

**Keywords:** CCSK; clear cell sarcoma of the kidney; relapse; clinical features; treatment; outcome

# Treatment and outcome of patients with relapsed clear cell sarcoma of the kidney: a combined SIOP and AIEOP study

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**Background:** Clear cell sarcoma of the kidney (CCSK) is an uncommon paediatric renal tumour. Relapses occur in about 15% of the patients. Since detailed clinical information on relapsed CCSK is scarce, the current study aims to describe outcome of patients with relapsed CCSK treated according to recent European protocols.

**Patients and methods:** We analysed prospectively collected data of all CCSK patients who developed a relapse after complete remission at the end of primary treatment, entered onto SIOP and AIEOP trials between 1992 and 2012.

**Results:** Thirty-seven of 237 CCSK patients (16%) treated according to SIOP and AIEOP protocols developed a relapse. Median time from initial diagnosis to relapse was 17 months (range, 5.5 months – 6.6 years). Thirty-five out of thirty-seven relapses (95%) were metastatic; the most common sites of relapse were the brain ( $n = 13$ ), lungs ( $n = 7$ ) and bone ( $n = 5$ ). Relapse treatment consisted of chemotherapy ( $n = 30$ ), surgery ( $n = 19$ ) and/or radiotherapy ( $n = 18$ ), followed by high-dose chemotherapy and autologous bone marrow transplantation (ABMT) in 14 patients. Twenty-two out of thirty-seven patients (59%) achieved a second complete remission (CR); 15 of whom (68%) developed a second relapse. Five-year event-free survival (EFS) after relapse was 18% (95% CI: 4%–32%), and 5-year overall survival (OS) was 26% (95% CI: 10%–42%).

**Conclusions:** In this largest series of relapsed CCSK patients ever described, overall outcome is poor. Most relapses are metastatic and brain relapses are more common than previously recognised. Intensive treatment aiming for local control, followed by high dose chemotherapy and ABMT, seems to be of benefit to enhance survival. Novel development of targeted therapy is urgently required.

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Clear cell sarcoma of the kidney (CCSK) is an uncommon type of childhood renal cancer (2%–5% of all primary renal tumours in children) that is observed most often in children under 3 years of age (Argani *et al*, 2000; Gooskens *et al*, 2012).

With current intensive treatment schedules, including radiotherapy and multi-agent chemotherapy, outcome of CCSK has significantly improved (5-year event-free survival 75%–85%, 5-year overall survival 85%–90%) (Argani *et al*, 2000; Gooskens *et al*, 2012, Furtwängler *et al*, 2013). Despite this improved survival, there is still a considerable relapse rate, especially in younger patients and patients with advanced stage disease (Argani *et al*, 2000; Seibel *et al*, 2006; Furtwängler *et al*, 2013).

Up until now, only three descriptive reports on clinical characteristics, treatment and outcome of relapsed CCSK have been published, including 11 patients in total (Table 1) (Kusumakumary *et al*, 1997; Yumura-Yagi *et al*, 1998; Radulescu *et al*, 2008). Therefore, data on clinical features of these patients are scarce and the contribution of chemotherapy, surgery, radiotherapy and high-dose chemotherapy followed by ABMT to optimal treatment of relapsed CCSK has not been established as yet. In addition, recent reports from the International Society for Pediatric Oncology (SIOP) and the National Wilms Tumor Study Group (NWTSG) have indicated that, following intensified upfront treatment, the pattern of relapses is changing with brain metastases now more common than the classical site of bone metastases in its original description as the 'bone metastasising renal tumour of childhood' (Marsden and Lawler, 1978; Furtwängler *et al*, 2005; Seibel *et al*, 2006).

This study aims to evaluate clinical characteristics, treatment and outcome of relapsed CCSK patients treated according to International Society of Paediatric Oncology (SIOP) and Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) protocols,

in order to find a rational for creating future international CCSK relapse treatment protocols.

