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Congenital Spindle Cell Rhabdomyosarcoma: An International Cooperative Analysis

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The corresponding author is responsible for ensuring that the descriptions are accurate and agreed by all authors.

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Abstract

Background—Spindle cell rhabdomyosarcoma (RMS) is a rare variant of RMS accounting for up to 10% of cases in infants. In older children and adults, spindle cell RMS is associated with *MYOD1* mutations and a poor prognosis. In infants, it is associated with recurring fusions involving *NCOA2* and *VGLL2.* Reports in the literature suggest a favorable prognosis for this subset, however, little is known about treatment and outcome data of infants with spindle cell RMS.

Methods—Characteristics, treatment, and outcome of an international cohort of 40 patients aged ≤12 months with spindle cell RMS treated from 1997–2018 were evaluated.

Results—Localized disease (LD) was diagnosed in 39 patients. The median age at diagnosis was 2.5 months (range 0–12 months). Expert pathologic review confirmed the diagnosis of spindle cell RMS in all patients. Among 26 tumors that had molecular evaluation, 13 had rearrangements of *NCOA* and/or *VGLL*. Multimodal treatment of infants with LD included conventional (age adjusted) chemotherapy (n=37), resection (n=31) and radiotherapy (RT) (n=5, brachytherapy in 3). Complete remission was achieved in 37/39 patients. Progressive disease occurred in two infants, relapsed disease in three. Microscopically complete surgical resection was associated with 5-year event-free survival (EFS) and overall survival (OS) of 100%. Two patients with tumors ≤ 5cm were treated with microscopically complete resection only and were alive 1 and 4.2 years after diagnosis. The 5-year EFS and OS for infants with LD were 86 % (±11; CI 95%) and 91% (±9;

CI 95%), respectively. One patient had metastatic disease (*NCOA* fusion positive) with primary tumor in head and neck and brain metastases. This patient died despite chemotherapy and delayed resection of the primary tumor due to respiratory failure secondary to cytomegalovirus infection 1.2 years after diagnosis.

Conclusion—Infants with spindle cell RMS have an excellent prognosis. Multimodal treatment including microscopically complete resection of the tumor is strongly recommended.

Table of contents:

The treatment and outcome of 39 infant patients with localized spindle cell rhabdomyosarcoma and a single patient with metastatic disease enrolled in international trials and registries (1997–2018) were analyzed.

Keywords

spindle cell rhabdomyosarcoma; NCOA; VGLL; infants; localized disease

INTRODUCTION:

Although the majority of rhabdomyosarcoma (RMS) is diagnosed in children under 6 years, the disease is uncommon in infants[1]. Historically, age ≤ 12 months has been reported as a poor prognostic factor [2, 3], in part because of high rates of local failure due to the difficulty in delivering aggressive local treatment, especially radiotherapy, in such young children[2, 4, 5]. More recent studies, however, have not shown this discrepancy in outcomes for infants, with infants demonstrating either no difference or improved overall survival (OS) compared to children 12–36 months [5, 6]. Spindle cell and sclerosing RMS is a rare variant which accounts for between 5 to 10% of all RMS. In infants, spindle cell RMS accounts for 10% of RMS cases [6]). In older children and adults, spindle cell and sclerosing RMS may be associated with *MYOD1* mutations and a poor prognosis[7, 8]. In contrast, infantile spindle cell RMS has been associated with recurring fusions involving *VGLL2* or *NCOA2*[9]. The majority of cases reported in the literature suggest that molecularly defined spindle cell RMS in infants may be a biologically distinct entity with a favorable prognosis and may not require the aggressive multimodal treatment used for other subtypes of RMS, with behavior more closely reminiscent of ETV6-NTRK3-positive infantile fibrosarcomas [9–11]. However, a recent publication described 4 infants with unresectable tumors harboring *VGLL* fusions with poor outcomes, calling into question the previous suggestion of favorable outcome[12]. We sought to describe the clinical characteristics, outcomes and prognostic factors of an international cohort of infants diagnosed with spindle cell RMS between 1997–2018.

METHODS:

Patients aged ≤12 months at the time of diagnosis of spindle cell RMS were identified from the Children's Oncology Group (COG), Cooperative Weichteilsarkom Studiengruppe (CWS), European paediatric Soft tissue sarcoma Study Group (EpSSG) and Italian Soft tissue Sarcoma Committee (STSC), clinical trial and registry databases as well as the Texas

Children's Hospital (TCH) pathology archives. Patients diagnosed between 1997 and 2018 were included. Guardians of patients who were enrolled in cooperative group clinical trials or registries had previously consented to data collection and retrospective chart review was performed per the requirements of the declaration of Helsinki and in accordance with the regulations of the respective ethical committee. Expert pathology review was performed either by the treating center or by central review for those enrolled on clinical trials. Gene fusions involving *VGLL2* and *NCOA2* were analyzed by fluorescence in situ hybridization (FISH) or reverse transcription polymerase chain reaction (RT)-PCR[10]. Fusion data were not available for all cases.

