Thesis

Management of rare molecularly defined soft tissue sarcomas in children and adolescents: A literature review and retrospective case study

submitted by

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Declaration of Academic Integrity

I hereby confirm that the present diploma thesis is the result of my own independent scholarly work. I also confirm that in all cases, where material from the work of others (in books, articles, essays, dissertations, and on the internet) is acknowledged, quotations and paraphrases are clearly indicated. No material other than that cited in the reference list has been used. I have read and understood the Medical University's regulations and procedures concerning plagiarism.

Graz, 05.12.2023 *Johanna Schuß m.p.*

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Zusammenfassung

Hintergrund: Die molekulare Diagnostik hat nicht nur die Klassifikation von Weichteilsarkomen (WTS) verändert und zur Definition von neuen Subtypen geführt, sondern ermöglicht auch den Einsatz neuer zielgerichteter Therapien. Aufgrund der Seltenheit dieser Tumoren fehlen Richtlinien zum Management dieser genetisch definierten Entitäten im klinischen Alltag.

Methoden: Es wurde eine Literaturrecherche zu den diagnostisch-therapeutischen Strategien bei seltenen fusionspositiven WTS durchgeführt. Zudem eingeschlossen wurden Fallberichte von 7 PatientInnen mit seltenen, molekulargenetisch definierten WTS, die an der Abteilung für Pädiatrische Hämato-Onkologie der Univ. Klinik für Kinder- und Jugendheilkunde der Medizinischen Universität Graz behandelt wurden (2010-2023).

Ergebnisse: Von 93 Patient*innen mit infantilen Fibrosarkomen (IFS) wurden bei 49 (53%) andere Genfusionen als *ETV6-NTRK3* detektiert (*NTRK1-3, BRAF, MET, ALK, RET*). In 79% (27/34) der Patient*innen mit lokalisierten IFSs war die alleinige (komplette oder inkomplette) chirurgische Resektion kurativ, wobei es bei 47% (7/15) mit inkompletter Resektion zu einem Rückfall kam. Von den 30 Patient*innen mit IFS, die eine zielgerichtete Therapie im Rahmen eines multimodalen Therapiekonzepts erhielten, waren alle am Leben, 15 (50%) in kompletter Remission. Von den 50 Patient*innen mit desmoplastischen klein- und rundzelligen Tumoren verstarben 64% (30/47 mit Follow-Up Information) trotz aggressiver multimodaler Therapie (medianes Überleben: 1,5 Jahre). Ähnlich schlecht ist die Prognose von Patient*innen mit *CIC*-fusionierten Sarkomen (67% [16/24] verstorben) und Patient*innen mit Klarzellsarkomen der Weichteile (60% [12/20] verstorben). Von 33 Patient*innen mit *BCOR*-fusionierten Weichteilsarkomen, die in der Regel eine multimodale Therapie erhielten, waren 81% (25/31) beim letzten Follow-Up am Leben, davon 61% in kompletter Remission. In der Gruppe der 24 *NTRK*-fusionierten Spindelzellsarkome waren alle Patient*innen - meist nach primärer oder sekundärer R0-Resektion - mit einem mittleren Follow-Up von 2 Jahren in Remission. Obwohl auch bei 88% der Patient*innen mit angiomatoiden fibrösen Histiozytomen (n=22) lediglich eine Resektion erfolgte, gab es vereinzelt Verläufe von metastasierter und letaler Erkrankung.

Schlussfolgerung: Bei *NTRK*-fusionierten Spindelzellsarkomen und bei angiomatoiden fibrösen Histiozytomen basiert die Therapie lediglich auf der Tumorresektion, bei den meisten anderen Entitäten (z.B. *BCOR*-fusionierten WTS) kommen multimodale Konzepte zum Einsatz. Die Prognose ist insbesondere bei *CIC*-fusionierten WTS, desmoplastischen klein- und rundzelligen Tumoren und Klarzellsarkomen der Weichteile schlecht. Nur bei infantilen Fibrosarkomen finden sich Genfusionen (v.a. *NTRK*-Fusionen), für die derzeit eine zielgerichtete Therapie zur Verfügung steht.

Abstract

Background: Molecular diagnostics has not only changed the way soft tissue sarcomas are classified by defining novel entities, but has also enabled the use of targeted therapy. Due to the rarity of these tumors, guidelines on the optimal clinical management of these molecularly defined entities are lacking.

Methods: The present work aims at providing an overview of diagnostic and therapeutic strategies based on a PubMed research and case reports of 7 patients with rare molecularly defined soft tissue sarcomas treated at the Division of Pediatric Hematology and Oncology, Medical University of Graz (2010-2023).

Results: 53% (49/93) of patients with IFS harbored gene fusions other than the canonical ETV6-NTRK3 (NTRK1-3, BRAF, MET, ALK, RET). Surgical resection only (complete or incomplete) was curative in 79% (27/34) of patients with localized IFS, while relapse occurred in 47% (7/15) of patients with incomplete resection. Of 30 patients with IFS receiving targeted therapy, 15 (50%) achieved CR, none of them died. Of 50 patients with DSRCT, 64% (30/47 with available follow-up) died despite aggressive multimodal treatment (median OS: 1.5 years). Similarly, prognosis is unfavorable in patients with CRS (67% [16/24] died) and CCSS (60% [12/20] died). Of 33 patients with BRS who commonly received multimodal treatment, 81% (25/31) were alive at last follow-up, including 61% in CR. In 24 patients with NTRK-rearranged spindle cell neoplasms, 100% (24/24) were alive at last follow-up (median: 2 years), mainly following primary or secondary R0-resection. Despite 88% of patients with AFH receiving surgery only (n=22), disease was reported extensive and letal in some patients.

Conclusion: In NTRK-rearranged spindle cell neoplasms and AFH, treatment is based on surgery only. In BRS, multimodal treatment concepts are advised. CRS, DSRCT and CCSS show an unfavorable prognosis. In tumors showing fusions related to the NTRK group of genes (including IFS), targeted therapy presents a safe and promising treatment option.

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List of Abbreviations

AFH	Angiomatoid fibrous histiocytoma
BID	Bis in die (twice a day)
BRS	BCOR-rearranged sarcoma
CCSS	Clear cell sarcoma of soft tissue
CR	Complete response
CRS	CIC-rearranged sarcoma
CT	Computed tomography
DSRCT	Desmoplastic small round cell tumor
EAM	Extra-abdominal metastases
FDG-PET	F-18-fluorodeoxyglucose-positron emission tomography
FISH	Fluorescence in situ hybridization
HIPEC	Hyperthermic intraperitoneal chemotherapy
IFS	Infantile fibrosarcoma
IL-6	Interleukin-6
MRI	Magnetic resonance imaging
NGS	Next generation sequencing
OS	Overall survival
PD	Progressive disease
PR	Partial response
RKI	Receptor kinase inhibitor
RT-PCR	Reverse transcriptase polymerase chain reaction
SD	Stable disease
TRK	Tyrosine kinase

1 INTRODUCTION

Soft tissue sarcomas (STS) are an extremely heterogenous group of neoplasms with over 50 different entities and even more subtypes described in the 2020 WHO Classification of Soft Tissue and Bone Tumours (1), most of them are ultrarare. Despite histopathology being the backbone of pathological and oncological diagnostics in the pre-molecular era, the detection of gene rearrangements resulting in gene fusions with oncogenic potential has revolutionized the way to classify and treat STS. These developments were driven by novel molecular technologies, including next generation sequencing, as well as the constantly evolving field of targeted therapy. To date, molecular genetic workup has become an integral part of routine diagnostics of STS, increasingly unveiling new molecularly defined entities. As such, genetical studies are now added to the histopathological and immunohistochemical work-ups in a complementary manner. The detection of the molecular characteristics of these tumors, including rearrangements related to the NTRK group of genes, has enabled targeted therapy in a subset of STS. As a result, molecular characterization of STS forms the basis of targeted therapy as a precision medicine approach to date. As clinical data are scarce and confined to small case series or case reports, management of pediatric patients with rare, molecular genetically defined STS is challenging. Because of the rarity of these entities, prospective clinical trials are infeasible. Thus, including these patients in registers is often the only way to gain data regarding symptoms, diagnosis, therapy and follow-up.

The present work aims at providing an overview of strategies based on literature research and case reports of patients with rare STS treated at the Division of Pediatric Hematology and Oncology, Medical University of Graz. Finally, it should serve as a basis for guiding management of these rare tumor entities.

2 LITERATURE SEARCH AND DATA EXTRACTION

First, a PubMed search using different search terms including ‘‘soft tissue sarcoma*,’’ ‘‘fusion sarcoma*,’’ ‘‘children/childhood,” “adolescents/adolescence,’’ ‘‘gene rearrangement*,’’ and ‘‘gene fusion*” was conducted. All articles written in English were available and read in full-length. References were then cross-checked to achieve - to the best of our knowledge - completeness of the reports to be included in this review. Due to the fact that the number of studies on molecularly defined STS in children and adolescents increased particularly during the last two decades, we

focused on reports that have been published during this period. Studies that reported on undifferentiated sarcoma without molecular confirmation were excluded, although it can be assumed that the majority of these cases harbored in fact gene rearrangements. Further, studies that reported on cases arising in the central nervous system and viscera were also excluded. A separation between the pre-molecular era and molecular era of STS by excluding older studies and reports seems reasonable to comprehensively summarize the current literature in pediatric STS. An age limit of 18 years was arbitrarily chosen. Clinical, pathological and molecular data of 275 children with molecularly defined STS in this age group are discussed in more detail and according to their underlying genetic alteration in separate sections. Study populations were overlapping in a few reports and the data of these studies were, therefore, combined. It was attempted to separate data of children with molecularly defined STS from those of adults in studies that included both age groups. However, this was not possible for some large series (2). In addition to cases from the published literature, we provide clinical and molecular data of seven patients treated between 01.01.2010 and 01.08.2023 at the Division of Pediatric Hematology and Oncology of the Department of Pediatrics and Adolescent Medicine, Medical University of Graz.

3 EPIDEMIOLOGY

STS are very uncommon among children and adolescents, comprising approximately 7% of all cancers in this population. In children under 20 years of age, the overall incidence rates of STS are reported as 11 per million (3). In the last two decades, novel molecularly defined entities have been described, some of them have been found to occur mainly in infants while others mostly affect adolescents. However, the incidence rate of different molecular subgroups of STS is difficult to establish. Given their frequent histologic similarity to a variety of other neoplasms it is likely that some subgroups have been previously underdiagnosed and grouped within a variety of other neoplastic categories. Due to the rarity of these entities, prospective trials are not feasible and prospective registers are needed to define epidemiological data of these neoplasms.

4 INFANTILE FIBROSARCOMA

4.1 INTRODUCTION

Infantile fibrosarcoma is the most common type of soft tissue sarcoma in children under 1 year of age. It is a locally aggressive tumor that only rarely metastasizes. Since its first description by Chung and Enzinger in 1976 (4), the advent of molecular diagnostics, including next generation sequencing, led to the recognition of a molecularly defined entity harboring oncogenic fusions involving the receptor tyrosine kinase genes NTRK1, NTRK2 and NTRK3. These fusion genes represent actionable molecular targets by TRK inhibitors such as larotrectinib (Vitravki®) or entrectinib (Rozlytrek®) which seem to be a promising and effective therapeutic option in this disease. Classic IFS is driven by t(12;15) creating a ETV6-NTRK3 chimeric protein, however, alternative fusions are being increasingly described.

4.2 CLINICAL PRESENTATION

A considerable number of articles describing children and adolescents with ETV6-NTRK3 positive IFS or IFS-like tumors harboring alternative gene fusions have been published (5-42). We identified 93 children below the age of 18 years including 3 from our institution with IFS providing data on treatment and/or outcome. While classic IFS predominantly affects infants before the age of 4 months including twenty-one cases (50%) being present at birth, IFS harboring alternative gene fusions (other than the canonical ETV6-NTRK3) may occur in older children up to 18 years of age. The median age of the patients included in the present review was 2 months (range, 0-18 years). Fifty patients (56%) were males and thirty-nine females (44%) with a female-to-male ratio of 1:1.28 (in four cases sex is not reported). On physical examination, IFS usually presents as a painless and rapidly enlarging mass with vascular appearance, often leading to misinterpretation as a benign vascular lesion (5, 6, 8, 14, 31, 34, 37). Approximately one third of all IFS are present at birth. The majority of pediatric IFS are located in the extremities (most commonly on the distal proportions of the upper or lower limb) (6-8, 12, 14-16, 18, 19, 22, 23, 25, 27, 30, 31, 34-36, 39, 40). The most common sites were the extremities (n=48), followed by back/trunk wall (n=19), head and neck (n=10), retroperitoneum (n=9), pelvis (n=5), and mediastinum (n=1) (tumor location was unavailable in one case). Data on the size of the primary tumor was available in 44 of the patients ranging from 2 to 22 cm (median: 6.3 cm). The lung is

the most common site of metastatic spread (10, 12, 16, 19, 21-23, 39, 40), but lung metastases are rarely present at diagnosis (10, 19). Rare cases of lymph nodes and bone as recurrence sites have been reported (12, 33, 40).

4.3 DIAGNOSIS

Imaging studies usually show a well-circumscribed, inhomogenous soft tissue mass with often intratumoral hypervascularity reminiscent of a vascular anomaly (5, 6, 8, 13, 31, 34, 36, 41). Pre-treatment diagnostic modalities for IFS include US, X-Ray, MRI and/or CT. MRI and CT are the preferred methods for assessment of IFS and are especially useful for monitoring therapy response. FDG-PET/CT is used as an additional surveillance modality (23). Staging is done by CT, and bone scans and/or bone marrow examinations are utilized for evaluation of osseous metastases (6, 7, 10-12, 15, 25). The final diagnosis is based on histology and immunohistochemistry and includes molecular confirmation of specific genetic alterations. Tissue samples are obtained either by diagnostic biopsy (mostly) or resection of the tumor. As surgical resection is the mainstay of treatment, it is mandatory in case of localized and resectable tumors.

The characteristic histopathology of IFS is described in detail in the recent World Health Classification of Soft Tissue and Bone Tumours. Immunohistochemically, these tumors show a rather nonspecific immunoprofile with variable expression of SMA, CD34, S100 and desmin. Pan-TRK immunohistochemistry in pediatric mesenchymal neoplasms has been shown to be a valuable time- and cost-effective diagnostic marker compared to molecular methods with a reported sensitivity and specificity of 96.7% and 97.9%, respectively (43), although this marker will be negative in the setting of alternative gene fusions (outside NTRK1/2/3). While many IFS harbor the rather specific ETV6-NTRK3 fusion resulting from t(12;15), a considerable number of tumors with an IFS-like histomorphology but harboring alternative fusions involving NTRK1, NTRK2, NTRK3, BRAF, MET, ALK or RET have been reported. In our cohort 43% (n=40) showed the ETV6-NTRK3 gene fusion while four cases with classic IFS histomorphology tested positive for ETV6-rearrangement by FISH, and more than half of the patients (n=49) showed variant gene fusions related to NTRK1 (n=25) (19-22, 32, 35, 39, 40), NTRK2 (n=1) (19), NTRK3 (n=3) (22, 23), BRAF (n=12) (24-27, 41), MET (n=2) (28, 42), ALK (n=2) (31), and RET (n=4) (29, 30). While FISH or RT-PCR is used to identify known fusion genes and to confirm the diagnosis, novel fusions may

still be missed using these methods. NGS presents a reliable tool for elucidation of the underlying molecular alteration including detection of yet unknown fusions genes. This seems especially important in NTRK-rearranged tumors (including IFS) in order to identify candidates for targeted therapy with RKI, thus increasing therapeutic options in these patients.

