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Rationale for the treatment of children with CCSK in the UMBRELLA SIOP–RTSG 2016 protocol

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Abstract | The International Society of Paediatric Oncology–Renal Tumour Study Group (SIOP–RTSG) has developed a new protocol for the diagnosis, treatment, and follow-up monitoring of childhood renal tumours — the UMBRELLA SIOP–RTSG 2016 protocol (the UMBRELLA protocol). This protocol has been designed to continue international collaboration in the treatment of childhood renal tumours and will be implemented in over 50 different countries. Clear cell sarcoma of the kidney, which is a rare paediatric renal tumour that most commonly occurs in children between 2 and 4 years of age, is specifically addressed in the UMBRELLA protocol.

Clear cell sarcoma of the kidney (CCSK) is an uncommon childhood renal tumour that comprises 2–5% of all primary renal malignancies in children[1–4]. CCSK is observed most often in children between 2 and 4 years of age and shows a slight male predominance (male:female ratio approximately 2:1)[3,5]. The majority of patients present with localized disease, and metastatic disease is identified in only 6–7% of patients at diagnosis, the most frequent sites being bone, lungs, and liver[2,3,5].

Histologically, CCSK shows a remarkable morphological diversity (including classic, myxoid, sclerosing, cellular, and epithelioid patterns, among others)[3]. These variant histological patterns do not seem to be of prognostic value, but they do often cause difficulties in distinguishing CCSK from other paediatric renal tumours, including blastemal-type nephroblastoma, mesoblastic nephroma, primitive neuroectodermal tumour, and rhabdoid tumour of the kidney, which might result in inappropriate or delayed treatment[2]. Tumour cells show diffuse and strong immunoreactivity for vimentin, cyclin D1, low-affinity nerve growth factor receptor (NGF receptor; also known as NGFR), and BCL6 corepressor (BCoR), which can assist in diagnosing CCSK[3,6–8].

Currently, the histogenesis of CCSK is uncertain. The genome of CCSK is rather stable, even at RNA and/or DNA deep-sequencing levels (mutations, copy number variations, and translocations are infrequent)[9–12]. A subgroup of CCSKs has been shown to harbour the translocation t(10;17)(q22;p13), resulting in fusion of *YWHAE* and *NUTM2B* or *NUTM2E*[13]. Three studies published in 2015 demonstrated that the majority of CCSKs have a somatic internal tandem duplication (ITD) in X-linked *BCOR* affecting the 3′ part of the exon 16 coding sequence[10,12,14]. These *BCOR* ITDs and t(10;17)(q22;p13) are mutually exclusive events in CCSK[15–17]. DNA methylation profiling identified hypermethylation of the tumour suppressor *TCF21* in CCSKs bearing *BCOR* ITDs[9,17]. Gene expression profiling studies reported strong and consistent upregulation of neural markers and members of the Sonic Hedgehog signalling pathway and the RACα serine/threonine-protein kinase (AKT) cell proliferation pathway[8,9]. The identified aberrations can be of use in the diagnosis of CCSK. To date, these aberrations have not been identified to be of prognostic or predictive value for patients with CCSK[18].

After the introduction of more intensive treatment schedules, including anthracyclines and alkylating agents (commencing in 1974 in National Wilms Tumour Study (NWTS) protocols and in 1980 in International Society of Paediatric Oncology (SIOP) protocols), the outcome of patients diagnosed with CCSK has increased substantially[2,3,19,20] (TABLE 1). However, a considerable

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minority of patients do not have a favourable prognostic clinical signature (especially patients with stage IV disease, young patients, and patients with relapsed disease), and a plateau in survival seems to have been reached as current treatment protocols already contain the maximum tolerated intensity of traditional cytotoxic agents that can cause consequential serious toxicity[2,3,21]. Thus, the development of new (targeted) therapies is necessary for this group of patients.

The main mission of the SIOP–Renal Tumour Study Group (SIOP–RTSG) is to increase survival and reduce the toxicity of treatment in children diagnosed with any renal tumour. In this context, the SIOP–RTSG is aiming to offer all paediatric patients with renal tumours who are enrolled in SIOP protocols standardized, high-quality diagnostics and treatment, independent of socioeconomic status or geographical region. To achieve these goals, the UMBRELLA SIOP–RTSG 2016 protocol (the UMBRELLA protocol), approved by the SIOP–RTSG and by the ethical committee in the country of the sponsor (Germany) (EudraCT number 2016-004180-39), is currently being implemented in over 50 countries[22,23]. The management of paediatric CCSK is addressed in the UMBRELLA protocol.

This Consensus Statement describes the rationale for the diagnosis, treatment, and follow-up recommendations for children with CCSK included in the UMBRELLA protocol. Importantly, owing to the rarity of CCSK, no randomized trials specifically investigating CCSK have been performed, which limits the level of evidence available. Consequently, recommendations for CCSK included in the UMBRELLA protocol are based on synthesis of collated evidence (including observational studies and randomized trials not specific to CCSK) by experts in the field of CCSK to select the current best-available treatment.

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Methods

The recommendations for CCSK have been developed by a multidisciplinary working group of selected SIOP–RTSG members (specialist paediatric oncologists, pathologists, radiologists, radiotherapists, surgeons, statisticians, and other experts in the field of CCSK). These experts designed the consensus regarding diagnostics, best-available treatment, and follow-up methods based on an extensive review of the literature on CCSK[5] and an analysis of treatment and outcomes of patients with CCSK treated according to the most recent SIOP 93–01 and SIOP 2001 protocols[2].