## PATIENTS AND METHODS

**Patients.** All patients with recurrent CCSK after complete remission at the end of primary treatment, registered by and treated according to SIOP 93-01 (1993–2001), SIOP 2001 (2001–2011), AIEOP CNR-92 (1992–1998) and AIEOP WT-2003 (2003–ongoing) clinical trials, were included in the current analyses. Prospectively collected data on patient- and treatment characteristics as well as relapse- and survival data were retrieved from SIOP and AIEOP databases. Informed consent for participating in the studies had been obtained from patients and parents before treatment, according to national law and regulations. Ethical approval was obtained from medical ethical committees of all participating international centres.

**Treatment at initial diagnosis.** Patients were treated upfront according to study-specific guidelines (Supplementary Table 1). Patients entered onto SIOP 93-01 and SIOP 2001 studies were treated with pre-operative chemotherapy. Immediate tumour nephrectomy was performed in SIOP 93-01 and SIOP 2001 patients younger than 6 months or older than 18 years, and in patients treated according to AIEOP protocols unless the tumour was judged inoperable. The United Kingdom used a different national guideline for their patients included in the SIOP 2001 trial, including initial biopsy and intensified pre-operative chemotherapy if the biopsy revealed CCSK (Supplementary Table 1) (Mitchell *et al*, 2006; Stoneham *et al*, 2009;

Table 1. Reported relapsed CCSK patients

Study	n	Initial treatment regimen	Time to relapse <sup>a</sup>	Site of relapse	Treatment at relapse				Outcome <sup>b</sup>
					CT	S	RT	HD-CT + ABMT	
Kusumakumary <i>et al</i> , 1997	1	AV	8.5y	Primary site	Palliative only	Yes (no sCR)	Yes	No	DOD 4m
Yumura-Yagi <i>et al</i> , 1998	2	NWTSG 3	10m	Bone	VP16, THP, CIS	No	Yes	IFO/MEL + BUS/THIO	NED 4.1y
			22m	Brain	ICE	Yes (sCR)	Yes	IFO/MEL + BUS/THIO	NED 1.6y
Radulescu <i>et al</i> , 2008	8	NWTS 5 (n = 7), SIOP 2001 (n = 1)	Median 25m (range 6–42m)	Brain (n = 6), brain and bone (n = 2)	8/8 (ICE +/- other chemotherapeutic agents)	7/8 (sCR n = 4)	6/8	4/8 (BUS/MEL/THIO, BUS/TOPO/MEL, CARBO/THIO/TOPO, THIO/CYCLO + CARBO/MEL)	- 6 NED (median FU 2.6y) - 1 DOD - 1 Died of sepsis
Gooskens <i>et al</i> , 2014 [Current study]	37	SIOP 93-01, SIOP 2001, AIEOP CNR-92, AIEOP WT-2003	Median 17m (range, 15m – 13.6y)	Brain (n = 13), lungs (n = 7), bone (n = 5), primary site (n = 2), soft tissue (n = 1), extra-abdominal (n = 1), multiple (n = 8)	30/37 (Table 4)	19/37 (sCR n = 11)	18/37	14/37 (Table 3)	- 10 NED (median FU 4.6y) - 1 AWD 4.3y - 22 DOD - 2 Died of sepsis - 1 Lost to follow-up - 1 Unknown

Abbreviations: AV = actinomycin/vincristine; AIEOP = Associazione Italiana Ematologia Oncologia Pediatrica; AWD = alive with disease; BUS = busulphan; CT = chemotherapy; CIS = cisplatin; CYCLO = cyclophosphamide; CARBO = carboplatin; DOD = dead of disease; FU = follow-up; HD-CT + ABMT = high-dose chemotherapy followed by autologous bone marrow transplantation; ICE = ifosfamide/carboplatin/etoposide; IFO = ifosfamide; m = month; MEL = melphalan; NED = no evidence of disease; NWTS = National Wilms Tumor Study; RT = radiotherapy; S = surgery; sCR = complete surgical remission; SIOP = International Society of Pediatric Oncology; THP = hydopyranyladriamycin, THIO = thiotepa, TOPO = topotecan, UK-CCLG = United Kingdom Children's Cancer and Leukaemia Group; VP16 = etoposide; y = year.

