



ORIGINAL RESEARCH**Desmoplastic small round cell tumors: Multimodality treatment and new risk factors**

Monika Scheer¹  | Christian Vokuhl² | Bernd Blank¹ | Erika Hallmen¹ |
 Thekla von Kalle³ | Marc Münter⁴ | Rüdiger Wessalowski⁵ | Maite Hartwig⁶ |
 Monika Sparber-Sauer¹  | Paul-Gerhardt Schlegel⁷ | Christof M. Kramm⁸ |
 Udo Kontny⁹ | Bernd Spriewald¹⁰ | Thomas Kegel¹¹ | Sebastian Bauer¹² |
 Bernarda Kazanowska¹³ | Felix Niggli¹⁴ | Ruth Ladenstein¹⁵ | Gustaf Ljungman¹⁶ |
 Kirsi Jahnukainen¹⁷ | Jörg Fuchs¹⁸ | Stefan S. Bielack^{1,19} | Thomas Klingebiel²⁰ |
 Ewa Koscielniak^{1,21} | on behalf of the Cooperative Weichteilsarkom Studiengruppe [CWS]

¹Pediatrics 5, Olgahospital, Klinikum Stuttgart, Stuttgart, Germany

²Kiel Pediatric Tumour Registry, Department of Pediatric Pathology, University Hospital Kiel, Germany

³Radiologisches Institut, Olgahospital, Klinikum Stuttgart, Stuttgart, Germany

⁴Radiation Oncology, Klinikum Stuttgart, Stuttgart, Germany

⁵Pediatric Oncology Clinic, Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany

⁶Pediatric Hematology and Oncology, University Hamburg-Eppendorf, Hamburg, Germany

⁷Children's Hospital, Pediatric Oncology, University Würzburg, Würzburg, Germany

⁸Pediatric Hematology and Oncology, University Medical Center Göttingen, Göttingen, Germany

⁹Pediatric Hematology and Oncology, University Medical Center Aachen, Aachen, Germany

¹⁰Internal Medicine 5, University Hospital Erlangen, Erlangen, Germany

¹¹Hematology/Oncology, University of Halle, Halle, Germany

¹²Sarcoma Center, West German Cancer Center, University of Duisburg-Essen, Essen, Germany

¹³Department of Pediatric Hematology/Oncology and BMT, University of Wrocław, Wrocław, Poland

¹⁴Pediatric Oncology, University of Zürich, Zürich, Switzerland

¹⁵St. Anna Kinderspital and St. Anna Kinderkrebsforschung e.V., Vienna, Austria

¹⁶Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden

¹⁷Pediatrics, Helsinki University Central Hospital, Helsinki, Finland

¹⁸Pediatric Surgery, University Hospital Tübingen, Tübingen, Germany

¹⁹Pediatric Hematology and Oncology, University Children's Hospital Münster, Münster, Germany

²⁰Department for Children and Adolescents, University Hospital, Goethe-University Frankfurt (Main), Frankfurt, Germany

²¹Pediatric Hematology and Oncology, University of Tübingen, Tübingen, Germany

Correspondence

Monika Scheer, Pediatrics 5, Klinikum Stuttgart, Olgahospital, Stuttgart, Germany.
 Emails: monika.scheer@olgahospital-stuttgart.de; m.scheer@klinikum-stuttgart.de

Abstract

Background: To evaluate optimal therapy and potential risk factors.

Methods: Data of DSRCT patients <40 years treated in prospective CWS trials 1997-2015 were analyzed.

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2019 The Authors. *Cancer Medicine* published by John Wiley & Sons Ltd.

Funding information

Supported by the German Childhood Cancer Foundation, Bonn; German Cancer Aid, Bonn; and the Förderkreis Krebskranke Kinder eV Stuttgart, Germany.

Results: Median age of 60 patients was 14.5 years. Male:female ratio was 4:1. Tumors were abdominal/retroperitoneal in 56/60 (93%). 6/60 (10%) presented with a localized mass, 16/60 (27%) regionally disseminated nodes, and 38/60 (63%) with extraperitoneal metastases. At diagnosis, 23/60 (38%) patients had effusions, 4/60 (7%) a thrombosis, and 37/54 (69%) elevated CRP. 40/60 (67%) patients underwent tumor resection, 21/60 (35%) macroscopically complete. 37/60 (62%) received chemotherapy according to CEVAIE (ifosfamide, vincristine, actinomycin D, carboplatin, epirubicin, etoposide), 15/60 (25%) VAIA (ifosfamide, vincristine, adriamycin, actinomycin D) and, 5/60 (8%) P6 (cyclophosphamide, doxorubicin, vincristine, ifosfamide, etoposide). Nine received high-dose chemotherapy, 6 received regional hyperthermia, and 20 received radiotherapy. Among 25 patients achieving complete remission, 18 (72%) received metronomic therapies. Three-year event-free (EFS) and overall survival (OS) were 11% (± 8 confidence interval [CI] 95%) and 30% (± 12 CI 95%), respectively, for all patients and 26.7% (± 18.0 CI 95%) and 56.9% (± 20.4 CI 95%) for 25 patients achieving remission. Extra-abdominal site, localized disease, no effusion or ascites only, absence of thrombosis, normal CRP, complete tumor resection, and chemotherapy with VAIA correlated with EFS in univariate analysis. In multivariate analysis, significant factors were no thrombosis and chemotherapy with VAIA. In patients achieving complete remission, metronomic therapy with cyclophosphamide/vinblastine correlated with prolonged time to relapse.

Conclusion: Pleural effusions, venous thrombosis, and CRP elevation were identified as potential risk factors. The VAIA scheme showed best outcome. Maintenance therapy should be investigated further.

KEYWORDS

C-reactive protein, desmoplastic small round cell tumor, maintenance therapy, soft tissue sarcoma, Trousseau's syndrome

1 | INTRODUCTION

Desmoplastic small round cell tumor (DSRCT) is a rare disease predominantly affecting adolescent and young adult males, which originates and spreads on peritoneal surfaces. Patients usually present with widespread intra-abdominal metastatic tumors related to serosal surfaces similar to carcinomatosis.¹ DSRCT consists of small round blue cell nests separated by desmoplastic stroma. It is characterized by the presence of t(11;22)(p13;q12) chromosomal translocation which leads to the fusion of the Ewing sarcoma gene (EWSR1) to the Wilms' tumor suppressor gene WT1.² First described as a distinct entity in 1989 by Gerald and Rosai,³ it remains poorly understood. Despite aggressive multimodal treatment, ~60%-70% of patients succumb to disease within 2-3 years.⁴

2 | PATIENTS AND METHODS

Eligible patients treated from 07/1997 to 06/2015 in the international European trials, CWS-96,⁵ CWS-2002P,⁶ and CWS-SoTiSaR conducted by the Cooperative Weichteilsarkomstudiengruppe CWS, had a confirmed diagnosis in central pathological review, aged <40 years, with no previous malignancy. All CWS trials were prospective and approved by appropriate ethics committees. Written informed consent according to the declaration of Helsinki was obtained from patients or guardians/parents. Data collection was performed as previously described.⁶ Patients received multimodal treatment including surgery, radiotherapy, and chemotherapy, according to the appropriate treatment protocols in use at the time of diagnosis.

2.1 | Staging and tumor distribution

Disease stage was classified according to IRS and TNM.^{7,8} For purpose of this analysis, localized disease was defined as one single tumor mass; regionally disseminated disease as multiple lesions in one affected cavity, detected by radiological assessment or inspection during surgical intervention. Extraperitoneal metastases were defined as lesions outside the affected cavity or in solid organs.

2.2 | Thrombosis

Venous thrombosis was diagnosed radiographically at diagnosis before implantation of a central venous line. No systematic screening for thromboses was performed.

2.3 | Pretreatment blood parameters

Coagulation parameters, blood counts, and C-reactive protein values (CRP) were evaluated. D-dimers were graded as normal (<500 µg/L), moderately increased (500-2000 µg/L), and markedly increased (>2000 µg/L). Scoring for disseminated intravascular coagulation (DIC) was done according to the scoring system of the International Society on Thrombosis and Hemostasis (ISTH).⁹

The inflammatory scores neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio were calculated by dividing the absolute neutrophil or platelet count, respectively, by the absolute lymphocyte count. The median was chosen as threshold. CRP was considered elevated when >5 mg/L.

