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# Conservative strategy in infantile fibrosarcoma is possible: The European paediatric Soft tissue sarcoma Study Group experience

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transcript

**Abstract** ***Background:*** Infantile fibrosarcoma (IFS) is a very rare disease occurring in young infants characterised by a high local aggressiveness but overall with a favourable survival. To try to reduce the total burden of therapy, the European pediatric Soft tissue sarcoma Study Group has developed conservative therapeutic recommendations according to initial resectability.

***Material and methods:*** Between 2005 and 2012, children with localised IFS were prospectively registered. Initial surgery was suggested only if possible without mutilation. Patients with initial complete (IRS-group I/R0) or microscopic incomplete (group II/R1) resection had no further therapy. Patients with initial inoperable tumour (group III/R2) received first-line vincristine-actinomycin-D chemotherapy (VA). Delayed conservative surgery was planned after tumour reduction. Aggressive local therapy (mutilating surgery or external radiotherapy) was discouraged.

***Results:*** A total of 50 infants (median age 1.4 months), were included in the study. ETV6-NTRK3 transcript was present in 87.2% of patients where investigation was performed. According to initial surgery, 11 patients were classified as group I, 8 as group II and 31 as group III. VA chemotherapy was first delivered to 25 children with IRS-III/R2 and one with IRS-II/R1 disease. Response rate to VA was 68.0%. Mutilating surgery was only performed in three cases. After a median follow-up of 4.7 years (range 1.9–9.0), 3-year event-free survival and overall survival were respectively 84.0% (95% confidence interval [CI] 70.5–91.7) and 94.0% (95% CI 82.5–98.0).

***Conclusions:*** Conservative therapy is possible in IFS as only three children required mutilating surgery, and alkylating or anthracycline based chemotherapy was avoided in 71.0% of patients needing chemotherapy. VA regimen should be first line therapy in order to reduce long term effects.



## 1. Introduction

Although infantile fibrosarcoma (IFS) is a rare tumour, it is the commonest soft tissue sarcoma in children less than 1 year of age. IFS is currently classified as a soft tissue tumour of intermediate malignancy characterised by a quite specific t(12;15)(p13;q25) translocation coding for a ETV6-NTRK3 gene fusion [1–3]. It arises below the age of 2–5 years with survival rates between 80 and 100% [1,4,5]. It often presents with initial rapid growth, sometimes with indolent evolution and metastatic spread is uncommon (1–13%). Local recurrence may occur after initial conservative surgery (17–43%), the latter being the mainstay of treatment, aiming for a conservative resection. However, IFS may present with locally advanced disease and surgery maybe mutilating or cause functional damage [4,5]. Since IFS is a chemosensitive tumour, chemotherapy may play a major role in the treatment strategy [1,6,7]. Recently, the VA regimen (vincristine-actinomycin-D), has confirmed its efficacy and allows important tumour reduction [1]. The International Society of Pediatric Oncology–Malignant Mesenchymal Tumour Committee and the Associazione Italiana Ematologia Oncologia Pediatrica–Soft Tissue Sarcoma Committee (previously called the Italian Cooperative Group) founded the European-paediatric-Soft-tissue-Sarcoma-Study Group (EpSSG) in 2005. The group developed treatment guidelines for IFS, with the major goal to make uniform the treatment of IFS patients across Europe, according to a conservative approach based on non-mutilating surgery and alkylating-anthracycline-free chemotherapy (EpSSG non-rhabdomyosarcoma soft tissue sarcomas [NRSTS] 2005 study – European Union Drug Regulating Authorities Clinical Trial No. 2005-001139-31) This present paper reports the results of a prospective cohort of IFS patients treated between 2005 and 2012 aiming to propose a conservative strategy in this disease.

