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CLINICAL STUDY

# Primary intracranial soft tissue sarcoma in children and adolescents: a cooperative analysis of the European CWS and HIT study groups

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**Abstract** Purely intracranial soft tissue sarcomas (ISTS) are very rare among children. A retrospective database analysis of the Cooperative Weichteilsarkom Studiengruppe (CWS) and brain tumor (HIT) registries was conducted to describe treatment and long-term outcome of children and adolescents with ISTS. Nineteen patients from Germany, Austria and Switzerland were reported between 1988 and 2009. Median age at diagnosis was 9.7 years (range, 0.5–17.8). Central pathological review was performed in 17 patients. Eleven patients underwent a total and five a subtotal tumor resection. A biopsy was done in one patient. In two patients no data concerning extent of initial resection was available. Radiotherapy was performed in 15 patients (first-line, $n = 11$; following progression, $n = 4$). All but one patient received chemotherapy (first-line, $n = 7$, following progression, $n = 5$; first-line and following progression, $n = 6$). With a median follow-up of 5.8 years (range, 0.6–19.8) ten patients were alive in either first or second complete remission. Seven patients died due to relapse or progression and two were alive with progressive disease. Estimated progression-free and overall survival at 5 years

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were 47 % (±12 %) and 74 % (±10 %), respectively. About 50 % of patients with ISTS remain relapse-free after 5 years. Multimodality treatment including complete tumor resection and radio-/chemotherapy is required to achieve sustained tumor control in patients with ISTS. Early initiation of post-operative non-surgical treatment seems to be important to prevent recurrence. Due to the intracranial localization local therapy should follow the recommendations used in brain tumors rather than in soft tissue sarcomas, whereas chemotherapy should be guided by histological subtype.

**Keywords** Soft tissue sarcomas · Children · Adolescents · Intracranial · Chemotherapy · Radiotherapy

## Introduction

Soft tissue sarcomas (STS) account for approximately 6 % of all childhood malignancies [1]. In Germany the age-standardized incidence for all pediatric STS is 0.9 per 100.000/year, 0.7 per 100.000/year for rhabdomyosarcoma (RMS)-like, and 0.18 per 100.000/year for non-RMS-like STS [1]. In terms of histopathology, location and biological behaviour STS are extremely heterogenous [2]. Both RMS and non-RMS STS can occur in the head and neck region. However, except for parameningeal RMS with intracranial extension purely intracranial STS (ISTS) are exceptionally rare among children [2]. The true incidence of ISTS remains unknown, but estimates between 0.1 and 4 % of intracranial tumors have been reported [3–7]. Reports on pediatric ISTS are limited to single-institutional case reports or small, single-institutional case series [4, 7–16].

Children with STS or primary tumors of the brain are treated in Germany, Austria and Switzerland according to the prospective multicenter trials of the Cooperative Weichteilsarkom Studiengruppe (CWS) and brain tumor (HIT) study groups of the Pediatric Oncology and Hematology Society of the German Language [17–23]. However, neither prospective clinical trials nor established treatment guidelines are available for children with ISTS so far. Thus, these study groups encourage participating centres to report also patients with rare entities like ISTS serving as a national platform for data acquisition and analysis. Furthermore, they provide the best available management recommendations for such uncommon tumors and allow also performing central cytological [cerebrospinal fluid (CSF)], neuroradiological, and pathological review within an established network. The aim of the present retrospective study was to report the clinical characteristics, treatment and outcome of children and adolescents with ISTS registered in the databases of the CWS and HIT study groups.

## Patients and methods

Between 1988 and 2009 nineteen patients (male, $n = 12$; female, $n = 7$) with non parameningeal RMS ISTS (ICD-O 8850/0-9364/3) from Germany, Austria and parts of Switzerland were reported as observational patients to the CWS ($n = 8$), HIT ($n = 7$) or both ($n = 4$) registries. The treating physicians decided which of the study centres (CWS, HIT or both) were contacted at the time of diagnosis. Institutional review board approval was obtained for all CWS and HIT trials. The HIT 2000 study was registered at the US National Cancer Institute (NCT00303810). All data were extracted without direct personal identification. Treatment centres were contacted by the CWS or HIT centres in order to obtain the most recent follow-up information. Patients' data were carefully checked to avoid double reporting. Study records were reviewed at the study centres prior to inclusion to ensure that only patients with purely ISTS were reported.