4.4 TREATMENT

Treatment is based primarily on surgical resection. The major goal is to achieve local resection with microscopic clear margins (R0) without jeopardizing functional outcome (44). A summary of reported therapies and the patients' outcome is shown in Table 1. According to guidelines, a conservative treatment strategy (e.g., surgery alone) in localized IFS is the main approach in patients with complete or microscopic incomplete resection (R1) and was curative in 27 of 34 (79%) with this strategy (7, 9, 16, 18-20, 22, 24, 27, 29-31). More radical procedures (e.g., amputation) were mostly reported in large tumors not easily amenable to resection or in case of tumor recurrence (12, 14, 19, 22, 23, 39). In light of available and possibly effective neo-adjuvant treatment including the use of TRK inhibitors which may improve tumor resectability, highly radical and mutilating procedures are not justified and should be critically discussed in interdisciplinary groups. Although lymph node involvement in pediatric IFS is rare, lymph node dissection has been described in two cases (11, 15). Treatment of lung metastases is generally approached by systemic chemotherapy and metastasectomy was reported in one patient (23).

Since IFS is a chemosensitive tumor, cytotoxic chemotherapy using alkylating agent- or anthracycline-based regimens was commonly administered and - when reported - was given as follows: neo-adjuvant, n=18; adjuvant, n=11; relapse, n=9; neo-adjuvant and adjuvant, n=3. The use of neo-adjuvant chemotherapy is recommended in tumors not amenable to non-mutilating curative surgery (45). In 21 patients of our cohort who were offered neo-adjuvant chemotherapy, objective responses were reported in 14: one showed a CR without the need for secondary surgery (15), and five patients showed a PR (10, 13, 15, 41, 42) facilitating limb-preserving surgery in two of them (10, 15). Four patients developed PD (6, 22, 35), but limb-preserving surgery with adequate margins was still achieved in two patients (6, 22). In two patients showing either no response or PD to neo-adjuvant chemotherapy subsequent amputation was performed (12, 22). Two of our cases receiving neo-adjuvant chemotherapy are

TABLE I. Treatment and outcome of children and adolescents with IFS

Number of pts. (Refs.)	Treatment	Disease course and/or outcome
1 (Hu et al. [5])	excision	NA
1 (Tsang et al. [9])	piece-meal resection	NED (1 year FU)
1 (Kang et al. [20])	complete resection	NED (1 year FU)
1 (Boulouadnine et al. [24])	complete resection	NED (2 years FU)
1 (Tan et al. [31])	excision (R0)	NED (0.5 years FU)
1 (Himori et al. [7])	en-bloc resection	NED (3 years FU)
1 (Davis et al. [30])	GTR	NED (1 year FU)
1 (Antonescu et al. [29])	resection (positive margins)	NED (9.5 years FU)
1 (Kao et al. [21])	piece-meal resection - resection of LR	LR x2, MD (lung), AWD (stable) (11 years FU)
2 (Alaggio et al. [16])	P2,4: resection	P2,4: NED (5-6 years FU)
2 (Davis et al. [22])	P3: wide resection (R0) P4: resection (R0)	P3: NED (4 years FU) P4: NED (3 years FU)
3 (Penning et al. [27])	P6,9,12: resection	P6: AWD (5 years FU) P9,12: NED (1 year FU)
6 (Sheng et al. [18])	P3,4,5,6,8,9: local excision with adequate margins	P3,4,5,6,8,9: NED (14 - 32 years FU)
9 (Davis et al. [19])	P5,15,16,21,22,24,30: excision (positive margins) P10: wide resection (R0) P20: biopsy	P5,15,16,21,22,24,30: NED (0.5 - 12 years FU) P10: NED (11 years FU) P20: wide-spread local disease, DOD
1 (Sivrikoz et al. [13])	CHT (VA)	AWD (1 year FU)
1 (Davis et al. [30])	CHT	AWD (0.5 years FU)
1 (McCahon et al. [15])	CHT (VAC, IA, ID)	NED [9 years off treatment]
2 (Steelman et al. [17])	P4,7: CHT	P4,7: NED
1 (Alias et al. [6])	CHT (VA) - near total resection - CHT (VA)	NED [2.5 years off treatment]
1 (Van Grotel et al. [10])	CHT (VAC) - surgery of primary - CHT (VC)	MD at diagnosis (lung), NED [10 months off treatment]
1 (McCahon et al. [15])	CHT (VAC, VDC) - inguinal ln dissection, tumor resection (R0)	NED [5 years off treatment]
1 (Punnett et al. [12])	CHT (VAC) - amputation (R0) - CHT for relapse (ICE)	MD (groin, pelvis, lung), DOC
1 (Kerl et al. [8])	size reduction (surgery, laser) - CHT for progression (VAC)	LR, NED (4 years FU)
1 (Alaggio et al. [16])	resection - CHT for relapse (VAC)	LR, MD (lung), NED (3 years FU)
1 (Fujikawa et al. [25])	complete resection - CHT for relapse (VDC,IE)	MD, AWD
1 (Hughes et al. [26])	debulking - CHT for relapse (VAC) + local RTX	LR, NED [5 months off treatment]
1 (Monsereenusorn et al. [11])	resection (positive margins) + retroperitoneal ln sampling - CHT (ID)	NED
1 (Steelman et al. [17])	incomplete resection - CHT	NED
1 (Flucke et al. [28])	incomplete resection - CHT (VAI)	ADW (stable) (1 year FU)
1 (Tannenbaum et al. [23])	amputation (negative margins) - CHT for relapse (ID) + RTX to right lung - complete resection of left lung residual disease - CHT (TC) - resection of right lung residual disease	MD (lung), NED [1 year off treatment]
2 (Yan et al. [14])	P1: surgical debulking - CHT (VAC, VDC) - amputation P3: CHT (VAC) - amputation	P1: NED (2 years FU) P3: NED (0.5 years FU)
3 (Penning et al. [27])	P10,11: resection - CHT P13: NA	P10: NED (1 year FU) P11: NED (2 years FU) P13: AWD (0.25 years FU)
4 (Davis et al. [22])	P1: CHT (VA) - GTR (positive margins) of primary and LR P2: CHT (VBL, MTX) - resection (positive margins) - STR of LR P5: CHT (ID) - amputation P6: none	P1: LR, NED (2.5 years FU) P2: LR, AWD (5 years FU) P5: MD (lung), AWD (5 years FU) P6: AWD (1 month FU)
5 (Davis et al. [19])	P1: debulking (positive margins), CHT P12: amputation (positive margins), CHT P27,28: excision (positive margins) - CHT P29: biopsy - CHT	P1: LR x2, NED (2 years FU) P12: LR, NED (10 years FU) P27: NED (5 years FU) P28: AWD (0.5 years FU) P29: MD (lung), DOD
Present case	wide resection (R0, focally marginal) - RTX (50.4 Gy) - CHT (VDC, IE) for relapse + photon-beam-radiation (15-50.4 Gy)	MD (lung), NED (3.25 years FU)

TABLE I. (Continued)

Patients treated with targ.th.

Case (Refs.)	Treatment	Disease course and/or outcome
#1 (Caldwell et al. [34])	larotrectinib	NED
#2 (Lapeña et al. [36])	larotrectinib	NED (1.25 years FU)
#3 (Corral Sanchez et al. [38])	larotrectinib	NED (1 year FU)
#4 (Lapeña et al. [36])	larotrectinib	NED [after 8 months of treatment]
#5 (Davis et al. [19])	larotrectinib	NED (1 year FU)
#6 (Davis et al. [19])	larotrectinib	NED (1.5 years FU)
#7 (Davis et al. [19])	larotrectinib	AWD (1.5 years FU)
#8 (Davis et al. [19])	larotrectinib	MD at diagnosis (lung) AWD (0.5 years FU)
#9 (Davis et al. [19])	CHT - larotrectinib	AWD (1 year FU)
#10 (Davis et al. [19])	surgery, CHT, larotrectinib	MD at diagnosis (lung) AWD (4 years FU)
#11 (Davis et al. [19])	debulking (positive margins), CHT, larotrectinib	LR x3 AWD (2 years FU)
#12 (Davis et al. [19])	debulking (positive margins), CHT, larotrectinib	LR AWD (4 years FU)
#13 (Davis et al. [19])	amputation (positive margins), CHT, larotrectinib	LR x2, MD (lung) AWD (1 year FU)
#14 (Davis et al. [19])	debulking (positive margins), CHT, larotrectinib	LR, MD (lung) AWD (2.5 years FU)
#15 (Baranov et al. [32])	CHT (VDC) - larotrectinib - excisional biopsy	NED (2.5 years FU)
#16 (Bielack et al. [33])	resection with close margins (R1/RX) - CHT for recurrence (VDC) - larotrectinib	MD (regional ln) NED
#17 (DuBois et al. [35])	CHT (VAC) - larotrectinib - resection (R0)	NED (1.25 years FU)
#18 (DuBois et al. [35])	CHT (VA) - larotrectinib - resection (R0)	NED (1 year FU)
#19 (DuBois et al. [35])	CHT (VAC) - excision (R1) - excision of LR (R1) - CHT (VAC) - radiology ablation of LR - CHT for progression (IE) - larotrectinib - excision (R1) - larotrectinib	LR x2 AWD (stable)
#20 (Nagasubramanian et al. [37])	debulking - CHT for LR (VAC) - debulking surgery + CHT (ID,IE) - GTR with positive margins - larotrectinib	LR AWD
#21 (Baranov et al. [32])	larotrectinib - resection (R0)	NED (5 years FU)
#22 (Present case)	CHT (IVAD) + larotrectinib - local proton beam radiation (50.4 Gy) - larotrectinib	NED (3.33 years FU)
#23 (Tan et al. [31])	crizotinib	AWD (0.75 years FU)
#24 (Bender et al. [39])	incomplete resection - CHT (ID) + local RTX - amputation - CHT for metastases (GD, VAC) - crizotinib	LR, MD x2 (lung) NED [1.5 years off treatment]
#25 (Wong et al. [40])	GTR - wide resection of LR (R0) - CHT for relapse (VAC, ID) - crizotinib	LR + MD (lung, bone) AWD (stable)
#26 (Penning et al. [27])	trametinib	AWD (stable) (1 year FU)
#27 (Vairy et al. [41])	CHT (VAC, ID) - trametinib	AWD [6 months after initiation of trametinib]
#28 (Gupta et al. [42])	CHT (VAC) - en-bloc resection (positive margins) - cabozantinib	NED (2 years FU)
#29 (Davis et al. [30])	vandetanib - LOXO-292	AWD (stable) (1 year FU)
#30 (Present case)	CHT (VAC) - entrectinib	NED (4.75 years FU)

Abbreviations: AWD alive with disease, CHT chemotherapy, DOC death of other cause, DOD death of disease, FU follow-up, GD gemcitabine/docetaxel, GTR gross total resection, IA ifosfamide/actinomycin-D, ICE ifosfamide/carboplatin/etoposide, ID ifosfamide/doxorubicin, IE ifosfamide/etoposide, IVAD ifosfamide/doxorubicin/vincristine/actinomycin-D, ln lymph nodes, LR local recurrence, MD metastatic disease, MTX methotrexate, NA not available, NED no evidence of disease, Pts. patients, Refs. references, RTX radiotherapy, STR subtotal resection, TC topotecan/cyclophosphamide, VA vincristine/actinomycin-D, VAC vincristine/actinomycin-

D/cyclophosphamide, VAI vincristine/actinomycin-D/ifosfamide, VBL vinblastine, VC vincristine/cyclophosphamide, VDC vincristine/doxorubicin/cyclophosphamide

described below. Similarly, CR or PR were observed in patients receiving initial chemotherapy for recurrent disease (CR, n=2; PR, n=1) (16, 23, 25). These results support the role of chemotherapy reported in the literature especially in a pre-operative setting. The upfront use of radiotherapy in children with IFS is strongly discouraged due to its known long-term risks and associated growth disturbances and was successfully avoided in 96% (n=89) of the patients included in this report.

A major break-through in the era of molecular medicine was the approval of receptor kinase inhibitors such as larotrectinib or entrectinib. This treatment modality targets NTRK gene fusions irrespective of tumor type (e.g., IFS and the emerging group of so-called NTRK rearranged spindle cell neoplasms). Although RKI are increasingly being used for treatment in adult and pediatric tumors harboring rearrangements of the NTRK group of genes (including IFS), the total number of reports on patients receiving RKI is low (Table 1). DuBois et al. reported on five pediatric patients with NTRK-rearranged tumors (including three IFS) part of a pediatric phase 1/2 clinical trial (46) receiving neo-adjuvant larotrectinib treatment orally twice daily (all for locally advanced disease). All five patients achieved a PR which allowed for limb-sparing surgery with negative margins (R0) in three and positive margins (R1/R2) in two. For the two patients with positive margins, larotrectinib was resumed after surgery: one remained in CR and one was without evidence of disease progression at the time of last follow-up. A small case series described the use of larotrectinib in two infants with a large localized IFS who did not undergo tumor resection (36). Larotrectinib was initiated at a dose of 100 mg/m² BID and in both patients the tumors disappeared by the second and third month of treatment with no recurrences being observed. Another patient with a recurrent, chemotherapy-refractory IFS of the tongue received 100 mg/m² larotrectinib BID and achieved a rapid and complete remission with a follow-up of 19+ months (33). A six-year-old girl from our institution had a TFG-NTRK3 positive IFS in the retroperitoneum infiltrating the lumbar spine and the psoas muscle, with a tumor volume of 390 ml. Chemotherapy was initiated consisting of vincristine, actinomycin-D, doxorubicin and ifosfamide concomitant with larotrectinib, leading to an impressive tumor shrinkage to a volume of 13 ml after 8 weeks of combined treatment. Local therapy consisted of proton beam radiation (50.4 Gy) to the primary site. Larotrectinib monotherapy was continued for a total of 19 months. Biopsy of the residual lumbar lesion showed

scattered viable spindle cells, immunohistochemically positive with a pan-TRK antibody, but the clinical impact of this finding was unclear. At last follow-up – 3 years after diagnosis – no residual mass could be detected radiologically. Another female patient from our institution diagnosed with a localized ETV6-NTRK3 positive IFS on the forearm at the age of five months received chemotherapy according to the CWS guidance for a total of 6 cycles and achieved PR. Targeted therapy using entrectinib was then initiated. After 7 months of treatment CR was observed. Following discontinuation of entrectinib treatment after a total of 19 months, the patient is closely observed and remains in CR almost 5 years after diagnosis. Our third patient, a 12-year-old boy, was diagnosed with a localized spindle cell sarcoma of the thigh showing a novel CLCN6-BRAF fusion not previously recognized in pediatric fibrosarcoma. Wide resection (R0), although focally marginal, was achieved. He then received adjuvant radiotherapy (50.4 Gy), however, a solitary (5 x 4 x 6 cm) left mediastinal lesion and a small subpleural nodule were noted a few weeks after end of treatment of the primary tumor. Chemotherapy consisting of vincristine, doxorubicin, cyclophosphamide, ifosfamide and etoposide was then initiated. After 3 cycles, a significant shrinkage of the pulmonary nodules was observed and was followed by photon beam radiation (15 Gy) to the left hemithorax with boost to the solid mediastinal lesion up to 50.4 Gy. Follow-up imaging showed no evidence of residual disease and the patient remains in CR 3 years after diagnosis.

