Outcomes in Clear Cell Sarcoma: Updated Insights from Electronic Health Records in a Patient-Led Registry

Lennie D. Woods[1], Jill Neal[1], Lisa A. Faulkner[1], Ann Lopez[1], Denise Reinke[2], Kelley M. Argraves[1]

[1]Clear Cell Sarcoma Foundation, [2]University of Michigan

Objective

Clear Cell Sarcoma (CCS) is a rare, aggressive soft tissue sarcoma driven by EWSR1-ATF1 gene fusion. It typically affects adolescents and young adults and is known for its resistance to conventional therapies and tendency to metastasize early. Clinical trial data are extremely limited due to its ultra-rare nature. To address this gap, the Clear Cell Sarcoma Foundation (CCSF) initiated a patient-participation registry with electronic health records (EHRs) aggregated through xCures to generate a longitudinal, real-world dataset. We previously reported early findings to help characterize the natural history of CCS. The objective of this study is to present updated analyses from this registry, reflecting expanded enrollment and additional real-world outcome data. This registry is designed to inform patients, clinicians, and researchers by capturing treatment histories and outcomes across multiple institutions.

Methods

Patients with confirmed CCS (or their caregivers) voluntarily enroll in the CCSF registry and authorize release of their medical records. EHRs are obtained from treating institutions and standardized into a research dataset via xCures, LLC. Records include demographic information, diagnostic details, treatment history (surgery, radiation, systemic therapy), tumor location and stage, and longitudinal outcomes. Data abstraction follows a retrospective design with ongoing prospective updates as new records are obtained. This model allows capture of treatment across both academic and community centers, reflecting real-world care beyond clinical trial cohorts.

Patient Demographics and Clinical Characteristics N=21

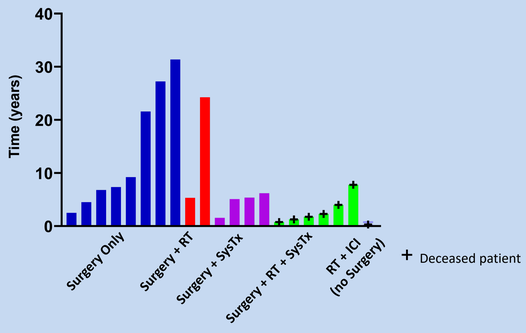
Median Age at Dx	Biomarkers	Location of Primary Tumor	Treatment Type
32 years (11-57)	• EWSR1-ATF1 81.0% (17/21) • EWSR1 (fusion partner not specified) additional histology 4.8% (1/21) • CCS by Histology 14.3% (3/21)	• Lower Extremity 52.4% (11/21) • Upper Extremity 14.3% (3/21) • Chest 9.5% (2/21) • Head/Neck 14.3% (3/21) • GI System 9.5% (2/21)	• Surgery 95.2% (20/21) • Cytotoxic Chemotherapy 19.0% (4/21) • Radiation 47.6% (10/21) • Tyrosine Kinase Inhibitor 14.3% (3/21) • Immunotherapy 38.1% (8/21) • Metabolic therapy (devimistat) 9.5% (2/21) • Repurposed drug protocols (Care Oncology) 9.5% (2/21)
Sex at Birth • Female 66.7% (14/21) • Male 33.3 % (7/21)	**Disease Status** • Localized 71.4% (15/21) • Metastatic 23.8% (5/21) • Unknown 4.8% (1/21)		
Race • Asian 14.3% (3/21) • White 71.4% (15/21) • Not Reported 14.3% (3/21)			

Alive to date 66.7% (14/21)

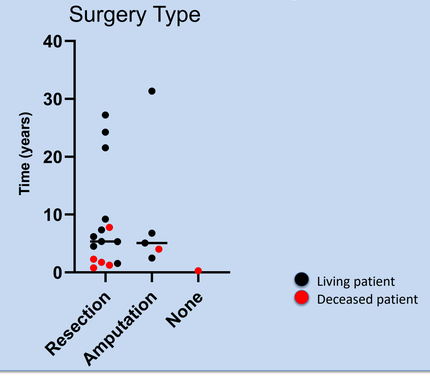
Results

A total of 21 patients with clear cell sarcoma (CCS) were included in this preliminary analysis. The median age at diagnosis was 32 years (range 11–57), with two-thirds female (66.7%). The majority of tumors arose in the lower extremity (52.4%). EWSR1::ATF1 fusions were identified in 81% of patients, while the remainder were diagnosed by histology to confirm CCS and exclude melanoma. At diagnosis, 71.4% of patients had localized disease, 23.8% had metastatic disease, and 4.8% had unknown status. Nearly all patients underwent surgery (95.2%).Treatment exposures were heterogeneous. Radiation therapy (RT) was given to 47.6%, cytotoxic chemotherapy to 19.0%, immune checkpoint inhibitors (ICI) to 38.1%, tyrosine kinase inhibitors to 14.3%, metabolic therapy (devimistat) to 9.5%, and repurposed drug regimens to 9.5%. At the time of analysis, 66.7% of patients were alive.