Local magnetic resonance imaging (MRI) of the brain was done preoperatively in all patients. None of the patients had documented metastatic disease at the time of diagnosis. However, complete CNS staging including spinal MRI and cytological analysis of cerebrospinal fluid (CSF) was performed in nine patients (47 %) only. In six patients neither spinal MRI nor CSF analysis was done. In the remaining patients exclusion of CNS dissemination was based on CSF analysis ($n = 2$) only. In two patients data on CNS staging was missing. Central pathological review was done at the time of diagnosis in 17 patients at the Neuropathology Reference Centre of the HIT network at the Institute of Neuropathology, University of Bonn and/or at the Kiel Pediatric Tumor Registry according to the current World Health Organization (WHO) classifications of tumors of the central nervous system (CNS) and tumors of soft tissue and bone [24, 25]. Additional institutions provided pathological reviews for five patients. Survival probability was estimated by the Kaplan–Meier method. Overall survival (OS) was defined as date of diagnosis to death of any cause or to the date of last visit; progression-free survival (PFS) was defined as date of diagnosis to date of death, first progression, relapse or occurrence of secondary malignancy.

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**Table 1** Basic clinical characteristics of study patients

| Patient | Gender | Age at diagnosis (yrs) | Diagnosis[a] | Symptoms | Duration of symptoms | Tumor location |
|---|---|---|---|---|---|---|
| 1 | F | 9.7 | Sarcoma (NOS) | Headache, seizures | 2 months | Left temporal lobe |
| 2 | F | 11.9 | Sarcoma (NOS) | n.r. | n.r. | Right temporal lobe |
| 3 | F | 7.8 | Sarcoma (NOS) | Headache, vomiting, vertigo | 4 weeks | Posterior cranial fossa |
| 4 | M | 14.1 | Embryonal rhabdomyosarcoma | Headache | 2 months | Posterior cranial fossa |
| 5 | M | 3.2 | Sarcoma (NOS) | Seizure | 1 week | Left frontal lobe |
| 6 | M | 10.9 | Small/spindle cell sarcoma (NF1) | Headache, vomiting, fatigue | 1 week | Right fronto-temporal lobe |
| 7 | F | 1.9 | Sarcoma (NOS) | Ataxia, torticollis | 2 weeks | Central midline/3rd ventricle |
| 8 | M | 3.4 | Alveolar rhabdomyosarcoma (break in the FKHR gene) | Vomiting | 2 weeks | Pinealis region |
| 9 | M | 17.8 | Myxoid/round cell liposarcoma t(12;16) (q13;p11) | Headache | 2 weeks | Left frontal lobe |
| 10 | M | 10.4 | Fibrosarcoma (adult type) | Headache, nausea, vomiting, drowsiness | 1 week | Right frontal lobe |
| 11 | M | 0 | Malignant mesenchymal tumor | Hydrocephalus | – | 3rd ventricle/pinealis region + temporo-parieto-occipitalcysts |
| 12 | F | 5.7 | Sarcoma (NOS) | Vomiting | 8 weeks | Left parieto-occipital lobe |
| 13 | M | 0.5 | Sarcoma (NOS) | Vomiting, macrocephalus | 1 day | Right cerebral hemisphere |
| 14 | M | 10.6 | Sarcoma (NOS) | Headache, diplopia | 2 weeks | Left fronto-temporal lobe |
| 15 | M | 12.2 | Chondrosarcoma | Headache | 1 year | Left parieto-occipital lobe |
| 16 | F | 9.5 | Malignant mesenchymal tumor | Headache, vomiting, diplopia | 3 days | Left temporo-parieto-occipital lobe |
| 17 | M | 12.1 | Mesenchymal chondrosarcoma | Headache | n.r. | Right parietal lobe |
| 18 | F | 4.7 | Embryonal rhabdomyosarcoma | Left hemiparesis | 2 days | Right fronto-parietal lobe |
| 19 | M | 13.4 | Anaplastic hemangiopericytoma | Headache | 4 months | Right occipito-parietal lobe |