<sup>a</sup>Time after date of initial diagnosis.

<sup>b</sup>Time after last treatment for relapse.

Pritchard-Jones *et al*, 2012). Administered post-operative treatment and applied radiotherapy per regimen is depicted in Supplementary Table 1.

**Histopathology.** All cases were centrally reviewed by panels of pathologists at time of nephrectomy. Tumours of SIOP trials were classified according to the SIOP Working Classification of Renal Tumours of Childhood and staged according to the SIOP 93-01 and SIOP 2001 trial criteria (Delemarre *et al*, 1996; Vujanic *et al*, 2002). Tumours of AIEOP trials were classified and staged according to NWTs criteria (Argani *et al*, 2000).

**Statistical analysis.** Statistical analysis was performed using the statistical software of SPSS (version 20.0) and GraphPad (version 5.01). Event-free survival (EFS) and overall survival (OS) were calculated using the Kaplan–Meier method, together with corresponding 95% confidence intervals (CIs). EFS was calculated from date of relapse to occurrence of a subsequent relapse or death, and OS was calculated from date of relapse to death for any reason. Patients with neither a further relapse nor death were censored at the time of the last follow-up record.

## RESULTS

**Clinical features and treatment at primary diagnosis.** This study describes all 37 relapses that occurred in the 237 CCSK patients treated according to the SIOP 93-01 ( $n = 98$ ), SIOP 2001 ( $n = 114$ ) and AIEOP ( $n = 25$ ) trials between 1992 and 2012. Clinical features and treatment of relapsed patients at initial diagnosis are depicted in Table 2. Forty-three percent of the patients presented with stage I and II disease, while the rest of the patients had more advanced disease stages.

Eighty-nine percent of the patients ( $n = 33$ ) were treated with three or more drugs at initial diagnosis (Table 2). Twenty-four out of thirty-seven patients were treated with alkylating agents (that is, ifosfamide or cyclophosphamide); patients who were treated with cyclophosphamide ( $n = 10$ ) had relapses located in the brain ( $n = 4$ ), lungs ( $n = 2$ ), bone ( $n = 1$ ) and multiple sites ( $n = 3$ ), while patients treated with ifosfamide ( $n = 13$ ) had relapses located in the brain ( $n = 8$ ), lungs ( $n = 3$ ), bone ( $n = 1$ ) and primary site ( $n = 1$ ) (Supplementary Table 2).

Forty-nine percent of the patients had been treated with radiotherapy at initial diagnosis. All four patients with a relapse located at the primary site had been treated upfront without local radiotherapy (3 stage I, 1 stage II) (Supplementary Table 2).

**Clinical features at relapse.** Median time from initial diagnosis to relapse was 17 months (range 5.5 months–6.6 years). Median age at the time of relapse was 42.5 months (range, 15 months–13.6 years). All patients younger than 12 months at initial diagnosis ( $n = 12$ ) had a relapse  $\leq 17$  months after initial diagnosis. Sites of relapse are depicted in Table 3; most relapses were metastatic ( $n = 35$ ) and the brain ( $n = 13$ ), lungs ( $n = 7$ ) and bone ( $n = 5$ ) were the most common sites of relapse. Three patients with a relapse located in the brain died shortly after the occurrence of relapse; two of them died immediately because of intra-cerebral bleeding of the tumour and one patient died 23 days later after palliative treatment.

**Treatment at relapse.** No standard treatment guideline was available for relapsed CCSK, except in the United Kingdom where relapsed patients were treated according to the recommendations of the UKWR trial including carboplatin, etoposide and cyclophosphamide followed by high-dose melphalan (Hale *et al*, 2008) (Supplementary Table 3). Detailed data on treatment of relapse were not available in two patients, and three patients with a relapse located in the brain died shortly after detection of the relapse, before treatment could be started. Thirty out of thirty-seven