In all cases, RKI therapy was well tolerated with no treatment discontinuations due to adverse effects. Children with NTRK-rearranged tumors who are considered for treatment with RKI should be included into prospective clinical trials. Otherwise, the decision to start treatment with RKI should be based on the risk profile of the patient. In agreement with the guidelines for treatment of adult NTRK fusion sarcoma (47, 48) treatment with RKI is recommended only in children with advanced NTRK-rearranged tumors (i.e., metastatic or initial curative resection not feasible) who have either failed upfront therapy or lack satisfactory treatment options. While recent evidence suggests that NTRK inhibitors might induce ongoing tumor response, there are currently insufficient data to recommend the duration of RKI therapy following complete clinical and radiological response. According to our experience, a total duration of at least 18 months seems feasible and reasonable.

To summarize, macroscopic complete resection without mutilation remains the mainstay of curative treatment in IFS. Because of these large tumors occurring in small

infants, neo-adjuvant chemotherapy might reduce the need for extensive surgery. Although the number of patients treated with TRK inhibitors is limited in this population, current evidence suggests that SD and CR can be achieved with the addition of TRK inhibitors.

4.5 PROGNOSIS

When completely resected, these tumors follow a benign clinical course even without adjuvant treatment. Surgery only, although not always microscopically complete, was curative in 27 of 34 (79%) patients. Relapse may occur, if complete resection can not be achieved. 7 of 15 (47%) patients with incomplete primary resection experienced local or distant recurrence. The recurrence rate (local or distant) differed between the classic fusion group (ETV6-positive) and the variant fusion group (ETV6-negative), with 9% and 35%, respectively, with an overall rate of 23%. Metastases may appear many years after diagnosis (e.g., one patient experienced pulmonary metastatic disease after 4 years (21)). Overall, follow-up time is short in most series and rarely exceeds 2 years. Of 93 patients in this review, the follow-up and disease status was reported in 70 and 92 of patients, respectively. Sixty-eight percent (n=63) were alive with no evidence of disease, 28% (n=26) were alive with disease and 3% (n=3) died at the time of publication.

5 DESMOPLASTIC SMALL ROUND CELL TUMOR

5.1 INTRODUCTION

Desmoplastic small round cell tumor is a highly aggressive malignancy with an extremely poor prognosis that affects children and young adults with a predilection for adolescent males. Its unique genetical feature is the fusion of EWSR1 and WT1, although EWSR1-WT1 negative cases have been described.

5.2 CLINICAL PRESENTATION

We identified 50 children including one patient from our institution below the age of 18 years with molecularly confirmed desmoplastic small round cell tumor providing data on treatment strategy and/or outcome. Although DSRCT has been observed even in infants (49), the majority of patients (86 %) become symptomatic during adolescence. The median age of the patients included in this review was 14.5 years (range, 2

months-18 years). There is a striking male predominance. Forty-one patients (82 %) were males and nine (18 %) were females with a female-to-male ratio of 1:4.55. Clinical signs and symptoms of the patients are summarized in Table 2. The duration of symptoms ranged from 3 days to 12 months (median: 6 months). The majority of primary pediatric DSRCTs are located in the abdominal cavity (50-59) frequently unrelated to any apparent primary visceral organ. The most common site was the abdominal cavity (n=20), followed by abdominal-pelvic (n=14) (50, 53, 58, 60-65) and pelvic sites (n=4) (50, 53, 59, 66) (in 2 cases location of the primary tumor was not reported). Rare cases affected the retroperitoneum (n=2) (52, 53) and non-abdominal sites including head and neck (n=6) (49, 52, 58, 67-69), shoulder (70) and mediastinum (58). Data on the size of the main tumor mass was available in eighteen of the patients. The tumors were mostly large, ranging from 1.5 to 24 cm (median: 9.5 cm). Patients are frequently found to have multiple intraabdominal tumor nodules (53, 54, 60-62, 65) and/or diffuse peritoneal implants (50, 53, 61, 62, 64). The liver and lymph nodes are the most common sites of metastatic spread, and liver or nodal metastases are often seen at diagnosis (49, 53, 54, 56-58, 60, 63-65). Peritoneal seeding may be present at diagnosis (53, 61, 64) and metastases affecting different organs throughout the body are reported (e.g., lung, bone, brain, pancreas, kidney, spleen, colon).

TABLE II. **Clinical signs and symptoms in children and adolescents with DSRCT**

	Refs.
Symptom/sign	
Abdominal pain	53, 54, 57, 60, 61, 64, 65
Abdomial distension/aszites	53, 62
Unspecific symptoms due to mass effect (constipation, pollakisuria, dysuria, urinary	53, 60, 61, 63-65
Palpable abdominal or pelvic mass (suggestive for a more advanced stage of disease)	56, 57, 60-62, 64
Weight loss	58, 61
Umbilical hernia	53
Enlarging abdominal mass	54, 56
Palpable axillary/inguinal lymph nodes	53, 60, 61

Abbreviations: Refs. references

5.3 DIAGNOSIS

Radiologically, DSRCT usually appears as a large intra-abdominal main tumor mass and multiple smaller peritoneal implants without any apparent primary organ of origin.

Infiltration into adjacent organs might be visible (54, 57, 60, 65). CT or MRI are essential in both the diagnostic work-up and follow-up of patients with DSRCT. Since DSRCT may show infiltration of bone and bone marrow (65, 71), bone scan and bone marrow examination are used as an additional staging modality in order to identify (osseous) DSRCT lesions (49, 55, 62, 65, 70). FDG-PET imaging with its ability to provide functional information is used for staging and to follow treatment response. The final diagnosis is based on histology and immunohistochemistry and includes molecular confirmation of the specific genetic alteration. Tumor samples can be obtained either by (percutaneous) biopsy or aspiration of peritoneal effusion. Obtaining tumor specimens through less invasive techniques, such as fine needle aspiration, may present a reliable alternative for open biopsy providing satisfactory material to confirm the (molecular) diagnosis in an appropriate clinical context (58, 59).

The characteristic histopathologic features of DSRCT are reported in detail in the latest WHO Classification of Soft Tissue and Bone Tumours (1). Immunohistochemically, these tumors typically show a multiphenotypic differentiation with expression of neural (CD57 and neuron-specific enolase [NSE]), epithelial (cytokeratins and epithelial membrane antigen [EMA]) and myogenic markers (desmin). WT1 C-terminal immunostaining serves as a useful diagnostic marker for DSRCT, especially when molecular methods are not available (72, 73). Despite its typical clinical presentation, DSRCT may show impressive variation in histomorphology and/or immunophenotype (54, 67) resulting in considerable diagnostic difficulty. Hence, molecular confirmation of the characteristic genetic alteration in DSRCTs is essential for recognizing these tumors. A reciprocal translocation, t(11;22), resulting in fusion of the EWSR1 gene on chromosome 22 to the WT1 gene on chromosome 11 has become the defining molecular feature of DSRCT helpful in differentiating these tumors from other small blue round cell sarcomas including extra-osseous Ewing sarcoma with resulting prognostic and therapeutic implications. EWSR1-WT1 fusion is the only type of gene fusion observed in adult and pediatric DSRCT to date. In our study, 50 of 50 (100%) patients showed the EWSR1-WT1 fusion. Detection of the fusion gene is possible using FISH or RT-PCR. However, tumors showing a morphology compatible with DSRCT but tested negative for EWSR1-WT1 by FISH or RT-PCR have been reported, suggesting a yet unknown fusion gene (50, 53, 58). In case of a molecular result incongruous with clinical, histopathological and immunohistochemical features, NGS might present a powerful tool for detection of variant fusion genes. Recently Gedminas

et al. provided interesting in vitro data on the pathogenesis of DSRCT by comprehensively demonstrating the dependence of the tumor on EWS-WT1 fusion for cell survival (74). Despite these recent advances in the understanding of tumor biology, there are currently no therapeutic drugs available to target this gene.

5.4 TREATMENT

A multidisciplinary approach combining systemic chemotherapy, surgery and adjuvant radiotherapy is the cornerstone of treatment in DSRCT. A summary of reported therapies and the patients' outcome is shown in Table 3.

Surgery is paramount when DSRCT presents as an abdominal disease in the absence of extra-abdominal metastases (75). The major goal is complete resection of all macroscopic disease within the abdomen; however, resection was incomplete or not possible in 12 of 13 evaluable patients presenting with abdominal disease (53-55, 58, 60-62). Surgical debulking is a common approach for reducing intraabdominal tumor burden as many patients present at the stage of a disseminated tumor and multiple peritoneal implants with and without EAM. When reported, upfront surgery was performed in 14 patients (52, 53, 56, 60, 67, 68, 70). 4 of these patients had limited and complete resection, and 8 patients had (incomplete) debulking surgery; with two not reported. 14 patients had delayed surgery after neo-adjuvant chemotherapy (52, 54, 55, 58, 61, 62, 64, 65, 69). In these patients, surgery was incomplete in 6 and complete or near-complete in 7; with one not reported. Of note, 5 of the 11 patients (45%) with complete or near-complete resection with or without preceding chemotherapy had non-abdominal tumors and are in CR after a minimum of 1 year, underlining the major role of surgery for DSRCT treatment. Surgical debulking may be performed after cytoreductive chemotherapy, allowing for resection of > 90% of tumor masses in some patients (58). In one patient from our institution, progression of intraabdominal residual disease was noted after incomplete debulking surgery including pre- and post-operative systemic chemotherapy. He then received hyperthermic intraperitoneal chemotherapy with radical surgery at an outside institution, resulting in pseudoprogression of his disease on imaging. He experienced severe adverse effects due to radical treatment and subsequently died of disease. The role of HIPEC as an adjunct intraoperative strategy has been controversially discussed (76-78). Current evidence suggests that HIPEC is feasible for local control if complete

TABLE III. Treatment and outcome of children and adolescents with DSRCT

Number of pts. (Refs.)	Treatment	Disease course and/or outcome
1 (Yamaguchi et al. [51])	NA	DOD (1.25 years FU)
1 (Barnoud et al. [66])	NA	DOD (4.25 years FU)
7 (Sydow et al. [50])	P1,7,9,10: Surgery, RTX, CHT	P1: MD (regional ln) D (2 years FU) P7: Alive (4.5 years FU) P9: MD (regional ln) Alive (3.25 years FU) P10: MD (liver, peritoneum) D (6 years FU)
	P3,4: Surgery, CHT P19: CHT	P3,4: D (2 - 3.5 years FU) P19: MD (liver, colon, intraabdominal ln) D (3 years FU)
2 (Rekhi et al. [52])	P21: Surgery - CHT (VACA,IE) P27: CHT (VACA,IE) - surgery - RTX	P21: NED (2 years FU) P27: DOD (2.5 years FU)
5 (Lae et al. [53])	P4,9: Debulking - CHT	P4: DOD (1.5 years FU) P9: NA
	P6: unresectable; CHT P11,15: Debulking	P6: AWD (0.5 years FU) P11: AWD (2 years FU) P15: DOD (1 year FU)
1 (Ali et al. [54])	CHT (VDC,IE) - resection (incomplete) + splenectomy	MD at diagnosis (intraabdominal ln)
1 (Slim et al. [60])	debulking (incomplete) - CHT (MTX, VBL) + RTX - CHT for relapse (VIDE)	Peritonealsarcomatosis + MD at diagnosis (intraabdominal ln), relapse (+ liver, intraabdominal ln) LFU (5 years FU)
1 (Shimizu et al. [61])	unresectable; CHT (CIS,VDC,IE) - complete resection - CHT	Peritonealsarcomatosis at diagnosis NED (2 years FU)
Present case	CHT (VIDE, VAC) - Debulking - CHT (VAC); outside institution: HIPEC - radical resection - HIPEC	Peritonealsarcomatosis + MD at diagnosis (intraabdominal ln) DOD
1 (Biswas et al. [55])	CHT (VDC,IE) - resection (incomplete) + RTX - CHT (VDC,IE)	DOD (1.5 years FU)
1 (Brodie et al. [62])	CHT (VDC,IE) - partial resection - CHT (VDC,IE); WART + CHT for progression, CHT for bone metastases	extensive MD (omentum, mesentery, peritoneum, abdominal wall, bones, brain, soft tissue) DOD (1.5 years FU)
1 (Saab et al. [58])	CHT (VDC,IE) - partial resection	MD at diagnosis (ln) DOD (2.5 years FU)
1 (Drugas et al. [56])	en-bloc resection (R0) - CHT (VDC,IE) + WART	MD at diagnosis (regional ln) NED (2 years FU)
1 (Hirano et al. [57])	CHT (TC) - CHT (VDC,IE) - CHT (IRIN)	MD at diagnosis (liver) DOD (1.5 years FU)
1 (Wang et al. [67])	resection (R0)	NED (1 year FU)
1 (He et al. [68])	resection	NED (1 year FU)
1 (Huang et al. [49])	CHT (VDC,IE)	MD at diagnosis (ln, lung, splen) AWD (stable) (1 year FU)
1 (Bengu et al. [69])	CHT (VDC,IE, TOPO) - CHT (IT) - RTX + CHT (IT) - en bloc resection (R0) - CHT (IT)	NED (1 year FU)
1 (Asadbeigi et al. [70])	excisional biopsy - re-excision (R0) - CHT (ES protocol)	NED (2 years FU)
1 (Antonescu et al. [63])	CHT (VDC,IE)	MD at diagnosis (mediastinal ln) AWD (0.5 years FU)
1 (Barnoud et al. [64])	CHT (vincristine/ifosfamide/actinomycin-D/etoposide/carboplatin/doxorubicin) - resection of residual disease + omentectomy - CHT (VIP)	Peritonealsarcomatosis + MD at diagnosis (regional and mediastinal ln, liver), LR DOD (4.25 years FU)
1 (Roberts et al. [65])	CHT (vincristine/carboplatin/epirubicin/actinomycin-D/mesna/ifosmide/etoposide) - incomplete surgery - CHT - RTX	MD at diagnosis (iliac ln, bone marrow), relapse DOD (1.25 years FU)
1 (Rekhi et al. [52])	Surgery - CHT (VACA,IE) + RTX (haemostasis)	DOD (1 year FU)
1 (Sydow et al. [50])	Surgery, RTX, CHT	MD (skin, abdominal) D (1.5 years FU)