2.4 | First-line chemotherapy

The induction therapy used was trial-dependent (Table S1). Early diagnosed patients had received the P6-scheme according to Kushner.¹⁰ Regional hyperthermia in combination with platinum-based chemotherapy¹¹ and high-dose chemotherapy with autologous stem cell rescue were administered on an individual basis.

Hyperthermic intraperitoneal chemotherapy (HIPEC) procedures with cisplatin and doxorubicin in combination with tumor resections were performed, a decision made by the treating oncologist.

2.5 | Maintenance chemotherapy

Remission was defined as no macroscopic residuals at therapy end (achieved with surgery and/or chemotherapy and/or radiotherapy). Maintenance chemotherapy with oral trofosamide, idarubicin, etoposide (O-TIE),¹² or with cyclophosphamide per os, vinblastine intravenously (Cyc/Vbl)^{6,13,14} was administered (Table S1) trial-dependent or individually. Some patients received individual therapy with irinotecan/

temozolomide or irinotecan/trabectedin. In addition to survival from diagnosis, time to relapse was calculated from end of intensive chemotherapy to eliminate the influence of different lengths of intensive therapies.

2.6 | Response evaluation

Response was assessed after three chemotherapy courses. For purpose of this analysis, response assessment was based on the CWS evaluation criteria for primary tumors^{15,16}: partial response $\geq 2/3$ volume reduction, minor response $\geq 1/3$ but $< 2/3$ reduction, objective response $< 1/3$ reduction, stable disease status idem, progression ($\geq 1/10$ volume increase).

In regionally disseminated nodular disease with variable response, the lesion showing the least volume reduction was evaluated.

2.7 | Local treatment

CWS protocols recommended local treatment of DSRCT analogous to non-rhabdomyosarcoma (NRSTS). Overall treatment strategies did not change substantially over the years. The mainstay of treatment for NRSTS was primary surgery with preferably complete or wide-ranging resection after biopsy. In metastatic disease, primary excision or biopsy of the primary tumor and/or metastases was performed and systemic therapy was administered to reduce tumor volume and improve respectability. This was followed by secondary surgery if feasible. Best surgery was defined as the best surgical result obtained at the end of treatment irrespective of procedure numbers. The surgical result was categorized as biopsy only, presence of macroscopic [R2], or microscopic [R1] residual tumor or as resection with free margins [R0].

Radiotherapy was to be administered with a total dose of 32-54.4 Gy (dose reduced hyperfractionated/accelerated radiotherapy) depending on primary resection status. Postoperative radiotherapy of the primary tumor (and metastases) was recommended. External beam irradiation with 44.8 Gy was recommended if a microscopically complete resection (R0) was not performed. In CWS-2002P, the recommendation was extended to include patients in whom an R0-resection had been performed if tumor size was >5 cm or age >10 years. In SoTiSaR, radiotherapy with 50.4 Gy (conventional fractionated irradiation) was added as an alternative. However, individual physician decisions did not always follow these recommendations.

2.8 | Statistical methods

Statistics were calculated using SPSS[®] 24 (Armonk, New York, NY, USA). Comparison of distribution was performed with the chi-square test. Event-free survival [EFS] and overall survival [OS] were calculated using the Kaplan-Meier

TABLE 1 Univariate analysis of characteristics at first diagnosis and pretreatment blood parameters

	60 included patients				25 patients achieving first remission				
	N (%)	3-y EFS (95% CI)	P value	3-y OS (95% CI)	N (%)	3-y EFS (95% CI)	P value	3-y OS (95% CI)	P value
Gender									
Female	11 (18)	27.3 ± 26.3	0.327	27.3 ± 26.3	6 (24)	50.0 ± 40.0	0.599	50.0 ± 40.0	0.471
Male	49 (82)	7.7 ± 7.6		31.9 ± 13.5	19 (76)	19.7 ± 18.6		60.2 ± 23.1	
Age [years]									
≤10	9 (15)	22.2 ± 27.2	0.201	64.8 ± 32.3	5 (20)	40.0 ± 42.9	0.494	50.0 ± 69.4	0.225
10-21	44 (73)	10.9 ± 9.4		26.7 ± 13.1	18 (72)	26.7 ± 21.0		48.9 ± 23.5	
≥21	7 (12)	0		16.7 ± 29.8	2 (8)	0		50.0 ± 69.4	
Site of primary									
Abdominal	56 (93)	6.7 ± 6.7	0.01	27.7 ± 12.2	21 (84)	17.9 ± 17.1	0.057	54.0 ± 22.3	0.31
Extra-abdominal	4 (7)	75.0 ± 42.5		75.0 ± 42.5	4 (16)	75.0 ± 42.5		75.0 ± 42.5	
Size of primary									
<10 cm	18 (30)	16.7 ± 17.2	0.145	35.4 ± 23.3	7 (28)	42.9 ± 36.7	0.138	83.3 ± 29.8	0.236
≥10 cm	40 (67)	9.4 ± 9.4		30.3 ± 14.7	18 (72)	20.8 ± 19.4		48.5 ± 23.7	
No information	2 (3)								
Tumor distribution									
Localized ^a	6 (20)	66.7 ± 37.6	0.004	83.3 ± 29.8	5 (20)	80.0 ± 35.1	0.005	100%	0.015
Regionally dissem.	16 (27)	6.3 ± 12.0		33.5 ± 23.9	9 (36)	11.1 ± 20.6		55.6 ± 32.5	
Extrap. metastases	38 (63)	5.3 ± 7.1		22.1 ± 13.3	11 (44)	18.2 ± 22.7		40.4 ± 30.4	
Extraperitoneal metastases in single or multiple organ									
No distant mets	22 (37)	22.7 ± 17.4	0.134	47.7 ± 21.4	14 (56)	35.7 ± 25.1	0.488	71.4 ± 23.7	0.038
Single organ mets	16 (27)	12.5 ± 16.3		27.5 ± 22.5	6 (24)	33.3 ± 37.6		60.0 ± 42.9	
Multiple organ mets	22 (37)	0%		18.2 ± 16.1	5 (20)	0%		20.2 ± 35.1	

(Continues)

TABLE 1 (Continued)

	60 included patients			25 patients achieving first remission						
	N (%)	3-y EFS (95% CI)	P value	3-y OS (95% CI)	P value	N (%)	3-y EFS (95% CI)	P value	3-y OS (95% CI)	P value
Effusion										
No effusion	37 (62)	13.0 ± 11.0	0.005	39.9 ± 16.5	<0.001	18 (72)	26.7 ± 21.0	0.347	57.6 ± 24.1	0.008
Ascites	14 (13)	14.3 ± 18.4		26.8 ± 24.1		5 (20)	40.0 ± 42.9		80.0 ± 35.1	
Pleural effusion	3 (5)	0%		0%		2 (8)	0%		0%	
Ascites + pleural eff	6 (10)	0%		0%		0 (0)				
Venous thrombosis										
No	53 (88)	12.6 ± 9.2	<0.001	34.7 ± 13.3	<0.001	23 (92)	29.0 ± 19.2	<0.001	61.8 ± 21.0	<0.001
Yes	4 (7)	0%		0%		2 (8)	0%		0%	
No information	3 (5)									
Elevation of CRP										
No	17 (28)	29.4 ± 21.8	0.002	51.8 ± 24.3	0.009	10 (40)	50.0 ± 31.0	0.011	78.8 ± 26.3	0.052
Yes	37 (62)	4.1 ± 7.1		25.6 ± 14.9		15 (60)	10.0 ± 17.2		41.3 ± 26.7	
No information	6 (10)									
Thrombocytes > 350/nL										
No	40 (67)	14.6 ± 11.2	0.318	32.8 ± 14.9	0.588	17 (68)	34.3 ± 23.1	0.117	63.3 ± 23.5	0.229
Yes	16 (27)	6.3 ± 12.0		34.4 ± 24.1		8 (32)	12.5 ± 22.9		43.8 ± 36.8	
No information	4 (6)									
Neutrophil-to-lymphocyte ratio										
<median	24 (40)	15.4 ± 13.9	0.379	41.2 ± 20.0	0.124	11 (44)	22.2 ± 25.1	0.525	68.6 ± 23.7	0.826
>median	26 (43)	11.1 ± 13.3		27.8 ± 18.4		12 (48)	36.4 ± 28.4		56.3 ± 29.0	
No information	10 (17)					2 (8)				
Platelet-to-lymphocyte ratio										
<median	27 (45)	18.5 ± 14.7	0.266	35.0 ± 18.4	0.356	13 (52)	25.0 ± 24.5	0.715	51.5 ± 31.0	0.781
>median	27 (45)	11.1 ± 11.8		33.6 ± 18.6		12 (48)	28.8 ± 25.7		61.5 ± 26.5	
No information	6 (10)									

P values are printed in italics, significant P values are bold ($P < 0.05$).