Definition of terms:

Initial staging procedures and assessment included imaging of the primary tumour and metastases by magnetic resonance imaging (MRI) or computed tomography (CT) with additional recommendation for whole body imaging with radionuclide bone scan or ^{18}F-fluorodeoxyglucose positron emission tomography, and bone marrow aspirate/biopsy dependent on the extent of the primary tumor. The TNM classification was used and differentiated pre-treatment TNM and postsurgical TNM stages [13–15]. The clinical grouping system adapted from the International Rhabdomyosarcoma Study Group (IRS) was used [16, 17]. Margins were defined at the time of pathological assessment. Resection was classified as microscopically complete (R0), microscopically incomplete (R1) and macroscopically incomplete (R2). Delayed surgical resection was defined as occurring after initiation of chemotherapy. "Extent of resection" was defined as the best surgical result in the sum of surgeries performed in an individual during primary treatment. Response was assessed after 3–4 courses of chemotherapy: Complete response (CR), partial response (PR), and stable disease (SD). Progressive disease (PD) as first event was defined as any increase in tumor volume in patients who did not achieve CR[18]. Response was not assessable after up front R0/R1 resection. "Best response" was the most available data on response without standardized timepoint after start chemotherapy. The interval between pathologic diagnosis and detection of relapse or progression was defined as time to event.

Statistical Methods:

Statistics were calculated using Statistica® version 6 (Statsoft) and IBM SPSS® 27 (Armonk, New York, U.S.). Graphs were created using R version 3.5.1. Overall survival (OS) and event-free survival (EFS), as well as post-relapse OS and EFS were calculated using the Kaplan-Meier estimator and confidence intervals (CI) stated at the 95% level [19]. For OS the time from diagnosis to death, either from therapy, disease, other reasons or last follow-up was calculated. For EFS the time from diagnosis to progression (any evidence of growth of a tumor which was not in clinical CR), first recurrence after CR, last follow-up, or death, was calculated. If there was no event the survival data was censored at last follow-up. For comparison of EFS levels the log-rank test was used in univariate analyses. P-values presented are not adjusted for multiplicity.

Treatment:

Patients were treated with a combination of therapies including chemotherapy, surgical resection, and radiation therapy (RT) according to their IRS stage and group. Therapy

was determined either by the clinical trial of enrolment or at the discretion of the treating physician for those not enrolled on treatment studies. The initial chemotherapy combinations always included vincristine and dactinomycin (VA), often in combination with cyclophosphamide or ifosfamide (VAC/IVA) or doxorubicin (VAIA). Some patients also received maintenance chemotherapy with cyclophosphamide and vinorelbine[20]. Every protocol recommended that infants ≤12 months should receive dose reduced chemotherapy due to patient age and weight [21]. Resection was performed if a non-mutilating procedure was reasonable. RT was left to the discretion of the treating center.

RESULTS

Patients Characteristics and Demography

Since 1997, 39 patients with localised spindle cell RMS fulfilled the inclusion criteria to be eligible for the analysis. In addition, one patient with metastatic disease was identified. This patient was excluded from the overall analysis but is described below. Patientś characteristics are given in Tables 1 and 2. Median age at initial diagnosis was 2.5 months (0–12 months). The median follow up time was 5.3 years (0.6–12 years), the median overall EFS was 4.8 years (0.1–14.2 years) as of the data cut-off of December 2020. Among 26 tumors that had molecular evaluation, 13 (50%) contained a molecular rearrangement of *VGLL2* or *NCOA2* (Table 2).

Patients with localized disease

Thirty-nine patients had localized disease: IRS I (n=12), IRS II (n=6) and IRS III (n=20); n.a. (n=1). Thirty patients were ≤ 6 months old at diagnosis, with 22 of them <3 months. Data for primary tumor size, chemotherapy regimens and response to chemotherapy are given in Table 1. One infant had regional lymph node involvement (primary in the extremity without molecular rearrangement). In 2 patients, no chemotherapy was given at the discretion of the treating center or parental refusal. Both patients achieved CR after upfront R0 resection (localisation was paratesticular and trunk, both less than 5 cm). Both are alive in CR 4.2 and 1 year after diagnosis. After initial chemotherapy, delayed primary resection was performed in 17 patients with IRS III disease. The extent of resections resulted in R0 (n=17, 44%), R1 (n=14, 36%) or R2 (n=6, 15%). RT was used in 5/39 patients, all of whom had IRS III disease and delayed resection resulted in a positive margin: R1 margin in 4 patients and R2 in 1 patient. Overall, 38/39 patients achieved CR, including 5/6 patients after R2 resection (one patient received additionally RT after R2 resection). Thirty-five patients had no relapse (92% of patients in CR) and 36 were alive in clinical remission at last follow up. One patient died of progressive disease despite chemotherapy after R2 resection and two of recurrent disease (one patient with N1 disease died from metastatic relapse, and one patient died with unknown site of recurrence). Of the three patients who died from disease, no molecular rearrangement could be found (n=2) or was not tested (n=1). The 5-year EFS was 86 % (±11; CI 95%), the 5-year OS was 91% (±9; CI 95%) (Figure 1).