TABLE III. **(Continued)**

Number of pts. (Refs.)	Treatment	Disease course and/or outcome
5 (Saab et al. [58])	P3: unresectable; CHT (VDC,IE) (refused therapy after 1 cycle)	P3: MD at diagnosis (bone, liver, pleura, kidney, ln) DOD (0.5 years FU)
	P8: CHT (VDC,IE) + RTX - complete resection - CHT (VACA,IE)	P8: MD at diagnosis (regional ln) NED (8 years FU)
	P9,10: CHT (VDC,IE) + WART, RTX to primary - near total resection	P9: MD at diagnosis (ln, mediastinum) Death due to toxicity (0.5 years FU)
		P10: MD at diagnosis (lung, ln) Death due to toxicity (1 year FU)
	P11: CHT (VDC,IE) + WART - near total resection - WART	P11: MD at diagnosis (ln, lung) NED (2 years FU)
4 (Lae et al. [53])	P10,13: Debulking - CHT + RTX	P10: MD (liver, lung, presacral) DOD (3.75 years FU)
		P13: Peritonealsarcomatosis + MD at diagnosis (liver, mediastinum) DOD (1 year FU)
	P20: Debulking - CHT	P20: MD at diagnosis (liver, retroperitoneal ln), MD (bones) DOD (1.5 years FU)
	P27: unresectable; CHT	P27: MD at diagnosis (axillary and retroperitoneal ln, liver), MD (lung, ln, mediastinum) DOD (4 years FU)
6 (Klijanienko et al. [59])	P2-5,7,8: according updated oncology chemotherapy protocols	P2,3,4: DOD (1- 3.5 years FU) P5: MD (pancreas, bones) DOD (0.75 years FU) P7: NED (3 years FU) P8: AWD (0.33 years FU)

Abbreviations: AWD alive with disease, CHT chemotherapy, CIS cisplatin, D death, DOD death of disease, ES Ewing sarcoma, FU follow-up, IE ifosfamide/etoposide, IT irinotecan/temozolomide, IRIN irinotecan, LFU lost to follow-up, ln lymph nodes, MD metastatic disease, MTX methotrexate, NA not available, NED no evidence of disease, Pts. patients, Refs. references, RTX radiotherapy, TC paclitaxel/carboplatin, TOPO topotecan, VAC vincristine/actinomycin-D/cyclophosphamide, VACA vincristine/actinomycin-D/doxorubicin/cyclophosphamide, VBL vinblastine, VDC vincristine/doxorubicin/cyclophosphamide, VIDE vincristine/ifosfamide/doxorubicin/etoposide, VIP etoposide/ifosfamide/cisplatin, WART whole abdominopelvic radiotherapy

surgical cytoreduction is achieved. Patients with DSRCT and disease outside the abdomen at the time of surgery do not benefit from HIPEC.

Most of the systemic chemotherapeutic regimes described in DSRCT were based on those used for the treatment of Ewing sarcoma, containing doxorubicin, vincristine, cyclophosphamide, ifosfamide and etoposide. Together with cytoreductive surgery, dose-intensive chemotherapy is a cornerstone of treatment in DSRCT, and was commonly administered first-line in patients presenting with an extra-abdominal primary tumor or EAM (49, 53, 58, 63-65, 69). Similarly, intensive chemotherapy was delivered to patients presenting with DSRCT confined to the abdomen (neo-adjuvant;

n=6, adjuvant; n=5, neo-adjuvant and adjuvant; n=4, relapse; n=2). Overall, the tumors responded well to systemic chemotherapy, however, the responses were short-lasting with relapse or PD being reported in the majority of patients.

The use of adjuvant radiotherapy in patients with DSRCT is well documented. Adjuvant whole abdominopelvic radiotherapy was shown to significantly improve survival when combined with systemic chemotherapy and aggressive cytoreductive surgery (79, 80). Because the role of WAP-RT remains unclear and may cause significant toxicity (81), WAP-RT should be used only in selected patients included into prospective trials.

In summary, aggressive cytoreductive surgery combined with perioperative chemotherapy and radiotherapy presents the mainstay in the treatment of DSRCT. However, no clear consensus has been reached concerning the optimal treatment strategy, which is – in light of the devastating prognosis - desperately needed.

5.5 PROGNOSIS

Although treatment was curative in a few patients (52, 56, 58, 59, 61, 67-70), prognosis is devastating with the vast majority of patients dying of extensive disease despite aggressive multimodal therapy (50-53, 55, 57-59, 62, 64-66). The study by Honore et al. identified 4 favorable prognostic factors: the absence of extra-peritoneal metastasis, complete surgical removal, post-operative WAP-RT and postoperative chemotherapy (75). Of 10 patients in our cohort with CR at the time of last follow-up, 9 had no evidence of extra-peritoneal metastasis including 5 with localized DSRCT arising at non-abdominal sites. Six of the patients with CR also received adjuvant chemotherapy. If CR is achieved, relapse may occur up to 2+ years following diagnosis (60, 64, 65). Overall follow-up time is short in most series and rarely exceeds 3 years (49, 51-53, 56, 57, 59, 61-63, 65, 67-70). Few series, however, report on a longer follow-up (50, 58, 60, 64, 66). DSCRT shows an aggressive clinical course with a median OS of only 1.5 years (range, 0.5-6 years). Overall in 47 of 50 patients in this review the follow-up (median time: 1.5 years) is reported with disease status in 47. Sixty-four percent died (including 2 patients with death due to aggressive treatment), and 36% are alive at the time of publication.

6 CIC-REARRANGED SARCOMA

6.1 INTRODUCTION

CIC-rearranged sarcoma is a high-grade round cell undifferentiated sarcoma with an unfavorable outcome and occurs over a very broad age range with the majority of cases described in older patients. It was first recognized by Richkind et al. in 1996 who found a t(4;19) associated metastatic sarcoma originating from the soft tissues in the ankle of a 12-year-old boy (82). Elucidation of the precise molecular events characterizing these tumors (e.g., CIC-DUX4 fusion creating a CIC-DUX4 chimeric protein) was published ten years later (83) and more recently the discovery of recurrent CIC fusions through the more routine use of molecular techniques added to better characterize a group of unclassified sarcoma mimicking Ewing sarcoma, but lacking the canonical EWSR1 gene rearrangement or rearrangements involving the FUS gene. In particular, CIC rearrangement is now emerging as the most frequent genetic alteration found in EWSR1-negative small blue round cell sarcomas (84, 85). According to these genetical differences and their significantly worse outcome (2), the current World Health Organization Classification of Soft Tissue and Bone Tumors now recognizes CRS as a stand-alone entity distinct from Ewing sarcoma.

6.2 CLINICAL PRESENTATION

There is a paucity of published literature on pediatric CRS (82, 84-101). We identified 25 children below the age of 18 years with CRS of the soft tissues providing data on treatment strategy and/or outcome. Although CRS have been observed in children as young as 3 years old (97), the majority of patients become symptomatic during the second decade of life. The median age of the patients included in the present review was 13 years (range, 3-18 years). Fifteen patients (60%) were males and ten were females (40%) with a female-to-male ratio of 1:1.5. CRS commonly presents as a large mass or swelling with or without pain. Duration of symptoms ranged from 1 month to 1 year with a median of 3 months. Pediatric CRS are located equally in the axial (including head and neck) and the extra-axial soft tissues with 14 and 11 cases, respectively. The most common axial site was the trunk wall (n=7) (84-86, 89, 91, 95, 97), followed by head and neck (n=4) (89, 97, 98), and one case each arose in the pelvis (89), perineum (93) and vulva (99). While only one case was located in the shoulder (87), the vast majority of extra-axial sites affected the lower extremity (91%,

n=10) (82, 84, 85, 88, 90, 94, 100, 101). These findings are in agreement with some larger studies including both children and adults (2, 85). Tumors mostly affected the deep soft tissues with or without infiltration of adjacent structures and only few cases had a primary superficial presentation. Of note, primary superficial presentation of CRS does not seem to favor clinical course as it does in other certain cancer types including Ewing sarcoma, stressing the aggressive nature of this malignancy (99). Data on the size of the primary tumor was available in 14 of the patients. The tumors were mostly large ranging from 1.5 to 31 cm (median: 7.5 cm). The lung is the most common site of metastatic spread, and lung metastases are often seen at diagnosis (82, 84, 86, 87, 90, 93, 100). Brain or bone metastases have not been reported at presentation, but are typical sites of recurrence (85, 88, 91, 93, 96, 97, 101).

6.3 DIAGNOSIS

Imaging studies usually show a single large deep-seated soft tissue mass with or without infiltration of adjacent muscle or bone which corresponds to a heterogeneously enhancing tumor with necrosis on contrast series. Since CRS have the propensity for infiltrative growth (87, 94, 96, 97) additional X-ray is used to identify osseous CIC lesions (87, 100). CT or MRI is mandatory in both the diagnostic work-up and follow-up of patients with CRS. FDG-PET/CT seems to be a useful staging and follow-up modality (93). Interestingly, FDG uptake was found to be higher in CRS than those of extra-skeletal Ewing sarcoma suggesting a more aggressive behavior compared to Ewing sarcoma (102). The final diagnosis is based on histology and immunohistochemistry and confirmed by the detection of CIC gene rearrangements on a molecular level. Tissue samples can be obtained either by (percutaneous) biopsy or resection of the tumor.

The histopathologic features in CRS are described in detail in the largest published series of 115 cases (2). Differentiating CRS from other small blue round cell sarcomas, especially Ewing sarcoma, represents a challenge due to partial overlap in both histopathology and immunohistochemistry. Helpful morphologic features supporting the diagnosis of CRS include geographical necrosis and more myxoid stroma which are not typically seen in Ewing sarcoma. Recent evidence suggests that diffuse ETV4 positivity by immunohistochemistry is a feature of CRS among small round cell sarcomas. A large study by Hung et al. reports a sensitivity and specificity of diffuse ETV4 expression for CRS of 90% and 95%, respectively (103). When combining the

studies by Hung et al. and Le Guellec et al. (104), 83 Ewing sarcomas (100%) were negative for diffuse ETV4 staining. Thus the distinct immunoprofile might be able to distinguish between CRS and other small round cell sarcomas, especially when molecular testing is not available. Definitive diagnosis of CRS, by definition, requires confirmation of the genetic abnormality on a molecular level. In the majority of CRS reported in the literature the CIC gene on chromosome 19 is fused to the DUX4 gene on either chromosome 4 or chromosome 10 with CIC-FOXO4 or CIC-NUTM1 fusions being less common. These findings have also been observed in the pediatric cases included in this review. 15 of 25 (60%) patients showed the CIC-DUX4/DUX4L fusion gene, while NUTM1 and FOXO4 were identified as fusion partners in 2 (8%) and 1 (4%) patients, respectively. In the remaining 7 (28%) patients, a CIC-rearrangement was detected by FISH. In light of possible false-negative results (105) a judicious interpretation of FISH results is recommended. In case of results discordant with morphological or immunohistochemical diagnosis, further molecular investigations by either RT-PCR or NGS must follow. While there is still the possibility of missing rare or yet unknown fusions partners using RT-PCR as published sets do not cover all variants of CIC fusion partners, NGS may constitute a key approach to reliably identify both fusion partners. The study by Kawamura-Saito et al. provided interesting in vitro data on the pathogenesis of CRS by demonstrating that the CIC-DUX4 fusion gene is a strong transcriptional activator, further identifying 22 downstream targets whose expression was significantly up-regulated in CIC-DUX4-positive cells (83). These targets included ETV1 and ERM/ETV5, both members of the PEA3 subclass of the ETS transcription factor gene family, which were suggested to play an important role in tumorigenesis (83). While this evidence suggests that the CIC-DUX4 fusion is a driver of tumor growth and metastasis in CRS, there are currently no therapeutic drugs available to target this oncogene, which might improve outcome in these patients.

6.4 TREATMENT

Since the biological behavior of this tumor entity is broadly unknown, the optimal treatment for CRS has not yet been defined.

As in adults, pediatric CRS is generally treated using a multimodal approach including Ewing sarcoma-based multi-agent chemotherapy. A summary of reported therapies and the patients' outcome is described in Table 4. Local excision with microscopic free

TABLE IV. Treatment and outcome of children and adolescents with CRS

Number of pts. (Refs.)	Treatment	Disease course and/or outcome
2 (Italiano et al. [84])	NA	P5: MD at diagnosis (lung) AWD (1 month FU) P7: MD (lung) DOD (1.25 years FU)
1 (Ko et al. [99])	incomplete excision - re-excision (R0)	MD (lung) DOD (2 years FU)
1 (Tang, Dodd [100])	CHT - en-bloc resection - CHT	MD at diagnosis (lung)
1 (Graham et al. [91], Somers et al. [92])	GTR - CHT (VAC,IE) for relapse	relapse (bone) NED (7.75 years FU)
1 (Chen et al. [94])	amputation - CHT for relapse	LR, relapse (lung) AWD (progressive)
1 (Solomon et al. [98])	excision (R0) - CHT (VDC,IE) - incomplete excision of LR - CHT for relapse (IT), cabozantinib	LR, MD (lung) DOD (2 years FU)
1 (Connolly et al. [101])	CHT (ID) - excision (R0) - CHT (ID) + RTX	MD (lung, brain, bone) DOD (3.5 years FU)
1 (Rakheja et al. [90])	GTR - CHT (VDC) - RTX to primary and lung	MD at diagnosis (lung) NED (0.25 years FU)
1 (Gambarotti et al. [87])	CHT (VDC,IE) - RTX to primary	MD at diagnosis (lung), relapse (lung) DOD (1 year FU)
1 (Richkind et al. [82])	excision - CHT (vincristine, melphalan) - RTX to primary and lungs - CHT for relapse (ICE)	MD at diagnosis (lung), relapse (groin) DOD (1 year FU)
1 (Krskova et al. [93])	radical resection - CHT (VIDE, VAI) + RTX to primary and ln - CHT for relapse (TC)	MD at diagnosis (lung, soft tissue, ln), relapse (lung, ln, bone) DOD (1 year FU)
1 (Yoshimoto et al. [95], Somers et al. [96])	wide resection - CHT (VAC) - excision and RTX of brain metastases - CHT for relapse (ICE)	relapse (brain, lung, bone) DOD (1 year FU)
1 (Ricker et al. [88])	re-excision (R0) - CHT for relapse (ID) - metastasectomy (R1) - pazopanib - pembrolizumab + RTX - radical resection of metastases, MGA-271	relapse (lung, pleura) DOD due to extensive MD (heart, diaphragm, chest wall, bowel, kidney, liver, spleen, ln)
1 (Nakai et al. [86])	CHT (VDC,IE) + RTX - excision - CHT (VAI) - lobectomy - CHT (IC) - CHT for relapse (IT), pazopanib	MD at diagnosis (lung), relapse (chest wall) DOD (1.5 years FU)
4 (Siegele et al. [89])	P1: resection - CHT + RTX P3: CHT + RTX - excision (R0) P4: CHT + RTX - hemipelvectomy P5: CHT + RTX - excision	P1: AWD (lung nodules) (1 year FU) P3: relapse (lung) AWD (2 years FU) P4: Alive (0.5 years FU) P5: relapse (myocard) DOD (0.5 years FU)
2 (Le Loarer et al. [97])	P1: excision (R1) - CHT (VAI) + RTX - CHT for relapse (VIT, doxorubicin) P3: excision (R2) - CHT (BEP) - excision (R1) of LR - CHT for relapse (cyclophosphamide/etoposide, vinorelbine/cyclophosphamide) + RTX	P1: relapse (brain), MD (meningeal) DOD (1.5 years FU) P3: LR x2 , MD (lung, bone, ileocolic, pancreas) DOD (3 years FU)
4 (Yoshida et al. [85])	P14: CHT (VAC, VDC/IE, irinotecan, TC) P16: surgery, CHT (VDC/IE, TC) P17: surgery, RTX, CHT (VDC, I) P18: surgery, RTX, CHT (VDC/IE, VACA, ICE)	P14: MD (lung, ln, brain, bone) DOD (1 year FU) P16: MD (lung) NED (6 years FU) P17: MD (lung) DOD (1 year FU) P18: MD (lung, pleura, liver, bone) DOD (0.75 years FU)