## 2. Patients and methods

### 2.1. Study population

All infants aged from birth to 24 months with localised IFS were prospectively registered in the EpSSG database using a web-based system, from October 2005 to 30th June 2012. Patients were classified according specific tumour sites [8]. Clinical staging was defined according to the tumour node metastases system: T1 or T2 according to the invasion of contiguous organs; N0/N1, and M0/M1 according to the presence of lymph node or distant metastases [8]. Lymph node involvement was evaluated clinically or by imaging and confirmed when necessary by cytological or histological biopsy. The status of resection margins was classified according to the UICC-R classification and the Intergroup

Rhabdomyosarcoma Staging (IRS) system which is generally used for primary surgery in paediatric rhabdomyosarcomas [9]. UICC-R R0 or IRS group I correspond to complete tumour resection with histologically free margins, UICC-R R1 or IRS II correspond to macroscopic resection, but invaded margins on histology, UICC-R R2 or IRS III correspond to macroscopic residual tumour after surgery (III b) or biopsy (III a). Patients with metastatic tumours were excluded from the analysis.

Cytogenetic and molecular evaluation to identify the presence of ETV6-NTRK3 transcript derived by the specific translocation by FISH and RT-PCR were recommended to confirm the diagnosis [10]. Where there was doubt, tumours were prospectively reviewed at the time of diagnosis by national and/or international panel of pathologists [11,12]. Exclusion criteria were: histological review did not confirm IFS diagnosis (n = 3); tumours negative for the ETV6-NTRK3 transcript or not tested in the absence of pathologic panel review (n = 4) (Fig. 1). Institutional ethics board approval was obtained for all participating centres according to the rules established in Europe. Written consent for treatment and the use of data were obtained from parents or guardians according to local research ethics requirements.

### 2.2. Treatment

Primary surgery after initial biopsy was recommended only when *en bloc* resection, removing the tumour through normal tissue with clear margins, might be achieved without significant long-term functional or cosmetic impairment. In the other cases, a biopsy was required followed by chemotherapy and, if necessary, delayed surgery. No adjuvant chemotherapy was recommended if resection was complete or microscopically-incomplete (IRS group-I/R0 or II/R1). The VA regimen was the treatment of choice in patients with unresectable disease (IRS group III/R2), with the exception of patients with congenital tumours (age <3 months at diagnosis), for which an optional 'wait and see' strategy was considered to evaluate the possibility of spontaneous regression or time to facilitate subsequent surgery. VA chemotherapy was continued, in a responsive tumour, until tumour resectability was possible. If the tumour shrinkage was not sufficient to permit conservative surgery, ifosfamide (IVA regimen) or cyclophosphamide (VAC regimen) was added (Fig. 2). Where there was no response to VA, or tumour progression, ifosfamide-doxorubicin (ID) chemotherapy was recommended. Mutilating surgery and external radiotherapy was strongly discouraged.

Additional dose reductions were applied for infants <8 kg and <6 months (30% reduction), and for newborns <5 kg and <3 months (50%). Moreover, the initial doses were delivered at 50%, progressively increasing to 75% and 100% to verify overall tolerance in infants, with specific attention to neurologic and hepatic toxicity, particularly constipation and veno-occlusive disease (VOD). No alkylating agent was administered before 1 month and no anthracycline before 3 months of age.

### 2.3. Response assessment

In patients with measurable disease, response to chemotherapy was assessed after three cycles of chemotherapy by assessment of radiologically-identified tumour volume reduction: i.e. complete response (CR)

