Received: 27 September 2020 | Revised: 21 November 2020 | Accepted: 5 December 2020

DOI: 10.1002/pbc.28860

Pediatric Blood & Cancer | SIOP International Society of Paediatric Oncology | aspho The American Society of Pediatric Hematology/Oncology | WILEY

ONCOLOGY: RESEARCH ARTICLE

Clear cell sarcoma of the kidney in Austrian children: Long-term survival after relapse

Waltraud Friesenbichler[1] | Roswitha Lüftinger[1] | Gabriele Kropshofer[2] | Martin Henkel[3] | Gabriele Amann[4] | Rhoikos Furtwängler[5] | Norbert Graf[5] | Leo Kager[1,6]

[1] Department of Paediatric Haematology and Oncology, St. Anna Children's Hospital, Medical University, Vienna, Austria

[2] Department of Paediatrics, University Hospital Innsbruck, Innsbruck, Austria

[3] Department of Paediatrics, Hospital of Barmherzige Schwestern Linz, Linz, Austria

[4] Institute of Pathology, Medical University of Vienna, Vienna, Austria

[5] Department of Paediatrics, University Hospital Homburg/Saar, Homburg, Germany

[6] Children's Cancer Research Institute, Vienna, Austria

Correspondence
Waltraud Friesenbichler, Department of Paediatric Haematology and Oncology, St. Anna Children's Hospital, Kinderspitalgasse 6, 1090 Vienna, Austria.
Email: w.friesenbichler@stanna.at

Abstract

Introduction: Clear cell sarcoma of the kidney (CCSK) is a rare malignant childhood renal tumour. Recently, the central nervous system (CNS) was found to be the most frequent site of relapse associated with a poor outcome. Optimal treatment strategies are scarce.

Patients and Methods: Retrospective data analysis of all Austrian children with CCSK. They were enrolled in the Austrian-Hungarian Wilms Tumour Study (AHWTS) 1989, the SIOP93-01 or the SIOP2001 study between 1990 and 2019. Demographic, diagnostic, treatment-related variables and survival data were analysed.

Results: We identified 12 children with CCSK (M = 7, F = 5; median age 1.6 years). All had localised disease (stage I: 2; stage II: 2; stage III: 8) at diagnosis, and a first complete remission (CR1) was achieved in 12/12. Six patients are in an ongoing CR1 (median follow-up 10 years). Six other patients had a relapse (local 1; brain 5) a median time of 2.4 years from diagnosis. Two patients died of the disease 4 months and 2.8 years after first relapse. Four of five patients with CNS relapse are in CR2 with a median follow-up time of 9.3 years after relapse diagnosis. Relapse treatment included a combination of chemotherapy, radiation and surgery. Two children received high-dose chemotherapy followed by autologous stem cell rescue, and one child received intrathecal mafosphamide. Long-term side effects after treatment were impaired tubular renal function (n = 4), cardiomyopathy (n = 1) and growth disorders (n = 1).

Conclusions: In this series, the brain was the most common site of relapse. Long-term survival after recurrence was achievable with intensive multimodal therapy.

KEYWORDS
central nervous system metastases, clear cell sarcoma of the kidney, relapse treatment, renal tumour

1 | INTRODUCTION

Clear cell sarcoma of the kidney (CCSK) accounts for approximately 2-5% of all childhood renal tumours. Although it is a rare entity, it is the second most common type of renal malignancy in children. The incidence rate is highest between the ages of 2 and 4 years, and the

Abbreviations: AHWTS, Austrian-Hungarian Wilms Tumour Study; AV, actinomycin-D and vincristine; AVD, actinomycin-D, vincristine and doxorubicin; CCSK, clear cell sarcoma of the kidney; CE, carboplatin and etoposide; CNS, central nervous system; CR1, first complete remission; CR2, second complete remission; CT, computed tomography; ECID, etoposide, carboplatin, ifosfamide and doxorubicin; EFS, event-free survival; ICE, ifosfamide, carboplatin and etoposide; MRI, magnetic resonance imaging; OS, overall survival; SIOP, International Society of Paediatric Oncology

male-to-female ratio is approximately 2:1.[1,2] First described in the 1970s, its initial name was 'bone metastasizing tumour of the kidney', reflecting its predilection for skeletal metastases.[3–5]