Background to the rationale

In general, the treatment of paediatric patients with renal tumours follows two contrasting recommendations internationally, which have been different from inception (TABLE 1). The European SIOP recommendations advocate preoperative chemotherapy consisting of two drugs (vincristine and actinomycin) in instances of localized disease and three drugs (vincristine, actinomycin, and doxorubicin) in instances of metastatic disease for children between 6 months and 16 years of age. The North American National Wilms Tumor Study Group (NWTS) and its successor, the Children's Oncology Group (COG), recommend immediate surgery for children of all ages when it can be performed safely. Both policies result in similar survival (TABLE 1). Preoperative chemotherapy given according to the SIOP policy has been shown to result in downstaging of paediatric renal tumours, leading to a reduction in therapy. The two regimens (SIOP and NWTS–COG) were compared in the UK Wilms Tumour trial 3 (UKW3), in which patients were randomly assigned either to immediate nephrectomy or to preoperative chemotherapy; 20% of renal tumour survivors were spared the late effects of doxorubicin and radiotherapy by treating them with preoperative chemotherapy[24]. In addition, the SIOP policy enables assessment of histological response to treatment[24]. Upfront resection according to the NWTS and COG protocol enables immediate, accurate assessment of the histological diagnosis and tumour extent as well as the harvesting of pretherapy tumour tissue, which is useful for research purposes. Consequently, most patients with CCSK treated according to SIOP protocols are diagnosed after preoperative chemotherapy, whereas patients treated according to NWTS and COG protocols are diagnosed before chemotherapeutic treatment. Historically, CCSK has been treated using chemotherapy regimens similar to those used for the treatment of high-risk Wilms tumour as the rarity of CCSK has limited studies or trials specifically tailored to CCSK.

Table 1 | **Previous and current treatment protocols including clear cell sarcoma of the kidney**

Study (period) and number of included patients with CCSK	Study design (quality of evidence[a]) and study limitations	Preoperative treatment	Postoperative treatment		Outcome		
			Chemotherapy	Radiotherapy	EFS	OS	Relapse rate
SIOP studies							
SIOP 1 (REFS 26,74) (1971–1974) NA[b]	• RCT (low) • Small CCSK cohort size • CCSKs were included in a study focused mainly on Wilms tumour • Outcome of patients with CCSK has been described only for combined studies (not for each study separately) • Patients with stage IV disease were excluded from the trial (all excluded patients were included in prospective registration studies)	Randomization: primary surgery versus radiotherapy (20 Gy)	Randomization: one course of AMD versus seven courses of AMD	Randomization: postoperative only (stage I: 20 Gy, stage II–III: 30 Gy) versus preoperative (20 Gy) and postoperative (stage II–III: 15 Gy)	30% (5-year)[b]	43% (5-year)[b]	NA
SIOP 2 (REFS 25,26,75) (1974–1976) NA[b]	• Observational (very low) • Small CCSK cohort size • CCSKs were included in a study focused mainly on Wilms tumour • Outcome of patients with CCSK has been described only for combined studies (not for each study separately) • Patients with stage IV disease were excluded from the trial (all excluded patients were included in prospective registration studies)	Radiotherapy (20 Gy)	Stage I–IV: AV (for 9 months or 15 months)	Stage II–III: 15 Gy	30% (5-year)[b]	43% (5-year)[b]	NA
SIOP 5 (REFS 25,26) (1977–1979) NA[b]	• RCT (low) • Small CCSK cohort size • CCSKs were included in a study focused mainly on Wilms tumour • Outcome of patients with CCSK has been described only for combined studies (not for each study separately) • Patients with stage IV disease were excluded from the trial (all excluded patients were included in prospective registration studies)	Randomization: radiotherapy (20 Gy) + AMD versus AV[c]	Stage I–IV: AV	Stage II–III: 15 Gy (in instances of preoperative radiotherapy) or 30 Gy (no preoperative radiotherapy)	30% (5-year)[b]	43% (5-year)[b]	NA
SIOP 6 (REF. 27) (1980–1987) *n* = 15	• RCT (no evidence[d]) • Small CCSK cohort size • CCSKs were included in a study focused mainly on Wilms tumour • Patients with stage IV disease were excluded from the trial (all excluded patients were included in prospective registration studies) • Exclusion of unfavourable-histology tumours (including CCSK; some CCSKs were included owing to initial misdiagnosis)	AV	• Stage I randomization: AV for 17 weeks versus AV for 38 weeks • Stage IIN0: AV for 38 weeks • Stage IIN1/III randomization: AV versus AVD	• Stage IIN0 randomization: radiotherapy (20 Gy) versus no radiotherapy • Stage IIN1 or III: 30 Gy	NA	NA	NA

Table 1 (cont.) | **Previous and current treatment protocols including clear cell sarcoma of the kidney**