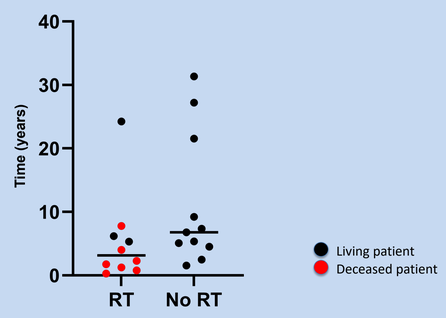
CCS Patient Survival Outcome by Treatment Approach



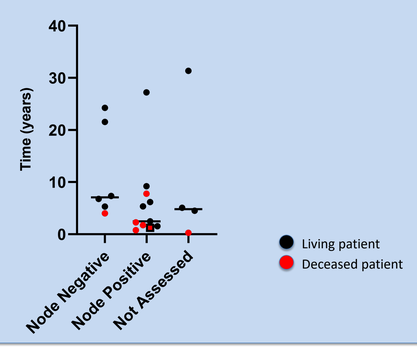
CCS Patient Survival Outcome by Surgery Type



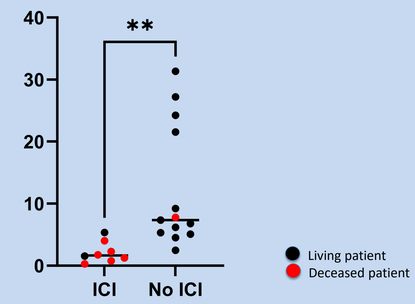
CCS Patient Survival Outcome by Radiation Therapy Status



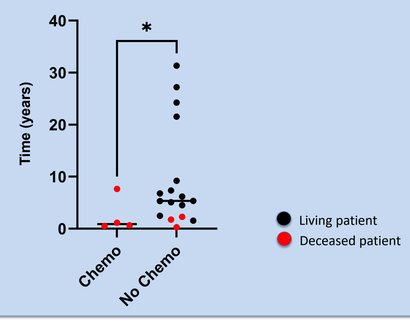
CCS Patient Survival Outcome by Lymph node status



CCS Patient Survival Outcome by Immune Checkpoint Inhibitor Therapy



CCS Patient Survival Outcome by Chemotherapy Treatment



Results (Continued)

Patients who received surgery as their only treatment appeared to have the longest survival durations, in some cases exceeding 20 years. No significant difference was observed between resection and amputation, but conclusions are limited by small sample size. Node-positive disease showed a trend toward shorter survival without statistical significance. Radiation therapy did not show a consistent impact on overall survival. Immune checkpoint inhibitor (ICI) therapy was associated with significantly shorter survival compared to those who did not receive ICI ($p < 0.01$**). Chemotherapy exposure was also linked to poorer outcomes overall, reaching statistical significance ($p < 0.05$*); however, some patients received only limited treatment (e.g., a single dose), which may influence interpretation.

Significance: $p < 0.05$ (*); $p < 0.01$ (**).

Conclusions and Future Directions

The CCSF–xCures registry demonstrates the feasibility of collecting multi-institutional, real-world data in ultra-rare CCS. Obtaining and harmonizing electronic health records is not a straightforward process, as records are often incomplete or fragmented across institutions. This requires additional effort to reconcile with patient-reported histories and registry notes to ensure accuracy and completeness. The registry will continue to expand enrollment to increase statistical power for addressing key clinical questions, including systemic therapy sequencing, the role of radiation relative to surgical margins, and outcomes in unique contexts such as pregnancy. Planned analyses will incorporate treatment tolerability, toxicity, and patient-reported outcomes to complement survival endpoints. By leveraging patient-driven, multi-institutional data, the CCSF registry aims to provide actionable evidence to guide care, support trial design, inform research priorities and improve outcomes for the CCS community.

Acknowledgements

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