^aAll with evidence of EWSR1-WT1 fusion transcript

TABLE 2 Univariate analysis of conducted first-line therapies

	60 included patients				25 patients achieving first remission				
	N (%)	3-y EFS (95% CI)	P value	3-y OS (95% CI)	P value	3-y EFS (95% CI)	N (%)	3-y OS (95% CI)	P value
Chemotherapy									
P6	5 (8)	0%	0.008	20.0 ± 35.1	0.043	0%	4 (16)	25.0 ± 42.5	0.001
VAIA	15 (25)	38.9 ± 25.3		53.3 ± 25.3		58.3 ± 31.6	10 (40)	80.0 ± 24.7	
CEVAIE	37 (62)	2.7 ± 5.3		22.2 ± 14.1		10.0 ± 18.6	10 (40)	38.9 ± 33.9	
Other	3 (5)					0%	1 (4)	100%	
Response									
Partial (≥2/3)	17 (28)	5.9 ± 11.2	0.738	23.5 ± 20.2	0.532	11.1 ± 20.6	9 (36)	44.4 ± 35.5	0.685
Minor (≥1/3)	12 (20)	16.7 ± 21.2		38.9 ± 28.8		40.0 ± 42.9	5 (20)	80.0 ± 35.1	
Objective (<1/3)	8 (13)	12.5 ± 22.9		37.5 ± 33.5		33.3 ± 53.3	3 (12)	66.7 ± 53.3	
Stable disease	10 (17)	0%		20.0 ± 24.7		0%	3 (12)	33.3 ± 53.3	
Progression (≥1/10)	5 (8)	20.0 ± 35.1		60.0 ± 42.9		50.0 ± 69.4	2 (8)	100%	
No information	8 (13)						3 (12)		
High-dose chemotherapy with stem cell transplant									
No	51 (85)	11.4 ± 8.8	0.613	32.0 ± 13.1	0.991	29.2 ± 20.4	20 (80)	68.1 ± 21.2	0.546
Yes	9 (15)	11.1 ± 20.6		19.0 ± 31.4		20.0 ± 35.1	5 (20)	0%	
Hyperthermia in combination with platinum-based chemotherapy									
No	54 (90)	12.3 ± 9.0	0.173	30.2 ± 12.7	0.403	27.8 ± 18.6	24 (96)	54.9 ± 21.0	0.551
Yes	6 (10)	0%		33.3 ± 37.6		0%	1 (4)	100%	
Best surgery at any time									
R0	5 (8)	40.0 ± 42.9	0.035	60.0 ± 42.9	0.005	40.0 ± 42.9	5 (20)	60.0 ± 42.9	0.709
R1	16 (27)	18.8 ± 19.2		45.8 ± 26.1		21.4 ± 21.6	14 (56)	52.4 ± 28.0	
R2	19 (32)	5.3 ± 10.0		25.1 ± 21.0		25.0 ± 42.5	4 (16)	66.7 ± 53.3	
Biopsy only	19 (32)	5.3 ± 10.0		15.8 ± 16.5		50.0 ± 69.4	2 (8)	50.0 ± 69.4	
No information	1 (2)						1 (4)		
Best surgery at any time in combination with HIPEC									
R0	5 (8)	40.0 ± 42.9	0.123	60.0 ± 42.9	0.021	40.0 ± 42.9	5 (20)	60.0 ± 42.9	0.866
R1	13 (22)	15.4 ± 19.6		35.2 ± 27.2		18.2 ± 22.7	11 (44)	41.6 ± 30.6	
R1 + HIPEC	3 (5)	33.3 ± 53.3		100%		33.3 ± 53.3	3 (12)	100%	
R2	17 (28)	5.9 ± 11.2		25.5 ± 21.6		33.3 ± 53.3	3 (12)	33.3 ± 53.3	
R2 + HIPEC	2 (3)	0%		0%		0%	1 (4)	100%	
Biopsy only	19 (32)	5.3 ± 10.0		15.8 ± 16.5		50.0 ± 69.4	2 (8)	50.0 ± 69.4	
No information	1 (2)						0		

(Continues)

TABLE 2 (Continued)

	60 included patients				25 patients achieving first remission				
	N (%)	3-y EFS (95% CI)	P value	3-y OS (95% CI)	P value	3-y EFS (95% CI)	P value	3-y OS (95% CI)	P value
Time of best surgery									
Biopsy only	19 (32)	5.3 ± 10.0	<i>0.071</i>	15.8 ± 16.5	0.008	50.0 ± 69.4	<i>0.08</i>	50.0 ± 69.4	<i>0.11</i>
Before Chemotherapy	7 (12)	42.9 ± 36.7		85.7 ± 25.9		60.0 ± 42.9		100%	
Up to 3rd round	12 (20)	8.3 ± 15.7		25.0 ± 24.5		11.1 ± 20.6		33.3 ± 30.8	
After 3rd round	21 (35)	0%		34.2 ± 21.8		0%		57.1 ± 39.0	
Irradiation									
No	40 (67)	5.0 ± 6.7	<i>0.228</i>	20.6 ± 12.7	0.021	22.2 ± 27.2	<i>0.591</i>	44.4 ± 32.5	<i>0.798</i>
Yes	20 (33)	25.0 ± 19.0		53.7 ± 22.3		31.3 ± 22.7		67.3 ± 23.5	
Metronomic chemotherapy									
No maint.	6 (24)					0%	<i>0.056</i>	33.3 ± 37.6	<i>0.193</i>
O-TIE	11 (44)					24.2 ± 27.0		51.9 ± 30.8	
Cyc/Vbl	5 (20)					60.0 ± 42.9		80.0 ± 35.1	
Irinotecan-con- taining	3 (12)					33.3 ± 53.3		100%	
Metronomic chemotherapy evaluated in patients who achieved a first remission									
No maint.	6 (24)					0%	0.006		
O-TIE	11 (44)					12.1 ± 21.8			
Cyc/Vbl	5 (20)					60.0 ± 42.9			
Irinotecan-con- taining	3 (12)					66.7 ± 53.3			

RFS, relapse-free survival calculated from end of intensive therapy.

P values are printed in italics, significant P values are bold ($P < 0.05$).

estimator.¹⁷ For OS, time from diagnosis to death or last follow-up was calculated, for EFS time from diagnosis to relapse/progression, death, or last follow-up. Confidence intervals [CI] for the Kaplan-Meier estimator were computed using Greenwoods Formula¹⁸ and stated at 95%-level. For comparison of EFS and OS levels, the log-rank test was used.

Multivariate analysis was conducted using Cox's proportional hazards regression method to establish independent prognostic significance. A stepwise variable selection procedure (combination of forward and backward selection techniques) was applied to covariates with *P*-value of at least 0.1 in EFS at univariate analysis. Hazard ratios (HRs) with 95% confidence intervals, calculated according to the Wald method, are reported for significant variables. Statistics were calculated using IBM SPSS[®] 24 for all other analyses.

3 | RESULTS

3.1 | Patient and tumor characteristics

Sixty patients registered from Germany (*n* = 51), Poland (*n* = 4), Sweden (*n* = 2), Austria (*n* = 2), and Switzerland (*n* = 1) were eligible. Median age at diagnosis was 14.5 years (6.0-38.0). Male:female ratio was 4:1 (Table 1). 56/60 patients (93%) had tumors in the abdominal cavity (abdominal and/or retroperitoneal). Four patients had extra-abdominal tumors, which included four thoracic, one paratesticular, and one parotid gland (all EWSR1-WT1-positive). 40/60 (67%) tumors were larger than 10 cm.

Six patients had a localized tumor (all EWSR1-WT1-positive, 3 extra-abdominal, 3 abdominal). An additional patient with a single primary in the abdomen also had extraperitoneal metastases (liver, lung, mediastinal lymph nodes).