Patient with primary metastatic disease

Only one patient with IRS group IV metastatic disease at diagnosis was identified. The patient was 1.2 months old at diagnosis and had a primary tumor located in the skull base measuring more than 5 cm, with metastatic disease in the brain. The tumor was found to have a *NCOA2* fusion by FISH (fusion partner unknown). The patient was treated with chemotherapy (regimen unknown) and underwent a delayed R2 resection of the primary tumor. RT was not administered. Partial response was achieved, but the patient died from respiratory failure due to cytomegalovirus pneumonitis 1.2 years after diagnosis which was 3 months after completion of therapy.

Univariate Analysis and Prognostic Factors:

The 39 patients with localized disease were included in the univariate analysis. Patients with either a *VGLL2* and/or *NCOA2* fusion had a 5 year EFS of 90% (±19; CI 95%) and OS of 100%, while those with no detected fusion had 5 year EFS 75% (±25; CI 95%) and OS of 82% (±23; CI 95%). The presence of the *VGLL2* and/or *NCOA2* fusion was not a statistically significant prognostic factor (Figure 2). Extent of surgical resection R0 and R1 were statistically significant favorable prognostic factors for the 5-year EFS of localized spindle cell RMS patients diagnosed in infancy (Figure 3, Table 1). Use of RT was not a statistically significant prognostic factor, and no difference between the different chemotherapy regimens was detected (Table 1).

DISCUSSION:

Localized RMS diagnosed in the first year of life has high rates of relapse with 5-year failure free survival (FFS) rates ranging from 42% to 72% in reports from various international cooperative groups [2–4, 6, 21, 22]. The 5 year OS for RMS in children less than a year old ranges from 61–88% [2, 4, 21, 22], with more recent studies suggesting that OS in this age range is no be worse than older children[5, 6]. Within our international cohort the 5-year EFS and OS for infants with localized spindle cell RMS were 86% and 91%, respectively, suggesting a favorable outcome for infants with spindle cell RMS, with lower rates of relapse and possibly death than combined histologic subtypes of infantile RMS. As previously reported, these tumors are frequently found in axial locations, and are almost always localized at presentation. Extent of resection was one prognostic factor resulting from univariate analysis, which has not been previously described [4]. Interestingly, while patients who had gross disease left behind surgically (R2 resection) had inferior EFS, no significant difference in OS could be shown. The small sample size limits the statistical power to show such an effect, especially considering that IRS III patients may have received additional intervention (resulting in microscopical complete resection) attenuating the impact on OS. We emphasize that from a statistical perspective a non-significant result in this small and exploratory study does not constitute proof that no relevant difference may exist between the examined groups [23].

Very few patients in our cohort received RT, and there was no statistically significant difference in outcomes based on the use of RT. RT in infants may lead to significant growth impairment, and is therefore generally avoided in this age group. Our data suggests the

majority of these patients can be cured without RT. Chemotherapy regimens varied widely with respect to specific agents used as well as doses of agents including cyclophosphamide. Overall, the common VA(C) regimen was used in most patients. Note that not only the very limited number of patients prevent us from making any strong scientific conclusions about the therapy, but that also a selection bias may influence results here, given that the choice of therapy may in general be related to the clinical presentation. However, the overall good prognosis for those who received VAC or IVA suggests that these additional therapies may not be necessary for these patients, underlying the importance of microscopically complete resection: Two patients with tumors <5cm and microscopically complete resections did not receive chemotherapy. Even omission of chemotherapy might be an option in patients with these small tumors and R0 resection. However, numbers of patients treated with resection only are limited not allowing us to draw conclusions.

The subset of spindle cell RMS in infants with fusions involving *VGLL2* or *NCOA2* have previously been reported to have a favorable prognosis [10, 11], although a recent report of four infants with unresectable *VGLL2* rearranged RMS who experienced local progression, metastatic disease, and 2 deaths from disease questioned these findings [12]. In that report, at initial diagnosis, 3 tumors were diagnosed as fibromatosis or infantile fibrosarcoma and initially managed as such, while 1 was a high-grade sarcoma. At relapse, 3 tumors showed high-grade morphology, while 1 retained a low-grade phenotype. These cases imply the importance of initial expert pathologic diagnosis, complete surgical resection, and suggest that RMS-type chemotherapy should be considered for unresectable low-grade tumors harboring these rearrangements, given the risk of high-grade transformation [12]. While our cohort did not demonstrate a significant difference in survival for those with *VGLL2* or *NCOA2* fusions, it is notable that no patients with a fusion died of their disease, though the one patient with metastatic disease and *NCOA2* fusion died of infection. The ability to draw conclusions specific to *NCOA2* or *VGLL2* fusion status is limited given the information was only available for half of the cohort due to lack of suitable banked tissues for analysis in the others. Additionally, within those for whom tissue was available for testing, we identified a *VGLL2* or *NCOA2* containing fusion in less than 60%. It is possible that the use of FISH limited our ability to detect these fusions and that next generation sequencing methods may detect other fusions analogous to the known *VGLL2* and *NCOA2* containing fusions. Larger studies with comprehensive molecular analysis will be needed to truly define the incidence and prognostic implications of *VGLL2* and *NCOA2* fusions.