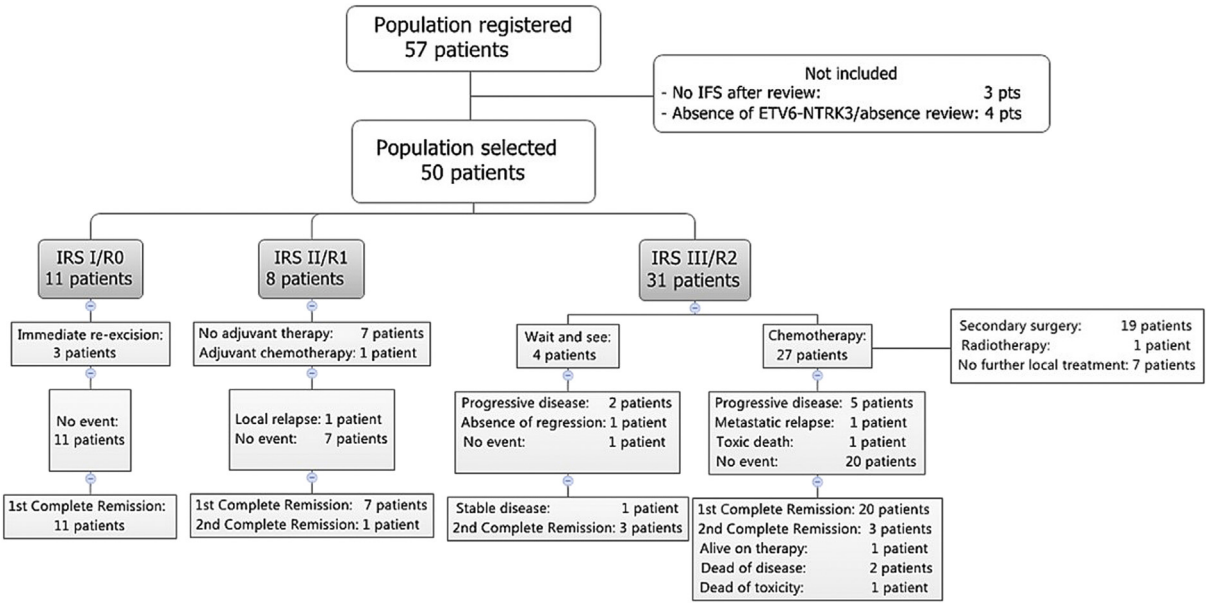


Fig. 1. Patient's charts. Abbreviations: IFS, infantile fibrosarcoma; IRS-I/R0, complete exeresis; IRS-II/R1, microscopic residue; IRS-III/R2, macroscopic residue; pts, patients.