*F* female, *FKHR* forkhead in RMS (rhabdomyosarcoma), *M* male, *NF1* neurofibromatosis type 1, *NOS* not otherwise specified, *n.r.* not reported

[a] Following central pathological review. In two patients (patient 2, 3) central pathological review was not done

Statistical analysis was done using SPSS software (IBM SPSS Statistics 19).

## Results

### Basic clinical characteristics

The clinical characteristics of study patients are shown in Table 1. Median age at diagnosis was 9.7 years (range, 0.5–17.8). Duration of symptoms was documented in 16 patients ranging from 1 day to 1 year (Table 1). Median duration of symptoms was 2 weeks. Histopathological diagnoses included sarcoma NOS (not otherwise specified) ($n = 8$), embryonal RMS ($n = 2$), chondrosarcoma ($n = 2$), malignant mesenchymal tumor ($n = 2$), alveolar RMS ($n = 1$), myxoid liposarcoma ($n = 1$), fibrosarcoma ($n = 1$), anaplastic hemangiopericytoma ($n = 1$) and small/spindle cell sarcoma ($n = 1$). In two cases (alveolar RMS, myxoid liposarcoma) diagnosis was confirmed by molecular genetics. In ten out of 17 patients local and central neuropathologies were concordant. Supratentorial tumor location was predominant. Two children had infratentorial tumors. In nine patients more than one lobe was involved (Table 1).

### Surgery and non-surgical treatment

Treatment-related and outcome data are summarized in Tables 2 and 3. Eleven patients underwent a complete and five a subtotal tumor resection. A biopsy was done in one patient. In the remaining two patients no data concerning extent of resection was available. Radiotherapy was performed in 15 patients (first line, $n = 11$). Median tumor dose was 54 Gy (range, 44.8-68). Four patients were irradiated following progression. All but one patient received chemotherapy (first-line, $n = 7$, following progression, $n = 5$; first-line and following progression, $n = 6$) according to STS, brain tumor or mixed/individualized protocols (Table 2).

**Table 2** Treatment characteristics of study patients

| Patient | Surgery | First line radiotherapy | First line chemotherapy | Treatment sequence |
|---|---|---|---|---|
| 1 | Total resection | Local (54 Gy) | HIT'91 (sandwich + maintenance chemotherapy) | S-CT-RT-CT |
| 2 | n.r. | No | No | S-S(LR + DR-CNS)-S(LR)-RT-S(LR)-CT(LR) |
| 3 | n.r. | Local | No | S-RT-S(DR-CNS)-RT-S(DR-CNS)-RT-S(DR-CNS)-CT-S(DR-CNS)-CT-S(DR-CNS) |
| 4 | Total resection | CS (55/35 Gy)[a] | HIT'91/CWS (EVAIA) | S-CT-RT-CT |
| 5 | Subtotal resection | Local (47.6 Gy) | HIT'91 (IFO/VP16) CWS-96 (VAIA) | S-CT-RT-CT |
| 6 | Total resection | CS (68/36 Gy)[a] | Weekly vincristine (during RT) followed by CWS-96 maintenance therapy (oral trofosfamide, idarubicine, VP16) | S-RT/CT-CT-S(LR)-CT(PD) |
| 7 | Total resection | Local (54 Gy), (at the age of 3 years) | Five courses HIT-SKK | S-CT-RT |
| 8 | Subtotal resection | No | CWS guidance (stage IV) | S-S(LR)-CT(DR-CNS)-CT/RT(PD) |
| 9 | Total resection | No | No | S |
| 10 | Total resection | No | No | S-S(LPD)-RT(DR-CNS)-γ-Knife-CHTH(PD) |
| 11 | Subtotal resection | No | No | S (following spontaneous regression)-S(LPD)-CT(PD) |
| 12 | Total resection | No | CWS-91 | S-CT-S(LR)-RT-CT |
| 13 | Biopsy | No | One course VCR, IFO, VP16 | Biopsy-CT-parental treatment refusal |
| 14 | Total resection | Local (44.8 Gy) | CWS-96 (IVA) | S-CT-RT-CT-S(LR)-CT-S(LR + DR-CNS) |
| 15 | Total resection | Local (60 Gy) | Two courses VIDE, two courses HD-MTX | S-CT-RT |
| 16 | Subtotal resection | CS (55.2/35.2 Gy)[a] | CWS-86 | S-S(LPD)-CT-RT |
| 17 | Subtotal resection | No | No | S-S(LPD)-CT |
| 18 | Total resection | Local (54.4 Gy) | CWS-86 Austria (VAIA + MTX, CIS, ARAC) | S-CT-RT-CT |
| 19 | Total resection | Local (54 Gy) | CWS-86 (VAIA) + cisplatin | S-CT-RT-CT-CT(DR-SYS)-RT-PSCT-IFN/IL-2/THAL(PD)-PEGIFN-S(PD)-RT-IFN/THAL(PD)-RT-BEVA-BEVA/THAL(PD)-BEVA/THAL(PD)-BEVA/LENA(PD)-ERLO/SORAF |