In addition to the lack of *NCOA2* and *VGLL2* fusion testing in half of our cohort, our study is also limited by its lack of complete genomic assessment of tumors including *HRAS* mutations which are frequently detected in *FOXO1* fusion negative infantile RMS[24], or presence of *MYOD1* mutations which are exceedingly rare in infants, but are associated with spindle cell RMS in older children and adults and carry important prognostic implications[24]. Knowledge about these and other genomic alterations would provide important contextual information related to prognosis in the patients with tumors lacking *NCOA2* or *VGLL2* fusions. In addition, the size of our study, potential selection bias, and a lack of complete treatment information for all patients made conclusions about best treatments for these patients difficult to determine. Nonetheless, this is the largest study of infants with spindle cell RMS and we internationally propose common first line treatment

recommendations: R0 resection (if feasible without mutilation) and systemic treatment with risk-adapted therapy using the VA (or VAC/IVA) regimen; if no R0 resection seems feasible, start with VAC (IVA) with the aim of secondary microscopically complete resection (Figure 4). Anthracyclines and external beam RT can be avoided in the majority of patients. Further international studies are needed to answer the question if further reduction of treatment might be possible as reducing the cumulative dose of alkylating agents in this age after microscopically complete resection. Continued international collaboration and a prospective molecular analysis of spindle cell RMS is undoubtedly needed to further investigate a common treatment approach in this subgroup of patients.

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Abbreviations

AIEOP	Associazione Italiana di Ematologia e Oncologia Pediatrica
CEVAIE	Carboplatin, epirubicin, vincristine, actinomycin-D, ifosfamide, etoposide
CI	confidence interval
CHT	chemotherapy
COG	Children's Oncology Group
CR	complete remission
CWS	Cooperative Weichteilsarkom Studiengruppe
EFS	event free survival
EpSSG	European Pediatric Soft Tissue Sarcoma Study Group
EVAIA	etoposide, vincristine, actinomycin-D, ifosfamide, doxorubicine
IRS	international rhabdomyosarcoma study group
LD	localized disease

MD	metastatic disease
mPR	minor partial response
MRI	magnetic resonance imaging
OS	overall survival
PFS	progression free survival
PD	progressive disease
PR	partial response
RD	relapsed disease
RMA	alveolar rhabdomyosarcoma
RME	embryonal rhabdomyosarcoma
RMS	habdomyosarcoma
AIEOP STSC	AIEOP Soft Tissue Sarcoma Committee
SD	stable disease
TNM	Tumor-node-metastasis
UICC	Union internationale contre le cancer
VAC	vincristine, actinomycin-D, cyclophosphamide
VACA	vincristine, actinomycin-D, cyclophosphamide, doxorubicine
VAIA	vincristine, actinomycin-D, ifosfamide, doxorubicine

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Highlights:

- international cohort of 40 patients aged ≤12 months with spindle cell rhabdomyosarcoma
- Characteristics, treatment, and outcome analyzed in 39 patients with localized disease
- Among 26 tumors that had molecular evaluation, 13 had rearrangements of *NCOA2* and/or *VGLL2*
- The 5-year EFS and OS for infants with localized disease were 86% and 91%, respectively.