Table 2. Clinical features and treatment at initial diagnosis

Clinical features	n (%)
<b>Protocol</b>	
SIOP 93-01	15 (41%)
SIOP 2001	18 (49%)
AIEOP 92	2 (5%)
AIEOP 2003	2 (5%)
<b>Gender</b>	
Male	24 (65%)
Female	13 (35%)
<b>Age (months)</b>	
Median	16 months
Range	2–143 months
<b>Stage</b>	
I	13 (35%)
II	3 (8%)
III	15 (41%)
IV	5 (14%) (lungs 4, bone 1)
Unknown	1 (3%)
<b>Initial treatment</b>	
Immediate surgery	4 (11%)
<b>Pre-operative chemotherapy</b>	
AV	27 (73%)
AVD	5 (14%)
AVE	1 (3%)
<b>Post-operative chemotherapy</b>	
VCCD	10 (27%)
EIVC	8 (22%)
AVD	8 (22%)
AVD + DIVC	3 (8%)
No post-operative chemotherapy <sup>a</sup>	2 (5%)
Other	6 (16%)
<b>Radiotherapy</b>	
Yes	18
No	18
NA	1

Abbreviations: AV = d-actinomycin/vincristine; AVD = d-actinomycin/vincristine/doxorubicin; AVE = d-actinomycin/vincristine/epirubicin; DIVC = doxorubicin/ifosfamide/etoposide/carboplatin; EIVC = epirubicin/ifosfamide/etoposide/carboplatin; NA = not available; VCCD = etoposide/carboplatin/cyclophosphamide/doxorubicin.

<sup>a</sup>No post-operative chemotherapy because of refusal by the parents.

patients (81%) were treated with different combinations of chemotherapy, in 19/37 patients (51%) surgical excision was performed (after biopsy confirming CCSK), 18/37 patients (49%) were treated with radiotherapy (median radiotherapy dose 27 Gy, range, 12–32 Gy) and 14/37 patients (38%) received subsequently high-dose chemotherapy and autologous bone marrow transplantation (ABMT) (Table 3 and Supplementary Table 3).

**Response to relapse treatment and outcome.** Median follow-up time after relapse was 19 months (range, 0–109 months). Twenty-two out of thirty-seven patients (59%) achieved a second CR after relapse treatment. Fifteen of these 22 patients (68%) developed a second relapse. Five-year EFS after relapse was 18% (95% CI:

Table 3. Clinical characteristics, treatment and outcome of relapsed CCSK patients

Treatment at relapse											
				S							
Site of relapse	N	Median time to relapse (range)	CT	sCR	No sCR	NA	RT	HD-CT + ABMT	2nd CR	2nd R	Outcome (median FU) <sup>a</sup>
Brain	13	21m (11–79m)	3 1 4 1	3 0 1 0	0 0 1 0	0 1 1 0	3 1 2 0	1 1 3 0	3 1 3 0	0 1 3 0	3 NED (58m) 1 AWD (51m) 8 DOD (10m) 1 Died (3m) <sup>a</sup>
Lungs	7	17m (14–35m)	0 5	1 3	0 2	0 1	0 4	1 1	1 5	1 5	1 NED (103m) 6 DOD (25.5m)
Bone	5	17m (5–21m)	3 2	1 1	0 0	0 0	3 1	2 1	3 1	1 1	3 NED (37.5m) 2 DOD (26m)
Primary	2	14m (13–15m)	1 1	0 0	0 0	1 0	1 0	1 0	1 0	0 0	1 NED (90m) 1 DOD (8m)
Soft tissue	1	15m	1	1	0	0	0	0	1	0	1 NED (109m)
Extra-abdominal	1	40m	NA	NA	NA	NA	NA	NA	NA	NA	NA
Multiple	8	18m (7–38m)	1 5 1 1	0 0 0 0	0 1 0 0	0 0 0 0	1 1 0 0	1 2 0 0	1 2 0 0	1 2 0 0	1 NED (35m) 5 DOD (19m) 1 Died (1m) <sup>a</sup> 1 lost to FU
Total	37	17m (5–79m)	30	11	4	5	17	14	22	15	10 NED (58m) 1 AWD (51m) 22 DOD (18m) 2 DOS (2m) 1 lost to FU 1 NA

Abbreviations: AWD = alive with disease; CT = chemotherapy; DOD = dead of disease; DOS = dead of sepsis; FU = follow-up; HD-CT + ABMT = high-dose chemotherapy followed by autologous bone marrow transplantation; m = month; NA = not available; NED = no evidence of disease; RT = radiotherapy; S = surgery; sCR = surgical complete remission; 2nd CR = second complete remission; 2nd R = second relapse.