Abbreviations: AWD alive with disease, BEP bleomycin/etoposide/platinum, CHT chemotherapy, DOD death of disease, FU follow-up, GTR gross total resection, I ifosfamide, IC irinotecan/carboplatin, ICE ifosfamide/carboplatin/etoposide, ID ifosfamide/doxorubicin, IE ifosfamide/etoposide, IT irinotecan/temozolomide, ln lymph nodes, LR local recurrence, MD metastatic disease, NED no evidence of disease, NA not available, Pts. patients, Refs. references, RTX radiotherapy, TC topotecan/cyclophosphamide, VAC vincristine/actinomycin-D/cyclophosphamide, VACA vincristine, actinomycin-D, cyclophosphamide, doxorubicin, VAI vincristine/actinomycin-D/ifosfamide, VDC

vincristine/doxorubicin/cyclophosphamide, VIDE vincristine/ifosfamide/doxorubicin/etoposide, VIT vincristine/irinotecan/temozolomide

margins (R0) is an important aspect of local disease control and can be achieved in the majority of patients. A more radical surgical procedure (e.g., hemipelvectomy) is reported in one patient; however, this is often associated with significant morbidity and the consequences of such (mutilating) operations should be critically discussed in an interdisciplinary group. Lymph node involvement in pediatric CRS is frequently reported (82, 85, 88, 93). However, nodal dissection was performed in only one of the patients (93). Removal of lung metastases is accomplished by partial or complete lobectomy or metastasectomy (86, 88).

The use of cytotoxic chemotherapy according to Ewing sarcoma protocols is a standard therapeutic approach (neo-adjuvant; n=3, adjuvant; n=9, relapse; n=9, first-line; n=1, neo-adjuvant and adjuvant, n=3). Currently, there is a lack of consensus on whether CRS should be treated with Ewing sarcoma-based approaches or according to high-grade sarcoma protocols (106). Using chemotherapeutic agents approved for Ewing sarcoma treatment (e.g., vincristine, doxorubicin, cyclophosphamide, ifosfamide, etoposide) the high response rate of Ewing sarcoma was not observed in CRS. Most tumors rapidly developed drug resistance and subsequently progressed. In 9 of 17 (53%) patients receiving Ewing sarcoma-based protocols for primary or recurrent CRS a CR (pathologic or radiologic) was reported. However, responses were short-lasting and only 1 of 7 (14%) patients with a reasonable follow-up period (> 6 months) remains in CR after 7+ years (91, 92). In 5 evaluable patients receiving cytotoxic chemotherapy +/- surgery as primary treatment, 5 (100%) patients achieved CR.

Targeted therapy with pazopanib and pembrolizumab has been administered in 2 patients (both for metastatic disease) (86, 88). In the first patient the tumor did not respond to pazopanib. In the second patient, the resected tumor showed near-complete pathological response after administration of ifosfamide/doxorubicin-chemotherapy. Treatment with pazopanib was initiated, but the disease progressed within 2 months. Following progression, he received 2 doses of pembrolizumab with palliative radiation therapy to the recurrence site and despite showing a mixed response with shrinkage of one tumor and appearance of another his disease eventually further progressed, leading to discontinuation of pembrolizumab after 4 months (88). The lack of response to pazopanib was also observed in adult CRS (101).

Radiotherapy to the primary site was administered in 11 patients, and local control was achieved in 10 (91%) patients (82, 86, 87, 89, 90, 93, 97, 101).
Children with CRS should be included into prospective trials and investigated as a separate entity.
To summarize, current evidence suggests that local control is best achieved by resection of the tumor with negative margins (R0) and radiotherapy might be beneficial in case of incomplete resection. Patients with CRS do respond to chemotherapy, and CR can be achieved with administration of multi-agent chemotherapy approved for Ewing sarcoma, however, the short progression-free survival interval suggests that "maintenance" treatment strategies might be considered.

6.5 PROGNOSIS

Despite a multimodal treatment approach including systemic chemotherapy, surgery and radiotherapy, prognosis is dismal with 16 of 24 (67%) patients dying from their (metastatic) disease, with a median OS of only 1 year (range, 0.5-3.5 years). Tumor recurrence is frequent and occurred at a median of 9 months following diagnosis (range, 3-16 months), but recurrence may occur even after several years (e.g., one patient died after relapsing at 3 years following diagnosis (101)). Overall follow-up time is short in most series and rarely exceeds 2 years. Few studies, however, report on longer follow-up (85, 91, 92, 97, 101). The final outcome of patients with tumor recurrence was death from disease in 81% (n=13) of patients. Of 25 patients included in this review, follow-up and disease status were reported in 22 and 24 patients, respectively. Median follow-up was 1 year (range, 1 month-7.75 years). Sixty-seven percent (n=16) died from disease, 17% (n=4) are alive with disease and 17% (n=4) had no evidence of disease at the time of publication.

7 CLEAR CELL SARCOMA OF SOFT TISSUE

7.1 INTRODUCTION

Clear cell sarcoma of soft tissue is a rare mesenchymal neoplasm frequently attached to tendons and aponeuroses that affects predominantly middle-aged adults. Previously termed malignant melanoma of soft parts, elucidation of the molecular genetic characteristics of this tumor (e.g., oncogenic EWSR1-ATF1 gene fusion) led to its recognition as a distinct tumor type requiring differentiation from malignant melanoma.

7.2 CLINICAL PRESENTATION

We identified 25 children including one patient from our institution below the age of 18 years with molecularly confirmed CCSS providing data on treatment strategy and/or outcome. Although there have been reports on children with CCSS (without molecular confirmation) as young as 2 years old (107), the majority of patients become symptomatic during the second decade of life. The median age of the patients included in this review was 13 years (range, 5 - 18 years). Sixteen patients (64%) were males and nine (36%) were females with a female-to-male ratio of 1:1.77. The tumors typically presented as a palpable slow-growing mass or swelling that has been noticed for up to 8 months prior to presentation with associated pain being occasionally reported (108-110). Seventeen CCSS (68%) were located in the lower extremity (108, 109, 111-116), mostly in the deep soft tissues, with slightly more than half described in or below the knee (e.g. knee [n=2] (112, 115), ankle [n=1] (111), tendon [n=1] (113), heel [n=2] (109, 112), foot [n=2] (115), and plantar aspect of the foot [n=1] (108)). Unusual sites involved the axial soft tissues, e.g., trunk wall (n=5) (112, 114-116), and one case each in the breast (115), pelvis (109), and shoulder (111). Data on the size of the primary tumor was available in 17 of the patients ranging from 1 to 10 cm (median: 4 cm). The lung and regional lymph nodes are the most common sites of metastatic spread (108-110, 112, 113) but lung or nodal metastases are rarely seen at diagnosis (110). Further, metastatic spread to the bones has been reported (113).

7.3 DIAGNOSIS

Imaging studies usually show a relatively small and homogenous mass in the deep soft tissues and in close proximity to tendons, fascia or aponeuroses (117). CT or MRI is mandatory in both the diagnostic work-up and follow-up of patients with CCSS. Bone scan is performed to identify osseous metastases (108). FDG-PET/CT may identify occult nodal metastases (118, 119). Detection of nodal metastases in patients with CCSS, making them amenable to targeted radiation or lymphadenectomy which might reduce tumor recurrence, is further of prognostic importance, as patients with positive lymph nodes show inferior OS (120). While PET/CT has been shown to miss a subset of nodal disease (121), routine lymph node sampling for early detection of microscopic disease in pediatric CCSS is recommended. In a comparative study, sentinel lymph node biopsy using a radioactive tracer and blue dye was superior to functional imaging

in this regard (121). The final diagnosis is based on histology and immunohistochemistry and recently includes detection of specific gene fusions (e.g., EWSR1-ATF1 fusion) on a molecular level, helping to differentiate these tumors from (metastatic) malignant melanoma. Tissue samples can be obtained either by (percutaneous) biopsy or resection of the tumor. As wide excision is the mainstay of treatment, tumor biopsy is unnecessary if the tumor is resectable.

The characteristic histopathology of CCSS and differential diagnoses are reported in detail elsewhere (122). Immunohistochemically these tumors show a phenotype identical to that of malignant melanoma with positivity for melanocytic markers (including HBM45, Melan-A and MITF) as well as S100 protein. Few studies specifically designed to elucidate the molecular genetic characteristics of CCSS include pediatric patients (111, 112, 114-116). In our cohort 88% (n=22) of pediatric CCSS harbored the reciprocal EWSR1-ATF1 fusion gene resulting from a t(12:22) which is similar to the 91% prevalence of EWSR1-ATF1 fusion of CCSS reported in adults (123). The remaining 12% (n=3) of pediatric CCSS tested positive for EWSR1-rearrangement by FISH, however, no fusion partner was identified. Of note, one of these cases tested negative for ATF1, CREB1 and CREM by FISH, suggesting a yet unknown fusion partner gene (116). Alternative fusions (e.g. EWSR1-CREB1) have been reported in clear cell sarcoma-like tumors of the gastrointestinal tract and more recently also in CCSS of adults (111), however, no alternative gene fusions other than EWSR1-ATF1 were found in pediatric CCSS to date. While detection of the pathognomonic EWSR1-ATF1 fusion is possible using FISH or RT-PCR analysis, NGS might be a powerful method to reliably detect both fusion partner genes, further aiding in the classification of these tumors. The study by Davis et al. provided interesting in vitro data on the oncogenic mechanisms of these tumors, showing that the EWSR1-ATF1 chimeric transcript directly activates the melanocyte-specific microphthalmia-associated transcription factor (MITF) which in the presence of SOX10 expression results in melanocytic differentiation and proliferation/survival of tumor cells, thus driving tumorigenesis (124). Despite those recent developments in the understanding of the biology of CCSS, there are currently no drugs available to treat these tumors by targeted therapy approaches, which could potentially improve outcome.

7.4 TREATMENT

Surgery is the backbone of treatment. As in adults, the major goal is to achieve wide surgical excision with negative margins (107). A summary of reported therapies and the patients' outcome is shown in Table 5.

Surgery of the primary tumor was reported in ten patients as follows: R0-resection; n=3 (108, 109), R1-resection; n=1 (109), wide resection; n=2 (113), excision; n=4 (112). Incomplete resection with microscopic residual disease has been reported after primary surgery (108, 109). Relapse was noted in 4 of 4 patients who received adjuvant radiotherapy (distant relapse; n=3, local relapse; n=2) and in 4 of 5 patients who had surgery without adjuvant radiotherapy (distant relapse; n=3, local relapse; n=1). When reviewing a large study by Ferrari et al. on 28 cases of pediatric CCSS (without molecular confirmation), adjuvant treatment seems unnecessary when complete resection was achieved (107). However, postoperative radiotherapy is recommended in case of incomplete resection to improve local tumor control (107). Radical surgical procedures (e.g. amputation) are not justified if negative margins can be achieved by wide resection (118). Involvement of loco-regional lymph nodes either at diagnosis or early in the course of disease is a common finding in CCSS, and lymph node dissection was reported in the series by Hocar et al. (109), in the patient reported by Moritake et al. (113) and in one patient included from our institution: An 18-year-old girl presented with a large CCSS in the buttock infiltrating the adjacent bone and metastases to loco-regional lymph nodes. After wide resection of the primary tumor (R0) and subsequent dissection of the metastatic lymph nodes (R0), the disease progressed within one month. Despite repeat lymph node dissection (R0), pelvic and paraaortal lymph node metastases were noted on imaging and the patient was subsequently referred to an outside institution, where she received radical resection of the intraabdominal and inguinal lymph nodes followed by abdominal and inguinal radiation therapy, which resulted in a CR. Despite systemic chemotherapy with vinblastine, cyclophosphamide and sunitinib, the patient eventually died of the disease. The decision on the extent of surgical resection should be made according to the results of intraoperative sentinel lymph node biopsy targeting the most clinically relevant nodes thus potentially reducing morbidity (e.g., lymphedema) due to excessive lymphadenectomy. Radical lymph node dissection is recommended in case of loco-regional failure to further improve the disease-free and overall survival. Surgical removal of lung metastases was reported in two patients (108, 113).