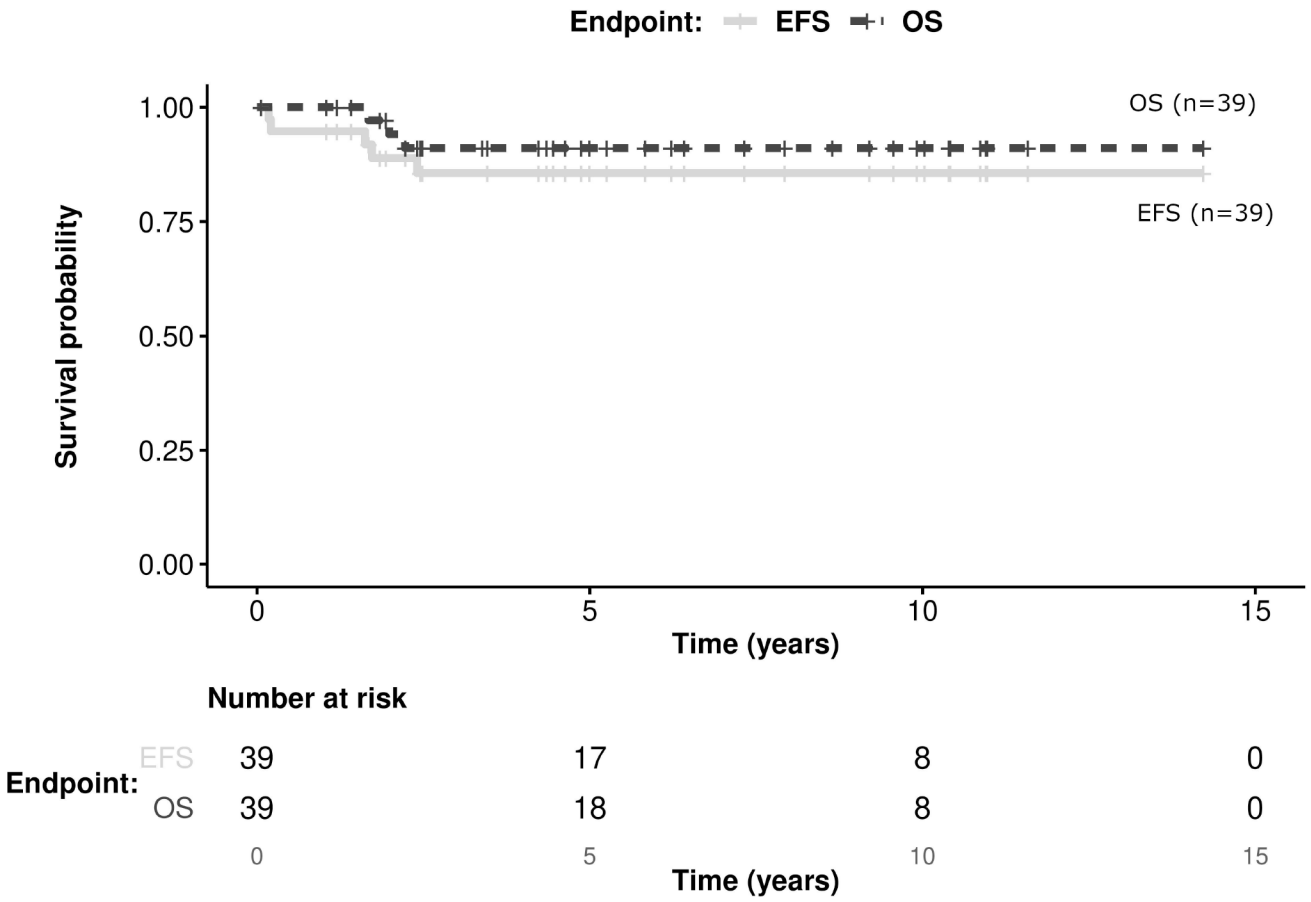

FIGURE 1.
Kaplan-Meier estimates presenting EFS and OS of 39 patients with localized disease. Total number of events: 5 in EFS, 3 in OS.

