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The impact of local control in the treatment of children with advanced infantile and adult-type fibrosarcoma: Experience of the cooperative weichteilsarkom studiengruppe (CWS)☆,☆☆,★,★★

Monika Sparber-Sauer [a,*], Christian Vokuhl [b], Guido Seitz [c], Sabine Stegmaier [a], Erika Hallmen [a], Thekla von Kalle [d], Monika Scheer [a], Marc Münter [e], Stefan S. Bielack [a,f], Ruth Ladenstein [g], Felix Niggli [h], Gustaf Ljungman [i], Joerg Fuchs [j], Thomas Klingebiel [k], Ewa Koscielniak [a,l], on behalf of the CWS Study Group

[a] Klinikum Stuttgart - Olgahospital, Stuttgart Cancer Center, Zentrum für Kinder-, Jugend- und Frauenmedizin, Pediatrics 5 (Oncology, Hematology, Immunology), Stuttgart, Germany
[b] Kiel Pediatric Tumor Registry, Section of Pediatric Pathology Department of Pathology, Kiel, Germany
[c] University Children's Hospital Marburg, Department of Pediatric Surgery, Marburg, Germany
[d] Klinikum Stuttgart - Olgahospital, Stuttgart Cancer Center, Zentrum für Kinder-, Jugend- und Frauenmedizin, Olgahospital, Institute of Radiology, Stuttgart, Germany
[e] Klinikum Stuttgart, Institute of Radiotherapy, Stuttgart, Germany
[f] University of Muenster, Department of Pediatric Hematology and Oncology, Muenster, Germany
[g] St. Anna Kinderspital, Pediatric Oncology, Wien, Austria
[h] Department of Pediatric Oncology, University of Zurich, Zurich, Switzerland
[i] University of Uppsala, Children's University Hospital, Department of Women's and Children's Health, Uppsala, Sweden
[j] University Children's Hospital, Department of Pediatric Surgery and Urology, Tuebingen, Germany
[k] University of Frankfurt, Department for Children and Adolescents, Goethe University, Frankfurt/M., Germany
[l] Children's Hospital, Department of Pediatric Hematology and Oncology, Tuebingen, Germany

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ABSTRACT

Background and objectives: This study aims at examining the potential survival benefits of primary versus secondary surgery of children diagnosed with advanced infantile (iFS) and adult-type fibrosarcoma (aFS).
Methods: Treatment and outcome of 89 children with FS treated within prospective Cooperative Studiengruppe (CWS) trials (1981–2016) were analyzed retrospectively.
Results: Localized disease (LD) was diagnosed in 87 patients: 64/66 patients with iFS (≤2 years) and 23 with aFS (>2 ≤ 18 years). Two patients (iFS) had metastatic disease. Resection was the mainstay of therapy of patients with LD resulting in microscopically complete (R0, IRS group I) ($n = 29/87$, 33%), microscopically incomplete (R1, IRS group II) ($n = 17/87$, 20%) and macroscopically incomplete (R2, IRS group III) ($n = 41/87$, 47%). Advanced LD (IRS group III) was present in 32/64 (50%) patients with iFS and in 9/23 (39%) with aFS. Chemotherapy was added predominantly in patients with advanced disease and an assessable objective response to CHT was seen in 71% iFS and 75% aFS. The 5-year event-free survival (EFS) of patients with iFS and aFS was 81% (±10, 95% CI) and 70% (±19, 95% CI) ($p = 0.24$); the 5-year overall survival (OS) was 98% (±3, 95% CI) and 82% (±16, 95% CI) ($p = 0.02$). Primary resection was no prognostic factor. Secondary R0/ R1 resection in patients with advanced disease improved 5-year EFS and OS in aFS ($p = 0.002$ and $p = 0.000$) but not in infants.
Conclusions: Secondary resection improves outcome in advanced aFS but not in infants. Mutilating surgery in infants should be avoided.
Type of study and level of evidence: Treatment study: patients were enrolled in five prospective studies and one registry, prognosis study: retrospective study.

Abbreviations: aFS, Adult-type Fibrosarcoma; CEVAIE, Carboplatin, epirubicin, vincristine, actinomycin-D, ifosfamide, etoposide; CI, confidence interval; CHT, Chemotherapy; CR, complete remission; CWS, Cooperative Weichteilsarkom Studiengruppe; EFS, event free survival; EVAIA, etoposide, vincristine, actinomycin-D, ifosfamide, doxorubicine; FNCLCC, French Federation of Cancer Centers Sarcoma Group; iFS, Infantile fibrosarcoma; IRS, international rhabdomyosarcoma study group; jFS, Juvenile fibrosarcoma; LD, localized disease; MD, metastatic disease; mPR, minor partial response; MRI, magnet resonance imaging; OS, overall survival; PFS, progression free survival; PD, progressive disease; PR, partial response; RD, relapsed disease; RT, Radiotherapy; 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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* Corresponding author. Tel.: +49 711 2787 04; fax +49 711 2787 2749.
E-mail address: M.Sparber-Sauer@klinikum-stuttgart.de (M. Sparber-Sauer).