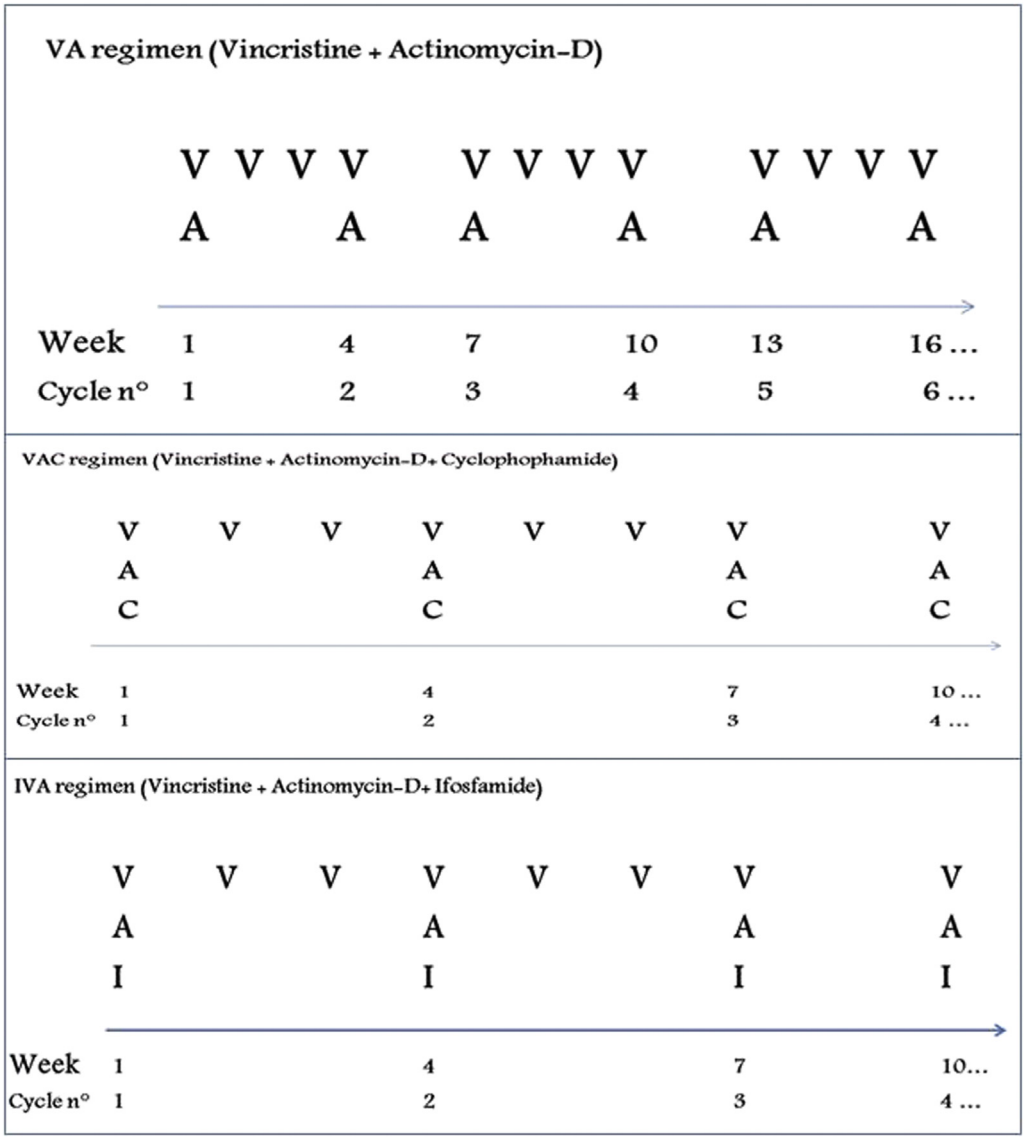


Fig. 2. Chemotherapy schedules. **Chemotherapy dosages**: Vincristine and actinomycin-D: 50 μg/kg/injection; if age >12 months and weight >10 kg: 1.5 mg/m$^2$. Endoxan®-cyclophosphamide: 50 mg/kg; if age >12 months and weight >10 kg: 1.5 g/m$^2$. Holoxan®-ifosfamide: 100 mg/kg × 2 d for patients >3 months and 5–10 kg; of age >12 months and weight >10 kg: 3 g/m$^2$ × 2 d. See text for further reductions in young children.

= complete disappearance of visible tumour with no residual disease; major partial response (PR ≥2/3) = volume response 66–99%; minor PR (<2/3) = volume response 34–65%; stable disease (SD) ≤ 33% reduction in tumour volume; progressive disease (PD) = more than 40% increase in the sum of the volumes of all measurable lesions, or the appearance of new lesions [13]. Response rate to specific regimen of chemotherapy was considered as follows: (CR+ PR ≥2/3+ PR <2/3).

### 2.4. Statistical methods

Data were analysed by the International Data Center (Istituto Oncologico Veneto I.R.C.C.S., Padua; Italy), considering information within the Remote Data Entry system as at May 2015. Outcome was defined as overall survival (OS) and event-free survival (EFS). The definition of OS was measured from the date of diagnosis to death from any cause. Events were defined for EFS as progression during chemotherapy, relapse after CR or death from any cause. Local control was defined as disappearance of all radiological signs of disease at the site of the primary or stable residual radiographic images for at least 6 months after completion of treatment. Survival curves were calculated by the Kaplan-Meier method [14]. The 3-year EFS and OS were reported along with their 95% confidence intervals (CI).