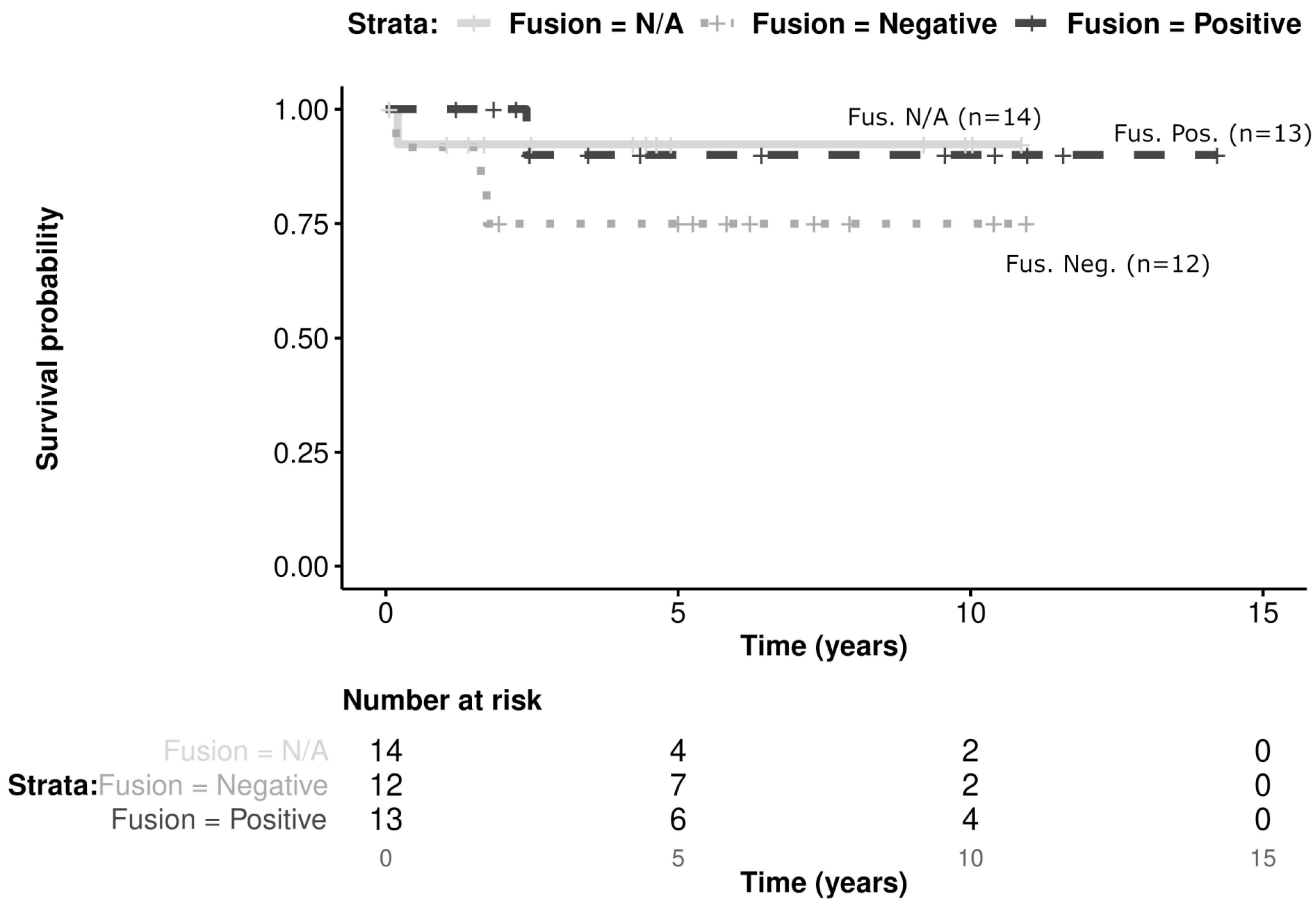

FIGURE 2.

Kaplan-Meier estimates presenting EFS of 39 patients with localized disease according to fusion status (p=0.38)

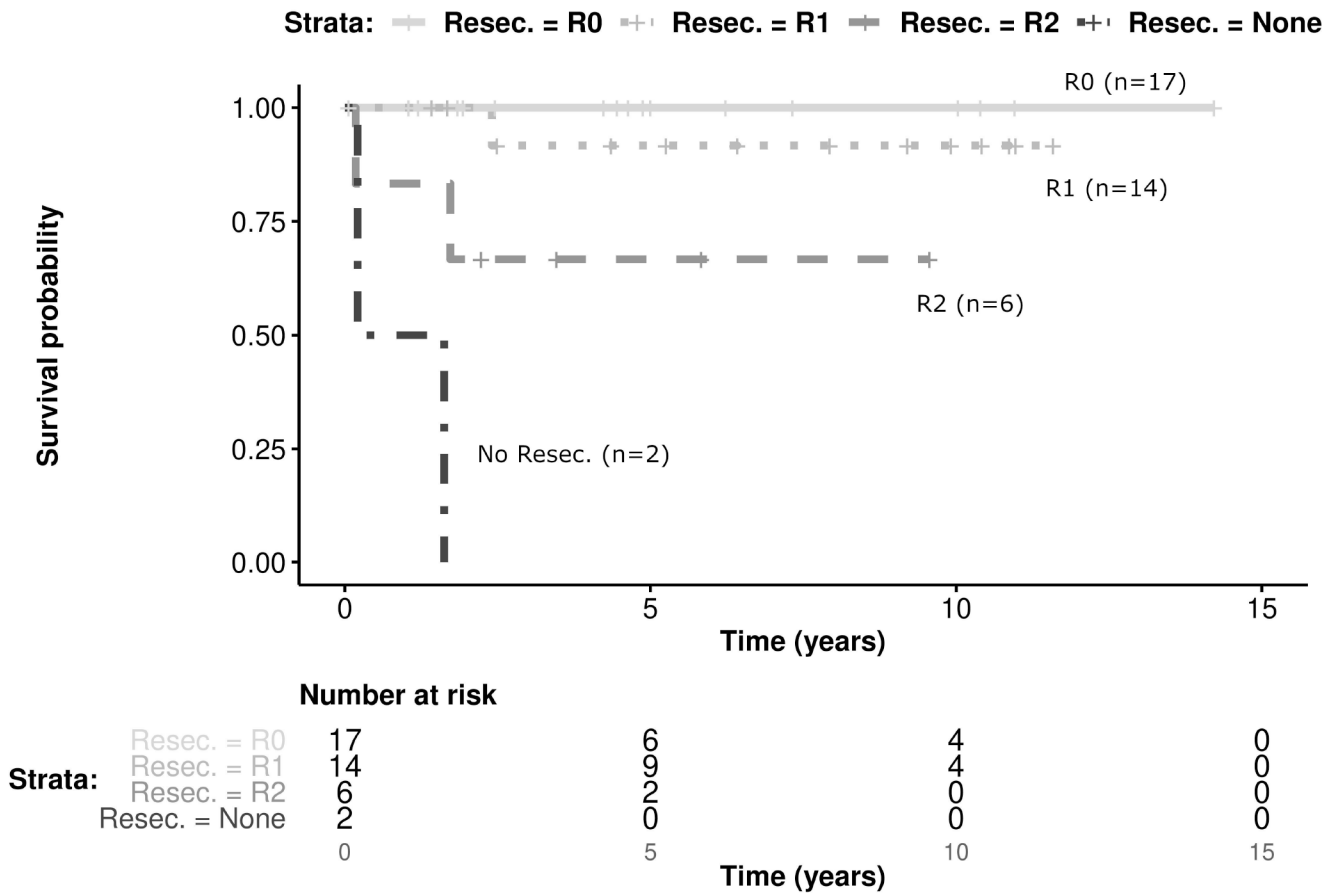

FIGURE 3:

Kaplan-Meier estimates presenting EFS of 39 patients with localized disease according to extent of resection, including the no-resection group ($p<0.001$)