The tumor was regionally disseminated in 53/60 patients (88%). Thirty-seven of these 53 (70%) had extraperitoneal metastases (Table S2).

23/60 patients (38%) had effusions, 14 ascites, six ascites in combination with pleural effusions, and three presented with pleural effusion only. Malignant cells were evident in 11/18 examined effusions.

Four patients presented with thrombosis before implantation of a central catheter. Two had a thrombosis in the vena cava, one in the iliac with extension into femoral and popliteal veins while the other had a brachiocephalic and jugular thrombosis.

In 56/60 patients, pretreatment laboratory parameters were available, which included coagulation results in 50 (83%). In 15 (25%), which included only two of the patients with thrombosis, D-dimers were determined. D-dimers were normal (*n* = 2), moderately increased (*n* = 6), and markedly increased (*n* = 7); the latter included two patients with thrombosis. Scoring for DIC according to the ISTH⁹ was

possible in 12 (20%) patients. All patients scored below 5, defined as nonovert DIC (*n* = 2 score 0; *n* = 4 score 2; *n* = 6 score 3).

Leukocytes ranged from 4.07 to 24.00/nL (median 8.1/nL) in 55/56 patients. Median neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios were 3.09 (0.56-9.20) and 170 (50.15-483.67) in 50 and 54 patients, respectively, with available data, and 2.96 (1.14-9.20) and 165 (61.63-435.16) in 23 and 25 patients achieving remission. Platelets ranged from 189 to 566/nL in 56/56 patients. 16/56 (27%) had thrombocytes >350/nL. CRP values were available for 54/56 (90%) and were elevated in 37/54 (69%).¹⁹

3.2 | Treatment

37/60 (62%) patients received chemotherapy according to the CEVAIE regimen¹² (ifosfamide, vincristine, actinomycin D, carboplatin, epirubicin, etoposide), 15/60 (25%) according to VAIA⁶ (ifosfamide, vincristine, adriamycin, actinomycin D) and 5/60 (8%) with P6-regimen¹⁰ (cyclophosphamide, doxorubicin, vincristine, ifosfamide, etoposide).

Two patients received alternative therapy (NB95 and Hyper-PEI, respectively). A single patient did not receive chemotherapy due to severe mental retardation.

Response to chemotherapy ranged from partial response to progression (Table 2). In six patients with regionally disseminated disease, a mixed response with reduction of some and stable or increased volume in other lesions was documented.

Nine patients received high-dose chemotherapy with autologous stem cell transplantation, and six other patients were treated with regional hyperthermia in combination with platinum-based chemotherapy¹¹ in addition to standard chemotherapy.

21/60 (35%) patients underwent complete resection of primary tumor manifestations (R0 *n* = 5, R1 *n* = 16). Two patients with R1 resection suffered disease progression shortly after resection and therefore were not considered as having achieved remission. Five patients were treated with HIPEC, three following R1- and two after R2-resection.

3.3 | Outcome

Overall, 51/60 patients died, 49 of disease and two of therapy-related causes (organ failure after chemotherapy, postoperative complications with peritonitis after anus praeter relocation). With a median follow-up of 3.2 years (1.2-10.6), 9/60 patients were alive, six in 1st, one in 2nd remission, one lost to follow-up without ever having achieved remission, and one in first relapse with active disease (Table S4).

Based upon follow-up data as of March 2017, 3-year EFS and 3-year OS were 11% (± 8 CI 95%) and 30% (± 12 CI 95%; Figure 1).

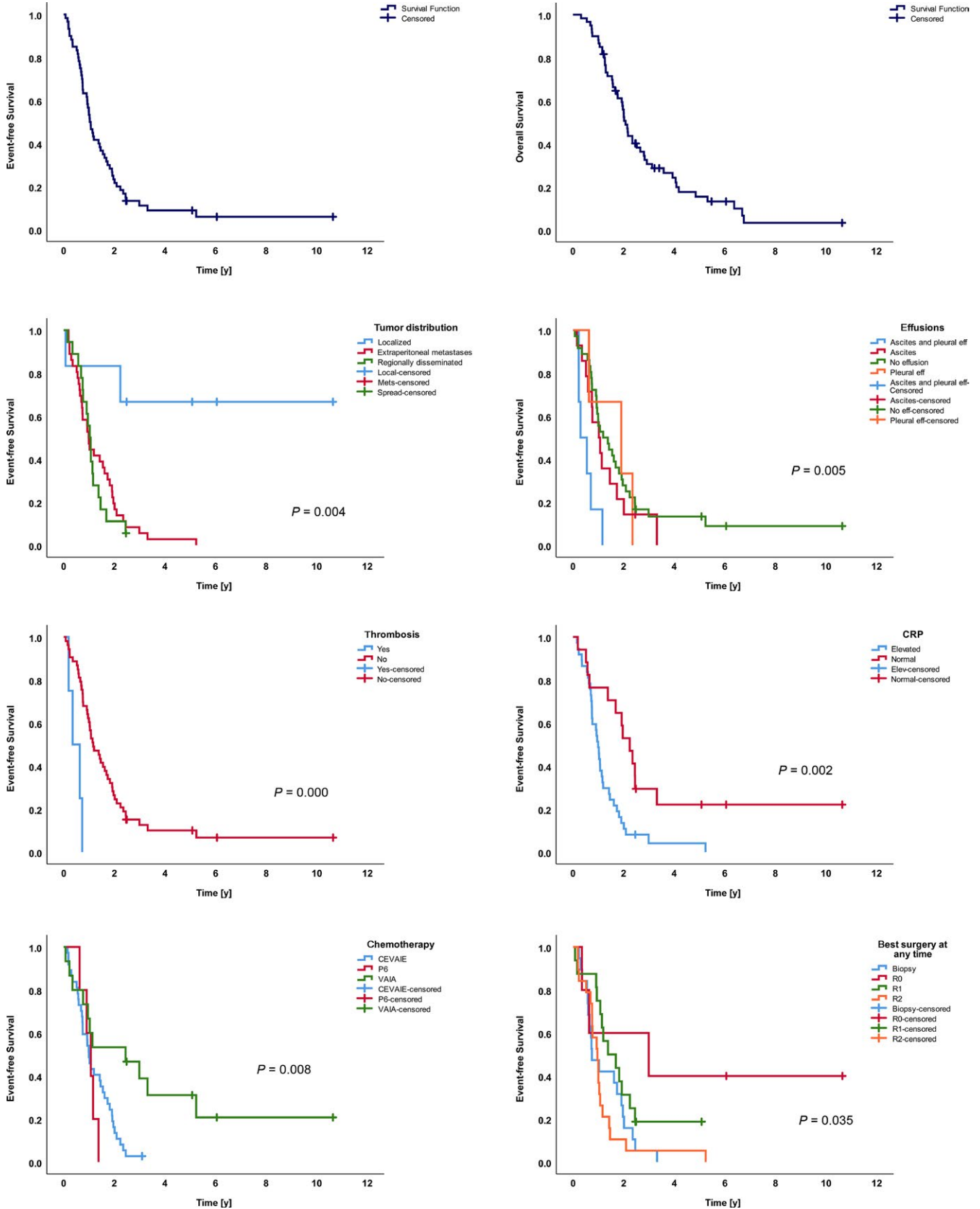


FIGURE 1 Event-free and overall survival probability of 60 DSRCT patients. Event-free survival probability according to the tumor distribution, the existence of effusions, thrombosis, elevated pretreatment CRP-value, and the conducted first-line chemotherapeutic regimens and best surgical result at any time in first-line therapy

25/60 patients (42%) achieved a complete remission at all disease sites, 6/25 (10%) remained in continuous remission and 19/25 (32%) remained in relapsed (Figure 2). For those 25 patients achieving remission, 3-year EFS and 3-year OS were 26.7% (± 18.0 CI 95%) and 56.9% (± 20.4 CI 95%), respectively.

35/60 patients (58%) did not achieve remission and died in a median of 1.5 years.

Among the four patients initially presenting with thrombosis, two showed progression while still on chemotherapy, while the remaining suffered early recurrences. None survived longer than 1.5 years.