Clinical features are nonspecific and closely resemble those of a Wilms tumour, such as abdominal mass, abdominal pain, haematuria or high blood pressure. Most patients present with localised disease, only 6-7% of patients have primary metastases, mainly in lymph nodes, bones, lungs and liver.[6]

CCSKs are treated with a multimodal therapy, including chemotherapy, surgery and radiation therapy where indicated. The originally poor prognosis was improved significantly by intensifying treatment with anthracyclines and alkylating agents. Currently, overall survival (OS) is reported to be approximately 85%.[6,7] However, the outcome after relapse remains poor with 5-year OS rates of approximately 26%.[8] After treatment intensification, the pattern of relapses changed, and they now tend to occur earlier. However, late relapses may occur up to 10 years after diagnosis, still significantly later than in Wilms tumours. Most remarkably, the brain has now overtaken bone as the most common site of relapse.[2,6–8]

Herein we report on the results of Austrian children who have been treated for CCSK over the last 30 years, with a special focus on treatment of central nervour system (CNS) relapse.

2 | PATIENTS AND METHODS

2.1 | Patient population

This retrospective data analyses included all patients with CCSK who were enrolled in the Austrian-Hungarian Wilms Tumour Study (AHWTS) 1989, the International Society of Paediatric Oncology (SIOP)93-01 Study and the SIOP2001 Study. The local ethics committee reviewed and approved the study protocols.

2.2 | Diagnosis

All eligible patients were previously untreated. Diagnostic workup included abdominal sonography and computed tomography (CT) or magnetic resonance imaging (MRI) with/without contrast enhancement. To exclude or confirm pulmonary metastasis chest X-rays at least were performed. In the AHWTS study, routine lung CT was recommended. In the other two studies, a scan was only performed if pulmonary lesions were suspected.

2.3 | Treatment

2.3.1 | Preoperative therapy

According to the treatment schedule for localised unilateral kidney tumours without visible distant metastases (stages I-III), all but one patient received 4-week preoperative chemotherapy with actinomycin-D and vincristine (AV). The cumulative doses were the same in all studies.[7,9]

2.3.2 | Surgery and histological classification

Approximately 1 week after the last preoperative chemotherapy, all patients underwent a tumour nephrectomy. One patient had primary surgery. Staging was done according to the Revised SIOP working classification of renal tumours in childhood (retrospectively for the AHWTS study).[9–11]

2.3.3 | Postoperative therapy

Adjuvant chemotherapy was given according to the respective high-risk protocols. In AHWTS89, all patients with stages I-III received a five-drug regimen including vincristine, actinomycin-D, adriamycin, ifosfamide and etoposide for 47 weeks (cumulative doses stages I-III: vincristine 24 mg/mš, actinomycin-D 600 μg/mš, adriamycin 360 mg/mš, ifosfamide 48 g/mš and etoposide 3600 mg/mš). In the SIOP93-01 trial, all patients received a four-drug regimen of etoposide, carboplatin, ifosfamide and doxorubicin (ECID) for 34 weeks (cumulative doses for stages I-III: etoposide 3000 mg/mš, carboplatin 3600 mg/mš, ifosfamide 36 g/mš and doxorubicin 300 mg/mš). In SIOP2001, patients with local stage I disease had a three-drug regimen consisting of actinomycin-D, vincristine and doxorubicin (AVD) for 28 weeks, while patients with local stages II or III received a comparable four-drug regimen as in protocol SIOP93-01. Instead of ifosfamide, cyclophosphamide was administered, and the dose of carboplatin was divided into three single doses and given on consecutive days. The cumulative dose of doxorubicin was 250 mg/mš for stage I and 300 mg/mš for stages II and III, the cumulative dose of cyclophosphamide was 8100 mg/mš.

All trials included additional irradiation to the flank for local stages II and III (AHWTS89: 14.4 Gy; SIOP93-01: 30-35 Gy; and SIOP2001: 25.2-36 Gy).[6,7,9]

3 | RESULTS

Between 1990 and 2019, 12 patients with CCSK were registered in Austria (AHWTS89, n = 1; SIOP93-01, n = 5; and SIOP2001, n = 6). Seven patients were male and five female, their ages ranged from 12 months to 6.9 years (median 1.6 years) at the time of the initial diagnosis. Nine patients presented with an abdominal mass, three patients additionally suffered from haematuria, one showed elevated blood pressure and two patients had abdominal pain. The diagnostic workup revealed eight patients with right-sided tumours and four with left-sided tumours. All patients had localised disease (Table 1).