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Level of evidence: II/ III.
Mini-abstract: Fibrosarcoma is a very rare malignant tumor. Little is known about differences of local treatment of advanced infantile and adult-type. Data of 89 patients registered in five prospective trials and one registry of the Cooperative Weichteilsarkom Studiengruppe (CWS) (1981–2016) were analyzed.

Infantile fibrosarcoma (iFS) predominantly occurs in children less than 24 months of age and a very good outcome of these infants with a 3-year EFS and OS of 84% and 94%, respectively, was recently reported [1–3]. IFS is classified as a soft tissue tumor of intermediate malignancy characterized by simulating classic adult fibrosarcoma histologically, but has a distinctive ETV6-NTRK3 gene fusion [2,4–7], which has also been described in other malignant diseases [4,8,9]. It is a densely cellular neoplasm composed of intersecting fascicles of primitive round, ovoid, and spindle cells with a focal herringbone pattern, or more commonly forming interlacing cords, sinusoids bands, or sheets [1,10,11]. Targeted therapies with tropomyosin-related kinase inhibitors are about to be evaluated in current clinical trials and first results have been published for patients with iFS (positive for ETV6-NTRK3 translocation) and advanced disease, metastatic disease or progression under CHT [12–14]. However, conservative surgery was the mainstay for the last decades and many data on chemotherapy show efficacy and important tumor reduction with few reported long term effects [2,3,15,16]. According to a recent analysis of retrospective data on 50 infants, conservative therapy with resection only appears possible in patients with resectable iFS, resulting in the International Rhabdomyosarcoma Study Group (IRS) [17] group I and II [2,3]. As this tumor is reported to be chemosensitive with a response rate of 68% specifically to vincristine/ actinomycin-D (VA), the authors were in favor of CHT for patients with IRS group III/R2 patients, who may not need any resection at all. The data showed that 35.4% of IRS III (macroscopically incomplete resected R2) patients did not need delayed resection owing to a radiologic complete remission or very good partial response after neoadjuvant chemotherapy [3] and a second surgery seems not necessary in this group of patients. Furthermore, surgery maybe mutilating or cause functional damage which should be avoided [2,3,18].

In contrast to iFS, FS in older children appears to be a clinically distinct entity with a poorer prognosis and a different cytogenetic profile despite histologic similarities [19–22]. This adult-type FS (aFS) is defined as histological FS composed of relatively monomorphic spindled cells, showing no more than a moderate degree of pleomorphism [23]. It is composed of fibroblasts with variable collagen production and a "herringbone" architecture with the absence of the ETV6-NTRK3 translocation [23,24]. AFS is most common in middle-aged and older adults and rarely occurs in children. Only few data exist on patients with aFS. A patient series on 26 adult patients that met World Health Organization (WHO) criteria for FS reported a poor outcome: 50% died of locally aggressive and/or metastatic disease [22] and optimal therapy is still unclear. No data exist on local treatment of older children with FS so far.

We therefore retrospectively analyzed infants, children and adolescents with FS registered in five consecutive trials and one registry of the Cooperative Weichteilsarkom Studiengruppe (CWS) comparing treatment and outcome of patients with infantile and adult-type FS focusing on the differences in local therapy in advanced disease.

1. Methods

1.1. Patients

Inclusion criteria for this analysis were: age 0–18, complete data set for assessment of therapy and follow up, and centrally reviewed histological diagnosis of FS [25–29] at the Kiel Pediatric Tumor Registry. The use of the grading system of the French Federation of Cancer Centers Sarcoma Group (FNCLCC) [30] was not recommended by the WHO classification [31]. Since CWS-2002P the presence of ETV6-NTRK3 translocation was examined by RT-PCR or FISH analysis. Infantile FS was defined analogous several previous publications according to histological criteria [24,32] and age ≤ 2 years of age at diagnosis [3,33–37]. To be consistent with previous analyses we used the same cutoff age [2,3,15,38]. However, we did a subanalysis of the infants positive for ETV6-NTRK3 translocation. Adult-type FS was defined according to histological criteria [23,24,32] and age > 2 years and < 18 years at age of diagnosis. Patients were enrolled prospectively onto the 5 CWS trials -81, -86, -91, -96, -2002P and the registry SoTiSaR between 1985 and 2015 with follow up until December 2017.

1.2. Treatment

The general treatment guidelines did not change over time or between the various protocols. Special recommendations for iFS were included since CWS-96. The mainstay of treatment for patients with iFS and aFS was primary surgery with complete excision after biopsy when microscopically complete, nonmutilating excision was believed to be possible. In other cases primary excision or biopsy of the primary tumor was performed and chemotherapy (CHT) to induce tumor shrinkage and improve resectability [39,40] was recommended: vincristine, actinomycin-D, cyclophosphamide, Adriamycin (VACA) in CWS-81, -86 and vincristine, actinomycin-D, cyclophosphamide (VAC) since CWS-91; dose was adapted to age since CWS-86 (30% reduction). This was followed by secondary surgery. Some patients received adjuvant CHT after microscopically complete or incomplete resection of the primary tumor as an individual decision of the treating center. Since CWS-96 a "wait and see" strategy was recommended after microscopically complete (R0, IRS group I) or microscopically incomplete (R1, IRS group II) resection. CHT with VAC was recommended for patients after macroscopically incomplete resection (R2 or biopsy, IRS group III) and in PD.