<sup>a</sup>Died of sepsis (treatment-related mortality).

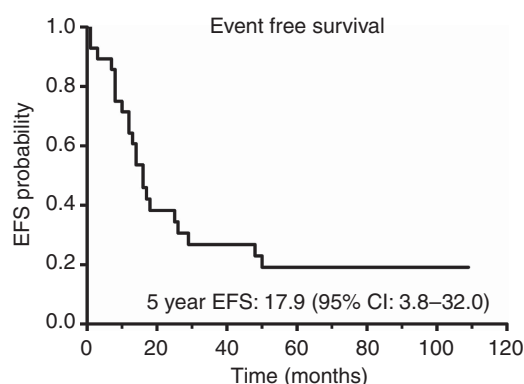


Figure 1. Event-free survival (EFS) after relapse. EFS = event-free survival, CI = confidence interval.

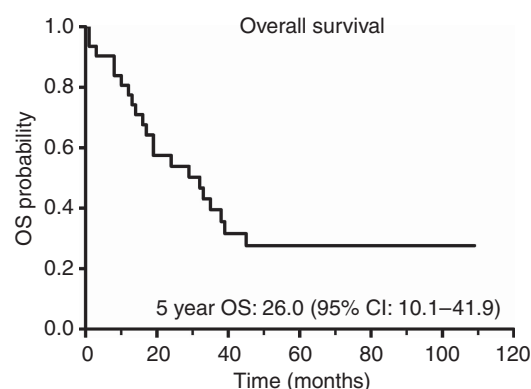


Figure 2. Overall survival (OS) after relapse. CI = confidence interval; OS = overall-survival.

4–32%), and 5-year OS after relapse was 26% (95% CI: 10–42%) (Figures 1 and 2).

Nine out of thirty-seven relapsed patients remained in long-term second CR after a median follow-up time from date of relapse of 4.8 years (range, 1.2–9.0 years) (Table 3). One out of thirty-seven patients is currently alive with disease (second relapse in the brain, 4.3 years after his first relapse in the brain). Two out of thirty-seven patients were lost to follow-up, and in one patient outcome data were not available. Twenty-four out of thirty-seven

relapsed patients (65%) died; causes of death were tumour progression ( $n=22$ ) or treatment-related mortality ( $n=2$ ) (patients died because of septic shock after one dose of topotecan and after one cycle of ICE (ifosfamide, carboplatin and etoposide), respectively).

The small number of the hereby described series of relapsed CCSK patients does not allow statistical analyses. In order to get some insight in clinical variables and successful treatments, we summarised characteristics of patients that achieved a second CR

separate from patients that did not reach second complete CR. We only included patients that completed intended relapse treatment ( $n=27$ ) (Table 4). Patients who died immediately after diagnosis ( $n=3$ ), patients who died early of treatment-related toxicity ( $n=2$ ), patients who are alive with disease ( $n=1$ ) and patients who had incomplete follow-up data ( $n=4$ ) were not included in this comparison. Patients who achieved a second CR ( $n=21$ ) were compared with patients who did not achieve a second CR ( $n=7$ ) (Table 4). In 11/21 second CR patients complete surgical resection was performed, whereas no complete surgical resection was performed in the 7 patients who did not achieve second CR. High-dose chemotherapy courses were applied in 13/21 second CR patients, whereas high-dose chemotherapy was applied in 1/7 patients who did not achieve second CR (Table 4). Subsequently, we focused on patients who achieved a second CR ( $n=20$ ). Of this group, 11 patients died of disease after second CR (median time to death 32 months) and 9 patients remained in long-term second CR (median follow up time 58 months) after

relapse treatment; clinical variables and administered treatment of these subgroups are depicted in Table 4.