*ARAC* cytarabine, *BEVA* bevacizumab, *CIS* cisplatin, *CS* craniospinal, *CT* chemotherapy, *DR-CNS* distant relapse within the CNS, *DR-SYS* distant relapse outside the CNS, *ERLO* erlotinib, *EVAIA* etoposide, vincristine, dactinomycin, ifosfamide, doxorubicin, *HD* high-dose, *IFN* interferon, *IFO* ifosfamide, *IL-2* interleukin 2, *IVA* ifosfamide, vincristine, dactinomycin, *LENA* lenalidomide, *LPD* progression of local residual tumors, *LR* local relapse, *MTX* methotrexate, *NED* no evidence of disease, *n.r.* not reported, *PD* progressive disease, *PEGIFN* pegylated interferon, *PSCT* peripheral blood stem cell transplantation, *RT* radiotherapy, *S* surgery, *SORA* sorafenib, *THAL* thalidomide, *VCR*, vincristine, *VAIA* vincristine, dactinomycin, ifosfamide, doxorubicin, *VIDE* vincristine, ifosfamide, doxorubicin, etoposide

[a] Tumor and craniospinal dose

## Clinical course and outcome

With a median follow-up of 5.8 years (range, 0.6–19.8) 10 patients were alive in either first ($n = 7$) or second ($n = 3$) complete remission (Table 3). Seven patients died due to relapse or progression and two were alive with progressive disease. The disease status according to the extent of resection and the use of postoperative non-surgical treatment is shown in Fig. 1. Estimated PFS and OS at 5 years were 47 % (±12 %) and 74 % (±10 %) (Fig. 2a, b).

**Table 3** Time to first progression and outcome

| Patient | Time to first progression (months) | Outcome [follow-up (years)] |
|---|---|---|
| 1 | – | NED (10.0) |
| 2 | 10 | AWPD (3.5) |
| 3 | 13 | AWPD (5.5) |
| 4 | – | NED (11.9) |
| 5 | – | NED (12.8) |
| 6 | 15 | DOD (1.8) |
| 7 | – | NED (8.3) |
| 8 | 1 | DOD (1.1) |
| 9 | – | NED (1.8) |
| 10 | 1.5 | DOD (0.9) |
| 11 | 65 | DOD (5.8) |
| 12 | 3 | NED (7.4) |
| 13 | 0.5 | DOD (0.6) |
| 14 | 10 | DOD (1.3) |
| 15 | – | NED (5.5) |
| 16 | 1 | NED (9.0) |
| 17 | 3 | NED (6.9) |
| 18 | – | NED (14.3) |
| 19 | 108 | DOD (19.8) |

*AWPD* alive with progressive disease, *DOD* dead of disease, *NED* no evidence of disease

Progression-free survival at 5 years was 64 % (±15 %) for patients following gross total resection (GTR) compared with 33 % (± 19 %) for patients in whom a less than GTR was achieved (log-rank test, $p = 0.072$; Fig. 2c). No difference in OS at 5 years between the two groups was observed [73 % (±13 %) vs. 66 % (±19 %); log-rank test, $p = 0.38$].