Patients with advanced aFS (IRS group III) were recommended to be treated with CHT analogous to patients with nonrhabdomyosarcoma (NRSTS) according to the protocols with a combination of vincristine and dactinomycin in combination with alkylating agent and anthracycline (VAIA). CHT was given in patients with IRS group I/II on an individual decision of the treating center.

Radiotherapy was not recommended in infants. In older patients with FS RT was administered analogous to recommendations for rhabdomyosarcoma with a total dose of 32 to 54.4 Gy if hyperfractionated accelerated (2 × 1.6 Gy/day) in CWS-86 and -91 [17,41,42]. Special recommendations for NRSTS were included since CWS-96: External beam irradiation with 44.8 Gy was recommended if a microscopically complete resection (R0) was not performed. In CWS-2002P, the recommendation was extended to include patients in whom an R0-resection had been performed if tumor size was >5 cm or age > 10 years. In the recent CWS Guidance, RT with 50.4 Gy (conventional fractionated irradiation) was recommended as an alternative to the regime of 44.8 Gy (hyperfractionated, accelerated irradiation).

1.3. Data collection and evaluation

Data were prospectively collected within the consecutive trials (CWS-81, -86, CWS-91, CWS-96, CWS-2002P) and the current registry SoTiSaR. Informed consent for data collection was obtained from the patients, guardians or parents by the responsible physician prior to

inclusion into the trial with respect to the requirements of the declaration of Helsinki and in accordance with the regulations of the respective ethical committee. Follow-up data were obtained from yearly status reports. Central pathological reviews and presence of the ETV6-NTRK3 translocation protein expression by RT-PCR or FISH analysis were performed at the reference center Kiel and Stuttgart, Germany. In addition to the data available in the data base, surgical, reference-histological, radiology and radiotherapy reports were studied by the first author.

1.4. Definition of terms

Initial staging procedures were recommended by the respective protocols and included imaging of the primary tumor and metastases by magnetic resonance imaging (MRI) or computed tomography (CT) of the chest. Initial tumor extension was assessed by MRI and CT. The TNM classification was applied to differentiate pretreatment and post-surgical stages [43–45]. A clinical staging system adapted from the International Rhabdomyosarcoma Study Group (IRS) was used [17]. Resection was classified as microscopically complete (R0) if the resection margins were free of tumor cells (IRS group I) or microscopically incomplete (R1) if a margin was positive (IRS group II). Surgical resection was considered macroscopically incomplete (R2) in the presence of gross residual disease after surgery (IRS group III). The surgical procedures were classified according to international recognized terms: Initial surgical approach was defined as initial surgical procedure (biopsy or resection) at diagnosis and within 4 weeks after biopsy prior to administration of any relevant chemotherapy. Secondary surgery was defined as a delayed surgical approach after initial surgery and/ or CHT. “Best surgery at any time” was defined as the best surgical result in the sum of surgeries performed in an individual during primary treatment.

Response was assessed after 3 to 4 courses of CHT by MRI or CT as previously described [46]: Complete remission (CR), minor partial response (mPR), 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 [41,47,48]. Response was not assessable after R0 or R1 resection. Regional lymph node sampling was recommended only for patients with clinically or radiographically suspicious regional lymph nodes.

Toxicity grading was documented as reported according to the common terminology criteria for adverse events (NCI CTCAE 3.0 [49]) and according to the respective versions at the time of the CWS study. “Severe late toxicity” was defined as persisting toxicity grade 3 or 4 [49] documented in the CWS database according to the late toxicity sheets at the time of last follow-up.

1.5. Statistical methods

Statistics were calculated using Statistica® version 6 (Statsoft) and IBM SPSS® 25 (Armonk, New York, U.S.). Overall survival (OS) and event-free survival (EFS) were calculated using the Kaplan–Meier estimator and confidence intervals (CI) stated at the 95% level [50]. 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, or last follow-up was calculated. If there was no event, the survival data were censored at last follow-up. OS of patients with relapsed disease (RD) was calculated from time of diagnosis of relapse to last follow-up or death. EFS of patients with RD was calculated from the time of diagnosis of relapse to event (second relapse) or last follow-up. For comparison of EFS and OS levels the log-rank test was used in univariate analysis.

2. Results

2.1. Patients characteristics and demography

Since 1981, 89 patients with FS registered in 5 prospective CWS trials (CWS-81 $n = 5$, CWS-86 $n = 5$, CWS-91 $n = 8$, CWS-96 $n = 25$, CWS-2002P $n = 23$) and the current registry SoTiSaR ($n = 23$), fulfilled the inclusion criteria and were eligible for the analysis. All 89 patients had the confirmed centrally reviewed histological diagnosis of FS (Kiel Pediatric Tumor Registry). The median follow up time of surviving patients was 7.78 years [range 1.86–17.2]; the median EFS for all patients was 5.70 years [range: 0.04–17.2] based on follow-up data as of December 2017.