Treatment outcome according to site of relapse is described in Table 3. Thirteen out of thirty-seven patients had a relapse located in the brain only, of whom four patients survived after relapse treatment. One patient who survived after relapse treatment recently suffered from a new (very late) recurrence in the brain (Table 3). Two patients with a relapse located in the brain died immediately after recognition of recurrence because of intra-tumoural bleeding, and one patient died shortly after diagnosis of treatment-related mortality after surgery and one dose of topotecan (Table 3). Seven out of thirty-seven patients had a relapse located in the lungs only, of which one patient survived after relapse treatment (Table 3). Isolated bone metastases occurred in 5 out of 37 patients, of which three patients survived after relapse treatment (Table 3). Two out of thirty-seven patients had a local relapse, of which one patient is in persistent second CR. One out of thirty-seven patients had a distant relapse located in the soft tissue

Table 4. Clinical variables of relapsed patients

2nd CR ( $n=21$ ) <sup>a</sup>		
Long-term 2nd CR ( $n=10$ )	DOD after 2nd CR ( $n=11$ )	No 2nd CR ( $n=7$ )
<b>Median time to relapse (range)<sup>b</sup></b>		
22 months (13–79 months)	16 months (14–30 months)	16 months (9–38 months)
<b>Median follow-up time (range)<sup>c</sup></b>		
54 months (14–109 months)	32 months (range 10–45 months)	14 months (range 8–29 months)
<b>Median age at initial diagnosis (range)</b>		
14 months (7–83 months)	22 months (2–143 months)	76 months (4–141 months)
<b>Site of relapse</b>		
Brain: 4 (40%) Bone: 2 (20%) Multiple: 1 (10%) Soft tissue: 1 (10%) Lungs: 1 (10%) Primary site: 1 (10%)	Lungs: 5 (45%) Brain: 3 (27%) Multiple: 2 (18%) Bone: 1 (9%)	Multiple: 3 (43%) Brain: 1 (14%) Lungs: 1 (14%) Bone: 1 (14%) Primary: 1 (14%)
<b>ICE chemotherapy</b>		
ICE: 5 (50%) No ICE: 5 (50%)	ICE: 6 (55%) No ICE: 5 (45%)	ICE: 4 (57%) No ICE: 3 (53%)
<b>Surgery</b>		
Surgery: 8 (80%) sCR: 6 (60%) No sCR: 2 (20%) No surgery: 2 (20%)	Surgery: 8 (73%) sCR: 5 (45%) No sCR: 3 (27%) No surgery: 3 (27%)	Surgery: 2 (29%) sCR: 0 (0%) No sCR: 2 (29%) No surgery: 5 (71%)
<b>Radiotherapy</b>		
Radiotherapy: 8 (80%) No radiotherapy: 2 (20%)	Radiotherapy: 5 (45%) No radiotherapy: 6 (55%)	Radiotherapy: 4 (57%) No radiotherapy: 3 (43%)
<b>HD-CT + ABMT</b>		
HD-CT: 7 (70%) No HD-CT: 3 (30%)	HD-CT: 6 (55%) No HD-CT: 5 (45%)	HD-CT: 1 (14%) No HD-ST: 6 (86%)
Abbreviations: ICE = ifosfamide/carboplatin/etoposide; HD-SCT + ABMT = high-dose chemotherapy followed by autologous bone marrow transplantation; 2nd CR = second complete remission; sCR = surgical complete remission.		
<sup>a</sup> One additional patient reached 2nd CR, but recently developed a 2nd relapse and is currently alive with disease.		
<sup>b</sup> Median time from initial diagnosis until first relapse.		
<sup>c</sup> Median time from first relapse until death or last date of follow-up.		