## 3. Results

A total of 50 cases with a diagnosis of IFS and age <2 years were considered during the study period. They represent 6.5% of all registered patients with NRSTS and 30.1% of those aged less than 2 years included in the NRSTS EpSSG database. Four older patients (>2 years) were registered during the same time in this database but their tumours did not manifest the specific transcript and were not included in the analysis. Overall clinical characteristics of the population are indicated in Table 1. Most tumours were not associated with specific congenital abnormalities (95.9%). Median age at diagnosis was 1.43 months (range: 0.03–18.73). The diagnosis was made before birth or during the first month of life for 40.0% of the patients and in 68.0% of the cases before the age of 3 months (so called 'congenital forms'). Tumours occurred mainly in the limbs (54.0%), with more than half ≥5 cm at diagnosis and none had lymph node spread. Histological local diagnosis was confirmed by national and/or international histology review in 39 and 15 cases respectively. The identification of ETV6-NTRK3 transcript was tested in 39/50 patients: FISH showed the presence of the fusion gene in 9/11 samples, RT-PCR was positive in 19/21 samples, and both tests were positive in 6/7 additional patients. All cases without histology review harboured the ETV6-NTRK3 translocation. In summary, the characteristic biological translocation was identified in 87.2% of tumours.

Table 1
Clinical characteristics of the population.

| | Number of patients n = 50 | % |
|---|---|---|
| **Age at diagnosis (months)** | | |
| <1 | 20 | 40.0 |
| 1–3 | 14 | 28.0 |
| 4–12 | 12 | 24.0 |
| >12 | 4 | 8.0 |
| **Congenital abnormalities associated** | | |
| Yes | 2 | 4.0 |
| *Ductus arteriosus persistens* | *1* | *50.0* |
| *Occipital haemangioma* | *1* | *50.0* |
| No | 47 | 94.0 |
| Missing data | 1 | 2.0 |
| **Gender** | | |
| Female | 18 | 36.0 |
| Male | 32 | 64.0 |
| **Post-surgical tumour staging (IRS)** | | |
| Group I (R0) | 11 | 22.0 |
| Group II (R1) | 8 | 16.0 |
| Group III a (biopsy) (R2) | 27 | 54.0 |
| Group III b (incomplete surgery) (R2) | 4 | 8.0 |
| **Primary tumour invasiveness (T)** | | |
| T1 – Localised to the organ or tissue of origin | 33 | 66.0 |
| T2 – Extending beyond the tissue or organ of origin | 17 | 34.0 |
| **Tumour size** | | |
| a:≤5 cm | 23 | 46.0 |
| b:>5 cm | 27 | 54.0 |
| **Regional lymph node involvement** | | |
| N0-No evidence of lymph node involvement | 50 | 100 |
| **Site of origin of primary tumour** | | |
| Extremities | 27 | 54.0 |
| Axial sites | 14 | 28.0 |
| *Abdomen* | *7* | |
| *Paraspinal* | *2* | |
| *Retroperitoneal* | *2* | |
| *Thorax* | *2* | |
| *Trunk* | *1* | |
| Non-parameningeal head and neck | 4 | 8.0 |
| Parameningeal | 3 | 6.0 |
| Genito-urinary non Bladder Prostate | 2 | 4.0 |
| *Kidney* | *2* | |

### 3.1. Treatment according to IRS group

According to initial surgery, eleven patients were classified as IRS-group I/R0, eight as IRS-group II/R1, thirty one as IRS-group III/R2, four after resection with macroscopic residual tumour and twenty seven after biopsy (Fig. 1).

**IRS I-II-group (n = 19)**: three out of 19 patients underwent primary re-excision of the tumour. No adjuvant chemotherapy was given according to the guideline recommendations in all but one case (a ruptured atypical hypercellular mesoblastic nephroma primary, IRS-group II/R1) that received 6 months of VA (treating physician's decision) with additional vincristine-cyclophosphamide for 2 months due to mild hepatic toxicity. Surgery comprised of wide tumour excision (18 cases), associated with a partial colectomy (three cases) or unilateral nephrectomy (two cases) and a limited chest wall excision (one case). One local relapse occurred in this group: a 17-d-old baby with a right wrist IFS who suffered a local relapse 2.5 months after microscopic incomplete surgery and then underwent radical surgery. He remains in 2nd CR 4 years after diagnosis. All 19 patients were alive in remission at the time of the analysis.