3.1 | Initial diagnosis

In accordance with the SIOP guidelines for childhood kidney tumours, all but one patient received preoperative chemotherapy. In a particular

TABLE 1 Clinical features, first-line treatment and outcome of Austrian patients with CCSK

Patient	Age (y)	Sex	Site	Signs/ symptoms	Protocol	Local stage	Preop. therapy	Surgery	Postop. therapy	Radiation (boost), Gy	Relapse	Outcome	Follow-up from diagnosis (y)
1	1.4	F	Right	Abd mass	AHWTS89	III	AV	Yes	HR-AVDIE	14.0	CNS	DOD	2.2
2	5.5	M	Right	Pain; haem	SIOP2001	III	AV	Yes	HR-ECCD	27.0		CR1	12.7
3	1.0	F	Right	Haem	SIOP2001	II	AV	Yes	HR-ECCD	25.5		CR1	16.8
4	1.0	F	Left	Abd mass	SIOP93-01	III	AV	Yes	HR-ECID	12.0 (18.0)	CNS	CR2	17.0
5	1.6	M	Right	Abd mass	SIOP93-01	III	AV	Yes	HR-ECID	19.5 (10.5)		CR1	14.1
6	3.7	M	Left	Abd mass; haem	SIOP93-01	I	AV	Yes	HR-ECID	No		CR1	11.2
7	6.9	M	Right	Pain	SIOP93-01	III	None	Yes	HR-ECID	20.4, 12 (lung)	Local	DOD	6.0
8	1.0	M	Right	Abd mass	SIOP93-01	III	AV	Yes	HR-ECID	30.0	CNS	CR2	21.5
9	1.7	F	Right	Abd mass	SIOP2001	III	AV	Yes	HR-ECCD	25.5		CR1	8.7
10	1.5	M	Left	Abd mass; hyp	SIOP2001	III	AV	Yes	HR-ECCD	25.2	CNS	CR2	6.6
11	1.2	F	Left	Abd mass	SIOP2001	II	AV	Yes	HR-ECCD	10.8	CNS	CR2	2.8
12	2.3	M	Right	Abd mass	SIOP2001	I	AV	Yes	HR-ECID	No		CR1	1.6

Abbrevations: Abd mass, abdominal mass; AHWTS, Austrian Hungarian Wilms Tumour Study; AV, actinomycin-D/vincristine; AVDIE, adriamycin/vincristine/actinomycin-D/ifosfamide/etoposide; CCSK, clear cell sarcoma of the kidney; CNS, central nervous system; DOD, died of disease; ECCD, etoposide/cyclophosphamide/carboplatin/doxorubicin; ECID, etoposide/carboplatin/ifosfamide/doxorubicin; haem, haematuria; HR, high risk; hyp, hyertension; Preop., preoperative; SIOP, International Society of Paediatric Oncology; y, year(s).

patient (Pat No. 7), neither imaging nor a fine needle biopsy could provide an unambiguous diagnosis. This patient therefore underwent primary surgery. All other patients had radical tumour nephrectomy after 4 weeks of VA. Histology revealed eight children to have local stage III, two had local stage II and two had local stage I (Table 1). Of the stage III patients, five had lymph node involvement, one patient had local spread to the mesocolon (Pat No. 8) and one patient had positive resection margins (Pat No. 9). In the single case of upfront surgery (Pat No. 7), the tumour infiltrated the diaphragm and intraoperative tumour rupture occurred.

Postoperatively, all patients were assigned to the high-risk treatment arm of the respective treatment protocols and received an anthracycline and alkylating agent-based chemotherapy (Table 1). One patient received only four of six anthracycline doses (Pat No. 5) due to cardiac dysfunction. Apart from this, no serious acute chemotherapy-related side effects occurred, and the chemotherapy was given as scheduled.

All stages II and III patients received flank irradiation involving the area of lymph node metastases (median dose 25.5 Gy, range 10.8-30.0) (Table 1). In the patient with diaphragmatic infiltration and tumour rupture (Pat No. 7), the entire abdomen (20.4 Gy) and lungs (12 Gy) were irradiated.