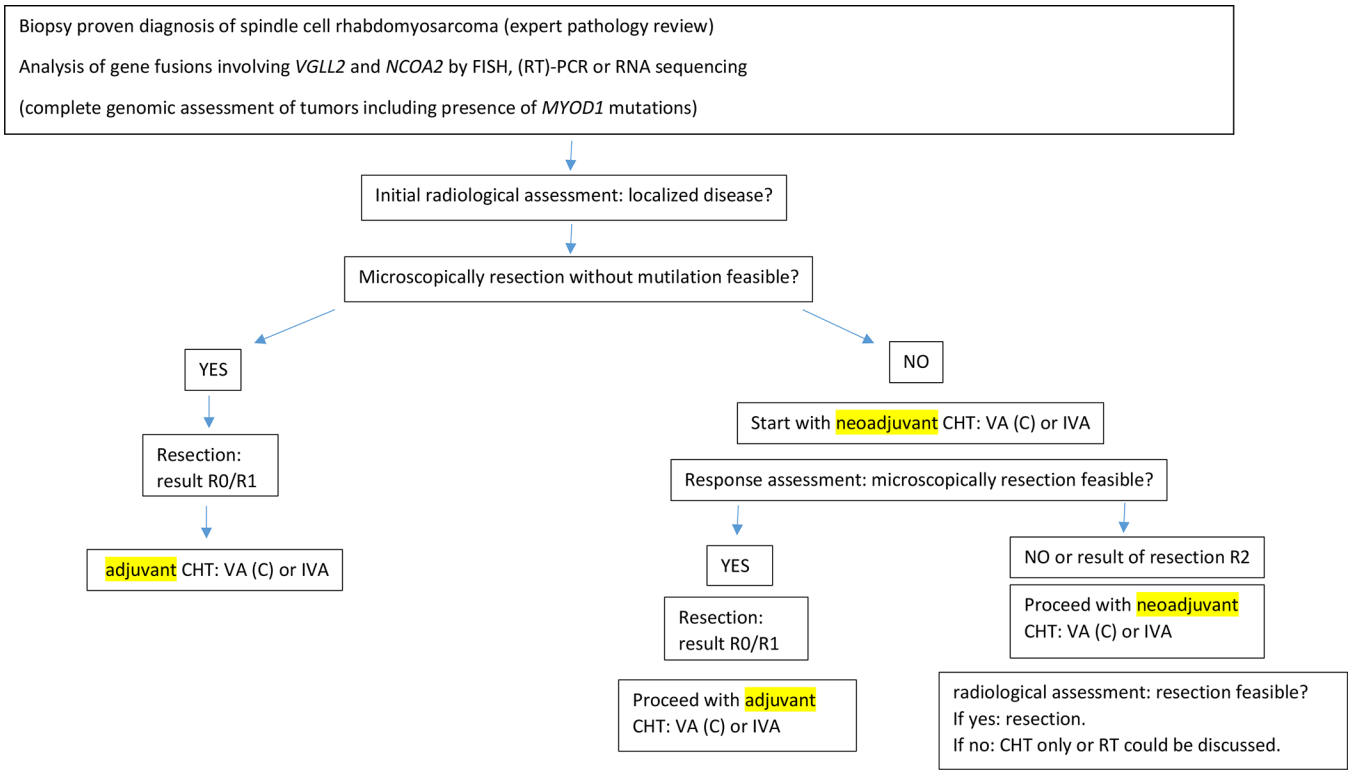

Figure 4.

International consensus on initial treatment of infants with congenital spindle cell rhabdomyosarcoma

CHT chemotherapy; FISH fluorescence in situ hybridization; IVA Vincristine, actinomycin-D, ifosfamide; VAC vincristine, actinomycin-D, cyclophosphamide; RT radiotherapy; (RT)-PCR reverse transcription polymerase chain reaction;

Table 1.

Univariate analysis of characteristics and treatment of patients with localized spindle cell RMS

	Total[1] (*N*=39)	5-year EFS,% (95% CI)	p-value	5-year OS, % (95% CI)	p-value
Sex	39				
female	18	100		100	
male	21	74±20	0.04	84±16	0.13
Age	39				
≤6 months	30	84±14		92±11	
>6 months≤12 months	9	89±21	0.75	89±21	0.79
Age-2	39				
≤3 months	22	83±14		100	
>3 months≤6 months	8	70±36		69±36	
>6 months≤12 months	9	89±21	0.39	89±21	0.05
Patients Origin	39				
COG/Texas	15	92±15		92±15	
CWS	9	64±41		100	
EpSSG	15	87±17	0.48	87±17	0.64
Fusion status	39				
VGLL2 and/or NCOA2-positive	13	90±19		100	
VGLL2 and/or NCOA2-negative	12	75±25	0.25	82±23	0.15
No fusion status available	14	92±15	0.38	90±17	0.37
Fusion status-2	13				
VGLL2 positive	6	83±30		100	
NCOA2 positive	5	100	0.56	100	-
VGLL2-NCOA2 positive	2	100	0.72	100	-
Tumor site	39				
favourable	7	86±26		100	
unfavourable	32	86±13	0.94	89±12	0.37
Tumor location	39				
Extremities	10	80±25		88±23	
Head and neck	3	67±53		100	
GU	8	86±26		88±23	
trunk	18	93±13	0.58	93±14	0.90
Initial tumor size	39				
≤ 5 cm	24	96±8		95±9	
>5 cm	15	72±24	0.07	86±18	0.40
Nodal status	36				
N0	35	87±12		93±9	
N1	1	0	0.002	0	<0.001
IRS group	38				
I	12	100		100	