**IRS III-group (n = 31)**: Chemotherapy was administered to 27 patients for a median duration of 4.14 months (range: 0.46–12.06). The remaining four had a 'wait and see' strategy. Overall 25 patients started chemotherapy according to the protocol with VA regimen for 14 d to 12 months, median 4.14 months. Six patients then switched chemotherapy to IVA (three cases), VAC (two cases), or ID regimen (one case) either due to SD or PD (three cases), to facilitate surgery (two cases) or for a life threatening scenario (one case). Finally, one patient received the IVA regimen due to an initially incorrect diagnosis and another one received VAC by physician preference due to rapid growth of the tumour after diagnosis.

A wait and see approach was used for four IRS group-III/R2 patients. Among them, three patients needed delayed VA chemotherapy from 2–4 months

after diagnosis, all with response (1 CR, 2 PR>2/3) and are alive in remission at the end of follow up. One is alive with a residual mass after spontaneous tumour reduction (Table 2).

The overall response rate to chemotherapy was 62.9% (17/27 evaluable patients) and 68.0% specifically to VA regimen (17/25 cases). Tolerance of chemotherapy was manageable overall but seven cases had specific grade III–IV toxicity: three reversible VOD, one peripheral neurotoxicity with ptosis, one haematological grade IV neutropenia with grade III anaemia, one haemorrhage in the tumour during progression. A 1-month old patient received by error an overdose (100 fold) of actinomycin-D and died despite supportive care.

Delayed tumour surgery was performed after a median of 4.9 months (range: 1.2–20.5) from diagnosis in 19 cases, with a wide excision in 13 patients including a conservative parotidectomy (one case), a limited perineal excision (one case), and nephrectomy with adrenalectomy (one case). Limb amputation was performed for two children and an exenteration in one patient. Overall, resection was complete in 14 cases, with microscopic residual in four cases and a macroscopically incomplete resection in one patient. No further surgery was done for 11 IRS-III/R2 patients. In seven cases, this was due to physician's decision (despite a residual images following chemotherapy in four cases; after an initial wait and see strategy in three cases), after histological remission of a residual mass confirmed by biopsy (two cases), and a clinical complete remission after chemotherapy (one case).

### 3.2. Total burden of therapy

Among the 50 cases, 40 (80.0%) had tumour surgery: resection alone in 19 cases and associated with chemotherapy in 21 cases. Surgery was mostly conservative (37 cases) whereas three needed mutilating surgery. Only one patient with a progressive orbital parameningeal IFS despite VA than VAC regimens received proton radiotherapy at 54 Gy after an orbital exenteration. Two other patients had limb amputation (finger, hand). Overall, among the 47 survivors, chemotherapy was delivered in 29 cases (61.7%) and comprised a VA regimen alone (22 cases), with additional alkylating agents (six cases) and/or anthracycline drug (one case).

### 3.3. Congenital cases

Among the 34 infants with congenital IFS, 59.0% were discovered antenatally or before 1 month of age. The site was the limbs (47.1%), 'other' sites (35.3%), head-and-neck (11.8%) and genito-urinary (5.9%).

### 3.4. Outcome

At the time of analysis, 35 patients are in first complete remission (CR), one is alive after 1st line chemotherapy; one is alive with a residual mass after therapy, seven are in 2nd or greater CR off therapy, three have died and three are lost to follow-up in CR (Fig. 1). Ten patients had a tumour event, nine initially classified as IRS group III/R2 and one as IRS group II/R1: seven tumours progressed, one patient experienced a metastatic relapse, one had a local relapse and one patient died due to toxicity. Among the 10 cases with tumour events, eight had tumours with ETV6-NTRK3 transcript, one without and in one case the analysis had not been performed. Tumour progression occurred in two cases after a wait and see strategy (Table 2), after VAC-IVA/ID regimens (two cases with refractory disease responsible for patients' death), and after the VA regimen (three cases were treated with VAC and surgery, surgery alone and ID regimen, and are in subsequent CR). One patient developed lung metastases 2.5 years after a head and neck tumour initially unresponsive to VA but