3.4 | Outcome according to surgery

In all those 19 patients who only underwent biopsy as best surgical procedure, an event (disease progression or relapse) was documented in a median of 0.7 years (range 0.2-3.3). Median overall survival was 1.6 years (0.6-5.3). None survived. In those other 19 patients with R2-resection as best surgical result at any time, all had an event in a median of 1.0 years (0.2-5.2). Median overall survival

was 1.7 years (0.3-6.4). Two were alive at the cutoff date, thereof one lost in progression and the other in first relapse with active disease. Of those 16 patients with R1 resection, 13 had an event in a median of 1.2 years (0.1-2.4). Median overall survival was 2.6 years (1.1-6.8). Four patients were in first remission at the cutoff date with a follow-up of 5.5, 3.2, 2.5, and 2.5 years, respectively. Five were alive. Of those five patients with R0-resection, 3 had an event in a median of 0.6 years (0.3-3.0). Median overall survival was 4.2 years (1.0-10.6). Two were alive at the cutoff date with a follow-up of 10.6 and 6.1 years, respectively.

3.5 | Outcome according to chemotherapy

The five patients treated according to the P6-regimen had a median EFS of 12.9 months (7.6-16.5), 15 treated with VAIA 29.4 months (1-127.7), and 37 who received CEVAIE 12.0 months (22.1-306.7). The remaining patient survived 9 months with palliative care. The VAIA scheme correlated with increased chance of R0 or R0/R1 resection (Table S3).

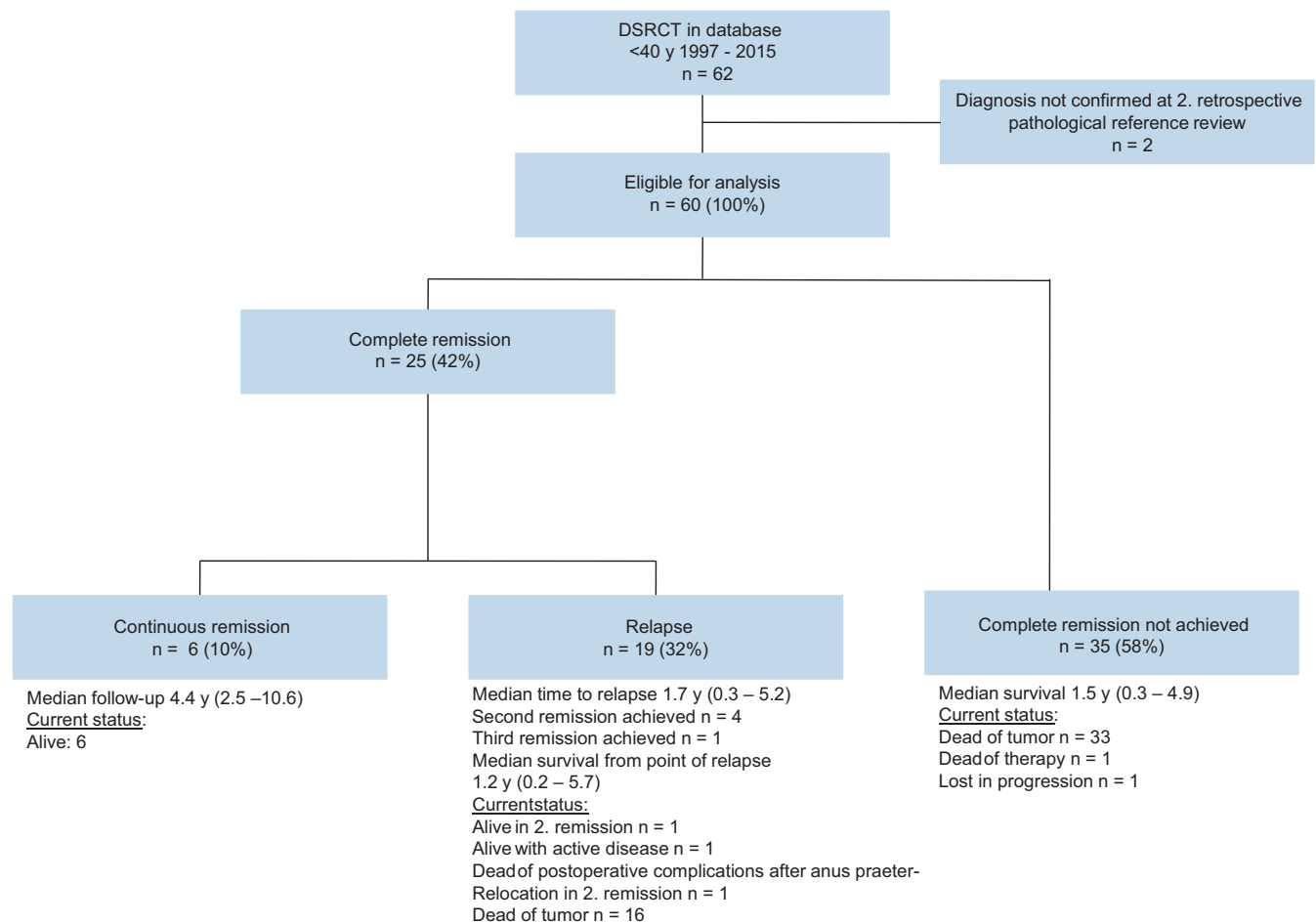


FIGURE 2 Flow diagram of evaluated patients

Potential correlations between maintenance therapy and outcome were analyzed in the subgroup of 25 patients achieving remission (Table 2, Figure 3). In six patients without maintenance therapy, the median time to relapse calculated from the end of intensive chemotherapy was 8.0 months (3.4-20.2), in 11 patients with O-TIE 17.2 months (5.2-31.8), in five patients with Cyc/Vbl 56.5 months (7.8-122.0), and in three patients with irinotecan-containing metronomic therapy 17.4 months (11.3-35.6).

3.6 | Pattern of relapse

Among those 19 patients with relapse, five suffered recurrence with merely intraperitoneal lesions. Nine other patients suffered metastatic recurrence with extraperitoneal lesions at different sites (n = 1 lung and bone lesions, n = 1 lymph node supraclavicular, n = 1 bone lesions, n = 1 mediastinal mass and lung lesions, n = 1 lung and liver lesions, n = 1 lung lesions, n = 1 one spleen lesion, n = 1 liver and brain lesions, and n = 1 pleural sarcomatosis). Five patients suffered relapse with combined intra- and extraperitoneal lesions. Extraperitoneal lesions were documented at liver and skin (n = 1), paratracheal and bone (n = 1), thoracic and lung (n = 1), thoracic lesions subpleural (n = 1), the site of the affected distant lymph nodes was not documented (n = 1).

3.7 | Uni- and multivariate analyses

In univariate analysis, extra-abdominal site, localized disease, no effusion or ascites only, absence of thrombosis, and normal CRP were associated with a significantly increased EFS (Table 1). Univariate analysis of metastatic sites did not show any differences in EFS whereas the existence of liver metastases correlated with reduced OS (Table S2).

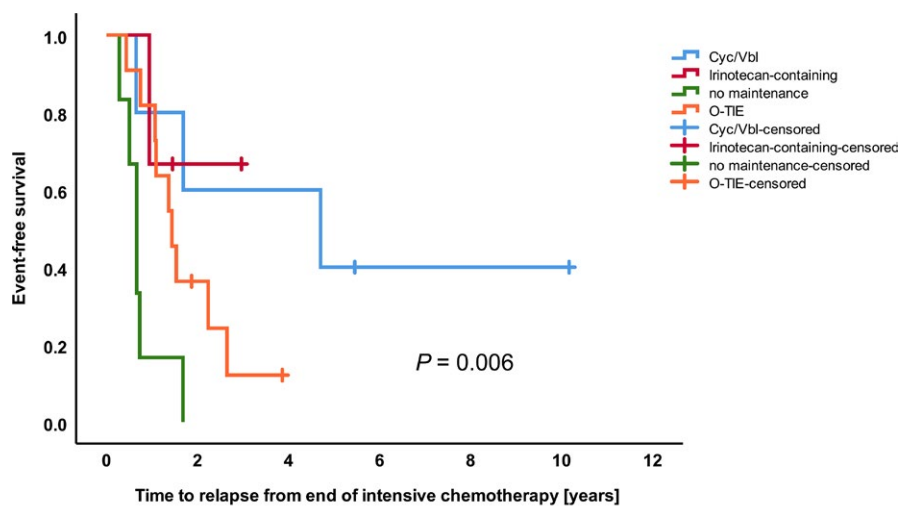
Among first-line treatment, chemotherapy with VAIA and complete resection of all primary tumor lesions at any time correlated with prolonged EFS (Table 2).