Study (period) and number of included patients with CCSK	Study design (quality of evidence[a]) and study limitations	Preoperative treatment	Postoperative treatment		Outcome		
			Chemotherapy	Radiotherapy	EFS	OS	Relapse rate
SIOP studies (cont.)							
SIOP 9 (REF. 28) (1987–1991) *n* = 16	• RCT (low) • Small CCSK cohort size • CCSKs were included in a study focused mainly on Wilms tumour • Patients with stage IV disease were excluded from the trial (all excluded patients were included in prospective registration studies)	Randomization: AV 4 weeks versus AV 8 weeks[c]	Stage I–IV: AVEI	Stage II–III: 30 Gy	75% (2-year)	88% (5-year)	NA
SIOP 93–01 (REF. 2) (1993–1999) *n* = 100	• Observational (low) • Outcome of patients with CCSK has been described only for combined studies (not for each study separately)	• Stage I–III: AV • Stage IV: AVD	Stage I–IV: ECID	Stage II–III: 25–30 Gy	78% (5-year)[e]	86% (5-year)[e]	15%
SIOP 2001 (REF. 2) (2001–2016) *n* = 91	• Observational (low) • Outcome of patients with CCSK has been described only for combined studies (not for each study separately)	• Stage I–III: AV • Stage IV: AVD	• Stage I: AVD • Stage II–IV: ECCD	Stage II–III: 25.2 Gy	78% (5-year)[e]	86% (5-year)[e]	15%
UK SIOP 2001 (2001–2011) NA	• Observational (no evidence[d]) • Number of included patients with CCSK unknown	AVD	• Stage I–III: AVD • Stage IV: ECCD	Stage II–III: 25.2 Gy (before 2009, only radiotherapy for stage III)	NA	NA	NA
UMBRELLA (2017–ongoing) NA	• Observational (NA) • NA	• Stage I–III: AV • Stage IV: AVD	Stage I–IV: ECICD	Stage II–III: 10.8 Gy	NA	NA	NA
NWTS and COG studies							
NWTS 1 (REFS 19,76) (1969–1973) *n* = 23	• RCT (low) • Small CCSK cohort size • CCSKs were included in a study focused mainly on Wilms tumour • Outcome of patients with CCSK has been described only for combined studies (not for each study separately)	• Stage I–III: primary surgery • Stage IV randomization: primary surgery versus VCR	• Stage I: AMD • Stage II–III randomization AMD versus VCR versus AV • Stage IV: AV	• Stage I randomization: radiotherapy (18–40 Gy) versus no radiotherapy • Stage II–IV: 18–40 Gy	• AV (*n* = 8): 25% (6-year) • AVD (*n* = 58): 64% (6-year) • AVDC (*n* = 30): 58% (6-year)[f]	• AV (*n* = 8): 25% (6-year) • AVD (*n* = 58): 72% (6-year) • AVDC (*n* = 30): 61% (6-year)[f]	NA
NWTS 2 (REFS 19,77) (1974–1978) *n* = 23	• RCT (low) • Small CCSK cohort size • CCSKs were included in a study focused mainly on Wilms tumour • Outcome of patients with CCSK has been described only for combined studies (not for each study separately)	Primary surgery	• Stage I randomization: AV for 6 months versus AV for 15 months • Stage II–IV randomization: AV versus AVD	Stage II–IV: 18–40 Gy	• AV (*n* = 8): 25% (6-year) • AVD (*n* = 58): 64% (6-year) • AVDC (*n* = 30): 58% (6-year)[f]	• AV (*n* = 8): 25% (6-year) • AVD (*n* = 58): 72% (6-year) • AVDC (*n* = 30): 61% (6-year)[f]	NA
NWTS 3 (REFS 19,78) (1979–1985) *n* = 73	• RCT (moderate) • CCSKs were included in a study focused mainly on Wilms tumour	Primary surgery	Stage I–IV randomization: AVD versus AVDC	Stage I–IV: 10.8–40 Gy	• AV (*n* = 8): 25% (6-year) • AVD (*n* = 58): 64% (6-year) • AVDC (*n* = 30): 58% (6-year) • NWTS 3: 60% (8-year)[f]	• AV (*n* = 8): 25% (6-year) • AVD (*n* = 58): 72% (6-year) • AVDC (*n* = 30): 61% (6-year) • NWTS 3: 67% (8-year)[f]	39%
NWTS 4 (REF. 29) (1986–1994) *n* = 86	• RCT (moderate) • CCSKs were included in a study focused mainly on Wilms tumour	Primary surgery	Stage I–IV randomization: AVD 6 months versus 16 months	Stage I–IV: 10.8 Gy	• AVD for 6 months: 61% (8-year) • AVD for 16 months: 88% (8-year) • Overall: 72% (8-year)	• AVD for 6 months: 86% (8-year) • AVD for 16 months: 88% (8-year) • Overall: 83% (8-year)	27%

Table 1 (cont.) | **Previous and current treatment protocols including clear cell sarcoma of the kidney**

Study (period) and number of included patients with CCSK	Study design (quality of evidence[a]) and study limitations	Preoperative treatment	Postoperative treatment		Outcome		
			Chemotherapy	Radiotherapy	EFS	OS	Relapse rate
NWTS and COG studies (cont)							
NWTS 5 (REF. 20) (1995–2002) *n* = 110	• Observational (low) • NA	Primary surgery	Stage I–IV: ECVD	Stage I–IV: 10.8 Gy	79% (5-year)	89% (5-year)	19%
AREN0321 (2006–2013) NA	• Observational (NA) • NA	Primary surgery	Stage I–III: ECVD Stage IV: ECVDC	Stage II–IV: 10.8 Gy	NA	NA	NA
Other studies							
UKW1 (REF. 79) (1980–1986) *n* = 14	• Observational (very low) • Small CCSK cohort size • CCSKs were included in a study focused mainly on Wilms tumour • EFS data not available for patients with CCSK	Primary surgery	Stage I–IV: AVDC	Stage II–IV: 30 Gy[g]	NA	79% (6-year)	NA
UKW2 (REF. 31) (1986–1991) *n* = 18	• Observational (very low) • Small CCSK cohort size • CCSKs were included in a study focused mainly on Wilms tumour	Primary surgery	Stage I–IV: AVD	Stage III–IV (stage IV: treatment with radiotherapy only in instances of local stage III disease): 30 Gy	82% (4-year)	88% (4-year)	NA
UKW3 (REF. 24) (1991–2001) *n* = 8	• RCT (no evidence[d]) • Small CCSK cohort size • CCSKs were included in a study focused mainly on Wilms tumour • Patients with stage IV disease were excluded from the trial (all excluded patients were included in prospective registration studies)	Randomization: AV versus primary surgery	Stage I–III: AVD	Stage III: 30 Gy	NA	NA	NA
AIEOP TW-2003 (REF. 33) (2003–2017) *n* = 14	• Observational (very low) • Small CCSK cohort size • CCSKs were included in a study focused mainly on Wilms tumour	Primary surgery	Stage I–IV: ECID	Stage I–III: 19.8 Gy	84% (5-year)	91% (5-year)	14%
JWiTs-1 (REF. 34) (1996–2005) *n* = 16	• Observational (very low) • Small CCSK cohort size • CCSKs were included in a study focused mainly on Wilms tumour	Primary surgery	Stage I–IV: ECVD	Stage I–IV: 10.8 Gy	73% (5-year)	75% (5-year)	NA