Table 2
IRS III/R2 patients with a 'wait and see' strategy.

| | Patient no 1 | Patient no 2 | Patient no 3 | Patient no 4 |
|---|---|---|---|---|
| Age at diagnosis | 10 d | 41 d | 68 d | 11 months |
| ETV6-NTRK3 transcript | Presence | Presence | Presence | Presence |
| Site of primary tumour | Foot | Shoulder | Retroperitoneal | Tight |
| Invasiveness | T1 | T2 | T1 | T1 |
| Tumour size | ≤5 cm | >5 cm | >5 cm | ≤5 cm |
| Time from diagnosis to start of CT | 4 months | – | 3 months | 2 months |
| Reason for treatment | Progressive disease | – | Progressive disease | Absence of regression |
| Therapy | CT (VA regimen for 5 months) | – | CT (VA regimen for 3 months) | CT (VA regimen for 5 months) + HCR after delayed surgery |
| Status | Alive in CR off therapy | Alive with tumour decreased from diagnosis | Alive in CR off therapy | Alive in 1st CR off therapy |
| Time from diagnosis to last FUP | 5 years and 7 months | 2 years and 11 months | 3 years | 7 years and 10 months |

**Abbreviations**: CT chemotherapy, HCR histologic complete response; CR complete remission; VA vincristine-actinomycin-D, FUP follow-up.

responding to subsequent ID chemotherapy, (allowing a R1 resection). At the time of the report, this patient was alive in secondary remission after second-line chemotherapy and pulmonary metastasectomy. One patient died due to an overdosage of chemotherapy. Two patients died from disease. The three patients that received mutilating surgery are alive and in continuing complete remission off therapy. After a median follow-up of 4.7 years (range 1.9–9.0), 3-year EFS and OS were respectively 84.0% (95% CI 70.5–91.7) and 94.0% (95% CI 82.5–98.0) (Fig. 3).

## 4. Discussion

This study demonstrates that a conservative treatment approach is feasible in young children with IFS without jeopardising survival. Despite many having large tumours at diagnosis, mutilating surgery was only required in three cases and alkylating-anthracycline-free chemotherapy sufficient to achieve cure in 74.2% of patients requiring chemotherapy. Our experience also confirms that prospective multi-institutional trials are possible even in very rare tumours in children at an European level [15]. The very good compliance with treatment guidelines within the different European countries involved, e.g. 94.7% of IRS I-II group patients were treated with surgery alone, and 93.3% of IRS group III patients received the VA regimen as first line therapy as recommended, shows that the goal to standardise the IFS treatment was achieved.

This series confirms some of the general clinical characteristics of IFS as a rare disease occurring in very young patients (median age 1.43 months), predominantly in males (64.0%), and mainly in limbs (54.0%) [16,17]. According to some authors, IFS can be either a histological or a biological defined entity [4,11,18]. This series reported that the ETV6-NTRK3 fusion gene

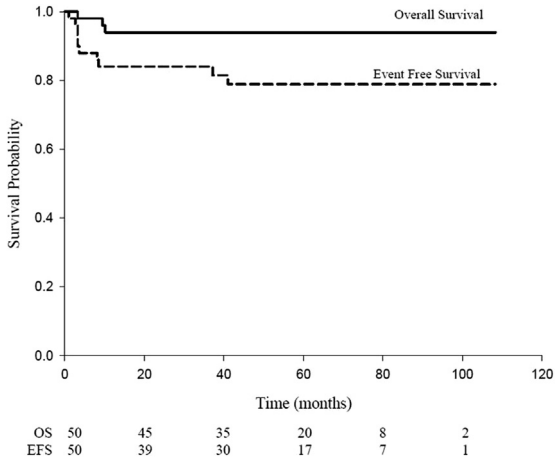


Fig. 3. Event-free survival and overall of the entire population. Abbreviations: OS, overall survival; EFS, event-free survival.