Median time to first progression was 6 months (range 0.5–108). Only two patients had late relapses 65 and 108 months after diagnosis. In the majority of cases the first recurrence was either a local progression after initial incomplete resection or a locoregional relapse after complete resection. Relapses involved CNS except in one patient who developed multifocal bone metastases. Following diagnosis of recurrence, the disease was rapidly progressing with a median survival time of 9.5 (range, 5–132) months.

Seven patients (patients 1, 4, 5, 7, 9, 15, 18) were in first continuous complete remission (CCR) for a median of 10 years (range, 1.8–14.3). Histopathological diagnoses in these patients were sarcoma NOS ($n = 3$), embryonal RMS ($n = 2$), chondrosarcoma ($n = 1$), and myxoid liposarcoma ($n = 1$). A total resection was accomplished in all but one patient who underwent a subtotal resection. The patient with myxoid liposarcoma was treated by surgery alone. All other patients received postoperative chemo- and radiotherapy. These six patients were given chemotherapy after tumor resection, followed by radiotherapy (local, $n = 5$; craniospinal, $n = 1$). Chemotherapy was then continued in four patients after radiotherapy (Table 2).

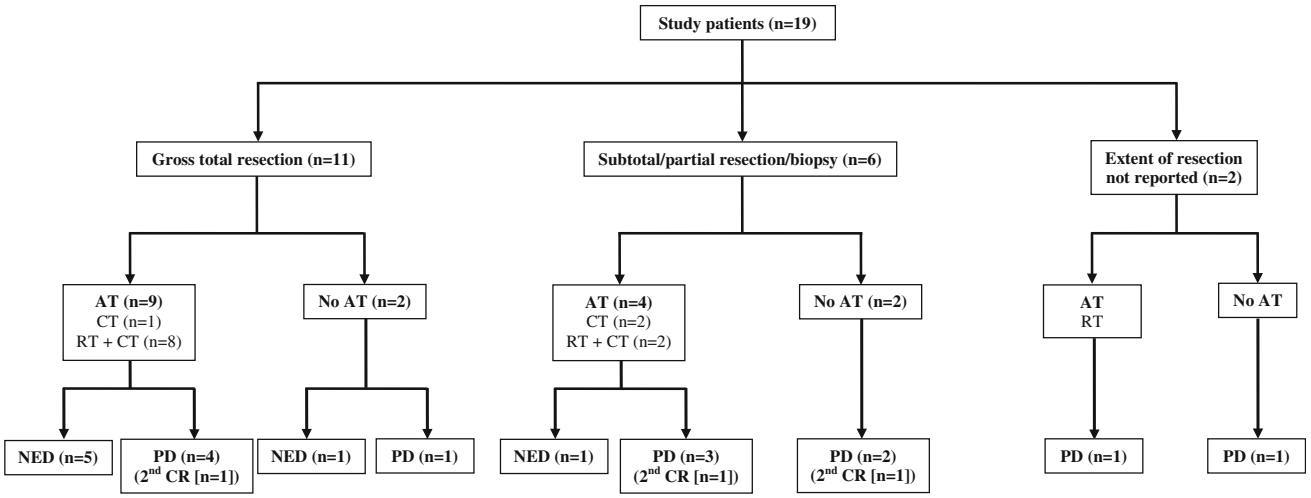
Three patients [patient 12 (sarcoma NOS), patient 16 (malignant mesenchymal tumor), patient 17 (chondrosarcoma)] developed early local relapse ($n = 1$) or local progressive disease ($n = 2$) 3, 1, and 3 months following primary total or subtotal resection. Secondary surgery—information about secondary surgery was missing in one patient—was performed immediately after diagnosis of relapse followed by chemotherapy in two and radiotherapy in three patients. All patients are alive in second complete remission for 82, 89 and 108 months.