AMD, actinomycin; AV, actinomycin and vincristine; AVD, actinomycin, vincristine, and doxorubicin; AVDC, actinomycin, vincristine, doxorubicin, and cyclophosphamide; AVEI, actinomycin, vincristine, epirubicin, and ifosfamide; CCSK, clear cell sarcoma of the kidney; COG, Children's Oncology Group; ECCD, etoposide, carboplatin, cyclophosphamide, and doxorubicin; ECICD, etoposide, carboplatin, ifosfamide, cyclophosphamide, and doxorubicin; ECID, etoposide, carboplatin, ifosfamide, and doxorubicin; ECVD, etoposide, cyclophosphamide, vincristine, and doxorubicin; ECVDC, etoposide, cyclophosphamide, vincristine, doxorubicin, and carboplatin; EFS, event-free survival; JWiTs, Japan Wilms Tumor Study group; NA, not applicable; NWTS, National Wilms Tumor Study; OS, overall survival; RCT, randomized controlled trial; SIOP, International Society of Paediatric Oncology; VCR, vincristine. [a]Studies were graded according to the GRADE system of the GRADE working group[80]. [b]Results of patients with CCSK treated in SIOP 1–5 studies were only described together, not separately for the SIOP 1, SIOP 2, and SIOP 5 studies. In total, 33 patients with CCSK were included in SIOP 1–5 studies. [c]SIOP 5 and SIOP 9 did not describe how randomization affected patients with CCSK; only outcomes of the whole group of patients with CCSK have been reported. [d]No evidence available because no outcome data have been reported for patients with CCSK. [e]Results of patients with CCSK treated in SIOP 93-01 and SIOP 2001 studies were only described together, not separately for both studies. [f]Results of patients with CCSK treated in NWTS 1–3 studies were described together, only results of patients with CCSK treated in NWTS 3 have also been described separately. [g]In the case of residual disease after second-look or delayed surgery.

SIOP trials

The first SIOP trials (SIOP 1, SIOP 2, and SIOP 5, conducted between 1971 and 1979), in which CCSKs were treated in the same way as Wilms tumours, used preoperative or postoperative radiotherapy and/or chemotherapy consisting of actinomycin alone or in combination with vincristine. The results of these trials showed a 5-year event-free survival (EFS) of 30% and a 5-year overall survival (OS) of 43% for patients with CCSK (*n* = 33, all three trials; TABLE 1)[25,26]. The results

of the first two SIOP trials demonstrated the benefit of preoperative radiotherapy (significantly fewer tumour ruptures, $P<0.001$). The SIOP 5 trial showed that preoperative chemotherapy was equivalent to preoperative radiotherapy in terms of prevention of tumour rupture. Thus, all subsequent SIOP treatment regimens contained recommendations for preoperative chemotherapy, at least in patients older than 6 months of age. Owing to the toxic effect of irradiation in small children, radiotherapy was used only as postoperative therapy in subsequent regimens. The sixth SIOP study (conducted between 1980 and 1987), in which patients were treated with preoperative actinomycin and vincristine and postoperative actinomycin and vincristine with or without additional doxorubicin and/or radiotherapy, included only patients with a favourable-histology Wilms tumour (TABLE 1). Some 15 patients with CCSK were included in this study after initial misdiagnosis, but outcomes of these patients were not reported separately[27]. The SIOP 9 study (conducted between 1987 and 1991), including patients with nonmetastatic renal tumours, showed a substantial increase in EFS and OS of patients with CCSK after the addition of an anthracycline (epirubicin or doxorubicin), an alkylating agent (ifosfamide), and radiotherapy to a dose of 30 Gy (in instances of local stage II and III disease) to the treatment protocol, resulting in a 2-year EFS of 75% and 5-year OS of 88% ($n=16$; TABLE 1)[28]. Patients with CCSK subsequently registered in SIOP 93–01 (conducted between 1993 and 2001) received adjuvant treatment consisting of etoposide, carboplatin, ifosfamide, and epirubicin or doxorubicin (doxorubicin in German, Austrian, and Swiss centres) ($n=100$; TABLE 1). Postoperative therapy was reduced to three drugs (actinomycin, vincristine, and doxorubicin) in patients with high-risk stage I tumours (including CCSK) registered in SIOP 2001 (conducted between 2001 and 2016) to decrease toxicity while maintaining doxorubicin as part of the treatment ($n=27$; TABLE 1). Etoposide, carboplatin, and doxorubicin, with cyclophosphamide replacing ifosfamide (because of the potential risk of tubular damage to the remaining kidney), continued to be used in patients with stage II–IV disease in SIOP 2001 ($n=64$; TABLE 1)[2]. SIOP 93–01 and SIOP 2001 protocols included additional irradiation to the flank (25–30 Gy in SIOP 93–01 and 25.2 Gy in SIOP 2001) in instances of local stage II and stage III disease. In terms of assessing responsiveness of CCSK to preoperative chemotherapy, in the SIOP 93–01 and SIOP 2001 trials, a partial response was observed in 21% of patients, a minor response in 15%, stable disease in 31%, and progressive disease in 33% (according to RECIST criteria)[2]. The 5-year EFS and OS of all 191 patients with CCSK registered in SIOP 93–01 and SIOP 2001 protocols were 78% and 86%, respectively[2]. Stage IV disease ($P=0.0315$) and age <12 months ($P=0.0004$) were significant adverse prognostic factors for EFS[2]. For patients treated with alkylating agents (ifosfamide or cyclophosphamide, $n=146$), 5-year EFS and OS were 83% and 88%, respectively, compared with 67% and 78%, respectively, for patients treated without alkylating agents ($n=28$)[2]. Notably, the 5-year EFS and OS of patients with stage I disease treated according to SIOP 93–01 (four drugs, including alkylating agent, $n=53$) were 83% and 90%, respectively, compared with 72% and 80%, respectively, for patients with stage I disease treated according to the SIOP 2001 protocol (three drugs, no alkylating agent, $n=27$)[2]. The data from this study suggest that postoperative treatment including alkylating agents might improve EFS and OS for patients with CCSK, although the study was an observational cohort study and not a randomized controlled trial. This difference in treatment protocols could explain why patients with stage I disease treated according to the SIOP 2001 protocol (without alkylating agents) had inferior survival to patients with stage I disease treated according to the SIOP 93–01 protocol (including alkylating agents).

