Introduction
Sarcoma is a type of cancer that occurs in connective tissue (such as tendons), supportive tissue (such as bones), and soft tissue (such as muscle). Only about 1% of adults with cancer suffer from sarcoma, but 15% of children with cancer suffer from sarcoma. About one-quarter of children with sarcomas have a wide variety of soft tissue sarcomas, most of which are more commonly diagnosed in adults.

Due to the diversity of sarcoma types, they can be particularly challenging to diagnose accurately and thus treat appropriately.

Although they are often called Paediatric Sarcomas because of their prevalence in children, they can occur in adults as well. When children are diagnosed with cancer, they have special needs. This means that the entire family is affected in a way that is not altogether true for adults with cancer.

Childhood Clear-Cell Sarcoma of the Kidney (CCSK)
Clear cell sarcoma of the kidney (CCSK) is a rare type of kidney cancer comprising 3% of all paediatric renal tumours. Clear-cell sarcoma of the kidney can spread from the kidney to other organs, most commonly the bone, but also including the lungs, brain, and soft tissues of the body. Despite the similarities in names, clear-cell sarcoma of the kidney is unrelated to clear-cell sarcoma of soft tissue, also known as malignant melanoma of soft parts.

This tumour may recur many years after its initial diagnosis. The average age at diagnosis is 2 to 4 years. External tumours histologically identical to CCSK have been reported in rare instances. This tumour may be confused with other paediatric renal tumours including blastemal-predominant Wilms’ tumour, malignant rhabdoid tumour, and cellular mesoblastic nephroma.
Several histologic variants of CCSK are recognised. The most common variant is the Myxoid CCSK. The nuclear accumulation of p53 in anaplastic tumours is thought to represent evidence of p53 gene mutation, a finding that has been well-documented in anaplastic Wilms’ tumours.

The frequency of different CCSK variants include:

- Myxoid pattern (50%)
- Sclerosing pattern (35%)
- Cellular pattern (26%)
- Epithelioid pattern (trabecular or acinar type) (13%)
- Palisading (verocay-body) pattern (11%)
- Spindle cell pattern (7%)
- Storiform pattern (4%)
- Anaplastic pattern (2.6%)

**Alder, A.P. & Pillay, K. 2019.**

“Clear cell sarcoma of the kidney is an uncommon malignant pediatric renal neoplasm that typically presents in the 2- to 3-year age group and has a propensity for aggressive behavior and late relapses. Histologically, this tumor exhibits a great diversity of morphologic patterns which can mimic most other pediatric renal neoplasms, often leading to confusion and misdiagnosis. Until recently, adjunct immunohistochemical and molecular genetic tests to support the diagnosis were lacking. The presence of internal tandem duplications in BCL-6 coreceptor (BCOR) and a translocation t(10;17) creating the fusion gene YWHAE-NUTM2B/E have now been well accepted. Immunohistochemistry for BCOR has also been shown to be a sensitive and specific marker for clear cell sarcoma of the kidney in the context of pediatric renal tumors. Improved intensive chemotherapy regimens have influenced the clinical course of the disease, with late relapses now being less frequent and the brain having overtaken the bone as the most common site of relapse.”

**Aw, S.J. & chang, K.T.E. 2019.**

“Clear cell sarcoma of the kidney is the second most common primary renal malignancy in childhood. It is histologically diverse, making accurate diagnosis challenging in some cases. Recent molecular studies have uncovered BCOR exon 15 internal tandem duplications in most cases, and YWHAE-NUTM2 fusion in a few cases, with the remaining cases having other genetic mutations, including BCOR-CCNB3 fusion and EGFR mutations. Although clear cell sarcoma of the kidney has no specific immunophenotype, several markers including cyclin D1, nerve growth factor receptor, and BCOR (BCL6 corepressor) have emerged as potential diagnostic aides. This review provides a concise account of recent advances in our understanding of clear cell sarcoma of the kidney to serve as a practical update for the practicing pathologist.”