Seven patients (patients 6, 8, 10, 11, 13, 14, 19) died of disease and two (patients 2, 3) were alive with progressive disease. Diagnoses included sarcoma NOS ($n = 4$), malignant mesenchymal tumor ($n = 1$), alveolar RMS ($n = 1$), fibrosarcoma ($n = 1$), anaplastic hemangiopericytoma ($n = 1$) and small/spindle cell sarcoma ($n = 1$) in a patient with neurofibromatosis type 1. Four of these patients underwent a complete and two a subtotal resection. A biopsy was done in one patient. In the remaining two patients no data concerning extent of initial resection was available. Three of the nine patients received both radiotherapy and chemotherapy following initial surgery; two patients received chemotherapy and one patient had radiotherapy only. In the remaining three patients no adjuvant therapy was given.

## Discussion

### Available data on childhood intracranial soft tissue sarcomas

Due to their rarity our current knowledge of ISTS is based on case reports and few retrospective case series, most of them published before the year 2000 [7–16]. The largest series to date was presented by a Canadian group in 2003 and included 16 patients; 14 of them had ISTS and two spinal STS [7]. This series comprised patients with undifferentiated sarcoma ($n = 7$), meningeal sarcoma ($n = 4$), sarcoma NOS ($n = 2$), and RMS ($n = 1$). Fifty-three percent of patients achieved a total and 47 % a subtotal resection. Adjuvant radiotherapy and chemotherapy were used in 9 and 12 of patients with ISTS [7]. Thus our and the Canadian study compare very well with regard to treatment-related parameters. Data on outcome was provided for 12 children with ISTS in the Canadian study; six of them died after a median of 6.5 months (range, 1–41). The other six patients were alive 2–16 years after diagnosis [7]. An unfavourable outcome of children and adolescents with ISTS was also observed in smaller series and case reports [4, 10–12].




Abbreviations: *AT*, adjuvant treatment; *CR*, complete remission; *CT*, chemotherapy; *NED*, no evidence of disease; *PD*, progressive disease; *RT*, radiotherapy.

**Fig. 1** Status of disease according to the extent of resection and use of postoperative non-surgical treatment

## Diagnostic work-up and reference pathology

Despite the fact that a high incidence of CNS dissemination in ISTS was already emphasized in historical series [7–9], the number of patients who underwent complete CNS staging (including spinal MRI and cytological analysis of CSF) in our study was surprisingly low (47 %). Thus initial diagnostic evaluation should include complete CNS imaging as well as examination of CSF in all patients with ISTS. To our knowledge central pathological review was not performed in any of the previously published studies on childhood ISTS. Considering the relatively high rate of discordant results between local and central pathology (37 %), central pathological review by experienced neuropathologists and pediatric pathologists is of outstanding importance in these patients and clearly contributed to the quality of our study. Because of their clinical relevance the results of central pathological review should be obtained as soon as possible following tumor resection. Additional molecular genetic analysis of tumor specimens might be helpful in selected cases to confirm diagnosis [26].

## Histological subtypes and outcome

Due to the variety of different tumor entities included in the present series it is difficult to assess the impact of a particular histopathology on prognosis. Histopathological diagnoses of the ten survivors in our series were sarcoma NOS ($n = 4$), embryonal RMS ($n = 2$), chondrosarcoma ($n = 2$), myxoid liposarcoma ($n = 1$), and malignant mesenchymal tumor ($n = 1$). Accordingly successful treatment is reported anecdotally in individual patients with intracranial fibrosarcoma [8, 13], chondrosarcoma [12, 14, 15], and embryonal RMS [7, 9, 16] following intensive multimodality treatment. In the Canadian study 4 out of 8 patients with undifferentiated or unclassifiable sarcoma and two out of three with meningeal sarcoma died [7]. In our series four out of eight patients with sarcoma NOS relapsed; two of them died and two were alive with progressive disease. Thus entities such as undifferentiated, unclassifiable or sarcoma NOS seem to have an unfavourable prognosis.