After a median follow-up of 10 years (range 1.7-21.5), six of 12 patients are in an ongoing first complete remission (CR1). The 5-year event-free survival (EFS) was 45% ± 0.15% (95% CI, 0.17-0.71) and 5-year OS 90% ± 0.09% (95% CI, 0.47-0.99). Chemotherapy-related long-term side effects were observed in two of six patients in CR1, one suffering from impaired renal function (Pat No. 5) and one from cardiomyopathy (Pat No. 9).

3.2 | Relapse

In six patients, the tumour relapsed. The median time from initial diagnosis to relapse was 2.4 years (range 1.6-4.1). The median age at the time of relapse was 3.7 years (range 2.8-10.1). Five of six relapses occurred in the CNS, three patients had a single metastasis in the cerebellum (Pat No. 4, 8, 10), two had multiple infra- and supratentorial lesions (Pat No. 1, 11). The patient with intraoperative tumour rupture (Pat No. 7) suffered a local recurrence within the irradiation field 3 years after primary disease. All but one patient had local stage III disease at initial diagnosis, and one had local stage II (Tables 1 and 2).

Of the six patients with relapse, three received front-line therapy according to SIOP93-01 study and two were treated according to SIOP2001 protocol. The only patient treated in the AHWTS89 study also relapsed (Table 2). None of the patients had dose reductions during first-line treatment, and all patients received local radiotherapy.

In total, five of six patients achieved a second CR (CR2) after the relapse therapy. Four of six are in an ongoing CR2 with a median follow-up time of 9.3 years (range 1.3-17.4). Two patients died 4 months (Pat No. 1) and 2.8 years (Pat No. 7) after relapse diagnosis (Table 1). Due to high doses of alkylating agents, three of five patients (Pat No. 4, 8, 10) in CR2 suffer from impaired tubular renal function with preserved glomerular filtration rate.

TABLE 2 Clinical features, treatment and outcome of patients with CNS relapse

Patient	First-line treatment	Time to relapse from initial diagnosis (y)	Site/solitary or multiple	Relapse treatment				Outcome	Follow-up after relapse diagnosis(y)
				CHT	Surgery	Radiation (Gy)	HD-CHT + ASCT		
1	AHWTS89	1.8	Supra- and infratento-rial/multiple	No	No	No	No	DOD	0.4
4	SIOP93-01	2.6	Cerebellum, solitary	CE ×6	Yes (in toto)	30.0 (focal)	No	CR2	14.4
8	SIOP93-01	4.1	Cerebellum, solitary	ICE ×2; M ith ×4	Yes (in toto)	30.6 (focal)	Yes (CET)	CR2	17.4
10	SIOP2001	2.2	Cerebellum, solitary	ICE ×4; CE ×2	Yes (in toto)	25.0 (focal)	No	CR2	4.3
11	SIOP2001	1.6	Supra- and infratento-rial/multiple	ICE ×4; CE ×2	Yes	19.8 (whole brain + spinal axis)	Yes (Mel)	CR2	1.3

Abbrevations: AHWTS, Austrian Hungarian Wilms Tumour Study; CE, carboplatin/etoposide; CET, carboplatin/etoposide/thiotepa; CHT, chemotherapy; CR2, second complete remission; DOD, died of disease; F, female; HD-CHT + ASCT, high-dose chemotherapy followed by autologous stem cell transplantation; ICE, ifosfamide/carboplatin/etoposide; M, male; Mel, melphalan; M ith, mafosphamide intrathekal; SIOP, International Society of Paediatric Oncology; y, year(s).

As there were no uniform treatment guidelines for recurrences, different treatment approaches were applied. The patient (Pat No. 1) who was treated according to the AHWTS89 study, suffered an early CNS relapse with multiple supra- and infratentorial lesions that were not amenable for surgical resection. Palliative care was initiated, and the patient died 4 months after relapse diagnosis. The remaining four patients with CNS relapse (Pat No. 4, 8, 10, 11) all underwent upfront CNS surgery. In all patients with singular cerebellar metastasis (Pat No. 4, 8, 10), a macroscopically total resection was achieved. In the patient with multiple cerebral lesions (Pat No. 11), four were completely resected and two suspicious cerebellar lesions disappeared under chemotherapy. All patients with singular cerebellar metastasis had local cranial irradiation with cumulative doses of 25.0-30.6 Gy. The patient with multiple cerebral lesions (Pat No. 11) received irradiation of the spinal axis with a total dose of 19.8 Gy in addition to whole-brain irradiation. One patient (Pat No. 8) received additional intrathecal therapy with mafosphamide (Table 2). Postoperative chemotherapy consisted of ifosfamide, carboplatin, etoposide (ICE) and/or carboplatin, etoposide (CE). Two patients (Pat No. 8, 11) received high-dose chemotherapy (one with carboplatin, etoposide, thiotepa and one with melphalan) followed by autologous stem cell rescue (Table 2).