2.2. Patients with IRS group I and II

Sixty-six patients with iFS were ≤ 2 years old at diagnosis (median 0.14 years, range 0.0–1.79 years). In 31/42 (74%) tested patients ETV6-NTRK translocation was present. The primary tumor was ≤5 cm in 30/66 (45%) patients and predominantly located in the extremities (67%). Patients of IRS group I ($n = 17$; 26%) and IRS group II ($n = 15$; 23%) were predominantly treated with surgery only ($n = 27/32$; 84%). CHT was added in 5/32 (16%) patients (VAC $n = 1$, VACA $n = 4$) as individual decision of the treating center.

Twenty-three patients with aFS were > 2 years old at diagnosis (median 10.5 years, range 2.16–17.12). In all tested patients ($n = 7$) ETV6-NTRK translocation was negative. Three patients had histological inflammatory FS (8.3–12.6 years old). In 9 patients the histopathological grading was documented in the pathology reports: grade 1 in 2 patients, grade 2 in 6 and grade 3 in 1 patient. The primary tumor was ≤5 cm in 13/23 (57%) patients and located in head and neck ($n = 9$; 39%), other (trunk, abdomen) ($n = 8$; 35%) and extremities ($n = 6$; 26%). After primary resection, 12 (52%) patients had IRS group I and 2 (9%) IRS group II. They were treated with surgery only except 4 patients. These were treated with adjuvant CHT (VAC $n = 2$, VACA $n = 2$) as individual decision (significant characteristics of patients are summarized in Table 1).

2.3. Treatment of patients with advanced iFS

Of 66 infants, 34 had advanced disease, IRS group III ($n = 32$; 48%). Regional lymph nodes were radiological suspicious in 1/32 patients with IRS group III and considered as positive (N1). Patients with IRS group III were all treated with CHT (VAC $n = 21$, IVA $n = 3$, VACA/VAIA $n = 5$, other $n = 2$) except two. One underwent an amputation of his extremity. The other was under “watch and wait” strategy until local PD 5 years after diagnosis, then achieved R1 resection without adjuvant CHT, no relapse and an OS of 11.74 years. The median duration of CHT was 4.6 months (range 1.4–13.4). Response was assessable in 28/32 patients treated with CHT: PR ($n = 21$), SD ($n = 4$) and PD ($n = 3$) resulting in an objective response (PR) of 75% (Table 1). A secondary resection was performed in 19/32 patients and resulted in best resection R0 ($n = 10$, amputation in 3), R1 ($n = 5$) and R2 ($n = 4$). Fourteen/32 (44%) patients achieved CR by CHT without secondary surgery ($n = 10$) or after secondary R2 status ($n = 4$) and did not relapse. RT (59.4 Gy) was administered to one infant with PR to VAC on musculus gluteus and intraspinal tumor achieving partial remission. Overall, CR was achieved by 29/32 (91%) patients with IRS group III; 3 achieved PR (Table 2).

Two patients had metastatic disease (MD) of iFS and both were treated with multimodal treatment including CHT (VAC/IVA). One (ETV6-NTRK positive iFS) had primary tumor >5 cm and skeletal metastases, suffered of PD despite R0 resection of the primary tumor and subsequently died. The other patient with MD could achieve CR after R0 resection of primary tumor (<5 cm) and CR of liver and pulmonary metastases by additional CHT and is alive in CR 12 years after diagnosis.

Table 1
Univariable analysis of significant characteristics of 64 patients with localized infantile fibrosarcoma and of 23 patients with localized "adult-type" fibrosarcoma.

	n (infantile FS *n* = 64) (%)	5 year EFS % ± 95% CI	p (EFS)	5 year OS % ± 95% CI	p (OS)	*n* (adult-type FS *n* = 23) (%)	5 year EFS % ± 95% CI	p (EFS)	5 year OS % ± 95% CI	p (OS)
Primary tumor size (cm)										
≤5 cm	29 (45)	76 ± 15		-		12 (52)	92 ± 16			
>5 cm	33 (52)	85 ± 12	0.53	97 ± 6	0.36	8 (35)	50 ± 35	0.09	75 ± 30	0.07
n.a.	2 (3)	-	0.64	-	0.64	3 (13)	33 ± 37	0.06	33 ± 27	0.02
IRS group										
I	17 (26)	100		-		12 (52)	75 ± 25		91 ± 17	
II	15 (23)	60 ± 25		-		2 (9)	-		-	
III	32 (48)	81 ± 14	0.02	96 ± 7	0.57	9 (39)	56 ± 33	0.46	67 ± 36	0.25
n.a.	4 (6)	75 ± 41	0.86	-	0.96	4 (17)	75 ± 43	0.93	75 ± 43	0.32
Best surgery at any time										
R0	30 (47)	83 ± 13		93 ± 9		16 (70)	81 ± 19		93 ± 13	
R1	15 (23)	73 ± 22		-		3 (13)	-		-	
R2/biopsy	19 (30)	84 ± 16	0.75	-	0.57	4 (17)	-	0.002	25 ± 22	0.000
Response to CHT										
CR/PR	22 (34)	77 ± 17		95 ± 10		6 (26)	67 ± 38	0.55	83 ± 30	
SD	4 (6)	-	0.32	-	0.76	1 (4)	-		-	0.68
PD	3 (5)	33 ± 27		-		1 (4)	-		-	
n.a.	6 (9)	83 ± 29		-		5 (22)	80 ± 35		80 ± 35	
no CHT	29 (46)	86 ± 15	0.06	-	0.76	10 (44)	70 ± 28	0.000	89 ± 21	0.20
RT										
yes	1 (2)	-		-		4 (17)	50 ± 49		75 ± 43	
no	63 (98)	83 ± 9	0.04	99 ± 3	0.89	19 (83)	79 ± 18	0.73	84 ± 16	0.53
CR										
yes	61 (94)	82 ± 10		-		20 (87)	75 ± 19		90 ± 14	
no	3 (6)	67 ± 53	0.14	98 ± 4	0.85	3 (13)	33 ± 27	0.06	33 ± 27	0.002