“Clear cell sarcoma of kidney (CCSK) is classified as a tumour of unfavourable histology by the National Wilms’ Tumor Study Group. It has worse clinical outcomes than Wilms’ tumour. Virtually nothing is known about CCSK biology, as there have been very few genetic aberrations identified to act as pointers in this cancer. Three cases of CCSK bearing a chromosomal translocation, t(10;17)(q22;p13), have been individually reported but not further investigated to date. The aim of this research was to characterize t(10;17)(q22;p13) in CCSK to identify the genes involved in the translocation breakpoints. Using fluorescently labelled bacterial artificial chromosomes (BACs) and a chromosome-walking strategy on an index case of CCSK with t(10;17)(q22;p13) by karyotype, we identified the chromosomal
breakpoints on 17p13.3 and 10q22.3. The translocation results in rearrangement of YWHAE on chromosome 17 and FAM22 on chromosome 10, producing an in-frame fusion transcript of ~3 kb, incorporating exons 1-5 of YWHAE and exons 2-7 of FAM22, as determined by RT-PCR using YWHAE- and FAM22-specific primers. The YWHAE-FAM22 transcript was detected in six of 50 further CCSKs tested, therefore showing an overall incidence of 12% in our cohort. No transcript-positive cases presented with stage I disease, despite this being the stage for 31% of our cohort. Tumour cellularity was significantly higher in the cases that were transcript-positive. Based on the chromosome 10 breakpoint identified by FISH and the sequences of the full-length transcripts obtained, the FAM22 members involved in the translocation in these CCSK cases include FAM22B and FAM22E. Elucidation of the role of YWHAE-FAM22 in CCSK will assist development of more efficient and targeted therapies for this childhood cancer, which currently has poor outcomes.”

Incidence of Childhood Clear-Cell Sarcoma of the Kidney
The South African National Cancer Registry (2014) does not provide any information regarding the incidence of childhood clear-cell sarcoma of the kidney.

Signs and Symptoms of Clear-Cell Sarcoma of the Kidney (CCSK)
The signs and symptoms of CCSK are very similar to that of Wilms’ tumour and include:

A lump or mass in the abdomen of an otherwise well child.

- Abdominal pain
- Blood in the urine (haematuria)
- High blood pressure
- Fever
- Diarrhoea
- Weight loss
- Urogenital infections

Diagnosis of Clear-Cell Sarcoma of the Kidney
Manifestations in patients with clear cell sarcoma of the kidney (CCSK) are similar to those in patients with Wilms’ tumour. Patients present with an abdominal mass, which is usually identified by a caregiver or family relative who has not seen the child in some time.

Often, abdominal swelling or the presence of an abdominal mass is noticed by a parent while bathing or dressing the child. Abdominal pain, gross haematuria, fever, and hypertension are other frequent findings.

Physical findings include a large palpable unilateral abdominal mass. Patients may have accompanying findings, such as hypertension and/or haematuria (gross or microscopic), depending on the size of the tumour. Extrarenal tumours with histologic features identical to those of clear-cell sarcoma of the kidney have been reported.
“Clear cell sarcoma of the kidney (CCSK) is a rare tumor that is diagnosed most often in children between 2- and 4-years-old of age. Usually, patients with CCSK are treated in international study for intrarenal tumors, preferentially Wilms tumor, according to bad histoprognostic group. The purpose of this paper is to review the most important features in 2015 about epidemiology, radiology, anatopathology and genetic of CCSK, and above all a synthesis about successive treatment strategies with their results. Second most common pediatric renal tumor in children less than 5-years-old, its prognosis has improved dramatically in recent years with the use of anthracyclines.”

“The largest series, to date, of fine-needle aspiration cytology (FNAC) findings in clear-cell sarcoma of the kidney (CCSK) is presented. All fine-needle aspirates of pediatric renal masses over a 17-yr period were reviewed. Eight out of 119 aspirates from late-stage childhood renal tumors (6.72%) were found to be CCSK. Ten aspirates from these eight patients and histopathological confirmation in six patients were available. Aspirates were cellular with three cell types: cord cells, septal cells, and small pyknotic cells. Cord cells, seen in all aspirates, were large polygonal cells with abundant eccentrically placed wispy cytoplasm, round to oval nuclei, and fine dusty chromatin. Occasional bare nuclei and frequent nuclear grooves were also seen. Small pyknotic cells were a degenerative change identified in 9 out of 10 aspirates. Stromal fragments with branching vascular cores were seen in 8 out of 10 aspirates, 6 of which had myxoid substance surrounding the vessel. Septal cells were spindle shaped and usually embedded in the stromal fragments. On the basis of cytology and histology, cases were classified into classical CCSK (5 cases), spindle-cell CCSK (1 case), and anaplastic CCSK (2 cases). Classical CCSK showed mostly cord cells with few stromal fragments. Spindle-cell CCSK showed preponderance of myxoid stromal fragments and septal cells. Anaplastic CCSK showed bizarre pleomorphic nuclei, coarse chromatin, and atypical mitosis. Cytology of CCSK is a spectrum with varying proportions of cord cells, septal cells, and mucopolysaccharide substance. Anaplastic CCSK is liable to misdiagnosis as Wilms tumor (WT) with unfavourable histology. Presence of eccentric cytoplasm in cord cells and nuclear grooves are the key to differentiation from Wilms tumor, including anaplastic variants.”

