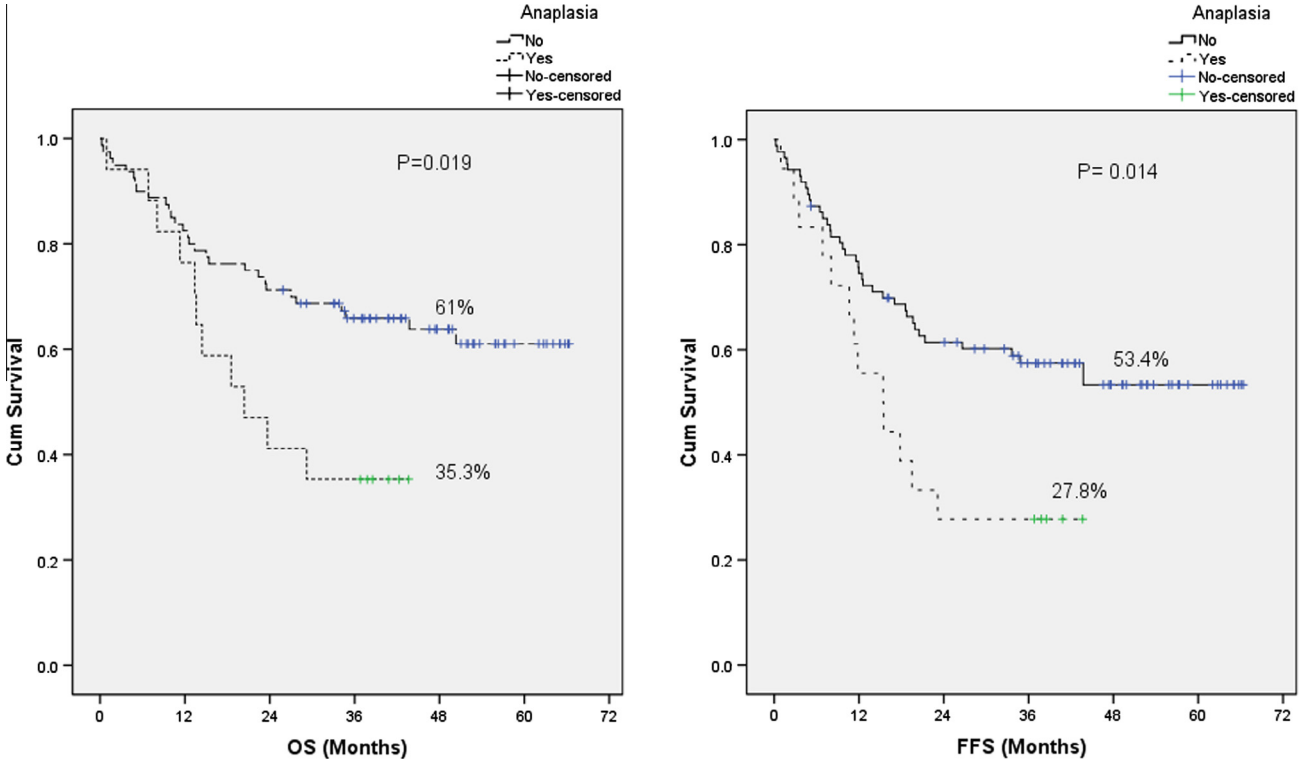

Figure 3 Failure free survival and overall survival in relation to the presence of anaplasia.

Table 3 Clinical and pathological features in relation to the presence or absence of diffuse or focal anaplasia.

	Anaplasia		*p*-value
	None ($n = 87$)	Anaplasia ($n = 18$)	
Age, years			0.09
⩽1 year	14 (16.1%)	1 (5.6%)	
>1 and <10 years	61 (70.1%)	11 (61.1%)	
⩾10 years	12 (13.8%)	6 (33.3%)	
Sex			1
Male	58 (66.7%)	12 (66.6%)	
Female	29 (33.3%)	6 (33.3%)	
Clinical group			0.14
I	9 (10.4%)	0	
II	4 (4.6%)	0	
III	62 (71.3%)	12 (66.6%)	
IV	12 (13.8%)	6 (33.3%)	
Stage			0.18
1	25 (28.7%)	3 (16.7%)	
2	14 (16.1%)	1 (5.6%)	
3	36 (41.4%)	8 (44.4%)	
4	12 (13.8%)	6 (33.3%)	
Primary site			0.28
Favorable	25 (28.7%)	7 (38.9%)	
Unfavorable	62 (71.3%)	11 (61.1%)	
Histology			0.04
Embryonal	76 (87.4%)	12 (66.6%)	
Non Embryonal	11 (12.6%)	6 (33.3%)	
Tumor invasiveness			0.8
T1	30 (34.5%)	8 (44.4%)	
T2	50 (57.5%)	9 (50%)	
Unknown	7 (8%)	1 (5.6%)	
Lymph node involvement			0.27
N0	45 (51.7%)	8 (44.4%)	
N1	27 (31%)	9 (50%)	
Unknown	15 (17.2%)	1 (5.6%)	
Tumor size, cm			0.77
⩽5	28 (32.2%)	6 (33.3%)	
>5	53 (60.9%)	10 (55.6%)	
Unknown	6 (6.9%)	2 (11.1%)	
Risk			0.08
Low	19 (21.8%)	1 (5.6%)	
Intermediate	56 (64.4%)	11 (61.1%)	
High	12 (13.8%)	6 (33.3%)	

when it is diffusely distributed and when identified at advanced stages. Focal anaplasia does not confer a poor prognosis, while diffuse anaplasia does [15,19]. In medulloblastomas, a study by the United Kingdom Children's Cancer Study Group demonstrated that children with anaplastic variant had significant worse event free survival than children with classic medulloblastomas [20]. On the other hand, another study reported that the group of patients with either moderate or severely anaplastic medulloblastomas showed only a trend toward shorter survival ($p = 0.11$), while severe anaplasia alone had significant worse clinical outcome ($p = 0.002$) [21].

As regards rhabdomyosarcoma, Kodet et al. reported that rhabdomyosarcoma patients with diffuse anaplasia had a worse clinical outcome [18]. In contrast, Qualman et al. reported that the presence of anaplasia regardless of its distribution (focal or diffuse), negatively influenced the failure-free survival rate on univariate analysis (63% vs 77% at 5 years) and overall survival (68% vs 82% at 5 years) rates in patients with embryonal rhabdomyosarcoma [5].

In this study, the presence of anaplasia had statistically significant negative impact on the 3-year FFS and OS rates being 27.8 ± 10.6% and 35.3 ± 11.6%, respectively *vs.* 53.4 ± 5.8%, and 61 ± 6%, for patients without anaplasia, respectively. The effect of diffuse versus focal anaplasia on survival cannot be assessed due to small number of patients in each group, however, percentage of patients with refractory and progressive disease were equal in both groups (4/8 and 5/10 patients with diffuse and focal anaplasia, respectively).

In conclusion, the current study demonstrated that anaplasia was present in 17.1% of the patients. Anaplasia was found in 6 (33%) of cases above 10 years, 6 (33%) cases were high risk, and 6 (33%) cases were of non-embryonal histology. Despite that most of correlations to anaplasia were found to be insignificant, it was found to be significant when correlated to survival.

Based on the small number of patients included in our study, further studies are needed to assess whether anaplasia is an independent prognostic factor in pediatric patients with rhabdomyosarcoma or not.

Disclosure

None.

Conflict of interest

None declared.

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