CR, complete remission; OS, overall survival; p, p-value; R0, microscopic complete resection; R1, microscopic incomplete resection; R2, macroscopic incomplete resection; RT, radiotherapy; SD, stable disease; y, years.

2.4. Treatment of patients with advanced aFS

All patients with IRS group III ($n = 9$) were treated with additional CHT (VAIA $n = 6$, VAC $n = 1$, IVA/other $n = 2$). The median duration of CHT was 4.05 months (range 0.7–13.2). Response was assessable in 8/9 patients with CR ($n = 1$), PR ($n = 5$), SD ($n = 1$) and PD ($n = 1$) resulting in an objective response rate of 75%. A secondary resection was performed in 7/9 patients with IRS group III with the result R0 ($n = 4$), R1 ($n = 1$) and R2 ($n = 2$). RT was administered to 3 patients with doses of 23 and 32 Gy and one patient with intraoperative radiation therapy after R2 resection/no resection ($n = 2$) and R0 resection ($n = 1$), the latter because of tumor size ≥5 cm and suspected R1 resection. One patient suffered of aFS as second malignancy located in the left thyroid after RT of Hodgkin lymphoma. This patient was cured by CHT (VAIA) and secondary R0 resection. CR was achieved by 6/9 (67%) patients with IRS group III; 1 achieved PR (Table 2).

2.5. Patients with progressive disease

In patients with iFS, progressive disease occurred in 3 patients of IRS group III under CHT. Two were cured by secondary R0 and R1 resection; the third achieved partial remission with CHT only. All were alive. In patients with aFS, progressive disease occurred in 3 patients of IRS group III under CHT. Two patients died of PD; 1 achieved CR by mutilating R0 resection but died of relapsed disease.

2.6. Patients with RD after CR of LD

Ten patients with LD of FS suffered a local ($n = 9$) or metastatic ($n = 1$) relapse at a median time of 0.21 years (range 0.04–0.92) after CR of primary disease: iFS ($n = 7$) and aFS ($n = 3$). Relapse therapy consisted of resection in all (no amputation) with the result of R0 ($n = 3$), R1 ($n = 4$) and R2 ($n = 3$), CHT ($n = 8/10$), RT ($n = 3/10$) and antihormonal therapy with tamoxifen ($n = 4/10$). Response to second line chemotherapy was assessable in 3 patients and was partial in all patients resulting in an objective response rate of 100%. Radiation was added in 3 patients with a median dose of 54 Gy (range 45–62). A second CR was achieved by 8/10 patients (80%). Progressive disease occurred in 2 patients (iFS $n = 1$, aFS $n = 1$) despite R1 resection in one and RT in both under CHT with VAC or Carbo-VP-16 and both subsequently died. At last follow up, eight/10 patients with RD (6 with iFS and 2 with aFS) were alive in CR ($n = 7$) and PR ($n = 1$). Median OS of patients with RD after diagnosis of RD was 11.45 years (range 8.50–15.62). 5-year EFS and OS for patients with RD were 70% (±28, 95% CI) and 80% (±25, 95% CI), respectively (Table 3).

2.7. Overall outcome and prognostic factors

The median follow up was 7.67 years [1.86–17.2]; 83/89 patients were alive at cutoff date. The 5-year EFS and OS of patients with iFS were 80% (± 10, 95% CI) and 97% (± 4, 95% CI), for patients with aFS were 70% (± 19, 95% CI) and 82% (± 16, 95% CI), respectively (Fig. 1). The 5-year OS was significantly different between patients with iFS and aFS ($p = 0.02$), whereas the EFS was not ($p = 0.24$). For patients with iFS, there was no significant difference concerning 5-year EFS or OS between ETV6-NTRK positive patients in comparison to patients who were not tested but had the reference-histological proven diagnosis. The 5-year event-free survival (EFS) of patients with advanced (IRS group III) iFS and aFS was 81% (±14, 95% CI) and 56% (±33, 95% CI); the 5-year overall survival (OS) was 96% (±7, 95% CI) and 67% (±36, 95% CI), respectively (Table 1, Fig. 2). For infants, primary R1 resection (IRS group II) seems to be a poor prognostic factor as patients with primary R0 resection (IRS group I) or with advanced disease (IRS group III) had a better 5-year EFS ($p = 0.02$). However, secondary surgery could not improve outcome of infants with advanced disease as best surgery was not a significant prognostic factor. In contrast, secondary surgery in IRS III patients with aFS could improve outcome as best surgery at any time was a significant prognostic factor for the 5-year EFS and OS ($p = 0.005$ and $p = 0.003$, respectively; Table 1, Fig. 3).