The patient (Pat No. 7) who presented with a local recurrence had a total of four abdominal relapses. Surgical resection was performed three times (first (again with minor spillage), second and third relapse). He received chemotherapy with four CE and two topotecan cycles (first relapse), five ICE cycles (third relapse) and two irinotecan, carboplatin, one topotecan, cyclophosphamide cycle and vinblastine (fourth relapse), and was locally irradiated with a cumulative dose of 20.8 Gy during his third relapse. He died of the disease 2.8 years after relapse diagnosis.

4 | DISCUSSION

This report provides a retrospective overview of paediatric patients treated for CCSK in Austria over a period of 30 years with a median follow-up time of 10 years (up to 21.5 years) after primary diagnosis and 9.3 years (up to 17.4 years) after relapse diagnosis. Since CCSK is an ultra-orphan childhood malignancy, the number of patients included in this analysis is limited and allows only a descriptive presentation of the data.

All our patients initially received an intensive chemotherapy regimen combined with surgery and, in the case of local stages II or III, additionally local radiotherapy. With more intensive adjuvant therapies, including anthracyclines, alkylating agents, topoisomerase II inhibitors and platinum compounds, EFS and OS rates in patients with CCSK have improved dramatically in recent decades.[1,2,7,12] The intensified chemotherapy regimens also influenced the clinical course of the disease, with relapses occurring now earlier and the brain becoming the most frequent site of relapse.[13] Our data confirm these observations and provide evidence that long-term survival after CNS relapse is achievable with an intensive multimodal therapy approach. In our cohort, six of 12 patients relapsed, five of which occurred in the brain. The time to relapse was relatively late, ranging from 1.6 to 4.1 years from initial diagnosis. Four of five patients with CNS relapse are in an ongoing stable CR2 after a median follow-up time of 9.3 years from relapse diagnosis. In fact, this is a surprisingly good result at a relevant follow-up time, and therefore deserves attention. In addition, the only deceased patient was diagnosed as early as 1992 and received palliative care only.

In the largest published series of Gooskens et al, 13 of 37 relapses occurred in the brain, and after a median follow-up time of 58 months,

three patients were alive without (including 2/4 of our survivors) and one with evidence of disease.[8] Though in this series, two patients died from cerebral haemorrhage at diagnosis, these results were suggestive of dismal outcome of CNS relapse in patients suffering from CCSK. However, already in 2008 Radulescu et al had described eight patients with recurrent CCSK involving the brain, six of them were in an ongoing CR2 after a median follow-up time of 30 months.[14] Our results are in line with this report, supporting a curative treatment approach with eventually encouraging outcome in these patients.

There are only few therapy recommendations available, and an optimal treatment strategy has not yet been determined.[1,14] Comparing the treatment modalities of surviving patients after CNS recurrence, some similarities can be found. Taking the two cited studies by Radulescu and Gooskens as well as the results of our cohort, eight of the 12 surviving patients with CNS relapse (Radulescu et al: 6 survivors; Gooskens et al: 2 survivors; our cohort: 4 survivors) achieved complete surgical remission. Although oligo-metastasised cases account for the majority of survivors, it is important that in the above-mentioned series, patients with multiple-site relapses achieved sustained CR2. Also in these cases, a combination of surgery and radiotherapy was used for local control. Sufficient local control thus appears to be a cornerstone of relapse management in patients with CNS recurrences.

All 12 surviving patients had whole (10.8-30 Gy) or partial brain irradiation with or without boost (up to 55 Gy), though the optimal dose has not yet been defined (Radulescu et al: range 30.6-55 Gy; Gooskens et al: range 12-32 Gy; our cohort: range 19.8-30.6 Gy). However, good local control for macroscopically completely resected CCSK can be achieved with 10.8 Gy.[6] Considering the specific surgical situation of CNS, a focal boost to the former tumour region seems reasonable and has been applied in the majority of the above-mentioned cases.