The distribution of prognostic factors among the chemotherapeutic regimens is shown in Table S3.

A multivariate analysis was conducted to establish independent prognostic significance of the evaluated factors (Table 3). Absence of thrombosis and chemotherapy according to the VAIA regimen remained significant.

4 | DISCUSSION

This study of 60 DSRCT patients confirms the poor prognosis. A small subgroup with reasonable outlook for long-term, disease-free survival could be identified, three individuals with localized and extra-abdominal disease, without pleural effusions, or thrombosis and normal CRP who were subsequently treated by complete tumor resection in conjunction



Metronomic chemotherapy	N (%)	3-yr relapse-free survival (95% CI)
no maintenance therapy	6 (24)	0%
O-TIE	11 (44)	12.1 ± 21.8%
Cyc/Vbl	5 (20)	60.0 ± 42.9%
Irinotecan-containing	3 (12)	66.7 ± 53.3%
<i>(Irinotecan-Temodal n = 2, Irinotecan-Trabectedin n = 1)</i>		

FIGURE 3 The effect of additional maintenance therapy after the end of intensive chemotherapy evaluated in 25 patients who achieved a first complete remission

with VAIA chemotherapy. All three patients were disease-free at last follow-up (6.1, 5.5, 2.5 years).

An inherent weakness of this study is the small number of patients due to the fact that DSRCT has only been recently described and is a very rare tumor. Nevertheless, to the best of our knowledge, it is the largest series of DSRCT patients enrolled in prospective trials to date. However, our analysis is retrospective and the base-line blood parameters are nonspecific. Further evaluation should be prospective and standardized.

Characteristics were similar to previous reports.^{20,21} Patients were principally adolescent, male and had large and widespread abdominal and/or retroperitoneal tumors. The majority had extraperitoneal metastases. No typical metastatic pattern was identifiable. No specific risk for disease progression or relapse of any specific metastatic site could be revealed. Nevertheless, though the existence of liver metastases did not correlate with reduced EFS in our series, it

correlated with a reduced overall survival probability. Liver metastases have been observed as a potential prognostic factor before.^{22,23} No specific pattern of disease recurrence could be determined; therefore, we were not able to identify specific treatment weaknesses.

In contrast to the literature, existence of extraperitoneal metastases did not correlate with survival.^{1,24,25} This supposed difference might have been caused by the fact that others had not differentiated between localized and regionally disseminated disease. However, others had estimated tumor burden based on peritoneal cancer index but survival did not differ.^{24,25}

In contrast to all other solid tumors, size and evidence of distant metastases did not correlate with survival. One cause might be the unique nature of dissemination. It seems that from the point, the cells lose the ability to organize within a single node and start disseminating into multiple nodules, survival decreases significantly. It remains to be elucidated

Variables	EFS hazard ratio	Confidence interval (95%)	P-value
Site of primary tumor			
Abdominal	1		
Extra-abdominal	1.958	0.12-32.13	0.638
Tumor distribution			
Localized	1		
Regionally disseminated	7.837	0.59-104.90	0.120
Extraperit. Metastases	5.582	0.49-63.21	0.165
Effusions			
No effusion	1		
Ascites	1.044	0.44-2.50	0.923
Pleural effusion	0.684	0.17-2.80	0.597
Ascites + pleural effusion	2.165	0.35-13.57	0.410
Venous thrombosis			
No	1		
Yes	10.96	2.77-43.31	0.001
Elevation of CRP			
No	1		
Yes	1.231	0.50-3.00	0.648
Chemotherapy			
VAIA	1		
CEVAIE	3.17	1.13-8.90	0.029
P6	2.58	0.47-14.26	0.277
Best surgery at any time			
R0	1		
R1	0.75	0.13-4.19	0.741
R2	1.22	0.24-6.15	0.807
Biopsy	0.88	0.15-5.09	0.890

TABLE 3 Multivariate analysis of factors predicting increased risk of progression or relapse

Bold values indicate statistical significance

whether this is due to the fact that local therapy is restricted or whether regionally disseminated disease indicates considerably more aggressive biology.

Though the presence of effusions has been described in DSRCT,²⁶ prognostic impact is unclear. In our series, pleural effusions correlated with inferior survival.

Four patients aged 8, 10, 11, and 17 years presented with venous thrombosis—detected coincidentally in the initial staging investigations. The association between thrombosis and cancer is well known as the Trousseau's syndrome.²⁷ Occurrence varies by age and cancer type.^{28–32} Pathogenesis is multifactorial.³³ A positive association can be observed with 1-year mortality of the cancer type as a measure of biological aggressiveness and associated thrombogenic potential.^{29,34} In our series, coagulation activation with thrombus formation seems to indicate more aggressive disease. Unfortunately, detailed analysis of the coagulation cascade was not possible. In only 15/60 (25%) patients, the necessary coagulation values including D-dimers were determined. Elevation was evident in 13 (86%). It is debatable, whether D-dimers alone or the ISTH scoring system is sufficient to capture or even quantify the pivotal phenomenon.^{35,36}

One contributing factor to coagulation activation is inflammation, which plays an important role in tumorigenesis.³⁷ Inflammatory scores are predictive in numerous cancers.^{19,38} In our series, merely CRP correlated with survival. As there are no acknowledged standard values for the applied ratios,³⁹ the median was chosen.⁴⁰ However, the predictive significance of CRP suggests need to determine clinical utility. It seems worth mentioning that among those 17 patients with normal CRP, five had localized, four regionally distributed, and eight widespread disease with extraperitoneal metastases.

Of interest are the underlying mechanisms. Malignancy is characterized by destructive tumor cell invasion of vascularized organ tissue and formation of leaky new vessels, so-called tumor angiogenesis. The procoagulant phenotype is likely to have profound effect on the hemostatic system as result of plasma leakage into the interstitial space, secretion of inflammatory cytokines, and direct invasion of tumor cells into blood or lymphatic vessels.²⁷ Coagulation activation, inflammation, and tumor biology form a triangular network with reciprocal interactions.^{33,41} The elucidation of these mechanisms might help to understand DSRCT biology.

The most effective chemotherapeutic regime still is debated. Most combinations are based on alkylating agents, similar to those in other small round cell tumors or Ewing sarcomas, which also carry EWSR1 fusions.^{25,42} Farhat reported five patients with disease stabilization lasting 4–9 months using a regimen consisting of cisplatin, etoposide, cyclophosphamide, and an anthracycline.⁴³ Kushner reported 12 patients with median survival of 19 months with the P6-protocol.¹⁰ Bertuzzi reported median survival of 14 months in 17 patients treated in

two prospective studies with induction chemotherapy of ifosfamide, epirubicin, and vincristine.^{44,45} Wong reported median time to progression of 14.6 months in 13 patients treated according to the VIDE-regimen (vincristine, ifosfamide, doxorubicin, etoposide).²⁰ Another report states survival of 1.7 years in a single case with VIDE.⁴⁶ The use of other agents has been reported, including irinotecan, temozolomide, and vinorelbine, but none of them showed superiority.^{47,48} Evidence is emerging on trabectedin.^{49–53} Activity was reported for pazopanib^{54,55} and eribulin.⁵⁶ A recent report gave negative results for imatinib.⁵⁷ Limited activity of the antiangiogenics sunitinib, sorafenib, and bevacizumab is reported.^{58–60}

In our series chemotherapy according to the VAIA scheme correlated with longer EFS than did the other investigated regimens. The median EFS of 15 patients treated with VAIA was 29.4 months. To the best of our knowledge, this is the first assessment of the VAIA scheme in DSRCT. Though the distribution of prognostic factors differed among the three analyzed chemotherapeutic regimens, the independent effect of the VAIA scheme was proven in the Cox regression analysis.

However, the fact that response to chemotherapy did not correlate with outcome is striking. 2/6 (33%) survivors had progressive disease. They were then treated with aggressive surgery.

6/60 (10%) patients showed mixed response of different tumor nodes suggesting heterogenous biology, which should be considered when adopting targeted therapeutic approaches.

In accordance with the recent literature, high-dose chemotherapy did not correlate with survival.⁶¹ The value of hyperthermia remains to be specified. However, in our series, patients did not benefit.