2.8. Long term toxicity and second malignancies

Thirteen of 64 (20%) surviving patients with iFS reported severe long term sequelae: 12/64 (19%) patients had impairment after amputation ($n = 4$), functional deficiencies after resection ($n = 5$), scoliosis ($n = 2$) or cosmetic defects ($n = 1$). Late toxicity sequelae were reported in

Table 2
Characteristics and local treatment of patients with advanced localized fibrosarcoma (IRS group III).

	n (infantile FS *n* = 32) (%)	*n* (adult-type FS *n* = 9) (%[a])
Age		
≤3 months	21 (66)	0
>3 months ≤24 months	11 (34)	0
>2 years ≤10 years	0	6 (67)
>10 years ≤18 years	0	3 (33)
Primary tumor size (cm)		
≤5 cm	7 (22)	4 (44)
>5 cm	24 (75)	4 (44)
n.a.	1 (3)	1 (11)
Primary tumor location		
Extremities	22 (69)	1 (11)
Head and Neck	2 (6)	5 (56)
other	8 (25)	3 (33)
Tumor invasiveness		
T1	12 (38)	3 (33)
T2	19 (59)	6 (67)
n.a.	1 (3)	0
N Status		
N0	30 (94)	4 (44)
N1	1 (3)	2 (22)
n.a.	1 (3)	3 (33)
CHT		
VAC/IVA	24 (75)	2 (22)
VACA/VAIA, other	9 (28)	7 (79)
none	2 (6)	0
Response to CHT		
CR/PR	21 (66)	6 (67)
SD	4 (13)	1 (11)
PD	3 (9)	1 (11)
n.a.	2 (6)	1 (11)
no CHT	2 (6)	0
Second surgery, *n* (%)		
R0	10 (31)	4 (45)
R1	5 (16)	1 (11)
R2	4 (13)	2 (22)
No second surgery	13 (40)	2 (22)
RT, *n* (%)		
yes	1 (3)	3 (33)
no	31 (97)	6 (67)
CR		
yes	29 (91)	6 (67)
no	3 (9)	3 (33)

R0, microscopic complete resection; R1, microscopic incomplete resection; R2, macroscopic incomplete resection; RT, radiotherapy.
[a] Some numbers do not total 100% for rounding reasons.

Table 3
Characteristics and treatment of 10 patients with RD after CR of LD.

	iFS (*n* = 7)	aFS (*n* = 3)
Gender		
female	5	1
male	2	2
Age at relapse median 0.42 years (0.06–17.81)		
≤15 months	7	0
>10 years	0	3
Histology		
iFS (ETV6-NTRK positive)	7 (4)	0
aFS (ETV6-NTRK negative)	0	3
IRS group		
I	0	3
II	6	0
III	1	0
Type of relapse		
local	7	2
metastatic	0	1
CHT at initial diagnosis		
yes	3	0
no	4	3
Best resection at initial diagnosis		
R0	3	3
R1	3	0
R2	1	0
CHT at relapse		
yes	5	3
no	2	0
Best surgery at relapse		
R0	2	1
R1	3	1
R2	1	1
n.a.	1	0
Radiotherapy at relapse		
yes	1	2
no	6	1
2. CR		
yes	6	2
no	1	1
Outcome		
ACR	6	1
APR	0	1
DOD	1	1

ACR, alive in complete remission; APR, alive in partial remission; DOD, dead of disease; CR, complete remission; LD, localized disease; R0, microscopic complete resection; R1, microscopic incomplete resection; R2, macroscopic incomplete resection; RD, relapsed disease; y, years.

1/65 (4%) surviving patients after CTH: Fanconi syndrome after ifosfamide containing CHT (IVA).

Four of 18 (22%) surviving patients with aFS reported functional deficiencies after resection ($n = 1$) or amputation ($n = 1$) and cosmetic defects ($n = 2$). One patient of 9 who had received CHT reported proteinuria after VAIA. One patient with aFS died of third malignancy (second malignancy was osteosarcoma, third malignancy was ductal invasive mamma carcinoma).