(left side lower lateral ribs) and is in persistent second CR (Table 3). Eight out of thirty-seven patients had relapses located at multiple sites, of which only one patient with relapses in the bone and brain is in persistent second CR after 4, 8 years of follow-up (Table 3). Two patients with disseminated disease were lost to follow-up shortly after diagnosis of relapse, and one patient with a relapse located at primary site and paravertebral died due to treatment-related mortality after one cycle of ICE chemotherapy (Table 3).

## DISCUSSION

This study reports on clinical characteristics, treatment and outcome of all children with relapsed CCSK after complete remission at the end of primary treatment, entered onto SIOP 93-01, SIOP 2001 and AIEOP trials. It represents the largest series of relapsed CCSK patients described so far (Table 1). We realise this is a descriptive study, nevertheless we consider it valuable to describe our series as data on treatment and outcome of relapsed CCSK patients are very scarce. This study reveals that outcome of relapsed CCSK patients is poor, that brain seems to have surpassed the bone as most common site of relapse and that intensive treatment, including chemotherapy as well as achieving local control by complete surgery and/or radiotherapy, is necessary to salvage CCSK patients.

We have demonstrated previously that survival rates are disappointing for younger children with CCSK (Furtwängler *et al*, 2013). Consequently, 32% of the relapsed patients were infants at the time of initial diagnosis, and the median age at the time of diagnosis was 16 months for relapsed CCSK patients, compared with a median age of 31 months of all CCSK patients described in a previous study (Furtwängler *et al*, 2013).

Our data show that relapses occur relatively late. This seems to be characteristic for CCSK according to smaller earlier reports that describe occurrence of recurrences up to 8 years after initial diagnosis (Kusumakumary *et al*, 1997). Green *et al* (1994) reported that 30% of relapses in NWTs 1-3 patients occurred more than 2 years after diagnosis. In the most recent North-American National Wilms Tumor Study (NWTs) trial, only 1 out of 21 relapses (5%) occurred beyond 3 years after diagnosis (Seibel *et al*, 2006). In our series, nine cases (24%) relapsed later than 2 years after initial diagnosis and four of these cases (11%) relapsed even more than 3 years after initial diagnosis (up to 6.6 years after initial diagnosis). Patients younger than 12 months at initial diagnosis all relapsed within 17 months after initial diagnosis, which might imply that the biological behaviour of CCSK is more aggressive in young children. Altogether this indicates that children with CCSK need extended and more intensive follow-up for detection of relapses than, for instance, patients with nephroblastoma. The late recurrences in CCSK are remarkable as it fundamentally is an aggressive tumour, illustrated by the fact that outcome on average is poor.

The pattern of relapse included distant metastases in more than 95% of our patients, similar to earlier reports (Argani *et al*, 2000). The most frequent locations of relapse were the brain, lungs and bone. Previous reports showed bone to be the most frequent site of CCSK recurrence, for which reason CCSK was initially referred to as 'bone metastasising tumour of the kidney' (Marsden and Lawler, 1978; Green *et al*, 1994). Bone is still the most common site of metastases at initial diagnosis, but interestingly, according to our study and previous studies, the brain seems to have surpassed the bone as the most common site of CCSK recurrence (Furtwängler *et al*, 2005; Seibel *et al*, 2006). This indicates that the brain might be a sanctuary for cells that are protected from intensive chemotherapy that patients currently receive. One would expect the highest rate of brain relapses in the group of patients less adequately treated with central nervous system (CNS)-penetrating drugs (vincristine, ifosfamide, carboplatin) (Yule *et al*, 1997). In Europe,