TABLE V. **Treatment and outcome of children and adolescents with CCSS**

Number of pts. (Refs.)	Treatment	Disease course and/or outcome
2 (Segawa et al. [116])	NA	P8: NED (8 years FU) P15: DOD (20.75 years FU)
2 (Panagopoulos et al. [114])	NA	P4: MD P5: AWD (1.5 years FU)
4 (Hisaoka et al. [111])	NA	P23: MD, DOD (0.25 years FU) P26: NA P27,28: NED (5 years FU)
5 (Wang et al. [115])	NA	P1,4: DOD (2 - 3.75 years FU) P10,13: LOF P11: AWD (5 years FU)
5 (Coindre et al. [112])	P9: CHT, excision, adj. RTX P17: excision, CHT, adj. RTX P16: excision P38: excision, CHT P43: NA	P9: MD (distant), DOD (3.33 years FU) P17: LR, DOD (9 years FU) P16: MD (ln + distant), DOD (4 years FU) P38: LR, DOD (7.5 years FU) P43: NA
1 (Curry et al. [108])	excision (positive margins) - complete re-excision - wedge resection of metastases	MD (lung), recurrent MD x2 (lung) AWD (4.75 years FU)
1 (Han et al. [110])	CHT (ID)	MD at diagnosis (lung) DOD (1 year FU)
1 (Moritake et al. [113])	CHT (cyclophosphamide/etoposide/pirarubicin/cisplatin) - wide resection - CHT (pirarubicin/ifosfamide, etoposide/carboplatin/melphalan) - resection of mets - CHT (cisplatin/vincristine/pirarubicin/docetaxel/ cyclophosphamide/peplomycin)	MD (ln, lung, bone) DOD (5 years FU)
3 (Hocar et al. [109])	P3: CHT (I) - complete resection (R0) - RTX P25: excision (R0) - CHT (ID) P37: resection (positive margins) - CHT (VAI) + RTX - resection of LR - reg. ln dissection	P3: MD (distant), DOD (3.33 years FU) P25: NED (5.5 years FU) P37: LR, MD (reg. ln) NED (10 years FU)
Present case	wide resection (R0) - (repeat) resection (R0) of ln metastases - radical ln dissection - RTX - CHT (vinblastine/cyclophosphamide/sunitinib)	MD at diagnosis (reg. ln) DOD

Abbreviations: Adj. adjuvant, AWD alive with disease, DOD death of disease, FU follow-up, I ifosfamide, ID ifosfamide/doxorubicin, ln lymph nodes, LOF lost to follow-up, LR local recurrence, MD metastatic disease, NA not available, NED no evidence of disease, Pts. patients, Refs. references, Reg. regional, RTX radiotherapy, VAI vincristine/actinomycin-D/ifosfamide

Despite the fact that chemotherapy has been shown to be not effective in CCSS, its use is documented in nine of the patients (109, 110, 112, 113). No response to cytotoxic chemotherapy was reported despite various chemotherapy regimens, most patients developing distant metastasis and eventually dying of disease.

In summary, local control is achieved by wide resection with negative margins (R0), with or without adjuvant radiation therapy. While there is still limited data on the systemic treatment of children with CCSS, current evidence suggest that there is no survival benefit using conventional chemotherapy.

7.5 PROGNOSIS

Although local control was achieved in most patients (108, 109, 111-114, 116), prognosis is dismal especially, when distant metastases occur. 7 of 10 (70%) patients with distant metastases died from disease; only one patient was free of disease ten

years after diagnosis despite local and distant relapse. Of note, pediatric CCSS was found to show an aggressive clinical course even without distant metastases, with two patients dying as a result of extensive and recurrent local disease. CCSS often shows a protracted clinical course with local or distant relapse occurring after many years, with a median-time of 26 months (range, 0-72) following diagnosis (108-112). Three patients experienced local recurrence after resection 19, 53 and 68 months after diagnosis, respectively (109, 112). Overall, follow-up time is long, and most studies report on follow-up periods of a minimum of 5 years. In 20 of 25 patients (80 %) included in this review, the follow-up (median time: 5 years) and disease status was reported. Sixty percent (n=12) died of disease, 25% (n=5) are alive with no evidence of disease and 15% (n=3) are alive with disease at the time of publication.

8 BCOR-REARRANGED SARCOMA

8.1 INTRODUCTION

BCOR-rearranged sarcoma is an aggressive small blue round cell sarcoma and occurs predominantly in the bones of male adolescents (125, 126). Due to its remarkable clinical and pathological similarities with Ewing sarcoma it was until recently grouped within the category of the so-called “Ewing-like” sarcomas together with EWSR1-non-ETS fusion sarcoma and CIC-rearranged sarcoma. These primitive round cell sarcomas lack the canonical EWSR1-ETS fusion found in Ewing sarcoma and instead harbor a distinct molecular alteration. In particular, the most frequent alteration in the pediatric population appears to be a X-chromosomal paracentric inversion, resulting in the BCOR-CCNB3 fusion. Due to their molecular genetical differences and more indolent behavior (127), BRS is now seen as a stand-alone entity distinct from Ewing sarcoma.

8.2 CLINICAL PRESENTATION

The number of reports on pediatric BRS of the soft tissues is scarce (126-138). We have identified 33 children below the age of 18 years with BRS of the soft tissues providing data on treatment strategy and/or outcome. Although these tumors have been described even in newborns (131, 138), the majority of patients become symptomatic during the second decade of life. The median age of the patients included in the present review was 13 years (range, 0-18 years). There was a predilection for

males. Twenty-five patients (76%) were males and eight were females (24%) with a female-to-male ratio of 1:3.13. Clinical symptoms of patients with BRS have not been described in this cohort. While BRS have a predilection for bone, the majority of pediatric tumors of the soft tissues are located in the trunk-wall (most commonly back/paraspinal) (127, 128, 131, 133, 134, 136-138). The most common site was back/trunk wall (n=13), followed by lower limb (n=11) (126, 127, 130, 135-137), pelvis (n=5) (126, 127, 134, 137) and others (shoulder, neck, n=4) (127, 129, 132). Data on the size of the primary tumor was available in 17 of the patients. The tumors were mostly large ranging from 1.5 to 27 cm (median: 10 cm). One patient was found to have multiple tumor implants within the thoracic and abdominal cavity from a paraspinal mass extending into the retroperitoneum (131). The lung is the most common site of metastatic spread (126, 127, 136), but lung metastasis is rarely seen at diagnosis (136).

8.3 DIAGNOSIS

Imaging studies usually show well-defined soft tissue masses with infiltrative growth into the adjacent bone (132, 134, 136, 137). CT or MRI is mandatory both in the diagnostic work-up and follow-up of patients with BRS of soft tissues. The final diagnosis is based on histology and immunohistochemistry, and the detection of BCOR gene rearrangements on a molecular level is essential to confirm the diagnosis. Tissue samples can be obtained either by biopsy (mostly diagnostic) or resection of the tumor. The characteristic histopathology of BRS is reported in detail elsewhere (139). BRS shows substantial overlap with classical Ewing sarcoma on both histopathology and immunohistochemistry. The presence of a spindle cell component embedded in a fibrous or myxoid stroma, typically absent in Ewing sarcoma, is highly suggestive for BRS (137). While CD99 positivity by immunohistochemistry is rather non-specific among the Ewing family of tumors, detection of the CCNB3 oncoprotein may be used as a helpful diagnostic marker as CCNB3 expression appears to be exclusive to BCOR-CCNB3 sarcoma (140). However, this marker will be negative in the absence of CCNB3 when BCOR is fused to alternative genes (e.g., KMT2D or MAML3 or yet unknown fusion partners), hence, molecular detection of BCOR rearrangement is needed to confirm the diagnosis. Molecular confirmation is vitally important for appropriate patient management, as survival of patients with BRS is significantly superior to that of other small blue round cell sarcomas (e.g., CIC-rearranged sarcoma)

(127). The majority of patients harbor BCOR-CCNB3 gene fusion resulting from a paracentric inversion on the X chromosome (141). Thirty-one (94%) of the patients included in this review showed the BCOR-CCNB3 fusion while one patient was found to harbor a KMT2D-BCOR fusion. The remaining patient tested positive for BCOR rearrangement by FISH, but negative for BCOR-CCNB3 by RT-PCR. Rare cases of BCOR-MAML3 and BCOR-ZC3H7B have been described in adults (142, 143), however, BCOR-MAML3 was reported in only one pediatric patient with a round cell sarcoma of the bone (143) and in none of the STSs in this cohort. While molecular detection of BCOR rearrangement is possible using FISH, and if the fusion partner is known also by RT-PCR, utilization of NGS is advised, if these methods fail to identify a gene fusion partner. Despite remarkable clinicopathologic and morphologic similarities, BRS and Ewing sarcoma have proven to be genetically and biologically distinct entities (129).

8.4 TREATMENT

The optimal treatment of BRS is not yet defined. Due to the rarity of these tumors there is currently no consensus or guidelines regarding the optimal therapeutic approach. A summary of reported therapies and the patients' outcome is described in Table 6.
As in adults BRS in children is generally treated using a multimodal approach including surgery, radiotherapy and Ewing sarcoma-based multi-agent chemotherapy. Surgery is an important aspect of treatment. The major goal is local excision with tumor-free margins (R0), but incomplete resection with microscopic residual disease has been reported after primary surgery (127). The combination of surgical resection and adjuvant therapy may play an important role in improving tumor control. Of twenty-six patients who had surgery, 20 (77%) received adjuvant therapy consisting of chemotherapy and/or radiotherapy, which was curative in 10 (50%) of the patients. 5 of 20 patients experienced local or distant recurrence, one of them after incomplete resection with adjuvant radiotherapy (127). While the data is limited to evaluate the disease course without adjuvant therapy, local recurrence was observed in one patient receiving surgery alone (137), whereas four patients benefitted from this approach with no relapse or progression being observed after a mean duration of 28 months after diagnosis (127, 137). Lymph node involvement in pediatric BRS has not been reported and nodal dissection was not performed. Resection of lung metastases was described in one patient (126).

TABLE VI. Treatment and outcome of children and adolescents with BRS

Number of pts. (Refs.)	Treatment	Disease course and/or outcome
1 (Pierron et al. [129])	NA	NED
1 (Gajdzis et al. [128])	NA	NED (3 years FU)
2 (Matsuyama et al. [130])	NA	P5: NED (8.25 years FU) P8: NED (5.5 years FU)
1 (Alfaro-Cervello et al. [131])	none	MD (mediastinum, pulmonary hilia and whole thoracic and abdominal periaortic region) DOD at 21h of life
2 (Peters et al. [137])	P2,5: GTR	P2: LR, DOD (3 years FU) P5: NED (0.25 years FU)
2 (Kao et al. [127])	P22,23: resection	P22: AWD (1 year FU) P23: NED (1.75 years FU)
1 (Li et al. [135])	CHT (VDC, IE)	AWD (0.75 years FU)
1 (Martín-Vaño et al. [138])	CHT (CE) - CHT for progression (VAI, CA)	DOC (0.5 years FU)
2 (Kao et al. [127])	P3: CHT (VAC-IE, IT) + RTX - resection P7: CHT (VAC-IE, IT) - resection	P3: NED (6.33 years FU) P7: DUC (3.33 years FU)
1 (Kao et al. [127])	CHT (ES) - resection - RTX	MD (lung)
1 (Li et al. [134])	excision - RTX	AWD (0.5 years FU)
1 (Huang et al. [132])	CHT (IVOx) - radical resection - CHT (I)	NED (0.5 years FU)
1 (Li et al. [134])	CHT - resection - CHT	AWD (1.5 years FU)
1 (Puls et al. [126])	excision - CHT (VIDE)	NED (11 years FU)
1 (Li et al. [135])	excision - CHT (VDC,IE)	NED (0.75 years FU)
3 (Kao et al. [127])	P14: resection - CHT (ES) + RTX P15: resection - CHT (ID, mesna) + RTX P20: resection (incomplete) - RTX - wide resection of LR	P14: NED (0.5 years FU) P15: NED (2 years FU) P20: LR, NED (3.66 years FU)
1 (Kyriazoglou et al. [133])	excision - CHT (VIDE, VAI) - RTX	Alive (1 year FU)
3 (Peters et al. [137])	P1: GTR - CHT (ID) + RTX P3: STR - CHT (ID) + RTX P4: open biopsy - CHT (VAC) + RTX	P1: NED (1 year FU) P3: NED (8 years FU) P4: LR, NED (7.75 years FU)
2 (Puls et al. [126])	P2: CHT (VIDE) + RTX - surgery - CHT (VAI) + RTX P9: resection - CHT (VIDE) + RTX - resection of lung mets	P2: DOD (2.33 years FU) P9: MD (lung), AWD (5 years FU)
1 (Kao et al. [127])	debulking surgery - CHT - re-excision	LR
4 (Krskova et al. [136])	surgery + neoadjuvant/adjuvant therapy	P1: NED (2.33 years FU) P2: MD at diagnosis (lung), DOD (2 years FU) P3: NED (15.5 years FU) P7: NED (11.5 years FU)

Abbreviations: AWD alive with disease, CA cisplatin/doxorubicin, CE carboplatin/etoposide, CHT chemotherapy, DOC death of other cause, DOD death of disease, DUC death of unknown cause, ES Ewing sarcoma protocol, FU follow-up, GTR gross total resection, I ifosfamide, ID ifosfamide/doxorubicin, IE ifosfamide/etoposide, IVOx ifosfamide/pirarubicin/oxaliplatin, LR local recurrence, MD metastatic disease, NA not available, NED no evidence of disease, Pts patients, Refs references, RTX radiotherapy, STR subtotal resection, VAC vincristine/actinomycin-D/cyclophosphamide, VAI vincristine/actinomycin-D/ifosfamide, VDC vincristine/doxorubicin/cyclophosphamide, VIDE vincristine/ifosfamide/doxorubicin/etoposide

Cytotoxic chemotherapy has been routinely administered in the majority of patients together with surgery (neo-adjuvant, n=5; adjuvant, n=14; neo-adjuvant and adjuvant, n=3), however, objective responses were rarely reported. Of eight patients receiving neo-adjuvant chemotherapy, two showed no response or PD (126, 127) and one patient achieved PR (138). Of the remaining five patients, two patients were free of disease after surgery with or without adjuvant therapy (127, 132), two were alive with

disease (134, 135), and one died of an unknown cause (127). Children with BRS should be included into prospective trials and in case of a EWSR1-negative small round cell tumor this disease should be considered.

To summarize, complete surgical resection is the mainstay of treatment in children and adolescents with BRS and adjuvant chemotherapy may be beneficial for the achievement of long-term remission. Most children with BRS benefit from treatment approved for Ewing sarcoma, however, their less aggressive clinical behavior compared to Ewing sarcoma suggests that other treatment modalities may be indicated for optimal patient management.

8.5 PROGNOSIS

Although BRS seems to have a relatively indolent course with multimodal therapy (126, 127, 132, 133, 135-137), prognosis is less favorable in case of metastatic disease (126, 131, 136). In the study by Puls et al. on 10 pediatric patients with BRS of both soft tissue and bone, a shorter survival was significantly related to location in the axial skeleton and soft tissues versus extremities (126). Recurrences have been reported up to 2+ years following diagnosis (127, 137). Overall, follow-up time is long in most series and often exceeds 2 years (128, 131-135). Some series report on a follow-up time over 5 years (126, 127, 130, 136, 137). The final outcome of patients who have developed tumor recurrence is described in the majority of reports, with two patients free of disease after 44 and 93 months and one patient dying of disease at 34 months following diagnosis. Overall in 30 of 33 patients in this review the follow-up (median time: 2.3 years) is reported with disease status in 30 (one additional patient was reported alive). Sixty-three percent (n=19) are alive with no evidence of disease, 20 % (n=6) died (including one of an unknown cause) and 17% (n=5) are alive with stable disease at the time of publication.