While there is considerable investment in the development of innovative therapies, metronomic approaches have been underinvestigated. In our series, metronomic therapy with cyclophosphamide/vinblastine correlated with prolonged time to relapse.

The crucial and decisive role of surgery can be confirmed.^{42,62} In our series, no patient who did not have a R0 resection or R1 resection survived long-term or was disease-free at the cutoff date. More precisely, of those 38 patients with only biopsy or R2-resection, only two were alive at the cutoff date, thereof one lost in progression and the other in first relapse with active disease. However, the feasibility of surgery due to extensively disseminated disease remains a problem. Interestingly, in the subgroup of 25 patients achieving remission, extent of surgery was not predictive of outcome. Two patients who only underwent biopsy achieved remission with chemotherapy alone, one with simultaneous irradiation. Unfortunately, the additional value of HIPEC^{1,24,63,64} cannot be further elucidated as only 5 patients with different resection results received HIPEC.

Although the CWS trials included radiotherapy recommendations, most patients were irradiated following an individual concept due to extensive disease. Radiotherapy mainly consisted of focused irradiation to particular tumor sites or nonresectable nodes. Whole-abdominal irradiation was performed in two patients. Thus, a reliable conclusion with regard to the specific effect of radiotherapy in DSRCT remains difficult. In our series, irradiation did not correlate with survival. Other authors suggested that a multimodal concept combining chemotherapy, surgery, and irradiation enables prolonged survival.^{25,63,65} In the future, the application and evaluation of standardized radiotherapeutic concepts and/or techniques are necessary to specify its potential benefit.^{22,23}

Nevertheless, in our series no specific pattern of disease recurrence was evident, so we were not able to identify specific treatment weaknesses.

In summary, the VAIA scheme could be specified as best chemotherapy in a multivariable model. The effect of maintenance therapy warrants further investigation. Pleural effusions, venous thrombosis, and CRP elevation were identified as novel potential risk factors for adverse outcomes. The elucidation of the underlying coagulation and inflammatory mechanisms may lead to a better understanding of disease biology, especially when investigating the observed coagulatory and inflammatory phenomena in conjunction with genetic analysis.

ACKNOWLEDGMENT


We are indebted to the personnel of all participating institutions and thank all patients, parents, and guardians for their willingness to participate in the CWS trials. We thank Iris Veit-Friedrich, Simone Feuchtgruber, and Agnieszka Bakowska CDM for their excellent data management and Mary Morgan for review of the manuscript.

CONFLICT OF INTEREST

None of the authors declared a conflict of interest related to the submitted material.

ORCID

Monika Scheer  <https://orcid.org/0000-0002-0665-6268>

Monika Sparber-Sauer  <https://orcid.org/0000-0001-9551-2399>

REFERENCES

- Hayes-Jordan A, Green HL, Lin H, et al. Complete cytoreduction and HIPEC improves survival in desmoplastic small round cell tumor. *Ann Surg Oncol*. 2014;21(1):220-224.
- Ladanyi M, Gerald W. Fusion of the EWS and WT1 genes in the desmoplastic small round cell tumor. *Cancer Res*. 1994;54(11):2837-2840.
- Gerald WL, Rosai J. Case 2. Desmoplastic small cell tumor with divergent differentiation. *Pediatr Pathol*. 1989;9(2):177-183.
- Stiles ZE, Dickson PV, Glazer ES, et al. Desmoplastic small round cell tumor: a nationwide study of a rare sarcoma. *J Surg Oncol*. 2018;117(8):1759-1767.
- Modritz D, Ladenstein R, Potschger U, et al. Treatment for soft tissue sarcoma in childhood and adolescence. Austrian results within the CWS 96 study. *Wien Klin Wochenschr*. 2005;117(5-6):196-209.
- Koscielniak E, Kosztyla D, Dantonello T, et al. Report of the CWS-2002-P study: treatment results for soft tissue sarcomas (STS) in childhood and adolescence. *Pediatr Blood Cancer*. 2013;60(S3):32.
- Harmer M, Denoix P, Hamperl H. The TNM-system. *Aktuelle Probl Chir*. 1970;14:25-36.
- Scheer M, Dantonello T, Brossart P, et al. Importance of whole-body imaging with complete coverage of hands and feet in alveolar rhabdomyosarcoma staging. *Pediatr Radiol*. 2018;48:648-657.
- Taylor FB Jr, Toh CH, Hoots WK, et al. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. *Thromb Haemost*. 2001;86(5):1327-1330.
- Kushner BH, LaQuaglia MP, Wollner N, et al. Desmoplastic small round-cell tumor: prolonged progression-free survival with aggressive multimodality therapy. *J Clin Oncol*. 1996;14(5):1526-1531.
- Wessalowski R, Schneider DT, Mills O, et al. Regional deep hyperthermia for salvage treatment of children and adolescents with refractory or recurrent non-testicular malignant germ-cell tumours: an open-label, non-randomised, single-institution, phase 2 study. *Lancet Oncol*. 2013;14(9):843-852.
- Klingebl T, Boos J, Beske F, et al. Treatment of children with metastatic soft tissue sarcoma with oral maintenance compared to high dose chemotherapy: report of the HD CWS-96 trial. *Pediatr Blood Cancer*. 2008;50(4):739-745.
- Scheer M, Dantonello T, Hallmen E, et al. Primary metastatic synovial sarcoma: experience of the CWS Study Group. *Pediatr Blood Cancer*. 2016;63(7):1198-1206.
- Scheer M, Dantonello T, Hallmen E, et al. Synovial sarcoma recurrence in children and young adults. *Ann Surg Oncol*. 2016;23(Suppl 5):618-626.
- Koscielniak E, Jurgens H, Winkler K, et al. Treatment of soft tissue sarcoma in childhood and adolescence. A report of the German Cooperative Soft Tissue Sarcoma Study. *Cancer*. 1992;70(10):2557-2567.
- Dantonello TM, Stark M, Timmermann B, et al. Tumour volume reduction after neoadjuvant chemotherapy impacts outcome in localised embryonal rhabdomyosarcoma. *Pediatr Blood Cancer*. 2015;62(1):16-23.
- Kaplan EL, Meyer P. Non-parametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53:457-481.
- Greenwood M. Reports on public health and medical subjects. The errors of sampling of the survivorship tables. London: HM Stationery Office; 1926.
- Dolan RD, Lim J, McSorley ST, et al. The role of the systemic inflammatory response in predicting outcomes in patients with operable cancer: Systematic review and meta-analysis. *Sci Rep*. 2017;7(1):16717.
- Wong HH, Hatcher HM, Benson C, et al. Desmoplastic small round cell tumour: characteristics and prognostic factors of 41 patients and review of the literature. *Clin Sarcoma Res*. 2013;3(1):14.