## Extent of resection, time to progression and outcome

In the study by Al-Gahtany et al. [7] mean survival following total resection was 6.2 years compared to 3.4 years in patients who underwent a subtotal resection, but no further statistical analysis to compare these figures was provided. In our series there was a trend toward improved PFS among patients who underwent a GTR compared with patients in whom a less than GTR was obtained (PFS 64 % vs. 33 %, $p = 0.072$). Thus a complete tumor resection seems to be a prerequisite for longer survival in patients with ISTS. Of note, very few histological subtypes such as liposarcoma, might be cured by complete surgical resection alone.

An aggressive clinical behaviour with early progression and death within months is reported in many series [4, 7–10, 13]. In our study the median time to progression was 6 months and only two patients had late relapses. In three patients who developed early local relapse or local

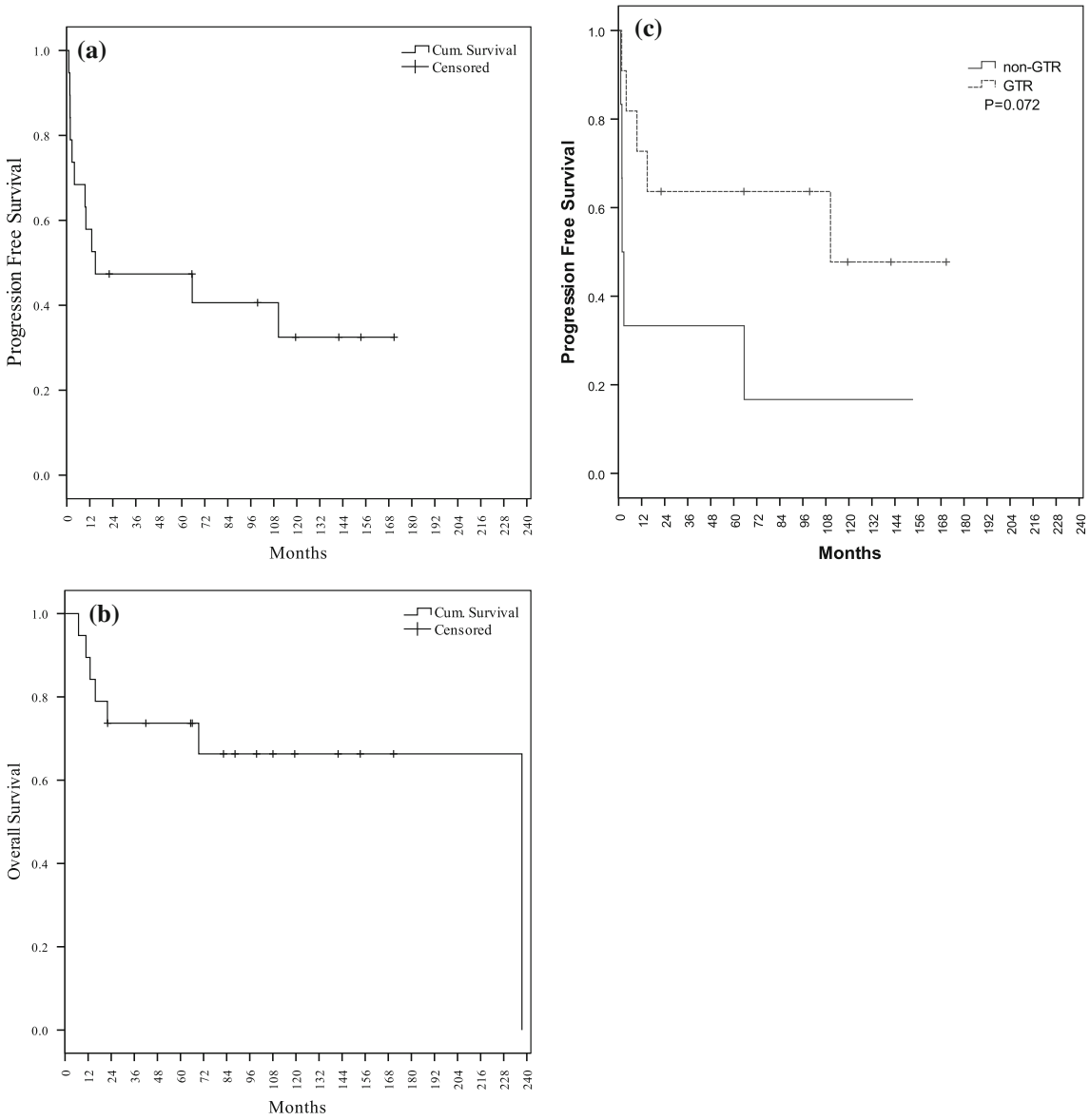



**Fig. 2** **a** Kaplan–Meier plots of the estimated progression-free survival rate for all 19 study patients. **b** Kaplan–Meier plots of the estimated overall survival rate for all 19 study patients. **c** Kaplan–Meier plots of the estimated progression-free of patients after GTR and less than GTR

progressive disease between 1 and 3 months following primary resection a second complete remission could be achieved. Thus, the short PFS seems to require rapid initiation of non-surgical treatment after tumor resection to improve local tumor control.

## Postoperative non-surgical treatment

Although postoperative local radiotherapy with adequate doses (44.8–54 Gy) seems to be essential to achieve local tumor control [7–10, 12–16], all our patients in first CCR started with postoperative chemotherapy before radiotherapy; four of them continued chemotherapy after radiotherapy. Thus administration of (one or two courses) of chemotherapy before the start of radiotherapy is one treatment option until completion of radiotherapy planning.

Since six out of seven patients in first CCR received first-line radiotherapy in contrast to five out of 12 patients who subsequently relapsed, radiotherapy is a prerequisite to achieve long-term disease control. Craniospinal irradiation (CSI) was done in three of our patients (patient 4, 6, 16), who all had localized disease at the time of diagnosis confirmed by complete CNS staging. Five patients received CSI in the study by Al-Gahtany et al. [7]; two of them had initial CNS spread. Following CSI two patients were alive, two died and in the remaining fifth patient follow-up data was