9 NTRK-REARRANGED SPINDLE CELL NEOPLASMS

9.1 INTRODUCTION

NTRK-rearranged spindle cell neoplasms are another group of molecularly defined rare soft tissue tumors described in the 2020 WHO Classification of Soft Tissue and Bone Tumours (1), representing a novel and emerging entity. These tumors are defined by a spectrum of histopathological patterns overlapping some well-known

entities (e.g., lipofibromatosis, malignant peripheral nerve sheath tumor and myopericytoma/haemangiopericytoma) and harbor recurrent rearrangements of the NTRK group of genes not previously recognized in either of their morphologic counterparts. To account for alternative gene fusions recently found in these tumors (outside NTRK), this provisional category according to the WHO includes tumors with BRAF- and RAF1-fusions.

9.2 CLINICAL PRESENTATION

There is a lack of reports on pediatric NTRK-rearranged soft tissue sarcomas in the published literature (27, 29, 30, 32, 144-152). We identified 24 children below the age of 18 years with NTRK-rearranged spindle cell neoplasm providing data on treatment strategy and/or outcome. Only cases with a distinct histomorphological pattern (lipofibromatosis-like, resembling malignant peripheral nerve sheath tumor, or myopericytoma/haemangiopericytoma-like) reported were included. Patient age ranged from 0 to 15 years (median: 5.5 years). Fifteen patients (63%) were females and nine (37%) were males with a male-to-female ratio of 1:1.7. Pediatric NTRK-rearranged soft tissue sarcoma affect more often the superficial (n=14) than deep (n=5) soft tissues, and mostly the extremities (27, 29, 144, 145, 147-149, 151). The most common sites were the lower limb (n=11), followed by the upper limb (n=6), back/trunk wall (n=5) and others (neck, retroperitoneum, n=2). Data on the size of the primary tumor was available in half of the patients, ranging from 1.4 to 14 cm (median: 3.3 cm). The tumors presented as a palpable non-tender mass sometimes consisting of multiple firm nodules with overlying purplish-red skin (146, 147). None of the patients had a history of type 1 neurofibromatosis reported. Metastases were not reported in the patients included in this report.

9.3 DIAGNOSIS

Imaging characteristics of NTRK-rearranged spindle cell neoplasms are scarcely described. The presence of an infiltrative boarder (also commonly reported on histology) as well as intratumoral hypovascularized nodules corresponding to areas of hyalinized vessels on histology may constitute a radiological finding suggestive of this tumor type, however, this is rather nonspecific and also found in other tumors (153). CT or MRI is mandatory for both the diagnostic and follow-up imaging of patients with NTRK-rearranged spindle cell neoplasms. Pre-treatment diagnostic modalities

included US, MRI and CT (146-149, 151, 152). Tissue samples are obtained by biopsy (mostly diagnostic).

Histomorphologically, NTRK-rearranged spindle cell neoplasms appear to form a wide spectrum ranging from lipofibromatosis-like to tumors resembling malignant peripheral nerve sheath tumor. Less commonly these neoplasms present with a myopericytoma/haemangiopericytoma-like pattern (Table 7). Importantly, as 50% (n=12) of the tumors reportedly showed multiple morphological patterns (27, 145, 149), tumor heterogeneity itself may be helpful in guiding diagnosis and may not be detected in small samples obtained by needle biopsy (19). There appears to be a continuum in the degree of malignancy within these tumors, revealing a variable degree of cellularity spanning from low to high cellularity accompanied by different levels of mitotic activity. These features have been shown to correlate with clinical behavior in a subset of adult cases (151). Immunohistochemistry is essential for differentiation of NTRK-rearranged spindle cell neoplasms from their NTRK fusion-negative counterparts. A striking characteristic is the frequent dual positivity of CD34 and S100 in the absence of SOX10 reactivity while H3K27me3 expression is consistently retained. Of note, tumors with a myopericytoma/haemangiopericytoma-like pattern share a rather nonspecific immunophenotype. Pan-TRK immunohistochemistry in pediatric mesenchymal neoplasms has been shown to be a valuable diagnostic marker, if NTRK-rearrangements are present (43). Screening for TRK protein expression by immunohistochemistry is recommended in case of tumors less likely to harbor NTRK-related gene fusions when sequencing platforms are not available (154), thus guiding further diagnostic steps. The final diagnosis, however, requires detection of specific gene rearrangements on a molecular basis. These tumors often harbor NTRK1 fusions with a variety of partners including LMNA, TPM3 and TPR. In our cohort sixteen patients harbored fusions related to the NTRK1 gene (most commonly LMNA-NTRK1). One patient showed a NTRK3-rearrangement and seven were found to harbor alternative fusions involving RET (n=3), BRAF (n=2), ROS (n=1) or ALK (n=1). The correlation of morphology and genotype remains challenging as comprehensive data on fusion frequencies in different histologic subtypes are limited (155). As a general approach, in neoplasms with a high frequency of recurrent NTRK fusions (e.g, lipofibromatosis-like tumors) molecular testing is of utmost importance, whereas the presence of a neoplasm with a low probability of harboring NTRK-related gene fusions should prompt RNA-based next generation sequencing following

immunohistochemistry to simultaneously identify a spectrum of targetable oncogenic drivers (48, 154).

9.4 TREATMENT

The major goal of surgical treatment is to achieve local excision with microscopic free margins (R0). A summary of reported therapies and the patients' outcome is described in Table 7.

Microscopic complete resection is curative in all cases without the need for adjuvant therapy. Incomplete resection with microscopic and/or macroscopic residual disease, however, has been reported after primary surgery (29, 144, 145, 152). Four of seven patients with incomplete primary resection experienced local recurrence whereas none of the six patients with microscopic complete resection, stressing the role of surgery in these tumors. Of the remaining three patients, one received adjuvant radiotherapy and he achieved a CR with an uneventful course after a follow-up of 3 years. In two patients without adjuvant treatment one had stable disease after 4 years and the other had no

TABLE VII. **Treatment and outcome of children and adolescents with NTRK-rearranged spindle cell neoplasm**

Number of pts. (Refs.)	Treatment	Disease course and/or outcome
Lipofibromatosis-like		
1 (Malik et al. [147])	close observation	uneventful since biopsy
1 (Antonescu et al. [29], Davis et al. [30])	biopsy only	AWD (stable) (2 years FU)
1 (Kohsaka et al. [148])	resection	NED (0.75 years FU)
1 (Bartenstein et al. [146])	wide resection (R0)	NED (0.66 years FU)
1 (Kao et al. [145])	primary incomplete excision	LR
7 (Agaram et al. [144], Kao et al. [145])	P1,10,11: primary excision with positive margins P2,3,6,12: excision (negative margins)	P1,10,11: LR (1-2x), NED (0.75 - 9.7 years FU) P2,3,6,12: NED (1 month - 3 years FU)
2 (Antonescu et al. [29], Davis et al. [30])	P1,3: excision (positive margins)	P1: AWD (stable) (4 years FU) P3: NED (2 years FU)
3 (Lao et al. [149])	P6,7,10: surgery	P6: LR P7: NED (0.5 years FU) P10: NA
1 (Baranov et al. [32])	trametinib - excisional biopsy	AWD (3 years FU)
1 (Penning et al. [27])	trametinib - trametinib/sirolimus	AWD (0.66 years FU)
MPNST-like		
1 (Suurmeijer et al. [150])	NA	AWD (0.33 years FU)
2 (Suurmeijer et al. [151])	P16,17: NA	P16,17: NED (0.25 - 1 year FU)
MPC/HPC-like		
2 (Haller et al. [152])	P1: excision (R1) - RTX P2: complete excision	P1: NED (2.5 years FU) P2: NED (2 years FU)

Abbreviations: AWD alive with disease, FU follow-up, HPC haemangiopericytoma, LR local recurrence, MPC myopericytoma, MPNST malignant peripheral nerve sheath tumor, NA not available, NED no evidence of disease, Pts. patients, Refs. references, RTX radiotherapy

evidence of disease after 2+ years. In two patients with a watch-and-wait strategy after biopsy, no recurrences were observed at the time of publication. Lymph node involvement in pediatric NTRK-rearranged spindle cell neoplasm has not been reported and nodal dissection was not described. Radiotherapy was delivered to one patient after resection with macroscopic residual disease, however, current evidence suggests that it can be safely omitted in most patients to potentially reduce the known long-term risks of radiotherapy (156). Chemotherapy was not administered in these patients.

Two infants with a BRAF-rearranged spindle cell neoplasm were treated first-line with the MEK-inhibitor trametinib: one patient achieved a radiological PR with 0% residual tumor on biopsy after 16 months of treatment (32) and in the other patient the disease progressed during trametinib-monotherapy; however, disease stabilization was achieved with a combination of trametinib and sirolimus (27).

In summary, surgical resection with microscopic free margins (R0) is the prerequisite for cure in children and adolescents with NTRK-rearranged spindle cell neoplasm. These tumors seem to follow a benign clinical course after conservative treatment without the need for adjuvant treatment. As the majority of these tumors harbor recurrent NTRK gene rearrangements, targeted therapy using receptor kinase inhibitors such as larotrectinib or entrectinib may provide a safe and promising treatment option in case of unresectable disease.

9.5 PROGNOSIS

These tumors show an excellent prognosis after surgery alone (29, 30, 144-146, 148, 149, 152), however, local recurrences are frequently observed, if the tumors are not amenable to complete resection (144, 145). Even without treatment the clinical course remains uneventful with stable disease being reported in one patient at 2 years following diagnosis (29, 30). Local recurrences may occur many years after diagnosis (e.g., two patients with incomplete resection relapsed after 4.2 and 7.5 years (144, 145)). In adult patients, histological grade may be associated with outcome (150, 151), however, in the pediatric population grading seems to have no impact on the course of disease. In eight evaluable patients with the tumors harboring at least one high grade feature (e.g., high mitotic rate [> 10/10 HPF], increased cellularity or scattered pleomorphic or multinucleated giant cells), none of the patients had an adverse outcome. Overall, follow-up time is short in most series and rarely exceeds 2 years

(27, 146, 148-151). Only a few series report on a longer follow-up (30, 32, 145, 152). The outcome of patients with tumor recurrence was reported in three of five patients. Of note, NTRK-rearranged spindle cell neoplasms were found to follow a benign clinical course, despite one (or multiple) tumor recurrences (144, 145). Overall, in 19 of 24 patients in this review the follow-up (median time: 2 years) and disease status were reported. Seventy-four percent (n=14) were alive with no evidence of disease, and 26% (n=5) were alive with disease at the time of publication. None of the patients died of disease.

10 ANGIOMATOID FIBROUS HISTIOCYTOMA

10.1 INTRODUCTION

Angiomatoid fibrous histiocytoma is a rare mesenchymal tumor of intermediate (rarely metastasizing) malignant potential, mostly affecting the soft tissues of children and young adults. Since its first description by Enzinger in 1979 who originally proposed the term angiomatoid malignant fibrous histiocytoma (157), elucidation of the molecular genetic signature of these tumors (e.g. oncogenic fusion resulting in EWSR1-CREB1) led to the recognition of a novel entity distinct from malignant fibrous histiocytoma with a much more favorable outcome after standard therapy.

10.2 CLINICAL PRESENTATION

Data on molecularly confirmed AFH is limited (158-169). We identified 25 children including 2 from our institution below the age of 18 years with fusion-positive AFH providing data on treatment strategy and/or outcome. The patients' age ranged from 3 to 17 years. The median age was 10 years. Sixteen patients (64%) were males and nine (36%) were females with a female-to-male ratio of 1:1.77. Clinical signs and symptoms were commonly reported as a slow-growing, painless, nontender lump or swelling sometimes mimicking a lymph node (167) without associated systemic symptoms. However, 3 cases including one of our patients with EWSR1-CREB1 positive AFH experienced paraneoplastic syndrome (158, 169) by showing elevated IL-6 and other inflammatory markers with or without systemic symptoms suggestive of tumoral cytokine production which promptly improved after surgical resection in one (158), but again increased paralleling progression in our case. The majority of pediatric AFH are located in the extremities (158, 159, 161, 162, 164-169). The most common

sites were the limbs (n=16), followed by trunk (n = 6) (163, 165-167) and scalp (n=3) (160, 165, 167). Two thirds (n=10) arose in the superficial soft tissues (e.g., deep dermis and/or subcutis), with one third (n=5) infiltrating or deep to the fascia. Data on the size of the primary tumor was available in 23 of the patients, ranging from 0.7 to 8.5 cm (median: 2 cm). Duration of symptoms ranged from 2-12 months with a median of 6.5 months. One patient had multiple satellite nodules without regional or distant metastases (163) and another patient, one of the three cases presenting with paraneoplastic syndrome, showed several enlarged lymph nodes, though pathologic examination showed reactive features but no metastasis (158). Lymph nodes and lungs were reported as metastatic sites (160, 166, 168), but metastatic events are rarely seen at diagnosis (169).

10.3 DIAGNOSIS

Imaging studies generally show single ovoid to round masses with well-defined margins. MRI findings in pediatric AFH are barely described in the literature. However, one of the features which should prompt for consideration of AFH are intralesional blood-filled cystic spaces with fluid-fluid levels, reflecting typical pseudoangiomatoid areas noted on histopathology, though not always present (170). CT or MRI is mandatory in both the diagnostic work-up and follow-up of patients with AFH. Of note, suspicious lymph nodes on imaging unraveling benign on pathologic examination is a common finding in patients with AFH (171), including one patient from our cohort (158). Hence, suspicious lymph nodes should be biopsied in order to achieve accurate staging. While definite diagnosis is based on the detection of specific molecular alterations, the results should be carefully correlated with clinical and histopathologic findings, as they may present diagnostic pitfalls due to overlapping features with other distinct entities. Tissue samples are obtained by biopsy (mostly non-diagnostic). As wide excision with negative margins represents the cornerstone for disease control in resectable and localized AFH, obtaining tissue samples by resection of the tumor is recommended in these cases.