NWTS trials

Results from the first three NWTS trials (conducted between 1969 and 1986) showed that the addition of doxorubicin to the combination of vincristine and actinomycin improved the 6-year EFS of patients with CCSK from 25% to 64% ($n=23$; TABLE 1)[19]. Argani *et al.*[3] confirmed the beneficial effect of doxorubicin in a retrospective review of 182 patients with CCSK treated according to the regimens in NWTS 1–4 (REF. 3). After these first NWTS trials, doxorubicin remained part of the treatment of patients with CCSK registered in NWTS protocols. The addition of cyclophosphamide did not further improve the 6-year EFS in NWTS 3; however, cyclophosphamide was administered at a fairly low dose and intensity (ten courses of 10 mg per kg daily for 3 days), which might have been too low to be effective ($n=73$; TABLE 1)[19]. Results of the NWTS 1–3 trials indicated that the frequency of flank relapses did not increase with the use of reduced radiotherapy doses to the lower flank; according to these data, a radiotherapy dose of 10.8 Gy has been used in all subsequent NWTS protocols[19]. Based on the results of NWTS 3, cyclophosphamide was not routinely used in the subsequent NWTS 4 regimen[19,29]. Results of NWTS 4 (conducted between 1986 and 1995) indicated that a 16-month course of vincristine, actinomycin, and doxorubicin results in superior 8-year EFS compared with a 6-month course (EFS 88% versus 61%), but long-term survival after both courses was equal (8-year OS 88% versus 86%, $n=86$; TABLE 1)[29]. NWTS 5 (conducted from 1995 to 2002) was designed to improve the EFS and OS for patients with CCSK by incorporating cyclophosphamide (at a higher dose than given on NWTS 3) and etoposide in combination with vincristine and doxorubicin (duration of treatment was 6 months) and postoperative radiotherapy ($n=110$; TABLE 1)[20]. Overall, 5-year EFS and OS were 79% and 89%, respectively, similar to outcomes of the NWTS 4 trial[20]. In total, 21 of 110 (19%) patients in the NWTS 5 trial developed a relapse, fewer than in previous studies. Only one of these recurrences occurred in the tumour bed and two relapses occurred elsewhere in the abdomen, indicating that local control was achieved in the majority of patients after radiotherapeutic treatment with a dose of only 10.8 Gy (J.S. Dome, former chair

COG renal tumour study group, personal communication). Retrospective analysis of patients with stage I CCSK (according to NWTS 5 staging criteria)[30] enrolled in NWTS 1–5 trials ($n = 53$) showed 100% EFS and OS at the last follow-up examination (median follow-up duration 17 years, range 2–36 years) despite the use of varying radiotherapy doses and chemotherapy regimens[30]. Treatment of patients with CCSK according to the AREN0321 COG protocol (conducted between 2006 and 2013) consisted of surgery of resectable tumours followed by adjuvant vincristine, cyclophosphamide, doxorubicin, and etoposide for patients with stage I–III disease, whereas stage IV patients were treated using an intensified regimen with additional carboplatin. Patients with local stage II–III disease received postoperative radiotherapy (10.8 Gy; TABLE 1). Based on the excellent survival of patients with stage I CCSK included in NWTS 1–5 protocols, the renal tumour committee of the COG decided to prospectively study the outcome of patients with stage I disease after treatment with surgery and chemotherapy alone, without additional radiotherapy (only if adequate surgical staging with lymph node sampling and central pathology review has been performed)[30]. The AREN0321 study has been closed since November 2013 and will be evaluated shortly.

Other trials

Treatment of patients with CCSK according to the UKW1 trial (conducted between 1980 and 1986) consisted of primary surgery and postoperative treatment with vincristine, actinomycin, doxorubicin, and cyclophosphamide. In addition, radiotherapy (30 Gy) was applied in instances of residual disease after second-look surgery in patients with stage II–IV disease (TABLE 1). The 6-year OS of patients with CCSK in this trial ($n = 14$) was 79% (EFS was not separately reported for CCSK patients). UKW2 (conducted from 1986 to 1991) was designed to improve the outcome of patients with tumours of unfavourable histology, including CCSK ($n = 18$), by intensification of chemotherapy scheduling of vincristine, actinomycin, and doxorubicin and addition of radiotherapy in patients with local stage III disease (30 Gy TABLE 1)[31]. In this trial, 4-year EFS and OS of CCSK patients were 82% and 88%, respectively. Patients with nonmetastatic CCSK ($n = 8$) treated according to the UKW3 protocol (conducted between 1991 and 2001) were randomized among all patients with kidney tumours to either immediate surgery or preoperative chemotherapy (vincristine and actinomycin). Adjuvant treatment was identical to that used in the UKW2 study (TABLE 1). EFS and OS were not separately reported for patients with CCSK (TABLE 1)[24]. After UKW3, the UK Children's Cancer Study Group joined the SIOP 2001 trial but continued to recommend vincristine, actinomycin, and doxorubicin for localized CCSK (TABLE 1). Combined analysis of patients with CCSK treated according to regimens in the UKW2, UKW3, and UK SIOP 2001 trials ($n = 55$) revealed a high local relapse rate (65%) in patients with stage II disease not treated with radiotherapy[32] (K.P.-J., unpublished preliminary UK CCSK data observation).