Due to the evident sensitivity to alkylating agents, particularly in combination with topoisomerase II inhibitors and platinum compounds, the most frequently used chemotherapeutic agents were ifosfamide, carboplatin and etoposide, combined as ICE or CE cycles. The topoisomerase II inhibitor etoposide and the platinum compound carboplatin were already used in the SIOP93-01 study in the adjuvant first-line treatment of stage I CCSK. The combination of four drugs (etoposide, carboplatin, ifosfamide, doxorubicin) resulted in better outcomes than the combination of three drugs (actinomycin-D, vincristine, doxorubicin) used in the SIOP2001 study.[7] To overcome the reduced drug levels caused by the blood-brain barrier, ifosfamide was also reintroduced into first-line treatment by SIOP-Renal Tumour Study Group (RTSG).[6] The role of high-dose chemotherapy is difficult to evaluate. In our cohort, two of four survivors after CNS relapse received high-dose chemotherapy followed by autologous stem cell rescue. In Radulescus series three of six survivors and in Gooskens' series one survivor being treated for a second relapse at the time of publication had high-dose chemotherapy. Additionally, Yumura-Yagi and colleagues published a case of relapsed CCSK in the brain, rescuing the child with tandem high-dose chemotherapy.[15] Overall, only half of the survivors were treated with high-dose chemotherapy. One of our patients received intrathecal mafosphamide, its benefit remains unclear, but it might be discussed in multilocular cerebral metastasis.

Aggressive anticancer therapy in children is associated with a high risk of chemotherapy-related long-term sequelae. Anthracyclines carry the lifelong risk of cardio-toxicity.[16,17] Renal dysfunction, infertility and an increased risk of secondary malignant neoplasms are associated with the use of alkylating agents such as ifosfamide. Radiation therapy further increases the risk of secondary malignancies.[18] In our series, follow-up examinations revealed one patient with cardiomyopathy, four patients with impaired renal function and one with hypogonadism and growth retardation (after cranial radiotherapy).

Major limitations of this report include the retrospective nature of the investigation and the small number of patients analysed. Furthermore, oligo-metastatic presentation at relapse made radical local control measures possible in all patients. Three of five patients had only a solitary metastasis in the cerebellum, allowing for a successful gross total resection combined with local radiotherapy. Even in the patient with multiple CNS metastases (Pat No. 11), surgical resection and local radiotherapy were feasible for all radiologically confirmed metastases.

Conclusions on maintained second remission in CCSK can be limited by its well-known propensity for late relapses. However, with the exception of the latter patient (Pat No. 11), who is now 1.3 years after relapse diagnosis, the extended median follow-up of 9.3 years is reassuring in our cohort.

Hence, we provide evidence that long-term survival is possible in patients with a CNS relapse of CCSK. A prerequisite is sufficient local tumour control, which is achieved by a combination of surgery and radiotherapy, as well as the administration of an intensive multiagent chemotherapy regimen. Further intensification of systemic therapy is not possible, taking into account the potential acute and long-term side effects. Therefore, alternative therapeutic strategies will be in demand in the future.

5 | CONCLUSIONS

Relapses of CCSK often occur in the CNS. To diagnose CNS recurrences at an early stage, regular cranial MRI controls directly after definitive histological diagnosis and during follow-up period are indicated to prevent irreversible CNS damage in a potentially curable relapse. By combining intensive chemotherapy, surgery and radiotherapy, a long-term cure is possible even in the case of relapse. The optimal treatment strategy and thus uniform treatment guidelines for recurrent CCSK are pending.

AUTHOR CONTRIBUTIONS

All the authors designed and planned the paper, and read and approved the final version of the manuscript.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ACKNOWLEDGEMENT

Many thanks to our colleague and native-English speaker Miriam Pajpach for proofreading the manuscript.