missing. Thus far, there are no data to suggest that CSI is able to prevent disease recurrence and/or dissemination in patients with non metastatic disease at diagnosis. Craniospinal irradiation, however, seems to be the most appropriate therapeutic option in case of initial CNS dissemination. The potential benefits and risks of CSI, particularly in younger children have to be carefully weighted and discussed with parents.

Chemotherapy is used in a considerable number of reported patients with ISTS [4, 7, 9, 16], even for chemoresistant histological subtypes [10, 13, 15], but its impact on outcome is still unknown. However, almost the vast majority of long-term survivors reported in the literature [7, 9, 13, 15, 16] has received multimodality treatment including chemotherapy. Although the optimal treatment schedule, duration and combination of drugs have not yet been established, a "sandwich" regimen that uses chemotherapy before and after radiotherapy might be appropriate. Six of seven patients were treated by such a "sandwich" approach. The early administration of chemotherapy when the blood brain barrier is disrupted postoperatively might have contributed to the more favourable outcome of patients treated by a "sandwich strategy". It is quite obvious to use cytotoxic drugs with known efficacy in STS such as vincristine, ifosfamide, etoposide, anthracyclines or dactinomycin. The type of chemotherapy in patients with ISTS should be guided by histology/histological subtype. Some of our patients continued to receive chemotherapy after radiotherapy, but the benefit of this approach is not defined for non-RMS ISTS.

## Conclusion

The present study is the first multi-institutional series on children and adolescents with centrally reviewed ISTS. The prospective collection of clinical, pathological, treatment-related and follow-up data of children and adolescents with ISTS within national or international registries is needed. This allows better defining favourable and unfavourable prognostic parameters and is a prerequisite for the development of risk-adapted therapeutic standards. The CWS and HIT study groups have, therefore, agreed on a common policy and close cooperation in patients with ISTS.

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