The characteristic histological features of AFH are described in detail in the largest morphologic series to date (172). AFH may show variant pleomorphism, but this does not seem to correlate with clinical behavior (173). Immunohistochemically, AFH stains variably positive for desmin, CD68, CD99 and epithelial membrane antigen (EMA), however, it is lacking a specific immunoprofile and immunohistochemistry should

therefore be considered supportive rather than diagnostic. Concomitant findings of CD99 positivity and a small blue round cell component with EWSR1 rearrangement detected by FISH without further molecular evaluation presented a diagnostic pitfall in three cases of AFH originally misclassified as Ewing sarcoma or high-grade undifferentiated sarcoma (167). EWSR1 gene rearrangement is not specific and has been found in a variety of different soft tissue sarcomas with sometimes near identical histomorphology (174), differing in behavior and treatment, thus stressing the importance of identification of the fusion partner gene. The use of RT-PCR as an adjunct diagnostic modality to histopathology is recommended in the diagnostic work-up of AFH, owing to its high specificity compared to FISH (175). The molecular genetic findings of the pediatric AFH included in this review support previous reports that EWSR1-CREB1 and EWSR1-ATF1 are the most common fusion types with FUS-ATF1 being very rare. 15 patients (60%) harbored the characteristic EWSR1-CREB1 gene, 3 patients (12%) harbored EWSR1-ATF1 and 1 patient (4%) harbored FUS-ATF1, while EWSR1-rearrangement by FISH without further molecular investigation was described in 6 patients (24%). Of note, these gene fusions are not unique to AFH with EWSR1-ATF1 being the genetic hallmark of clear cell sarcoma of soft tissue (CCSS), suggesting a molecular homology between these two entities despite CCSS sharing a distinct phenotype and melanocytic differentiation. Interestingly, in a gene expression data analysis, the melanocyte-specific microphthalmia-associated transcription factor gene MITF-M was found to be constantly expressed in EWSR1-ATF1 fused CCSS (124), but in none of the previously reported AFH harboring the same gene fusion (162, 163, 167). In the presence of SOX10 expression, the EWSR1-ATF1 fusion protein activates MITF, which results in melanocytic differentiation and survival/proliferation of tumor cells. SOX10 expression is constantly found in CCSS, whereas negative in AFH. This finding implicates differences in the molecular biology of these two entities despite sharing the same fusion gene and is in line with the more aggressive clinical behavior of CCSS compared to AFH.

10.4 TREATMENT

Surgery is the mainstay of treatment. As in adults the major goal is to achieve local excision with microscopic free margins (R0). A summary of reported therapies and the patients' outcome is described in Table 8.

Surgical resection was performed without preoperative treatment in 100% (n=24) of patients presenting with localized disease and was curative in 75% (n=18) without the need for further treatment. Of the remaining five patients with local and/or distant relapse, primary excision was reported marginal in two, incomplete in two, and complete in one, whereas in one patient, follow-up was not available. In one of the patients with metastatic disease, subsequent R0-resection of the metastatic lesions was performed and he remained in complete remission after a follow-up of almost 3.5 years (160).

The use of cytotoxic chemotherapy was described in two patients (both for metastatic disease). In one of the patients, the pulmonary metastatic nodules resolved after chemotherapy while the primary tumor and lymph node metastases showed no response (169). The other patient achieved PR of both local and distant relapse and the residual disease remained stable at 9 months following the end of treatment (168).

Two patients were treated at our institution for a localized AFH harboring the EWSR1-CREB1 fusion. The first patient was a 12-year-old male presenting with a fusion-positive AFH of the thigh without evidence of distant metastasis. Wide surgical excision with negative margins was performed and the patient is currently alive with no evidence

TABLE VIII. **Treatment and outcome of children and adolescents with AFH**

Number of pts. (Refs.)	Treatment	Disease course and/or outcome
2 (Hallor et al. [163])	resection	NED (0.5 - 5 years FU)
1 (Tornoczky et al. [159])	excision	NED (2 years FU)
3 (Shi et al. [164])	excision	NED
3 (Kao et al. [165])	excision	NED (0.5 - 2.75 years FU)
5 (Antonescu et al. [167])	excision	NED (0.5 - 3 years FU)
1 (Akiyama et al. [158])	complete excision	NA
Present case	wide resection (R0)	NED (3.33 years FU)
1 (Hallor et al. [162])	marginal excision	NED (0.5 years FU)
3 (Matsumura et al. [166])	P2: marginal excision P6: marginal excision P9: wide resection	P2: LR x2, MD (lung), DOD (17.5 years FU) P6: NED (3.5 years FU) P9: NED (0.25 years FU)
1 (Waters et al. [161])	complete excision - excision of recurrence	LR
1 (Thway et al. [160])	excision (R1) - excision of relapse (R0)	MD (ln), NED (3.5 years FU)
1 (Ogden et al. [168])	marginal excision - ln dissection - CHT for 2nd relapse (ID)	MD x2 (ln), LR AWD (stable) [9 months after end of treatment]
1 (Potter et al. [169])	CHT (VAC) - tocilizumab 10mg/kg	MD at diagnosis (ln, lung)
Present case	resection (R1/RX) - re-excision (R1) - wide resection (R1/RX) - local RTX - CHT (CEVAIE, tocilizumab, TRABIRI, crizotinib, pazopanib) - surgery of lung and soft tissue metastases + photon beam radiation to lungs and regional ln - CHT (temozolomide), pembrolizumab	MD (lungs, ln, soft tissue) DOD (2 years FU)

Abbreviations: AWD alive with disease, CEVAIE carboplatin/epirubicin/vincristine/actinomycin-D/ifosfamide/etoposide, CHT chemotherapy, DOD death of disease, FU follow-up, ID ifosfamide/doxorubicin, ln lymph nodes, LR local recurrence, MD metastatic disease, NA not available,

NED no evidence of disease, Pts patients, Refs references, RTX radiotherapy, TRABIRI trabectedin/irinotecan, VAC vincristine/actinomycin-D/cyclophosphamide

of relapse at a follow-up of 40 months. The second patient was a 16-year-old male presenting with a large AFH of the buttock with infiltration into the gluteal muscle showing elevated IL-6 and other inflammatory markers and aggressive behavior resistant to multimodal therapy. After incomplete first resection and second excision with positive margins, the residual disease rapidly progressed within 2 months. Radical resection with adjuvant radiotherapy was subsequently performed, however, widespread disease to the lungs and lymph nodes was noted a few weeks later. Despite different therapeutic attempts including multi-agent chemotherapy, radiotherapy and targeted therapy using tocilizumab, pazopanib and crizotinib, the disease further progressed and the patient subsequently succumbed to his disease 2 years following diagnosis. The study by Potter et al. described the use of tocilizumab in another patient with paraneoplastic syndrome treated for metastatic disease (169). SD was achieved with administration of tocilizumab for one year at a dose of 10 mg/kg with normalization of inflammatory markers.

To summarize, surgical resection with microscopic free margins (R0) is the prerequisite for cure in children and adolescents with AFH. Although the number of patients treated with tocilizumab is limited in this cohort, current evidence suggests that SD can be achieved with administration of tocilizumab.

10.5 PROGNOSIS

Although 75% (n=18) of patients with AFH can be cured with complete surgical resection alone (159, 160, 162-167), prognosis is less favorable, if the tumor and/or metastatic lesions are not amenable to complete resection (166, 168, 169). Repeated relapses may occur and several years following diagnosis (e.g., one patient died after disease duration of 17.5 years) (166). Overall, follow-up time is short in most patients and rarely exceeds 3 years (159, 162, 165, 167). Few studies, however, report on longer follow-up (160, 163, 166). The outcome of patients with tumor recurrence was reported in 4 of 5 patients (160, 166, 168). Of note, recurrent pediatric AFH may show a benign clinical course, if the tumor is completely excised (160). Of the 25 patients included in this review, the follow-up was reported in 18 (median time: 2 years), with reported disease status in 22. Eighty-six percent (n=19) are alive with no evidence of

disease, 9% (n=2) died of disease and 5% (n=1) are alive with stable disease at the time of publication.

11 SUMMARY AND FUTURE PERSPECTIVES

We present the first review on the management of a variety of rare molecularly confirmed STS in children and adolescents. The rarity of STS is illustrated by the lack of data available on the optimal clinical management. Classification of STS according to their underlying molecular profile seems reasonable, as some neoplasms with near identical histomorphology are – in fact – distinct entities with a distinct molecular signature, further highlighted by their different clinical behavior.

BRS typically occurs in the bones of adolescent males, with soft tissue presentation being less common (129). In our pediatric cohort of 33 patients with BRS of the soft tissues, we observed 70% to be less than 15 years old, while a similar large study including both children and adults showed a slight shift towards adults with 47% less than 15 years of age (127). This may be due to the fact that BRS of the bones had been included that might occur more often in older children. We noted a distribution towards the axial vs. extra-axial soft tissues (61% vs. 39%), with a high proportion of pelvic/paraspinal tumors among the axial tumors (65%).

Clinical presentation of BRS differs from those of CRS, which is an important differential diagnosis. CRS mainly affects the soft tissues of middle aged adults (mean 32 years), while osseous presentation is quite rare (2). In our series of 25 pediatric patients with CRS originating from the soft tissues, we observed an equal distribution between axial and extra-axial sites (56% vs. 44%), with a predilection for the deep soft tissues of the lower limb among extra-axial tumors (91%; 10/11), a pattern that has already been described by other authors (2, 85). The overall metastatic rate was 96% (24/25). This percentage is higher than the one observed in the largest study on CRS to date, including both children and adults (53% [30/57]) (2). This may be due to the relatively small number of patients included in our cohort. Metastases most commonly affected the lungs (88% [21/24] of all patients with metastatic disease), and were often seen at diagnosis.

Although the EWSR1-ATF1 fusion is the genetical hallmark of CCSS, AFH may share the same gene fusion (3/25 patients [12%] in our cohort). CCSS most commonly affects the lower extremity (68% [17/25]), often in close proximity to tendons and aponeuroses of the distal proportions of the leg (53% [9/17]), while AFH usually

presents in the superficial tissues. Both entities may show suspicious lymph nodes on imaging. While lymph node metastases are a common finding in CCSS, AFH rarely metastasizes and suspicious lymph nodes are often found benign on pathologic examination (171). Presenting a case from our institution, however, we showed that the disease in AFH may indeed be extensive with distant metastases and letal.

In our cohort of 50 patients with DSRCT, we confirm the striking male predilection (F:M ratio 1:4.55) and predilection for abdominal/pelvic sites (83% [40/48]) which has already been reported (F:M 1:3.32 and 84% [76/90]) (176).

Interestingly, the majority of pediatric IFSs in our cohort (53% [49/93]) harbored gene fusions other than the canonical ETV6-NTRK3, half of these (n=25) related to NTRK1. Furthermore, we observed 50% (21/42) of classic IFS to be present at birth, while alternatively fused IFS often occurred in older children. To consider clinical data like age at presentation seems especially important in these cases, as it may guide molecular work-up (e.g., the use of RT-PCR or NGS) while suggesting alternative fusions. Further of note, IFS is important to include in the differential diagnosis of vascular tumors, as 9 IFSs (10%) of our cohort were misinterpreted as benign vascular lesions like vascular malformations.

In the latest WHO Classification of Soft Tissue and Bone Tumours, the group of NTRK-rearranged spindle cell neoplasms as a distinct entity was recently added to the field of molecularly defined soft tissue malignancies. In our relatively small cohort of 24 pediatric patients the median age was 5.5 years, two thirds (63% [15/24]) affected females. 50% (n=12) of cases reportedly showed multiple histological patterns. This feature that needs to be further looked into in larger cohorts as it may be helpful in guiding diagnosis, because these tumors histologically overlap some well-known entities, thus avoiding diagnostic pitfalls.

When testing for gene fusions, it seems important to reconcile the prevalence of known fusion genes in certain neoplasms with the molecular techniques used.

In CRS and BRS, for example, the use of FISH – in most cases – seems adequate for detection of CIC-rearrangements and BCOR-rearrangements, respectively, as these are obligate to confirm diagnosis in these tumors and identification of the fusion partner seems to be more of statistical than practical use.

In other certain neoplasms, including AFH and CCSS, identification of the fusion partner is of utmost importance. For instance, AFH and Ewing sarcoma both may share gene fusions related to EWSR1, and the detection of only EWSR1-rearrangement by

FISH may not be sufficient to confirm diagnosis, especially when histopathology is inconclusive (167). Hence, the use of RT-PCR as an adjunct diagnostic modality is recommended in AFH to reliably identify both fusion partners (e.g. EWSR1-CREB1, EWSR1-ATF1, FUS-ATF1).

While the use of FISH or RT-PCR seems adequate in most cases of CCSS (88% [22/25] harbored EWSR1-ATF1) and DSRCT (100% [50/50] harbored EWSR1-WT1), one case in our cohort of CCSS tested positive for EWSR1-rearrangement by FISH but negative for ATF1, CREB1 and CREM, suggesting a yet unknown fusion partner. Further, EWSR1-WT1 negative cases in DSRCT have been described (50, 53, 58). The use of NGS might present a powerful method to confirm diagnosis in these cases. Lastly, IFS and NTRK-rearranged spindle cell neoplasm both may share fusions related to the NTRK group of genes, although they are seen as distinct entities with different clinical behavior. In our cohort of NTRK-rearranged spindle cell neoplasms, 67% (16/24) involved NTRK1, 4% (1/24) involved NTRK3 and 29% (7/24) involved alternative genes including RET (n=3), BRAF (n=2), ROS (n=1) or ALK (n=1). In our cohort of IFS, alternative fusions other than the canonical ETV6-NTRK3 were present in 53% [49/93] of cases, including NTRK1 (n=25), NTRK2 (n=1), NTRK3 (n=3), BRAF (n=12), MET (n=2), ALK (n=2) and RET (n=4). The correlation of histomorphology and genotype is crucial in these cases for confirming diagnosis, including the detection of the fusion partner gene by NGS.

Despite multimodal treatment, the prognosis of patients with CRS was dismal and consistent with previous reports. The median OS in this cohort was only 1 year. CRS appears to be less chemo-sensitive than Ewing sarcoma, although transient responses were noted. Similarly, patients with DSRCT show a devastating prognosis, with a median OS of 1.5 years in our cohort. Further, deaths due to aggressive treatment were reported.

The treatment in IFS and NTRK-rearranged spindle cell neoplasms mainly consists of complete surgical resection. In these tumors, targeted therapy using NTRK-inhibitors such as larotrectinib or entrectinib presents a safe and promising treatment option when standard therapy fails. In our cohort of 30 patients with IFS treated with targeted therapy, 50% (15/30) achieved CR and none of them died.

The fact that BRS seems to follow a more indolent course with multimodal therapy compared to Ewing sarcoma suggests that other treatment modalities may be indicated for optimal patient management.

Despite the majority of patients with AFH in our cohort showing a favorable outcome with complete resection, the disease may be extensive and letal, when not completely resected, including one of our cases who died despite multimodal treatment. Similarly, prognosis in patients with CCSS is less favorable in case of metastatic disease, with 70% (7/10) of patients in our cohort dying of metastatic disease.

The bonding of molecular and histopathologic diagnostics has greatly contributed to better classify the broad landscape of undifferentiated soft tissue sarcomas. At the same time, the number of molecularly defined entities is expected to increase in the future, and it can be argued that this will render identification of these tumors even more difficult. As prospective clinical trials are not feasible due to the rarity of these tumors, evidence on the optimal treatment will be difficult to obtain. As for now, including patients into registers is the only way to generate data on adequate clinical management.

While molecular characterization has enabled targeted therapy to evolve, this is – to date - only available in a subset of these tumors. For the future, identification of specific molecular cancer vulnerabilities could be the basis to generate new targeted therapy approaches for many more entities.

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