In the TW-2003 protocol of the Associazione Italiana di Ematologia e Oncologia Pediatrica (AIEOP; conducted between 2003 and 2017), patients with CCSK were treated according to the regimen for high-risk Wilms tumours, consisting of immediate surgery, unless the tumour is considered inoperable, followed by treatment with etoposide, ifosfamide, carboplatin, and doxorubicin (TABLE 1). Radiotherapy (19.8 Gy) was recommended for stage I–III disease. This regimen has resulted in a 5-year EFS of 84% and 5-year OS of 91% ($n = 14$)[33].

The first Japan Wilms Tumour Study Group trial (JWiTs-1; conducted between 1996 and 2005) used similar treatment regimens for CCSK patients to the NWTS 5 trial (vincristine, doxorubicin, cyclophosphamide, etoposide, and postoperative radiotherapy to a dose of 10.8 Gy for all patients, regardless of stage; TABLE 1). In this trial, 5-year EFS and OS were 73% and 75%, respectively ($n = 15$)[34].

The latter trials supported the evidence from SIOP and NWTS–COG studies that have informed the decisions made in the UMBRELLA protocol.

Recommendations in the UMBRELLA protocol

Diagnostics

All patients with renal tumours enrolled in the UMBRELLA protocol will be diagnosed in a standardized way, which simplifies the procedure for clinicians and enables the interpretation of results of a large cohort of patients in a uniform manner. An overview of standard diagnostic investigations during the preoperative and postoperative phase is provided in the UMBRELLA protocol (available at www.siop-rtsg.eu).

Pathology. The morphology of CCSK shows a remarkable diversity, which can result in considerable diagnostic difficulty[2,3]. In the SIOP 93–01 and SIOP 2001 studies, 27% of CCSKs were initially diagnosed as other renal tumours by local pathologists[2]. This misidentification stresses the importance of a rapid and central pathology review of all suspected instances of CCSK by national pathology panels, which work in coordination with the SIOP pathology panel. This procedure has become standard for all patients with renal tumours registered in SIOP studies since SIOP 2001. Central pathology review should be completed within 2 weeks after nephrectomy, which will enable communication of the results of the review back to the institutional team before decisions on postoperative therapy are implemented. Similarly, the COG includes central pathology review in their diagnostic protocol (since the first NWTS trials)[35].

Radiology. The only reported retrospective study that has investigated the radiolographical characteristics of CCSK concluded that no features can reliably distinguish CCSK from other paediatric renal tumours[36,37]. In general, radiological diagnostic work-up of patients diagnosed with CCSK follows the standard work-up for paediatric renal tumours. Once the diagnosis of CCSK is made, brain MRI is advised as a complementary baseline investigation, as observational studies of the

AIEOP, SIOP, and COG renal tumour study groups have identified the brain to be a preferential site for CCSK metastasis, especially in the relapse setting (approximately 40% of relapses are located in the brain)[20,21]. Furthermore, whole-body FDG–PET (sensitivity ± 90%), whole-body MRI (sensitivity ± 82%), or ^{99m}Tc bone scan (sensitivity ± 71%) is recommended as bone is one of the most common metastatic sites at diagnosis (in SIOP 93–01 and SIOP 2001, 69% of metastases at diagnosis occurred in the bone, and in NWTS 5 22% of metastasis at diagnosis occurred in the bone)[2,20,38].

Genetic counselling. No CCSK-related syndromes have been reported; thus, counselling by a clinical geneticist is not routinely recommended in individuals without a family history of multiple cancers at a young age.

Treatment recommendations

The UMBRELLA protocol aims to include chemotherapy regimens that have been shown to be of value for patients with CCSK in order to maintain excellent survival for patients with localized CCSK and to further improve survival if possible. Moreover, the UMBRELLA protocol takes into account that survival is already reasonable for some groups of patients, but at the cost of fairly intensive treatment. Thus, this protocol aims to de-intensify standard therapy selectively to minimize serious short-term and long-term toxicity if feasible.

Many national and international randomized trials and observational studies on renal tumours in which patients with CCSK have been included provide only a very low to moderate level of evidence to direct further improvement using conventional chemotherapy and radiotherapy (TABLE 1). Hence, the recommendations for treatment of CCSK in the UMBRELLA protocol are based on expert opinion of a synthesis of this collated evidence to select treatments associated with the best reported outcomes to date.

General treatment recommendations. The UMBRELLA protocol recommends continuing to treat all patients with renal tumours (including CCSK) between 6 months and 16 years of age with preoperative chemotherapy (vincristine and actinomycin for localized disease and vincristine, actinomycin, and doxorubicin for metastatic disease) based on the demonstrated downstaging effect of preoperative chemotherapy, resulting in treatment reduction[24] (TABLE 2).

The addition of anthracyclines (doxorubicin) to the postoperative treatment regimen of patients diagnosed with CCSK has been shown to result in a significant improvement in outcome (relative risk 0.22 ($P < 0.001$))[3]. Thus, doxorubicin will continue to be part of the treatment of all patients diagnosed with CCSK in the UMBRELLA protocol. Dosing of doxorubicin in the UMBRELLA protocol is mainly based on the recommendations described for CCSK in the previous SIOP 2001 protocol. The only adjustment is a reduction of the cumulative dose from 300 mg/m^2 to 250 mg/m^2 for CCSK patients with stage II or stage III disease with the aim of decreasing cardiotoxicity and toxicity in general, as COG studies have shown that reduced anthracycline doses seem to be sufficient in these patients (the maximum total cumulative doses of doxorubicin included in the UMBRELLA protocol for CCSK are 250 mg/m^2 for localized disease and 300 mg/m^2 for metastatic disease) (TABLE 2).