brain relapses occurred in 8 out of 15 cases (53%) treated with ifosfamide (SIOP 93-01, AIEOP CNR-92, AIEOP WT-2003) versus 6 out of 15 cases (40%) treated with cyclophosphamide (SIOP 2001). All these cases, either treated with ifosfamide or cyclophosphamide were also treated with carboplatin. In NWTs-5, 11 out of 21 (52%) relapses occurred in the brain; these patients were treated with vincristine, doxorubicin, cyclophosphamide and etoposide, but without carboplatin and ifosfamide (Seibel *et al*, 2006). This indicates that other factors than CNS penetration of the applied agents may have a role in this preference location of CCSK relapses. Radulescu *et al* (2008) describe eight NWTs CCSK patients with a relapse in the brain, all treated with a variable number of courses of ICE (ifosfamide, carboplatin, etoposide); 7 out of 8 patients achieved a second complete response, and 1 out of 8 patients died from complications of bacteraemia (Radulescu *et al*, 2008). In our series, 5 out of 13 patients with an isolated relapse in the brain were treated with ICE chemotherapy, of which three patients achieved a long-term complete response. This may indicate that treatment including ICE is promising for patients with a relapse in the brain, although we currently have no data on the influence of other factors like type of upfront treatment and hence, development of resistance. As the brain is the most common site of relapse, a logical consequence would be to include MRI of the brain in follow-up protocols of CCSK patients. However, relapses occur in only 16% of all CCSK patients, and 41% of these relapses are located in the brain. This indicates that all CCSK patients have to be screened by MRI of the brain during follow-up in order to detect brain relapses in only 7% of these patients. Besides practical objections such as anaesthesia in young children, this does not seem to be cost-effective. Nevertheless, brain MRI seems to be of value in case of suspicion of a brain relapse in an individual CCSK patient and as work-up for patients with a relapse detected elsewhere.

As the number of relapsed patients reported is too small to draw conclusions regarding the contributions of chemotherapy, high-dose chemotherapy followed by stem-cell transplantation, radiotherapy and surgery to the treatment of recurrent CCSK, no standard treatment guidelines are available for this patient group (Table 1).

More than half of the patients achieved a second CR after relapse treatment, but 68% of these patients subsequently developed a second relapse, indicating that consolidation of a second CR seems to be a challenge in relapsed CCSK patients. Intensive treatment, including chemotherapy as well as achieving local control by complete surgery (where possible) and/or radiotherapy, seems to enhance consolidation of second CR. Summarising our study and previous reports, in total 24 relapsed CCSK patients received high-dose chemotherapy followed by ABMT, of which 12 patients (50%) were alive without disease after a median follow-up of 52 months (range, 9–103 months) (Kullendorff and Bekassy, 1997; Pein *et al*, 1998; Yumura-Yagi *et al*, 1998; Radulescu *et al*, 2008; Furtwängler *et al*, 2013). This seems to be promising, although it should be emphasised that this high-dose chemotherapy is mostly applied in a selected group of patients who already achieved a second CR. In addition, high-dose chemotherapy followed by ABMT may cause treatment-related direct and late toxicity and needs to be weighed against the risk of disease-related mortality (Radulescu *et al*, 2008).

As treatment options for relapsed CCSK are limited and survival is poor, development of new targeted therapies based on biological characteristics of CCSK is necessary to improve survival of these children. Although the molecular background of CCSK is poorly understood, a few genetic aberrations have been described, that is, upregulation of the Sonic hedgehog signalling pathway and the PI3K/Akt signalling pathway and *EGFR* gene amplification and mutation (Cutcliffe *et al*, 2005; Little *et al*, 2007). In addition, a recurrent translocation of chromosome 10 and chromosome 17

has been described, including *YWHA*E and *FAM22* genes (O'Meara *et al*, 2012). These molecular changes might be possible targets for therapy for early-phase trials.

For other sarcomas in children, new chemotherapeutic agents, such as irinotecan and temozolomide, are currently being studied in clinical trials (Raciborska *et al*, 2013). So far, it is unknown whether the biological character of these sarcomas is comparable to that of CCSK and whether these drugs are of any value for CCSK.

In conclusion, this largest series of relapsed CCSK patients ever described shows that outcome of relapsed CCSK patients is poor. Relapses tend to occur late, so extensive follow-up is desirable. Nearly all relapses are metastatic and the brain seems to have surpassed the bone as the most common site of relapse. Intensive treatment aiming for local control followed by high-dose chemotherapy and ABMT seems to be of benefit to enhance survival. International collaboration to develop new targeted therapies based on biological characteristics of CCSK is warranted to improve survival of CCSK patients that suffer from a relapse.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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