	Total[1] (*N*=39)	5-year EFS,% (95% CI)	p-value	5-year OS, % (95% CI)	p-value
II	6	75±43		80±35	
III	20	80±17	0.34	90±14	0.44
CHT	34				
VA	6	75±43		100	
VAC/IVA	14	92±16		92±16	
VAC/IVA+MT	9	78±27		88±23	
VAIA	5	75±43	0.79	80±35	0.76
Best response to CHT	19				
CR	10	100		100	
PR	9	100	-	100	-
RT	35				
yes	5	100		100	
no	30	85±14	0.37	92±10	0.52
Surgical resection	39				
yes	37	91±10		91±10	
no	2	0	<0.001	100	0.66
Time of surgical resection	35				
upfront	18	92±16		93±14	
delayed	17	94±11	0.99	94±12	0.91
Extend of resection	37				
R0	17	100		100	
R1	14	92±16		93±15	
R2	6	67±38	0.03	83±30	0.39

Abbreviations: EFS event free survival; OS overall survival; CHT chemotherapy; CR complete response; IVA Vincristine, actinomycin-D, ifosfamide; PR partial response; R0 complete resection; R1 microscopic incomplete resection; R2 macroscopic incomplete resection; RT radiotherapy; VA vincristine, actinomycin-D; VAC vincristine, actinomycin-D, cyclophosphamide; VAIA Vincristine, actinomycin-D, ifosfamide, doxorubicin; y years.

[1]Variables displayed may have missing values. For each variable the available cases are used and therefore subcategories do not always sum up to *N*=39.

Table 2.

Characteristics and treatment of 39 patients with localized disease according to fusion status

Fusion	N	Age (mo)	Tumor location	Initial tumor size	N-status	IRS Group	CHT	Extend of resection	RT	Outcome
NCOA2-VGLL2	2	0.24 and 1.6	extremity (n=1) trunk (n=1)	≤5cm (n=1) >5 (n=1)	N0	III (n=2)	VA(C) (n=1) VAIA (n=1)	R1 (n=1) R2 (n=1)	no (n=2)	A1.CR (n=2)
NCOA2-	5[1]	1.3 (0.3–8)	extremity (n=3) trunc (n=2)	≤5cm (n=3) >5 (n=2)	N0	I (n=2) II (n=1) III (n=2)	VA(C) (n=4) IVA (n=1)	R0 (n=3) R1 (n=1) R2 (n=1)	no (n=5)	A1.CR (n=5)
VGLL2-	6[2]	0.4 (0.2–3.0)	extremity (n=1) trunc (n=5) head and neck (n=1)	≤5cm (n=1) >5 (n=6)	N0	II (n=1) III (n=5) n.a. (n=1)	VA(C)/IVA(n=2) IVA+MT (n=3) VAIA (n=2)	R0 (n=1) R1 (n=5) R2 (n=1)	no (n=6= yes (n=1)	A1.CR (n=6) relapse and A2.CR (n=1)
No fusion identified	12[3]	4.3 (0–12)	extremity (n=4) trunc (n=3) head and neck (n=1) GU (n=4)	≤5cm (n=8) >5 (n=4)	N0 (n=11) N1 (n=1)	I (n=5) II (n=7)	VA(C)/IVA(n=6) IVA+MT (n=2) VAIA (n=1) n.a. (n=2)	R0 (n=6) R1 (n=2) R2 (n=3) n.a. (n=1)	no (n=11) yes (n=2)	A1-CR (n=5) DOD (n=2)
Not tested/ Insufficient sample	14	3.9 (0.2–12.4)	extremity (n=1) trunc (n=8) head and neck (n=1) GU (n=4)	≤5cm (n=11) >5 (n=3)	N0 (n=13) n.a. (n=1)	I (n=5) II (n=4) III (n=5)	VA(C)/IVA(n=7) IVA+MT (n=3) VAIA (n=2) No CHT (n=2) n.a. (n=1)	R0 (n=7) R1 (n=6) n.a. (n=1)	no (n=12) yes (n=2)	A1.CR (n=13) DOD (n=1)

Abbreviations: A1.CR alive in 1st complete remission; A2. CR alive in 2nd complete remisison; CHT chemotherapy; CR complete response; DOD dead of disease; GU genitourinary tract; IVA Vincristine, actinomycin-D, ifosfamide; n.a. not available; PR partial response; R0 complete resection; R1 microscopic incomplete resection; R2 macroscopic incomplete resection; RT radiotherapy; VAC vincristine, actinomycin-D, cyclophosphamide; VAIA Vincristine, actinomycin-D, ifosfamide, doxorubicin

[1] TEAD1-NCOA2 n=4, partner unknown n=1

[2] VGLL2-CITED2 n=2, partner unknown n=4

[3] One sample only tested for *NCOA2* and 2 samples only tested for *VGLL2* containing fusions