3. Discussion

We retrospectively analyzed children and adolescents with FS registered in five consecutive trials and one registry of the Cooperative Weichteilsarkom Studiengruppe (CWS) focusing on primary versus secondary surgery of patients with advanced iFS and aFS. Despite histologic similarities, we confirm aFS as a clinically distinct entity with other prognostic factors than iFS and significant different overall survival. For patients with iFS, this series reported that the ETV6-NTRK fusion gene documented by FISH of RT-PCR was present in 74% of the patients where the investigation was performed analogous to previously reported 87% [3]. Recurrent iatrogenic rearrangements of EGFR and BRAF were found in some of the included infants with the histologic diagnosis of iFS but lacked the canonical NTRK3-ETV6 fusion gene [51]. For patients with localized iFS, we can confirm primary surgery as the mainstay of therapy for patients with resectable tumors resulting in IRS group I/II. However, secondary resection did not improve outcome in infants with IRS group III as best resection was not a significant prognostic factor. Interestingly, 14/32 (44%) patients with advanced disease successfully reached CR with CHT alone and are still alive in first remission. We confirm this good outcome with CHT alone as previously described [3]. Incomplete R1 resection in infants seems to be a risk factor for relapse, more than advanced disease treated with CHT. Other aspects of importance concerning patients with iFS are the long term sequelae after resection or amputation: 12/64 (19%) surviving patients reported functional impairment. These mutilating resections should be avoided in the future. The CWS documentation of long term sequelae relies on a very long duration with a median follow up time of 7.78 years but there might be a bias as mainly the events are reported and some underestimation of the frequency of late effects might be possible. For patients with IRS group III, CHT with VA [2,3] or VAC should be started. As no long term toxicity is reported, we can confirm VAC as a safe and successful systemic regime [3] over the last 36 years without reported long term sequelae. However, actinomycin-D bears the risk of venoocclusive disease in infants and should be considered with caution in this very young group of patients. Thirteen of 64 (20%) surviving patients with iFS reported severe long term sequelae because of amputation, resection, scoliosis, cosmetic

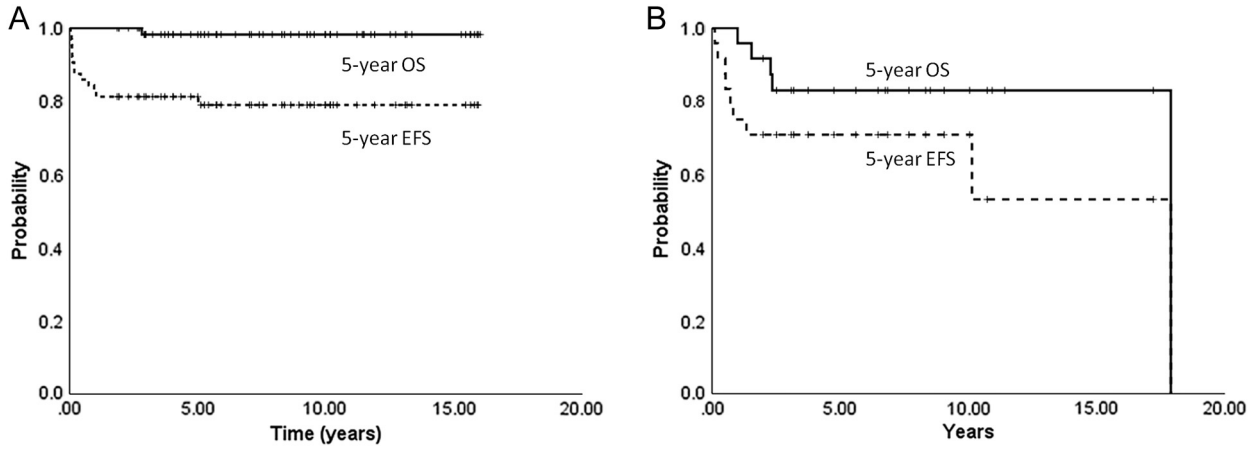

Fig. 1. (A) Kaplan–Meier estimates presenting 5-year EFS % and OS % of infants with fibrosarcoma ($n = 66$). (B) Kaplan–Meier estimates presenting 5-year EFS % and OS % of patients with adult type fibrosarcoma ($n = 23$).

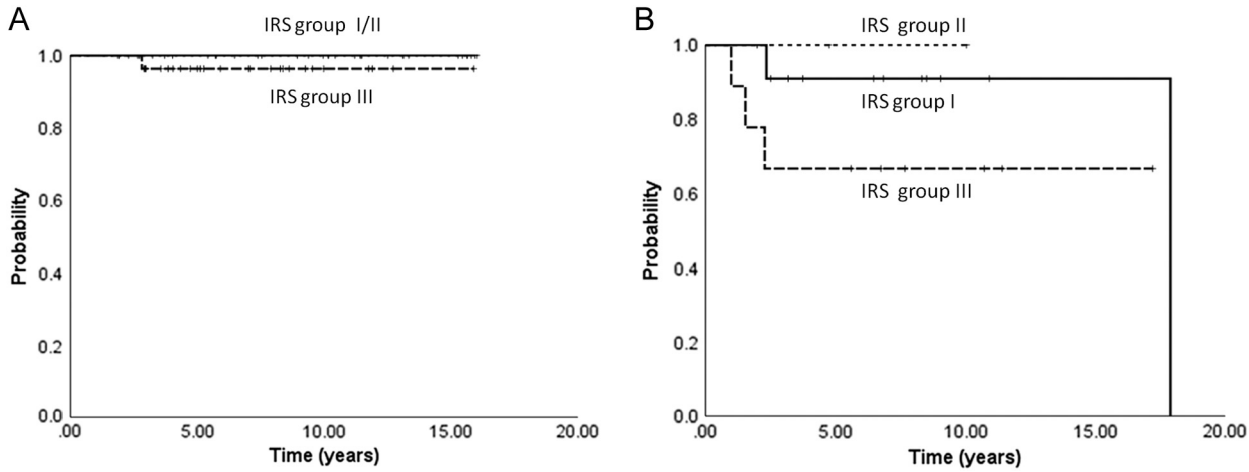

Fig. 2. (A) Kaplan–Meier estimates presenting 5-year EFS % and OS % of patients with iFS according to primary resection (IRS group) (p = 0.57). (B) Kaplan–Meier estimates presenting 5-year EFS % and OS % of patients with aFS according to primary resection (IRS group) (p = 0.46).