documented by FISH or RT-PCR was present in 87.2% of the patients with IFS where the investigation was performed. This is a helpful tool where there is pathological difficulty in confirming the diagnosis of IFS [10]. Nevertheless, it is important to note that the ETV6-NTRK3 fusion gene is not totally specific to IFS. It has been described in congenital hypercellular mesoblastic nephroma, mammary analogue secretory carcinoma of salivary glands and of the breast, and in some leukaemias [19]. The definition of the 'infantile' nature of fibrosarcoma is not precise in the literature and an age limit up to 2 years is used by most authors [16,17,20,21]. Even if some rare series consider patients with IFS up to 3 years, we focused on the population of very young children (≤2 years of age at diagnosis) for whom the consequences of treatment (chemotherapy, radical surgery and radiotherapy) are a major factor guiding treatment decisions, and also to be consistent with other analyses [1,6,22].

Other studies previously reported the very good OS of children with IFS, and emphasised the challenge of tumour resectability without anatomical or functional damage. Even if surgery should still be seen as the cornerstone of therapy in this tumour, our experience highlighted that the use of chemotherapy may also play a critical role in large diffuse inoperable tumours. Initial grossly tumour resection (IRS-I/II–R0/1) was only possible in 38.0% of patients but tumour shrinkage achieved with chemotherapy in the majority of initially unresected tumours allowed a secondary conservative surgical approach in the majority. It is clear, however, that postoperative chemotherapy is not necessary after a delayed complete macroscopic tumour resection (IRSI/II-R0/1) or total necrosis. Similarly, adjuvant chemotherapy was unnecessary for IRS group I/R0 patients but also for IRS group II/R1. In this cohort, only one local recurrence occurred out of 19 patients, and was successfully treated with further surgery. Nevertheless, the overall consensus should be to try to avoid incomplete surgery with macroscopic residue.

The VA regimen, a combination that does not contain alkylating agents or anthracyclines, appears to be very active in IFS. Acute toxicity was not negligible but despite three mild episodes of VOD and one toxic death (associated with a dose error) we believe that VA is more advantageous compared with VAC chemotherapy (cyclophosphamide) or anthracycline containing regimens, as it reduces the gonadal and mutagenic toxicity of cyclophosphamide/ifosfamide and the cardiac toxicity of anthracyclines in very young children, previously used in up to 53–87% of all patients [6,20,23,24]. The optimal duration of preoperative chemotherapy was not defined in our protocol and still needs to be clarified.

Previously it was unclear whether it is possible to avoid delayed surgery in IRS-group III/R2 patients, after successful use of neoadjuvant chemotherapy with

radiological complete remission. In our experience, 35.4% (11/31) of IRS-III/R2 patients did not need delayed resection due to a radiologic CR or VGPR after neoadjuvant chemotherapy, and we therefore recommend this approach.

The possibility of spontaneous regression in IFS has already been reported [25–27]. The observation that one patient in our series showed a spontaneous tumour shrinkage supports a 'wait and see' strategy especially in very young patients, i.e. patients <3 months with a non-resectable primary in a non-threatening situation, in whom tolerance to chemotherapy may be poor. This approach may be extended to older infants, if strict follow-up could be ensured. If progression does occur, then neoadjuvant chemotherapy with VA should be started.

The small number of relapses in our cohort does not allow further analysis of prognostic factors and subsequent risk-stratification. A recent epidemiological retrospective study among a large cohort of 224 children ≤2 years with IFS did not show any significant survival difference according to various risk factors such as margin status, nodal involvement, tumour size or treatment modalities [17].

In conclusion, this study highlights the importance of paediatric international cooperation in developing prospective studies for very rare childhood tumours. Due to the rarity of this tumour all medical decisions should be shared through multidisciplinary discussions at a regional, national or international level [15]. This should allow a conservative treatment approach where feasible in young children with IFS without jeopardising survival.

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## Conflict of interest statement

All authors disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organisations within that could inappropriately influence (bias) their work.

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