Moreover, the benefit of including alkylating agents in the treatment of patients diagnosed with CCSK is incorporated in the UMBRELLA protocol[2], to reduce the risk of serious renal toxicity caused by ifosfamide[39–42] as well as the occurrence of second tumours or fertility problems caused by cyclophosphamide[43–45]. Combining the alkylating agents ifosfamide and cyclophosphamide in an alternating setting to reduce the total cumulative dose of either drug was decided by consensus (TABLE 2). Irrespective of disease stage, patients will be treated with postoperative alternating ifosfamide and cyclophosphamide in combination with etoposide, carboplatin, and doxorubicin, including patients with stage I disease, on the basis of the superior survival of patients with stage I disease treated according to the SIOP 93–01 protocol (TABLE 2)[2].

Observational cohort studies have shown that the pattern of relapses is changing, as the most common site

Table 2 | **Overview of therapy according to stage**

Stage	Preoperative chemotherapy[a]	Postoperative chemotherapy	Abdominal radiotherapy
I	AV	Etoposide, carboplatin, ifosfamide alternating with cyclophosphamide, and doxorubicin	No
II	AV	Etoposide, carboplatin, ifosfamide alternating with cyclophosphamide, and doxorubicin	Yes[b]
III	AV	Etoposide, carboplatin, ifosfamide alternating with cyclophosphamide, and doxorubicin	Yes[b]
IV	AVD	Etoposide, carboplatin, ifosfamide alternating with cyclophosphamide, and doxorubicin or vincristine[c]	According to local stage and radiotherapy of metastatic sites[b,d]

AV, actinomycin and vincristine; AVD, actinomycin, vincristine, and doxorubicin; NA, not applicable. [a]If clear cell sarcoma of the kidney has been confirmed by biopsy before the start of preoperative chemotherapy, starting treatment with five drugs (postoperative chemotherapy schedule) is advised instead of standard preoperative chemotherapy; evaluate the possibility of surgery after two cycles of chemotherapy (performing surgery within 6 weeks after the start of chemotherapy is recommended). [b]For detailed radiotherapy recommendations, see the 'Radiotherapeutic Guidelines' chapter of the UMBRELLA protocol. [c]Replace doxorubicin with vincristine after reaching a total cumulative dose of 300 mg/m^2. [d]Abdominal radiotherapy in instances of local stage II–III disease. Radiotherapy to metastases is indicated regardless of response to preoperative chemotherapy or surgical treatment (radiotherapy doses for metastases are described in the UMBRELLA protocol).

of CCSK recurrence is now brain rather than bone[20,21]. This observation suggests that the brain might be a sanctuary that protects tumour cells from the intensive chemotherapy that patients currently receive. For this reason, agents that penetrate the central nervous system, such as ifosfamide and carboplatin, will continue to be included in the treatment regimen[46–49] (TABLE 2).

Radiotherapy seems to be beneficial in the treatment of selected patients diagnosed with CCSK[3,5,32]. Children undergoing abdominal radiotherapy are at an increased risk of developing orthopaedic, renal, metabolic, hepatic, gonadal, and vascular problems in addition to an increased risk of treatment-induced neoplasms[50–52]. The new UMBRELLA protocol has implemented the local radiotherapy dose of 10.8 Gy used by the COG following the efficacy of the low-dose radiotherapy (10.8 Gy) used in the NWTS 4, NWTS 5, and AREN0321 trials[20] (TABLES 1,2). A stopping rule has been defined for early detection of unexpectedly high local relapse rates. Quantitative limits set for the stopping rule for patients with CCSK treated with the new radiotherapy dose, designed by the SIOP–RTSG statistician (H.v.T.), are described in detail in the UMBRELLA protocol (available at www.siop-rtsg.eu). In line with previous SIOP 93–01 and SIOP 2001 protocols and the current COG protocol, patients with local stage II–III CCSK should receive postoperative abdominal radiotherapy; treatment with radiotherapy is not indicated for patients with stage I disease (TABLES 1,2).

Treatment recommendations for metastatic disease. For patients with haematogenous or lymph node metastases outside the abdominal–pelvic region (stage IV disease) still present after treatment with preoperative chemotherapy (three drugs), metastasectomy is advised whenever surgery can be performed without mutilation or loss of vital organs. Regardless of response to preoperative chemotherapy or surgical treatment, radiotherapy to metastatic sites is indicated in patients with stage IV CCSK (TABLE 2). Based on extrapolating the results of prospective and review studies on adults and expert opinion, the use of highly conformal techniques can be considered in patients with metastatic CCSK, especially in instances of solitary metastasis or oligometastases, depending on the anatomical site[53,54]. Postoperative treatment is consistent with previous SIOP 93–01 and SIOP 2001 protocols, with the specific outlined differences, and consists of the five chemotherapeutic agents used for localized disease and abdominal radiotherapy (dose 10.8 Gy as in COG) for local stage II or III disease (TABLES 1,2). To limit cardiotoxicity and toxicity in general, doxorubicin will be replaced by vincristine after exceeding the maximum cumulative dose of 300 mg/m^2, which is similar to what was recommended in the previous SIOP 2001 protocol[20]. The benefit of high-dose chemotherapy for metastatic CCSK patients has not been reported to date.