21. Lettieri CK, Garcia-Filion P, Hingorani P. Incidence and outcomes of desmoplastic small round cell tumor: results from the surveillance, epidemiology, and end results database. *J Cancer Epidemiol.* 2014;2014:680126.
22. Osborne EM, Briere TM, Hayes-Jordan A, et al. Survival and toxicity following sequential multimodality treatment including whole abdominopelvic radiotherapy for patients with desmoplastic small round cell tumor. *Radiother Oncol.* 2016;119(1):40-44.
23. Desai NB, Stein NF, LaQuaglia MP, et al. Reduced toxicity with intensity modulated radiation therapy (IMRT) for desmoplastic small round cell tumor (DSRCT): an update on the whole abdominopelvic radiation therapy (WAP-RT) experience. *Int J Radiat Oncol Biol Phys.* 2013;85(1):e67-72.
24. Hayes-Jordan A, Green H, Lin H, et al. Cytoreductive surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for children, adolescents, and young adults: the first 50 cases. *Ann Surg Oncol.* 2015;22(5):1726-1732.
25. Honore C, Amroun K, Vilcot L, et al. Abdominal desmoplastic small round cell tumor: multimodal treatment combining chemotherapy, surgery, and radiotherapy is the best option. *Ann Surg Oncol.* 2015;22(4):1073-1079.
26. Hayes-Jordan A, LaQuaglia MP, Modak S. Management of desmoplastic small round cell tumor. *Semin Pediatr Surg.* 2016;25(5):299-304.
27. Varki A. Trousseau's syndrome: multiple definitions and multiple mechanisms. *Blood.* 2007;110(6):1723-1729.
28. Walker AJ, Card TR, West J, et al. Incidence of venous thromboembolism in patients with cancer - a cohort study using linked United Kingdom databases. *Eur J Cancer.* 2013;49(6):1404-1413.
29. Timp JF, Braekkan SK, Versteeg HH, et al. Epidemiology of cancer-associated venous thrombosis. *Blood.* 2013;122(10):1712-1723.
30. Athale U, Siciliano S, Thabane L, et al. Epidemiology and clinical risk factors predisposing to thromboembolism in children with cancer. *Pediatr Blood Cancer.* 2008;51(6):792-797.
31. Athale U, Cox S, Siciliano S, et al. Thromboembolism in children with sarcoma. *Pediatr Blood Cancer.* 2007;49(2):171-176.
32. Paz-Priel I, Long L, Helman LJ, et al. Thromboembolic events in children and young adults with pediatric sarcoma. *J Clin Oncol.* 2007;25(12):1519-1524.
33. Dicke C, Langer F. Pathophysiology of Trousseau's syndrome. *Hamostaseologie.* 2015;35(1):52-59.
34. Ahlbrecht J, Dickmann B, Ay C, et al. Tumor grade is associated with venous thromboembolism in patients with cancer: results from the Vienna Cancer and Thrombosis Study. *J Clin Oncol.* 2012;30(31):3870-3875.
35. Asakura H, Takahashi H, Uchiyama T, et al. Proposal for new diagnostic criteria for DIC from the Japanese Society on Thrombosis and Hemostasis. *Thromb J.* 2016;14:42.
36. Soundar EP, Jariwala P, Nguyen TC, et al. Evaluation of the International Society on Thrombosis and Haemostasis and institutional diagnostic criteria of disseminated intravascular coagulation in pediatric patients. *Am J Clin Pathol.* 2013;139(6):812-816.
37. Diakos CI, Charles KA, McMillan DC, et al. Cancer-related inflammation and treatment effectiveness. *Lancet Oncol.* 2014;15(11):e493-503.
38. Nayak A, McDowell DT, Kellie SJ, et al. Elevated preoperative neutrophil-lymphocyte ratio is predictive of a poorer prognosis for pediatric patients with solid tumors. *Ann Surg Oncol.* 2017;24(11):3456-3462.
39. Forget P, Khalifa C, Defour JP, et al. What is the normal value of the neutrophil-to-lymphocyte ratio? *BMC Res Notes.* 2017;10(1):12.
40. Dolan RD, McSorley ST, Horgan PG, et al. The role of the systemic inflammatory response in predicting outcomes in patients with advanced inoperable cancer: systematic review and meta-analysis. *Crit Rev Oncol Hematol.* 2017;116:134-146.
41. Langer F, Bokemeyer C. Crosstalk between cancer and haemostasis. Implications for cancer biology and cancer-associated thrombosis with focus on tissue factor. *Hamostaseologie.* 2012;32(2):95-104.
42. Lal DR, Su WT, Wolden SL, et al. Results of multimodal treatment for desmoplastic small round cell tumors. *J Pediatr Surg.* 2005;40(1):251-255.
43. Farhat F, Culine S, Lhomme C, et al. Desmoplastic small round cell tumors: results of a four-drug chemotherapy regimen in five adult patients. *Cancer.* 1996;77(7):1363-1366.
44. Bertuzzi A, Castagna L, Nozza A, et al. High-dose chemotherapy in poor-prognosis adult small round-cell tumors: clinical and molecular results from a prospective study. *J Clin Oncol.* 2002;20(8):2181-2188.
45. Bertuzzi A, Castagna L, Quagliuolo V, et al. Prospective study of high-dose chemotherapy and autologous peripheral stem cell transplantation in adult patients with advanced desmoplastic small round-cell tumour. *Br J Cancer.* 2003;89(7):1159-1161.
46. Frank JA, Ranft A, Paulussen M, et al. Results for patients with sarcoma not otherwise specified and other diagnoses than Ewing sarcoma treated according to the Euro-EWING 99 trial. *Pediatr Blood Cancer.* 2017;64(10):e26524.
47. Rosoff PM, Bayliff S. Successful clinical response to irinotecan in desmoplastic round blue cell tumor. *Med Pediatr Oncol.* 1999;33(5):500-503.
48. Ferrari A, Grosso F, Stacchiotti S, et al. Response to vinorelbine and low-dose cyclophosphamide chemotherapy in two patients with desmoplastic small round cell tumor. *Pediatr Blood Cancer.* 2007;49(6):864-866.
49. Chuk MK, Aikin A, Whitcomb T, et al. A phase I trial and pharmacokinetic study of a 24-hour infusion of trabectedin (Yondelis(R), ET-743) in children and adolescents with relapsed or refractory solid tumors. *Pediatr Blood Cancer.* 2012;59(5):865-869.
50. Lopez-Gonzalez A, Cantos B, Tejerina E, et al. Activity of trabectedin in desmoplastic small round cell tumor. *Med Oncol.* 2011;28(Suppl 1):S644-646.
51. Brunetti AE, Delcuratolo S, Lorusso V, et al. Third-line trabectedin for a metastatic desmoplastic small round cell tumour treated with multimodal therapy. *Anticancer Res.* 2014;34(7):3683-3688.
52. Frezza AM, Whelan JS, Dileo P. Trabectedin for desmoplastic small round cell tumours: a possible treatment option? *Clin Sarcoma Res.* 2014;4:3.
53. Verret B, Honore C, Dumont S, et al. Trabectedin in advanced desmoplastic round cell tumors: a retrospective single-center series. *Anticancer Drugs.* 2017;28(1):116-119.
54. Ikeue T, Ohi I, Noguchi S, et al. Desmoplastic small round cell tumor of the pleura successfully treated with a lower dose of pazopanib. *Intern Med.* 2016;55(17):2463-2467.
55. Menegaz BA, Cuglievan B, Benson J, et al. Clinical activity of pazopanib in patients with advanced desmoplastic small round cell tumor. *Oncologist.* 2017;23(3):360-366.

56. Emambux S, Kind M, Le Loarer F, et al. Clinical activity of eribulin in advanced desmoplastic small round-cell tumor. *Anticancer Drugs*. 2017;28(9):1053-1055.
57. De Sanctis R, Bertuzzi A, Bisogno G, et al. Imatinib mesylate in desmoplastic small round cell tumors. *Future Oncol*. 2017;13(14):1233-1237.
58. Italiano A, Kind M, Cioffi A, et al. Clinical activity of sunitinib in patients with advanced desmoplastic round cell tumor: a case series. *Target Oncol*. 2013;8(3):211-213.
59. de Araujo RA, Araujo BJ. Desmoplastic small round cell tumor: report of 2 cases treated with chemotherapy alone or in combination with bevacizumab. *Case Rep Oncol*. 2014;7(1):102-108.
60. Betrian S, Bergeron C, Blay JY, et al. Antiangiogenic effects in patients with progressive desmoplastic small round cell tumor: data from the French national registry dedicated to the use of off-labeled targeted therapy in sarcoma (OUTC's). *Clin Sarcoma Res*. 2017;7:10.
61. Forlenza CJ, Kushner BH, Kernan N, et al. Myeloablative chemotherapy with autologous stem cell transplant for desmoplastic small round cell tumor. *Sarcoma*. 2015;2015:269197.
62. Schwarz RE, Gerald WL, Kushner BH, et al. Desmoplastic small round cell tumors: prognostic indicators and results of surgical management. *Ann Surg Oncol*. 1998;5(5):416-422.
63. Honore C, Atallah V, Mir O, et al. Abdominal desmoplastic small round cell tumor without extraperitoneal metastases: Is there a benefit for HIPEC after macroscopically complete cytoreductive surgery? *PLoS ONE*. 2017;12(2):e0171639.
64. Hayes-Jordan A. Cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy in DSRCT: progress and pitfalls. *Curr Oncol Rep*. 2015;17(8):38.
65. Atallah V, Honore C, Orbach D, et al. Role of adjuvant radiation therapy after surgery for abdominal desmoplastic small round cell tumors. *Int J Radiat Oncol Biol Phys*. 2016;95(4):1244-1253.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Scheer M, Vokuhl C, Blank B, et al. Desmoplastic small round cell tumors: Multimodality treatment and new risk factors. *Cancer Med*. 2019;8:527–542. <https://doi.org/10.1002/cam4.1940>