Treatment of Childhood Clear-Cell Sarcoma of the Kidney (CCSK)
The approach for treating clear-cell sarcoma of the kidney (CCSK) is different from the approach for Wilms’ tumour because the overall survival of children with clear-cell sarcoma of the kidney remains considerably lower than that of patients with favourable-histology Wilms’ tumour.

In the third National Wilms’ Tumour Study (NWTS-3), the addition of doxorubicin to the combination of vincristine, dactinomycin, and radiation therapy resulted in an improvement in disease-free survival in patients with clear-cell sarcoma of the kidney.

NWTS-4 showed that patients treated with vincristine, doxorubicin, and dactinomycin for 15 months had an improved relapse-free survival rate compared with patients treated for 6 months (87.5% vs 60.6% at 8 y). The overall survival has improved for patients with clear-cell sarcoma of the kidney from NWTS-3 to NWTS-4 (83% vs 66.9% at 8 y). The 8-year relapse-free survival rate for localised clear-cell sarcoma of the kidney stages I-III is 88%, but late relapses have been known to occur. In the NWTS-5 protocol, patients with all stages of CCSK are treated with the same regimen used in patients who have Wilms’ tumour with diffuse anaplasia (excluding stage I); this treatment consists of a radical nephrectomy followed by radiotherapy and chemotherapy with cyclophosphamide, etoposide, vincristine, and doxorubicin for 24 weeks.
In the NWTSG series that was reviewed by Argani et al, a better prognosis was indicated in the subset of patients with clear-cell sarcoma of the kidney that was characterised by stage I tumours in patients aged 2-4 years in whom no tumour necrosis was identified.

In the current Children's Oncology Group protocol (AREN0321), all patients with clear-cell sarcoma of the kidney, except patients with stage IV, continue treatment as in NWTS-5. However, patients with stage I who undergo lymph node sampling do not undergo radiation therapy to the tumour bed. Any patient with stage I who has not undergone lymph node sampling is upstaged to stage II. Patients with stage IV undergo treatment with irinotecan and vincristine in an upfront window approach before treatment with cyclophosphamide, etoposide, vincristine, doxorubicin, and cyclophosphamide.

Surgical Care - at presentation, radical nephrectomy is the initial treatment of choice if the lesion is resectable. If the size or extension of the lesion is in question, a biopsy is performed, and chemotherapy is administered, followed by surgical resection after a response has been obtained.


PURPOSE: Clear Cell Sarcoma of the Kidney (CCSK) is a rare childhood renal tumour. Only a few homogeneously treated CCSK cohorts have been reported. This study aims to describe clinical characteristics and survival of CCSK patients treated according to recent International Society of Pediatric Oncology (SIOP) protocols.

PATIENTS AND METHODS: We analysed the prospectively collected data of patients with a histologically verified CCSK, entered onto SIOP 93-01/2001 trials.

RESULTS: A total of 191 CCSK patients (64% male) were analysed, with a median age at diagnosis of 2.6 years. Stage distribution for stages I, II, III and IV was 42%, 23%, 28% and 7%, respectively. Pre-operative chemotherapy was administered to 169/191 patients. All patients underwent total nephrectomy and 189/191 patients received post-operative chemotherapy. Radiotherapy was applied in 2/80 stage I, 33/44 stage II, 44/54 stage III and 6/13 stage IV patients. Five year event-free survival (EFS) and overall survival (OS) were 79% (95% confidence interval (CI): 73-85%) and 86% (95% CI: 80-92%) respectively. Stage IV disease and young age were significant adverse prognostic factors for event-free survival. Factors such as gender, tumour volume and type of initial treatment were not found to be prognostic for EFS and OS.

CONCLUSION: In this largest SIOP cohort described so far, overall outcome of CCSK is reasonable, although treatment of young and advanced-stage disease patients is challenging. As further intensification of treatment is hampered by direct and late toxicity, future directions should include the development of targeted therapy based on specific molecular aberrations of CCSK.

About Clinical Trials
Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:
- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers

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Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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Sources and References Consulted or Utilised


Atlas of Genetics and Cytogenetics in Oncology and Haematology
http://atlasgeneticsoncology.org/Tumors/t1017ClCellSarclD5412.html


Children’s Oncology Group


Medscape
http://emedicine.medscape.com/article/993245-clinical

National Cancer Institute
http://www.cancer.gov/clinicaltrials/learningabout/what-are-clinical-trials


Sarcoma

Sarcoma Alliance


The Liddy Shriver Sarcoma Initiative
http://sarcomahelp.org/clear-cell-sarcoma.html

Wikipedia