defects or Fanconi syndrome. These infants might have profited from the new therapy with NTRK inhibitors and targeted therapy with NTRK inhibitors should be taken into consideration analogous to recent reported data [12–14]. One of the major future challenges of this rare disease is progressive and metastatic disease. Treatment data on NTRK inhibitors on this patient collective appear to be very promising, even though no data about

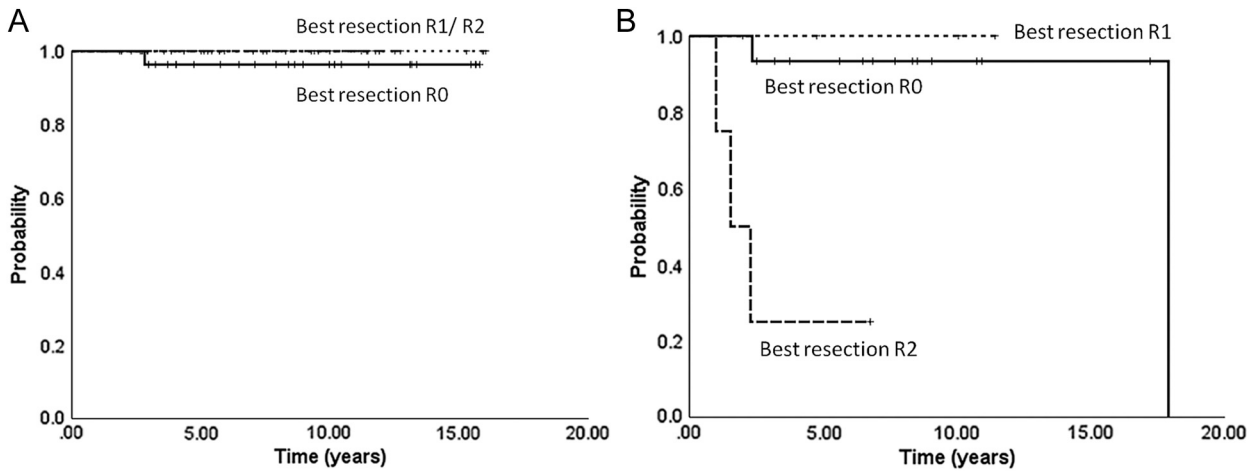

Fig. 3. (A) Kaplan–Meier estimates presenting 5-year EFS % and OS % of patients with iFS according to best resection (p = 0.57). (B) Kaplan–Meier estimates presenting 5-year EFS % and OS % of patients with aFS according to best resection (p = 0.002).

late toxicity or long term sequelae exist and the role of resection still remains to be defined. Future strategies for treatment of iFS in a prospective international trial including classification according to molecular profile (NTRK fusion positive and negative patients) are undoubtedly needed.

The major strength of this analysis is the data on older children with FS. Very limited data exist on this very rare "adult-type" FS [22]. All our 23 patients met WHO criteria for FS and were reviewed by expert pediatric reference pathologists from one single center. However, limitations might be the cutoff age and the histological variability of aFS. We included 4 patients <3 years in the group of patients with aFS who might be iFS (not fusion tested) as we used the age limit up to 2 years used by most authors [3,33,34,36,37]. Furthermore, we included three patients with inflammatory FS [52,53] because of their age > 5 years and the reference histological proven diagnosis of FS. Or data indicate that older children with FS should be treated differently than infants. Best resection was a significant prognostic factor in our analysis which was not reported previously and every effort should be made to achieve local control. Secondary resection after CHT inducing tumor shrinkage in patients with aFS and IRS group III improves 5-year EFS and OS significantly. However, patient numbers are not very high in this group of very rare disease and results must be interpreted carefully. The prognosis of our cohort of children with aFS was significantly poorer than with iFS. Despite more aggressive local therapy including RT, more patients suffered of PD and died. The role of RT needs to be further evaluated; the number of our patients was too low to draw conclusions. We can further add data on relapsed disease with a fair prognosis as 5-year EFS and OS for patients with RD were 70% (± 28, 95% CI) and 80% (±25, 95% CI), respectively, which are not reported so far. Surgery seems one of the main treatment strategies within multimodal treatment of the relapsed disease; however, the small number of relapses in our cohort does not allow further analysis of risk factors.

In conclusion, for all patients with FS, international collaboration and studies are necessary mainly for patients with advanced, progressive and metastatic disease. New treatment options as NTRK inhibitors need to be implicated for defined patient groups in international consensus recommendations for optimal treatment of all patients and further evaluation of potentially long term sequelae.

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