ORCID

Waltraud Friesenbichler https://orcid.org/0000-0001-9275-5109
Rhoikos Furtwängler https://orcid.org/0000-0002-1967-8343

REFERENCES

1. Gooskens SL, Furtwängler R, Vujanic GM, Dome JS, Graf N, van den Heuvel-Eibrink MM. Clear cell sarcoma of the kidney: a review. *Eur J Cancer*. 2012;48(14):2219-2226.
2. Argani P, Perlman EJ, Breslow NE, et al. Clear cell sarcoma of the kidney: a review of 351 cases from the National Wilms Tumour Study Group Pathology Center. *Am J Surg Pathol*. 2000;24(1):4-18.
3. Beckwith JB, Palmer NF. Histopathology and prognosis of Wilms tumours: results from the First National Wilms' Tumour Study. *Cancer*. 1978;41(5):1937-1948.
4. Morgan E, Kidd JM. Undifferentiated sarcoma of the kidney: a tumour of childhood with histopathologic and clinical characteristics distinct from Wilms' tumour. *Cancer*. 1978;42(4):1916-1921.
5. Marsden HB, Lawler W, Kumar PM. Bone metastasizing renal tumour of childhood: morphological and clinical features, and differences from Wilms' tumour. *Cancer*. 1978;42(4):1922-1928.
6. Gooskens SL, Graf N, Furtwängler R, et al. Position paper: rationale for the treatment of children with CCSK in the UMBRELLA SIOP-RTSG 2016 protocol. *Nat Rev Urol*. 2018;15(5):309-319.
7. Furtwängler R, Gooskens SL, van Tinteren H, et al. Clear cell sarcomas of the kidney registered on International Society of Pediatric Oncology (SIOP) 93-01 and SIOP 2001 protocols: a report of the SIOP Renal Tumour Study Group. *Eur J Cancer*. 2013;49(16):3497-3506.
8. Gooskens SL, Furtwängler R, Spreafico F, et al. Treatment and outcome of patients with relapsed clear cell sarcoma of the kidney: a combined SIOP and AIEOP study. *Br J Cancer*. 2014;111(2):227-233.
9. Zimmermann C, Pötschger U, Amann G, et al. Results of children with renal tumours treated in the Austrian-Hungarian Wilms tumour Study 1989 and the International Society of Pediatric Oncology (SIOP) 93-01/GPOH trial in Austria. *Memo*. 2012;5:289-295.
10. Delemarre JF, Sandstedt B, Harms D, Boccon-Gibod L, Vujanić GM. The new SIOP (Stockholm) working classification of renal tumours of childhood. *Med Pediatr Oncol*. 1996;26(2):145-146.
11. Vujanić GM, Sandstedt B, Harms D, et al. Revised International Society of Paediatric Oncology (SIOP) working classification of renal tumours of childhood. *Med Pediatr Oncol*. 2002;38(2):79-82.
12. Seibel NL, Li S, Breslow NE, et al. Effect of duration of treatment on treatment outcome for patients with clear-cell sarcoma of the kidney: a report from the National Wilms' Tumour Study Group. *J Clin Oncol*. 2004;22(3):468-473.
13. Aldera AP, Pillay K. Clear cell sarcoma of the kidney. *Arch Pathol Lab Med*. 2020;144(1):119-123.
14. Radulescu VC, Gerrard M, Moertel C, et al. Treatment of recurrent clear cell sarcoma of the kidney with brain metastasis. *Pediatr Blood Cancer*. 2008;50(2):246-249.
15. Yumura-Yagi K, Inoue M, Wakabayashi R, et al. Successful double autografts for patients with relapsed clear cell sarcoma of the kidney. *Bone Marrow Transplant*. 1998;22(4):381-383.
16. Sadurska E. Current views on anthracycline cardiotoxicity in childhood cancer survivors. *Pediatr Cardiol*. 2015;36(6):1112-1119.
17. Robison LL, Melissa M. Hudson survivors of childhood/adolescent cancer: life-long risks and responsibilities. *Nat Rev Cancer*. 2014;14(1):61-70.
18. Lee JS, DuBois SG, Coccia PF, Bleyer A, Olin RL, Goldsby RE. Increased risk of second malignant neoplasms in adolescents and young adults with cancer. *Cancer*. 2016;122(1):116-123.

How to cite this article: Friesenbichler W, Lüftinger R, Kropshofer G, et al. Clear cell sarcoma of the kidney in Austrian children: Long-term survival after relapse. *Pediatr Blood Cancer*. 2021;68:e28860. https://doi.org/10.1002/pbc.28860