Treatment recommendations for relapsed disease. A descriptive cohort study of SIOP–RTSG and AIEOP trials including 37 patients in total, the largest cohort of patients with CCSK who experienced relapse described to date, reported that outcome after relapse is poor (5-year EFS 18%, 5-year OS 26%)[21]. Results of the analysis of the SIOP–RTSG and SIOP–AIEOP studies ($n = 37$) and a descriptive study by Radulescu *et al.*[53] ($n = 8$) indicate that intensive treatment, including chemotherapy as well as achieving local control by surgery and/or radiotherapy, seems to increase survival of patients with relapsed CCSK[21,55]. However, statistical evidence is lacking, owing to the small number of patients included in these studies. Furthermore, treatment with high-dose chemotherapy (extremely high, potentially toxic doses of chemotherapy) followed by autologous stem cell transplantation (HD-ASCT) to consolidate the second complete remission seems to be of value[21,55]. In total, the outcomes of 24 patients with CCSK who experienced relapse and received HD-ASCT have been reported in the literature, of whom 50% were alive without disease after a median follow-up duration of 52 months, whereas the average 5-year OS of patients with relapsed CCSK is about 26%[21,55–58]. Importantly, this HD-ASCT treatment was mostly given to a selected group of patients with relapsed disease who already achieved second complete remission; thus, the positive effect of HD-ASCT might (in part) be attributable to this selection of patients. Furthermore, the risk of HD-ASCT-related toxicity needs to be weighed against the risk of disease-related mortality. Providing a recommendation regarding the best high-dose chemotherapy schedule for relapsed patients with CCSK is not possible owing to the small number of patients treated in this manner and the many drug combinations used. To enable evaluation of treatment, the high-dose treatment schedule in the UMBRELLA protocol has been defined as melphalan (200 mg/m^2 total dose over 1 hour) by consensus, which is similar to the high-dose regimen recommended for relapsed Wilms tumour in the UMBRELLA protocol. Melphalan was the most commonly used high-dose agent in the SIOP–AIEOP relapsed CCSK study; eight patients were treated with high-dose melphalan, of whom four patients were alive without disease and four patients died of disease after a median follow-up time of 29 months[21]. Moreover, high-dose melphalan has previously been successfully used in the treatment of other recurrent paediatric solid tumours, such as neuroblastoma[59,60].

For other sarcomas and solid tumours in children (for example, Ewing sarcoma and Wilms tumour), next-generation chemotherapeutic agents such as irinotecan, temozolomide, temsirolimus, topotecan, gemcitabine, and docetaxel are currently being studied in phase I and II trials; retrospective cohort studies show that these drugs seem to be active and well tolerated in children with recurrent, metastatic, or refractory disease[61–70]. Whether these drugs are of any value for CCSK is not currently known.

Follow-up monitoring

To date, no studies have been performed on the surveillance of patients with CCSK after finishing treatment; thus, follow-up monitoring will be performed as conducted in SIOP 2001 (Supplementary Table 1).

Cohort studies and case reports have shown that relapses in patients with CCSK can occur fairly late (relapses up to 8 years after initial diagnosis have been reported); thus, vigilance even after 5 years of follow-up duration is important[21,71]. Awareness of relapses in the brain is required, and a neurological examination should be part of the physical examination during follow-up monitoring owing to the fairly high rate of relapses in the brain in patients with CCSK reported in the SIOP–AIEOP and NWTS cohort studies[20,21]. Moreover, brain MRI is advised if any suspicion of a cerebral relapse exists and if a relapse is detected at another site. The SIOP–AIEOP cohort study and NWTS studies also reported bone to be a common site of relapse; thus, whole-body MRI, bone scan, or FDG–PET scan[38] is advised in addition to standard follow-up examinations if bone relapse is suspected and for patients with a relapse detected elsewhere[3,21].

The follow-up recommendation includes screening for early (within 5 years after diagnosis) and late (>5 years after diagnosis or initial treatment) toxicity after intensive chemotherapy, including sampling urine (using a dipstick test), sampling blood (full blood count, urea, creatinine, cystatin C, calcium, phosphate, magnesium, albumin, aspartate aminotransferase, alanine aminotransferase, bilirubin, and blood gas), echocardiography (after anthracyclines), and audiometry (after carboplatin), on the basis of recommendations in national and sometimes international guidelines (for example, the recommendations for cardiomyopathy surveillance for survivors of childhood cancer[72]) and consensus within the SIOP–RTSG.

Future perspectives

Future studies need to include the effect of highly conformal radiotherapy and type of postoperative chemotherapeutic treatment on survival and toxicity, preferably in international or worldwide randomized controlled trials. The limited number of patients in current trial settings hampers the design of such studies, especially in instances of relapsed disease. Furthermore, development of targeted therapies, based on specific molecular aberrations of CCSK, is desirable for this group of patients. Potential targets for new treatments for CCSK patients might be *BCOR* ITDs (identified in about 80–90% of CCSKs), hypermethylation of *TCF21* (identified in about 80–90% of CCSKs) or the *YWHAE–NUTM2* fusion gene (identified in 5–10% of CCSKs)[9,13,14]. Finally, immunotherapy might be a therapeutic option for patients with CCSK in the future[73].

Conclusions

To improve survival and reduce short-term and long-term toxicity of treatment for children diagnosed with CCSK, an updated best-available treatment protocol (including diagnostic work-up and follow-up schedule) has been developed within the framework of the UMBRELLA protocol. The combination of the alkylating agents ifosfamide and cyclophosphamide in an alternating pattern and the reduction of radiotherapy dose from 25.2 to 10.8 Gy (as in COG) to limit serious toxicity are hallmarks of this best-available treatment regimen, which is based on expert consensus.

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Author contributions

S.L.G. researched data for the manuscript. S.L.G. and M.M.v.d.H.-E. wrote the article. S.L.G., N.G., R.F., F.S., C.B., G.L.R.-V., J.G., C.R., G.O.J., G.M.V., I.L., A.C.-L.'H., A.M.S., B.d.C., S.S., H.v.T., K.P.-J. and M.M.v.d.H.-E. made substantial contributions to discussions of content. N.G., R.F., F.S., C.B., G.L.R.-V., J.G., C.R., G.O.J., G.M.V., I.L., A.C.-L.'H., A.M.S., B.d.C., S.S., H.v.T., K.P.-J. and M.M.v.d.H.-E. reviewed and edited the manuscript before submission

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